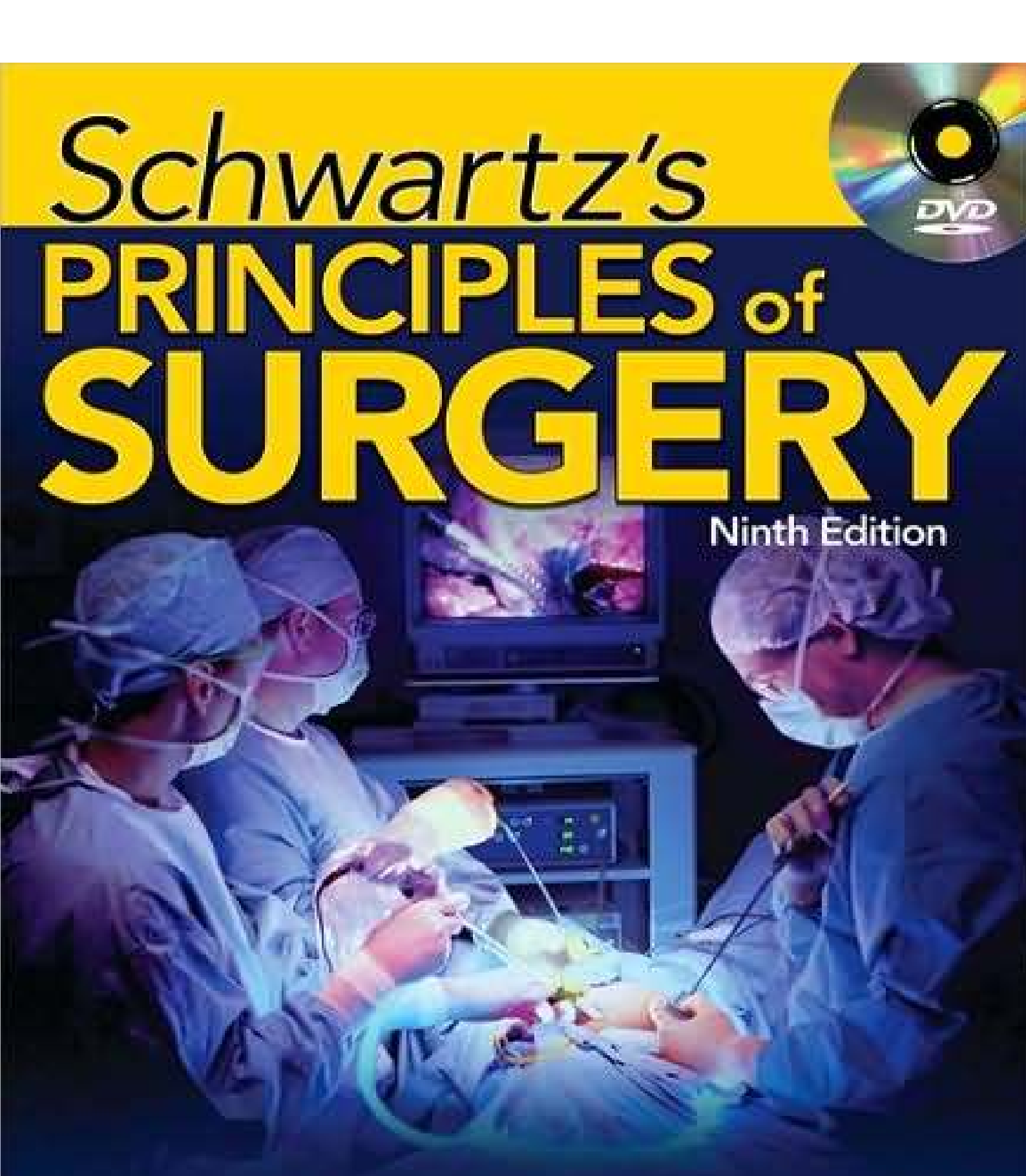
Schwartz's PRINCIPLES of SURGERY

Ninth Edition



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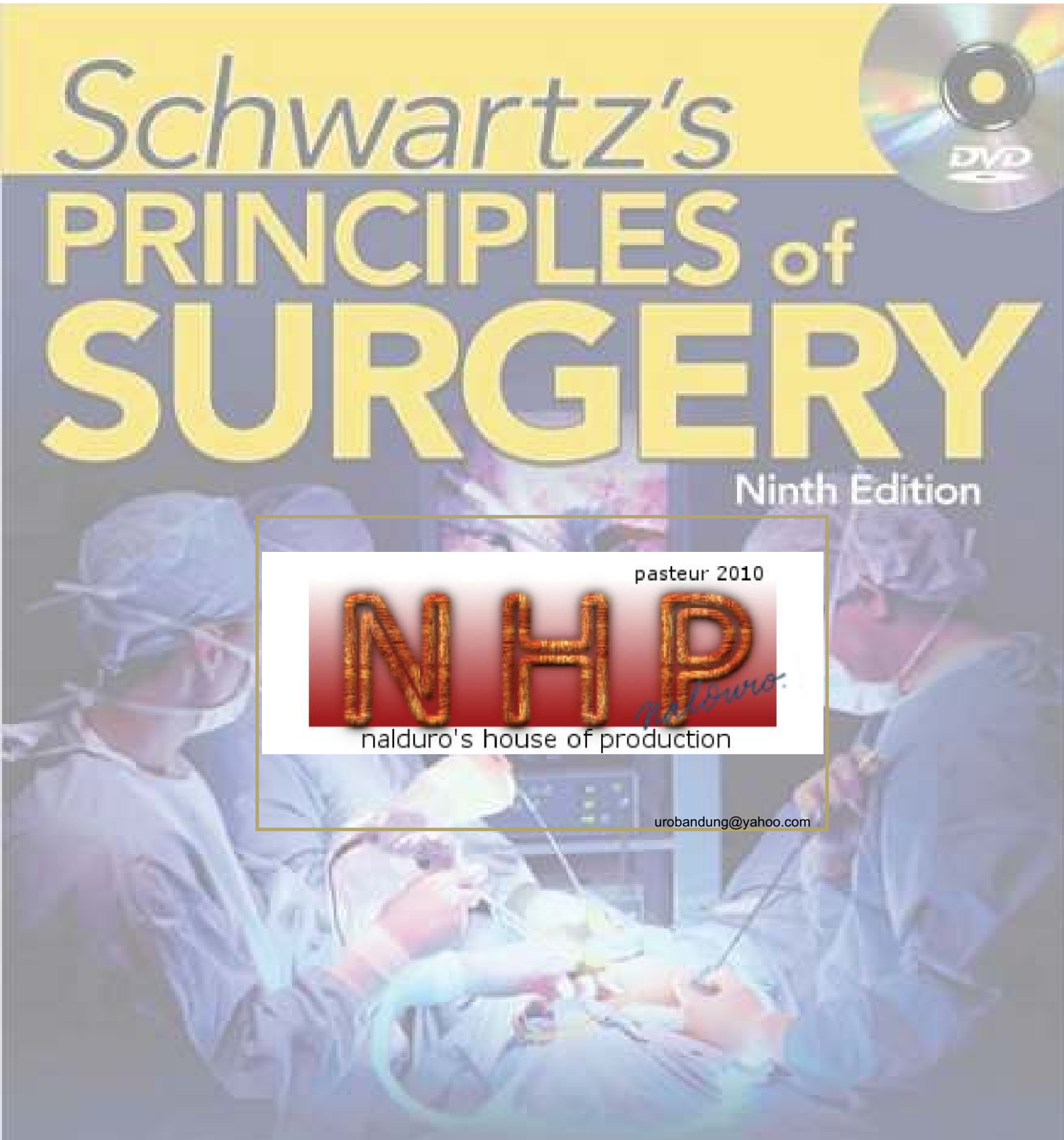

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Preface

When I was asked to serve as editor-in-chief of this historic textbook of surgery, my goal was to preserve its excellent reputation, honoring the commitment of Dr. Seymour Schwartz and previous co-editors and contributors who upheld the highest standard for seven prior editions. I would like to thank all who helped achieve this goal, namely the outstanding contributions by the individual chapter authors and the meticulous dedication of the editorial board, all of whom share a passion for patient care, teaching, and surgery.

It is this shared passion that has been channeled now into the creation of this new ninth edition; updating, improving, and finetuning it to secure its place as a leading international textbook of surgery. Each chapter has either been fastidiously updated or created anew by leaders in their respective surgical fields to ensure the highest quality of surgical teaching. Additionally, each chapter has been outfitted with quick-reference key points; highlighted evidenced-based references; and full-color illustrations, images, and information tables. Two new chapters have been added to this edition: *Accreditation Council for Graduate Medical Core Competencies* and *Ethics, Palliative Care, and Care at the End of Life*.

One new component of this edition is the inclusion of a digital video disc of surgical videos. Many students already augment their more traditional classroom and practical education through the breadth of information available in the electronic realm, such as that available on AccessSurgery.com. This collection of operative and instructional videos, generously provided by chapter authors and editors, provides accurate visual instruction and technique to round out students' surgical training. It is the sincere hope of all who have contributed to this textbook that the knowledge of craft contained within will provide a solid foundation for the acquisition of skill, a haven for the continuation of education, and motivation for the pursuit of excellence.

I wish to thank all of those responsible for the publication of this new edition, including the newest member of the editorial board, Dr. Jeffrey Matthews, as well as those who fearlessly signed on as contributors to our newly established international editorial board to provide regional perspective and commentary. I extend many thanks and gratitude to Marsha Loeb, Christie Naglieri, and all at McGraw-Hill for their guidance and knowledge throughout this process. I wish to thank Katie Elsbury for her dedication to the organization and editing of this textbook. I would also like to thank our families, whose love and support *continue* to make this book possible.

F. Charles Brunicardi, MD, FACS

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Knot Tying
Suturing
Laparoscopic Cholecystectomy on a Patient with Biliary Colic and Gall Stones
Laparoscopic Nissen Fundoplication
Laparoscopic Distal Pancreatectomy
Totally Extra-Peritoneal (TEP) Hernia Repair
Laparoscopic Adjustable Gastric Band and Hiatal Hernia Repair
Laparoscopic Sleeve Gastrectomy

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Open Surgical Treatment of Extent IV Thoracoabdominal Aortic Aneurysms

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Open Surgical Treatment of Extent IV Thoracoabdominal Aortic Aneurysms

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KEY POINTS

1. The Accreditation Council for Graduate Medical Education (ACGME) Outcomes Project changes the focus of graduate medical education from how programs are *potentially* educating residents to how programs are *actually* educating residents through assessment of competencies.

2. The six core competencies are patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice.

3. The Residency Review Committee recognizes the importance of simulators for technical training and mandated that all training programs have a skills laboratory by July 2008. A Surgical Skills Curriculum Task Force has developed a National Skills Curriculum to assist programs with training and assessing competency through simulators.

4. The ACGME has developed a professional development tool called the *ACGME Learning Portfolio.* This interactive web-based portfolio can be used as a tool for residents, faculty, and programs directors to allow for reflection, competency assessment, and identification of weaknesses.

5. There is much to be learned still, and programs should continue to share their experiences to identify benchmark programs.

ACCREDITATION COUNCIL FOR GRADUATE MEDICAL EDUCATION OUTCOMES PROJECT

Technologic and molecular advances have fundamentally changed the way medicine is practiced. The Internet has revolutionized the way both physicians and patients learn about diseases. In addition, political and economic pressures have altered the way society views and reimburses medical care. The end result of these changes is that access to medical care, access to information about medical care, and the very nature of the doctor-patient relationship has changed.[1] In response to this situation, the Accreditation Council for Graduate Medical Education (ACGME) Outcomes Project was developed. Dr. Leach stated that this initiative was based on three principles: (1) whatever we measure we tend to improve; (2) focusing on outcomes instead of processes allows programs flexibility to adapt based on their needs and resources; and (3) the public deserves to have access to data demonstrating that graduating physicians are competent.[2] This initiative changed the focus of graduate medical education from how programs were *potentially* educating residents by complying with the accreditation requirements to how programs are *actually* educating residents through assessment of the program's outcomes. In 1999, the Outcomes Project identified six core competencies that would provide a conceptual framework to train residents to competently and compassionately treat patients in today's changing health care system. The six core competencies as designated by the ACGME are patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice (Table 1-1).[3] Starting in July 2001, the ACGME

implemented a 10-year timeline to implement these concepts into medical education. The timeline was divided into four phases, allowing flexibility for individual programs to meet these goals (Table 1-2).[4]

Table 1-1 Accreditation Council for Graduate Medical Education Core Competencies

Core Competency	Description
Patient care	To be able to provide compassionate and effective health care in the modern-day health care environment
Medical knowledge	To effectively apply current medical knowledge in patient care and to be able to use medical tools (i.e., PubMed) to stay current in medical education
Practice-based learning and improvement	To critically assimilate and evaluate information in a systematic manner to improve patient care practices
Interpersonal and communication skills	To demonstrate sufficient communication skills that allow for efficient information exchange in physician-patient interactions and as a member of a health care team
Professionalism	To demonstrate the principles of ethical behavior (i.e., informed consent, patient confidentiality) and integrity that promote the highest level of medical care
Systems-based practice	To acknowledge and understand that each individual practice is part of a larger health care delivery system and to be able to use the system to support patient care

Table 1-2 Accreditation Council for Graduate Medical Education Timeline

Phase	Dates	Program Focus	Accreditation Focus
1. Forming an initial response to changes in requirements	July 2001–June 2002	▪ Define objectives for residents to demonstrate learning the competencies ▪ Review current approaches to evaluation of resident learning ▪ Begin integrating the teaching and learning of competencies into residents' didactic and clinic experience	▪ Develop operational definitions of compliance ▪ Provide constructive citations and recommendations with no consequences
2. Sharpening the focus	July 2002–June 2006	▪ Provide learning opportunities in all six competencies ▪ Improve evaluation process to obtain accurate resident performance on the six core competencies ▪ Provide aggregated resident performance data for the program's GMEC internal review	▪ Review evidence that programs are teaching and assessing the competencies ▪ Provide constructive citations early in the phase and transition to citations with consequences later ▪ Review evidence that GMECs' internal reviews of programs include consideration of aggregated performance data
3. Full integration	July 2006–June 2011	▪ Use resident performance data as basis for improvement and provide evidence for accreditation review ▪ Use external measures to verify resident and program performance	▪ Review evidence that programs are making data-driven improvements ▪ Review external program performance measures and input from GMECs as evidence for achieving educational goals

		levels	
4. Expansion	July 2011–beyond	—	• Identify benchmark programs • Adapt and adopt generalizable information about models of excellence • Invoke community about building knowledge about good graduate medical education

GMEC = graduate medical education committee.

CORE COMPETENCIES

The core competencies include six specific areas that have been designated as critical for general surgery resident training. Each surgical training program must provide an environment that is conducive to learning the core competencies, establish a curriculum that addresses each of the competencies, and assess that learning has taken place (see Table 1-1). The six core competencies are as follows[5] :

1. Patient Care. Residents must be able to provide patient care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health. Residents:

a. Will demonstrate manual dexterity appropriate for their level;

b. Will develop and execute patient care plans appropriate for the resident's level, including management of pain;

c. Will participate in a program that must document a clinical curriculum that is sequential, comprehensive, and organized from basic to complex. The clinical assignments should be carefully structured to ensure that graded levels of responsibility, continuity in patient care, a balance between education and service, and progressive clinical experience are achieved for each resident.

2. Medical Knowledge. Residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiological, and social-behavioral sciences, as well as the application of this knowledge to patient care. Residents:

a. Will critically evaluate and demonstrate knowledge of pertinent scientific information, and

b. Will participate in an educational program that should include the fundamentals of basic science as applied to clinical surgery, including applied surgical anatomy and surgical pathology; the elements of wound healing; homeostasis, shock and circulatory physiology; hematologic disorders; immunobiology and transplantation; oncology; surgical endocrinology; surgical nutrition, fluid and electrolyte balance; and the metabolic response to injury, including burns.

3. Practice-Based Learning and Improvement. Residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and life-long learning. Residents are expected to develop skills and habits to be able to meet the following goals:

a. Identify strengths, deficiencies, and limits in one's knowledge and expertise;

b. Set learning and improvement goals;

c. Identify and perform appropriate learning activities;

d. Systematically analyze practice using quality improvement methods, and implement changes with the goal of practice improvement;

e. Incorporate formative evaluation feedback into daily practice;

f. Locate, appraise, and assimilate evidence from scientific studies related to their patients' health problems;

g. Use information technology to optimize learning;

h. Participate in the education of patients, families, students, residents and other health professions;

i. Participate in mortality and morbidity conferences that evaluate and analyze patient care outcomes; and

j. Utilize an evidence-based approach to patient care.

4. Interpersonal and Communication Skills. Residents must demonstrate interpersonal and communication skills that result in effective exchange of information and collaboration with patients, their families, and health professionals. Residents are expected to:

a. Communicate effectively with patients, families, and the public, as appropriate, across a broad range of socioeconomic and cultural backgrounds;

b. Communicate effectively with physicians, other health professionals, and health related agencies;

c. Work effectively as a member or leader of a health care team or other professional group;

d. Act in a consultative role to other physicians and health professionals;

e. Maintain comprehensive, timely, and legible medical records, if applicable.

f. Counsel and educate patients and families; and

g. Effectively document practice activities.

5. Professionalism. Residents must demonstrate a commitment to carrying out professional responsibilities and an adherence to ethical principles. Residents are expected to demonstrate:

a. Compassion, integrity, and respect for others;

b. Responsiveness to patient needs that supersedes self-interest;

c. Respect for patient privacy and autonomy;

d. Accountability to patients, society and the profession;

e. Sensitivity and responsiveness to a diverse patient population, including but not limited to diversity in gender, age, culture, race, religion, disabilities, and sexual orientation;

f. High standards of ethical behavior; and

g. A commitment to continuity of patient care.

6. Systems-Based Practice. Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care. Residents are expected to:

a. Work effectively in various health care delivery settings and systems relevant to their clinical specialty;

b. Coordinate patient care within the health care system relevant to their clinical specialty;

c. Incorporate considerations of cost awareness and risk-benefit analysis in patient and/or population-based care as appropriate;

d. Advocate for quality patient care and optimal patient care systems;

e. Work in inter-professional teams to enhance patient safety and improve patient care quality;

f. Participate in identifying system errors and implementing potential systems solutions;

g. Practice high quality, cost effective patient care;

h. Demonstrate knowledge of risk-benefit analysis; and

i. Demonstrate an understanding of the role of different specialists and other health care professionals in overall patient management.

The goal of any surgical training program is to train physicians to provide the highest quality of patient care. The core competency mandates have set into motion changes in education that result in measurable outcome-based training. The challenge of the surgical educator is to develop innovative and focused learning techniques to accomplish this mandate within an 80-hour work week.

Patient Care

Patient care is the foundation for the practice of clinical medicine and must be addressed early and continuously during residency. Historically, patient care has been taught by an apprenticeship model; in other words, by the residents' spending time with attending physicians on the wards or in the operating rooms.[6] However, this training method has to be re-evaluated as a result of the ever-increasing constraints and changes in our health care system. Increasing public awareness of medical legal errors has resulted in heightened scrutiny with regard to patient safety issues.[1] In addition, there are increasing concerns related to the perceived financial setback and medical-legal impact of resident training in the operating room.[7] Even with the inherent flexibility provided by the ACGME, all of these factors, coupled with the work hour restrictions,[8] make surgical training in the modern health care system an especially challenging endeavor. Not only must educators impart the medical knowledge of caring for patients and new advances in patient care, but they must also impart the technical skills necessary to perform complex surgical procedures.

One of the subcompetencies under patient care is that residents "will demonstrate manual dexterity appropriate for their level."[5] Traditionally, the operating room has been used to train residents in the technical aspects of patient care by "see one, do one, and teach one." A study by Velmahos and colleagues evaluated the knowledge and technical skills of residents who were randomly assigned either to training using the traditional approach or to training in a surgical skills laboratory using the principles of cognitive task analysis. This study revealed that the residents who trained using the laboratory approach had improved medical knowledge and technical skills.[9] Multiple studies like the one previously mentioned have revealed improved performance with simulators and advocated their use in technical skills training.[10–12] Having recognized the importance of incorporating simulation training into today's residency, the Residency Review Committee (RRC) mandated that all surgery programs be required to have a surgical skills laboratory by July 2008 to maintain their accreditation.[13] To assist programs, the Surgical Skills Curriculum Task Force, a joint project of the American College of Surgeons (ACS) and the Association of Program Directors in Surgery, developed a standardized skills curriculum.[14,15] This curriculum was developed in three phases (Table 1-3): phase I with modules for junior residents, phase II for senior residents, and phase III for team training. Another resource that programs may use in developing a surgical skills curriculum is the Fundamentals of Laparoscopic Surgery (FLS) program. This program is endorsed by the ACS and the Society of Gastrointestinal and Endoscopic Surgeons. The FLS consists of a comprehensive curriculum with hands-on skills training and an assessment tool designed to teach and assess the fundamentals of laparoscopic surgery.[16] Future goals for surgical education include a method to ensure that residents are "certified" and deemed competent to perform a procedure in a simulator environment before allowing residents to perform that particular procedure in the operating room.[17]

Table 1-3 National Skills Curriculum Phases and Launch Dates	
Phase	**Dates**

I	Basic/core skills and tasks	July 2007
II	Advanced procedures	January 2008
III	Team-based skills	July 2008

The RRC has mandated that all residency programs develop a surgical skills laboratory, and the majority of program directors feel that this is an important part of residency training. However, a study by Korndorffer and associates just before the mandate was issued revealed that only 55% of the 162 programs that replied to the survey had a surgical skills laboratory facility.[18] The average cost to develop a laboratory has been reported as $133,000 to $450,000, but the cost can range from $300 to $3 million.[18,19] Kapadia and colleagues surveyed 40 programs with surgical skills laboratories in place and found that funding came from industry (68%), surgery departments (64%), hospitals (46%), and other sources (29%). They also found a wide variation in the size of the facility, location, availability of simulators, protected time for skills training, and curriculum. This study also revealed that 65% of the programs believed that it was somewhat difficult to recruit faculty members to staff the laboratory; however, this could be related to the fact that 69% of the laboratories did not offer any faculty incentive to teach.[19] These studies suggest that although most surgical educators believe that surgical skills laboratories are important for resident education, there is still much room for improvement and standardization.

In addition to technical competency, residents are expected to "develop and execute patient care plans appropriate for the resident's level, including management of pain."[5] This can be reinforced during attendance at rounds and integrated into many of the conferences that are currently available in many surgery programs, such as grand rounds and the morbidity and mortality conference.[20,21] Prince and others demonstrated in an institutional study that use of an interactive format for the morbidity and mortality conference improved the educational value of the conference for residents at all levels.[22] Rosenfeld restructured the morbidity and mortality conference to make it more competence based. For example, each patient case was further divided into separate categories such as patient communication, ethical dilemmas, system problems, and practice-based improvement to enhance patient care.[20] Stiles and associates developed a morning report conference after the implementation of the night float system to improve patient sign-out procedures. They found that this forum not only helped to improve communication but also allowed for teaching, discussion of patient care plans, and direct evaluation of resident competence.[23]

Medical Knowledge

The ACGME has mandated that "residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiological, and social-behavioral sciences, as well as the application of this knowledge to patient care."[5] Surgery has undergone an exponential growth in new procedures and technology. With this explosion in medical innovation, training programs are posed with the daunting task of not only teaching the technical aspects of surgery, but also imparting the basic science and fundamentals of surgical diseases. Furthermore, development of the field of molecular biology and its application to surgical diseases has mandated that surgeons understand the basic molecular mechanisms of each disease process.[24,25] The new era of molecular biology requires understanding the complex science that can lead to advances such as molecular fingerprinting techniques to tailor treatments that are specific for each individual patient. Other, more cognitive tools such as how to critically review literature and how to logically evaluate the relevance of a study must also be imparted to residents so that they can correctly apply findings of the latest medical studies to each individual patient.

The ACGME mandates that residents "will participate in an educational program that should include the fundamentals of basic science as applied to clinical surgery, including applied surgical anatomy and surgical pathology; the elements of wound

healing; homeostasis, shock and circulatory physiology; hematologic disorders; immunobiology and transplantation; oncology; surgical endocrinology; surgical nutrition, fluid and electrolyte balance; and the metabolic response to injury, including burns."[5] The ability of a surgical program to adequately meet this educational challenge can be improved by using innovative learning techniques. Educational systems such as the SQR3 (Survey, Question, Read, Recite, and Review) system of studying,[26] the Pimsleur model,[27] and Rosetta Stone learning techniques[28] are all tools that can aid in the understanding and application of advances in a rapidly changing surgical field. The authors' surgery residency program combined adult learning principles with some of these learning techniques into a problem-based learning program that met weekly after grand rounds. This mandatory, focused curriculum for the residents incorporated both basic science and its clinical application in an interactive and collaborative format. This educational format led to high resident satisfaction and also a sustainable increase in resident American Board of Surgery In-Training Examination scores.[29,30]

Residents are also expected to "critically evaluate and demonstrate knowledge of pertinent scientific information."[5] Residents can be taught early how to critically review the literature using the format of a journal club. The journal club is a widely used technique through which to disseminate the latest in medical knowledge. Even as early as the late 1980s, a study in the *Journal of the American Medical Association* found that residents who participated in a journal club had improved reading habits and improved medical knowledge compared with their peers who did not participate in a journal club.[31] The wide use of journal clubs in surgery education can be seen as a necessary foundation for medical education. In one survey, over 65% of general surgery residency programs have a journal club that meets at least once a month to discuss relevant surgical and medical topics.[32] MacRae and others took this approach a step further by evaluating the effect of a multifaceted Internet-based journal club and found that this learning format improved the skills of the surgical residents to critically appraise the medical literature.[33] Many online resources are available for residents that provide an abundant amount of material for study, reference, and interactive learning.[34–36] In particular, AccessSurgery provides an extensive online resource with medical data and operative techniques, with a core curriculum organized around the ACGME mandates.[34] Finally, and perhaps most importantly, it must be conveyed to surgical trainees that surgery is a lifelong learning process, and the ability to continue building on one's medical knowledge is critical for a successful surgical career.

Practice-Based Learning and Improvement

The third ACGME mandate states that "residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and life-long learning."[5] This mandate comes from the increasing public demand for accountability and increased demand for data regarding outcomes for specific surgeon.[2] Practice-based learning and improvement involves a cycle of four steps: identify areas for improvement, engage in learning, apply the new knowledge and skills to a practice, and check for improvement.[37] This ability to critically and impartially analyze one's practice patterns to continually improve patient care should start early during training, so that this behavior becomes second nature for residents when they become practicing surgeons.

In residency training, the simplest example of practice-based learning is the surgical morbidity and mortality conference. This conference traditionally allows for in-depth discussions of surgical cases and adverse patient outcomes. Complications are categorized (preventable, probably preventable, possibly preventable, and unpreventable) and areas of improvement are identified. Rosenfeld as well as Williams and Dunnington have reformatted this conference to make it more competence based by having residents assess themselves. Residents are required to fill out a practice-based improvement form and identify areas of improvement.[20,38] Another innovative modality to teach practice-based learning was described by Canal and

colleagues, who developed a 6-week curriculum in continuous quality improvement for surgery residents that included a specific project. In this project, the residents identified a need for quality improvement, implemented a plan for improvement, and developed a method to measure the improvement. These residents scored significantly higher in knowledge of and experience in quality improvement after completing this curriculum and felt that it was an effective and formal way to teach them the science of practice-based improvement.[39]

Clearly, for surgeons to identify areas of improvement, there has to be some method to allow for comparison and reflection. An interesting Internet-based learning portfolio called *Computerized Obstetrics and Gynecology Automated Learning Analysis (KOALA)* was developed for the obstetrics and gynecology residents in Canada. This portfolio encouraged self-analysis and self-directed learning by allowing residents to log patient encounters, list critical events and questions derived from these events, look up data used to answer these questions, and state how their practice patterns would be altered based on their reflections. Residents who used this method to reflect and critically analyze their performance scored significantly higher on the Self-Directed Learning Readiness Scale, looked forward to learning for life, and had a strong desire to learn new things.[40] An avenue currently available for practicing surgeons and residents to analyze their outcomes is the ACS Case Log System. This system was developed to support practice-based learning and improvement by allowing surgeons to voluntarily report their own results and compare them to those of other surgeons enrolled in the system. This allows surgeons to critically evaluate their practice outcomes and identify areas that need improvement.[41]

To further improve practice patterns, the ACGME has mandated that trainees must understand the use of information technology systems to manage patient information and support clinical care. Technology is rapidly improving, and hospitals are increasing their efficiency by using electronic medical records. One of the best examples of this is the Computerized Patient Record System (CPRS) used by the Veterans Affairs (VA) hospital system. This fully computerized patient database allows easy access to all patient clinical data, including laboratory tests, radiographic studies, physician notes, and appointment times. Use of this central core information system also has allowed the VA health system to develop the National Surgical Quality Improvement Program (NSQIP).[42] Using information from the CPRS, nurse reviewers are able to gather and input information into the NSQIP system. NSQIP has been the first prospective risk-adjusted outcomes-based program for comparing and improving surgical outcomes across multiple institutions. This program has revolutionized the reporting and quality control of surgical services within the VA system.

Practice-based learning is complex and involves many components, including self-awareness, critical thinking, problem solving, self-directed learning, analysis of outcomes, use of information technology, and focus on evidence-based medicine to improve practice outcomes and patient care.[5] This competency is multifaceted, and an extensive literature review by Ogrinc and associates found little instruction on how to impart these important skills to our residents. Much work appears to be needed before an ideal curriculum can be developed. Future plans should be made for faculty to develop these skills and for programs to continually share their experiences.[43]

Interpersonal and Communication Skills

The fourth competency mandated by the ACGME is that "residents must demonstrate interpersonal and communication skills that result in effective exchange of information and collaboration with patients, their families, and health professionals."[5] Effective communication between physicians, patients, and other health care professionals is essential to the successful and competent practice of medicine and patient care. Studies reveal that physicians with good communication and interpersonal skills have improved patient outcomes and are subject to less medical litigation.[44–46] In support of this, a root cause analysis by the Joint Commission identified breakdown in communication as the leading cause of wrong-site operations and

other sentinel events.[47] The ACS has developed a Task Force on Communication and Interpersonal Skills to specifically address this issue and encourage practicing surgeons to develop these important skills.[48] The goal of this task force is to appropriately address the core competency of interpersonal skills and communication and to use novel educational techniques to improve these skills. Certain areas, such as palliative care and patient mortality, have not been a focus for surgeons or surgical trainees but are critical in the surgeon-patient relationship. Four areas in which surgeons can improve their communication skills have been identified in palliative care: the preoperative visit, and discussion of a poor prognosis, surgical complications, and death.[49] These are situations that all surgeons will face at some point in their careers, and the ability to communicate effectively and compassionately with patients during these stressful times is an important skill to develop. Fortunately, multiple techniques for imparting this particular skill have been described in the literature. The group at Southern Illinois University had teams of senior surgical faculty and a faculty member from the Department of Medical Humanities develop a case-based ethics curriculum that covered topics such as resource allocation, research ethics, substituted consent, competition of interests, truth telling, and communication.[17] Other methods to teach communication skills have relied on the use of standardized patients.[38,50,51] Yudkowsky and associates assessed the use of a patient-based communication skills examination. Their conclusion was that the use of a patient-based examination was able to demonstrate consistent results and that verbal feedback was beneficial for resident education on improvement of communication skills.[50] Other recommended teaching strategies include observation with real-time feedback, role modeling, self-assessment, and videotaping.[52]

Residents also are expected to "work effectively as a member or leader of a health care team or other professional group"[5] (Fig. 1-1). This is particularly important for surgeons, because caring for surgical patients requires a team approach to safely get the patient from the preoperative evaluation process, to the operating room, and through the postoperative course. Surgeons are typically the leaders of such teams; hence, it is important for residents to develop the necessary leadership skills during training. With less time spent in the hospital, the ability to learn from real-life situations is limited. Therefore, these principles need to be taught through other creative means such as didactic lectures or problem-based learning. Studies have revealed that formal leadership training not only improves communication skills[53,54] but also helps to develop conflict resolution skills.[55] Awad and colleagues instituted a formal collaborative leadership training program and found that this format significantly increased the residents' views of leadership in the areas of alignment, communication, and integrity.[56] Having recognized leadership training as a necessity for surgeons to thrive in today's medical environment, the ACS offers a course called "Surgeons as Leaders: From Operating Room to Boardroom," whose purpose is to provide surgeons with the skills needed for effective leadership.[57]

Fig. 1-1.

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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Establishing interpersonal and communication skills equips residents with the necessary tools to communicate effectively with both patients and health professionals.

A subcompetency under communication and interpersonal skills is to "maintain comprehensive, timely, and legible medical records."[5] Not only does communication occur in person, but physicians commonly communicate their plans and thoughts in the medical record. One of the predominant issues in health care is medical errors related to poor communication. The consequences of poor communication have been shown to cause delays in patient care, improper use of resources, and serious adverse events that lead to significant morbidity and mortality.[58] This is especially important now, as many programs have instituted the night float system to maintain compliance with the work hour restrictions. For this system to work effectively, communication is integral for safe patient care during shift changes.[59,60] One example of a creative approach to this new challenge of information transfer is a web-based system that allows for secure storage of patient information, maintenance of patient lists, access to laboratory values and vital sign data, and ability to compile this information to a sign-out list that can be passed on to a coverage team.[61] The residents that participated in the study of this system reported better sign-out quality, decreased time collecting data on prerounds, increased patient contact time, and improved continuity of care. Other medical centers also have begun to institute the use of computerized web-based systems for resident sign-out, and this format may become more widespread as the efficiency and safety of these systems become more apparent.

Not only should surgeons be technically competent and medically knowledgeable, but interpersonal and communication skills are also vital to patient care. The inherent nature of surgery often requires the bearing of bad news, disclosure of complications, and discussion of end-of-life issues. Learning and harnessing the skill of doing these things well during residency will provide a lifelong tool to effectively and compassionately care for patients.

Professionalism

The core competency of professionalism is expressed as follows: "residents must demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population."[5] The trainee

should demonstrate respect, compassion, and integrity while involved in patient care. In addition, residents should understand that their patients' needs supersede their own self-interest and that they are to be held accountable to their patients, society, and the profession.[5]

The ACS endorsed the Charter of Medical Professionalism as its Code of Professional Conduct in 2002.[62,63] This model of professionalism is based on three principles. First, the physician should be dedicated to the patient's welfare. This should supersede all financial, societal, and administrative forces. Second, the physician should have respect for the patient's autonomy. This entails being honest and providing the patient with all the necessary information to make an informed decision. Third, the medical profession should promote justice in the health care system by removing discrimination due to any societal barriers.[64] The ACS also has developed a Task Force on Professionalism to address the competency of professionalism for practicing surgeons and surgical residents. In 2004, this task force stated that professionalism is not just a desirable trait for surgeons to acquire peripherally but is the "central core" of the profession of surgery. The task force has stated the principles of professionalism and defined the responsibility of surgeons to commit to excellence.[65] In addition, it also has created a multimedia program geared toward teaching residents and surgeons about the principles of professionalism through clinical vignettes and discussions.[66] Kumar and associates evaluated this learning tool and found that residents who watched the ACS DVD had improved conceptual understanding of professionalism and scored higher on tests that evaluated these concepts than their peers who had not watched the video.[67]

Professionalism also has been taught by various other methods reported in the literature. A training program at the University of Washington set out to see if professionalism was teachable, learnable, and measurable. This group defined professionalism, developed a curriculum to teach professionalism, and evaluated these traits by a previously validated tool known as the *Global Resident Competency Rating Form.* They found that, after implementation of the curriculum, residents evaluated by the faculty were given significantly higher scores for traits that demonstrate professionalism such as (a) demonstrating respect, compassion, integrity, and reliability; (b) showing commitment to ethical principles; and (c) displaying sensitivity to patient culture, age, sex, and disabilities.[68] Rosenfeld also described a curriculum for professionalism taught by leaders in the community. This 2-year course on professionalism dealt with various topics such as ethics, communication, professional development, respect, sensitivity, and health care delivery. The topics were presented in various formats via lectures, discussion panels, small groups, and videos. The residents were then assessed for competency through quizzes on clinical vignettes and 360-degree evaluations. The preliminary results revealed that residents were treating their patients and other health care workers in a more professional manner.[69] Heru described the use of role playing and instructional videotapes in teaching professionalism to residents. The residents who were taught using this format showed an increased awareness of unprofessional behavior and increased sensitivity to others, and were able to better deal with conflict.[70] Teaching residents how to navigate through difficult situations and manage conflict is also another important aspect of professionalism, which can further promote an environment of integrity and mutual respect. Fisher and Ury have described four principles for successful conflict resolution: (a) maintain objectivity by not focusing on the participants but focusing on the problem, (b) relinquish the position of power and inflexibility to concentrate more on individual interests, (c) create outcomes in which both parties will have gains, and (d) make sure there are objective criteria for the negotiating process. All of these principles are related to maintaining an open mind and dialogue and yielding to principles, not pressure.[71] These four principles can be integrated into a curriculum through various teaching techniques to help residents deal with conflict in a nonhostile and productive manner.

The ACS has set standards on professional behavior in the Code of Professional Conduct. With these standards used as a

conceptual framework, the development of professionalism should be a continuous process for any physician. Surgeons should constantly analyze and reflect on their behavior and continue to work toward actions based on integrity, honesty, respect, altruism, compassion, accountability, excellence, and leadership. This is an area in which surgical educators, acting as mentors and role models through daily interactions with their patients, residents, and peers, may be the most powerful teaching tool (Fig. 1-2).[72,73]

Fig. 1-2.

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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Dr. Michael E. DeBakey, a surgical pioneer and transformational health care leader, served as a mentor and role model to generations of residents and inspired professionalism and the pursuit of excellence. He is pictured here with a group of chief residents at the Baylor College of Medicine.

Systems-Based Practice

The ACGME has mandated that "residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care."[5] In today's medical world, resources and finances are limited, and each health care provider must understand that the business aspect of medicine is closely interrelated with the effective delivery of care. As health care costs have grown, so have health care management organizations. Learning how to interact with these organizations is crucial for the improvement of health care delivery and allocation of resources. Some reports have demonstrated that surgeons feel deficient in the understanding of public health and the business aspects of surgery.[74]

The ACS has developed a Task Force on Systems-Based Practice to specifically address this particular competency.[75] Systems-based practice is not inherently integrated into the surgical curriculum; therefore, it may be more challenging to incorporate and teach. Several methods for educating residents about systems-based practice have been described in the literature. Dunnington and Williams have arranged for residents to participate in hospital committees that focus on quality improvement and patient safety. The residents keep a journal of the issues that are discussed during the meetings and reflect on how these issues will affect the way that they practice medicine in the future. Both committee members and

residents have found this to be a constructive learning process.[17] Davison and colleagues described a longitudinal systems-based practice into their 3-year-long core curriculum which included group discussions (risk management, discharge planning, patient relations), didactic lectures (structure of health care, pathway to surgery, current procedural terminology, governance, contract negotiations), and hospital training sessions. Personnel with expertise in health care delivery systems and health care management were enlisted to teach some of these courses.[76] Englander and associates applied systems-based practice by involving residents in the process of cost-reduction efforts. The residents identified a project that was cost inefficient then identified key issues, devised improvement plans, and subsequently implemented them. This educational exercise saved the hospital over $500,000 per year. The authors concluded that involving residents in cost-reduction efforts helps to teach and assess the skill of systems-based practice.[77] Conferences such as grand rounds, morbidity and mortality conferences, and morning reports have also been modified to teach the principles of systems-based practice.[20,21,23]

Given today's changing health care economics, surgeons are faced with the need to understand the business aspects of medicine to care optimally for patients. This involves being able to work effectively in different health care settings, incorporating cost awareness and risk-benefit analysis in patient care, improving patient safety and quality of care, and identifying system errors and implementing solutions (Fig. 1-3).[5] Unfortunately, this has not been an inherent part of surgical training, and many physicians do not feel that they have an adequate understanding of these concepts.[74] However, there are strides in the right direction with various novel methods to incorporate systems-based practice into surgical curriculums.

Fig. 1-3.

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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One of the ACGME core competencies requires that residents demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care. The Texas Medical Center in Houston, Texas, encompasses 740 acres and 42 member institutions where residents must learn to navigate, comprehend, and utilize the larger health care system as a whole.

ASSESSMENT AND THE ACCREDITATION COUNCIL FOR GRADUATE

MEDICAL EDUCATION LEARNING PORTFOLIO

The ACGME not only has mandated the teaching of the six core competencies but also has stated that residents must be evaluated to ensure that they have acquired these necessary skills. There is little doubt that, in the future, these or similar core competencies will be used to assess practicing surgeons as well. Hence, the need to document the acquisition and maintenance of these competencies is important to all surgeons, not just those in training.

Competence has been defined as "the ability to do something well measured against a standard, especially ability acquired through training."[78] Miller has described a model of competency that consists of four levels: "knows," "knows how," "shows how," and "performs." Residents, early in their training, would most likely attain the level of "knows" and "knows how." This would be comparable to a resident's understanding the pathology and clinical diagnosis of appendicitis and the appropriate treatment algorithms. The "shows how" level would be demonstrated by a resident who could demonstrate how to perform an appendectomy while being supervised by faculty on a simulator or animal model. The "performs" level is the competence level at which the surgeon could perform this operation without any supervision or assistance in a real-life clinical situation. The levels of competency are not based on postgraduate year but are based on the ability to specifically meet a defined objective set forth by a surgical curriculum.[79]

The most pressing question is how to implement a competency-based curriculum and, perhaps even more of a challenge, how to assess the six core competencies. An assessment tool should ideally be reliable, valid, reproducible, and also practical.[80] The two most common evaluation tools in surgical programs have been the American Board of Surgery In-Training Examination (ABSITE) and the ward evaluation. The ABSITE is administered once a year and attempts to test the general medical knowledge and patient care knowledge of surgical trainees. A direct linear correlation has been described between the ABSITE score and the American Board of Surgery Qualifying Examination score,[81] which emphasizes the need to perform at an adequate level on the ABSITE. ABSITE scores also have been found to be higher in programs that have instituted mandatory reading programs and focused problem-based learning education programs.[29,82] Overall, the ABSITE remains a tried and true method of assessing the basic medical knowledge of surgical trainees.

The second method of evaluation has been the ward evaluation. These evaluations are typically performed at the end of the rotation and are subject to biases related to factors such as memory and the general impression of the surgery faculty of the given resident. These evaluations often consist of subjective terms that globally define the residents, for example, *excellent, good,* and *very good.* However, these ratings do not provide any objective data on competence.[83] Even though the ward evaluation provides general information on achievement of educational goals, the new ACGME mandates will require either revising these evaluations to make them more competence based or developing new methods for measuring outcomes.

A number of programs have instituted novel evaluation tools to assess for competency in patient care and medical knowledge. The Operative Performance Rating System (OPRS) is an innovative tool used to assess the competence of patient care that was developed by Larson and colleagues. It is an Internet-based system for evaluating sentinel procedures performed by residents that assesses not only technical skills but also the intraoperative decision-making process. They found this to be a feasible and reliable method. The authors concluded that this may be a way to evaluate competence in patient care, track the development of surgical skills, identify problems early on, and certify competence in a particular procedure.[84] Schell and Flynn described a web-based program for teaching and assessing medical knowledge and patient care. Residents were allowed to follow a self-paced curriculum by viewing a CD-ROM didactic lesson and participating in a minimally invasive skills laboratory to assess competency in the basics of minimally invasive surgery. They found that

residents showed significant improvement in their surgical skills, and the trainees described a high satisfaction with this program and felt that it should be an integral component of their education.[10] The Objective Structured Assessment of Technical Skills (OSATS) test was developed at the University of Toronto to assess technical competency. The test is administered in stations that simulate tasks performed in the operating room, such as a small-bowel anastomosis, placement of a T tube, control of inferior vena cava hemorrhage, and so on. The participants are graded by a surgical evaluator who completes two standardized grading forms for each station. One grading form covers the specific steps and technical points of the station (i.e., correct suture, use of forceps, etc), whereas the second form is a global rating scale that evaluates the flow of operation and more subjective but important aspects of an operation. The authors concluded that this method has high reliability and construct validity for assessing competency in technical skills.[85] Furthermore, the OSATS examination has been validated in a number of studies as accurately representing the technical skills of a surgical trainee when compared with performance in carrying out a procedure on a live patient.[86,87] Virtual simulators have also been used effectively to teach and assess surgical skills, medical knowledge, and practice-based learning and improvement in a controlled environment.[12,88]

Other competencies, such as communication and professionalism, may require a more interactive and direct means for true assessment. The methods most described in the literature involve standardized patients and the 360-degree evaluations. Yudkowsky and colleagues described a method to assess communication and interpersonal skills, patient care, and professionalism known as the *Communication and Interpersonal Skills Objective Structured Clinical Assessment (CIS-OSCE) examination.* This examination was administered to residents in multiple specialties at the University of Illinois at Chicago and consisted of resident interaction with standardized patients on various matters such as obtaining informed consent, relaying bad news, and discussing domestic violence. They found this method of evaluation to be valid and feasible.[50] The Patient Assessment and Management Examination (PAME) to access competencies such as patient care, communication and interpersonal skills, and professionalism has also been described. This examination consists of six stations with standardized patients. It entails an initial assessment, ordering and interpretation of test, discussion of the findings with the patient, and evaluation of a higher level of thinking with implementation of a treatment plan. These interactions are observed by a staff physician, which allows for direct assessment of competencies.[38,51] The 360-degree evaluation to assess communication and professionalism has been described for various specialties. This process involves evaluation of the resident by various people who have had interactions with the resident, including patients as well as nurses and other ancillary staff. The resident's ability to communicate effectively and behave in a professional manner is evaluated based on a scale. This method has been found to be a valid and reliable method to assess for the competencies; however, it can be difficult to carry out.[89–91]

Practice-based learning and systems-based practice have been assessed through existing conferences. Rosenfeld as well as Williams and Dunnington revised their morbidity and mortality conference to allow for assessment of practice-based learning by having residents fill out a practice-based learning log. This allowed staff to determine whether the residents were able to identify key issues and implement improved practice patterns.[20,38] Stiles and associates developed a competency-based morning report format and felt that this was an ideal environment in which to directly assess many of the core competencies, including systems-based practice and practice-based learning, through direct interactions with the residents.[23]

In 2004, the Association of Program Directors and the ACS worked together to develop a web-based system to evaluate all of the core competencies at the end of residents' rotations. This evaluation system was studied throughout multiple institutions and found to be both a reliable and valid method to assess the core competencies.[92] In addition, the ACGME has developed a professional developmental tool called the *ACGME Learning Portfolio.* This portfolio is an interactive web-based

portfolio that allows residents to record, organize, and reflect back on their learning experiences. Residents, faculty, and program directors can use this portfolio as a tool to allow for constructive feedback, to monitor a resident's progress, and to identify areas of weakness. It will also enable program directors to evaluate the quality of their curriculums and isolate deficiencies that require improvement.[93] Both of these tools use the web for data collection and evaluation, which allows for centralization and ease in interpretation of the data, permits use of real-time data to identify strengths and weaknesses, and may allow programs to provide competency-based performance data for the RRC. The number of assessment tools for the core competencies continues to increase as programs learn from trial and error. Programs should continue to share their work through publications to identify programs with models of excellence that can be adopted at other institutions (see Table 1-2).

CONCLUSION

The goal of the ACGME core competency mandate has been to ensure that patient care continues to improve into the twenty-first century with the development of benchmark programs and best educational practices. The goal of the modern surgical educator is to develop a better means to ensure that the material is properly taught and, even more importantly, truly learned. The defined core competencies provide an excellent framework for surgical education. This supplies an exciting foundation for the introduction of new educational initiatives and the development of novel educational programs through collaboration. These innovations should serve to move surgical education forward and allow for improved training of the surgeons of the future.

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KEY POINTS

1. Systemic inflammation is characterized by exaggerated immune responses to either a sterile or infectious process. The cause of inflammatory activation needs to be addressed to resolve the dysregulated immune state.

2. An understanding of the signaling mechanisms and pathways underlying systemic inflammation can help guide therapeutic interventions in injured and/or septic patients.

3. Management of such patients is optimized with the use of evidence-based and algorithm-driven therapy.

4. Nutritional assessments, whether clinical or laboratory guided, and intervention should be considered at an early juncture in all surgical and critically ill patients.

5. Excessive feeding should be avoided in an effort to limit complications, including ventilator dependency, aspiration events, and infections.

SYSTEMIC RESPONSE TO INJURY AND METABOLIC SUPPORT: INTRODUCTION

The immune system has developed to respond to and neutralize pathogenic micro-organisms as well as coordinate tissue repair. The inflammatory response to injury or infection involves cell signaling, cell migration, and mediator release. Minor host insults instigate a local inflammatory response that is transient and in most cases beneficial. Major host insults may propagate reactions that can become amplified, resulting in systemic inflammation and potentially detrimental responses. This topic is highly relevant because systemic inflammation is a central feature[1] of both sepsis and severe trauma. Understanding the complex pathways that regulate local and systemic inflammation is necessary to develop therapies to intervene during overwhelming sepsis or after severe injury. Sepsis, defined by a systemic inflammatory response to infection, is a disease process with an increasing incidence of over 900,000 cases per year. Trauma is the leading cause of mortality and morbidity for individuals under 50 years of age.

This chapter reviews the autonomic, cellular, and hormonal responses to injury. These facets of the inflammatory response to injury and infection are discussed in reference to the specific response being considered.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The systemic inflammatory response syndrome (SIRS) is characterized by a sequence of host phenotypic and metabolic responses to systemic inflammation that includes changes in heart rate, respiratory rate, blood pressure, temperature regulation, and immune cell activation (Table 2-1). The systemic inflammatory response includes two general phases: (1) an acute proinflammatory state resulting from innate immune system recognition of ligands, and (2) an anti-inflammatory phase that may serve to modulate the proinflammatory phase. Under normal circumstances, these coordinated responses direct a return to homeostasis[2] (Fig. 2-1).

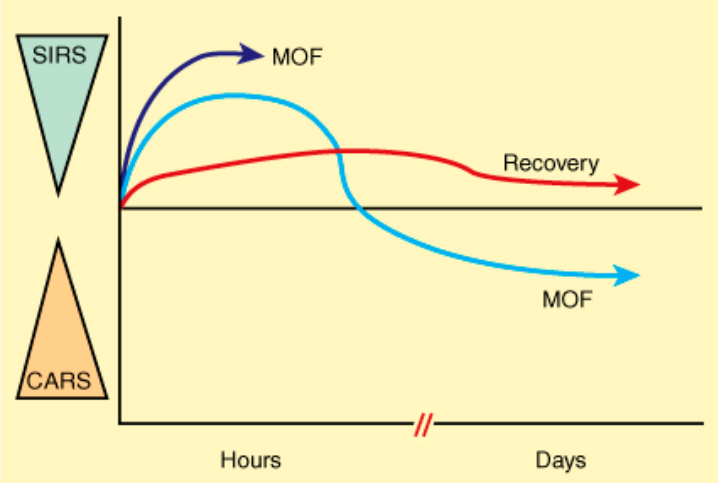
Table 2-1 Clinical Spectrum of Infection and Systemic Inflammatory Response Syndrome (SIRS)

Term	Definition
Infection	Identifiable source of microbial insult

SIRS	Two or more of following criteria are met:
	Temperature ≥38°C (100.4°F) or ≤36°C (96.8°F)
	Heart rate ≥90 beats per minute
	Respiratory rate ≥20 breaths per minute or $PaCO_2$ ≤32 mmHg or mechanical ventilation
	White blood cell count ≥12,000/μL or ≤4000/μL or ≥10% band forms
Sepsis	Identifiable source of infection + SIRS
Severe sepsis	Sepsis + organ dysfunction
Septic shock	Sepsis + cardiovascular collapse (requiring vasopressor support)

$PaCO_2$ = partial pressure of arterial carbon dioxide.

Fig. 2-1.



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Schematic representation of the systemic inflammatory response syndrome (SIRS) after injury, followed by a period of convalescence mediated by the counterregulatory anti-inflammatory response syndrome (CARS). Severe inflammation may lead to acute multiple organ failure (MOF) and early death after injury (*dark blue arrow*). A lesser inflammatory response followed by excessive CARS may induce a prolonged immunosuppressed state that can also be deleterious to the host (*light blue arrow*). Normal recovery after injury requires a period of systemic inflammation followed by a return to homeostasis (*red arrow*).

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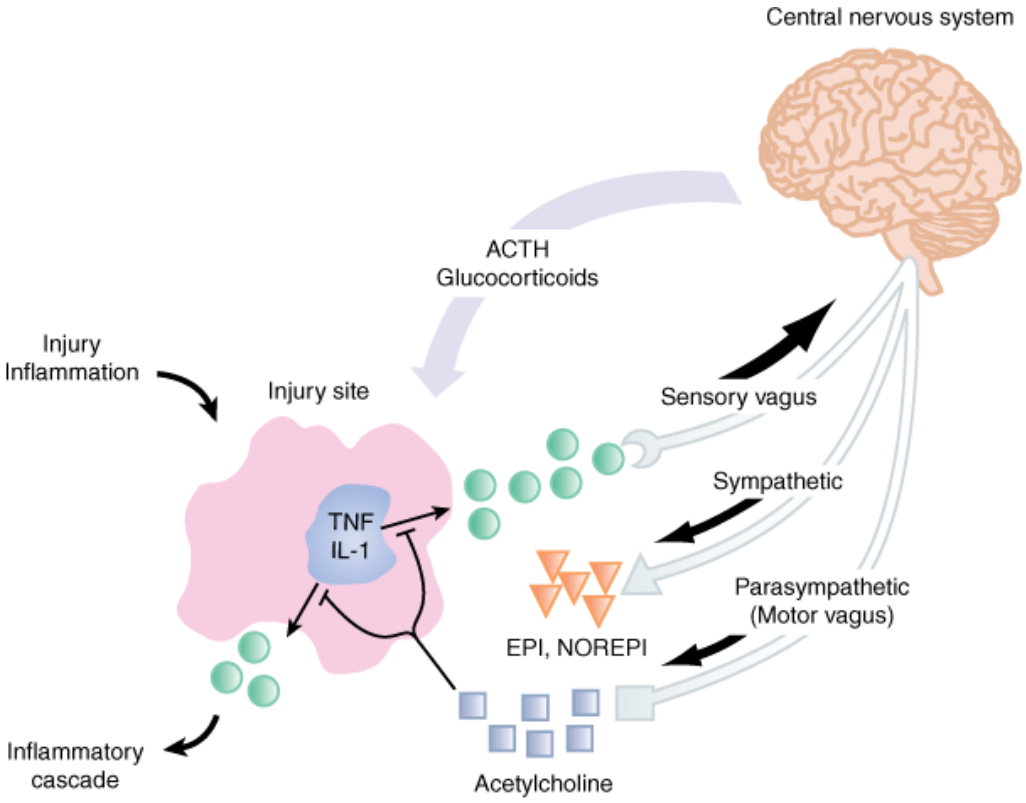
CENTRAL NERVOUS SYSTEM REGULATION OF INFLAMMATION

Afferent Signals to the Brain

The central nervous system (CNS) plays a key role in orchestrating the inflammatory response. The CNS influences multiple organs through both neurohormonal and endocrine signals. Injury or infection signals are recognized by the CNS through afferent signal pathways (Fig. 2-2). The CNS may respond to peripheral inflammatory stimuli through both circulatory and neuronal pathways. Inflammatory mediators activate CNS receptors and establish phenotypic responses such as fever and anorexia. The vagus nerve has been described as highly influential in mediating afferent

sensory input to the CNS.[3]

Fig. 2-2.



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Neural circuit relaying messages of localized injury to the brain (nucleus tractus solitarius). The brain follows with a hormone release (adrenocorticotropic hormone [ACTH], glucocorticoids) into the systemic circulation and by sympathetic response. The vagal response rapidly induces acetylcholine release directed at the site of injury to curtail the inflammatory response elicited by the activated immunocytes. This vagal response occurs in real time and is site specific. EPI = epinephrine; IL-1 = interleukin-1; NOREPI = norepinephrine; TNF = tumor necrosis factor.

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Cholinergic Anti-Inflammatory Pathways

The vagus nerve exerts several homeostatic influences, including enhancing gut motility, reducing heart rate, and regulating inflammation. Central to this pathway is the understanding of neurally controlled anti-inflammatory pathways of the vagus nerve. Parasympathetic nervous system activity transmits vagus nerve efferent signals primarily through the neurotransmitter acetylcholine. This neurally mediated anti-inflammatory pathway allows for a rapid response to inflammatory stimuli and also for the potential regulation of early proinflammatory mediator release, specifically tumor necrosis factor (TNF).[4] Vagus nerve activity in the presence of systemic inflammation may inhibit cytokine activity and reduce injury from disease processes such as pancreatitis, ischemia and reperfusion, and hemorrhagic shock. This activity is primarily mediated through nicotinic acetylcholine receptors on immune mediator cells such as tissue macrophages. Furthermore, enhanced inflammatory profiles are

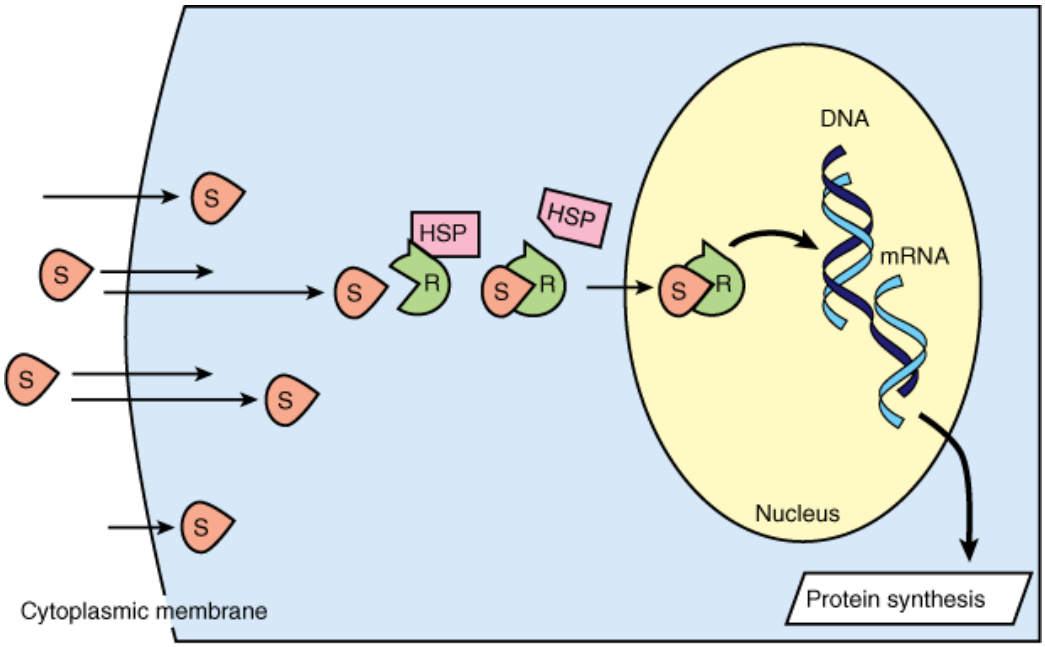
observed after vagotomy, during stress conditions.[4] Experimental trials have studied this pathway to develop therapeutic interventions. Specifically, nicotine, which also activates nicotinic acetylcholine receptors on immune cells, has been shown to reduce cytokine release after endotoxemia in animal models.[5]

HORMONAL RESPONSE TO INJURY

Hormone Signaling Pathways

Hormones are chemical signals that are released to modulate the function of target cells. Humans release hormones in several chemical categories, including polypeptides (e.g., cytokines, glucagon, and insulin), amino acids (e.g., epinephrine, serotonin, and histamine), and fatty acids (e.g., glucocorticoids, prostaglandins, and leukotrienes). Hormone receptors are present on or within the target cells and allow signal transduction to progress intracellularly mostly through three major pathways: (1) receptor kinases such as insulin and insulin-like growth factor (IGF) receptors, (2) guanine nucleotide-binding or G-protein receptors such as neurotransmitter and prostaglandin receptors, and (3) ligand-gated ion channels that permit ion transport when activated. On activation, the signal is then amplified through the action of secondary signaling molecules. Intracellular signaling leads to downstream effects such as protein synthesis and further mediator release. Protein synthesis is mediated through intracellular receptor binding either by hormone ligands or through subsequently released secondary signaling molecules. These, together with the targeted DNA sequences, activate transcription. The prototype of the intracellular hormone receptor is the glucocorticoid receptor (Fig. 2-3). This receptor is regulated by the stress-induced protein known as *heat shock protein (HSP),* which maintains the glucocorticoid receptor in the cytosol; however, on ligand binding, HSP is released, and the receptor-ligand complex is transported to the nucleus for DNA transcription.[6]

Fig. 2-3.



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Simplified schematic of steroid transport into the nucleus. Steroid molecules (S) diffuse readily across cytoplasmic membranes. Intracellularly the receptors (R) are rendered inactive by being coupled to heat shock protein (HSP). When S and R bind, HSP dissociates, and the S-R

complex enters the nucleus, where the S-R complex induces DNA transcription, resulting in protein synthesis. mRNA = messenger RNA.

Virtually every hormone of the hypothalamic-pituitary-adrenal axis influences the physiologic response to injury and stress (Table 2-2), but some with direct influence on the inflammatory response or immediate clinical impact are highlighted here.

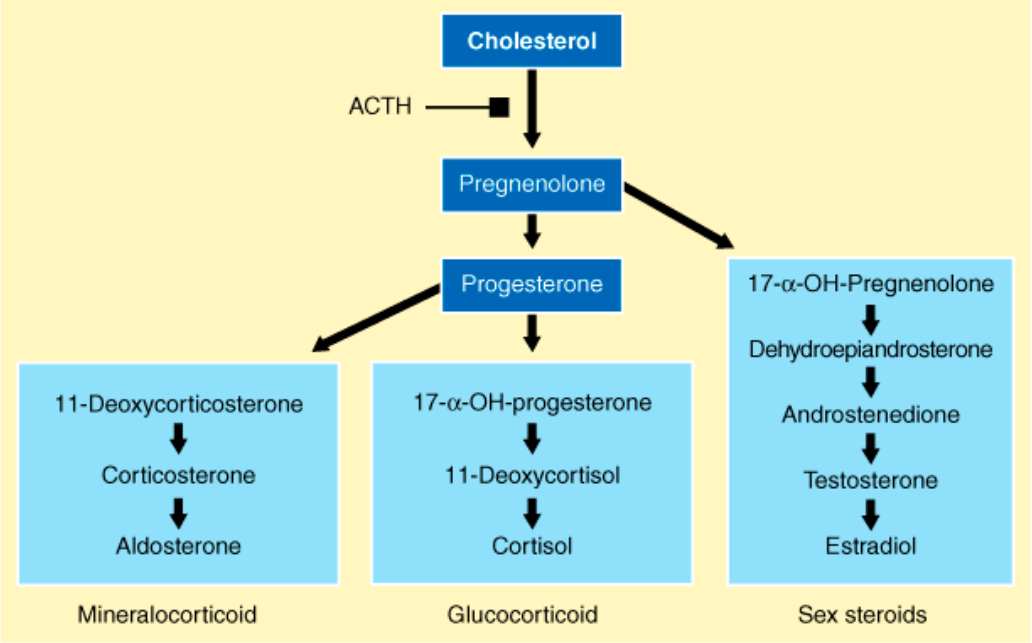
Table 2-2 Hormones Regulated by the Hypothalamus, Pituitary, and Autonomic System
Hypothalamic Regulation
Corticotropin-releasing hormone
Thyrotropin-releasing hormone
Growth hormone–releasing hormone
Luteinizing hormone–releasing hormone
Anterior Pituitary Regulation
Adrenocorticotropic hormone
Cortisol
Thyroid-stimulating hormone
Thyroxine
Triiodothyronine
Growth hormone
Gonadotrophins
Sex hormones
Insulin-like growth factor
Somatostatin
Prolactin
Endorphins
Posterior Pituitary Regulation
Vasopressin
Oxytocin
Autonomic System
Norepinephrine
Epinephrine
Aldosterone
Renin-Angiotensin System
Insulin
Glucagon
Enkephalins

Adrenocorticotropic Hormone

Adrenocorticotropic hormone (ACTH) is a polypeptide hormone released by the anterior pituitary gland. ACTH binds with receptors in the zona fasciculata of the adrenal gland, which mediate intracellular signaling and subsequent cortisol release. ACTH release follows circadian rhythms in healthy humans; however, during times of stress this diurnal pattern becomes blunted because ACTH release is elevated in proportion to the severity of injury. Several important stimuli for ACTH release are present in the injured patient, including corticotropin-releasing hormone, pain,

anxiety, vasopressin, angiotensin II, cholecystokinin, vasoactive intestinal polypeptide, catecholamines, and proinflammatory cytokines. Within the zona fasciculata of the adrenal gland, ACTH signaling activates intracellular pathways that lead to glucocorticoid production (Fig. 2-4). Conditions of excess ACTH stimulation result in adrenocortical hypertrophy.[7]

Fig. 2-4.



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Steroid synthesis from cholesterol. Adrenocorticotropic hormone (ACTH) is a principal regulator of steroid synthesis. The end products are mineralocorticoids, glucocorticoids, and sex steroids.

Cortisol and Glucocorticoids

Cortisol is a glucocorticoid steroid hormone released by the adrenal cortex in response to ACTH. Cortisol release is increased during times of stress and may be chronically elevated in certain disease processes. For example, burn-injured patients may exhibit elevated levels for 4 weeks.

Metabolically, cortisol potentiates the actions of glucagon and epinephrine that manifest as hyperglycemia. Cortisol acts on liver enzymes by decreasing glycogenesis, while increasing gluconeogenesis. In skeletal muscle, cortisol facilitates the breakdown of protein and amino acids, and mediates the release of lactate. Subsequently, these substrates are used by the liver for gluconeogenesis. In adipose tissue cortisol stimulates the release of free fatty acids, triglycerides, and glycerol to increase circulating energy stores. Wound healing also is impaired, because cortisol reduces transforming growth factor beta (TGF-β) and insulin-like growth factor I (IGF-I) in the wound. This effect can be partially ameliorated by the administration of vitamin A.

Adrenal insufficiency represents a clinical syndrome highlighted largely by inadequate amounts of circulating cortisol and aldosterone. Classically, adrenal insufficiency is described in patients with atrophic adrenal glands caused by exogenous steroid administration who undergo a stressor such as surgery. These patients subsequently manifest signs and symptoms such as tachycardia, hypotension, weakness, nausea, vomiting, and fever. Critical illness may be associated with a relative adrenal insufficiency such that the adrenal gland cannot mount an effective cortisol

response to match the degree of injury. Laboratory findings in adrenal insufficiency include hypoglycemia from decreased gluconeogenesis, hyponatremia from impaired renal tubular sodium resorption, and hyperkalemia from diminished kaliuresis. Diagnostic tests include baseline cortisol levels and ACTH-stimulated cortisol levels, both of which are lower than normal during adrenal insufficiency. Treatment strategies are controversial; however, they include low-dose steroid supplementation.[8]

Glucocorticoids have immunosuppressive properties that have been used when needed, as in organ transplantation. Immunologic changes associated with glucocorticoid administration include thymic involution, depressed cell-mediated immune responses reflected by decreases in T-killer and natural killer cell function, T-lymphocyte blastogenesis, mixed lymphocyte responsiveness, graft-versus-host reactions, and delayed hypersensitivity responses. In addition glucocorticoids inhibit leukocyte migration to sites of inflammation by inhibiting the expression of adhesion molecules. In monocytes, glucocorticoids inhibit intracellular killing while maintaining chemotactic and phagocytic properties. Glucocorticoids inhibit neutrophil superoxide reactivity, suppress chemotaxis, and normalize apoptosis signaling mechanisms but maintain neutrophil phagocytic function. In clinical settings manifested by hypoperfusion, such as septic shock, trauma, and coronary artery bypass grafting, glucocorticoid administration is associated with attenuation of the inflammatory response.

Macrophage Migration–Inhibiting Factor

Macrophage migration–inhibiting factor (MIF) is a neurohormone that is stored and secreted by the anterior pituitary and by intracellular pools within macrophages. MIF is a counterregulatory mediator that potentially reverses the anti-inflammatory effects of cortisol. During times of stress, hypercortisolemia, and host immunosuppression, MIF may modulate the inflammatory response by inhibiting the immunosuppressive effect of cortisol on immunocytes and thereby increasing their activity against foreign pathogens.[9]

Growth Hormones and Insulin-Like Growth Factors

Growth hormone (GH) is a neurohormone expressed primarily by the pituitary gland that has both metabolic and immunomodulatory effects. GH promotes protein synthesis and insulin resistance, and enhances the mobilization of fat stores. GH secretion is upregulated by hypothalamic GH–releasing hormone and downregulated by somatostatin. GH primarily exerts its downstream effects through direct interaction with GH receptors and secondarily through the enhanced hepatic synthesis of IGF-I. IGF circulates primarily bound to various IGF-binding proteins and also has anabolic effects, including increased protein synthesis and lipogenesis. In the liver, IGF stimulates protein synthesis and glycogenesis; in adipose tissue, it increases glucose uptake and lipid utilization; and in skeletal muscles, it mediates glucose uptake and protein synthesis. Critical illness is associated with an acquired GH resistance and contributes to decreased levels of IGF. This effect in part mediates the overall catabolic phenotype manifested during critical illness. In addition, GH enhances phagocytic activity of immunocytes through increased lysosomal superoxide production. GH also increases the proliferation of T-cell populations.[10] Exogenous GH administration has been studied in critically ill patients and may be associated with worse outcomes, including increased mortality, prolonged ventilator dependence, and increased susceptibility to infection.[11] The mechanisms through which GH is associated with these outcomes are unclear, although GH-induced insulin resistance and hyperglycemia may contribute.

Catecholamines

Catecholamines are hormones secreted by the chromaffin cells of the adrenal medulla and function as neurotransmitters in the CNS. The most common catecholamines are epinephrine, norepinephrine, and dopamine, which have metabolic, immunomodulatory, and vasoactive effects. After severe injury, plasma catecholamine levels are increased threefold to fourfold, with elevations lasting 24 to 48 hours before returning toward baseline levels.

Catecholamines act on both alpha and beta receptors, which are widely distributed on several cell types, including vascular endothelial cells, immunocytes, myocytes, adipose tissue, and hepatocytes. Epinephrine has been shown to induce a catabolic state and hyperglycemia through

hepatic gluconeogenesis and glycogenolysis as well as by peripheral lipolysis and proteolysis. In addition epinephrine promotes insulin resistance in skeletal muscle. Catecholamines also increase the secretion of thyroid hormone, parathyroid hormones, and renin, but inhibit the release of aldosterone.

Epinephrine also has immunomodulatory properties mediated primarily through the activation of $beta_2$ receptors on immunocytes. Epinephrine has been shown to inhibit the release of inflammatory cytokines, including TNF, interleukin-1, and interleukin-6, while also enhancing the release of the anti-inflammatory mediator interleukin-10.[12] Similar to cortisol, epinephrine increases leukocyte demargination with resultant neutrophilia and lymphocytosis. The immunomodulatory sequelae of catecholamines in patients during septic shock have yet to be clearly elucidated.

Catecholamines exert several hemodynamic effects, including increased cardiac oxygen demand, vasoconstriction, and increased cardiac output. Catecholamines are used to treat systemic hypotension during septic shock. Because of the increased cardiac stress induced by catecholamines, however, cardioprotective strategies, including beta blockade for patients undergoing surgery, have shown significant benefit in reducing cardiac-related deaths.

Aldosterone

Aldosterone is a mineralocorticoid released by the zona glomerulosa of the adrenal cortex. Aldosterone increases intravascular volume by acting on the renal mineralocorticoid receptor of the distal convoluted tubules to retain sodium and eliminate potassium and hydrogen ions. Aldosterone secretion is stimulated by ACTH, angiotensin II, decreased intravascular volume, and hyperkalemia. Aldosterone deficiency is manifested by hypotension and hyperkalemia, whereas aldosterone excess is manifested by edema, hypertension, hypokalemia, and metabolic alkalosis.

Insulin

Hyperglycemia and insulin resistance are hallmarks of critical illness due to the catabolic effects of circulating mediators, including catecholamines, cortisol, glucagon, and growth hormone. Insulin is secreted by the islets of Langerhans in the pancreas. Insulin mediates an overall host anabolic state through hepatic glycogenesis and glycolysis, peripheral glucose uptake, lipogenesis, and protein synthesis.[13]

Hyperglycemia during critical illness has immunosuppressive effects, including glycosylation of immunoglobulins and decreased phagocytosis and respiratory burst of monocytes, and thus is associated with an increased risk for infection. Insulin therapy to manage hyperglycemia has grown in favor and has been shown to be associated with both decreased mortality and a reduction in infectious complications in select patient populations; however, caution should be exercised to avoid the deleterious sequelae of hypoglycemia from overaggressive glycemic control.[14] The ideal blood glucose range within which to maintain critically ill patients and avoid hypoglycemia has yet to be determined.

ACUTE PHASE PROTEINS

Acute phase proteins are a class of proteins produced by the liver that manifest either increased or decreased plasma concentration in response to inflammatory stimuli such as traumatic injury and infection. Specifically, C-reactive protein has been studied as a marker of proinflammatory response in many clinical settings, including appendicitis, vasculitis, and ulcerative colitis. Importantly, C-reactive protein levels do not show diurnal variations and are not modulated by feeding. Acute phase protein levels may be unreliable as an index of inflammation in the setting of hepatic insufficiency.

MEDIATORS OF INFLAMMATION

Cytokines

Cytokines are a class of protein signaling compounds that are essential for both innate and adaptive immune responses. Cytokines mediate a broad sequence of cellular responses, including cell migration, DNA replication, cell turnover, and immunocyte proliferation (Table 2-3). When

functioning locally at the site of injury and infection, cytokines mediate the eradication of invading micro-organisms and also promote wound healing. However, an exaggerated proinflammatory cytokine response to inflammatory stimuli may result in hemodynamic instability (i.e., septic shock) and metabolic derangements (i.e., muscle wasting).

Table 2-3 Cytokines and Their Sources

Cytokine	Source	Comment
TNF	*Macrophages/monocytes*	Among earliest responders after injury; half-life <20 min; activates TNF receptors 1 and 2; induces significant shock and catabolism
	Kupffer cells	
	Neutrophils	
	NK cells	
	Astrocytes	
	Endothelial cells	
	T lymphocytes	
	Adrenal cortical cells	
	Adipocytes	
	Keratinocytes	
	Osteoblasts	
	Mast cells	
	Dendritic cells	
IL-1	*Macrophages/monocytes*	Two forms (IL-1α and IL-1β); similar physiologic effects as TNF; induces fevers through prostaglandin activity in anterior hypothalamus; promotes β-endorphin release from pituitary; half-life <6 min
	B and T lymphocytes	
	NK cells	
	Endothelial cells	
	Epithelial cells	
	Keratinocytes	
	Fibroblasts	
	Osteoblasts	
	Dendritic cells	
	Astrocytes	
	Adrenal cortical cells	
	Megakaryocytes	
	Platelets	
	Neutrophils	
	Neuronal cells	
IL-2	*T lymphocytes*	Promotes lymphocyte proliferation, immunoglobulin production, gut barrier integrity; half-life <10 min; attenuated production after major blood loss leads to immunocompromise; regulates lymphocyte apoptosis
IL-3	*T lymphocytes*	
	Macrophages	
	Eosinophils	
	Mast cells	
IL-4	*T lymphocytes*	Induces B-lymphocyte production of IgG4 and IgE, mediators of allergic and anthelmintic response;

	Mast cells	downregulates TNF, IL-1, IL-6, IL-8
	Basophils	
	Macrophages	
	B lymphocytes	
	Eosinophils	
	Stromal cells	
IL-5	*T lymphocytes*	Promotes eosinophil proliferation and airway inflammation
	Eosinophils	
	Mast cells	
	Basophils	
IL-6	*Macrophages*	Elicited by virtually all immunogenic cells; long half-life; circulating levels proportional to injury severity; prolongs activated neutrophil survival
	B lymphocytes	
	Neutrophils	
	Basophils	
	Mast cells	
	Fibroblasts	
	Endothelial cells	
	Astrocytes	
	Synovial cells	
	Adipocytes	
	Osteoblasts	
	Megakaryocytes	
	Chromaffin cells	
	Keratinocytes	
IL-8	*Macrophages/monocytes*	Chemoattractant for neutrophils, basophils, eosinophils, lymphocytes
	T lymphocytes	
	Basophils	
	Mast cells	
	Epithelial cells	
	Platelets	
IL-10	*T lymphocytes*	Prominent anti-inflammatory cytokine; reduces mortality in animal sepsis and ARDS models
	B lymphocytes	
	Macrophages	
	Basophils	
	Mast cells	
	Keratinocytes	
IL-12	*Macrophages/monocytes*	Promotes T_H1 differentiation; synergistic activity with IL-2
	Neutrophils	
	Keratinocytes	
	Dendritic cells	

	B lymphocytes	
IL-13	*T lymphocytes*	Promotes B-lymphocyte function; structurally similar to IL-4; inhibits nitric oxide and endothelial activation
IL-15	*Macrophages/monocytes*	Anti-inflammatory effect; promotes lymphocyte activation; promotes neutrophil phagocytosis in fungal infections
	Epithelial cells	
IL-18	*Macrophages*	Similar to IL-12 in function; levels elevated in sepsis, particularly gram-positive infections; high levels found in cardiac deaths
	Kupffer cells	
	Keratinocytes	
	Adrenal cortical cells	
	Osteoblasts	
IFN-γ	*T lymphocytes*	Mediates IL-12 and IL-18 function; half-life of days; found in wounds 5–7 d after injury; promotes ARDS
	NK cells	
	Macrophages	
GM-CSF	*T lymphocytes*	Promotes wound healing and inflammation through activation of leukocytes
	Fibroblasts	
	Endothelial cells	
	Stromal cells	
IL-21	*T lymphocytes*	Preferentially secreted by T_H2 cells; structurally similar to IL-2 and IL-15; activates NK cells, B and T lymphocytes; influences adaptive immunity
HMGB1	*Monocytes/lymphocytes*	High mobility group box chromosomal protein; DNA transcription factor; late (downstream) mediator of inflammation (ARDS, gut barrier disruption); induces "sickness behavior"

ARDS = acute respiratory distress syndrome; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; Ig = immunoglobulin; IL = interleukin; NK = natural killer; T_H1 = helper T cell subtype 1; T_H2 = helper T cell subtype 2; TNF = tumor necrosis factor.

Anti-inflammatory cytokines also are released, at least in part as an opposing influence to the proinflammatory cascade. These anti-inflammatory mediators also may result in immunocyte dysfunction and host immunosuppression. Cytokine signaling after an inflammatory stimulus is manifested by a fluctuating and counterregulated balance of opposing influences and should not be oversimplified into dichotomic proinflammatory and anti-inflammatory responses.[2]

Heat Shock Proteins

Heat shock proteins (HSPs) are a group of intracellular proteins that are increasingly expressed during times of stress, such as burn injury, inflammation, and infection. HSPs participate in many physiologic processes, including protein folding and protein targeting. The formation of HSPs requires gene induction by the heat shock transcription factor. HSPs bind both autologous and foreign proteins and thereby function as intracellular chaperones for ligands such as bacterial DNA and endotoxin. HSPs are presumed to protect cells from the deleterious effects of traumatic stress[15] and, when released by damaged cells, alert the immune system of the tissue damage.

Reactive Oxygen Species

Reactive oxygen species (ROS) are small molecules that are highly reactive due to the presence of unpaired outer orbit electrons. They can cause cellular injury to both host cells and invading pathogens through the oxidation of unsaturated fatty acids within cell membranes.

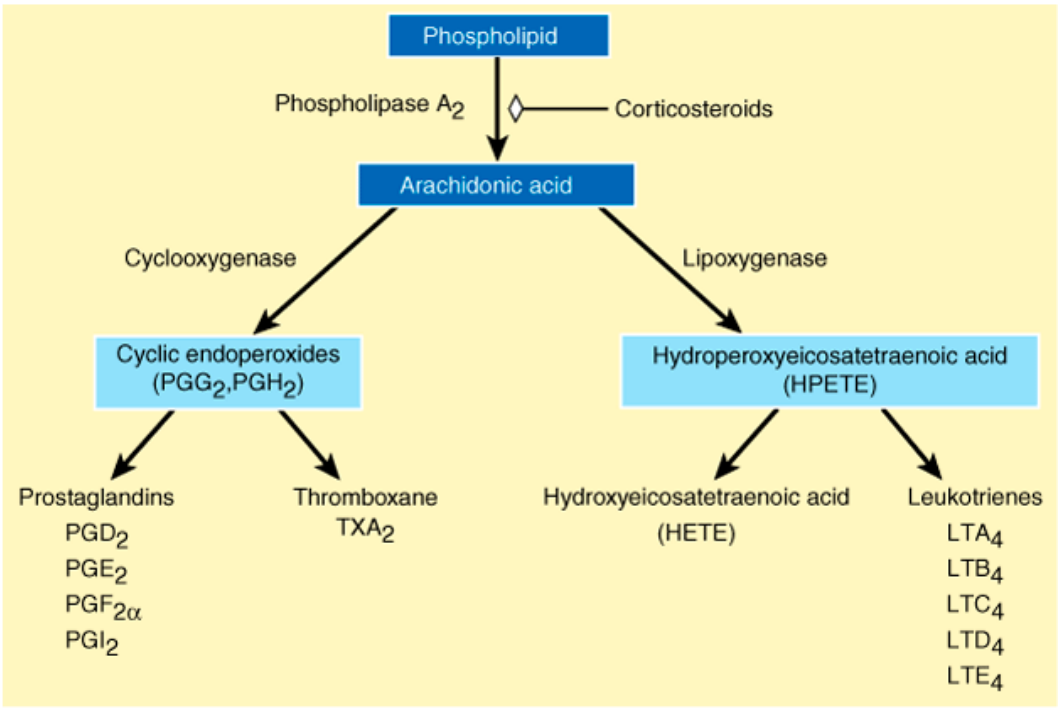
Oxygen radicals are produced as a by-product of oxygen metabolism as well as by anaerobic processes. Potent oxygen radicals include oxygen, superoxide, hydrogen peroxide, and hydroxyl radicals. The main areas of ROS production include mitochondrial electron transport, peroxisomal

fatty acid metabolism, cytochrome P-450 reactions, and the respiratory burst of phagocytic cells. Host cells are protected from the damaging effects of ROS through the activity of endogenous antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. Under normal physiologic conditions ROS are balanced by antioxidative enzymes. During times of stress or ischemia, however, enzymatic clearance mechanisms are consumed, and on restoration of perfusion, the unbalanced production of ROS leads to reperfusion injury.[16]

Eicosanoids

Eicosanoids are derived primarily by oxidation of the membrane phospholipid arachidonic acid (eicosatetraenoic acid) and are composed of subgroups, including prostaglandins, prostacyclins, hydroxyeicosatetraenoic acids (HETEs), thromboxanes, and leukotrienes. The synthesis of arachidonic acid from phospholipids requires the enzymatic activation of phospholipase A2 (Fig. 2-5). Products of the COX pathway include all of the prostaglandins and thromboxanes. The lipoxygenase pathway generates leukotrienes and HETE. Eicosanoids are not stored within cells but are instead generated rapidly in response to many stimuli, including hypoxic injury, direct tissue injury, endotoxin (lipopolysaccharide, or LPS), norepinephrine, vasopressin, angiotensin II, bradykinin, serotonin, acetylcholine, cytokines, and histamine. Eicosanoid pathway activation also leads to the formation of the anti-inflammatory compound lipoxin, which inhibits chemotaxis and nuclear factor κB (NF-κB) activation. Glucocorticoids, NSAIDs, and leukotriene inhibitors block the end products of eicosanoid pathways.

Fig. 2-5.



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Schematic diagram of arachidonic acid metabolism. LT = leukotriene; PG = prostaglandin; TXA_2 = thromboxane A_2.

Eicosanoids have a broad range of physiologic roles, including neurotransmission, vasomotor regulation, and immune cell regulation (Table 2-4). Eicosanoids mostly generate a proinflammatory response with deleterious host effects and are associated with acute lung injury, pancreatitis, and renal failure. Leukotrienes are potent mediators of capillary leakage as well as leukocyte adherence, neutrophil activation, bronchoconstriction,

and vasoconstriction. Experimental models of sepsis have shown a benefit to inhibiting eicosanoid production. However, human sepsis trials have failed to show a mortality benefit using NSAIDs.[17]

Table 2-4 Systemic Stimulatory and Inhibitory Actions of Eicosanoids

Organ/Function	Stimulator	Inhibitor
Pancreas		
Glucose-stimulated insulin secretion	12-HPETE	PGE2
Glucagon secretion	PGD_2, PGE2	
Liver		
Glucagon-stimulated glucose production	PGE2	
Fat		
Hormone-stimulated lipolysis	PGE2	
Bone		
Resorption	PGE2 , PGE-m, 6-K-PGE1 , $PGF_{1\alpha}$, PGI2	
Pituitary		
Prolactin	PGE1	
Luteinizing hormone	PGE1 , PGE2 , 5-HETE	
Thyroid-stimulating hormone	PGA_1, PGB_1, PGE1 , PGE1	
Growth hormone	PGE1	
Parathyroid		
Parathyroid hormone	PGE2	PGF_2
Lung		
Bronchoconstriction	$PGF_{2\alpha}$ TXA_2, LTC_4, LTD_4, LTE_4	PGE2
Kidney		
Stimulation of renin secretion	PGE2 , PGI2	
Gastrointestinal system		
Cytoprotective effect	PGE2	
Immune response		
Suppression of lymphocyte activity	PGE2	
Hematologic system		
Platelet aggregation	TXA_2	PGI2

5-HETE = 5-hydroxyeicosatetraenoic acid; 12-HPETE = 12-hydroxyperoxyeicosatetraenoic acid; 6-K-PGE1 = 6-keto-prostaglandin E1 ; LT = leukotriene; PG = prostaglandin; PGE-m = 13,14-dihydro-15-keto-PGE2 (major urine metabolite of PGE_2); TXA_2 = thromboxane A_2.

Eicosanoids also have several recognized metabolic effects. Cyclooxygenase pathway products inhibit pancreatic β-cell release of insulin, whereas

lipoxygenase pathway products stimulate β-cell activity. Prostaglandins such as prostaglandin E2 can inhibit gluconeogenesis through the binding of hepatic receptors and also can inhibit hormone-stimulated lipolysis.[18]

Fatty Acid Metabolites

Fatty acid metabolites function as inflammatory mediators and as such have significant roles in the inflammatory response. As previously discussed, eicosanoids participate in inflammatory signaling; however, dietary omega-3 and omega-6 fatty acids also influence inflammation. Eicosanoids are produced primarily through two major pathways: (1) with arachidonic acid (omega-6 fatty acid) as substrate and (2) eicosapentaenoic acid (omega-3 fatty acid) as substrate. Many lipid preparations are soy based and are primarily composed of omega-6 fatty acids. Nutritional supplementation with either omega-6 or omega-3 fatty acid can significantly modulate the inflammatory response, because omega-6 substrate is associated with increased downstream mediator production. Omega-3 fatty acids have specific anti-inflammatory effects, including inhibition of NF-κB activity, TNF release from hepatic Kupffer cells, as well as leukocyte adhesion and migration. The anti-inflammatory effects of omega-3 fatty acids on chronic autoimmune diseases such as rheumatoid arthritis, psoriasis, and lupus have been documented in both animals and humans. In experimental models of sepsis, omega-3 fatty acids inhibit inflammation, ameliorate weight loss, increase small-bowel perfusion, and may increase gut barrier protection. In human studies, omega-3 supplementation is associated with decreased production of TNF, interleukin-1β, and interleukin-6 by endotoxin-stimulated monocytes. In a study of surgical patients, preoperative supplementation with omega-3 fatty acid was associated with reduced need for mechanical ventilation, decreased hospital length of stay, and decreased mortality with a good safety profile.[19]

Kallikrein-Kinin System

The kallikrein-kinin system is a group of proteins that contribute to inflammation, blood pressure control, coagulation, and pain responses. Prekallikrein is activated by stimuli such as Hageman factor, trypsin, plasmin, factor XI, glass surfaces, kaolin, and collagen to produce the serine protease kallikrein, which subsequently plays a role in the coagulation cascade. High molecular weight kininogen is produced by the liver and is metabolized by kallikrein to form bradykinin.

Kinins mediate several physiologic processes, including vasodilation, increased capillary permeability, tissue edema, pain pathway activation, inhibition of gluconeogenesis, and increased bronchoconstriction. They also increase renal vasodilation and consequently reduce renal perfusion pressure. Decreased renal perfusion leads to activation of the renin-angiotensin-aldosterone system, which acts on the nephron to actively resorb sodium and subsequently increase intravascular volume.

Bradykinin and kallikrein levels are increased during gram-negative bacteremia, hypotension, hemorrhage, endotoxemia, and tissue injury. The degree of elevation in the levels of these mediators has been associated with the magnitude of injury and mortality. Clinical trials using bradykinin antagonists have shown some benefit in patients with gram-negative sepsis.[20]

Serotonin

Serotonin is a monoamine neurotransmitter (5-hydroxytryptamine) derived from tryptophan. Serotonin is synthesized by neurons in the CNS as well as by enterochromaffin cells of the GI tract and platelets. This neurotransmitter stimulates vasoconstriction, bronchoconstriction, and platelet aggregation. Serotonin also increases cardiac inotropy and chronotropy through nonadrenergic cyclic adenosine monophosphate (cAMP) pathways. Serotonin receptors are located in the CNS, GI tract, and monocytes.[21] Ex vivo study has shown that serotonin receptor blockade is associated with decreased production of TNF and interleukin-1 in endotoxin-treated monocytes. Serotonin is released at sites of injury, primarily by platelets; however, its role in inflammatory modulation has yet to be clearly defined.

Histamine

Histamine is synthesized by the decarboxylation of the amino acid histidine. Histamine is either rapidly released or stored in neurons, skin, gastric mucosa, mast cells, basophils, and platelets. There are four histamine receptor (H) subtypes with varying physiologic roles. H_1 binding mediates vasodilation, bronchoconstriction, intestinal motility, and myocardial contractility. H_2 binding stimulates gastric parietal cell acid secretion. H_3 is an autoreceptor found on presynaptic histamine-containing nerve endings and leads to downregulation of histamine release. H_4 is expressed primarily in bone marrow, eosinophils, and mast cells. H_4 binding interactions have not been fully delineated but have been associated with eosinophil and mast cell chemotaxis. Increased histamine release has been documented in hemorrhagic shock, trauma, thermal injury, endotoxemia, and sepsis.[22]

CYTOKINE RESPONSE TO INJURY

Tumor Necrosis Factor

Tumor necrosis factor alpha (TNF) is a cytokine that is rapidly mobilized in response to stressors such as injury and infection, and is a potent mediator of the subsequent inflammatory response. TNF is primarily synthesized by macrophages, monocytes, and T cells, which are abundant in peritoneum and splanchnic tissues. Although the circulating half-life of TNF is brief, the activity of TNF elicits many metabolic and immunomodulatory activities. TNF stimulates muscle breakdown and cachexia through increased catabolism, insulin resistance, and redistribution of amino acids to hepatic circulation as fuel substrates. In addition, TNF also mediates coagulation activation, cell migration, and macrophage phagocytosis, and enhances the expression of adhesion molecules, prostaglandin E2 , platelet-activating factor, glucocorticoids, and eicosanoids.[23]

Tumor necrosis factor receptors (TNFRs) are composed of two subtypes: TNFR-1 and TNFR-2. TNFR-1 is ubiquitously expressed in most tissues and, on ligand binding, mediates apoptosis through proteolytic caspases. TNFR-2 is expressed primarily on immunocytes and, on ligand binding, leads to NF-κB activation and subsequent amplification of the inflammatory signal. TNFRs exist in both transmembrane and soluble form. In response to inflammatory stimuli such as injury and infection, TNFRs are proteolytically cleaved from cell membranes and are readily detectable in soluble form. This may represent a mechanism of inflammatory regulation, because soluble TNFRs maintain their affinity for TNF and thereby compete with and limit the activation of transmembrane TNFR.[24]

Interleukin-1

Interleukin-1 (IL-1) is represented by two active subtypes, IL-1α and IL-1β. IL-1α is primarily membrane associated and functions through cellular contact. IL-1β is readily detectable in soluble form and mediates an inflammatory sequence similar to that of TNF. IL-1 is primarily synthesized by monocytes, macrophages, endothelial cells, fibroblasts, and epidermal cells. IL-1 is released in response to inflammatory stimuli, including cytokines (TNF, IL-2, interferon-γ [IFN-γ]) and foreign pathogens, and requires the formation of the inflammasome in the cell for processing and release. High doses of either IL-1 or TNF are associated with profound hemodynamic compromise. Interestingly, low doses of both IL-1 and TNF combined elicit hemodynamic events similar to those elicited by high doses of either mediator, which suggests a synergistic effect. IL-1 is an endogenous pyrogen because it acts on the hypothalamus by stimulating prostaglandin activity and thereby mediates a febrile response.

IL-1 is autoregulated by endogenous IL-1 receptor antagonists, which are released in response to inflammatory stimuli and compete with IL-1 at receptor binding sites. There are two primary receptor types for IL-1: IL-1R1 and IL-1R2. IL-1R1 is widely expressed and mediates inflammatory signaling on ligand binding. IL-1R2 is proteolytically cleaved from the membrane surface to soluble form on activation and thus serves as another mechanism for competition and regulation of IL-1 activity.[25]

Interleukin-2

Interleukin-2 (IL-2) is upregulated in response to IL-1 and is primarily a promoter of T-lymphocyte proliferation and differentiation,

immunoglobulin production, and gut barrier integrity. IL-2 binds to IL-2 receptors, which are expressed on leukocytes. Partly due to its short half-life of <10 minutes, IL-2 is not readily detectable after acute injury. IL-2 receptor blockade induces immunosuppressive effects and can be pharmacologically used for organ transplantation. Attenuated IL-2 expression observed during major injury or blood transfusion may contribute to the relatively immunosuppressed state of the surgical patient.[26]

Interleukin-4

Interleukin-4 (IL-4) is released by activated helper T cells and stimulates the differentiation of T cells, and also stimulates T-cell proliferation and B-cell activation. It is also important in antibody-mediated immunity and in antigen presentation. IL-4 induces class switching of differentiating B lymphocytes to produce predominantly immunoglobulin G4 and immunoglobulin E, which are important immunoglobulins in allergic and antihelmintic responses. IL-4 has anti-inflammatory effects on macrophages, exhibited by an attenuated response to proinflammatory mediators such as IL-1, TNF, interleukin-6, and interleukin-8. In addition, IL-4 appears to increase macrophage susceptibility to the anti-inflammatory effects of glucocorticoids.

Interleukin-6

Interleukin-6 (IL-6) release by macrophages is stimulated by inflammatory mediators such as endotoxin, TNF, and IL-1. IL-6 is increasingly expressed during times of stress, as in septic shock. After injury, IL-6 levels in the circulation are detectable by 60 minutes, peak between 4 and 6 hours, and can persist for as long as 10 days. Plasma levels of IL-6 are proportional to the degree of injury during surgery. Interestingly, IL-6 has counterregulatory effects on the inflammatory cascade through the inhibition of TNF and IL-1. IL-6 also promotes the release of soluble tumor necrosis factor receptors and IL-1 receptor antagonists, and stimulates the release of cortisol. High plasma IL-6 levels have been associated with mortality during intra-abdominal sepsis.[27]

Interleukin-8

Interleukin-8 (IL-8) is synthesized by macrophages as well as other cell lines such as endothelial cells. Critical illness as manifested during sepsis is a potent stimulus for IL-8 expression. IL-8 stimulates the release of IFN-γ and functions as a potent chemoattractant for neutrophils. Elevated plasma IL-8 also has been associated with disease severity and end organ dysfunction during sepsis.[28]

Interleukin-10

Interleukin-10 (IL-10) is an anti-inflammatory cytokine synthesized primarily by monocytes; however, it is also released by other lymphocytes. IL-10 is increasingly expressed during times of systemic inflammation, and its release is specifically enhanced by TNF and IL-1. IL-10 inhibits the secretion of proinflammatory cytokines, including TNF and IL-1, partly through the downregulation of NF-κB and thereby functions as a negative feedback regulator of the inflammatory cascade. Experimental models of inflammation have shown that neutralization of IL-10 increases TNF production and mortality, whereas restitution of circulating IL-10 reduces TNF levels and subsequent deleterious effects. Increased plasma levels of IL-10 also have been associated with mortality and disease severity after traumatic injury. IL-10 may significantly contribute to the underlying immunosuppressed state during sepsis through the inhibition and subsequent anergy of immunocytes.[29]

Interleukin-12

Interleukin-12 (IL-12) has been described as a regulator of cell mediated immunity. IL-12 is released by activated phagocytes, including monocytes, macrophages, neutrophils, and dendritic cells, and is increasingly expressed during endotoxemia and sepsis. IL-12 stimulates lymphocytes to increase secretion of IFN-γ with the costimulus of interleukin-18 and also stimulates natural killer cell cytotoxicity and helper T cell differentiation. IL-12 release is inhibited by IL-10. IL-12 deficiency inhibits phagocytosis in neutrophils. In experimental models of inflammatory stress, IL-12 neutralization conferred a mortality benefit in mice during endotoxemia. However, in a cecal ligation and puncture

model of intraperitoneal sepsis, IL-12 blockade was associated with increased mortality. Furthermore, later studies of intraperitoneal sepsis observed no difference in mortality with IL-12 administration; however, IL-12 knockout mice exhibited increased bacterial counts and inflammatory cytokine release, which suggests that IL-12 may contribute to an antibacterial response. IL-12 administration in chimpanzees is capable of stimulating the release of proinflammatory mediators such as IFN-γ and also anti-inflammatory mediators, including IL-10, soluble TNFR, and IL-1 receptor antagonists. In addition, IL-12 enhances coagulation as well as fibrinolysis. Despite evidence of both proinflammatory and anti-inflammatory pathway activation, most evidence suggests that IL-12 contributes to an overall proinflammatory response.[30]

Interleukin-13

Interleukin-13 (IL-13) exerts many of the same immunomodulatory effects as does IL-4. IL-13 inhibits monocyte release of TNF, IL-1, IL-6, and IL-8, while increasing the secretion of IL-1R antagonist. However, unlike IL4, IL-13 has no identifiable effect on T lymphocytes and only has influence on selected B-lymphocyte populations. Increased IL-13 expression is observed during septic shock and mediates neutropenia, monocytopenia, and leukopenia. In addition, IL-13 inhibits leukocyte interaction with activated endothelial surfaces. Similar to IL-4 and IL-10, IL-13 has a net anti-inflammatory effect.[31]

Interleukin-15

Interleukin-15 (IL-15) is synthesized in many cell types, including macrophages and skeletal muscle after endotoxin administration. IL-15 stimulates natural killer cell activation as well as B-cell and T-cell proliferation and thus functions as a regulator of cellular immunity. IL-15 has immunomodulatory effects similar to those of IL-2, in part due to shared receptor subunits. Furthermore, IL-15 acts as a potent inhibitor of lymphocyte apoptosis by enhancing the expression of antiapoptotic molecules such as Bcl-2.[32]

Interleukin-18

Interleukin-18 (IL-18), formerly IFN-γ–inducing factor, is synthesized primarily by macrophages. IL-18 and its receptor complex are members of the IL-1 superfamily. As with IL-1, macrophages release IL-18 in response to inflammatory stimuli, including endotoxin, TNF, IL-1, and IL-6. IL-18 level also is elevated during sepsis. IL-18 activates NF-κB through an Myeloid differentiation primary response gene (88) (MyD88)-dependent pathway with subsequent proinflammatory mediator release. IL-18 regulation is in part mediated through IL-18–binding protein (IL-18BP). This molecule is not a soluble receptor isoform but rather a specific endogenous antagonist. IL-18 also mediates hepatotoxicity associated with Fas ligand and TNF. The viral skin pathogen molluscum contagiosum secretes an IL-18BP–like protein, which neutralizes IL-18 and thereby inhibits the inflammatory response. IL-18 and IL-12 act synergistically to release IFN-γ from T cells. In a murine model of systemic inflammation, IL-18 neutralization reduced lethal endotoxemia. IL-18 signaling also is associated with increased expression of intercellular adhesion molecule-1. Interestingly, in a murine model of systemic inflammation, a reversal of left ventricular dysfunction was observed with IL-18 blockade, which suggests that IL-18 may contribute to the hemodynamic compromise during septic shock.[33]

Interferons

Interferons were first recognized as soluble mediators that inhibited viral replication through the activation of specific antiviral genes in infected cells. Interferons are categorized into two major subtypes based on receptor specificity and sequence homology. Type I interferons include IFN-α, IFN-β, and IFN-ω, which are structurally related and bind to a common receptor, IFN-α receptor. Type I interferons are expressed in response to many stimuli, including viral antigens, double-stranded DNA, bacteria, tumor cells, and LPS. Type I interferons influence adaptive immune responses by inducing the maturation of dendritic cells and by stimulating class I MHC expression. IFN-α and IFN-β also enhance immune responses by increasing the cytotoxicity of natural killer cells both in culture and in vivo. In murine models, the absence of IFN-α receptor results in greater susceptibility to viral infection as well as diminished LPS-induced lethality. Furthermore, type I interferons have also been studied as therapeutic agents in hepatitis C and relapsing multiple sclerosis.

Many of the physiologic effects observed with increased levels of IL-12 and IL-18 are mediated through IFN-γ. IFN-γ is a type II interferon secreted by T lymphocytes, natural killer cells, and antigen-presenting cells in response to bacterial antigens, IL-2, IL-12, and IL-18. IFN-γ stimulates the release of IL-12 and IL-18. Negative regulators of IFN-γ include IL4, IL-10, and glucocorticoids. IFN-γ binding with a cognate receptor activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, leading to subsequent induction of biologic responses. Macrophages stimulated by IFN-γ demonstrate enhanced phagocytosis and microbial killing, and increased release of oxygen radicals, partly through a nicotinamide adenosine dinucleotide phosphate–dependent phagocyte oxidase. IFN-γ mediates macrophage stimulation and thus may contribute to acute lung injury after major surgery or trauma. Diminished IFN-γ level, as seen in knockout mice, is associated with increased susceptibility to both viral and bacterial pathogens. IFN-γ regulates trafficking of immunocytes to sites of inflammation via upregulation of chemoattractants [e.g., monokine induced by IFN-γ (MIG), macrophage inflammatory protein 1-alpha and 1-beta] and adhesion molecules (e.g., intercellular adhesion molecule-1, vascular cell adhesion molecule-1). In addition, IFN-γ promotes differentiation of T cells to the helper T cell subtype 1 and also enhances B-cell isotype switching to immunoglobulin G.[34]

Granulocyte-Macrophage Colony-Stimulating Factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF), as the name suggests, upregulates both granulocyte and monocyte cell lines from hematopoietic bone marrow stem cells. GM-CSF plasma levels are low to undetectable but rapidly increase in response to inflammatory stimuli such as TNF. GM-CSF inhibits both monocyte and neutrophil apoptosis and enhances macrophage cytokine release in response to inflammatory stimuli. GM-CSF also potentiates the release of neutrophil superoxide as well as the cytotoxicity of monocytes. Administration of GM-CSF has proven beneficial during the treatment of fungal infections in immunocompromised patients. GM-CSF may potentiate acute lung injury during critical illness, because GM-CSF blockade has been found to be associated with decreased alveolar macrophage activity and NF-κB intensity. This growth factor is effective in promoting the maturation and recruitment of functional leukocytes necessary for normal inflammatory cytokine responses and also may be effective in wound healing.[35]

High Mobility Group Box 1

High mobility group box 1 (HMGB1) is a DNA transcription factor that facilitates the binding of regulatory protein complexes to DNA. HMGB1 is actively secreted by macrophages, natural killer cells, and enterocytes. Endotoxin, TNF, and IFN-γ promote the release of HMGB1, and in a murine model of intraperitoneal sepsis, increased circulating HMGB1 was associated with increased mortality. HMGB1 also appears to have cytokine-like activities, because it promotes the release of TNF from monocytes. Interestingly, elevation of plasma HMGB1 levels after experimental induction of endotoxemia is delayed relative to that of other inflammatory mediators, with levels peaking at 16 hours and remaining elevated beyond 30 hours. This response contrasts with that of acute inflammatory mediators such as TNF, which peaks at 1 to 2 hours and becomes undetectable by 12 hours. Furthermore, HMGB1 blockade is associated with decreased mortality even when initiated 4 to 24 hours after the inflammatory stimulus.[36]

HMGB1 is passively released by necrotic cells. Thus, HMGB1 alone or in combination with other molecules may contribute to the regulation of inflammation after tissue injury. Receptors for HMGB1 are receptors for advanced glycation end products and toll-like receptor 4. Binding leads to the proinflammatory response through the activation of NF-κB. Clinical trials have demonstrated increased plasma HMGB1 during systemic inflammation, as in sepsis, hemorrhagic shock, pancreatitis, myocardial infarction, and major surgery.

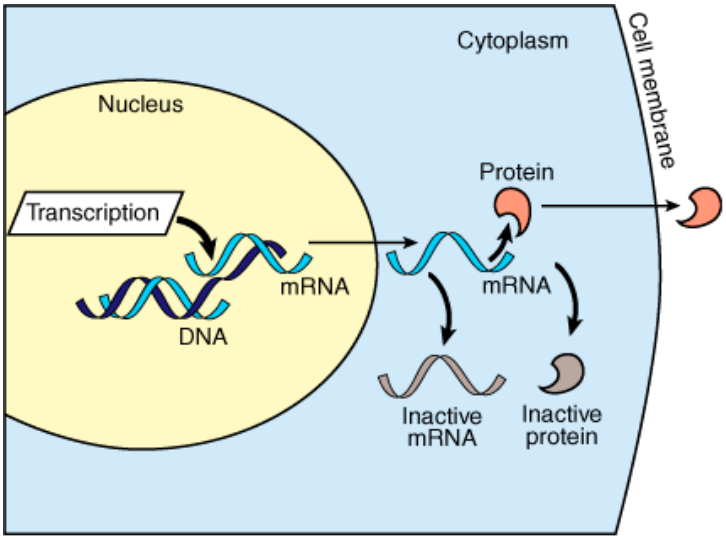
CELLULAR RESPONSE TO INJURY

Gene Expression and Regulation

Many genes are regulated at the point of DNA transcription and thus influence whether messenger RNA (mRNA) and its subsequent product are expressed (Fig. 2-6). These mRNA transcripts are also regulated by modulation mechanisms, including (a) splicing, which can cleave mRNA and

remove noncoding regions; (b) capping, which modifies the 5' ends of the mRNA sequence to inhibit breakdown by exonucleases; (c) and the addition of a polyadenylated tail, which adds a noncoding sequence to the mRNA, effectively increasing the half-life of the transcript. Once out of the nucleus, the mRNA can be inactivated or translated to form proteins. Many protein products are also further modified for specific function or trafficking.

Fig. 2-6.



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Gene expression and protein synthesis can occur within a 24-hour period. The process can be regulated at various stages: transcription, messenger RNA (mRNA) processing, or protein packaging. At each stage, it is possible to inactivate the mRNA or protein, rendering these molecules nonfunctional.

Gene expression relies on the coordinated action of transcription factors and coactivators (i.e., regulatory proteins), which are complexes that bind to highly specific DNA sequences upstream of the target gene known as the *promoter region.* Enhancer sequences of DNA mediate gene expression, whereas repressor sequences are noncoding regions that bind proteins to inhibit gene expression. During systemic inflammation, transcription factors are highly important, because regulation of cytokine gene expression may have profound effects on the clinical phenotype.

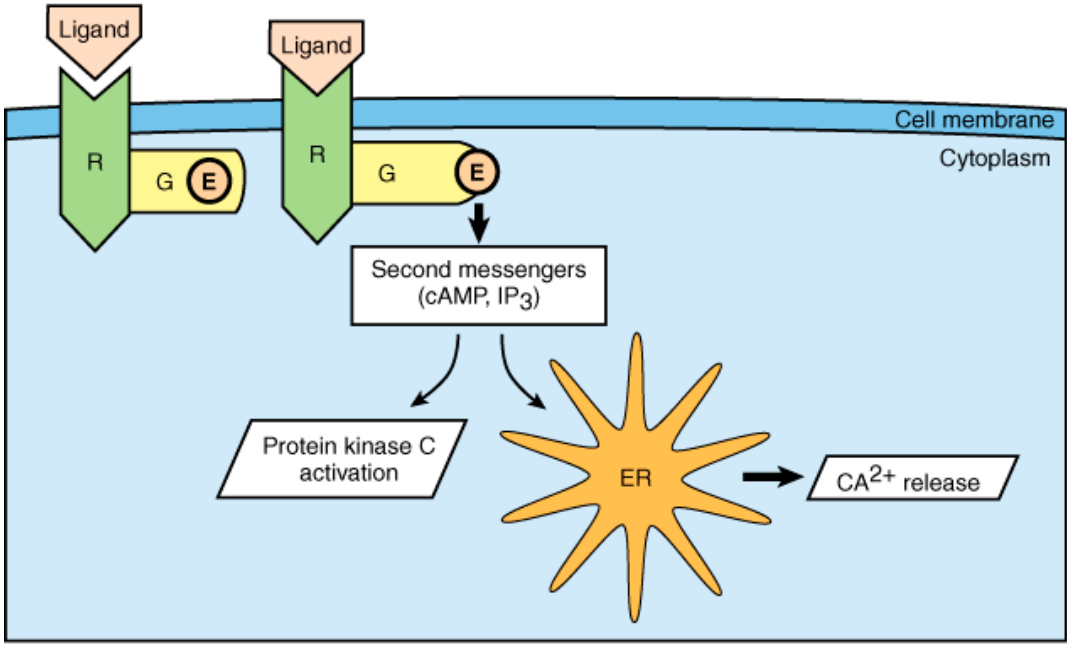
CELL SIGNALING PATHWAYS

G-Protein Receptors

G-protein receptors (GPRs) are a large family of transmembrane receptors. They bind a multitude of ligands (e.g., epinephrine, bradykinin, leukotriene) and are involved in signal transduction during the inflammatory response. Extracellular ligands bind to GPR, which result in a conformational change and activation of associated proteins. The two major second messengers of the G-protein pathway are (1) cAMP, and (2) calcium, released from the endoplasmic reticulum (Fig. 2-7). Increased intracellular cAMP can activate gene transcription through the activity of intracellular signal transducers such as protein kinase A. Increased intracellular calcium can activate the intracellular signal transducer phospholipase C with further subsequent downstream effects. GPR binding also can promote the activity of protein kinase C, which can subsequently stimulate NF-κB as well as other transcription factors.

Fig. 2-7.

G-protein receptors
(vasoactive polypeptides, mitogens, phospholipids,
neurotransmitters, prostaglandins)



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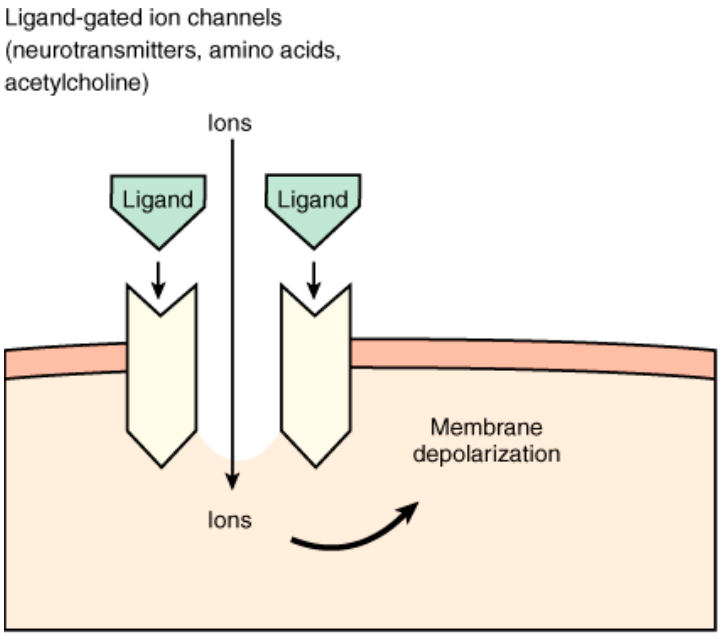
G-protein–coupled receptors are transmembrane proteins. The G-protein receptors respond to ligands such as adrenaline and serotonin. On ligand binding to the receptor (R), the G protein (G) undergoes a conformational change through guanosine triphosphate–guanosine diphosphate conversion and in turn activates the effector (E) component. The E component subsequently activates second messengers. The role of inositol triphosphate (IP_3) is to induce release of calcium from the endoplasmic reticulum (ER). cAMP = cyclic adenosine triphosphate.

Ligand-Gated Ion Channels

Ligand-gated ion channels (LGICs) are transmembrane receptors that allow the rapid influx of ions (e.g., sodium, calcium, potassium, chloride) and are central to the signal transduction of neurotransmitters. On ligand binding LGICs effectively convert a chemical signal into an electrical signal. The prototypical LGIC is the nicotinic acetylcholine receptor (Fig. 2-8).

Fig. 2-8.



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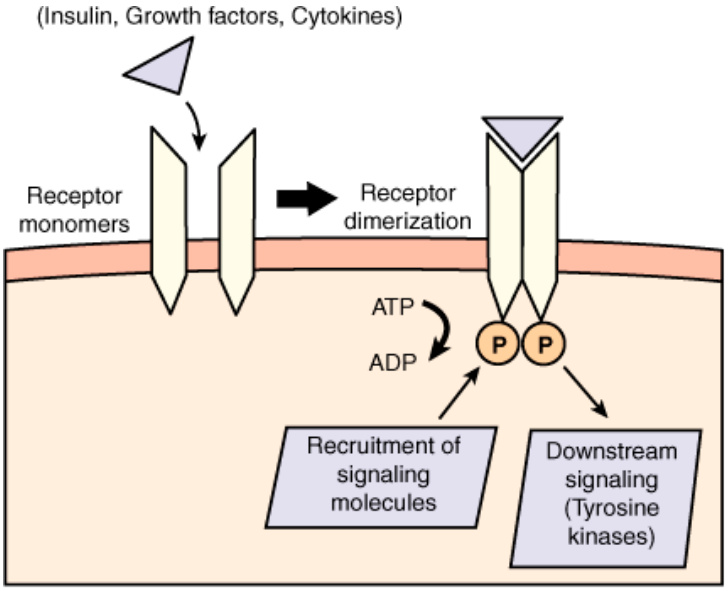
Ligand-gated ion channels convert chemical signals into electrical signals, inducing a change in cell membrane potential. On activation of the channel, millions of ions per second influx into the cell. These channels are composed of many subunits, and the nicotinic acetylcholine receptor is one such example.

Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs) are transmembrane receptors that are involved in cell signaling for several growth factors, including platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, and vascular endothelial growth factor. On ligand binding, RTKs dimerize with adjacent receptors, undergo autophosphorylation, and recruit secondary signaling molecules (e.g., phospholipase C) (Fig. 2-9). Activation of RTK is important for gene transcription as well as cell proliferation and may have influence in the development of many types of cancer.

Fig. 2-9.



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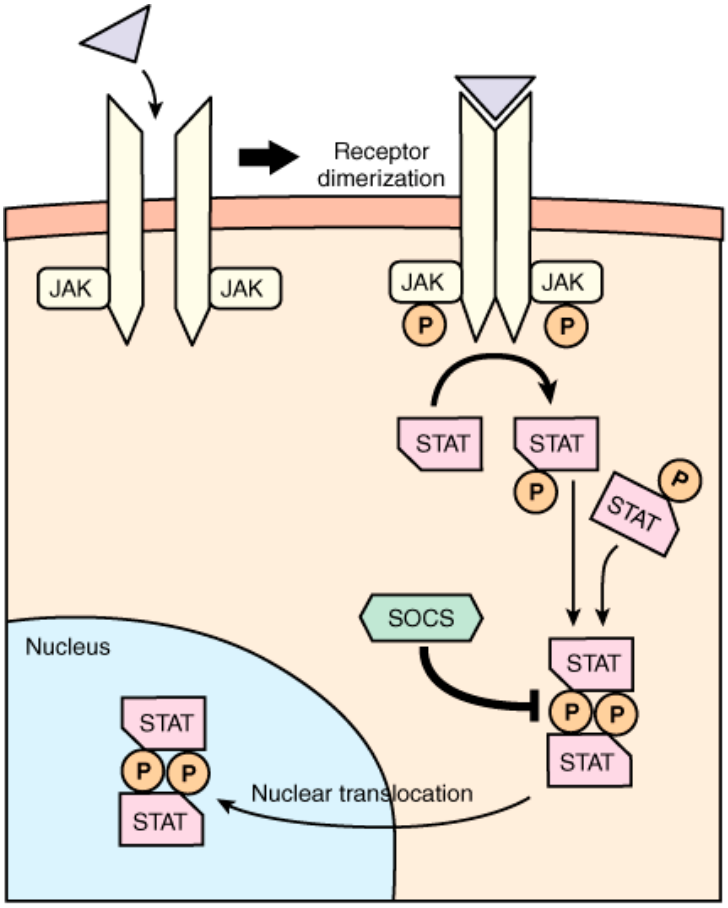
The receptor tyrosine kinase requires dimerization of monomeric units. These receptors possess intrinsic enzymatic activity that requires multiple autophosphorylation steps to recruit and activate intracellular signaling molecules. ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Janus Kinase/Signal Transducer and Activator of Transcription Signaling

The Janus kinases (JAKs) represent a family of tyrosine kinases that mediate signal transduction of several cytokines, including IFN-γ, IL-6, IL-10, IL-12, and IL-13. JAKs bind to cytokines, and on ligand binding and dimerization, activated JAKs recruit and phosphorylate signal transducer and activator of transcription (STAT) molecules (Fig. 2-10). Activated STAT proteins further dimerize and translocate into the nucleus and modulate the transcription of target genes. Interestingly, STAT-DNA binding can be observed within minutes of cytokine binding. The JAK/STAT system is a rapid pathway for membrane to nucleus signal transduction. The JAK/STAT pathway is inhibited by the action of phosphatase, the export of STATs from the nucleus, as well the interaction of antagonistic proteins.[37]

Fig. 2-10.



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The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway also requires dimerization of monomeric units. STAT molecules possess "docking" sites that allow for STAT dimerization. The STAT complexes translocate into the nucleus and serve as gene transcription factors. JAK/STAT activation occurs in response to cytokines (e.g., interleukin-6) and cell stressors, and has been found to induce cell proliferation and inflammatory function. Intracellular molecules that inhibit STAT function, known as *suppressors of cytokine signaling (SOCSs),* have been identified. P = phosphate.

Suppressors of Cytokine Signaling

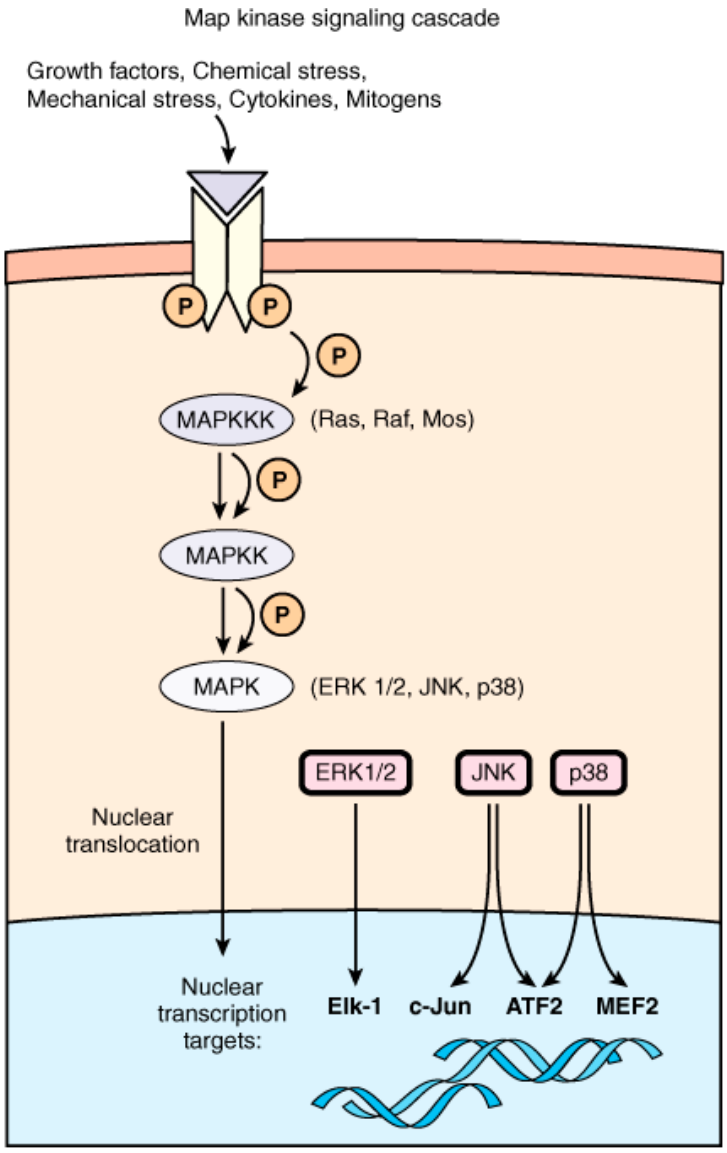
Suppressor of cytokine signaling (SOCS) molecules are a group of cytokine-induced proteins that function as a negative feedback loop by downregulating the JAK/STAT pathway. SOCSs exert an inhibitory effect partly by binding with JAK and thus competing with STAT. A deficiency of SOCS activity may render a cell hypersensitive to certain stimuli, such as inflammatory cytokines and growth hormones. Interestingly, in a murine model, SOCS knockout resulted in a lethal phenotype in part because of unregulated interferon-ϒ signaling. An example of this pathway is highlighted by an attenuated IL-6 response in macrophages via suppressor of cytokine signaling 3 (SOCS-3) inhibition of signal transducer and activator of transcription 3 (STAT3).[38]

Mitogen-Activated Protein Kinases

Pathways mediated through mitogen-activated protein kinase (MAPK) contribute to inflammatory signaling and regulation of cell proliferation and cell death (Fig. 2-11). MAPK pathways involve sequential stages of mediator phosphorylation resulting in the activation of downstream effectors,

including c-Jun N-terminal kinase (JNK), extracellular signal regulated protein kinase (ERK), and p38 kinase, with subsequent gene modulation. Dephosphorylation of MAPK pathway mediators inhibit their function. Activated JNK phosphorylates c-Jun, which dimerizes to form the transcription factor activated protein 1. The protein MAP/ERK kinase kinase (MEKK) has several functions, including protein kinase and ubiquitin ligase, and also has been shown to downregulate MAPK pathways. JNK is activated by TNF and IL-1 and is a regulator of apoptosis. Pharmacologic blockade of JNK was associated with decreased pulmonary injury and TNF and IL-1 secretion in an ischemia/reperfusion model. The p38 kinase is activated in response to endotoxin, viruses, IL-1, IL-2, IL-7, IL-17, IL-18, and TNF. The p38 also plays a role in immunocyte development, because p38 inactivation is a critical step in the differentiation of thymic T cells. These MAPK isoforms do not function independently but rather exhibit significant counteraction and cosignaling, which can influence the inflammatory response.[39]

Fig. 2-11.



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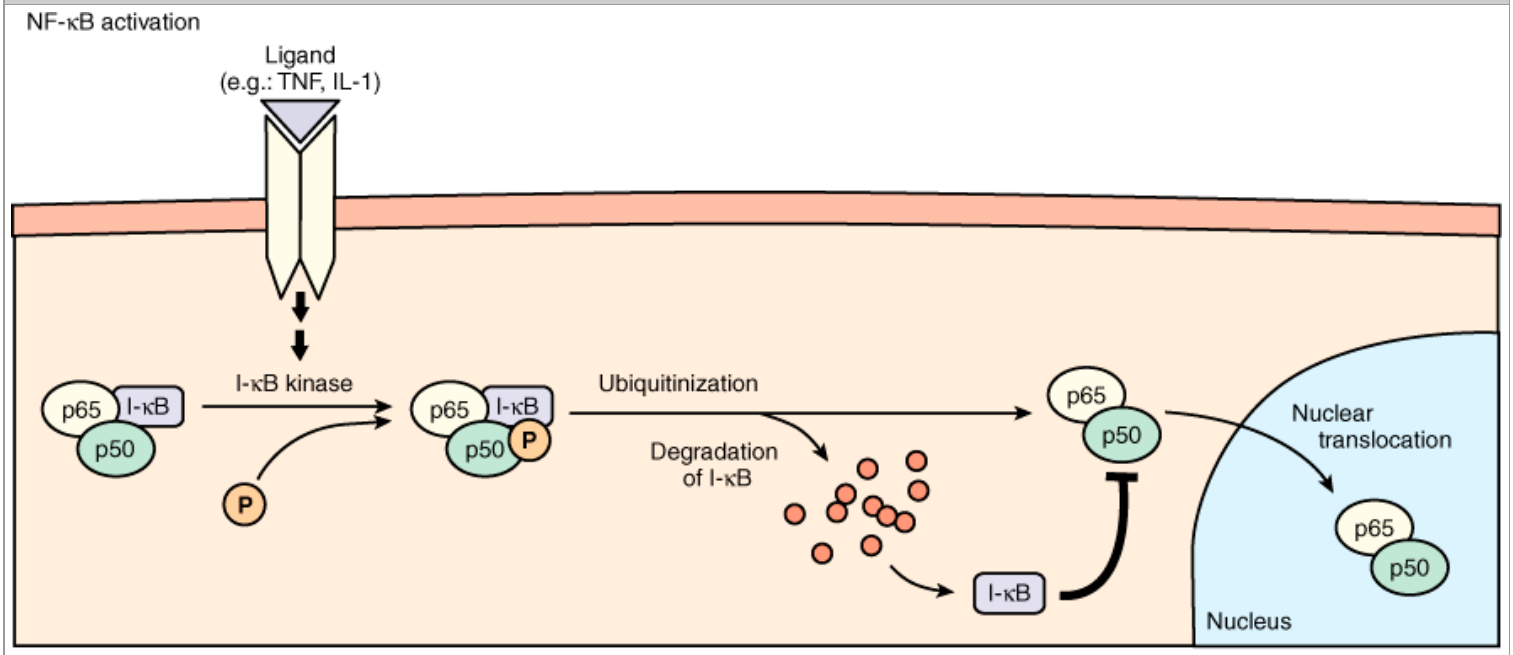
The mitogen-activated protein kinase (MAPK) signaling pathway requires multiple phosphorylation steps. Ras, Raf, and Mos are examples of the MAPK kinase kinase (MAPKKK) and are upstream molecules. Well-characterized downstream kinases are extracellular signal regulated kinases 1 and 2 (ERK 1/2), c-Jun N-terminal kinases (JNKs) or stress-activated protein kinases (SAPKs), and p38 MAPKs that target specific gene transcription sites in the nucleus. ATF2 = activating transcription factor 2; MAPKK = mitogen-activated protein kinase kinase; MEF2 = myocyte-enhancing factor 2; P = phosphate.

Nuclear Factor κB

Nuclear factor κB (NF-κB) is a transcription factor that has a central role in regulating the gene products expressed after inflammatory stimuli (Fig. 2-12). NF-κB is composed of two smaller polypeptides, p50 and p65. NF-κB resides in the cytosol in the resting state primarily through the inhibitory binding of inhibitor of κB (I-κB). In response to an inflammatory stimulus such as TNF, IL-1, or endotoxin, a sequence of intracellular mediator phosphorylation reactions leads to the degradation of I-κB and subsequent release of NF-κB. On release, NF-κB travels to the nucleus

and promotes gene expression. NF-κB also stimulates the gene expression for I-κB, which results in negative feedback regulation. In clinical appendicitis, for example, increased NF-κB activity was associated with initial disease severity, and levels returned to baseline within 18 hours after appendectomy in concert with resolution of the inflammatory response.[40]

Fig. 2-12.



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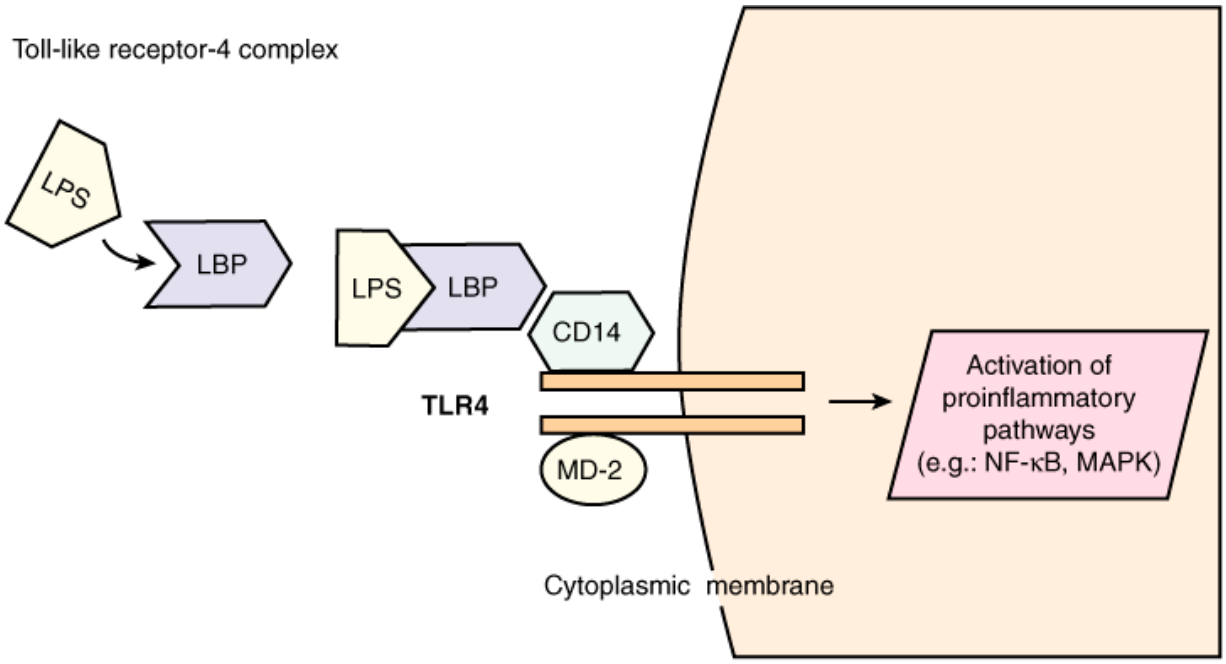
Inhibitor of κB (I-κB) binding to the p50-p65 subunits of nuclear factor κB (NF-κB) inactivates the molecule. Ligand binding to the receptor activates a series of downstream signaling molecules, of which I-κB kinase is one. The phosphorylated NF-κB complex further undergoes ubiquitinization and proteosome degradation of I-κB, activating NF-κB, which translocates into the nucleus. Rapid resynthesis of I-κB is one method of inactivating the p50-p65 complex. IL-1 = interleukin-1; P = phosphate; TNF = tumor necrosis factor.

Toll-Like Receptors and CD14

The innate immune system responds to pathogen-associated molecular patterns (PAMPs) such as microbial antigens and LPS. Toll-like receptors (TLRs) are a group of pattern recognition receptors activated by PAMPs that function as effectors of the innate immune system and belong to the IL-1 superfamily. Immunocyte recognition of LPS is mediated primarily by TLR4. LPS-binding proteins chaperone LPS to the CD14/TLR4 complex, which sets into effect cellular mechanisms that activate MAPK, NF-κB, and cytokine gene expression (Fig. 2-13). In contrast to TLR4, TLR2 recognizes PAMPs from gram-positive bacteria, including lipoproteins, lipopeptides, peptidoglycans, and phenol-soluble modulin from *Staphylococcus* species. Interestingly, loss-of-function single nucleotide polymorphisms of TLR are associated with an increased risk of infection in susceptible critically ill patients.[41] As multiligand receptors, TLRs also bind damage-associated molecular pattern molecules (DAMPs), which are endogenous cellular products released during times of stress or injury. DAMPs include products such as HMGB1, heat shock proteins, and hyaluronic acid. Innate immune activation by DAMPs stimulates the recruitment of inflammatory cells to the site of injury and also mediates proinflammatory signaling.[42]

Fig. 2-13.



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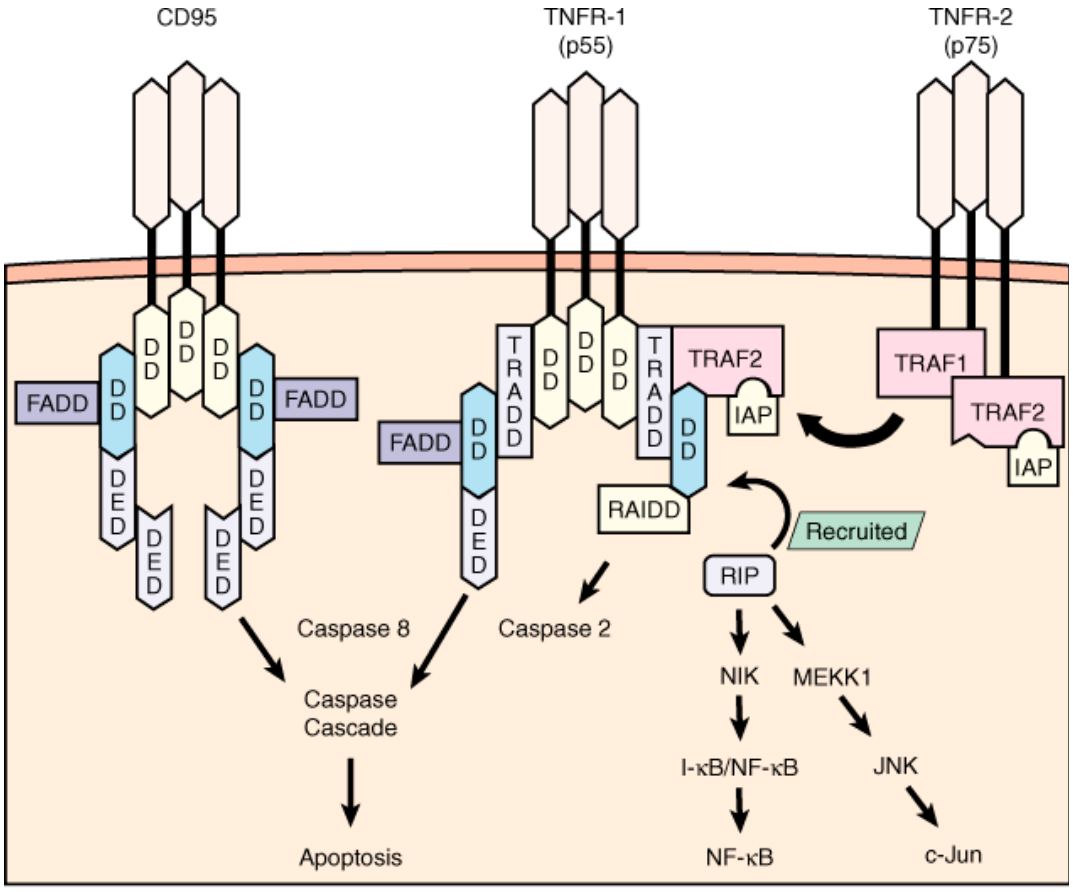
Lipopolysaccharide (LPS) recognition by immune cells is primarily by the toll-like receptor-4 (TLR4)/CD14/MD-2 complex. LPS is transported by LPS-binding protein (LBP) to the cell surface complex. Other cell surface LPS sensors include ion-gated channels, CD11b/CD18, and macrophage scavenger receptors. MAPK = mitogen-activated protein kinase; NF-κB = nuclear factor B.

APOPTOSIS

Apoptosis (regulated cell death) is an energy-dependent, organized mechanism for clearing senescent or dysfunctional cells, including macrophages, neutrophils, and lymphocytes, without promoting an inflammatory response. Conversely, cell necrosis results in a disorganized sequence of intracellular molecular releases with subsequent immune activation and inflammatory response. Systemic inflammation modulates apoptotic signaling in active immunocytes, which subsequently influences the inflammatory response through the loss of effector cells.

Apoptosis proceeds primarily through two pathways: the extrinsic pathway and the intrinsic pathway. The extrinsic pathway is activated through the binding of death receptors (e.g., Fas, TNFR), which leads to the recruitment of Fas-associated death domain protein and subsequent activation of caspase 3 (Fig. 2-14). On activation, caspases are the effectors of apoptotic signaling because they mediate the organized breakdown of nuclear DNA. The intrinsic pathway proceeds through protein mediators (e.g., Bcl-2, Bcl-2-associated death promoter, Bcl-2–associated X protein, Bim) that influence mitochondrial membrane permeability. Increased membrane permeability leads to the release of mitochondrial cytochrome C, which ultimately activates caspase 3 and thus induces apoptosis. These pathways do not function in a completely autonomous manner, because there is significant interaction and crosstalk between mediators of both extrinsic and intrinsic pathways. Apoptosis is modulated by several regulatory factors, including inhibitor of apoptosis proteins and regulatory caspases (e.g., caspases 1, 8, 10).

Fig. 2-14.



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Signaling pathway for tumor necrosis factor receptor 1 (TNFR-1) (55 kDa) and TNFR-2 (75 kDa) occurs by the recruitment of several adapter proteins to the intracellular receptor complex. Optimal signaling activity requires receptor trimerization. TNFR-1 initially recruits TNFR-associated death domain (TRADD) and induces apoptosis through the actions of proteolytic enzymes known as *caspases,* a pathway shared by another receptor known as *CD95 (Fas).* CD95 and TNFR-1 possess similar intracellular sequences known as *death domains (DDs),* and both recruit the same adapter proteins known as *Fas-associated death domains (FADDs)* before activating caspase 8. TNFR-1 also induces apoptosis by activating caspase 2 through the recruitment of receptor-interacting protein (RIP). RIP also has a functional component that can initiate nuclear factor κB (NF-κB) and c-Jun activation, both favoring cell survival and proinflammatory functions. TNFR-2 lacks a DD component but recruits adapter proteins known as TNFR-associated factors 1 and 2 (TRAF1, TRAF2) that interact with RIP to mediate NF-κB and c-Jun activation. TRAF2 also recruits additional proteins that are antiapoptotic, known as inhibitor of apoptosis proteins (IAPs). DED = death effector domain; I-κB = inhibitor of κB; I-κB/NF-κB = inactive complex of NF-κB that becomes activated when the I-κB portion is cleaved; JNK = c-Jun N-terminal kinase; MEKK1 = mitogen-activated protein/extracellular regulatory protein kinase kinase kinase-1; NIK = NF-κB–inducing kinase; RAIDD = RIP-associated interleukin-1b-converting enzyme and ced-homologue-1–like protein with death domain, which activates proapoptotic caspases.

(Adapted with permission from Lin E, Calvano SE, Lowry SF: Tumor necrosis factor receptors in systemic inflammation, in Vincent J-L (series ed), Marshall JC, Cohen J (eds): *Update in Intensive Care and Emergency Medicine: Vol. 31: Immune Response in Critical Illness.* Berlin: Springer-Verlag, 1999, p 365. With kind permission from Springer Science + Business Media.)

Apoptosis during sepsis may influence the ultimate competency of the acquired immune response. In a murine model of peritoneal sepsis, increased lymphocyte apoptosis was associated with mortality, which may be due to a resultant decrease in IFN-γ release. In postmortem analysis of patients who expired from overwhelming sepsis, there was an increase in lymphocyte apoptosis, whereas macrophage apoptosis did not appear to be affected. Clinical trials have observed an association between the degree of lymphopenia and disease severity in sepsis. In

addition, after the phagocytosis of apoptotic cells by macrophages, anti-inflammatory mediators such as IL-10 are released that may exacerbate immune suppression during sepsis. Neutrophil apoptosis is inhibited by inflammatory products, including TNF, IL-1, IL-3, IL-6, GM-CSF, and IFN-γ. This retardation in regulated cell death may prolong and exacerbate secondary injury through neutrophil free radical release as the clearance of senescent cells is delayed.[28]

CELL-MEDIATED INFLAMMATORY RESPONSE

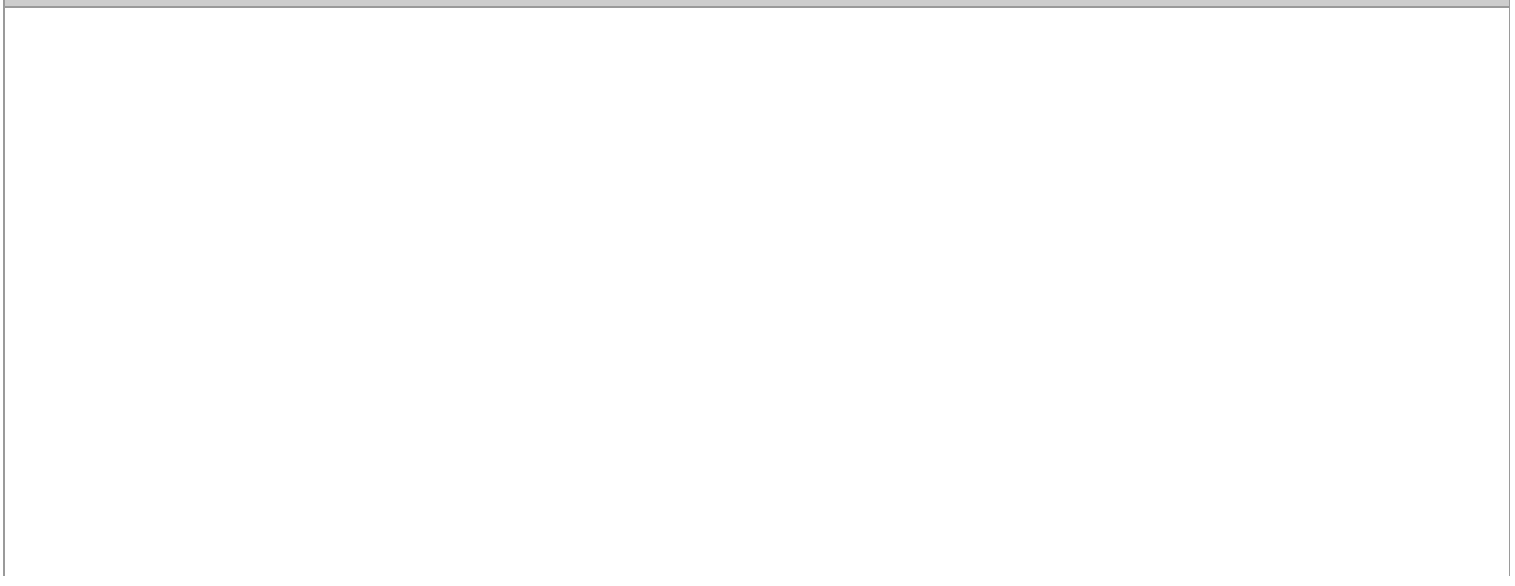
Platelets

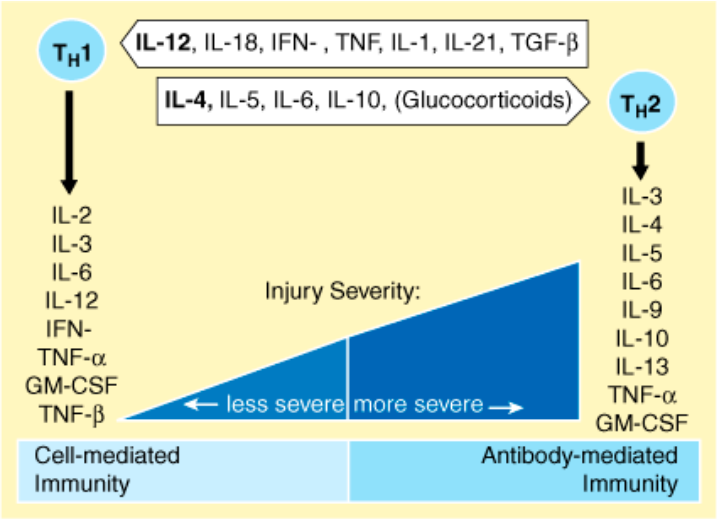
Platelets are nonnucleated structures containing both mitochondria and mediators of coagulation and inflammatory signaling. Platelets are derived from bone marrow megakaryocytes. Platelets are critically important in the hemostatic response and are activated by several factors, including exposed collagen. Activated platelets at the site of injury release inflammatory mediators that serve as the principal chemoattractant for neutrophils and monocytes. The migration of platelets and neutrophils through the vascular endothelium occurs within 3 hours of injury and is enhanced by serotonin release, platelet-activating factor, and prostaglandin E2 . Platelets are an important source of eicosanoids and vasoactive mediators. A hallmark of the septic response includes thrombocytopenia; however, the mechanism is unclear and likely multifactorial. Pharmaceutical agents such as NSAIDs inhibit platelet function through the blockade of COX.[43]

Lymphocytes and T-Cell Immunity

Lymphocytes are circulating immune cells composed primarily of B cells, T cells, and natural killer cells. As mediators of adaptive immunity, T lymphocytes are recruited to sites of injury. Helper T lymphocytes are broadly categorized into two groups: T_H1 and T_H2. T_H1 cells favor cellular immune responses and secrete IFN-γ, IL-2, and IL-12, whereas T_H2 cells favor humoral responses and produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. T_H1 activation is paramount in the defense against bacterial pathogens; however, during critical illness induced by severe trauma or sepsis, there appears to be a predominance of T_H2 over T_H1 cytokine responses, which may exacerbate immune dysregulation through amplified cytokine signaling (Fig. 2-15). In burn injury, T regulatory cells are associated with T-cell suppression via the release of transforming growth factor beta (TGF-β), which can downregulate T-cell function. Nutritional supplementation may confer a benefit in T-cell responses, because arginine is essential for T-cell proliferation and receptor function.[44]

Fig. 2-15.





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Specific immunity mediated by helper T lymphocytes subtype 1 (T_H1) and subtype 2 (T_H2) after injury. A T_H1 response is favored in lesser injuries, with intact cell-mediated and opsonizing antibody immunity against microbial infections. This cell-mediated immunity includes activation of monocytes, B lymphocytes, and cytotoxic T lymphocytes. A shift toward the T_H2 response from naïve helper T cells is associated with injuries of greater magnitude and is not as effective against microbial infections. A T_H2 response includes the activation of eosinophils, mast cells, and B-lymphocyte immunoglobulin 4 and immunoglobulin E production. (Primary stimulants and principal cytokine products of such responses are in **bold** characters.) Interleukin-4 (IL-4) and IL-10 are known inhibitors of the T_H1 response. Interferon-ϒ (IFN-ϒ) is a known inhibitor of the T_H2 response. Although not cytokines, glucocorticoids are potent stimulants of a T_H2 response, which may partly contribute to the immunosuppressive effects of cortisol. GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor.

(Adapted with permission from Lin E, Calvano SE, Lowry SF: Inflammatory cytokines and cell response in surgery. *Surgery* 127:117, 2000. Copyright Elsevier.)

Eosinophils

Eosinophils are immunocytes whose primary functions are antihelmintic. Eosinophils are found mostly in tissues such as the lung and GI tract, which may suggest a role in immune surveillance. Eosinophils can be activated by IL-3, IL-5, GM-CSF, chemoattractants, and platelet-activating factor. Eosinophil activation can lead to subsequent release of toxic mediators, including reactive oxygen species, histamine, and peroxidase.[45]

Mast Cells

Mast cells are important in the primary response to injury because they are located in tissues. TNF release from mast cells has been found to be crucial for neutrophil recruitment and pathogen clearance. Mast cells are also known to play an important role in the anaphylactic response to allergens. On activation from stimuli including allergen binding, infection, and trauma, mast cells produce histamine, cytokines, eicosanoids, proteases, and chemokines, which leads to vasodilatation, capillary leakage, and immunocyte recruitment. Mast cells are thought to be important cosignaling effector cells of the immune system via the release of IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-14, as well as macrophage migration–inhibiting factor.[46]

Monocytes

Monocytes are mononuclear phagocytes that circulate in the bloodstream and can differentiate into macrophages, osteoclasts, and dendritic cells

on migrating into tissues. Macrophages are the main effector cells of the immune response to infection and injury, primarily through mechanisms that include phagocytosis of microbial pathogens, release of inflammatory mediators, and clearance of apoptotic cells. In humans, downregulation of monocyte and neutrophil TNFR expression has been demonstrated experimentally and clinically during systemic inflammation. In clinical sepsis, nonsurviving patients with severe sepsis have an immediate reduction in monocyte surface TNFR expression with failure to recover, whereas surviving patients have normal or near-normal receptor levels from the onset of clinically defined sepsis. In patients with congestive heart failure, there is also a significant decrease in the amount of monocyte surface TNFR expression compared with control patients. In experimental models, endotoxin has been shown to differentially regulate over 1000 genes in murine macrophages with approximately 25% of these corresponding to cytokines and chemokines. During sepsis, macrophages undergo phenotypic reprogramming highlighted by decreased surface human leukocyte antigen DR (a critical receptor in antigen presentation), which also may contribute to host immunocompromise during sepsis.[47]

Neutrophils

Neutrophils are among the first responders to sites of infection and injury and as such are potent mediators of acute inflammation. Chemotactic mediators from a site of injury induce neutrophil adherence to the vascular endothelium and promote eventual cell migration into the injured tissue. Neutrophils are circulating immunocytes with short half-lives (4 to 10 hours). On activation by inflammatory stimuli, including TNF, IL-1, and microbial pathogens, neutrophils are able to phagocytose, release lytic enzymes, and generate large amounts of toxic reactive oxygen species.[48]

ENDOTHELIUM-MEDIATED INJURY

Vascular Endothelium

Under physiologic conditions, vascular endothelium has overall anticoagulant properties mediated via the production and cell surface expression of heparin sulfate, dermatan sulfate, tissue factor pathway inhibitor, protein S, thrombomodulin, plasminogen, and tissue plasminogen activator. Endothelial cells also perform a critical function as barriers that regulate tissue migration of circulating cells. During sepsis, endothelial cells are differentially modulated, which results in an overall procoagulant shift via decreased production of anticoagulant factors, which may lead to microthrombosis and organ injury.

Neutrophil-Endothelium Interaction

The regulated inflammatory response to infection facilitates neutrophil and other immunocyte migration to compromised regions through the actions of increased vascular permeability, chemoattractants, and increased endothelial adhesion factors referred to as *selectins* that are elaborated on cell surfaces (Table 2-5). Prolonged and unremitting neutrophil activation and mediator release can lead to tissue injury through the production of toxic oxygen metabolites and lysosomal enzymes that degrade tissue basal membranes, cause microvascular thrombosis, and activate myeloperoxidases. In response to inflammatory stimuli, including chemokines, thrombin, IL-1, histamine, and TNF, vascular endothelium increases surface expression of the adhesion molecule P-selectin, which is observable in 10 to 20 minutes and mediates neutrophil rolling (Fig. 2-16). After 2 hours, however, cell surface expression favors E-selectin expression. L-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) are responsible for over 85% of monocyte-to-monocyte and monocyte-to-endothelium adhesion activity. Endothelial selectins interact with leukocyte selectins (PSGL-1, L-selectin) to mediate leukocyte rolling, which allows targeted immunocyte migration. Also important are secondary leukocyte-leukocyte interactions in which PGSL-1 and L-selectin binding facilitates further leukocyte tethering. Although there are distinguishable properties among individual selectins in leukocyte rolling, effective rolling most likely involves a significant degree of functional overlap.[49]

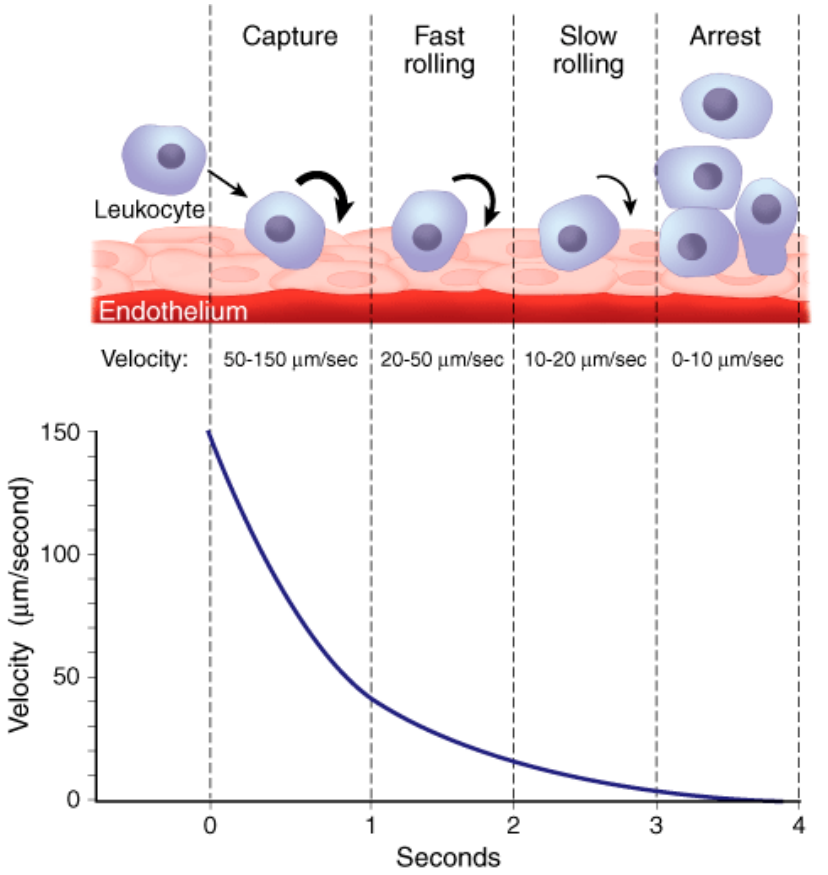
Table 2-5 Molecules that Mediate Leukocyte-Endothelial Adhesion, Categorized by Family

Adhesion Molecule	Action	Origin	Inducers of Expression	Target Cells

Selectins				
L-selectin	Fast rolling	Leukocytes	Native	Endothelium, platelets, eosinophils
P-selectin	Slow rolling	Platelets and endothelium	Thrombin, histamine	Neutrophils, monocytes
E-selectin	Very slow rolling	Endothelium	Cytokines	Neutrophils, monocytes, lymphocytes
Immunoglobulins				
ICAM-1	Firm adhesion/transmigration	Endothelium, leukocytes, fibroblasts, epithelium	Cytokines	Leukocytes
ICAM-2	Firm adhesion	Endothelium, platelets	Native	Leukocytes
VCAM-1	Firm adhesion/transmigration	Endothelium	Cytokines	Monocytes, lymphocytes
PECAM-1	Adhesion/transmigration	Endothelium, platelets, leukocytes	Native	Endothelium, platelets, leukocytes
β_2-*(CD18) Integrins*				
CD18/11a	Firm adhesion/transmigration	Leukocytes	Leukocyte activation	Endothelium
CD18/11b (Mac-1)	Firm adhesion/transmigration	Neutrophils, monocytes, natural killer cells	Leukocyte activation	Endothelium
CD18/11c	Adhesion	Neutrophils, monocytes, natural killer cells	Leukocyte activation	Endothelium
β_1-*(CD29) Integrins*				
VLA-4	Firm adhesion/transmigration	Lymphocytes, monocytes	Leukocyte activation	Monocytes, endothelium, epithelium

ICAM-1 = intercellular adhesion molecule-1; ICAM-2 = intercellular adhesion molecule-2; Mac-1 = macrophage antigen 1; PECAM-1 = platelet-endothelial cell adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1; VLA-4 = very late antigen-4.

Fig. 2-16.



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Simplified sequence of selectin-mediated neutrophil-endothelium interaction after an inflammatory stimulus. *CAPTURE* (tethering), predominantly mediated by cell L-selectin with contribution from endothelial P-selectin, describes the initial recognition between leukocyte and endothelium, in which circulating leukocytes marginate toward the endothelial surface. *FAST ROLLING* (20 to 50 µm/s) is a consequence of rapid L-selectin shedding from cell surfaces and formation of new downstream L-selectin to endothelium bonds, which occur in tandem. *SLOW ROLLING* (10 to 20 µm/s) is predominantly mediated by P-selectins. The slowest rolling (3 to 10 µm/s) before arrest is predominantly mediated by E-selectins, with contribution from P-selectins. *ARREST* (firm adhesion) leading to transmigration is mediated by β-integrins and the immunoglobulin family of adhesion molecules. In addition to interacting with the endothelium, activated leukocytes also recruit other leukocytes to the inflammatory site by direct interactions, which are mediated in part by selectins.

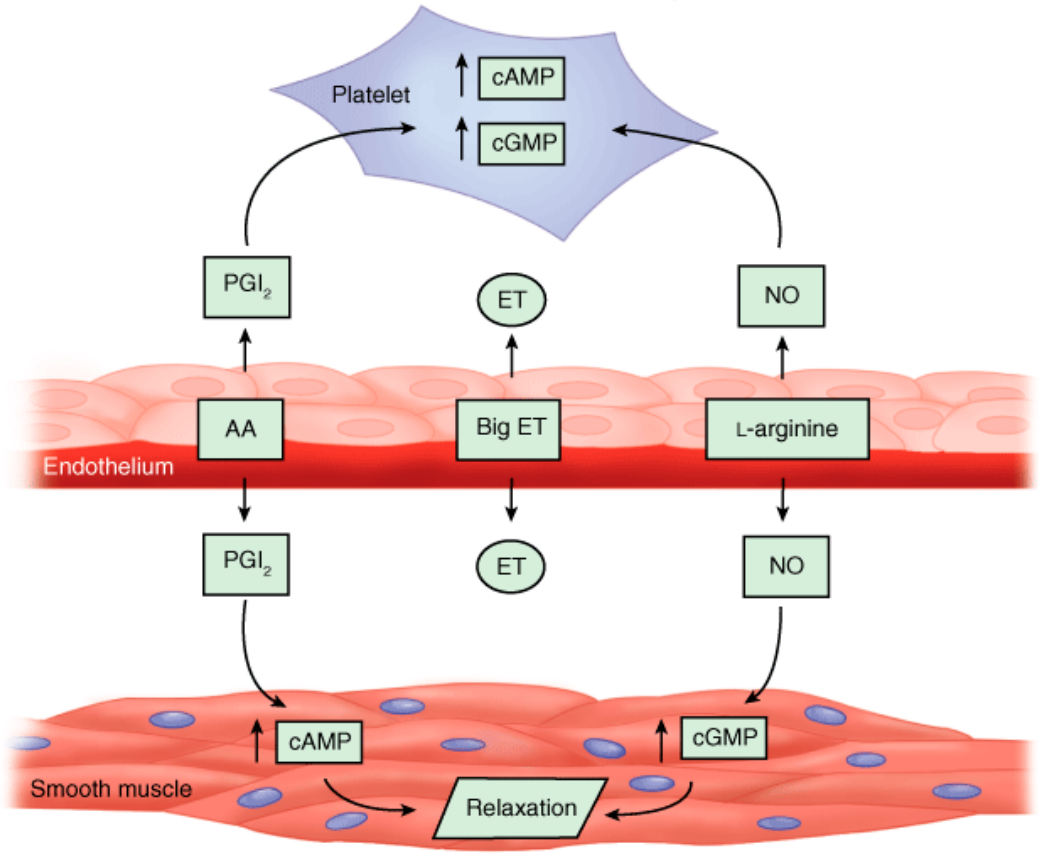
(Adapted with permission from Lin E, Calvano SE, Lowry SF: Selectin neutralization: Does it make biological sense? *Crit Care Med* 27:2050, 1999.)

Nitric Oxide

Nitric oxide (NO) was initially known as *endothelium-derived relaxing factor* due to its effect on vascular smooth muscle and has important functions in both physiologic and pathologic control of vascular tone. Normal vascular smooth muscle relaxation is maintained by a constant output of NO and subsequent activation of soluble quanylyl cyclase. NO also can reduce microthrombosis by reducing platelet adhesion and aggregation (Fig. 2-17). NO easily traverses cell membranes and has a short half-life of a few seconds and is oxidized into nitrate and nitrite. NO is constitutively expressed by endothelial cells; however, inducible NO synthase, which is normally not expressed, is upregulated in response to inflammatory stimuli, which increases NO production. Increased NO is detectable in septic shock and in response to TNF, IL-1, IL-2, and hemorrhage. NO mediates hypotension observed during septic shock; however, a clinical trial of a nonselective NOS inhibitor showed increased

organ dysfunction and mortality.[50]

Fig. 2-17.



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Endothelial interaction with smooth muscle cells and with intraluminal platelets. Prostacyclin (prostaglandin I_2, or PGI2) is derived from arachidonic acid (AA), and nitric oxide (NO) is derived from L-arginine. The increase in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) results in smooth muscle relaxation and inhibition of platelet thrombus formation. Endothelins (ETs) are derived from "big ET," and they counter the effects of prostacyclin and NO.

Prostacyclin

Prostacyclin is a member of the eicosanoid family and is primarily produced by endothelial cells. Prostacyclin is an effective vasodilator and also inhibits platelet aggregation. During systemic inflammation, endothelial prostacyclin expression is impaired, and thus the endothelium favors a more procoagulant profile. Prostacyclin therapy during sepsis has been shown to reduce the levels of cytokines, growth factors, and adhesion molecules through a cAMP-dependent pathway. In clinical trials, prostacyclin infusion is associated with increased cardiac output, splanchnic blood flow, and oxygen delivery and consumption with no significant decrease in mean arterial pressure. However, further study is required before the widespread use of prostacyclin is recommended.[51]

Endothelins

Endothelins (ETs) are potent mediators of vasoconstriction and are composed of three members: ET-1, ET-2, and ET-3. ETs are 21-amino-acid peptides derived from a 38-amino-acid precursor molecule. ET-1, synthesized primarily by endothelial cells, is the most potent endogenous vasoconstrictor and is estimated to be 10 times more potent than angiotensin II. ET release is upregulated in response to hypotension, LPS, injury, thrombin, TGF-β, IL-1, angiotensin II, vasopressin, catecholamines, and anoxia. ETs are primarily released to the abluminal side of endothelial cells, and very little is stored in cells; thus a plasma increase is associated with a marked increase in production. The half-life of plasma ET is between 4 and 7 minutes, which suggests that ET release is primarily regulated at the transcriptional level. Three endothelin receptors, referred to as ET_A , ET_B , and ET_C , have been identified and function via the G-protein–coupled receptor mechanism. ET_B receptors are associated with increased NO and prostacyclin production, which may serve as a feedback mechanism. Atrial ET_A receptor activation has been associated with increased inotropy and chronotropy. ET-1 infusion is associated with increased pulmonary vascular resistance and pulmonary edema and may contribute to pulmonary abnormalities during sepsis. At low levels, in conjunction with NO, ETs regulate vascular tone. However, at increased concentrations, ETs can disrupt the normal blood flow and distribution and may compromise oxygen delivery to the tissue. In addition, increased plasma ET concentration correlates with the severity of injury after major trauma or major surgical procedures, and in patients with cardiogenic or septic shock.[52]

Platelet-Activating Factor

Another endothelium-derived product is platelet-activating factor (PAF), a natural phospholipid constituent of cell membranes that is minimally expressed under normal physiologic conditions. During acute inflammation, PAF is released by neutrophils, platelets, mast cells, and monocytes, and is expressed at the outer leaflet of endothelial cells. PAF can further activate neutrophils and platelets, and increase vascular permeability. Antagonists to PAF receptors have been experimentally shown to mitigate the effects of ischemia and reperfusion injury. Human sepsis is associated with a reduction in levels of PAF-acetylhydrolase, which is the endogenous inhibitor of PAF. Indeed, PAF-acetylhydrolase administration in patients with severe sepsis has yielded some reduction in multiple organ dysfunction and mortality.[53]

Atrial Natriuretic Peptides

Atrial natriuretic peptides (ANPs) are a family of peptides that are released primarily by atrial tissue but are also synthesized by the gut, kidney, brain, adrenal glands, and endothelium. They induce vasodilation as well as fluid and electrolyte excretion. ANPs are potent inhibitors of aldosterone secretion and prevent reabsorption of sodium. There is some experimental evidence to suggest that ANP can reverse acute renal failure or early acute tubular necrosis.

SURGICAL METABOLISM

The initial hours after surgical or traumatic injury are metabolically associated with a reduced total body energy expenditure and urinary nitrogen wasting. On adequate resuscitation and stabilization of the injured patient, a reprioritization of substrate use ensues to preserve vital organ function and to support repair of injured tissue. This phase of recovery also is characterized by functions that participate in the restoration of homeostasis, such as augmented metabolic rates and oxygen consumption, enzymatic preference for readily oxidizable substrates such as glucose, and stimulation of the immune system.

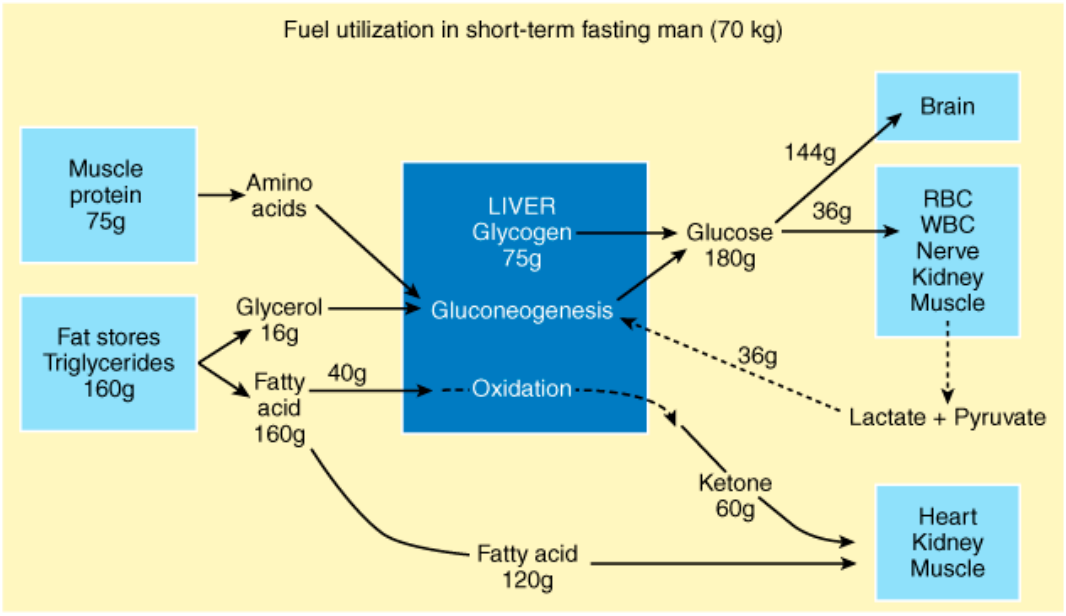
Understanding of the collective alterations in amino acid (protein), carbohydrate, and lipid metabolism characteristic of the surgical patient lays the foundation upon which metabolic and nutritional support can be implemented.

Metabolism during Fasting

Fuel metabolism during unstressed fasting states has historically served as the standard to which metabolic alterations after acute injury and critical illness are compared (Fig. 2-18). To maintain basal metabolic needs (i.e., at rest and fasting), a normal healthy adult requires

approximately 22 to 25 kcal/kg per day drawn from carbohydrate, lipid, and protein sources. This requirement can be as high as 40 kcal/kg per day in severe stress states, such as those seen in patients with burn injuries.

Fig. 2-18.



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Fuel utilization in a 70-kg man during short-term fasting with an approximate basal energy expenditure of 1800 kcal. During starvation, muscle proteins and fat stores provide fuel for the host, with the latter being most abundant. RBC = red blood cell; WBC = white blood cell.

(Adapted with permission from Cahill GF: Starvation in man. *N Engl J Med* 282:668, 1970. Copyright © Massachusetts Medical Society. All rights reserved.)

In the healthy adult, principal sources of fuel during short-term fasting (<5 days) are derived from muscle protein and body fat, with fat being the most abundant source of energy (Table 2-6). The normal adult body contains 300 to 400 g of carbohydrates in the form of glycogen, of which 75 to 100 g are stored in the liver. Approximately 200 to 250 g of glycogen are stored within skeletal, cardiac, and smooth muscle cells. The greater glycogen stores within the muscle are not readily available for systemic use due to a deficiency in glucose-6-phosphatase but are available for the energy needs of muscle cells. Therefore, in the fasting state, hepatic glycogen stores are rapidly and preferentially depleted, which results in a fall of serum glucose concentration within hours (<16 hours).

Table 2-6 A. Body Fuel Reserves in a 70-kg Man

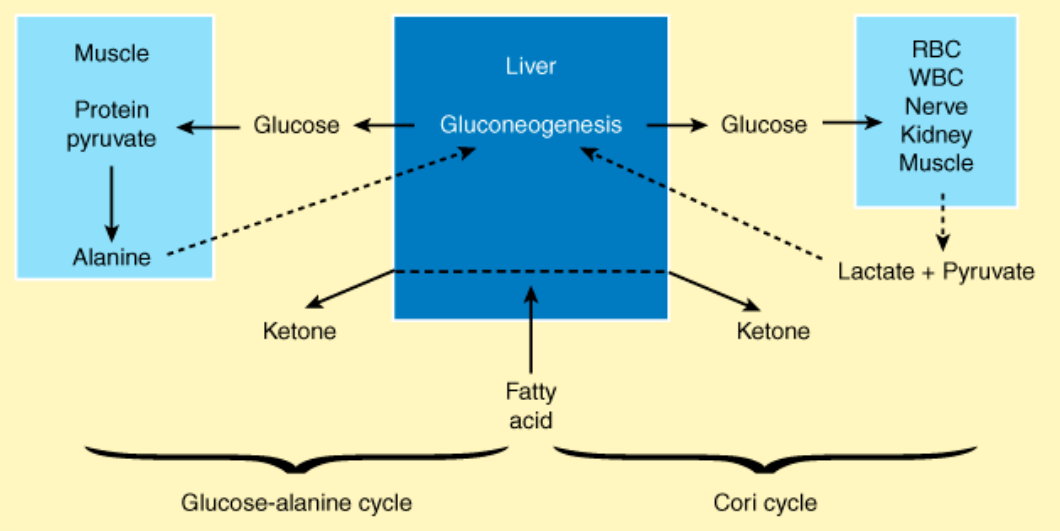
A. Component	Mass (kg)	Energy (kcal)	Days Available
Water and minerals	49	0	0
Protein	6.0	24,000	13.0
Glycogen	0.2	800	0.4
Fat	15.0	140,000	78.0
Total	70.2	164,800	91.4

B. Energy Equivalent of Substrate Oxidation					
B. Substrate	**O_2 Consumed (L/g)**	**CO_2 Produced (L/g)**	**Respiratory Quotient**	**kcal/g**	**Recommended Daily Requirement**
Glucose	0.75	0.75	1.0	4.0	7.2 g/kg per day
Dextrose	—	—	—	3.4	—
Lipid	2.0	1.4	0.7	9.0	1.0 g/kg per day
Protein	1.0	0.8	0.8	4.0	0.8 g/kg per day

During fasting, a healthy 70-kg adult will utilize 180 g of glucose per day to support the metabolism of obligate glycolytic cells such as neurons, leukocytes, erythrocytes, and the renal medullae. Other tissues that use glucose for fuel are skeletal muscle, intestinal mucosa, fetal tissues, and solid tumors.

Glucagon, norepinephrine, vasopressin, and angiotensin II can promote the utilization of glycogen stores (glycogenolysis) during fasting. Although glucagon, epinephrine, and cortisol directly promote gluconeogenesis, epinephrine and cortisol also promote pyruvate shuttling to the liver for gluconeogenesis. Precursors for hepatic gluconeogenesis include lactate, glycerol, and amino acids such as alanine and glutamine. Lactate is released by glycolysis within skeletal muscles, as well as by erythrocytes and leukocytes. The recycling of lactate and pyruvate for gluconeogenesis is commonly referred to as the *Cori cycle,* which can provide up to 40% of plasma glucose during starvation (Fig. 2-19).

Fig. 2-19.



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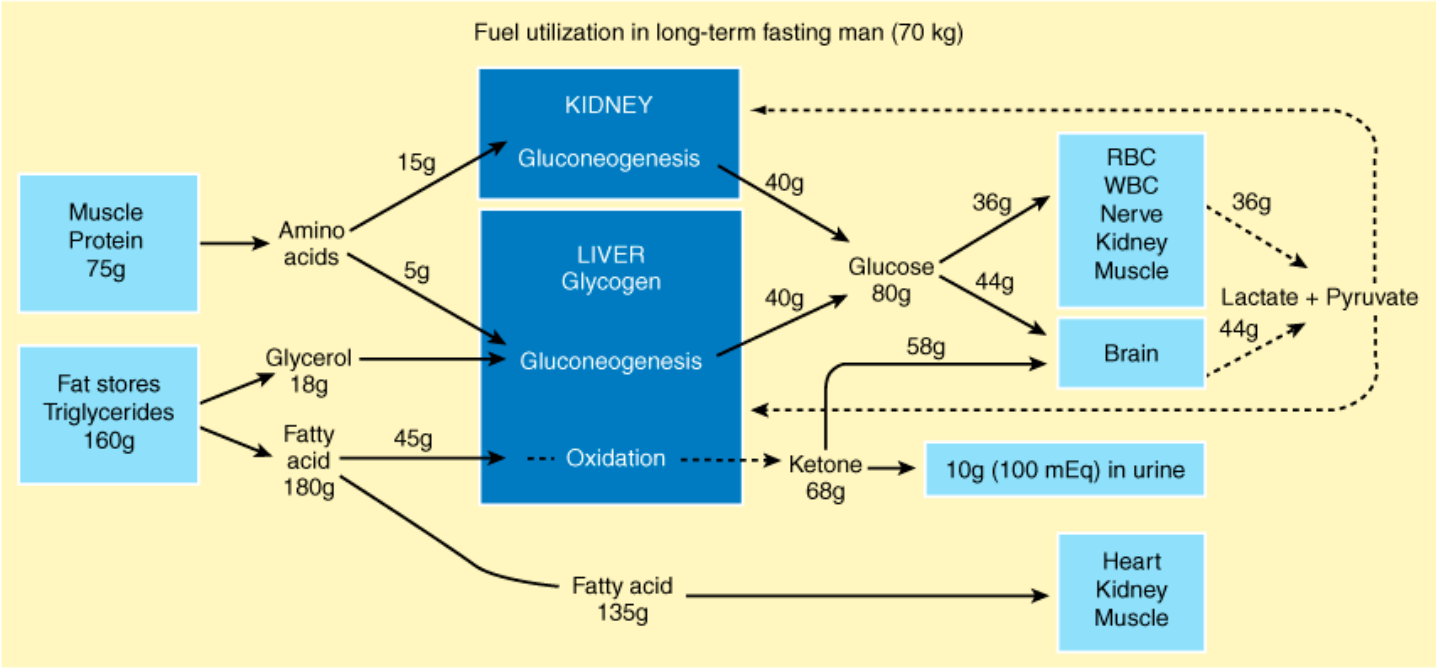
The recycling of peripheral lactate and pyruvate for hepatic gluconeogenesis is accomplished by the Cori cycle. Alanine within skeletal muscles can also be used as a precursor for hepatic gluconeogenesis. During starvation, such fatty acid provides fuel sources for basal hepatic enzymatic function. RBC = red blood cell; WBC = white blood cell.

Lactate production from skeletal muscle is insufficient to maintain systemic glucose needs during short-term fasting (simple starvation).

Therefore, significant amounts of protein must be degraded daily (75 g/d for a 70-kg adult) to provide the amino acid substrate for hepatic gluconeogenesis. Proteolysis during starvation, which results primarily from decreased insulin and increased cortisol release, is associated with elevated urinary nitrogen excretion from the normal 7 to 10 g per day up to 30 g or more per day.[54] Although proteolysis during starvation occurs mainly within skeletal muscles, protein degradation in solid organs also occurs.

In prolonged starvation, systemic proteolysis is reduced to approximately 20 g/d and urinary nitrogen excretion stabilizes at 2 to 5 g/d (Fig. 2-20). This reduction in proteolysis reflects the adaptation by vital organs (e.g., myocardium, brain, renal cortex, and skeletal muscle) to using ketone bodies as their principal fuel source. In extended fasting, ketone bodies become an important fuel source for the brain after 2 days and gradually become the principal fuel source by 24 days.

Fig. 2-20.



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Fuel utilization in extended starvation. Liver glycogen stores are depleted, and there is adaptive reduction in proteolysis as a source of fuel. The brain uses ketones for fuel. The kidneys become important participants in gluconeogenesis. RBC = red blood cell; WBC = white blood cell.

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Enhanced deamination of amino acids for gluconeogenesis during starvation consequently increases renal excretion of ammonium ions. The kidneys also participate in gluconeogenesis by the use of glutamine and glutamate, and can become the primary source of gluconeogenesis during prolonged starvation, accounting for up to one half of systemic glucose production.

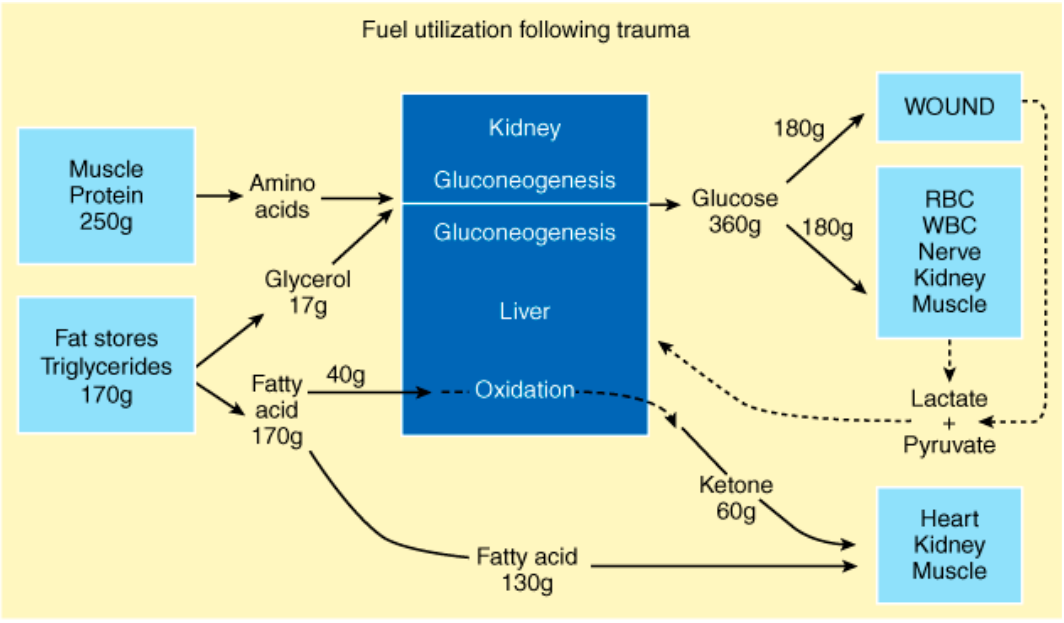
Lipid stores within adipose tissue provide 40% or more of caloric expenditure during starvation. Energy requirements for basal enzymatic and muscular functions (e.g., gluconeogenesis, neural transmission, and cardiac contraction) are met by the mobilization of triglycerides from adipose tissue. In a resting, fasting, 70-kg person, approximately 160 g of free fatty acids and glycerol can be mobilized from adipose tissue per day. Free fatty acid release is stimulated in part by a reduction in serum insulin levels and in part by the increase in circulating glucagon and

catecholamine. Such free fatty acids, like ketone bodies, are used as fuel by tissues such as the heart, kidney (renal cortex), muscle, and liver. The mobilization of lipid stores for energy importantly decreases the rate of glycolysis, gluconeogenesis, and proteolysis, as well as the overall glucose requirement to sustain the host. Furthermore, ketone bodies spare glucose utilization by inhibiting the enzyme pyruvate dehydrogenase.

Metabolism after Injury

Injuries or infections induce unique neuroendocrine and immunologic responses that differentiate injury metabolism from that of unstressed fasting (Fig. 2-21). The magnitude of metabolic expenditure appears to be directly proportional to the severity of insult, with thermal injuries and severe infections having the highest energy demands (Fig. 2-22). The increase in energy expenditure is mediated in part by sympathetic activation and catecholamine release, which has been replicated by the administration of catecholamines to healthy human subjects. Lipid metabolism after injury is intentionally discussed first, because this macronutrient becomes the primary source of energy during stressed states.[55]

Fig. 2-21.



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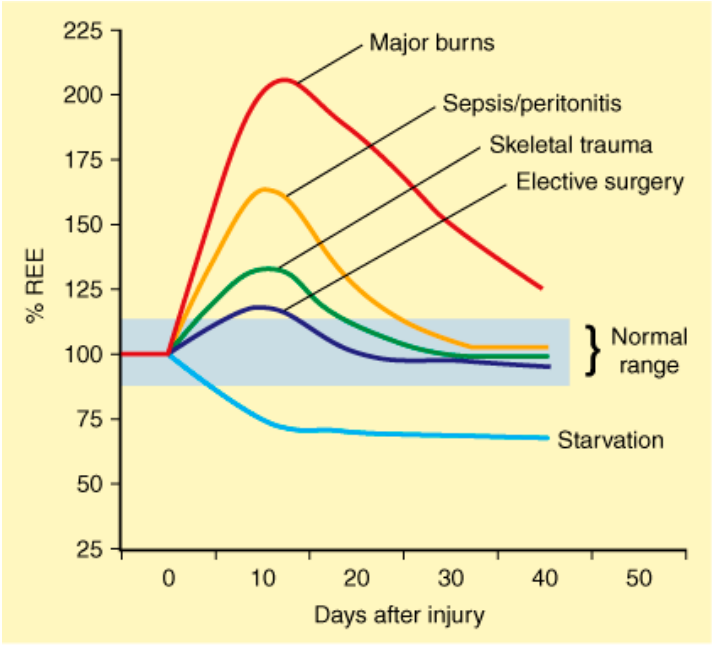
Acute injury is associated with significant alterations in substrate utilization. There is enhanced nitrogen loss, indicative of catabolism. Fat remains the primary fuel source under these circumstances. RBC = red blood cell; WBC = white blood cell.

Fig. 2-22.



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Influence of injury severity on resting metabolism (resting energy expenditure, or REE). The shaded area indicates normal REE.

(Adapted with permission from Long CL et al: Metabolic response to injury and illness: Estimation of energy and protein needs from indirect calorimetry and nitrogen balance. *JPEN J Parenter Enteral Nutr* 3:452, 1979.)

LIPID METABOLISM AFTER INJURY

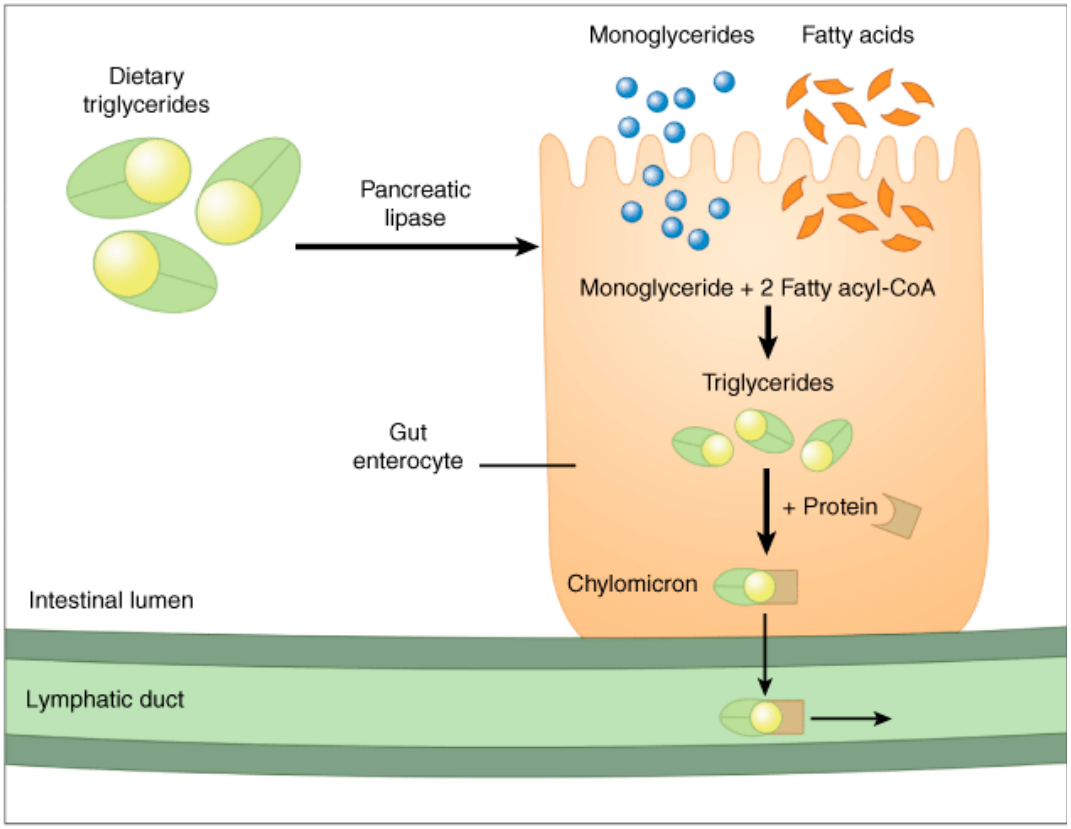
Lipids are not merely nonprotein, noncarbohydrate fuel sources that minimize protein catabolism in the injured patient. Lipid metabolism potentially influences the structural integrity of cell membranes as well as the immune response during systemic inflammation. Adipose stores within the body (triglycerides) are the predominant energy source (50 to 80%) during critical illness and after injury. Fat mobilization (lipolysis) occurs mainly in response to catecholamine stimulus of the hormone-sensitive triglyceride lipase. Other hormonal influences which potentiate lipolysis include adrenocorticotropic hormone (ACTH), catecholamines, thyroid hormone, cortisol, glucagon, growth hormone release, reduction in insulin levels, and increased sympathetic stimulus.[56]

Lipid Absorption

Although the process is poorly understood, adipose tissue provides fuel for the host in the form of free fatty acids and glycerol during critical illness and injury. Oxidation of 1 g of fat yields approximately 9 kcal of energy. Although the liver is capable of synthesizing triglycerides from carbohydrates and amino acids, dietary and exogenous sources provide the major source of triglycerides. Dietary lipids are not readily absorbable in the gut but require pancreatic lipase and phospholipase within the duodenum to hydrolyze the triglycerides into free fatty acids and monoglycerides. The free fatty acids and monoglycerides are then readily absorbed by gut enterocytes, which resynthesize triglycerides by esterification of the monoglycerides with fatty acyl coenzyme A (acyl-CoA) (Fig. 2-23). Long-chain triglycerides (LCTs), defined as those with 12 carbons or more, generally undergo this process of esterification and enter the circulation through the lymphatic system as chylomicrons. Shorter fatty acid chains directly enter the portal circulation and are transported to the liver by albumin carriers. Hepatocytes use free fatty acids as a fuel source during stress states but also can synthesize phospholipids or triglycerides (i.e., very-low-density lipoproteins) during fed states. Systemic tissue (e.g., muscle and the heart) can use chylomicrons and triglycerides as fuel by hydrolysis with lipoprotein lipase at the luminal surface of

capillary endothelium.[57] Trauma or sepsis suppresses lipoprotein lipase activity in both adipose tissue and muscle, presumably mediated by TNF.

Fig. 2-23.



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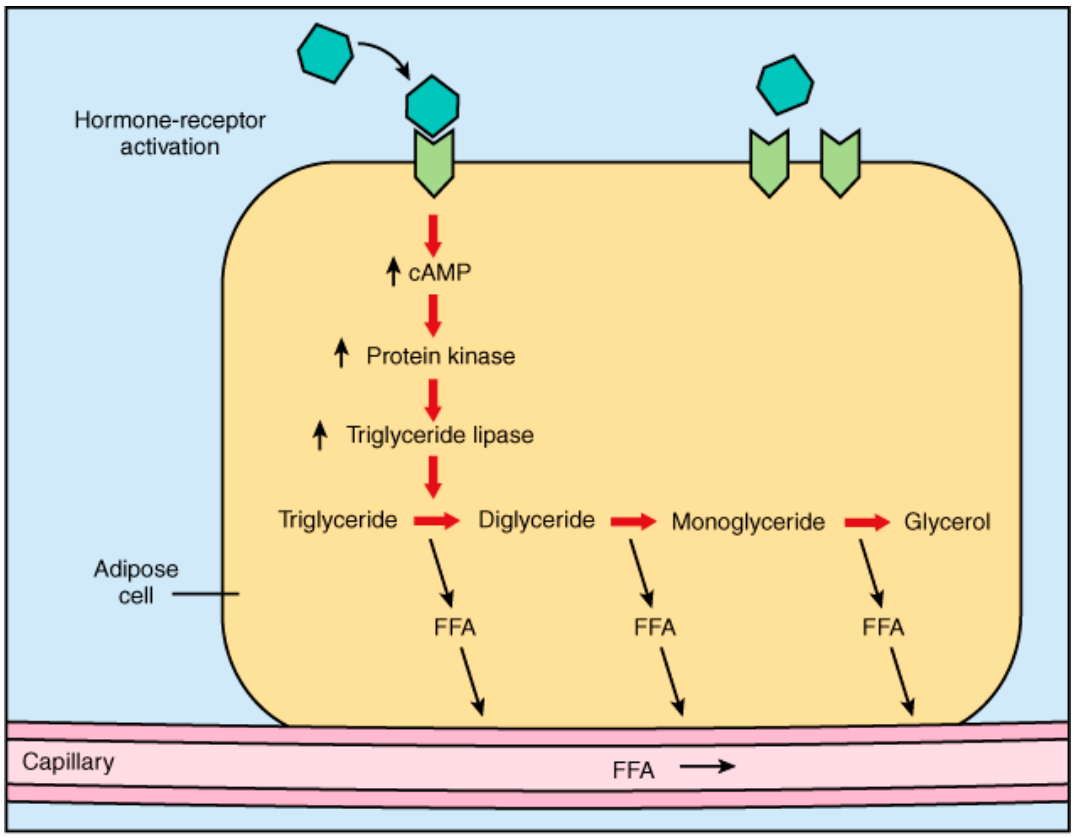
Pancreatic lipase within the small intestinal brush borders hydrolyzes triglycerides into monoglycerides and fatty acids. These components readily diffuse into the gut enterocytes, where they are re-esterified into triglycerides. The resynthesized triglycerides bind carrier proteins to form chylomicrons, which are transported by the lymphatic system. Shorter triglycerides (those with <10 carbon atoms) can bypass this process and directly enter the portal circulation for transport to the liver. CoA = coenzyme A.

Lipolysis and Fatty Acid Oxidation

Periods of energy demand are accompanied by free fatty acid mobilization from adipose stores. This is mediated by hormonal influences (e.g., catecholamines, ACTH, thyroid hormones, growth hormone, and glucagon) on triglyceride lipase through a cAMP pathway (Fig. 2-24). In adipose tissues, triglyceride lipase hydrolyzes triglycerides into free fatty acids and glycerol. Free fatty acids enter the capillary circulation and are transported by albumin to tissues requiring this fuel source (e.g., heart and skeletal muscle). Insulin inhibits lipolysis and favors triglyceride synthesis by augmenting lipoprotein lipase activity as well as intracellular levels of glycerol-3-phosphate. The use of glycerol for fuel depends on the availability of tissue glycerokinase, which is abundant in the liver and kidneys.

Fig. 2-24.



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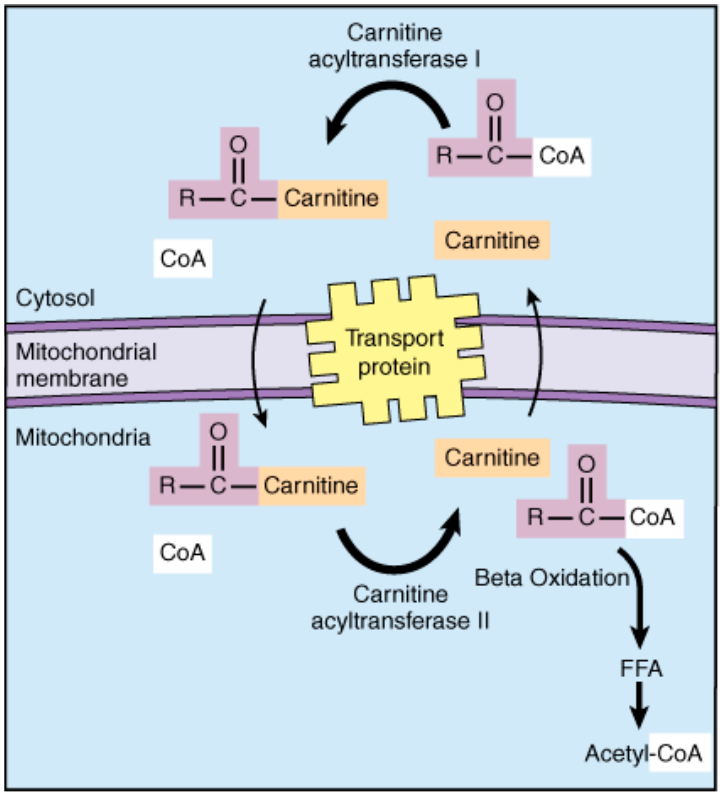
Fat mobilization in adipose tissue. Triglyceride lipase activation by hormonal stimulation of adipose cells occurs through the cyclic adenosine monophosphate (cAMP) pathway. Triglycerides are serially hydrolyzed with resultant free fatty acid (FFA) release at every step. The FFAs diffuse readily into the capillary bed for transport. Tissues with glycerokinase can use glycerol for fuel by forming glycerol-3-phosphate. Glycerol-3-phosphate can esterify with FFAs to form triglycerides or can be used as a precursor for renal and hepatic gluconeogenesis. Skeletal muscle and adipose cells have little glycerokinase and thus do not use glycerol for fuel.

Free fatty acids absorbed by cells conjugate with acyl-CoA within the cytoplasm. The transport of fatty acyl-CoA from the outer mitochondrial membrane across the inner mitochondrial membrane occurs via the carnitine shuttle (Fig. 2-25). Medium-chain triglycerides (MCTs), defined as those 6 to 12 carbons in length, bypass the carnitine shuttle and readily cross the mitochondrial membranes. This accounts in part for the fact that MCTs are more efficiently oxidized than LCTs. Ideally, the rapid oxidation of MCTs makes them less prone to fat deposition, particularly within immune cells and the reticuloendothelial system—a common finding with lipid infusion in parenteral nutrition.[58] However, exclusive use of MCTs as fuel in animal studies has been associated with higher metabolic demands and toxicity, as well as essential fatty acid deficiency.

Fig. 2-25.



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Free fatty acids (FFAs) in the cells form fatty acyl coenzyme A (CoA) with CoA. Fatty acyl-CoA cannot enter the inner mitochondrial membrane and requires carnitine as a carrier protein (carnitine shuttle). Once inside the mitochondria, carnitine dissociates and fatty acyl-CoA is re-formed. The carnitine molecule is transported back into the cytosol for reuse. The fatty acyl-CoA undergoes beta oxidation to form acetyl-CoA for entry into the tricarboxylic acid cycle. "R" represents a part of the acyl group of acyl-CoA.

Within the mitochondria, fatty acyl-CoA undergoes beta oxidation, which produces acetyl-CoA with each pass through the cycle. Each acetyl-CoA molecule subsequently enters the tricarboxylic acid (TCA) cycle for further oxidation to yield 12 adenosine triphosphate (ATP) molecules, carbon dioxide, and water. Excess acetyl-CoA molecules serve as precursors for ketogenesis. Unlike glucose metabolism, oxidation of fatty acids requires proportionally less oxygen and produces less carbon dioxide. This is frequently quantified as the ratio of carbon dioxide produced to oxygen consumed for the reaction and is known as the *respiratory quotient (RQ).* An RQ of 0.7 would imply greater fatty acid oxidation for fuel, whereas an RQ of 1 indicates greater carbohydrate oxidation (overfeeding). An RQ of 0.85 suggests the oxidation of equal amounts of fatty acids and glucose.

KETOGENESIS

Carbohydrate depletion slows the entry of acetyl-CoA into the TCA cycle secondary to depleted TCA intermediates and enzyme activity. Increased lipolysis and reduced systemic carbohydrate availability during starvation diverts excess acetyl-CoA toward hepatic ketogenesis. A number of extrahepatic tissues, but not the liver itself, are capable of using ketones for fuel. Ketosis represents a state in which hepatic ketone production exceeds extrahepatic ketone utilization.

The rate of ketogenesis appears to be inversely related to the severity of injury. Major trauma, severe shock, and sepsis attenuate ketogenesis by increasing insulin levels and by causing rapid tissue oxidation of free fatty acids. Minor injuries and infections are associated with modest

elevations in plasma free fatty acid concentrations and ketogenesis. However, in minor stress states ketogenesis does not exceed that in nonstressed starvation.

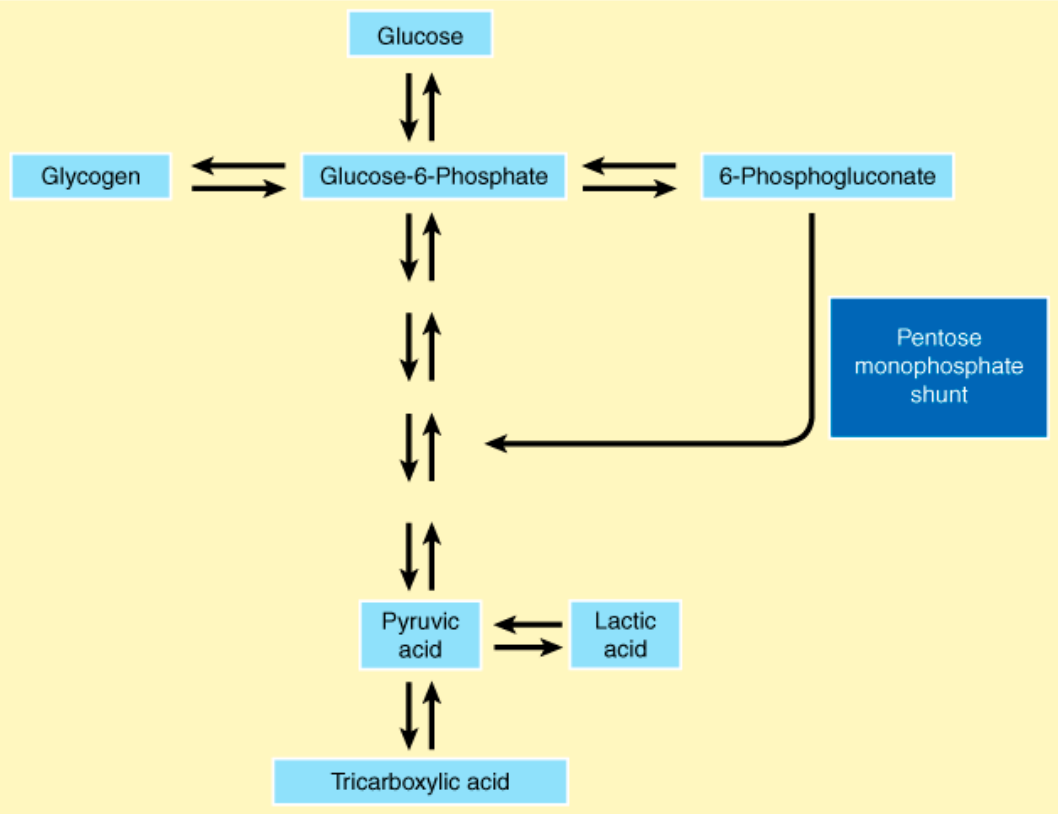
CARBOHYDRATE METABOLISM

Ingested and enteral carbohydrates are primarily digested in the small intestine, where pancreatic and intestinal enzymes reduce the complex carbohydrates to dimeric units. Disaccharidases (e.g., sucrase, lactase, and maltase) within intestinal brush borders dismantle the complex carbohydrates into simple hexose units, which are transported into the intestinal mucosa. Glucose and galactose are primarily absorbed by energy-dependent active transport coupled to the sodium pump. Fructose absorption, however, occurs by concentration-dependent facilitated diffusion. Neither fructose and galactose within the circulation nor exogenous mannitol (for neurologic injury) evokes an insulin response. Intravenous administration of low-dose fructose in fasting humans has been associated with nitrogen conservation, but the clinical utility of fructose administration in human injury remains to be demonstrated.

Discussion of carbohydrate metabolism primarily refers to the utilization of glucose. The oxidation of 1 g of carbohydrate yields 4 kcal, but sugar solutions such as those found in intravenous fluids or parenteral nutrition provide only 3.4 kcal/g of dextrose. In starvation, glucose production occurs at the expense of protein stores (i.e., skeletal muscle). Hence, the primary goal for maintenance glucose administration in surgical patients is to minimize muscle wasting. The exogenous administration of small amounts of glucose (approximately 50 g/d) facilitates fat entry into the TCA cycle and reduces ketosis. Unlike in starvation in healthy subjects, in septic and trauma patients provision of exogenous glucose never has been shown to fully suppress amino acid degradation for gluconeogenesis. This suggests that during periods of stress, other hormonal and proinflammatory mediators have a profound influence on the rate of protein degradation and that some degree of muscle wasting is inevitable. The administration of insulin, however, has been shown to reverse protein catabolism during severe stress by stimulating protein synthesis in skeletal muscles and by inhibiting hepatocyte protein degradation. Insulin also stimulates the incorporation of elemental precursors into nucleic acids in association with RNA synthesis in muscle cells.

In cells, glucose is phosphorylated to form glucose-6-phosphate. Glucose-6-phosphate can be polymerized during glycogenesis or catabolized in glycogenolysis. Glucose catabolism occurs by cleavage to pyruvate or lactate (pyruvic acid pathway) or by decarboxylation to pentoses (pentose shunt) (Fig. 2-26).

Fig. 2-26.



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Simplified schema of glucose catabolism through the pentose monophosphate pathway or by breakdown into pyruvate. Glucose-6-phosphate becomes an important "crossroad" for glucose metabolism.

Excess glucose from overfeeding, as reflected by RQs >1.0, can result in conditions such as glucosuria, thermogenesis, and conversion to fat (lipogenesis). Excessive glucose administration results in elevated carbon dioxide production, which may be deleterious in patients with suboptimal pulmonary function, as well as hyperglycemia, which may contribute to infectious risk and immune suppression.

Injury and severe infections acutely induce a state of peripheral glucose intolerance, despite ample insulin production at levels severalfold above baseline. This may occur in part due to reduced skeletal muscle pyruvate dehydrogenase activity after injury, which diminishes the conversion of pyruvate to acetyl-CoA and subsequent entry into the TCA cycle. The three-carbon structures (e.g., pyruvate and lactate) that consequently accumulate are shunted to the liver as substrate for gluconeogenesis. Furthermore, regional tissue catheterization and isotope dilution studies have shown an increase in net splanchnic glucose production by 50 to 60% in septic patients and a 50 to 100% increase in burn patients.[59] The increase in plasma glucose levels is proportional to the severity of injury, and this net hepatic gluconeogenic response is believed to be under the influence of glucagon. Unlike in the nonstressed subject, in the hypermetabolic, critically ill patient the hepatic gluconeogenic response to injury or sepsis cannot be suppressed by exogenous or excess glucose administration but rather persists. Hepatic gluconeogenesis, arising primarily from alanine and glutamine catabolism, provides a ready fuel source for tissues such as those of the nervous system, wounds, and erythrocytes, which do not require insulin for glucose transport. The elevated glucose concentrations also provide a necessary energy source for leukocytes in inflamed tissues and in sites of microbial invasions.

The shunting of glucose away from nonessential organs such as skeletal muscle and adipose tissues is mediated by catecholamines. Experiments

with infusing catecholamines and glucagon in animals have demonstrated elevated plasma glucose levels as a result of increased hepatic gluconeogenesis and peripheral insulin resistance. Interestingly, although glucocorticoid infusion alone does not increase glucose levels, it does prolong and augment the hyperglycemic effects of catecholamines and glucagon when glucocorticoid is administered concurrently with the latter.

Glycogen stores within skeletal muscles can be mobilized by epinephrine activation of beta−adrenergic receptors, GTP-binding proteins (G-proteins), which subsequently activates the second messenger, cAMP. The cAMP activates phosphorylase kinase, which in turn leads to conversion of glycogen to glucose-1-phosphate. Phosphorylase kinase also can be activated by the second messenger, calcium, through the breakdown of phosphatidylinositol phosphate, which is the case in vasopressin-mediated hepatic glycogenolysis.[60]

Glucose Transport and Signaling

Hydrophobic cell membranes are relatively impermeable to hydrophilic glucose molecules. There are two distinct classes of membrane glucose transporters in human systems. These are the facilitated diffusion glucose transporters (GLUTs) that permit the transport of glucose down a concentration gradient (Table 2-7) and the Na^+/glucose secondary active transport system (SGLT), which transports glucose molecules against concentration gradients by active transport.

Table 2-7 Human Facilitated Diffusion Glucose Transporter (GLUT) Family

Type	Amino Acids	Major Expression Sites
GLUT1	492	Placenta, brain, kidney, colon
GLUT2	524	Liver, pancreatic β-cells, kidney, small intestine
GLUT3	496	Brain, testis
GLUT4	509	Skeletal muscle, heart muscle, brown and white fat
GLUT5	501	Small intestine, sperm

Five functional human GLUTs have been cloned since 1985. GLUT1 is the transporter in human erythrocytes. It is expressed on several other tissues, but little is found in the liver and skeletal muscle. Importantly, it is a constitutive part of the endothelium in the blood-brain barrier. GLUT2 is predominantly expressed in the sinusoidal membranes of liver, renal tubules, enterocytes, and insulin-secreting β-cells of the pancreas. GLUT2 is important for rapid export of glucose resulting from gluconeogenesis. GLUT3 is highly expressed in neuronal tissue of the brain, the kidney, and placenta, but GLUT3 mRNA has been detected in almost every human tissue. GLUT4 is significant to human metabolism because it is the primary glucose transporter of insulin-sensitive tissues, adipose tissue, and skeletal and cardiac muscle. These transporters are usually packaged as intracellular vesicles, but insulin induces rapid translocation of these vesicles to the cell surface. GLUT4 function has important implications in the physiology of patients with insulin-resistant diabetes. GLUT5 has been identified in several tissues but is primarily expressed in the jejunum. Although it possesses some capacity for glucose transport, it is predominantly a fructose transporter.[61]

SGLTs are distinct glucose transport systems found in the intestinal epithelium and in the proximal renal tubules. These systems transport both sodium and glucose intracellularly, and glucose affinity for this transporter increases when sodium ions are attached. SGLT1 is prevalent on brush borders of small intestine enterocytes and primarily mediates the active uptake of luminal glucose. In addition, SGLT1 within the intestinal lumen also enhances gut retention of water through osmotic absorption. SGLT1 and SGLT2 are both associated with glucose reabsorption at proximal renal tubules.

Protein and Amino Acid Metabolism

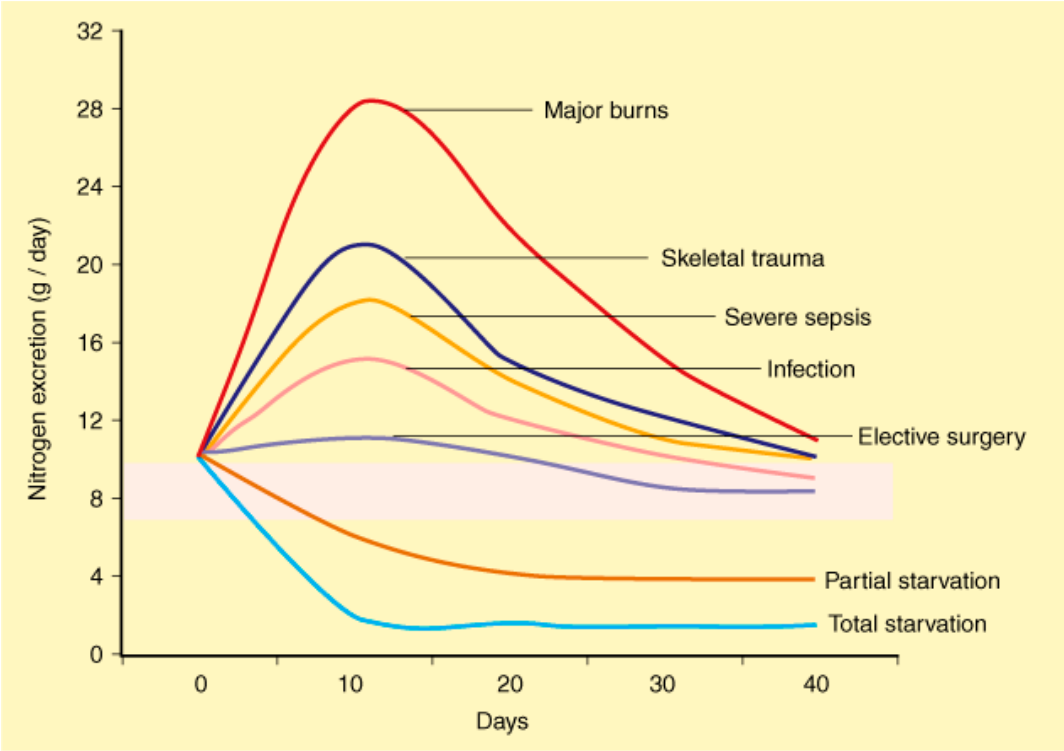
The average protein intake in healthy young adults ranges from 80 to 120 g/d, and every 6 g of protein yields approximately 1 g of nitrogen. The degradation of 1 g of protein yields approximately 4 kcal of energy, similar to the yield in carbohydrate metabolism.

After injury the initial systemic proteolysis, mediated primarily by glucocorticoids, increases urinary nitrogen excretion to levels in excess of 30 g/d, which roughly corresponds to a loss in lean body mass of 1.5% per day. An injured individual who does not receive nutrition for 10 days can theoretically lose 15% lean body mass. Therefore, amino acids cannot be considered a long-term fuel reserve, and indeed excessive protein depletion (i.e., 25 to 30% of lean body weight) is not compatible with sustaining life.[62]

Protein catabolism after injury provides substrates for gluconeogenesis and for the synthesis of acute phase proteins. Radiolabeled amino acid incorporation studies and protein analyses confirm that skeletal muscles are preferentially depleted acutely after injury, whereas visceral tissues (e.g., the liver and kidney) remain relatively preserved. The accelerated urea excretion after injury also is associated with the excretion of intracellular elements such as sulfur, phosphorus, potassium, magnesium, and creatinine. Conversely, the rapid utilization of elements such as potassium and magnesium during recovery from major injury may indicate a period of tissue healing.

The net changes in protein catabolism and synthesis correspond to the severity and duration of injury (Fig. 2-27). Elective operations and minor injuries result in lower protein synthesis and moderate protein breakdown. Severe trauma, burns, and sepsis are associated with increased protein catabolism. The rise in urinary nitrogen and negative nitrogen balance can be detected early after injury and peak by 7 days. This state of protein catabolism may persist for as long as 3 to 7 weeks. The patient's prior physical status and age appear to influence the degree of proteolysis after injury or sepsis.

Fig. 2-27.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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The effect of injury severity on nitrogen wasting.

(Adapted with permission from Long CL et al: Metabolic response to injury and illness: Estimation of energy and protein needs from indirect

calorimetry and nitrogen balance. *JPEN J Parenter Enteral Nutr* 3:452, 1979.)

Activation of the ubiquitin-proteosome system in muscle cells is one of the major pathways for protein degradation during acute injury. This response is accentuated by tissue hypoxia, acidosis, insulin resistance, and elevated glucocorticoid levels.

NUTRITION IN THE SURGICAL PATIENT

The goal of nutritional support in the surgical patient is to prevent or reverse the catabolic effects of disease or injury. Although several important biologic parameters have been used to measure the efficacy of nutritional regimens, the ultimate validation for nutritional support in surgical patients should be improvement in clinical outcome and restoration of function.

Estimation of Energy Requirements

Overall nutritional assessment is undertaken to determine the severity of nutrient deficiencies or excess and to aid in predicting nutritional requirements. Pertinent information is obtained by determining the presence of weight loss, chronic illnesses, or dietary habits that influence the quantity and quality of food intake. Social habits predisposing to malnutrition and the use of medications that may influence food intake or urination should also be investigated. Physical examination seeks to assess loss of muscle and adipose tissues, organ dysfunction, and subtle changes in skin, hair, or neuromuscular function reflecting frank or impending nutritional deficiency. Anthropometric data (i.e., weight change, skinfold thickness, and arm circumference muscle area) and biochemical determinations (i.e., creatinine excretion, albumin level, prealbumin level, total lymphocyte count, and transferrin level) may be used to substantiate the patient's history and physical findings. It is imprecise to rely on any single or fixed combination of the aforementioned findings to accurately assess nutritional status or morbidity. Appreciation for the stresses and natural history of the disease process, in combination with nutritional assessment, remains the basis for identifying patients in acute or anticipated need of nutritional support.

A fundamental goal of nutritional support is to meet the energy requirements for metabolic processes, core temperature maintenance, and tissue repair. Failure to provide adequate nonprotein energy sources will lead to consumption of lean tissue stores. The requirement for energy may be measured by indirect calorimetry and trends in serum markers (e.g., prealbumin level) and estimated from urinary nitrogen excretion, which is proportional to resting energy expenditure.[60] However, the use of indirect calorimetry, particularly in the critically ill patient, is labor intensive and often leads to overestimation of caloric requirements.

Basal energy expenditure (BEE) may also be estimated using the Harris-Benedict equations:

$$\text{BEE (men)} = 66.47 + 13.75\,(W) + 5.0\,(H) - 6.76\,(A)\ \text{kcal/d}$$

$$\text{BEE (women)} = 655.1 + 9.56\,(W) + 1.85\,(H) - 4.68\,(A)\ \text{kcal/d}$$

where W = weight in kilograms; H = height in centimeters; and A = age in years.

These equations, adjusted for the type of surgical stress, are suitable for estimating energy requirements in the majority of hospitalized patients. It has been demonstrated that the provision of 30 kcal/kg per day will adequately meet energy requirements in most postsurgical patients, with a low risk of overfeeding. After trauma or sepsis, energy substrate demands are increased, necessitating greater nonprotein calories beyond calculated energy expenditure (Table 2-8). These additional nonprotein calories provided after injury are usually 1.2 to 2.0 times greater than calculated resting energy expenditure, depending on the type of injury. It is seldom appropriate to exceed this level of nonprotein energy intake during the height of the catabolic phase.

Table 2-8 Caloric Adjustments above Basal Energy Expenditure (BEE) in Hypermetabolic Conditions

Condition	kcal/kg per Day	Adjustment above BEE	Grams of Protein/kg per Day	Nonprotein Calories: Nitrogen
Normal/moderate malnutrition	25–30	1.1	1.0	150:1

Mild stress	25–30	1.2	1.2	150:1
Moderate stress	30	1.4	1.5	120:1
Severe stress	30–35	1.6	2.0	90–120:1
Burns	35–40	2.0	2.5	90–100:1

The second objective of nutritional support is to meet the substrate requirements for protein synthesis. An appropriate nonprotein-calorie:nitrogen ratio of 150:1 (e.g., 1 g N = 6.25 g protein) should be maintained, which is the basal calorie requirement provided to limit the use of protein as an energy source. There is now greater evidence suggesting that increased protein intake, and a lower calorie:nitrogen ratio of 80:1 to 100:1, may benefit healing in selected hypermetabolic or critically ill patients. In the absence of severe renal or hepatic dysfunction precluding the use of standard nutritional regimens, approximately 0.25 to 0.35 g of nitrogen per kilogram of body weight should be provided daily.[64]

Vitamins and Minerals

The requirements for vitamins and essential trace minerals usually can be met easily in the average patient with an uncomplicated postoperative course. Therefore, vitamins usually are not given in the absence of preoperative deficiencies. Patients maintained on elemental diets or parenteral hyperalimentation require complete vitamin and mineral supplementation. Commercial enteral diets contain varying amounts of essential minerals and vitamins. It is necessary to ensure that adequate replacement is available in the diet or by supplementation. Numerous commercial vitamin preparations are available for intravenous or intramuscular use, although most do not contain vitamin K and some do not contain vitamin B12 or folic acid. Supplemental trace minerals may be given intravenously via commercial preparations. Essential fatty acid supplementation also may be necessary, especially in patients with depletion of adipose stores.

Overfeeding

Overfeeding usually results from overestimation of caloric needs, as occurs when actual body weight is used to calculate the BEE in patient populations such as the critically ill with significant fluid overload and the obese. Indirect calorimetry can be used to quantify energy requirements but frequently overestimates BEE by 10 to 15% in stressed patients, particularly if they are receiving ventilatory support. In these instances, estimated dry weight should be obtained from preinjury records or family members. Adjusted lean body weight also can be calculated. Overfeeding may contribute to clinical deterioration via increased oxygen consumption, increased carbon dioxide production and prolonged need for ventilatory support, fatty liver, suppression of leukocyte function, hyperglycemia, and increased risk of infection.

ENTERAL NUTRITION

Rationale for Enteral Nutrition

Enteral nutrition generally is preferred over parenteral nutrition based on the lower cost of enteral feeding and the associated risks of the intravenous route, including vascular access complications.[65] Laboratory models have long demonstrated that luminal nutrient contact reduces intestinal mucosal atrophy compared with parenteral or no nutritional support. Studies comparing postoperative enteral and parenteral nutrition in patients undergoing gastrointestinal surgery have demonstrated reduced infectious complications and acute phase protein production in those fed by the enteral route. Yet prospectively randomized studies of patients with adequate nutritional status (albumin ≥4 g/dL) undergoing gastrointestinal surgery demonstrate no differences in outcome and complications between those administered enteral nutrition and those given maintenance intravenous fluids alone in the initial days after surgery.[66] Furthermore, intestinal permeability studies in well-nourished patients undergoing upper gastrointestinal cancer surgery demonstrated normalization of intestinal permeability and barrier function by the fifth postoperative day.[67] At the other extreme, meta-analysis of studies involving critically ill patients demonstrates a 44% reduction in infectious complications in those receiving enteral nutritional support compared with those receiving parenteral nutrition. Most prospectively randomized

studies in patients with severe abdominal and thoracic trauma demonstrate significant reductions in infectious complications in patients given early enteral nutrition compared with those who were unfed or received parenteral nutrition. The exception has been in studies of patients with closed-head injury, in which no significant differences in outcome were demonstrated between early jejunal feeding and other nutritional support modalities. Moreover, early gastric feeding after closed-head injury was frequently associated with underfeeding and calorie deficiency due to the difficulties in overcoming gastroparesis and the high risk of aspiration.

The early initiation of enteral feeding in burn patients, while sensible and supported by retrospective analysis, is an empiric practice supported by limited prospective trials.

Recommendations for instituting early enteral nutrition in surgical patients with moderate malnutrition (albumin level of 2.9 to 3.5 g/dL) can only be made by inference due to a lack of data directly pertaining to this population. For these patients, it is prudent to offer enteral nutrition based on measured energy expenditure of the recovering patient, or if complications arise that may alter the anticipated course of recovery (e.g., anastomotic leaks, return to surgery, sepsis, or failure to wean from the ventilator). Other clinical scenarios for which the benefits of enteral nutritional support have been substantiated include permanent neurologic impairment, oropharyngeal dysfunction, short-bowel syndrome, and bone marrow transplantation.

Collectively, the data support the use of early enteral nutritional support after major trauma and in patients who are anticipated to have prolonged recovery after surgery. Healthy patients without malnutrition undergoing uncomplicated surgery can tolerate 10 days of partial starvation (i.e., maintenance intravenous fluids only) before any clinically significant protein catabolism occurs. Earlier intervention is likely indicated in patients with poorer preoperative nutritional reserves.

Initiation of enteral nutrition should occur immediately after adequate resuscitation, most readily determined by adequate urine output. The presence of bowel sounds and the passage of flatus or stool are not absolute prerequisites for initiation of enteral nutrition, but in the setting of gastroparesis feedings should be administered distal to the pylorus. Gastric residuals of 200 mL or more in a 4- to 6-hour period or abdominal distention requires cessation of feeding and adjustment of the infusion rate. Concomitant gastric decompression with distal small-bowel feedings may be appropriate in certain patients such as closed-head injury patients with gastroparesis. There is no evidence to support withholding enteric feedings for patients after bowel resection or for those with low-output enterocutaneous fistulas of <500 mL/d, but low-residue formulations may be preferred. Enteral feeding should also be offered to patients with short-bowel syndrome or clinical malabsorption, but necessary calories, essential minerals, and vitamins should be supplemented using parenteral modalities.

Enteral Formulas

The functional status of the gastrointestinal tract determines the type of enteral solutions to be used. Patients with an intact gastrointestinal tract will tolerate complex solutions, but patients who have not been fed via the gastrointestinal tract for prolonged periods are less likely to tolerate complex carbohydrates such as lactose. In patients with malabsorption, such as in inflammatory bowel diseases, absorption may be improved by provision of dipeptides, tripeptides, and MCTs. However, MCTs are deficient in essential fatty acids, which necessitates supplementation with some LCTs.

Factors that influence the choice of enteral formula include the extent of organ dysfunction (e.g., renal, pulmonary, hepatic, or gastrointestinal), the nutrients needed to restore optimal function and healing, and the cost of specific products. There are still no conclusive data to recommend one category of product over another, and nutritional support committees typically develop the most cost-efficient enteral formulary for the most commonly encountered disease categories within the institution.

LOW-RESIDUE ISOTONIC FORMULAS

Most low-residue isotonic formulas provide a caloric density of 1.0 kcal/mL, and approximately 1500 to 1800 mL are required to meet daily

requirements. These low-osmolarity compositions provide baseline carbohydrates, protein, electrolytes, water, fat, and fat-soluble vitamins (some do not have vitamin K) and typically have a nonprotein-calorie:nitrogen ratio of 150:1. These contain no fiber bulk and therefore leave minimum residue. These solutions usually are considered to be the standard or first-line formulas for stable patients with an intact gastrointestinal tract.

ISOTONIC FORMULAS WITH FIBER

Isotonic formulas with fiber contain soluble and insoluble fiber, which is most often soy based. Physiologically, fiber-based solutions delay intestinal transit time and may reduce the incidence of diarrhea compared with nonfiber solutions. Fiber stimulates pancreatic lipase activity and is degraded by gut bacteria into short-chain fatty acids, an important fuel for colonocytes. There are no contraindications for using fiber-containing formulas in critically ill patients.

IMMUNE-ENHANCING FORMULAS

Immune-enhancing formulas are fortified with special nutrients that are purported to enhance various aspects of immune or solid organ function. Such additives include glutamine, arginine, branched-chain amino acids, omega-3 fatty acids, nucleotides, and beta carotene.[68] Although several trials have proposed that one or more of these additives reduce surgical complications and improve outcome, these results have not been uniformly corroborated by other trials.[69] The addition of amino acids to these formulas generally doubles the amount of protein (nitrogen) found in standard formula; however, their cost can be prohibitive.[70]

CALORIE-DENSE FORMULAS

The primary distinction of calorie-dense formulas is a greater caloric value for the same volume. Most commercial products of this variety provide 1.5 to 2 kcal/mL and therefore are suitable for patients requiring fluid restriction or those unable to tolerate large-volume infusions. As expected, these solutions have higher osmolality than standard formulas and are suitable for intragastric feedings.

HIGH-PROTEIN FORMULAS

High-protein formulas are available in isotonic and nonisotonic mixtures and are proposed for critically ill or trauma patients with high protein requirements. These formulas have nonprotein-calorie:nitrogen ratios between 80:1 and 120:1.

ELEMENTAL FORMULAS

Elemental formulas contain predigested nutrients and provide proteins in the form of small peptides. Complex carbohydrates are limited, and fat content, in the form of MCTs and LCTs, is minimal. The primary advantage of such a formula is ease of absorption, but the inherent scarcity of fat, associated vitamins, and trace elements limits its long-term use as a primary source of nutrients. Due to its high osmolarity, dilution or slow infusion rates usually are necessary, particularly in critically ill patients. These formulas have been used frequently in patients with malabsorption, gut impairment, and pancreatitis, but their cost is significantly higher than that of standard formulas.

RENAL-FAILURE FORMULAS

The primary benefits of renal formulas are the lower fluid volume and concentrations of potassium, phosphorus, and magnesium needed to meet daily calorie requirements. This type of formulation almost exclusively contains essential amino acids and has a high nonprotein-calorie:nitrogen ratio; however, it does not contain trace elements or vitamins.

PULMONARY-FAILURE FORMULAS

In pulmonary-failure formulas, fat content is usually increased to 50% of the total calories, with a corresponding reduction in carbohydrate content. The goal is to reduce carbon dioxide production and alleviate ventilation burden for failing lungs.

HEPATIC-FAILURE FORMULAS

Close to 50% of the proteins in hepatic-failure formulas are branched-chain amino acids (e.g., leucine, isoleucine, and valine). The goal of such a formula is to reduce aromatic amino acid levels and increase the levels of branched-chain amino acids, which can potentially reverse encephalopathy in patients with hepatic failure.[71] The use of these formulas is controversial, however, because no clear benefits have been proven by clinical trials. Protein restriction should be avoided in patients with end-stage liver disease, because such patients have significant protein energy malnutrition that predisposed them to additional morbidity and mortality.[72]

ACCESS FOR ENTERAL NUTRITIONAL SUPPORT

The available techniques and repertoire for enteral access have provided multiple options for feeding the gut. Presently used methods and preferred indications are summarized in Table 2-9.[73]

Table 2-9 Options for Enteral Feeding Access

Access Option	Comments
Nasogastric tube	Short-term use only; aspiration risks; nasopharyngeal trauma; frequent dislodgment
Nasoduodenal/nasojejunal tube	Short-term use; lower aspiration risks in jejunum; placement challenges (radiographic assistance often necessary)
Percutaneous endoscopic gastrostomy (PEG)	Endoscopy skills required; may be used for gastric decompression or bolus feeds; aspiration risks; can last 12–24 mo; slightly higher complication rates with placement and site leaks
Surgical gastrostomy	Requires general anesthesia and small laparotomy; procedure may allow placement of extended duodenal/jejunal feeding ports; laparoscopic placement possible
Fluoroscopic gastrostomy	Blind placement using needle and T-prongs to anchor to stomach; can thread smaller catheter through gastrostomy into duodenum/jejunum under fluoroscopy
PEG-jejunal tube	Jejunal placement with regular endoscope is operator dependent; jejunal tube often dislodges retrograde; two-stage procedure with PEG placement, followed by fluoroscopic conversion with jejunal feeding tube through PEG
Direct percutaneous endoscopic jejunostomy (DPEJ)	Direct endoscopic tube placement with enteroscope; placement challenges; greater injury risks
Surgical jejunostomy	Commonly carried out during laparotomy; general anesthesia; laparoscopic placement usually requires assistant to thread catheter; laparoscopy offers direct visualization of catheter placement
Fluoroscopic jejunostomy	Difficult approach with injury risks; not commonly done

Nasoenteric Tubes

Nasogastric feeding should be reserved for those with intact mentation and protective laryngeal reflexes to minimize risks of aspiration. Even in intubated patients, nasogastric feedings often can be recovered from tracheal suction. Nasojejunal feedings are associated with fewer pulmonary complications, but access past the pylorus requires greater effort to accomplish. Blind insertion of nasogastric feeding tubes is fraught with misplacement, and air instillation with auscultation is inaccurate for ascertaining proper positioning. Radiographic confirmation is usually required to verify the position of the nasogastric feeding tube.

Several methods have been recommended for the passage of nasoenteric feeding tubes into the small bowel, including use of prokinetic agents, right lateral decubitus positioning, gastric insufflation, tube angulation, and application of clockwise torque. However, the successful placement of feeding tubes by these methods is highly variable and operator dependent. Furthermore, it is time consuming, and success rates for intubation past the duodenum into the jejunum by these methods are <20%. Fluoroscopy-guided intubation past the pylorus has a >90% success rate, and more than half of these intubations result in jejunal placement. Similarly, endoscopy-guided placement past the pylorus has high success rates, but attempts to advance the tube beyond the second portion of the duodenum using a standard gastroduodenoscope is unlikely to be successful.

Small-bowel feeding is more reliable for delivering nutrition than nasogastric feeding. Furthermore, the risks of aspiration pneumonia can be reduced by 25% with small-bowel feeding compared with nasogastric feeding. The disadvantages of the use of nasoenteric feeding tubes are clogging, kinking, and inadvertent displacement or removal of the tube, and nasopharyngeal complications. If nasoenteric feeding will be required for longer than 30 days, access should be converted to a percutaneous one.[74]

Percutaneous Endoscopic Gastrostomy

The most common indications for percutaneous endoscopic gastrostomy (PEG) include impaired swallowing mechanisms, oropharyngeal or esophageal obstruction, and major facial trauma. It is frequently used for debilitated patients requiring caloric supplementation, hydration, or frequent medication dosing. It is also appropriate for patients requiring passive gastric decompression. Relative contraindications for PEG placement include ascites, coagulopathy, gastric varices, gastric neoplasm, and lack of a suitable abdominal site. Most tubes are 18F to 28F in size and may be used for 12 to 24 months.

Identification of the PEG site requires endoscopic transillumination of the anterior stomach against the abdominal wall. A 14-gauge angiocatheter is passed through the abdominal wall into the fully insufflated stomach. A guidewire is threaded through the angiocatheter, grasped by snares or forceps, and pulled out through the mouth. The tapered end of the PEG tube is secured to the guidewire and is pulled into position out of the abdominal wall. The PEG tube is secured without tension against the abdominal wall, and many have reported using the tube within hours of placement. It has been the practice of some to connect the PEG tube to a drainage bag for passive decompression for 24 hours before use, allowing more time for the stomach to seal against the peritoneum.

If endoscopy is not available or technical obstacles preclude PEG placement, the interventional radiologist can attempt the procedure percutaneously under fluoroscopic guidance by first insufflating the stomach against the abdominal wall with a nasogastric tube. If this also is unsuccessful, surgical gastrostomy tube placement can be considered, particularly with minimally invasive methods. When surgery is contemplated, it may be wise to consider directly accessing the small bowel for nutrition delivery.

Although PEG tubes enhance nutritional delivery, facilitate nursing care, and are superior to nasogastric tubes, serious complications occur in approximately 3% of patients. These complications include wound infection, necrotizing fasciitis, peritonitis, aspiration, leaks, dislodgment, bowel perforation, enteric fistulas, bleeding, and aspiration pneumonia.[75] For patients with significant gastroparesis or gastric outlet obstruction, feedings through PEG tubes are hazardous. In such cases, the PEG tube can be used for decompression and allow access for converting the PEG tube to a transpyloric feeding tube.

Percutaneous Endoscopic Gastrostomy-Jejunostomy and Direct Percutaneous Endoscopic Jejunostomy

Although gastric bolus feedings are more physiologic, patients who cannot tolerate gastric feedings or who have significant aspiration risks should be fed directly past the pylorus. In the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) method, a 9F to 12F tube is passed through an existing PEG tube, past the pylorus, and into the duodenum. This can be achieved by endoscopic or fluoroscopic guidance. With weighted catheter tips and guidewires, the tube can be further advanced past the ligament of Treitz. However, the incidence of long-term PEG-J tube malfunction has been reported to be >50% as a result of retrograde tube migration into the stomach, kinking, or clogging.

Direct percutaneous endoscopic jejunostomy (DPEJ) tube placement uses the same techniques as PEG tube placement but requires an enteroscope or colonoscope to reach the jejunum. DPEJ tube malfunctions are probably less frequent than PEG-J tube malfunctions, and kinking or clogging is usually averted by placement of larger-caliber catheters. The success rate of DPEJ tube placement is variable because of the complexity of endoscopic skills required to locate a suitable jejunal site. In such cases where endoscopic means are not feasible, surgical jejunostomy tube placement is more appropriate, especially when minimally invasive techniques are available.

Surgical Gastrostomy and Jejunostomy

For a patient undergoing complex abdominal or trauma surgery, thought should be given during surgery to the possible routes for subsequent nutritional support, because laparotomy affords direct access to the stomach or small bowel. The only absolute contraindication to feeding jejunostomy is distal intestinal obstruction. Relative contraindications include severe edema of the intestinal wall, radiation enteritis, inflammatory bowel disease, ascites, severe immunodeficiency, and bowel ischemia. Needle-catheter jejunostomies also can be done with a minimal learning curve. The biggest drawback usually is possible clogging and knotting of the 6F catheter.[76]

Abdominal distention and cramps are common adverse effects of early enteral nutrition. Some have also reported impaired respiratory mechanics as a result of intolerance to enteral feedings. These are mostly correctable by temporarily discontinuing feedings and resuming at a lower infusion rate.

Pneumatosis intestinalis and small-bowel necrosis are infrequent but significant problems in patients receiving jejunal tube feedings. Several contributing factors have been proposed, including the hyperosmolarity of enteral solutions, bacterial overgrowth, fermentation, and accumulation of metabolic breakdown products. The common pathophysiology is believed to be bowel distention and consequent reduction in bowel wall perfusion. Risk factors for these complications include cardiogenic and circulatory shock, vasopressor use, diabetes mellitus, and chronic obstructive pulmonary disease. Therefore, enteral feedings in the critically ill patient should be delayed until adequate resuscitation has been achieved. As alternatives, diluting standard enteral formula, delaying the progression to goal infusion rates, or using monomeric solutions with low osmolality requiring less digestion by the gastrointestinal tract all have been successfully used.

PARENTERAL NUTRITION

Parenteral nutrition is the continuous infusion of a hyperosmolar solution containing carbohydrates, proteins, fat, and other necessary nutrients through an indwelling catheter inserted into the superior vena cava. To obtain the maximum benefit, the calorie:protein ratio must be adequate (at least 100 to 150 kcal/g nitrogen), and both carbohydrates and proteins must be infused simultaneously. When the sources of calories and nitrogen are given at different times, there is a significant decrease in nitrogen utilization. These nutrients can be given in quantities considerably greater than the basic caloric and nitrogen requirements, and this method has proved to be highly successful in achieving growth and development, positive nitrogen balance, and weight gain in a variety of clinical situations. Clinical trials and meta-analysis of studies of parenteral feeding in the perioperative period have suggested that preoperative nutritional support may benefit some surgical patients, particularly those with extensive malnutrition. Short-term use of parenteral nutrition in critically ill patients (i.e., duration of <7 days) when enteral nutrition may have been instituted is associated with higher rates of infectious complications. After severe injury, parenteral nutrition is associated with higher rates of infectious risks than is enteral feeding (Table 2-10). Clinical studies have demonstrated that parenteral feeding with complete bowel rest results in augmented stress hormone and inflammatory mediator response to an antigenic challenge. However, parenteral feeding still is associated with fewer infectious complications than no feeding at all. In cancer patients, delivery of parenteral nutrition has not been shown to benefit clinical response, prolong survival, or ameliorate the toxic effects of chemotherapy, and infectious complications are increased.

Table 2-10 Incidence of Septic Morbidity in Parenterally and Enterally Fed Trauma Patients

	Blunt Trauma		**Penetrating Trauma**		**Total**	
Complication	**TEN n = 48**	**TPN n = 44**	**TEN n = 38**	**TPN n = 48**	**TEN n = 44**	**TPN n = 84**
Abdominal abscess	2	1	2	6	4	7
Pneumonia	4	10	1	2	5	12
Wound infection	0	2	3	1	3	3
Bacteremia	1	4	0	1	1	5

Urinary tract	1	1	0	1	1	2
Other	5	4	1	1	6	5
Total complications	**13**	**22**	**7**	**12**	**20**	**34**
% Complications per patient group	**27%**	**50%**	**18%**	**30%**	**23%**	**39%**

TEN = total enteral nutrition; TPN = total parenteral nutrition.

Source: Reproduced with permission from Moore FA, Feliciano DV, Andrassy RJ et al: Early enteral feeding, compared with parenteral, reduces postoperative septic complications. *Ann Surg* 216(2):172–183, 1992.

Rationale for Parenteral Nutrition

The principal indications for parenteral nutrition are malnutrition, sepsis, or surgical or traumatic injury in seriously ill patients for whom use of the gastrointestinal tract for feedings is not possible. In some instances, intravenous nutrition may be used to supplement inadequate oral intake. The safe and successful use of parenteral nutrition requires proper selection of patients with specific nutritional needs, experience with the technique, and an awareness of the associated complications. As with enteral nutrition, the fundamental goals are to provide sufficient calories and nitrogen substrate to promote tissue repair and to maintain the integrity or growth of lean tissue mass. The following are patient groups for whom parenteral nutrition has been used in an effort to achieve these goals:

1. Newborn infants with catastrophic gastrointestinal anomalies, such as tracheoesophageal fistula, gastroschisis, omphalocele, or massive intestinal atresia

2. Infants who fail to thrive due to gastrointestinal insufficiency associated with short-bowel syndrome, malabsorption, enzyme deficiency, meconium ileus, or idiopathic diarrhea

3. Adult patients with short-bowel syndrome secondary to massive small-bowel resection (<100 cm without colon or ileocecal valve, or <50 cm with intact ileocecal valve and colon)

4. Patients with enteroenteric, enterocolic, enterovesical, or high-output enterocutaneous fistulas (>500 mL/d)

5. Surgical patients with prolonged paralytic ileus after major operations (>7 to 10 days), multiple injuries, or blunt or open abdominal trauma, or patients with reflex ileus complicating various medical diseases

6. Patients with normal bowel length but with malabsorption secondary to sprue, hypoproteinemia, enzyme or pancreatic insufficiency, regional enteritis, or ulcerative colitis

7. Adult patients with functional gastrointestinal disorders such as esophageal dyskinesia after cerebrovascular accident, idiopathic diarrhea, psychogenic vomiting, or anorexia nervosa

8. Patients with granulomatous colitis, ulcerative colitis, or tuberculous enteritis in which major portions of the absorptive mucosa are diseased

9. Patients with malignancy, with or without cachexia, in whom malnutrition might jeopardize successful use of a therapeutic option

10. Patients in whom attempts to provide adequate calories by enteral tube feedings or high residuals have failed

11. Critically ill patients who are hypermetabolic for >5 days or for whom enteral nutrition is not feasible

Patients in whom hyperalimentation is *contraindicated* include the following:

1. Patients for whom a specific goal for patient management is lacking or for whom, instead of extending a meaningful life, inevitable dying would be delayed

2. Patients experiencing hemodynamic instability or severe metabolic derangement (e.g., severe hyperglycemia, azotemia, encephalopathy, hyperosmolality, and fluid-electrolyte disturbances) requiring control or correction before hypertonic intravenous feeding is attempted

3. Patients for whom gastrointestinal tract feeding is feasible; in the vast majority of instances, this is the best route by which to provide nutrition

4. Patients with good nutritional status

5. Infants with <8 cm of small bowel, because virtually all have been unable to adapt sufficiently despite prolonged periods of parenteral nutrition

6. Patients who are irreversibly decerebrate or otherwise dehumanized

Total Parenteral Nutrition

TPN, also referred to as *central parenteral nutrition,* requires access to a large-diameter vein to deliver the entire nutritional requirements of the individual. Dextrose content of the solution is high (15 to 25%), and all other macronutrients and micronutrients are deliverable by this route.

Peripheral Parenteral Nutrition

The lower osmolarity of the solution used for peripheral parenteral nutrition (PPN), secondary to reduced levels of dextrose (5 to 10%) and protein (3%), allows its administration via peripheral veins. Some nutrients cannot be supplemented because they cannot be concentrated into small volumes. Therefore, PPN is not appropriate for repleting patients with severe malnutrition. It can be considered if central routes are not available or if supplemental nutritional support is required. Typically, PPN is used for short periods (<2 weeks). Beyond this time, TPN should be instituted.

Initiation of Parenteral Nutrition

The basic solution for parenteral nutrition contains a final concentration of 15 to 25% dextrose and 3 to 5% crystalline amino acids. The solutions usually are prepared in sterile conditions in the pharmacy from commercially available kits containing the component solutions and transfer apparatus. Preparation in the pharmacy under laminar flow hoods reduces the incidence of bacterial contamination of the solution. Proper preparation with suitable quality control is absolutely essential to avoid septic complications.

The proper provision of electrolytes and amino acids must take into account routes of fluid and electrolyte loss, renal function, metabolic rate, cardiac function, and the underlying disease state.

Intravenous vitamin preparations also should be added to parenteral formulas. Vitamin deficiencies are rare occurrences if such preparations are used. In addition, because vitamin K is not part of any commercially prepared vitamin solution, it should be supplemented on a weekly basis. During prolonged parenteral nutrition with fat-free solutions, essential fatty acid deficiency may become clinically apparent and manifests as dry, scaly dermatitis and loss of hair. The syndrome may be prevented by periodic infusion of a fat emulsion at a rate equivalent to 10 to 15% of total calories. Essential trace minerals may be required after prolonged TPN and may be supplied by direct addition of commercial preparations. The most frequent presentation of trace mineral deficiencies is the eczematoid rash developing both diffusely and at intertriginous areas in zinc-deficient patients. Other rare trace mineral deficiencies include a microcytic anemia associated with copper deficiency, and glucose intolerance presumably related to chromium deficiency. The latter complications are seldom seen except in patients receiving parenteral nutrition for extended periods. The daily administration of commercially available trace mineral supplements will obviate most such problems.

Depending on fluid and nitrogen tolerance, parenteral nutrition solutions generally can be increased over 2 to 3 days to achieve the desired infusion rate. Insulin may be supplemented as necessary to ensure glucose tolerance. Administration of additional intravenous fluids and electrolytes may occasionally be necessary in patients with persistently high fluid losses. The patient should be carefully monitored for development of electrolyte, volume, acid-base, and septic complications. Vital signs and urinary output should be measured regularly, and the patient should be weighed regularly. Frequent adjustments of the volume and composition of the solutions are necessary during the course of therapy. Samples for measurement of electrolytes are drawn daily until levels are stable and every 2 or 3 days thereafter. Blood counts, blood urea nitrogen level, levels of liver function indicators, and phosphate and magnesium levels are determined at least weekly.

The urine or capillary blood glucose level is checked every 6 hours and serum glucose concentration is checked at least once daily during the first

few days of the infusion and at frequent intervals thereafter. Relative glucose intolerance, which often manifests as glycosuria, may occur after initiation of parenteral nutrition. If blood glucose levels remain elevated or glycosuria persists, the dextrose concentration may be decreased, the infusion rate slowed, or regular insulin added to each bottle. The rise in blood glucose concentration observed after initiating parenteral nutrition may be temporary, as the normal pancreas increases its output of insulin in response to the continuous carbohydrate infusion. In patients with diabetes mellitus, additional insulin may be required.

Potassium is essential to achieve positive nitrogen balance and replace depleted intracellular stores. In addition, a significant shift of potassium ion from the extracellular to the intracellular space may take place because of the large glucose infusion, with resultant hypokalemia, metabolic alkalosis, and poor glucose utilization. In some cases as much as 240 mEq of potassium ion daily may be required. Hypokalemia may cause glycosuria, which would be treated with potassium, not insulin. Thus, before giving insulin, the serum potassium level must be checked to avoid exacerbating the hypokalemia.

Patients with insulin-dependent diabetes mellitus may exhibit wide fluctuations in blood glucose levels while receiving parenteral nutrition. This may require protocol-driven intravenous insulin therapy. In addition, partial replacement of dextrose calories with lipid emulsions may alleviate these problems in selected patients.

Lipid emulsions derived from soybean or safflower oils are widely used as an adjunctive nutrient to prevent the development of essential fatty acid deficiency. There is no evidence of enhanced metabolic benefit when >10 to 15% of calories are provided as lipid emulsions. Although the administration of 500 mL of 20% fat emulsion one to three times a week is sufficient to prevent essential fatty acid deficiency, it is common to provide fat emulsions on a daily basis to provide additional calories. The triple mix of carbohydrate, fat, and amino acids is infused at a constant rate during a 24-hour period. The theoretical advantages of a constant fat infusion rate include increased efficiency of lipid utilization and reduction in the impairment of reticuloendothelial function normally identified with bolus lipid infusions. The addition of lipids to an infusion bag may alter the stability of some micronutrients in a dextrose–amino acid preparation.

INTRAVENOUS ACCESS METHODS

Temporary or short-term access can be achieved with a 16-gauge percutaneous catheter inserted into a subclavian or internal jugular vein and threaded into the superior vena cava. More permanent access with the intention of providing long-term or home parenteral nutrition can be achieved by placement of a catheter with a subcutaneous port for access by tunneling a catheter with a substantial subcutaneous length or threading a long catheter through the basilic or cephalic vein into the superior vena cava.

COMPLICATIONS OF PARENTERAL NUTRITION

Technical Complications

One of the more common and serious complications associated with long-term parenteral feeding is sepsis secondary to contamination of the central venous catheter. Contamination of solutions should be considered, but is rare when proper pharmacy protocols have been followed. This problem occurs more frequently in patients with systemic sepsis and in many cases is due to hematogenous seeding of the catheter with bacteria.[77] One of the earliest signs of systemic sepsis may be the sudden development of glucose intolerance (with or without temperature increase) in a patient who previously has been maintained on parenteral alimentation without difficulty. When this occurs, or if high fever (>38.5°C [101.3°F]) develops without obvious cause, a diligent search for a potential septic focus is indicated. Other causes of fever should also be investigated. If fever persists, the infusion catheter should be removed and submitted for culture. If the catheter is the cause of the fever, removal of the infectious source is usually followed by rapid defervescence. Some centers are now replacing catheters considered at low risk for infection over a guidewire. Should evidence of infection persist over 24 to 48 hours without a definable source, the catheter should be replaced into the opposite subclavian vein or into one of the internal jugular veins and the infusion restarted. It is prudent to delay reinserting the catheter

by 12 to 24 hours, especially if bacteremia is present.[78]

Other complications related to catheter placement include the development of pneumothorax, hemothorax, hydrothorax, subclavian artery injury, thoracic duct injury, cardiac arrhythmia, air embolism, catheter embolism, and cardiac perforation with tamponade. All of these complications may be avoided by strict adherence to proper techniques.

The use of multilumen catheters may be associated with a slightly increased risk of infection. This is most likely associated with greater catheter manipulation and intensive use. The rate of catheter infection is highest for those placed in the femoral vein, lower for those in the jugular vein, and lowest for those in the subclavian vein. When catheters are indwelling for <3 days, infection risks are negligible. If indwelling time is 3 to 7 days, the infection risk is 3 to 5%. Indwelling times of >7 days are associated with a catheter infection risk of 5 to 10%. Strict adherence to barrier precautions also reduces the rate of infection.

Metabolic Complications

Hyperglycemia may develop with normal rates of infusion in patients with impaired glucose tolerance or in any patient if the hypertonic solutions are administered too rapidly. This is a particularly common complication in patients with latent diabetes and in patients subjected to severe surgical stress or trauma. Treatment of the condition consists of volume replacement with correction of electrolyte abnormalities and the administration of insulin. This complication can be avoided with careful attention to daily fluid balance and frequent monitoring of blood glucose levels and serum electrolytes.

Increasing experience has emphasized the importance of not overfeeding the parenterally nourished patient. This is particularly true for the depleted patient in whom excess calorie infusion may result in carbon dioxide retention and respiratory insufficiency. In addition, excess feeding also has been related to the development of hepatic steatosis or marked glycogen deposition in selected patients. Cholestasis and formation of gallstones are common in patients receiving long-term parenteral nutrition. Mild but transient abnormalities of serum transaminase, alkaline phosphatase, and bilirubin levels occur in many parenterally nourished patients. Failure of the liver enzymes to plateau or return to normal over 7 to 14 days should suggest another etiology.

Intestinal Atrophy

Lack of intestinal stimulation is associated with intestinal mucosal atrophy, diminished villous height, bacterial overgrowth, reduced lymphoid tissue size, reduced immunoglobulin A production, and impaired gut immunity. The full clinical implications of these changes are not well realized, although bacterial translocation has been demonstrated in animal models. The most efficacious method to prevent these changes is to provide at least some nutrients enterally. In patients requiring TPN, it may be feasible to infuse small amounts of feedings via the gastrointestinal tract.

SPECIAL FORMULATIONS

Glutamine and Arginine

Glutamine is the most abundant amino acid in the human body, comprising nearly two thirds of the free intracellular amino acid pool. Of this, 75% is found within the skeletal muscles. In healthy individuals, glutamine is considered a nonessential amino acid, because it is synthesized within the skeletal muscles and the lungs. Glutamine is a necessary substrate for nucleotide synthesis in most dividing cells and hence provides a major fuel source for enterocytes. It also serves as an important fuel source for immunocytes such as lymphocytes and macrophages, and is a precursor for glutathione, a major intracellular antioxidant. During stress states such as sepsis, or in tumor-bearing hosts, peripheral glutamine stores are rapidly depleted, and the amino acid is preferentially shunted as a fuel source toward the visceral organs and tumors, respectively. These situations create, at least experimentally, a glutamine-depleted environment, with consequences including enterocyte and immunocyte starvation.

Glutamine metabolism during stress in humans, however, may be more complex than is indicated in previously reported animal data. Advanced methods of detecting glutamine traffic in patients with gastrointestinal cancer have not demonstrated more sequestration of glutamine in tumors than in normal intestine. There are data demonstrating decreased dependency on TPN in severe cases of short-bowel syndrome when glutamine therapy with modified diets and growth hormones are used. However, in patients with milder forms of short-bowel syndrome and better nutritional status, glutamine supplementation did not lead to appreciable enhancement in intestinal absorption. Although it is hypothesized that provision of glutamine may preserve immune cell and enterocyte function and enhance nitrogen balance during injury or sepsis, the clinical evidence in support of these phenomena in human subjects remains inconclusive.[79]

Arginine, also a nonessential amino acid in healthy subjects, first attracted attention for its immunoenhancing properties, wound-healing benefits, and association with improved survival in animal models of sepsis and injury. As with glutamine, the benefits of experimental arginine supplementation during stress states are diverse. In clinical studies involving critically ill and injured patients and patients who have undergone surgery for certain malignancies, enteral administration of arginine has led to net nitrogen retention and protein synthesis, whereas isonitrogenous diets have not. Some of these studies also provide in vitro evidence of enhanced immunocyte function. The clinical utility of arginine supplementation in improving overall patient outcome remains an area of investigation.

Omega-3 Fatty Acids

The provision of omega-3 polyunsaturated fatty acids (canola oil or fish oil) displaces omega-6 fatty acids in cell membranes, which theoretically reduces the proinflammatory response from prostaglandin production.[80]

Nucleotides

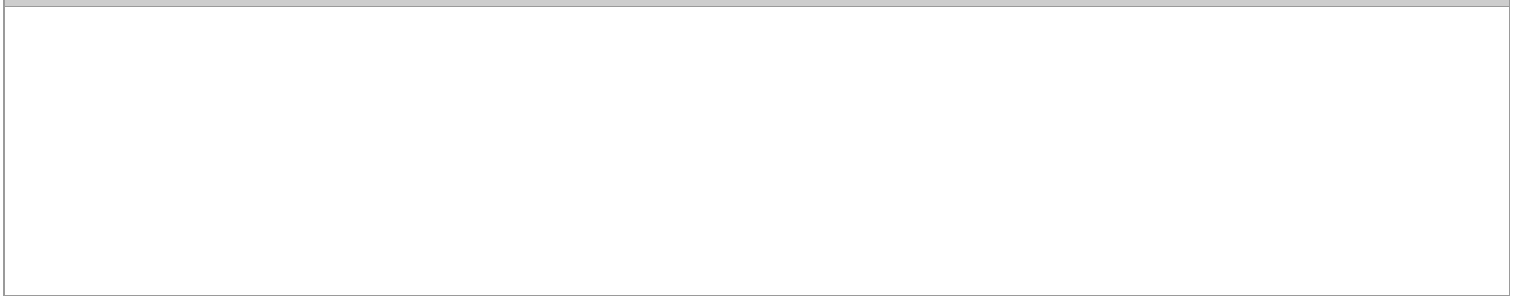
RNA supplementation in solutions is purported, at least experimentally, to increase cell proliferation, provide building blocks for DNA synthesis, and improve helper T cell function.

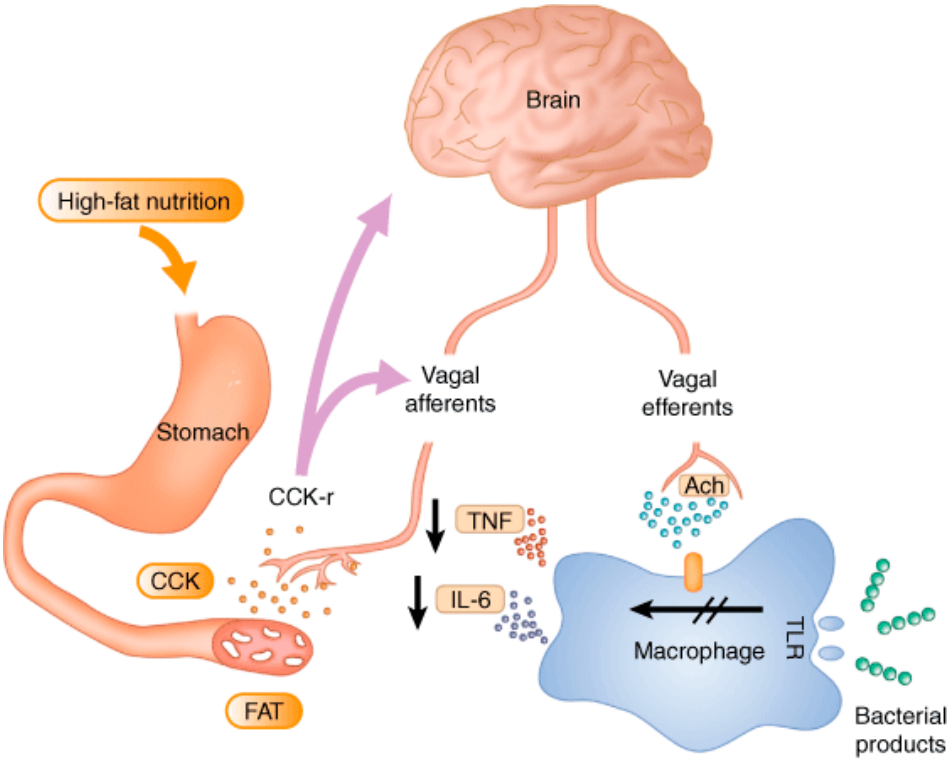
NUTRITION-INDUCED INFLAMMATORY MODULATION

Studies have demonstrated that the mode of nutritional supplementation, either enteral or parenteral, may influence stress-induced inflammatory responses. Intravenously fed subjects demonstrate a heightened response to proinflammatory stimuli such as endotoxin. Enteral feedings have been regarded as the feeding mode of choice when possible, and although advantages have been suggested, including improved GI barrier function, the mechanisms through which enteral feedings mediate efficacious effects have yet to be fully determined.

Providing further insight into the benefit of enteral feedings, Luyer and colleagues have demonstrated that enteral fat maintains both afferent and efferent vagal pathway signaling via intestinal cholecystokinin receptor activation. They observed that consumption of a high-density fat meal before stress induced by hemorrhage resulted in reduced systemic inflammation and improved outcome.[81] Thus, enteral nutrients may act as agonists for endogenous neuroendocrine anti-inflammatory pathways (Fig. 2-28).[82]

Fig. 2-28.





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Vagal afferent system senses peripheral inflammatory focus and also responses to intestinal luminal substrates, in this case enteral lipid signaling via cholecystokinin receptors (CCK-r). Efferent vagal signals limit proinflammatory cytokine production via activation of cholinergic nicotinic receptors on visceral immune cells. Clinical conditions that disrupt the integrity of this circuit may enhance inflammatory responses. Ach = acetylcholine; CCK = cholecystokinin; IL-6 = interleukin-6; TLR = toll-like receptor; TNF = tumor necrosis factor.

(Adapted with permission from Luyer MD, et al. Nutritional stimulation of cholecystokinin receptors inhibits inflammation via the vagus nerve. *J Exp Med* 202:1023, 2005. By copyright permission of The Rockefeller University Press.)

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KEY POINTS

1. Proper management of fluid and electrolytes facilitates crucial homeostasis that allows cardiovascular perfusion, organ system function, and cellular mechanisms to respond to surgical illness.

2. Knowledge of the compartmentalization of body fluids forms the basis for understanding pathologic shifts in these fluid spaces in disease states. Although difficult to quantify, a deficiency in the functional extracellular fluid compartment often requires resuscitation with isotonic fluids in surgical and trauma patients.

3. Alterations in the concentration of serum sodium have profound effects on cellular function due to water shifts between the intracellular and extracellular spaces.

4. Different rates of compensation between respiratory and metabolic components of acid-base homeostasis require frequent laboratory reassessment during therapy.

5. Most acute surgical illnesses are accompanied by some degree of volume loss or redistribution. Consequently, isotonic fluid administration is the most common initial IV fluid strategy, while attention is being given to alterations in concentration and composition.

6. Although active investigation continues, alternative resuscitation fluids have limited clinical utility, other than the correction of specific electrolyte abnormalities.

7. Some surgical patients with neurologic illness, malnutrition, acute renal failure, or cancer require special attention to well-defined, disease-specific abnormalities in fluid and electrolyte status.

FLUID AND ELECTROLYTE MANAGEMENT OF THE SURGICAL PATIENT: INTRODUCTION

Fluid and electrolyte management is paramount to the care of the surgical patient. Changes in both fluid volume and electrolyte composition occur preoperatively, intraoperatively, and postoperatively, as well as in response to trauma and sepsis. The sections that follow review the normal anatomy of body fluids, electrolyte composition and concentration abnormalities and treatments, common metabolic derangements, and alternative resuscitative fluids. These concepts are then discussed in relationship to management of specific surgical patients and their commonly encountered fluid and electrolyte abnormalities.

BODY FLUIDS

Total Body Water

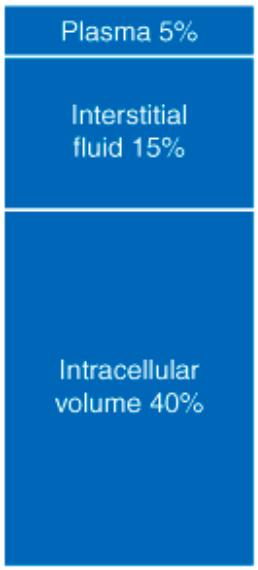
Water constitutes approximately 50 to 60% of total body weight. The relationship between total body weight and total body

water (TBW) is relatively constant for an individual and is primarily a reflection of body fat. Lean tissues such as muscle and solid organs have higher water content than fat and bone. As a result, young, lean males have a higher proportion of body weight as water than elderly or obese individuals. Deuterium oxide and tritiated water have been used in clinical research to measure TBW by indicator dilution methods. In an average young adult male 60% of total body weight is TBW, whereas in an average young adult female it is 50%.[1] The lower percentage of TBW in females correlates with a higher percentage of adipose tissue and lower percentage of muscle mass in most. Estimates of percentage of TBW should be adjusted downward approximately 10 to 20% for obese individuals and upward by 10% for malnourished individuals. The highest percentage of TBW is found in newborns, with approximately 80% of their total body weight comprised of water. This decreases to approximately 65% by 1 year of age and thereafter remains fairly constant.

Fluid Compartments

TBW is divided into three functional fluid compartments: plasma, extravascular interstitial fluid, and intracellular fluid (Fig. 3-1). The extracellular fluids (ECF), plasma and interstitial fluid, together comprise about one third of the TBW and the intracellular compartment the remaining two thirds. The extracellular water comprises 20% of the total body weight and is divided between plasma (5% of body weight) and interstitial fluid (15% of body weight). Intracellular water makes up approximately 40% of an individual's total body weight, with the largest proportion in the skeletal muscle mass. ECF is measured using indicator dilution methods. The distribution volumes of NaBr and radioactive sulfate have been used to measure ECF in clinical research. Measurement of the intracellular compartment is then determined indirectly by subtracting the measured ECF from the simultaneous TBW measurement.

Fig. 3-1.



% of Total body weight	Volume of TBW	Male (70 kg)	Female (60 kg)
Plasma 5%	Extracellular volume	14,000 mL	10,000 mL
Interstitial fluid 15%	Plasma	3500 mL	2500 mL
	Interstitial	10,500 mL	7500 mL
Intracellular volume 40%	Intracellular volume	28,000 mL	20,000 mL
		42,000 mL	30,000 mL

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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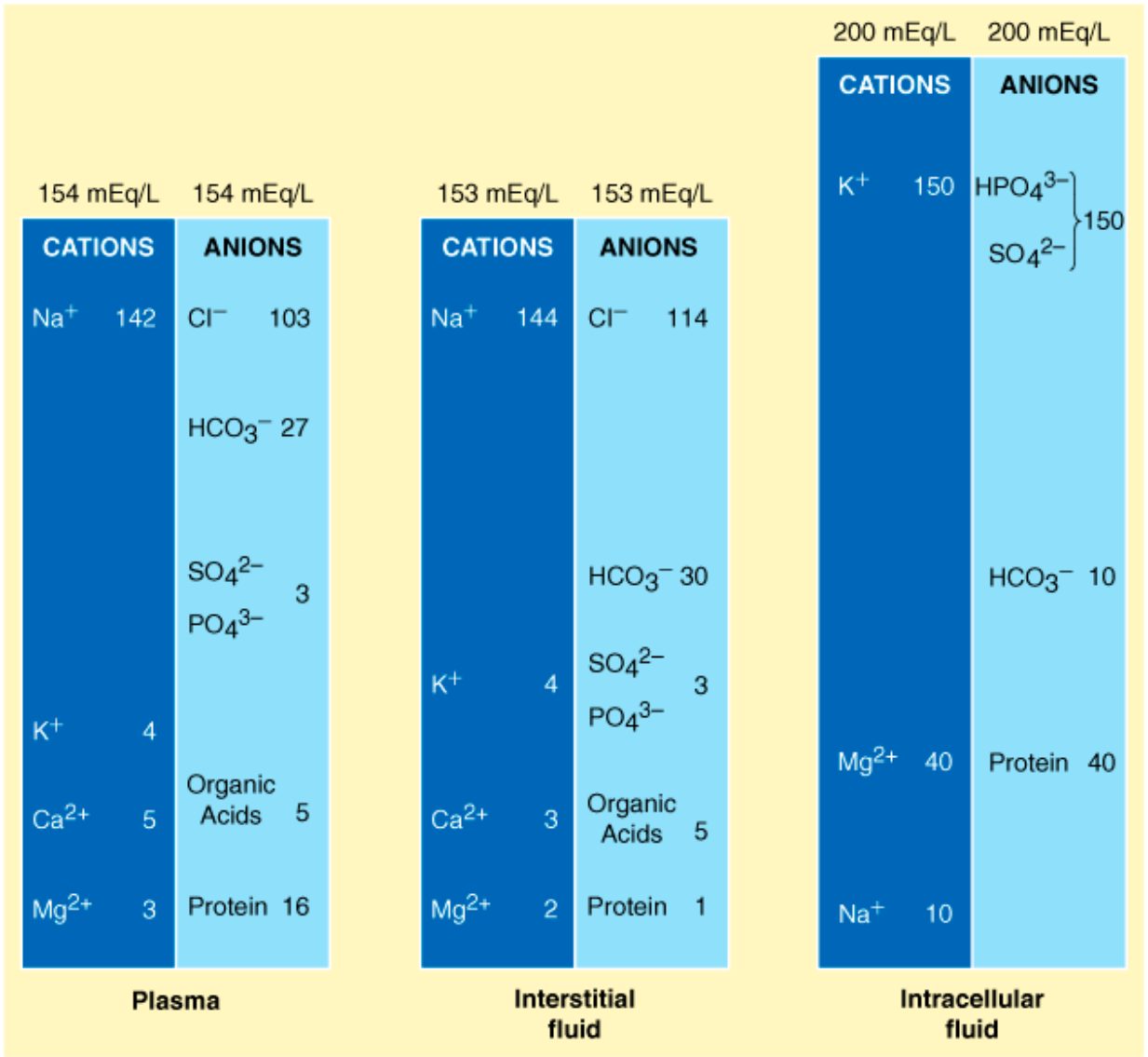
Functional body fluid compartments. TBW = total body water.

Composition of Fluid Compartments

The normal chemical composition of the body fluid compartments is shown in Fig. 3-2. The ECF compartment is balanced between sodium, the principal cation, and chloride and bicarbonate, the principal anions. The intracellular fluid compartment is comprised primarily of the cations potassium and magnesium, and the anions phosphate and proteins. The concentration gradient between compartments is maintained by adenosine triphosphate–driven sodium-potassium pumps located with the cell membranes. The composition of the plasma and interstitial fluid differs only slightly in ionic composition. The slightly higher protein content (organic anions) in plasma results in a higher plasma cation composition relative to the interstitial fluid, as explained by the Gibbs-Donnan equilibrium equation. Proteins add to the osmolality of the plasma and contribute to the balance of forces that determine fluid balance across the capillary endothelium. Although the movement of ions and proteins between the various fluid compartments is restricted, water is freely diffusible. Water is distributed evenly throughout all fluid compartments of the body, so that a given volume of water increases the volume of any one compartment relatively little. Sodium, however, is confined to the ECF compartment, and because of its osmotic and electrical properties, it remains associated with water. Therefore, sodium-containing fluids are distributed throughout the ECF and add to the volume of both the intravascular and interstitial spaces. Although the administration of sodium-containing fluids expands the intravascular volume, it also expands the interstitial space by approximately three times as much as the plasma.

Fig. 3-2.



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Chemical composition of body fluid compartments.

Osmotic Pressure

The physiologic activity of electrolytes in solution depends on the number of particles per unit volume (millimoles per liter, or mmol/L), the number of electric charges per unit volume (milliequivalents per liter, or mEq/L), and the number of osmotically active ions per unit volume (milliosmoles per liter, or mOsm/L). The concentration of electrolytes usually is expressed in terms of the chemical combining activity, or equivalents. An equivalent of an ion is its atomic weight expressed in grams divided by the valence:

$$\text{Equivalent} = \text{atomic weight (g)}/\text{valence}$$

For univalent ions such as sodium, 1 mEq is the same as 1 mmol. For divalent ions such as magnesium, 1 mmol equals 2 mEq. The number of milliequivalents of cations must be balanced by the same number of milliequivalents of anions. However, the expression of molar equivalents alone does not allow a physiologic comparison of solutes in a solution.

The movement of water across a cell membrane depends primarily on osmosis. To achieve osmotic equilibrium, water moves

across a semipermeable membrane to equalize the concentration on both sides. This movement is determined by the concentration of the solutes on each side of the membrane. Osmotic pressure is measured in units of osmoles (osm) or milliosmoles (mOsm) that refer to the actual number of osmotically active particles. For example, 1 mmol of sodium chloride contributes to 2 mOsm (one from sodium and one from chloride). The principal determinants of osmolality are the concentrations of sodium, glucose, and urea (blood urea nitrogen, or BUN):

$$\text{Calculated serum osmolality} = 2\,\text{sodium} + (\text{glucose}/18) + (\text{BUN}/2.8)$$

The osmolality of the intracellular and extracellular fluids is maintained between 290 and 310 mOsm in each compartment. Because cell membranes are permeable to water, any change in osmotic pressure in one compartment is accompanied by a redistribution of water until the effective osmotic pressure between compartments is equal. For example, if the ECF concentration of sodium increases, there will be a net movement of water from the intracellular to the extracellular compartment. Conversely, if the ECF concentration of sodium decreases, water will move into the cells. Although the intracellular fluid shares in losses that involve a change in concentration or composition of the ECF, an isotonic change in volume in either one of the compartments is not accompanied by the net movement of water as long as the ionic concentration remains the same. For practical clinical purposes, most significant gains and losses of body fluid are directly from the extracellular compartment.

BODY FLUID CHANGES

Normal Exchange of Fluid and Electrolytes

The healthy person consumes an average of 2000 mL of water per day, approximately 75% from oral intake and the rest extracted from solid foods. Daily water losses include 800 to 1200 mL in urine, 250 mL in stool, and 600 mL in insensible losses. Insensible losses of water occur through both the skin (75%) and lungs (25%), and can be increased by such factors as fever, hypermetabolism, and hyperventilation. Sensible water losses such as sweating or pathologic loss of GI fluids vary widely, but these include the loss of electrolytes as well as water (Table 3-1). To clear the products of metabolism, the kidneys must excrete a minimum of 500 to 800 mL of urine per day, regardless of the amount of oral intake.

Table 3-1 Water Exchange (60- to 80-kg Man)

Routes	Average Daily Volume (mL)	Minimal (mL)	Maximal (mL)
H_2O gain:			
Sensible:			
Oral fluids	800–1500	0	1500/h
Solid foods	500–700	0	1500
Insensible:			
Water of oxidation	250	125	800
Water of solution	0	0	500
H_2O loss:			
Sensible:			
Urine	800–1500	300	1400/h
Intestinal	0–250	0	2500/h

Sweat	0	0	4000/h
Insensible:			
Lungs and skin	600	600	1500

The typical individual consumes 3 to 5 g of dietary salt per day, with the balance maintained by the kidneys. With hyponatremia or hypovolemia, sodium excretion can be reduced to as little as 1 mEq/d or maximized to as much as 5000 mEq/d to achieve balance except in people with salt-wasting kidneys. Sweat is hypotonic, and sweating usually results in only a small sodium loss. GI losses are isotonic to slightly hypotonic and contribute little to net gain or loss of free water when measured and appropriately replaced by isotonic salt solutions.

Classification of Body Fluid Changes

Disorders in fluid balance may be classified into three general categories: disturbances in (a) volume, (b) concentration, and (c) composition. Although each of these may occur simultaneously, each is a separate entity with unique mechanisms demanding individual correction. Isotonic gain or loss of salt solution results in extracellular volume changes, with little impact on intracellular fluid volume. If free water is added or lost from the ECF, water will pass between the ECF and intracellular fluid until solute concentration or osmolarity is equalized between the compartments. Unlike with sodium, the concentration of most other ions in the ECF can be altered without significant change in the total number of osmotically active particles, producing only a compositional change. For instance, doubling the serum potassium concentration will profoundly alter myocardial function without significantly altering volume or concentration of the fluid spaces.

Disturbances in Fluid Balance

Extracellular volume deficit is the most common fluid disorder in surgical patients and can be either acute or chronic. Acute volume deficit is associated with cardiovascular and central nervous system signs, whereas chronic deficits display tissue signs, such as a decrease in skin turgor and sunken eyes, in addition to cardiovascular and central nervous system signs (Table 3-2). Laboratory examination may reveal an elevated blood urea nitrogen level if the deficit is severe enough to reduce glomerular filtration and hemoconcentration. Urine osmolality usually will be higher than serum osmolality, and urine sodium will be low, typically <20 mEq/L. Serum sodium concentration does not necessarily reflect volume status and therefore may be high, normal, or low when a volume deficit is present. The most common cause of volume deficit in surgical patients is a loss of GI fluids (Table 3-3) from nasogastric suction, vomiting, diarrhea, or enterocutaneous fistula. In addition, sequestration secondary to soft tissue injuries, burns, and intra-abdominal processes such as peritonitis, obstruction, or prolonged surgery can also lead to massive volume deficits.

Table 3-2 Signs and Symptoms of Volume Disturbances

System	Volume Deficit	Volume Excess
Generalized	Weight loss	Weight gain
	Decreased skin turgor	Peripheral edema
Cardiac	Tachycardia	Increased cardiac output
	Orthostasis/hypotension	Increased central venous pressure
	Collapsed neck veins	Distended neck veins
		Murmur
Renal	Oliguria	—

	Azotemia	
GI	Ileus	Bowel edema
Pulmonary	—	Pulmonary edema

Table 3-3 Composition of GI Secretions

Type of Secretion	Volume (mL/24 h)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	HCO_3^- (mEq/L)
Stomach	1000–2000	60–90	10–30	100–130	0
Small intestine	2000–3000	120–140	5–10	90–120	30–40
Colon	—	60	30	40	0
Pancreas	600–800	135–145	5–10	70–90	95–115
Bile	300–800	135–145	5–10	90–110	30–40

Extracellular volume excess may be iatrogenic or secondary to renal dysfunction, congestive heart failure, or cirrhosis. Both plasma and interstitial volumes usually are increased. Symptoms are primarily pulmonary and cardiovascular (see Table 3-2). In fit patients, edema and hyperdynamic circulation are common and well tolerated. However, the elderly and patients with cardiac disease may quickly develop congestive heart failure and pulmonary edema in response to only a moderate volume excess.

Volume Control

Volume changes are sensed by both osmoreceptors and baroreceptors. Osmoreceptors are specialized sensors that detect even small changes in fluid osmolality and drive changes in thirst and diuresis through the kidneys.[2] For example, when plasma osmolality is increased, thirst is stimulated and water consumption increases.[3] Additionally, the hypothalamus is stimulated to secrete vasopressin, which increases water reabsorption in the kidneys. Together, these two mechanisms return the plasma osmolality to normal. Baroreceptors also modulate volume in response to changes in pressure and circulating volume through specialized pressure sensors located in the aortic arch and carotid sinuses.[4] Baroreceptor responses are both neural, through sympathetic and parasympathetic pathways, and hormonal, through substances including renin-angiotensin, aldosterone, atrial natriuretic peptide, and renal prostaglandins. The net result of alterations in renal sodium excretion and free water reabsorption is restoration of volume to the normal state.

Concentration Changes

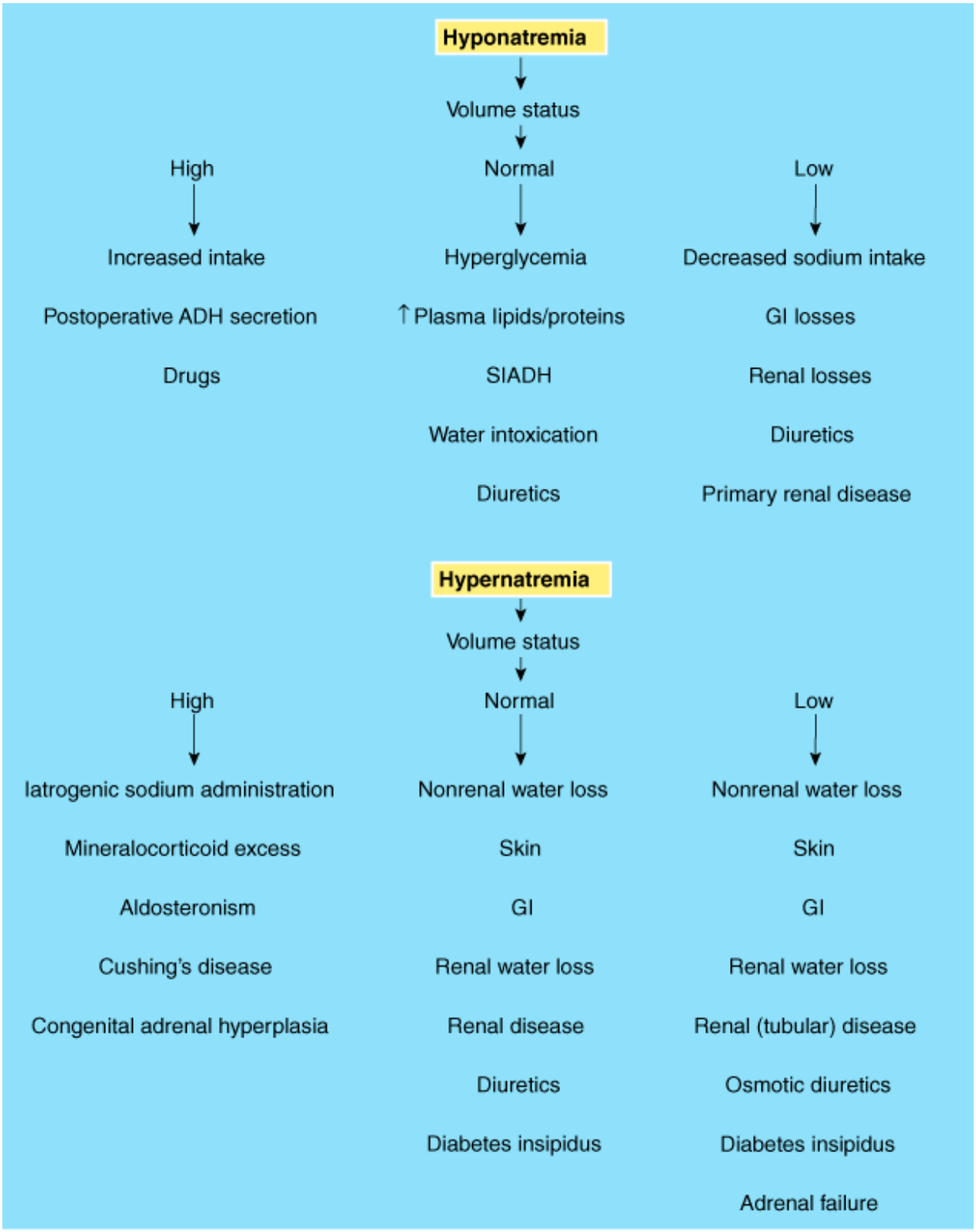
Changes in serum sodium concentration are inversely proportional to TBW. Therefore, abnormalities in TBW are reflected by abnormalities in serum sodium levels.

HYPONATREMIA

A low serum sodium level occurs when there is an excess of extracellular water relative to sodium. Extracellular volume can be high, normal, or low (Fig. 3-3). In most cases of hyponatremia, sodium concentration is decreased as a consequence of either sodium depletion or dilution.[5] Dilutional hyponatremia frequently results from excess extracellular water and therefore is associated with a high extracellular volume status. Excessive oral water intake or iatrogenic IV excess free water administration can cause hyponatremia. Postoperative patients are particularly prone to increased secretion of antidiuretic

hormone (ADH), which increases reabsorption of free water from the kidneys with subsequent volume expansion and hyponatremia. This is usually self-limiting in that both hyponatremia and volume expansion decrease ADH secretion. Additionally, a number of drugs can cause water retention and subsequent hyponatremia, such as the antipsychotics and tricyclic antidepressants as well as angiotensin-converting enzyme inhibitors. The elderly are particularly susceptible to drug-induced hyponatremia. Physical signs of volume overload usually are absent, and laboratory evaluation reveals hemodilution. Depletional causes of hyponatremia are associated with either a decreased intake or increased loss of sodium-containing fluids. A concomitant ECF volume deficit is common. Causes include decreased sodium intake, such as consumption of a low-sodium diet or use of enteral feeds, which are typically low in sodium; GI losses from vomiting, prolonged nasogastric suctioning, or diarrhea; and renal losses due to diuretic use or primary renal disease.

Fig. 3-3.



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Evaluation of sodium abnormalities. ADH = antidiuretic hormone; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

Hyponatremia also can be seen with an excess of solute relative to free water, such as with untreated hyperglycemia or mannitol administration. Glucose exerts an osmotic force in the extracellular compartment, causing a shift of water from the

intracellular to the extracellular space. Hyponatremia therefore can be seen when the effective osmotic pressure of the extracellular compartment is normal or even high. When hyponatremia in the presence of hyperglycemia is being evaluated, the corrected sodium concentration should be calculated as follows:

For every 100-mg/dL increment in plasma glucose above normal,
the plasma sodium should decrease by 1.6 mEq/L

Lastly, extreme elevations in plasma lipids and proteins can cause pseudohyponatremia, because there is no true decrease in extracellular sodium relative to water.

Signs and symptoms of hyponatremia (Table 3-4) are dependent on the degree of hyponatremia and the rapidity with which it occurred. Clinical manifestations primarily have a central nervous system origin and are related to cellular water intoxication and associated increases in intracranial pressure. Oliguric renal failure also can be a rapid complication in the setting of severe hyponatremia.

Table 3-4 Clinical Manifestations of Abnormalities in Serum Sodium Level

Body System	**Hyponatremia**
Central nervous system	Headache, confusion, hyperactive or hypoactive deep tendon reflexes, seizures, coma, increased intracranial pressure
Musculoskeletal	Weakness, fatigue, muscle cramps/twitching
GI	Anorexia, nausea, vomiting, watery diarrhea
Cardiovascular	Hypertension and bradycardia if significant increases in intracranial pressure
Tissue	Lacrimation, salivation
Renal	Oliguria
Body System	**Hypernatremia**
Central nervous system	Restlessness, lethargy, ataxia, irritability, tonic spasms, delirium, seizures, coma
Musculoskeletal	Weakness
Cardiovascular	Tachycardia, hypotension, syncope
Tissue	Dry sticky mucous membranes, red swollen tongue, decreased saliva and tears
Renal	Oliguria
Metabolic	Fever

A systematic review of the etiology of hyponatremia should reveal its cause in a given instance. Hyperosmolar causes, including hyperglycemia or mannitol infusion and pseudohyponatremia, should be easily excluded. Next, depletional versus dilutional causes of hyponatremia are evaluated. In the absence of renal disease, depletion is associated with low urine sodium levels (<20 mEq/L), whereas renal sodium wasting shows high urine sodium levels (>20 mEq/L). Dilutional causes of hyponatremia usually are associated with hypervolemic circulation. A normal volume status in the setting of hyponatremia should prompt an evaluation for a syndrome of inappropriate secretion of ADH.

HYPERNATREMIA

Hypernatremia results from either a loss of free water or a gain of sodium in excess of water. Like hyponatremia, it can be associated with an increased, normal, or decreased extracellular volume (see Fig. 3-3). Hypervolemic hypernatremia usually is caused either by iatrogenic administration of sodium-containing fluids, including sodium bicarbonate, or mineralocorticoid

excess as seen in hyperaldosteronism, Cushing's syndrome, and congenital adrenal hyperplasia. Urine sodium concentration is typically >20 mEq/L and urine osmolarity is >300 mOsm/L. Normovolemic hypernatremia can result from renal causes, including diabetes insipidus, diuretic use, and renal disease, or from nonrenal water loss from the GI tract or skin, although the same conditions can result in hypovolemic hypernatremia. When hypovolemia is present, the urine sodium concentration is <20 mEq/L and urine osmolarity is <300 to 400 mOsm/L. Nonrenal water loss can occur secondary to relatively isotonic GI fluid losses such as that caused by diarrhea, to hypotonic skin fluid losses such as loss due to fever, or to losses via tracheotomies during hyperventilation. Additionally, thyrotoxicosis can cause water loss, as can the use of hypertonic glucose solutions for peritoneal dialysis. With nonrenal water loss, the urine sodium concentration is <15 mEq/L and the urine osmolarity is >400 mOsm/L.

Symptomatic hypernatremia usually occurs only in patients with impaired thirst or restricted access to fluid, because thirst will result in increased water intake. Symptoms are rare until the serum sodium concentration exceeds 160 mEq/L but, once present, are associated with significant morbidity and mortality. Because symptoms are related to hyperosmolarity, central nervous system effects predominate (see Table 3-4). Water shifts from the intracellular to the extracellular space in response to a hyperosmolar extracellular space, which results in cellular dehydration. This can put traction on the cerebral vessels and lead to subarachnoid hemorrhage. Central nervous system symptoms can range from restlessness and irritability to seizures, coma, and death. The classic signs of hypovolemic hypernatremia, (tachycardia, orthostasis, and hypotension) may be present, as well as the unique findings of dry, sticky mucous membranes.

Composition Changes: Etiology and Diagnosis

POTASSIUM ABNORMALITIES

The average dietary intake of potassium is approximately 50 to 100 mEq/d, which in the absence of hypokalemia is excreted primarily in the urine. Extracellular potassium is maintained within a narrow range, principally by renal excretion of potassium, which can range from 10 to 700 mEq/d. Although only 2% of the total body potassium (4.5 mEq/L x 14 L = 63 mEq) is located within the extracellular compartment, this small amount is critical to cardiac and neuromuscular function; thus, even minor changes can have major effects on cardiac activity. The intracellular and extracellular distribution of potassium is influenced by a number of factors, including surgical stress, injury, acidosis, and tissue catabolism.

Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration above the normal range of 3.5 to 5.0 mEq/L. It is caused by excessive potassium intake, increased release of potassium from cells, or impaired potassium excretion by the kidneys (Table 3-5).[6] Increased intake can be either from oral or IV supplementation, or from red cell lysis after transfusion. Hemolysis, rhabdomyolysis, and crush injuries can disrupt cell membranes and release intracellular potassium into the ECF. Acidosis and a rapid rise in extracellular osmolality from hyperglycemia or IV mannitol can raise serum potassium levels by causing a shift of potassium ions to the extracellular compartment.[7] Because 98% of total body potassium is in the intracellular fluid compartment, even small shifts of intracellular potassium out of the intracellular fluid compartment can lead to a significant rise in extracellular potassium. A number of medications can contribute to hyperkalemia, particularly in the presence of renal insufficiency, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and NSAIDs. Spironolactone and angiotensin-converting enzyme inhibitors interfere with aldosterone activity, inhibiting the normal renal mechanism of potassium excretion. Acute and chronic renal insufficiency also impairs potassium excretion.

Table 3-5 Etiology of Potassium Abnormalities

Hyperkalemia
Increased intake
Potassium supplementation
Blood transfusions
Endogenous load/destruction: hemolysis, rhabdomyolysis, crush injury, gastrointestinal hemorrhage
Increased release
Acidosis
Rapid rise of extracellular osmolality (hyperglycemia or mannitol)
Impaired excretion
Potassium-sparing diuretics
Renal insufficiency/failure
Hypokalemia
Inadequate intake
Dietary, potassium-free intravenous fluids, potassium-deficient TPN
Excessive potassium excretion
Hyperaldosteronism
Medications
GI losses
Direct loss of potassium from GI fluid (diarrhea)
Renal loss of potassium (gastric fluid, either as vomiting or high nasogastric output)

Symptoms of hyperkalemia are primarily GI, neuromuscular, and cardiovascular (Table 3-6). GI symptoms include nausea, vomiting, intestinal colic, and diarrhea. Neuromuscular symptoms range from weakness to ascending paralysis to respiratory failure. Early cardiovascular signs may be apparent from electrocardiogram (ECG) changes and eventually lead to hemodynamic symptoms of arrhythmia and cardiac arrest. ECG changes that may be seen with hyperkalemia include high peaked T waves (early), widened QRS complex, flattened P wave, prolonged PR interval (first-degree block), sine wave formation, and ventricular fibrillation.

Table 3-6 Clinical Manifestations of Abnormalities in Potassium, Magnesium, and Calcium Levels

	Increased Serum Levels		
System	**Potassium**	**Magnesium**	**Calcium**
GI	Nausea/vomiting, colic, diarrhea	Nausea/vomiting	Anorexia, nausea/vomiting, abdominal pain
Neuromuscular	Weakness, paralysis, respiratory failure	Weakness, lethargy, decreased reflexes	Weakness, confusion, coma, bone pain
Cardiovascular	Arrhythmia, arrest	Hypotension, arrest	Hypertension, arrhythmia, polyuria
Renal	—	—	Polydipsia
	Decreased Serum Levels		
System	**Potassium**	**Magnesium**	**Calcium**
GI	Ileus, constipation	—	—

Neuromuscular	Decreased reflexes, fatigue, weakness, paralysis	Hyperactive reflexes, muscle tremors, tetany, seizures	Hyperactive reflexes, paresthesias, carpopedal spasm, seizures
Cardiovascular	Arrest	Arrhythmia	Heart failure

Hypokalemia

Hypokalemia is much more common than hyperkalemia in the surgical patient. It may be caused by inadequate potassium intake; excessive renal potassium excretion; potassium loss in pathologic GI secretions, such as with diarrhea, fistulas, vomiting, or high nasogastric output; or intracellular shifts from metabolic alkalosis or insulin therapy (see Table 3-5). The change in potassium associated with alkalosis can be calculated by the following formula:

Potassium decreases by 0.3 mEq/L for every
0.1 increase in pH above normal.

Additionally, drugs such as amphotericin, aminoglycosides, foscarnet, cisplatin, and ifosfamide that induce magnesium depletion cause renal potassium wastage.[8,9] In cases in which potassium deficiency is due to magnesium depletion,[10] potassium repletion is difficult unless hypomagnesemia is first corrected.

The symptoms of hypokalemia (see Table 3-6), like those of hyperkalemia, are primarily related to failure of normal contractility of GI smooth muscle, skeletal muscle, and cardiac muscle. Findings may include ileus, constipation, weakness, fatigue, diminished tendon reflexes, paralysis, and cardiac arrest. In the setting of ECF depletion, symptoms may be masked initially and then worsened by further dilution during volume repletion. ECG changes suggestive of hypokalemia include U waves, T-wave flattening, ST-segment changes, and arrhythmias (with digitalis therapy).

CALCIUM ABNORMALITIES

The vast majority of the body's calcium is contained within the bone matrix, with <1% found in the ECF. Serum calcium is distributed among three forms: protein found (40%), complexed to phosphate and other anions (10%), and ionized (50%). It is the ionized fraction that is responsible for neuromuscular stability and can be measured directly. When total serum calcium levels are measured, the albumin concentration must be taken into consideration:

Adjust total serum calcium down by 0.8 mg/dL
for every 1-g/dL decrease in albumin.

Unlike changes in albumin, changes in pH will affect the ionized calcium concentration. Acidosis decreases protein binding, thereby increasing the ionized fraction of calcium.

Daily calcium intake is 1 to 3 g/d. Most of this is excreted via the bowel, with urinary excretion relatively low. Total body calcium balance is under complex hormonal control, but disturbances in metabolism are relatively long term and less important in the acute surgical setting. However, attention to the critical role of ionized calcium in neuromuscular function often is required.

Hypercalcemia

Hypercalcemia is defined as a serum calcium level above the normal range of 8.5 to 10.5 mEq/L or an increase in the ionized calcium level above 4.2 to 4.8 mg/dL. Primary hyperparathyroidism in the outpatient setting and malignancy in hospitalized patients, from either bony metastasis or secretion of parathyroid hormone–related protein, account for most cases of symptomatic hypercalcemia.[11] Symptoms of hypercalcemia (see Table 3-6), which vary with the degree of severity, include neurologic impairment, musculoskeletal weakness and pain, renal dysfunction, and GI symptoms of nausea, vomiting, and abdominal pain. Cardiac symptoms can be manifest as hypertension, cardiac arrhythmias, and a worsening of digitalis

toxicity. ECG changes in hypercalcemia include shortened QT interval, prolonged PR and QRS intervals, increased QRS voltage, T-wave flattening and widening, and atrioventricular block (which can progress to complete heart block and cardiac arrest).

Hypocalcemia

Hypocalcemia is defined as a serum calcium level below 8.5 mEq/L or a decrease in the ionized calcium level below 4.2 mg/dL. The causes of hypocalcemia include pancreatitis, massive soft tissue infections such as necrotizing fasciitis, renal failure, pancreatic and small bowel fistulas, hypoparathyroidism, toxic shock syndrome, abnormalities in magnesium levels, and tumor lysis syndrome. In addition, transient hypocalcemia commonly occurs after removal of a parathyroid adenoma due to atrophy of the remaining glands and avid bone remineralization, and sometimes requires high-dose calcium supplementation.[12] Additionally, malignancies associated with increased osteoclastic activity, such as breast and prostate cancer, can lead to hypocalcemia from increased bone formation.[13] Calcium precipitation with organic anions is also a cause of hypocalcemia and may occur during hyperphosphatemia from tumor lysis syndrome or rhabdomyolysis. Pancreatitis may sequester calcium via chelation with free fatty acids. Massive blood transfusion with citrate binding is another mechanism.[14,15] Hypocalcemia rarely results solely from decreased intake, because bone reabsorption can maintain normal levels for prolonged periods.

Asymptomatic hypocalcemia may occur when hypoproteinemia results in a normal ionized calcium level. Conversely, symptoms can develop with a normal serum calcium level during alkalosis, which decreases ionized calcium. In general, neuromuscular and cardiac symptoms do not occur until the ionized fraction falls below 2.5 mg/dL (see Table 3-6). Clinical findings may include paresthesias of the face and extremities, muscle cramps, carpopedal spasm, stridor, tetany, and seizures. Patients will demonstrate hyperreflexia and may exhibit positive Chvostek's sign (spasm resulting from tapping over the facial nerve) and Trousseau's sign (spasm resulting from pressure applied to the nerves and vessels of the upper extremity with a blood pressure cuff). Hypocalcemia may lead to decreased cardiac contractility and heart failure. ECG changes of hypocalcemia include prolonged QT interval, T-wave inversion, heart block, and ventricular fibrillation.

PHOSPHORUS ABNORMALITIES

Phosphorus is the primary intracellular divalent anion and is abundant in metabolically active cells. Phosphorus is involved in energy production during glycolysis and is found in high-energy phosphate products such as adenosine triphosphate. Serum phosphate levels are tightly controlled by renal excretion.

Hyperphosphatemia

Hyperphosphatemia can be due to decreased urinary excretion, increased intake, or endogenous mobilization of phosphorus. Most cases of hyperphosphatemia are seen in patients with impaired renal function. Hypoparathyroidism or hyperthyroidism also can decrease urinary excretion of phosphorus and thus lead to hyperphosphatemia. Increased release of endogenous phosphorus can be seen in association with any clinical condition that results in cell destruction, including rhabdomyolysis, tumor lysis syndrome, hemolysis, sepsis, severe hypothermia, and malignant hyperthermia. Excessive phosphate administration from IV hyperalimentation solutions or phosphorus-containing laxatives may also lead to elevated phosphate levels. Most cases of hyperphosphatemia are asymptomatic, but significant prolonged hyperphosphatemia can lead to metastatic deposition of soft tissue calcium-phosphorus complexes.

Hypophosphatemia

Hypophosphatemia can be due to a decrease in phosphorus intake, an intracellular shift of phosphorus, or an increase in phosphorus excretion. Decreased GI uptake due to malabsorption or administration of phosphate binders and decreased dietary intake from malnutrition are causes of chronic hypophosphatemia. Most acute cases are due to an intracellular shift of phosphorus in association with respiratory alkalosis, insulin therapy, refeeding syndrome, and hungry bone syndrome. Clinical manifestations of hypophosphatemia usually are absent until levels fall significantly. In general, symptoms are related to adverse effects on the oxygen availability of tissue and to a decrease in high-energy phosphates, and can be manifested as cardiac dysfunction or muscle weakness.

MAGNESIUM ABNORMALITIES

Magnesium is the fourth most common mineral in the body and, like potassium, is found primarily in the intracellular compartments. Approximately one half of the total body content of 2000 mEq is incorporated in bone and is slowly exchangeable. Of the fraction found in the extracellular space, one third is bound to serum albumin. Therefore, the plasma level of magnesium may be a poor indicator of total body stores in the presence of hypoalbuminemia. Magnesium should be replaced until levels are in the upper limit of normal. The normal dietary intake is approximately 20 mEq/d and is excreted in both the feces and urine. The kidneys have a remarkable ability to conserve magnesium, with renal excretion <1 mEq/d during magnesium deficiency.

Hypermagnesemia

Hypermagnesemia is rare but can be seen with severe renal insufficiency and parallel changes in potassium excretion. Magnesium-containing antacids and laxatives can produce toxic levels in patients with renal failure. Excess intake in conjunction with TPN, or rarely massive trauma, thermal injury, and severe acidosis, may be associated with symptomatic hypermagnesemia. Clinical examination (see Table 3-6) may find nausea and vomiting; neuromuscular dysfunction with weakness, lethargy, and hyporeflexia; and impaired cardiac conduction leading to hypotension and arrest. ECG changes are similar to those seen with hyperkalemia and include increased PR interval, widened QRS complex, and elevated T waves.

Hypomagnesemia

Magnesium depletion is a common problem in hospitalized patients, particularly in the critically ill.[16] The kidney is primarily responsible for magnesium homeostasis through regulation by calcium/magnesium receptors on the renal tubular cells that respond to serum magnesium concentrations.[17] Hypomagnesemia may result from alterations of intake, renal excretion, and pathologic losses. Poor intake may occur in cases of starvation, alcoholism, prolonged IV fluid therapy, and TPN with inadequate supplementation of magnesium. Losses are seen in cases of increased renal excretion from alcohol abuse, diuretic use, administration of amphotericin B, and primary aldosteronism, as well as GI losses from diarrhea, malabsorption, and acute pancreatitis. The magnesium ion is essential for proper function of many enzyme systems. Depletion is characterized by neuromuscular and central nervous system hyperactivity. Symptoms are similar to those of calcium deficiency, including hyperactive reflexes, muscle tremors, tetany, and positive Chvostek's and Trousseau's signs (see Table 3-6). Severe deficiencies can lead to delirium and seizures. A number of ECG changes also can occur and include prolonged QT and PR intervals, ST-segment depression, flattening or inversion of P waves, torsades de pointes, and arrhythmias.
Hypomagnesemia is important not only because of its direct effects on the nervous system but also because it can produce hypocalcemia and lead to persistent hypokalemia. When hypokalemia or hypocalcemia coexists with hypomagnesemia, magnesium should be aggressively replaced to assist in restoring potassium or calcium homeostasis.

Acid-Base Balance

ACID-BASE HOMEOSTASIS

The pH of body fluids is maintained within a narrow range despite the ability of the kidneys to generate large amounts of HCO_3^- and the normal large acid load produced as a by-product of metabolism. This endogenous acid load is efficiently neutralized by buffer systems and ultimately excreted by the lungs and kidneys.

Important buffers include intracellular proteins and phosphates and the extracellular bicarbonate–carbonic acid system. Compensation for acid-base derangements can be by respiratory mechanisms (for metabolic derangements) or metabolic mechanisms (for respiratory derangements). Changes in ventilation in response to metabolic abnormalities are mediated by hydrogen-sensitive chemoreceptors found in the carotid body and brain stem. Acidosis stimulates the chemoreceptors to increase ventilation, whereas alkalosis decreases the activity of the chemoreceptors and thus decreases ventilation. The kidneys provide compensation for respiratory abnormalities by either increasing or decreasing bicarbonate reabsorption in response to respiratory acidosis or alkalosis, respectively. Unlike the prompt change in ventilation that occurs with metabolic abnormalities, the compensatory response in the kidneys to respiratory abnormalities is delayed. Significant compensation may not begin for 6 hours and then may continue for several days. Because of this delayed compensatory response, respiratory acid-base derangements before renal compensation are classified as acute, whereas those persisting after renal compensation are categorized as chronic. The predicted compensatory changes in response to metabolic or respiratory derangements are listed in Table 3-7.[18] If the predicted change in pH is exceeded, then a mixed acid-base abnormality may be present (Table 3-8).

Table 3-7 Predicted Changes in Acid-Base Disorders

Disorder	Predicted Change
Metabolic	
Metabolic acidosis	$Pco_2 = 1.5 \times HCO_3^- + 8$
Metabolic alkalosis	$Pco_2 = 0.7 \times HCO_3^- + 21$
Respiratory	
Acute respiratory acidosis	Δ pH = $(Pco_2 - 40) \times 0.008$
Chronic respiratory acidosis	Δ pH = $(Pco_2 - 40) \times 0.003$
Acute respiratory alkalosis	Δ pH = $(40 - Pco_2) \times 0.008$
Chronic respiratory alkalosis	Δ pH = $(40 - Pco_2) \times 0.017$

Pco_2 = partial pressure of carbon dioxide.

Table 3-8 Respiratory and Metabolic Components of Acid-Base Disorders

		Acute Uncompensated		Chronic (Partially Compensated)

Type of Acid-Base Disorder	pH	Pco_2 (Respiratory Component)	Plasma HCO_3^{-a} (Metabolic Component)	pH	Pco_2 (Respiratory Component)	Plasma HCO_3^{-a} (Metabolic Component)
Respiratory acidosis	↓↓	↑↑	N	↓	↑↑	↑
Respiratory alkalosis	↑↑	↓↓	N	↑	↓↓	↓
Metabolic acidosis	↓↓	N	↓↓	↓	↓	↓
Metabolic alkalosis	↑↑	N	↑↑	↑	↑?	↑

[a]Measured as standard bicarbonate, whole blood buffer base, CO_2 content, or CO_2 combining power. The *base excess value* is positive when the standard bicarbonate is above normal and negative when the standard bicarbonate is below normal.

N = normal; Pco_2 = partial pressure of carbon dioxide.

METABOLIC DERANGEMENTS

Metabolic Acidosis

Metabolic acidosis results from an increased intake of acids, an increased generation of acids, or an increased loss of bicarbonate (Table 3-9). The body responds by several mechanisms, including producing buffers (extracellular bicarbonate and intracellular buffers from bone and muscle), increasing ventilation (Kussmaul's respirations), and increasing renal reabsorption and generation of bicarbonate. The kidney also will increase secretion of hydrogen and thus increase urinary excretion of NH_4^+ ($H^+ + NH_3^+ = NH_4^+$). Evaluation of a patient with a low serum bicarbonate level and metabolic acidosis includes determination of the anion gap (AG), an index of unmeasured anions.

Table 3-9 Etiology of Metabolic Acidosis
Increased Anion Gap Metabolic Acidosis
Exogenous acid ingestion
Ethylene glycol
Salicylate
Methanol
Endogenous acid production
Ketoacidosis
Lactic acidosis
Renal insufficiency
Normal Anion Gap
Acid administration (HCl)
Loss of bicarbonate
GI losses (diarrhea, fistulas)
Ureterosigmoidoscopy
Renal tubular acidosis

Carbonic anhydrase inhibitor

$$AG = (Na) - (Cl + HCO_3)$$

The normal AG is <12 mmol/L and is due primarily to the albumin effect, so that the estimated AG must be adjusted for albumin (hypoalbuminemia reduces the AG).[19]

$$\text{Corrected AG} = \text{actual AG} - [2.5(4.5 - \text{albumin})]$$

Metabolic acidosis with an increased AG occurs either from ingestion of exogenous acid such as from ethylene glycol, salicylates, or methanol, or from increased endogenous acid production of the following:

- β-Hydroxybutyrate and acetoacetate in ketoacidosis
- Lactate in lactic acidosis
- Organic acids in renal insufficiency

A common cause of severe metabolic acidosis in surgical patients is lactic acidosis. In circulatory shock, lactate is produced in the presence of hypoxia from inadequate tissue perfusion. The treatment is to restore perfusion with volume resuscitation rather than to attempt to correct the abnormality with exogenous bicarbonate. With adequate perfusion, the lactic acid is rapidly metabolized by the liver and the pH level returns to normal. The administration of bicarbonate for the treatment of metabolic acidosis is controversial, because it is not clear that acidosis is deleterious.[20] The overzealous administration of bicarbonate can lead to metabolic alkalosis, which shifts the oxyhemoglobin dissociation curve to the left; this interferes with oxygen unloading at the tissue level and can be associated with arrhythmias that are difficult to treat. An additional disadvantage is that sodium bicarbonate actually can exacerbate intracellular acidosis. Administered bicarbonate can combine with the excess hydrogen ions to form carbonic acid; this is then converted to CO_2 and water, which thus raises the partial pressure of CO_2 (PCO_2). This hypercarbia could compound ventilation abnormalities in patients with underlying acute respiratory distress syndrome. This CO_2 can diffuse into cells, but bicarbonate remains extracellular, which thus worsens intracellular acidosis. Clinically, lactate levels may not be useful in directing resuscitation, although lactate levels may be higher in nonsurvivors of serious injury.[21]

Metabolic acidosis with a normal AG results either from exogenous acid administration (HCl or NH_4^+), from loss of bicarbonate due to GI disorders such as diarrhea and fistulas or ureterosigmoidostomy, or from renal losses. In these settings, the bicarbonate loss is accompanied by a gain of chloride; thus, the AG remains unchanged. To determine if the loss of bicarbonate has a renal cause, the urinary [NH_4^+] can be measured. A low urinary [NH_4^+] in the face of hyperchloremic acidosis would indicate that the kidney is the site of loss, and evaluation for renal tubular acidosis should be undertaken. Proximal renal tubular acidosis results from decreased tubular reabsorption of HCO_3^-, whereas distal renal tubular acidosis results from decreased acid excretion. The carbonic anhydrase inhibitor acetazolamide also causes bicarbonate loss from the kidneys.

Metabolic Alkalosis

Normal acid-base homeostasis prevents metabolic alkalosis from developing unless both an increase in bicarbonate generation and impaired renal excretion of bicarbonate occur (Table 3-10). Metabolic alkalosis results from the loss of fixed acids or the gain of bicarbonate and is worsened by potassium depletion. The majority of patients also will have hypokalemia, because extracellular potassium ions exchange with intracellular hydrogen ions and allow the hydrogen ions to buffer excess HCO_3^-. Hypochloremic, hypokalemic, and metabolic alkalosis can occur from isolated loss of gastric contents in infants with

pyloric stenosis or adults with duodenal ulcer disease. Unlike vomiting associated with an open pylorus, which involves a loss of gastric as well as pancreatic, biliary, and intestinal secretions, vomiting with an obstructed pylorus results only in the loss of gastric fluid, which is high in chloride and hydrogen, and therefore results in a hypochloremic alkalosis. Initially the urinary bicarbonate level is high in compensation for the alkalosis. Hydrogen ion reabsorption also ensues, with an accompanied potassium ion excretion. In response to the associated volume deficit, aldosterone-mediated sodium reabsorption increases potassium excretion. The resulting hypokalemia leads to the excretion of hydrogen ions in the face of alkalosis, a paradoxic aciduria. Treatment includes replacement of the volume deficit with isotonic saline and then potassium replacement once adequate urine output is achieved.

Table 3-10 Etiology of Metabolic Alkalosis
Increased bicarbonate generation
1. Chloride losing (urinary chloride >20 mEq/L)
Mineralocorticoid excess
Profound potassium depletion
2. Chloride sparing (urinary chloride <20 mEq/L)
Loss from gastric secretions (emesis or nasogastric suction)
Diuretics
3. Excess administration of alkali
Acetate in parenteral nutrition
Citrate in blood transfusions
Antacids
Bicarbonate
Milk-alkali syndrome
Impaired bicarbonate excretion
1. Decreased glomerular filtration
2. Increased bicarbonate reabsorption (hypercarbia or potassium depletion)

RESPIRATORY DERANGEMENTS

Under normal circumstances blood P_{CO_2} is tightly maintained by alveolar ventilation, controlled by the respiratory centers in the pons and medulla oblongata.

Respiratory Acidosis

Respiratory acidosis is associated with the retention of CO_2 secondary to decreased alveolar ventilation. The principal causes are listed in Table 3-11. Because compensation is primarily a renal mechanism, it is a delayed response. Treatment of acute respiratory acidosis is directed at the underlying cause. Measures to ensure adequate ventilation are also initiated. This may entail patient-initiated volume expansion using noninvasive bilevel positive airway pressure or may require endotracheal intubation to increase minute ventilation. In the chronic form of respiratory acidosis, the partial pressure of arterial CO_2 remains elevated and the bicarbonate concentration rises slowly as renal compensation occurs.

Table 3-11 Etiology of Respiratory Acidosis: Hypoventilation

Narcotics
Central nervous system injury
Pulmonary: significant
Secretions
Atelectasis
Mucus plug
Pneumonia
Pleural effusion
Pain from abdominal or thoracic injuries or incisions
Limited diaphragmatic excursion from intra-abdominal pathology
Abdominal distention
Abdominal compartment syndrome
Ascites

Respiratory Alkalosis

In the surgical patient, most cases of respiratory alkalosis are acute and secondary to alveolar hyperventilation. Causes include pain, anxiety, and neurologic disorders, including central nervous system injury and assisted ventilation. Drugs such as salicylates, fever, gram-negative bacteremia, thyrotoxicosis, and hypoxemia are other possibilities. Acute hypocapnia can cause an uptake of potassium and phosphate into cells and increased binding of calcium to albumin, leading to symptomatic hypokalemia, hypophosphatemia, and hypocalcemia with subsequent arrhythmias, paresthesias, muscle cramps, and seizures. Treatment should be directed at the underlying cause, but direct treatment of the hyperventilation using controlled ventilation may also be required.

FLUID AND ELECTROLYTE THERAPY

Parenteral Solutions

A number of commercially available electrolyte solutions are available for parenteral administration. The most commonly used solutions are listed in Table 3-12. The type of fluid administered depends on the patient's volume status and the type of concentration or compositional abnormality present. Both lactated Ringer's solution and normal saline are considered isotonic and are useful in replacing GI losses and correcting extracellular volume deficits. Lactated Ringer's is slightly hypotonic in that it contains 130 mEq of lactate. Lactate is used rather than bicarbonate because it is more stable in IV fluids during storage. It is converted into bicarbonate by the liver after infusion, even in the face of hemorrhagic shock. Evidence has suggested that resuscitation using lactated Ringer's may be deleterious because it activates the inflammatory response and induces apoptosis. The component that has been implicated is the D isomer of lactate, which unlike the L isomer is not a normal intermediary in mammalian metabolism.[22] However, subsequent in vivo studies showed significantly lower levels of apoptosis in lung and liver tissue after resuscitation with any of the various Ringer's formulations.[23]

Table 3-12 Electrolyte Solutions for Parenteral Administration

	Electrolyte Composition (mEq/L)						
Solution	**Na**	**CL**	**K**	**HCO_3^-**	**Ca**	**Mg**	**mOsm**

Extracellular fluid	142	103	4	27	5	3	280–310
Lactated Ringer's	130	109	4	28	3		273
0.9% Sodium chloride	154	154					308
D_5 0.45% Sodium chloride	77	77					407
D5W							253
3% Sodium chloride	513	513					1026

D_5 = 5% dextrose; D5W = 5% dextrose in water.

Sodium chloride is mildly hypertonic, containing 154 mEq of sodium that is balanced by 154 mEq of chloride. The high chloride concentration imposes a significant chloride load on the kidneys and may lead to a hyperchloremic metabolic acidosis. Sodium chloride is an ideal solution, however, for correcting volume deficits associated with hyponatremia, hypochloremia, and metabolic alkalosis.

The less concentrated sodium solutions, such as 0.45% sodium chloride, are useful for replacement of ongoing GI losses as well as for maintenance fluid therapy in the postoperative period. This solution provides sufficient free water for insensible losses and enough sodium to aid the kidneys in adjustment of serum sodium levels. The addition of 5% dextrose (50 g of dextrose per liter) supplies 200 kcal/L, and dextrose is always added to solutions containing <0.45% sodium chloride to maintain osmolality and thus prevent the lysis of red blood cells that may occur with rapid infusion of hypotonic fluids. The addition of potassium is useful once adequate renal function and urine output are established.

Alternative Resuscitative Fluids

A number of alternative solutions for volume expansion and resuscitation are available (Table 3-13).[24] Hypertonic saline solutions (3.5% and 5%) are used for correction of severe sodium deficits and are discussed elsewhere in this chapter. Hypertonic saline (7.5%) has been used as a treatment modality in patients with closed head injuries. It has been shown to increase cerebral perfusion and decrease intracranial pressure, thus decreasing brain edema.[25] However, there also have been concerns of increased bleeding, because hypertonic saline is an arteriolar vasodilator. A meta-analysis of the results of prospective randomized controlled trials in trauma patients suggests that hypertonic saline may be no better than standard-of-care isotonic saline.[26] In subgroup analysis, however, patients with shock and concomitant closed head injury did demonstrate benefit.

Table 3-13 Alternative Resuscitative Fluids

Solution	Molecular Weight	Osmolality (mOsm/L)	Sodium (mEq/L)
Hypertonic saline (7.5%)	—	2565	1283
Albumin 5%	70,000	300	130–160
Albumin 25%	70,000	1500	130–160
Dextran 40	40,000	308	154
Dextran 70	70,000	308	154
Hetastarch	450,000	310	154
Hextend	670,000	307	143
Gelofusine	30,000	NA	154

NA = not available.

Colloids also are used in surgical patients, and their effectiveness as volume expanders compared with isotonic crystalloids has long been debated. Due to their molecular weight, they are confined to the intravascular space, and their infusion results in more efficient transient plasma volume expansion. However, under conditions of severe hemorrhagic shock, capillary membrane permeability increases; this permits colloids to enter the interstitial space, which can worsen edema and impair tissue oxygenation. The theory that these high molecular weight agents "plug" capillary leaks which occur during neutrophil-mediated organ injury has not been confirmed.[27,28] Four major types of colloids are available—albumin, dextrans, hetastarch, and gelatins—that are described by their molecular weight and size in Table 3-13. Colloid solutions with smaller particles and lower molecular weights exert a greater oncotic effect but are retained within the circulation for a shorter period of time than larger and higher molecular weight colloids.

Albumin (molecular weight 70,000) is prepared from heat-sterilized pooled human plasma. It is typically available as either a 5% solution (osmolality of 300 mOsm/L) or 25% solution (osmolality of 1500 mOsm/L). Because it is a derivative of blood, it can be associated with allergic reactions. Albumin has been shown to induce renal failure and impair pulmonary function when used for resuscitation in hemorrhagic shock.[29]

Dextrans are glucose polymers produced by bacteria grown on sucrose media and are available as either 40,000 or 70,000 molecular weight solutions. They lead to initial volume expansion due to their osmotic effect but are associated with alterations in blood viscosity. Thus dextrans are used primarily to lower blood viscosity rather than as volume expanders. Dextrans have been used, in association with hypertonic saline, to help maintain intravascular volume.

Hydroxyethyl starch solutions are another group of alternative plasma expanders and volume replacement solutions. Hetastarches are produced by the hydrolysis of insoluble amylopectin, followed by a varying number of substitutions of hydroxyl groups for carbon groups on the glucose molecules. The molecular weights can range from 1000 to 3,000,000. The high molecular weight hydroxyethyl starch hetastarch, which comes as a 6% solution, is the only hydroxyethyl starch approved for use in the United States. Administration of hetastarch can cause hemostatic derangements related to decreases in von Willebrand's factor and factor VIII:c, and its use has been associated with postoperative bleeding in cardiac and neurosurgery patients.[30,31] Hetastarch also can induce renal dysfunction in patients with septic shock and in recipients of kidneys procured from brain-dead donors.[32,33] Currently, hetastarch has a limited role in massive resuscitation because of the associated coagulopathy and hyperchloremic acidosis (due to its high chloride content). Hextend is a modified, balanced, high molecular weight hydroxyethyl starch that is suspended in a lactate-buffered solution, rather than in saline. A phase III clinical study comparing Hextend to a similar 6% hydroxyethyl starch in patients undergoing major abdominal surgery demonstrated no adverse effects on coagulation with Hextend other than the known effects of hemodilution.[34] Hextend has not been tested for use in massive resuscitation, and not all clinical studies show consistent results.[35]

Gelatins are the fourth group of colloids and are produced from bovine collagen. The two major types are urea-linked gelatin and succinylated gelatin (modified fluid gelatin, Gelofusine). Gelofusine has been used abroad with mixed results.[36] Like many other artificial plasma volume expanders, it has been shown to impair whole blood coagulation time in human volunteers.[37]

Correction of Life-Threatening Electrolyte Abnormalities[38]

SODIUM

Hypernatremia

Treatment of hypernatremia usually consists of treatment of the associated water deficit. In hypovolemic patients, volume should be restored with normal saline before the concentration abnormality is addressed. Once adequate volume has been achieved, the water deficit is replaced using a hypotonic fluid such as 5% dextrose, 5% dextrose in $^1/_4$ normal saline, or enterally administered water. The formula used to estimate the amount of water required to correct hypernatremia is as follows:

$$\text{Water deficit (L)} = \frac{\text{serum sodium} - 140}{140} \times \text{TBW}$$

Estimate TBW as 50% of lean body mass in men and 40% in women

The rate of fluid administration should be titrated to achieve a decrease in serum sodium concentration of no more than 1 mEq/h and 12 mEq/d for the treatment of acute symptomatic hypernatremia. Even slower correction should be undertaken for chronic hypernatremia (0.7 mEq/h), because overly rapid correction can lead to cerebral edema and herniation. The type of fluid used depends on the severity and ease of correction. Oral or enteral replacement is acceptable in most cases, or IV replacement with half- or quarter-normal saline can be used. Caution also should be exercised when using 5% dextrose in water to avoid overly rapid correction. Frequent neurologic evaluation as well as frequent evaluation of serum sodium levels also should be performed.

Hyponatremia

Most cases of hyponatremia can be treated by free water restriction and, if severe, the administration of sodium. In patients with normal renal function, symptomatic hyponatremia does not occur until the serum sodium level is ≤20 mEq/L. If neurologic symptoms are present, 3% normal saline should be used to increase the sodium by no more than 1 mEq/L per hour until the serum sodium level reaches 130 mEq/L or neurologic symptoms are improved. Correction of asymptomatic hyponatremia should increase the sodium level by no more than 0.5 mEq/L per hour to a maximum increase of 12 mEq/L per day, and even more slowly in chronic hyponatremia. The rapid correction of hyponatremia can lead to pontine myelinolysis,[39] with seizures, weakness, paresis, akinetic movements, and unresponsiveness, and may result in permanent brain damage and death. Magnetic resonance imaging may assist in the diagnosis.[40]

POTASSIUM

Hyperkalemia

Treatment options for symptomatic hyperkalemia are listed in Table 3-14. The goals of therapy include reducing the total body potassium, shifting potassium from the extracellular to the intracellular space, and protecting the cells from the effects of increased potassium. For all patients exogenous sources of potassium should be removed, including potassium supplementation in IV fluids and enteral and parenteral solutions. Potassium can be removed from the body using a cation-exchange resin such as Kayexalate that binds potassium in exchange for sodium. It can be administered either orally, in alert patients, or rectally. Immediate measures also should include attempts to shift potassium intracellularly with glucose and bicarbonate infusion. Nebulized albuterol (10 to 20 mg) may also be used. Use of glucose alone will cause a rise in insulin secretion, but in the acutely ill this response may be blunted, and therefore both glucose and insulin may be necessary. Circulatory overload and hypernatremia may result from the administration of Kayexalate and bicarbonate, so care should be exercised when administering these agents to patients with fragile cardiac function. When ECG changes are present, calcium chloride or calcium gluconate (5 to 10 mL of 10% solution) should be administered immediately to counteract the myocardial

effects of hyperkalemia. Calcium infusion should be used cautiously in patients receiving digitalis, because digitalis toxicity may be precipitated. All of the aforementioned measures are temporary, lasting from 1 to approximately 4 hours. Dialysis should be considered in severe hyperkalemia when conservative measures fail.

Table 3-14 Treatment of Symptomatic Hyperkalemia
Potassium removal
Kayexalate
Oral administration is 15–30 g in 50–100 mL of 20% sorbitol
Rectal administration is 50 g in 200 mL of 20% sorbitol
Dialysis
Shift potassium
Glucose 1 ampule of D_{50} and regular insulin 5–10 units IV
Bicarbonate 1 ampule IV
Counteract cardiac effects
Calcium gluconate 5–10 mL of 10% solution

D_{50} = 50% dextrose.

Hypokalemia

Treatment for hypokalemia consists of potassium repletion, the rate of which is determined by the symptoms (Table 3-15). Oral repletion is adequate for mild, asymptomatic hypokalemia. If IV repletion is required, usually no more than 10 mEq/h is advisable in an unmonitored setting. This amount can be increased to 40 mEq/h when accompanied by continuous ECG monitoring, and even more in the case of imminent cardiac arrest from a malignant arrhythmia associated hypokalemia. Caution should be exercised when oliguria or impaired renal function is coexistent.

Table 3-15 Electrolyte Replacement Therapy Protocol
Potassium
Serum potassium level <4.0 mEq/L:
Asymptomatic, tolerating enteral nutrition: KCl 40 mEq per enteral access x 1 dose
Asymptomatic, not tolerating enteral nutrition: KCl 20 mEq IV q2h x 2 doses
Symptomatic: KCl 20 mEq IV q1h x 4 doses
Recheck potassium level 2 h after end of infusion; if <3.5 mEq/L and asymptomatic, replace as per above protocol
Magnesium
Magnesium level 1.0–1.8 mEq/L:
Magnesium sulfate 0.5 mEq/kg in normal saline 250 mL infused IV over 24 h x 3 d
Recheck magnesium level in 3 d
Magnesium level <1.0 mEq/L:
Magnesium sulfate 1 mEq/kg in normal saline 250 mL infused IV over 24 h x 1 d, then 0.5 mEq/kg in normal saline 250 mL infused IV over 24 h x 2 d
Recheck magnesium level in 3 d

If patient has gastric access and needs a bowel regimen:
Milk of magnesia 15 mL (approximately 49 mEq magnesium) q24h per gastric tube; hold for diarrhea
Calcium
Normalized calcium level <4.0 mg/dL:
With gastric access and tolerating enteral nutrition: Calcium carbonate suspension 1250 mg/5 mL q6h per gastric access; recheck ionized calcium level in 3 d
Without gastric access or not tolerating enteral nutrition: Calcium gluconate 2 g IV over 1 h x 1 dose; recheck ionized calcium level in 3 d
Phosphate
Phosphate level 1.0–2.5 mg/dL:
Tolerating enteral nutrition: Neutra-Phos 2 packets q6h per gastric tube or feeding tube
No enteral nutrition: $KPHO_4$ or $NaPO_4$ 0.15 mmol/kg IV over 6 h x 1 dose
Recheck phosphate level in 3 d
Phosphate level <1.0 mg/dL:
Tolerating enteral nutrition: $KPHO_4$ or $NaPO_4$ 0.25 mmol/kg over 6 h x 1 dose
Recheck phosphate level 4 h after end of infusion; if <2.5 mg/dL, begin Neutra-Phos 2 packets q6h
Not tolerating enteral nutrition: $KPHO_4$ or $NaPO_4$ 0.25 mmol/kg (LBW) over 6 h x 1 dose; recheck phosphate level 4 h after end of infusion; if <2.5 mg/dL, then $KPHO_4$ or $NaPO_4$ 0.15 mmol/kg (LBW) IV over 6 h x 1 dose

3 mmol $KPHO_4$ = 3 mmol Phos and 4.4 mEq K^+ = 1 mL

3 mmol $NaPO_4$ = 3 mmol Phos and 4 mEq Na^+ = 1 mL

Neutra-Phos 1 packet = 8 mmol Phos, 7 mEq K^+, 7 mEq Na^+

Use patient's lean body weight (LBW) in kilograms for all calculations.

Disregard protocol if patient has renal failure, is on dialysis, or has a creatinine clearance <30 mL/min.

CALCIUM

Hypercalcemia

Treatment is required when hypercalcemia is symptomatic, which usually occurs when the serum level exceeds 12 mg/dL. The critical level for serum calcium is 15 mg/dL, when symptoms noted earlier may rapidly progress to death. The initial treatment is aimed at repleting the associated volume deficit and then inducing a brisk diuresis with normal saline. Treatment of hypercalcemia associated with malignancies is discussed later in this chapter.

Hypocalcemia

Asymptomatic hypocalcemia can be treated with oral or IV calcium (see Table 3-15). Acute symptomatic hypocalcemia should be treated with IV 10% calcium gluconate to achieve a serum concentration of 7 to 9 mg/dL. Associated deficits in magnesium, potassium, and pH must also be corrected. Hypocalcemia will be refractory to treatment if coexisting hypomagnesemia is not corrected first. Routine calcium supplementation is no longer recommended in association with massive blood transfusions.[41]

PHOSPHORUS

Hyperphosphatemia

Phosphate binders such as sucralfate or aluminum-containing antacids can be used to lower serum phosphorus levels. Calcium acetate tablets also are useful when hypocalcemia is simultaneously present. Dialysis usually is reserved for patients with renal failure.

Hypophosphatemia

Depending on the level of depletion and tolerance to oral supplementation, a number of enteral and parenteral repletion strategies are effective for the treatment of hypophosphatemia (see Table 3-15).

MAGNESIUM

Hypermagnesemia

Treatment for hypermagnesemia consists of measures to eliminate exogenous sources of magnesium, correct concurrent volume deficits, and correct acidosis if present. To manage acute symptoms, calcium chloride (5 to 10 mL) should be administered to immediately antagonize the cardiovascular effects. If elevated levels or symptoms persist, hemodialysis may be necessary.

Hypomagnesemia

Correction of magnesium depletion can be oral if asymptomatic and mild. Otherwise, IV repletion is indicated and depends on severity (see Table 3-15) and clinical symptoms. For those with severe deficits (<1.0 mEq/L) or those who are symptomatic, 1 to 2 g of magnesium sulfate may be administered IV over 15 minutes. Under ECG monitoring, it may be given over 2 minutes if necessary to correct torsades de pointes (irregular ventricular rhythm). Caution should be taken when giving large amounts of magnesium, because magnesium toxicity may develop. The simultaneous administration of calcium gluconate will counteract the adverse side effects of a rapidly rising magnesium level and correct hypocalcemia, which is frequently associated with hypomagnesemia.

Preoperative Fluid Therapy

The administration of maintenance fluids should be all that is required in an otherwise healthy individual who may be under orders to receive nothing by mouth for some period before the time of surgery. This does not, however, include replenishment of a pre-existing deficit or ongoing fluid losses. The following is a frequently used formula for calculating the volume of maintenance fluids in the absence of pre-existing abnormalities:

For the first 0 to 10 kg	Give 100 mL/kg per day
For the next 10 to 20 kg	Give an additional 50 mL/kg per day
For weight >20 kg	Give an additional 20 mL/kg per day

For example, a 60-kg female would receive a total of 2100 mL of fluid daily: 1000 mL for the first 10 kg of body weight (10 kg x 100 mL/kg per day), 500 mL for the next 20 kg (10 kg x 50 mL/kg per day), and 80 mL for the last 40 kg (40 kg x 20 mL/kg per day).

An alternative approach is to replace the calculated daily water losses in urine, stool, and insensible loss with a hypotonic

saline solution rather than water alone, which allows the kidney some sodium excess to adjust for concentration. Although there should be no "routine" maintenance fluid orders, both of these methods would yield an appropriate choice of 5% dextrose in 0.45% sodium chloride at 100 mL/h as initial therapy, with potassium added for patients with normal renal function. However, many surgical patients have volume and/or electrolyte abnormalities associated with their surgical disease. Preoperative evaluation of a patient's volume status and pre-existing electrolyte abnormalities is an important part of overall preoperative assessment and care. Volume deficits should be considered in patients who have obvious GI losses, such as through emesis or diarrhea, as well as in patients with poor oral intake secondary to their disease. Less obvious are those fluid losses known as *third-space* or *nonfunctional* ECF losses that occur with GI obstruction, peritoneal or bowel inflammation, ascites, crush injuries, burns, and severe soft tissue infections such as necrotizing fasciitis. The diagnosis of an acute volume deficit is primarily clinical (see Table 3-2), although the physical signs may vary with the duration of the deficit. Cardiovascular signs of tachycardia and orthostasis predominate with acute volume loss, usually accompanied by oliguria and hemoconcentration. Acute volume deficits should be corrected as much as possible before the time of operation.

Once a volume deficit is diagnosed, prompt fluid replacement should be instituted, usually with an isotonic crystalloid, depending on the measured serum electrolyte values. Patients with cardiovascular signs of volume deficit should receive a bolus of 1 to 2 L of isotonic fluid followed by a continuous infusion. Close monitoring during this period is imperative. Resuscitation should be guided by the reversal of the signs of volume deficit, such as restoration of acceptable values for vital signs, maintenance of adequate urine output ($^{1}/_{2}$ to 1 mL/kg per hour in an adult), and correction of base deficit. Patients whose volume deficit is not corrected after this initial volume challenge and those with impaired renal function and the elderly should be considered for more intensive monitoring in an intensive care unit setting. In these patients, early invasive monitoring of central venous pressure or cardiac output may be necessary.

If symptomatic electrolyte abnormalities accompany volume deficit, the abnormality should be corrected to the point that the acute symptom is relieved before surgical intervention. For correction of severe hypernatremia associated with a volume deficit, an unsafe rapid fall in extracellular osmolarity from 5% dextrose infusion is avoided by slowly correcting the hypernatremia with 0.45% saline or even lactated Ringer's solution rather than 5% dextrose alone. This will safely and slowly correct the hypernatremia while also correcting the associated volume deficit.

Intraoperative Fluid Therapy

With the induction of anesthesia, compensatory mechanisms are lost, and hypotension will develop if volume deficits are not appropriately corrected before the time of surgery. Hemodynamic instability during anesthesia is best avoided by correcting known fluid losses, replacing ongoing losses, and providing adequate maintenance fluid therapy preoperatively. In addition to measured blood loss, major open abdominal surgeries are associated with continued extracellular losses in the form of bowel wall edema, peritoneal fluid, and the wound edema during surgery. Large soft tissue wounds, complex fractures with associated soft tissue injury, and burns are all associated with additional third-space losses that must be considered in the operating room. These represent distributional shifts, in that the functional volume of ECF is reduced but fluid is not externally lost from the body. These functional losses have been referred to as *parasitic losses, sequestration,* or *third-space edema,* because the lost volume no longer participates in the normal functions of the ECF.

Until the 1960s saline solutions were withheld during surgery. Administered saline was retained and was felt to be an inappropriate challenge to a physiologic response of intraoperative salt intolerance. Basic and clinical research began to change this concept,[42,43] eventually leading to the current concept that saline administration is necessary to restore the

obligate ECF losses noted earlier. Although no accurate formula can predict intraoperative fluid needs, replacement of ECF during surgery often requires 500 to 1000 mL/hr of a balanced salt solution to support homeostasis. The addition of albumin or other colloid-containing solutions to intraoperative fluid therapy is not necessary. Manipulation of colloid oncotic forces by albumin infusion during major vascular surgery showed no advantage in supporting cardiac function or avoiding the accumulation of extravascular lung water.[44]

Postoperative Fluid Therapy

Postoperative fluid therapy should be based on the patient's current estimated volume status and projected ongoing fluid losses. Any deficits from either preoperative or intraoperative losses should be corrected and ongoing requirements should be included along with maintenance fluids. Third-space losses, although difficult to measure, should be included in fluid replacement strategies. In the initial postoperative period, an isotonic solution should be administered. The adequacy of resuscitation should be guided by the restoration of acceptable values for vital signs and urine output and, in more complicated cases, by the correction of base deficit or lactate. If uncertainty exists, particularly in patients with renal or cardiac dysfunction, a central venous catheter or Swan-Ganz catheter may be inserted to help guide fluid therapy. After the initial 24 to 48 hours, fluids can be changed to 5% dextrose in 0.45% saline in patients unable to tolerate enteral nutrition. If normal renal function and adequate urine output are present, potassium may be added to the IV fluids. Daily fluid orders should begin with assessment of the patient's volume status and assessment of electrolyte abnormalities. There is rarely a need to check electrolyte levels in the first few days of an uncomplicated postoperative course. However, postoperative diuresis may require attention to replacement of urinary potassium loss. All measured losses, including losses through vomiting, nasogastric suctioning, drains, and urine output, as well as insensible losses, are replaced with the appropriate parenteral solutions as previously reviewed.

Special Considerations for the Postoperative Patient

Volume excess is a common disorder in the postoperative period. The administration of isotonic fluids in excess of actual needs may result in excess volume expansion. This may be due to the overestimation of third-space losses or to ongoing GI losses that are difficult to measure accurately. The earliest sign of volume overload is weight gain. The average postoperative patient who is not receiving nutritional support should lose approximately 0.25 to 0.5 lb/d (0.11 to 0.23 kg/d) from catabolism. Additional signs of volume excess may also be present as listed in Table 3-2. Peripheral edema may not necessarily be associated with volume overload, because overexpansion of total ECF may exist in association with a deficit in the circulating plasma volume.

Volume deficits also can be encountered in surgical patients if preoperative losses were not completely corrected, intraoperative losses were underestimated, or postoperative losses were greater than appreciated. The clinical manifestations are described in Table 3-2 and include tachycardia, orthostasis, and oliguria. Hemoconcentration also may be present. Treatment will depend on the amount and composition of fluid lost. In most cases of volume depletion, replacement with an isotonic fluid will be sufficient while alterations in concentration and composition are being evaluated.

ELECTROLYTE ABNORMALITIES IN SPECIFIC SURGICAL PATIENTS

Neurologic Patients

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur after head injury or surgery to the

central nervous system, but it also is seen in association with administration of drugs such as morphine, nonsteroidals, and oxytocin, and in a number of pulmonary and endocrine diseases, including hypothyroidism and glucocorticoid deficiency. Additionally, it can be seen in association with a number of malignancies, most often small cell cancer of the lung but also pancreatic carcinoma, thymoma, and Hodgkin's disease.[45] SIADH should be considered in patients who are euvolemic and hyponatremic with elevated urine sodium levels and urine osmolality. ADH secretion is considered inappropriate when it is not in response to osmotic or volume-related conditions. Correction of the underlying problem should be attempted when possible. In most cases, restriction of free water will improve the hyponatremia. The goal is to achieve net water balance while avoiding volume depletion that may compromise renal function. Furosemide also can be used to induce free water loss. If hyponatremia persists after fluid restriction, the addition of isotonic or hypertonic fluids may be effective. The administration of isotonic saline may sometimes worsen the problem if the urinary sodium concentration is higher than the infused sodium concentration. The use of loop diuretics may be helpful in this situation by preventing further urine concentration. In chronic SIADH, when long-term fluid restriction is difficult to maintain or is ineffective, demeclocycline and lithium can be used to induce free water loss.

DIABETES INSIPIDUS

Diabetes insipidus (DI) is a disorder of ADH stimulation and is manifested by dilute urine in the case of hypernatremia. Central DI results from a defect in ADH secretion, and nephrogenic DI from a defect in end-organ responsiveness to ADH. Central DI is frequently seen in association with pituitary surgery, closed head injury, and anoxic encephalopathy.[46] Nephrogenic DI occurs in association with hypokalemia, administration of radiocontrast dye, and use of certain drugs such as aminoglycosides and amphotericin B. In patients tolerating oral intake, volume status usually is normal because thirst stimulates increased intake. However, volume depletion can occur rapidly in patients incapable of oral intake. The diagnosis can be confirmed by documenting a paradoxical increase in urine osmolality in response to a period of water deprivation. In mild cases, free water replacement may be adequate therapy. In more severe cases, vasopressin can be added. The usual dosage of vasopressin is 5 U SC every 6 to 8 hours. However, serum electrolytes and osmolality should be monitored to avoid excess vasopressin administration with resulting iatrogenic SIADH.

CEREBRAL SALT WASHING

Cerebral salt wasting is a diagnosis of exclusion that occurs in patients with a cerebral lesion and renal wasting of sodium and chloride with no other identifiable cause.[47] Natriuresis in a patient with a contracted extracellular volume should prompt the possible diagnosis of cerebral salt wasting. Hyponatremia is frequently observed but is nonspecific and occurs as a secondary event, which differentiates it from SIADH.

Malnourished Patients: Refeeding Syndrome

Refeeding syndrome is a potentially lethal condition that can occur with rapid and excessive feeding of patients with severe underlying malnutrition due to starvation, alcoholism, delayed nutritional support, anorexia nervosa, or massive weight loss in obese patients.[48] With refeeding, a shift in metabolism from fat to carbohydrate substrate stimulates insulin release, which results in the cellular uptake of electrolytes, particularly phosphate, magnesium, potassium, and calcium. However, severe hyperglycemia may result from blunted basal insulin secretion. The refeeding syndrome can be associated with enteral or parenteral refeeding, and symptoms from electrolyte abnormalities include cardiac arrhythmias, confusion, respiratory failure, and even death. To prevent the development of refeeding syndrome, underlying electrolyte and volume deficits should be corrected. Additionally, thiamine should be administered before the initiation of feeding. Caloric repletion should be instituted

slowly, at 20 kcal/kg per day, and should gradually increase over the first week.[49] Vital signs, fluid balance, and electrolytes should be closely monitored and any deficits corrected as they evolve.

Acute Renal Failure Patients

A number of fluid and electrolyte abnormalities are specific to patients with acute renal failure. With the onset of renal failure, an accurate assessment of volume status must be made. If prerenal azotemia is present, prompt correction of the underlying volume deficit is mandatory. Once acute tubular necrosis is established, measures should be taken to restrict daily fluid intake to match urine output and insensible and GI losses. Oliguric renal failure requires close monitoring of serum potassium levels. Measures to correct hyperkalemia as reviewed in Table 3-14 should be instituted early, including consideration of early hemodialysis. Hyponatremia is common in established renal failure as a result of the breakdown of proteins, carbohydrates, and fats, as well the administration of free water. Dialysis may be required for severe hyponatremia. Hypocalcemia, hypermagnesemia, and hyperphosphatemia also are associated with acute renal failure. Hypocalcemia should be verified by measuring ionized calcium, because many patients also are hypoalbuminemic. Phosphate binders can be used to control hyperphosphatemia, but dialysis may be required in more severe cases. Metabolic acidosis is commonly seen with renal failure, as the kidneys lose their ability to clear acid by-products. Bicarbonate can be useful, but dialysis often is needed. Although dialysis may be either intermittent or continuous, normalization of sodium, potassium, and bicarbonate levels may be best achieved using continuous therapy.[50]

Cancer Patients

Fluid and electrolyte abnormalities are common in patients with cancer. The causes may be common to all patient populations or may be specific to cancer patients and their treatment.[51] Hyponatremia is frequently hypovolemic due to renal loss of sodium caused by diuretics or salt-wasting nephropathy as seen with some chemotherapeutic agents such as cisplatin. Cerebral salt wasting also can occur in patients with intracerebral lesions. Normovolemic hyponatremia may occur in association with SIADH from cervical cancer, lymphoma, and leukemia, or from certain chemotherapeutic agents. Hypernatremia in cancer patients most often is due to poor oral intake or GI volume losses, which are common side effects of chemotherapy. Central DI also can lead to hypernatremia in patients with central nervous system lesions.

Hypokalemia can develop from GI losses associated with diarrhea caused by radiation enteritis or chemotherapy, or from tumors such as villous adenomas of the colon. Tumor lysis syndrome can precipitate severe hyperkalemia from massive tumor cell destruction.

Hypocalcemia can be seen after removal of a thyroid or parathyroid tumor or after a central neck dissection, which can damage the parathyroid glands. Hungry bone syndrome produces acute and profound hypocalcemia after parathyroid surgery for secondary or tertiary hyperparathyroidism because calcium is rapidly taken up by bones. Prostate and breast cancer can result in increased osteoblastic activity, which decreases serum calcium by increasing bone formation. Acute hypocalcemia also can occur with hyperphosphatemia, because phosphorus complexes with calcium. Hypomagnesemia is a side effect of ifosfamide and cisplatin therapy. Hypophosphatemia can be seen in hyperparathyroidism, due to decreased phosphorus reabsorption, and in oncogenic osteomalacia, which increases the urinary excretion of phosphorus. Other causes of hypophosphatemia in cancer patients include renal tubular dysfunction from multiple myeloma, Bence Jones proteins, and certain chemotherapeutic agents. Acute hypophosphatemia can occur as rapidly proliferating malignant cells take up phosphorus in acute leukemia. Tumor lysis syndrome or the use of bisphosphonates to treat hypercalcemia also can result in hyperphosphatemia.

Malignancy is the most common cause of hypercalcemia in hospitalized patients and is due to increased bone resorption or decreased renal excretion. Bone destruction occurs from bony metastasis as seen in breast or renal cell cancer but also can occur in multiple myeloma. With Hodgkin's and non-Hodgkin's lymphoma, hypercalcemia results from increased calcitriol formation, which increases both absorption of calcium from the GI tract and mobilization from bone. Humoral hypercalcemia of malignancy is a common cause of hypercalcemia in cancer patients. As in primary hyperparathyroidism, a parathyroid-related protein is secreted that binds to parathyroid receptors, stimulating calcium resorption from bone and decreasing renal excretion of calcium. The treatment of hypercalcemia of malignancy should begin with saline volume expansion, which will decrease renal reabsorption of calcium as the associated volume deficit is corrected. Once an adequate volume status has been achieved, a loop diuretic may be added. Unfortunately, these measures are only temporary, and additional treatment is often necessary. A variety of drugs are available with varying times of onset, duration of action, and side effects.[52] The bisphosphonates etidronate and pamidronate inhibit bone resorption and osteoclastic activity. They have a slow onset of action, but effects can last for 2 weeks. Calcitonin also is effective, inhibiting bone resorption and increasing renal excretion of calcium. It acts quickly, within 2 to 4 hours, but its use is limited by the development of tachyphylaxis. Corticosteroids may decrease tachyphylaxis in response to calcitonin and can be used alone to treat hypercalcemia. Gallium nitrates are potent inhibitors of bone resorption. They display a long duration of action but can cause nephrotoxicity. Mithramycin is an antibiotic that blocks osteoclastic activity, but it can be associated with liver, renal, and hematologic abnormalities, which limits its use to the treatment of Paget's disease of bone. For patients with severe, refractory hypercalcemia who are unable to tolerate volume expansion due to pulmonary edema or congestive heart failure, dialysis is an option.

Tumor lysis syndrome results when the release of intracellular metabolites overwhelms the kidneys' excretory capacity. This rapid release of uric acid, potassium, and phosphorus can result in marked hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, and acute renal failure. It is typically seen with poorly differentiated lymphomas and leukemias but also can occur with a number of solid tumor malignancies. Tumor lysis syndrome most commonly develops during treatment with chemotherapy or radiotherapy. Once it develops, volume expansion should be undertaken and any associated electrolyte abnormalities corrected. In this setting, hypocalcemia should not be treated unless it is symptomatic to avoid metastatic calcifications. Dialysis may be required for management of impaired renal function or correction of electrolyte abnormalities.

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KEY POINTS

1. Therapeutic anticoagulation preoperatively and postoperatively is becoming increasingly more common. The patient's risk of intraoperative and postoperative bleeding should guide the need for reversal of anticoagulation therapy preoperatively and the timing of its reinstatement postoperatively.

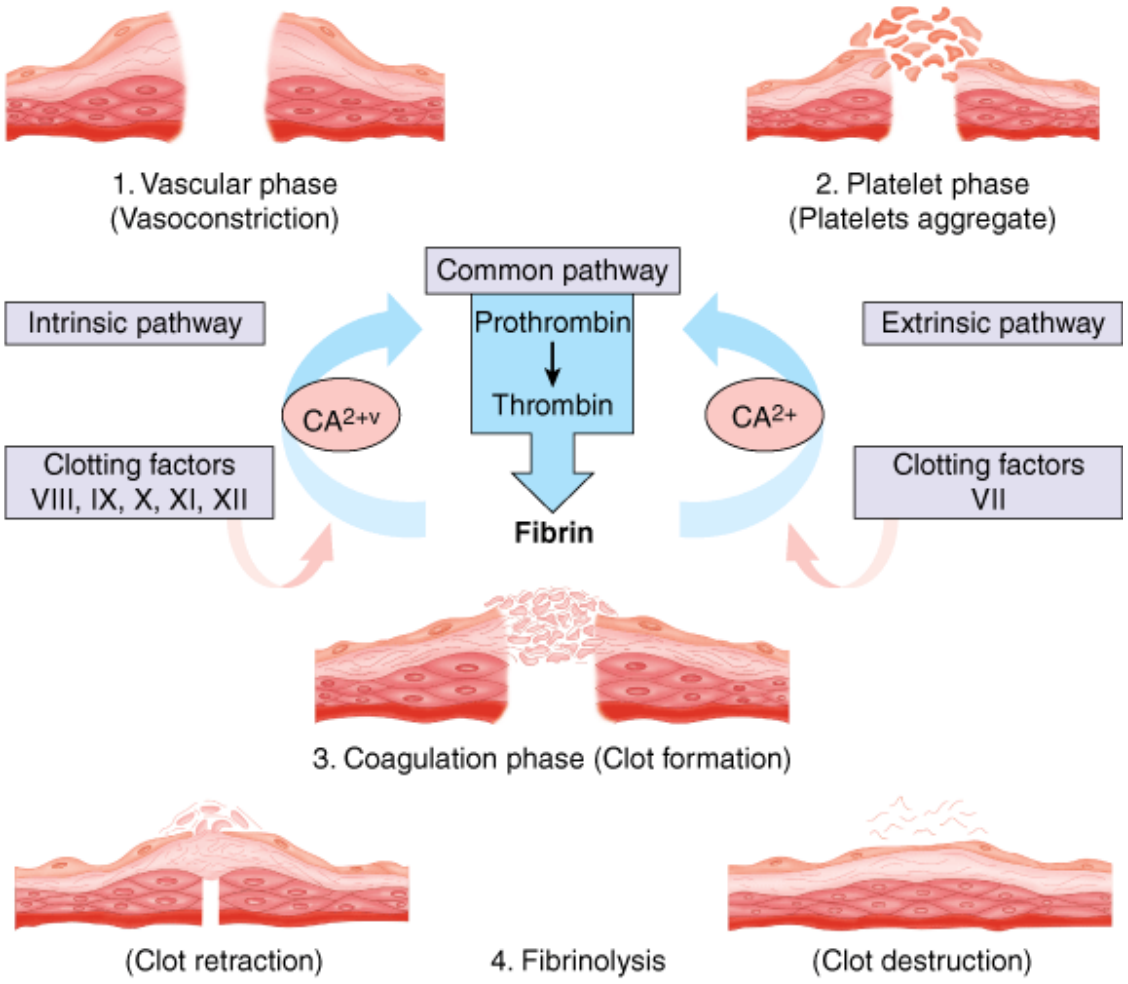
2. The need for massive transfusion should be anticipated and guidelines should be in place to provide the simultaneous administration of blood, plasma, and platelets.

3. The acute coagulopathy of trauma results from a combination of activation of protein C and fibrinolysis. It is distinct from disseminated intravascular coagulation, is present on arrival to the emergency department, and is associated with an increase in mortality.

BIOLOGY OF HEMOSTASIS

Hemostasis is a complex process whose function is to limit blood loss from an injured vessel. Four major physiologic events participate in the hemostatic process: vascular constriction, platelet plug formation, fibrin formation, and fibrinolysis. Although each tends to be activated in order, the four processes are interrelated so that there is a continuum and multiple reinforcements. The process is shown schematically in Fig. 4-1.

Fig. 4-1.



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Biology of hemostasis. The four physiologic processes that interrelate to limit blood loss from an injured vessel are illustrated and include vascular constriction, platelet plug formation, fibrin clot formation, and fibrinolysis.

Vascular Constriction

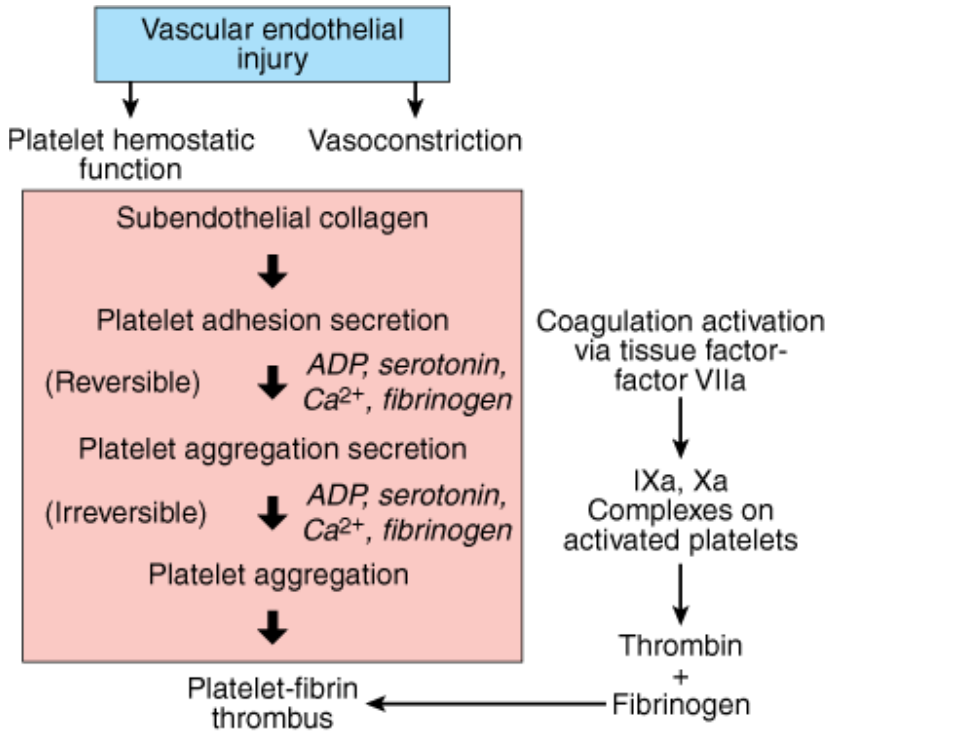
Vascular constriction is the initial response to vessel injury. It is more pronounced in vessels with medial smooth muscles and is dependent on local contraction of smooth muscle. Vasoconstriction is subsequently linked to platelet plug formation. Thromboxane A_2 (TXA_2) is produced locally at the site of injury via the release of arachidonic acid from platelet membranes and is a potent constrictor of smooth muscle. Similarly, endothelin synthesized by injured endothelium and serotonin (5-hydroxytryptamine) released during platelet aggregation are potent vasoconstrictors. Lastly, bradykinin and fibrinopeptides, which are involved in the coagulation scheme, also are capable of contracting vascular smooth muscle. The extent of vasoconstriction varies with the degree of vessel injury. A small artery with a lateral incision may remain open due to physical forces, whereas a similarly sized vessel that is completely transected may contract to the extent that bleeding ceases spontaneously.

Platelet Function

Platelets are anucleate fragments of megakaryocytes. The normal circulating number of platelets ranges between 150,000 and 400,000/μL. Up to 30% of circulating platelets may be sequestered in the spleen. If not consumed in a clotting reaction, platelets are normally removed by the spleen and have an average life span of 7 to 10 days.

Platelets play an integral role in hemostasis by forming a hemostatic plug and by contributing to thrombin formation (Fig. 4-2). Platelets do not normally adhere to each other or to the vessel wall but can form a plug that aids in cessation of bleeding when vascular disruption occurs. Injury to the intimal layer in the vascular wall exposes subendothelial collagen to which platelets adhere. This process requires von Willebrand's factor (vWF), a protein in the subendothelium that is lacking in patients with von Willebrand's disease. The vWF binds to glycoprotein I/IX/V on the platelet membrane. After adhesion, platelets initiate a release reaction that recruits other platelets from the circulating blood to seal the disrupted vessel. Up to this point, this process is known as *primary hemostasis.* Platelet aggregation is reversible and is not associated with secretion. Additionally, heparin does not interfere with this reaction, and thus hemostasis can occur in the heparinized patient. Adenosine diphosphate (ADP) and serotonin are the principal mediators in platelet aggregation.

Fig. 4-2.



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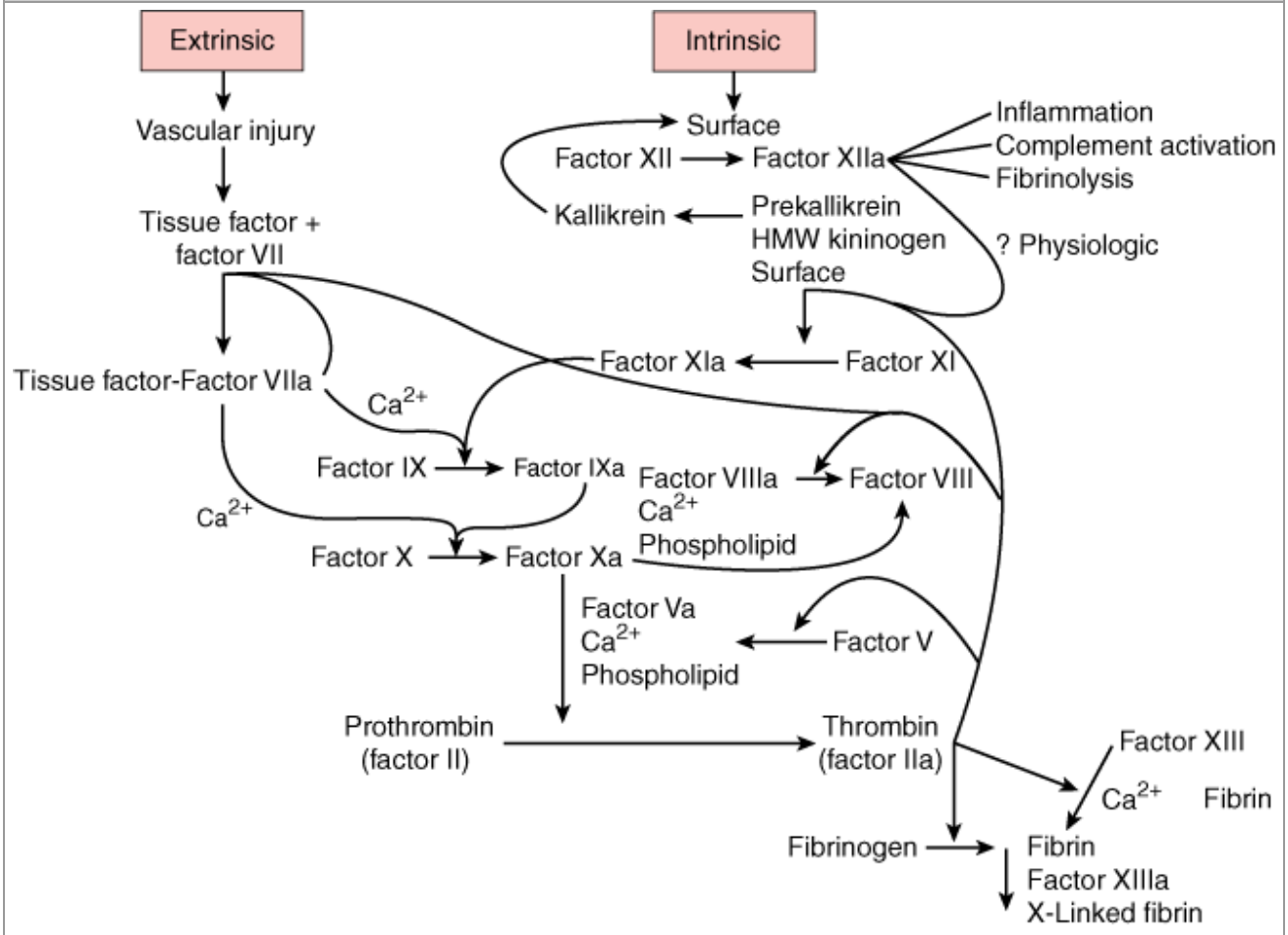
Schematic of platelet activation and thrombus function. ADP = adenosine diphosphate.

Arachidonic acid released from the platelet membranes is converted by COX to prostaglandin G_2 (PGG_2) and then to prostaglandin H_2 (PGH_2), which, in turn, is converted to TXA_2. TXA_2 has potent vasoconstriction and platelet aggregation effects. Arachidonic acid may also be shuttled to adjacent endothelial cells and converted to prostacyclin (PGI2), which is a vasodilator and acts to inhibit platelet aggregation. Platelet COX is irreversibly inhibited by aspirin and reversibly blocked by NSAIDs but is not affected by COX-2 inhibitors.

In the second wave of platelet aggregation, a release reaction occurs in which several substances, including ADP, Ca^{2+}, serotonin, TXA_2, and α-granule proteins are discharged. Fibrinogen is a required cofactor for this process, acting as a bridge for the glycoprotein IIb/IIIa receptor on the activated platelets. The release reaction results in compaction of the platelets

into a plug, a process that is no longer reversible. Thrombospondin, another protein secreted by the α-granule, stabilizes fibrinogen binding to the activated platelet surface and strengthens the platelet-platelet interactions. Platelet factor 4 (PF4) and β-thromboglobulin also are secreted during the release reaction. PF4 is a potent heparin antagonist. The second wave of platelet aggregation is inhibited by aspirin and NSAIDs, by cyclic adenosine monophosphate (cAMP), and by nitric oxide. As a consequence of the release reaction, alterations occur in the phospholipids of the platelet membrane that allow calcium and clotting factors to bind to the platelet surface, forming enzymatically active complexes. The altered lipoprotein surface (sometimes referred to as *platelet factor 3*) catalyzes reactions that are involved in the conversion of prothrombin (factor II) to thrombin (factor IIa) (Fig. 4-3) by activated factor X (Xa) in the presence of factor V and calcium, and it is involved in the reaction by which activated factor IX (IXa), factor VIII, and calcium activate factor X. Platelets may also play a role in the initial activation of factors XI and XII.

Fig. 4-3.



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Schematic of the coagulation system. HMW = high molecular weight.

Coagulation

Under physiologic conditions, hemostasis is accomplished by a complex sequence of interactions between platelets, the endothelium, and multiple circulating or membrane-bound coagulation factors. As shown in Fig. 4-3, the coagulation cascade typically has been depicted as two intersecting pathways. The intrinsic pathway begins with factor XII and through a cascade

of enzymatic reactions activates factors XI, IX, and VII in sequence. In the intrinsic pathway all of the components leading ultimately to fibrin clot formation are intrinsic to the circulating plasma and no surface is required to initiate the process. In contrast, the extrinsic pathway requires exposure of tissue factor on the surface of the injured vessel wall to initiate the arm of the cascade beginning with factor VII. The two arms of the coagulation cascade merge to a common pathway at factor X, and activation proceeds in sequence of factors II (prothrombin) and I (fibrinogen). Clot formation occurs after proteolytic conversion of fibrinogen to fibrin.

One convenient feature of depicting the coagulation cascade with two merging arms is that commonly used laboratory tests segregate abnormalities of clotting to one of the two arms (Table 4-1). An elevated activated partial thromboplastin time (aPTT) is associated with abnormal function of the intrinsic arm of the cascade, whereas an elevated prothrombin time (PT) is associated with the extrinsic arm. Vitamin K deficiency and warfarin use affect factors II, VII, IX, and X. Fibrinogen levels usually need to be <50 mg/dL to cause prolongation of the PT and aPTT. Recently, efforts have been made to present the coagulation cascade in a more physiologically relevant format. The primary physiologic pathway for coagulation is initiated by the exposure of subendothelial tissue factor when the luminal surface of a vessel is injured. Propagation of the clotting reaction then ensues with a sequence of four enzymatic reactions, each of which involves a proteolytic enzyme that generates the next enzyme in the cascade by cleavage of a proenzyme and a phospholipid surface, such as a platelet membrane. Each reaction requires a helper protein. Factor VIIa binds to tissue factor on exposure of the latter molecule through injury to the vascular wall. The tissue factor VIIa complex catalyzes the activation of factor X to factor Xa. The reaction takes place on the phospholipid surface of activated platelets. This complex is four orders of magnitude more active at converting factor X than is factor VIIa alone and also activates factor IX to factor IXa. Factor Xa, together with factor Va and Ca^{2+} and phospholipid, comprises the prothrombinase complex that converts prothrombin to thrombin. Thrombin has multiple functions in the clotting process, including conversion of fibrinogen to fibrin and activation of factors V, VII, VIII, XI, and XIII, as well as activation of platelets.

Table 4-1 Coagulation Factors Tested by the PT and the aPTT

PT	**aPTT**
VII	XII
X	High molecular weight kininogen
V	Prekallikrein
II (prothrombin)	XI
Fibrinogen	IX
	VIII
	X
	V
	II
	Fibrinogen

aPTT = activated partial thromboplastin time; PT = prothrombin time.

Factor VIIIa combines with factor IXa to form the intrinsic factor complex, which is responsible for the bulk of the conversion of factor X to Xa. This intrinsic complex (VIIIa-IXa) is approximately 50 times more effective at catalyzing factor X activation than is the extrinsic (tissue factor VIIa) complex and five to six orders of magnitude more effective than is factor IXa alone.

Factor Xa combines with factor Va, also on the activated platelet membrane surface, to form the prothrombinase complex, which is responsible for converting prothrombin to thrombin. As with the VIIIa-IXa complex, the prothrombinase is significantly more effective at catalyzing its substrate than is factor Xa alone. Once formed, thrombin leaves the membrane surface and converts fibrinogen by two cleavage steps into fibrin and two small peptides termed *fibrinopeptides A* and *B.* Removal of fibrinopeptide A permits end-to-end polymerization of the fibrin molecules, whereas cleavage of fibrinopeptide B allows side-to-side polymerization of the fibrin clot. This latter step is facilitated by thrombin-activatable fibrinolysis inhibitor (TAFI), which acts to stabilize the resultant clot.

The coagulation system is exquisitely regulated. In addition to clot formation that must occur to prevent bleeding at the time of vascular injury, two related processes must exist to prevent propagation of the clot beyond the site of injury. First, there is a feedback inhibition on the coagulation cascade, which deactivates the enzyme complexes leading to thrombin formation. Second, mechanisms of fibrinolysis allow for breakdown of the fibrin clot and subsequent repair of the injured vessel with deposition of connective tissue.

Tissue factor pathway inhibitor (TFPI) blocks the extrinsic tissue factor–VIIa complex, eliminating this catalyst's production of factors Xa and IXa. Antithrombin III effectively neutralizes all of the procoagulant serine proteases and only weakly inhibits the tissue factor–VIIa complex. The primary effect is to halt the production of thrombin. A third major mechanism of inhibition of thrombin formation is the protein C system. On its formation, thrombin binds to thrombomodulin and activates protein C to activated protein C (APC), which then forms a complex with its cofactor, protein S, on a phospholipid surface. The APC–protein S complex cleaves factors Va and VIIIa so they are no longer able to participate in the formation of tissue factor–VIIa or prothrombinase complexes. Of interest is an inherited form of factor V that carries a genetic mutation, called *factor V Leiden,* that is resistant to cleavage by APC and thus remains active (procoagulant). Patients with factor V Leiden are predisposed to venous thromboembolic events. As a result of the three systems described earlier, feedback inhibition of thrombin formation exists at upstream, intermediate, and downstream portions of the coagulation cascade to "turn off" thrombin formation once the procoagulant sequence is initially activated.

The same thrombin-thrombomodulin complex that leads to formation of APC also activates TAFI. In addition to stabilizing the clot, removal of the terminal lysine on the fibrin molecule by TAFI renders the clot more susceptible to lysis by plasmin. Degradation of fibrin clot is accomplished by plasmin, a serine protease derived from the proenzyme plasminogen. Plasmin formation occurs as a result of one of several plasminogen activators. Tissue plasminogen activator (tPA) is made by the endothelium and other cells of the vascular wall and is the main circulating form of this family of enzymes. The tPA is selective for fibrin-bound plasminogen so that endogenous fibrinolytic activity occurs predominately at the site of clot formation. The other major plasminogen activator, urokinase plasminogen activator (uPA), also produced by endothelial cells as well as by urothelium, is not selective for fibrin-bound plasminogen.

Because of the complex nature of hemostasis, potential interference in the process can occur at many levels. Platelet number or function can be insufficient to adequately support coagulation. Alternatively, abnormalities in the clotting factors may underlie an abnormality of hemostasis, either from an intrinsic defect in one of the factors or as the result of pharmacotherapy.

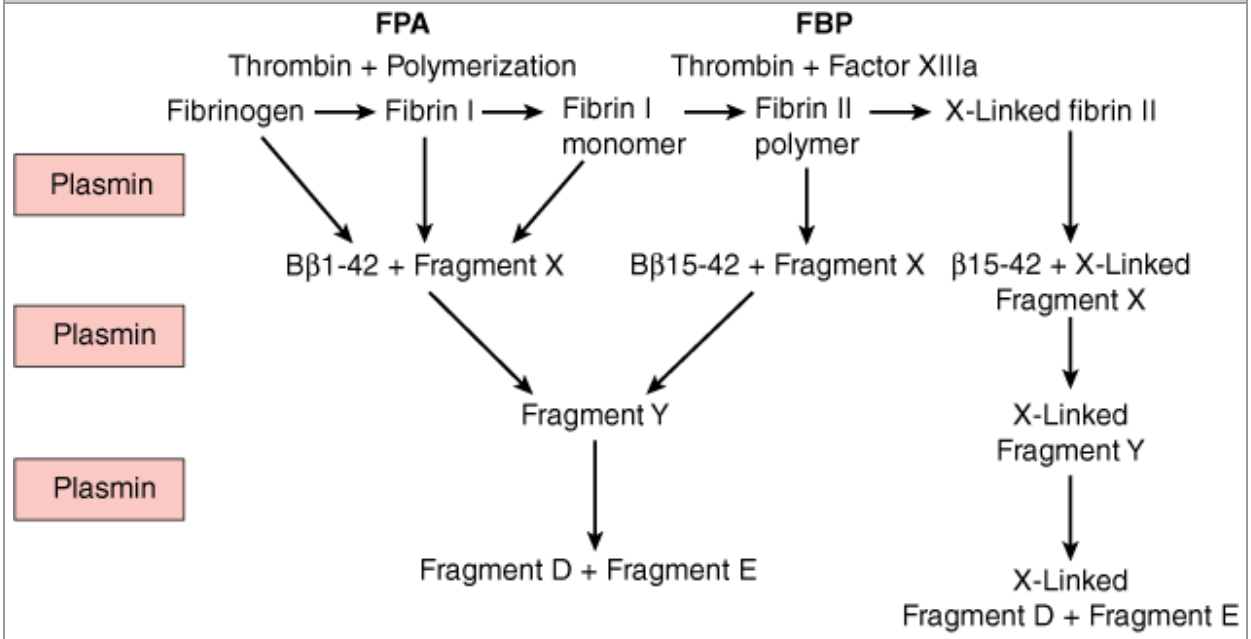
Fibrinolysis

During the wound-healing process, the fibrin clot undergoes clot lysis, which permits restoration of blood flow. The main enzyme, plasmin, degrades the fibrin mesh at various places, which leads to the production of circulating fragments that are

cleared by other proteases or by the kidney and liver. Fibrinolysis is initiated at the same time as the clotting mechanism under the influence of circulating kinases, tissue activators, and kallikrein, which are present in many organs, including the vascular endothelium. Fibrin is degraded by plasmin, a serine protease derived from the proenzyme plasminogen. Plasminogen may be converted by one of several plasminogen activators, including tPA and uPA. The tPA is synthesized by endothelial cells and released by the cells on thrombin stimulation as single-chain tPA. This is then cleaved by plasmin to form two-chain tPA. Bradykinin, a potent endothelium-dependent vasodilator cleaved from high molecular weight kininogen by kallikrein, causes contraction of nonvascular smooth muscle, increases vascular permeability, and enhances release of tPA. Both tPA and plasminogen bind to fibrin as it forms, and this trimolecular complex cleaves fibrin very efficiently. After plasmin is generated it cleaves fibrin, somewhat less efficiently, and it also will degrade fibrinogen. Fully cross-linked fibrin is also a relatively poor substrate for plasmin. Plasminogen activation may be initiated by activation of factor XII, which leads to the generation of kallikrein from prekallikrein and cleavage of high molecular weight kininogen by kallikrein.

Several characteristics of the enzymatic reactions ensure that fibrinolysis occurs at a controlled rate and preferentially at the site of clot formation. The tPA activates plasminogen more efficiently when it is bound to fibrin, so that plasmin is formed selectively on the clot. Plasmin is inhibited by α_2-antiplasmin, a protein that is cross-linked to fibrin by factor XIII, which helps to ensure that clot lysis does not occur too quickly. Any circulating plasmin also is inhibited by α_2-antiplasmin and circulating tPA or urokinase. Clot lysis yields fibrin degradation products, including E-nodules and D-dimers. The smaller fragments interfere with normal platelet aggregation and the larger fragments may be incorporated into the clot in lieu of normal fibrin monomers. This may result in an unstable clot. Presence of D-dimers in the circulation may be a marker of thrombosis or other conditions in which a significant activation of the fibrinolytic system is present. The final inhibitor for the fibrinolytic system is TAFI, a procarboxypeptidase that is activated by the thrombin-thrombomodulin complex. The active enzyme removes lysine residues from fibrin that are essential for binding plasminogen. The sequence of fibrin formation and its dissolution by plasmin is presented in schematic form in Fig. 4-4.

Fig. 4-4.



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Schematic of fibrin formation and dissolution. FBP = fibrin breakdown product; FPA = fibrinopeptide A.

CONGENITAL FACTOR DEFICIENCIES

Coagulation Factor Deficiencies

Inherited deficiencies of all of the coagulation factors are seen. However, the three most frequent are factor VIII deficiency (hemophilia A and von Willebrand's disease), factor IX deficiency (hemophilia B or Christmas disease), and factor XI deficiency. Hemophilia A and hemophilia B are inherited as sex-linked recessive disorders with males being affected almost exclusively. The clinical severity of hemophilia A and hemophilia B depends on the measurable level of factor VIII or factor IX in the patient's plasma. Plasma factor levels <1% of normal are considered severe disease, factor levels between 1 and 5% moderately severe, and levels of 5 to 30% mild disease. Patients with severe hemophilia have severe spontaneous bleeds, frequently into joints, which leads to crippling arthropathies. Intramuscular hematomas, retroperitoneal hematomas, and GI, genitourinary, and retropharyngeal bleeding are added clinical sequelae seen with severe disease. Intracranial bleeding and bleeding from the tongue or lingual frenulum may be life-threatening with severe disease. Patients with moderately severe hemophilia have less spontaneous bleeding but are likely to bleed severely after trauma or surgery. Those with mild disease do not bleed spontaneously and frequently have only minor bleeding after major trauma or surgery. Because platelet function is normal in individuals with hemophilia, patients may not bleed immediately after an injury or minor surgery because they have a normal response with platelet activation and formation of a platelet plug. At times, the diagnosis of hemophilia is not made in these patients until after their first minor procedure (e.g., tooth extraction or tonsillectomy).

Patients with hemophilia A or B are treated with factor VIII or factor IX concentrate, respectively. Recombinant factor VIII is strongly recommended for patients not treated previously and generally is recommended for patients who are both HIV and hepatitis C virus seronegative. For factor IX replacement, the preferred products are recombinant or high-purity factor IX, because of the risk of thrombosis with the intermediate factor IX (prothrombin complex) concentrates. Intermediate factor IX concentrates contain varying amounts of factors II, VII, and X and are reported to induce thrombosis when used in high doses. Furthermore, the cost of concentrates increases with the specific activity of factor VIII or factor IX.

Up to 20% of hemophiliac patients with factor VIII deficiency develop inhibitors. Some patients have low titers of the inhibitors and can be treated with higher dosages of factor VIII to achieve the desired plasma level. For patients with high titers of inhibitors alternate treatments must be used. These include porcine factor VIII, prothrombin complex concentrates, activated prothrombin complex concentrates, and recombinant factor VIIa. Factor VII is the most effective but must be given every 2 hours in situations with active bleeding and can be very expensive. Recombinant factor VIIa may be useful in factor IX–deficient patients with inhibitors. Additionally ε-aminocaproic acid, or Amicar, an inhibitor of fibrinolysis, is frequently a useful adjunct to factor VIII or IX or desmopressin acetate (DDAVP) in treatment of bleeding in patients with hemophilia. Excess ε-aminocaproic acid can lead to thrombosis, so the drug should be used with caution.

VON WILLEBRAND'S DISEASE

von Willebrand's disease (vWD), the most common congenital bleeding disorder, is characterized by low levels of factor VIII. It is an autosomal dominant disorder, and the primary defect is a low level of vWF, a large glycoprotein responsible for carrying factor VIII and platelet adhesion. The latter is important for normal platelet adhesion to exposed subendothelium and for aggregation under high-shear conditions. Patients with vWD have bleeding that is characteristic of platelet disorders (i.e., easy bruising and mucosal bleeding). Menorrhagia is common in women. vWD is classified into three types. Type I is a partial quantitative deficiency, type II is a qualitative defect, and type III is total deficiency. One treatment for vWD is an

intermediate-purity factor VIII concentrate such as Humate-P that contains vWF as well as factor VIII. The second treatment strategy is desmopressin acetate, which raises endogenous vWF levels by triggering release of the factor from endothelial cells. Desmopressin acetate is used once a day because time is needed for synthesis of new stores of vWF within the endothelial cells. Historically, patients with type I disease have been found to respond well to desmopressin acetate. Type II patients may respond, depending on the particular defect. Type III patients are usually unresponsive.

FACTOR XI DEFICIENCY

Factor XI deficiency, an autosomal recessive inherited condition sometimes referred to as *hemophilia C,* is more prevalent in the Ashkenazi Jewish population. Spontaneous bleeding is rare, but bleeding may occur after surgery, trauma, or invasive procedures. Patients with factor XI deficiency who present with bleeding or for whom surgery is planned and who are known to have bled previously are treated with fresh-frozen plasma (FFP). Each milliliter of plasma contains 1 unit of factor XI activity, so the volume needed depends on the patient's baseline level, the desired level, and the plasma volume. Recombinant factor VIIa treatment has been used successfully in children with severe factor XI deficiency who require major operations such as open heart surgery.[1] Desmopressin acetate also may be useful in the prevention of surgical bleeding in these patients.

DEFICIENCY OF FACTORS II (PROTHROMBIN), V, AND X

Inherited deficiencies of factors II, V, and X are rare. These deficiencies are inherited in an autosomal recessive pattern. Significant bleeding is encountered in homozygotes with <1% of normal activity. In any of these deficiencies, bleeding is treated with FFP. As with factor XI, FFP contains 1 unit of activity of each per milliliter. However, factor V activity is decreased because of its inherit instability. The half-life of prothrombin (factor II) is long (approximately 72 hours) and only approximately 25% of the normal level is needed for hemostasis. Prothrombin complex concentrates can be used to treat deficiencies of prothrombin or factor X. Daily infusions of FFP are used to treat bleeding in factor V deficiency, with a goal of 20 to 25% activity. Factor V deficiency may be coinherited with factor VIII deficiency. Treatment of bleeding in individuals with the combined deficiency requires factor VIII concentrate and FFP. Some patients with factor V deficiency also are lacking the factor V normally present in platelets and may need platelet transfusions as well as FFP.

FACTOR VII DEFICIENCY

Inherited factor VII deficiency is a rare autosomal recessive disorder. Clinical bleeding can widely vary and does not always correlate with the level of factor VII coagulant activity in plasma. Bleeding is uncommon unless the level is <3%. The most common bleeding manifestations are easy bruising and mucosal bleeding, particularly epistaxis or oral mucosal bleeding. Postoperative bleeding is also common, reported in 30% of surgical procedures in such patients.[2] Treatment is with FFP or recombinant factor VIIa. The half-life of recombinant factor VIIa is only approximately 2 hours, but excellent hemostasis can be achieved with frequent infusions. The half-life of factor VII in FFP is up to 4 hours.

FACTOR XIII DEFICIENCY

Congenital factor XIII deficiency, originally recognized by François Duckert in 1960, is a rare autosomal recessive disease usually associated with a severe bleeding diathesis.[3] The male:female ratio is 1:1. Although acquired factor XIII deficiency has been described in association with hepatic failure, inflammatory bowel disease, and myeloid leukemia, the only significant association with bleeding in children is the inherited deficiency.[4] Bleeding typically is delayed, because clots form normally but are susceptible to fibrinolysis. Umbilical stump bleeding is characteristic, and there is a high risk of intracranial

bleeding. Spontaneous abortion is usual in women with factor XIII deficiency unless they receive replacement therapy. Replacement can be accomplished with FFP, cryoprecipitate, or a factor XIII concentrate. Levels of 1 to 2% are usually adequate for hemostasis.

Platelet Functional Defects

Inherited platelet functional defects include abnormalities of platelet surface proteins, abnormalities of platelet granules, and enzyme defects. The major surface protein abnormalities are thrombasthenia and Bernard-Soulier syndrome. Thrombasthenia or Glanzmann thrombasthenia is a rare genetic platelet disorder, inherited in an autosomal recessive pattern, in which the platelet glycoprotein IIb/IIIa complex is either lacking or present but dysfunctional. This defect leads to faulty platelet aggregation and subsequent bleeding. The disorder was first described by Dr. Eduard Glanzmann in 1918.[5] Bleeding in thrombasthenic patients must be treated with platelet transfusions. The Bernard-Soulier syndrome, caused by a defect in the glycoprotein Ib/IX/V receptor for vWF, is necessary for platelet adhesion to the subendothelium. Transfusion of normal platelets is required to treat bleeding in these patients.

The most common intrinsic platelet defect is storage pool disease. It involves loss of dense granules [storage sites for ADP, adenosine triphosphate (ATP), Ca^{2+}, and inorganic phosphate] and ¤-granules. Dense granule deficiency is the most prevalent of these. It may be an isolated defect or occur with partial albinism in the Hermansky-Pudlak syndrome. Bleeding is variable, depending on the severity of the granule defect. Bleeding is caused by the decreased release of ADP from these platelets. An isolated defect of the ¤-granules is known as *gray platelet syndrome* because of the appearance of the platelets on Wright's stain preparations. A few patients have been reported who have decreased numbers of both dense and ¤-granules. They have a more severe bleeding disorder. Patients with mild bleeding as a consequence of a form of storage pool disease can be treated with desmopressin acetate. It is likely that the high levels of vWF in the plasma after desmopressin acetate administration somehow compensate for the intrinsic platelet defect. With more severe bleeding, platelet transfusion is required.

ACQUIRED HEMOSTATIC DEFECTS

Platelet Abnormalities

Acquired abnormalities of platelets may be quantitative or qualitative, although some patients have both types of defects. Quantitative defects may be a result of failure of production, shortened survival, or sequestration. Failure of production is generally a result of bone marrow disorders such as those caused by leukemia, myelodysplastic syndrome, severe vitamin B12 or folate deficiency, chemotherapeutic drug use, radiation therapy, acute ethanol intoxication, or viral infection. If a quantitative abnormality exists and treatment is indicated, either due to symptoms or the need for an invasive procedure, platelet transfusion is used. The etiology of both qualitative and quantitative defects is reviewed in Table 4-2.

Table 4-2 Etiology of Platelet Disorders
A. Quantitative disorders
1. Failure of production: related to impairment of bone marrow function
a. Leukemia
b. Myeloproliferative disorders
c. Vitamin B12 or folate deficiency
d. Chemotherapy or radiation therapy

e. Acute alcohol intoxication
f. Viral infections
2. Decreased survival
a. Immune-mediated disorders
1) Idiopathic thrombocytopenia
2) Heparin-induced thrombocytopenia
3) Autoimmune disorders or B-cell malignancies
4) Secondary thrombocytopenia
b. Disseminated intravascular coagulation
c. Disorders related to platelet thrombi
1) Thrombocytopenic purpura
2) Hemolytic uremic syndrome
3. Sequestration
a. Portal hypertension
b. Sarcoid
c. Lymphoma
d. Gaucher's disease
B. Qualitative disorders
1. Massive transfusion
2. Therapeutic administration of platelet inhibitors
3. Disease states
a. Myeloproliferative disorders
b. Monoclonal gammopathies
c. Liver disease

QUANTITATIVE DEFECTS

Failure of platelet production can occur when bone marrow production of platelets is affected by marrow-related disease such as leukemia or myelodysplasia, vitamin B12 or folate deficiencies, chemotherapy or radiation therapy, acute alcohol intoxication, or viral illnesses.

Shortened platelet survival is seen in immune thrombocytopenia, disseminated intravascular coagulation, and disorders characterized by platelet thrombi such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Immune thrombocytopenia may be idiopathic or associated with other autoimmune disorders or low-grade B-cell malignancies, and it may also be secondary to viral infections (including HIV infection) or use of certain drugs. Secondary immune thrombocytopenia often presents with a very low platelet count, petechiae and purpura, and epistaxis. Large platelets are seen on peripheral smear. Initial treatment consists of corticosteroids, IV gamma globulin, or anti-D immunoglobulin in patients who are Rh-positive. Effects of both gamma globulin and anti-D immunoglobulin are rapid in onset. Platelet transfusions usually are not needed unless central nervous system bleeding or active bleeding from other sites occurs. Survival of the transfused platelets is usually short.

Primary immune thrombocytopenia also is known as *idiopathic thrombocytopenic purpura* (ITP). In children it is usually acute

and short lived, and typically follows a viral illness. In contrast, ITP in adults is gradual in onset, chronic, and has no identifiable cause. Because the circulating platelets in ITP are young and functional, bleeding is less for a given platelet count than when there is failure of platelet production. The pathophysiology of ITP is believed to involve both impaired platelet production and T cell–mediated platelet destruction.[6] Management options are summarized in Table 4-3. Treatment of drug-induced immune thrombocytopenia may simply entail withdrawal of the offending drug, but administration of corticosteroids, gamma globulin, and anti-D immunoglobulin may hasten recovery of the count.

Table 4-3 Management of Idiopathic Thrombocytopenic Purpura (ITP) in Adults
First Line
a. Corticosteroids: The majority of patients respond, but only a few long term.
b. IV immunoglobulin: Indicated with clinical bleeding, along with platelet transfusion, and when condition is steroid unresponsive. Response is rapid but transient.
c. Anti-D immunoglobulin: Active only in Rh-positive patients before splenectomy. Response is transient.
Second Line
a. Splenectomy: Open or laparoscopic. Criteria include severe thrombocytopenia, high risk of bleeding, and continued need for steroids. Treatment failure may be due to retained accessory splenic tissue.
Third Line
a. Patients for whom first- and second-line therapies fail are considered to have chronic ITP. The objective in this subset of patients is to maintain the platelet count >20–30 x 10^9/L and to minimize side effects of medications.
b. Rituximab, an anti-CD20 monoclonal antibody: Acts by eliminating B cells.
c. Alternative medications producing mixed results and a limited response: Danazol, cyclosporine A, dapsone, azathioprine, and vinca alkaloids.
d. Thrombopoietic agents: A new class of drugs for patients with impaired production of platelets rather than accelerated destruction of platelets. Second-generation drugs still in clinical trials include AMG531 and eltrombopag.

Heparin-induced thrombocytopenia (HIT) is a form of drug-induced immune thrombocytopenia. It is an immunologic disorder in which antibodies against PF4 formed during exposure to heparin affect platelet activation and endothelial function with resultant thrombocytopenia and intravascular thrombosis.[7] The platelet count typically begins to fall 5 to 7 days after heparin has been started, but if it is a re-exposure, the decrease in count may occur within 1 to 2 days. HIT should be suspected if the platelet count falls to <100,000/μL or if it drops by 50% from baseline in a patient receiving heparin. Although HIT is more common with full-dose unfractionated heparin (1 to 3%), it also can occur with prophylactic doses or with low molecular weight heparins. Interestingly, approximately 17% of patients receiving unfractionated heparin and 8% of those receiving low molecular weight heparin develop antibodies against PF4, yet a much smaller percentage develop thrombocytopenia and even fewer clinical HIT.[8] In addition to the mild to moderate thrombocytopenia, this disorder is characterized by a high incidence of thrombosis, which may be arterial or venous. Importantly, the absence of thrombocytopenia in these patients does not preclude the diagnosis of HIT.

The diagnosis of HIT may be made by using either a serotonin release assay or an enzyme-linked immunosorbent assay (ELISA). The serotonin release assay is highly specific but not sensitive, so that a positive test result supports the diagnosis but a negative result does not exclude HIT.[7] On the other hand, the ELISA has a low specificity, so although a positive ELISA result confirms the presence of anti–heparin-PF4, it does not help in the diagnosis of clinical HIT. A negative ELISA result, however, essentially rules out HIT.

The initial treatment of suspected HIT is to stop heparin and begin an alternative anticoagulant. Stopping heparin without adding another anticoagulant is not adequate to prevent thrombosis in this setting. Alternative anticoagulants are primarily thrombin inhibitors. Those available in the United States are lepirudin, argatroban, and bivalirudin. In Canada and Europe, danaparoid also is available. Danaparoid is a heparinoid that has approximately 20% cross reactivity with HIT antibodies in vitro but a much lower cross reactivity in vivo. Because of warfarin's early induction of a hypercoagulable state, only once full anticoagulation with an alternative agent has been accomplished and the platelet count has begun to recover should warfarin be instituted.

There are also disorders in which thrombocytopenia is a result of platelet activation and formation of platelet thrombi. In thrombotic thrombocytopenic purpura (TTP), large vWF molecules interact with platelets, which leads to activation. These large molecules result from inhibition of a metalloproteinase enzyme, ADAMTS13, which cleaves the large vWF molecules.[9] TTP is classically characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, and renal and neurologic signs or symptoms. The finding of schistocytes on a peripheral blood smear aids in the diagnosis. The most effective treatment for TTP is plasmapheresis, although plasma infusion also has been attempted. A recent study comparing these two modalities reported a higher relapse rate and a higher mortality with plasma infusions. Platelet transfusions are contraindicated.[10] Additionally, rituximab, a monoclonal antibody against the CD20 protein on B lymphocytes, has shown promise as an immunomodulatory therapy directed against acquired TTP, which in the majority of cases is autoimmune mediated.[11]

Hemolytic uremic syndrome (HUS) often occurs secondary to infection by *Escherichia coli* 0157:H7 or other Shiga toxin–producing bacteria. The metalloproteinase is normal in these cases. HUS usually is associated with some degree of renal failure, with many patients requiring renal replacement therapy. Neurologic symptoms are less frequent. A number of patients develop features of both TTP and HUS. This may occur with autoimmune diseases, especially systemic lupus erythematosus, and HIV infection, or in association with certain drugs (such as ticlopidine, mitomycin C, gemcitabine), and immunosuppressive agents (such as cyclosporine and tacrolimus). Discontinuation of the involved drug is the mainstay of therapy. Plasmapheresis frequently is used, but it is not clear what etiologic factor is being removed by the pheresis.

Sequestration is another important cause of thrombocytopenia and usually involves sequestration of platelets in an enlarged spleen, typically related to portal hypertension, sarcoid, lymphoma, or Gaucher's disease. The total body platelet mass is essentially normal in patients with hypersplenism, but a much larger fraction of the platelets are in the enlarged spleen. Platelet survival is mildly decreased. Bleeding is less than anticipated from the count, because sequestered platelets can be mobilized to some extent and enter the circulation. Platelet transfusion does not increase the platelet count as much as it would in a normal person, because the transfused platelets are similarly sequestered in the spleen. Splenectomy is not indicated to correct the thrombocytopenia of hypersplenism caused by portal hypertension.

Thrombocytopenia is the most common abnormality of hemostasis that results in bleeding in the surgical patient. The patient may have a reduced platelet count as a result of a variety of disease processes as discussed earlier. In these circumstances, the marrow usually demonstrates a normal or increased number of megakaryocytes. By contrast, when thrombocytopenia occurs in patients with leukemia or uremia and in patients receiving cytotoxic therapy, there are generally a reduced number of megakaryocytes in the marrow. Thrombocytopenia also occurs in surgical patients as a result of massive blood loss and replacement with product deficient in platelets. Thrombocytopenia may also be induced by heparin administration in patients with cardiac and vascular disorders, as in the case of HIT, or may be associated with thrombotic and hemorrhagic complications. When thrombocytopenia is present in a patient for whom an elective operation is being considered,

management is contingent on the extent and cause of platelet reduction. A count of >50,000/μL generally requires no specific therapy.

Prophylactic platelet administration has now become part of massive transfusion protocols. Platelets also are administered preoperatively to rapidly increase the platelet count in surgical patients with underlying thrombocytopenia. One unit of platelet concentrate contains approximately 5.5×10^{10} platelets and would be expected to increase the circulating platelet count by approximately 10,000/μL in the average 70-kg person. Fever, infection, hepatosplenomegaly, and the presence of antiplatelet alloantibodies decrease the effectiveness of platelet transfusions. In patients whose thrombocytopenia is refractory to standard platelet transfusion, the use of human leukocyte antigen (HLA)–compatible platelets coupled with special processors has proved effective.

QUALITATIVE PLATELET DEFECTS

Impaired platelet function often accompanies thrombocytopenia. Impaired ADP-stimulated aggregation occurs with massive transfusion (>10 units of packed red blood cells). Uremia may be associated with increased bleeding time and impaired aggregation and can be corrected by hemodialysis or peritoneal dialysis. Defective aggregation and platelet secretion can occur in patients with thrombocythemia, polycythemia vera, or myelofibrosis.

Drugs that interfere with platelet function by design include aspirin, clopidogrel, dipyridamole, and the glycoprotein IIb/IIIa inhibitors. Both aspirin and clopidogrel irreversibly inhibit platelet function, clopidogrel through selective irreversible inhibition of ADP-induced platelet aggregation and aspirin through irreversible acetylation of platelet prostaglandin synthase. There are no prospective randomized trials in general surgical patients to guide the timing of surgery in patients taking aspirin and/or clopidogrel. The general recommendation is that, for each, a period of approximately 7 days is required from the time the drug is stopped until an elective procedure can be performed.[12] Timing of urgent and emergent surgeries is even more unclear. Preoperative platelet transfusions may be beneficial, but again there are no good data to guide their administration. The problem is that accurate tests of platelet function are lacking. Other disorders associated with abnormal platelet function include uremia, myeloproliferative disorders, monoclonal gammopathies, and liver disease. In the surgical patient, platelet dysfunction of uremia often can be corrected by dialysis or the administration of desmopressin acetate. Platelet transfusion may not be helpful if the patient is uremic when the platelets are given. Platelet dysfunction in myeloproliferative disorders is intrinsic to the platelets and usually improves if the platelet count can be reduced to normal with chemotherapy. If possible, surgery should be delayed until the count has been decreased. These patients are at risk for both bleeding and thrombosis. Platelet dysfunction in patients with monoclonal gammopathies is a result of interaction of the monoclonal protein with platelets. Treatment with chemotherapy, or occasionally plasmapheresis, to lower the amount of monoclonal protein improves hemostasis.

Acquired Hypofibrinogenemia

DISSEMINATED INTRAVASCULAR COAGULATION

The official definition of disseminated intravascular coagulation (DIC), as put forth by the Scientific Subcommittee on DIC of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (SSC/ISTH), is that "DIC is an acquired syndrome characterized by the intravascular activation of coagulation with the loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."[13] Excessive thrombin generation leads to microthrombus formation, followed by consumption and depletion of coagulation factors and platelets, which leads to the classic picture of diffuse bleeding. The presence of an

underlying condition that predisposes a patient to DIC is required for the diagnosis. Specific injuries include central nervous system injuries with embolization of brain matter, fractures with embolization of bone marrow, and amniotic fluid embolization. Embolized materials are potent thromboplastins that activate the DIC cascade.[14] Additional causes include malignancy, organ injury (such as severe pancreatitis), liver failure, certain vascular abnormalities (such as large aneurysms), snakebites, illicit drugs, transfusion reactions, transplant rejection, and sepsis.[13] DIC frequently accompanies sepsis and may be associated with multiple organ failure. As of yet, scoring systems for organ failure do not routinely incorporate DIC.[14] The important interplay between sepsis and coagulation abnormalities was demonstrated by Dhainaut and colleagues, who showed that administration of activated protein C was particularly effective in septic patients with DIC.[15] The diagnosis of DIC is made on the basis of an inciting cause with associated thrombocytopenia, prolongation of the PT, low fibrinogen level, and elevated levels of fibrin markers (fibrin degradation products, D-dimer, soluble fibrin monomers). A scoring system developed by the SSC/ISTH assigns a score between 0 and 1 to the measured value on each of these laboratory tests; a score of 5 or greater is considered to be overt DIC.[16]

The most important facets of treatment are relieving the patient's causative primary medical or surgical problem and maintaining adequate perfusion. If there is active bleeding, hemostatic factors should be replaced using FFP, which generally is sufficient to correct the hypofibrinogenemia, although cryoprecipitate and platelet concentrates also may be needed. Because microthrombi are generated during DIC, heparin therapy has been proposed. Most studies, however, have shown that heparin is not helpful in acute forms of DIC but may be indicated for purpura fulminans or venous thromboembolism.

PRIMARY FIBRINOLYSIS

An acquired hypofibrinogenic state in the surgical patient also can be a result of pathologic fibrinolysis. This may occur in patients after prostate resection when urokinase is released during surgical manipulation of the prostate or in patients undergoing extracorporeal bypass. The severity of fibrinolytic bleeding is dependent on the concentration of breakdown products in the circulation. The synthetic amino acidε-aminocaproic acid interferes with fibrinolysis by inhibiting plasminogen activation.

Myeloproliferative Diseases

Polycythemia, particularly with marked thrombocytosis, presents a major surgical risk. In such patients, operations should be considered only for the most grave surgical emergencies. If possible, the operation should be deferred until medical management has restored normal blood volume, hematocrit level, and platelet count. Spontaneous thrombosis is a complication of polycythemia vera and can be explained in part by increased blood viscosity, increased platelet count, and an increased tendency toward stasis. Paradoxically, a significant tendency toward spontaneous hemorrhage also is noted in these patients. Myeloid metaplasia frequently represents part of the natural history of polycythemia vera. Approximately 50% of patients with myeloid metaplasia are postpolycythemic. Abnormalities in platelet aggregation and release have been demonstrated in these patients.

Thrombocytosis can be reduced by the administration of hydroxyurea or anagrelide. Elective surgical procedures should be delayed until the institution of appropriate treatment. Ideally, the hematocrit level should be kept below 48% and the platelet count under 400,000/µL. When an emergency procedure is required, phlebotomy and blood replacement with lactated Ringer's solution may be beneficial.

Coagulopathy of Liver Disease

The liver plays a key role in hemostasis because it is responsible for the synthesis of many of the coagulation factors (Table 4-4). The most common coagulation abnormalities associated with liver dysfunction are thrombocytopenia and impaired humoral coagulation function manifested as prolongation of the PT and increase in the International Normalized Ratio (INR).[17] Thrombocytopenia in patients with liver disease typically is related to hypersplenism, reduced production of thrombopoietin, and immune-mediated destruction of platelets. As noted earlier, in patients with hypersplenism the total body platelet mass is basically normal, but an abnormally high proportion of the platelets are found in the enlarged spleen. Less bleeding is seen than would be anticipated from the platelet count, because some of the sequestered platelets can be released into the circulation. Thrombopoietin, the primary stimulus for thrombopoiesis, may be responsible for some cases of thrombocytopenia in cirrhotic patients, although its role is not well delineated. Finally, immune-mediated thrombocytopenia may also occur in cirrhotic patients, especially those with hepatitis C and primary biliary cirrhosis.[18] Before any therapy to ameliorate thrombocytopenia is initiated, the actual need for correction should be strongly considered. In general, correction based solely on a low platelet count should be discouraged. Most often, treatment should be withheld for invasive procedures and surgery. Platelet transfusions are the mainstay of therapy; however, the effect typically lasts only several hours. Risks associated with transfusions in general, and the development of antiplatelet antibodies in a patient population likely to need recurrent correction, should be considered. A potential alternative strategy is administration of interleukin-11, a cytokine that stimulates proliferation of hematopoietic stem cells and megakaryocyte progenitors.[16] Most studies using interleukin-11 have been in patients with cancer, although some evidence exists that it may be beneficial in cirrhotic patients as well. Significant side effects limit its usefulness.[19] A less well accepted option is splenectomy or splenic embolization to reduce hypersplenism. Not only are there risks associated with these techniques, but reduced splenic blood flow can reduce portal vein flow with subsequent portal vein thrombosis. Results are mixed after transjugular intrahepatic portosystemic shunt (TIPS). Therefore, treatment of thrombocytopenia should not be the primary indication for a TIPS procedure.

Table 4-4 Coagulation Factors Synthesized by the Liver
Vitamin K–dependent factors: II (prothrombin factor), VII, IX, X
Fibrinogen
Factor V
Factor VIII
Factors XI, XII, XIII
Antithrombin III
Plasminogen
Protein C and protein S

Decreased production or increased destruction of coagulation factors as well as a vitamin K deficiency can contribute to a prolonged PT and increased INR in patients with liver disease. As liver dysfunction worsens, so does the liver's synthetic function, which results in decreased production of coagulation factors. Additionally, abnormalities in laboratory results may mimic those of DIC. Elevated D-dimer levels have been reported to increase the risk of variceal bleeding.[20] The absorption of vitamin K is dependent on bile production. Therefore, patients with liver disease who have impaired bile production, such as those with cholestatic disease, may be at risk for vitamin K deficiency.

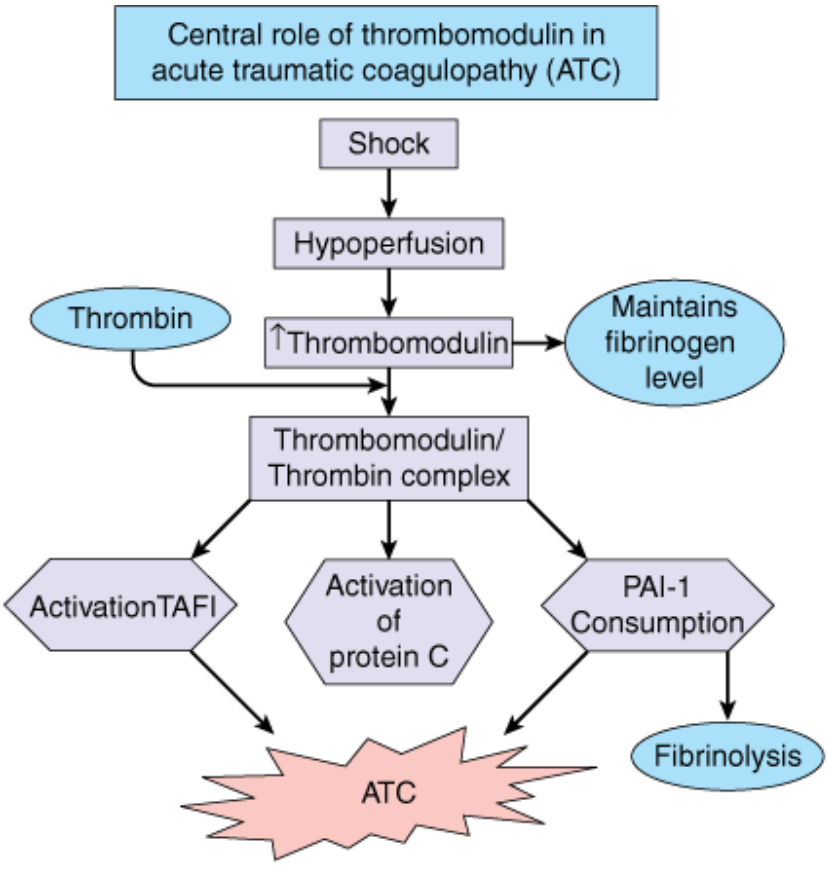
As with thrombocytopenia, correction of coagulopathy should be reserved for treatment of active bleeding and prophylaxis for invasive procedures and surgery. Coagulopathy caused by liver disease is most often treated with FFP, but because the

coagulopathy generally is not a result of decreased levels of factor V, complete correction usually is not possible. If the fibrinogen level is <100 mg/dL, administration of cryoprecipitate may be helpful. Cryoprecipitate is also a source of factor VIII for the rare patient with a low factor VIII level.

Coagulopathy of Trauma

Traditionally recognized causes of traumatic coagulopathy include acidosis, hypothermia, and dilution of coagulation factors. However, a significant proportion of trauma patients arrive at the emergency department coagulopathic, and this early coagulopathy is associated with a significant increase in mortality.[21,22] Brohi and colleagues have demonstrated that only patients in shock arrive coagulopathic and that it is the shock that induces coagulopathy through systemic activation of anticoagulant and fibrinolytic pathways.[23] As shown in Fig. 4-5, hypoperfusion causes activation of thrombomodulin on the surface of endothelial cells. Circulating thrombin complexes with thrombomodulin. This complex not only induces an anticoagulant state through activation of protein C but also enhances fibrinolysis by deinhibition of tPA through the consumption of plasminogen activator inhibitor 1.

Fig. 4-5.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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Illustration of the pathophysiologic mechanism responsible for the acute coagulopathy of trauma. PAI-1 = plasminogen activator inhibitor 1; TAFI = thrombin-activatable fibrinolysis inhibitor.

Lastly, the thrombin-thrombomodulin complex limits the availability of thrombin to cleave fibrinogen to fibrin, which may explain why injured patients rarely have low levels of fibrinogen.

Acquired Coagulation Inhibition

Among the most common acquired disorder of coagulation inhibition is the antiphospholipid syndrome (APLS), in which the lupus anticoagulant and anticardiolipin antibodies are present. These antibodies may be associated with either venous or arterial thrombosis, or both. In fact, patients who show recurrent thrombosis should be evaluated for APLS. The presence of antiphospholipid antibodies is very common in patients with systemic lupus erythematosus but also may be seen in association with rheumatoid arthritis and Sjögren's syndrome. There are also individuals who have no autoimmune disorders but develop transient antibodies in response to infections or who develop drug-induced APLS. The hallmark of APLS is a prolonged aPTT in vitro but an increased risk of thrombosis in vivo.[24]

Paraprotein Disorders

Paraprotein disorders are characterized by production of an abnormal globulin or fibrinogen that interferes with clotting or platelet function. This may be an immunoglobulin M in Waldenström's macroglobulinemia, an immunoglobulin G or immunoglobulin A in multiple myeloma, a cryoglobulin in liver disease (especially hepatitis C) or autoimmune diseases, or a cryofibrinogen. Chemotherapy usually is effective in lowering the level of paraproteins in macroglobulinemia and myeloma, although for rapid removal before surgery, plasmapheresis may be needed. Cryoglobulins and cryofibrinogens are usually removed by plasmapheresis.

Anticoagulation and Bleeding

Spontaneous bleeding can be a complication of anticoagulant therapy with either heparin, warfarin, low molecular weight heparins, or factor Xa inhibitors. The risk of spontaneous bleeding related to heparin administration is reduced when a continuous infusion technique is used. Therapeutic anticoagulation is more reliably achieved with a low molecular weight heparin. Laboratory testing is not routinely used to monitor dosing of these agents, which makes them attractive options for outpatient anticoagulation. If monitoring is needed for low molecular weight heparins (e.g., in the presence of renal insufficiency or severe obesity), the drug effect should be determined with an assay for anti-Xa activity.

Warfarin is used for long-term anticoagulation in various clinical conditions, including deep vein thrombosis, pulmonary embolism, valvular heart disease, atrial fibrillation, recurrent systemic embolism, and recurrent myocardial infarction, as well as in patients with prosthetic heart valves and prosthetic implants.[25–27] Due to the interaction of the P-450 system, the anticoagulant effect of the warfarin is reduced (e.g., higher dosage is required) in patients receiving barbiturates as well as in patients with diets low in vitamin K. Warfarin requirements also may be increased in patients taking contraceptives or estrogen-containing compounds, corticosteroids, or adrenocorticotropic hormone. A number of medications can alter warfarin requirements (Table 4-5).

Table 4-5 Medications That Can Alter Warfarin Dosing

↓ Warfarin effect	Barbiturates, oral contraceptives, estrogen-containing compounds, corticosteroids, adrenocorticotropic hormone
↑ Warfarin requirements	
↑ Warfarin effect	Phenylbutazone, clofibrate, anabolic steroids, L-thyroxine, glucagons, amiodarone, quinidine, cephalosporins
↓ Warfarin requirements	

Bleeding complications are frequent in patients taking anticoagulants. Examples include hematuria, soft tissue bleeding, intracerebral bleeding, skin necrosis, and abdominal bleeding. Bleeding into the abdominal cavity is by far the most common complication of warfarin therapy and may be either intraperitoneal, extraperitoneal, or retroperitoneal.[28–30] An intramural bowel hematoma is the most common cause of abdominal pain in patients receiving anticoagulation therapy.[31–33] Fortunately, most intramural bowel hematomas respond to nonoperative treatment. Bleeding secondary to anticoagulation therapy is also not an uncommon cause of rectus sheath hematomas. In most of these cases, reversal of anticoagulation is the only treatment that is necessary. Lastly, it is important to remember that one of the first symptoms of an underlying tumor may be bleeding in a patient who is receiving anticoagulation therapy.

Surgical intervention may prove necessary in patients receiving anticoagulation therapy. Increasing experience suggests that surgical treatment can be undertaken without discontinuing the anticoagulant program, depending on the procedure being performed.[34] Furthermore, the risk of thrombotic complications may be increased when anticoagulation therapy is discontinued abruptly. When the aPTT is <1.3 times the control value in a patient receiving heparin or when the INR is <1.5 in a patient taking warfarin, reversal of anticoagulation therapy may not be necessary. However, meticulous surgical technique is mandatory, and the patient must be observed closely throughout the postoperative period.

Certain surgical procedures should not be performed in concert with anticoagulation; this applies, in particular, to circumstances in which even minor bleeding can cause great morbidity, such as procedures involving the central nervous system or the eye. Emergency operations are occasionally necessary in patients who have been receiving heparin. The first step for these patients is to discontinue heparin. For more rapid reversal of anticoagulation, use of protamine sulfate is effective. However, significant adverse reactions may be encountered when administering protamine, especially in patients with severe fish allergies.[35,36] Symptoms include hypotension, flushing, bradycardia, nausea, and vomiting. Prolongation of the aPTT after heparin neutralization with protamine may also be a result of the anticoagulant effect of protamine. In a patient undergoing elective surgery who is receiving coumarin-derivative therapy sufficient to effect anticoagulation, the drug can be discontinued several days before the operation and the prothrombin concentration then checked (a level >50% is considered safe).[37] Rapid reversal of anticoagulation can be accomplished with FFP in an emergent situation. Parenteral administration of vitamin K also is indicated in elective surgical treatment of patients with biliary obstruction or malabsorption who may be vitamin K deficient. However, if low levels of factors II, VII, IX, and X (vitamin K–dependent factors) are a result of hepatocellular dysfunction, vitamin K administration is ineffective. For patients who were taking warfarin preoperatively and are at high risk for thrombosis, low molecular weight heparin should be administered while the INR is decreasing and should be restarted at prophylactic dosages as soon as possible after surgery. The perioperative management of patients receiving long-term oral anticoagulation therapy is an increasingly common problem. Firm evidence-based guidelines regarding which patients require perioperative "bridging" anticoagulation and the most effective way to bridge are lacking. IV unfractionated heparin and SC low molecular weight heparin in therapeutic dosages reduce the risk of venous thromboembolism but have not been proven to reduce the risk of arterial thromboembolism.[38] Bridging anticoagulation involves discontinuation of oral anticoagulation before surgery and the use of IV or SC agents for several days before and (sometimes) after surgery. Most studies have shown that preoperative bridging is associated with an acceptably low postoperative bleeding rate (1.8 to 5.8%). Not unexpectedly, the risk of bleeding can be substantially higher for procedures associated with intraoperative and postoperative bleeding.

CARDIOPULMONARY BYPASS

The predisposing factors that are associated with excessive bleeding are prolonged perfusion times, prior use of oral

anticoagulants or antiplatelet drugs, cyanotic heart disease, and hypothermia. Two factors triggering excessive bleeding associated with cardiopulmonary bypass are excessive fibrinolysis and platelet function defects, with the latter being more important.

The laboratory evaluation of patients with cardiopulmonary bypass hemorrhage should include INR, aPTT, complete blood count, platelet count, peripheral blood smear examination, and measurement of fibrin degradation products. The management entails empiric administration of platelets, and if hyperheparinemia is believed to be the major factor, 25% of the calculated dose of protamine should be administered and repeated every 30 to 60 minutes until the bleeding ceases. If there is laboratory evidence of excess fibrinolysis, ε-aminocaproic acid can be given at an initial dose of 5 to 10 g followed by 1 to 2 g/h until bleeding ceases. Aprotinin, a protease inhibitor that acts as an antifibrinolytic agent, has been shown to reduce transfusion requirements associated with cardiac surgery and orthotopic liver transplantation.[39]

Desmopressin acetate, which stimulates release of factor VIII from endothelial cells, also may be effective in reducing blood loss during cardiac surgery. Laboratory evidence of heparin-induced thrombocytopenia (HIT) often is found after cardiopulmonary bypass; however, clinically significant HIT is rare unless the patient has had previous heparin exposure or heparin continues to be administered in the postoperative period.

LOCAL HEMOSTASIS

Significant surgical bleeding usually is caused by ineffective local hemostasis. The goal is therefore to prevent further blood loss from a disrupted vessel that has been incised or transected. Hemostasis may be accomplished by interrupting the flow of blood to the involved area or by direct closure of the blood vessel wall defect.

Mechanical Procedures

The oldest mechanical method of halting bleeding is digital pressure. When pressure is applied to an artery proximal to an area of bleeding, profuse bleeding may be reduced so that more definitive action is permitted. Application of an extremity tourniquet that occludes a major vessel proximal to the bleeding site and the Pringle maneuver for liver bleeding are good examples. Direct digital pressure over a bleeding site often is effective and has the advantage of being less traumatic than a hemostatic clamp. Even an "atraumatic" vascular clamp results in damage to the intimal wall of a blood vessel.

When a small vessel is transected, a simple ligature is sufficient. For large arteries with pulsation, a transfixion suture to prevent slipping is indicated. All sutures represent foreign material, and selection is based on their intrinsic characteristics and the state of the wound. Direct pressure applied by packs affords the best method of controlling diffuse bleeding from large areas, such as in the trauma situation. Bleeding from cut bone can be controlled by packing bone wax on the raw surface to achieve pressure.

The Harmonic scalpel is an instrument that cuts and coagulates tissue via vibration at 55 kHz. The device converts electrical energy into mechanical motion. The motion of the blade causes collagen molecules within the tissue to become denatured, forming a coagulum. No significant electrical current flows through the patient. The instrument has proved advantageous in performing thyroidectomy, hemorrhoidectomy, and transsection of the short gastric veins during splenectomy, and in transecting hepatic parenchyma.[40–42]

Thermal Agents

Heat achieves hemostasis by denaturation of protein that results in coagulation of large areas of tissue. With cautery, heat is transmitted from the instrument by conduction directly to the tissue. When electrocautery is used, heating occurs by

induction from an alternating current source. The amplitude setting should be high enough to produce prompt coagulation but not so high as to set up an arc between the tissue and the cautery tip. This avoids burns outside the operative field and prevents the exit of current through electrocardiographic leads, other monitoring devices, or permanent pacemakers or defibrillators. A negative grounding plate should be placed beneath the patient to avoid severe skin burns. Certain anesthetic agents (diethyl ether, divinyl ether, ethyl chloride, ethylene, and cyclopropane) cannot be used with electrocautery because of the hazard of explosion.

Use of direct current also can result in hemostasis. Because the protein moieties and cellular elements of blood have a negative surface charge, they are attracted to a positive pole, where a thrombus is formed. Direct currents in the 20- to 100-mA range have successfully controlled diffuse bleeding from raw surfaces, as has argon gas.

Topical Hemostatic Agents

Topical hemostatic agents play an important role in common or complex general surgical procedures. These agents can be classified based on their mechanism of action and include physical or mechanical, caustic, biologic, and physiologic agents. Some agents induce protein coagulation and precipitation that results in occlusion of small cutaneous vessels, whereas others take advantage of later stages in the coagulation cascade, activating biologic responses to bleeding.[43] The ideal topical hemostatic agent has significant hemostatic action, shows minimal tissue reactivity, is nonantigenic, biodegrades in vivo, provides ease of sterilization, is low in cost, and can be tailored to specific needs.[44] Table 4-6 reviews only some of the commonly used products on the market.

Table 4-6 Common Hemostatic Agents

Hemostatic Agent	Manufacturer	Cost	Comments
Thrombin Products			
Floseal	Baxter	$1500 per 6 pack/5 mL	Disseminated intravascular coagulation may result from intravascular exposure. Solution soaked in gauze or injected over wound bed, forming attachment.
Thrombostat	Parke-Davis	$56–60/5000–10,000 vial	
Thrombin-JMI	King Pharmaceuticals	$285/10,000 units	
Fibrin Sealant			
Tisseel	Baxter	$135/2 mL	Useful in skin grafts or anticoagulated patients. Crosseal contains no aprotinin, reduces anaphylaxis risk.
Crosseal	Johnson & Johnson	$100–150/1 mL	
Gelatin Agents			
Gelfoam	Pfizer	$90/1 g	Forms hydrated meshwork to promote clotting. Can swell. May cause granulomatous reaction.
Surgifoam	Johnson & Johnson	$8–14/gelatin square	

Thrombin-derivative products direct the conversion of fibrinogen to fibrin, aiding in clot formation. Thrombin takes advantage

of natural physiologic processes, thereby avoiding foreign body or inflammatory reactions, and the wound bed is not disturbed.[44] Caution must be taken in judging vessel caliber in the wound, because thrombin entry into larger-caliber vessels can result in systemic exposure to thrombin with a risk of disseminated intravascular clotting or death.

Fibrin sealants are prepared from cryoprecipitate (homologous or synthetic) and have the advantage of not promoting inflammation or tissue necrosis.[45] The sealant is administered using a dual syringe compartment system. In one compartment is fibrinogen, factor XIII, fibronectin, and fibrinolysis inhibitors. The second compartment contains thrombin and calcium chloride.[46] The use of fibrin glue is particularly helpful in patients who have received heparin or who have deficiencies in coagulation (e.g., hemophilia or von Willebrand's disease).[47–49]

Purified gelatin solution can be prepared into several vehicles, including powders, sponges or foams, and sheets or films.[43] Gelatin is hygroscopic, absorbing many times its weight in water or liquid. It is effectively metabolized and degraded by proteinases in the wound bed over a period of 4 to 6 weeks.[43] Gelfoam provides effective hemostasis for operative fields with diffuse small-vessel oozing.[50] Thrombin may be applied to this vehicle to boost hemostasis. Gelatin is relatively inexpensive, readily available, pliable, and easy to handle. Although relatively inert, the implanted gelatin can serve as a nidus for infection.[44]

These agents are not a substitute for meticulous surgical technique. The advantages and disadvantages of each agent must be weighed in selecting the correct agent to control bleeding. In general, the minimum amount of each topical hemostatic agent should be used to minimize toxic effects and adverse reactions, interference with wound healing, and procedural cost.

TRANSFUSION

Background

Human blood replacement therapy was accepted in the late nineteenth century. This was followed by the introduction of blood grouping by Dr. Karl Landsteiner, who identified the major A, B, and O groups in 1900. In 1939 Dr. Philip Levine and Dr. Rufus Stetson followed with the concept of Rh grouping. These breakthroughs established the foundation from which the field of transfusion medicine has grown. Whole blood was considered the standard in transfusion until the late 1970s, when goal-directed component therapy began to take prominence. This change in practice was made possible by the development of improved collection strategies, testing for infection, and advances in preservative solutions and storage.

Replacement Therapy

TYPING AND CROSS-MATCHING

Serologic compatibility for A, B, O, and Rh groups is established routinely. Cross-matching between donors' red blood cells and recipients' sera (the major cross-match) is performed. Rh-negative recipients should receive transfusions only of Rh-negative blood. However, this group represents only 15% of the population. Therefore, the administration of Rh-positive blood is acceptable if Rh-negative blood is not available. However, Rh-positive blood should not be transfused to Rh-negative females who are of childbearing age.

In emergency situations, type O-negative blood may be transfused to all recipients. O-negative and type-specific red blood cells are equally safe for emergency transfusion. Problems are associated with the administration of 4 or more units of O-negative blood, because there is a significant increase in the risk of hemolysis. In patients with clinically significant levels of cold agglutinins, blood should be administered through a blood warmer. If these antibodies are present in high titer,

hypothermia is contraindicated.

In patients who have been transfused multiple times and who have developed alloantibodies or who have autoimmune hemolytic anemia with pan–red blood cell antibodies, typing and cross-matching is often difficult, and sufficient time should be allotted preoperatively to accumulate blood that might be required during the operation. Cross-matching should always be performed before the administration of dextran, because it interferes with the typing procedure.

The use of autologous transfusion is growing. Up to 5 units can be collected for subsequent use during elective procedures. Patients can donate blood if their hemoglobin concentration exceeds 11 g/dL or if the hematocrit is >34%. The first procurement is performed 40 days before the planned operation and the last one is performed 3 days before the operation. Donations can be scheduled at intervals of 3 to 4 days. Administration of recombinant human erythropoietin accelerates generation of red blood cells and allows for more frequent harvesting of blood.

BANKED WHOLE BLOOD

Banked whole blood, once the gold standard, is rarely available. The shelf life is now around 6 weeks. At least 70% of the transfused erythrocytes remain in the circulation for 24 hours after transfusion and are viable. The age of red cells may play a significant role in the inflammatory response and incidence of multiple organ failure. The changes in the red blood cells that occur during storage include reduction of intracellular ADP and 2,3-diphosphoglycerate, which alters the oxygen dissociation curve of hemoglobin and results in a decrease in oxygen transport. Although all clotting factors are relatively stable in banked blood except for factors V and VIII, banked blood progressively becomes acidotic with elevated levels of lactate, potassium, and ammonia. The hemolysis that occurs during storage is insignificant.

FRESH WHOLE BLOOD

Fresh whole blood refers to blood that is administered within 24 hours of its donation. Advances in testing for infectious disease now make fresh whole blood another option. Recent evidence has shown that the use of fresh whole blood may improve outcomes in patients with trauma-associated coagulopathy in the combat situation,[51] and a civilian study will soon be under way. An advantage to the use of fresh whole blood is that it provides greater coagulation activity than equal units of component therapy.

PACKED RED BLOOD CELLS AND FROZEN RED BLOOD CELLS

Packed red blood cells are the product of choice for most clinical situations. Concentrated suspensions of red blood cells can be prepared by removing most of the supernatant plasma after centrifugation. This preparation reduces, but does not eliminate, reaction caused by plasma components. It also reduces the amount of sodium, potassium, lactic acid, and citrate administered. Frozen red blood cells are not available for use in emergencies. They are used for patients who are known to have been previously sensitized. By freezing red blood cells viability is theoretically improved, and the ATP and 2,3-diphosphoglycerate concentrations are maintained. Little clinical outcome data are available to substantiate these findings.

LEUKOCYTE-REDUCED AND LEUKOCYTE-REDUCED/WASHED RED BLOOD CELLS

Leukocyte-reduced and leukocyte-reduced/washed red blood cell products are prepared by filtration that removes approximately 99.9% of the white blood cells and most of the platelets (leukocyte-reduced red blood cells), and if necessary, by additional saline washing (leukocyte-reduced/washed red blood cells). Leukocyte reduction prevents almost all febrile, nonhemolytic transfusion reactions (fever and/or rigors), alloimmunization to HLA class I antigens, and platelet transfusion refractoriness as well as cytomegalovirus transmission. In most western nations, it is the standard red blood cell transfusion

product. Opponents of universal leukoreduction believe that the additional costs associated with this process are not justified because they are of the opinion that transfused allogenic white blood cells have no significant immunomodulatory effects. Supporters of universal leukocyte reduction argue that allogenic transfusion of white cells predisposes to postoperative bacterial infection and multiorgan failure. Reviews of randomized trials and meta-analysis have not provided convincing evidence either way,[52,53] although a large Canadian retrospective study suggests a decrease in mortality and infections when leukocyte-reduced red blood cells are used.[54]

PLATELET CONCENTRATES

The indications for platelet transfusion include thrombocytopenia caused by massive blood loss and replacement with platelet-poor products, thrombocytopenia caused by inadequate platelet production, and qualitative platelet disorders. The shelf life of platelets is 120 hours from time of donation. One unit of platelet concentrate has a volume of approximately 50 mL. Platelet preparations are capable of transmitting infectious diseases and can provoke allergic reactions similar to those caused by blood transfusion. Therapeutic levels of platelets reached after therapy are in the range of 50,000 to 100,000/μL. However, there is a growing body of information suggesting that platelet transfusion thresholds can safely be lowered in patients who have no signs of hemostatic deficiency and who have no history of poor tolerance to low platelet counts. Prevention of HLA alloimmunization can be achieved by leukocyte reduction through filtration. In rare cases, such as in patients who have become alloimmunized through previous transfusion or patients who are refractory from sensitization through prior pregnancies, HLA-matched platelets can be used.

FRESH-FROZEN PLASMA

Fresh-frozen plasma (FFP) prepared from freshly donated blood is the usual source of the vitamin K–dependent factors and is the only source of factor V. However, FFP carries infectious risks similar to those of other component therapies. FFP has come to the forefront with the inception of damage control resuscitation in patients with trauma-associated coagulopathy. In an effort to increase the shelf life and avoid the need for refrigeration, lyophilized plasma is being tested. Preliminary animal studies suggest that this process preserves the beneficial effects of FFP.[55]

CONCENTRATES AND RECOMBINANT DNA TECHNOLOGY

Technologic advancements have made the majority of clotting factors and albumin readily available as concentrates. These products are readily obtainable and carry no inherent infectious risks as do other component therapies.

HUMAN POLYMERIZED HEMOGLOBIN (POLYHEME)

Human polymerized hemoglobin (PolyHeme) is a universally compatible, immediately available, disease-free, oxygen-carrying resuscitative fluid that has been successfully used in massively bleeding patients when red blood cells were not transfused. Advantages of an artificial oxygen carrier include the absence of blood-type antigens (no cross-match needed) and viral infections and long-term stability, which allows prolonged periods of storage. Disadvantages include shorter half-life in the bloodstream and the potential to increase cardiovascular complications. This product has not yet been approved for use in patients.

Indications for Replacement of Blood and Its Elements

GENERAL INDICATIONS

Improvement in Oxygen-Carrying Capacity

Oxygen-carrying capacity is primarily a function of the red blood cells. Thus, transfusion of red blood cells should augment oxygen-carrying capacity. Additionally, hemoglobin is fundamental to arterial oxygen content and thus oxygen delivery. Despite this obvious association, there is little evidence that actually supports the premise that transfusion of red blood cells equates with enhanced cellular delivery and utilization. The reasons for this apparent discrepancy are related to changes that occur with the storage of blood. The decrease in 2,3-diphosphoglycerate and p50 impair oxygen offloading, and deformation of the red cells impairs microcirculatory perfusion.[56]

Treatment of Anemia: Transfusion Trigger

A 1988 National Institutes of Health Consensus Report challenged the dictum that a hemoglobin value of <10 g/dL or a hematocrit level of <30% indicates a need for preoperative red blood cell transfusion. This was verified in a prospective randomized controlled trial in critically ill patients that compared use of a restrictive transfusion threshold with use of a more liberal strategy and demonstrated that maintaining hemoglobin levels between 7 and 9 g/dL had no adverse effect on mortality. In fact, patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of 20 or less and patients 55 years or younger actually had a lower mortality.[57]

Despite these results, little has changed in transfusion practice. Critically ill patients frequently receive transfusions, with the hemoglobin level at which transfusion is initiated approaching 9 g/dL in a large observational study.[58]

One unresolved issue related to transfusion triggers is the safety of maintaining a hemoglobin level of 7 g/dL in a patient with ischemic heart disease. Data on this subject are mixed, and many studies have significant design flaws, including their retrospective nature. However, the majority of the published literature favors a restrictive transfusion trigger for patients with acute coronary syndrome without ST elevation, and many report worse outcomes in those patients receiving transfusions. Patients with acute myocardial infarctions with ST elevation may, however, benefit from receiving red blood cell transfusions for anemia.[56,58] Clearly, further investigation is warranted.

Volume Replacement

The most common indication for blood transfusion in surgical patients is the replenishment of the blood volume, a deficit of which is difficult to evaluate.

Measurements of hemoglobin levels or hematocrit are frequently used to assess blood loss. These measurements can be misleading in the face of acute loss, because the levels can be normal in spite of severely contracted blood volume. Both the amount and the rate of bleeding are factors in the development of signs and symptoms of blood loss.[56] A healthy adult can lose up to 15% of total blood volume (class I hemorrhage or up to 750 mL) with only minor effects on the circulation. Loss of 15 to 30% of blood volume (class II hemorrhage or 750 to 1500 mL) is associated with tachycardia and decreased pulse pressure but, importantly, a normal blood pressure. Loss of 30 to 40% (class III hemorrhage or 1500 to 2000 mL) results in tachycardia, tachypnea, hypotension, oliguria, and changes in mental status. Class IV hemorrhage is loss of >40% of blood volume and is considered life-threatening.

Loss of blood in the operating room can be evaluated by estimating the amount of blood in the wound and on the drapes, weighing the sponges, and quantifying blood suctioned from the operative field. In patients with normal preoperative values, blood loss of up to 20% of total blood volume can be replaced with crystalloid solution. Blood loss above this amount may require the addition of packed red blood cells and, in the case of massive transfusion, the addition of FFP (detailed later in this chapter). Transfusion of platelets and/or FFP may be indicated in specific patients before or during an operative

procedure (Table 4-7).

Table 4-7 Replacement of Clotting Factors

Factor	Normal Level	Life Span In Vivo (Half-Life)	Fate during Coagulation	Level Required for Safe Hemostasis	Ideal Agent ACD Bank Blood [4°C (39.2°F)]	Ideal Agent for Replacing Deficit
I (fibrinogen)	200–400 mg/100 mL	72 h	Consumed	60–100 mg/100 mL	Very stable	Bank blood; concentrated fibrinogen
II (prothrombin)	20 mg/100 mL (100% of normal level)	72 h	Consumed	15–20%	Stable	Bank blood; concentrated preparation
V (proaccelerin, accelerator globulin, labile factor)	100% of normal level	36 h	Consumed	5–20%	Labile (40% of normal level at 1 wk)	Fresh-frozen plasma; blood under 7 d
VII (proconvertin, serum prothrombin conversion accelerator, stable factor)	100% of normal level	5 h	Survives	5–30%	Stable	Bank blood; concentrated preparation
VIII (antihemophilic factor, antihemophilic globulin)	100% of normal level (50–150% of normal level)	6–12 h	Consumed	30%	Labile (20–40% of normal level at 1 wk)	Fresh-frozen plasma; concentrated antihemophilic factor; cryoprecipitate
IX (Christmas factor, plasma thromboplastin component)	100% of normal level	24 h	Survives	20–30%	Stable	Fresh-frozen plasma; bank blood; concentrated preparation
X (Stuart-Prower factor)	100% of normal level	40 h	Survives	15–20%	Stable	Bank blood; concentrated preparation
XI (plasma thromboplastin antecedent)	100% of normal level	Probably 40–80 h	Survives	10%	Probably stable	Bank blood
XII (Hageman factor)	100% of normal level	Unknown	Survives	Deficit produces no bleeding tendency	Stable	Replacement not required
XIII (fibrinase, fibrin-stabilizing factor)	100% of normal level	4–7 d	Survives	Probably <1%	Stable	Bank blood
Platelets	150,000–400,000/μL	8–11 d	Consumed	60,000–100,000/μL	Very labile (40% of normal level at 20 h; 0 at 48 h)	Fresh blood or plasma; fresh platelet concentrate (not frozen plasma)

ACD = acid-citrate-dextrose.

Source: Reproduced with permission from Salzman EW: Hemorrhagic disorders, in Kinney JM, Egdahl RH, Zuidema GD (eds): *Manual of Preoperative and Postoperative Care,* 2nd ed. Philadelphia: WB Saunders, 1971, p 157. Copyright Elsevier.

DAMAGE CONTROL RESUSCITATION

Current resuscitation algorithms are based on the sequence of crystalloid followed by red blood cells and then plasma and platelet transfusions and have been in widespread use since the 1970s. Recently, the damage control resuscitation (DCR) strategy, aimed at halting and/or preventing rather than treating the lethal triad of coagulopathy, acidosis, and hypothermia, has challenged traditional thinking on early resuscitation strategies.

Rationale

In civilian trauma systems nearly half of all deaths occur before a patient reaches the hospital, and few of these deaths are preventable.[59–61] Those patients who survive until arrival at an emergency center have a high incidence of truncal hemorrhage, and deaths in this group of patients may be potentially preventable. Truncal hemorrhage patients in shock often present with the early coagulopathy of trauma in the emergency department and are at significant risk of dying.[21,22,62]

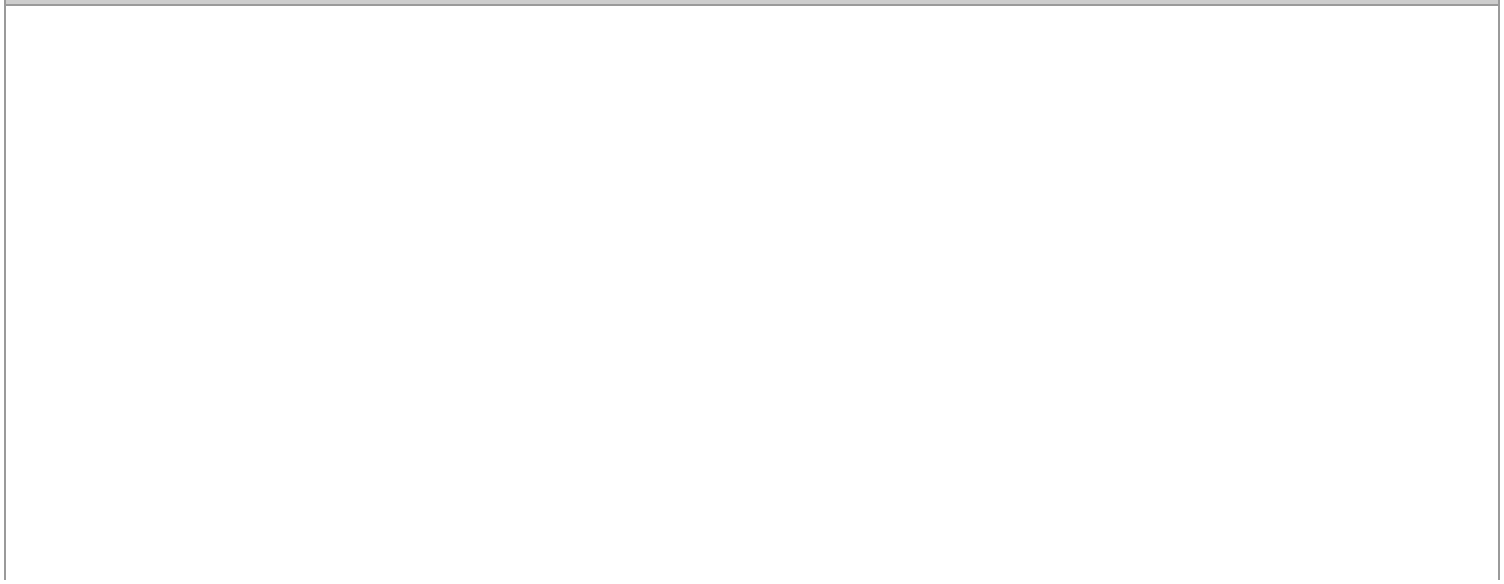
Many of these patients receive a massive transfusion, generally defined as the administration of 10 or more units of packed red blood cells within 24 hours of admission. Although 25% of all trauma patients admitted receive a unit of blood early after admission, only a small percentage of patients receive a massive transfusion. In the military setting, however, the percentage of patients receiving a massive transfusion almost doubles.[63]

New Concepts in Resuscitation Strategies

Standard advanced trauma life support guidelines start resuscitation with crystalloid, followed by packed red blood cells.[64] Only after liters of crystalloid have been transfused does transfusion of units of plasma or platelets begin. This conventional massive transfusion practice was based on a small uncontrolled retrospective study that used blood products containing increased amounts of plasma, which are no longer available.[65]

More recently, multiple retrospective studies have suggested that this standard resuscitation practice exacerbates the initial coagulopathy of trauma, thus increasing mortality, whereas transfusing a higher ratio of plasma and platelets to red blood cells is associated with improved survival.[66,67] An example of an adult massive transfusion clinical guideline specifying the early use of component therapy is shown in Fig. 4-6. Specific recommendations for the administration of component therapy during a massive transfusion are shown in Table 4-8. Recent data suggest that plasma should be given earlier to patients who are significantly injured and massively transfused, because they arrive in the intensive care unit coagulopathic.[68]

Fig. 4-6.



A. Initial Transfusion of Red Blood Cells (RBCs):

1. Notify Blood Bank immediately of urgent need for RBCs.
   O Negative Uncrossmatched (available immediately).
   As soon as possible switch to O-negative for females and O-positive for males
   Type-Specific Uncrossmatched (available in approximately 5–10 minutes)
   Completely Crossmatched (available in approximately 40 minutes)
2. A blood sample must be sent to Blood Bank for a Type & Cross.
3. The Emergency Release of Blood form must be completed. If the blood type is not known and blood is needed immediately, O Negative RBCs should be issued.
4. RBCs will be transfused in the standard fashion. All patients must be identified (name and number) prior to transfusion.
5. Patients who are unstable or receive 1–2 RBCs and do not rapidly respond should be considered candidates for the massive transfusion (MT) guideline.

B. Adult Massive Transfusion Guideline:

1. The **Massive Transfusion Guideline (MTG)** should be initiated as soon as it is anticipated that a patient will require massive transfusion (≥10 U RBCs in 24 hours). The Blood Bank should strive to deliver plasma, platelets, and RBCs in a 1:1:1 ratio. To be effective and minimize further dilutional coagulopathy, the 1:1:1 ratio must be initiated early, ideally with the first 2 units of transfused RBCs. Crystalloid infusion should be minimized.
2. Once the MTG is activated, the Blood Bank will have 6 RBCs, 6 FFP, and a 6-pack of platelets packed in a cooler available for rapid transport. If 6 units of thawed FFP are not immediately available, the Blood Bank will issue units that are ready and notify appropriate personnel when the remainder is thawed. Every attempt should be made to obtain a 1:1:1 ratio of plasma:platelets:RBCs.
3. Once initiated, the MT will continue until stopped by the attending physician. MT should be terminated once the patient is no longer actively bleeding.
4. No blood components will be issued without a pickup slip with the recipient's medical record number and name.
5. Basic laboratory tests should be drawn immediately on ED arrival and optimally performed on point-of-care devices, facilitating timely delivery of relevant information to the attending clinicians. These tests should be repeated as clinically indicated (e.g., after each cooler of products has been transfused). Suggested laboratory values are:
   - CBC
   - INR, fibrinogen
   - pH and/or Base deficit
   - TEG, where available

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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Adult transfusion clinical practice guidelines. ED = emergency department; CBC = complete blood count; INR = International Normalized Ratio; TEG = thromboelastography.

Table 4-8 Component Therapy Administration during Massive Transfusion

Fresh-frozen plasma (FFP)	As soon as the need for massive transfusion is recognized. For every 6 units of red blood cells (RBCs), give 6 units of FFP (1:1 ratio).
Platelets	For every 6 units of RBCs and plasma, give one 6-pack of platelets. Six random-donor platelet packs = 1 apheresis platelet unit. Keep platelet counts >100,000 μ/L during active hemorrhage control.
Cryoprecipitate	After first 6 units of RBCs, check fibrinogen level. If ≤100 mg/dL, give 20 units of cryoprecipitate (2 g fibrinogen). Repeat as needed, depending on fibrinogen level.

When one center modified its transfusion practice so that plasma was started when the first units of red cells were administered rather than waiting until after 6 units of red cells were transfused, a significant decrease in 30-day mortality was demonstrated.[69] This work documents the importance of starting increased amounts of plasma early and supports a 1:1 ratio of plasma to red cells in patients receiving massive transfusion. This is a shift from traditional resuscitation strategies that called for the early use of crystalloids followed by packed red cells and the administration of plasma only after large amounts of blood products were transfused or to treat the resultant coagulopathy. As noted earlier, this new strategy has been termed *damage control resuscitation* and represents an alternative to traditional resuscitation standards. The central tenet of DCR is transfusion of plasma and red blood cells in a 1:1 ratio, started within minutes of the patient's arrival to the emergency department. In Iraq and Afghanistan, DCR practices are demonstrating unprecedented success with improved overall survival.[70] Greater use of platelets recently has been added to the DCR approach, because survival is improved with their early and increased use. As an adjunct to DCR, recombinant activated factor VII is used by the military and many major civilian trauma centers. Retrospective studies in combat wounded reveals an association with decreased transfusions and improved 30-day survival.[71] However, some studies have reported increased thrombotic complications after administration of factor VII.[72]

To verify military and single-institution civilian data on DCR, a multicenter retrospective study of modern transfusion practices at 17 leading civilian trauma centers was recently completed.[73] There was significant variation among centers, with plasma:platelet:red blood cell ratios varying from 1:1:1 to 0.3:0.1:1 and corresponding survival rates ranging from 71 to 41%. Centers using ratios approximating 1:1:1 demonstrated significantly fewer truncal hemorrhagic deaths and significantly lower 30-day mortality without a concomitant increase in multiple organ failure as a cause of death. A prospective observational study will soon commence to study the practice of the early use of plasma.

Because only a small percentage of trauma patients require a massive transfusion and blood products in general are in short supply, attempts have been made to develop early prediction models. A comparison of results from both civilian and military studies is shown in Table 4-9.[74–78] Although they are compelling, none of these algorithms has yet been prospectively validated.

Table 4-9 Comparison of Massive Transfusion Prediction Studies

Authors	Variables	ROC AUC Value
McLaughlin et al[73]	SBP, HR, pH, Hct	0.839
Yücel et al[74]	SBP, HR, BD, Hgb, male gender, + FAST, long bone/pelvic fracture	0.892
Moore et al[75]	SBP, pH, ISS >25	0.804

Schreiber et al[76]	Hgb ≤11, INR >1.5, penetrating injury	0.80
Wade et al[77]	SBP, HR, pH, Hct	0.78

AUC = area under the curve; BD = base deficit; FAST = focused assessment by sonography in trauma; Hct = hematocrit; Hgb = hemoglobin level; HR = heart rate; INR = International Normalized Ratio; ISS = injury severity score; ROC = receiver operating characteristic; SBP = systolic blood pressure.

Complications of Transfusion (Table 4-10)

Complications of transfusion are primarily related to blood-induced proinflammatory responses. Transfusion-related events are estimated to occur in approximately 10% of all transfusions, but <0.5% are serious. Transfusion-related deaths, although rare, do occur and are caused primarily by transfusion-related acute lung injury (16 to 22%), ABO hemolytic transfusion reactions (12 to 15%), and bacterial contamination of platelets (11 to 18%).[79]

Table 4-10 Transfusion-Related Complications

Abbreviation	Complication	Signs & Symptoms	Frequency	Mechanism	Prevention
NHTR	Febrile, nonhemolytic transfusion reaction	Fever	0.5–1.5% of transfusions	Preformed cytokines	Use leukocyte-reduced blood
				Host Ab to donor lymphocytes	
	Bacterial contamination	High fever, chills	<<0.05% of blood	Infusion of contaminated blood	Store platelets <5 d
		Hemodynamic changes	0.05% of platelets		
		DIC			
		Emesis, diarrhea			
		Hemoglobinuria			
	Allergic reactions	Rash, hives	0.1–0.3% of units	Soluble transfusion constituents	Provide antihistamine prophylaxis
		Itching			
TACO	Transfusion-associated circulatory overload	Pulmonary edema	? 1:200–1:10,00 of transfused patients	Large volume of blood transfused into an older patient with CHF	Increase transfusion time
					Administer diuretics
					Minimize associated fluids
TRALI	Transfusion-related acute lung injury	Acute (<6 h) hypoxemia		Anti-HLA or anti-HNA Ab in transfused blood attacks circulatory and pulmonary leukocytes	Limit female donors
		Bilateral infiltrates			
		± Tachycardia, hypotension			
	Hemolytic reactions				

	Acute	Fever	1:33,000–1:1,500,000 units	Transfusion of ABO incompatible blood	Transfuse appropriately matched blood
		Hypotension			
		DIC		Preformed IgM Ab to ABO Ag	
		Hemoglobinuria			
		Hemoglobinemia			
		Renal insufficiency			
	Delayed (2–10 d)	Anemia		IgG mediated	Identify patient's Ag to prevent recurrence
		Indirect hyperbilirubinemia			
		Elevated haptoglobin level			
		Positive result on direct Coombs' test			

Ab = antibody; Ag = antigen; CHF = congestive heart failure; DIC = disseminated intravascular coagulation; HLA = human leukocyte antigen; HNA = anti–human neutrophil antigen; IgG = immunoglobulin G; IgM = immunoglobulin M.

NONHEMOLYTIC REACTIONS

Febrile nonhemolytic reactions are defined as an increase in temperature [>1°C (1.8°F)] associated with a transfusion and are fairly common (approximately 1% of all transfusions). Preformed cytokines in donated blood and recipient antibodies reacting with donated antibodies are postulated causes. The incidence of febrile reactions can be greatly reduced by the use of leukocyte-reduced blood products. Pretreatment with acetaminophen reduces the severity of the reaction.

Bacterial contamination of infused blood is rare. Gram-negative organisms, especially *Yersinia enterocolitica* and *Pseudomonas* species, which are capable of growth at 4°C (39.2°F), are the most common cause. Most cases, however, are associated with the administration of platelets that are stored at 20°C (68°F) or even more commonly with apheresis platelets stored at room temperature. Bacterial contamination results in sepsis and death in up to 25% of patients.[80] Clinical manifestations include systemic signs such as fever and chills, tachycardia, and hypotension, and GI symptoms (abdominal cramps, vomiting, and diarrhea). There also can be hemorrhagic manifestations such as hemoglobinemia, hemoglobinuria, and disseminated intravascular coagulation. If the diagnosis is suspected, the transfusion should be discontinued and the blood cultured. Emergency treatment includes administration of oxygen, adrenergic blocking agents, and antibiotics. Prevention includes avoidance of out-of-date platelets.

ALLERGIC REACTIONS

Allergic reactions are relatively frequent, occurring in approximately 1% of all transfusions. Reactions usually are mild and consist of rash, urticaria, and fever occurring within 60 to 90 minutes of the start of the transfusion. In rare instances, anaphylactic shock develops. Allergic reactions are caused by the transfusion of antibodies from hypersensitive donors or the transfusion of antigens to which the recipient is hypersensitive. Allergic reactions can occur after the administration of any blood product. Treatment and prophylaxis consist of the administration of antihistamines. In more serious cases, use of epinephrine or steroids may be indicated.

RESPIRATORY COMPLICATIONS

Respiratory compromise may be associated with transfusion-associated circulatory overload, which is an avoidable complication. It can occur with rapid infusion of blood, plasma expanders, and crystalloids, particularly in older patients with underlying heart disease. Central venous pressure monitoring should be considered whenever large amounts of fluid are administered. Overload is manifest by a rise in venous pressure, dyspnea, and cough. Rales generally can be heard at the lung bases. Treatment consists of initiating diuresis, slowing the rate of blood administration, and minimizing delivery of fluids while blood products are being transfused.

The *syndrome of transfusion-related acute lung injury (TRALI)* is defined as noncardiogenic pulmonary edema related to transfusion.[81] It can occur with the administration of any plasma-containing blood product. Symptoms are similar to those of circulatory overload with dyspnea and associated hypoxemia. However, TRALI is characterized as noncardiogenic and often is accompanied by fever, rigors, and bilateral pulmonary infiltrates on chest radiograph. It most commonly occurs within 1 to 2 hours after the onset of transfusion, but virtually always before 6 hours. The actual incidence is unknown, because most cases are not reported (or not diagnosed). The etiology is not well established, but TRALI is thought to be related to anti-HLA or anti–human neutrophil antigen antibodies in transfused blood that primes neutrophils in the pulmonary circulation. Multiparity of the donor is considered a major risk factor for the development of TRALI. In a recent study by Gajic and colleagues, critically ill patients who received high volumes of plasma had worsened gas exchange after transfusion of components from female but not male donors.[82] This association of TRALI with components from female donors has prompted the American Association of Blood Banks to propose the use of male-only donor plasma. Treatment of TRALI entails discontinuation of any transfusion, notification of the transfusion service, and provision of pulmonary support, which may vary from supplemental oxygen to mechanical ventilation.

HEMOLYTIC REACTIONS

Hemolytic reactions can be classified as either acute of delayed. Acute hemolytic reactions occur with the administration of ABO-incompatible blood and are fatal in up to 6% of cases. Contributing factors include technical or clerical errors in the laboratory and administration of blood of the wrong blood type. Immediate hemolytic reactions are characterized by intravascular destruction of red blood cells and consequent hemoglobinemia and hemoglobinuria. DIC can be initiated activation of factor XII and complement by antibody-antigen complexes, which leads to initiation of the coagulation cascade. Finally, acute renal insufficiency results from the toxicity associated with free hemoglobin in the plasma, leading to tubular necrosis and precipitation of hemoglobin within the tubules.

Delayed hemolytic transfusion reactions occur 2 to 10 days after transfusion and are characterized by extravascular hemolysis, mild anemia, and indirect (unconjugated) hyperbilirubinemia. They occur when an individual has a low antibody titer at the time of transfusion but the titer increases after transfusion as a result of an anamnestic response. Reactions to non-ABO antigens involve immunoglobulin G–mediated clearance by the reticuloendothelial system.

If the patient is awake, the most common symptoms of acute transfusion reactions are pain at the site of transfusion, facial flushing, and back and chest pain. Associated symptoms include fever, respiratory distress, hypotension, and tachycardia. In anesthetized patients, diffuse bleeding and hypotension are the hallmarks. A high index of suspicion is needed to make the diagnosis. The laboratory criteria for a transfusion reaction are hemoglobinuria and serologic findings that show incompatibility of the donor and recipient blood. A positive Coombs' test result indicates the presence of transfused cells coated with patient antibody and is diagnostic. Delayed hemolytic transfusion reactions may also be manifested by fever and recurrent anemia. Jaundice and decreased haptoglobin levels usually occur, and low-grade hemoglobinemia and hemoglobinuria may be seen. The Coombs' test usually yields a positive result, and the blood bank must identify the antigen

to prevent subsequent reactions.

If an immediate hemolytic transfusion reaction is suspected, the transfusion should be stopped immediately and a sample of the recipient's blood drawn and sent along with the suspect unit to the blood bank for comparison with the pretransfusion samples. Urine output should be monitored and adequate hydration maintained to prevent precipitation of hemoglobin within the tubules. Delayed hemolytic transfusion reactions do not usually require specific intervention.

TRANSMISSION OF DISEASE

Among the diseases that have been transmitted by transfusion are malaria, Chagas' disease, brucellosis, and, very rarely, syphilis. Malaria can be transmitted by all blood components. The species most commonly implicated is *Plasmodium malariae.* The incubation period ranges from 8 to 100 days. The initial manifestations are shaking chills and spiking fever. Cytomegalovirus infection resembling infectious mononucleosis also has occurred.

Transmission of hepatitis C virus and HIV-1 has been dramatically minimized by the introduction of better antibody and nucleic acid screening for these pathogens. The infection rate for these pathogens is now estimated to be <1 per 1,000,000 units transfused. Hepatitis B virus transmission may still occur in about 1 in 100,000 transfusions in nonimmune recipients. Hepatitis A virus is very rarely transmitted because there is no asymptomatic carrier state. Recent concerns about the rare transmission of these and other pathogens, such as West Nile virus, are being addressed by current trials of "pathogen inactivation systems" that reduce infectious levels of all viruses and bacteria known to be transmittable by transfusion. Prion disorders (e.g., Creutzfeldt-Jakob disease) also are transmissible by transfusion, but there is currently no information on inactivation of prions in blood products for transfusion.

TESTS OF HEMOSTASIS AND BLOOD COAGULATION

The initial approach to assessing hemostatic function is a careful review of the patient's clinical history (including previous abnormal bleeding or bruising) and drug use, and basic laboratory testing. Common screening laboratory testing includes platelet count, PT or INR, and aPTT. Platelet dysfunction can occur at either extreme of platelet count. The normal platelet count ranges from 150,000 to 400,000/μL. Platelet counts >1,000,000/μL may be associated with bleeding or thrombotic complications. Increased bleeding complications may be seen with major surgical procedures when the platelet count is <100,000/μL and with minor surgical procedures when counts are <50,000/μL. Spontaneous hemorrhage can occur when the count falls below 20,000/μL.

The PT and aPTT are variations of plasma recalcification times initiated by the addition of a thromboplastic agent. The PT reagent contains thromboplastin and calcium that, when added to plasma, leads to the formation of a fibrin clot. The PT test measures the function of factors I, II, V, VII, and X. Factor VII is part of the extrinsic pathway and the remaining factors are part of the common pathway. Factor VII has the shortest half-life of the coagulation factors, and its synthesis is vitamin K dependent. The PT test is best suited to detection of abnormal coagulation caused by vitamin K deficiencies and warfarin therapy.

Due to variations in thromboplastin activity, it can be difficult to accurately assess the degree of anticoagulation on the basis of PT alone. To account for these variations, determination of the INR is now the method of choice for reporting PT values. The International Sensitivity Index (ISI) is unique to each batch of thromboplastin and is furnished by the manufacturer to the hematology laboratory. Human brain thromboplastin has an ISI of 1, and the optimal reagent has an ISI between 1.3 and 1.5.

The INR is a calculated number derived from the following equation:

$$\text{INR} = (\text{measured PT}/\text{normal PT})^{\text{ISI}}$$

The aPTT reagent contains a phospholipid substitute, activator, and calcium, which in the presence of plasma leads to fibrin clot formation. The aPTT measures function of factors I, II, and V of the common pathway and factors VIII, IX, X, and XII of the intrinsic pathway. Heparin therapy is often monitored by following aPTT values, with a therapeutic target range of 1.5 to 2.5 times the control value (approximately 50 to 80 seconds). Low molecular weight heparins are selective factor Xa inhibitors and may mildly elevate the aPTT, but therapeutic monitoring is not routinely recommended.

The bleeding time is used to evaluate platelet and vascular dysfunction, although not so frequently as in the past. Several standard methods have been described; however, the Ivy bleeding time is most commonly used. It is determined by placing a sphygmomanometer on the upper arm and inflating it to 40 mmHg and then making a 5-mm stab incision on the flexor surface of the forearm. The time is measured to cessation of bleeding, and the upper limit of normal bleeding time with Ivy's test is 7 minutes. A template aids in administering the test uniformly and adds to the reproducibility of the results. An abnormal bleeding time suggests either platelet dysfunction (intrinsic or drug induced), vWD, or certain vascular defects. Many laboratories are replacing the template bleeding time with an in vitro test in which blood is sucked through a capillary and the platelets adhere to the walls of the capillary and aggregate. The closure time in this system appears to be more reproducible than the bleeding time and also correlates with bleeding in patients with vWD, primary platelet function disorders, or other platelet dysfunction disorders and patients who are taking aspirin.

Additional medications may significantly impair hemostatic function, such as antiplatelet agents (clopidogrel and glycoprotein IIb/IIIa inhibitors), anticoagulant agents (hirudin, chondroitin sulfate, dermatan sulfate), and thrombolytic agents (streptokinase, tPA). If abnormal results on any of the coagulation studies cannot be explained by known medications, congenital abnormalities of coagulation or comorbid disease should be considered.

Thromboelastography (TEG) was originally described by Hartert in 1948.[83] Continuous improvements in this technique have made this test a valuable tool. TEG monitors hemostasis as a dynamic process rather than revealing isolated information as in conventional coagulation screens.[84] TEG measures the viscoelastic properties of blood as it is induced to clot in a low-shear environment (resembling sluggish venous flow). The patterns of change in shear elasticity allow the kinetics of clot formation and growth as well as the strength and stability of the formed clot to be determined. The strength and stability data provide information about the ability of the clot to perform the work of hemostasis, whereas the kinetic data determine the adequacy of quantitative factors available for clot formation. A sample of celite-activated whole blood is placed into a prewarmed cuvette. A suspended piston is then lowered into the cuvette, which is rotated through a 4.5-degree arc backwards and forwards. The normal clot goes through an acceleration and strengthening phase. The fiber strands that interact with activated platelets attach to the surface of the cuvette and the suspended piston. The clot forming in the cuvette transmits its movement onto the suspended piston. A weak clot stretches and therefore delays the arc movement of the piston, which is graphically expressed as a narrow thromboelastogram. A strong clot, in contrast, will move the piston simultaneously and proportionally to the cuvette's movements, creating a thick thromboelastogram.[85]

The strength of a clot is graphically represented over time as a characteristic cigar-shaped figure (Fig. 4-7). There are five parameters of the TEG(r) tracing: R, k, alpha angle, MA, and MA60, all of which measure different stages of clot development.

R is the time from the commencement of the test to the initial fibrin formation.

k is a measure of the time from the beginning of clot formation until the amplitude of the TEG tracing reaches 20 mm and represents the dynamics of clot formation.

alpha angle is the angle between the line in the middle of the TEG(r) tracing and the line tangential to the developing body of the TEG(r) tracing. The alpha angle represents the acceleration (kinetics) of fibrin buildup and cross-linking.

MA is the maximum amplitude and reflects the strength of the clot, which is dependent on the number and function of platelets and the clot's interaction with fibrin.

MA60 is the rate of amplitude reduction 60 minutes after MA and represents the stability of the clot.

Fig. 4-7.

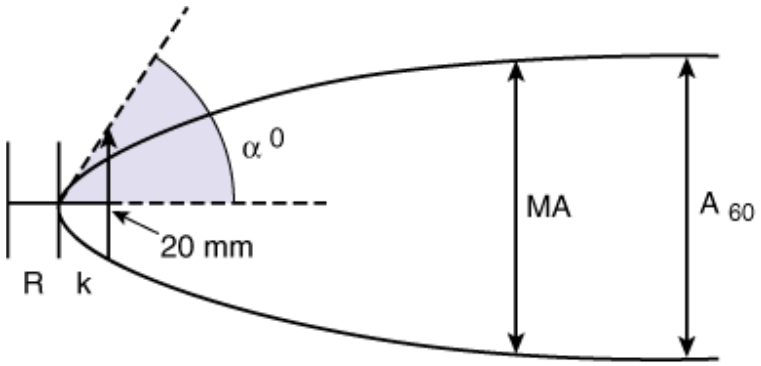

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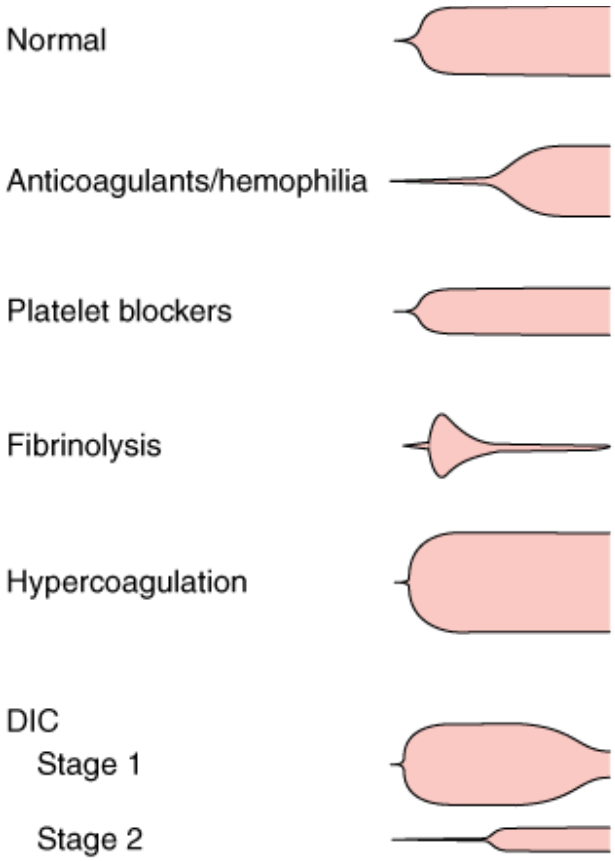
Illustration of a thromboelastographic tracing. See text for explanation of parameters.

Examples of normal and abnormal TEG tracings are shown in Fig. 4-8. The usefulness of TEG has been sufficiently documented in general surgery,[86,87] cardiac surgery,[88] urologic surgery,[89] obstetrics,[90] pediatrics,[91] and liver transplantation.[92,93] It is the only test measuring all dynamic steps of clot formation until eventual clot lysis or retraction. Its role in evaluating coagulopathic patients is still being investigated.

Fig. 4-8.



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Examples of normal and abnormal thromboelastographic tracings. DIC = disseminated intravascular coagulation.

EVALUATION OF HEMOSTATIC RISK IN THE SURGICAL PATIENT

Preoperative Evaluation of Hemostasis

Several hematologic disorders may have an impact on the outcome of surgery. The more common clinical situations faced by the surgeon are pre-existing anemia and oral anticoagulation therapy. Assessment of bleeding risk should also be considered in patients with liver or renal dysfunction.

When feasible, diagnostic evaluation of the patient with previously unrecognized anemia should be carried out before surgery, because certain types of anemia (particularly sickle cell disease and immune hemolytic anemias) may have implications for perioperative management. Hemoglobin levels below 7 or 8 g/dL appear to be associated with significantly more perioperative complications than higher levels.[94] Determination of the need for preoperative transfusion in an individual patient must consider factors other than the absolute hemoglobin level, including the presence of cardiopulmonary disease, the type of surgery, and the likelihood of surgical blood loss. Many patients have anemia postoperatively secondary to blood loss and hemodilution and do not necessarily require transfusion.

The most important component of the bleeding risk assessment is a directed bleeding history. A detailed patient history can provide meaningful clues to the presence of a bleeding tendency, such as easy bruising or a family history of bleeding problems. Patients who are reliable historians and who reveal no suggestion of abnormal bleeding on directed bleeding history and physical examination are at very low risk for having an occult bleeding disorder. Laboratory tests of hemostatic

parameters in patients with low risk of bleeding are not required. When the directed bleeding history is unreliable or incomplete or when abnormal bleeding is suggested, a formal evaluation of hemostasis should be performed before surgery including measurement of the PT, the aPTT, and the platelet count.[95]

Evaluation of Excessive Intraoperative or Postoperative Bleeding

Excessive bleeding during or after a surgical procedure may be the result of ineffective hemostasis, blood transfusion, undetected hemostatic defect, consumptive coagulopathy, and/or fibrinolysis. Excessive bleeding from the operative field unassociated with bleeding from other sites usually suggests inadequate mechanical hemostasis.

Massive blood transfusion is a well-known cause of thrombocytopenia. Bleeding after massive transfusion can occur due to hypothermia, dilutional coagulopathy, platelet dysfunction, fibrinolysis, or hypofibrinogenemia. Another cause of hemostatic failure related to the administration of blood is hemolytic transfusion reaction. The first sign of a transfusion reaction may be diffuse bleeding. The pathogenesis of this bleeding is thought to be related to the release of ADP from hemolyzed red blood cells, resulting in diffuse platelet aggregation, after which the platelet clumps are removed out of the circulation.

Transfusion purpura occurs when the donor platelets are of the uncommon Pl(A1) group. This is an uncommon cause of thrombocytopenia and associated bleeding after transfusion. The platelets sensitize the recipient, who makes antibody to the foreign platelet antigen. The foreign platelet antigen does not completely disappear from the recipient circulation but attaches to the recipient's own platelets. The antibody then destroys the recipient's own platelets. The resultant thrombocytopenia and bleeding may continue for several weeks. This uncommon cause of thrombocytopenia should be considered if bleeding follows transfusion by 5 or 6 days. Platelet transfusions are of little help in the management of this syndrome, because the new donor platelets usually are subject to the binding of antigen and damage from the antibody. Corticosteroids may be of some help in reducing the bleeding tendency. Posttransfusion purpura is self-limited, and the passage of several weeks inevitably leads to subsidence of the problem.

DIC is characterized by systemic activation of the blood coagulation system, which results in the generation and deposition of fibrin, leading to microvascular thrombi in various organs and contributing to the development of multiorgan failure. Consumption and subsequent exhaustion of coagulation proteins and platelets due to the ongoing activation of the coagulation system may induce severe bleeding complications.

Lastly, severe hemorrhagic disorders due to thrombocytopenia have occurred as a result of gram-negative sepsis. The pathogenesis of endotoxin-induced thrombocytopenia has been suggested to be related to lability of factor V, which appears necessary for this interaction. Defibrination and hemostatic failure also may occur with meningococcemia, *Clostridium perfringens* sepsis, and staphylococcal sepsis. Hemolysis appears to be one mechanism in sepsis leading to defibrination.

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KEY POINTS

1. Shock is defined as a failure to meet the metabolic demands of cells and tissues and the consequences that ensue.

2. A central component of shock is decreased tissue perfusion. This may be a direct consequence of the etiology of shock, such as in hypovolemic/hemorrhagic, cardiogenic, or neurogenic etiologies, or may be secondary to elaborated or released molecules or cellular products that result in endothelial/cellular activation, such as in septic shock or traumatic shock.

3. Physiologic responses to shock are based upon a series of afferent (sensing) signals and efferent responses that include neuroendocrine, metabolic, and immune/inflammatory signaling.

4. The mainstay of treatment of hemorrhagic/hypovolemic shock includes volume resuscitation with blood products and fluids. In the case of hemorrhagic shock, timely control of bleeding is essential and influences outcome.

5. Prevention of hypothermia, acidemia, and coagulopathy are essential in the management of patients in hemorrhagic shock.

6. The mainstay of treatment of septic shock is fluid resuscitation, initiation of appropriate antibiotic therapy, and control of the source of infection. This includes drainage of infected fluid collections, removal of infected foreign bodies, and débridement of devitalized tissues.

7. A combination of physiologic parameters and markers of organ perfusion/tissue oxygenation are used to determine if patients are in shock and to follow the efficacy of resuscitation.

EVOLUTION IN UNDERSTANDING SHOCK

"Shock is the manifestation of the rude unhinging of the machinery of life."[1]

—Samuel V. Gross, 1872

Overview

Shock, at its most rudimentary definition and regardless of the etiology, is the failure to meet the metabolic needs of the cell and the consequences that ensue. The initial cellular injury that occurs is reversible; however, the injury will become irreversible if tissue perfusion is prolonged or severe enough such that, at the cellular level, compensation is no longer possible. Our evolution in the understanding of shock and the disease processes that result in shock made its most significant advances throughout the twentieth century as our appreciation for the physiology and pathophysiology of shock matured. Most notably, this includes the sympathetic and neuroendocrine stress responses on the cardiovascular system. The clinical manifestations of these physiologic responses are most often what lead practitioners to the diagnosis of shock as well as guide the management of patients in shock. However, hemodynamic parameters such as blood pressure and heart rate are relatively insensitive measures of shock, and additional considerations must be used to help aid in early diagnosis and treatment of patients in shock. The general approach to the management of patients in shock has been empiric: assuring a secure airway with adequate ventilation and restoration of vascular volume and tissue perfusion.

Historical Background

Integral to our understanding of shock is the appreciation that our bodies attempt to maintain a state of homeostasis. Claude Bernard suggested in the mid-nineteenth century that the organism attempts to maintain constancy in the internal environment against external forces that attempt to disrupt the *milieu interieur*.[2] Walter B. Cannon carried Bernard's observations further and introduced the term *homeostasis*, emphasizing that an organism's ability to survive was related to maintenance of homeostasis.[3] The failure of physiologic

systems to buffer the organism against external forces results in organ and cellular dysfunction, what is clinically recognized as shock. He first described the "*fight or flight response*," generated by elevated levels of catecholamines in the bloodstream. Cannon's observations on the battlefields of World War I led him to propose that the initiation of shock was due to a disturbance of the nervous system that resulted in vasodilation and hypotension. He proposed that secondary shock, with its attendant capillary permeability leak, was caused by a "toxic factor" released from the tissues.

In a series of critical experiments, Alfred Blalock documented that the shock state in hemorrhage was associated with reduced cardiac output due to volume loss, not a "toxic factor."[4] In 1934, Blalock proposed four categories of shock: hypovolemic, vasogenic, cardiogenic, and neurogenic. *Hypovolemic shock*, the most common type, results from loss of circulating blood volume. This may result from loss of whole blood (hemorrhagic shock), plasma, interstitial fluid (bowel obstruction), or a combination. *Vasogenic shock* results from decreased resistance within capacitance vessels, usually seen in sepsis. *Neurogenic shock* is a form of vasogenic shock in which spinal cord injury or spinal anesthesia causes vasodilation due to acute loss of sympathetic vascular tone. *Cardiogenic shock* results from failure of the heart as a pump, as in arrhythmias or acute myocardial infarction (MI).

This categorization of shock based on etiology persists today (Table 5-1). In recent clinical practice, further classification has described six types of shock: hypovolemic, septic (vasodilatory), neurogenic, cardiogenic, obstructive, and traumatic shock. *Obstructive shock* is a form of cardiogenic shock that results from mechanical impediment to circulation leading to depressed cardiac output rather than primary cardiac failure. This includes etiologies such as pulmonary embolism or tension pneumothorax. In *traumatic shock*, soft tissue and bony injury lead to the activation of inflammatory cells and the release of circulating factors, such as cytokines and intracellular molecules that modulate the immune response. Recent investigations have revealed that the inflammatory mediators released in response to tissue injury [damage-associated molecular patterns (DAMPs)] are recognized by many of the same cellular receptors [pattern recognition receptors (PRRs)] and activate similar signaling pathways as do bacterial products elaborated in sepsis (pathogen-associated molecular patterns), such as lipopolysaccharide.[5] These effects of tissue injury are combined with the effects of hemorrhage, creating a more complex and amplified deviation from homeostasis.

Table 5-1 Classification of Shock
Hypovolemic
Cardiogenic
Septic (vasogenic)
Neurogenic
Traumatic
Obstructive

In the mid- to later twentieth century, the further development of experimental models contributed significantly to the understanding of the pathophysiology of shock. In 1947, Wiggers developed a sustainable, irreversible model of hemorrhagic shock based on uptake of shed blood into a reservoir to maintain a set level of hypotension.[6] G. Tom Shires added further understanding of hemorrhagic shock with a series of clinical studies demonstrating that a large extracellular fluid deficit, greater than could be attributed to vascular refilling alone, occurred in severe hemorrhagic shock.[7,8] The phenomenon of fluid redistribution after major trauma involving blood loss was termed *third spacing* and described the translocation of intravascular volume into the peritoneum, bowel, burned tissues, or crush injury sites. These seminal studies form the scientific basis for the current treatment of hemorrhagic shock with red blood cells and lactated Ringer's solution or isotonic saline.

As resuscitation strategies evolved and patients survived the initial consequences of hemorrhage, new challenges of sustained shock became apparent. During the Vietnam War, aggressive fluid resuscitation with red blood cells and crystalloid solution or plasma resulted in survival of patients who previously would have succumbed to hemorrhagic shock. Renal failure became a less frequent clinical problem; however, a new disease process, acute fulminant pulmonary failure, appeared as an early cause of death after seemingly successful surgery to control hemorrhage. Initially called *DaNang lung* or *shock lung*, the clinical problem became recognized as acute respiratory distress syndrome (ARDS). This led to new methods of prolonged mechanical ventilation. Our current concept of ARDS is a component in the spectrum of multiple organ system failure.

Studies and clinical observations over the past two decades have extended the early observations of Canon, that "restoration of blood pressure prior to control of active bleeding may result in loss of blood that is sorely needed," and challenged the appropriate endpoints in resuscitation of uncontrolled hemorrhage.[9] Core principles in the management of the critically ill or injured patient include: (a) definitive control of the airway must be secured, (b) control of active hemorrhage must occur promptly (delay in control of bleeding increases mortality and recent battlefield data would suggest that in the young and otherwise healthy population commonly injured in combat, that control of bleeding is the paramount priority), (c) volume resuscitation with red blood cells, plasma, and crystalloid must occur while operative control of bleeding is achieved, (d) unrecognized or inadequately corrected hypoperfusion increases morbidity and mortality (i.e., inadequate resuscitation results in avoidable early deaths from shock), and (e) excessive fluid resuscitation may exacerbate bleeding (i.e., uncontrolled resuscitation is harmful). Thus both inadequate and uncontrolled volume resuscitation is harmful.

Current Definitions and Challenges

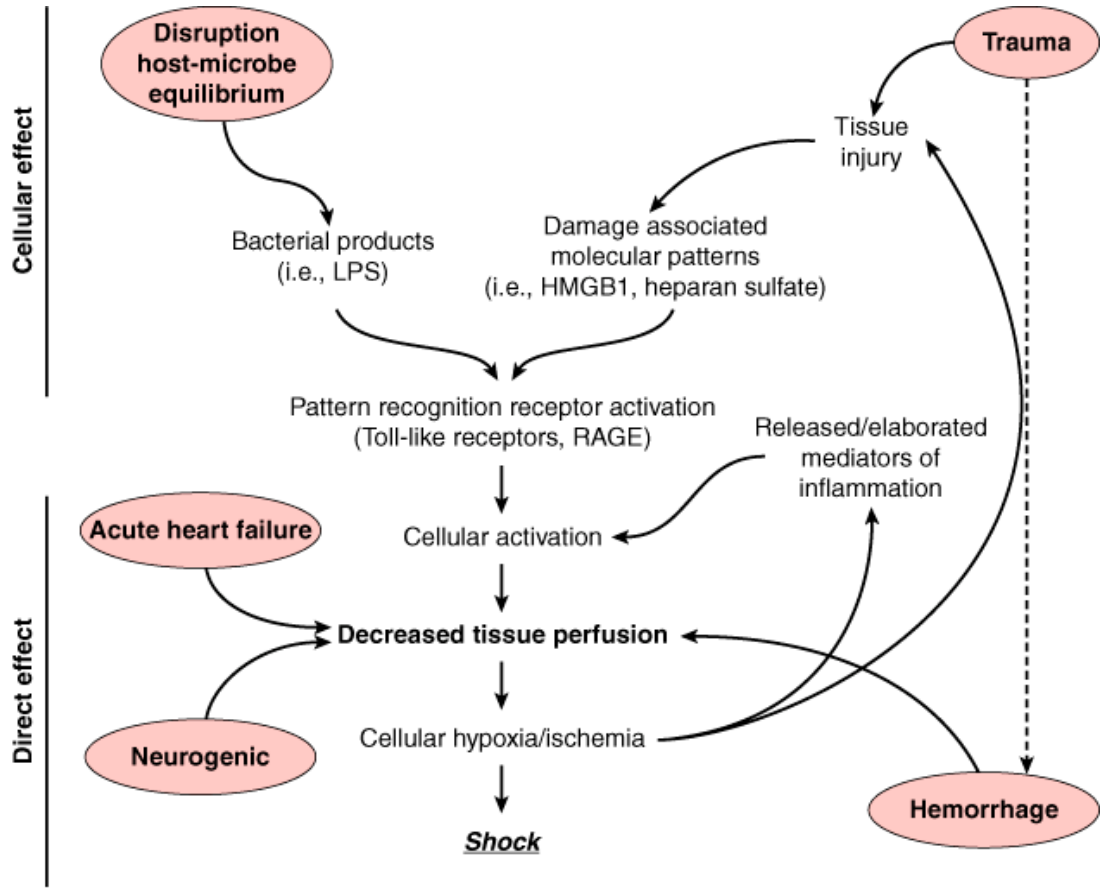
A modern definition and approach to shock acknowledges that shock consists of inadequate tissue perfusion marked by decreased delivery of required metabolic substrates and inadequate removal of cellular waste products. This involves failure of oxidative metabolism that can involve defects of oxygen (O_2) delivery, transport, and/or utilization. Current challenges include moving beyond fluid resuscitation based upon endpoints of tissue oxygenation, and using therapeutic strategies at the cellular and molecular level. This approach will help to identify compensated patients or patients early in the course of their disease, initiate appropriate treatment, and allow for continued evaluation for the efficacy of resuscitation and adjuncts.

Current investigations focus on determining the cellular events that often occur in parallel to result in organ dysfunction, shock irreversibility, and death. This chapter will review our current understanding of the pathophysiology and cellular responses of shock states. Current and experimental diagnostic and therapeutic modalities for the different categories of shock are reviewed, with a focus on hemorrhagic/hypovolemic shock and septic shock.

PATHOPHYSIOLOGY OF SHOCK

Regardless of etiology, the initial physiologic responses in shock are driven by tissue hypoperfusion and the developing cellular energy deficit. This imbalance between cellular supply and demand leads to neuroendocrine and inflammatory responses, the magnitude of which is usually proportional to the degree and duration of shock. The specific responses will differ based on the etiology of shock, as certain physiologic responses may be limited by the inciting pathology. For example, the cardiovascular response driven by the sympathetic nervous system is markedly blunted in neurogenic or septic shock. Additionally, decreased perfusion may occur as a consequence of cellular activation and dysfunction, such as in septic shock and to a lesser extent traumatic shock (Fig. 5-1). Many of the organ-specific responses are aimed at maintaining perfusion in the cerebral and coronary circulation. These are regulated at multiple levels including (a) stretch receptors and baroreceptors in the heart and vasculature (carotid sinus and aortic arch), (b) chemoreceptors, (c) cerebral ischemia responses, (d) release of endogenous vasoconstrictors, (e) shifting of fluid into the intravascular space, and (f) renal reabsorption and conservation of salt and water.

Fig. 5-1.



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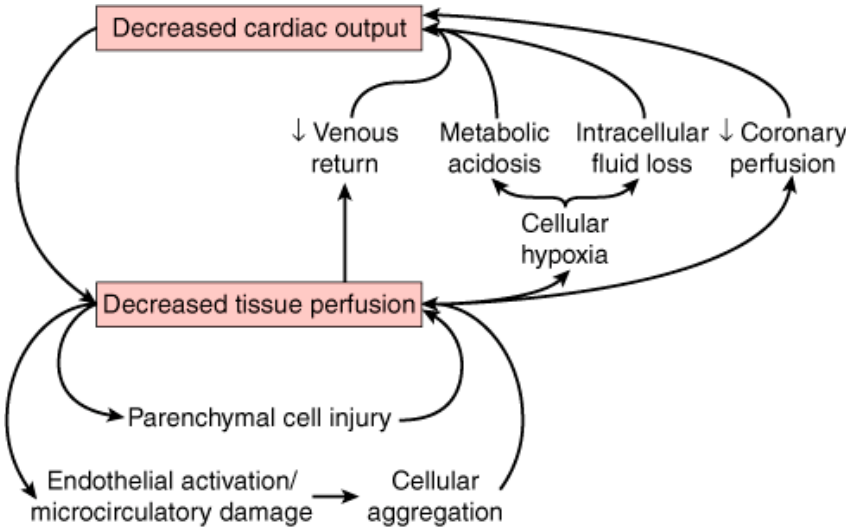
Pathways leading to decreased tissue perfusion and shock. Decreased tissue perfusion can result directly from hemorrhage/hypovolemia, cardiac failure, or neurologic injury. Decreased tissue perfusion and cellular injury can then result in immune and inflammatory responses. Alternatively, elaboration of microbial products during infection or release of endogenous cellular products from tissue injury can result in cellular activation to subsequently influence tissue perfusion and the development of shock. HMGB1 = high mobility group box 1; LPS = lipopolysaccharide; RAGE = receptor for advanced glycation end products.

Furthermore, the pathophysiologic responses vary with time and in response to resuscitation. In hemorrhagic shock, the body can compensate for the initial loss of blood volume primarily through the neuroendocrine response to maintain hemodynamics. This represents the *compensated phase* of shock. With continued hypoperfusion, which may be unrecognized, cellular death and injury are ongoing and the *decompensation phase* of shock ensues. Microcirculatory dysfunction, parenchymal tissue damage, and inflammatory cell activation can perpetuate hypoperfusion. Ischemia/reperfusion injury will often exacerbate the initial insult. These effects at the cellular level, if untreated, will lead to compromise of function at the organ system level, thus leading to the "*vicious cycle*" of shock (Fig. 5-2). Persistent hypoperfusion results in further hemodynamic derangements and cardiovascular collapse. This has been termed the *irreversible phase* of shock and can develop quite insidiously and may only be obvious in retrospect. At this point there has occurred extensive enough parenchymal and microvascular injury such that volume resuscitation fails to reverse the process, leading to death of the patient. In experimental animal models of hemorrhagic shock (modified Wiggers model), this is represented by the "uptake phase" or "compensation endpoint" when shed blood must be returned to the animal to sustain the hypotension at the set level to prevent further hypotension and death.[10] If shed blood volume is slowly returned to maintain the set level of hypotension, eventually the injury progresses to irreversible shock, where further volume will not reverse the process and the animal dies (Fig. 5-3).

Fig. 5-2.



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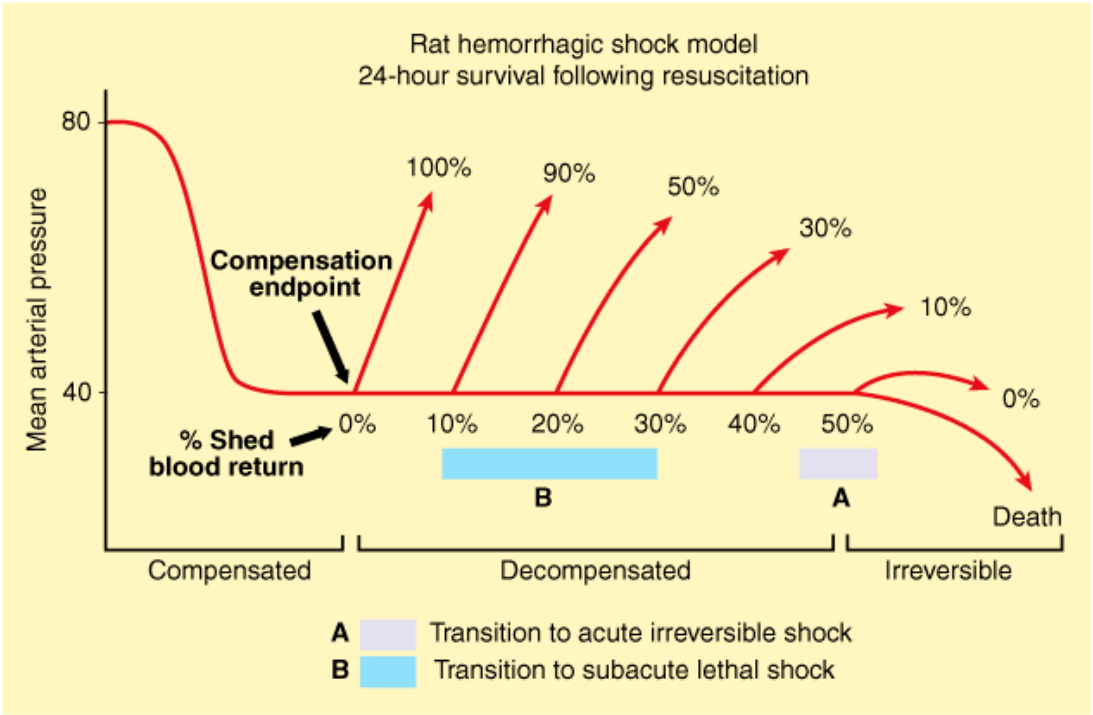
The "vicious cycle of shock." Regardless of the etiology, decreased tissue perfusion and shock results in a feed-forward loop that can exacerbate cellular injury and tissue dysfunction.

Fig. 5-3.



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Rat model of hemorrhagic shock through the phases of compensation, decompensation, and irreversibility. The percentages shown above the curve represent survival rates. (From Shah et al,[10] with permission.)

Neuroendocrine and Organ-Specific Responses to Hemorrhage

The goal of the neuroendocrine response to hemorrhage is to maintain perfusion to the heart and the brain, even at the expense of other organ systems. Peripheral vasoconstriction occurs, and fluid excretion is inhibited. The mechanisms include autonomic control of peripheral

vascular tone and cardiac contractility, hormonal response to stress and volume depletion, and local microcirculatory mechanisms that are organ specific and regulate regional blood flow. The initial stimulus is loss of circulating blood volume in hemorrhagic shock. The magnitude of the neuroendocrine response is based on both the volume of blood lost and the rate at which it is lost.

Afferent Signals

Afferent impulses transmitted from the periphery are processed within the central nervous system (CNS) and activate the reflexive effector responses or efferent impulses. These effector responses are designed to expand plasma volume, maintain peripheral perfusion and tissue O_2 delivery, and restore homeostasis. The afferent impulses that initiate the body's intrinsic adaptive responses and converge in the CNS originate from a variety of sources. The initial inciting event usually is loss of circulating blood volume. Other stimuli that can produce the neuroendocrine response include pain, hypoxemia, hypercarbia, acidosis, infection, change in temperature, emotional arousal, or hypoglycemia. The sensation of pain from injured tissue is transmitted via the spinothalamic tracts, resulting in activation of the hypothalamic-pituitary-adrenal axis, as well as activation of the autonomic nervous system (ANS) to induce direct sympathetic stimulation of the adrenal medulla to release catecholamines.

Baroreceptors also are an important afferent pathway in initiation of adaptive responses to shock. Volume receptors, sensitive to changes in both chamber pressure and wall stretch, are present within the atria of the heart. They become activated with low volume hemorrhage or mild reductions in right atrial pressure. Receptors in the aortic arch and carotid bodies respond to alterations in pressure or stretch of the arterial wall, responding to larger reductions in intravascular volume or pressure. These receptors normally inhibit induction of the ANS. When activated, these baroreceptors diminish their output, thus disinhibiting the effect of the ANS. The ANS then increases its output, principally via sympathetic activation at the vasomotor centers of the brain stem, producing centrally mediated constriction of peripheral vessels.

Chemoreceptors in the aorta and carotid bodies are sensitive to changes in O_2 tension, H^+ ion concentration, and carbon dioxide (CO_2) levels. Stimulation of the chemoreceptors results in vasodilation of the coronary arteries, slowing of the heart rate, and vasoconstriction of the splanchnic and skeletal circulation. In addition, a variety of protein and nonprotein mediators are produced at the site of injury as part of the inflammatory response, and they act as afferent impulses to induce a host response. These mediators include histamine, cytokines, eicosanoids, and endothelins, among others that are discussed in greater detail later in this chapter in the Immune and Inflammatory Responses section.

Efferent Signals

CARDIOVASCULAR RESPONSE

Changes in cardiovascular function are a result of the neuroendocrine response and ANS response to shock, and constitute a prominent feature of both the body's adaptive response mechanism, and the clinical signs and symptoms of the patient in shock. Hemorrhage results in diminished venous return to the heart and decreased cardiac output. This is compensated by increased cardiac heart rate and contractility, as well as venous and arterial vasoconstriction. Stimulation of sympathetic fibers innervating the heart leads to activation of $beta_1$-adrenergic receptors that increase heart rate and contractility in this attempt to increase cardiac output. Increased myocardial O_2 consumption occurs as a result of the increased workload; thus, myocardial O_2 supply must be maintained or myocardial dysfunction will develop. The cardiovascular response in hemorrhage/hypovolemia differs from the responses elicited with the other etiologies of shock. These are compared in Table 5-2.

Table 5-2 Hemodynamic Responses to Different Types of Shock

Type of Shock	Cardiac Index	SVR	Venous Capacitance	CVP/PCWP	Svo_2	Cellular/Metabolic Effects
Hypovolemic	↓	↑	↓	↓	↓	Effect
Septic	↑↑	↓	↑	↑ ↓	↑↓	Cause
Cardiogenic	↓↓	↑↑	→	↑	↓	Effect
Neurogenic	↑	↓	→	↓	↓	Effect

The hemodynamic responses are indicated by arrows to show an increase (↑), severe increase (↑↑), decrease (↓), severe decrease (↓ ↓), ↑↓ →

varied response ( ), or little effect ( ). CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; Svo_2 = mixed venous oxygen saturation; SVR = systemic vascular resistance.

Direct sympathetic stimulation of the peripheral circulation via the activation of $alpha_1$-adrenergic receptors on arterioles induces vasoconstriction and causes a compensatory increase in systemic vascular resistance and blood pressure. The arterial vasoconstriction is not uniform; marked redistribution of blood flow results. Selective perfusion to tissues occurs due to regional variations in arteriolar resistance, with blood shunted away from less essential organ beds such as the intestine, kidney, and skin. In contrast, the brain and heart have autoregulatory mechanisms that attempt to preserve their blood flow despite a global decrease in cardiac output. Direct sympathetic stimulation also induces constriction of venous vessels, decreasing the capacitance of the circulatory system and accelerating blood return to the central circulation.

Increased sympathetic output induces catecholamine release from the adrenal medulla. Catecholamine levels peak within 24 to 48 hours of injury, and then return to baseline. Persistent elevation of catecholamine levels beyond this time suggests ongoing noxious afferent stimuli. The majority of the circulating epinephrine is produced by the adrenal medulla, while norepinephrine is derived from synapses of the sympathetic nervous system. Catecholamine effects on peripheral tissues include stimulation of hepatic glycogenolysis and gluconeogenesis to increase circulating glucose availability to peripheral tissues, an increase in skeletal muscle glycogenolysis, suppression of insulin release, and increased glucagon release.

HORMONAL RESPONSE

The stress response includes activation of the ANS as discussed above in the Afferent Signals secition, as well as activation of the hypothalamic-pituitary-adrenal axis. Shock stimulates the hypothalamus to release corticotropin-releasing hormone, which results in the release of adrenocorticotropic hormone (ACTH) by the pituitary. ACTH subsequently stimulates the adrenal cortex to release cortisol. Cortisol acts synergistically with epinephrine and glucagon to induce a catabolic state. Cortisol stimulates gluconeogenesis and insulin resistance, resulting in hyperglycemia as well as muscle cell protein breakdown and lipolysis to provide substrates for hepatic gluconeogenesis. Cortisol causes retention of sodium and water by the nephrons of the kidney. In the setting of severe hypovolemia, ACTH secretion occurs independently of cortisol negative feedback inhibition.

The renin-angiotensin system is activated in shock. Decreased renal artery perfusion, beta-adrenergic stimulation, and increased renal tubular sodium concentration cause the release of renin from the juxtaglomerular cells. Renin catalyzes the conversion of angiotensinogen (produced by the liver) to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme (ACE) produced in the lung. While angiotensin I has no significant functional activity, angiotensin II is a potent vasoconstrictor of both splanchnic and peripheral vascular beds, and also stimulates the secretion of aldosterone, ACTH, and antidiuretic hormone (ADH). Aldosterone, a mineralocorticoid, acts on the nephron to promote reabsorption of sodium, and as a consequence, water. Potassium and hydrogen ions are lost in the urine in exchange for sodium.

The pituitary also releases vasopressin or ADH in response to hypovolemia, changes in circulating blood volume sensed by baroreceptors and left atrial stretch receptors, and increased plasma osmolality detected by hypothalamic osmoreceptors. Epinephrine, angiotensin II, pain, and hyperglycemia increase production of ADH. ADH levels remain elevated for about 1 week after the initial insult, depending on the severity and persistence of the hemodynamic abnormalities. ADH acts on the distal tubule and collecting duct of the nephron to increase water permeability, decrease water and sodium losses, and preserve intravascular volume. Also known as *arginine vasopressin*, ADH acts as a potent mesenteric vasoconstrictor, shunting circulating blood away from the splanchnic organs during hypovolemia.[11] This may contribute to intestinal ischemia and predispose to intestinal mucosal barrier dysfunction in shock states. Vasopressin also increases hepatic gluconeogenesis and increases hepatic glycolysis.

In septic states, endotoxin directly stimulates arginine vasopressin secretion independently of blood pressure, osmotic, or intravascular volume changes. Proinflammatory cytokines also contribute to arginine vasopressin release. Interestingly, patients on chronic therapy with ACE inhibitors are more at risk of developing hypotension and vasodilatory shock with open heart surgery. Low plasma levels of arginine vasopressin were confirmed in these patients.[12]

Circulatory Homeostasis

PRELOAD

At rest, the majority of the blood volume is within the venous system. Venous return to the heart generates ventricular end-diastolic wall tension, a major determinant of cardiac output. Gravitational shifts in blood volume distribution are quickly corrected by alterations in venous capacity. With decreased arteriolar inflow, there is active contraction of the venous smooth muscle and passive elastic recoil in the thin-walled systemic veins. This increases venous return to the heart, thus maintaining ventricular filling.

Most alterations in cardiac output in the normal heart are related to changes in preload. Increases in sympathetic tone have a minor effect on skeletal muscle beds but produce a dramatic reduction in splanchnic blood volume, which normally holds 20% of the blood volume.

The normal circulating blood volume is maintained within narrow limits by the kidney's ability to manage salt and water balance with external losses via systemic and local hemodynamic changes and hormonal effects of renin, angiotensin, and ADH. These relatively slow responses maintain preload by altering circulating blood volume. Acute responses to intravascular volume include changes in venous tone, systemic vascular resistance, and intrathoracic pressure, with the slower hormonal changes less important in the early response to volume loss. Furthermore, the net effect of preload on cardiac output is influenced by cardiac determinants of ventricular function, which include coordinated atrial activity and tachycardia.

VENTRICULAR CONTRACTION

The Frank-Starling curve describes the force of ventricular contraction as a function of its preload. This relationship is based on force of contraction being determined by initial muscle length. Intrinsic cardiac disease will shift the Frank-Starling curve and alter mechanical performance of the heart. In addition, cardiac dysfunction has been demonstrated experimentally in burns and in hemorrhagic, traumatic, and septic shock.

AFTERLOAD

Afterload is the force that resists myocardial work during contraction. Arterial pressure is the major component of afterload influencing the ejection fraction. This vascular resistance is determined by precapillary smooth muscle sphincters. Blood viscosity also will increase vascular resistance. As afterload increases in the normal heart, stroke volume can be maintained by increases in preload. In shock, with decreased circulating volume and therefore diminished preload, this compensatory mechanism to sustain cardiac output is impeded. The stress response with acute release of catecholamines and sympathetic nerve activity in the heart increases contractility and heart rate.

MICROCIRCULATION

The microvascular circulation plays an integral role in regulating cellular perfusion and is significantly influenced in response to shock. The microvascular bed is innervated by the sympathetic nervous system and has a profound effect on the larger arterioles. Following hemorrhage, larger arterioles vasoconstrict; however, in the setting of sepsis or neurogenic shock, these vessels vasodilate. Additionally, a host of other vasoactive proteins, including vasopressin, angiotensin II, and endothelin-1, also lead to vasoconstriction to limit organ perfusion to organs such as skin, skeletal muscle, kidneys, and the GI tract to preserve perfusion of the myocardium and CNS.

Flow in the capillary bed often is heterogeneous in shock states, which likely is secondary to multiple local mechanisms, including endothelial cell swelling, dysfunction, and activation marked by the recruitment of leukocytes.[13] Together, these mechanisms lead to diminished capillary perfusion that may persist after resuscitation. In hemorrhagic shock, correction of hemodynamic parameters and restoration of O_2 delivery generally leads to restoration of tissue O_2 consumption and tissue O_2 levels. In contrast, regional tissue dysoxia often persists in sepsis, despite similar restoration of hemodynamics and O_2 delivery. Whether this defect in O_2 extraction in sepsis is the result of heterogeneous impairment of the microcirculation (intraparenchymal shunting) or impaired tissue parenchymal cell oxidative phosphorylation and O_2 consumption by the mitochondria is not resolved.[14] Interesting data suggest that in sepsis the response to limit O_2 consumption by the tissue parenchymal cells is an adaptive response to the inflammatory signaling and decreased perfusion.[15]

An additional pathophysiologic response of the microcirculation to shock is failure of the integrity of the endothelium of the microcirculation and development of capillary leak, intracellular swelling, and the development of an extracellular fluid deficit. Seminal work by Shires helped to define this phenomenon.[7,16] There is decreased capillary hydrostatic pressure secondary to changes in blood flow and increased cellular

uptake of fluid. The result is a loss of extracellular fluid volume. The cause of intracellular swelling is multifactorial, but dysfunction of energy-dependent mechanisms, such as active transport by the sodium-potassium pump contributes to loss of membrane integrity.

Capillary dysfunction also occurs secondary to activation of endothelial cells by circulating inflammatory mediators generated in septic or traumatic shock. This exacerbates endothelial cell swelling and capillary leak, as well as increases leukocyte adherence. This results in capillary occlusion, which may persist after resuscitation, and is termed *no-reflow*. Further ischemic injury ensues as well as release of inflammatory cytokines to compound tissue injury. Experimental models have shown that neutrophil depletion in animals subjected to hemorrhagic shock produces fewer capillaries with no-reflow and lower mortality.[13]

METABOLIC EFFECTS

Cellular metabolism is based primarily on the hydrolysis of adenosine triphosphate (ATP). The splitting of the phosphoanhydride bond of the terminal or γ-phosphate from ATP is the source of energy for most processes within the cell under normal conditions. The majority of ATP is generated in our bodies through aerobic metabolism in the process of oxidative phosphorylation in the mitochondria. This process is dependent on the availability of O_2 as a final electron acceptor in the electron transport chain. As O_2 tension within a cell decreases, there is a decrease in oxidative phosphorylation, and the generation of ATP slows. When O_2 delivery is so severely impaired such that oxidative phosphorylation cannot be sustained, the state is termed *dysoxia*.[17] When oxidative phosphorylation is insufficient, the cells shift to anaerobic metabolism and glycolysis to generate ATP. This occurs via the breakdown of cellular glycogen stores to pyruvate. Although glycolysis is a rapid process, it is not efficient, allowing for the production of only 2 mol of ATP from 1 mol of glucose. This is compared to complete oxidation of 1 mol of glucose that produces 38 mol of ATP. Additionally, under hypoxic conditions in anaerobic metabolism, pyruvate is converted into lactate, leading to an intracellular metabolic acidosis.

There are numerous consequences secondary to these metabolic changes. The depletion of ATP potentially influences all ATP-dependent cellular processes. This includes maintenance of cellular membrane potential, synthesis of enzymes and proteins, cell signaling, and DNA repair mechanisms. Decreased intracellular pH also influences vital cellular functions such as normal enzyme activity, cell membrane ion exchange, and cellular metabolic signaling.[18] These changes also will lead to changes in gene expression within the cell. Furthermore, acidosis leads to changes in calcium metabolism and calcium signaling. Compounded, these changes may lead to irreversible cell injury and death.

Epinephrine and norepinephrine have a profound impact on cellular metabolism. Hepatic glycogenolysis, gluconeogenesis, ketogenesis, skeletal muscle protein breakdown, and adipose tissue lipolysis are increased by catecholamines. Cortisol, glucagon, and ADH also contribute to the catabolism during shock. Epinephrine induces further release of glucagon, while inhibiting the pancreatic α-cell release of insulin. The result is a catabolic state with glucose mobilization, hyperglycemia, protein breakdown, negative nitrogen balance, lipolysis, and insulin resistance during shock and injury. The relative underuse of glucose by peripheral tissues preserves it for the glucose-dependent organs such as the heart and brain.

Cellular Hypoperfusion

Hypoperfused cells and tissues experience what has been termed *oxygen debt*, a concept first proposed by Crowell in 1961.[19] The O_2 debt is the deficit in tissue oxygenation over time that occurs during shock. When O_2 delivery is limited, O_2 consumption can be inadequate to match the metabolic needs of cellular respiration, creating a deficit in O_2 requirements at the cellular level. The measurement of O_2 deficit uses calculation of the difference between the estimated O_2 demand and the actual value obtained for O_2 consumption. Under normal circumstances, cells can "repay" the O_2 debt during reperfusion. The magnitude of the O_2 debt correlates with the severity and duration of hypoperfusion. Surrogate values for measuring O_2 debt include base deficit and lactate levels, and are discussed later in the Hypovolemic/Hemorrhagic section.

In addition to induction of changes in cellular metabolic pathways, shock also induces changes in cellular gene expression. The DNA binding activity of a number of nuclear transcription factors is altered by hypoxia and the production of O_2 radicals or nitrogen radicals that are produced at the cellular level by shock. Expression of other gene products such as heat shock proteins, vascular endothelial growth factor, inducible nitric oxide synthase (iNOS), heme oxygenase-1, and cytokines also are clearly increased by shock.[20] Many of these shock-induced gene products, such as cytokines, have the ability to subsequently alter gene expression in specific target cells and tissues. The involvement

of multiple pathways emphasizes the complex, integrated, and overlapping nature of the response to shock.

IMMUNE AND INFLAMMATORY RESPONSES

The inflammatory and immune responses are a complex set of interactions between circulating soluble factors and cells that can arise in response to trauma, infection, ischemia, toxic, or autoimmune stimuli.[20] The processes are well regulated and can be conceptualized as an ongoing surveillance and response system that undergoes a coordinated escalation following injury to heal disrupted tissue and restore host-microbe equilibrium, as well as active suppression back to baseline levels. Failure to adequately control the activation, escalation, or suppression of the inflammatory response can lead to systemic inflammatory response syndrome and potentiate multiple organ failure.

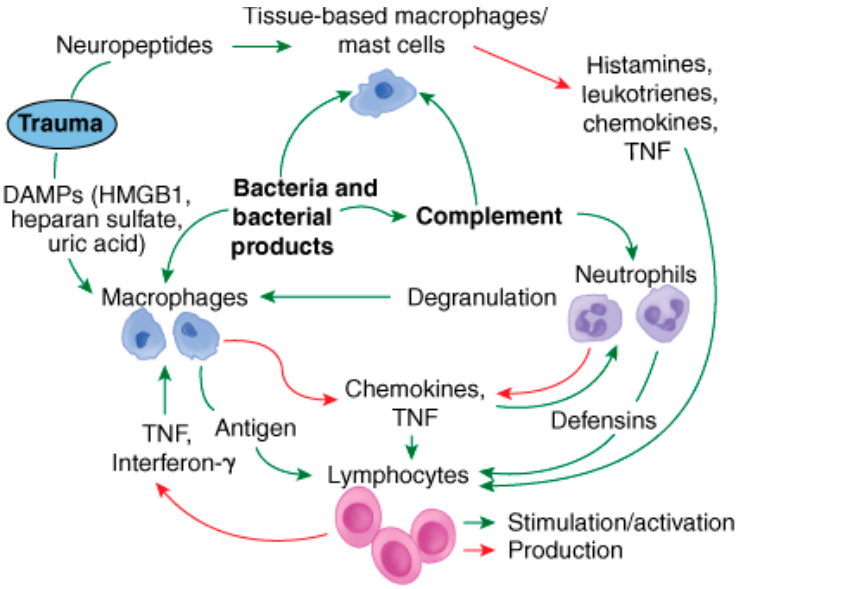
Both the innate and adaptive branches of the immune system work in concert to rapidly respond in a specific and effective manner to challenges that threaten an organism's well-being. Each arm of the immune system has its own set of functions, defined primarily by distinct classes of effector cells and their unique cell membrane receptor families. Alterations in the activity of the innate host immune system can be responsible for both the development of shock (i.e., septic shock following severe infection and traumatic shock following tissue injury with hemorrhage) and the pathophysiologic sequelae of shock such as the proinflammatory changes seen following hypoperfusion (see Fig. 5-1). When the predominantly paracrine mediators gain access to the systemic circulation, they can induce a variety of metabolic changes that are collectively referred to as the *host inflammatory response*. Understanding of the intricate, redundant, and interrelated pathways that comprise the inflammatory response to shock continues to expand. Despite limited understanding of how our current therapeutic interventions impact the host response to illness, inappropriate or excessive inflammation appears to be an essential event in the development of ARDS, multiple organ dysfunction syndrome (MODS), and posttraumatic immunosuppression that can prolong recovery.[21]

Following direct tissue injury or infection, there are several mechanisms that lead to the activation of the active inflammatory and immune responses. These include release of bioactive peptides by neurons in response to pain and the release of intracellular molecules by broken cells, such as heat shock proteins, mitochondrial peptides, heparan sulfate, high mobility group box 1, and RNA. Only recently has it been realized that the release of intracellular products from damaged and injured cells can have paracrine and endocrine-like effects on distant tissues to activate the inflammatory and immune responses.[22] This hypothesis, which was first proposed by Matzinger, is known as *danger signaling*. Under this novel paradigm of immune function, endogenous molecules are capable of signaling the presence of danger to surrounding cells and tissues. These molecules that are released from cells are known as *damage associated molecular patterns* (DAMPs, Table 5-3). DAMPs are recognized by cell surface receptors to effect intracellular signaling that primes and amplifies the immune response. These receptors are known as *pattern recognition receptors (PRRs)* and include the Toll-like receptors (TLRs) and the receptor for advanced glycation end products. Interestingly, TLRs and PRRs were first recognized for their role in signaling as part of the immune response to the entry of microbes and their secreted products into a normally sterile environment. These bacterial products, including lipopolysaccharide, are known as *pathogen-associated molecular patterns*. The salutary consequences of PRR activation most likely relate to the initiation of the repair process and the mobilization of antimicrobial defenses at the site of tissue disruption. However, in the setting of excessive tissue damage, the inflammation itself may lead to further tissue damage amplifying the response both at the local and systemic level.[20] PRR activation leads to intracellular signaling and release of cellular products including cytokines (Fig. 5-4).

Table 5-3 Endogenous Damage Associated Molecular Pattern Molecules
Hyaluronan oligomers
Heparan sulfate
Extra domain A of fibronectin
Heat shock proteins 60, 70, Gp96
Surfactant Protein A
β-Defensin 2
Fibrinogen
Biglycan
High mobility group box 1
Uric acid

Interleukin-1α
S-100s
Nucleolin

Fig. 5-4.



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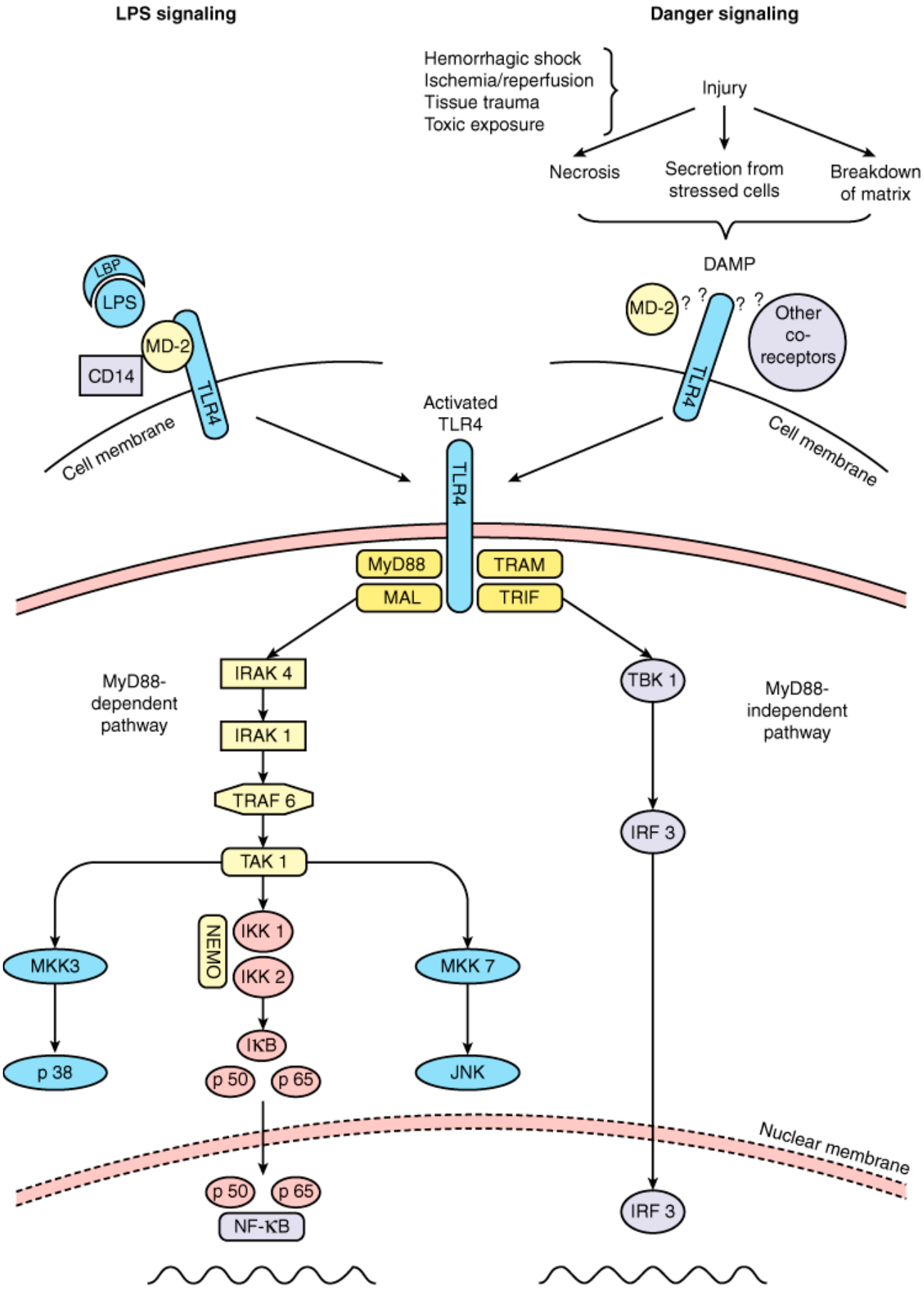
A schema of information flow between immune cells in early inflammation following tissue injury and infection. Cells require multiple inputs and stimuli before activation of a full response. DAMPs = damage associated molecular patterns; HMGB1 = high mobility group box 1; TNF = tumor necrosis factor.

Before the recruitment of leukocytes into sites of injury, tissue-based macrophages or mast cells act as sentinel responders, releasing histamines, eicosanoids, tryptases, and cytokines (Fig. 5-5). Together these signals amplify the immune response by further activation of neurons and mast cells, as well as increasing the expression of adhesion molecules on the endothelium. Furthermore, these mediators cause leukocytes to release platelet-activating factor, further increasing the stickiness of the endothelium. Additionally, the coagulation and kinin cascades impact the interaction of endothelium and leukocytes.

Fig. 5-5.



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Signaling via the pattern recognition receptor TLR4. LPS signaling via TLR4 requires the cofactors LPS binding protein (LBP), MD-2, and CD14. Endogenous danger signals released from a variety of sources also signal in a TLR4-dependent fashion, although it is as yet unknown what cofactors may be required for this activity. Once TLR4 is activated, an intracellular signaling cascade is initiated that involves both a MyD88-dependent and independent pathway. DAMP = damage associated molecular pattern; LPS = lipopolysaccharide; MD-2 = myeloid differentiation factor-2; MyD88 = myeloid differentiation primary response gene 88; NF-κB = nuclear factor κB; TLR4 = Toll-like receptor-4.

(From Mollen et al,[74] with permission.)

Cytokines

The immune response to shock encompasses the elaboration of mediators with both proinflammatory and anti-inflammatory properties (Table 5-4). Furthermore, new mediators, new relationships between mediators, and new functions of known mediators are continually being identified. As new pathways are uncovered, understanding of the immune response to injury and the potential for therapeutic intervention by manipulating the immune response following shock will expand. What seems clear at present, however, is that the innate immune response can help restore homeostasis, or if it is excessive, promote cellular and organ dysfunction.

Table 5-4 Inflammatory Mediators of Shock

Proinflammatory	Anti-Inflammatory
Interleukin-1α/β	Interleukin-4
Interleukin-2	Interleukin-10
Interleukin-6	Interleukin-13
Interleukin-8	Prostaglandin E2
Interferon	TGFβ
TNF	
PAF	

PAF = platelet activating factor; TGFβ = transforming growth factor beta; TNF = tumor necrosis factor.

Multiple mediators have been implicated in the host immune response to shock. It is likely that some of the most important mediators have yet to be discovered, and the roles of many known mediators have not been defined. A comprehensive description of all of the mediators and their complex interactions is beyond the scope of this chapter. For a general overview, a brief description of the more extensively studied mediators, as well as some of the known effects of these substances, see the discussion below. A more comprehensive review can be found in Chap. 2.

Tumor necrosis factor alpha (TNF-α) was one of the first cytokines to be described, and is one of the earliest cytokines released in response to injurious stimuli. Monocytes, macrophages, and T cells release this potent proinflammatory cytokine. TNF-α levels peak within 90 minutes of stimulation and return frequently to baseline levels within 4 hours. Release of TNF-α may be induced by bacteria or endotoxin, and leads to the development of shock and hypoperfusion, most commonly observed in septic shock. Production of TNF-α also may be induced following other insults, such as hemorrhage and ischemia. TNF-α levels correlate with mortality in animal models of hemorrhage.[23] In contrast, the increase in serum TNF-α levels reported in trauma patients is far less than that seen in septic patients.[24] Once released, TNF-α can produce peripheral vasodilation, activate the release of other cytokines, induce procoagulant activity, and stimulate a wide array of cellular metabolic changes. During the stress response, TNF-α contributes to the muscle protein breakdown and cachexia.

Interleukin-1 (IL-1) has actions that are similar to those of TNF-α. IL-1 has a very short half-life (6 minutes) and primarily acts in a paracrine fashion to modulate local cellular responses. Systemically, IL-1 produces a febrile response to injury by activating prostaglandins in the posterior hypothalamus, and causes anorexia by activating the satiety center. This cytokine also augments the secretion of ACTH, glucorticoids, and α-endorphins. In conjunction with TNF-α, IL-1 can stimulate the release of other cytokines such as IL-2, IL-4, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and interferon-γ.

IL-2 is produced by activated T cells in response to a variety of stimuli and activates other lymphocyte subpopulations and natural killer cells. The lack of clarity regarding the role of IL-2 in the response to shock is intimately associated with that of understanding immune function

after injury. Some investigators have postulated that increased IL-2 secretion promotes shock-induced tissue injury and the development of shock. Others have demonstrated that depressed IL-2 production is associated with, and perhaps contributes to, the depression in immune function after hemorrhage that may increase the susceptibility of patients who develop shock to suffer infections.[25,26] It has been postulated that overly exuberant proinflammatory activation promotes tissue injury, organ dysfunction, and the subsequent immune dysfunction/suppression that may be evident later.[21] Emphasizing the importance of temporal changes in the production of mediators, both the initial excessive production of IL-2 and later depressed IL-2 production are probably important in the progression of shock.

IL-6 is elevated in response to hemorrhagic shock, major operative procedures, or trauma. Elevated IL-6 levels correlate with mortality in shock states. IL-6 contributes to lung, liver, and gut injury after hemorrhagic shock.[27] Thus, IL-6 may play a role in the development of diffuse alveolar damage and ARDS. IL-6 and IL-1 are mediators of the hepatic acute phase response to injury, and enhance the expression and activity of complement, C-reactive protein, fibrinogen, haptoglobin, amyloid A, and alpha1-antitrypsin, and promote neutrophil activation.[28]

IL-10 is considered an anti-inflammatory cytokine that may have immunosuppressive properties. Its production is increased after shock and trauma, and it has been associated with depressed immune function clinically, as well as an increased susceptibility to infection.[29] IL-10 is secreted by T cells, monocytes, and macrophages, and inhibits proinflammatory cytokine secretion, O_2 radical production by phagocytes, adhesion molecule expression, and lymphocyte activation.[29,30] Administration of IL-10 depresses cytokine production and improves some aspects of immune function in experimental models of shock and sepsis.[31,32]

Complement

The complement cascade can be activated by injury, shock, and severe infection, and contributes to host defense and proinflammatory activation. Significant complement consumption occurs after hemorrhagic shock.[33] In trauma patients, the degree of complement activation is proportional to the magnitude of injury and may serve as a marker for severity of injury. Patients in septic shock also demonstrate activation of the complement pathway, with elevations of the activated complement proteins C3a and C5a. Activation of the complement cascade can contribute to the development of organ dysfunction. Activated complement factors C3a, C4a, and C5a are potent mediators of increased vascular permeability, smooth muscle cell contraction, histamine and arachidonic acid by-product release, and adherence of neutrophils to vascular endothelium. Activated complement acts synergistically with endotoxin to induce the release of TNF-α and IL-1. The development of ARDS and MODS in trauma patients correlates with the intensity of complement activation.[34] Complement and neutrophil activation may correlate with mortality in multiply injured patients.

Neutrophils

Neutrophil activation is an early event in the upregulation of the inflammatory response; neutrophils are the first cells to be recruited to the site of injury. Polymorphonuclear leukocyte (PMNs) remove infectious agents, foreign substances that have penetrated host barrier defenses, and nonviable tissue through phagocytosis. However, activated PMNs and their products may also produce cell injury and organ dysfunction. Activated PMNs generate and release a number of substances that may induce cell or tissue injury, such as reactive O_2 species, lipid-peroxidation products, proteolytic enzymes (elastase, cathepsin G), and vasoactive mediators (leukotrienes, eicosanoids, and platelet-activating factor). Oxygen free radicals, such as superoxide anion, hydrogen peroxide, and hydroxyl radical, are released and induce lipid peroxidation, inactivate enzymes, and consume antioxidants (such as glutathione and tocopherol). Ischemia-reperfusion activates PMNs and causes PMN-induced organ injury. In animal models of hemorrhagic shock, activation of PMNs correlates with irreversibility of shock and mortality, and neutrophil depletion prevents the pathophysiologic sequelae of hemorrhagic and septic shock. Human data corroborate the activation of neutrophils in trauma and shock and suggest a role in the development of MODS.[35] Plasma markers of PMN activation, such as elastase, correlate with severity of injury in humans.

Interactions between endothelial cells and leukocytes are important in the inflammatory process. The vascular endothelium contributes to regulation of blood flow, leukocyte adherence, and the coagulation cascade. Extracellular ligands such as intercellular adhesion molecules, vascular cell adhesion molecules, and the selectins (E-selectin, P-selectin) are expressed on the surface of endothelial cells, and are responsible for leukocyte adhesion to the endothelium. This interaction allows activated neutrophils to migrate into the tissues to combat infection, but also can lead to PMN-mediated cytotoxicity and microvascular and tissue injury.

Cell Signaling

A host of cellular changes occur following shock. Although many of the intracellular and intercellular pathways that are important in shock are being elucidated, undoubtedly there are many more that have yet to be identified. Many of the mediators produced during shock interact with cell surface receptors on target cells to alter target cell metabolism. These signaling pathways may be altered by changes in cellular oxygenation, redox state, high-energy phosphate concentration, gene expression, or intracellular electrolyte concentration induced by shock. Cells communicate with their external environment through the use of cell surface membrane receptors which, once bound by a ligand, transmit their information to the interior of the cell through a variety of signaling cascades. These signaling pathways may subsequently alter the activity of specific enzymes, the expression or breakdown of important proteins, or affect intracellular energy metabolism. Intracellular calcium (Ca^{2+}) homeostasis and regulation represents one such pathway. Intracellular Ca^{2+} concentrations regulate many aspects of cellular metabolism; many important enzyme systems require Ca^{2+} for full activity. Profound changes in intracellular Ca^{2+} levels and Ca^{2+} transport are seen in models of shock.[36,37] Alterations in Ca^{2+} regulation may lead to direct cell injury, changes in transcription factor activation, alterations in the expression of genes important in homeostasis, and the modulation of the activation of cells by other shock-induced hormones or mediators.[38–40]

A proximal portion of the intracellular signaling cascade consists of a series of kinases that transmit and amplify the signal through the phosphorylation of target proteins. The O_2 radicals produced during shock and the intracellular redox state are known to influence the activity of components of this cascade, such as protein tyrosine kinases, mitogen activated kinases, and protein kinase C.[41–44] Either through changes in these signaling pathways, changes in the activation of enzyme systems through Ca^{2+}-mediated events, or direct conformational changes to oxygen-sensitive proteins, O_2 radicals also regulate the activity of a number of transcription factors that are important in gene expression, such as nuclear factor κB, APETALA1, and hypoxia-inducible factor 1.[45,46] It is therefore becoming increasingly clear that oxidant-mediated direct cell injury is merely one consequence of the production of O_2 radicals during shock.

The study of the effects of shock on the regulation of gene expression as an important biologic effect was stimulated by the work of Buchman and colleagues.[47] The effects of shock on the expression and regulation of numerous genes and gene products has been studied in both experimental animal models and human patients. These studies include investigations into single genes of interest as well as large-scale genomic and proteomic analysis.[48–50] Changes in gene expression are critical for adaptive and survival cell signaling. Polymorphisms in gene promoters that lead to a differential level of expression of gene products are also likely to contribute significantly to varied responses to similar insults.[51,52]

FORMS OF SHOCK

Hypovolemic/Hemorrhagic

The most common cause of shock in the surgical or trauma patient is loss of circulating volume from hemorrhage. Acute blood loss results in reflexive decreased baroreceptor stimulation from stretch receptors in the large arteries, resulting in decreased inhibition of vasoconstrictor centers in the brain stem, increased chemoreceptor stimulation of vasomotor centers, and diminished output from atrial stretch receptors. These changes increase vasoconstriction and peripheral arterial resistance. Hypovolemia also induces sympathetic stimulation, leading to epinephrine and norepinephrine release, activation of the renin-angiotensin cascade, and increased vasopressin release. Peripheral vasoconstriction is prominent, while lack of sympathetic effects on cerebral and coronary vessels and local autoregulation promote maintenance of cardiac and CNS blood flow.

DIAGNOSIS

Treatment of shock is initially empiric. A secure airway must be confirmed or established and volume infusion initiated while the search for the cause of the hypotension is pursued. Shock in a trauma patient and postoperative patient should be presumed to be due to hemorrhage until proven otherwise. The clinical signs of shock may be evidenced by agitation, cool clammy extremities, tachycardia, weak or absent peripheral pulses, and hypotension. Such apparent clinical shock results from at least 25 to 30% loss of the blood volume. However, substantial volumes of blood may be lost before the classic clinical manifestations of shock are evident. Thus, when a patient is significantly tachycardic or hypotensive, this represents both significant blood loss and physiologic decompensation. The clinical and physiologic response

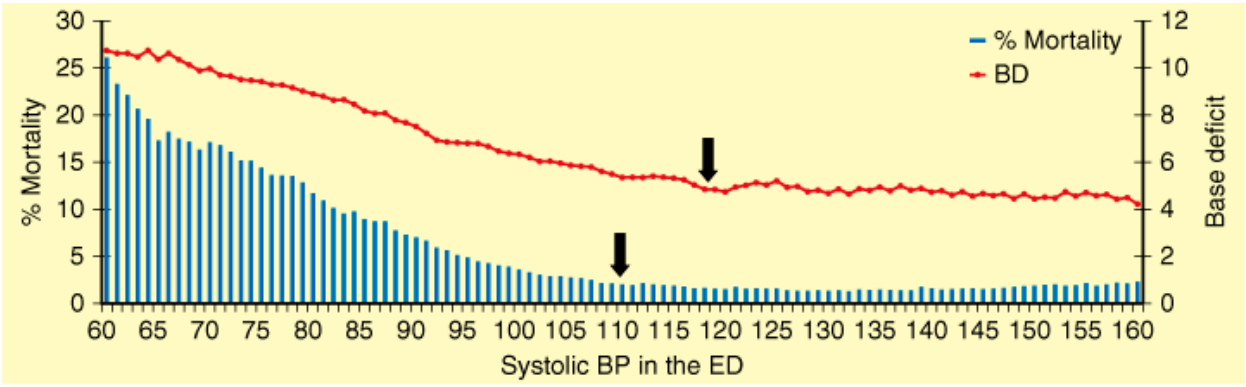
to hemorrhage has been classified according to the magnitude of volume loss. Loss of up to 15% of the circulating volume (700 to 750 mL for a 70-kg patient) may produce little in terms of obvious symptoms, while loss of up to 30% of the circulating volume (1.5 L) may result in mild tachycardia, tachypnea, and anxiety. Hypotension, marked tachycardia [i.e., pulse greater than 110 to 120 beats per minute (bpm)], and confusion may not be evident until more than 30% of the blood volume has been lost; loss of 40% of circulating volume (2 L) is immediately life threatening, and generally requires operative control of bleeding (Table 5-5). Young healthy patients with vigorous compensatory mechanisms may tolerate larger volumes of blood loss while manifesting fewer clinical signs despite the presence of significant peripheral hypoperfusion. These patients may maintain a near-normal blood pressure until a precipitous cardiovascular collapse occurs. Elderly patients may be taking medications that either promote bleeding (e.g., warfarin or aspirin), or mask the compensatory responses to bleeding (e.g., beta blockers). In addition, atherosclerotic vascular disease, diminishing cardiac compliance with age, inability to elevate heart rate or cardiac contractility in response to hemorrhage, and overall decline in physiologic reserve decrease the elderly patient's ability to tolerate hemorrhage. Recent data in trauma patients suggest that a systolic blood pressure (SBP) of less than 110 mmHg is a clinically relevant definition of hypotension and hypoperfusion based upon an increasing rate of mortality below this pressure (Fig. 5-6).[53]

Table 5-5 Classification of Hemorrhage

	Class			
Parameter	**I**	**II**	**III**	**IV**
Blood loss (mL)	<750	750–1500	1500–2000	>2000
Blood loss (%)	<15	15–30	30–40	>40
Heart rate (bpm)	<100	>100	>120	>140
Blood pressure	Normal	Orthostatic	Hypotension	Severe hypotension
CNS symptoms	Normal	Anxious	Confused	Obtunded

bpm = beats per minute; CNS = central nervous system.

Fig. 5-6.



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The relationship between systolic blood pressure and mortality in trauma patients with hemorrhage. These data suggest that a systolic blood pressure of less than 110 mmHg is a clinically relevant definition of hypotension and hypoperfusion based upon an increasing rate of mortality below this pressure. Base deficit (BD) is also shown on this graph. ED = emergency department.

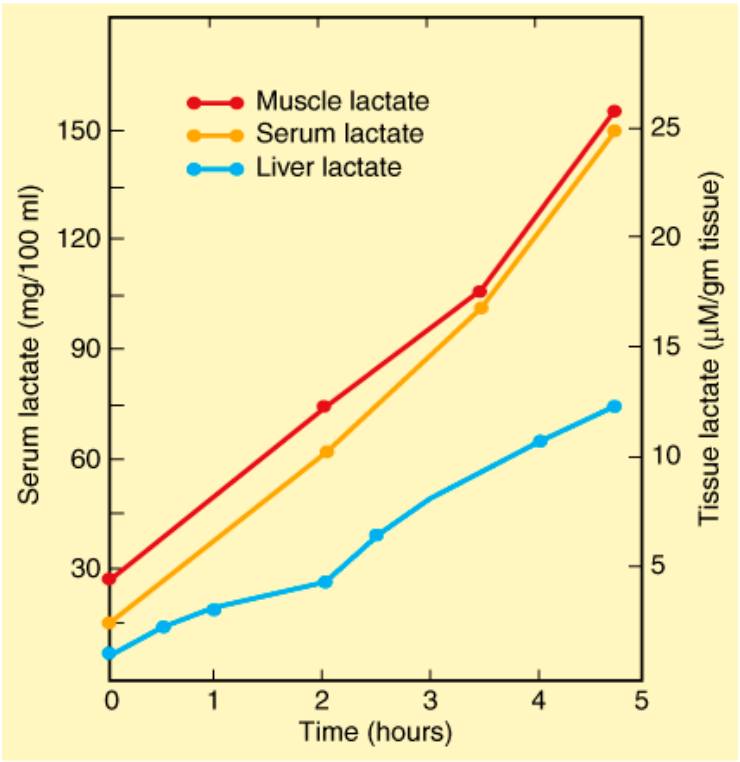
(From Eastridge et al,[53] with permission.)

In addressing the sensitivity of vital signs and identifying major thoracoabdominal hemorrhage, a study retrospectively identified patients with injury to the trunk and an abbreviated injury score of 3 or greater who required immediate surgical intervention and transfusion of at least 5 units of blood within the first 24 hours. Ninety-five percent of patients had a heart rate greater than 80 bpm at some point during their postinjury course. However, only 59% of patients achieved a heart rate greater than 120 bpm. Ninety-nine percent of all patients had a

recorded blood pressure of less than 120 mmHg at some point. Ninety-three percent of all patients had a recorded SBP of less than 100 mmHg.[54] A more recent study corroborated that tachycardia was not a reliable sign of hemorrhage following trauma, and was present in only 65% of hypotensive patients.[55]

Serum lactate and base deficit are measurements that are helpful to both estimate and monitor the extent of bleeding and shock. The amount of lactate that is produced by anaerobic respiration is an indirect marker of tissue hypoperfusion, cellular O_2 debt, and the severity of hemorrhagic shock. Several studies have demonstrated that the initial serum lactate and serial lactate levels are reliable predictors of morbidity and mortality with hemorrhage following trauma (Fig. 5-7).[56] Similarly, base deficit values derived from arterial blood gas analysis provide clinicians with an indirect estimation of tissue acidosis from hypoperfusion. Davis and colleagues stratified the extent of base deficit into mild (−3 to −5 mmol/L), moderate (−6 to −9 mmol/L), and severe (less than −10 mmol/L), and from this established a correlation between base deficit upon admission with transfusion requirements, the development of multiple organ failure, and death (Fig. 5-8).[57] Both base deficit and lactate correlate with the extent of shock and patient outcome, but interestingly do not firmly correlate with each other.[58–60] Evaluation of both values may be useful in trauma patients with hemorrhage.

Fig. 5-7.



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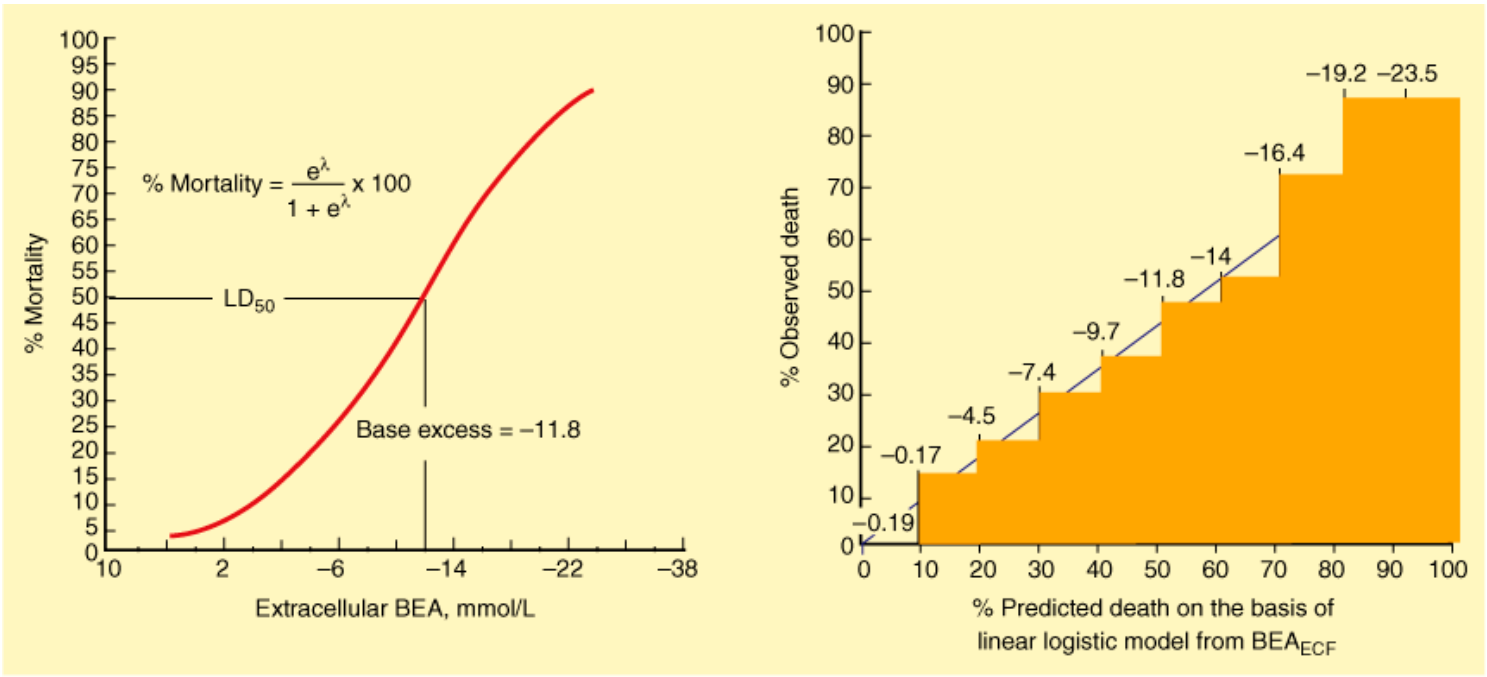
Progressive increases in serum lactate, muscle lactate, and liver lactate in a baboon model of hemorrhagic shock. (From Peitzman et al,[8] with permission.)

Fig. 5-8.

From Lycan / Dr. MV



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The relationship between base deficit (negative base excess) and mortality in trauma patients. BEA = base excess arterial; ECF = extracellular fluid.

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In management of trauma patients, understanding the patterns of injury of the patient in shock will help direct the evaluation and management. Identifying the sources of blood loss in patients with penetrating wounds is relatively simple because potential bleeding sources will be located along the known or suspected path of the wounding object. Patients with penetrating injuries who are in shock usually require operative intervention. Patients who suffer multisystem injuries from blunt trauma have multiple sources of potential hemorrhage. Blood loss sufficient to cause shock is generally of a large volume, and there are a limited number of sites that can harbor sufficient extravascular blood volume to induce hypotension (e.g., external, intrathoracic, intra-abdominal, retroperitoneal, and long bone fractures). In the nontrauma patient, the GI tract must always be considered as a site for blood loss. Substantial blood loss externally may be suspected from prehospital medical reports documenting a substantial blood loss at the scene of an accident, history of massive blood loss from wounds, visible brisk bleeding, or presence of a large hematoma adjacent to an open wound. Injuries to major arteries or veins with associated open wounds may cause massive blood loss rapidly. Direct pressure must be applied and sustained to minimize ongoing blood loss. Persistent bleeding from uncontrolled smaller vessels can, over time, precipitate shock if inadequately treated.

When major blood loss is not immediately visible in the setting of trauma, internal (intracavitary) blood loss should be suspected. Each pleural cavity can hold 2 to 3 L of blood and can therefore be a site of significant blood loss. Diagnostic and therapeutic tube thoracostomy may be indicated in unstable patients based on clinical findings and clinical suspicion. In a more stable patient, a chest radiograph may be obtained to look for evidence of hemothorax. Major retroperitoneal hemorrhage typically occurs in association with pelvic fractures, which is confirmed by pelvic radiography in the resuscitation bay. Intraperitoneal hemorrhage is probably the most common source of blood loss inducing shock. The physical exam for detection of substantial blood loss or injury is insensitive and unreliable; large volumes of intraperitoneal blood may be present before physical examination findings are apparent. Findings with intra-abdominal hemorrhage include abdominal distension, abdominal tenderness, or visible abdominal wounds. Hemodynamic abnormalities generally stimulate a search for blood loss before the appearance of obvious abdominal findings. Adjunctive tests are essential in the diagnosis of intraperitoneal bleeding; intraperitoneal blood may be rapidly identified by diagnostic ultrasound or diagnostic peritoneal lavage. Furthermore, patients that have sustained high-energy blunt trauma that are hemodynamically stable or that have normalized their vital signs in response to initial volume resuscitation should undergo computed tomography scans to assess for head, chest, and/or abdominal bleeding.

TREATMENT

Control of ongoing hemorrhage is an essential component of the resuscitation of the patient in shock. As mentioned in Diagnosis above, treatment of hemorrhagic shock is instituted concurrently with diagnostic evaluation to identify a source. Patients who fail to respond to initial resuscitative efforts should be assumed to have ongoing active hemorrhage from large vessels and require prompt operative intervention. Based on trauma literature, patients with ongoing hemorrhage demonstrate increased survival if the elapsed time between the injury and control of bleeding is decreased. Although there are no randomized controlled trials, retrospective studies provide compelling evidence in this regard. To this end, Clarke and colleagues[61] demonstrated that trauma patients with major injuries isolated to the abdomen requiring emergency laparotomy had an increased probability of death with increasing length of time in the emergency department for patients who were in the emergency department for 90 minutes or less. This probability increased approximately 1% for each 3 minutes in the emergency department.

The appropriate priorities in these patients are (a) secure the airway, (b) control the source of blood loss, and (c) IV volume resuscitation. In trauma, identifying the body cavity harboring active hemorrhage will help focus operative efforts; however, because time is of the essence, rapid treatment is essential and diagnostic laparotomy or thoracotomy may be indicated. The actively bleeding patient cannot be resuscitated until control of ongoing hemorrhage is achieved. Our current understanding has led to the management strategy known as *damage control resuscitation*.[62] This strategy begins in the emergency department, continues into the operating room, and into the intensive care unit (ICU). Initial resuscitation is limited to keep SBP around 90 mmHg. This prevents renewed bleeding from recently clotted vessels. Resuscitation and intravascular volume resuscitation is accomplished with blood products and limited crystalloids, which is addressed further later in this section. Too little volume allowing persistent severe hypotension and hypoperfusion is dangerous, yet too vigorous of a volume resuscitation may be just as deleterious. Control of hemorrhage is achieved in the operating room, and efforts to warm patients and to prevent coagulopathy using multiple blood products and pharmacologic agents are used in both the operating room and ICU.

Cannon and colleagues first made the observation that attempts to increase blood pressure in soldiers with uncontrolled sources of hemorrhage is counterproductive, with increased bleeding and higher mortality.[3] This work was the foundation for the "hypotensive resuscitation" strategies. Several laboratory studies confirmed the observation that attempts to restore normal blood pressure with fluid infusion or vasopressors was rarely achievable and resulted in more bleeding and higher mortality.[63] A prospective, randomized clinical study compared delayed fluid resuscitation (upon arrival in the operating room) with standard fluid resuscitation (with arrival by the paramedics) in hypotensive patients with penetrating torso injury.[64] The authors reported that delayed fluid resuscitation resulted in lower patient mortality. Further laboratory studies demonstrated that fluid restriction in the setting of profound hypotension resulted in early deaths from severe hypoperfusion. These studies also showed that aggressive crystalloid resuscitation attempting to normalize blood pressure resulted in marked hemodilution, with hematocrits of 5%.[63] Reasonable conclusions in the setting of uncontrolled hemorrhage include: Any delay in surgery for control of hemorrhage increases mortality; with uncontrolled hemorrhage attempting to achieve normal blood pressure may increase mortality, particularly with penetrating injuries and short transport times; a goal of SBP of 80 to 90 mmHg may be adequate in the patient with penetrating injury; and profound hemodilution should be avoided by early transfusion of red blood cells. For the patient with blunt injury, where the major cause of death is a closed head injury, the increase in mortality with hypotension in the setting of brain injury must be avoided. In this setting, a SBP of 110 mmHg would seem to be more appropriate.

Patients who respond to initial resuscitative effort but then deteriorate hemodynamically frequently have injuries that require operative intervention. The magnitude and duration of their response will dictate whether diagnostic maneuvers can be performed to identify the site of bleeding. However, hemodynamic deterioration generally denotes ongoing bleeding for which some form of intervention (i.e., operation or interventional radiology) is required. Patients who have lost significant intravascular volume, but whose hemorrhage is controlled or has abated, often will respond to resuscitative efforts if the depth and duration of shock have been limited.

A subset of patients exists who fail to respond to resuscitative efforts despite adequate control of ongoing hemorrhage. These patients have ongoing fluid requirements despite adequate control of hemorrhage, have persistent hypotension despite restoration of intravascular volume necessitating vasopressor support, and may exhibit a futile cycle of uncorrectable hypothermia, hypoperfusion, acidosis, and coagulopathy that cannot be interrupted despite maximum therapy. These patients have deteriorated to decompensated or irreversible shock with

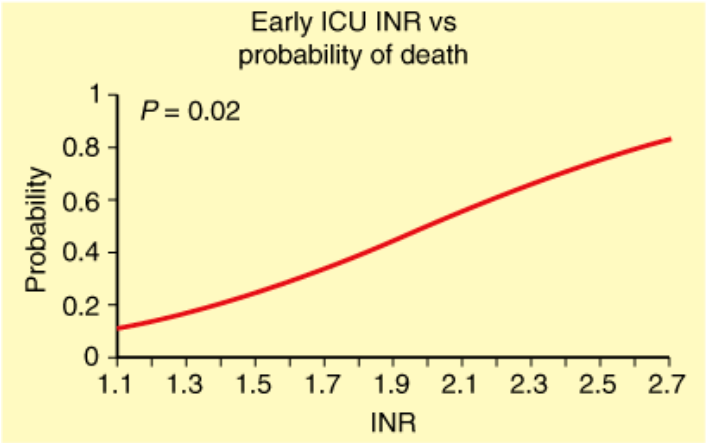
peripheral vasodilation and resistance to vasopressor infusion. Mortality is inevitable once the patient manifests shock in its terminal stages. Unfortunately, this is all too often diagnosed in retrospect.

Fluid resuscitation is a major adjunct to physically controlling hemorrhage in patients with shock. The ideal type of fluid to be used continues to be debated; however, crystalloids continue to be the mainstay of fluid choice. Several studies have demonstrated increased risk of death in bleeding trauma patients treated with colloid compared to patients treated with crystalloid.[65] In patients with severe hemorrhage, restoration of intravascular volume should be achieved with blood products.[66]

Ongoing studies continue to evaluate the use of hypertonic saline as a resuscitative adjunct in bleeding patients.[67] The benefit of hypertonic saline solutions may be immunomodulatory. Specifically, these effects have been attributed to pharmacologic effects resulting in decreased reperfusion-mediated injury with decreased O_2 radical formation, less impairment of immune function compared to standard crystalloid solution, and less brain swelling in the multi-injured patient. The reduction of total volume used for resuscitation makes this approach appealing as a resuscitation agent for combat injuries and may contribute to a decrease in the incidence of ARDS and multiple organ failure.

Transfusion of packed red blood cells and other blood products is essential in the treatment of patients in hemorrhagic shock. Current recommendations in stable ICU patients aim for a target hemoglobin of 7 to 9 g/dL;[68,69] however, no prospective randomized trials have compared restrictive and liberal transfusion regimens in trauma patients with hemorrhagic shock. Fresh frozen plasma (FFP) should also be transfused in patients with massive bleeding or bleeding with increases in prothrombin or activated partial thromboplastin times 1.5 times greater than control. Civilian trauma data show that severity of coagulopathy early after ICU admission is predictive of mortality (Fig. 5-9).[70] Evolving data suggest more liberal transfusion of FFP in bleeding patients, but the clinical efficacy of FFP requires further investigation. Recent data collected from a U.S. Army combat support hospital in patients that received massive transfusion of packed red blood cells (>10 units in 24 hours) suggests that a high plasma to RBC ratio (1:1.4 units) was independently associated with improved survival (Fig. 5-10).[71] Platelets should be transfused in the bleeding patient to maintain counts above 50×10^9/L. There is a potential role for other blood products, such as fibrinogen concentrate of cryoprecipitate, if bleeding is accompanied by a drop in fibrinogen levels to less than 1 g/L. Pharmacologic agents such as recombinant activated coagulation factor 7, and antifibrinolytic agents such as ε-aminocaproic acid, tranexamic acid (both are synthetic lysine analogues that are competitive inhibitors of plasmin and plasminogen), and aprotinin (protease inhibitor) may all have potential benefits in severe hemorrhage but require further investigation.

Fig. 5-9.



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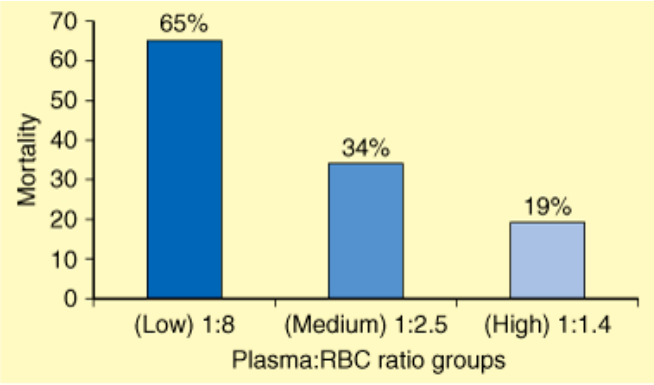
The relationship between coagulopathy and mortality in trauma patients. Civilian trauma data show that severity of coagulopathy as determined by an increasing International Normalized Ratio (INR) early after intensive care unit (ICU) admission is predictive of mortality.

(From Gonzalez et al,[70] with permission.)

Fig. 5-10.



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Increasing ratio of transfusion of fresh frozen plasma to red blood cells improves outcome of trauma patients receiving massive transfusions. RBC = red blood cell.

(From Borgman et al,[71] with permission.)

Additional resuscitative adjuncts in patients with hemorrhagic shock include minimization of heat loss and maintaining normothermia. The development of hypothermia in the bleeding patient is associated with acidosis, hypotension, and coagulopathy. Hypothermia in bleeding trauma patients is an independent risk factor for bleeding and death. This likely is secondary to impaired platelet function and impairments in the coagulation cascade. Several studies have investigated the induction of controlled hypothermia in patients with severe shock based on the hypothesis of limiting metabolic activity and energy requirements, creating a state of "suspended animation." These studies are promising and continue to be evaluated in large trials.

Traumatic Shock

The systemic response after trauma, combining the effects of soft tissue injury, long bone fractures, and blood loss, is clearly a different physiologic insult than simple hemorrhagic shock. Multiple organ failure, including acute respiratory distress syndrome (ARDS), develops relatively often in the blunt trauma patient, but rarely after pure hemorrhagic shock (such as a GI bleed). The hypoperfusion deficit in traumatic shock is magnified by the proinflammatory activation that occurs following the induction of shock. In addition to ischemia or ischemia-reperfusion, accumulating evidence demonstrates that even simple hemorrhage induces proinflammatory activation that results in many of the cellular changes typically ascribed only to septic shock.[72,73] At the cellular level, this may be attributable to the release of cellular products termed *damage associated molecular patterns* (*DAMPs*, i.e., riboxynucleic acid, uric acid, and high mobility group box 1) that activate the same set of cell surface receptors as bacterial products, initiating similar cell signaling.[5,74] These receptors are termed *pattern recognition receptors* (*PRRs)* and include the TLR family of proteins. Examples of traumatic shock include small volume hemorrhage accompanied by soft tissue injury (femur fracture, crush injury), or any combination of hypovolemic, neurogenic, cardiogenic, and obstructive shock that precipitate rapidly progressive proinflammatory activation. In laboratory models of traumatic shock, the addition of a soft tissue or long bone injury to hemorrhage produces lethality with significantly less blood loss when the animals are stressed by hemorrhage. Treatment of traumatic shock is focused on correction of the individual elements to diminish the cascade of proinflammatory activation, and includes prompt control of hemorrhage, adequate volume resuscitation to correct O_2 debt, débridement of nonviable tissue, stabilization of bony injuries, and appropriate treatment of soft tissue injuries.

Septic Shock (Vasodilatory Shock)

In the peripheral circulation, profound vasoconstriction is the typical physiologic response to the decreased arterial pressure and tissue perfusion with hemorrhage, hypovolemia, or acute heart failure. This is not the characteristic response in vasodilatory shock. Vasodilatory shock is the result of dysfunction of the endothelium and vasculature secondary to circulating inflammatory mediators and cells or as a response to prolonged and severe hypoperfusion. Thus, in vasodilatory shock, hypotension results from failure of the vascular smooth muscle to constrict appropriately. Vasodilatory shock is characterized by peripheral vasodilation with resultant hypotension and resistance to

treatment with vasopressors. Despite the hypotension, plasma catecholamine levels are elevated, and the renin-angiotensin system is activated in vasodilatory shock. The most frequently encountered form of vasodilatory shock is septic shock. Other causes of vasodilatory shock include hypoxic lactic acidosis, carbon monoxide poisoning, decompensated and irreversible hemorrhagic shock, terminal cardiogenic shock, and postcardiotomy shock (Table 5-6). Thus, vasodilatory shock seems to represent the final common pathway for profound and prolonged shock of any etiology.[75]

Table 5-6 Causes of Septic and Vasodilatory Shock
Systemic response to infection
Noninfectious systemic inflammation
Pancreatitis
Burns
Anaphylaxis
Acute adrenal insufficiency
Prolonged, severe hypotension
Hemorrhagic shock
Cardiogenic shock
Cardiopulmonary bypass
Metabolic
Hypoxic lactic acidosis
Carbon monoxide poisoning

Despite advances in intensive care, the mortality rate for severe sepsis remains at 30 to 50%. In the United States, 750,000 cases of sepsis occur annually, one third of which are fatal.[76] Sepsis accounts for 9.3% of deaths in the United States, as many yearly as MI.[77] Septic shock is a by-product of the body's response to disruption of the host-microbe equilibrium, resulting in invasive or severe localized infection.

In the attempt to eradicate the pathogens, the immune and other cell types (e.g., endothelial cells) elaborate soluble mediators that enhance macrophage and neutrophil killing effector mechanisms, increase procoagulant activity and fibroblast activity to localize the invaders, and increase microvascular blood flow to enhance delivery of killing forces to the area of invasion. When this response is overly exuberant or becomes systemic rather than localized, manifestations of sepsis may be evident. These findings include enhanced cardiac output, peripheral vasodilation, fever, leukocytosis, hyperglycemia, and tachycardia. In septic shock, the vasodilatory effects are due, in part, to the upregulation of the inducible isoform of nitric oxide synthase (iNOS or NOS 2) in the vessel wall. iNOS produces large quantities of nitric oxide for sustained periods of time. This potent vasodilator suppresses vascular tone and renders the vasculature resistant to the effects of vasoconstricting agents.

DIAGNOSIS

Attempts to standardize terminology have led to the establishment of criteria for the diagnosis of sepsis in the hospitalized adult. These criteria include manifestations of the host response to infection in addition to identification of an offending organism. The terms *sepsis*, *severe sepsis*, and *septic shock* are used to quantify the magnitude of the systemic inflammatory reaction. Patients with *sepsis* have evidence of an infection, as well as systemic signs of inflammation (e.g., fever, leukocytosis, and tachycardia). Hypoperfusion with signs of organ dysfunction is termed *severe sepsis. Septic shock* requires the presence of the above, associated with more significant evidence of tissue hypoperfusion and systemic hypotension. Beyond the hypotension, maldistribution of blood flow and shunting in the microcirculation further compromise delivery of nutrients to the tissue beds.[78]

Recognizing septic shock begins with defining the patient at risk. The clinical manifestations of septic shock will usually become evident and prompt the initiation of treatment before bacteriologic confirmation of an organism or the source of an organism is identified. In addition to fever, tachycardia, and tachypnea, signs of hypoperfusion such as confusion, malaise, oliguria, or hypotension may be present. These should prompt an aggressive search for infection, including a thorough physical examination, inspection of all wounds, evaluation of intravascular

catheters or other foreign bodies, obtaining appropriate cultures, and adjunctive imaging studies, as needed.

TREATMENT

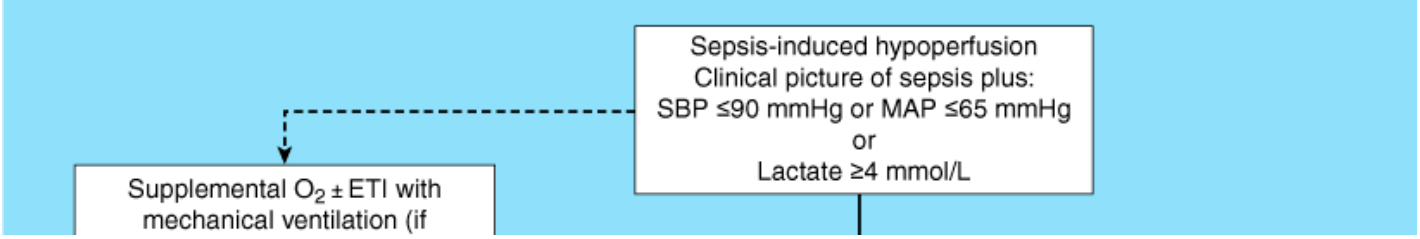
Evaluation of the patient in septic shock begins with an assessment of the adequacy of their airway and ventilation. Severely obtunded patients and patients whose work of breathing is excessive require intubation and ventilation to prevent respiratory collapse. Because vasodilation and decrease in total peripheral resistance may produce hypotension, fluid resuscitation and restoration of circulatory volume with balanced salt solutions is essential. Empiric antibiotics must be chosen carefully based on the most likely pathogens (gram-negative rods, gram-positive cocci, and anaerobes) because the portal of entry of the offending organism and its identity may not be evident until culture data return or imaging studies are completed. Knowledge of the bacteriologic profile of infections in an individual unit can be obtained from most hospital infection control departments and will suggest potential responsible organisms. Antibiotics should be tailored to cover the responsible organisms once culture data are available, and if appropriate, the spectrum of coverage narrowed. Long-term, empiric, broad-spectrum antibiotic use should be minimized to reduce the development of resistant organisms and to avoid the potential complications of fungal overgrowth and antibiotic-associated colitis from overgrowth of *Clostridium difficile*. IV antibiotics will be insufficient to adequately treat the infectious episode in the settings of infected fluid collections, infected foreign bodies, and devitalized tissue. This situation is termed *source control* and involves percutaneous drainage and operative management to target a focus of infection. These situations may require multiple operations to ensure proper wound hygiene and healing.

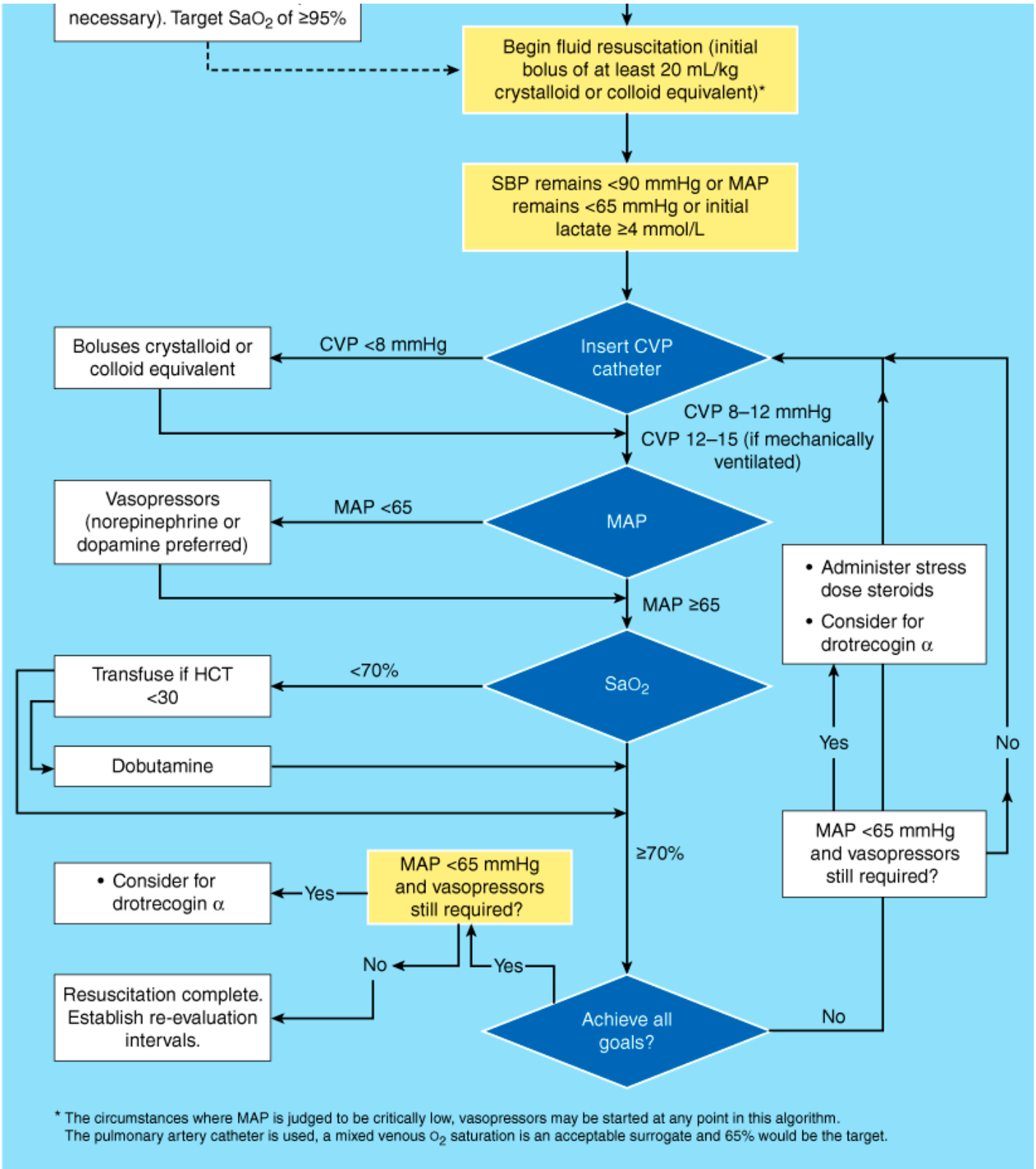
After first-line therapy of the septic patient with antibiotics, IV fluids, and intubation if necessary, vasopressors may be necessary to treat patients with septic shock. Catecholamines are the vasopressors used most often. Occasionally, patients with septic shock will develop arterial resistance to catecholamines. Arginine vasopressin, a potent vasoconstrictor, is often efficacious in this setting.

The majority of septic patients have hyperdynamic physiology with supranormal cardiac output and low systemic vascular resistance. On occasion, septic patients may have low cardiac output despite volume resuscitation and even vasopressor support. Mortality in this group is high. Despite the increasing incidence of septic shock over the past several decades, the overall mortality rates have changed little. Studies of interventions, including immunotherapy, resuscitation to pulmonary artery endpoints with hemodynamic optimization (cardiac output and O_2 delivery, even to supranormal values), and optimization of mixed venous O_2 measurements up to 72 hours after admission to the ICU, have not changed mortality.

Over the past decade, multiple advances have been made in the treatment of patients with sepsis and septic shock (Fig. 5-11).[78,79] Negative results from previous studies have led to the suggestion that earlier interventions directed at improving global tissue oxygenation may be of benefit. To this end, Rivers and colleagues reported that goal-directed therapy of septic shock and severe sepsis initiated in the emergency department and continued for 6 hours significantly improved outcome.[80] This approach involved adjustment of cardiac preload, afterload, and contractility to balance O_2 delivery with O_2 demand. They found that goal-directed therapy during the first 6 hours of hospital stay (initiated in the emergency department) had significant effects, such as higher mean venous O_2 saturation, lower lactate levels, lower base deficit, higher pH, and decreased 28-day mortality (49.2 vs. 33.3%) compared to the standard therapy group. The frequency of sudden cardiovascular collapse was also significantly less in the group managed with goal-directed therapy (21.0 vs. 10.3%). Interestingly, the goal-directed therapy group received more IV fluids during the initial 6 hours, but the standard therapy group required more IV fluids by 72 hours. The authors emphasize that continued cellular and tissue decompensation is subclinical and often irreversible when obvious clinically. Goal-directed therapy allowed identification and treatment of these patients with insidious illness (global tissue hypoxia in the setting of normal vital signs).

Fig. 5-11.





Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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An algorithm for the treatment of patients presenting with sepsis syndrome. CVP = central venous pressure; ETI = ejective time index; HCT = hematocrit; MAP = mean arterial pressure; O_2 = oxygen; SaO_2 = oxygen saturation; SBP = systolic blood pressure.

(From Cinel et al,[79] with permission.)

Hyperglycemia and insulin resistance are typical in critically ill and septic patients, including patients without underlying diabetes mellitus. A

recent study reported significant positive impact of tight glucose management on outcome in critically ill patients.[81] The two treatment groups in this randomized, prospective study were assigned to receive intensive insulin therapy (maintenance of blood glucose between 80 and 110 mg/dL) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dL, with a goal between 180 and 200 mg/dL). The mean morning glucose level was significantly higher in the conventional treatment as compared to the intensive insulin therapy group (153 vs. 103 mg/dL). Mortality in the intensive insulin treatment group (4.6%) was significantly lower than in the conventional treatment group (8.0%), representing a 42% reduction in mortality. This reduction in mortality was most notable in the patients requiring longer than 5 days in the ICU. Furthermore, intensive insulin therapy reduced episodes of septicemia by 46%, reduced duration of antibiotic therapy, and decreased the need for prolonged ventilatory support and renal replacement therapy.

Another treatment protocol that has been demonstrated to increase survival in patients with ARDS investigated the use of lower ventilatory tidal volumes compared to traditional tidal volumes.[82] The majority of the patients enrolled in this multicenter, randomized trial developed ARDS secondary to pneumonia or sepsis. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 mL/kg of predicted body weight and an airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) of 50 cm of water or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 mL/kg of predicted body weight and a plateau pressure of 30 cm of water or less. The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 vs. 39.8%, $P = .007$), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean ± SD, 12 ± 11 vs. 10 ± 11; $P = .007$). The investigators concluded that in patients with acute lung injury and ARDS, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use.

A recent study reported benefit from IV infusion of recombinant human activated protein C for severe sepsis.[83] Activated protein C is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation. The authors conducted a randomized, prospective, multicenter trial assessing the efficacy of activated protein C in patients with systemic inflammation and organ failure due to acute infection. Treatment with activated protein C reduced the 28-day mortality rate from 31 to 25%; the reduction in relative risk of death was 19.4%. However, several follow-up studies have suggested that activated protein C may not improve mortality when patients are followed up to 6 months.

The use of corticosteroids in the treatment of sepsis and septic shock has been controversial for decades. The observation that severe sepsis often is associated with adrenal insufficiency or glucocorticoid receptor resistance has generated renewed interest in therapy for septic shock with corticosteroids. A single IV dose of 50 mg of hydrocortisone improved mean arterial blood pressure response relationships to norepinephrine and phenylephrine in patients with septic shock, and was most notable in patients with relative adrenal insufficiency. A more recent study evaluated therapy with hydrocortisone (50 mg IV every 6 hours) and fludrocortisone (50 μg orally once daily) vs. placebo for 1 week in patients with septic shock.[84] As in earlier studies, the authors performed corticotropin tests on these patients to document and stratify patients by relative adrenal insufficiency. In this study, 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly and safely lowered the risk of death in patients with septic shock and relative adrenal insufficiency. In an international, multicenter, randomized trial of corticosteroids in sepsis (CORTICUS study; 499 analyzable patients), steroids showed no benefit in intent to treat mortality or shock reversal.[85] This study suggested that hydrocortisone therapy cannot be recommended as routine adjuvant therapy for septic shock. However, if SBP remains less than 90 mmHg despite appropriate fluid and vasopressor therapy, hydrocortisone at 200 mg/day for 7 days in four divided doses or by continuous infusion should be considered.

Additional adjunctive immune modulation strategies have been developed for the treatment of septic shock. These include the use of antiendotoxin antibodies, anticytokine antibodies, cytokine receptor antagonists, immune enhancers, a non–isoform-specific nitric oxide synthase inhibitor, and O_2 radical scavengers. These compounds are each designed to alter some aspect of the host immune response to shock that is hypothesized to play a key role in its pathophysiology. However, most of these strategies have failed to demonstrate efficacy in human patients despite utility in well-controlled animal experiments. It is unclear whether the failure of these compounds is due to poorly designed clinical trials, inadequate understanding of the interactions of the complex host immune response to injury and infection, or animal models of shock that poorly represent the human disease.

Cardiogenic Shock

Cardiogenic shock is defined clinically as circulatory pump failure leading to diminished forward flow and subsequent tissue hypoxia, in the setting of adequate intravascular volume. Hemodynamic criteria include sustained hypotension (i.e., SBP <90 mmHg for at least 30 minutes), reduced cardiac index (<2.2 L/min per square meter), and elevated pulmonary artery wedge pressure (>15 mmHg).[86] Mortality rates for cardiogenic shock are 50 to 80%. Acute, extensive MI is the most common cause of cardiogenic shock; a smaller infarction in a patient with existing left ventricular dysfunction also may precipitate shock. Cardiogenic shock complicates 5 to 10% of acute MIs. Conversely, cardiogenic shock is the most common cause of death in patients hospitalized with acute MI. Although shock may develop early after MI, it typically is not found on admission. Seventy-five percent of patients who have cardiogenic shock complicating acute MIs develop signs of cardiogenic shock within 24 hours after onset of infarction (average 7 hours).

Recognition of the patient with occult hypoperfusion is critical to prevent progression to obvious cardiogenic shock with its high mortality rate; early initiation of therapy to maintain blood pressure and cardiac output is vital. Rapid assessment, adequate resuscitation, and reversal of the myocardial ischemia are essential in optimizing outcome in patients with acute MI. Prevention of infarct extension is a critical component. Large segments of nonfunctional but viable myocardium contribute to the development of cardiogenic shock after MI. In the setting of acute MI, expeditious restoration of cardiac output is mandatory to minimize mortality; the extent of myocardial salvage possible decreases exponentially with increased time to restoration of coronary blood flow. The degree of coronary flow after percutaneous transluminal coronary angioplasty correlates with inhospital mortality (i.e., 33% mortality with complete reperfusion, 50% mortality with incomplete reperfusion, and 85% mortality with absent reperfusion).[87] Inadequate cardiac function can be a direct result of cardiac injury, including profound myocardial contusion, blunt cardiac valvular injury, or direct myocardial damage (Table 5-7).[86–88] The pathophysiology of cardiogenic shock involves a vicious cycle of myocardial ischemia that causes myocardial dysfunction, which results in more myocardial ischemia. When sufficient mass of the left ventricular wall is necrotic or ischemic and fails to pump, the stroke volume decreases. An autopsy series of patients dying from cardiogenic shock have found damage to 40% of the left ventricle.[89] Ischemia distant from the infarct zone may contribute to the systolic dysfunction in patients with cardiogenic shock. The majority of these patients have multivessel disease, with limited vasodilator reserve and pressure-dependent coronary flow in multiple areas of the heart. Myocardial diastolic function is impaired in cardiogenic shock as well. Decreased compliance results from myocardial ischemia, and compensatory increases in left ventricular filling pressures progressively occur.

Table 5-7 Causes of Cardiogenic Shock
Acute myocardial infarction
Pump failure
Mechanical complications
Acute mitral regurgitation
Acute ventricular septal defect
Free wall rupture
Pericardial tamponade
Arrhythmia
End-stage cardiomyopathy
Myocarditis
Severe myocardial contusion
Left ventricular outflow obstruction
Aortic stenosis
Hypertrophic obstructive cardiomyopathy
Obstruction to left ventricular filling
Mitral stenosis
Left atrial myxoma
Acute mitral regurgitation
Acute aortic insufficiency

Metabolic
Drug reactions

Diminished cardiac output or contractility in the face of adequate intravascular volume (preload) may lead to underperfused vascular beds and reflexive sympathetic discharge. Increased sympathetic stimulation of the heart, either through direct neural input or from circulating catecholamines, increases heart rate, myocardial contraction, and myocardial O_2 consumption, which may not be relieved by increases in coronary artery blood flow in patients with fixed stenoses of the coronary arteries. Diminished cardiac output may also decrease coronary artery blood flow, resulting in a scenario of increased myocardial O_2 demand at a time when myocardial O_2 supply may be limited. Acute heart failure may also result in fluid accumulation in the pulmonary microcirculatory bed, decreasing myocardial O_2 delivery even further.

DIAGNOSIS

Rapid identification of the patient with pump failure and institution of corrective action are essential in preventing the ongoing spiral of decreased cardiac output from injury causing increased myocardial O_2 needs that cannot be met, leading to progressive and unremitting cardiac dysfunction. In evaluation of possible cardiogenic shock, other causes of hypotension must be excluded, including hemorrhage, sepsis, pulmonary embolism, and aortic dissection. Signs of circulatory shock include hypotension, cool and mottled skin, depressed mental status, tachycardia, and diminished pulses. Cardiac exam may include dysrhythmia, precordial heave, or distal heart tones. Confirmation of a cardiac source for the shock requires electrocardiogram and urgent echocardiography. Other useful diagnostic tests include chest radiograph, arterial blood gases, electrolytes, complete blood count, and cardiac enzymes. Invasive cardiac monitoring, which generally is not necessary, can be useful to exclude right ventricular infarction, hypovolemia, and possible mechanical complications.

Making the diagnosis of cardiogenic shock involves the identification of cardiac dysfunction or acute heart failure in a susceptible patient. In the setting of blunt traumatic injury, hemorrhagic shock from intra-abdominal bleeding, intrathoracic bleeding, and bleeding from fractures must be excluded, before implicating cardiogenic shock from blunt cardiac injury. Relatively few patients with blunt cardiac injury will develop cardiac pump dysfunction. Those who do generally exhibit cardiogenic shock early in their evaluation. Therefore, establishing the diagnosis of blunt cardiac injury is secondary to excluding other etiologies for shock and establishing that cardiac dysfunction is present. Invasive hemodynamic monitoring with a pulmonary artery catheter may uncover evidence of diminished cardiac output and elevated pulmonary artery pressure.

TREATMENT

After ensuring that an adequate airway is present and ventilation is sufficient, attention should be focused on support of the circulation. Intubation and mechanical ventilation often are required, if only to decrease work of breathing and facilitate sedation of the patient. Rapidly excluding hypovolemia and establishing the presence of cardiac dysfunction are essential. Treatment of cardiac dysfunction includes maintenance of adequate oxygenation to ensure adequate myocardial O_2 delivery and judicious fluid administration to avoid fluid overload and development of cardiogenic pulmonary edema. Electrolyte abnormalities, commonly hypokalemia and hypomagnesemia, should be corrected. Pain is treated with IV morphine sulfate or fentanyl. Significant dysrhythmias and heart block must be treated with antiarrhythmic drugs, pacing, or cardioversion, if necessary. Early consultation with cardiology is essential in current management of cardiogenic shock, particularly in the setting of acute MI.[86]

When profound cardiac dysfunction exists, inotropic support may be indicated to improve cardiac contractility and cardiac output. Dobutamine primarily stimulates cardiac $beta_1$ receptors to increase cardiac output but may also vasodilate peripheral vascular beds, lower total peripheral resistance, and lower systemic blood pressure through effects on $beta_2$ receptors. Ensuring adequate preload and intravascular volume is therefore essential prior to instituting therapy with dobutamine. Dopamine stimulates receptors (vasoconstriction), β_1 receptors (cardiac stimulation), and $BETA_2$ receptors (vasodilation), with its effects on beta receptors predominating at lower doses. Dopamine may be preferable to dobutamine in treatment of cardiac dysfunction in hypotensive patients. Tachycardia and increased peripheral resistance from dopamine infusion may worsen myocardial ischemia. Titration of both dopamine and dobutamine infusions may be required in some patients.

Epinephrine stimulates alpha and beta receptors and may increase cardiac contractility and heart rate; however, it also may have intense peripheral vasoconstrictor effects that impair further cardiac performance. Catecholamine infusions must be carefully controlled to maximize

coronary perfusion, while minimizing myocardial O_2 demand. Balancing the beneficial effects of impaired cardiac performance with the potential side effects of excessive reflex tachycardia and peripheral vasoconstriction requires serial assessment of tissue perfusion using indices such as capillary refill, character of peripheral pulses, adequacy of urine output, or improvement in laboratory parameters of resuscitation such as pH, base deficit, and lactate. Invasive monitoring generally is necessary in these unstable patients. The phosphodiesterase inhibitors amrinone and milrinone may be required on occasion in patients with resistant cardiogenic shock. These agents have long half-lives and induce thrombocytopenia and hypotension, and use is reserved for patients unresponsive to other treatment.

Patients whose cardiac dysfunction is refractory to cardiotonics may require mechanical circulatory support with an intra-aortic balloon pump.[90] Intra-aortic balloon pumping increases cardiac output and improves coronary blood flow by reduction of systolic afterload and augmentation of diastolic perfusion pressure. Unlike vasopressor agents, these beneficial effects occur without an increase in myocardial O_2 demand. An intra-aortic balloon pump can be inserted at the bedside in the ICU via the femoral artery through either a cutdown or using the percutaneous approach. Aggressive circulatory support of patients with cardiac dysfunction from intrinsic cardiac disease has led to more widespread application of these devices and more familiarity with their operation by both physicians and critical care nurses.

Preservation of existing myocardium and preservation of cardiac function are priorities of therapy for patients who have suffered an acute MI. Ensuring adequate oxygenation and O_2 delivery, maintaining adequate preload with judicious volume restoration, minimizing sympathetic discharge through adequate relief of pain, and correcting electrolyte imbalances are all straightforward nonspecific maneuvers that may improve existing cardiac function or prevent future cardiac complications. Anticoagulation and aspirin are given for acute MI. Although thrombolytic therapy reduces mortality in patients with acute MI, its role in cardiogenic shock is less clear. Patients in cardiac failure from an acute MI may benefit from pharmacologic or mechanical circulatory support in a manner similar to that of patients with cardiac failure related to blunt cardiac injury. Additional pharmacologic tools may include the use of beta blockers to control heart rate and myocardial O_2 consumption, nitrates to promote coronary blood flow through vasodilation, and ACE inhibitors to reduce ACE-mediated vasoconstrictive effects that increase myocardial workload and myocardial O_2 consumption.

Current guidelines of the American Heart Association recommend percutaneous transluminal coronary angiography for patients with cardiogenic shock, ST elevation, left bundle-branch block, and age less than 75 years.[91] Early definition of coronary anatomy and revascularization is the pivotal step in treatment of patients with cardiogenic shock from acute MI.[92] When feasible, percutaneous transluminal coronary angioplasty (generally with stent placement) is the treatment of choice. Coronary artery bypass grafting seems to be more appropriate for patients with multiple vessel disease or left main coronary artery disease.

Obstructive Shock

Although obstructive shock can be caused by a number of different etiologies that result in mechanical obstruction of venous return (Table 5-8), in trauma patients this is most commonly due to the presence of tension pneumothorax. Cardiac tamponade occurs when sufficient fluid has accumulated in the pericardial sac to obstruct blood flow to the ventricles. The hemodynamic abnormalities in pericardial tamponade are due to elevation of intracardiac pressures with limitation of ventricular filling in diastole with resultant decrease in cardiac output. Acutely, the pericardium does not distend; thus small volumes of blood may produce cardiac tamponade. If the effusion accumulates slowly (e.g., in the setting of uremia, heart failure, or malignant effusion), the quantity of fluid producing cardiac tamponade may reach 2000 mL. The major determinant of the degree of hypotension is the pericardial pressure. With either cardiac tamponade or tension pneumothorax, reduced filling of the right side of the heart from either increased intrapleural pressure secondary to air accumulation (tension pneumothorax) or increased intrapericardial pressure precluding atrial filling secondary to blood accumulation (cardiac tamponade) results in decreased cardiac output associated with increased central venous pressure.

Table 5-8 Causes of Obstructive Shock
Pericardial tamponade
Pulmonary embolus
Tension pneumothorax
IVC obstruction
Deep venous thrombosis

Gravid uterus on IVC
Neoplasm
Increased intrathoracic pressure
Excess positive end-expiratory pressure
Neoplasm

IVC = inferior vena cava.

DIAGNOSIS AND TREATMENT

The diagnosis of tension pneumothorax should be made on clinical examination. The classic findings include respiratory distress (in an awake patient), hypotension, diminished breath sounds over one hemithorax, hyperresonance to percussion, jugular venous distention, and shift of mediastinal structures to the unaffected side with tracheal deviation. In most instances, empiric treatment with pleural decompression is indicated rather than delaying to wait for radiographic confirmation. When a chest tube cannot be immediately inserted, such as in the prehospital setting, the pleural space can be decompressed with a large caliber needle. Immediate return of air should be encountered with rapid resolution of hypotension. Unfortunately, not all of the clinical manifestations of tension pneumothorax may be evident on physical examination. Hyperresonance may be difficult to appreciate in a noisy resuscitation area. Jugular venous distention may be absent in a hypovolemic patient. Tracheal deviation is a late finding and often is not apparent on clinical examination. Practically, three findings are sufficient to make the diagnosis of tension pneumothorax: respiratory distress or hypotension, decreased lung sounds, and hypertympany to percussion. Chest x-ray findings that may be visualized include deviation of mediastinal structures, depression of the hemidiaphragm, and hypo-opacification with absent lung markings. As discussed above, definitive treatment of a tension pneumothorax is immediate tube thoracostomy. The chest tube should be inserted rapidly, but carefully, and should be large enough to evacuate any blood that may be present in the pleural space. Most recommend placement in the fourth intercostal space (nipple level) at the anterior axillary line.

Cardiac tamponade results from the accumulation of blood within the pericardial sac, usually from penetrating trauma or chronic medical conditions such as heart failure or uremia. Although precordial wounds are most likely to injure the heart and produce tamponade, any projectile or wounding agent that passes in proximity to the mediastinum can potentially produce tamponade. Blunt cardiac rupture, a rare event in trauma victims who survive long enough to reach the hospital, can produce refractory shock and tamponade in the multiply-injured patient. The manifestations of cardiac tamponade, such as total circulatory collapse and cardiac arrest, may be catastrophic, or they may be more subtle. A high index of suspicion is warranted to make a rapid diagnosis. Patients who present with circulatory arrest from cardiac tamponade require emergency pericardial decompression, usually through a left thoracotomy. The indications for this maneuver are discussed in Chap. 7. Cardiac tamponade also may be associated with dyspnea, orthopnea, cough, peripheral edema, chest pain, tachycardia, muffled heart tones, jugular venous distention, and elevated central venous pressure. Beck's triad consists of hypotension, muffled heart tones, and neck vein distention. Unfortunately, absence of these clinical findings may not be sufficient to exclude cardiac injury and cardiac tamponade. Muffled heart tones may be difficult to appreciate in a busy trauma center and jugular venous distention and central venous pressure may be diminished by coexistent bleeding. Therefore, patients at risk for cardiac tamponade whose hemodynamic status permits additional diagnostic tests frequently require additional diagnostic maneuvers to confirm cardiac injury or tamponade.

Invasive hemodynamic monitoring may support the diagnosis of cardiac tamponade if elevated central venous pressure, pulsus paradoxus (i.e., decreased systemic arterial pressure with inspiration), or elevated right atrial and right ventricular pressure by pulmonary artery catheter are present. These hemodynamic profiles suffer from lack of specificity, the duration of time required to obtain them in critically injured patients, and their inability to exclude cardiac injury in the absence of tamponade. Chest radiographs may provide information on the possible trajectory of a projectile, but rarely are diagnostic because the acutely filled pericardium distends poorly. Echocardiography has become the preferred test for the diagnosis of cardiac tamponade. Good results in detecting pericardial fluid have been reported, but the yield in detecting pericardial fluid depends on the skill and experience of the ultrasonographer, body habitus of the patient, and absence of wounds that preclude visualization of the pericardium. Standard two-dimensional or transesophageal echocardiography are sensitive techniques to evaluate the pericardium for fluid, and are typically performed by examiners skilled at evaluating ventricular function, valvular abnormalities, and integrity of the proximal thoracic aorta. Unfortunately, these skilled examiners are rarely immediately available at all hours of the night,

when many trauma patients present; therefore, waiting for this test may result in inordinate delays. In addition, although both ultrasound techniques may demonstrate the presence of fluid or characteristic findings of tamponade (large volume of fluid, right atrial collapse, poor distensibility of the right ventricle), they do not exclude cardiac injury per se. Pericardiocentesis to diagnose pericardial blood and potentially relieve tamponade may be used. Performing pericardiocentesis under ultrasound guidance has made the procedure safer and more reliable. An indwelling catheter may be placed for several days in patients with chronic pericardial effusions. Needle pericardiocentesis may not evacuate clotted blood and has the potential to produce cardiac injury, making it a poor alternative in busy trauma centers.

Diagnostic pericardial window represents the most direct method to determine the presence of blood within the pericardium. The procedure is best performed in the operating room under general anesthesia. It can be performed through either the subxiphoid or transdiaphragmatic approach. Adequate equipment and personnel to rapidly decompress the pericardium, explore the injury, and repair the heart should be present. Once the pericardium is opened and tamponade relieved, hemodynamics usually improve dramatically and formal pericardial exploration can ensue. Exposure of the heart can be achieved by extending the incision to a median sternotomy, performing a left anterior thoracotomy, or performing bilateral anterior thoracotomies ("clamshell").

Neurogenic Shock

Neurogenic shock refers to diminished tissue perfusion as a result of loss of vasomotor tone to peripheral arterial beds. Loss of vasoconstrictor impulses results in increased vascular capacitance, decreased venous return, and decreased cardiac output. Neurogenic shock is usually secondary to spinal cord injuries from vertebral body fractures of the cervical or high thoracic region that disrupt sympathetic regulation of peripheral vascular tone (Table 5-9). Rarely, a spinal cord injury without bony fracture, such as an epidural hematoma impinging on the spinal cord, can produce neurogenic shock. Sympathetic input to the heart, which normally increases heart rate and cardiac contractility, and input to the adrenal medulla, which increases catecholamine release, may also be disrupted, preventing the typical reflex tachycardia that occurs with hypovolemia. Acute spinal cord injury results in activation of multiple secondary injury mechanisms: (a) vascular compromise to the spinal cord with loss of autoregulation, vasospasm, and thrombosis, (b) loss of cellular membrane integrity and impaired energy metabolism, and (c) neurotransmitter accumulation and release of free radicals. Importantly, hypotension contributes to the worsening of acute spinal cord injury as the result of further reduction in blood flow to the spinal cord. Management of acute spinal cord injury with attention to blood pressure control, oxygenation, and hemodynamics, essentially optimizing perfusion of an already ischemic spinal cord, seems to result in improved neurologic outcome. Patients with hypotension from spinal cord injury are best monitored in an ICU and carefully followed for evidence of cardiac or respiratory dysfunction.

Table 5-9 Causes of Neurogenic Shock
Spinal cord trauma
Spinal cord neoplasm
Spinal/epidural anesthetic

DIAGNOSIS

Acute spinal cord injury may result in bradycardia, hypotension, cardiac dysrhythmias, reduced cardiac output, and decreased peripheral vascular resistance. The severity of the spinal cord injury seems to correlate with the magnitude of cardiovascular dysfunction. Patients with complete motor injuries are over five times more likely to require vasopressors for neurogenic shock compared to those with incomplete lesions.[93] The classic description of neurogenic shock consists of decreased blood pressure associated with bradycardia (absence of reflexive tachycardia due to disrupted sympathetic discharge), warm extremities (loss of peripheral vasoconstriction), motor and sensory deficits indicative of a spinal cord injury, and radiographic evidence of a vertebral column fracture. Patients with multisystem trauma that includes spinal cord injuries often have head injuries that may make identification of motor and sensory deficits difficult in the initial evaluation. Furthermore, associated injuries may occur that result in hypovolemia, further complicating the clinical presentation. In a subset of patients with spinal cord injuries from penetrating wounds, most of the patients with hypotension had blood loss as the etiology (74%) rather than neurogenic causes, and few (7%) had the classic findings of neurogenic shock.[94] In the multiply injured patient, other causes of hypotension including hemorrhage, tension pneumothorax, and cardiogenic shock, must be sought and excluded.

TREATMENT

After the airway is secured and ventilation is adequate, fluid resuscitation and restoration of intravascular volume often will improve perfusion in neurogenic shock. Most patients with neurogenic shock will respond to restoration of intravascular volume alone, with satisfactory improvement in perfusion and resolution of hypotension. Administration of vasoconstrictors will improve peripheral vascular tone, decrease vascular capacitance, and increase venous return, but should only be considered once hypovolemia is excluded as the cause of the hypotension, and the diagnosis of neurogenic shock established. If the patient's blood pressure has not responded to what is felt to be adequate volume resuscitation, dopamine may be used first. A pure alpha agonist, such as phenylephrine, may be used primarily or in patients unresponsive to dopamine. Specific treatment for the hypotension is often of brief duration, as the need to administer vasoconstrictors typically lasts 24 to 48 hours. On the other hand, life-threatening cardiac dysrhythmias and hypotension may occur up to 14 days after spinal cord injury.

The duration of the need for vasopressor support for neurogenic shock may correlate with the overall prognosis or chances of improvement in neurologic function. Appropriate rapid restoration of blood pressure and circulatory perfusion may improve perfusion to the spinal cord, prevent progressive spinal cord ischemia, and minimize secondary cord injury. Restoration of normal blood pressure and adequate tissue perfusion should precede any operative attempts to stabilize the vertebral fracture.

ENDPOINTS IN RESUSCITATION

Shock is defined as inadequate perfusion to maintain normal organ function. With prolonged anaerobic metabolism, tissue acidosis and O_2 debt accumulate. Thus, the goal in the treatment of shock is restoration of adequate organ perfusion and tissue oxygenation. Resuscitation is complete when O_2 debt is repaid, tissue acidosis is corrected, and aerobic metabolism restored. Clinical confirmation of this endpoint remains a challenge.

Resuscitation of the patient in shock requires simultaneous evaluation and treatment; the etiology of the shock often is not initially apparent. Hemorrhagic shock, septic shock, and traumatic shock are the most common types of shock encountered on surgical services. To optimize outcome in bleeding patients, early control of the hemorrhage and adequate volume resuscitation, including both red blood cells and crystalloid solutions, are necessary. Expedient operative resuscitation is mandatory to limit the magnitude of activation of multiple mediator systems and to abort the microcirculatory changes, which may evolve insidiously into the cascade that ends in irreversible hemorrhagic shock. Attempts to stabilize an actively bleeding patient anywhere but in the operating room are inappropriate. Any intervention that delays the patient's arrival in the operating room for control of hemorrhage increases mortality, thus the important concept of *operating room resuscitation* of the critically injured patient.

Recognition by care providers of the patient who is in the compensated phase of shock is equally important, but more difficult based on clinical criteria. Compensated shock exists when inadequate tissue perfusion persists despite normalization of blood pressure and heart rate. Even with normalization of blood pressure, heart rate, and urine output, 80 to 85% of trauma patients have inadequate tissue perfusion, as evidenced by increased lactate or decreased mixed venous O_2 saturation.[56,95] Persistent, occult hypoperfusion is frequent in the ICU, with a resultant significant increase in infection rate and mortality in major trauma patients. Patients failing to reverse their lactic acidosis within 12 hours of admission (acidosis that was persistent despite normal heart rate, blood pressure, and urine output) developed an infection three times as often as those who normalized their lactate levels within 12 hours of admission. In addition, mortality was fourfold higher in patients who developed infections. Both injury severity score and occult hypotension (lactic acidosis) longer than 12 hours were independent predictors of infection.[96] Thus, recognition of subclinical hypoperfusion requires information beyond vital signs and urinary output.

Endpoints in resuscitation can be divided into *systemic* or *global parameters* , *tissue-specific parameters*, and *cellular parameters*. Global endpoints include vital signs, cardiac output, pulmonary artery wedge pressure, O_2 delivery and consumption, lactate, and base deficit (Table 5-10).

Table 5-10 Endpoints in Resuscitation
Systemic/global
Lactate

Base deficit
Cardiac output
Oxygen delivery and consumption
Tissue specific
Gastric tonometry
Tissue pH, oxygen, carbon dioxide levels
Near infrared spectroscopy
Cellular
Membrane potential
Adenosine triphosphate

Assessment of Endpoints in Resuscitation

OXYGEN TRANSPORT

Attaining supranormal O_2 transport variables has been proposed as a means to correct O_2 debt. Shoemaker and associates published the first randomized study examining supranormal O_2 consumption and delivery as endpoints in resuscitation.[97] The supranormal O_2 transport variables include O_2 delivery greater than 600 mL/min per square meter, cardiac index greater than 4.5 L/min per square meter, and O_2 consumption index greater than 170 mL/min per square meter. These authors reported a significant reduction in mortality in the patients achieving supranormal endpoints. More recent publications suggest that patients unable to increase O_2 delivery have a higher mortality, as opposed to it being a true benefit of the therapy.[98–100] This observation strongly correlates with age of the patient, with older patients less able to generate supranormal O_2 delivery. Gattinoni and colleagues reported effects of hemodynamic therapy in critically ill patients on 10,726 patients in 56 ICUs.[101] Seven hundred sixty-two patients met the predefined diagnostic categories and were assigned to one of three groups: control group, supranormal cardiac index group, and O_2 saturation group (with a goal of achieving normal venous O_2 saturation). The authors found that hemodynamic therapy aimed at reaching supranormal values for cardiac index or normal values for mixed venous O_2 saturation did not reduce morbidity or mortality among critically ill patients. In this paper's accompanying editorial, it was noted that failure to achieve both values is a relatively common problem, particularly among older or more severely ill patients. These results emphasize the importance of adequate volume replacement, maintenance of normal blood pressure, and the use of minor doses of inotropic drugs to maintain a normal cardiac output. In a recent paper from Shoemaker's group, supranormal values were achieved intentionally in 70% of the treatment group and spontaneously by 40% of the control group.[98] Mortality, incidence of organ failure and sepsis, and length of stay were no different between the treatment and control groups. Patients in each group who attained supranormal values had better outcomes than those who could not, and mortality was 30% in patients unable to reach supranormal values and 0% in patients with supranormal indices. Age younger than 40 years was the sole independent variable that predicted ability to reach these supraphysiologic endpoints. Thus, the evidence is insufficient to support the routine use of a strategy to maximize O_2 delivery in a group of unselected patients.

Inability to repay O_2 debt is a predictor of mortality and organ failure; the probability of death has been directly correlated to the calculated O_2 debt in hemorrhagic shock. Direct measurement of the O_2 debt in the resuscitation of patients is difficult. The easily obtainable parameters of arterial blood pressure, heart rate, urine output, central venous pressure, and pulmonary artery occlusion pressure are poor indicators of the adequacy of tissue perfusion. Therefore, surrogate parameters have been sought to estimate the O_2 debt; serum lactate and base deficit have been shown to correlate with O_2 debt.

LACTATE

Lactate is generated by conversion of pyruvate to lactate by lactate dehydrogenase in the setting of insufficient O_2. Lactate is released into the circulation and is predominantly taken up and metabolized by the liver and kidneys. The liver accounts for approximately 50% and the kidney for about 30% of whole body lactate uptake. Elevated serum lactate is an indirect measure of the O_2 debt, and therefore an approximation of the magnitude and duration of the severity of shock. The admission lactate level, highest lactate level, and time interval to normalize the serum lactate are important prognostic indicators for survival. For example, in a study of 76 consecutive patients, 100% survival was observed among the patients with normalization of lactate within 24 hours, 78% survival when lactate normalized between 24

and 48 hours, and only 14% survivorship if it took longer than 48 hours to normalize the serum lactate.[56] In contrast, individual variability of lactate may be too great to permit accurate prediction of outcome in any individual case. Base deficit and volume of blood transfusion required in the first 24 hours of resuscitation may be better predictors of mortality than the plasma lactate alone.

BASE DEFICIT

Base deficit is the amount of base in millimoles that is required to titrate 1 L of whole blood to a pH of 7.40 with the sample fully saturated with O_2 at 37°C (98.6°F) and a partial pressure of CO_2 of 40 mmHg. It usually is measured by arterial blood gas analysis in clinical practice as it is readily and quickly available. The mortality of trauma patients can be stratified according to the magnitude of base deficit measured in the first 24 hours after admission.[60] In a retrospective study of over 3000 trauma admissions, patients with a base deficit worse than 15 mmol/L had a mortality of 70%. Base deficit can be stratified into mild (3 to 5 mmol/L), moderate (6 to 14 mmol/L), and severe (15 mmol/L) categories, with a trend toward higher mortality with worsening base deficit in patients with trauma. Both the magnitude of the perfusion deficit as indicated by the base deficit and the time required to correct it are major factors determining outcome in shock.

Indeed, when elevated base deficit persists (or lactic acidosis) in the trauma patient, ongoing bleeding is often the etiology. Trauma patients admitted with a base deficit greater than 15 mmol/L required twice the volume of fluid infusion and six times more blood transfusion in the first 24 hours compared to patients with mild acidosis. Transfusion requirements increased as base deficit worsened and ICU and hospital lengths of stay increased. Mortality increased as base deficit worsened; the frequency of organ failure increased with greater base deficit.[57] The probability of trauma patients developing ARDS has been reported to correlate with severity of admission base deficit and lowest base deficit within the first 24 hours postinjury.[59] Persistently high base deficit is associated with abnormal O_2 utilization and higher mortality. Monitoring base deficit in the resuscitation of trauma patients assists in assessment of O_2 transport and efficacy of resuscitation.[58]

Factors that may compromise the utility of the base deficit in estimating O_2 debt are the administration of bicarbonate, hypothermia, hypocapnia (overventilation), heparin, ethanol, and ketoacidosis. However, the base deficit remains one of the most widely used estimates of O_2 debt for its clinical relevance, accuracy, and availability.

GASTRIC TONOMETRY

Lactate and base deficit indicate global tissue acidosis. Several authors have suggested that tissue-specific endpoints, rather than systemic endpoints, are more predictive of outcome and adequate resuscitation in trauma patients. With heterogeneity of blood flow, regional tissue beds may be hypoperfused. Gastric tonometry has been used to assess perfusion of the GI tract. The concentration of CO_2 accumulating in the gastric mucosa can be sampled with a specially designed nasogastric tube. With the assumption that gastric bicarbonate is equal to serum levels, gastric intramucosal pH (pHi) is calculated by applying the Henderson-Hasselbalch equation. pHi should be greater than 7.3; pHi will be lower in the setting of decreased O_2 delivery to the tissues. pHi is a good prognostic indicator; patients with normal pHi have better outcomes than those patients with pHi less than 7.3.[102–104] Goal-directed human studies, with pHi as an endpoint in resuscitation, have shown normalization of pHi to correlate with improved outcome in several studies, and with contradictory findings in other studies. Use of pHi as a singular endpoint in the resuscitation of critically ill patients remains controversial.[105]

NEAR INFRARED SPECTROSCOPY

Near infrared (NIR) spectroscopy can measure tissue oxygenation and redox state of cytochrome a,a_3 on a continuous, noninvasive basis. The NIR probe emits multiple wavelengths of light in the NIR spectrum (650 to 1100 nm). Photons are then either absorbed by the tissue or reflected back to the probe. Maximal exercise in laboratory studies resulted in reduction of cytochrome a,a_3; this correlated with tissue lactate elevation. NIR spectroscopy can be used to compare tissue oxyhemoglobin levels (indicating tissue O_2 supply to cytochrome a,a_3 with mitochondrial O_2 consumption), thus demonstrating flow-independent mitochondrial oxidative dysfunction and the need for further resuscitation. Trauma patients with decoupled oxyhemoglobin and cytochrome a,a_3 have redox dysfunction and have been shown to have a higher incidence of organ failure (89 vs. 13%).[106,107]

TISSUE PH, OXYGEN, AND CARBON DIOXIDE CONCENTRATION

Tissue probes with optical sensors have been used to measure tissue pH and partial pressure of O_2 and CO_2 in subcutaneous sites, muscle, and the bladder. These probes may use transcutaneous methodology with Clark electrodes or direct percutaneous probes.[108,109] The

percutaneous probes can be inserted through an 18-gauge catheter and hold promise as continuous monitors of tissue perfusion.

RIGHT VENTRICULAR END-DIASTOLIC VOLUME INDEX

Right ventricular end-diastolic volume index (RVEDVI) seems to more accurately predict preload for cardiac index than does pulmonary artery wedge pressure.[110] Chang and colleagues reported that 50% of trauma patients had persistent splanchnic ischemia that was reversed by increasing RVEDVI. RVEDVI is a parameter that seems to correlate with preload-related increases in cardiac output. More recently, these authors have described left ventricular power output as an endpoint (LVP >320 mmHg·L/min per square meter), which is associated with improved clearance of base deficit and a lower rate of organ dysfunction following injury.[111]

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Note: Large images and tables on this page may necessitate printing in landscape mode.

KEY POINTS

1. The incidence of surgical site infections can be reduced by appropriate patient preparation, timely perioperative antibiotic administration, maintenance of perioperative normothermia and normoglycemia, and appropriate wound management.

2. Principles relevant to appropriate antibiotic prophylaxis for surgery: (a) select an agent with activity against common organisms at the site of surgery, (b) the initial dose of the antibiotic should be given within 30 minutes of incision, (c) antibiotics should be redosed every 1 to 2 half-lives during surgery to ensure adequate tissue levels, and (d) antibiotics should not be continued for more than 24 hours after surgery for routine prophylaxis.

3. Source control is a key concept in the treatment of most surgically relevant infections. Infected or necrotic material must be drained or removed as part of the treatment plan in this setting. Delays in adequate source control are associated with worsened outcomes.

4. Sepsis is both the presence of infection and the host response to infection (systemic inflammatory response syndrome, SIRS). Sepsis is a clinical spectrum, ranging from sepsis (SIRS plus infection) to severe sepsis (organ dysfunction), to septic shock (hypotension requiring vasopressors). Outcomes in patients with sepsis are improved with an organized approach to therapy that includes rapid resuscitation, antibiotics, and source control.

5. When using antimicrobial agents for therapy of serious infection, several principles should be followed: (a) identify likely sources of infection, (b) choose an agent (or agents) that covers likely organisms for these sources, (c) remember that inadequate or delayed antibiotic therapy results in increased mortality, so it is important to begin therapy with broader coverage, (d) when possible, obtain cultures early and use results to tailor therapy, (e) if there is no infection identified after 3 days, strongly consider discontinuation of antibiotics, and (f) stop antibiotics after an appropriate course of therapy.

6. The keys to good outcomes in patients with necrotizing soft tissue infection are early recognition and appropriate débridement of infected tissue with repeated débridement until no further signs of infection are present.

7. Transmission of HIV and other infections spread by blood and body fluid from patient to health care worker can be minimized by observation of universal precautions, which include routine use of barriers when anticipating contact with blood or body fluids, washing of hands and other skin surfaces immediately after contact with blood or body fluids, and careful handling and disposal of sharp instruments during and after use.

HISTORICAL BACKGROUND

Although treatment of infection has been an integral part of the surgeon's practice since the dawn of time, the body of knowledge that led to the present field of surgical infectious disease was derived from the evolution of germ theory and antisepsis. Application of the latter to clinical practice, concurrent with the development of anesthesia, was pivotal in allowing surgeons to expand their repertoire to encompass complex procedures that previously were associated with extremely high rates of morbidity and mortality due to postoperative infections. However, until recently, the occurrence of infection related to the surgical wound was the rule rather than the exception. In fact, the development of modalities to effectively prevent and treat infection has occurred only within the last several decades.

A number of observations by nineteenth-century physicians and investigators were critical to our current understanding of the pathogenesis, prevention, and treatment of surgical infections. In 1846, Ignaz Semmelweis, a Magyar physician, took a post at the Allgemein Krankenhaus in Vienna. He noticed that the mortality from puerperal ("childbed") fever was much higher in the teaching ward (1:11) than in the ward where patients were delivered by midwives (1:29). He also made the interesting observation that women who delivered before arrival on the

teaching ward had a negligible mortality rate. The tragic death of a colleague due to overwhelming infection after a knife scratch received during an autopsy of a woman who had died of puerperal fever led Semmelweis to observe that pathologic changes in his friend were identical to those of women dying from this postpartum disease. He then hypothesized that puerperal fever was caused by putrid material transmitted from patients dying of this disease by carriage on the examining fingers of the medical students and physicians who frequently went from the autopsy room to the wards. The low mortality noted in the midwives' ward, Semmelweis realized, was due to the fact that midwives did not participate in autopsies. Fired with the zeal of his revelation, he posted a notice on the door to the ward requiring all caregivers to rinse their hands thoroughly in chlorine water before entering the area. This simple intervention reduced mortality from puerperal fever to 1.5%, surpassing the record of the midwives. In 1861, he published his classic work on childbed fever based on records from his practice. Unfortunately, Semmelweis' ideas were not well accepted by the authorities of the time.[1] Despondent, he committed suicide in 1865 by intentionally cutting his finger during the autopsy of a woman who died of puerperal fever, presumably as the ultimate proof of his tenets.

Louis Pasteur performed a body of work during the latter part of the nineteenth century that provided the underpinnings of modern microbiology, at the time known as *germ theory*. His work in humans followed experiments identifying infectious agents in silkworms. He was able to elucidate the principle that contagious diseases are caused by specific microbes and that these microbes are foreign to the infected organism. Using this principle, he developed techniques of sterilization critical to oenology and identified several bacteria responsible for human illnesses, including *Staphylococcus*, *Streptococcus*, and pneumococcus.

Joseph Lister, the son of a wine merchant, was appointed professor of surgery at the Glasgow Royal Infirmary in 1859. In his early practice, he noted that more than 50% of his patients undergoing amputation died due to postoperative infection. After hearing of Pasteur's theory, Lister experimented with the use of a solution of carbolic acid, which he knew was being used to treat sewage. He first reported his findings to the British Medical Association in 1867 using dressings saturated with carbolic acid on 12 patients with compound fractures; 10 recovered without amputation, one survived with amputation, and one died of causes unrelated to the wound. In spite of initial resistance, his methods were quickly adopted throughout Europe.

From 1878 until 1880, Robert Koch was the District Medical Officer for Wollstein (then Prussia, now a part of Poland), which was an area in which anthrax was endemic. Performing experiments in his home, without the benefit of scientific equipment and academic contact, Koch developed techniques for culture of *Bacillus anthracis* and proved the ability of this organism to cause anthrax in healthy animals. He developed the following four postulates to identify the association of organisms with specific diseases: (a) the suspected pathogenic organism should be present in all cases of the disease and absent from healthy animals, (b) the suspected pathogen should be isolated from a diseased host and grown in a pure culture in vitro, (c) cells from a pure culture of the suspected organism should cause disease in a healthy animal, and (d) the organism should be reisolated from the newly diseased animal and shown to be the same as the original. He used these same techniques to identify the organisms responsible for cholera and tuberculosis. During the next century, *Koch's postulates*, as they came to be called, became critical to our understanding of surgical infections and remain so today.[2]

The first intra-abdominal operation to treat infection via "source control" (i.e., surgical intervention to eliminate the source of infection) was appendectomy. This operation was pioneered by Charles McBurney at the New York College of Physicians and Surgeons, among others.[3] McBurney's classic report on early operative intervention for appendicitis was presented before the New York Surgical Society in 1889. Appendectomy for the treatment of appendicitis, previously an often fatal disease, was popularized after the 1902 coronation of King Edward VII of England was delayed due to his need for an appendectomy, which was performed by Sir Frederick Treves. The king desperately needed an appendectomy but strongly opposed going into the hospital, protesting, "I have a coronation on hand." However, Treves was adamant, stating, "It will be a funeral, if you don't have the operation." Treves carried the debate, and the king lived.

During the twentieth century, the discovery of effective antimicrobials added another tool to the armamentarium of modern surgeons. Sir Alexander Fleming, after serving in the British Army Medical Corps during World War I, continued work on the natural antibacterial action of the blood and antiseptics. In 1928, while studying influenza virus, he noted a zone of inhibition around a mold colony (*Penicillium notatum*) that serendipitously grew on a plate of *Staphylococcus*, and he named the active substance *penicillin*. This first effective antibacterial agent subsequently led to the development of hundreds of potent antimicrobials, set the stage for their use as prophylaxis against postoperative infection, and became a critical component of the armamentarium to treat aggressive, lethal surgical infections.

Concurrent with the development of numerous antimicrobial agents were advances in the field of clinical microbiology. Many new microbes

were identified, including numerous anaerobes; the autochthonous microflora of the skin, GI tract, and other parts of the body that the surgeon encountered in the process of an operation were characterized in great detail. However, it remained unclear whether these organisms, anaerobes in particular, were commensals or pathogens. Subsequently, the initial clinical observations of surgeons such as Frank Meleney, William Altemeier, and others provided the key, when they observed that aerobes and anaerobes could synergize to cause serious soft tissue and severe intra-abdominal infection.[4,5] Thus, the concepts that resident microbes were nonpathogenic until they entered a sterile body cavity at the time of surgery, and that many, if not most, surgical infections were polymicrobial in nature, became critical ideas and were promulgated by a number of clinician-scientists over the last several decades.[6,7] These tenets became firmly established after microbiology laboratories demonstrated the invariable presence of aerobes and anaerobes in peritoneal cultures obtained at the time of surgery for intra-abdominal infection due to a perforated viscus or gangrenous appendicitis. Clinical trials provided evidence that optimal therapy for these infections required effective source control, plus the administration of antimicrobial agents directed against both types of pathogens.

William Osler, a prolific writer and one of the fathers of American medicine, made an observation in 1904 in his treatise *The Evolution of Modern Medicine* that was to have profound implications for the future of treatment of infection: "Except on few occasions, the patient appears to die from the body's response to infection rather than from it."[8] The discovery of the first cytokines began to allow insight into the organism's response to infection, and led to an explosion in our understanding of the host inflammatory response. Expanding knowledge of the multiple pathways activated during the response to invasion by infectious organisms has permitted the design of new therapies targeted at modifying the inflammatory response to infection, which seems to cause much of the end-organ dysfunction and failure. Preventing and treating this process of multiple organ failure during infection is one of the major challenges of modern critical care and surgical infectious disease.

PATHOGENESIS OF INFECTION

Host Defenses

The mammalian host possesses several layers of endogenous defense mechanisms that serve to prevent microbial invasion, limit proliferation of microbes within the host, and contain or eradicate invading microbes. These defenses are integrated and redundant so that the various components function as a complex, highly regulated system that is extremely effective in coping with microbial invaders. They include site-specific defenses that function at the tissue level, as well as components that freely circulate throughout the body in both blood and lymph. Systemic host defenses invariably are recruited to a site of infection, a process that begins immediately upon introduction of microbes into a sterile area of the body. Perturbation of one or more components of these defenses (e.g., via immunosuppressants, chronic illness, and burns) may have substantial negative impact on resistance to infection.

Entry of microbes into the mammalian host is precluded by the presence of a number of barriers that possess either an epithelial (integument) or mucosal (respiratory, gut, and urogenital) surface. However, barrier function is not solely limited to physical characteristics: Host barrier cells may secrete substances that limit microbial proliferation or prevent invasion. Also, resident or commensal microbes (endogenous or autochthonous host microflora) adherent to the physical surface and to each other may preclude invasion, particularly of virulent organisms (colonization resistance).[9]

The most extensive physical barrier is the integument or skin. In addition to the physical barrier posed by the epithelial surface, the skin harbors its own resident microflora that may block the attachment and invasion of noncommensal microbes. Microbes also are held in check by chemicals that sebaceous glands secrete and by the constant shedding of epithelial cells. The endogenous microflora of the integument primarily comprises gram-positive aerobic microbes belonging to the genera *Staphylococcus* and *Streptococcus*, as well as *Corynebacterium* and *Propionibacterium* species. These organisms, plus *Enterococcus faecalis* and *faecium*, *Escherichia coli*, and other Enterobacteriaceae, and yeast such as *Candida albicans*, can be isolated from the infraumbilical regions of the body. Diseases of the skin (e.g., eczema and dermatitis) are associated with overgrowth of skin commensal organisms, and barrier breaches invariably lead to the introduction of these microbes.

The respiratory tract possesses several host defense mechanisms that facilitate the maintenance of sterility in the distal bronchi and alveoli under normal circumstances. In the upper respiratory tract, respiratory mucus traps larger particles, including microbes. This mucus is then

passed into the upper airways and oropharynx by ciliated epithelial cells, where the mucus is cleared via coughing. Smaller particles arriving in the lower respiratory tract are cleared via phagocytosis by pulmonary alveolar macrophages. Any process that diminishes these host defenses can lead to development of bronchitis or pneumonia.

The urogenital, biliary, pancreatic ductal, and distal respiratory tracts do not possess resident microflora in healthy individuals, although microbes may be present if these barriers are affected by disease (e.g., malignancy, inflammation, calculi, or foreign body), or if microorganisms are introduced from an external source (e.g., urinary catheter or pulmonary aspiration). In contrast, significant numbers of microbes are encountered in many portions of the GI tract, with vast numbers being found within the oropharynx and distal colorectum, although the specific organisms differ.

One would suppose that the entire GI tract would be populated via those microbes found in the oropharynx, but this is not the case. This is because after ingestion, these organisms routinely are killed in the highly acidic, low-motility environment of the stomach during the initial phases of digestion. Thus, small numbers of microbes populate the gastric mucosa [approximately 10^2 to 10^3 colony-forming units (CFU)/mL]; this population expands in the presence of drugs or disease states that diminish gastric acidity. Microbes that are not destroyed within the stomach enter the small intestine, in which a certain amount of microbial proliferation takes place, such that approximately 10^5 to 10^8 CFU/mL are present in the terminal ileum.

The relatively low-oxygen, static environment of the colon is accompanied by the exponential growth of microbes that comprise the most extensive host endogenous microflora. Anaerobic microbes outnumber aerobic species approximately 100:1 in the distal colorectum, and approximately 10^{11} to 10^{12} CFU/g are present in feces. Large numbers of facultative and strict anaerobes (*Bacteroides fragilis*, *distasonis*, and *thetaiotaomicron*, *Bifidobacterium*, *Clostridium*, *Eubacterium*, *Fusobacterium*, *Lactobacillus* , and *Peptostreptococcus* species) as well as several orders of magnitude fewer aerobic microbes (*E. coli* and other Enterobacteriaceae, *E. faecalis* and *faecium*, *C. albicans* and other *Candida* spp.) are present. Intriguingly, although colonization resistance on the part of this extensive, well-characterized host microflora effectively prevents invasion of enteric pathogens such as *Salmonella*, *Shigella*, *Vibrio*, and other enteropathogenic bacterial species, these same organisms provide the initial inoculum for infection should perforation of the GI tract occur. It is of great interest that only some of these microbial species predominate in established intra-abdominal infection.

Once microbes enter a sterile body compartment (e.g., pleural or peritoneal cavity) or tissue, additional host defenses act to limit and/or eliminate these pathogens. Initially, several primitive and relatively nonspecific host defenses act to contain the nidus of infection, which may include microbes as well as debris, devitalized tissue, and foreign bodies, depending on the nature of the injury. These defenses include the physical barrier of the tissue itself, as well as the capacity of proteins such as lactoferrin and transferrin to sequester the critical microbial growth factor iron, thereby limiting microbial growth. In addition, fibrinogen within the inflammatory fluid has the ability to trap large numbers of microbes during the process in which it polymerizes into fibrin. Within the peritoneal cavity, unique host defenses exist, including a diaphragmatic pumping mechanism whereby particles such as microbes within peritoneal fluid are expunged from the abdominal cavity via specialized structures on the undersurface of the diaphragm. Concurrently, containment by the omentum, the so-called *gatekeeper* of the abdomen and intestinal ileus, serves to wall off infection. However, the latter processes and fibrin trapping have a high likelihood of contributing to the formation of an intra-abdominal abscess.

Microbes also immediately encounter a series of host defense mechanisms that reside within the vast majority of tissues of the body. These include resident macrophages and low levels of complement (C) proteins and immunoglobulins (Ig, antibodies).[10] Resident macrophages secrete a wide array of substances in response to the above-mentioned processes, some of which appear to regulate the cellular components of the host defense response. Macrophage cytokine synthesis is upregulated. Secretion of tumor necrosis factor alpha (TNF-α), of interleukins (IL)-1β, 6, and 8; and of interferon-gamma (INF-γ) occurs within the tissue milieu, and, depending on the magnitude of the host defense response, the systemic circulation.[11] Concurrently, a counterregulatory response is initiated consisting of binding proteins (TNF-BP), cytokine receptor antagonists (IL-1ra) and anti-inflammatory cytokines (IL-4 and IL-10).

The interaction of microbes with these first-line host defenses leads to microbial opsonization (C1q, C3bi, and IgFc), phagocytosis, and both extracellular (C5b6-9 membrane attack complex) and intracellular microbial destruction (phagocytic vacuoles). Concurrently, the classic and alternate complement pathways are activated both via direct contact with and via IgM > IgG binding to microbes, leading to the release of a number of different complement protein fragments (C3a, C4a, C5a) that are biologically active, acting to markedly enhance vascular

permeability. Bacterial cell wall components and a variety of enzymes that are expelled from leukocyte phagocytic vacuoles during microbial phagocytosis and killing act in this capacity as well.

Simultaneously, the release of substances to which polymorphonuclear leukocytes (PMNs) in the bloodstream are attracted takes place. These consist of C5a, microbial cell wall peptides containing *N*-formyl-methionine, and macrophage secretion of cytokines such as IL-8. This process of host defense recruitment leads to further influx of inflammatory fluid into the area of incipient infection, and is accompanied by diapedesis of large numbers of PMNs, a process that begins within several minutes and may peak within hours or days. The magnitude of the response and eventual outcome generally are related to several factors: (a) the initial number of microbes, (b) the rate of microbial proliferation in relation to containment and killing by host defenses, (c) microbial virulence, and (d) the potency of host defenses. In regard to the latter, drugs or disease states that diminish any or multiple components of host defenses are associated with higher rates and potentially more grave infections.

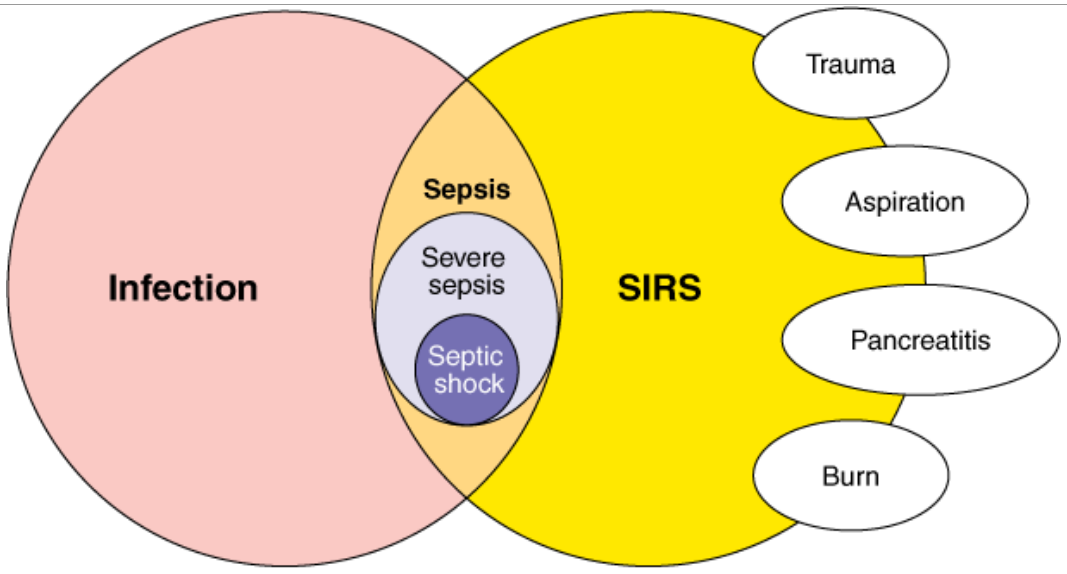
Definitions

Several possible outcomes can occur subsequent to microbial invasion and the interaction of microbes with resident and recruited host defenses: (a) eradication, (b) containment, often leading to the presence of purulence—the hallmark of chronic infection (e.g., a furuncle in the skin and soft tissue or abscess within the parenchyma of an organ or potential space), (c) locoregional infection (cellulitis, lymphangitis, and aggressive soft tissue infection) with or without distant spread of infection (metastatic abscess), or (d) systemic infection (bacteremia or fungemia). Obviously, the latter represents the failure of resident and recruited host defenses at the local level, and is associated with significant morbidity and mortality in the clinical setting. In addition, it is not uncommon that disease progression occurs such that serious locoregional infection is associated with concurrent systemic infection. A chronic abscess also may intermittently drain and/or be associated with bacteremia.

Infection is defined by identification of microorganisms in host tissue or the bloodstream, plus an inflammatory response to their presence. At the site of infection, the classic findings of rubor, calor, and dolor in areas such as the skin or subcutaneous tissue are common. Most infections in normal individuals with intact host defenses are associated with these local manifestations, plus systemic manifestations such as elevated temperature, elevated white blood cell (WBC) count, tachycardia, or tachypnea. The systemic manifestations noted above comprise the *systemic inflammatory response syndrome* (SIRS).

SIRS can be caused by a variety of disease processes, including pancreatitis, polytrauma, malignancy, and transfusion reaction, as well as infection (Fig. 6-1). Strict criteria for SIRS (tachycardia, tachypnea, fever, and elevated WBC count) have been broadened to include additional clinical indicators noted in Table 6-1.[12] SIRS caused by infection is termed *sepsis* and is mediated by the production of a cascade of proinflammatory mediators produced in response to exposure to microbial products. These products include lipopolysaccharide (endotoxin) derived from gram-negative organisms; peptidoglycans and teichoic acids from gram-positive organisms; multiple cell wall components such as mannan from yeast and fungi; and many others. Patients have developed sepsis if they have met clinical criteria for SIRS and have evidence of a local or systemic source of infection.

Fig. 6-1.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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Relationship between infection and systemic inflammatory response syndrome (SIRS). Sepsis is the presence both of infection and the systemic inflammatory response, shown here as the intersection of these two areas. Other conditions may cause SIRS as well (trauma, aspiration, etc.). Severe sepsis (and septic shock) are both subsets of sepsis.

Table 6-1 Criteria for Systemic Inflammatory Response Syndrome
General variables
Fever [core temp >38.3°C (100.9°F)]
Hypothermia [core temp <36°C (96.8°F)]
Heart rate >90 bpm
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC >12,000)
Leukopenia (WBC <4000)
Bandemia (>10% band forms)
Plasma C-reactive protein > 2 s.d. above normal value
Plasma procalcitonin >2 s.d. above normal value
Hemodynamic variables
Arterial hypotension (SBP <90 mmHg, MAP <70, or SBP decrease >40 mmHg)
SvO_2 >70%
Cardiac index >3.5 L/min per square meter
Organ dysfunction variables
Arterial hypoxemia
Acute oliguria
Creatinine increase
Coagulation abnormalities
Ileus

Thrombocytopenia	
Hyperbilirubinemia	
Tissue perfusion variables	
Hyperlactatemia	
Decreased capillary filling	

bpm = beats per minute; MAP = mean arterial pressure; SBP = systolic blood pressure; s.d. = standard deviations; Svo_2 = venous oxygen saturation; WBC = white blood cell count.

Severe sepsis is characterized as sepsis (defined above) combined with the presence of new-onset organ failure. Severe sepsis is the most common cause of death in noncoronary critical care units, with a mortality rate of 51 cases/100,000 population per year in 2003.[13] A number of organ dysfunction scoring systems have been described.[14–16] With respect to clinical criteria, a patient with sepsis and the need for ventilatory support, with oliguria unresponsive to aggressive fluid resuscitation or with hypotension requiring vasopressors, should be considered to have developed severe sepsis. *Septic shock* is a state of acute circulatory failure identified by the presence of persistent arterial hypotension (systolic blood pressure <90 mmHg) despite adequate fluid resuscitation, without other identifiable causes. Septic shock is the most severe manifestation of infection, occurring in approximately 40% of patients with severe sepsis; it has an attendant mortality rate of 45 to 60%.[17,18]

Clinicians dedicated to improving the treatment of sepsis have recently developed a new classification scheme for this entity.[12] This scheme has borrowed from the tumor-node-metastasis staging scheme developed for oncology. The impetus for development of this scheme was related to the heterogeneity of the patient population developing sepsis, an example of which would include two patients, both in the intensive care unit (ICU), who develop criteria consistent with septic shock. Although both have infection and sepsis-associated hypotension, one might expect a different outcome in a young, healthy patient who develops urosepsis than in an elderly, immunosuppressed lung transplant recipient who develops invasive fungal infection. The PIRO Staging System stratifies patients based on their predisposing conditions (P), the nature and extent of the infection (I), the nature and magnitude of the host response (R), and the degree of concomitant organ dysfunction (O). Current definitions using this system are listed in Table 6-2. Published trials using this classification system have confirmed the validity of this concept.[19] Further investigation is ongoing to evaluate the clinical utility of this scheme.

Table 6-2 PIRO Classification Scheme

Domain	**Means of Classification**
*P*redisposition	Premorbid illness that affects probability of survival (e.g., immunosuppression, age, genetics)
*I*nsult (infection)	Type of infecting organisms, location of disease, intervention (source control)
*R*esponse	SIRS, other signs of sepsis, presence of shock, tissue markers (e.g., C-reactive protein, IL-6)
*O*rgan dysfunction	Organ dysfunction as a number of failing organs or composite score

IL-6 = interleukin-6; SIRS = systemic inflammatory response syndrome.

MICROBIOLOGY OF INFECTIOUS AGENTS

A partial list of common pathogens that cause infections in surgical patients is provided in Table 6-3.

Table 6-3 Common Pathogens in Surgical Patients
Gram-positive aerobic cocci
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes
Streptococcus pneumoniae
Enterococcus faecium, E. faecalis
Gram-negative aerobic bacilli

Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis
Enterobacter cloacae, E. aerogenes
Serratia marcescens
Acinetobacter calcoaceticus
Citrobacter freundii
Pseudomonas aeruginosa
Xanthomonas maltophilia
Anaerobes
Gram-positive
Clostridium difficile
Clostridium perfringens, *C. tetani*, *C. septicum*
Peptostreptococcus spp.
Gram-negative
Bacteroides fragilis
Fusobacterium spp.
Other bacteria
Mycobacterium avium-intracellulare
Mycobacterium tuberculosis
Nocardia asteroides
Legionella pneumophila
Listeria monocytogenes
Fungi
Aspergillus fumigatus, *A. niger*, *A. terreus*, *A. flavus*
Blastomyces dermatitidis
Candida albicans
Candida glabrata, *C. parapsilosis*, *C. krusei*
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Mucor/Rhizopus
Viruses
Cytomegalovirus
Epstein-Barr virus
Hepatitis A, B, C viruses
Herpes simplex virus
HIV
Varicella-zoster virus

Bacteria

Bacteria are responsible for the majority of surgical infections. Specific species are identified using Gram's stain and growth characteristics on specific media. The Gram's stain is an important evaluation that allows rapid classification of bacteria by color. This color is related to the staining characteristics of the bacterial cell wall: gram-positive bacteria stain blue and gram-negative bacteria stain red. Bacteria are

classified based upon a number of additional characteristics including morphology (cocci and bacilli), the pattern of division [e.g., single organisms, groups of organisms in pairs (diplococci), clusters (staphylococci), and chains (streptococci)], and the presence and location of spores.

Gram-positive bacteria that frequently cause infections in surgical patients include aerobic skin commensals (*Staphylococcus aureus* and *epidermidis* and *Streptococcus pyogenes*) and enteric organisms such as *E. faecalis* and *faecium*. Aerobic skin commensals cause a large percentage of surgical site infections (SSIs), either alone or in conjunction with other pathogens; enterococci can cause nosocomial infections [urinary tract infections (UTIs) and bacteremia] in immunocompromised or chronically ill patients, but are of relatively low virulence in healthy individuals.

There are many pathogenic gram-negative bacterial species that are capable of causing infection in surgical patients. Most gram-negative organisms of interest to the surgeon are bacilli belonging to the family Enterobacteriaceae, including *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Enterobacter*, *Citrobacter*, and *Acinetobacter* spp. Other gram-negative bacilli of note include *Pseudomonas* spp., including *P. aeruginosa* and *fluorescens* and *Xanthomonas* spp.

Anaerobic organisms are unable to grow or divide poorly in air, as most do not possess the enzyme catalase, which allows for metabolism of reactive oxygen species. Anaerobes are the predominant indigenous flora in many areas of the human body, with the particular species dependent on the site. For example, *Propionibacterium acnes* and other species are a major component of the skin microflora and cause the infectious manifestation of acne. As noted above, large numbers of anaerobes contribute to the microflora of the oropharynx and colorectum.

Infection due to *Mycobacterium tuberculosis* was once one of the most common causes of death in Europe, causing one in four deaths in the seventeenth and eighteenth centuries. In the nineteenth and twentieth centuries, thoracic surgical intervention often was required for severe pulmonary disease, now an increasingly uncommon occurrence in developed countries. This organism and other related organisms (*M. avium-intracellulare* and *M. leprae*) are known as *acid-fast bacilli*. Other acid-fast bacilli include *Nocardia* spp. These organisms typically are slow-growing, sometimes necessitating observation in culture for weeks to months before final identification, although DNA-based analysis is increasingly available to provide a means for preliminary, rapid detection.

Fungi

Fungi typically are identified by use of special stains (e.g., potassium hydroxide, India ink, methenamine silver, or Giemsa). Initial identification is assisted by observation of the form of branching and septation in stained specimens or in culture. Final identification is based on growth characteristics in special media, similar to bacteria, as well as on the capacity for growth at a different temperature [25 vs. 37°C (77 vs. 98.6°F)]. Fungi of relevance to surgeons include those that cause nosocomial infections in surgical patients as part of polymicrobial infections or fungemia (e.g., *C. albicans* and related species), rare causes of aggressive soft tissue infections (e.g., *Mucor*, *Rhizopus*, and *Absidia* spp.), and so-called *opportunistic pathogens* that cause infection in the immunocompromised host (e.g., *Aspergillus fumigatus*, *niger*, *terreus*, and other spp., *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Cryptococcus neoformans*). Agents currently available for antifungal therapy are described in Table 6-4.

Table 6-4 Antifungal Agents and Their Characteristics

Antifungal	**Advantages**	**Disadvantages**	**Approximate Daily Cost**
Amphotericin B	Broad-spectrum, inexpensive	Renal toxicity, premeds, IV only	$11
Liposomal amphotericin B	Broad-spectrum	Expensive, IV only, renal toxicity	$600
Azoles			
Fluconazole	IV and PO availability	Narrow-spectrum, drug interactions	$21 (IV), <$1 (PO)
Itraconazole	IV and PO availability	Narrow-spectrum, no CSF penetration, drug interactions, decreased cardiac contractility	$200 (IV), $3 (PO)
Posaconazole	Broad-spectrum, zygomycete activity	PO only	$100

Voriconazole	IV and PO availability, broad-spectrum	IV diluent accumulates in renal failure, visual disturbances	$200 (IV), $70 (PO)
Echinocandins			
Anidulafungin, caspofungin, micafungin	Broad-spectrum	IV only, poor CNS penetration	$100–250

CSF = cerebrospinal fluid.

Viruses

Due to their small size and necessity for growth within cells, viruses are difficult to culture, requiring a longer time than is typically optimal for clinical decision making. Previously, viral infection was identified by indirect means (i.e., the host antibody response). Recent advances in technology have allowed for the identification of the presence of viral DNA or RNA using methods such as polymerase chain reaction. Similarly to many fungal infections, most viral infections in surgical patients occur in the immunocompromised host, particularly those receiving immunosuppression to prevent rejection of a solid organ allograft. Relevant viruses include adenoviruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus. Surgeons must be aware of the manifestations of hepatitis B and C virus, as well as HIV infections, including their capacity to be transmitted to health care workers (see Blood-Borne Pathogens below). Prophylactic and therapeutic use of antiviral agents is discussed in Chap. 11.

PREVENTION AND TREATMENT OF SURGICAL INFECTIONS

General Principles

Maneuvers to diminish the presence of exogenous (surgeon and operating room environment) and endogenous (patient) microbes are termed *prophylaxis*, and consist of the use of mechanical, chemical, and antimicrobial modalities, or a combination of these methods.

As described above in Bacteria, the host resident microflora of the skin (patient and surgeon) and other barrier surfaces represent a potential source of microbes that can invade the body during trauma, thermal injury, or elective or emergent surgical intervention. For this reason, operating room personnel are versed in mild mechanical exfoliation of the skin of the hands and forearms using antibacterial preparations, and intraoperatively sterile technique is used. Similarly, application of an antibacterial agent to the skin of the patient at the proposed operative site takes place before creating an incision. Also, if necessary, hair removal should take place using a clipper rather than a razor; the latter promotes overgrowth of skin microbes in small nicks and cuts. Dedicated use of these modalities clearly has been shown to diminish the quantity of skin microflora, and although a direct correlation between praxis and reduced infection rates has not been demonstrated, comparison to infection rates before the use of antisepsis and sterile technique makes clear their utility and importance.

The aforementioned modalities are not capable of sterilizing the hands of the surgeon or the skin or epithelial surfaces of the patient, although the inoculum can be reduced considerably. Thus, entry through the skin, into the soft tissue, and into a body cavity or hollow viscus invariably is associated with the introduction of some degree of microbial contamination. For that reason, patients who undergo procedures that may be associated with the ingress of significant numbers of microbes (e.g., colonic resection) or in whom the consequences of any type of infection due to said process would be dire (e.g., prosthetic vascular graft infection) should receive an antimicrobial agent.

Source Control

The primary precept of surgical infectious disease therapy consists of drainage of all purulent material, débridement of all infected, devitalized tissue, and debris, and/or removal of foreign bodies at the site of infection, plus remediation of the underlying cause of infection.[20] A discrete, walled-off purulent fluid collection (i.e., an abscess) requires drainage via percutaneous drain insertion or an operative approach in which incision and drainage take place. An ongoing source of contamination (e.g., bowel perforation) or the presence of an aggressive, rapidly-spreading infection (e.g., necrotizing soft tissue infection) invariably requires expedient, aggressive operative intervention, both to remove contaminated material and infected tissue (e.g., radical débridement or amputation) and to remove the initial cause of infection (e.g., bowel resection). Other treatment modalities such as antimicrobial agents, albeit critical, are of secondary importance to effective surgery with regard to treatment of surgical infections and overall outcome. Rarely, if ever, can an aggressive surgical infection be cured only by the administration of antibiotics, and never in the face of an ongoing source of contamination. Also, it has been repeatedly demonstrated that

delay in operative intervention, whether due to misdiagnosis or the need for additional diagnostic studies, is associated with increased morbidity and occasional mortality.[21–23]

Appropriate Use of Antimicrobial Agents

A classification of antimicrobial agents, mechanisms of action, and spectrum of activity is shown in Table 6-5. *Prophylaxis* consists of the administration of an antimicrobial agent or agents before initiation of certain specific types of surgical procedures to reduce the number of microbes that enter the tissue or body cavity. Agents are selected according to their activity against microbes likely to be present at the surgical site, based on knowledge of host microflora. For example, patients undergoing elective colorectal surgery should receive antimicrobial prophylaxis directed against skin flora, gram-negative aerobes, and amoebic bacteria. There are a wide variety of agents that meet these criteria.

Table 6-5 Antimicrobial Agents

Antibiotic Class, Generic Name			**Organism**								
	Trade Name	**Mechanism of Action**	***S. pyogenes***	**MSSA**	**MRSA**	***S. epidermidis***	**Enterococcus**	**VRE**	***E. coli***	***P. aeruginosa***	**Anaerobes**
Penicillins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Penicillin G	—		1	0	0	0	±	0	0	0	1
Nafcillin	Nallpen, Unipen		1	1	0	±	0	0	0	0	0
Piperacillin	Pipracil		1	0	0	0	±	0	1	1	±
Penicillin/beta lactamase inhibitor combinations		Cell wall synthesis inhibitors/beta lactamase inhibitors									
Ampicillin-sulbactam	Unasyn		1	1	0	±	1	±	1	0	1
Ticarcillin-clavulanate	Timentin		1	1	0	±	±	0	1	1	1
Piperacillin-tazobactam	Zosyn		1	1	0	1	±	0	1	1	1
First-generation cephalosporins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Cefazolin, cefalexin	Ancef, Keflex		1	1	0	±	0	0	1	0	0
Second-generation cephalosporins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									

Cefoxitin	Mefoxin		1	1	0	±	0	0	1	0	1
Cefotetan	Cefotan		1	1	0	±	0	0	1	0	1
Cefuroxime	Ceftin		1	1	0	±	0	0	1	0	0
Third- and fourth-generation cephalosporins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Ceftriaxone	Rocephin		1	1	0	±	0	0	1	0	0
Ceftazidime	Fortaz		1	±	0	±	0	0	1	1	0
Cefepime	Maxipime		1	1	0	±	0	0	1	1	0
Cefotaxime	Cefotaxime		1	1	0	±	0	0	1	±	0
Carbapenems		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Imipenem-cilastatin	Primaxin		1	1	0	1	±	0	1	1	1
Meropenem	Merrem		1	1	0	1	0	0	1	1	1
Ertapenem	Invanz		1	1	0	1	0	0	1	±	1
Aztreonam	Azactam	Cell wall synthesis inhibitor (bind penicillin-binding protein)	0	0	0	0	0	0	1	1	0
Aminoglycosides		Alteration of cell membrane, binding and inhibition of 30S ribosomal unit									
Gentamicin	—		0	1	0	±	1	0	1	1	0
Tobramycin, amikacin	—		0	1	0	±	0	0	1	1	0
Fluoroquinolones		Inhibit topoisomerase II and IV (DNA synthesis inhibition)									
Ciprofloxacin	Cipro		±	1	0	1	0	0	1	1	0
Levofloxacin	Levaquin		1	1	0	1	0	0	1	±	0
Glycopeptides		Cell wall synthesis inhibition (peptidoglycan synthesis inhibition)									

Vancomycin	Vancocin		1	1	1	1	1	0	0	0	0
Quinupristin-dalfopristin	Synercid	Inhibits two sites on 50S ribosome (protein synthesis inhibition)	1	1	1	1	1	1	0	0	±
Linezolid	Zyvox	Inhibits 50S ribosomal activity (protein synthesis inhibition)	1	1	1	1	1	1	0	0	±
Daptomycin	Cubicin	Binds bacterial membrane, results in depolarization, lysis	1	1	1	1	1	1	0	0	0
Rifampin	—	Inhibits DNA-dependent RNA polymerase	1	1	1	1	±	0	0	0	0
Clindamycin	Cleocin	Inhibits 50S ribosomal activity (protein synthesis inhibition)	1	1	0	0	0	0	0	0	1
Metronidazole	Flagyl	Production of toxic intermediates (free radical production)	0	0	0	0	0	0	0	0	1
Macrolides		Inhibit 50S ribosomal activity (protein synthesis inhibition)									
Erythromycin	—		1	±	0	±	0	0	0	0	0
Azithromycin	Zithromax		1	1	0	0	0	0	0	0	0
Clarithromycin	Biaxin		1	1	0	0	0	0	0	0	0
Trimethoprim-sulfamethoxazole	Bactrim, Septra	Inhibits sequential steps of folate metabolism	±	1	0	±	0	0	1	0	0
Tetracyclines		Bind 30S ribosomal unit (protein synthesis inhibition)									
Minocycline	Minocin		1	1	0	0	0	0	0	0	±
Doxycycline	Vibramycin		1	±	0	0	0	0	1	0	±
Tigecycline	Tygacil		1	1	1	1	1	1	1	0	1

E. coli = *Escherichia coli*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; *P. aeruginosa* = *Pseudomonas aeruginosa*; *S. epidermidis* = *Staphylococcus epidermidis*; *S. pyogenes* = *Streptococcus pyogenes*; VRE = vancomycin-resistant enterococcus.

1 = reliable activity; ± = variable activity; 0 = no activity.

The sensitivities presented are generalizations. The clinician should confirm sensitivity patterns at the locale where the patient is being treated because these patterns may vary widely depending on location.

By definition, prophylaxis is limited to the time before and during the operative procedure; in the vast majority of cases only a single dose of antibiotic is required, and only for certain types of procedures (see Surgical Site Infections below). However, patients who undergo complex, prolonged procedures in which the duration of the operation exceeds the serum drug half-life should receive an additional dose or doses of the antimicrobial agent. *Nota bene:* There is no evidence that administration of postoperative doses of an antimicrobial agent provides additional benefit, and this practice should be discouraged, as it is costly and is associated with increased rates of microbial drug resistance. Guidelines for prophylaxis are provided in Table 6-6.

Table 6-6 Prophylactic Use of Antibiotics

Site	Antibiotic	Alternative (e.g., penicillin allergic)
Cardiovascular surgery	Cefazolin, cefuroxime	Vancomycin
Gastroduodenal area	Cefazolin, cefotetan, cefoxitin, ampicillin-sulbactam	Fluoroquinolone
Biliary tract with active infection (e.g., cholecystitis)	Ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam	Fluoroquinolone plus clindamycin or metronidazole
Colorectal surgery, obstructed small bowel	Cefazolin plus metronidazole, ertapenem, ticarcillin-clavulanate, piperacillin-tazobactam	Gentamicin or fluoroquinolone plus clindamycin or metronidazole
Head and neck	Cefazolin	Aminoglycoside plus clindamycin
Neurosurgical procedures	Cefazolin	Vancomycin
Orthopedic surgery	Cefazolin, ceftriaxone	Vancomycin
Breast, hernia	Cefazolin	Vancomycin

Empiric therapy comprises the use of an antimicrobial agent or agents when the risk of a surgical infection is high, based on the underlying disease process (e.g., ruptured appendicitis), or when significant contamination during surgery has occurred (e.g., inadequate bowel preparation or considerable spillage of colon contents). Obviously, prophylaxis merges into empiric therapy in situations in which the risk of infection increases markedly because of intraoperative findings. Empiric therapy also often is used in critically ill patients in whom a potential site of infection has been identified and severe sepsis or septic shock occurs. Invariably, empiric therapy should be limited to a short course of drug (3 to 5 days), and should be curtailed as soon as possible based on microbiologic data (i.e., absence of positive cultures) coupled with improvements in the clinical course of the patient.

Similarly, empiric therapy merges into therapy of established infection in some patients as well. However, among surgical patients, the manner in which therapy is used, particularly in relation to the use of microbiologic data (culture and antibiotic sensitivity patterns), differs depending on whether the infection is monomicrobial or polymicrobial. Monomicrobial infections frequently are nosocomial infections occurring in postoperative patients, such as UTIs, pneumonia, or bacteremia. Evidence of SIRS (fever, tachycardia, tachypnea, or elevated leukocyte count) in such individuals, coupled with evidence of local infection (e.g., an infiltrate on chest roentgenogram plus a positive Gram's stain in bronchoalveolar lavage samples) should lead the surgeon to initiate empiric antibiotic therapy. Drug selection must be based on initial evidence (gram-positive vs. gram-negative microbes, yeast), coupled with institutional and unit-specific drug sensitivity patterns. It is important, however, to ensure that the antimicrobial coverage chosen is adequate, because delay in appropriate antibiotic treatment has been shown to be associated with increased mortality. Within 24 to 72 hours, culture and sensitivity reports will allow refinement of the antibiotic regimen to select the most efficacious agent. The clinical course of the patient is monitored closely, and in some cases (e.g., UTI) follow-up studies (urine culture) should be obtained after completion of therapy.

Although the primary therapeutic modality to treat polymicrobial surgical infections is source control as delineated above in Source Control, antimicrobial agents play an important role as well. Culture results are of lesser importance in managing these types of infections, as it has been repeatedly demonstrated that only a limited cadre of microbes predominate in the established infection, selected from a large number present at the time of initial contamination. Invariably, it is difficult to identify all microbes that comprise the initial polymicrobial inoculum.

For this reason, the antibiotic regimen should not be modified solely on the basis of culture information, as it is less important than the clinical course of the patient. For example, patients who undergo appendectomy for gangrenous, perforated appendicitis, or bowel resection for intestinal perforation, should receive an antimicrobial agent or agents directed against aerobes and anaerobes for 3 to 5 days, occasionally longer. A survey of several decades of clinical trials examining the effect of antimicrobial agent selection on the treatment of intra-abdominal infection revealed striking similarities in outcome among regimens that possessed aerobic and anaerobic activity (~10 to 30% failure rates): Most failures could not be attributed to antibiotic selection, but rather were due to the inability to achieve effective source control.[24]

Duration of antibiotic administration should be decided at the time the drug regimen is prescribed. As noted below in Surgical Site Infections, prophylaxis is limited to a single dose administered immediately before creating the incision. Empiric therapy should be limited to 3 to 5 days or less, and should be curtailed if the presence of a local site or systemic infection is not revealed.[25] This precept is highlighted by a study in which patients in whom SIRS was identified were closely monitored for the presence of infection: Less than half of them were found to harbor infection.[26]

Therapy for monomicrobial infections follows standard guidelines: 3 to 5 days for UTIs, 7 to 10 days for pneumonia, and 7 to 14 days for bacteremia. Longer courses of therapy in this setting do not result in improved care but are associated with increased risk of resistant organisms.[27,28] Antibiotic therapy for osteomyelitis, endocarditis, or prosthetic infections in which it is hazardous to remove the device consists of prolonged courses of an antibiotic or several agents in combination for 6 to 12 weeks. The specific agents are selected based on analysis of the degree to which the organism is killed in vitro using the minimum inhibitory concentration of a standard pure inoculum of 10^5 CFU/mL of the organism isolated from the site of infection or bloodstream. Sensitivities are reported in relation to the achievable blood level of each antibiotic in a panel of agents. The least toxic, least expensive agent to which the organism is most sensitive should be selected, although the latter parameter is of paramount importance. Serious or recrudescent infection may require therapy with two or more agents, particularly if a multidrug-resistant pathogen is causative, limiting therapeutic options to drugs to which the organism is only moderately sensitive. Commonly, an agent may be administered IV for 1 to 2 weeks, following which the treatment course is completed with oral drug. However, this should only be undertaken in patients who demonstrate progressive clinical improvement, and the oral agent should be capable of achieving high serum levels as well (e.g., fluoroquinolones).

The majority of studies examining the optimal duration of antibiotic therapy for the treatment of polymicrobial infection have focused on patients who develop peritonitis. Cogent data exist to support the contention that satisfactory outcomes are achieved with 12 to 24 hours of therapy for penetrating GI trauma in the absence of extensive contamination, 3 to 5 days of therapy for perforated or gangrenous appendicitis, 5 to 7 days of therapy for treatment of peritoneal soilage due to a perforated viscus with moderate degrees of contamination, and 7 to 14 days of therapy to adjunctively treat extensive peritoneal soilage (e.g., feculent peritonitis) or that occurring in the immunosuppressed host.[29] It bears repeating that the eventual outcome is more closely linked to the ability of the surgeon to achieve effective source control than to the duration of antibiotic administration.

In the later phases of postoperative antibiotic treatment of serious intra-abdominal infection, the absence of an elevated WBC count, lack of band forms of PMNs on peripheral smear, and lack of fever [<38.6°C (100.5°F)] provide close to complete assurance that infection has been eradicated.[30] Under these circumstances, antibiotics can be discontinued with impunity. However, the presence of one or more of these indicators does not mandate continuing antibiotics or altering the antibiotic(s) administered. Rather, a search for an extra-abdominal source of infection or a residual or ongoing source of intra-abdominal infection (e.g., abscess or leaking anastomosis) should be sought, the latter mandating maneuvers to effect source control.

Allergy to antimicrobial agents must be considered before prescribing them. First, it is important to ascertain whether a patient has had any type of allergic reaction in association with administration of a particular antibiotic. However, one should take care to ensure that the purported reaction consists of true allergic symptoms and signs, such as urticaria, bronchospasm, or other similar manifestations, rather than indigestion or nausea. Penicillin allergy is quite common, the reported incidence ranging from 0.7 to 10%. Although avoiding the use of any beta-lactam drug is appropriate in patients who manifest significant allergic reactions to penicillins, the incidence of cross reactivity appears highest for carbapenems, much lower for cephalosporins (~5 to 7%), and extremely small or nonexistent for monobactams.

Severe allergic manifestations to a specific class of agents, such as anaphylaxis, generally preclude the use of any agents in that class, except under circumstances in which use of a certain drug represents a lifesaving measure. In some centers, patients undergo intradermal testing

using a dilute solution of a particular antibiotic to determine whether a severe allergic reaction would be elicited by parenteral administration. A pathway including such intradermal testing has been effective in reduction of vancomycin use to 16% in surgical patients with reported allergy to penicillin.[31] This type of testing is rarely used because it is simpler to select an alternative class of agent. Should administration of a specific agent to which the patient is allergic become necessary, desensitization using progressively higher doses of antibiotic can be undertaken, providing the initial testing does not cause severe allergic manifestations.

Misuse of antimicrobial agents is rampant in the inpatient and outpatient setting, and is associated with an enormous financial impact on health care costs, adverse reactions due to drug toxicity and allergy, the occurrence of new infections such as *Clostridium difficile* colitis, and the development of multiagent drug resistance among nosocomial pathogens. Each of these factors has been directly correlated with overall drug administration. It has been estimated that in the United States, in excess of $20 billion is spent on antibiotics each year, and the appearance of so-called *super bugs*—microbes sensitive to few if any agents—has been sobering.[32] The responsible practitioner limits prophylaxis to the period during the operative procedure, does not convert prophylaxis into empiric therapy except under well-defined conditions, sets the duration of antibiotic therapy from the outset, curtails antibiotic administration when clinical and microbiologic evidence does not support the presence of an infection, and limits therapy to a short course in every possible instance. The utility of prophylactic antibiotics to prevent infections related to thoracostomy tube insertion has been demonstrated,[33,34] but prolonged treatment while a thoracostomy tube remains in situ, or prolonged therapy of biliary, intra-abdominal, or abscess drain cultures is not to be condoned.

INFECTIONS OF SIGNIFICANCE IN SURGICAL PATIENTS

Surgical Site Infections

SSIs are infections of the tissues, organs, or spaces exposed by surgeons during performance of an invasive procedure. SSIs are classified into incisional and organ/space infections, and the former are further subclassified into superficial (limited to skin and subcutaneous tissue) and deep incisional categories.[35] The development of SSIs is related to three factors: (a) the degree of microbial contamination of the wound during surgery, (b) the duration of the procedure, and (c) host factors such as diabetes, malnutrition, obesity, immune suppression, and a number of other underlying disease states. Table 6-7 lists risk factors for development of SSIs. By definition, an incisional SSI has occurred if a surgical wound drains purulent material or if the surgeon judges it to be infected and opens it.

Table 6-7 Risk Factors for Development of Surgical Site Infections
Patient factors
Older age
Immunosuppression
Obesity
Diabetes mellitus
Chronic inflammatory process
Malnutrition
Peripheral vascular disease
Anemia
Radiation
Chronic skin disease
Carrier state (e.g., chronic *Staphylococcus* carriage)
Recent operation
Local factors
Poor skin preparation
Contamination of instruments
Inadequate antibiotic prophylaxis
Prolonged procedure
Local tissue necrosis

Hypoxia, hypothermia
Microbial factors
Prolonged hospitalization (leading to nosocomial organisms)
Toxin secretion
Resistance to clearance (e.g., capsule formation)

Surgical wounds are classified based on the presumed magnitude of the bacterial load at the time of surgery (Table 6-8).[36] *Clean wounds* (class I) include those in which no infection is present; only skin microflora potentially contaminate the wound, and no hollow viscus that contains microbes is entered. Class ID wounds are similar except that a prosthetic device (e.g., mesh or valve) is inserted. *Clean/contaminated wounds* (class II) include those in which a hollow viscus such as the respiratory, alimentary, or genitourinary tracts with indigenous bacterial flora is opened under controlled circumstances without significant spillage of contents. Interestingly, while elective colorectal cases have classically been included as class II cases, a number of studies in the last decade have documented higher SSI rates (9 to 25%).[37–39] One study identified two thirds of infections presenting after discharge from hospital, highlighting the need for careful follow-up of these patients.[37] Infection is also more common in cases involving entry into the rectal space.[39] *Contaminated wounds* (class III) include open accidental wounds encountered early after injury, those with extensive introduction of bacteria into a normally sterile area of the body due to major breaks in sterile technique (e.g., open cardiac massage), gross spillage of viscus contents such as from the intestine, or incision through inflamed, albeit nonpurulent, tissue. *Dirty wounds* (class IV) include traumatic wounds in which a significant delay in treatment has occurred and in which necrotic tissue is present, those created in the presence of overt infection as evidenced by the presence of purulent material, and those created to access a perforated viscus accompanied by a high degree of contamination. The microbiology of SSIs is reflective of the initial host microflora such that SSIs following creation of a class I wound are invariable, due solely to skin microbes found on that portion of the body, while SSIs subsequent to a class II wound created for the purpose of elective colon resection may be caused by either skin microbes or colonic microflora, or both.

Table 6-8 Wound Class, Representative Procedures, and Expected Infection Rates

Wound Class	Examples of Cases	Expected Infection Rates
Clean (class I)	Hernia repair, breast biopsy	1.0–5.4%
Clean/contaminated (class II)	Cholecystectomy, elective GI surgery (not colon)	2.1–9.5%
Clean/contaminated (class II)	Colorectal surgery	9.4–25%
Contaminated (class III)	Penetrating abdominal trauma, large tissue injury, enterotomy during bowel obstruction	3.4–13.2%
Dirty (class IV)	Perforated diverticulitis, necrotizing soft tissue infections	3.1–12.8%

In the United States, hospitals are required to conduct surveillance for the development of SSIs for a period of 30 days after the operative procedure.[40] Such surveillance has been associated with greater awareness and a reduction in SSI rates, probably in large part based upon the impact of observation and promotion of adherence to appropriate care standards. Several different SSI risk stratification schemes have been developed via retrospective, multivariate analysis of large surveillance data sets. The National Nosocomial Infection Surveillance (NNIS) risk index is commonly used and assesses three factors: (a) American Society of Anesthesiologists Physical Status score greater than 2, (b) class III/IV wound, and (c) duration of operation greater than the 75th percentile for that particular procedure, to refine the risk of infection beyond that achieved by use of wound classification alone. Intriguingly, the risk of SSIs for class I wounds varies from approximately 1 to 2% for patients with low NNIS scores, to approximately 15% for patients with high NNIS scores (e.g., long operations and/or high American Society of Anesthesiologists scores), and it seems clear that additional refinements are required.[41]

SSIs are associated with considerable morbidity and occasional lethality, as well as substantial health care costs and patient inconvenience and dissatisfaction.[42] For that reason, surgeons strive to avoid SSIs by using the maneuvers described in the previous section Prevention and Treatment of Surgical Infections. Also, the use of prophylactic antibiotics may serve to reduce the incidence of SSI rates during certain types

of procedures. For example, it is well accepted that a single dose of an antimicrobial agent should be administered immediately before commencing surgery for class ID, II, III, and IV types of wounds.[43] It seems reasonable that this practice should be extended to patients in any category with high NNIS scores, although this remains to be proven. Thus the utility of prophylactic antibiotics in reducing the rate of wound infection subsequent to clean surgery remains controversial, and these agents should not be used under routine circumstances (e.g., in healthy young patients). However, because of the potential dire consequences of a wound infection after clean surgery in which prosthetic material is implanted into tissue, patients who undergo such procedures should receive a single preoperative dose of an antibiotic.

A number of health care organizations within the United States have become interested in evaluating performance of hospitals and physicians with respect to implementing standard of care therapies, one of which being reduction in SSIs, because the morbidity (and subsequent cost) of this complication is high. Several of these organizations are noted in Table 6-9. Appropriate guidelines in this area incorporating the principles discussed above in Prevention and Treatment of Surgical Infections have been developed and published.[44] However, adherence to these guidelines has been poor.[45] Driving incorporation of these guidelines into routine clinical practice is the belief that better adherence to evidence-based practice recommendations and more attention to designing systems of care with redundant safeguards will result in reduction of surgical complications and better patient outcomes. Importantly, the Center for Medicare and Medicaid Services, the largest third party payer in the United States, has required reporting by hospitals of many processes related to reduction of surgical infections, including appropriate use of perioperative antibiotics. This information, which is currently reported publicly by hospital, has led to significant improvement in reported rates of these process measures. The effects of this approach on SSIs are not known at this time.

Table 6-9 Quality Improvement Organizations of Interest to Surgeons in the United States

Abbreviation	Organization	Website
SCIP	Surgical Care Improvement Project	http://www.medqic.org (Enter SCIP in search)
NSQIP	National Surgical Quality Improvement Program	http://acsnsqip.org
IHI	Institute for Healthcare Improvement	http://www.ihi.org
CMS	Center for Medicare and Medicaid Services	http://www.hospitalcompare.hhs.gov
NCQA	National Committee for Quality Assurance	http://www.ncqa.org

Surgical management of the wound is also a critical determinant of the propensity to develop an SSI. In healthy individuals, class I and II wounds may be closed primarily, while skin closure of class III and IV wounds is associated with high rates of incisional SSIs (approximately 25 to 50%). The superficial aspects of these latter types of wounds should be packed open and allowed to heal by secondary intention, although selective use of delayed primary closure has been associated with a reduction in incisional SSI rates.[46] It remains to be determined whether NNIS-type stratification schemes can be used prospectively to target specific subgroups of patients who will benefit from the use of prophylactic antibiotic and/or specific wound management techniques. One clear example based on cogent data from clinical trials is that class III wounds in healthy patients undergoing appendectomy for perforated or gangrenous appendicitis can be primarily closed as long as antibiotic therapy directed against aerobes and anaerobes is administered. This practice leads to SSI rates of approximately 3 to 4%.[47]

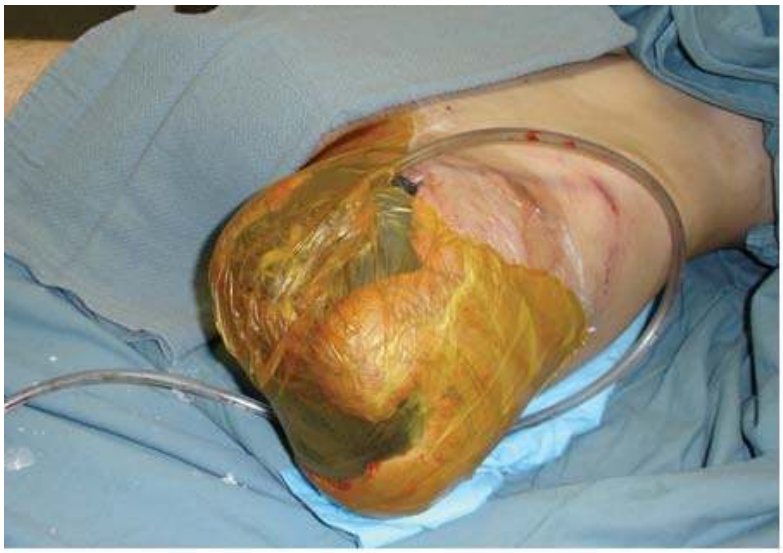
Recent investigations have studied the effect of additional maneuvers in an attempt to further reduce the rate of SSIs. The adverse effects of hyperglycemia on WBC function have been well described.[48] A number of recent studies have reported the effects of hyperglycemia in vivo in diabetic patients, with increased SSI rates being associated with hyperglycemia in cardiac surgery patients undergoing bypass.[49,50] On this basis, it is recommended that clinicians maintain appropriate blood sugar control in diabetic patients in the perioperative period to minimize the occurrence of SSIs.

The effects of the level of inhaled oxygen and prewarming of the wound on SSI rates also have been studied. Although an initial study provided evidence that patients who received high levels of inhaled oxygen during colorectal surgery developed fewer SSIs,[51] data to the contrary recently have been reported.[52,53] In another study, preoperative warming of the wound site for 30 minutes before surgery among patients undergoing clean surgery was associated with a decrease in SSIs (5% with warmed wounds vs. 14% without).[54] Unfortunately, several of the aforementioned studies report SSI rates among study patients that are higher than those reported and expected among similar groups of patients, making comparison difficult. Of note, stratification using the NNIS classification methodology was not used. Further

evaluation via multicenter studies is needed before implementation of these modalities as standard therapies.

Effective therapy for incisional SSIs consists solely of incision and drainage without the addition of antibiotics. Antibiotic therapy is reserved for patients in whom evidence of significant cellulitis is present, or who manifest concurrent SIRS. The open wound often is allowed to heal by secondary intention, with dressings being changed twice a day. The use of topical antibiotics and antiseptics to further wound healing remains unproven, although anecdotal studies indicate their potential utility in complex wounds that do not heal with routine measures.[55] Despite a paucity of prospective studies,[56] vacuum-assisted closure is increasingly used in management of problem wounds and can be applied to complex wounds in difficult locations (Fig. 6-2). Although culture results are of epidemiologic interest, they rarely serve to direct therapy because antibiotics are not routinely withheld until results are known. The treatment of organ/space infections is discussed in Intra-Abdominal Infections, below.

Fig. 6-2.



A

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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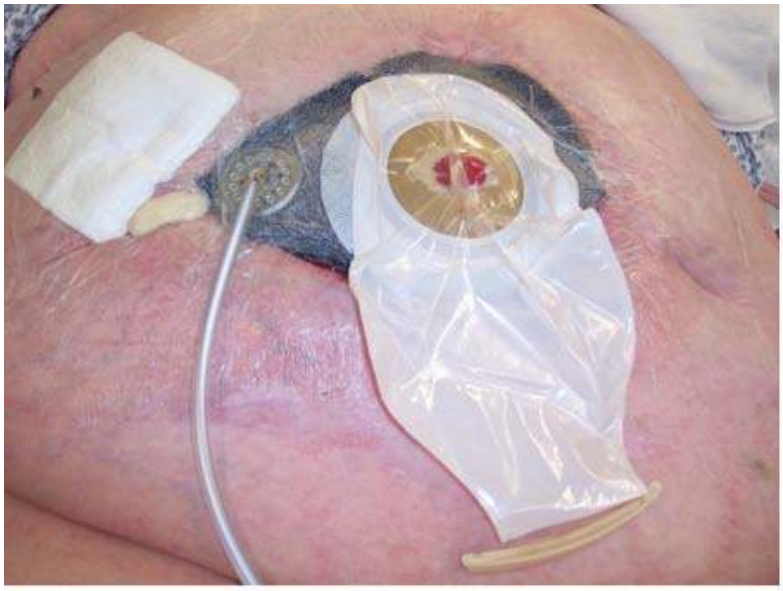

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Negative pressure wound therapy in a patient after amputation for wet gangrene (**A**), and in a patient with enterocutaneous fistula (**B**). It is possible to adapt these dressings to fit difficult anatomy and provide appropriate wound care while reducing frequency of dressing change. It is important to evaluate the wound under these dressings if patient demonstrates signs of sepsis with an unidentified source, because typical clues of wound sepsis, such as odor and drainage, are hidden by the suction apparatus.

Intra-Abdominal Infections

Microbial contamination of the peritoneal cavity is termed *peritonitis* or *intra-abdominal infection*, and is classified according to etiology. *Primary microbial peritonitis* occurs when microbes invade the normally sterile confines of the peritoneal cavity via hematogenous dissemination from a distant source of infection or direct inoculation. This process is more common among patients who retain large amounts of peritoneal fluid due to ascites, and in those individuals who are being treated for renal failure via peritoneal dialysis. These infections invariably are monomicrobial and rarely require surgical intervention. The diagnosis is established based on a patient who has ascites for medical reasons, physical examination that reveals diffuse tenderness and guarding without localized findings, absence of pneumoperitoneum on abdominal flat plate and upright roentgenograms, the presence of more than 100 WBCs/mL, and microbes with a single morphology on Gram's stain performed on fluid obtained via paracentesis. Subsequent cultures will typically demonstrate the presence of gram-positive organisms in patients receiving peritoneal dialysis. In patients without this risk factor organisms can include *E. coli*, *K. pneumoniae*, pneumococci, and others, although many different pathogens can be causative. Treatment consists of administration of an antibiotic to which the organism is sensitive; often 14 to 21 days of therapy are required. Removal of indwelling devices (e.g., peritoneal dialysis catheter or peritoneovenous shunt) may be required for effective therapy of recurrent infections.

Secondary microbial peritonitis occurs subsequent to contamination of the peritoneal cavity due to perforation or severe inflammation and infection of an intra-abdominal organ. Examples include appendicitis, perforation of any portion of the GI tract, or diverticulitis. As noted previously in Source Control, effective therapy requires source control to resect or repair the diseased organ; débridement of necrotic, infected tissue and debris; and administration of antimicrobial agents directed against aerobes and anaerobes.[57] This type of antibiotic regimen should be chosen because in most patients the precise diagnosis cannot be established until exploratory laparotomy is performed, and the most morbid form of this disease process is colonic perforation, due to the large number of microbes present. A combination of agents or single agents with a broad spectrum of activity can be used for this purpose; conversion of a parenteral to an oral regimen when the patient's ileus resolves will provide results similar to those achieved with IV antibiotics.[58] Effective source control and antibiotic therapy is associated with low failure rates and a mortality rate of approximately 5 to 6%; inability to control the source of infection leads to mortality greater than 40%.[59]

The response rate to effective source control and use of appropriate antibiotics has remained approximately 70 to 90% over the past several decades.[24,60] Patients in whom standard therapy fails develop an intra-abdominal abscess, leakage from a GI anastomosis leading to postoperative peritonitis, or *tertiary (persistent) peritonitis*. The latter is a poorly understood entity that is more common in immunosuppressed patients in whom peritoneal host defenses do not effectively clear or sequester the initial secondary microbial peritoneal infection. Microbes such as *E. faecalis* and *faecium*, *S. epidermidis*, *C. albicans*, and *P. aeruginosa* can be identified, typically in combination, and may be selected based on their lack of responsiveness to the initial antibiotic regimen, coupled with diminished activity of host defenses. Unfortunately, even with effective antimicrobial agent therapy, this disease process is associated with mortality rates in excess of 50%.[61,62]

Formerly, the presence of an intra-abdominal abscess mandated surgical re-exploration and drainage. Today, the vast majority of such abscesses can be effectively diagnosed via abdominal computed tomographic (CT) imaging techniques and drained percutaneously. Surgical intervention is reserved for those individuals who harbor multiple abscesses, those with abscesses in proximity to vital structures such that percutaneous drainage would be hazardous, and those in whom an ongoing source of contamination (e.g., enteric leak) is identified. The necessity of antimicrobial agent therapy and precise guidelines that dictate duration of catheter drainage have not been established. A short course (3 to 7 days) of antibiotics that possess aerobic and anaerobic activity seems reasonable, and most practitioners leave the drainage catheter in situ until it is clear that cavity collapse has occurred, output is less than 10 to 20 mL/d, no evidence of an ongoing source of contamination is present, and the patient's clinical condition has improved.

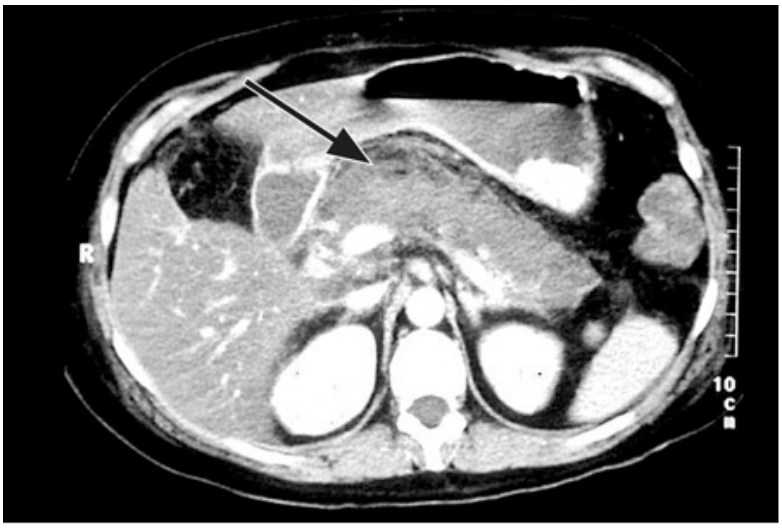
Organ-Specific Infections

Hepatic abscesses are rare, currently accounting for approximately 15 per 100,000 hospital admissions in the United States. Pyogenic

abscesses account for approximately 80% of cases, the remaining 20% being equally divided among parasitic and fungal forms.[63] Formerly, pyogenic liver abscesses were caused by pylephlebitis due to neglected appendicitis or diverticulitis. Today, manipulation of the biliary tract to treat a variety of diseases has become a more common cause, although in nearly 50% of patients no cause is identified. The most common aerobic bacteria identified in recent series include *E. coli*, *K. pneumoniae*, and other enteric bacilli, enterococci, and *Pseudomonas* spp., while the most common anaerobic bacteria are *Bacteroides* spp., anaerobic streptococci, and *Fusobacterium* spp. *C. albicans* and other similar yeasts cause the majority of fungal hepatic abscesses. Small (<1 cm), multiple abscesses should be sampled and treated with a 4- to 6-week course of antibiotics. Larger abscesses invariably are amenable to percutaneous drainage, with parameters for antibiotic therapy and drain removal similar to those mentioned above in Intra-Abdominal Infections. Splenic abscesses are extremely rare and are treated in a similar fashion. Recurrent hepatic or splenic abscesses may require operative intervention—unroofing and marsupialization or splenectomy, respectively.

Secondary pancreatic infections (e.g., infected pancreatic necrosis or pancreatic abscess) occur in approximately 10 to 15% of patients who develop severe pancreatitis with necrosis. The surgical treatment of this disorder was pioneered by Bradley and Allen, who noted significant improvements in outcome for patients undergoing repeated pancreatic débridement of infected pancreatic necrosis.[64] Current care of patients with severe acute pancreatitis includes staging with dynamic, contrast-enhanced helical CT scan with 3-mm tomographs to determine the extent of pancreatic necrosis, coupled with the use of one of several prognostic scoring systems. Patients who exhibit significant pancreatic necrosis (grade greater than C, Fig. 6-3) should be carefully monitored in the ICU and undergo follow-up CT examination. A recent change in practice has been the elimination of the routine use of prophylactic antibiotics for prevention of infected pancreatic necrosis. Early results were promising;[65] however, several randomized multicenter trials have failed to show benefit and three meta-analyses have confirmed this finding.[66–68]

Fig. 6-3.



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Contrast-enhanced computed tomographic scan of pancreas with severe pancreatic necrosis. Note lack of IV contrast within the boggy pancreatic bed (*large black arrow*).

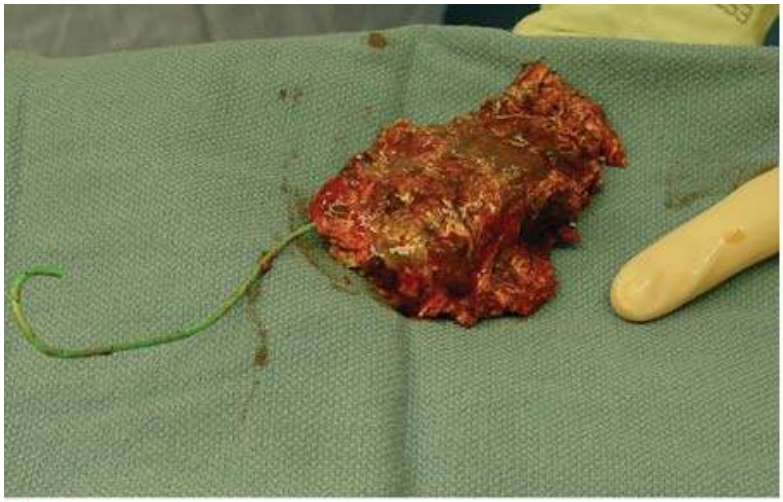
In two small studies, enteral feedings initiated early, using nasojejunal feeding tubes placed past the ligament of Treitz, have been associated with decreased development of infected pancreatic necrosis, possibly due to a decrease in gut translocation of bacteria. Recent guidelines support the practice of enteral alimentation in these patients, with the addition of parenteral nutrition if nutritional goals cannot be met by tube feeding alone.[69,70]

The presence of secondary pancreatic infection should be suspected in patients whose systemic inflammatory response (fever, elevated WBC count, or organ dysfunction) fails to resolve, or in those individuals who initially recuperate, only to develop sepsis syndrome 2 to 3 weeks

later. CT-guided aspiration of fluid from the pancreatic bed for performance of Gram's stain and culture analysis is of critical importance. A positive Gram's stain or culture from CT-guided aspiration, or identification of gas within the pancreas on CT scan, mandate operative intervention.

Surgery for secondary pancreatic infection is designed to remove the infected inflammatory focus. It is the practice of the authors to expose the pancreatic bed through a transverse incision in the abdominal wall and lesser sac (Fig. 6-4). A jejunal feeding tube, gastrostomy tube, and cholecystectomy (if indicated) are all performed at the index operation if patient condition permits. The gastrocolic omentum is tacked to the abdominal wall on the peritoneal edges of the wound to sequester the intestines from the inflammatory process. After initial gentle débridement of necrotic tissue, the pancreatic bed is packed with gauze dressings and the abdomen closed temporarily with a permanent mesh or packed open. This mesh allows repeated reoperations without damage to the remaining fascia. In a similar fashion to surgery for necrotizing soft tissue infection, the surgeon should plan on scheduled relaparotomy and undertake débridement until necrotic tissue and purulence are absent and granulation tissue forms. Approximately 20 to 25% of patients will develop a GI fistula, which either heals or is amenable to surgical repair after resolution of the pancreatic infection. The laparoscopic approach to débridement first described in 1996 has been described using various techniqes.[71,72]

Fig. 6-4.



A

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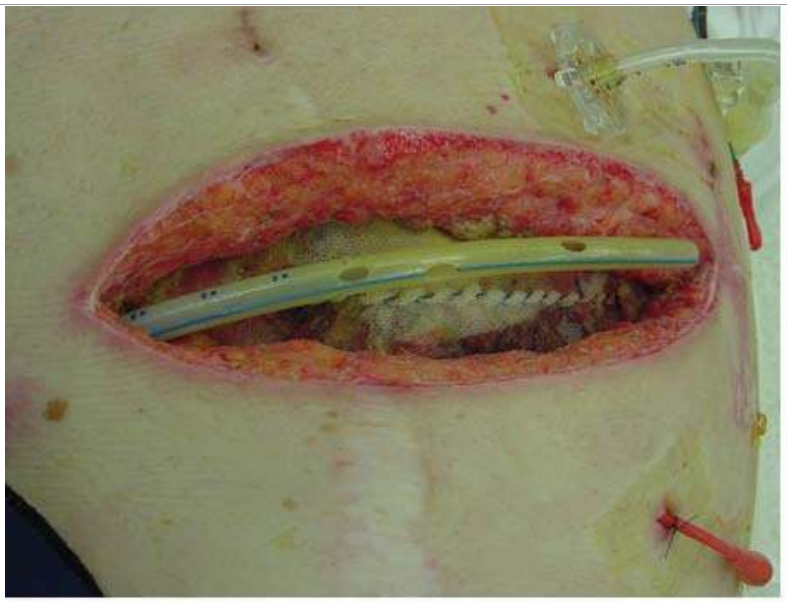

B

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Infected pancreatic necrosis. **A.** Necrosectomy specimen with pancreatic stent in situ. It is important to gently débride only necrotic pancreatic tissue, relying on repeated operation to ensure complete removal. **B.** Typical incision for infected pancreatic necrosis. Polypropylene mesh has been secured to fascia and is used for re-entry into the pancreatic bed. Note gastrostomy and feeding jejunostomy tubes. The chest tube in the wound is placed to allow closed continuous suction.

Infections of the Skin and Soft Tissue

Infections of the skin and soft tissue can be classified according to whether surgical intervention is required. For example, superficial skin and skin structure infections, such as cellulitis, erysipelas, and lymphangitis, invariably are effectively treated with antibiotics alone, although a search for a local source of infection should be undertaken. Generally, drugs that possess activity against the gram-positive skin microflora that are causative are selected. Furuncles or boils may drain spontaneously or require surgical incision and drainage. Antibiotics are prescribed if significant cellulitis is present or if cellulitis does not rapidly resolve after surgical drainage. Commonly acquired methicillin-resistant *S. aureus* infection should be suspected if infection persists after treatment with adequate drainage and antibiotics. These infections may require more aggressive drainage and altered antimicrobial therapy.[73]

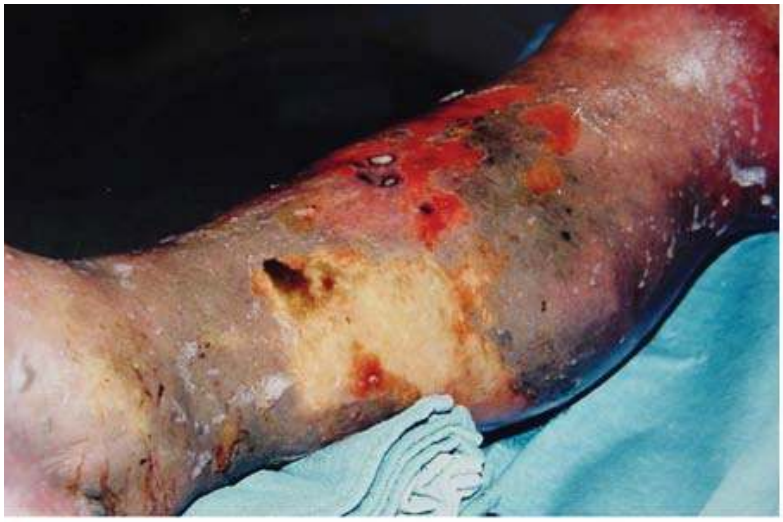
Aggressive soft tissue infections are rare, difficult to diagnose, and require immediate surgical intervention plus administration of antimicrobial agents. Failure to do so results in an extremely high mortality rate (approximately 80 to 100%), and even with rapid recognition and intervention, current mortality rates remain high, approximately 16 to 25%.[74,75] Eponyms and classification in the past have been a hodgepodge of terminology, such as Meleney's synergistic gangrene, rapidly spreading cellulitis, gas gangrene, and necrotizing fasciitis, among others. Today, it seems best to delineate these serious infections based on the soft tissue layer(s) of involvement (e.g., skin and superficial soft tissue, deep soft tissue, and muscle) and the pathogen(s) that causes them.[76]

Patients at risk for these types of infections include those who are elderly, immunosuppressed, or diabetic; those who suffer from peripheral vascular disease; or those with a combination of these factors. The common thread among these host factors appears to be compromise of the fascial blood supply to some degree, and if this is coupled with the introduction of exogenous microbes, the result can be devastating. However, it is of note that over the last decade, extremely aggressive necrotizing soft tissue infections among healthy individuals due to streptococci have been described as well.

Initially, the diagnosis is established solely upon a constellation of clinical findings, not all of which are present in every patient. Not surprisingly, patients often develop sepsis syndrome or septic shock without an obvious cause. The extremities, perineum, and torso are most commonly affected, in that order. Careful examination should be undertaken for an entry site such as a small break or sinus in the skin from which grayish, turbid semipurulent material ("dishwater pus") can be expressed, as well as for the presence of skin changes (bronze hue or

brawny induration), blebs, or crepitus. The patient often develops pain at the site of infection that appears to be out of proportion to any of the physical manifestations. Any of these findings mandates immediate surgical intervention, which should consist of exposure and direct visualization of potentially infected tissue (including deep soft tissue, fascia, and underlying muscle) and radical resection of affected areas. Radiologic studies should be undertaken only in patients in whom the diagnosis is not seriously considered, as they delay surgical intervention and frequently provide confusing information. Unfortunately, surgical extirpation of infected tissue frequently entails amputation and/or disfiguring procedures; however, incomplete procedures are associated with higher rates of morbidity and mortality (Fig. 6-5).

Fig. 6-5.



A

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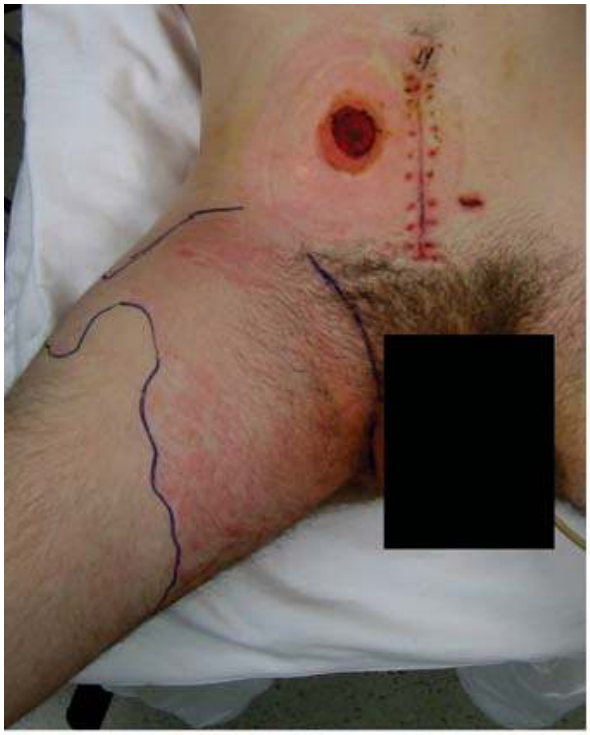

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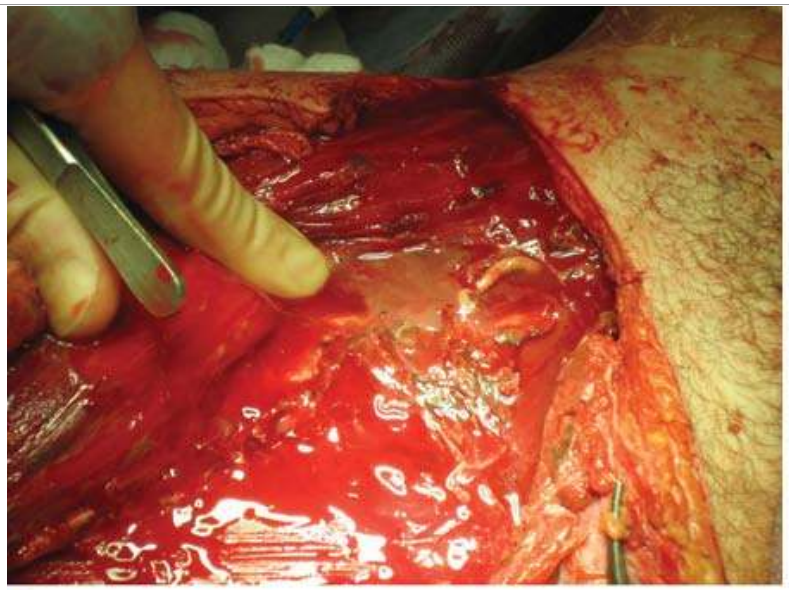

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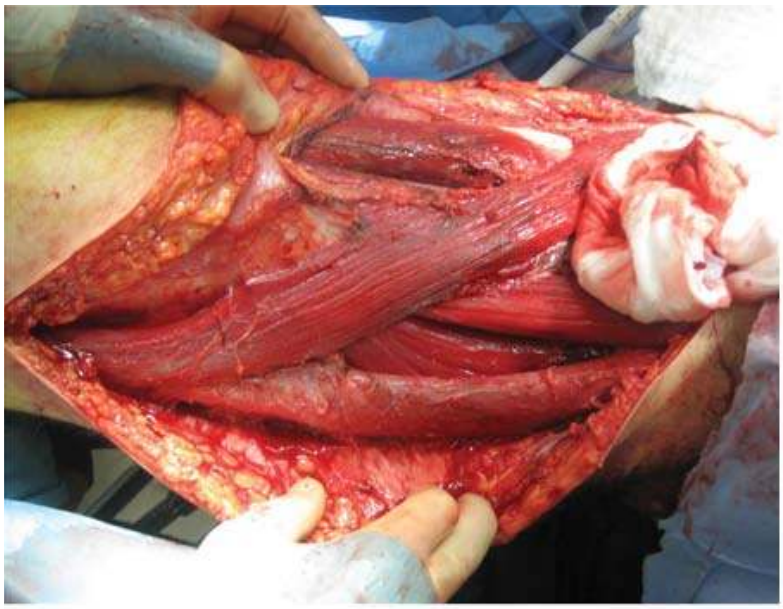

D

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Necrotizing soft tissue infection. **A.** This patient presented with hypotension due to severe late necrotizing fasciitis and myositis due to beta-hemolytic streptococcal infection. The patient succumbed to his disease after 16 hours despite aggressive débridement. **B.** This patient presented with spreading cellulites and pain on motion of his right hip 2 weeks after total colectomy. Cellulitis on right anterior thigh is outlined. **C.** Classic dishwater edema of tissues with necrotic fascia. **D.** Right lower extremity after débridement of fascia to viable muscle.

During the procedure, a Gram's stain should be performed on tissue fluid. Antimicrobial agents directed against gram-positive and gram-negative aerobes and anaerobes (e.g., vancomycin plus a carbapenem), as well as high-dose aqueous penicillin G (16,000 to 20,000 U/d), the latter to treat clostridial pathogens, should be administered. Approximately 50% of such infections are polymicrobial, the remainder being caused by a single organism such as *S. pyogenes, P. aeruginosa, or C. perfringens*. The microbiology of these polymicrobial infections is similar to that of secondary microbial peritonitis, with the exception that gram-positive cocci are more commonly encountered. Most patients should be returned to the operating room on a scheduled basis to determine if disease progression has occurred. If so, additional resection of

infected tissue and débridement should take place. Antibiotic therapy can be refined based on culture and sensitivity results, particularly in the case of monomicrobial soft tissue infections. Adjunctive treatments, including treatment with hyperbaric oxygen or IV Ig, have been described with contradictory results. Hyperbaric oxygen therapy should be strongly considered in patients with infection caused by gas-forming organisms (e.g., *C. perfringens*). It may be reasonable to consider IV Ig in patients with group A streptococcal infection with toxic shock syndrome and in those patients with a high risk of death, such as the elderly or those with hypotension or bacteremia.[77]

Postoperative Nosocomial Infections

Surgical patients are prone to develop a wide variety of nosocomial infections during the postoperative period, which include SSIs, UTIs, pneumonia, and bacteremic episodes.[78] SSIs are discussed above in Surgical Site Infections, and the latter types of nosocomial infections are related to prolonged use of indwelling tubes and catheters for the purpose of urinary drainage, ventilation, and venous and arterial access, respectively.

The presence of a postoperative UTI should be considered based on urinalysis demonstrating WBCs or bacteria, a positive test for leukocyte esterase, or a combination of these elements. The diagnosis is established after more than 10^4 CFU/mL of microbes are identified by culture techniques in symptomatic patients, or more than 10^5 CFU/mL in asymptomatic individuals. Treatment for 3 to 5 days with a single antibiotic that achieves high levels in the urine is appropriate. Postoperative surgical patients should have indwelling urinary catheters removed as quickly as possible, typically within 1 to 2 days, as long as they are mobile.

Prolonged mechanical ventilation is associated with an increased incidence of pneumonia, and is frequently due to pathogens common in the nosocomial environment.[79] Frequently these organisms are highly resistant to many different agents.[80] The diagnosis of hospital-acquired pneumonia should be made using the presence of a purulent sputum, elevated leukocyte count, fever, and new chest x-ray abnormality. The presence of two of the clinical findings, plus chest x-ray findings, significantly increases the likelihood of ventilator-associated pneumonia.[81] Consideration should be given to performing bronchoalveolar lavage to obtain samples to assess by Gram's stain and obtaining a culture to assess for the presence of microbes. Surgical patients should be weaned from mechanical ventilation as soon as feasible, based on oxygenation and inspiratory effort.

Infection associated with indwelling intravascular catheters has become a common problem among hospitalized patients. Because of the complexity of many surgical procedures, these devices are increasingly used for physiologic monitoring, vascular access, drug delivery, and hyperalimentation. Among the several million catheters inserted each year in the United States, approximately 25% will become colonized, and approximately 5% will be associated with bacteremia. Duration of catheterization, insertion or manipulation under emergency or nonsterile conditions, use for hyperalimentation, and perhaps the use of multilumen catheters increase the risk of infection. Although no randomized trials have been performed, peripherally inserted central venous catheters have a similar catheter-related infection rate.[82]

Many patients who develop intravascular catheter infections are asymptomatic, often exhibiting an elevation in the blood WBC count. Blood cultures obtained from a peripheral site and drawn through the catheter that reveal the presence of the same organism increase the index of suspicion for the presence of a catheter infection. Obvious purulence at the exit site of the skin tunnel, severe sepsis syndrome due to any type of organism when other potential causes have been excluded, or bacteremia due to gram-negative aerobes or fungi should lead to catheter removal. Selected catheter infections due to low-virulence microbes such as *S. epidermidis* can be effectively treated in approximately 50 to 60% of patients with a 14- to 21-day course of an antibiotic, which should be considered when no other vascular access site exists.[83] The use of antibiotic-bonded catheters is associated with lower rates of colonization.[84] Routine, scheduled catheter changes over a guidewire are associated with slightly lower rates of infection, but an increase in the insertion-related complication rate.[85] The surgeon should carefully consider the need for any type of vascular access device, rigorously attend to their maintenance to prevent infection, and remove them as quickly as possible. Use of antibacterial or antifungal agents to prevent catheter infection is of no utility and is contraindicated.

Sepsis

Severe sepsis is increasing in incidence, with over 750,000 cases estimated per year in the United States. This rate is expected to increase as the population of aged in the United States increases. The treatment of sepsis has improved dramatically over the last decade, with mortality rates dropping to under 30%.[86] Factors contributing to this improvement in mortality relate both to recent randomized prospective trials

demonstrating improved outcomes with new therapies, and to improvements in the process of care delivery to the sepsis patient. The "Surviving Sepsis Campaign," a multidisciplinary group that worked to develop treatment recommendations, has published guidelines incorporating evidence-based treatment strategies most recently in 2008.[87] These guidelines are summarized in Table 6-10.

Table 6-10 Summary of Surviving Sepsis Campaign Guidelines
Initial evaluation and infection issues
Initial resuscitation: Begin resuscitation immediately in patients with hypotension or elevated serum lactate with resuscitation goal of CVP 8–12 mmHg, mean arterial pressure of ≥65 mmHg, and urine output of ≥0.5 mL/kg per hour.
Diagnosis: Obtain appropriate cultures before antibiotics but do not delay antibiotic therapy.
Antibiotic therapy: Begin IV antibiotic therapy as early as possible: Should be within the first hour after recognition of severe sepsis/septic shock; use broad-spectrum antibiotic regimen with penetration into presumed source; reassess regimen daily; discontinue antibiotics in 7–10 d for most infections; stop antibiotics for noninfectious issues.
Source control: Establish anatomic site of infection as rapidly as possible, implement source control measures as soon as possible after initial resuscitation. Remove intravascular access devices if potentially infected.
Hemodynamic support and adjunctive therapy
Fluid therapy: Fluid resuscitate using crystalloid or colloid, using fluid volumes of 1000 mL (crystalloid), target CVP of 8–12 mmHg.
Vasopressors/inotropic therapy: Maintain MAP of ≥65 mmHg; centrally administered norepinephrine or dopamine are first-line choices; dopamine should not be used for "renal protection"; insert arterial catheters for patients requiring vasopressors. Do not increase cardiac index to predetermined supranormal levels.
Steroids: Consider IV hydrocortisone (dose ≤300 mg/d) for adult septic shock when hypotension responds poorly to fluids and vasopressors.
Recombinant human activated protein C: Consider rhAPC in adult patients with sepsis-induced organ dysfunction and high risk of death if there are no contraindications.
Other supportive therapy
Blood product administration: Transfuse red blood cells when hemoglobin decreases to <7.0 g/dL.
Mechanical ventilation: Target an initial tidal volume of 6 mL/kg body weight and plateau pressure of ≤30 cm H_2O in patients with acute lung injury. Use PEEP to avoid lung collapse. Use a weaning protocol to evaluate the potential for discontinuing mechanical ventilation. Pulmonary artery catheter is not indicated for routine monitoring.
Glucose control: Use IV insulin to control hyperglycemia in patients with severe sepsis.
Prophylaxis: Use stress ulcer (proton pump inhibitor or H_2 blocker) and deep venous thrombosis (low-dose unfractionated or fractionated heparin) prophylaxis.
Limitation of support: Discuss advance care planning with patients and families and set realistic expectations.

CVP = central venous pressure; MAP = mean arterial pressure; PEEP = positive end-expiratory pressure; rhAPC = recombinant human activated protein C.

Source: Reproduced with permission from Dellinger et al.[87]

Patients presenting with severe sepsis should receive resuscitation fluids to a central venous pressure target of 8 to 12 mmHg, with a goal of mean arterial pressure of 65 mmHg or greater and urine output of 0.5 mL/kg per hour or greater. Delaying this resuscitative step for as little as 3 hours until arrival in the ICU has been shown to result in poor outcome.[88] Typically, this goal necessitates early placement of central venous catheter.

A number of studies have demonstrated the importance of early empiric antibiotic therapy in patients who develop sepsis or nosocomial infection. This therapy should be initiated as soon as possible with broad-spectrum antibiotics directed against most likely organisms, because early appropriate antibiotic therapy has been associated with significant reductions in mortality,[89,90] and delays in appropriate antibiotic administration are associated with increased mortality.[91] Use of institutional and unit specific sensitivity patterns are critical in selecting an appropriate agent for patients with nosocomial infection. It is key, however, to obtain cultures of appropriate areas without delaying initiating antibiotics so that appropriate adjustment of antibiotic therapy can take place when culture results return.

Additionally, early identification and treatment of septic sources is key for improved outcomes in patients with sepsis. Although there are no randomized trials demonstrating this concept, repeated evidence in series including intra-abdominal infection, necrotizing soft tissue infection, and others demonstrate increased mortality with delayed treatment. A possible exception is that of infected pancreatic necrosis.

Multiple trials have evaluated the use of vasopressors and inotropes for treatment of septic shock. Current suggestions for first-line agents based on effects on splanchnic perfusion include norepinephrine, dopamine, and vasopressin.[92,93] It is important to titrate therapy based on other parameters such as mixed venous oxygen saturation and plasma lactate levels as well as mean arterial pressure to reduce the risk of vasopressor-induced perfusion deficits. Several recent randomized trials have failed to demonstrate benefit with use of pulmonary arterial catheterization, leading to a significant decrease in its use.

A number of other adjunctive therapies are useful in treatment of the patient with severe sepsis and septic shock. Corticosteroids, first evaluated unsuccessfully in the 1980s for treatment of sepsis (high dose), have recently been reintroduced to the armamentarium of the practitioner after the observation that many patients with septic shock have a relative adrenal insufficiency. Low-dose corticosteroids (hydrocortisone at 300 mg/d or less) can be used in patients with septic shock who are not responsive to fluids and vasopressors. However, a recent randomized trial failed to show survival benefit. Recombinant human activated protein C (drotrecogin alfa, Xigris) has been associated with significant survival benefit in patients with severe sepsis and at least one organ failure.[94] In surgical patients, this therapy should be reserved for patients with at least two organ failures or for patients with septic shock. Patients with acute lung injury associated with sepsis should receive mechanical ventilation with tidal volumes of 6 mL/kg and pulmonary airway plateau pressures of 30 cm H_2O or less. Finally, red blood cell transfusion should be reserved for patients with hemoglobin of less than 7 g/dL, with a more liberal transfusion strategy reserved for those patients with severe coronary artery disease, ongoing blood loss, or severe hypoxemia.

Blood-Borne Pathogens

Although alarming to contemplate, the risk of HIV transmission from patient to surgeon is low. By December 31, 2001, there had been six cases of surgeons with HIV seroconversion from a possible occupational exposure, from a total of 469,850 HIV cases to that date reported to the Centers for Disease Control and Prevention. Of the groups of health care workers with likely occupationally acquired HIV infection (n = 195), surgeons were one of the lower risk groups (compared to nurses at 59 cases and nonsurgeon physicians at 18 cases).[95] Transmission of HIV (and other infections spread by blood and body fluid) from patient to health care worker can be minimized by observation of universal precautions, which include the following: (a) routine use of barriers (such as gloves and/or goggles) when anticipating contact with blood or body fluids, (b) washing of hands and other skin surfaces immediately after contact with blood or body fluids, and (c) careful handling and disposal of sharp instruments during and after use. The current estimate of the risk of transmission is 0.3% after needlestick.

Postexposure prophylaxis for HIV has significantly decreased the risk of seroconversion for health care workers with occupational exposure to HIV. Steps to initiate postexposure prophylaxis should be initiated within hours rather than days for the most effective preventive therapy. Postexposure prophylaxis with a two- or three-drug regimen should be initiated for health care workers with significant exposure to patients with an HIV-positive status. If a patient's HIV status is unknown, it may be advisable to begin postexposure prophylaxis while testing is carried out, particularly if the patient is at high risk for infection due to HIV (e.g., IV narcotic use). Generally, postexposure prophylaxis is not warranted for exposure to sources with unknown status, such as deceased persons or needles from a sharps container.

The risks for surgeons of acquiring HIV infection have recently been evaluated by Goldberg and coauthors.[96] They noted that the risks are related to the prevalence of HIV infection in the population being cared for, the probability of transmission from a percutaneous injury suffered while caring for an infected patient, the number of such injuries sustained, and the use of postexposure prophylaxis. Annual calculated risks in Glasgow, Scotland, ranged from one in 200,000 for general surgeons not utilizing postexposure prophylaxis to as low as one in 10,000,000 with use of routine postexposure prophylaxis after significant exposures.

Hepatitis B virus (HBV) is a DNA virus that affects only humans. Primary infection with HBV generally is self-limited (~6% of those infected are over 5 years of age), but can progress to a chronic carrier state. Death from chronic liver disease or hepatocellular cancer occurs in roughly 30% of chronically infected persons. Surgeons and other health care workers are at high risk for this blood-borne infection and should receive the HBV vaccine; children are routinely vaccinated in the United States.[97] This vaccine has contributed to a significant decline in the number of new cases of HBV per year in the United States, from approximately 27,000 new cases in 1984 to 4700 new cases in 2006.[98] In

the postexposure setting, hepatitis B immune globulin confers approximately 75% protection from HBV infection.[99]

Hepatitis C virus (HCV), previously known as non-A, non-B hepatitis, is a RNA flavivirus first identified specifically in the late 1980s. This virus is confined to humans and chimpanzees. A chronic carrier state develops in 75 to 80% of patients with the infection, with chronic liver disease occurring in three fourths of patients developing chronic infection. The number of new infections per year has declined since the 1980s due to the incorporation of testing of the blood supply for this virus. Fortunately, HCV virus is not transmitted efficiently through occupational exposures to blood, with the seroconversion rate after accidental needlestick reported to be approximately 2%.[100] To date, a vaccine to prevent HCV infection has not been developed. Experimental studies in chimpanzees with HCV Ig using a model of needlestick injury have failed to demonstrate a protective effect of this treatment in seroconversion after exposure, and no effective antiviral agents for postexposure prophylaxis are available. Early treatment of infection with INF-γ has been considered; however, this exposes patients who may not develop HCV infection–related sequelae to the side effects of this drug.[101]

BIOLOGIC WARFARE AGENTS

Several infectious organisms have been studied by the United States and the former Soviet Union and presumably other entities for potential use as biologic weapons. Programs involving biologic agents in the United States were halted by presidential decree in 1971. However, concern remains that these agents could be used by rogue states or terrorist organizations as alternatives to nuclear weapons as weapons of mass destruction, as they are relatively inexpensive to make in terms of infrastructure development. If so, all physicians including surgeons would need to familiarize themselves with the manifestations of infection due to these pathogens. The typical agent is selected for the ability to be spread via the inhalational route, as this is the most efficient mode of mass exposure. Some potential agents are discussed in the *Bacillus anthracis* (Anthrax), *Yersinia pestis* (Plague), Smallpox, and *Francisella tularensis* (Tularemia) sections that follow.

Bacillus anthracis (Anthrax)

Anthrax is a zoonotic disease occurring in domesticated and wild herbivores. The first identification of inhalational anthrax as a disease occurred among woolsorters in England in the late 1800s. The largest recent epidemic of inhalational anthrax occurred in Sverdlovsk, Russia, in 1979 after accidental release of anthrax spores from a military facility. Inhalational anthrax develops after a 1- to 6-day incubation period, with nonspecific symptoms including malaise, myalgia, and fever. Over a short period of time, these symptoms worsen, with development of respiratory distress, chest pain, and diaphoresis. Characteristic chest roentgenographic findings include a widened mediastinum and pleural effusions. A key aspect in establishing the diagnosis is eliciting an exposure history. Rapid antigen tests are currently under development for identification of this gram-positive rod. Drugs such as cephalosporins and trimethoprim-sulfamethoxazole are not active against this agent. Postexposure prophylaxis consists of administration of either ciprofloxacin or doxycycline.[102] If an isolate is demonstrated to be penicillin-sensitive, the patient should be switched to amoxicillin. Inhalational exposure followed by the development of symptoms is associated with a high mortality rate. Treatment options include combination therapy with ciprofloxacin, clindamycin, and rifampin, with clindamycin added to block production of toxin, and rifampin for its ability to penetrate the central nervous system and intracellular locations.

Yersinia pestis (Plague)

Plague is caused by the gram-negative organism *Yersinia pestis*. The naturally occurring disease in humans is transmitted via flea bites from rodents. It was the first biologic warfare agent, and was used in the Crimean city of Caffa by the Tartar army, whose soldiers catapulted bodies of plague victims at the Genoese. When plague is used as a biologic warfare agent, clinical manifestations include epidemic pneumonia with blood-tinged sputum if aerosolized bacteria were used, or bubonic plague if fleas were used as carriers. Individuals who develop a painful lesion termed a *bubo* associated with fever, severe malaise, and exposure to fleas should be suspected to have plague. Diagnosis is confirmed via aspirate of the bubo and a direct antibody stain to detect plague bacillus. Typical morphology for this organism is that of a bipolar safety-pin–shaped gram-negative organism. Postexposure prophylaxis for patients exposed to plague consists of doxycycline. Treatment of the pneumonic or bubonic/septicemic form includes administration of aminoglycosides, doxycycline, ciprofloxacin, and chloramphenicol.[103]

Smallpox

Variola, the causative agent of smallpox, was a major cause of infectious morbidity and mortality until its eradication in the late 1970s.

During the European colonization of North America, British commanders may have used it against native inhabitants and the colonists by distribution of blankets from smallpox victims. Even in the absence of laboratory-preserved virus, the prolonged viability of variola virus has been demonstrated in scabs up to 13 years after collection; the potential for reverse genetic engineering using the known sequence of smallpox also makes it a potential biologic weapon.[104] This has resulted in the United States undertaking a vaccination program for key health care workers. Variola virus is highly infectious in the aerosolized form: After an incubation period of 10 to 12 days, clinical manifestations of malaise, fever, vomiting, and headache appear, followed by development of a characteristic centripetal rash (which is found to predominate on the face and extremities). The fatality rate may reach 30%. Postexposure prophylaxis with smallpox vaccine has been noted to be effective for up to 4 days postexposure. Cidofovir, an acyclic nucleoside phosphonate analogue, has demonstrated activity in animal models of poxvirus infections and may offer promise for the treatment of smallpox.[105]

Francisella tularensis (Tularemia)

The principal reservoir of this gram-negative aerobic organism is the tick. After inoculation, this organism proliferates within macrophages. This organism has been considered a potential bioterrorist threat due to a very high infectivity rate after aerosolization. Patients with tularemia pneumonia develop a cough and demonstrate pneumonia on chest roentgenogram. Enlarged lymph nodes are seen in approximately 85% of patients. The organism can be cultured from tissue samples, but this is difficult. Alternative diagnosis is based on acute-phase agglutination tests. Treatment of inhalational tularemia consists of administration of aminoglycosides or second-line agents such as doxycycline and ciprofloxacin.

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a silverchair information system

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KEY POINTS

1. Trauma remains the most common cause of death for all individuals between the ages of 1 and 44 years and is the third most common cause of death regardless of age.

2. The initial management of seriously injured patients consists of performing the primary survey (the "ABCs"—*A*irway with cervical spine protection, *B*reathing, and *C*irculation); the goals of the primary survey are to identify and treat conditions that constitute an immediate threat to life.

3. Patients with ongoing hemodynamic instability, whether "nonresponders" or "transient responders," require prompt intervention; one must consider the four categories of shock that may represent the underlying pathophysiology: hemorrhagic, cardiogenic, neurogenic, and septic.

4. All patients with blunt injury should be assumed to have unstable cervical spine injuries until proven otherwise; one must maintain cervical spine precautions and in-line stabilization.

5. Indications for immediate operative intervention for penetrating cervical injury include hemodynamic instability and significant external arterial hemorrhage; the management algorithm for hemodynamically stable patients is based on the presenting symptoms and anatomic location of injury, with the neck being divided into three distinct zones.

6. Blunt injuries to the carotid and vertebral arteries are usually managed with systemic antithrombotic therapy.

7. The abdomen is a diagnostic black box. However, physical examination and ultrasound can rapidly identify patients requiring emergent laparotomy. Computed tomographic (CT) scanning is the mainstay of evaluation in the remaining patients to more precisely identify the site and magnitude of injury.

8. Manifestation of the "bloody vicious cycle" (the lethal combination of coagulopathy, hypothermia, and metabolic acidosis) is the most common indication for damage control surgery. The primary objectives of damage control laparotomy are to control bleeding and limit GI spillage.

9. The abdominal compartment syndrome may be primary (i.e., due to the injury of abdominal organs, bleeding, and packing) or secondary (i.e., due to reperfusion gut edema and ascites).

10. The gold standard for determining if there is a blunt descending torn aorta injury is CT scanning; indications are primarily based on injury mechanisms.

TRAUMA: INTRODUCTION

Trauma, or injury, is defined as cellular disruption caused by an exchange with environmental energy that is beyond the body's resilience. Trauma remains the most common cause of death for all individuals between the ages of 1 and 44 years and is the third most common cause of death regardless of age.[1] It is also the number one cause of years of productive life lost. The U.S. government classifies injury-related death into the following categories: accidents (unintentional injuries), intentional self-harm (suicide), assault (homicide), legal intervention or war, and undetermined causes. Unintentional injuries account for over 110,000 deaths per year, with motor vehicle collisions accounting for over 40%. Homicides, suicides, and other causes are responsible for another 50,000 deaths each year. However, death is a poor indicator of the magnitude of the problem, because most injured patients survive. For example, in 2004 there were approximately 167,000 injury-related deaths, but 29.6 million injured patients treated in emergency departments (EDs).[2] Injury-related medical expenditures are estimated to be $117 billion each year in the United States.[2] The aggregate lifetime cost for all injured patients is estimated to be in excess of $260 trillion. For these reasons, trauma must be considered a major public health issue. The American College of Surgeons Committee on Trauma addresses this issue by assisting in the development of trauma centers and systems. The organization of trauma systems has had a significant favorable impact on patient outcomes.[3–5]

INITIAL EVALUATION AND RESUSCITATION OF THE INJURED PATIENT

Primary Survey

The Advanced Trauma Life Support (ATLS) course of the American College of Surgeons Committee on Trauma was developed in the late 1970s, based on the assumption that appropriate and timely care can significantly improve the outcome for the injured patient.[6] ATLS provides a structured approach to the trauma patient with standard algorithms of care; it emphasizes the "golden hour" concept that timely prioritized interventions are necessary to prevent death. The ATLS format and basic tenets are followed throughout this chapter, with minor modifications. The initial management of seriously injured patients consists of the primary survey, concurrent resuscitation, the secondary survey, diagnostic evaluation, and definitive care. The first step in patient management is performing the primary survey, the goal of which is to identify and treat conditions that constitute an immediate threat to life. The ATLS course refers to the primary survey as assessment of the "ABCs" (*A*irway with cervical spine protection, *B*reathing, and *C*irculation). Although the concepts within the primary survey are presented in a sequential fashion, in reality they often proceed simultaneously. Life-threatening injuries must be identified (Table 7-1) and treated before advancing to the secondary survey.

Table 7-1 Immediately Life-Threatening Injuries to Be Identified during the Primary Survey
Airway

Airway obstruction
Airway injury
Breathing
Tension pneumothorax
Open pneumothorax
Flail chest with underlying pulmonary contusion
Circulation
Hemorrhagic shock
Massive hemothorax
Massive hemoperitoneum
Mechanically unstable pelvis fracture
Extremity losses
Cardiogenic shock
Cardiac tamponade
Neurogenic shock
Cervical spine injury
Disability
Intracranial hemorrhage/mass lesion

AIRWAY MANAGEMENT WITH CERVICAL SPINE PROTECTION

Ensuring a patent airway is the first priority in the primary survey. This is essential, because efforts to restore cardiovascular integrity will be futile unless the oxygen content of the blood is adequate. Simultaneously, all patients with blunt trauma require cervical spine immobilization until injury is excluded. This is typically accomplished by applying a hard collar or placing sandbags on both sides of the head with the patient's forehead taped across the bags to the backboard. Soft collars do not effectively immobilize the cervical spine.

In general, patients who are conscious, do not show tachypnea, and have a normal voice do not require early attention to the airway. Exceptions are patients with penetrating injuries to the neck and an expanding hematoma; evidence of chemical or thermal injury to the mouth, nares, or hypopharynx; extensive subcutaneous air in the neck; complex maxillofacial trauma; or airway bleeding. Although these patients may initially have a satisfactory airway, it may become obstructed if soft tissue swelling, hematoma formation, or edema progresses. In these cases, elective intubation should be performed before evidence of airway compromise.

Patients who have an abnormal voice, abnormal breathing sounds, tachypnea, or altered mental status require further airway evaluation. Blood, vomit, the tongue, foreign objects, and soft tissue swelling can cause airway obstruction; suctioning affords immediate relief in many patients. In the comatose patient, the tongue may fall backward and obstruct the hypopharynx; this may be relieved by either a chin lift or jaw thrust. An oral airway or a nasal trumpet also can be helpful in maintaining airway patency, although the former is not usually tolerated by an awake patient. Establishment of a definitive airway (i.e., endotracheal intubation) is indicated in patients with apnea; inability to protect the airway due to altered mental status; impending airway compromise due to inhalation injury, hematoma, facial bleeding, soft tissue swelling, or aspiration; and inability to maintain oxygenation. Altered mental status is the most common indication for intubation. Agitation or obtundation, often attributed to intoxication or drug use, may actually be due to hypoxia.

Options for endotracheal intubation include nasotracheal, orotracheal, or surgical routes. Nasotracheal intubation can be accomplished only in patients who are breathing spontaneously. Although nasotracheal intubation is frequently used by prehospital providers, the primary application for this technique in the ED is in those patients requiring emergent airway support in whom chemical paralysis cannot be used. Orotracheal intubation is the most common technique used to establish a definitive airway. Because all patients are presumed to have cervical spine injuries, manual in-line cervical immobilization is essential.[6] Correct endotracheal placement is verified with direct laryngoscopy, capnography, audibility of bilateral breath sounds, and finally a chest film. The GlideScope, a video laryngoscope that uses fiberoptics to visualize the vocal cords, is being employed more frequently.[7] Advantages of orotracheal intubation include the direct visualization of the vocal cords, ability to use larger-diameter endotracheal tubes, and applicability to apneic patients. The disadvantage of orotracheal intubation is that conscious patients usually require neuromuscular blockade, which may result in inability to intubate, aspiration, or medication complications. Those who attempt rapid-sequence induction must be thoroughly familiar with the procedure (see Chap. 13).

Patients in whom attempts at intubation have failed or who are precluded from intubation due to extensive facial injuries require surgical establishment of an airway. Cricothyroidotomy (Fig. 7-1) is performed through a generous vertical incision, with sharp division of the subcutaneous tissues and strap muscles. Visualization may be improved by having an assistant retract laterally on the neck incision using army-navy retractors. The cricothyroid membrane is verified by digital palpation through the space into the airway. The airway may be stabilized before incision of the membrane using a tracheostomy hook; the hook should be placed under the thyroid cartilage to elevate the airway. A 6.0 tracheostomy tube (maximum diameter in adults) is then advanced through the cricothyroid opening and sutured into place. In patients under the age of 8, cricothyroidotomy is contraindicated due to the risk of subglottic stenosis, and tracheostomy should be performed.

Fig. 7-1.

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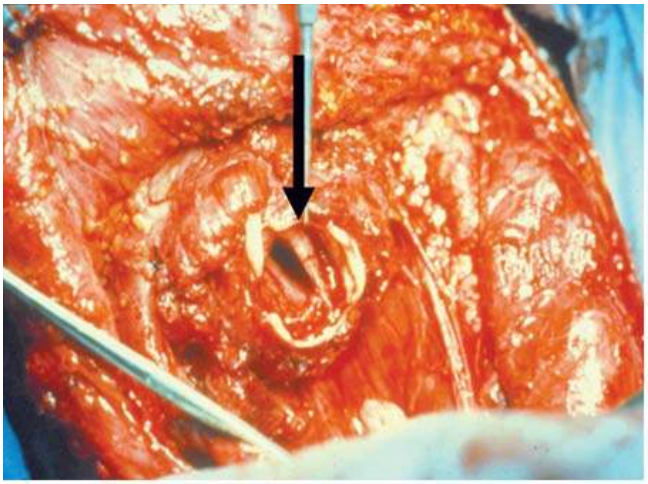
Cricothyroidotomy is recommended for emergent surgical establishment of a patent airway. A vertical skin incision avoids injury to the anterior jugular veins, which are located just lateral to the midline. Hemorrhage from these vessels obscures vision and prolongs the procedure. When a transverse incision is made in the cricothyroid membrane, the blade of the knife should be angled inferiorly to avoid injury to the vocal cords. **A.** Use of a tracheostomy hook stabilizes the thyroid cartilage and facilitates tube insertion. **B.** A 6.0 tracheostomy tube or endotracheal tube is inserted after digital confirmation of airway access.

Emergent tracheostomy is indicated in patients with laryngotracheal separation or laryngeal fractures, in whom cricothyroidotomy may cause further damage or result in complete loss of the airway. This procedure is best performed in the OR where there is optimal lighting and availability of more equipment (e.g., sternal saw). In these cases, often after a "clothesline" injury, direct visualization and instrumentation of the trachea usually is done through the traumatic anterior neck defect or after a collar skin incision (Fig. 7-2). If the trachea is completely transected, a nonpenetrating clamp should be placed on the distal aspect to prevent tracheal retraction into the mediastinum; this is particularly important before placement of the endotracheal tube.

Fig. 7-2.



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A "clothesline" injury can partially or completely transect the anterior neck structures, including the trachea. With complete tracheal transection, the endotracheal tube is placed directly into the distal aperture, with care taken not to push the trachea into the mediastinum.

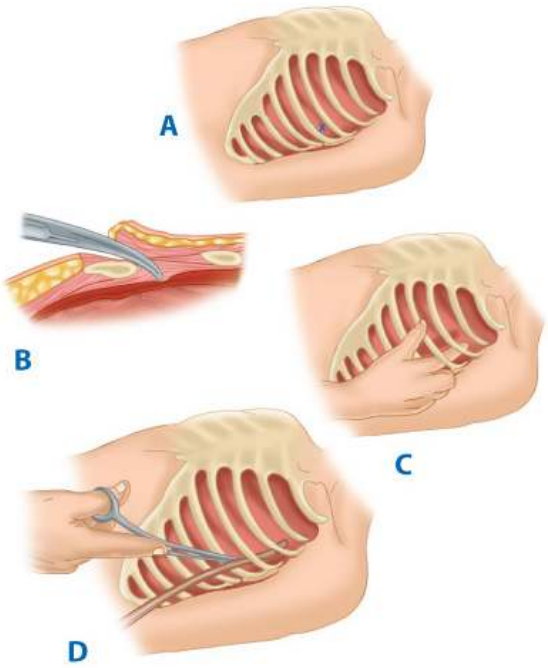
BREATHING AND VENTILATION

Once a secure airway is obtained, adequate oxygenation and ventilation must be assured. All injured patients should receive supplemental oxygen and be monitored by pulse oximetry. The following conditions constitute an immediate threat to life due to inadequate ventilation and should be recognized during the primary survey: tension pneumothorax, open pneumothorax, and flail chest with underlying pulmonary contusion. All of these diagnoses should be made during the initial physical examination.

The diagnosis of tension pneumothorax is implied by respiratory distress and hypotension in combination with any of the following physical signs in patients with chest trauma: tracheal deviation away from the affected side, lack of or decreased breath sounds on the affected side, and subcutaneous emphysema on the affected side. Patients may have distended neck veins due to impedance of the superior vena cava, but the neck veins may be flat due to systemic hypovolemia. Vital signs differentiate a tension pneumothorax from a simple pneumothorax; each can have similar signs, symptoms, and examination findings, but hypotension qualifies the pneumothorax as a tension pneumothorax. Although immediate needle thoracostomy decompression with a 14-gauge angiocatheter in the second intercostal space in the midclavicular line may be indicated in the field, tube thoracostomy should be performed immediately in the ED before a chest radiograph is obtained (Fig. 7-3). In cases of tension pneumothorax, the parenchymal tear in the lung acts as a one-way valve, with each inhalation allowing additional air to accumulate in the pleural space. The normally negative intrapleural pressure becomes positive, which depresses the ipsilateral hemidiaphragm and shifts the mediastinal structures into the contralateral chest. Subsequently, the contralateral

lung is compressed and the heart rotates about the superior and inferior vena cava; this decreases venous return and ultimately cardiac output, which results in cardiovascular collapse.

Fig. 7-3.



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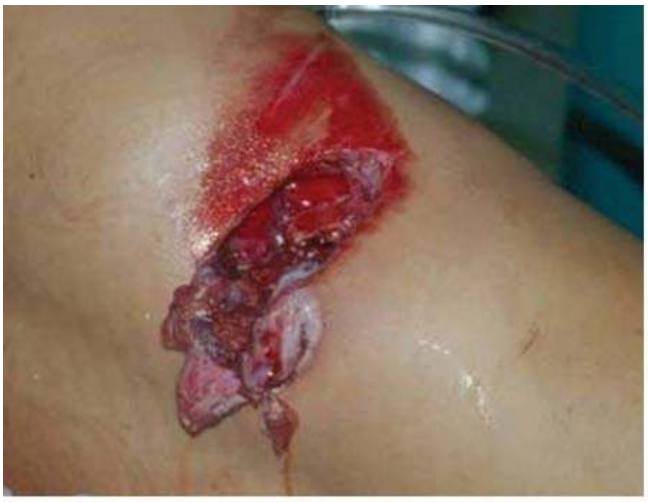
A. Tube thoracostomy is performed in the midaxillary line at the fourth or fifth intercostal space (inframammary crease) to avoid iatrogenic injury to the liver or spleen. **B.** Heavy scissors are used to cut through the intercostal muscle into the pleural space. This is done on top of the rib to avoid injury to the intercostal bundle located just beneath the rib. **C.** The incision is digitally explored to confirm intrathoracic location and identify pleural adhesions. **D.** A 36F chest tube is directed superiorly and posteriorly with the aid of a large clamp.

An open pneumothorax or "sucking chest wound" occurs with full-thickness loss of the chest wall, permitting free communication between the pleural space and the atmosphere (Fig. 7-4). This compromises ventilation due to equilibration of atmospheric and pleural pressures, which prevents lung inflation and alveolar ventilation, and results in hypoxia and hypercarbia. Complete occlusion of the chest wall defect without a tube thoracostomy may convert an open pneumothorax to a tension pneumothorax. Temporary management of this injury includes covering the wound with an occlusive dressing that is taped on three sides. This acts as a flutter valve, permitting effective ventilation on inspiration while allowing accumulated air to escape from the pleural space on the untaped side, so that a tension pneumothorax is prevented. Definitive treatment requires closure of the chest wall defect and tube thoracostomy remote from the wound.

Fig. 7-4.



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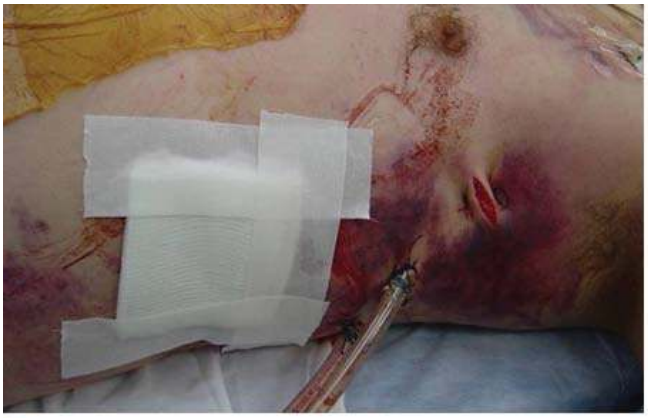

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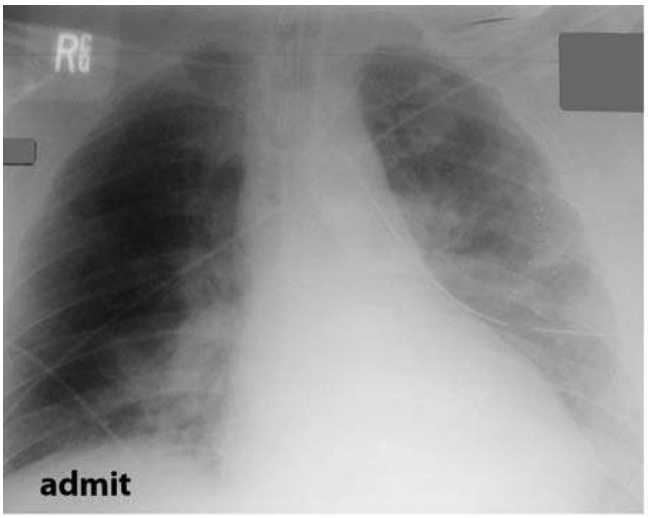
A. Full-thickness loss of the chest wall results in an open pneumothorax. **B.** The defect is temporarily managed with an occlusive dressing that is taped on three sides, which allows accumulated air to escape from the pleural space and thus prevents a tension pneumothorax. Repair of the chest wall defect and tube thoracostomy remote from the wound is definitive treatment.

Flail chest occurs when three or more contiguous ribs are fractured in at least two locations. Paradoxical movement of this free-floating segment of chest wall may be evident in patients with spontaneous ventilation, due to the negative intrapleural pressure of inspiration. Rarely the additional work of breathing and chest wall pain caused by the flail segment is sufficient to compromise ventilation. However, it is the decreased compliance and increased shunt fraction caused by the associated pulmonary contusion that is typically the source of postinjury pulmonary dysfunction. Pulmonary contusion often progresses during the first 12 hours. Resultant hypoventilation and hypoxemia may require presumptive intubation and mechanical ventilation. The patient's initial chest radiograph often underestimates the extent of the pulmonary parenchymal damage (Fig. 7-5); close monitoring and frequent clinical re-evaluation are warranted.

Fig. 7-5.



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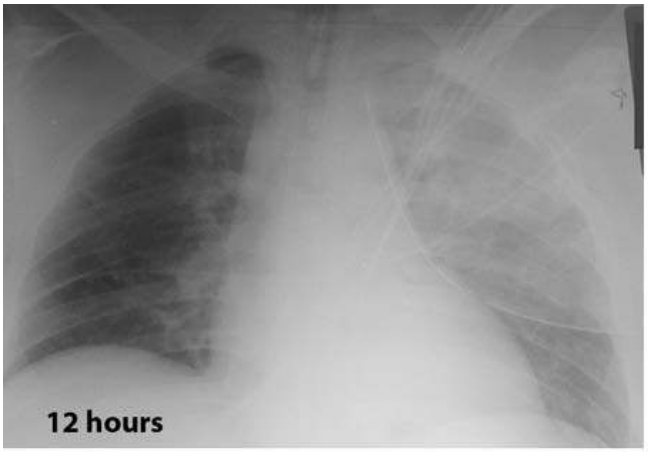

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A. Admission chest film may not show the full extent of the patient's thoracic injury. **B.** This patient's left pulmonary contusion blossomed 12 hours later, and its associated opacity is noted on repeat chest film.

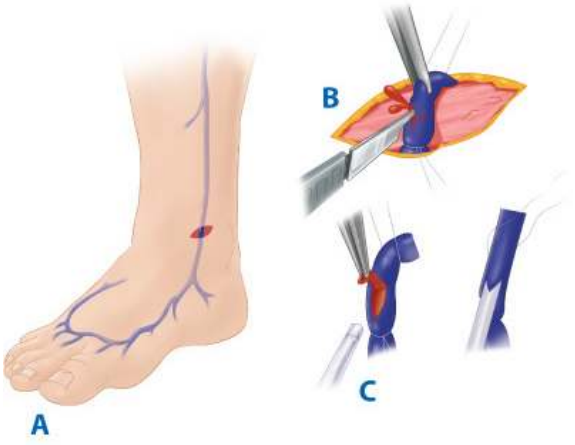
CIRCULATION WITH HEMORRHAGE CONTROL

With a secure airway and adequate ventilation established, circulatory status is the next priority. An initial approximation of the patient's cardiovascular status can be obtained by palpating peripheral pulses. In general, systolic blood pressure (SBP) must be 60 mmHg for the carotid pulse to be palpable, 70 mmHg for the femoral pulse, and 80 mmHg for the radial pulse. At this point in the patient's evaluation, any episode of hypotension (defined as a SBP <90 mmHg) is assumed to be caused by hemorrhage until proven otherwise. Blood pressure and pulse should be measured manually at least every 5 minutes in patients with significant blood loss until normal vital sign values are restored.

IV access for fluid resuscitation is obtained with two peripheral catheters, 16-gauge or larger in adults. Blood should be drawn simultaneously and sent for measurement of hematocrit level, as well as for typing and cross-matching for possible blood transfusion in patients with evidence of hypovolemia. According to Poiseuille's law, the flow of liquid through a tube is proportional to the diameter and inversely proportional to the length; therefore, venous lines for volume resuscitation should be short with a large diameter. If peripheral access with large-bore angiocatheters is inadequate, Cordis introducer catheters are preferred over triple-lumen catheters. In general, initial access in trauma patients is best secured in the groin or ankle, so that the catheter will not interfere with the performance of other diagnostic and therapeutic thoracoabdominal procedures. For patients requiring vigorous fluid resuscitation in whom peripheral angiocatheter access is difficult, saphenous vein cutdowns at the ankle provide excellent access (Fig. 7-6). The saphenous vein is reliably found 1 cm anterior and 1 cm superior to the medial malleolus. Standard 14-gauge catheters can be quickly placed, even in an exsanguinating patient with collapsed veins. Additional venous access often is obtained through the femoral or subclavian veins with Cordis introducer catheters. A rule of thumb to consider is placement of femoral access for thoracic trauma and jugular or subclavian access for abdominal trauma. However, placement of jugular or

subclavian central venous catheters provides a more reliable measurement of central venous pressure (CVP), which is helpful in determining the volume status of the patient and excluding cardiac tamponade. In hypovolemic patients under 6 years of age, an intraosseous needle can be placed in the proximal tibia (preferred) or distal femur of an unfractured extremity (Fig. 7-7). Flow through the needle should be continuous and does not require pressure. All medications administered IV may be administered in a similar dosage intraosseously. Although safe for emergent use, the needle should be removed once alternative access is established to prevent osteomyelitis.

Fig. 7-6.



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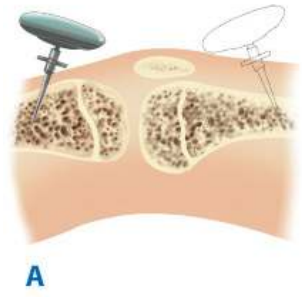
Saphenous vein cutdowns are excellent sites for fluid resuscitation access. **A.** The vein is consistently found 1 cm anterior and 1 cm superior to the medial malleolus. **B.** Proximal and distal traction sutures are placed with the distal suture ligated. **C.** A 14-gauge IV catheter is introduced and secured with sutures and tape to prevent dislodgment.

Fig. 7-7.



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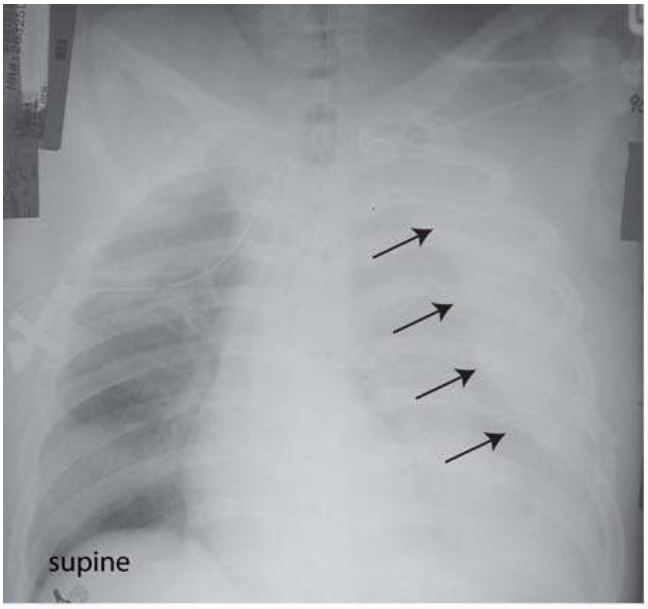
Intraosseous infusions are indicated for children <6 years of age in whom one or two attempts at IV access have failed. **A.** The proximal tibia is the preferred location.

Alternatively, the distal femur can be used if the tibia is fractured. **B.** The needle should be directed away from the epiphyseal plate to avoid injury. The position is satisfactory if bone marrow can be aspirated and saline can be easily infused without evidence of extravasation.

External control of hemorrhage should be achieved promptly while circulating volume is restored. Manual compression of open wounds with ongoing bleeding should be done with a single 4 x 4 gauze and a gloved hand. Covering the wound with excessive dressings may permit ongoing unrecognized blood loss that is hidden underneath the dressing. Blind clamping of bleeding vessels should be avoided because of the risk to adjacent structures, including nerves. This is particularly true for penetrating injuries of the neck, thoracic outlet, and groin, where bleeding may be torrential and arising from deep within the wound. In these situations, a gloved finger is placed through the wound directly onto the bleeding vessel and enough pressure is applied to control active bleeding. The surgeon performing this maneuver must then walk with the patient to the OR for open definitive treatment. For bleeding of the extremities it is tempting to apply tourniquets for hemorrhage control, but digital occlusion will usually control the bleeding, and complete vascular occlusion risks permanent neuromuscular impairment. For patients with open fractures, fracture reduction with stabilization via splints will limit bleeding externally and into the subcutaneous tissues. Scalp lacerations through the galea aponeurotica tend to bleed profusely; these can be temporarily controlled with skin staples, Rainey clips, or a large full-thickness continuous running nylon stitch.

During the circulation section of the primary survey, four life-threatening injuries that must be identified are (a) massive hemothorax, (b) cardiac tamponade, (c) massive hemoperitoneum, and (d) mechanically unstable pelvic fractures. Massive hemoperitoneum and mechanically unstable pelvic fractures are discussed in "Emergent Abdominal Exploration" and "Pelvic Fractures and Emergent Hemorrhage Control," respectively. Three critical tools used to differentiate these in the multisystem trauma patient are chest radiograph, pelvis radiograph, and focused abdominal sonography for trauma (FAST) (see "Regional Assessment and Special Diagnostic Tests"). A massive hemothorax (life-threatening injury number one) is defined as >1500 mL of blood or, in the pediatric population, one third of the patient's blood volume in the pleural space (Fig. 7-8). Although it may be suspected on chest radiograph, tube thoracostomy is the only reliable means to quantify the amount of hemothorax. After blunt trauma, a hemothorax usually is due to multiple rib fractures with severed intercostal arteries, but occasionally bleeding is from lacerated lung parenchyma. After penetrating trauma, a systemic or pulmonary hilar vessel injury should be presumed. In either scenario, a massive hemothorax is an indication for operative intervention, but tube thoracostomy is critical to facilitate lung re-expansion, which may provide some degree of tamponade.

Fig. 7-8.



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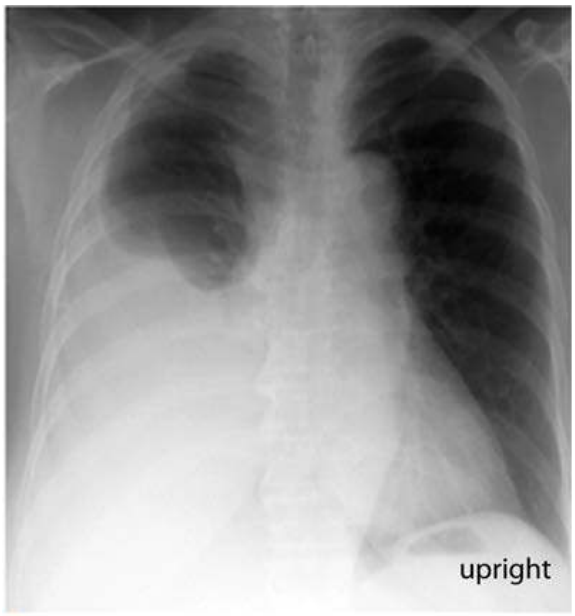

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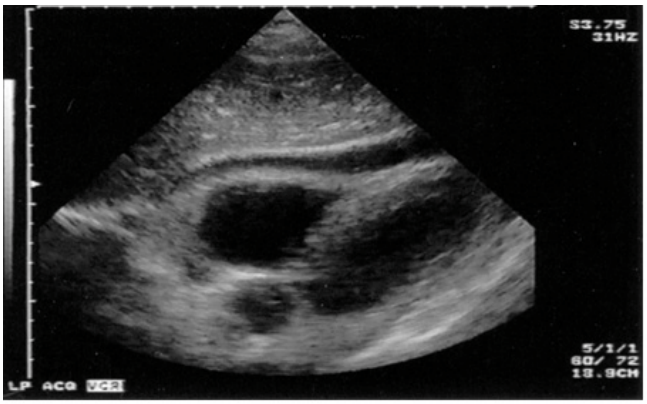
More than 1500 mL of blood in the pleural space is a massive hemothorax. Chest film findings reflect the positioning of the patient. **A.** In the supine position, blood tracks along the entire posterior section of the chest and is most notable pushing the lung away from the chest wall. **B.** In the upright position, blood is visible dependently in the pleural space.

Cardiac tamponade (life-threatening injury number two) occurs most commonly after penetrating thoracic injuries, although occasionally blunt rupture of the heart, particularly the atrial appendage, is seen. Acutely, <100 mL of pericardial blood may cause pericardial tamponade. The classic diagnostic Beck's triad—dilated neck veins, muffled heart tones, and a decline in arterial pressure—often is not observed in the trauma bay because of the noisy environment and hypovolemia. Because the pericardium is not acutely distensible, the pressure in the pericardial sac will rise to match that of the injured chamber. When this pressure exceeds that of the right atrium, right atrial filling is impaired and right ventricular preload is reduced. This leads to decreased right ventricular output and increased CVP. Increased intrapericardial pressure also impedes myocardial blood flow, which leads to subendocardial ischemia and a further reduction in cardiac output.

Diagnosis is best achieved by bedside ultrasound of the pericardium (Fig. 7-9). Early in the course of tamponade, blood pressure and cardiac output will transiently improve with fluid administration. In patients with any hemodynamic disturbance, a pericardial drain is placed using ultrasound guidance (Fig. 7-10). Removing as little as 15 to 20 mL of blood will often temporarily stabilize the patient's hemodynamic status, prevent subendocardial ischemia and associated lethal arrhythmias, and allow transport to the OR for sternotomy. Pericardiocentesis is successful in decompressing tamponade in approximately 80% of cases; the majority of failures are due to the presence of clotted blood within the pericardium. Patients with a SBP <70 mmHg warrant emergency department thoracotomy (EDT) with opening of the pericardium to address the injury.

Fig. 7-9.



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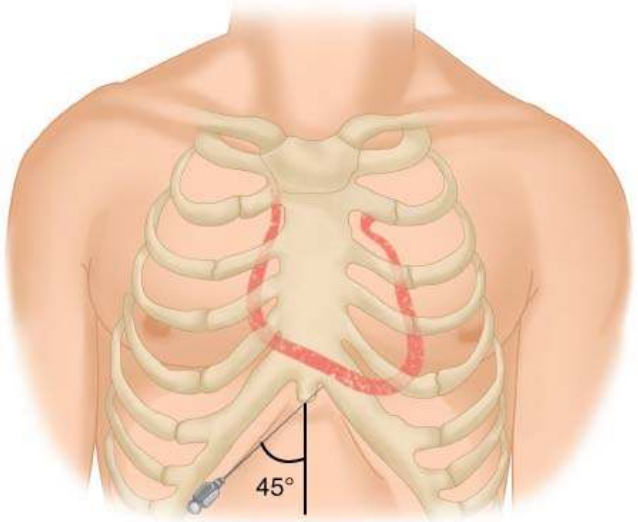
Subxiphoid pericardial ultrasound reveals a large pericardial fluid collection.

Fig. 7-10.



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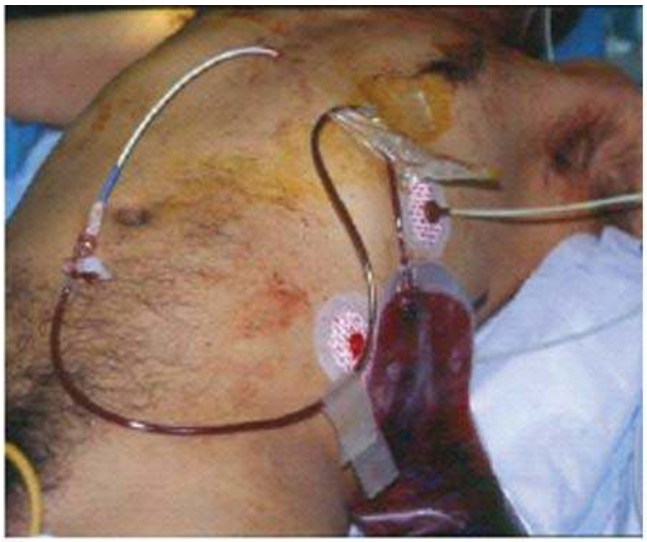

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Pericardiocentesis is indicated for patients with evidence of pericardial tamponade. **A.** Access to the pericardium is obtained through a subxiphoid approach, with the needle angled 45 degrees up from the chest wall and toward the left shoulder. **B.** Seldinger technique is used to place a pigtail catheter. Blood can be repeatedly aspirated with a syringe or the tubing may be attached to a gravity drain. Evacuation of unclotted pericardial blood prevents subendocardial ischemia and stabilizes the patient for transport to the operating room for sternotomy.

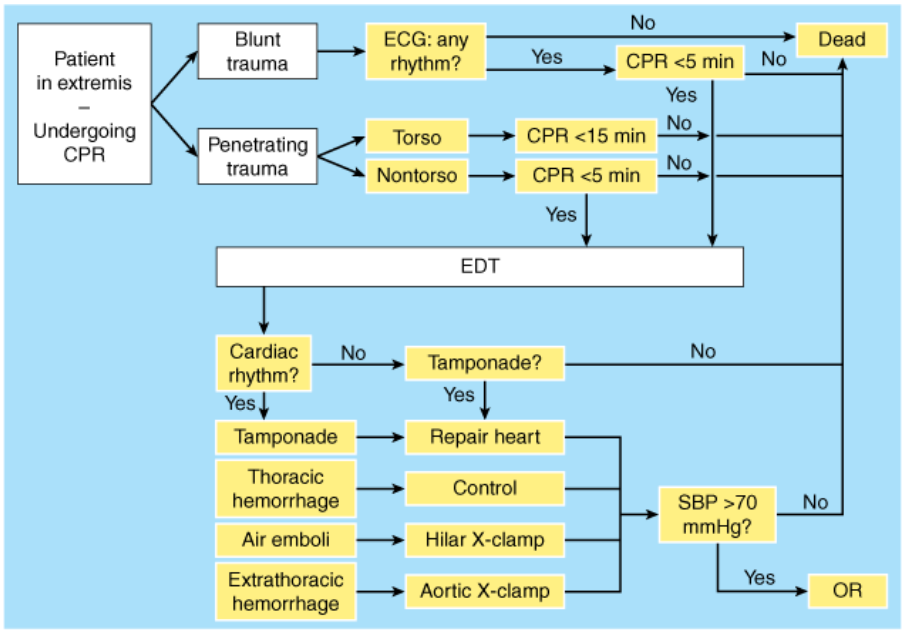
The utility of EDT has been debated for many years. Current indications are based on 30 years of prospective data (Table 7-2).[7] EDT is associated with the highest survival rate after isolated cardiac injury; 35% of patients presenting in shock and 20% without vital signs (i.e., pulse or obtainable blood pressure) are resuscitated after isolated penetrating injury to the heart. For all penetrating wounds, survival rate is 15%. Conversely, patient outcome is poor when EDT is done for blunt trauma, with 2% survival among patients in shock and <1% survival among those with no vital signs. Thus, patients undergoing cardiopulmonary resuscitation upon arrival to the ED should undergo EDT selectively based on injury and transport time (Fig. 7-11). EDT is best accomplished using a left anterolateral thoracotomy, with the incision started to the right of the sternum (Fig. 7-12). A longitudinal pericardiotomy anterior to the phrenic nerve releases cardiac tamponade and allows access to the heart for cardiac repair and open cardiac massage. Cross-clamping of the aorta sustains central circulation, augments cerebral and coronary blood flow, and limits any abdominal blood loss (Fig. 7-13). The patient must sustain an SBP of 70 mmHg after EDT and associated interventions to be considered resuscitatable and hence transported to the OR.[8]

Table 7-2 Current Indications and Contraindications for Emergency Department Thoracotomy

Indications
Salvageable postinjury cardiac arrest:
Patients sustaining witnessed penetrating trauma with <15 min of prehospital CPR
Patients sustaining witnessed blunt trauma with <5 min of prehospital CPR
Persistent severe postinjury hypotension (SBP ≤60 mmHg) due to:
Cardiac tamponade
Hemorrhage—intrathoracic, intra-abdominal, extremity, cervical
Air embolism
Contraindications
Penetrating trauma: CPR >15 min and no signs of life (pupillary response, respiratory effort, motor activity)
Blunt trauma: CPR >5 min and no signs of life or asystole

CPR = cardiopulmonary resuscitation; SBP = systolic blood pressure.

Fig. 7-11.



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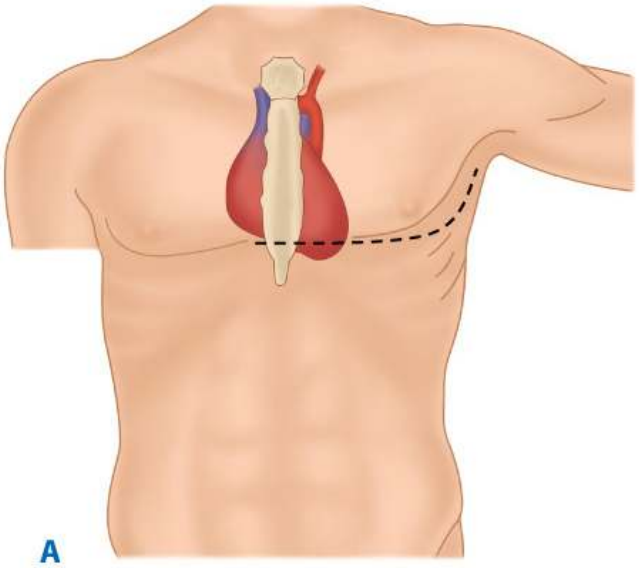
Algorithm directing the use of emergency department thoracotomy (EDT) in the injured patient undergoing cardiopulmonary resuscitation (CPR). ECG = electrocardiogram; OR = operating room; SBP = systolic blood pressure.

Fig. 7-12.



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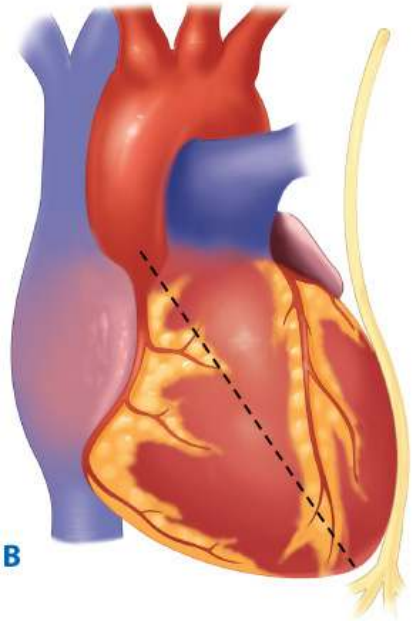

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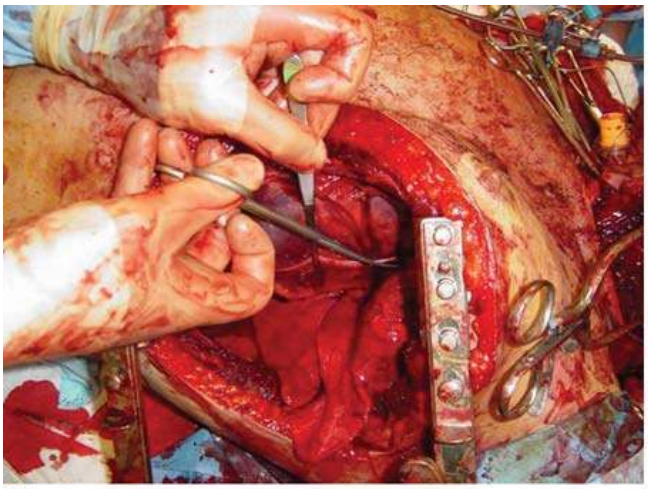

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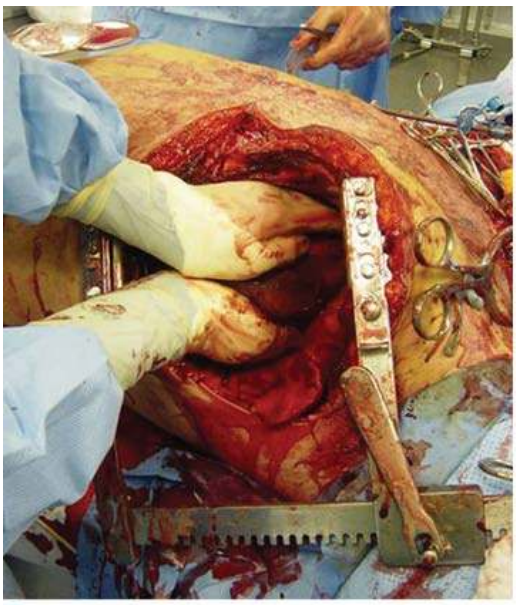

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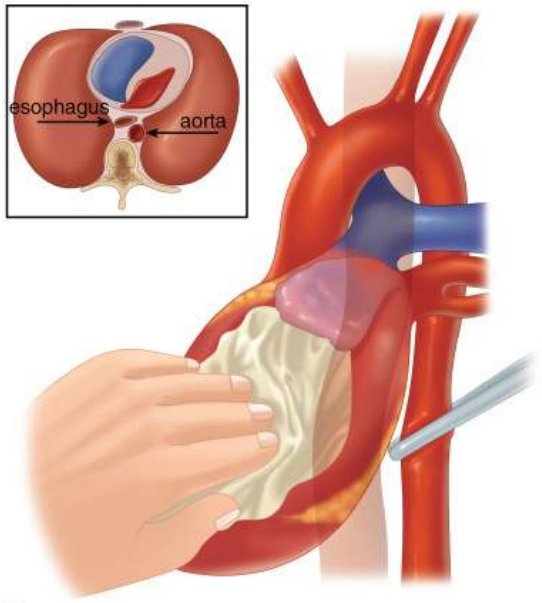
A. Emergency department thoracotomy is performed through the fifth intercostal space using the anterolateral approach. **B** and **C.** The pericardium is opened anterior to the phrenic nerve, and the heart is rotated out for repair. **D.** Open cardiac massage should be performed with a hinged, clapping motion of the hands, with sequential closing from palms to fingers. The two-handed technique is strongly recommended because the one-handed massage technique poses the risk of myocardial perforation with the thumb.

Fig. 7-13.



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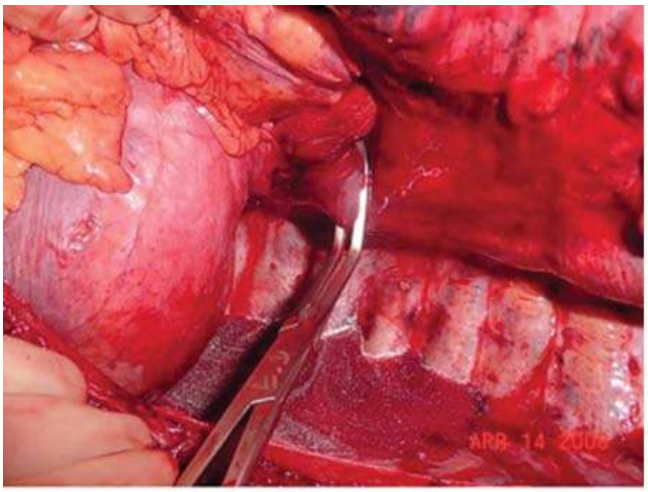

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Aortic cross-clamp is applied with the left lung retracted superiorly, below the inferior pulmonary ligament, just above the diaphragm. The flaccid aorta is identified as the first structure encountered on top of the spine when approached from the left chest.

DISABILITY AND EXPOSURE

The Glasgow Coma Scale (GCS) score should be determined for all injured patients (Table 7-3). It is calculated by adding the scores of the best motor response, best verbal response, and eye opening. Scores range from 3 (the lowest) to 15 (normal). Scores of 13 to 15 indicate mild head injury, 9 to 12 moderate injury, and <9 severe injury. The GCS is a quantifiable determination of neurologic function that is useful for both triage and prognosis.

Table 7-3 Glasgow Coma Scale[a]

		Adults	**Infants/Children**
Eye opening	4	Spontaneous	Spontaneous
	3	To voice	To voice
	2	To pain	To pain
	1	None	None
Verbal	5	Oriented	Alert, normal vocalization
	4	Confused	Cries but consolable

	3	Inappropriate words	Persistently irritable
	2	Incomprehensible words	Restless, agitated, moaning
	1	None	None
Motor response	6	Obeys commands	Spontaneous, purposeful
	5	Localizes pain	Localizes pain
	4	Withdraws	Withdraws
	3	Abnormal flexion	Abnormal flexion
	2	Abnormal extension	Abnormal extension
	1	None	None

[a] Score is calculated by adding the scores of the best motor response, best verbal response, and eye opening. Scores range from 3 (the lowest) to 15 (normal).

Neurologic evaluation before administration of neuromuscular blockade for intubation is critical. Subtle changes in mental status can be caused by hypoxia, hypercarbia, or hypovolemia, or may be an early sign of increasing intracranial pressure. An abnormal mental status should prompt an immediate re-evaluation of the ABCs and consideration of central nervous system injury. Deterioration in mental status may be subtle and may not progress in a predictable fashion. For example, previously calm, cooperative patients may become anxious and combative as they become hypoxic. However, a patient who is agitated and combative from drugs or alcohol may become somnolent if hypovolemic shock develops. Seriously injured patients must have all of their clothing removed to avoid overlooking limb- or life-threatening injuries.

SHOCK CLASSIFICATION AND INITIAL FLUID RESUSCITATION

Classic signs and symptoms of shock are tachycardia, hypotension, tachypnea, mental status changes, diaphoresis, and pallor (Table 7-4). The quantity of acute blood loss correlates with physiologic abnormalities. For example, although patients in class II shock may be tachycardic, they do not exhibit a reduction in blood pressure until over 1500 mL of blood loss, or class III shock. Physical findings should be viewed as a constellation and aid in the evaluation of the patient's response to treatment. The goal of fluid resuscitation is to re-establish tissue perfusion. Fluid resuscitation begins with a 2 L (adult) or 20 mL/kg (child) IV bolus of isotonic crystalloid, typically Ringer's lactate. For persistent hypotension, this is repeated once in an adult and twice in a child before red blood cells (RBCs) are administered. Patients who have a good response to fluid infusion (i.e., normalization of vital signs, clearing of the sensorium) and evidence of good peripheral perfusion (warm fingers and toes with normal capillary refill) are presumed to have adequate overall perfusion. Urine output is a quantitative, reliable indicator of organ perfusion. Adequate urine output is 0.5 mL/kg per hour in an adult, 1 mL/kg per hour in a child, and 2 mL/kg per hour in an infant <1 year of age. Because measurement of this resuscitation-related variable is time dependent, it is more useful in the OR and intensive care unit (ICU) setting than in initial evaluation in the trauma bay.

Table 7-4 Signs and Symptoms of Advancing Stages of Hemorrhagic Shock

	Class I	**Class II**	**Class III**	**Class IV**
Blood loss (mL)	Up to 750	750–1500	1500–2000	>2000
Blood loss (%BV)	Up to 15%	15–30%	30–40%	>40%
Pulse rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Urine output (mL/h)	>30	20–30	5–15	Negligible
CNS/mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic

BV = blood volume; CNS = central nervous system.

There are several caveats to be considered and pitfalls to be avoided when evaluating the injured patient for shock. Tachycardia is often the earliest sign of ongoing blood loss. However, individuals in good physical condition with a resting pulse rate in the fifties may manifest a relative tachycardia in the nineties; although clinically significant, this does not meet the standard definition of tachycardia. Conversely, patients receiving cardiac medications such as beta blockers may not be capable of increasing their heart rate despite significant stress. Bradycardia occurs with severe blood loss; this is an ominous sign, often heralding impending cardiovascular collapse. Other physiologic stresses, aside from hypovolemia, may produce tachycardia, such as hypoxia, pain, anxiety, and stimulant drugs (cocaine, amphetamines). As noted previously, hypotension is not a reliable early sign of hypovolemia, because blood volume must decrease by >30% before hypotension occurs. Additionally, younger patients with good sympathetic tone may surprise even the experienced clinician by maintaining SBP despite severe intravascular deficits until they are on the verge of cardiac arrest. Pregnant patients have a progressive increase in circulating blood volume over gestation; therefore, they must lose a relatively larger volume of blood before manifesting signs and symptoms of hypovolemia (see "Special Trauma Populations" below).

Based on the initial response to fluid resuscitation, hypovolemic injured patients can be separated into three broad categories: responders, transient responders, and nonresponders. Individuals who are stable or have a good response to the initial fluid therapy as evidenced by normalization of vital signs, mental status, and urine output are unlikely to have significant ongoing hemorrhage, and further diagnostic evaluation for occult injuries can proceed in an orderly fashion (see "Secondary Survey" below). At the other end of the spectrum are patients classified as "nonresponders" who have persistent hypotension despite aggressive resuscitation. These patients require immediate identification of the source of hypotension with appropriate intervention to prevent a fatal outcome. Patients considered as "transient responders" are those who respond initially to volume loading by an increase in blood pressure only to then hemodynamically deteriorate once more. This group of patients can be challenging to triage

for definitive management.

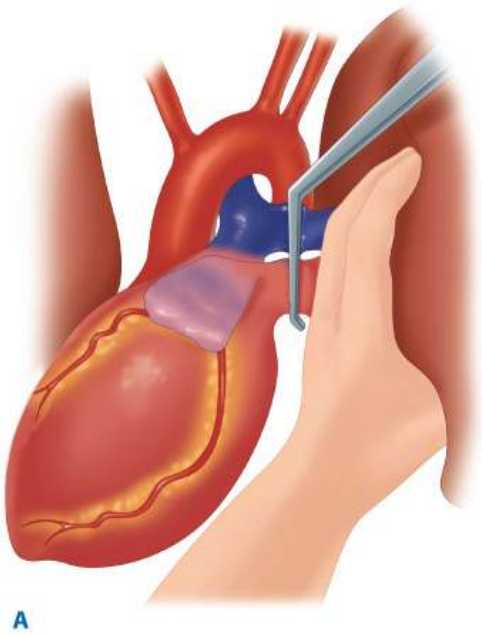
PERSISTENT HYPOTENSION

Patients with ongoing hemodynamic instability, whether "nonresponders" or "transient responders," require systematic evaluation and prompt intervention. The spectrum of disease in patients with persistent hypotension ranges from nonsurvivable multisystem injury to easily reversible problems such as a tension pneumothorax. One must first consider the four categories of shock that may be the underlying cause: hemorrhagic, cardiogenic, neurogenic, and septic. Except for patients transferred from outside facilities >12 hours after injury, few patients present in septic shock in the trauma bay. Patients with neurogenic shock as a component of hemodynamic instability often are recognized during the disability section of the primary survey to have paralysis, but those patients chemically paralyzed before physical examination may be misdiagnosed. In most cases, however, the two broad categories of shock causing persistent hypotension are hemorrhagic and cardiogenic. An evaluation of the CVP will usually distinguish between these two categories. A patient with flat neck veins and a CVP of <5 cm H_2O is hypovolemic and is likely to have ongoing hemorrhage. A patient with distended neck veins or a CVP of >15 cm H_2O is likely to be in cardiogenic shock. The CVP may be falsely elevated, however, if the patient is agitated and straining, or fluid administration is overzealous; isolated readings must be interpreted with caution. Serial base deficit measurements also are helpful; a persistent base deficit of >8 mmol/L implies ongoing cellular shock. Evolving technology, such as near infrared spectroscopy, will provide noninvasive monitoring of oxygen delivery to tissue.[9]

The differential diagnosis of cardiogenic shock in trauma patients is: (a) tension pneumothorax, (b) pericardial tamponade, (c) blunt cardiac injury, (d) myocardial infarction, and (e) bronchovenous air embolism. Tension pneumothorax, the most frequent cause of cardiac failure, and pericardial tamponade have been discussed earlier. Although as many as one third of patients sustaining significant blunt chest trauma experience blunt cardiac injury, few such injuries result in hemodynamic embarrassment. Patients with electrocardiographic (ECG) abnormalities or dysrhythmias require continuous ECG monitoring and antidysrhythmic treatment as needed. Unless myocardial infarction is suspected, there is no role for measurement of cardiac enzyme levels—they lack specificity and do not predict significant dysrhythmias.[10] The patient with hemodynamic instability requires aggressive resuscitation and may benefit from the placement of a pulmonary artery catheter to optimize preload and guide inotropic support. Echocardiography may be indicated to exclude pericardial tamponade or valvular or septal injuries. It typically demonstrates right ventricular dyskinesia but is less helpful in titrating treatment and monitoring the response to therapy unless done repeatedly. Patients with refractory cardiogenic shock may require placement of an intra-aortic balloon pump to decrease myocardial work and enhance coronary perfusion. Acute myocardial infarction may be the cause of a motor vehicle collision or other trauma in older patients. Although optimal initial management includes treatment for the evolving infarction, such as lytic therapy and emergent angioplasty, these decisions must be individualized in accordance with the patient's other injuries.

Air embolism is a frequently overlooked or undiagnosed lethal complication of pulmonary injury. Air emboli can occur after blunt or penetrating trauma, when air from an injured bronchus enters an adjacent injured pulmonary vein (bronchovenous fistula) and returns air to the left heart. Air accumulation in the left ventricle impedes diastolic filling, and during systole air is pumped into the coronary arteries, disrupting coronary perfusion. The typical case is a patient with a penetrating thoracic injury who is hemodynamically stable but experiences arrest after being intubated and placed on positive pressure ventilation. The patient should immediately be placed in Trendelenburg's position to trap the air in the apex of the left ventricle. Emergency thoracotomy is followed by cross-clamping of the pulmonary hilum on the side of the injury to prevent further introduction of air (Fig. 7-14). Air is aspirated from the apex of the left ventricle and the aortic root with an 18-gauge needle and 50-mL syringe. Vigorous massage is used to force the air bubbles through the coronary arteries; if this is unsuccessful, a tuberculin syringe may be used to aspirate air bubbles from the right coronary artery. Once circulation is restored, the patient should be kept in Trendelenburg's position with the pulmonary hilum clamped until the pulmonary venous injury is controlled operatively.

Fig. 7-14.



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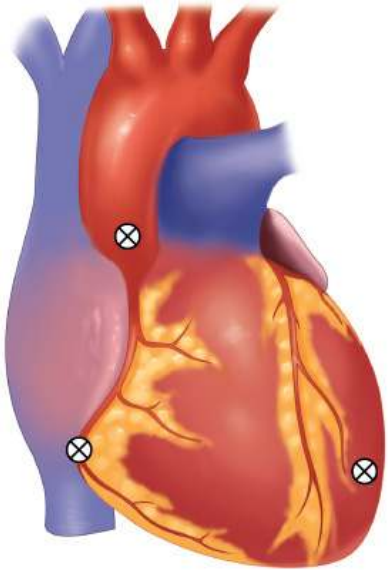

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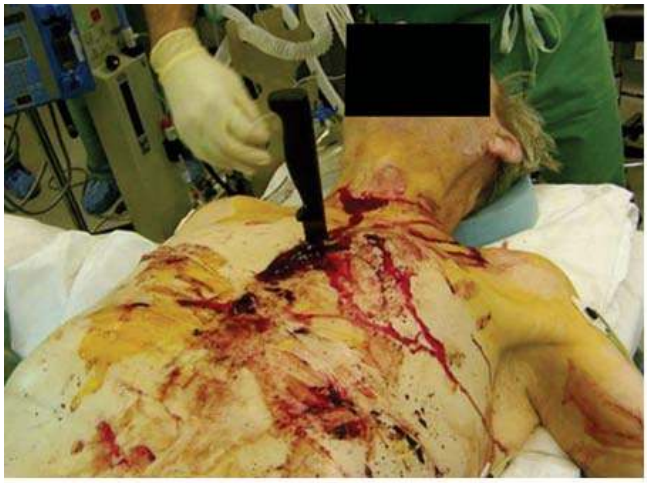
A. A Satinsky clamp is used to clamp the pulmonary hilum to prevent further bronchovenous air embolism. **B.** Sequential sites of aspiration include the left ventricle, the aortic root, and the right coronary artery.

Persistent hypotension due to uncontrolled hemorrhage is associated with high mortality. A rapid search for the source or sources of hemorrhage includes visual inspection with knowledge of the injury mechanism, FAST, and chest and pelvic radiographs. During diagnostic evaluation, type O RBCs (O-negative for women of childbearing age) and type-specific RBCs, when available, should be administered. In patients with penetrating trauma and clear indications for operation, essential films should be taken and the patient should be transported to the OR immediately. Such patients include those with massive hemothorax, those with initial chest tube output of >1 L with ongoing output of >200 mL/h, and those with abdominal trauma and ultrasound evidence of hemoperitoneum. In patients with gunshot wounds to the chest or abdomen, a chest and abdominal film, with radiopaque markers at the wound sites, should be obtained to determine the trajectory of the bullet or location of a retained fragment. For example, a patient with a gunshot wound to the upper abdomen should have a chest radiograph to ensure that the bullet did not traverse the diaphragm causing intrathoracic injury. Similarly, physical examination and chest radiograph of a patient with a gunshot wound to the right chest must evaluate the left hemithorax. If a patient has a penetrating weapon remaining in place, the weapon should *not* be removed in the ED, because it could be tamponading a lacerated blood vessel (Fig. 7-15). The surgeon should extract the offending instrument in the controlled environment of the OR, ideally once an incision has been made with adequate exposure. In situations

in which knives are embedded in the head or neck, preoperative imaging may be useful to exclude arterial injuries. Blunt trauma patients with clear operative indications include hypotensive patients with massive hemothorax and those with a FAST examination documenting extensive free intraperitoneal fluid.

Fig. 7-15.



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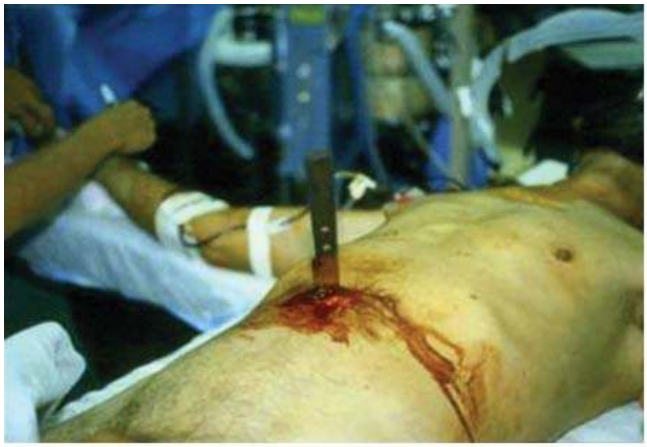

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If a weapon is still in place, it should be removed in the operating room, because it could be tamponading a lacerated blood vessel.

In patients without clear operative indications and persistent hypotension, one should systematically evaluate the five potential sources of blood loss: scalp, chest, abdomen, pelvis, and extremities. Significant bleeding at the scene may be noted by paramedics, but its quantification is unreliable. Examination should detect active bleeding from a scalp laceration that may be readily controlled with clips or staples. Thoracoabdominal trauma should be evaluated with a combination of chest radiograph, FAST, and pelvic radiograph. If the FAST results are negative and no other source of hypotension is obvious, diagnostic peritoneal aspiration should be entertained.[11] Extremity examination and radiographs should be used to search for associated fractures. Fracture-related blood loss, when additive, may be a potential source of the patient's hemodynamic instability. For each rib fracture there is approximately 100 to 200 mL of blood loss; for tibial fractures, 300 to 500 mL; for femur fractures, 800 to 1000 mL; and for pelvic fractures >1000 mL. Although no single injury may appear to cause a patient's hemodynamic instability, the sum of the injuries may result in life-threatening blood loss. The diagnostic measures advocated earlier are those that can be easily performed in the trauma bay. Transport of a hypotensive patient out of the ED for computed tomographic (CT) scanning may be hazardous; monitoring is compromised, and the environment is suboptimal for dealing with acute problems. The surgeon must accompany the patient and be prepared to abort the CT scan with direct transport to the OR. This dilemma is becoming less common in large trauma centers where CT scanning can be accomplished in the ED.

The role of treatment of hypotension in the ED remains controversial, and it is primarily relevant for patients with penetrating vascular injuries. Experimental work suggests that an endogenous sealing clot of an injured artery may be disrupted at an SBP of >90 mmHg[12] ; thus, many believe that this should be the preoperative blood pressure target for patients with torso arterial injuries. On the other hand, optimal management of traumatic brain injury (TBI) includes maintaining the SBP at >90 mmHg.[13]

Secondary Survey

Once the immediate threats to life have been addressed, a thorough history is obtained and the patient is examined in a systematic fashion. The patient and surrogates should be queried to obtain an AMPLE history (*A*llergies, *M*edications, *P*ast illnesses or Pregnancy, *L*ast meal, and *E*vents related to the injury). The physical examination

should be head to toe, with special attention to the patient's back, axillae, and perineum, because injuries here are easily overlooked. All potentially seriously injured patients should undergo digital rectal examination to evaluate for sphincter tone, presence of blood, rectal perforation, or a high-riding prostate; this is particularly critical in patients with suspected spinal cord injury, pelvic fracture, or transpelvic gunshot wounds. Vaginal examination with a speculum also should be performed in women with pelvic fractures to exclude an open fracture. Specific injuries, their associated signs and symptoms, diagnostic options, and treatments are discussed in detail later in this chapter.

Adjuncts to the physical examination include vital sign and CVP monitoring, ECG monitoring, nasogastric tube placement, Foley catheter placement, repeat FAST, laboratory measurements, and radiographs. A nasogastric tube should be inserted in all intubated patients to decrease the risk of gastric aspiration but may not be indicated in the awake patient. Nasogastric tube placement in patients with complex facial fractures is contraindicated; rather, a tube should be placed orally if required. Nasogastric tube evaluation of stomach contents for blood may suggest occult gastroduodenal injury or the path of the nasogastric tube on a chest film may suggest a diaphragm injury. A Foley catheter should be inserted in patients unable to void to decompress the bladder, obtain a urine specimen, and monitor urine output. Gross hematuria demands evaluation of the genitourinary system for injury. Foley catheter placement should be deferred until urologic evaluation in patients with signs of urethral injury: blood at the meatus, perineal or scrotal hematomas, or a high-riding prostate. Although policies vary at individual institutions, patients in extremis with need for Foley catheter placement should undergo one attempt at catheterization; if the catheter does not pass easily, a percutaneous suprapubic cystostomy should be considered. Repeat FAST is performed if there are any signs of abdominal injury or occult blood loss.

Selective radiography and laboratory tests are done early in the evaluation after the primary survey. For patients with severe blunt trauma, lateral cervical spine, chest, and pelvic radiographs should be obtained, often termed *the big three.* For patients with truncal gunshot wounds, anteroposterior and lateral radiographs of the chest and abdomen are warranted. It is important to mark the entrance and exit sites of penetrating wounds with ECG pads, metallic clips, or staples so that the trajectory of the missile can be estimated. Limited one-shot extremity radiographs also may be taken. In critically injured patients, blood samples for a routine trauma panel (type and cross-match, complete blood count, blood chemistries, coagulation studies, lactate level, and arterial blood gas analysis) should be sent to the laboratory. For less severely injured patients only a complete blood count and urinalysis may be required. Because older patients may present in subclinical shock, even with minor injuries, routine analysis of arterial blood gases in patients over the age of 55 should be considered.

Many trauma patients cannot provide specific information about the mechanism of their injury. Emergency medical service personnel and police are trained to evaluate an injury scene and should be questioned. For automobile collisions, the speed of the vehicles involved, angle of impact (if any), use of restraints, airbag deployment, condition of the steering wheel and windshield, amount of intrusion, ejection or nonejection of the patient from the vehicle, and fate of other passengers should all be ascertained. For other injury mechanisms, critical information includes such things as height of a fall, surface impact, helmet use, and weight of an object by which the patient was crushed. In patients sustaining gunshot wounds, velocity, caliber, and presumed path of the bullet are important, if known. For patients with stab wounds, the length and type of object is helpful. Finally, some patients experience a combination of blunt and penetrating trauma. Do not assume that someone who was stabbed was not also assaulted; the patient may have a multitude of injuries and cannot be presumed to have only injuries associated with the more obvious penetrating mechanism. In sum, these details of information are critical to the clinician to determine overall mechanism of injury and anticipate its associated injury patterns.

Mechanisms and Patterns of Injury

In general, more energy is transferred over a wider area during blunt trauma than from a gunshot or stab wound. As a result, blunt trauma is associated with multiple widely distributed injuries, whereas in penetrating wounds the damage is localized to the path of the bullet or knife. In blunt trauma, organs that cannot yield to impact by elastic deformation are most likely to be injured, namely, the solid organs (liver, spleen, and kidneys). For penetrating trauma, organs with the largest surface area when viewed from the front are most prone to injury (small bowel, liver, and colon). Additionally, because bullets and knives usually follow straight lines, adjacent structures are commonly injured (e.g., the pancreas and duodenum).

Trauma surgeons often separate patients who have sustained blunt trauma into categories according to their risk for multiple injuries: those sustaining high energy transfer injuries and those sustaining low energy transfer injuries. Injuries involving high energy transfer include auto-pedestrian accidents, motor vehicle collisions in which the car's change of velocity (ΔV) exceeds 40 km/h or in which the patient has been ejected, motorcycle collisions, and falls from heights >20 ft.[14] In fact, for motor vehicle accidents the variables strongly associated with life-threatening injuries, and hence reflective of the magnitude of the mechanism, are death of another occupant in the vehicle, extrication time of >20 minutes, ΔV >40 km/h, lack of restraint use, and lateral impact.[14] Low-energy trauma, such as being struck with a club or falling from a bicycle, usually does not result in widely distributed injuries. However, potentially lethal lacerations of internal organs still can occur, because the net energy transfer to any given location may be substantial.

In blunt trauma, particular constellations of injury or injury patterns are associated with specific injury mechanisms. Frontal impact collisions typically produce multisystem trauma. When an unrestrained driver sustains a frontal impact, the head strikes the windshield, the chest and upper abdomen hit the steering column, and the legs or knees contact the dashboard. The resultant injuries can include facial fractures, cervical spine fractures, laceration of the thoracic aorta, myocardial contusion, injury to the spleen and liver, and fractures of the pelvis and lower extremities. When such patients are evaluated, the discovery of one of these injuries should prompt a search for others. Collisions with side impact also carry the risk of cervical spine and thoracic trauma, diaphragm rupture, and crush injuries of the pelvic ring, but solid organ injury usually is limited to either the liver or spleen based on the direction of impact. Not surprisingly, any time a patient is ejected from the vehicle or thrown a significant distance from a motorcycle, the risk of any injury increases.

Penetrating injuries are classified according to the wounding agent (i.e., stab wound, gunshot wound, or shotgun wound). Gunshot wounds are subdivided further into high- and low-velocity injuries, because the speed of the bullet is much more important than its weight in determining kinetic energy. High-velocity gunshot wounds (bullet speed >2000 ft/s) are infrequent in the civilian setting. Shotgun injuries are divided into close-range (<7 m) and long-range wounds. Close-range shotgun wounds are tantamount

to high-velocity wounds because the entire energy of the load is delivered to a small area, often with devastating results. Long-range shotgun blasts result in a diffuse pellet pattern in which many pellets miss the victim, and those that do strike are dispersed and of comparatively low energy.

Regional Assessment and Special Diagnostic Tests

Based on mechanism, location of injuries identified on physical examination, screening radiographs, and the patient's overall condition, additional diagnostic studies often are indicated. However, the seriously injured patient is in constant jeopardy when undergoing special diagnostic testing; therefore, the surgeon must be in attendance and must be prepared to alter plans as circumstances demand. Hemodynamic, respiratory, and mental status will determine the most appropriate course of action. With these issues in mind, additional diagnostic tests are discussed on an anatomic basis.

HEAD

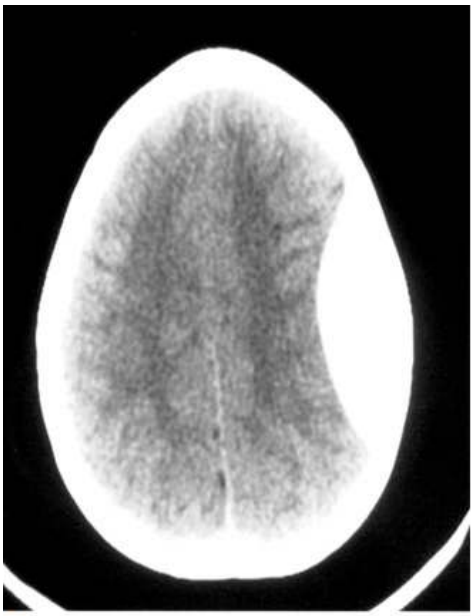
Evaluation of the head includes examination for injuries to the scalp, eyes, ears, nose, mouth, facial bones, and intracranial structures. Palpation of the head will identify scalp lacerations, which should be evaluated for depth, and depressed or open skull fractures. The eye examination includes not only pupillary size and reactivity, but also examination for visual acuity and for hemorrhage within the globe. Ocular entrapment, caused by orbital fractures with impingement on the ocular muscles, is evident when the patient cannot move his or her eyes through the entire range of motion. It is important to perform the eye examination early, because significant orbital swelling may prevent later evaluation. The tympanic membrane is visualized to identify hemotympanum, otorrhea, or rupture, which may signal an underlying head injury. Otorrhea, rhinorrhea, raccoon eyes, and Battle's sign (ecchymosis behind the ear) suggest a basilar skull fracture. Although such fractures may not require treatment, there is an association with blunt cerebrovascular injuries and a small risk of development of meningitis.

Anterior facial structures should be examined to rule out fractures. This entails palpating for bony step-off of the facial bones and instability of the midface (by grasping the upper palate and seeing if this moves separately from the patient's head). A good question to ask awake patients is whether their bite feels normal to them; abnormal dental closure suggests malalignment of facial bones and a possibility for a mandible or maxillary fracture. Nasal fractures, which may be evident on direct inspection or palpation, typically bleed vigorously. This may result in the patient's having airway compromise due to blood running down the posterior pharynx, or there may be vomiting provoked by swallowed blood. Nasal packing or balloon tamponade may be necessary to control bleeding. Examination of the oral cavity includes inspection for open fractures, loose or fractured teeth, and sublingual hematomas.

All patients with a significant closed head injury (GCS score <14) should undergo CT scanning of the head. For penetrating injuries, plain skull films may be helpful in the trauma bay to determine the extent of injury in hemodynamically unstable patients who cannot be transported for CT scan. The presence of lateralizing findings (e.g., a unilateral dilated pupil unreactive to light, asymmetric movement of the extremities either spontaneously or in response to noxious stimuli, or unilateral Babinski's reflex) suggests an intracranial mass lesion or major structural damage.

Such lesions include hematomas, contusions, hemorrhage into ventricular and subarachnoid spaces, and diffuse axonal injury (DAI). Epidural hematomas occur when blood accumulates between the skull and dura, and are caused by disruption of the middle meningeal artery or other small arteries in that potential space, typically after a skull fracture (Fig. 7-16). Subdural hematomas occur between the dura and cortex and are caused by venous disruption or laceration of the parenchyma of the brain. Due to associated parenchymal injury, subdural hematomas typically have a worse prognosis than epidural collections. Hemorrhage into the subarachnoid space may cause vasospasm and reduce cerebral blood flow. Intraparenchymal hematomas and contusions can occur anywhere within the brain. DAI results from high-speed deceleration injury and represents direct axonal damage. CT scan may demonstrate blurring of the gray and white matter interface and multiple small punctate hemorrhages, but magnetic resonance imaging is a more sensitive test. Although prognosis for these injuries is extremely variable, early evidence of DAI is associated with a poor outcome. Stroke syndromes should prompt a search for carotid or vertebral artery injury using standard four-vessel angiography or 16-slice CT angiography (Fig. 7-17).

Fig. 7-16.



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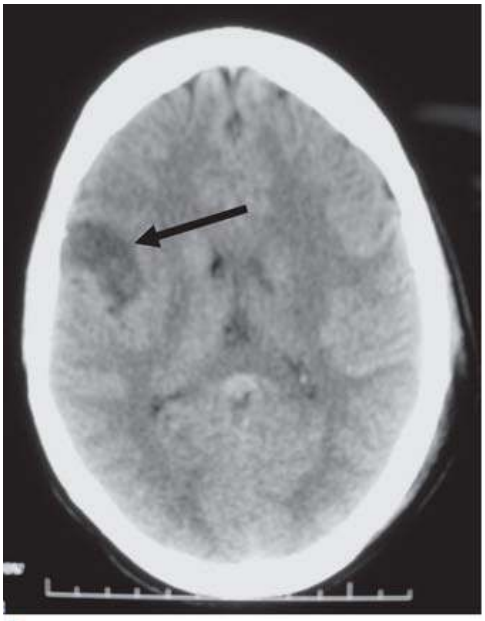
Epidural hematomas (**A**) have a distinctive convex shape on computed tomographic scan, whereas subdural hematomas (**B**) are concave along the surface of the brain.

Fig. 7-17.



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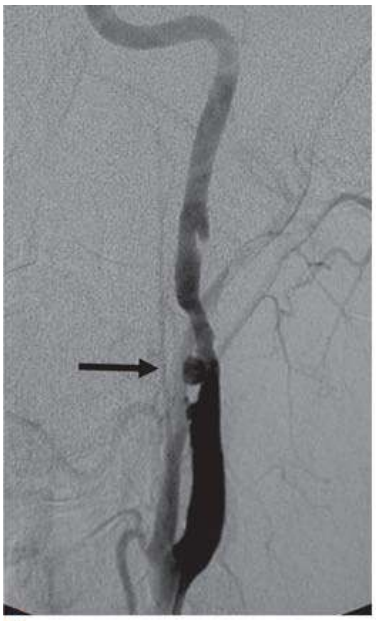

B

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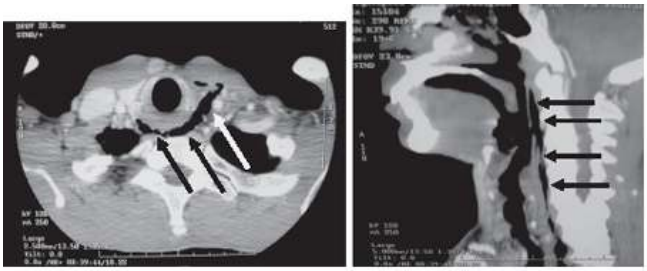
A. A right middle cerebral infarct noted on a computed tomographic scan of the head. Such a finding should prompt imaging to rule out an associated extracranial cerebrovascular injury. **B.** An internal carotid artery pseudoaneurysm documented by angiography.

Significant intracranial penetrating injuries usually are produced by bullets from handguns, but an array of other weapons or instruments can injure the cerebrum via the orbit or through the thinner temporal region of the skull. Although the diagnosis usually is obvious, in some instances wounds in the auditory canal, mouth, and nose can be elusive. Prognosis is variable, but most supratentorial wounds that injure both hemispheres are fatal.

NECK

All blunt trauma patients should be assumed to have cervical spine injuries until proven otherwise. During cervical examination one must maintain cervical spine precautions and in-line stabilization. During the primary survey, identification of penetrating injuries to the neck with exsanguination, expanding hematomas, and airway obstruction is a priority. A more subtle injury that may not be identified is a fracture of the larynx due to blunt trauma. Signs and symptoms include hoarseness, subcutaneous emphysema (Fig. 7-18), and a palpable fracture.

Fig. 7-18.



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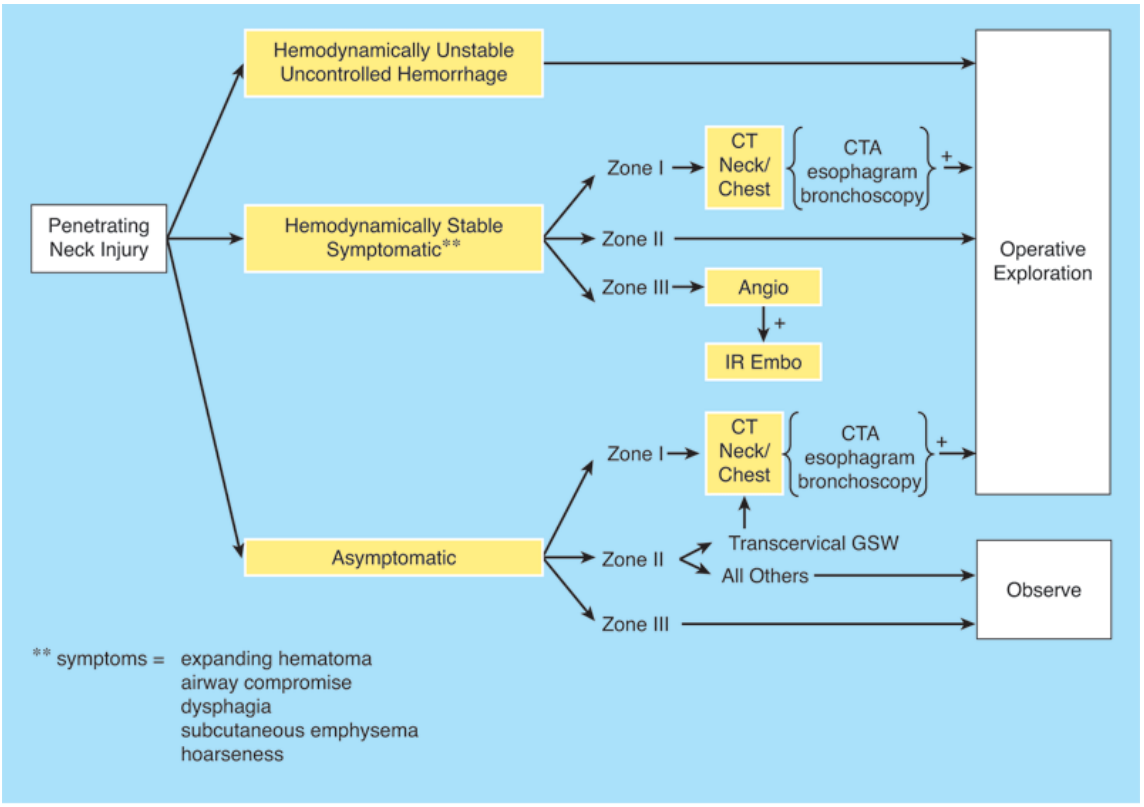
A laryngeal fracture results in air tracking around the trachea along the prevertebral space (*arrows*).

Due to the devastating consequences of quadriplegia, a diligent evaluation for occult cervical spine injuries is mandatory. In the awake patient, the presence of posterior midline pain or tenderness should provoke a thorough radiologic evaluation. Additionally, intubated patients, patients experiencing trauma associated with significant injury mechanisms, and patients with distracting injuries or another identified spine fracture should undergo imaging. Imaging options include CT scan or five plain radiograph views of the cervical spine: lateral view with visualization of C7 through T1, anteroposterior view, transoral odontoid views, and bilateral oblique views. If pain or tenderness persists but no injuries are identified on plain radiographs, or if the patient cannot be examined in a timely manner, a CT scan should be performed. However, a ligamentous injury may not be visible with standard imaging techniques.[15] Flexion and extension views are typically obtained after a delay in patients with persistent pain but negative imaging findings. However, this should be done only in the presence of an experienced spinal surgeon, because patients can be rendered permanently quadriplegic when flexed and extended by inexperienced individuals.

Spinal cord injuries can be complete or partial. Complete injuries cause either permanent quadriplegia or paraplegia, depending on the level of injury. These patients have a complete loss of motor function and sensation two or more levels below the bony injury. Patients with high spinal cord disruption are at risk for shock due to physiologic disruption of sympathetic fibers. Significant neurologic recovery is rare. There are several partial or incomplete spinal cord injury syndromes. Central cord syndrome usually occurs in older persons who experience hyperextension injuries. Motor function and pain and temperature sensation are preserved in the lower extremities but diminished in the upper extremities. Some functional recovery usually occurs, but is often not a return to normal. Anterior cord syndrome is characterized by diminished motor function and pain and temperature sensation below the level of the injury, but position sensing, vibratory sensation, and crude touch are maintained. Prognosis for recovery is poor. Brown-Séquard syndrome is usually the result of a penetrating injury in which the right or left half of the spinal cord is transected. This rare lesion is characterized by the ipsilateral loss of motor function, proprioception, and vibratory sensation, whereas pain and temperature sensation are lost on the contralateral side.

Penetrating injuries of the anterior neck that violate the platysma are potentially life-threatening because of the density of critical structures in this region. Although presumptive exploration may be appropriate in some circumstances, selective nonoperative management is practiced in most centers (Fig. 7-19).[16,17] Indications for immediate operative intervention for penetrating cervical injury include hemodynamic instability or significant external hemorrhage. The management algorithm for hemodynamically stable patients is based on the presenting symptoms and anatomic location of injury, with the neck being divided into three distinct zones (Fig. 7-20). Zone I is between the clavicles and cricoid cartilage, zone II is between the cricoid cartilage and the angle of the mandible, and zone III is above the angle of the mandible. Due to technical difficulties of injury exposure and varying operative approaches, a precise preoperative diagnosis is desirable for symptomatic zone I and III injuries. Therefore, these patients should ideally undergo diagnostic imaging before operation if they remain hemodynamically stable. CT scanning of the neck and chest determines the injury track, and further studies are performed based on proximity to major structures.[18] Such additional imaging includes CT angiography, angiography of the great vessels, soluble contrast esophagram followed by barium esophagram, esophagoscopy, or bronchoscopy. Angiographic diagnosis, particularly of zone III injuries, may be followed by endovascular intervention for definitive treatment.

Fig. 7-19.



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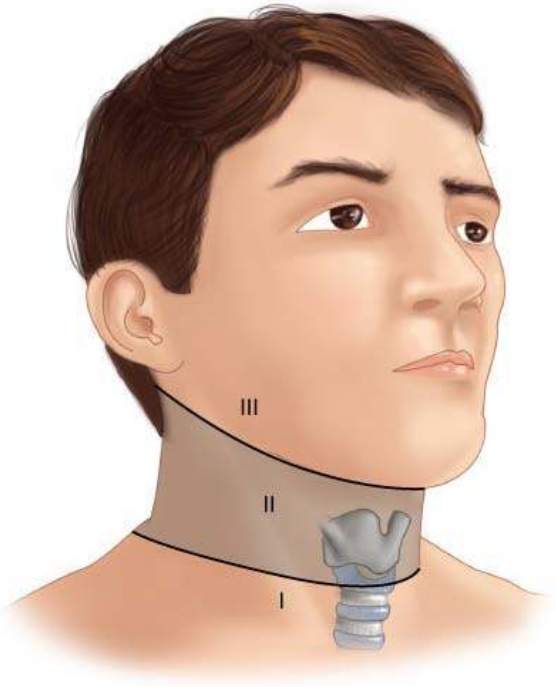
Algorithm for the selective management of penetrating neck injuries. CT = computed tomography; CTA = computed tomographic angiography; GSW = gunshot wound; IR Embo = interventional radiology embolization.

Fig. 7-20.



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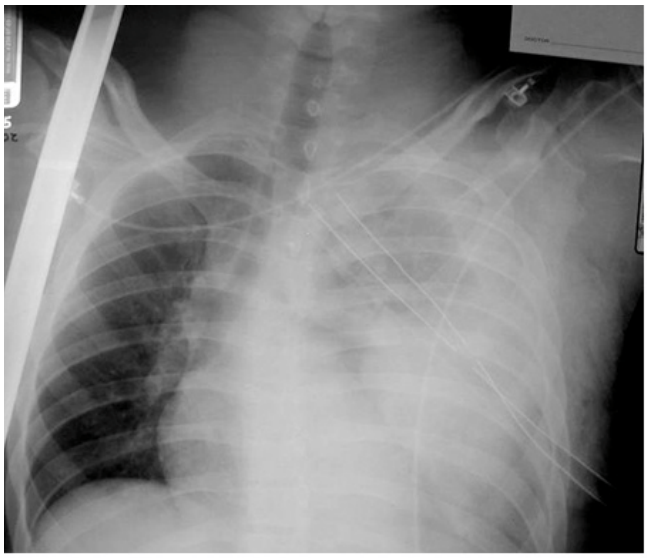
For the purpose of evaluating penetrating injuries, the neck is divided into three zones. Zone I is up to the level of the cricoid and is also known as the *thoracic outlet.* Zone II is located between the cricoid cartilage and the angle of the mandible. Zone III is above the angle of the mandible.

Patients with zone II wounds that do not penetrate the platysma can be discharged from the ED. Patients with zone II penetrating wounds are divided into those who are symptomatic and those who are not. Specific symptoms that should be elucidated include airway compromise, an expanding or pulsatile hematoma, dysphagia, hoarseness, and subcutaneous emphysema. Symptomatic patients should undergo emergent neck exploration. Asymptomatic patients with zone II injuries should be further divided into those with and those without a transcervical gunshot wound. Those without a transcervical component may be observed for 12 to 24 hours, whereas those with transcervical gunshot wounds should undergo CT scanning to determine the track of the bullet. Based on location of the track and transfer of kinetic injury, further diagnostic imaging with angiography, esophagram, or bronchoscopy should be performed.

CHEST

Blunt trauma to the chest may involve the chest wall, thoracic spine, heart, lungs, thoracic aorta and great vessels, and rarely the esophagus. Most of these injuries can be evaluated by physical examination and chest radiography, with supplemental CT scanning based on initial findings. Any patient who undergoes intervention—intubation, central line placement, tube thoracostomy—needs a repeat chest radiograph to document the adequacy of the procedure. This is particularly true in patients undergoing tube thoracostomy for a pneumothorax or hemothorax. Patients with persistent pneumothorax, large air leaks after tube thoracostomy, or difficulty ventilating should undergo fiber-optic bronchoscopy to exclude a bronchial injury or presence of a foreign body. Patients with hemothorax must have a chest radiograph documenting complete evacuation of the chest; a persistent hemothorax that is not drained by two chest tubes is termed a *caked hemothorax* and mandates prompt thoracotomy (Fig. 7-21).

Fig. 7-21.



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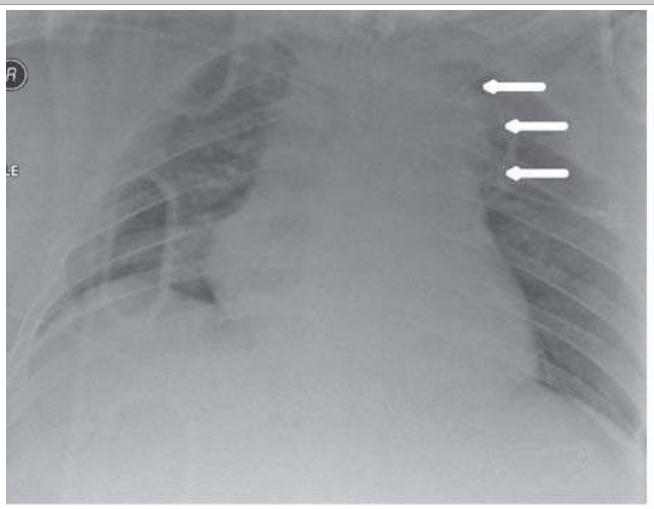
Persistence of a hemothorax despite two tube thoracostomies is termed a *caked hemothorax* and is an indication for prompt thoracotomy.

Occult thoracic vascular injury must be diligently sought due to the high mortality of a missed lesion. Widening of the mediastinum on initial anteroposterior chest radiograph, caused by a hematoma around an injured vessel that is contained by the mediastinal pleura, suggests an injury of the great vessels. The mediastinal abnormality may suggest the location of the arterial injury (i.e., left-sided hematomas are associated with descending torn aortas, whereas right-sided hematomas are commonly seen with innominate injuries) (Fig. 7-22). Posterior rib fractures, sternal fractures, and laceration of small vessels also can produce similar hematomas. Other chest radiographic findings suggestive of an aortic tear are summarized in Table 7-5 (Fig. 7-23). However, at least 7% of patients with a descending torn aorta have a normal chest radiograph.[19] Therefore, screening spiral CT scanning is performed based on the mechanism of injury: high-energy deceleration motor vehicle collision with frontal or lateral impact, motor vehicle collision with ejection, falls of >25 ft, or direct impact (horse kick to chest, snowmobile or ski collision with tree).[20] In >95% of patients who survive to reach the ED, the aortic injury occurs just distal to the left subclavian artery, where it is tethered by the ligamentum arteriosum (Fig. 7-24). In 2 to 5% of patients the injury occurs in the ascending aorta, in the transverse arch, or at the diaphragm. Reconstructions with multislice CT scanning obviate the need for invasive angiography.[20]

Fig. 7-22.



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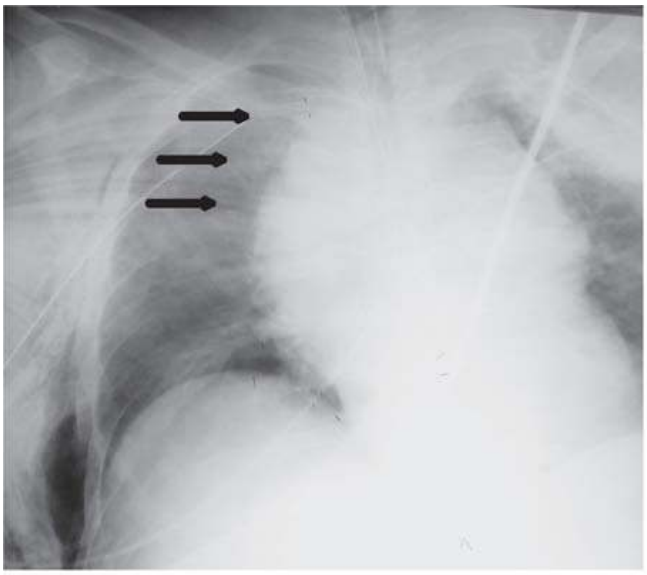

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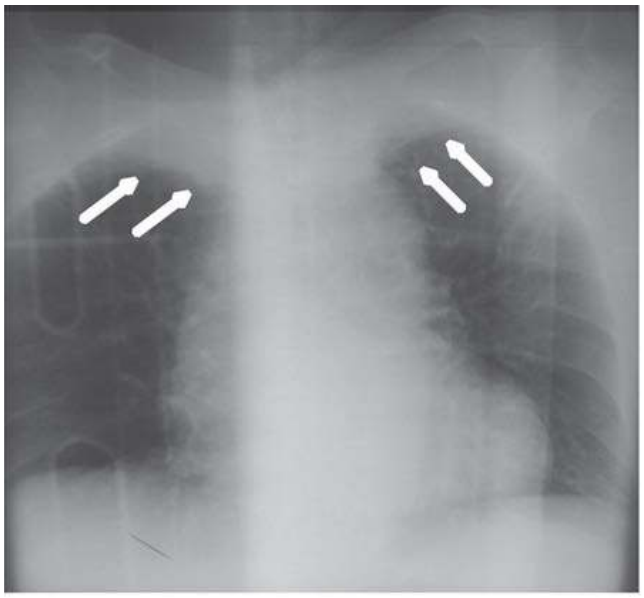
Location of the hematoma within the mediastinal silhouette suggests the type of great vessel injury. A predominant hematoma on the left suggests the far more common descending torn aorta (**A;***arrows*), whereas a hematoma on the right indicates a relatively unusual but life-threatening innominate artery injury (**B;***arrows*).

Table 7-5 Findings on Chest Radiograph Suggestive of a Descending Thoracic Aortic Tear
1. Widened mediastinum
2. Abnormal aortic contour
3. Tracheal shift
4. Nasogastric tube shift
5. Left apical cap
6. Left or right paraspinal stripe thickening
7. Depression of the left main bronchus
8. Obliteration of the aorticopulmonary window
9. Left pulmonary hilar hematoma

Fig. 7-23.



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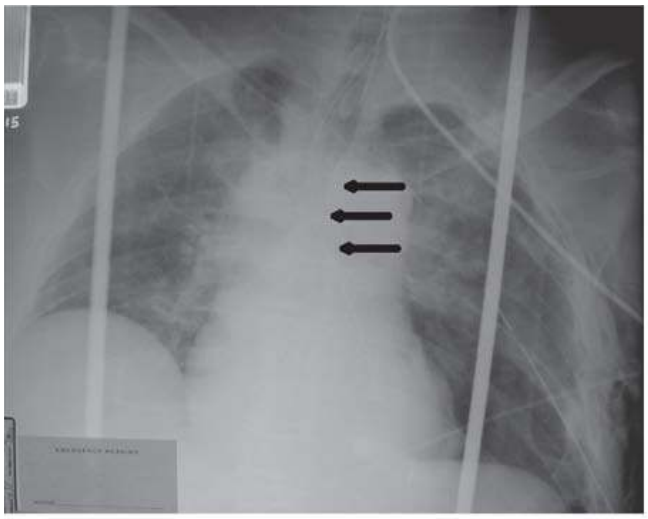

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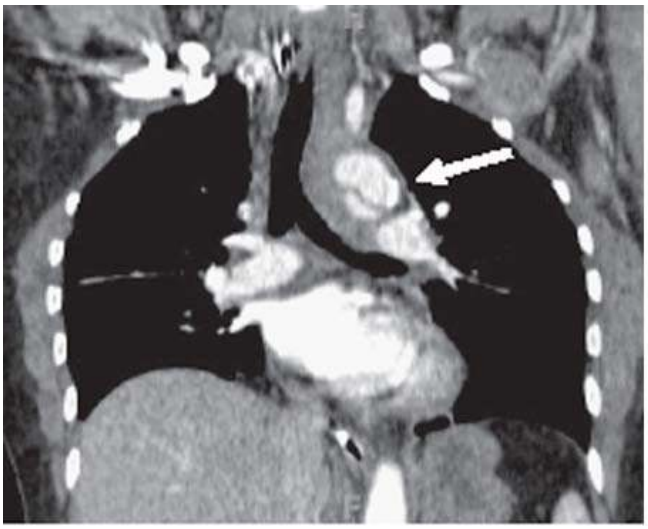
Chest film findings associated with descending torn aorta include apical capping (**A;***arrows*) and tracheal shift (**B;***arrows*).

Fig. 7-24.



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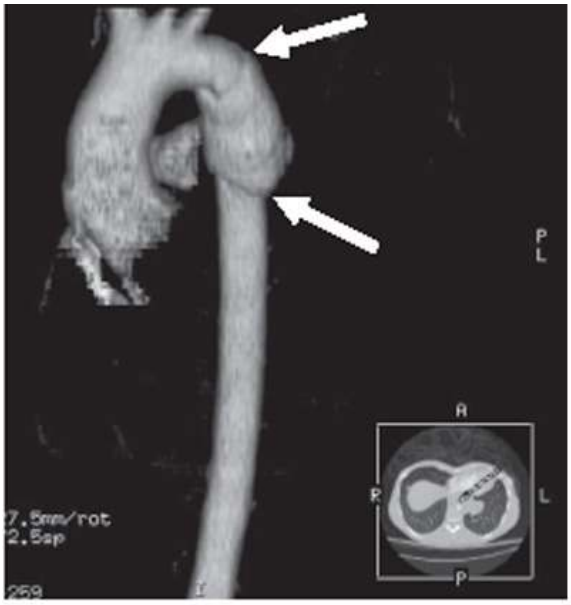

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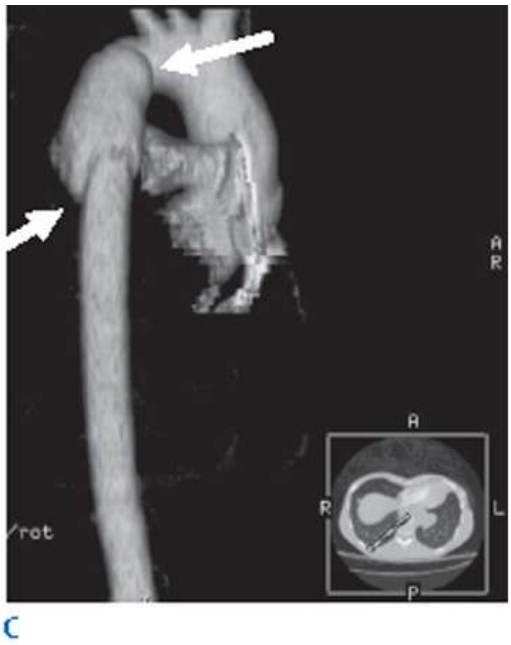

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Imaging to diagnose descending torn aorta includes computed tomographic angiography (**A**), with three-dimensional reconstructions (**B,** anterior; **C,** posterior) demonstrating the proximal and distal extent of the injury (*arrows*).

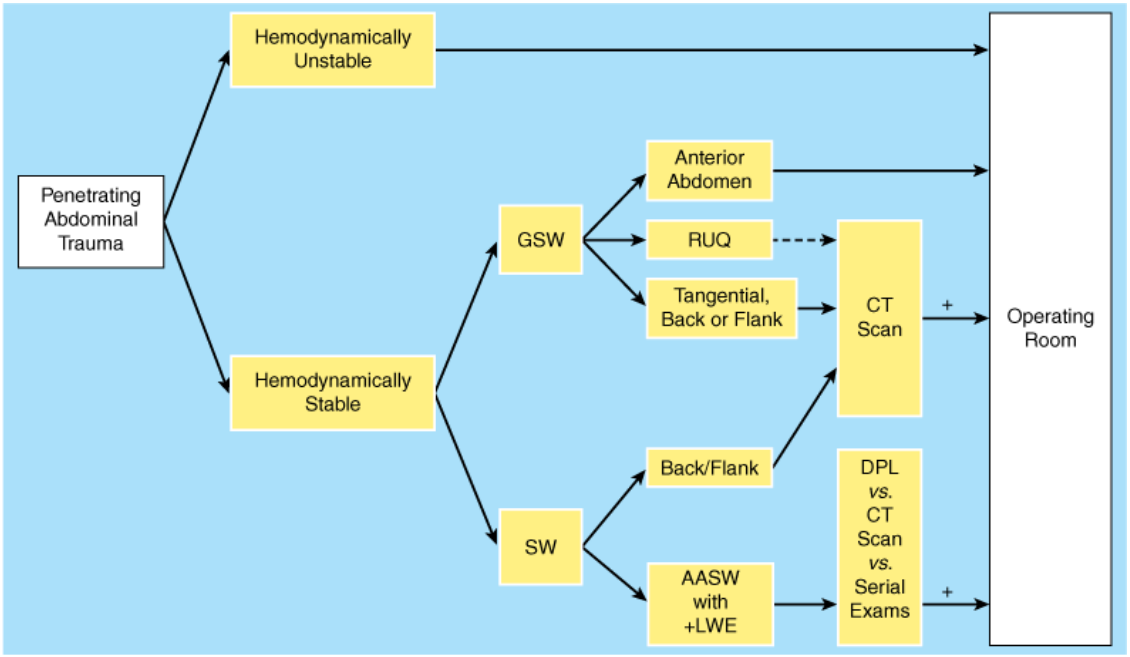
For penetrating thoracic trauma physical examination, plain posteroanterior and lateral chest radiographs with metallic markings of entrance and exit wounds, pericardial ultrasound, and CVP measurement will identify the majority of injuries. Injuries of the esophagus and trachea are exceptions. Bronchoscopy should be performed to evaluate the trachea in patients with a persistent air leak from the chest tube or mediastinal air. Because esophagoscopy can miss injuries, patients at risk should undergo soluble contrast esophagraphy followed by barium examination to look for extravasation of contrast to identify an injury.[21] As with neck injuries, hemodynamically stable patients with transmediastinal gunshot wounds should undergo CT scanning to determine the path of the bullet; this identifies the vascular or visceral structures at risk for injury and directs angiography or endoscopy as appropriate. If there is a suspicion of a subclavian artery injury, brachial-brachial indices should be measured, but >60% of patients with an injury may not have a pulse deficit.[22] Therefore, CT angiography should be performed based on injury proximity to intrathoracic vasculature. Finally, despite entry wounds on the chest, penetrating trauma should not be presumed to be isolated to the thorax. Injury to contiguous body cavities (i.e., the abdomen and neck) must be excluded.

ABDOMEN

The abdomen is a diagnostic black box. Fortunately, with few exceptions, it is not necessary to determine in the ED which intra-abdominal organs are injured, only whether an exploratory laparotomy is necessary. Physical examination of the abdomen is unreliable in making this determination, and drugs, alcohol, and head and spinal cord injuries complicate clinical evaluation. However, the presence of abdominal rigidity or hemodynamic compromise is an indication for prompt surgical exploration. For the remainder of patients, a variety of diagnostic adjuncts are used to identify abdominal injury.

The diagnostic approach differs for penetrating trauma and blunt abdominal trauma. As a rule, minimal evaluation is required before laparotomy for gunshot or shotgun wounds that penetrate the peritoneal cavity, because over 90% of patients have significant internal injuries. Anterior truncal gunshot wounds between the fourth intercostal space and the pubic symphysis whose trajectory as determined by radiograph or entrance and exit wounds indicates peritoneal penetration should be operatively explored (Fig. 7-25). The exception is penetrating trauma isolated to the right upper quadrant; in hemodynamically stable patients with bullet trajectory confined to the liver by CT scan, nonoperative observation may be considered.[23,24] Gunshot wounds to the back or flank are more difficult to evaluate because of the retroperitoneal location of the injured abdominal organs. Triple-contrast CT scan can delineate the trajectory of the bullet and identify peritoneal violation or retroperitoneal entry, but may miss specific injuries.[25] Similarly, in obese patients, if the gunshot wound is thought to be tangential through the subcutaneous tissues, CT scan can delineate the track and exclude peritoneal violation. Laparoscopy is another option to assess peritoneal penetration and is followed by laparotomy to repair injuries if found. If there is doubt, it is always safer to explore the abdomen than to equivocate.

Fig. 7-25.



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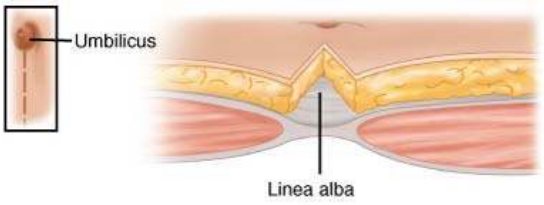
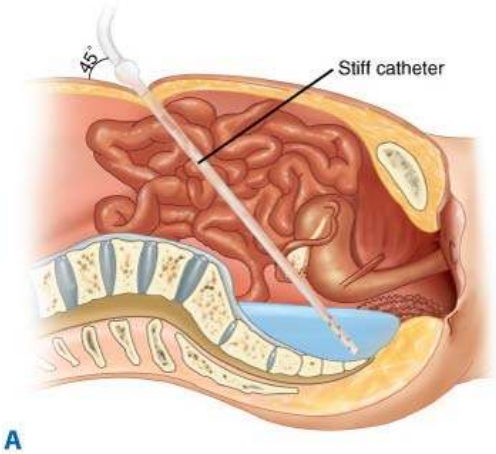
Algorithm for the evaluation of penetrating abdominal injuries. AASW = anterior abdominal stab wound; CT = computed tomography; DPL = diagnostic peritoneal lavage; GSW = gunshot wound; LWE = local wound exploration; RUQ = right upper quadrant; SW = stab wound.

In contrast to gunshot wounds, stab wounds that penetrate the peritoneal cavity are less likely to injure intra-abdominal organs. Anterior abdominal stab wounds (from costal margin to inguinal ligament and bilateral midaxillary lines) should be explored under local anesthesia in the ED to determine if the fascia has been violated. Injuries that do not penetrate the peritoneal cavity do not require further evaluation, and the patient is discharged from the ED. Patients with fascial penetration must be further evaluated for intra-abdominal injury, because there is up to a 50% chance of requiring laparotomy. Debate remains over whether the optimal diagnostic approach is serial examination, diagnostic peritoneal lavage (DPL), or CT scanning.[26] If DPL is pursued, an infraumbilical approach is used (Fig. 7-26). After placement of the catheter, a 10-mL syringe is connected and the abdominal contents aspirated (termed a *diagnostic peritoneal aspiration*). The aspirate is considered to show positive findings if >10 mL of blood is aspirated. If <10 mL is withdrawn, a liter of normal saline is instilled. The effluent is withdrawn via siphoning and sent to the laboratory for RBC count, white blood cell (WBC) count, and determination of amylase, bilirubin, and alkaline phosphatase levels. Values representing positive findings are summarized in Table 7-6.

Fig. 7-26.





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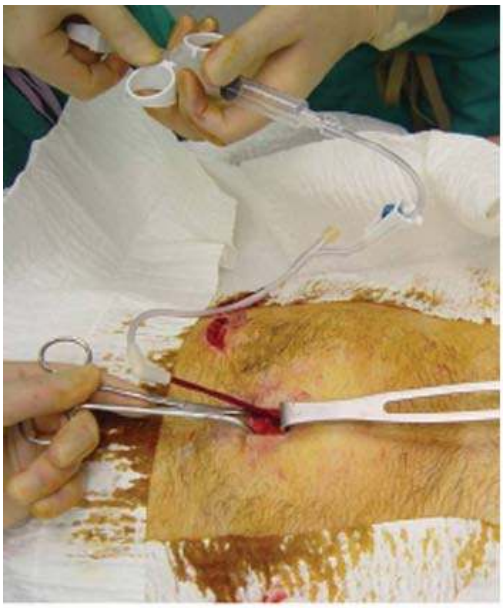

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Diagnostic peritoneal lavage is performed through an infraumbilical incision unless the patient has a pelvic fracture or is pregnant. **A.** The linea alba is sharply incised, and the catheter is directed into the pelvis. **B.** The abdominal contents should initially be aspirated using a 10-mL syringe.

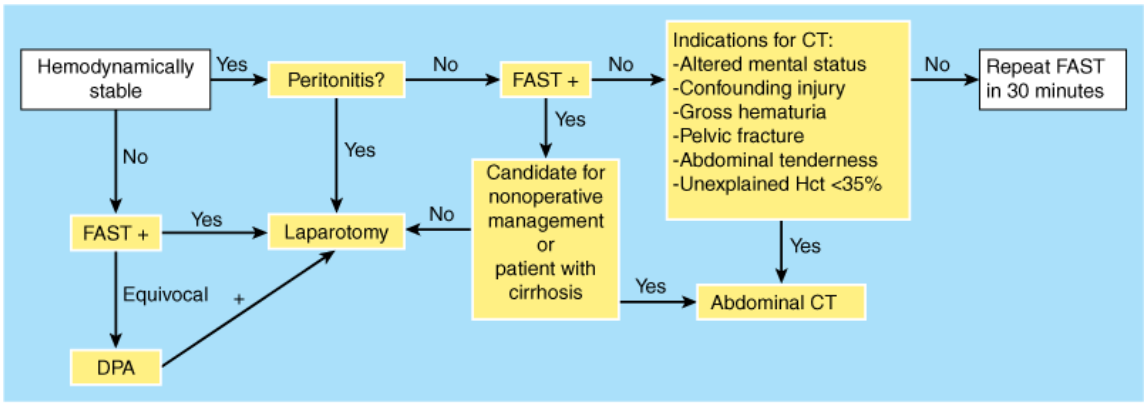
Table 7-6 Criteria for "Positive" Finding on Diagnostic Peritoneal Lavage

	Anterior Abdominal Stab Wounds	Thoracoabdominal Stab Wounds
Red blood cell count	>100,000/mL	>10,000/mL
White blood cell count	>500/mL	>500/mL
Amylase level	>19 IU/L	>19 IU/L
Alkaline phosphatase level	>2 IU/L	>2 IU/L
Bilirubin level	>0.01 mg/dL	>0.01 mg/dL

Abdominal stab wounds in three body regions require a unique diagnostic approach: thoracoabdominal stab wounds, right upper quadrant stab wounds, and back and flank stab wounds. Occult injury to the diaphragm must be ruled out in patients with stab wounds to the lower chest. For patients undergoing DPL evaluation, laboratory value cutoffs are different for those with thoracoabdominal stab wounds and for those with standard anterior abdominal stab wounds (see Table 7-6). An RBC count of >10,000/μL is considered a positive finding and an indication for laparotomy; patients with a DPL RBC count between 1000/μL and 10,000/μL should undergo laparoscopy or thoracoscopy. Patients with stab wounds to the right upper quadrant can undergo CT scanning to determine trajectory and confinement to the liver for potential nonoperative care.[23,24] Those with stab wounds to the flank and back should undergo triple-contrast CT to detect occult retroperitoneal injuries of the colon, duodenum, and urinary tract.[25]

Blunt abdominal trauma initially is evaluated by FAST examination in most major trauma centers, and this has largely supplanted DPL (Fig. 7-27).[27] FAST is not 100% sensitive, however, so diagnostic peritoneal aspiration is still advocated in hemodynamically unstable patients without a defined source of blood loss to rule out abdominal hemorrhage.[11] FAST is used to identify free intraperitoneal fluid (Fig. 7-28) in Morison's pouch, the left upper quadrant, and the pelvis. Although this method is exquisitely sensitive for detecting intraperitoneal fluid of >250 mL, it does not reliably determine the source of hemorrhage nor grade solid organ injuries.[28,29] Patients with fluid on FAST examination, considered a "positive FAST," who do not have immediate indications for laparotomy and are hemodynamically stable undergo CT scanning to quantify their injuries. Injury grading using the American Association for the Surgery of Trauma grading scale (Table 7-7) is a key component of nonoperative management of solid organ injuries. Additional findings that should be noted on CT scan in patients with solid organ injury include contrast extravasation (i.e., a "blush"), the amount of intra-abdominal hemorrhage, and presence of pseudoaneurysms (Fig. 7-29). CT also is indicated for hemodynamically stable patients for whom the physical examination is unreliable. Despite the increasing diagnostic accuracy of multislice CT scanners, CT still has limited sensitivity for identification of intestinal injuries. Bowel injury is suggested by findings of thickened bowel wall, "streaking" in the mesentery, free fluid without associated solid organ injury, or free intraperitoneal air.[30] Patients with free intra-abdominal fluid without solid organ injury are closely monitored for evolving signs of peritonitis; if patients have a significant closed head injury or cannot be serially examined, DPL should be performed to exclude bowel injury.

Fig. 7-27.



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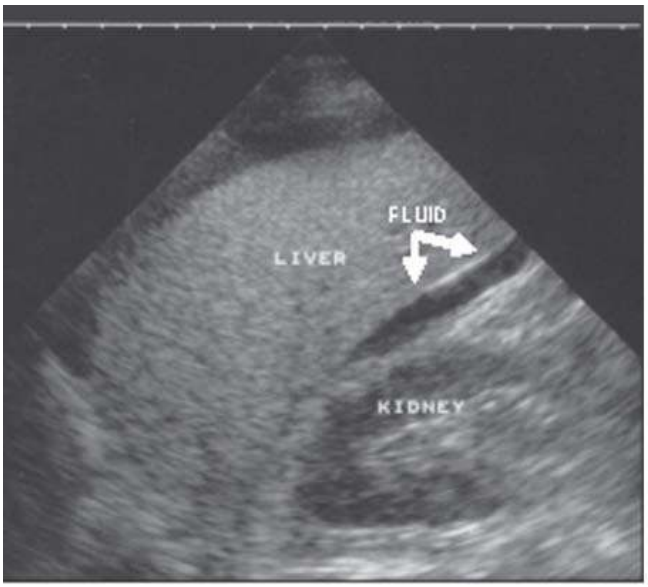
Algorithm for the initial evaluation of a patient with suspected blunt abdominal trauma. CT = computed tomography; DPA = diagnostic peritoneal aspiration; FAST = focused abdominal sonography for trauma; Hct = hematocrit.

Fig. 7-28.



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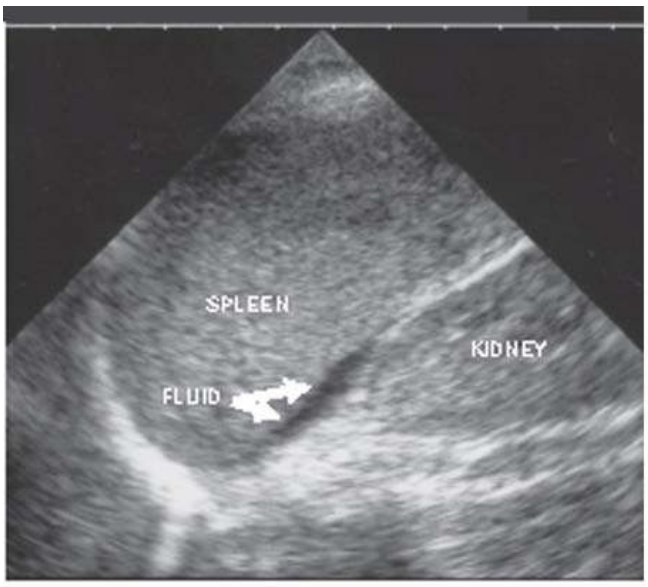

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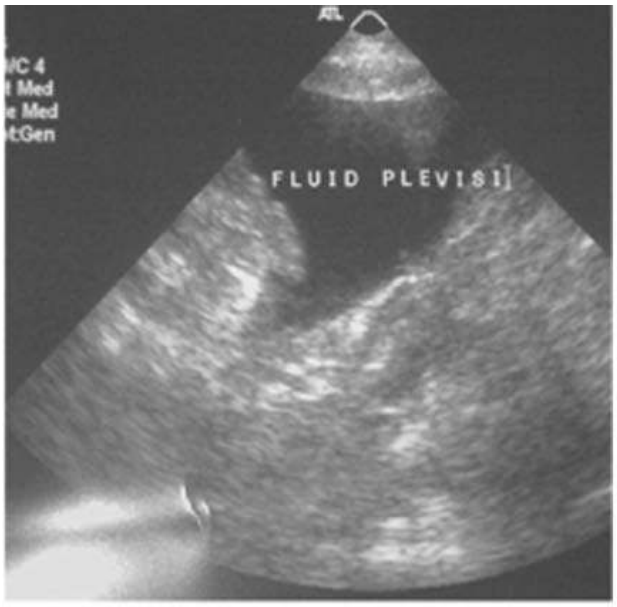

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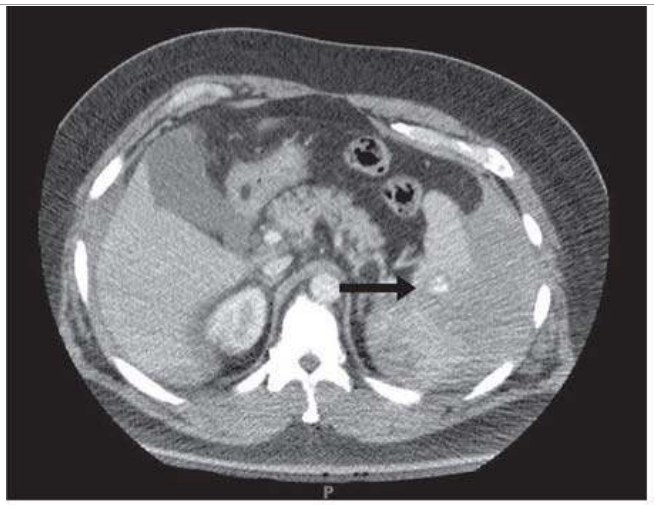
Focused abdominal sonography for trauma imaging detects intra-abdominal hemorrhage. Hemorrhage is presumed when a fluid stripe is visible between the right kidney and liver (**A**), between the left kidney and spleen (**B**), or in the pelvis (**C**).

Table 7-7 American Association for the Surgery of Trauma Grading Scales for Solid Organ Injuries

	Subcapsular Hematoma	**Laceration**
Liver Injury Grade		
Grade I	<10% of surface area	<1 cm in depth
Grade II	10–50% of surface area	1–3 cm
Grade III	>50% of surface area or >10 cm in depth	>3 cm
Grade IV	25–75% of a hepatic lobe	
Grade V	>75% of a hepatic lobe	
Grade VI	Hepatic avulsion	
Splenic Injury Grade		
Grade I	<10% of surface area	<1 cm in depth
Grade II	10–50% of surface area	1–3 cm
Grade III	>50% of surface area or >10 cm in depth	>3 cm
Grade IV	>25% devascularization	Hilum
Grade V	Shattered spleen	
	Complete devascularization	

Fig. 7-29.



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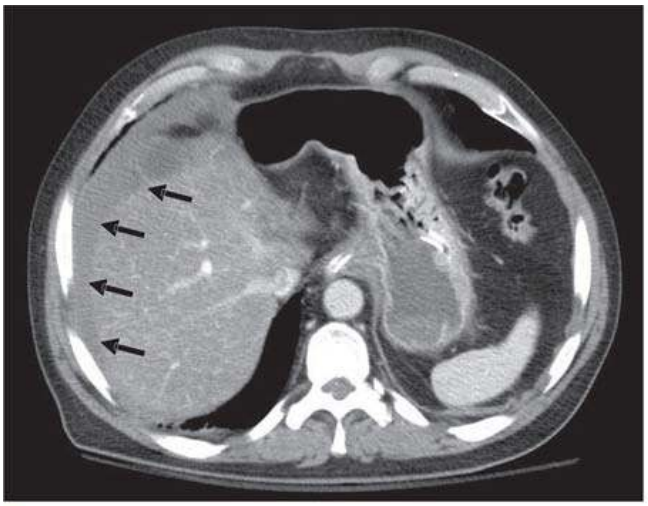

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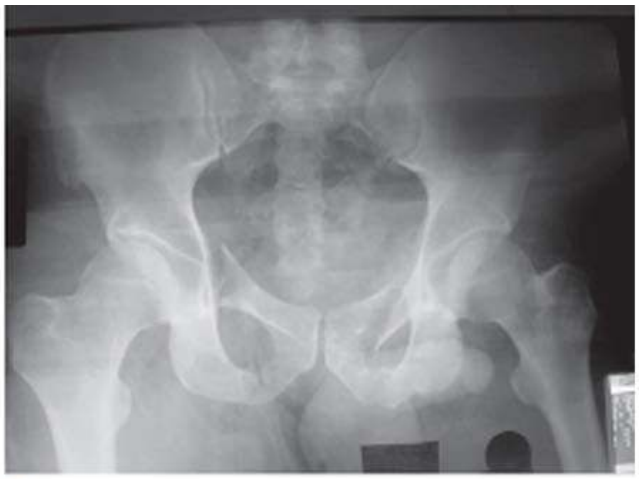
Computed tomographic images reveal critical information about solid organ injuries, such as associated contrast extravasation from a grade IV laceration of the spleen (**A;***arrows*) and the amount of subcapsular hematoma in a grade III liver laceration (**B;***arrows*).

PELVIS

Blunt injury to the pelvis may produce complex fractures with major hemorrhage (Fig. 7-30). Plain radiographs will reveal gross abnormalities, but CT scanning may be necessary to determine the precise geometry. Sharp spicules of bone can lacerate the bladder, rectum, or vagina. Alternatively, bladder rupture may result from the direct blow to the torso if the bladder is full. CT cystography is performed if the urinalysis findings are positive for RBCs. Urethral injuries are suspected if examination reveals blood at the meatus, scrotal or perineal hematomas, or a high-riding prostate on rectal examination. Urethrograms should be obtained for stable patients before placing a Foley catheter to avoid false passage and subsequent stricture. Major vascular injuries causing exsanguination are uncommon in blunt pelvic trauma; however, thrombosis of either the arteries or veins in the iliofemoral system may occur, and CT angiography or formal angiography is diagnostic. Life-threatening hemorrhage can be associated with pelvic fractures and may initially preclude definitive imaging. Treatment algorithms for patients with complex pelvic fractures and hemodynamic instability are presented later in the chapter.

Fig. 7-30.



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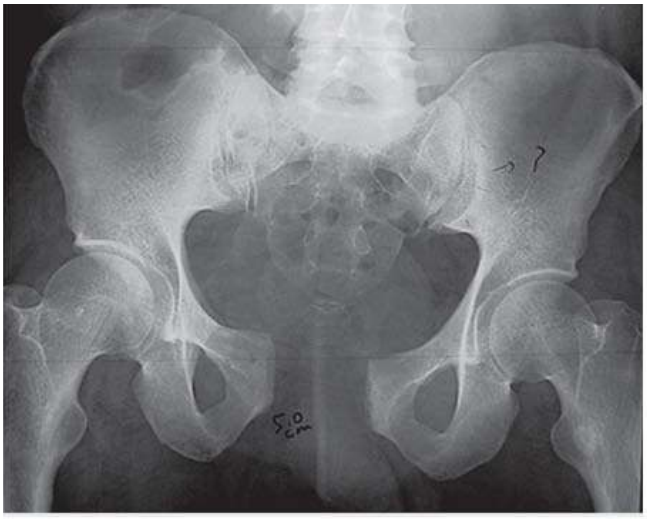

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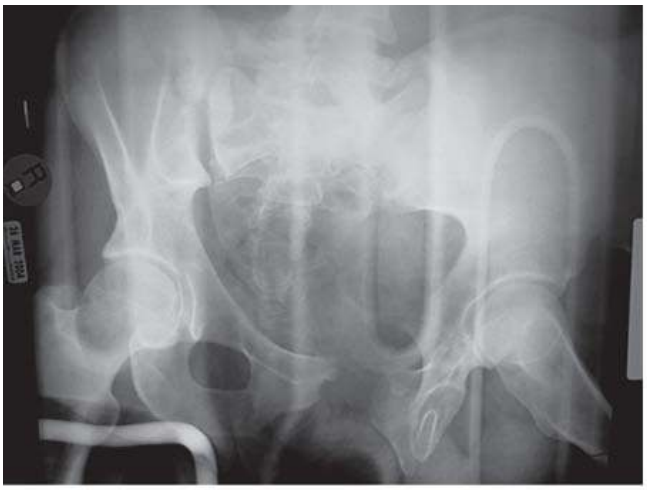

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The three types of mechanically unstable pelvis fractures are lateral compression (**A**), anteroposterior compression (**B**), and vertical shear (**C**).

EXTREMITIES

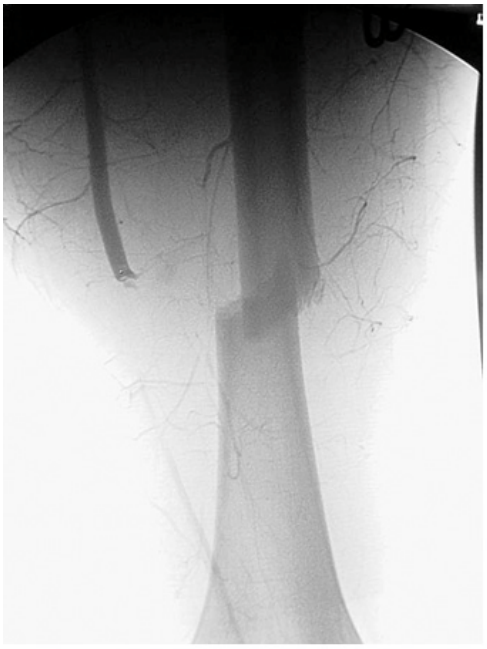
Blunt or penetrating trauma to the extremities requires an evaluation for fractures, ligamentous injury, and neurovascular injury. Plain radiographs are used to evaluate fractures, whereas ligamentous injuries, particularly those of the knee and shoulder, can be imaged with magnetic resonance imaging. Physical examination often identifies arterial injuries, and findings are classified as either hard signs or soft signs of vascular injury (Table 7-8). In general, hard signs constitute indications for operative exploration, whereas soft signs are indications for further testing or observation. Bony fractures or knee dislocations should be realigned before definitive vascular examination. On-table angiography may be useful to localize the arterial injury and thus limit tissue dissection in patients with hard signs of vascular injury. For example, a patient with an absent popliteal pulse and femoral shaft fracture due to a bullet that entered the lateral hip and exited below the medial knee could have injured either the femoral or popliteal artery anywhere along its course (Fig. 7-31).

Table 7-8 Signs and Symptoms of Peripheral Arterial Injury

Hard Signs (Operation Mandatory)	**Soft Signs (Further Evaluation Indicated)**
Pulsatile hemorrhage	Proximity to vasculature
Absent pulses	Significant hematoma
Acute ischemia	Associated nerve injury
	A-A index of <0.9
	Thrill or bruit

A-A index = systolic blood pressure on the injured side compared with that on the uninjured side.

Fig. 7-31.



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On-table angiography in the operating room isolates the area of vascular injury to the superficial femoral artery in a patient with a femoral fracture.

In management of vascular trauma, controversy exists regarding the treatment of patients with soft signs of injury, particularly those with injuries in proximity to major vessels. It is known that some of these patients will have arterial injuries that require repair. One approach has been to measure SBP using Doppler ultrasonography and compare the value for the injured side with that for the uninjured side, termed the *A-A index*.[31] If the pressures are within 10% of each other, a significant injury is unlikely and no further evaluation is performed. If the difference is >10%, CT angiography or arteriography is indicated. Others argue that there are occult injuries, such as pseudoaneurysms or injuries of the profunda femoris or peroneal arteries, which may not be detected with this technique. If hemorrhage occurs from these injuries, compartment syndrome and limb loss may occur. Although busy trauma centers continue to debate this issue, the surgeon who is obliged to treat the occasional injured patient may be better served by performing CT angiography in selected patients with soft signs.

GENERAL PRINCIPLES OF MANAGEMENT

Over the past 20 years there has been a remarkable change in management practices and operative approach for the injured patient. With the advent of CT scanning, nonoperative management of solid organ injuries has replaced routine operative exploration. Those patients who do require operation may be treated with less radical

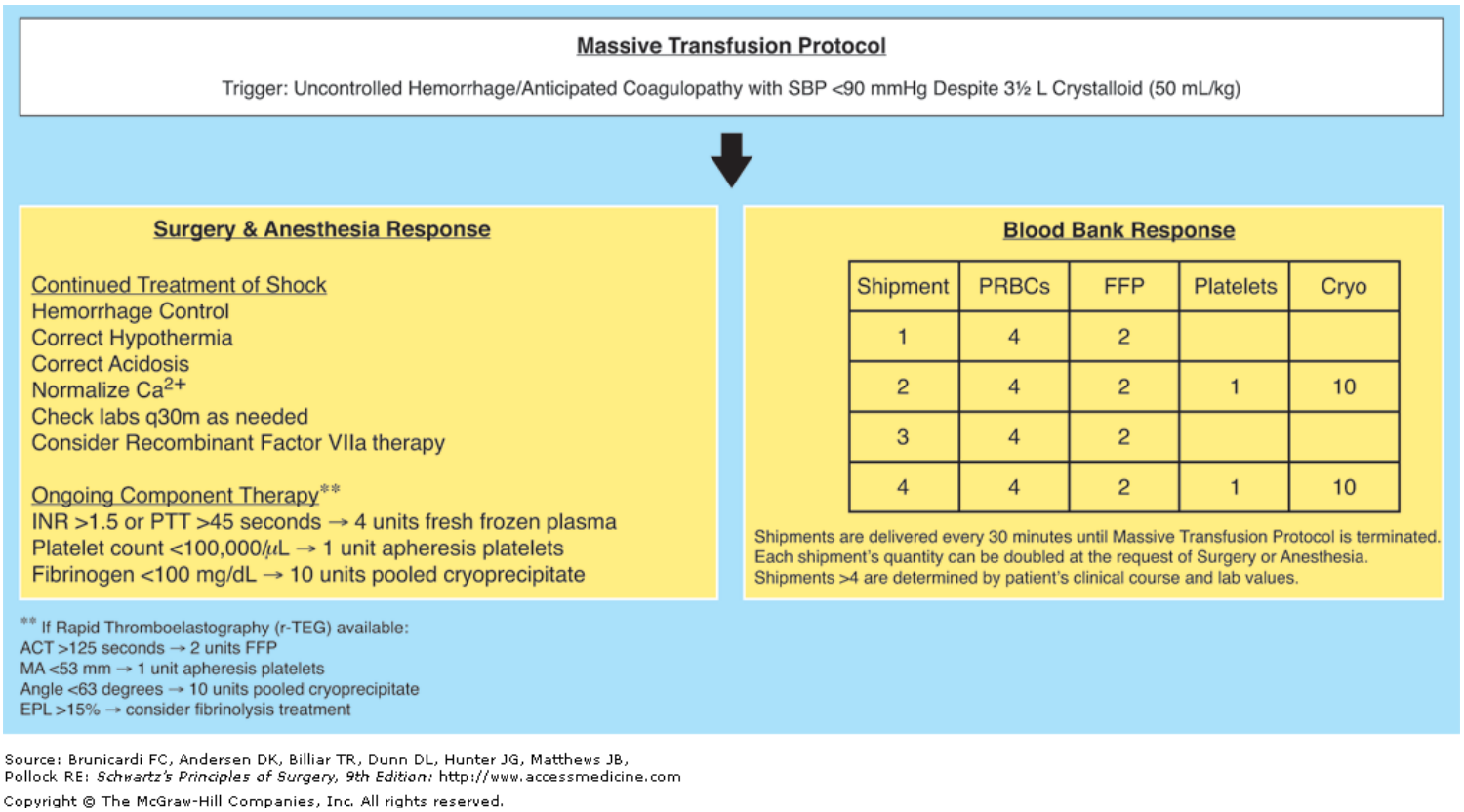
resection techniques such as splenorrhaphy or partial nephrectomy. Colonic injuries, previously mandating colostomy, are now repaired primarily in virtually all cases. Additionally, the type of anastomosis has shifted from a double-layer closure to a continuous running single-layer closure; this method is technically equivalent to and faster than the interrupted multilayer techniques.[32] Adoption of damage control surgical techniques in physiologically deranged patients has resulted in limited initial operative time, with definitive injury repair delayed until after resuscitation in the surgical intensive care unit (SICU) with physiologic restoration.[33] Abdominal drains, once considered mandatory for parenchymal injuries and some anastomoses, have disappeared; fluid collections are managed by percutaneous techniques. Newer endovascular techniques such as stenting of arterial injuries and angioembolization are routine adjuncts. Blunt cerebrovascular injuries have been recognized as a significant, preventable source of neurologic morbidity and mortality. The use of preperitoneal pelvic packing for unstable pelvic fractures as well as early fracture immobilization with external fixators are paradigm shifts in management. Finally, the institution of massive transfusion protocols balances the benefit of blood component therapy against immunologic risk. These conceptual changes have significantly improved survival of critically injured patients; they have been promoted and critically reviewed by academic trauma centers via forums such as the American College of Surgeons Committee on Trauma, the American Association for the Surgery of Trauma, the International Association of Trauma Surgery and Intensive Care, the Pan-American Trauma Congress, and other surgical organizations.

Transfusion Practices

Injured patients with life-threatening hemorrhage may develop marked coagulopathy requiring clotting factor replacement. Fresh whole blood, arguably the optimal replacement, is no longer available in the United States. Rather, its component parts, packed red blood cells (PRBCs), fresh-frozen plasma, platelets, and cryoprecipitate, are administered. Specific transfusion triggers for individual blood components exist. Although current critical care guidelines indicate that PRBC transfusion should occur once the patient's hemoglobin level is <7 g/dL,[34] in the acute phase of resuscitation the endpoint is 10 g/dL.[35] Fresh-frozen plasma is transfused to keep the patient's International Normalized Ratio (INR) less than 1.5 and partial thromboplastin time (PTT) <45 seconds. Primary hemostasis relies on platelet adherence and aggregation to injured endothelium, and a platelet count of 50,000/μL is considered adequate if platelet function is normal. With massive transfusion, however, platelet dysfunction is common, and therefore a target of 100,000/μL is advocated. If fibrinogen levels drop below 100 mg/dL, cryoprecipitate should be administered. Such guidelines are designed to limit the transfusion of immunologically active blood components and decrease the risk of transfusion-associated lung injury and multiple organ failure.[36,37]

In the critically injured patient requiring large amounts of blood component therapy, a massive transfusion protocol should be followed (Fig. 7-32). This approach calls for administration of various components in a specific ratio during transfusion to achieve restoration of blood volume and correction of coagulopathy. Although the optimal ratio is yet to be determined,[38] the majority of trauma centers use a presumptive 1:1 or 1:2 red cell:plasma ratio in patients at risk for massive transfusion (10 units of PRBCs in 6 hours). Because complete typing and cross-matching takes up to 45 minutes, patients requiring emergent transfusions are given type O, type-specific, or biologically compatible RBCs. Blood typing, and to a lesser extent cross-matching, is essential to avoid life-threatening intravascular hemolytic transfusion reactions. Trauma centers and their associated blood banks must have the capability of transfusing tremendous quantities of blood components, because it is not unusual to have 100 component units transfused during one procedure and have the patient survive. Massive transfusion protocols, established preemptively, permit coordination of the activities of surgeons, anesthesiologists, and blood bank directors to facilitate transfusion at these rates should a crisis occur.

Fig. 7-32.



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Denver Health Medical Center's Massive Transfusion Protocol. ACT = activated clotting time; Cryo = cryoprecipitate; EPL = estimated percent lysis; FFP = fresh-frozen plasma; INR = International Normalized Ratio; MA = maximum amplitude; PRBCs = packed red blood cells; PTT = partial thromboplastin time; SBP = systolic blood pressure.

Postinjury coagulopathy is associated with core hypothermia and metabolic acidosis, termed the *bloody vicious cycle.*[33] The pathophysiology is multifactorial and includes inhibition of temperature-dependent enzyme-activated coagulation cascades, platelet dysfunction, endothelial abnormalities, and a poorly understood fibrinolytic activity. Such coagulopathy may be insidious, so the surgeon must be cognizant of subtle signs such as excessive bleeding from the cut edges of skin. Although the coagulopathic "ooze" may seem minimal compared with the torrential hemorrhage from a hole in the aorta, blood loss from the entire area of dissection can lead to exsanguination. Obtaining results for the usual laboratory tests of coagulation capability (i.e., INR, PTT, and platelet count) requires approximately 30 minutes. Such a delay is particularly troublesome for patients who have lost two blood volumes while waiting for the test results to return. Under such conditions, transfusion of fresh-frozen plasma and platelets must be empiric. Using damage control techniques to limit operative time and provide physiologic restoration in the SICU can be life saving (see "Damage Control Surgery" later).

Prophylactic Measures

All injured patients undergoing an operation should receive preoperative antibiotics. The type of antibiotic is determined by the anticipated source of contamination in the abdomen or other operative region; additional doses should be administered during the procedure based on blood loss and the half-life of the antibiotic. Extended postoperative antibiotic therapy is administered only for open fractures or significant intra-abdominal contamination. Tetanus prophylaxis is administered to all patients according to published guidelines.

Trauma patients are at risk for venous thromboembolism and its associated complications. In fact, pulmonary embolus can occur much earlier in the patient's hospital course than previously believed.[39] Patients at higher risk for venous thromboembolism are (a) those with multiple fractures of the pelvis and lower extremities, (b) those with coma or spinal cord injury, and (c) those requiring ligation of large veins in the abdomen and lower extremities. Morbidly obese patients and those over 55 years of age are at additional risk. Administration of low molecular weight heparin is initiated as soon as bleeding has been controlled and there is no intracranial pathology. In high-risk patients, removable inferior vena caval filters should be considered if there are contraindications to administration of low molecular weight heparin. Additionally, pulsatile compression stockings (also termed *sequential compression devices*) are used routinely unless there is a fracture.

A final prophylactic measure that is usually not considered is thermal protection. Hemorrhagic shock impairs perfusion and metabolic activity throughout the body, with resultant decrease in heat production and body temperature. Removing the patient's clothes causes a second thermal insult, and infusion of cold RBCs or room temperature crystalloid exacerbates the problem. As a result, injured patients can become hypothermic, with temperatures below 34°C (93.2°F) upon arrival in the OR. Hypothermia causes coagulopathy and myocardial irritability. Therefore, prevention must begin in the ED by maintaining a comfortable ambient temperature, covering stabilized patients with warm blankets, and administering warmed IV fluids and blood products. Additionally, in the OR a Bair Hugger warmer (the upper body or lower body blanket) and heated inhalation via the ventilatory circuit is instituted. For cases of severe hypothermia [temperature <30°C (86°F)], arteriovenous rewarming should be considered.

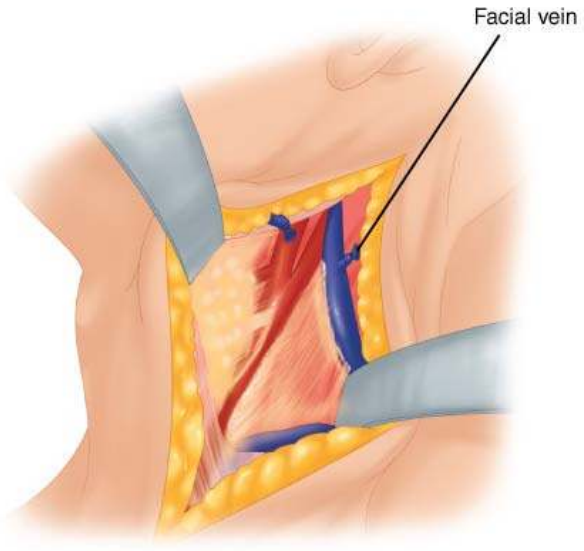
Operative Approaches and Exposure

CERVICAL EXPOSURE

Operative exposure for midline structures of the neck (trachea, thyroid, bilateral carotid sheaths) is obtained through a collar incision; this is typically performed two finger breadths above the sternal notch, but can be varied based on the level of injury. After subplatysmal flap elevation, the strap muscles are divided in the midline to gain access to the central neck compartment. More superior and lateral structures are accessed by extending the collar incision upward along the sternocleidomastoid muscle; this may be done bilaterally if necessary. Unilateral neck exploration is done through an incision extending from the mastoid down to the clavicle, along the anterior border of the sternocleidomastoid muscle (Fig. 7-33). The carotid sheath, containing the carotid artery, jugular vein, and vagus nerve, is opened widely to examine these structures. The facial vein, which marks the carotid bifurcation, is usually ligated for exposure of the internal carotid artery.

Fig. 7-33.

From Lycan / Dr. MV



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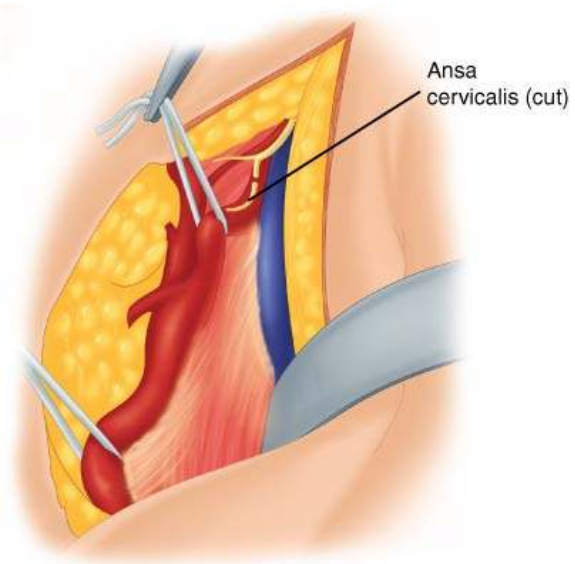

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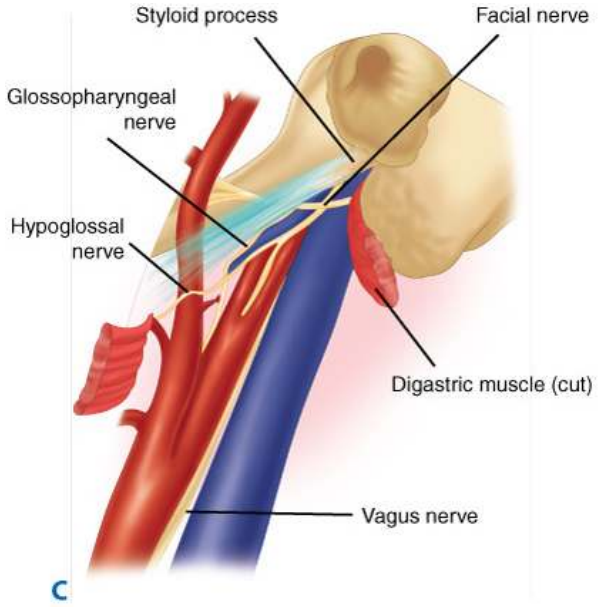

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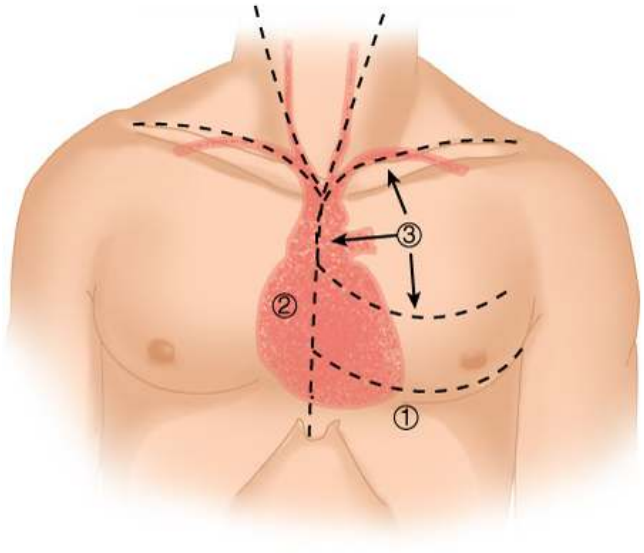
A. Unilateral neck exploration is performed through an incision along the anterior border of the sternocleidomastoid muscle; exposure of the carotid artery requires early division of the facial vein. **B.** The distal internal carotid artery is exposed by dividing the ansa cervicalis, which permits mobilization of the hypoglossal nerve. **C.** Further exposure is facilitated by resection of the posterior belly of the digastric muscle.

Exposure of the distal carotid artery in zone III is difficult (see Fig. 7-33). The first step is division of the ansa cervicalis to facilitate mobilization of the hypoglossal nerve. Next, the posterior portion of the digastric muscle, which overlies the internal carotid, is transected. The glossopharyngeal and vagus nerves are mobilized and retracted as necessary. If accessible, the styloid process and attached muscles are removed. At this point anterior displacement of the mandible (subluxation) may be helpful. In desperate situations, the vertical ramus of the mandible may be divided. However, this maneuver often entails resection of the parotid gland and facial nerve for exposure of the distal internal carotid.

THORACIC INCISIONS

An anterolateral thoracotomy, with the patient placed supine, is the most versatile incision for emergent thoracic exploration. The location of the incision is in the fifth interspace, in the inframammary line (Fig. 7-34). If access is needed to bilateral pleural cavities, the original incision can be extended across the sternum with a Lebsche knife, into a "clamshell" thoracotomy (Fig. 7-35). If the sternum is divided, the internal mammary arteries should be ligated to prevent blood loss. The heart, lungs, descending aorta, pulmonary hilum, and esophagus are accessible with this approach. For control of the great vessels, the superior portion of the sternum may be opened and extension of the incision into the neck considered. A method advocated for access to the proximal left subclavian artery is through a fourth interspace anterolateral thoracotomy, superior sternal extension, and left supraclavicular incision ("trap door" thoracotomy). Although the trap door procedure is appropriate after resuscitative thoracotomy, the proximal left subclavian artery can be accessed more easily via a sternotomy with a supraclavicular extension. If the left subclavian artery is injured outside the thoracic outlet, vascular control can be obtained via the sternotomy and definitive repair done through the supraclavicular incision. Median sternotomy is of limited utility in cases of cardiac trauma but can be used for anterior stab wounds to the heart. Typically, these patients have pericardial tamponade and undergo placement of a pericardial drain before a semiurgent median sternotomy is performed. Patients in extremis, however, should undergo anterolateral thoracotomy.

Fig. 7-34.



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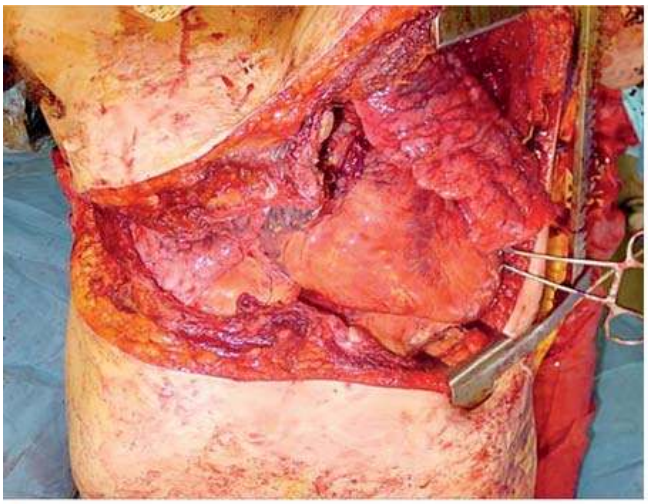
Options for thoracic exposure include the most versatile incision, the anterolateral thoracotomy (*1*), as well as a median sternotomy (*2*) and a "trap door" thoracotomy (*3*). Any thoracic incision may be extended into a supraclavicular or anterior neck incision for wider exposure.

Fig. 7-35.



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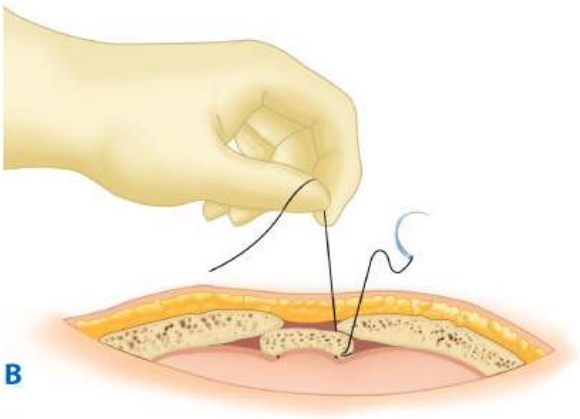

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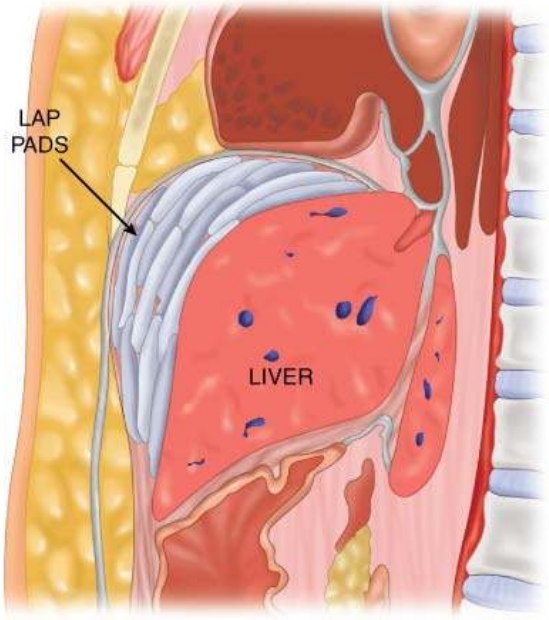
A. A "clamshell" thoracotomy provides exposure to bilateral thoracic cavities. **B.** Sternal transection requires individual ligation of both the proximal and distal internal mammary arteries on the undersurface of the sternum.

Median sternotomy with cervical extension may also be used for rapid exposure in patients with presumed proximal subclavian, innominate, or proximal carotid artery injuries. Care must be taken to avoid injury to the phrenic and vagus nerves that pass over the subclavian artery and to the recurrent laryngeal nerve passing posteriorly. Posterolateral thoracotomies are used for exposure of injuries to the posterior aspect of the trachea or main stem bronchi near the carina (right posterolateral thoracotomy), tears of the descending thoracic aorta (left posterolateral thoracotomy with left heart bypass), and intrathoracic esophageal injuries.

EMERGENT ABDOMINAL EXPLORATION

Abdominal exploration in adults is performed using a generous midline incision because of its versatility. For children under the age of 6, a transverse incision may be advantageous. Making the incision is faster with a scalpel than with an electrosurgical unit; incisional abdominal wall bleeding should be ignored until intra-abdominal sources of hemorrhage are controlled. Liquid and clotted blood is evacuated with multiple laparotomy pads and suction to identify the major source(s) of active bleeding. After blunt trauma the spleen and liver should be palpated and packed if fractured, and the infracolic mesentery inspected to exclude injury. In contrast, after a penetrating wound the search for bleeding should pursue the trajectory of the penetrating device. If the patient has an SBP of <70 mmHg when the abdomen is opened, digital pressure or a clamp should be placed on the aorta at the diaphragmatic hiatus. After the source of hemorrhage is localized, direct digital occlusion (vascular injury) or laparotomy pad packing (solid organ injury) is used to control bleeding (Fig. 7-36). If the liver is the source in a hemodynamically unstable patient, additional control of bleeding is obtained by clamping the hepatic pedicle (Pringle maneuver) (Fig. 7-37). Similarly, clamping the splenic hilum may more effectively control bleeding than packing alone. When the spleen is mobilized, it should be gently rotated medially to expose the lateral peritoneum; this peritoneum and endoabdominal fascia are incised, which allows blunt dissection of the spleen and pancreas as a composite from the retroperitoneum (Fig. 7-38).

Fig. 7-36.



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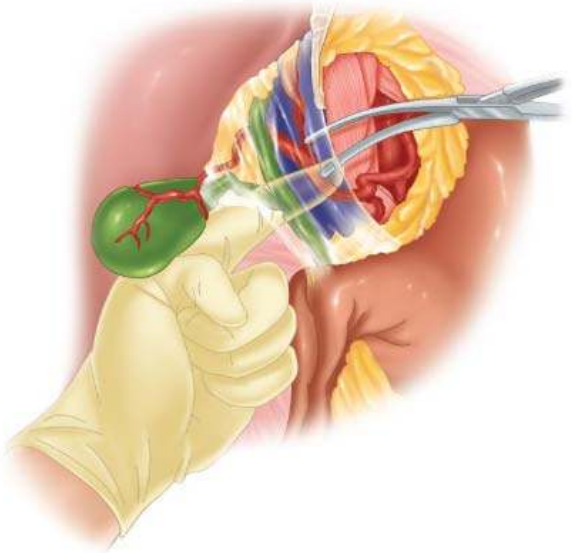
A sagittal view of packs placed to control hepatic hemorrhage. Lap = laparotomy.

Fig. 7-37.



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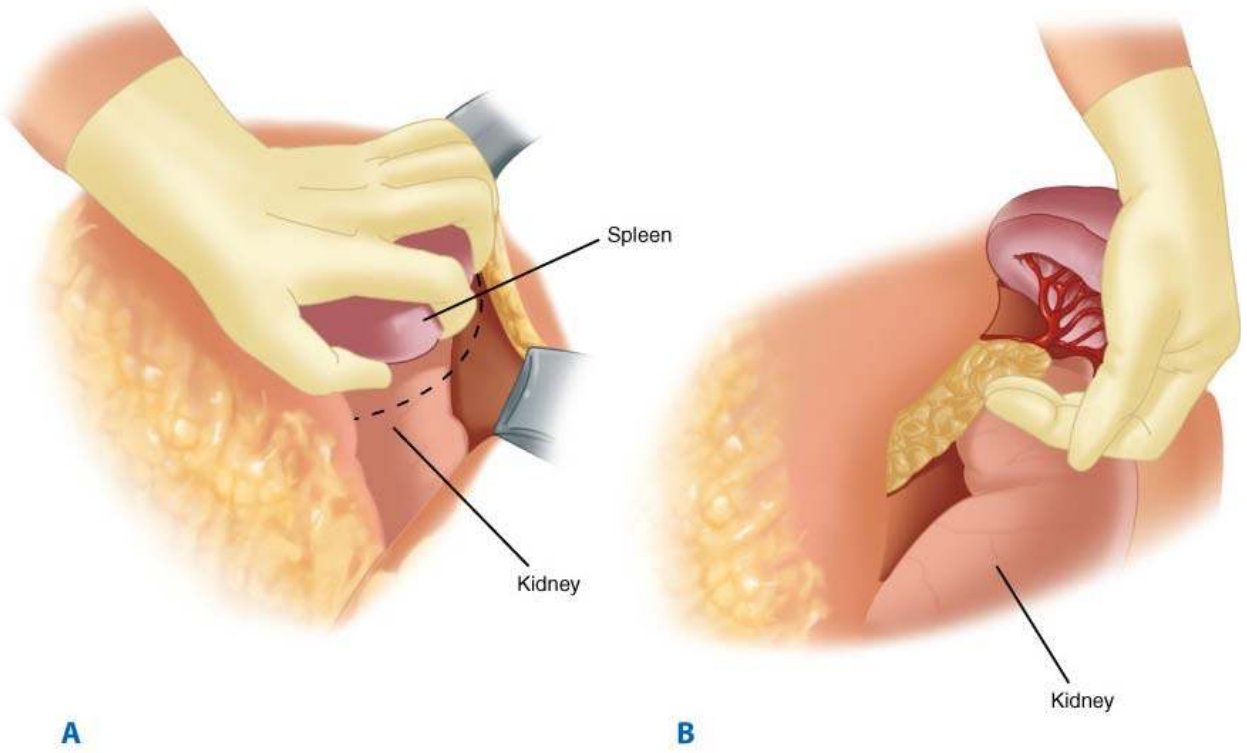
The Pringle maneuver, performed with a vascular clamp, occludes the hepatic pedicle containing the portal vein, hepatic artery, and common bile duct.

Fig. 7-38.



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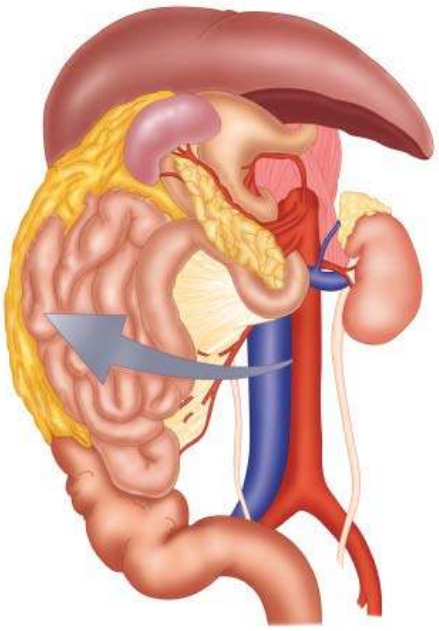
To mobilize the spleen, an incision is made into the endoabdominal fascia 1 cm lateral to the reflection of the peritoneum onto the spleen (**A**). While the spleen is gently rotated medially, a plane is developed between the pancreas and left kidney (**B**). With complete mobilization, the spleen can reach the level of the abdominal incision.

Rapid exposure of the intra-abdominal vasculature can prove challenging in the face of exsanguinating hemorrhage. The aorta, celiac axis, proximal superior mesenteric artery (SMA), and left renal arteries can be exposed with a left medial visceral rotation (Fig. 7-39). This is done by incising the lateral peritoneal reflection (white line of Toldt) beginning at the distal descending colon and extending the incision along the colonic splenic flexure, around the posterior aspect of the spleen, and behind the gastric fundus, ending at the esophagus. The left colon, spleen, pancreas, and stomach are then rotated toward the midline. The authors prefer to leave the kidney in situ when mobilizing the viscera because this exaggerates the separation of the renal vessels from the SMA. Proximal control of the aorta is obtained at the diaphragmatic hiatus; if an aortic injury is supraceliac, transecting the left crus of diaphragm or performing left thoracotomy may be necessary. Inferior vena cava injuries are approached by a right medial visceral rotation (Fig. 7-40). Proximal control is obtained just above the aortic bifurcation with direct pressure via a sponge stick; the injury is identified by cephalad dissection along the anterior surface of the inferior vena cava. The operative approach for SMA injuries is based on the level of injury. Fullen zone I SMA injuries, located posterior to the pancreas, can be exposed by a left medial visceral rotation. Fullen zone II SMA injuries, extending from the pancreatic edge to the middle colic branch, are approached via the lesser sac along the inferior edge of the pancreas at the base of the transverse mesocolon; the pancreatic body may be divided to gain proximal vascular access. More distal SMA injuries, Fullen zones III and IV, are approached directly within the mesentery. A venous injury behind the pancreas, from the junction of the superior mesenteric, splenic, and portal veins, is accessed by dividing the neck of the pancreas.

Fig. 7-39.



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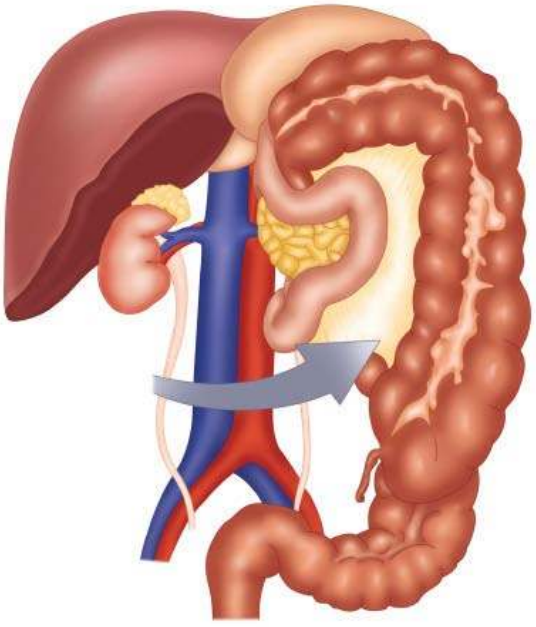
A left medial visceral rotation is used to expose the abdominal aorta.

Fig. 7-40.



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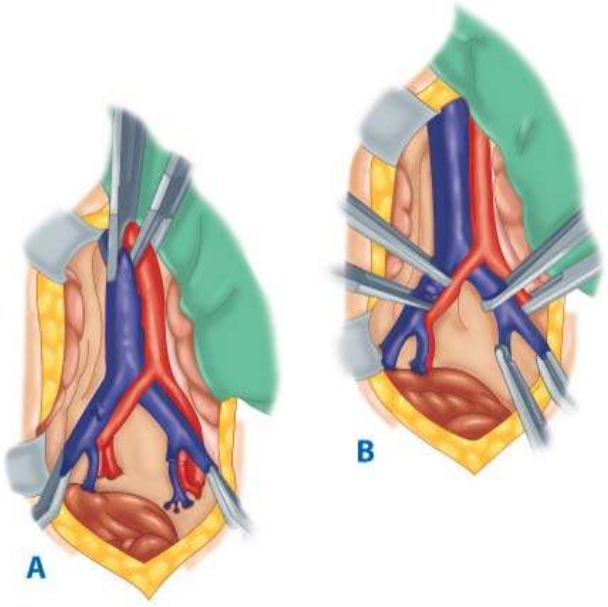
A right medial visceral rotation is used to expose the infrahepatic vena cava.

Injuries of the iliac vessels pose a unique problem for emergent vascular control due to the number of vessels, their close proximity, and cross circulation. Proximal control at the infrarenal aorta arrests the arterial bleeding and avoids splanchnic and renal ischemia; however, venous injuries are not controlled with aortic clamping. Tamponade with a folded laparotomy pad held directly over the bleeding site usually will establish hemostasis sufficient to prevent exsanguination. If hemostasis is not adequate to expose the vessel proximal and distal to the injury, sponge sticks can be strategically placed on either side of the injury and carefully adjusted to improve hemostasis. Alternatively, complete pelvic vascular isolation (Fig. 7-41) may be required to control hemorrhage for adequate visualization of the injuries. The right common iliac artery obscures the bifurcation of the vena cava and the right iliac vein; the iliac artery can be divided to expose venous injuries of this area (Fig. 7-42). The artery must be

repaired after the venous injury is treated, however, because of limb-threatening ischemia.

Fig. 7-41.



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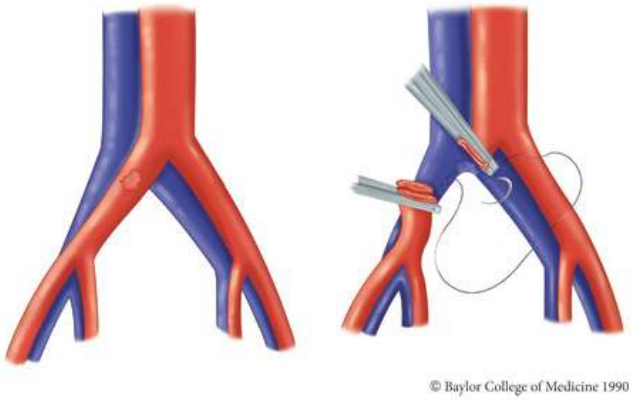
Pelvic vascular isolation. **A.** Initially, clamps are placed on the aorta, inferior vena cava, and bilateral external iliac vessels. **B.** With continued dissection, the clamps can be moved progressively closer to the vascular injury to limit unwarranted ischemia.

Fig. 7-42.



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The right common iliac artery can be divided to expose the bifurcation of the inferior vena cava and the right common iliac vein.

Once overt hemorrhage is controlled, sources of enteric contamination are identified by serially running along the small and large bowel, looking at all surfaces. Associated hematomas should be unroofed to rule out adjacent bowel injury. The anterior and posterior aspects of the stomach should be inspected, which requires opening the lesser sac for complete visualization. Duodenal injuries should be evaluated with a wide Kocher maneuver. During exploration of the lesser sac, visualization and palpation of the pancreas is done to exclude injury. Palpating the anterior surface is not sufficient, because the investing fascia may mask a pancreatic injury; mobilization, including evaluation of the posterior aspect, is critical. After injuries are identified, whether to use damage control techniques or perform primary repair of injuries is based on the patient's intraoperative physiologic status (see "Damage Control Surgery" and "Treatment of Specific Injuries" later). In a patient with multisystem trauma, enteral access via gastrostomy tube and needle-catheter jejunostomy should be considered. If abdominal closure is indicated after the patient's injuries are addressed, the abdomen is irrigated with warm saline and the midline fascia is closed with a running heavy suture. The skin is closed selectively based on the amount of intra-abdominal contamination.

VASCULAR REPAIR TECHNIQUES

Initial control of vascular injuries is accomplished digitally by applying enough direct pressure to stop the hemorrhage. Sharp dissection with fine scissors defines the injury and mobilizes sufficient length for proximal and distal control. Heparinized saline (50 units/mL) is injected into the proximal and distal ends of the injured vessel to prevent

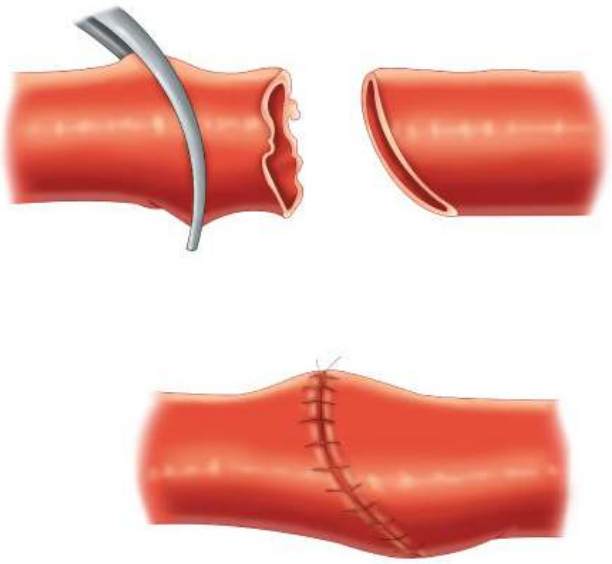
small clot formation on the exposed intima and media. Ragged edges of the injury site should be judiciously débrided using sharp dissection.

Options for the treatment of vascular injuries are listed in Table 7-9. Arterial repair should always be done for the aorta and the carotid, innominate, brachial, superior mesenteric, proper hepatic, renal, iliac, femoral, and popliteal arteries. In the extremities, at least one artery with distal runoff should be salvaged. Venous repair should be attempted for injuries of the superior vena cava, the inferior vena cava proximal to the renal veins, and the portal vein, although the portal vein may be ligated in extreme cases. Arterial injuries that may be treated conservatively include small pseudoaneurysms, intimal dissections, small intimal flaps, and small arteriovenous fistulas in the extremities. Follow-up imaging is performed 1 to 2 weeks after injury to confirm healing.

Table 7-9 Options for the Treatment of Vascular Injuries
Observation
Ligation
Lateral suture repair
End-to-end primary anastomosis
Interposition grafts
Autogenous vein
Polytetrafluoroethylene graft
Dacron graft
Transpositions
Extra-anatomic bypass
Interventional radiology
Stents
Embolization

The type of operative repair for a vascular injury is based on the extent and location of injury. Lateral suture repair is preferred for arterial injuries with minimal loss of tissue. End-to-end primary anastomosis is performed if the vessel can be repaired without tension. Arterial defects of 1 to 2 cm often can be bridged by mobilizing the severed ends of the vessel after ligating small branches. The surgeon should not be reluctant to divide small branches to obtain additional length, because most injured patients have normal vasculature, and the preservation of potential collateral flow is not as important as in surgery for atherosclerosis. The aorta, subclavian artery, and brachial artery, however, are difficult to mobilize for additional length. To avoid postoperative stenosis, particularly in smaller arteries, beveling or spatulation should be used so that the completed anastomosis is slightly larger in diameter than the native artery (Fig. 7-43). The authors emphasize the parachute technique to ensure precision placement of the posterior suture line (Fig. 7-44). If this technique is used, traction must be maintained on both ends of the suture, or leakage from the posterior aspect of the suture line may occur. A single temporary suture 180 degrees from the posterior row may be used to maintain alignment for challenging anastomoses.

Fig. 7-43.



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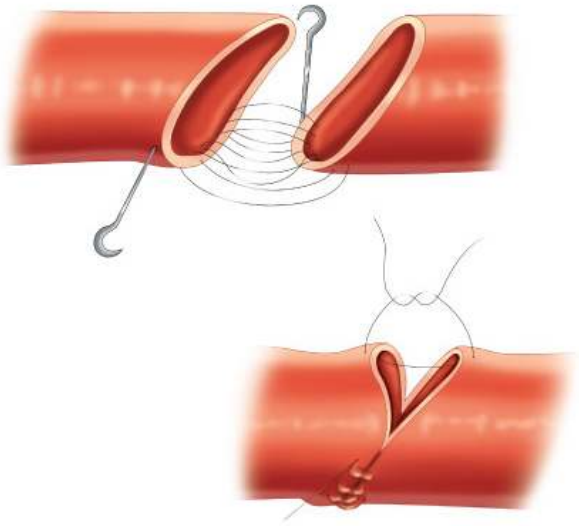
Small arteries repaired with an end-to-end anastomosis are prone to stricture. Enlarging the anastomosis by beveling the cut ends of the injured vessel can minimize this problem. A curved hemostat is a useful adjunct to create the curve.

Fig. 7-44.



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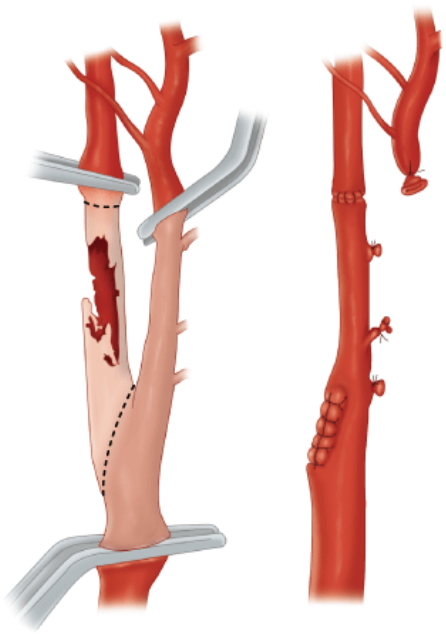
The parachute technique is helpful for accurate placement of the posterior sutures of an anastomosis when the arterial end is fixed and an interposition graft is necessary. Traction must be maintained on both ends of the suture to prevent loosening and leakage of blood. Six stitches should be placed before the graft is pulled down to the artery.

Interposition grafts are used when end-to-end anastomosis cannot be accomplished without tension despite mobilization. For vessels <6 mm in diameter (e.g., internal carotid, brachial, superficial femoral, and popliteal arteries), autogenous saphenous vein from the contralateral groin should be used, because polytetrafluoroethylene (PTFE) grafts of <6 mm have a prohibitive rate of thrombosis. Larger arteries (e.g., subclavian, innominate, aorta, common iliac) are bridged by PTFE grafts. Aortic or iliac arterial injuries may be complicated by enteric contamination from colon or small bowel injuries. There is a natural reluctance to place artificial grafts in such circumstances, but graft infections are rare and the time required to perform an axillofemoral bypass is excessive. Therefore, after the control of hemorrhage, bowel contamination is contained and the abdomen irrigated before placing PTFE grafts. After placement of the graft, it is covered with peritoneum or omentum before definitive treatment of the enteric injuries.

Transposition procedures can be used when an artery has a bifurcation and one vessel can safely be ligated. Injuries of the proximal internal carotid can be treated by mobilizing the adjacent external carotid, dividing it distal to the internal injury, and performing an end-to-end anastomosis between it and the distal internal carotid (Fig. 7-45). The proximal stump of the internal carotid is oversewn, with care taken to avoid a blind pocket where a clot may form. Injuries of the common and external iliac arteries can be handled in a similar fashion (Fig. 7-46), while maintaining flow in at least one internal iliac artery.

Fig. 7-45.



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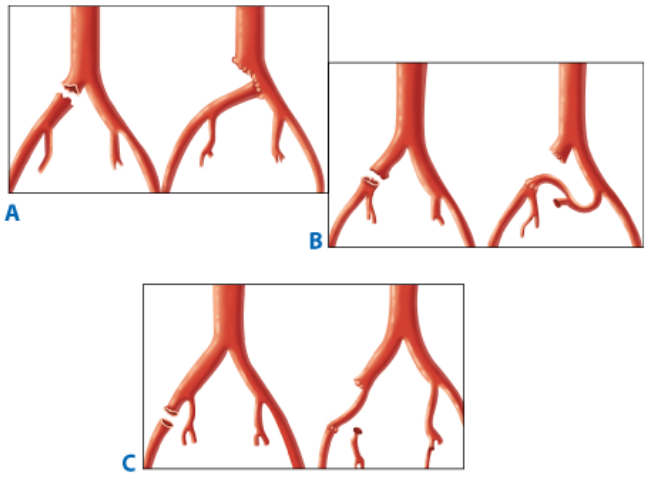
Carotid transposition is an effective approach for treating injuries of the proximal internal carotid artery.

Fig. 7-46.



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Transposition procedures can be used for iliac artery injuries to eliminate the dilemma of placing an interposition polytetrafluoroethylene graft in the presence of enteric contamination. **A.** Right common iliac artery transposed to left common iliac artery. **B.** Left internal iliac artery transposed to the distal right common iliac artery. **C.** Right internal iliac artery transposed to the right external iliac artery.

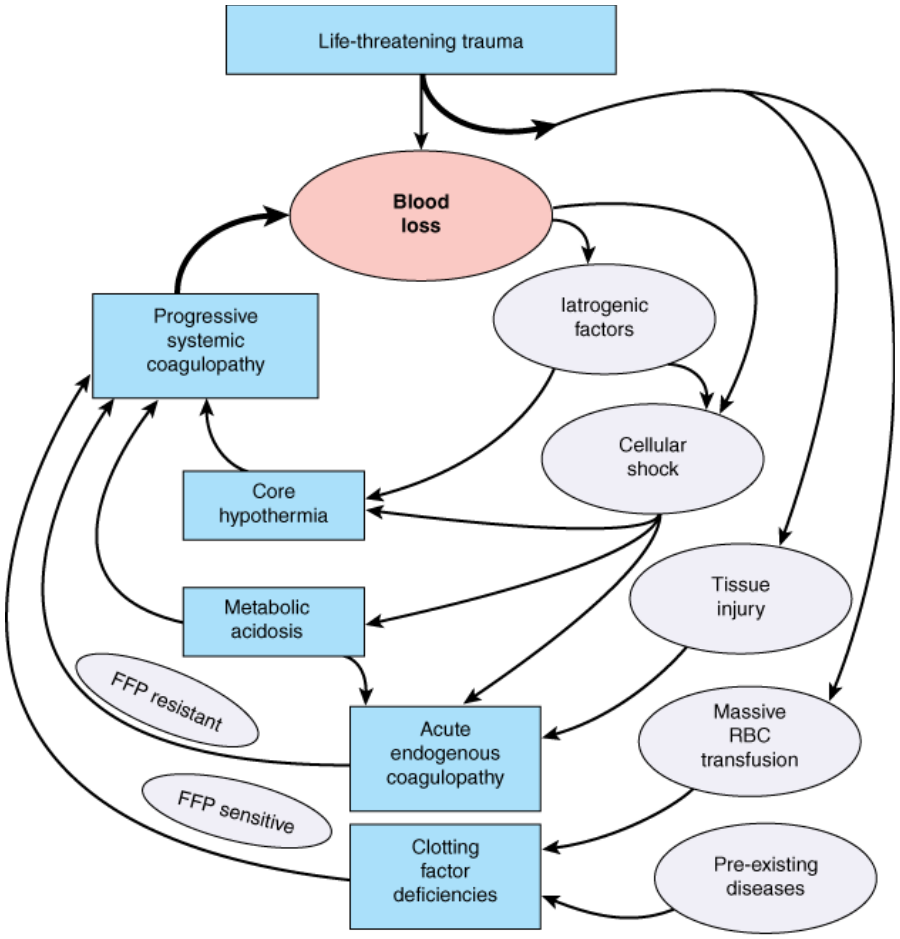
Venous injuries are inherently more difficult to reconstruct due to their propensity to thrombose. Small injuries without loss of tissue can be treated with lateral suture repair. More complex repairs with interposition grafts often fail; this typically does not occur acutely but rather gradually over 1 to 2 weeks. During this time adequate collateral circulation typically develops, which is sufficient to avoid acute venous hypertension. Therefore, it is reasonable to use PTFE for venous interposition grafting and accept a gradual, but eventual, thrombosis while allowing time for collateral circulation to develop. Such an approach is reasonable for venous injuries of the superior vena cava, suprarenal vena cava, and popliteal vein because ligation of these is associated with significant morbidity. In the remainder of venous injuries the vein may be ligated. In such patients, chronic venous hypertensive complications in the lower extremities often can be avoided by (a) temporary use of elastic bandages (Ace wraps) applied from the toes to the hips at the end of the procedure, and (b) temporary continuous elevation of the lower extremities to 30 to 45 degrees. These measures should be maintained for 1 week; if the patient has no peripheral edema with ambulation, these maneuvers are no longer required.

Damage Control Surgery

The recognition of the bloody vicious cycle and the introduction of damage control surgery (DCS) have improved the survival of critically injured patients. The bloody vicious

cycle, first described in 1981, is the lethal combination of coagulopathy, hypothermia, and metabolic acidosis (Fig. 7-47).[33] Hypothermia from evaporative and conductive heat loss and diminished heat production occurs despite the use of warming blankets and blood warmers. The metabolic acidosis of shock is exacerbated by aortic clamping, administration of vasopressors, massive transfusions, and impaired myocardial performance. Coagulopathy is caused by dilution, hypothermia, and acidosis. Once the cycle starts, each component magnifies the others, which leads to a downward spiral and ultimately a fatal arrhythmia. The purpose of DCS is to limit operative time so that the patient can be returned to the SICU for physiologic restoration and the cycle thus broken. Indications to limit the initial operation and institute DCS techniques include temperature <35°C (95°F), arterial pH <7.2, base deficit <15 mmol/L (or <6 mmol/L in patients over 55 years of age), and INR or PTT >50% of normal. The decision to abbreviate a trauma laparotomy is made intraoperatively as laboratory values become available and the patient's clinical course becomes clearer.

Fig. 7-47.



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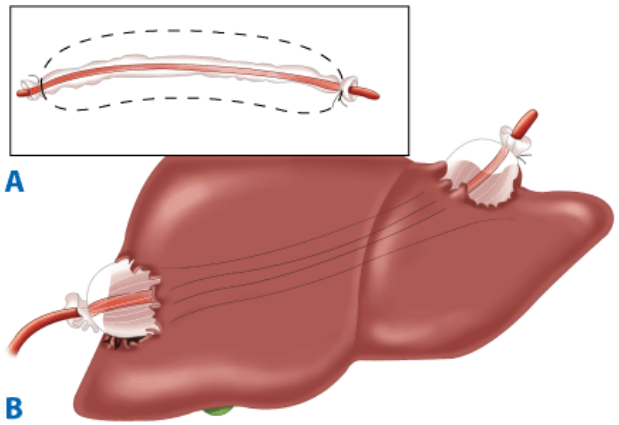
The bloody vicious cycle. FFP = fresh-frozen plasma; RBC= red blood cell.

The goal of DCS is to control surgical bleeding and limit GI spillage. The operative techniques used are temporary measures, with definitive repair of injuries delayed until the patient is physiologically replete. Controlling surgical bleeding while preventing ischemia is of utmost importance during DCS. Aortic injuries must be repaired using an interposition PTFE graft. Although celiac artery injuries may be ligated, the SMA must maintain flow, and the insertion of an intravascular shunt is advocated. Similarly, perfusion of the iliac system and infrainguinal vessels can be restored with a vascular shunt, with interposition graft placement delayed until hours later. Venous injuries are preferentially treated with ligation in damage control situations, except for the suprarenal inferior vena cava and popliteal vein. For solid organ injuries to the spleen or one kidney, excision is indicated rather than an attempt at repair such as splenorrhaphy. For hepatic injuries, packing of the liver causes compression tamponade of bleeding (see Fig. 7-36). Translobar gunshot wounds of the liver are best controlled with balloon catheter tamponade, whereas deep lacerations can be controlled with Foley catheter inflation deep within the injury track (Fig. 7-48). For thoracic injuries requiring DCS several options exist. For bleeding peripheral pulmonary injuries, wedge resection using a gastrointestinal anastomosis (GIA) stapler is performed. In penetrating injuries, pulmonary tractotomy is used to divide the parenchyma (Fig. 7-49); individual vessels and bronchi are then ligated using a 3-0 polydioxanone (PDS) suture and the track left open. Patients who sustain more proximal injuries may require pulmonary lobectomy or pneumonectomy to control bleeding. Cardiac injuries may be temporarily controlled using a running 3-0 nonabsorbable polypropylene suture or skin staples. If this technique does not definitely control hemorrhage, pledgeted repair of the injury should be performed.

Fig. 7-48.



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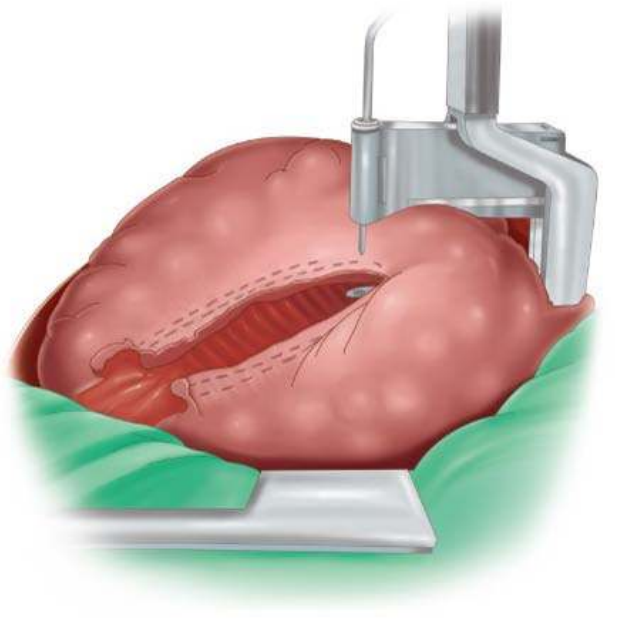
A. An intrahepatic balloon used to tamponade hemorrhage from transhepatic penetrating injuries is made by placing a red rubber catheter inside a 1-inch Penrose drain, with both ends of the Penrose drain ligated. **B.** Once placed inside the injury track, the balloon is inflated with saline until hemorrhage stops. **C.** A Foley catheter with a 30-mL balloon can be used to halt hemorrhage from deep lacerations to the liver.

Fig. 7-49.



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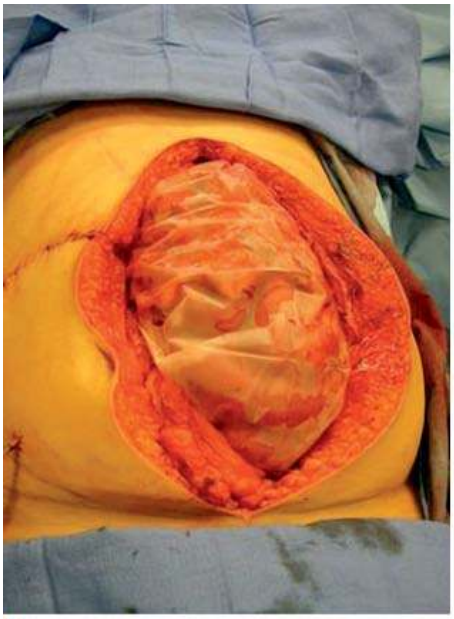
Pulmonary tractotomy divides the pulmonary parenchyma using either a transection/anastomosis (TA) or gastrointestinal anastomosis (GIA) stapler. The opened track permits direct access to injured vessels or bronchi for individual ligation.

The second key component of DCS is limiting enteric content spillage. Small GI injuries (stomach, duodenum, small intestine, and colon) may be controlled using a rapid whipstitch of 2-0 nonabsorbable polypropylene. Complete transection of the bowel or segmental damage is controlled using a GIA stapler, often with resection of the injured segment. Alternatively, open ends of the bowel may be ligated using umbilical tapes to limit spillage. Pancreatic injuries, regardless of location, are packed and the evaluation of ductal integrity postponed. Before the patient is returned to the SICU, the abdomen must be temporarily closed. Originally, penetrating towel clips were used to approximate the skin; however, the ensuing bowel edema often produced a delayed abdominal compartment syndrome. Currently, temporary closure of the abdomen is accomplished using an antimicrobial surgical incise drape (Ioban) (Fig. 7-50). In this technique, the bowel is covered with a fenestrated subfascial sterile drape (45 x 60 cm Steri-Drape), and two Jackson-Pratt drains are placed along the fascial edges; this is then covered using an Ioban drape, which allows closed suction to control reperfusion-related ascitic fluid egress while providing adequate space for bowel expansion to prevent abdominal compartment syndrome. During the initial DCS stage, the subfascial sterile drape is not covered by a blue towel so that the status of the bowel and hemorrhage control can be assessed. Return to the OR in 12 to 24 hours is planned once the patient clinically improves, as evidenced by normothermia, normalization of coagulation test results, and correction of acidosis.

Fig. 7-50.



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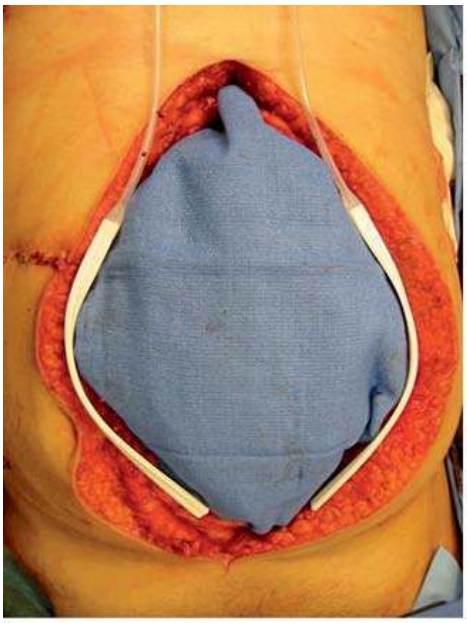

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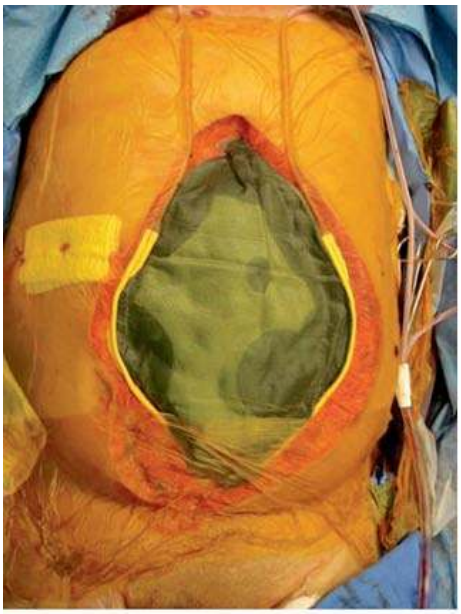

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Temporary closure of the abdomen entails covering the bowel with a fenestrated subfascial 45 x 60 cm sterile drape (**A**), placing Jackson-Pratt drains and a blue towel (**B**), and then occluding with an Ioban drape (**C**).

TREATMENT OF SPECIFIC INJURIES

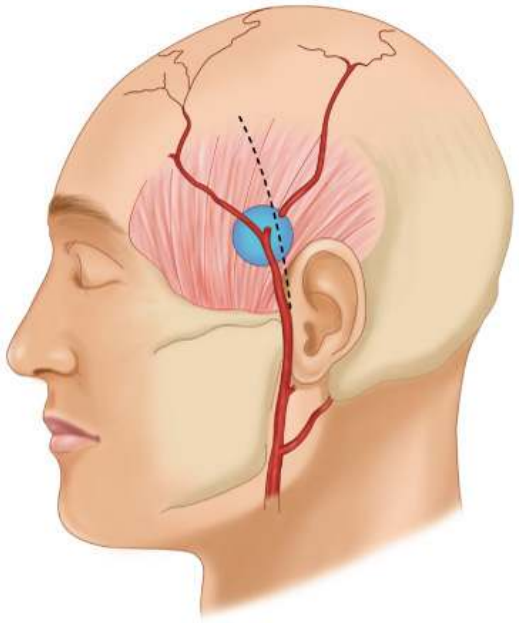
Head Injuries

INTRACRANIAL INJURIES

CT scanning, performed on all patients with a significant closed head injury (GCS score <14), identifies and quantitates intracranial lesions. Patients with intracranial hemorrhage, including epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intracerebral hematoma or contusion, and diffuse axonal injury, are admitted to the SICU. In patients with abnormal findings on CT scans and GCS scores of ð8, intracranial pressure (ICP) should be monitored using fiber-optic intraparenchymal devices or intraventricular catheters.[13] Although an ICP of 10 mmHg is believed to be the upper limit of normal, therapy is not initiated until ICP is >20 mmHg.[13] Indications for operative intervention to remove space-occupying hematomas are based on the clot volume, amount of midline shift, location of the clot, GCS score, and ICP.[13] A shift of >5 mm typically is considered an indication for evacuation, but this is not an absolute rule. Smaller hematomas that are in treacherous locations, such as the posterior fossa, may require drainage due to brain stem compression or impending herniation. Removal of small hematomas may also improve ICP and cerebral perfusion in patients with elevated ICP that is refractory to medical therapy. Patients with diffuse cerebral edema resulting in excessive ICP may require a decompressive craniectomy. Patients with open or depressed skull fractures, with or without sinus involvement, may require operative intervention. Penetrating injuries to the head require operative intervention for hemorrhage control, evacuation of blood, skull fracture fixation, or débridement.

General surgeons in communities without emergency neurosurgical coverage should have a working knowledge of burr hole placement in the event that emergent evacuation is required for a life-threatening epidural hematoma (Fig. 7-51).[40] The typical clinical course of an epidural hematoma is an initial loss of consciousness, a lucid interval, recurrent loss of consciousness with an ipsilateral fixed and dilated pupil, and finally cardiac arrest. The final stages of this sequence are caused by blood accumulation that forces the temporal lobe medially, with resultant compression of the third cranial nerve and eventually the brain stem. The burr hole is made on the side of the dilated pupil to decompress the intracranial space. After stabilization, the patient is transferred to a facility with emergency neurosurgical capability for formal craniotomy.

Fig. 7-51.



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A burr hole is made for decompression of an epidural hematoma as a life-saving maneuver. One or more branches of the external carotid artery usually must be ligated to gain access to the skull. No attempt should be made to control intracranial hemorrhage through the burr hole. Rather, the patient's head should be wrapped with a bulky absorbent dressing and the patient transferred to a neurosurgeon for definitive care.

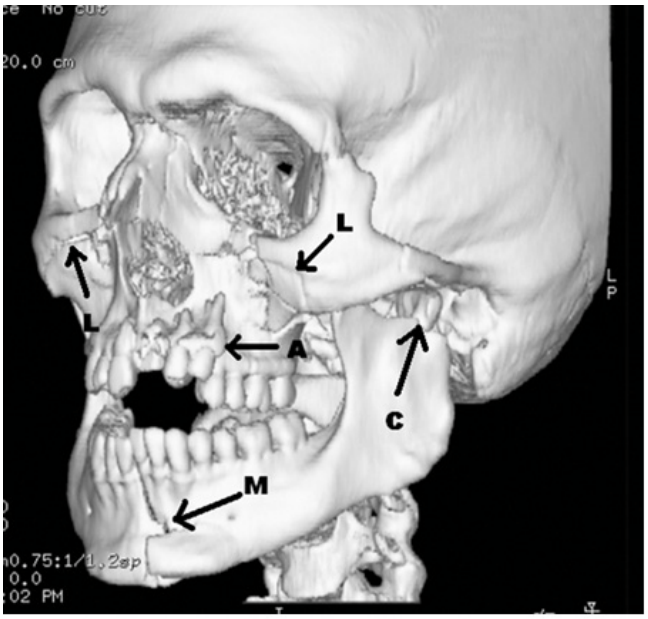
In addition to operative intervention, postinjury care directed at limiting secondary injury to the brain is critical. The goal of resuscitation and management in patients with head injuries is to avoid hypotension (SBP of <90 mmHg) and hypoxia (partial pressure of arterial oxygen of <60 or arterial oxygen saturation of <90).[13] Attention, therefore, is focused on maintaining cerebral perfusion rather than merely lowering ICP. Resuscitation efforts aim for a euvolemic state and an SBP of >90 mmHg. Cerebral perfusion pressure (CPP) is equal to the mean arterial pressure minus the ICP, with a target range of 50 to 70 mmHg.[13] CPP can be increased by either lowering ICP or raising mean arterial pressure. Sedation, osmotic diuresis, paralysis, ventricular drainage, and barbiturate coma are used in sequence, with coma induction being the last resort. The partial pressure of carbon dioxide (P_{CO_2}) should be maintained in a normal range (35 to 40 mmHg), but for temporary management of acute intracranial hypertension, inducing cerebral vasoconstriction by hyperventilation to a P_{CO_2} of <30 mmHg is occasionally warranted. Moderate hypothermia [32° to 33°C (89.6° to 91.4°F)] may decrease mortality risk and improve neurologic outcomes when maintained for at least 48 hours, but its ultimate role remains to be defined.[13] Patients with intracranial hemorrhage should be monitored for postinjury seizures, and prophylactic anticonvulsant therapy (e.g., phenytoin [Dilantin]) is indicated for 7 days after injury.[13]

MAXILLOFACIAL INJURIES

Maxillofacial injuries are common with multisystem trauma and require coordinated management by the trauma surgeon and the specialists in otolaryngology, plastic surgery, ophthalmology, and oral and maxillofacial surgery. Delay in addressing these systems that control vision, hearing, smelling, breathing, eating, and phonation may produce dysfunction and disfigurement with serious psychologic impact. The maxillofacial complex is divided into three regions; the *upper face* containing the frontal sinus and brain, the *midface* containing the orbits, nose, and zygomaticomaxillary complex, and the *lower face* containing the mandible. High-impact kinetic energy is required to fracture the frontal sinus, orbital rims, and mandible, whereas low-impact forces will injure the nasal bones and zygoma.

The most common scenario, which at times may be life-threatening, is bleeding from facial fractures.[41] Temporizing measures include nasal packing, Foley catheter tamponade of posterior nasal bleeding, and oropharyngeal packing. Prompt angioembolization will halt exsanguinating hemorrhage. Fractures of tooth-bearing bone are considered open fractures and require antibiotic therapy and semiurgent repair to preserve the airway as well as the functional integrity of the occlusion (bite) and the aesthetics of the face. Orbital fractures may compromise vision, produce muscle injury causing diplopia, or change orbital volume to produce a sunken appearance to the orbit. Nose and nasoethmoidal fractures should be assessed carefully to identify damage to the lacrimal drainage system or to the cribriform plate producing cerebrospinal fluid rhinorrhea. After initial stabilization, a systematic physical examination of the head and neck should be performed that also includes cranial nerve examination and coronal and three-dimensional CT scanning of the maxillofacial complex (Fig. 7-52). Early consultation with the surgical specialists in this area is essential to prevent complications to these vital structures.

Fig. 7-52.



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Three-dimensional computed tomographic scan illustrating Le Fort II maxillary (*L*) and alveolar (*A*) fractures, and fracture of the mandible (*M*) at the midline and at the weaker condyle (*C*).

(Image courtesy of Vincent D. Eusterman, MD, DDS.)

Neck and Cervical Spine Injuries

Blunt trauma can involve virtually every structure in the neck. Treatment of injuries to the cervical spine is based on the level of injury, the stability of the spine, the presence of subluxation, the extent of angulation, the level of neurologic deficit, and the overall condition of the patient. In general, physician-supervised axial traction, via cervical tongs or the more commonly used halo vest, is used to reduce subluxations and stabilize the injury. Immobilization of injuries also is achieved with spinal orthoses (braces), particularly in those with associated thoracolumbar injuries. Surgical fusion typically is performed in patients with neurologic deficit, those with angulation of >11 degrees or translation of >3.5 mm, and those who remain unstable after external fixation. Indications for immediate operative intervention are deterioration in neurologic function and fractures or dislocations with incomplete deficit. Methylprednisolone generally is administered to patients with acute spinal cord injury. Although controversy exists, clinical data suggest initiating a 24-hour infusion if started within 3 hours and a 48-hour infusion if started 3 to 8 hours.[42] Current guidelines suggest an initial bolus of 30 mg/kg methylprednisolone followed by a 5.4-mg/kg infusion for 23 hours in patients with nonpenetrating injuries. The role and timing of operative surgical decompression after acute spinal cord injury is a matter of debate. However, evidence supports urgent decompression of bilateral locked facets in patients with incomplete tetraplegia or with neurologic deterioration. Urgent decompression in acute cervical spinal cord injury is safe. Performing surgery within 24 hours may decrease length of stay and complications.[43] Complete injuries of the spinal cord remain essentially untreatable. However, approximately 3% of patients who present with flaccid quadriplegia have concussive injuries, and these patients represent the very few who seem to have miraculous recoveries.

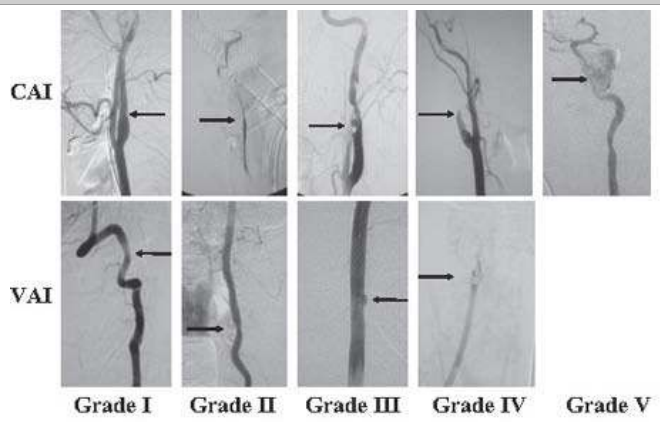
Subclinical fractures of the larynx and trachea may manifest as cervical emphysema, but fractures documented by CT scan often are repaired. Common injuries include thyroid cartilage fractures, rupture of the thyroepiglottic ligament, disruption of the arytenoids or vocal cord tears, and cricoid fractures. After necessary débridement of devitalized tissue, tracheal injuries are repaired end to end using a single layer of interrupted absorbable sutures. Associated injuries of the esophagus are common in penetrating injuries due to its close proximity. After débridement and repair, vascularized tissue is interposed between the repair and the injured trachea, and a closed suction drain is placed. The sternocleidomastoid muscle or strap muscles are useful for interposition and help prevent postoperative fistulas.

Cervical vascular injuries due to either blunt or penetrating trauma can result in devastating neurologic sequelae or exsanguination. Penetrating injuries to the carotid artery and internal jugular vein usually are obvious on operative neck exploration. The principles of vascular repair techniques (discussed previously) apply to carotid injuries, and options for repair include end-to-end primary repair (often possible with mobilization of the common carotid), graft interposition, and transposition procedures. All carotid injuries that can be repaired without undue physiologic ramifications should be. However, in patients who present in coma, particularly with a delay, ligation should be considered. In patients with uncontrolled hemorrhage, an alternative is temporary vascular control and revascularization using a Pruitt-Inahara shunt. Tangential wounds of the internal jugular vein should be repaired by lateral venorrhaphy, but extensive wounds are efficiently addressed by ligation. However, it is not advisable to ligate both jugular veins. Vertebral artery injuries due to penetrating trauma are difficult to control operatively because of the artery's protected location within the foramen transversarium. Although exposure from an anterior approach can be accomplished by removing the anterior elements of the bony canal and the tough fascia covering the artery between the elements, typically the most efficacious control of such injuries is angioembolization. Fogarty catheter balloon occlusion may be useful for controlling acute bleeding.

Blunt injury to the carotid or vertebral arteries may cause dissection, thrombosis, or pseudoaneurysm, typically in the surgically inaccessible distal internal carotid (Fig. 7-53).[44] Early recognition and management of these injuries is paramount, because patients treated with antithrombotics have a stroke rate of <1% compared with stroke

rates between 5 and 50% in untreated patients based on grade of injury. Because treatment must be instituted during the latent period between injury and onset of neurologic sequelae, diagnostic imaging is performed based on identified screening criteria (Fig. 7-54).[45] After identification of an injury, antithrombotics are administered if the patient does not have contraindications (intracranial hemorrhage, falling hemoglobin level with solid organ injury or pelvic fracture). Heparin, started without a loading dose at 15 units/kg per hour, is titrated to achieve a PTT between 40 and 50 seconds or antiplatelet agents are initiated (aspirin 325 mg/d and clopidogrel 75 mg/d). The types of antithrombotic treatment appear equivalent in published studies to date, and the duration of treatment is empirically recommended to be 6 months.[46,47] Thrombosis of the internal jugular veins caused by blunt trauma can occur unilaterally or bilaterally and is often discovered incidentally, because most patients are asymptomatic. Bilateral thrombosis can aggravate cerebral edema in patients with serious head injuries; stent placement should be considered in such patients if ICP remains elevated.

Fig. 7-53.



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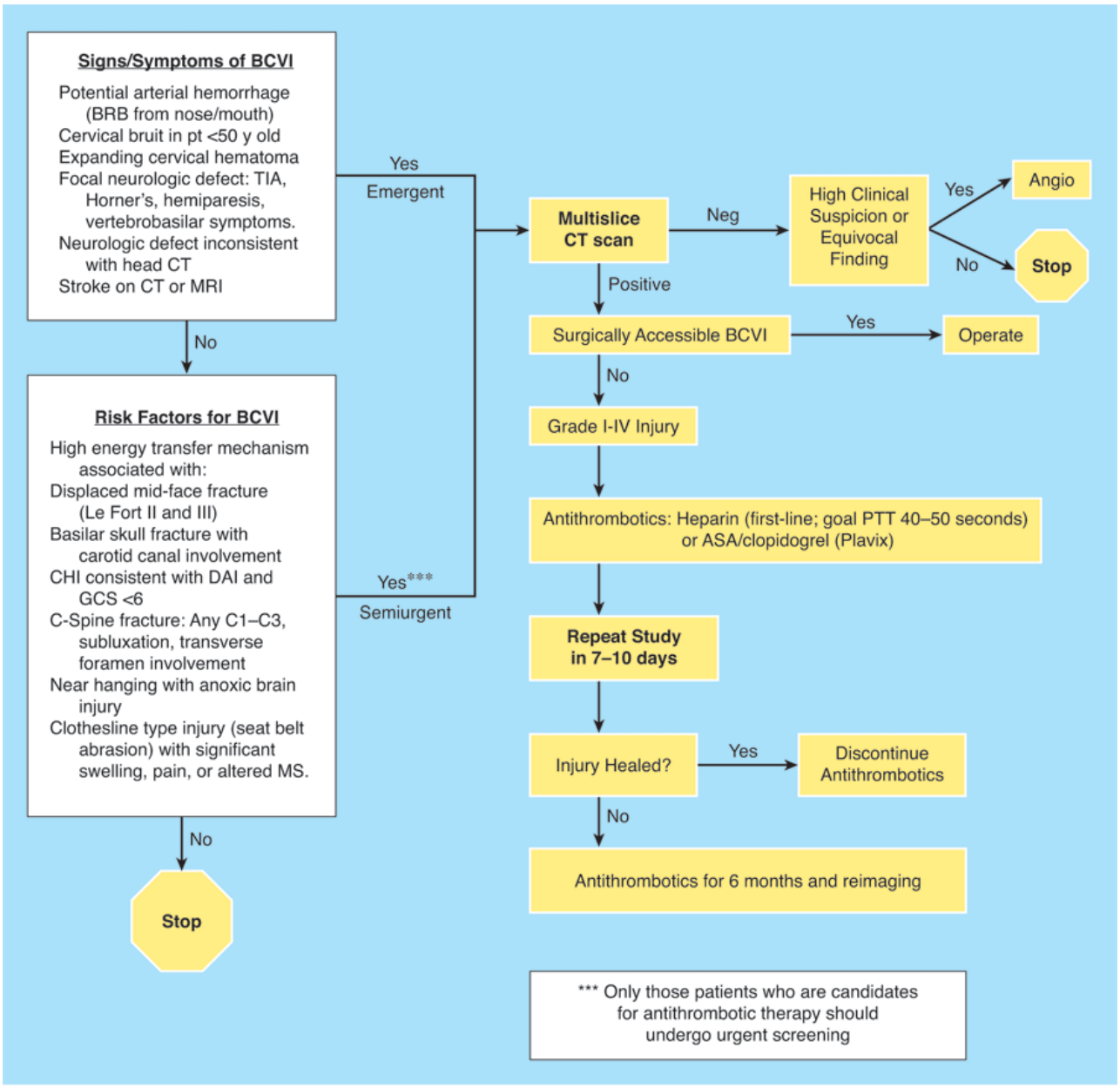
The Denver grading scale for blunt cerebrovascular injuries. Grade I: irregularity of the vessel wall, dissection/intramural hematoma with <25% luminal stenosis. Grade II: visualized intraluminal thrombus or raised intimal flap, or dissection/intramural hematoma with 25% or more luminal narrowing. Grade III: pseudoaneurysm. Grade IV: vessel occlusion. Grade V: vessel transection. CAI = carotid artery injury; VAI = vertebral artery injury.

Fig. 7-54.



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Screening and treatment algorithm for blunt cerebrovascular injuries (BCVIs). Angio = angiography; ASA = acetylsalicylic acid; BRB = bright red blood; CHI = closed head injury; C-spine = cervical spine; CT = computed tomography; DAI = diffuse axonal injury; GCS = Glasgow Coma Scale score; MRI = magnetic resonance imaging; MS = mental status; Neg = negative; pt = patient; PTT = partial thromboplastin time; TIA = transient ischemic attack.

Chest Injuries

The most common injuries from both blunt and penetrating thoracic trauma are hemothorax and pneumothorax. Few require operative intervention because >85% of patients can be definitively treated with a chest tube. The indications for thoracotomy include significant initial or ongoing hemorrhage from the tube thoracostomy and specific imaging-identified diagnoses (Table 7-10). One caveat concerns the patient who presents after a delay. Even when the initial chest tube output is 1.5 L, if the output ceases and the lung is re-expanded, the patient may be managed through observation.

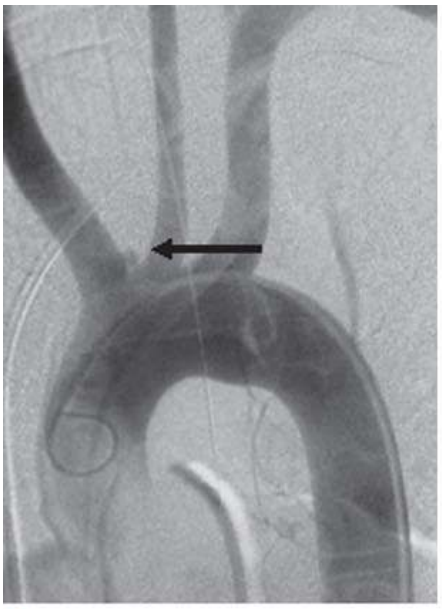
Table 7-10 Indications for Operative Treatment of Thoracic Injuries
• Initial tube thoracostomy drainage of >1000 mL (penetrating injury) or >1500 mL (blunt injury)
• Ongoing tube thoracostomy drainage of >200 mL/h for 3 consecutive hours in noncoagulopathic patients
• Caked hemothorax despite placement of two chest tubes
• Selected descending torn aortas
• Great vessel injury (endovascular techniques may be used in selected patients)
• Pericardial tamponade

• Cardiac herniation
• Massive air leak from the chest tube with inadequate ventilation
• Tracheal or main stem bronchial injury diagnosed by endoscopy or imaging
• Open pneumothorax
• Esophageal perforation

GREAT VESSELS

Over 90% of thoracic great vessel injuries are due to penetrating trauma, although blunt injury to the innominate, subclavian, or descending aorta may cause a pseudoaneurysm or frank rupture.[22,48,49] Simple lacerations of the ascending or transverse aortic arch can be repaired with lateral aortorrhaphy. Repair of posterior injuries, or those requiring interposition grafting of the arch, call for cardiopulmonary bypass, and repair of complex injuries may require circulatory arrest. Innominate artery injuries are repaired using the bypass exclusion technique,[49] which avoids the need for cardiopulmonary bypass. Bypass grafting from the proximal aorta to the distal innominate with a prosthetic tube graft is performed before the postinjury hematoma is entered. The PTFE graft is anastomosed end to side from the proximal undamaged aorta and anastomosed end to end to the innominate artery (Fig. 7-55). The origin of the innominate is then oversewn at its base to exclude the pseudoaneurysm or other injury. Subclavian artery injuries can be repaired using lateral arteriorrhaphy or PTFE graft interposition; due to its multiple branches and tethering of the artery, end-to-end anastomosis is not advocated.

Fig. 7-55.



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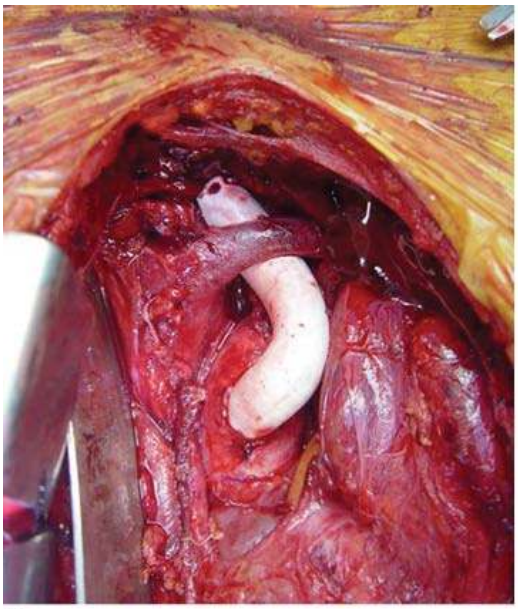

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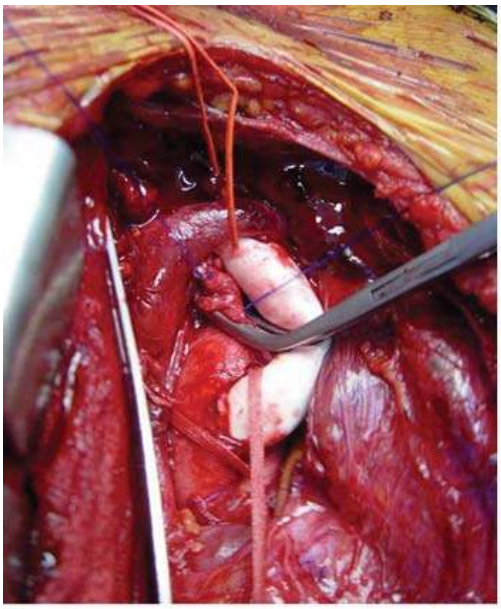

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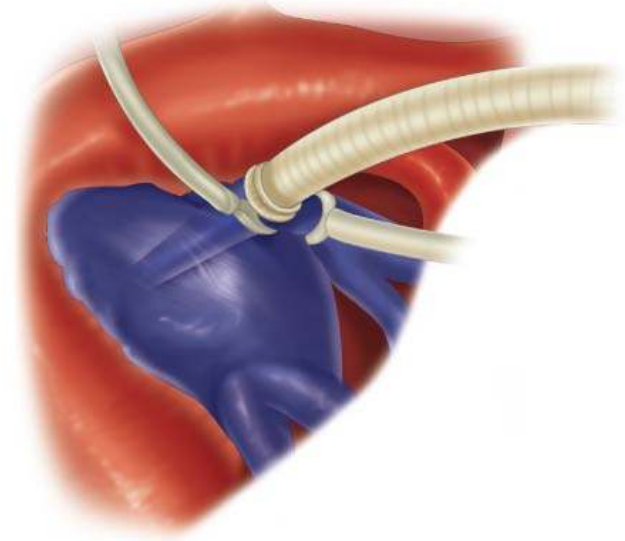
A. Angiography reveals a 1-cm pseudoaneurysm of the innominate artery origin. **B.** In the first stage of the bypass exclusion technique, a 12-mm polytetrafluoroethylene graft is anastomosed end to side from the proximal undamaged aorta, tunneled under the vein, and anastomosed end to end to the innominate artery. **C.** The origin of the innominate is then oversewn at its base to exclude the pseudoaneurysm.

Descending thoracic aortic injuries may require urgent if not emergent intervention. However, operative intervention for intracranial or intra-abdominal hemorrhage or unstable pelvic fractures takes precedence. To prevent aortic rupture, pharmacologic therapy with an esmolol infusion should be instituted in the trauma bay, with a target SBP of <100 mmHg and heart rate of <100/min.[50] Open operative reconstruction of the thoracic aorta remains the mainstay of treatment,[19,51] although endovascular stenting is being used more frequently as the technology improves.[52] Endovascular techniques are particularly appealing in patients who cannot tolerate single lung ventilation, patients >65 years old who are at risk for cardiac decompensation with aortic clamping, or patients with uncontrolled intracranial hypertension. The major limitations are current endograft sizes, which are too large compared to the diameter of the thoracic aorta, and a lack of long-term follow-up data in young patients.

Open repair of the descending aorta entails placement of an interposition graft using partial left heart bypass.[53] With the patient in a right lateral decubitus position, the patient's hips and legs are rotated 45 degrees toward the supine position to gain access to the left groin for common femoral artery cannulation. Using a left posterolateral thoracotomy, the fourth rib is transected to expose the aortic arch and left pulmonary hilum. Partial left heart bypass is performed by cannulating the superior pulmonary

vein with return through the left common femoral artery (Fig. 7-56). A centrifugal pump provides flow rates of 2.5 to 4 L/min to maintain a distal perfusion pressure of >65 mmHg. This prevents ischemic injury of the spinal cord as well as the splanchnic bed, and reduces left ventricular afterload.[19] Heparinization is not required, a significant benefit in patients with multiple injuries, particularly in those with intracranial hemorrhage. Unless contraindicated, however, low-dose heparin (100 units/kg) typically is administered to prevent thromboembolic events. Once bypass is initiated, vascular clamps are applied on the aorta between the left common carotid and left subclavian arteries, on the left subclavian, and on the aorta distal to the injury. In most patients a short PTFE graft (usually 18 mm in diameter) is placed using a running 3-0 polypropylene suture. Primary arterial repair should be done when possible. Air and thrombus are flushed from the aortic graft before the final suture is tied, and the occluding vascular clamps are removed. The patient is then weaned from the centrifugal pump, the cannulas are removed, and primary repair of the cannulated vessels is performed.

Fig. 7-56.



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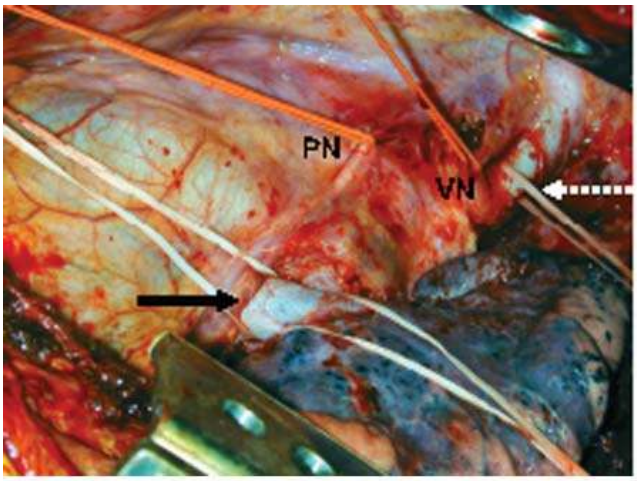

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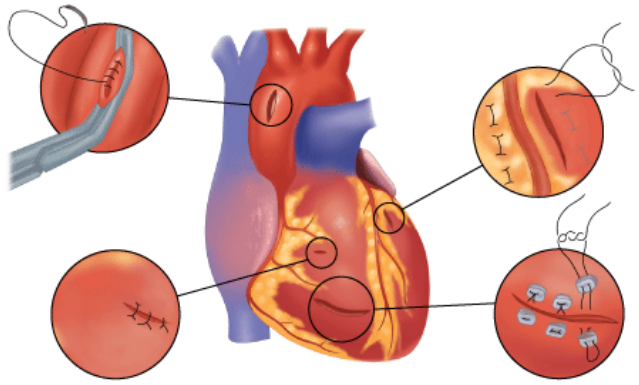
When a tear of the descending thoracic aorta is repaired, perfusion of the spinal cord while the aorta is clamped is achieved by using partial left heart bypass. The venous cannula is inserted into the left superior pulmonary vein (*solid arrow*) because it is less prone to tearing than the left atrium. The subclavian artery (*dashed arrow*) is identified for vascular control. The phrenic nerve (PN) and vagus nerve (VN) should be identified during mediastinal exploration to prevent inadvertent injury.

HEART

Blunt and penetrating cardiac injuries have widely differing presentations and therefore disparate treatments. Survivable penetrating cardiac injuries consist of wounds that can be closed; most are stab wounds. Before repair of the injury is attempted, hemorrhage should be controlled; injuries to the atria can be clamped with a Satinsky vascular clamp, whereas digital pressure occludes the majority of ventricular wounds. Foley catheter occlusion of larger stellate lesions may be effective, but even minimal traction may enlarge the original injury. Temporary control of hemorrhage, and at times definitive repair, may be accomplished with skin staples for left ventricular lacerations. Definitive repair of cardiac injuries is performed with either running 3-0 polypropylene suture or interrupted, pledgeted 2-0 polypropylene suture (Fig. 7-57).[54]

Use of pledgets may be particularly effective in the right ventricle to prevent sutures from pulling through the thinner myocardium. Injuries adjacent to coronary arteries should be repaired using horizontal mattress sutures, because use of running sutures results in coronary occlusion and distal infarction. Gunshot wounds may result in stellate lesions or contused, extremely friable myocardium adjacent to the wound. When the edges of such complex wounds cannot be fully approximated and hence the repair is not hemostatic, the authors have used surgical adhesive (BioGlue) to achieve hemostasis. Occasionally, interior structures of the heart may be damaged. Intraoperative auscultation or postoperative hemodynamic assessment usually identifies such injuries.[55] Echocardiography can diagnose the injury and quantitate its effect on cardiac output. Immediate repair of valvular damage or septal defects rarely is necessary and would require cardiopulmonary bypass, which is associated with a high mortality in this situation.

Fig. 7-57.



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A variety of techniques may be necessary to repair cardiac wounds. Generally, pledget support is used for the relatively thin-walled right ventricle.

Patients with blunt cardiac injury typically present with persistent tachycardia or rhythm disturbances, but occasionally present with tamponade due to atrial or right ventricular rupture. There are no pathognomonic ECG findings, and cardiac enzyme levels do not correlate with the risk of cardiac complications.[10] Therefore, patients for whom there is high clinical suspicion of cardiac contusion and who are hemodynamically stable should be monitored for dysrhythmias for 24 hours by telemetry. Patients with hemodynamic instability should undergo echocardiography to evaluate for wall motion abnormalities, valvular dysfunction, chordae rupture, or diminished ejection fraction. If such findings are noted or if vasoactive agents are required, cardiac function can be continuously monitored using a pulmonary artery catheter. A precisely timed blow to the precordium can provoke sudden cardiac death, termed *commotio cordis.*[56] This phenomenon, affecting primarily adolescent males, usually is fatal unless cardiopulmonary resuscitation and defibrillation are instituted immediately.

TRACHEA, BRONCHI, PULMONARY PARENCHYMA, AND ESOPHAGUS

Fewer than 1% of all injured patients sustain intrathoracic tracheobronchial injuries, and only a small number require operative intervention. Although penetrating injuries may occur throughout the tracheobronchial system, blunt injuries occur within 2.5 cm of the carina. For patients with a massive air leak requiring emergent exploration, initial control of the injury to provide effective ventilation is obtained by passing an endotracheal tube either beyond the injury or into the contralateral mainstem bronchus. Principles of repair are similar to those for repair of cervical tracheal injuries. Devitalized tissue is débrided, and primary end-to-end anastomosis with 3-0 PDS suture is performed. Dissection should be careful and limited to the area of injury to prevent disruption of surrounding bronchial vasculature and ensuing ischemia and stricture. Suture lines should be encircled with vascularized tissue, either pericardium, intercostal muscle, or pleura. Expectant management is employed for bronchial injuries that are less than one-third the circumference of the airway and have no evidence of a persistent major air leak. In patients with peripheral bronchial injuries, indicated by persistent air leaks from the chest tube and documented by endoscopy, bronchoscopically directed fibrin glue sealing is occasionally required.

Injuries to the pulmonary parenchyma typically are discovered during exploration for a massive hemothorax after penetrating trauma. Peripheral lacerations with persistent bleeding can be managed with stapled wedge resection. More central injuries traditionally have been managed with pulmonary lobectomy or pneumonectomy. But current treatment relies on pulmonary tractotomy, which permits selective ligation of individual bronchioles and bleeders, prevents the development of an intraparenchymal hematoma or air embolism, and reduces the need for formal lobar resection (see Fig. 7-49).[57,58] A stapling device, preferably the longest GIA stapler available, is inserted directly into the injury track and positioned along the thinnest section of overlying parenchyma. The injury track is thus filleted open, which allows direct access to the bleeding vessels and leaking bronchi. The majority of injuries are definitively managed with selective ligation, and the defect is left open. Occasionally, tractotomy reveals a more proximal vascular injury that must be treated with formal lobectomy. Parenchymal injuries severe enough to mandate pneumonectomy usually are fatal because of right heart decompensation, and major pulmonary hilar injuries necessitating pneumonectomy are usually lethal in the field.[59]

One parenchymal injury that may be incidentally discovered during thoracic imaging is a posttraumatic pulmonary pseudocyst, colloquially termed a *pneumatocele.* Traumatic pneumatoceles typically follow a benign clinical course and are treated with aggressive pain management, pulmonary toilet, and serial chest radiography to monitor for resolution of the lesion. If the patient has persistent fever or leukocytosis, however, chest CT is done to evaluate for an evolving abscess, because up to 30% of pneumatoceles become infected. CT-guided catheter drainage may be required in such cases, because 25% of patients do not respond to antibiotic therapy alone. Surgery, ranging from partial resection to anatomic lobectomy, is indicated for unresolving complex pneumatoceles or infected lesions refractory to antibiotic therapy and drainage.

The most common complication after thoracic injury is development of an empyema. Management is based on CT diagnostic criteria. Percutaneous drainage is indicated for single loculations without appreciable rind. Early decortication via video-assisted thoracic surgery is pursued in patients with multiple loculations or a pleural rind of >1 cm.[60] Antibiotic treatment is based on definitive culture results.

Due to the proximity of the structures, esophageal injuries often occur with tracheobronchial injuries, particularly in cases of penetrating trauma. Operative options are based on the extent and location of esophageal injury. With sufficient mobilization, a primary single-layer end-to-end anastomosis may be performed after appropriate débridement. As with cervical repairs, if there are two suture lines in close approximation (trachea or bronchi and esophagus) interposition of a vascularized pedicle will prevent fistula formation. Perforations close to the gastroesophageal junction may be best treated with segmental resection and gastric pull-up. With large destructive injuries or delayed presentation of injuries, esophageal exclusion with wide drainage, diverting loop esophagostomy, and placement of a gastrostomy tube should be considered.

CHEST WALL AND DIAPHRAGM

Virtually all chest wall injuries, consisting of rib fractures and laceration of intercostal vessels, are treated nonoperatively with pain control, pulmonary toilet or ventilatory management, and drainage of the pleural space as indicated. Early institution of effective pain control is essential. The authors advocate rib blocks with 0.25% bupivacaine hydrochloride (Marcaine) in the trauma bay, followed by epidural placement supplemented with patient-controlled anesthesia. Persistent hemorrhage from a chest tube after blunt trauma most often is due to injured intercostal arteries; for unusual persistent bleeding (see Table 7-10), thoracotomy with direct ligation or angioembolization may be required to arrest hemorrhage. In rare cases of extensive flail chest segments or markedly displaced rib fractures, open reduction and internal fixation of the fracture with plates may be warranted. Chest wall defects, particularly those seen with open pneumothorax, are repaired using local approximation of tissues or tissue transfer for coverage. Scapular and sternal fractures rarely require operative intervention but are markers for significant thoracoabdominal force during injury. Careful examination and imaging should exclude associated injuries, including blunt cardiac injury and aortic tears. On the other hand, clavicle fractures often are isolated injuries and should be managed with pain control and immobilization. The exception is posterior dislocation of the clavicular head, which may injure the subclavian vessels.

Blunt diaphragmatic injuries result in a linear tear in the central tendon, whereas penetrating injuries are variable in size and location depending on the agent of injury. Regardless of the etiology, acute injuries are repaired through an abdominal incision or with thoracoscopy/laparoscopy. After delineation of the injury, the chest should be evacuated of all blood and particulate matter, and thoracostomy tube placed if not previously done. Allis clamps are used to approximate the diaphragmatic edges, and the defect is closed with a running No. 1 polypropylene suture. Occasionally, large avulsions or shotgun wounds with extensive tissue loss will require polypropylene mesh or acellular dermal matrix (AlloDerm) to bridge the defect. Alternatively, transposition of the diaphragm cephalad one to two intercostal spaces may allow repair without undue tension.[61]

Abdominal Injuries

LIVER AND GALLBLADDER

The liver's large size makes it the organ most susceptible to blunt trauma, and it is frequently involved in upper torso penetrating wounds. Nonoperative management of solid organ injuries is pursued in hemodynamically stable patients who do not have overt peritonitis or other indications for laparotomy. These patients should be admitted to the SICU with frequent hemodynamic monitoring, determination of hematocrit, and abdominal examination. The only absolute contraindication to nonoperative management is hemodynamic instability. Factors such as high injury grade, large hemoperitoneum, contrast extravasation, or pseudoaneurysms may predict complications or failure of nonoperative management. However, angioembolization and endoscopic retrograde cholangiopancreatography (ERCP) are useful adjuncts that can improve the success rate of nonoperative management.[62,63] The indication for angiography to control hepatic hemorrhage is transfusion of 4 units of RBCs in 6 hours or 6 units of RBCs in 24 hours without hemodynamic instability.

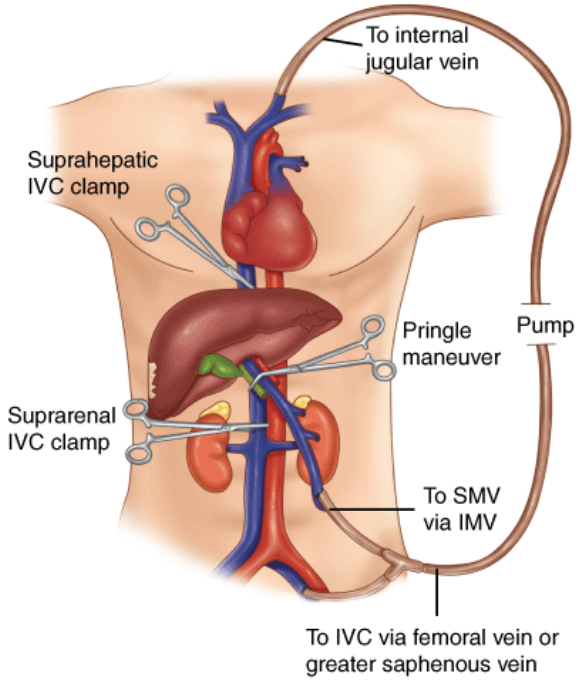
In the >10% of patients for whom emergent laparotomy is mandated, the primary goal is to arrest hemorrhage. Initial control of hemorrhage is best accomplished using perihepatic packing and manual compression. In either case, the edges of the liver laceration should be opposed for local pressure control of bleeding. Hemorrhage from most major hepatic injuries can be controlled with effective perihepatic packing. The right costal margin is elevated, and the pads are strategically placed over and around the bleeding site (see Fig. 7-36). Additional pads should be placed between the liver, diaphragm, and anterior chest wall until the bleeding has been controlled. Ten to 15 pads may be required to control the hemorrhage from an extensive right lobar injury. Packing of injuries of the left lobe is not as effective, because there is insufficient abdominal and thoracic wall anterior to the left lobe to provide adequate compression with the abdomen open. Fortunately, hemorrhage from the left lobe usually can be controlled by mobilizing the lobe and compressing it between the surgeon's hands. If the patient has persistent bleeding despite packing, injuries to the hepatic artery, portal vein, and retrohepatic vena cava should be considered. The Pringle maneuver can help delineate the source of hemorrhage. Hemorrhage from hepatic artery and portal vein injuries will halt with the application of a vascular clamp across the portal triad, whereas bleeding from the hepatic veins and retrohepatic vena cava will not.

Injuries of the portal triad vasculature should be addressed immediately. In general, ligation from the celiac axis to the level of the common hepatic artery at the gastroduodenal arterial branch is tolerated due to the extensive collaterals, but the proper hepatic artery should be repaired. The right or left hepatic artery, or in urgent situations the portal vein, may be selectively ligated; occasionally, lobar necrosis will necessitate delayed anatomic resection. If the right hepatic artery is ligated, cholecystectomy also should be performed. If the vascular injury is a stab wound with clean transection of the vessels, primary end-to-end repair is done. If the injury is destructive, temporary shunting should be performed followed by interposition reversed saphenous vein graft (RSVG). Blunt avulsions of the portal structures are particularly problematic if located at the hepatic plate, flush with the liver; hemorrhage control at the liver can be attempted with directed packing or Fogarty catheters. If the avulsion is more proximal, flush with the border of the pancreatic body or even retropancreatic, the pancreas must be transected to gain access for hemorrhage control and repair.

If massive venous hemorrhage is seen from behind the liver despite use of the Pringle maneuver, the patient likely has a hepatic vein or retrohepatic vena cava injury. If bleeding is controlled, the packing should be left undisturbed and the patient observed in the SICU. If bleeding continues despite repeat perihepatic packing, then direct

repair, with or without hepatic vascular isolation, should be attempted. Three techniques have been used to accomplish hepatic vascular isolation: (a) isolation with clamps on the diaphragmatic aorta, the suprarenal vena cava, and the suprahepatic vena cava; (b) atriocaval shunt; and (c) Moore-Pilcher balloon shunt. All techniques are performed with an associated Pringle maneuver. Even in experienced centers with readily available equipment, however, such techniques carry a mortality rate of >80%. Instead, recent efforts to control this highly lethal injury have used venovenous bypass (Fig. 7-58).[64]

Fig. 7-58.



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Venovenous bypass permits hepatic vascular isolation with continued venous return to the heart. IMV = inferior mesenteric vein; IVC = inferior vena cava; SMV = superior mesenteric vein.

Numerous methods for the definitive control of hepatic parenchymal hemorrhage have been developed. Minor lacerations may be controlled with manual compression applied directly to the injury site. Topical hemostatic techniques include the use of an electrocautery (with the device set at 100 watts), argon beam coagulator, microcrystalline collagen, thrombin-soaked gelatin foam sponge, fibrin glue, and BioGlue. Suturing of the hepatic parenchyma is an effective hemostatic technique. However, the "liver suture," blunt 0 chromic suture, may tear the liver capsule, and its use generally is discouraged due to the associated hepatic necrosis. A running suture is used to approximate the edges of shallow lacerations, whereas deeper lacerations are approximated using interrupted horizontal mattress sutures placed parallel to the edge of the laceration. When the suture is tied, tension is adequate when visible hemorrhage ceases or the liver blanches around the suture. This technique of placing large liver sutures controls bleeding through reapproximation of the liver laceration rather than direct ligation of bleeding vessels. Aggressive finger fracture to identify bleeding vessels followed by individual clip or suture ligation was advocated previously but currently has a limited role in hemostasis. Hepatic lobar arterial ligation may be appropriate for patients with recalcitrant arterial hemorrhage from deep within the liver and is a reasonable alternative to a deep hepatotomy, particularly in unstable patients. Omentum can be used to fill large defects in the liver. The tongue of omentum not only obliterates potential dead space with viable tissue but also provides an excellent source of macrophages. Additionally, the omentum can provide buttressing support for parenchymal sutures.

Translobar penetrating injuries are particularly challenging, because the extent of the injury cannot be fully visualized. As discussed later in "Damage Control Surgery," options include intraparenchymal tamponade with a Foley catheter or balloon occlusion (see Fig. 7-48).[65] If tamponade is successful with either modality, the balloon is left inflated for 24 to 48 hours followed by judicious deflation in the SICU and removal at a second laparotomy. Hepatotomy, using the finger fracture technique, with ligation of individual bleeders occasionally may be required. However, division of the overlying viable hepatic tissue may cause considerable blood loss in the coagulopathic patient. Finally, angioembolization is an effective adjunct in any of these scenarios and should be considered early in the course of treatment.

Several centers have reported patients with devastating hepatic injuries or necrosis of the entire liver who have undergone successful hepatic transplantation. Clearly this is dramatic therapy, and the patient must have all other injuries delineated, particularly those of the central nervous system, and have an excellent chance of survival excluding the hepatic injury. Because donor availability will limit such procedures, hepatic transplantation for trauma will continue to be performed only in extraordinary circumstances.

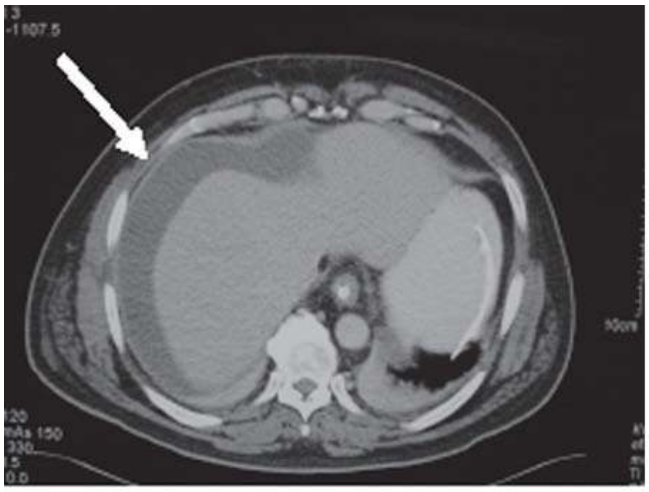
Cholecystectomy is performed for injuries of the gallbladder and after operative ligation of the right hepatic artery. Injuries of the extrahepatic bile ducts are a challenge due to their small size and thin walls. Because of the proximity of other portal structures and the vena cava, associated vascular injuries are common. These factors may preclude primary repair. Small lacerations with no accompanying loss or devitalization of adjacent tissue can be treated by the insertion of a T tube through the wound or by

lateral suturing using 6-0 monofilament absorbable suture. Virtually all transections and any injury associated with significant tissue loss will require a Roux-en-Y choledochojejunostomy.[66] The anastomosis is performed using a single-layer interrupted technique with 4-0 or 5-0 monofilament absorbable suture. To reduce anastomotic tension, the jejunum can be sutured to the areolar tissue of the hepatic pedicle or porta hepatis. Injuries of the hepatic ducts are almost impossible to satisfactorily repair under emergent circumstances. One approach is to intubate the duct for external drainage and attempt a repair when the patient recovers. Alternatively, the duct can be ligated if the opposite lobe is normal and uninjured.

Patients undergoing perihepatic packing for extensive liver injuries typically are returned to the OR for pack removal 24 to 48 hours after initial injury. Earlier exploration may be indicated in patients with evidence of ongoing hemorrhage. Signs of rebleeding include a falling hematocrit, accumulation of blood clots under the temporary abdominal closure device, and bloody output from drains; the magnitude of hemorrhage is reflected in hemodynamic instability and the findings of metabolic monitoring. Patients with hepatic ischemia due to prolonged intraoperative use of the Pringle maneuver have an expected elevation but subsequent resolution of transaminases levels, whereas patients requiring hepatic artery ligation may have frank hepatic necrosis. Although patients should be evaluated for infectious complications, patients with complex hepatic injuries typically have intermittent "liver fever" for the first 5 days after injury.

The complications after significant hepatic trauma include delayed hemorrhage, bilomas, hepatic necrosis, arterial pseudoaneurysms, and various fistulas (Fig. 7-59). In patients requiring perihepatic packing, postoperative hemorrhage should be re-evaluated in the OR once the patient's coagulopathy is corrected. Alternatively, angioembolization is appropriate for complex injuries. Bilomas are loculated collections of bile, which may or may not be infected. If infected, they should be treated like an abscess via percutaneous drainage. Although small, sterile bilomas eventually will be reabsorbed, larger fluid collections should also be drained. Biliary ascites, due to the disruption of a major bile duct, often requires reoperation and wide drainage. Primary repair of the injured duct is unlikely to be successful. Resectional débridement is indicated for the removal of peripheral portions of nonviable hepatic parenchyma.

Fig. 7-59.



A

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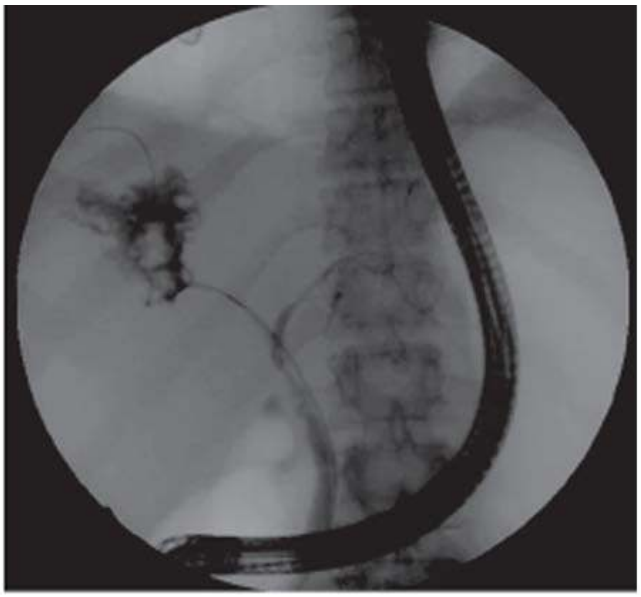

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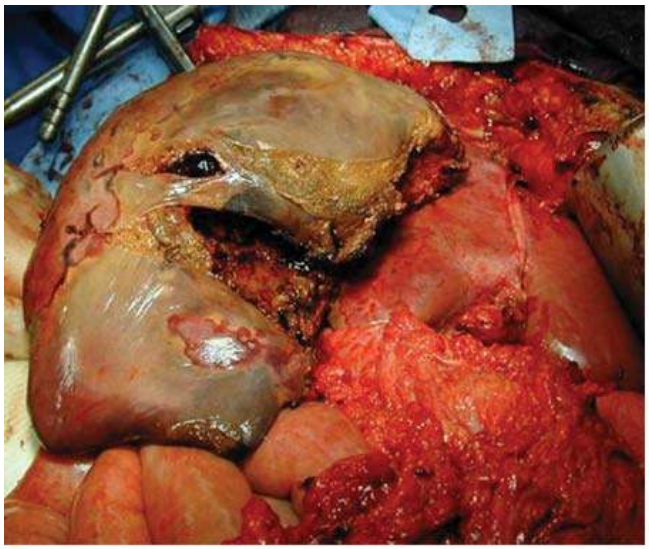

C

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Complications after hepatic trauma include bilomas (**A;***arrow*), hepatic duct injuries (**B**), and hepatic necrosis after hepatic artery ligation or embolization (**C**).

Pseudoaneurysms and biliary fistulas are rare complications in patients with hepatic injuries. Because hemorrhage from hepatic injuries often is treated without isolating individual bleeding vessels, arterial pseudoaneurysms may develop, with the potential for rupture. Rupture into a bile duct results in hemobilia, which is characterized by intermittent episodes of right upper quadrant pain, upper GI hemorrhage, and jaundice. If the aneurysm ruptures into a portal vein, portal venous hypertension with bleeding esophageal varices may occur. Either scenario is best managed with hepatic arteriography and embolization. Biliovenous fistulas, causing jaundice due to rapid increases in serum bilirubin levels, should be treated with ERCP and sphincterotomy. Rarely, a biliary fistulous communication will form with intrathoracic structures in patients with associated diaphragm injuries, resulting in a bronchobiliary or pleurobiliary fistula. Due to the pressure differential between the biliary tract (positive) and the pleural cavity (negative), the majority require operative closure. Occasionally, endoscopic sphincterotomy with stent placement will effectively address the pressure differential, and the pleurobiliary fistula will close spontaneously.

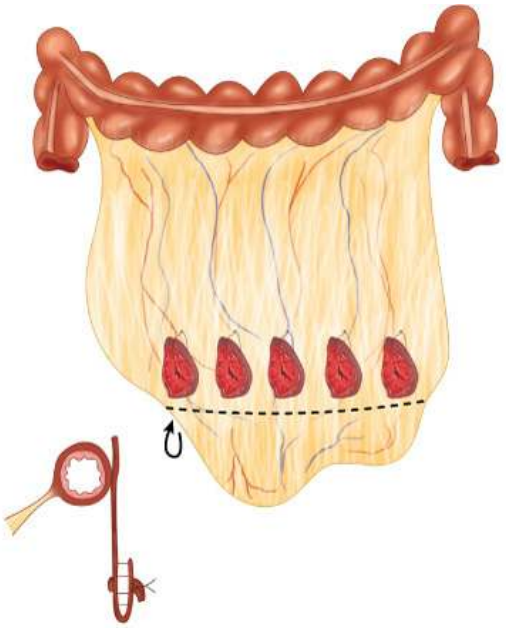
SPLEEN

Until the 1970s, splenectomy was considered mandatory for all splenic injuries. Recognition of the immune function of the spleen refocused efforts on operative splenic salvage in the 1980s.[67,68] After success in pediatric patients, nonoperative management has become the preferred means of splenic salvage. The identification of contrast extravasation as a risk factor for failure of nonoperative management led to liberal use of angioembolization. The true value of angioembolization in splenic salvage has not been rigorously evaluated. It is clear, however, that 20 to 30% of patients with splenic trauma deserve early splenectomy and that failure of nonoperative management

often represents poor patient selection.[69,70] Unlike hepatic injuries, which rebleed in 24 to 48 hours, delayed hemorrhage or rupture of the spleen can occur up to weeks after injury. Indications for prompt laparotomy include initiation of blood transfusion within the first 12 hours and hemodynamic instability.

Splenic injuries are managed operatively by splenectomy, partial splenectomy, or splenic repair (splenorrhaphy), based on the extent of the injury and the physiologic condition of the patient. Splenectomy is indicated for hilar injuries, pulverized splenic parenchyma, or any injury of grade II or higher in a patient with coagulopathy or multiple injuries. The authors use autotransplantation of splenic implants (Fig. 7-60) to achieve partial immunocompetence in younger patients.[71] Drains are not used. Partial splenectomy can be employed in patients in whom only the superior or inferior pole has been injured. Hemorrhage from the raw splenic edge is controlled with horizontal mattress sutures, with gentle compression of the parenchyma (Fig. 7-61). As in repair of hepatic injuries, in splenorrhaphy hemostasis is achieved by topical methods (electrocautery; argon beam coagulation; application of thrombin-soaked gelatin foam sponges, fibrin glue, or BioGlue), envelopment of the injured spleen in absorbable mesh, and pledgeted suture repair.

Fig. 7-60.



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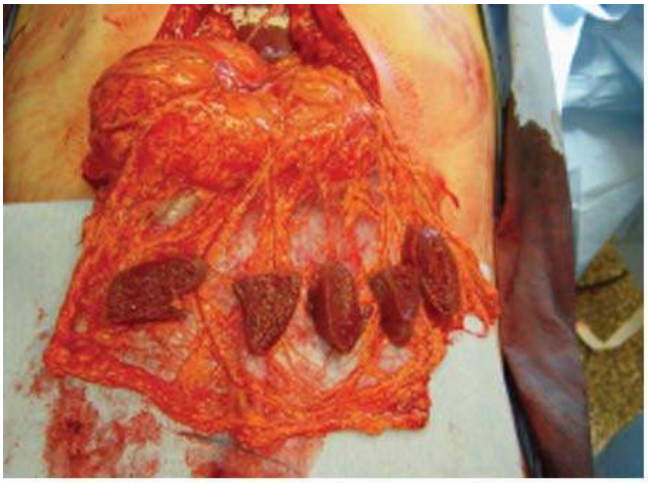

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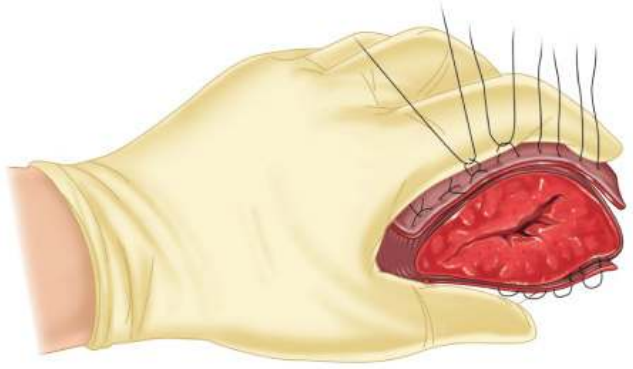
Autologous splenic transplantation is performed by placing sections of splenic parenchyma, 40 x 40 x 3 mm in size, into pouches in the greater omentum.

Fig. 7-61.



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Interrupted pledgeted sutures may effectively control hemorrhage from the cut edge of the spleen.

After splenectomy or splenorrhaphy, postoperative hemorrhage may be due to loosening of a tie around the splenic vessels, an improperly ligated or unrecognized short gastric artery, or recurrent bleeding from the spleen if splenic repair was used. An immediate postsplenectomy increase in platelets and WBCs is normal; however, beyond postoperative day 5, a WBC count above 15,000/mm^3 and a platelet/WBC ratio of <20 are strongly associated with sepsis and should prompt a thorough search for underlying infection.[72] A common infectious complication after splenectomy is a subphrenic abscess, which should be managed with percutaneous drainage. Additional sources of morbidity include a concurrent but unrecognized iatrogenic injury to the pancreatic tail during rapid splenectomy resulting in pancreatic ascites or fistula. Enthusiasm for splenic salvage was driven by the rare, but often fatal, complication of overwhelming postsplenectomy sepsis. Overwhelming postsplenectomy sepsis is caused by encapsulated bacteria, *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis,* which are resistant to antimicrobial treatment. In patients undergoing splenectomy, prophylaxis against these bacteria is provided via vaccines administered optimally at 14 days.

STOMACH AND SMALL INTESTINE

Little controversy exists regarding the repair of injuries to the stomach or small bowel. Gastric wounds can be oversewn with a running single-layer suture line or closed with a transection/anastomosis (TA) stapler. If a single-layer closure is chosen, full-thickness bites should be taken to ensure hemostasis from the well-vascularized gastric wall. The most commonly missed gastric injury is the posterior wound of a through-and-through penetrating injury. Injuries also can be overlooked if the wound is located within the mesentery of the lesser curvature or high in the posterior fundus. To delineate a questionable injury, the stomach can be digitally occluded at the pylorus while methylene blue–colored saline is instilled via a nasogastric tube. Partial gastrectomy may be required for destructive injuries, with resections of the distal antrum or pylorus reconstructed using a Billroth I or II procedure. Patients with injuries that damage both Latarjet nerves or vagi should undergo a drainage procedure (see Chap. 26). Small intestine injuries can be repaired using a transverse running 3-0 PDS suture if the injury is less than one third the circumference of the bowel. Destructive injuries or multiple penetrating injuries occurring close together are treated with segmental resection followed by end-to-end anastomosis using a continuous, single-layer 3-0 polypropylene suture.[73] Mesenteric injuries may result in an ischemic segment of intestine, which mandates resection.

Following repair of GI tract injuries, there is an obligatory postoperative ileus. Return of bowel function is indicated by a decrease in gastrostomy or nasogastric tube output. The topic of nutrition is well covered in other chapters, but a few issues warrant mention. Multiple studies have confirmed the importance of early total enteral nutrition (TEN) in the trauma population, particularly its impact in reducing septic complications.[74] The route of enteral feedings (stomach vs. small bowel) tends to be less important, because gut tolerance appears equivalent unless there is upper GI tract pathology. Although early enteral nutrition is the goal, one should be wary with any bowel anastomoses; evidence of bowel function should be apparent before advancing to goal tube feedings. Overzealous jejunal feeding can lead to small bowel necrosis in the patient recovering from profound shock. Patients undergoing monitoring for nonoperative management of grade II or higher solid organ injuries should receive nothing by mouth for at least 48 hours in case they require an operation. Although there is general reluctance to initiate TEN in patients with an open abdomen, tube feeding by any route may be started within 24 hours of abdominal closure, because over 90% of patients will tolerate TEN. Moreover, in patients relegated to an open abdomen, TEN is frequently tolerated at low volumes—that is, trophic tube feeds (25 mL/h)—while active attempts are made to close fascia.

In general, wounds sustained from trauma should be examined daily for progression of healing and signs of infection. Complex soft tissue wounds of the abdomen, such as degloving injuries after blunt trauma (termed *Morel-Lavallee lesions*), shotgun wounds, and other destructive blast injuries, are particularly difficult to manage. Following initial débridement of devitalized tissue, wound care includes wet-to-dry dressing changes twice daily or application of a vacuum-assisted wound closure (VAC) device. Repeated operative débridement may be necessary, and early involvement of the reconstructive surgery service for possible flap coverage is advised. Midline laparotomy wounds are inspected 48 hours postoperatively by removing the sterile surgical dressing. If an ileostomy or colostomy was required, one should inspect it daily to ensure that it is viable. If the patient develops high-grade fever, the wound should be inspected sooner to exclude an early necrotizing infection. If a wound infection is identified—as evidenced by erythema, pain along the wound, or purulent drainage—the wound should be widely opened by removing skin staples. After ensuring that the midline fascia is intact with digital palpation, the wound is initially managed with wet-to-dry dressing changes. The most common intra-abdominal complications are anastomotic failure and abscess. The choice between percutaneous and operative therapy is based on the location, timing, and extent of the collection.

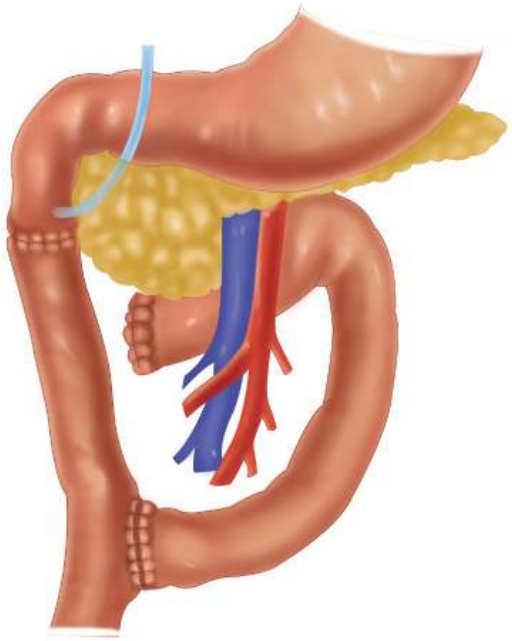
DUODENUM AND PANCREAS

The spectrum of injuries to the duodenum includes hematomas, perforation (blunt blow-outs, lacerations from stab wounds, or blast injury from gunshot wounds), and

combined pancreaticoduodenal injuries. The majority of duodenal hematomas are managed nonoperatively with nasogastric suction and parenteral nutrition. Patients with suspected associated perforation, suggested by clinical deterioration or imaging with retroperitoneal free air or contrast extravasation, should undergo operative exploration. A marked drop in nasogastric tube output heralds resolution of the hematoma, which typically occurs within 2 weeks; repeat imaging to confirm these clinical findings is optional. If the patient shows no clinical or radiographic improvement within 3 weeks, operative evaluation is warranted.

Small duodenal perforations or lacerations can be treated by primary repair using a running single-layer suture of 3-0 monofilament. The wound should be closed in a direction that results in the largest residual lumen. Challenges arise when there is a substantial loss of duodenal tissue. Extensive injuries of the first portion of the duodenum (proximal to the duct of Santorini) can be repaired by débridement and end-to-end anastomosis because of the mobility and rich blood supply of the distal gastric atrium and pylorus. In contrast, the second portion is tethered to the head of the pancreas by its blood supply and the ducts of Wirsung and Santorini; therefore, no more than 1 cm of duodenum can be mobilized away from the pancreas, and this does not effectively alleviate tension on the suture line. Moreover, suture repair using an end-to-end anastomosis in the second portion often results in an unacceptably narrow lumen. Therefore, defects in the second portion of the duodenum should be patched with a vascularized jejunal graft. Duodenal injuries with tissue loss distal to the papilla of Vater and proximal to the superior mesenteric vessels are best treated by Roux-en-Y duodenojejunostomy with the distal portion of the duodenum oversewn (Fig. 7-62). In particular, injuries in the distal third and fourth portions of the duodenum (behind the mesenteric vessels) should be resected, and a duodenojejunostomy performed on the left side of the superior mesenteric vessels.

Fig. 7-62.



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Roux-en-Y duodenojejunostomy is used to treat duodenal injuries between the papilla of Vater and superior mesenteric vessels when tissue loss precludes primary repair.

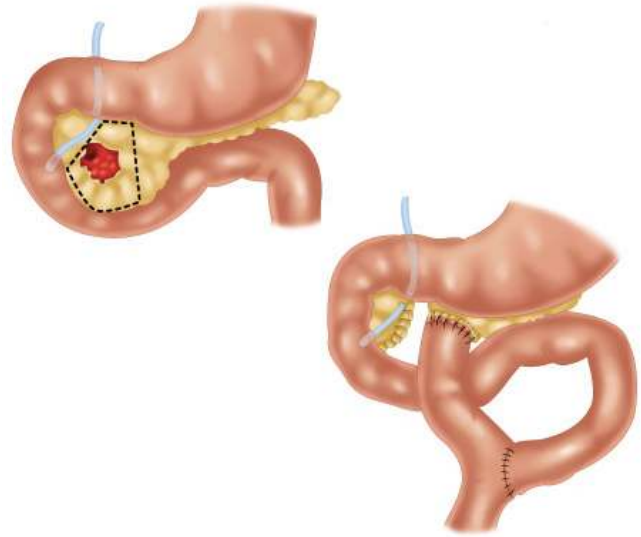
Optimal management of pancreatic trauma is determined by where the parenchymal damage is located and whether the intrapancreatic common bile duct and main pancreatic duct remain intact. Patients with pancreatic contusions (defined as injuries that leave the ductal system intact) can be treated nonoperatively or with closed suction drainage if undergoing laparotomy for other indications. In contrast, pancreatic injuries associated with ductal disruption require intervention to prevent a pancreatic fistula or ascites. To determine the integrity of the pancreatic duct, several options exist. Direct exploration of the parenchymal laceration will often confirm the diagnosis of a ductal injury. Operative pancreatography can be performed through a duodenotomy by cannulating the duct using a 5F pediatric feeding tube. Under fluoroscopy, full-strength contrast material is slowly injected while observing for obstruction or extravasation. An alternative to pancreatography is to pass a 1.5- to 2.0-mm coronary artery dilator into the main duct via the papilla and observe the depth of the pancreatic wound. If the dilator is seen in the wound, a ductal injury is confirmed. Either technique requires the creation of a duodenal wound and hence the potential for anastomotic leak and a lateral duodenal fistula; this possibility may dampen a surgeon's enthusiasm for this approach. A third method for identifying pancreatic ductal injuries is endoscopic retrograde pancreatography. Although challenging to perform emergently in the OR, it can be performed postoperatively once resuscitation is accomplished and is particularly advantageous in stable patients or those with a delayed presentation.

Several options exist for treating injuries of the pancreatic body and tail when the pancreatic duct is transected. In stable patients, spleen-preserving distal pancreatectomy should be performed. An alternative, which preserves both the spleen and distal transected end of the pancreas, is either a Roux-en-Y pancreaticojejunostomy or pancreaticogastrostomy. If the patient is physiologically compromised, distal pancreatectomy with splenectomy is the preferred approach. Regardless of the choice of definitive procedure, the pancreatic duct in the proximal edge of transected pancreas should be individually ligated or occluded with a TA stapler. Application of fibrin glue over the stump may be advantageous.

Injuries to the pancreatic head add an additional element of complication because the intrapancreatic portion of the common bile duct traverses this area and often

converges with the pancreatic duct. In contrast to diagnosis of pancreatic duct injuries, identification of intrapancreatic common bile duct disruption is relatively simple. The first method is to squeeze the gallbladder and look for bile leaking from the pancreatic wound. Otherwise, cholangiography, optimally via the cystic duct, is diagnostic. Definitive treatment of this injury entails division of the common bile duct superior to the first portion of the duodenum, with ligation of the distal duct and reconstruction with a Roux-en-Y choledochojejunostomy. For injuries to the head of the pancreas that involve the main pancreatic duct but not the intrapancreatic bile duct, there are few options. Distal pancreatectomy alone is rarely indicated due to the extended resection of normal gland and the resultant risk of pancreatic insufficiency. Central pancreatectomy preserves the common bile duct, and mobilization of the pancreatic body permits drainage into a Roux-en-Y pancreaticojejunostomy (Fig. 7-63). Although this approach avoids a pancreaticoduodenectomy (Whipple procedure), the complexity may make the pancreaticoduodenectomy more appropriate in patients with multiple injuries. Some injuries of the pancreatic head do not involve either the pancreatic or common bile duct; if no clear ductal injury is present, drains are placed. Rarely, patients sustain destructive injuries to the head of the pancreas or combined pancreaticoduodenal injuries that require pancreaticoduodenectomy. Examples of such injuries include transection of both the intrapancreatic bile duct and the main pancreatic duct in the head of the pancreas, avulsion of the papilla of Vater from the duodenum, and destruction of the entire second portion of the duodenum.

Fig. 7-63.



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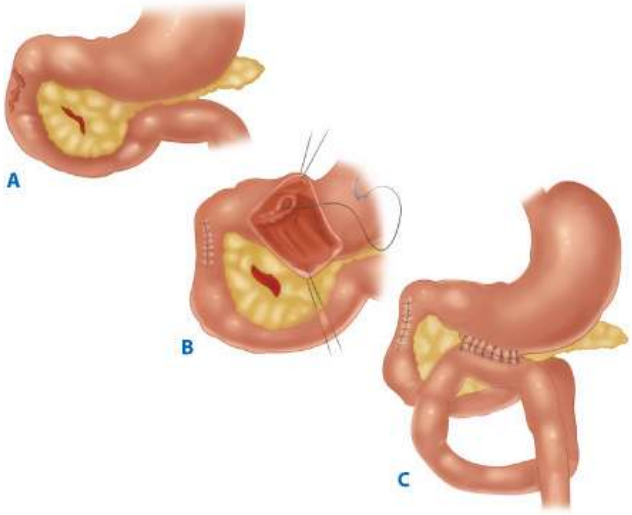
For injuries of the pancreatic head that involve the pancreatic duct but spare the common bile duct, central pancreatic resection with Roux-en-Y pancreaticojejunostomy prevents pancreatic insufficiency.

Pyloric exclusion often is used to divert the GI stream after high-risk, complex duodenal repairs (Fig. 7-64).[75] If the duodenal repair breaks down, the resultant fistula is an end fistula, which is easier to manage and more likely to close than a lateral fistula. To perform a pyloric exclusion, first a gastrostomy is made on the greater curvature near the pylorus. The pylorus is then grasped with a Babcock clamp, via the gastrostomy, and oversewn with an O polypropylene suture. A gastrojejunostomy restores GI tract continuity. Vagotomy is not necessary because a risk of marginal ulceration has not been documented. Perhaps surprisingly, the sutures maintain diversion for only 3 to 4 weeks. Alternatively, the most durable pyloric closure is a double external staple line across the pylorus using a TA stapler.

Fig. 7-64.



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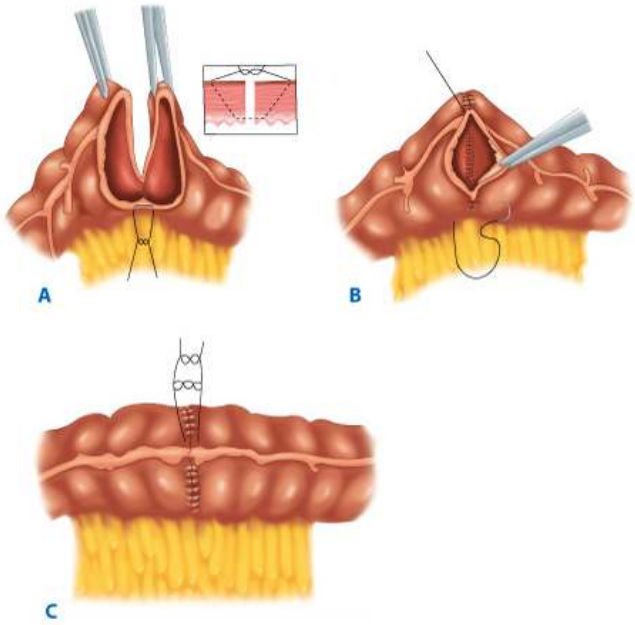
A. Pyloric exclusion is used to treat combined injuries of the duodenum and the head of the pancreas as well as isolated duodenal injuries when the duodenal repair is less than optimal. **B** and **C.** The pylorus is oversewn through a gastrotomy, which is subsequently used to create a gastrojejunostomy. The authors frequently use needle-catheter jejunostomy tube feedings for these patients.

Complications should be expected after such injuries. Delayed hemorrhage is rare but may occur with pancreatic necrosis or abdominal infection; this usually can be managed by angioembolization. If closed suction drains have been inserted for major pancreatic trauma, these should remain in place until the patient is tolerating an oral diet or enteral nutrition. Pancreatic fistula is diagnosed after postoperative day 5 in patients with drain output of >30 mL/d and a drain amylase level three times the serum value. Pancreatic fistula develops in over 20% of patients with combined injuries and should be managed similar to fistulas after elective surgery (see Chap. 33). Similarly, a duodenal fistula, presumptively an end fistula if a pyloric exclusion has been done, will typically heal in 6 to 8 weeks with adequate drainage and control of intra-abdominal sepsis. Pancreatic pseudocysts in patients managed nonoperatively suggest a missed injury, and ERCP should be done to evaluate the integrity of the pancreatic duct. Late pseudocysts may be a complication of operative management and are treated much like those in patients with pancreatitis (see Chap. 33). Intra-abdominal abscesses are common and routinely managed with percutaneous drainage.

COLON AND RECTUM

Currently, three methods for treating colonic injuries are used: primary repair, end colostomy, and primary repair with diverting ileostomy. Primary repairs include lateral suture repair or resection of the damaged segment with reconstruction by ileocolostomy or colocolostomy. All suturing and anastomoses are performed using a running single-layer technique (Fig. 7-65).[73] The advantage of definitive treatment must be balanced against the possibility of anastomotic leakage if suture lines are created under suboptimal conditions. Alternatively, although use of an end colostomy requires a second operation, an unprotected suture line with the potential for breakdown is avoided. Numerous large retrospective and several prospective studies have now clearly demonstrated that primary repair is safe and effective in virtually all patients with penetrating wounds.[76] Colostomy is still appropriate in a few patients, but the current dilemma is how to select which patients should undergo the procedure. Currently, the overall physiologic status of the patient, rather than local factors, directs decision making. Patients with devastating left colon injuries requiring damage control are clearly candidates for temporary colostomy. Ileostomy with colocolostomy, however, is used for most other high-risk patients.

Fig. 7-65.



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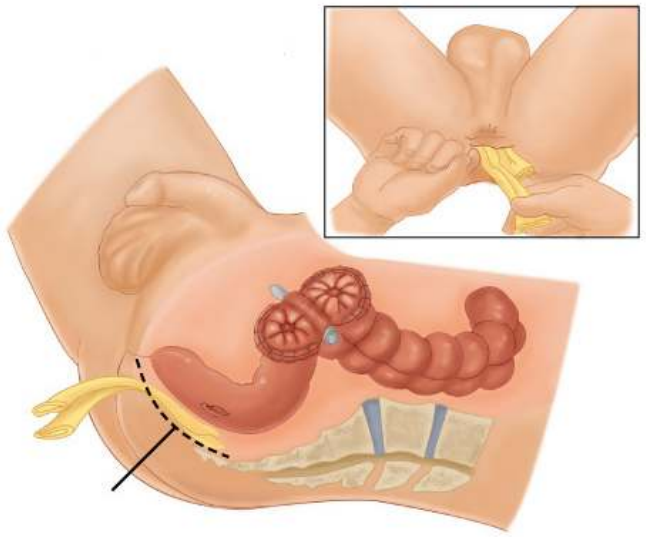
Technique for bowel repair and anastomosis. **A.** The running, single-layer suture is started at the mesenteric border. **B.** Stitches are spaced 3 to 4 mm from the edge of the bowel and advanced 3 to 4 mm, including all layers except the mucosa. **C.** The continuous suture is tied near the antimesenteric border.

Rectal injuries are similar to colonic injuries with respect to the ecology of the luminal contents, overall structure, and blood supply of the wall, but access to extraperitoneal injuries is limited due to the surrounding bony pelvis. Therefore, indirect treatment with intestinal diversion usually is required. The current options are loop ileostomy and sigmoid loop colostomy. These are preferred because they are quick and easy to perform, and provide essentially total fecal diversion. For sigmoid colostomy, technical elements include (a) adequate mobilization of the sigmoid colon so that the loop will rest on the abdominal wall without tension, (b) maintenance of the spur of the colostomy (the common wall of the proximal and distal limbs after maturation) above the level of the skin with a one-half-inch nylon rod or similar device, (c) longitudinal incision in the tenia coli, and (d) immediate maturation in the OR (Fig. 7-66). If the injury is accessible (e.g., in the posterior intraperitoneal portion of the rectum), repair of the injury should also be attempted. However, it is not necessary to explore the extraperitoneal rectum to repair a distal perforation. If the rectal injury is extensive, another option is to divide the rectum at the level of the injury, oversew or staple the distal rectal pouch if possible, and create an end colostomy (Hartmann's procedure). Extensive injuries may warrant presacral drainage with Penrose drains placed along Waldeyer's fascia via a perianal incision (see Fig. 7-66). In rare instances in which destructive injuries are present, an abdominoperineal resection may be necessary to avert lethal pelvic sepsis.

Fig. 7-66.



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Loop colostomy will completely divert the fecal flow, allowing the low rectal injury to heal. For extensive wounds, presacral drains are inserted through a perianal incision

(*box*) and advanced along Waldeyer's fascia (*dashed line*).

Complications related to colorectal injuries include intra-abdominal abscess, fecal fistula, wound infection, and stomal complications. Intra-abdominal abscesses occur in approximately 10% of patients, and most are managed with percutaneous drainage. Fistulas occur in 1 to 3% of patients and usually present as an abscess or wound infection with subsequent continuous drainage of fecal output; the majority will heal spontaneously with routine care (see Chap. 29). Stomal complications (necrosis, stenosis, obstruction, and prolapse) occur in 5% of patients and may require either immediate or delayed reoperation. Stomal necrosis should be carefully monitored, because spread beyond the mucosa may result in septic complications, including necrotizing fasciitis of the abdominal wall. Penetrating injuries that involve both the rectum and adjacent bony structures are prone to development of osteomyelitis. Bone biopsy is performed for diagnosis and bacteriologic analysis, and treatment entails long-term IV antibiotic therapy and occasionally débridement.

ABDOMINAL VASCULATURE

Injury to the major arteries and veins in the abdomen are a technical challenge.[77–83] Although penetrating trauma indiscriminately affects all blood vessels, blunt trauma most commonly involves renal vasculature and rarely the abdominal aorta. Patients with a penetrating aortic wound who survive to reach the OR frequently have a contained hematoma within the retroperitoneum. Due to lack of mobility of the abdominal aorta, few injuries are amenable to primary repair. Small lateral perforations may be controlled with 4-0 polypropylene suture or a PTFE patch, but end-to-end interposition grafting with a PTFE tube graft is the most common repair. In contrast, blunt injuries are typically intimal tears of the infrarenal aorta and are readily exposed via a direct approach. To avoid future vascular-enteric fistulas, the vascular suture lines should be covered with omentum.

Penetrating wounds to the superior mesenteric artery (SMA) are typically encountered upon exploration for a gunshot wound, with "black bowel" and associated supramesocolic hematoma being pathognomonic. Blunt avulsions of the SMA are rare but should be considered in patients with a seat belt sign who have midepigastric pain or tenderness and associated hypotension. For injuries of the SMA, temporary damage control with a Pruitt-Inahara shunt can prevent extensive bowel necrosis; additionally, temporary shunting allows control of visceral contamination before placement of a PTFE graft. For definitive repair, end-to-end interposition RSVG from the proximal SMA to the SMA past the point of injury can be performed if there is no associated pancreatic injury. Alternatively, if the patient has an associated pancreatic injury, the graft should be tunneled from the distal aorta beneath the duodenum to the distal SMA. For proximal SMV injuries, digital compression for hemorrhage control is followed by attempted venorrhaphy; ligation is an option in a life-threatening situation, but the resultant bowel edema requires aggressive fluid resuscitation. Temporary abdominal closure and a second-look operation to evaluate bowel viability should be done.

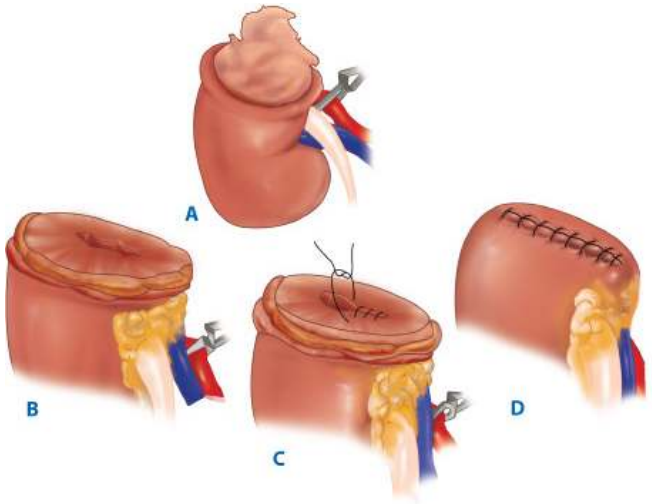
Transpelvic gunshot wounds or blunt injuries with associated pelvic fractures are the most common scenarios in patients with iliac artery injuries. A Pruitt-Inahara shunt can be used for temporary shunting of the vessel for damage control. Definitive interposition grafting with excision of the injured segment is appropriate (see "Vascular Repair Techniques"). Careful monitoring for distal embolic events and reperfusion injury necessitating fasciotomy is imperative.

In general, outcome after vascular injuries is related to (a) the technical success of the vascular reconstruction and (b) associated soft tissue and nerve injuries. Vascular repairs rarely fail after the first 12 hours, whereas, soft tissue infection is a limb threat for several weeks. Following aortic interposition grafting, the patient's SBP should not exceed 120 mmHg for at least the first 72 hours postoperatively. Patients requiring ligation of an inferior vena cava injury often develop marked bilateral lower extremity edema. To limit the associated morbidity the patient's legs should be wrapped with elastic bandages from the toes to the hips and elevated at a 45- to 60-degree angle. For superior mesenteric vein injuries, either ligation or thrombosis after venorrhaphy results in marked bowel edema; fluid resuscitation should be aggressive and abdominal pressure monitoring routine in these patients. Prosthetic graft infections are rare complications, but prevention of bacteremia is imperative; administration of antibiotics perioperatively and treatment of secondary infections is indicated. Long-term arterial graft complications such as stenosis or pseudoaneurysms are uncommon, and routine graft surveillance rarely is performed. Consequently, long-term administration of antiplatelet agents or antithrombotics is not routine.

GENITOURINARY TRACT

When undergoing laparotomy for trauma, the best policy is to explore all penetrating wounds to the kidneys. Parenchymal renal injuries are treated with hemostatic and reconstructive techniques similar to those used for injuries of the liver and spleen: topical methods (electrocautery; argon beam coagulation; application of thrombin-soaked gelatin foam sponge, fibrin glue, or BioGlue) and pledgeted suture repair. Two caveats are recognized, however: The collecting system should be closed separately, and the renal capsule should be preserved to close over the repair of the collecting system (Fig. 7-67). Renal vascular injuries are common after penetrating trauma and may be deceptively tamponaded, which results in delayed hemorrhage. Arterial reconstruction using graft interposition should be attempted for renal preservation. For destructive parenchymal or irreparable renovascular injuries, nephrectomy may be the only option; a normal contralateral kidney must be palpated, because unilateral renal agenesis occurs in 0.1% of patients.

Fig. 7-67.



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When renorrhaphy is undertaken, effective repair is assisted by attention to several key points: **A.** Vascular occlusion controls bleeding and permits adequate visualization. **B.** The renal capsule is carefully preserved. **C.** The collecting system is closed separately with absorbable suture. **D.** The preserved capsule is closed over the collecting system repair.

Over 90% of all blunt renal injuries are treated nonoperatively. Hematuria typically resolves within a few days with bed rest, although rarely bleeding is so persistent that bladder irrigation to dispel blood clots is warranted. Persistent gross hematuria may require embolization, whereas urinomas can be drained percutaneously. Operative intervention after blunt trauma is limited to renovascular injuries and destructive parenchymal injuries that result in hypotension. The renal arteries and veins are uniquely susceptible to traction injury caused by blunt trauma. As the artery is stretched, the inelastic intima and media may rupture, which causes thrombus formation and resultant stenosis or occlusion. The success rate for renal artery repair approaches 0%, but an attempt is reasonable if the injury is <3 hours old or if the patient has a solitary kidney or bilateral injuries.[84] Reconstruction after blunt renal injuries may be difficult, however, because the injury is typically at the level of the aorta. If repair is not possible within this time frame, leaving the kidney in situ does not necessarily lead to hypertension or abscess formation. The renal vein may be torn or completely avulsed from the vena cava due to blunt trauma. Typically, the large hematoma causes hypotension, which leads to operative intervention. During laparotomy for blunt trauma, expanding or pulsatile perinephric hematomas should be explored. If necessary, emergent vascular control can be obtained by placing a curved vascular clamp across the hilum from an inferior approach. Techniques of repair and hemostasis are similar to those described earlier.

Injuries to the ureters are uncommon but may occur in patients with pelvic fractures and penetrating trauma. An injury may not be identified until a complication (i.e., a urinoma) becomes apparent. If an injury is suspected during operative exploration but is not clearly identified, methylene blue or indigo carmine is administered IV with observation for extravasation. Injuries are repaired using 5-0 absorbable monofilament, and mobilization of the kidney may reduce tension on the anastomosis. Distal ureteral injuries can be treated by reimplantation facilitated with a psoas hitch and/or Boari flap. In damage control circumstances, the ureter can be ligated on both sides of the injury and a nephrostomy tube placed.

Bladder injuries are subdivided into those with intraperitoneal extravasation and those with extraperitoneal extravasation. Ruptures or lacerations of the intraperitoneal bladder are operatively closed with a running, single-layer, 3-0 absorbable monofilament suture. Laparoscopic repair is becoming common in patients not requiring laparotomy for other injuries. Extraperitoneal ruptures are treated nonoperatively with bladder decompression for 2 weeks. Urethral injuries are managed by bridging the defect with a Foley catheter, with or without direct suture repair. Strictures are not uncommon but can be managed electively.

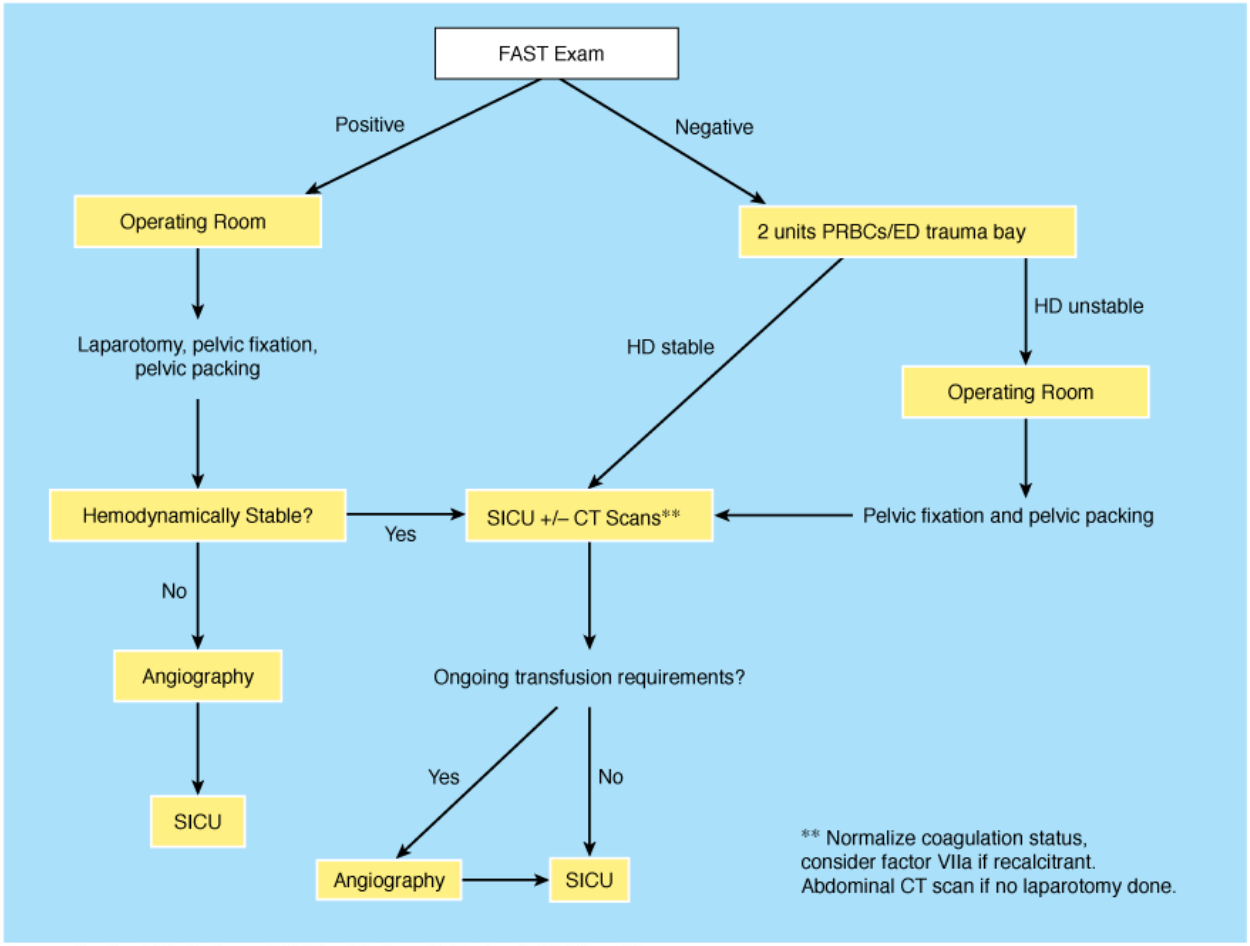
FEMALE REPRODUCTIVE TRACT

Gynecologic injuries are rare. Occasionally the vaginal wall will be lacerated by a bone fragment from a pelvic fracture. Although repair is not mandated, it should be performed if physiologically feasible. More important, however, is recognition of the open fracture, need for possible drainage, and potential for pelvic sepsis. Penetrating injuries to the vagina, uterus, fallopian tubes, and ovaries are also uncommon, and routine hemostatic techniques are used. Repair of a transected fallopian tube can be attempted but probably is unjustified, because a suboptimal repair will increase the risk of tubal pregnancy. Transection at the injury site with proximal ligation and distal salpingectomy is a more prudent approach.

Pelvic Fractures and Emergent Hemorrhage Control

Patients with pelvic fractures who are hemodynamically unstable are a diagnostic and therapeutic challenge for the trauma team. These injuries often occur in conjunction with other life-threatening injuries, and there is no universal agreement among clinicians on management. Current management algorithms in the United States incorporate variable time frames for bony stabilization and fixation, as well as hemorrhage control by preperitoneal pelvic packing and/or angioembolization. Early institution of a multidisciplinary approach with the involvement of trauma surgeons, orthopedic surgeons, interventional radiologists, the director of the blood bank, and anesthesiologists is imperative due to high associated mortality rates (Fig. 7-68).

Fig. 7-68.



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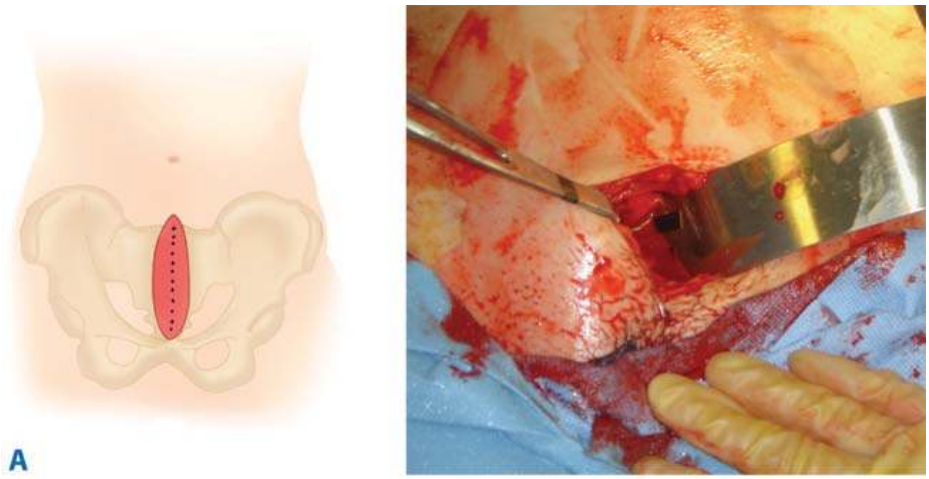
Management algorithm for patients with pelvic fractures with hemodynamic instability. CT = computed tomography; ED = emergency department; FAST = focused abdominal sonography for trauma; HD = hemodynamic; PLT = platelets; PRBCs = packed red blood cells; SICU = surgical intensive care unit.

Evaluation in the ED focuses on identification of injuries mandating operative intervention (e.g., massive hemothorax, ruptured spleen) and injuries related to pelvic fracture that alter management (e.g., injuries to the iliac artery). Immediate temporary stabilization with sheeting of the pelvis or application of commercially available compression devices should be performed. If the patient's primary source of bleeding is the fracture-related hematoma, several options exist for hemorrhage control. Because 85% of bleeding due to pelvic fractures is venous or bony in origin the authors advocate immediate external fixation and preperitoneal pelvic packing.[85] Anterior external fixation decreases pelvic volume, which promotes tamponade of venous bleeding and prevents secondary hemorrhage from the shifting of bony elements. Pelvic packing, in which six laparotomy pads (four in children) are placed directly into the paravesical space through a small suprapubic incision, provides tamponade for the bleeding (Fig. 7-69). Pelvic packing also eliminates the often difficult decision by the trauma surgeon: OR vs. Interventional Radiology? All patients can be rapidly transported to the OR and packing can be accomplished in under 30 minutes. In the authors' experience, this results in hemodynamic stability and abrupt cessation of the need for ongoing blood transfusion in the majority of cases. Patients also can undergo additional procedures such as laparotomy, thoracotomy, external fixation of extremity fractures, open fracture débridement, or craniotomy. Currently, angiography is reserved for patients with evidence of ongoing pelvic bleeding after admission to the SICU. Patients undergo standard posttrauma resuscitative SICU care, and the pelvic packs are removed within 48 hours, a time frame chosen empirically based on the authors' experience with liver packing. The authors elect to repack the patient's pelvis if there is persistent oozing and perform serial washouts of the preperitoneal space if it appears infected.

Fig. 7-69.



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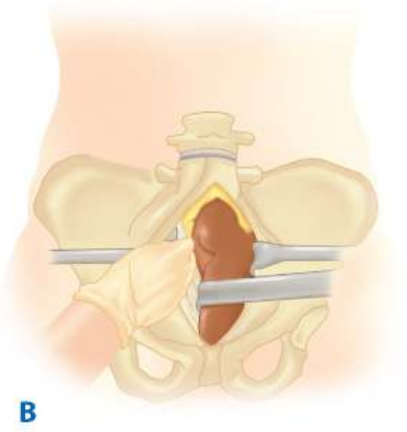

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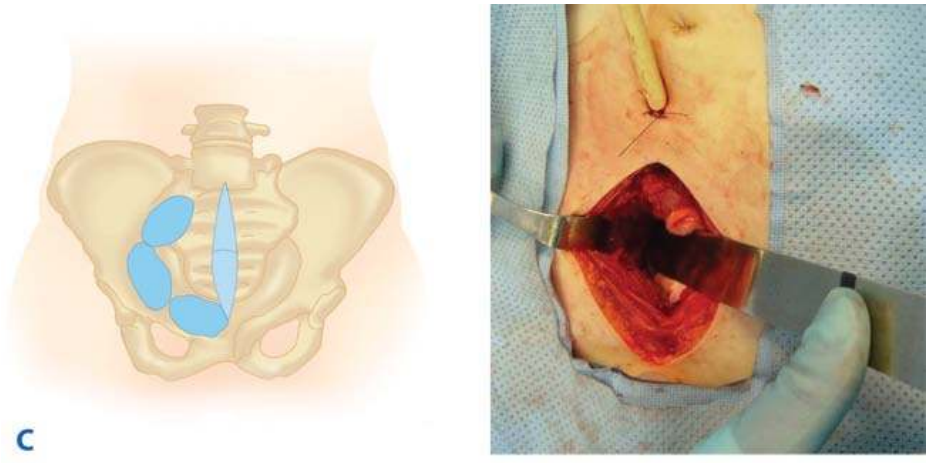

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A. Pelvic packing is performed through a 6- to 8-cm midline incision made from the pubic symphysis cephalad, with division of the midline fascia. **B.** The pelvic hematoma often dissects the preperitoneal and paravesical space down to the presacral region, which facilitates packing; alternatively, blunt digital dissection opens the preperitoneal space for packing. **C.** Three standard surgical laparotomy pads are placed on each side of the bladder, deep within the preperitoneal space; the fascia is closed with an O polydioxanone monofilament suture and the skin with staples.

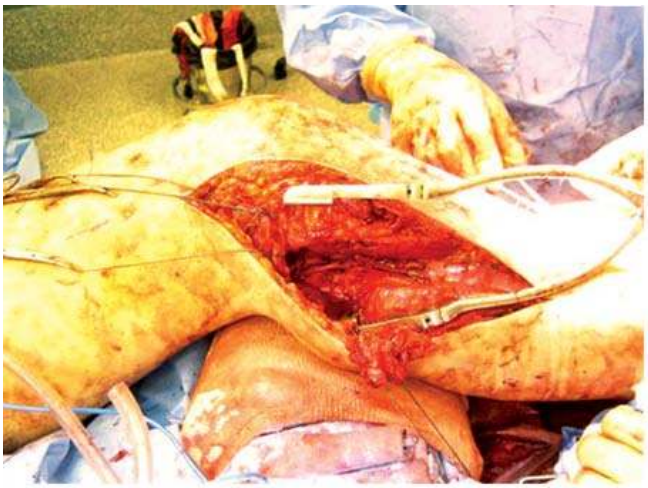
Another clinical challenge is the open pelvic fracture. In many instances the wounds are located in the perineum, and the risk of pelvic sepsis and osteomyelitis is high. To reduce the risk of infection, performance of a diverting sigmoid colostomy is recommended. The pelvic wound is manually débrided and then irrigated daily with a high-pressure pulsatile irrigation system until granulation tissue covers the wound. The wound is then left to heal by secondary intention with a wound VAC device.

Extremity Fractures, Vascular Injuries, and Compartment Syndromes

Patients with injured extremities often require a multidisciplinary approach with involvement of trauma, orthopedic, and plastic surgeons to address vascular injuries, fractures, soft tissues injuries, and compartment syndromes. Immediate stabilization of fractures or unstable joints is done in the ED using Hare traction, knee immobilizers, or plaster splints. In patients with open fractures the wound should be covered with povidone iodine (Betadine)–soaked gauze and antibiotics administered. Options for fracture fixation include external fixation or open reduction and internal fixation with plates or intramedullary nails. Vascular injuries, either isolated or in combination with fractures, require emergent repair. Common combined injuries include clavicle/first rib fractures and subclavian artery injuries, dislocated shoulder/proximal humeral fractures and axillary artery injuries, supracondylar fractures/elbow dislocations and brachial artery injuries, femur fracture and superficial femoral artery injuries, and knee dislocation and popliteal vessel injuries. On-table angiography in the OR facilitates rapid intervention and is warranted in patients with evidence of limb threat at ED arrival. Arterial access for on-table lower extremity angiography can be obtained percutaneously at the femoral vessels with a standard arterial catheter, via femoral vessel exposure and direct cannulation, or with superficial femoral artery (SFA) exposure just above the medial knee. Controversy exists regarding which should be done first, fracture fixation or arterial repair. The authors prefer placement of temporary intravascular shunts with arterial occlusions to minimize ischemia during fracture treatment, with definitive vascular repair following. Rarely, immediate amputation may be considered due to the severity of orthopedic and neurovascular injuries. This is particularly true if primary nerve transection is present in addition to fracture and arterial injury.[86] Collaborative decision making by the trauma, orthopedic, and plastic/reconstructive team is encouraged.

Operative intervention for vascular injuries should follow standard principles of repair (see "Vascular Repair Techniques"). For subclavian or axillary artery repairs, 6-mm PTFE graft and RSVG are used. Because associated injuries of the brachial plexus are common, a thorough neurologic examination of the extremity is mandated before operative intervention. Operative approach for a brachial artery injury is via a medial upper extremity longitudinal incision; proximal control may be obtained at the axillary artery, and an S-shaped extension through the antecubital fossa provides access to the distal brachial artery. The injured vessel segment is excised, and an end-to-end interposition RSVG graft is performed. Upper extremity fasciotomy is rarely required unless the patient manifests preoperative neurologic changes or diminished pulse upon revascularization, or the time to operative intervention is extended. For SFA injuries, external fixation of the femur typically is performed, followed by end-to-end RSVG of the injured SFA segment. Close monitoring for calf compartment syndrome is mandatory. Preferred access to the popliteal space for an acute injury is the medial one-incision approach with detachment of the semitendinosus, semimembranosus, and gracilis muscles (Fig. 7-70). Another option is a medial approach with two incisions using a longer RSVG, but this requires interval ligation of the popliteal artery and geniculate branches. Rarely, with open wounds a straight posterior approach with an S-shaped incision can be used. If the patient has an associated popliteal vein injury, this should be repaired first with a PTFE interposition graft while the artery is shunted. For an isolated popliteal artery injury, RSVG is performed with an end-to-end anastomosis. Compartment syndrome is common, and presumptive four-compartment fasciotomies are warranted in patients with combined arterial and venous injury. Once the vessel is repaired and restoration of arterial flow documented, completion angiography should be done in the OR if there is no palpable distal pulse. Vasoparalysis with verapamil, nitroglycerin, and papaverine may be used to treat vasoconstriction (Table 7-11).

Fig. 7-70.



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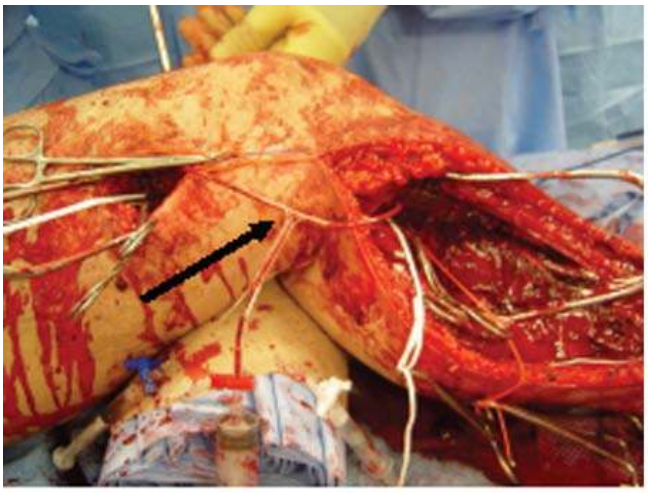

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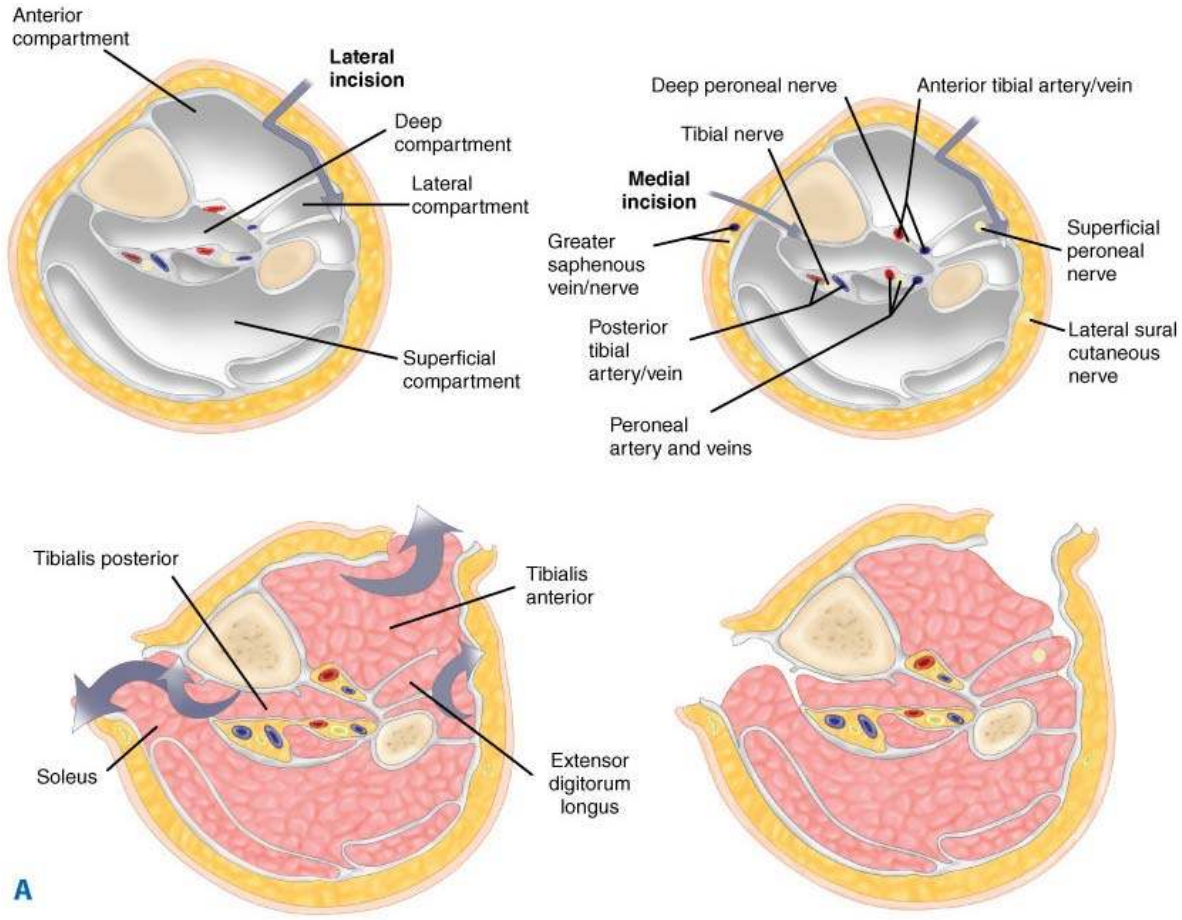
A. The popliteal space is commonly accessed using a single medial incision (the detached semitendinosus, semimembranosus, and gracilis muscles are identified by different suture types). **B.** Alternatively, a medial approach with two incisions may be used. Insertion of a Pruitt-Inahara shunt (*arrow*) provides temporary restoration of blood flow, which prevents ischemia during fracture treatment.

Table 7-11 Arterial Vasospasm Treatment Guideline
Step 1: Intra-arterial alteplase (tissue plasminogen activator) 5 mg/20 mL bolus
If spasm continues, proceed to step 2.
Step 2: Intra-arterial nitroglycerin 200 μg/20 mL bolus
Repeat same dose once as needed.
If spasm continues, proceed to step 3.
Step 3: Inter-arterial verapamil 10 mg/10 mL bolus
If spasm continues, proceed to step 4.
Step 4: Inter-arterial papaverine drip 60 mg/50 mL given over 15 min

Compartment syndromes, which can occur anywhere in the extremities, involve an acute increase in pressure inside a closed space, which impairs blood flow to the structures within. Causes of compartment syndrome include arterial hemorrhage into a compartment, venous ligation or thrombosis, crush injuries, and ischemia and reperfusion. In conscious patients, pain is the prominent symptom, and active or passive motion of muscles in the involved compartment increases the pain. Paresthesias may also be described. In the lower extremity, numbness between the first and second toes is the hallmark of early compartment syndrome in the exquisitely sensitive anterior compartment and its enveloped deep peroneal nerve. Progression to paralysis can occur, and loss of pulses is a late sign. In comatose or obtunded patients, the diagnosis is more difficult to secure. In patients with a compatible history and a tense extremity, compartment pressures should be measured with a hand-held Stryker device. Fasciotomy is indicated in patients with a gradient of <35 mmHg (gradient = diastolic pressure – compartment pressure), ischemic periods of >6 hours, or combined arterial and venous injuries. The lower extremity is most frequently involved, and compartment release is performed using a two-incision, four-compartment fasciotomy (Fig. 7-71). Of note, the soleus muscle must be detached from the tibia to decompress the deep flexor compartment.

Fig. 7-71.



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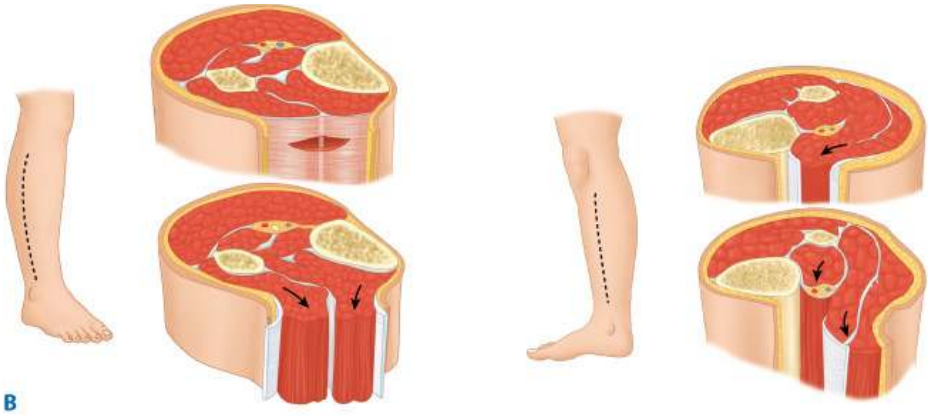

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A. The anterior and lateral compartments are approached from a lateral incision, with identification of the fascial raphe between the two compartments. Care must be taken to avoid the superficial peroneal nerve running along the raphe. **B.** To decompress the deep flexor compartment, which contains the tibial nerve and two of the three arteries to the foot, the soleus muscle must be detached from the tibia.

INTENSIVE CARE UNIT MANAGEMENT AND POSTOPERATIVE CONSIDERATIONS

Postinjury Resuscitation

ICU management of the trauma patient, either with direct admission from the ED or after emergent operative intervention, is considered in distinct phases, because there are differing goals and priorities. The period of acute resuscitation, typically lasting for the first 12 to 24 hours after injury, combines several key principles: optimizing tissue perfusion, ensuring normothermia, and restoring coagulation. There are a multitude of management algorithms aimed at accomplishing these goals, the majority of which involve goal-directed resuscitation with initial volume loading to attain adequate preload, followed by judicious use of inotropic agents or vasopressors.[87] Although the optimal hemoglobin level remains debated, during shock resuscitation a hemoglobin level of >10 g/dL is generally accepted to optimize oxygen delivery. After the first 24

hours of resuscitation, a more judicious transfusion trigger of a hemoglobin level of <7 g/dL in the euvolemic patient limits the adverse inflammatory effects of stored RBCs. The resuscitation of the severely injured trauma patient may require what appears to be an inordinate amount of crystalloid resuscitation. Infusion volumes of 10 L during the initial 6 to 12 hours may be required to attain an adequate preload. Although early colloid administration is appealing, evidence to date does not support this concept. In fact, optimizing crystalloid administration is a challenging aspect of early care (i.e., balancing cardiac performance against generation of an abdominal compartment syndrome and generalized tissue edema).

Invasive monitoring with pulmonary artery catheters is controversial but may be a critical adjunct in patients with multiple injuries who require advanced inotropic support. Not only do such devices allow minute-to-minute monitoring of the patient, but the added information on the patient's volume status, cardiac function, peripheral vascular tone, and metabolic response to injury permits appropriate therapeutic intervention. With added information on the patient's cardiac function, cardiac indices and oxygen delivery become important variables in the ongoing ICU management. Resuscitation to values of >500 mL/min per square meter for the oxygen delivery index and >3.8 L/min per square meter for the cardiac index are the goals. Pulmonary artery catheters also enable the physician to monitor response to vasoactive agents. Although norepinephrine is the agent of choice for patients with low systemic vascular resistance who are unable to maintain a mean arterial pressure of >60 mmHg, patients may have an element of myocardial dysfunction requiring inotropic support. The role of relative adrenal insufficiency is another controversial area.

Optimal early resuscitation is mandatory and determines when the patient can undergo definitive diagnosis as well as when the patient can be returned to the OR after initial damage control surgery. Specific goals of resuscitation before repeated "semielective" transport include a core temperature of >35°C (95°F), base deficit of <6 mmol/L, and normal coagulation indices. Although correction of metabolic acidosis is desirable, how quickly this should be accomplished requires careful consideration. Adverse sequelae of excessive crystalloid resuscitation include increased intracranial pressure, worsening pulmonary edema, and intra-abdominal visceral and retroperitoneal edema resulting in secondary abdominal compartment syndrome. Therefore, it should be the overall trend of the resuscitation rather than a rapid reduction of the base deficit that is the goal. Exogenous bicarbonate, occasionally given to improve cardiovascular function and response to vasoactive agents if the serum pH is below 7.2, obfuscates the base deficit trending, and lactate level is a more reliable indicator of adequate perfusion after the first 12 hours.

Abdominal Compartment Syndrome

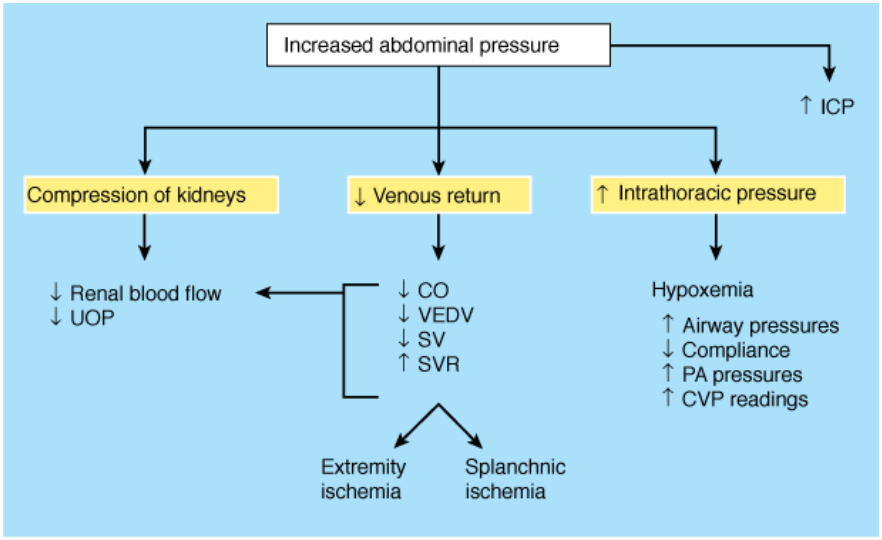
Abdominal compartment syndrome is classified as intra-abdominal hypertension due to intra-abdominal injury (primary) or splanchnic reperfusion after massive resuscitation (secondary). Secondary abdominal compartment syndrome may result from any condition requiring extensive crystalloid resuscitation, including extremity trauma, chest trauma, or even postinjury sepsis. The sources of increased intra-abdominal pressure include gut edema, ascites, bleeding, and packs, among others. A diagnosis of intra-abdominal hypertension cannot reliably be made by physical examination; therefore, it is obtained by measuring the intraperitoneal pressure. The most common technique is to measure a patient's bladder pressure. Fifty milliliters of saline is instilled into the bladder via the aspiration port of the Foley catheter with the drainage tube clamped, and a three-way stopcock and water manometer is placed at the level of the pubic symphysis. Bladder pressure is then measured on the manometer in centimeters of water (Table 7-12) and correlated with the physiologic impact of abdominal compartment syndrome. Conditions in which the bladder pressure is unreliable include bladder rupture, external compression from pelvic packing, neurogenic bladder, and adhesive disease.

Table 7-12 Abdominal Compartment Syndrome Grading System

	Bladder Pressure	
Grade	**mmHg**	**cm H_2O**
I	10–15	13–20
II	16–25	21–35
III	26–35	36–47
IV	>35	>48

Increased abdominal pressure affects multiple organ systems (Fig. 7-72). Abdominal compartment syndrome, as noted earlier, is defined as intra-abdominal hypertension and frequently manifests via such end-organ sequelae as decreased urine output, increased pulmonary inspiratory pressures, decreased cardiac preload, and increased cardiac afterload. Because any of these clinical symptoms of abdominal compartment syndrome may be attributed to the primary injury, a heightened awareness of this syndrome must be maintained. Organ failure can occur over a wide range of recorded bladder pressures. Generally, no specific bladder pressure prompts therapeutic intervention, except when the pressure is >35 mmHg. Rather, emergent decompression is carried out when intra-abdominal hypertension reaches a level at which end-organ dysfunction occurs. Mortality is directly affected by decompression, with 60% mortality in patients undergoing presumptive decompression, 70% mortality in patients with a delay in decompression, and nearly uniform mortality in those not undergoing decompression. Decompression is performed operatively either in the ICU if the patient is hemodynamically unstable or in the OR. ICU bedside laparotomy is easily accomplished, avoids transport of hemodynamically compromised patients, and requires minimal equipment (e.g., scalpel, suction device, cautery, and dressings for temporary abdominal closure). In patients with significant intra-abdominal fluid as the primary component of abdominal compartment syndrome, rather than bowel or retroperitoneal edema, decompression may be accomplished effectively via a percutaneous drain. This method is particularly applicable for nonoperative management of major liver injuries. These patients are identified by bedside ultrasound, and the morbidity of a laparotomy is avoided. When operative decompression is required with egress of the abdominal contents, temporary coverage is obtained using a subfascial 45 x 60 cm sterile drape and Ioban application (see Fig. 7-50).

Fig. 7-72.



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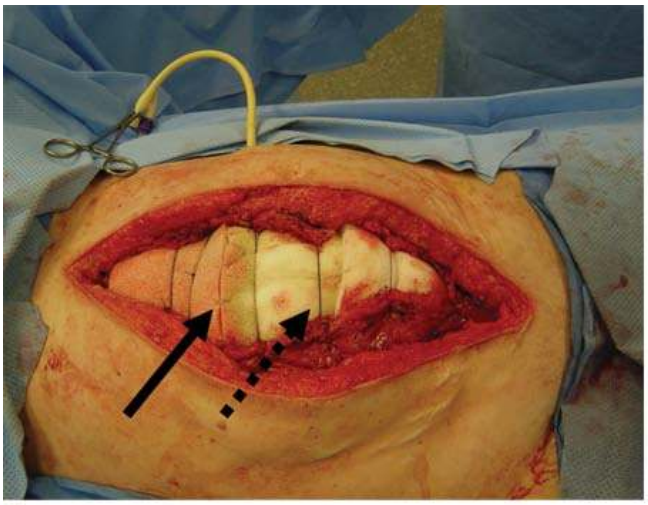
Abdominal compartment syndrome is defined by the end organ sequelae of intra-abdominal hypertension. CO = cardiac output; CVP = central venous pressure; ICP = intracranial pressure; PA = pulmonary artery; SV = stroke volume; SVR = systemic vascular resistance; UOP = urine output; VEDV = ventricular end diastolic volume.

The performance of damage control surgery and recognition of abdominal compartment syndrome have dramatically improved patient survival, but at the cost of an open abdomen. Several management points deserve attention. Despite having a widely open abdomen, patients can develop recurrent abdominal compartment syndrome, which increases their morbidity and mortality; therefore, bladder pressure should be monitored every 4 hours, with significant increases in pressures alerting the clinician to the possible need for repeat operative decompression. Patients with an open abdomen lose between 500 and 2500 mL per day of abdominal effluent. Appropriate volume compensation for this albumin-rich fluid remains controversial, with regard to both the amount administered (replacement based on clinical indices vs. routine $^{1}/_{2}$ mL replacement for every milliliter lost) as well as the type of replacement (crystalloid vs. colloid/blood products).

Following resuscitation and management of specific injuries, the goal of the operative team is to close the abdomen as quickly as possible. Multiple techniques have been introduced to obtain fascial closure of the open abdomen to minimize morbidity and cost of care. Historically, for patients who could not be closed at repeat operation, approximation of the fascia with mesh (prosthetic or biologic) was used, with planned reoperation. Another option was split-thickness skin grafts applied directly to the exposed bowel for coverage; removal of the skin grafts was planned 9 to 12 months after the initial surgery, with definitive repair of the hernia by component separation. However, delayed abdominal wall reconstruction was resource invasive, with considerable patient morbidity. The advent of VAC technology has revolutionized fascial closure. The authors currently use a sequential closure technique with the wound VAC device that provides constant fascial tension and return to the OR every 48 hours until closure is complete (Fig. 7-73). The authors' success rate with this approach exceeds 95%. Among patients not attaining fascial closure, 20% suffer GI tract complications that prolong their hospital course. These include intra-abdominal abscess, enteric fistula, and bowel perforations (Fig. 7-74). Management includes operative or percutaneous drainage of abscesses, control of fistulas, and nutritional support for bowel complications.

Fig. 7-73.



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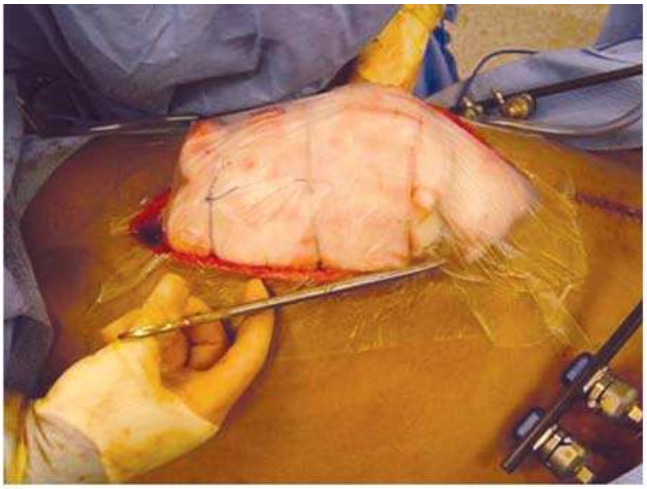

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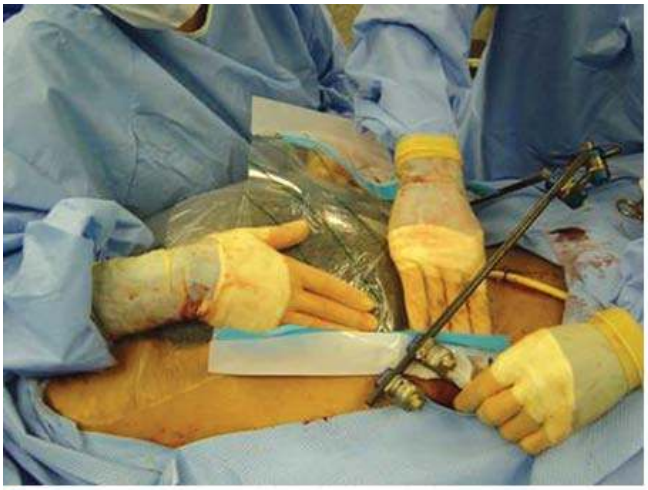

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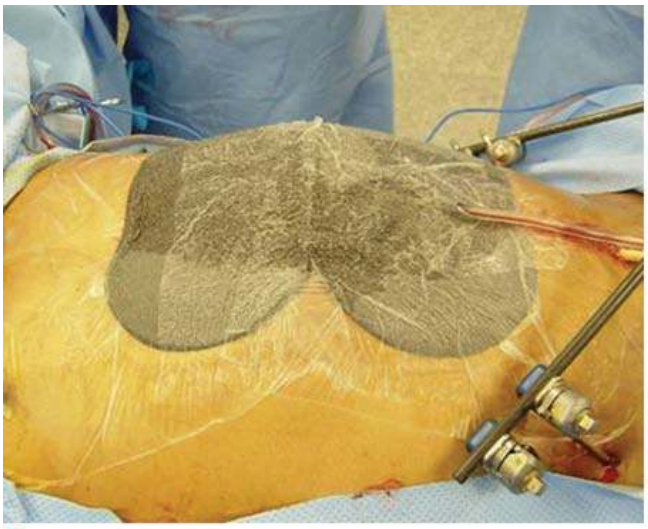

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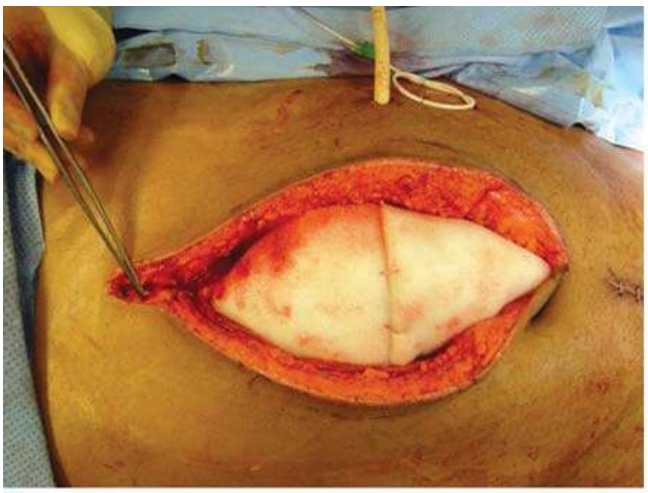

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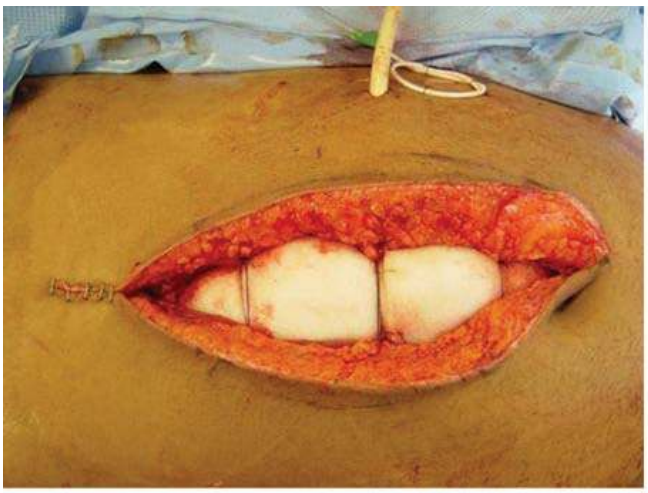

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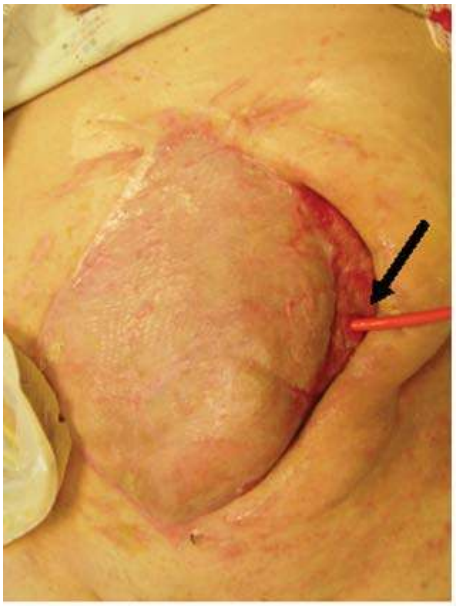
The authors' sequential closure technique for the open abdomen. **A.** Multiple white sponges (*solid arrow*), stapled together, are placed on top of the bowel underneath the

fascia. Interrupted No. 1 polydioxanone sutures are placed approximately 5 cm apart (*dashed arrow*), which puts the fascia under moderate tension over the white sponge. **B.** After the sticky clear plastic vacuum-assisted closure (VAC) dressing is placed over the white sponges and adjacent 5 cm of skin, the central portion is removed by cutting along the wound edges. **C** and **D.** Black VAC sponges are placed on top of the white sponges and plastic-protected skin with standard occlusive dressing and suction. **E.** On return to the operating room (OR) 48 hours later, fascial sutures are placed from both the superior and inferior directions until tension precludes further closure; skin is closed over the fascial closure with skin staples. **F.** White sponges (fewer in number) are again applied and fascial retention sutures are placed with planned return to the OR in 48 hours.

Fig. 7-74.



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Complications after split-thickness skin graft closure of the abdomen include enterocutaneous fistulas (intubated here with a red rubber catheter) (**A;***arrow*) and rupture of the graft with exposure of the bowel mucosa (**B**).

SPECIAL TRAUMA POPULATIONS

Pregnant Patients

Seven percent of women are injured during their pregnancy. Motor vehicle collisions and falls are the leading causes of injury, accounting for 70% of cases. Fetal death after trauma most frequently occurs after motor vehicle collisions, but only 11% of fetal deaths are due to the death of the mother; therefore, early trauma resuscitation and management is directed not only at the mother but also at the fetus. Domestic violence is also common, affecting between 10 and 30% of pregnant women and resulting in

fetal mortality of 5%.

Pregnancy results in physiologic changes that may impact postinjury evaluation (Table 7-13). Heart rate increases by 10 to 15 beats per minute during the first trimester and remains elevated until delivery. Blood pressure diminishes during the first two trimesters due to a decrease in systemic vascular resistance and rises again slightly during the third trimester (mean values: first = 105/60, second = 102/55, third = 108/67). Intravascular volume is increased by up to 8 L, which results in a relative anemia but also a relative hypervolemia. Consequently a pregnant woman may lose 35% of her blood volume before exhibiting signs of shock. Pregnant patients have an increase in tidal volume and minute ventilation but a decreased functional residual capacity; this results in a diminished P_{CO_2} reading and respiratory alkalosis. Also, pregnant patients may desaturate more rapidly, particularly in the supine position and during intubation. Supplemental oxygen is always warranted in the trauma patient but is particularly critical in the injured pregnant patient, because the oxygen dissociation curve is shifted to the left for the fetus compared to the mother (i.e., small changes in maternal oxygenation result in larger changes for the fetus because the fetus is operating in the steep portions of the dissociation curve). Anatomic changes contribute to these pulmonary functional alterations and are relevant in terms of procedures. With the gravid uterus enlarged, diagnostic peritoneal lavage (DPL) should be performed in a supraumbilical site with the catheter directed cephalad. In addition, the upward pressure on the diaphragm calls for caution when placing a thoracostomy tube; standard positioning may result in an intra-abdominal location or perforation of the diaphragm.

Table 7-13 Physiologic Effects of Pregnancy
Cardiovascular
Increase in heart rate by 10–15 bpm
Decreased systemic vascular resistance resulting in:
(a) Increased intravascular volume
(b) Decreased blood pressure during the first two trimesters
Pulmonary
Elevated diaphragm
Increased tidal volume
Increased minute ventilation
Decreased functional residual capacity
Hematopoietic
Relative anemia
Leukocytosis
Hypercoagulability
(a) Increased levels of factors VII, VIII, IX, X, XII
(b) Decreased fibrinolytic activity
Other
Decreased competency of lower esophageal sphincter
Increased enzyme levels on liver function tests
Impaired gallbladder contractions
Decreased plasma albumin level
Decreased blood urea nitrogen and creatinine levels
Hydronephrosis and hydroureter

Other physiologic changes during pregnancy affect the GI, renal, and hematologic systems. The lower esophageal sphincter has decreased competency, which increases the risk for aspiration. Liver function test values increase, with the alkaline phosphatase level nearly doubling. The high levels of progesterone impair gallbladder contractions, which results in bile stasis and an increased incidence of gallstone formation; this may not affect the trauma bay evaluation but becomes important in a prolonged ICU stay. Plasma albumin level decreases from a normal of around 4.3 g/dL to an average of 3.0 g/dL. Renal blood flow increases by 30% during pregnancy, which causes a decrease in serum level of blood urea nitrogen and creatinine. The uterus may also compress the ureters and bladder, causing hydronephrosis and hydroureter. Finally, as noted earlier there is a relative anemia during pregnancy, but a hemoglobin level of <11 g/dL is considered abnormal. Additional hematologic changes include a moderate leukocytosis (up to 20,000 mm^3) and a relative hypercoagulable state due to increased levels of factors VII, VIII, IX, X, and XII and decreased fibrinolytic activity.

During evaluation in the ED, the primary and secondary surveys commence, with mindfulness that the mother always receives priority while conditions are still optimized for the fetus. This management includes provision of supplemental oxygen (to prevent maternal and fetal hypoxia), aggressive fluid resuscitation (the hypervolemia of pregnancy may mask signs of shock), and placement of the patient in the left lateral decubitus position (or tilting of the backboard to the left) to avoid caval compression. Assessment of the fetal heart rate is the most valuable information regarding fetal viability. Fetal monitoring should be performed with a cardiotocographic device that measures both contractions and fetal heart tones (FHTs). Because change in heart rate is the primary response of the fetus to hypoxia or hypotension, anything above an FHT of 160 is a cause for concern, whereas bradycardia (FHT of <120) is considered fetal distress. Ideally, if possible, a member of the obstetrics team will be present during initial evaluation to perform a pelvic examination using a sterile speculum. Vaginal bleeding can signal early cervical dilation and labor, abruptio placentae, or placenta previa. Amniotic sac rupture can result in prolapse of the umbilical cord with fetal compromise. Strong contractions are associated with true labor and should prompt consideration of delivery and resuscitation of the neonate. Focused prenatal history taking should elicit a history of pregnancy-induced hypertension, gestational diabetes, congenital heart disease, preterm labor, or placental abnormalities. Asking the patient when the baby first moved and if she is currently experiencing movement of

the fetus is important. Determining fetal age is important for considerations of viability. Gestational age may be estimated by noting fundal height, with the fundus approximating the umbilicus at 20 weeks and the costal margin at 40 weeks. Discrepancy in dates and size may be due to uterine rupture or hemorrhage.

Initial evaluation for abdominopelvic trauma in pregnant patients should proceed in the standard manner. Ultrasound (FAST) of the abdomen should evaluate the four windows (pericardial, right and left upper quadrant, and bladder) and additionally assess FHTs, fetal movement, and sufficiency of amniotic fluid. DPL can be performed in pregnant women via a supraumbilical, open technique. Trauma radiography of pregnant patients presents a conundrum. Radiation damage has three distinct phases of damage and effect: preimplantation, during the period of organogenesis from 3 to 16 weeks, and after 16 weeks. Generally, it is accepted that "safe" doses of radiation from radiography are <5 rad.[88] A chest radiograph results in a dose of 0.07 mrad; CT scan of the chest, <1 rad; and CT scan of the abdomen, 3.5 rad. It is important, therefore, to limit radiographs to those that are essential and to shield the pelvis with a lead apron when possible. If clinically warranted, however, a radiograph should be obtained.

The vast majority of injuries are treated similarly whether the patient is pregnant or not. Following standard protocols for nonoperative management of blunt trauma avoids the risks associated with general anesthesia. A particular challenge in the pregnant trauma patient is a major pelvic fracture. Because uterine and retroperitoneal veins may dilate to 60 times their original size, hemorrhage from these vessels may be torrential. Fetal loss may be related to both maternal shock and direct injury to the uterus or fetal head. Penetrating injuries in this patient population also carry a high risk. The gravid uterus is a large target, and any penetrating injury to the abdomen may result in fetal injury depending on trajectory and uterine size. Gunshot wounds to the abdomen are associated with a 70% injury rate to the uterus and 35% mortality rate of the fetus. If the bullet traverses the uterus and the fetus is viable, cesarean section should be performed. On the other hand, stab wounds do not often penetrate the thick wall of the uterus. Indications for emergent cesarean section include (a) severe maternal shock or impending death (if the fetus is delivered within 5 minutes, survival is estimated at 70%), (b) uterine injury or significant fetal distress (anticipated survival rates of >70% if FHTs are present and fetal gestational age is >28 weeks).[89]

Any patient with a viable pregnancy should be monitored after trauma, with the length of monitoring determined by the injury mechanism and patient physiology. Patients who are symptomatic, defined by the presence of uterine irritability or contractions, abdominal tenderness, vaginal bleeding, or blood pressure instability, should be monitored in the hospital for at least 24 hours. In addition, patients at high risk for fetal loss (those experiencing vehicle ejection or involved in motorcycle or pedestrian collisions and those with maternal tachycardia, Injury Severity Score of >9, gestational period of >35 weeks, or history of prior assault) also warrant careful monitoring.[90] Patients without these risk factors who are asymptomatic can be monitored for 6 hours in the ED and sent home if no problems develop. They should be counseled regarding warning signs that mandate prompt return to the ED.

Geriatric Patients

Elderly trauma patients (>65 years of age) are hospitalized twice as often as those in any other age group, and this population accounts for one quarter of all trauma admissions. Although the physiology of aging separates older trauma patients from the younger generation (Table 7-14), treatment must remain individualized (some octogenarians look and physiologically act 50 years old, whereas others appear closer to 100 years). No chronologic age is associated with a higher morbidity or mortality, but a patient's comorbidities do impact the individual's postinjury course and outcome. For example, recognition that a patient is taking beta blockers affects the physician's evaluation of vital signs in the ED and impacts treatment course in the ICU, particularly if the patient's reflex tachycardia is being managed. These patients have limited cardiac and physiologic reserve; early monitoring of arterial blood gas values will identify occult shock. A base deficit of >6 mmol/L is associated with a twofold higher risk of mortality in patients over the age of 55 than in younger patients (67% vs. 30%).[91]

Table 7-14 Physiologic Effects of Aging
Cardiovascular
Increased prevalence of heart disease
Fatty deposition in the myocardium, resulting in:
(a) Progressive stiffening and loss of elasticity
(b) Diminished stroke volume, systolic contraction, and diastolic relaxation
Decrease in cardiac output of 0.5% per year
Atherosclerotic disease that limits cardiac response to stress
Increased risk of coronary ischemia
Thickening and calcification of the cardiac valves, which results in valvular incompetence
Pulmonary
Loss of compliance
Progressive loss of alveolar size and surface area
Air trapping and atelectasis
Intracranial
Loss of cerebral volume, resulting in:
(a) Increased risk of tearing of bridging veins with smaller injuries
(b) Accumulation of a significant amount of blood before symptoms occur
Senescence of the senses
Other
Decline in creatinine clearance by 80–90%

Osteoporosis, which causes a greater susceptibility to fractures

Although the published literature on geriatric traumatic brain injury is relatively sparse and uncontrolled with regard to management, some interesting points are noted. First, outcomes are worse in this age group than in their younger counterparts. Based on data from the Traumatic Coma Databank, mortality in patients with severe head injury more than doubles after the age of 55. Moreover, 25% of patients with a normal GCS score of 15 had intracranial bleeding, with an associated mortality of 50%.[92] Just as there is no absolute age that predicts outcome, admission GCS score is a poor predictor of individual outcome. Therefore, the majority of trauma centers advocate an initial aggressive approach with re-evaluation at the 72-hour mark to determine subsequent care.

One of the most common sequelae of blunt thoracic trauma is rib fractures. In the aging population, perhaps due to osteoporosis, less force is required to cause a fracture. In fact, in one study, 50% of patients >65 years old sustained rib fractures from a fall of <6 ft, compared with only 1% of patients <65 years of age. Concurrent pulmonary contusion is noted in up to 35% of patients, and pneumonia complicates the injuries in 10 to 30% of patients with rib fractures, not surprisingly leading to longer ICU stays.[93,94] Additionally, mortality increases linearly with the number of rib fractures. Patients who sustain more than six rib fractures have pulmonary morbidity rates of >50% and overall mortality rates of >20%.

Chronologic age is not the best predictor of outcome, but the presence of pre-existing conditions, which affect a patient's physiologic age, is associated with increased mortality rates.[95,96] Injury Severity Score is probably the best overall predictor of patient outcome in the elderly[97] ; however, for any given individual its sensitivity may not be precise, and there is a time delay in obtaining sufficient information to calculate the final score. In addition to pre-existing conditions and severity of injury, the occurrence of complications compounds the risk for mortality.

Pediatric Patients

Twenty million children, or almost one in four children, are injured each year, with an associated cost of treating the injured child of $16 billion per year. Injury is the leading cause of death among children over the age of 1 year, with 15,000 to 25,000 pediatric deaths per year. Disability after traumatic injury is more devastating, with rates 3 to 10 times that of the death rate. Pediatric trauma involves different mechanisms, different constellations of injury, and the potential for long-term problems related to growth and development. As with adult trauma, over 85% of pediatric trauma has a blunt mechanism, with boys injured twice as often as girls.[98] Falls are the most common cause of injury in infants and toddlers. In children, bicycle mishaps are the most common cause of severe injury, whereas motor vehicle–related injury predominates in adolescence. Although unintentional injuries are by far the most common type of injuries in childhood, the number of intentional injuries, such as firearm-related injury and child abuse, is increasing.

ED preparation for the pediatric trauma patient includes assembling age-appropriate equipment (e.g., intubation equipment; IV catheters, including intraosseous needles and 4F single-lumen lines), laying out the Broselow Pediatric Emergency Tape (which allows effective approximation of the patient's weight, medication doses, size of endotracheal tube, and chest tube size), and turning on heat lamps. Upon the pediatric patient's arrival, the basic tenets of the ABCs apply, with some caveats. In children, the airway is smaller and more cephalad in position compared with that of adults, and in children younger than 10 years, the larynx is funnel shaped rather than cylindrical as in adults. Additionally, the child's tongue is much larger in relation to the oropharynx. Therefore, a small amount of edema or obstruction can significantly reduce the diameter of the airway (thus increasing the work of breathing), and the tongue may posteriorly obstruct the airway, causing intubation to be difficult. During intubation, a Miller (straight) blade rather than a Macintosh (curved) blade may be more effective due to the acute angle of the cephalad, funnel-shaped larynx. Administration of atropine before rapid-sequence intubation will prevent bradycardia. Adequate ventilation is critical, because oxygen consumption in infants and young children is twice that in adults; onset of hypoxemia, followed by cardiac arrest, may be precipitous. Because gastric distension can inhibit adequate ventilation, placement of a nasogastric tube may facilitate effective gas exchange. Approximately one third of preventable deaths in children are related to airway management; therefore, if airway control cannot be obtained using a standard endotracheal method, surgical establishment of an airway should be considered. In children older than 11 years, standard cricothyroidotomy is performed. Due to the increased incidence of subglottic stenosis in younger patients, needle cricothyroidotomy with either a 14- or 16-gauge catheter is advocated, although it is rarely used. Alternatively, tracheostomy may be performed. In children, the standard physiologic response to hypovolemia is peripheral vasoconstriction and reflex tachycardia; this may mask significant hemorrhagic injury, because children can compensate for up to a 25% loss of circulating blood volume with minimal external signs. "Normal" values for vital signs should not necessarily make one feel more secure about the child's volume status. Volume restoration is based on the child's weight; two to three boluses of 20 mL/kg of crystalloid is appropriate.

After initial evaluation based on the trauma ABCs, identification and management of specific injuries proceeds. Acute traumatic brain injury is the most common cause of death and disability in any pediatric age group. Although falls are the most common mechanism overall, severe brain injury most often is due to child abuse (in children <2 years) or motor vehicle collisions (in those >2 years). Head CT should be performed to determine intracranial pathology, followed by skull radiography to diagnose skull fractures. As in adults, CPP is monitored, and appropriate resuscitation is critical to prevent the secondary insults of hypoxemia and hypovolemia. Although some data indicate that the pediatric brain recovers from traumatic injury better than the adult brain, this advantage may be eliminated if hypotension is allowed to occur.

As is true in adults, the vast majority of thoracic trauma is also blunt. However, because a child's skeleton is not completely calcified, it is more pliable. Significant internal organ damage may occur without overlying bony fractures. For example, adult patients with significant chest trauma have a 70% incidence of rib fractures, whereas only 40% of children with significant chest trauma do. Pneumothorax is treated similarly in the pediatric population; patients who are asymptomatic with a pneumothorax of <15% are admitted for observation, whereas those who have a pneumothorax of >15% or who require positive pressure ventilation undergo tube decompression. Presence of a hemothorax in this age group may be particularly problematic, because the child's chest may contain his or her entire blood volume. If the chest tube output is initially 20% of the patient's blood volume (80 mL/kg) or is persistently >1 to 2 mL/kg per hour, thoracotomy should be considered. Aortic injuries are rare in children, and tracheobronchial injuries are more amenable to nonoperative management. Thoracic injuries are second only to brain injuries as the main cause of death according to the National Pediatric Trauma Registry; however, the overall mortality rate of 15% correlates with the levels in many adult studies.

The evaluation for abdominal trauma in the pediatric patient is similar to that in the adult. FAST is valid in the pediatric age group to detect intra-abdominal fluid.[99] The mechanism of injury often correlates with specific injury patterns. A child sustaining a blow to the epigastrium (e.g., hitting the handlebars during a bike accident) should be evaluated for a duodenal hematoma and/or a pancreatic transection. After a motor vehicle collision in which the patient was wearing a passenger restraint, injuries comprising the "lap belt complex" or "seat belt syndrome" (i.e., abdominal wall contusion, small bowel perforation, flexion-distraction injury of the lumbar spine, diaphragm rupture, and occasionally abdominal aortic dissection) may exist. Nonoperative management of solid organ injuries, first used in children, is the current standard of care in the hemodynamically stable patient. If the patient shows clinical deterioration or hemodynamic lability, has a hollow viscus injury, or requires >40 mL/kg of packed RBCs, continued nonoperative management is not an option. Success rates of nonoperative management approach 95%, with an associated 10 to 23% transfusion rate. Blood transfusion rates are significantly lower in patients managed nonoperatively than in patients undergoing operation (13 vs. 44%).[100]

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KEY POINTS

1. Follow American Burn Association criteria for transfer of a patient to a regional burn center.

2. IV fluid resuscitation for patients with burns greater than 20% total body surface area (children with >15% total body surface area) should be titrated to mean arterial pressure (MAP) greater than 60 mmHg and urine output greater than 30 mL/h.

3. Never administer prophylactic antibiotics other than tetanus vaccination.

4. Patients with upper airway injury, partial pressure of arterial oxygen:fraction of inspired oxygen ratio less than 200 or carbon monoxide toxicity should be intubated for inhalation injury.

5. Early excision and grafting of full thickness and deep partial thickness burns improves outcomes.

GROWING NEED FOR BURN EXPERTISE

Surgical care of the burn patient has evolved into a specialized field incorporating the interdisciplinary skills of burn surgeons, nurses, therapists, and other health care specialists. However, recent mass casualty events have been a reminder that health systems may be rapidly pressed to care for large numbers of burn patients. Naturally, general surgeons will be at the forefront in these events, so it is crucial that they are comfortable with the care of burned patients and well equipped to provide standard of care.

BACKGROUND

Burn injury historically carried a poor prognosis. With advances in fluid resuscitation[1] and the advent of early excision of the burn wound,[2] survival has become an expectation even for patients with severe burns. Continued improvements in critical care and progress in skin bioengineering herald a future in which functional and psychological outcomes are equally important as survival alone. With this shift in priority, the American Burn Association has emphasized referral to specialized burn centers after early stabilization. Specific criteria should guide transfer of patients with more complex injuries or other medical needs to a burn center (Table 8-1). The American Burn Association has published standards of care [3] and created a verification process to ensure that burn centers meet those standards.[4] Because of increased prehospital safety measures, burn patients are being transferred longer distances to receive definitive care at regional burn centers; recent data from one burn center with a particularly wide catchment area confirmed that even transport times averaging 7 hours did not affect the long-term outcomes of burn patients.[5]

Table 8-1 Guidelines for Referral to a Burn Center
Partial-thickness burns greater than 10% TBSA
Burns involving the face, hands, feet, genitalia, perineum, or major joints
Third-degree burns in any age group
Electrical burns, including lightning injury
Chemical burns
Inhalation injury
Burn injury in patients with complicated pre-existing medical disorders

Patients with burns and concomitant trauma in which the burn is the greatest risk. If the trauma is the greater immediate risk, the patient may be stabilized in a trauma center before transfer to a burn center.
Burned children in hospitals without qualified personnel for the care of children
Burn injury in patients who will require special social, emotional, or rehabilitative intervention

TBSA = total body surface area.

INITIAL EVALUATION

Initial evaluation of the burn patient involves four crucial assessments: airway management, evaluation of other injuries, estimation of burn size, and diagnosis of carbon monoxide and cyanide poisoning. With direct thermal injury to the upper airway or smoke inhalation, rapid and severe airway edema is a potentially lethal threat. Anticipating the need for intubation and establishing an early airway is critical. Perioral burns and singed nasal hairs are signs that the oral cavity and pharynx should be further evaluated for mucosal injury, but in themselves these physical findings do not indicate an upper airway injury. Signs of impending respiratory compromise may include a hoarse voice, wheezing, or stridor; subjective dyspnea is a particularly concerning symptom, and should trigger prompt elective endotracheal intubation. In patients with combined multiple trauma, especially oral trauma, nasotracheal intubation may be useful but should be avoided if oral intubation is safe and easy.

Burn patients should be first considered trauma patients, especially when details of the injury are unclear. A primary survey should be conducted in accordance with advanced trauma life support guidelines. Concurrently with the primary survey, large-bore peripheral IV catheters should be placed and fluid resuscitation should be initiated; for a burn larger than 40% total body surface area (TBSA), two large-bore IVs are ideal. IV placement through burned skin is safe and effective but requires attention to securing the catheters. Central venous access may be necessary in the severely burned patient, and provides useful information as to volume status in the intensive care unit. Pediatric patients may require intraosseous access in emergent situations. An early and comprehensive secondary survey must be performed on all burn patients, but especially those with a history of associated trauma such as with a motor vehicle collision and a fire. Also, patients from structural fires in which the manner of egress is not known should be carefully evaluated for injuries from a possible jump or fall. Urgent radiology studies, such as a chest x-ray should be performed in the emergency department, but nonurgent skeletal evaluation (i.e., extremity x-rays) can be done in the intensive care unit to avoid hypothermia and delays in burn resuscitation. Hypothermia is one of the common prehospital complications that contributes to resuscitation failure. Patients should be wrapped with clean blankets in transport. Cooling blankets should be avoided in patients with moderate or large burns.

Patients with acute burn injuries should never receive prophylactic antibiotics. This intervention has been clearly demonstrated to promote development of fungal infections and resistant organisms and was abandoned in the mid-1980s. A tetanus booster should be administered in the emergency room.

Pain management for these patients has been widely recognized over the past 25 years. However, one must also consider treatment of the contribution of long-term anxiety. Therefore, it is important to administer an anxiolytic such as a benzodiazepine with the initial narcotics.

Most burn resuscitation formulas (Table 8-2) estimate fluid requirements using the burn size as a percent of TBSA burned. The "rule of nines" is a crude but quick and effective method of estimating burn size (Fig. 8-1). In adults, the anterior and posterior trunk each account for 18%, each lower extremity is 18%, each upper extremity is 9%, and the head is 9%. In children younger than 3 years old, the head accounts for a larger relative surface area and should be taken into account when estimating burn size. Diagrams such as the Lund and Browder chart give a more accurate accounting of the true burn size in children. The importance of an accurate burn size assessment cannot be overemphasized. Superficial or first-degree burns should not be included when calculating the percent of TBSA, and thorough cleaning of soot and debris is mandatory to avoid confusing areas of soiling with burns. Examination of referral data suggests that physicians inexperienced with burns tend to overestimate the size of small burns and underestimate the size of large burns, with potentially detrimental effects on pretransfer resuscitation.[6]

Table 8-2 Burn Resuscitation Formulas

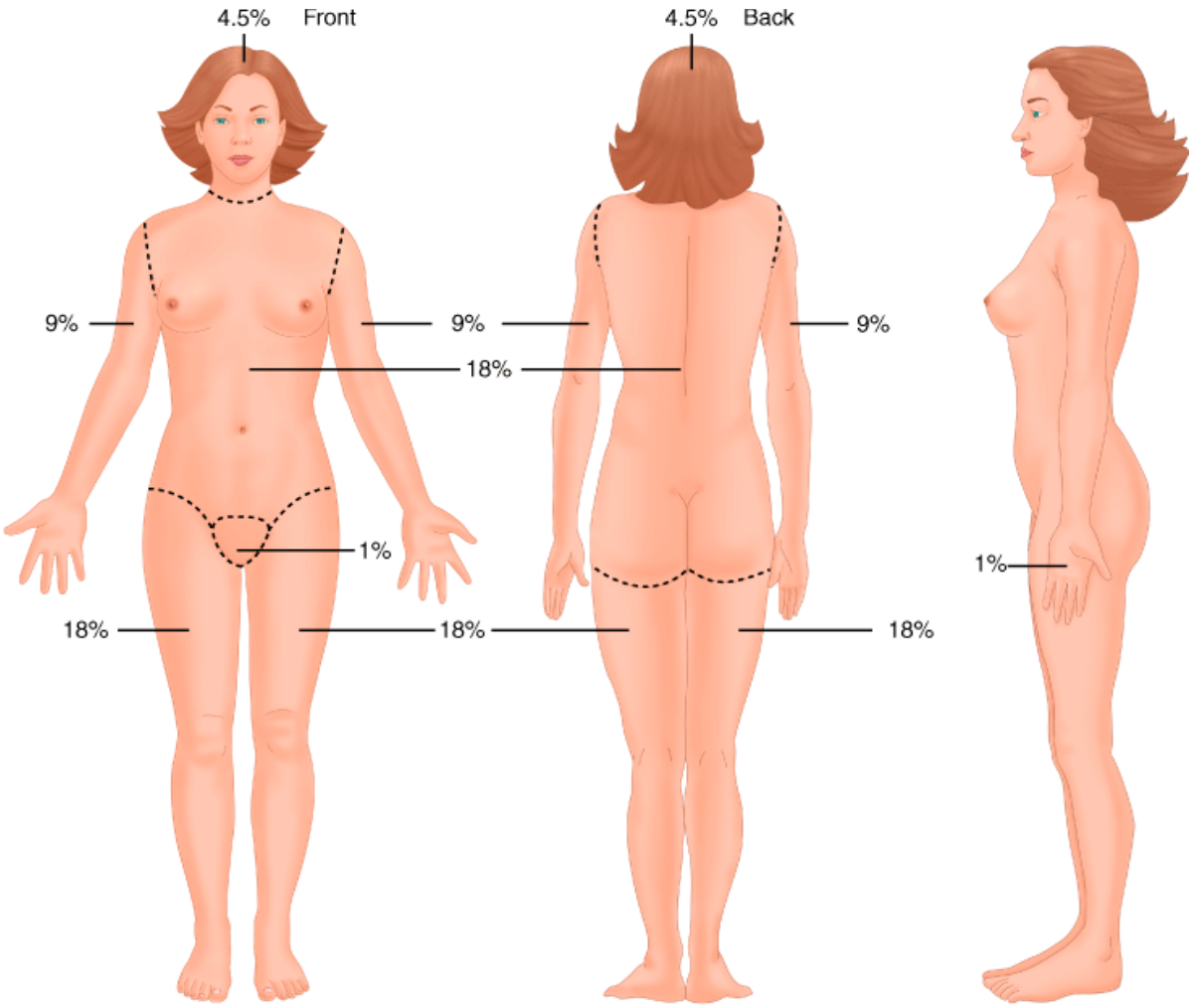
	Electrolyte Solution	**Colloid Solution**	**D_5W**
Isotonic crystalloid formulas			

Parkland formula	Lactated Ringer's		
	4 mL/kg per % TBSA burn		
	$^1/_2$ volume during first 8 h postinjury;		
	$^1/_2$ during next 16 h postinjury		
Modified Brooke formula	Lactated Ringer's		
	2.0 mL/kg per % TBSA burn		
Haifa formula	Lactated Ringer's	Fresh-frozen plasma	
	1 mL/kg per % TBSA burn	1.5 mL/kg per % TBSA burn	
	$^1/_2$ volume during first 8 h postinjury;	$^1/_2$ volume during first 8 h postinjury;	
	$^1/_2$ during next 16 h postinjury	$^1/_2$ during next 16 h postinjury	
Hypertonic formulas			
Monafo formula	25 mEq/L NaCl		
	Volume titrated to UOP 30 mL/h		
Warden formula	Lactated Ringer's plus 50 mEq NaHCO3 (180 mEq Na/L) titrated to UOP 30–50 mL/h for 8 h postinjury		
	Lactated Ringer's titrated to UOP 30–50 mL/h beginning 8 h postburn		
Colloid formulas			
Evans formula	0.9% saline 1 mL/kg per % TBSA burn	Fresh-frozen plasma	2000 mL
		1 mL/kg per % TBSA burn	
Brooke formula	Lactated Ringer's	Fresh-frozen plasma	2000 mL
	1.5 mL/kg per % TBSA burn	0.5 mL/kg per % TBSA burn	
Slater formula	Lactated Ringer's	Fresh-frozen plasma	
	2000 mL/24 h	75 mL/kg per 24 h	
Demling formula	Dextran 40 in 0.9% NaCl	Fresh-frozen plasma	
	2 mL/kg per hour for 8 h postinjury;	0.5 mL/kg per hour starting 8 h postburn continued for 18 h	
	Lactated Ringer's titrated to UOP >30 mL/h for next 18 h postburn		

Note: Individual burn centers may modify these basic formulas for their own needs.

D_5W = 5% dextrose in water; NaCl = sodium chloride; NaHCO3 = sodium bicarbonate; TBSA = total body surface area; UOP = urine output.

Fig. 8-1.



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The Rule of Nines can be used as a quick reference for estimating a patient's burn size by dividing the body into regions to which total body surface area is allocated in multiples of nine.

Another important contributor to early mortality in burns is carbon monoxide (CO) poisoning resulting from smoke inhalation. The affinity of CO for hemoglobin is approximately 200–250 times more than that of oxygen, which decreases the levels of normal oxygenated hemoglobin and can quickly lead to anoxia and death.[7] Unexpected neurologic symptoms should raise the level of suspicion, and an arterial carboxyhemoglobin level must be obtained because pulse oximetry is falsely elevated. Administration of 100% oxygen is the gold standard for treatment of CO poisoning, and reduces the half-life of CO from 250 minutes in room air to 40 to 60 minutes.[8] Some authors have proposed hyperbaric oxygen as an adjunctive therapy for CO poisoning.[9] However, the data are mixed regarding the success of hyperbaric oxygen, and its associated logistic difficulties and complications have limited its usefulness for patients with moderate or large burns.[10,11] Patients who sustain a cardiac arrest as a result of their CO poisoning have an extremely poor prognosis regardless of the success of initial resuscitation attempts.[12] Hydrogen cyanide toxicity may also be a component of smoke inhalation injury. Afflicted patients may have a persistent lactic acidosis or S-T elevation on electrocardiogram (ECG).[13] Cyanide inhibits cytochrome oxidase, which in turn inhibits cellular oxygenation.[14] Treatment consists of sodium thiosulfate, hydroxocobalamin, and 100% oxygen. Sodium thiosulfate works by transforming cyanide into a nontoxic thiocyanate derivative; however, it works slowly and is not effective for acute therapy. Hydroxocobalamin quickly complexes with cyanide and is excreted by the kidney, and is recommended for immediate therapy.[9] In the majority of patients, the lactic acidosis will resolve with ventilation and

sodium thiosulfate treatment becomes unnecessary.[15]

CLASSIFICATION OF BURNS

Burns are commonly classified as thermal, electrical, or chemical burns, with thermal burns consisting of flame, contact, or scald burns. Flame burns are not only the most common cause for hospital admission of burns, but also have the highest mortality. This is primarily related to their association with structural fires and the accompanying inhalation injury and/or CO poisoning.[16]

Electrical burns make up only 4% of U.S. hospital admissions but have special concerns, including the potential for cardiac arrhythmias and compartment syndromes with concurrent rhabdomyolysis. A baseline ECG is recommended in all patients with electrical injury, and a normal ECG in a low-voltage injury may preclude hospital admission. Because compartment syndrome and rhabdomyolysis are common in high-voltage electrical injuries, vigilance must be maintained for neurologic or vascular compromise, and fasciotomies should be performed even in cases of moderate clinical suspicion. Long-term neurologic and visual symptoms are not uncommon with high voltage electrical injuries, and ophthalmologic and neurologic consultation should be obtained to better define a patient's baseline function.[17]

Chemical burns are less common, but potentially are severe burns. The most important components of initial therapy are careful removal of the toxic substance from the patient and irrigation of the affected area with water for a minimum of 30 minutes. An exception to this is in cases of concrete powder or powdered forms of lye, which should be swept from the patient to avoid activating the aluminum hydroxide with water. The offending agents in chemical burns can be systemically absorbed and may cause specific metabolic derangements. Formic acid has been known to cause hemolysis and hemoglobinuria, and hydrofluoric acid causes hypocalcemia. Hydrofluoric acid is a particularly common offender due to its widespread industrial uses. Calcium-based therapies are the mainstay of treating hydrofluoric acid burns, with topical calcium gluconate applied to wounds,[18] and subcutaneous or IV infiltration of calcium gluconate for systemic symptoms. Intra-arterial infusion of calcium gluconate may be effective in the most severe cases.[19,20] Patients undergoing intra-arterial therapy need continuous cardiac monitoring. Persistent electrocardiac abnormalities or refractory hypocalcemia may signal the need for emergent excision of the burned areas.

BURN DEPTH

Burn wounds are commonly classified as superficial (first degree), partial thickness (second degree), full thickness (third degree), and fourth-degree burns, which affect underlying soft tissue. Partial-thickness burns are then classified as either superficial or deep partial thickness burns by depth of involved dermis. Clinically, first-degree burns are painful but do not blister, second-degree burns have dermal involvement and are extremely painful with weeping and blisters, and third-degree burns are hard, painless, and nonblanching. Jackson described three zones of tissue injury following burn injury.[21] The zone of coagulation is the most severely burned portion and is typically in the center of the wound. As the name implies, the affected tissue is coagulated and sometimes frankly necrotic, and will need excision and grafting. Peripheral to that is a zone of stasis, which has a local response of vasoconstriction and resultant ischemia. Appropriate resuscitation and wound care may help prevent conversion to a deeper wound, but infection or suboptimal perfusion may result in an increase in burn depth. This is clinically relevant because many superficial partial-thickness burns will heal with expectant management, while the majority of deep partial-thickness burns require excision and skin grafting. The last area of a burn is called the *zone of hyperemia*, which will heal with minimal or no scarring.

Unfortunately, even experienced burn surgeons have limited ability to accurately predict the healing potential of partial-thickness burns; one reason is that burn wounds evolve over 48–72 hours after a burn injury. Numerous techniques have been developed with the idea that better early prediction of burn depth will expedite appropriate surgical decision making. One of the most effective ways to determine burn depth is full-thickness biopsy, but this has several limitations. Not only is the procedure painful and potentially scarring, but accurate interpretation of the histopathology requires a specialized pathologist and may have slow turnaround times.[22] Laser Doppler can measure skin perfusion and use those measurements to predict burn depth, with a positive predictive value of up to 80% in some studies.[23,24] Noncontact ultrasound has been postulated as a painless modality to predict nonhealing wounds, and has the advantage of easily performed serial measurements.[25] Unfortunately, none of these newer therapies have proven adequately superior to justify their cost, and so have not yet substituted serial examination by experienced burn surgeons.

PROGNOSIS

The Baux score (mortality = age + percent TBSA) was used for many years to predict mortality in burns, and analysis of multiple risk factors for burn mortality validated age and percent

TBSA as the strongest predictors of mortality.[26] Advancements in burn care have lowered overall mortality to the point that the Baux score may no longer be accurate. However, age and burn size, as well as inhalation injury, continue to be the most robust markers for burn mortality.[27] Age, even as a single variable, strongly predicts mortality in burns,[28] and inhospital mortality in elderly burn patients is a function of age regardless of other comorbidities.[29] In nonelderly patients, comorbidities such as preinjury HIV, metastatic cancer, and kidney or liver disease may influence mortality and length of stay.[30] A recent large database study of 68,661 burn patients found that the variables with the highest predictive value for mortality were age, percent TBSA, inhalation injury, coexistent trauma, and pneumonia.[31]

RESUSCITATION

A myriad of formulas exist for calculating fluid needs during burn resuscitation, suggesting that no one formula benefits all patients. The most commonly used formula, the Parkland or Baxter formula, consists of 3 to 4 mL/kg per percent burned of lactated Ringer's, of which half is given during the first 8 hours postburn, and the remaining half over the subsequent 16 hours. The concept behind the continuous fluid needs are simple. The burn (and/or inhalation injury) drives an inflammatory response that leads to capillary leak; as the plasma leaks into the extravascular space, crystalloid administration maintains the intravascular volume. Therefore, if a patient receives a large fluid bolus in a prehospital setting or emergency department, that fluid has likely leaked into the interstitium and the patient will still require ongoing burn resuscitation, according to the estimates. Continuation of fluid volumes should depend on the time since injury, urine output, and MAP; as the leak closes, the patient will require less volume to maintain these two resuscitation endpoints. Children under 20 kg have the additional requirement that they do not have sufficient glycogen stores to maintain an adequate glucose level in response to the inflammatory response. Specific pediatric formulas have been described, but the simplest approach is to add maintenance IV fluid with glucose supplementation in addition to the calculated resuscitation fluid with lactated Ringer's.

It is important to remember that any formula for burn resuscitation is merely a guideline, and fluid must be titrated based on appropriate measures of adequate resuscitation. A number of parameters are widely used to gauge burn resuscitation, but the most common remain the simple outcomes of blood pressure and urine output. As in any critically ill patient, the target MAP is 60 mmHg to ensure optimal end-organ perfusion. Goals for urine output should be 30 mL/h in adults and 1 to 1.5 mL/kg per hour in pediatric patients. Because blood pressure and urine output may not correlate perfectly with true tissue perfusion, the search continues for other adjunctive parameters that may more accurately reflect adequate resuscitation. Some centers have found serum lactate to be a better predictor of mortality in severe burns;[32,33] others have found that base deficit may be a better predictor of eventual organ dysfunction and mortality.[34,35] Burned patients with normal blood pressures and serum lactate levels may still have compromised gastric mucosal blood flow. However, continuous measurement of gastric mucosal pH is logistically difficult and has not been widely implemented.[36,37]

Invasive monitoring with pulmonary artery catheters typically results in significant excessive fluid administration without resulting in improved cardiac output or preload measurements, and the use of invasive monitoring seems to have variable effects on long-term outcomes.[38]

Actual administrated fluid volumes typically exceed volumes predicted by standard formulas.[39] One survey of burn centers showed that 58% of patients receive more fluids than would be predicted by Baxter's formula.[40] A comparison of modern-day patients with historical controls shows that this over-resuscitation may be a relatively recent trend.[41] One theory is that increased opioid analgesic use results in peripheral vasodilation and hypotension and thus the need for greater volumes of bloused resuscitative fluids.[42] A classic study by Navar and associates showed that burned patients with inhalation injury required an average of 5.76 mL/kg per percent burned, versus 3.98 mL/kg per percent burned for patients without inhalation injury. This finding has been corroborated by subsequent studies.[43,44] Prolonged mechanical ventilation may also play a role in increased fluid needs.[45] A recent multicenter study found that age, weight, percent TBSA, and intubation on admission were significant predictors that the patient would receive more fluid during the resuscitation period. Those patients receiving higher fluid volumes were at increased risk of complications and death.[46] Common complications include abdominal compartment syndrome, extremity compartment syndrome, intraocular compartment syndrome, and pleural effusions. Monitoring bladder pressures can provide valuable information about the development of intra-abdominal hypertension.

The use of colloid as part of the burn resuscitation has generated much interest. In late resuscitation when the capillary leak has closed, colloid administration may decrease overall fluid volumes, and potentially may decrease associated complications such as intra-abdominal hypertension.[47] However, the use of albumin has never been shown to improve outcomes in burn patients and has controversial effects on mortality in critically ill patients.[48,49] Attempts to minimize fluid volumes in burn resuscitation have also led to the study of hypertonic solutions. Hypertonic solutions decrease initial resuscitation volumes as expected, but it appears to be a transient benefit and has the downside of causing hyperchloremic acidosis.[50]

Other adjuncts are being increasingly used during initial burn resuscitation. High-dose ascorbic acid (vitamin C) may decrease fluid volume requirements and ameliorate respiratory embarrassment during resuscitation.[51] Plasmapheresis may also decrease fluid requirements in patients who require higher volumes than predicted to maintain adequate urine output and

MAP. It is postulated that plasmapheresis may filter out inflammatory mediators, thus decreasing ongoing vasodilation and capillary leak.[52]

TRANSFUSION

The role of blood transfusion in burns has undergone a re-evaluation in recent years. A large multicenter study found that increased numbers of transfusions were associated with increased infections and a higher mortality rate in burn patients, even when correcting for burn severity.[53] A follow-up study implanting a restrictive transfusion policy in burned children showed that a hemoglobin threshold of 7 g/dL had no more adverse outcomes versus a traditional transfusion trigger of 10 g/dL. In addition, costs incurred to the institution were significantly less.[54] These data, in concert with other reported complications such as transfusion-related lung injury,[55] have led to recommendations that blood transfusions be used only when there is an apparent physiologic need. Attempts to minimize blood transfusion in nonburned, critically ill patients have led to the use of erythropoietin by some centers. Unfortunately, a randomized study in burn patients showed that recombinant human erythropoietin did not effectively prevent anemia or decrease the number of transfusions given.[56]

INHALATION INJURY AND VENTILATOR MANAGEMENT

Inhalation injuries are commonly seen in tandem with burn injuries and are known to drastically increase mortality in burn patients.[57] Smoke inhalation is present in as many as 35% of hospitalized burn patients, and may triple the hospital stay compared to isolated burn injuries.[58] The combination of burns, inhalation injury, and pneumonia increases mortality by up to 60% over burns alone.[59] Subsequent development of the adult respiratory distress syndrome (ARDS) is common in these patients and may be caused in part by recruitment of alveolar leukocytes with an enhanced endotoxin-activated cytokine response.[60] When ARDS complicates burn and inhalation injury, it may result in mortality of up to 66%, and in one study, patients with 60% TBSA or greater in combination with inhalation injury and ARDS had 100% mortality.[61]

Smoke inhalation causes injury in two ways: by direct heat injury to the upper airways, and by inhalation of combustion products into the lower airways. Direct injury to the upper airway causes airway swelling that typically leads to maximal edema in the first 24 to 48 hours after injury, and will require a short course of endotracheal intubation for airway protection. Lower airway injury is caused by combustion products found in smoke, most commonly from synthetic substances burned in structural fires. These irritants cause direct mucosal injury, which in turn leads to mucosal sloughing, edema, reactive bronchoconstriction, and finally obstruction of the lower airways. Injury to both the epithelium and to pulmonary alveolar macrophages causes release of prostaglandins and chemokines, migration of neutrophils and other inflammatory mediators, a rise in tracheobronchial blood flow, and finally increased capillary permeability, leading to ARDS.

The physiologic effects of smoke inhalation are numerous. Inhalation injury decreases lung compliance [62] and increases airway resistance work of breathing.[63] Inhalation injury in the presence of burns will also increase overall metabolic demands.[64] The most common physiologic derangement seen with inhalation injury is an increase in fluid requirements during resuscitation of patients with burn injuries. Bronchoscopic findings, including carbon deposits, erythema, edema, bronchorrhea, and a hemorrhagic appearance, can be useful for confirmation of inhalation injury. Severe inhalation injury may result in mucosal sloughing with obstruction of smaller airways. Because bronchoscopy is an invasive test, attempts have been made to use other diagnostic modalities, such as thoracic computed tomographic scans[65] and xenon ventilation-perfusion scanning.[66] Many of these techniques do not change therapeutic protocols or outcomes,[67] and for this reason many centers still rely on a clinical diagnosis of inhalation injury.[68] A decreased partial pressure of arterial oxygen:fraction of inspired oxygen ratio <200 on admission may not only predict inhalation injury but also indicate increased fluid needs more accurately than bronchoscopic grading of the severity of inhalation.[69]

Treatment of inhalation injury consists primarily of supportive care. Aggressive pulmonary toilet and routine use of nebulized bronchodilators such as albuterol are recommended. Other nebulized agents have shown mixed results. Nebulized *N*-acetylcysteine is an antioxidant free-radical scavenger designed to decrease the toxicity of high oxygen concentrations. Aerosolized heparin aims to prevent formation of fibrin plugs and decrease the formation of airway casts. These agents seem to improve pulmonary toilet, but have no demonstrated effect on mortality.[70] Aerosolized tissue plasminogen activator[71] and recombinant human antithrombin[72] have shown promise in sheep models, but have not yet seen widespread clinical use. Administration of intrabronchial surfactant has been used as a salvage therapy in patients with severe burns and inhalation injury.[73] Inhaled nitric oxide may also be useful as a last effort in burn patients with severe lung injury for whom other means of ventilatory support have failed.[74] The use of steroids traditionally has been avoided due to worse outcomes in burn patients,[75] but new promising data in late ARDS have prompted scientific review of steroid use in this situation.[76]

New ventilator strategies have played an enormous role in improving the mortality of ARDS. Although ARDS still contributes to mortality in burn patients, treatments have improved so

that mortality is primarily from multisystem organ failure rather than isolated respiratory causes.[77] The ARDS Network Study examined low tidal volume or "lung-protective ventilation" by comparing traditional tidal volumes of 12 mL/kg to low tidal volumes of 6 mL/kg. They found that patients on low tidal volume settings had a 22% lower mortality than patients with traditional tidal volumes.[78] A similar approach had previously been shown to improve outcomes in pediatric burn patients.[79] In patients with refractory hypoxemia despite lung-protective ventilation, prone positioning may help improve oxygenation, but has not shown a definitive effect on mortality.[80] No specific studies have examined prone positioning in burn patients, and caution must be used in patients with facial burns who are already at risk for loss of the endotracheal tube. High-frequency percussive ventilation (HFPV) is an alternative mode which has shown some early promise in patients with inhalation injury.[81] A recent study showed notable decreases in both morbidity and mortality with HFPV, especially in patients with less than 40% TBSA and inhalation injury.[82] A related technique is high-frequency oscillatory ventilation, which has been used primarily as a salvage modality in patients refractory to more conventional measure.[83] Extracorporeal membrane oxygenation also typically is reserved for salvage situations, and experience with this modality is limited to small numbers of patients.[84] A promising area of future study is arteriovenous carbon dioxide removal. This technique has proven superior to both low tidal volume ventilation and HFPV in a sheep model, but has not yet made the transition to clinical use.[85]

TREATMENT OF THE BURN WOUND

There are multitudes of topical therapies for the treatment of burn wounds. Of these, silver sulfadiazine is the most widely used in clinical practice. Silver sulfadiazine has a wide range of antimicrobial activity, primarily as prophylaxis against burn wound infections rather than treatment of existing infections. It has the added benefits of being inexpensive and easily applied, and has some soothing qualities. It is not significantly absorbed systemically and thus has minimal metabolic derangements. Silver sulfadiazine has a reputation for causing neutropenia, but this association is more likely to be a result of neutrophil margination due to the inflammatory response to the burn injury. True allergic reactions to the sulfa component of silver sulfadiazine are rare, and at-risk patients can have a small amount applied to identify a burning sensation or rash. Silver sulfadiazine will destroy skin grafts and is contraindicated on burns in proximity to newly grafted areas.

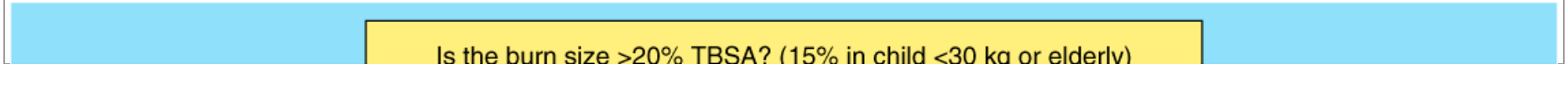
Mafenide acetate, either in cream or solution form, is an effective topical antimicrobial. It is effective even in the presence of eschar and can be used in both treating and preventing wound infections, and the solution form is an excellent antimicrobial for fresh skin grafts. The use of mafenide acetate may be limited by pain with application to partial-thickness burns. Mafenide is absorbed systemically, and a major side effect is metabolic acidosis resulting from carbonic anhydrase inhibition.

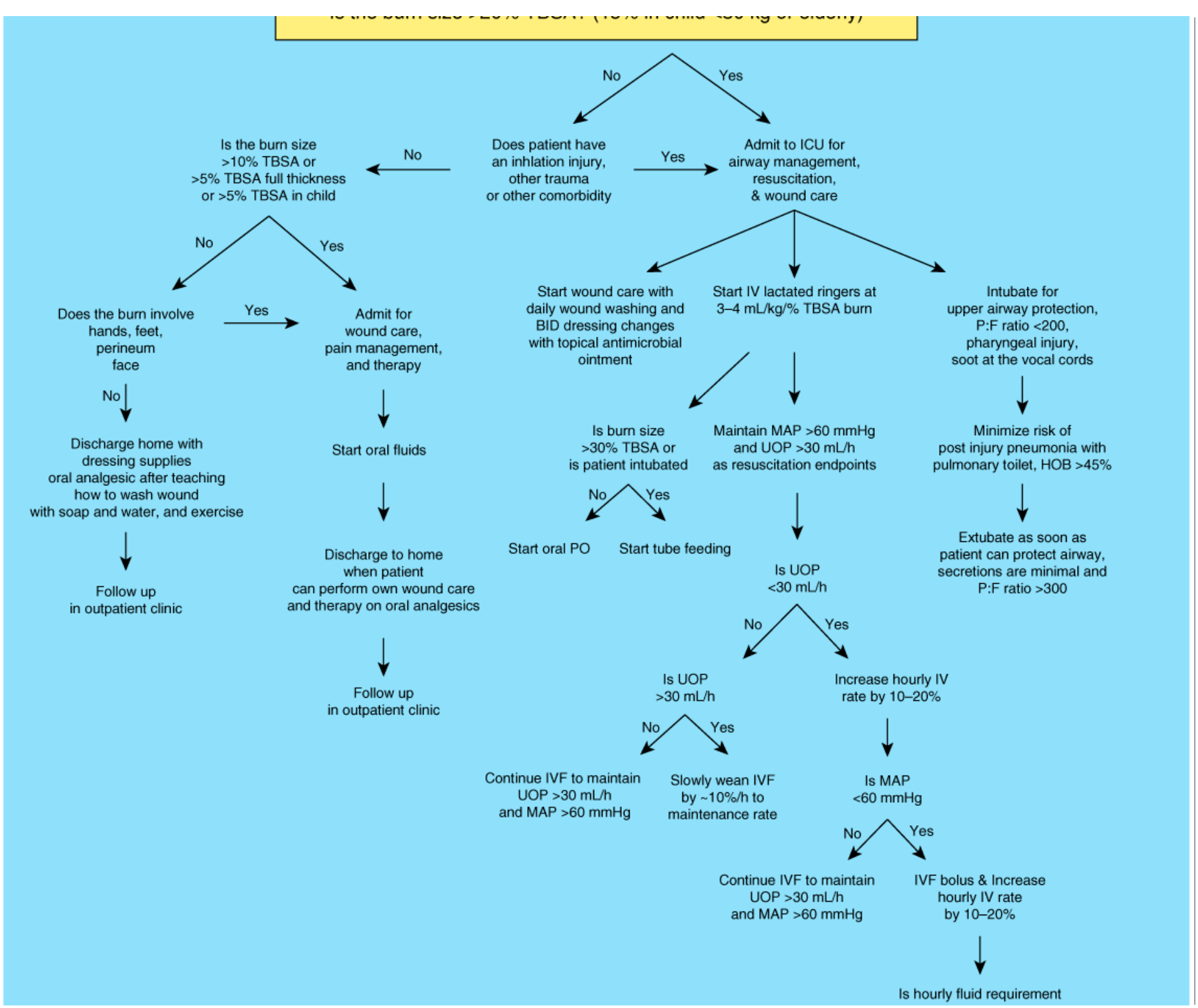
Silver nitrate is another topical agent with broad-spectrum antimicrobial activity. The solution used must be dilute (0.5%), and topical application can lead to electrolyte extravasation with resulting hyponatremia. A rare complication is methemoglobinemia. Although inexpensive, silver nitrate solution causes black stains and laundry costs may offset any fiscal benefit to the hospital.

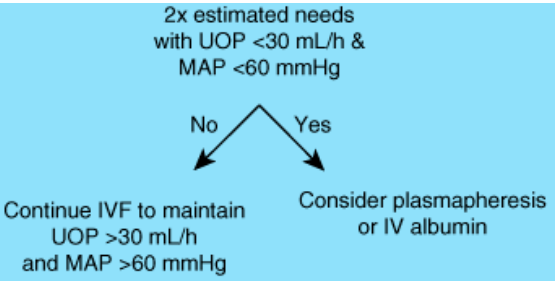
For burns that are nearly healed, small or large, topical ointments such as bacitracin, neomycin, and polymyxin B can be used. These are also useful for superficial partial-thickness facial burns as they can be applied and left open to air without dressing coverage. Meshed skin grafts, in which the interstices are nearly closed, are another indication for use of these agents, preferably with greasy gauze to help retain the ointment in the affected area. All three have been rarely reported to cause nephrotoxicity and should not be used in large burns. The recent media fascination with methicillin-resistant *Staphylococcus aureus* has led to widespread use by community practitioners of mupirocin for new burns. Unless the patient has known risk factors for methicillin-resistant *S. aureus*, mupirocin should only be used in culture-positive burn wound infections to prevent encouragement of further resistance.

Silver-impregnated dressings such as Acticoat (Smith & Nephew, London, England) and Aquacel Ag (Convatec, Princeton, NJ) are increasingly being used for both donor sites and skin grafts, as well as for burns that are clearly partial-thickness on admission. These help reduce the number of dressing changes and may be more comfortable for the patient, but should not be used in wounds of heterogeneous depth, as they prevent serial examinations of the wound. Biologic membranes such as Biobrane (Dow-Hickham, Sugarland, TX) provide a prolonged barrier under which wounds may heal. Because of the occlusive nature of these dressings, these are typically used only on fresh superficial partial-thickness burns that are clearly not contaminated. Fig. 8-2 provides an algorithm that may assist in selecting the appropriate burn treatment.

Fig. 8-2.




No
Yes
Is the burn size >10% TBSA or >5% TBSA full thickness or >5% TBSA in child
No
Does patient have an inhlation injury, other trauma or other comorbidity
Yes
Admit to ICU for airway management, resuscitation, & wound care
No
Yes
Does the burn involve hands, feet, perineum face
Yes
Admit for wound care, pain management, and therapy
No
Discharge home with dressing supplies oral analgesic after teaching how to wash wound with soap and water, and exercise
Follow up in outpatient clinic
Start oral fluids
Discharge to home when patient can perform own wound care and therapy on oral analgesics
Follow up in outpatient clinic
Start wound care with daily wound washing and BID dressing changes with topical antimicrobial ointment
Start IV lactated ringers at 3–4 mL/kg/% TBSA burn
Intubate for upper airway protection, P:F ratio <200, pharyngeal injury, soot at the vocal cords
Is burn size >30% TBSA or is patient intubated
Maintain MAP >60 mmHg and UOP >30 mL/h as resuscitation endpoints
Minimize risk of post injury pneumonia with pulmonary toilet, HOB >45%
No
Yes
Start oral PO
Start tube feeding
Extubate as soon as patient can protect airway, secretions are minimal and P:F ratio >300
Is UOP <30 mL/h
No
Yes
Is UOP >30 mL/h
Increase hourly IV rate by 10–20%
No
Yes
Continue IVF to maintain UOP >30 mL/h and MAP >60 mmHg
Slowly wean IVF by ~10%/h to maintenance rate
Is MAP <60 mmHg
No
Yes
Continue IVF to maintain UOP >30 mL/h and MAP >60 mmHg
IVF bolus & Increase hourly IV rate by 10–20%
Is hourly fluid requirement



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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Algorithm for burn treatment. HOB = head of bed; MAP = mean arterial pressure; P:F = partial pressure of arterial oxygen:fraction of inspired oxygen; TBSA = total body surface area; UOP = urine output.

NUTRITION

Nutritional support may be more important in patients with large burns than in any other patient population. Not only does adequate nutrition play a role in acute issues such as immune responsiveness, but the hypermetabolic response in burn injury may raise baseline metabolic rates by as much as 200%.[86] This can lead to catabolism of muscle proteins and decreased lean body mass that may delay functional recovery.[87] Early enteral feeding for patients with burns larger than 20% TBSA is not only safe, but it may help prevent loss of lean body mass,[88] slow the hypermetabolic response,[89] and result in more efficient protein metabolism.[90] If the enteral feeds are started within the first few hours after admission, gastric ileus can often be avoided. Adjuncts such as metoclopramide can promote GI motility; alternatively, advancing the tube into the small bowel with nasojejunal feeding can be attempted if other measures for gastric feeding are unsuccessful.[91] In endotracheally intubated patients, trips to the operating room do not necessitate holding enteral feedings.[92] Immune modulating supplements such as glutamine may decrease infectious complications and mortality in burn patients,[93] likely via prevention of T-cell suppression in mesenteric lymph nodes.[94]

Calculating the appropriate caloric needs of the burn patient can be challenging. A commonly used formula in nonburned patients is the Harris-Benedict equation, which calculates caloric needs using factors such as gender, age, height, and weight. This formula uses an activity factor for specific injuries, and for burns the basal energy expenditure is multiplied by two. The Harris-Benedict equation may be inaccurate in burns of less than 40% TBSA, and in these patients, the Curreri formula may be more appropriate. This formula estimates caloric needs = 25 kcal/kg per day + 40 kcal/% TBSA per day.[95] Indirect calorimetry also can be used to calculate resting energy expenditure, but in burn patients a "metabolic cart" has not been documented to be more beneficial than the predictive equations.[96] Titrating caloric needs closely is important because overfeeding patients will lead to storage of fat instead of muscle anabolism.[97]

Modifying the hypermetabolic response is an area of intense study with several recent findings. Beta blocker use in pediatric patients decreases heart rate and resting energy expenditure and abrogates protein catabolism, even in long-term use.[98] There may be benefits to beta blocker use in adult patients as well,[99] and many centers have begun using them routinely in the adult population. The anabolic steroid oxandrolone has been extensively studied in pediatric patients as well, and has demonstrated improvements in lean body mass and bone density in severely burned children.[100] The weight gain and functional improvements seen with oxandrolone may persist even after stopping administration of the drug.[101] A recent double-blinded, randomized study of oxandrolone showed decreased length of stay, improved hepatic protein synthesis, and no adverse effects on the endocrine function, although the authors noted a rise in transaminases with unclear clinical significance.[102] Intensive insulin therapy in critically ill patients has shown benefit, presumably from avoidance of hyperglycemia.[103] However, in burn patients, the insulin itself may have a metabolic benefit, with improvements in lean body mass and amelioration of the inflammatory response to burn injury.[104,105] Oral hypoglycemic agents such as metformin also help to avoid hyperglycemia and may contribute to prevention of muscle catabolism.[106]

COMPLICATIONS IN BURN CARE

There are several complications commonly associated with treatment of burn patients. Although not always avoidable, maintaining vigilance for typical complications and using appropriate techniques for prevention may limit the frequency and severity of complications. Ventilator-associated pneumonia, as with all critically ill patients, is a significant problem in burn patients.

However, it is so common in patients with inhalation injury, a better nomenclature may be postinjury pneumonia. Unfortunately, commonly used scores in critical illness such as the Clinical Pulmonary Infection Score have not been shown to be reliable in burn patients. Quantitative bronchoscopic cultures in the setting of clinical suspicion of pneumonia should guide treatment of pneumonia.[107] Simple measures such as elevating the head of the bed and maintaining excellent oral hygiene and pulmonary toilet are recommended to help decrease the risk of postinjury pneumonia. There is some question as to whether early tracheostomy will decrease infectious morbidity in burn patients, and whether it will affect long-term outcomes. There do not seem to be any major differences in the rates of pneumonia with early tracheostomy, although there may be less subglottic stenosis than in burn patients with prolonged endotracheal intubation.[108] It also appears that overall outcomes are not affected by early tracheostomy,[109] but practical considerations such as protection of facial skin grafts may play a role in deciding the timing of tracheostomy. One major consideration in deciding whether to perform a tracheostomy has been the presence of eschar at the insertion site, which complicates tracheostomy site care and increases the risk of airway infection. Bedside percutaneous dilatational tracheostomy is a facile method for performing tracheostomy and is reported to be as safe as open tracheostomy in the burn population.[110]

Massive resuscitation of burn patients may lead to an abdominal compartment syndrome characterized by increased airway pressures with hypoventilation, and decreased urine output and hemodynamic compromise. Decompressive laparotomy is the standard of care for refractory abdominal compartment syndrome but carries an especially lethal prognosis in burn patients.[111] Adjunctive measures such as minimizing fluid, performing truncal escharotomies, decreasing tidal volumes, and chemical paralysis should be initiated before resorting to decompressive laparotomy.

Deep vein thrombosis (DVT) has been commonly believed to be a rare phenomenon in burn patients, and there is a paucity of controlled studies regarding heparin prophylaxis in this population.[112] However, recent data show that 6 to 25% of burn patients may have DVT, and fatal pulmonary embolus has been reported in burn patients.[113,114] A large retrospective study in patients with routine prophylaxis found DVT in only 0.25% of patients, and reported no bleeding complications.[115] Thus, it appears that heparin prophylaxis is safe in burn patients and may help prevent thrombotic complications.

Unfortunately, the use of both prophylaxis and therapeutic heparin may be associated with heparin-induced thrombocytopenia (HIT). One study of HIT in burn patients showed an incidence of 1.6% in heparinized burn patients. Thrombotic complications included DVT, pulmonary embolus, and even arterial thrombosis requiring limb amputation. Nonheparin anticoagulation for HIT commonly caused bleeding complications requiring transfusion.[116] Although rare, a high index of suspicion for HIT should be maintained in thrombocytopenic burn patients, particularly if the platelet counts drop in hospital days 7 to 10.

Burn patients often require central venous access for fluid resuscitation and hemodynamic monitoring. Because of the anatomic relation of their burns to commonly used access sites, burn patients may be at higher risk for catheter-related bloodstream infections. Because burn patients may commonly exhibit leukocytosis with a documented bloodstream infection, practice has been to rewire lines over a guidewire and then culture the catheter. However, this may increase the risk of catheter-related infections in burn patients and a new site should be used if at all possible.[117]

SURGERY

Full-thickness burns with a rigid eschar can form a tourniquet effect as the edema progresses, leading to compromised venous outflow and eventually arterial inflow. The resulting compartment syndrome is most common in circumferential extremity burns, but abdominal and thoracic compartment syndromes also occur. Warning signs of impending compartment syndrome may include paresthesias, pain, decreased capillary refill, and progression to loss of distal pulses; in an intubated patient, the surgeon should anticipate the compartment syndrome and perform frequent vascular evaluations. Abdominal compartment syndrome should be suspected with decreased urine output, increased ventilator airway pressures, and hypotension. Thoracic compartment syndrome may also be characterized by hypoventilation, increased airway pressures, and hypotension. Escharotomies are rarely needed within the first 8 hours following injury and should not be performed unless indicated because of the terrible aesthetic sequelae. When indicated, they usually are performed at the bedside preferably with electrocautery. Extremity incisions are made on the lateral and medial aspects of the limbs in an anatomic position and may extend onto thenar and hypothenar eminences of the hand. Digital escharotomies do not usually result in any meaningful salvage of functional tissue and are not recommended. Inadequate perfusion despite proper escharotomies may indicate the need for fasciotomy; however, this procedure should not be routinely performed as part of the eschar release. Thoracic escharotomies should be placed along the anterior axillary lines with bilateral subcostal and subclavicular extensions. Extension of the anterior axillary incisions down the lateral abdomen typically will allow adequate release of abdominal eschar.

The strategy of early excision and grafting in burned patients revolutionized survival outcomes in burn care. Not only did it improve mortality, but early excision decreased reconstruction surgery, improved hospital length of stay, and reduced costs of care.[118,119] After the initial resuscitation is complete and the patient is hemodynamically stable, attention should be turned to excising the burn wound. Burn excision and wound coverage should ideally start within the first several days, and in larger burns, serial excisions can be performed as the patient's condition allows. Excision is performed with repeated tangential slices using a Watson or Goulian blade until only nonburned tissue remains. It is appropriate to leave healthy dermis, which will appear white with punctate areas of bleeding. Excision to fat or fascia may be necessary in deeper burns. The downside of tangential excision is a high blood loss, though this may be ameliorated using techniques such as instillation of an epinephrine clysis solution underneath the burn. Pneumatic tourniquets are helpful in extremity burns, and compresses soaked in a dilute epinephrine solution are necessary adjuncts after excision. A fibrinogen and thrombin spray sealant (Tisseel Fibrin Sealant; Baxter, Deerfield, Illinois) also has beneficial effects on both hemostasis and graft adherence to the wound bed. The use of these techniques has markedly decreased the number of blood transfusions given during burn surgery.[120] For patients with clearly deep burns and concern for excessive blood loss, fascial excision may be used. In this technique, electrocautery is used to excise the burned tissue and the underlying subcutaneous tissue down to muscle fascia. This technique markedly decreases blood loss but results in a cosmetically inferior appearance due to the loss of subcutaneous tissue. For excision of burns in difficult anatomic areas such as the face, eyelids, or hands, a pressurized water dissector may offer more precision but is time consuming, has a steep learning curve, and is expensive.[121]

WOUND COVERAGE

Because full-thickness grafts are impractical for most burn wounds, split-thickness sheet autografts harvested with a power dermatome make the most durable wound coverings and have a decent cosmetic appearance. In larger burns, meshing of autografted skin provides a larger area of wound coverage. This also allows drainage of blood and serous fluid to prevent accumulation under the skin graft with subsequent graft loss. Areas of cosmetic importance such as the face, neck, and hands should be grafted with nonmeshed sheet grafts to ensure optimal appearance. Unfortunately, even extensive meshing of skin grafts in patients with limited donor sites may not provide adequate amounts of skin. Options for temporary wound coverage include human cadaveric allograft, which is incorporated into the wound but is rejected by the immune system and must be eventually replaced. This will allow time for donor sites to heal enough so that they may be reharvested. The search for a perfect permanent synthetic skin substitute remains elusive, but there are some products in use that help expedite removal of burn eschar and provide temporary wound coverage. Integra (Integra LifeSciences Corporation, Plainsboro, NJ) is a bilayer product with a porous collagen-chondroitin 6-sulphate inner layer that is attached to an outer sheet of silastic. The silastic barrier helps prevent fluid loss and infection, and the inner layer becomes vascularized, creating an artificial neodermis. At approximately 2 weeks, the silastic layer is removed and a thin autograft placed over the neodermis. This results in faster healing of the more superficial donor sites, and seems to have less hypertrophic scarring and improved joint function.[122] AlloDerm (LifeCell Corporation, The Woodlands, TX) is another dermal substitute consisting of cryopreserved acellular human dermis. This must also be used in combination with thin split-thickness skin grafts.[123]

Epidermal skin substitutes such as cultured epithelial autografts are an option in patients with massive burns and very limited donor sites.[124] Their clinical use has been limited by a long turnaround time for culturing, as well as the fragility of the cultured skin, which creates great difficulty with intraoperative handling and graft take. There are promising developments in skin culturing techniques, but none of the final products have yet become commercially available.[125]

Thighs make convenient anatomic donor sites, which are easily harvested and relatively hidden from an aesthetic standpoint. The thicker skin of the back is useful in older patients, who have thinner skin elsewhere and may have difficulty healing donor sites. The buttocks are an excellent donor site in infants and toddlers; Silvadene can be applied to the donor site with a diaper as coverage. The scalp is also an excellent donor site; the skin is thick and there are many hair follicles so it heals quickly. It has the added advantage of being completely hidden once hair regrows. Epinephrine clysis is necessary for harvesting the scalp, for both hemostasis of this hypervascular area and also to create a smooth surface for harvesting.

The list of commonly used donor site dressings is lengthy and includes simple transparent films to hydrocolloids, petrolatum gauzes, and silver-impregnated dressings. Donor sites close to fresh grafts may be dressed with a porous nonadherent gauze, and both the donor sites and grafts can be soaked with mafenide acetate for ease of care. Principles behind choosing a dressing should balance ease of care, comfort, infection control, and cost. The choice of donor site dressing is largely institution dependent and few data support the clear superiority of any single treatment plan.

REHABILITATION

The rehabilitation of the burn patient is an integral part of their clinical care and should be initiated on admission. Immediate and ongoing physical and occupational therapy is mandatory to prevent loss of physical function. Patients that are unable to participate due to mechanical ventilation or other reasons should have passive range of motion done at least twice a day. This includes patients with burns over joints, such as with hand burns. Patients should be taught exercises they can do themselves to maintain full range of motion. Patients with foot and extremity burns should be instructed to walk independently without the help of crutches to prevent extremity swelling, desensitize the burned areas, and prevent disuse atrophy; when patients are not ambulating, they must elevate the affected extremity to minimize swelling. If postoperative immobilization is used for graft protection, the graft should be evaluated early and at frequent intervals so that active exercise can be resumed at the earliest possible occasion. The transition to outpatient care should also include physical and occupational therapy, with introduction of exercises designed to accelerate return to activities of daily living as well as specific job-related tasks. Tight-fitting pressure garments provide vascular support in burns that are further along in the healing process. However, they do provide vascular support that many patients find more comfortable.

Psychological rehabilitation is equally important in the burn patient. Depression, posttraumatic stress disorder, concerns about cosmetic appearance, and anxiety about returning to society constitute predictable barriers to progress in both the inpatient and outpatient setting. Psychological distress occurs in as many as 34% of burn patients, and persists in severity long after discharge.[126] Despite this, many patients will be able to quickly return to work or school, and goals should be set accordingly. The return to school for pediatric patients is typically prompt, averaging about 10 days after discharge. However, further study is needed to determine whether attendance and performance suffer despite early re-entry to school.[127] The involvement of clinical psychologists and psychiatrists is invaluable in providing guidance and coping techniques to lessen the significant psychological burden of burn injury.

PREVENTION

Despite many areas of progress in prevention, burns continue to be a common source of injury. Some successful initiatives have included community-based interventions targeting simple home safety measures. Smoke alarms are known to decrease mortality from structural fires, but not all homes are equipped with proper smoke alarms, particularly in low-income households. Mandatory smoke alarm installation via community initiatives can be successful, but appears to be contingent on close, long-term follow up to ensure proper maintenance and function.[128,129] Regulation of hot water heater temperatures has had some success, and may be even more effective in conjunction with community-based programs emphasizing education and in-home inspections.[130,131]

FUTURE AREAS OF STUDY

It has long been anecdotally noted that two patients of similar ages and burn size may have very divergent responses to their burn injuries. Attention is being increasingly turned to identifying genetic differences among burn patients and how they affect response to injury. Specific allele variants have been linked with increased mortality in burn patients.[132] It may be that genetic differences may predispose burn patients to severe sepsis,[133] perhaps by downregulating the immune response.[134] Inflammation and the Host Response to Injury is a prospective, multicenter, federally-funded study that aims to define specific genetic pathways that differ in the response to both burns and traumatic injury. Blood and tissue samples taken from a strictly defined patient population are analyzed using gene arrays to determine whether differential expression in certain genetic pathways affects clinical outcomes.[135]

With the progress achieved, the functional outcomes of burn survivors have become more important to clinical outcomes than survival. Since 1993, the National Institute of Disability and Rehabilitation Research has included burns as a model system for improving outcomes for survivors. These studies have been crucial for understanding the barriers that these patients face in returning to their communities, to the workplace, or to school.

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KEY POINTS

1. Wound healing is a complex cellular and biochemical cascade that leads to restitution of integrity and function.

2. Although individual tissues may have unique healing characteristics, all tissues heal by similar mechanisms, and the process undergoes phases of inflammation, cellular migration, proliferation, matrix deposition, and remodeling.

3. Factors that impede normal healing include local, systemic, and technical conditions that the surgeon must take into account.

4. Optimal outcome of acute wounds relies on complete evaluation of the patient and of the wound, and application of best practices and techniques.

5. Clinically, excess healing can be as significant a problem as impaired healing; genetic, technical, and local factors play a major role.

6. Future advances in growth factor understanding, tissue engineering, and dressing design are expected to increase the armamentarium in improving wound outcomes.

HISTORY OF WOUND HEALING

The earliest accounts of wound healing date back to about 2000 B.C., when the Sumerians employed two modes of treatment: a spiritual method consisting of incantations and a physical method of applying poultice-like materials to the wound. The Egyptians were the first to differentiate between infected and diseased wounds compared to noninfected wounds. The 1650 B.C. Edwin Smith Surgical Papyrus, a copy of a much older document, describes at least 48 different types of wounds. A later document (Ebers Papyrus, 1550 B.C.) relates the use of concoctions containing honey (antibacterial properties), lint (absorbent properties), and grease (barrier) for treating wounds. These same properties are still considered essential in contemporary daily wound management.

The Greeks, equipped with the knowledge bequeathed by the Egyptians, went even further and classified wounds as acute or chronic in nature. Galen of Pergamum (120–201 A.D.), appointed as the doctor to the Roman gladiators, had an enormous number of wounds to deal with after gladiatorial combats. He emphasized the importance of maintaining a moist environment to ensure adequate healing. It took almost 19 centuries for this important concept to be proven scientifically, when it was shown that the epithelialization rate increases by 50% in a moist wound environment when compared to a dry wound environment.[1]

The next major stride in the history of wound healing was the discovery of antiseptics and their importance in reducing wound infections. Ignaz Philipp Semmelweis, a Hungarian obstetrician (1818–1865), noted that the incidence of puerperal fever was much lower if medical students, after cadaver-dissection class and before attending childbirth, washed their hands with soap and hypochlorite. Louis Pasteur (1822–1895) was instrumental in dispelling the theory of spontaneous generation

of germs and proving that germs were always introduced into the wound from the environment. Joseph Lister probably made one of the most significant contributions to wound healing. On a visit to Glasgow, Scotland, Lister noted that some areas of the city's sewer system were less murky than the rest. He discovered that the water from pipes that were dumping waste containing carbolic acid (phenol) was clear. In 1865, Lister began soaking his instruments in phenol and spraying the operating rooms, reducing the mortality rates from 50 to 15%. This practice led to the suspension of Lister, although subsequent confirmation of his results paved the way for his triumphant return to Edinburgh.

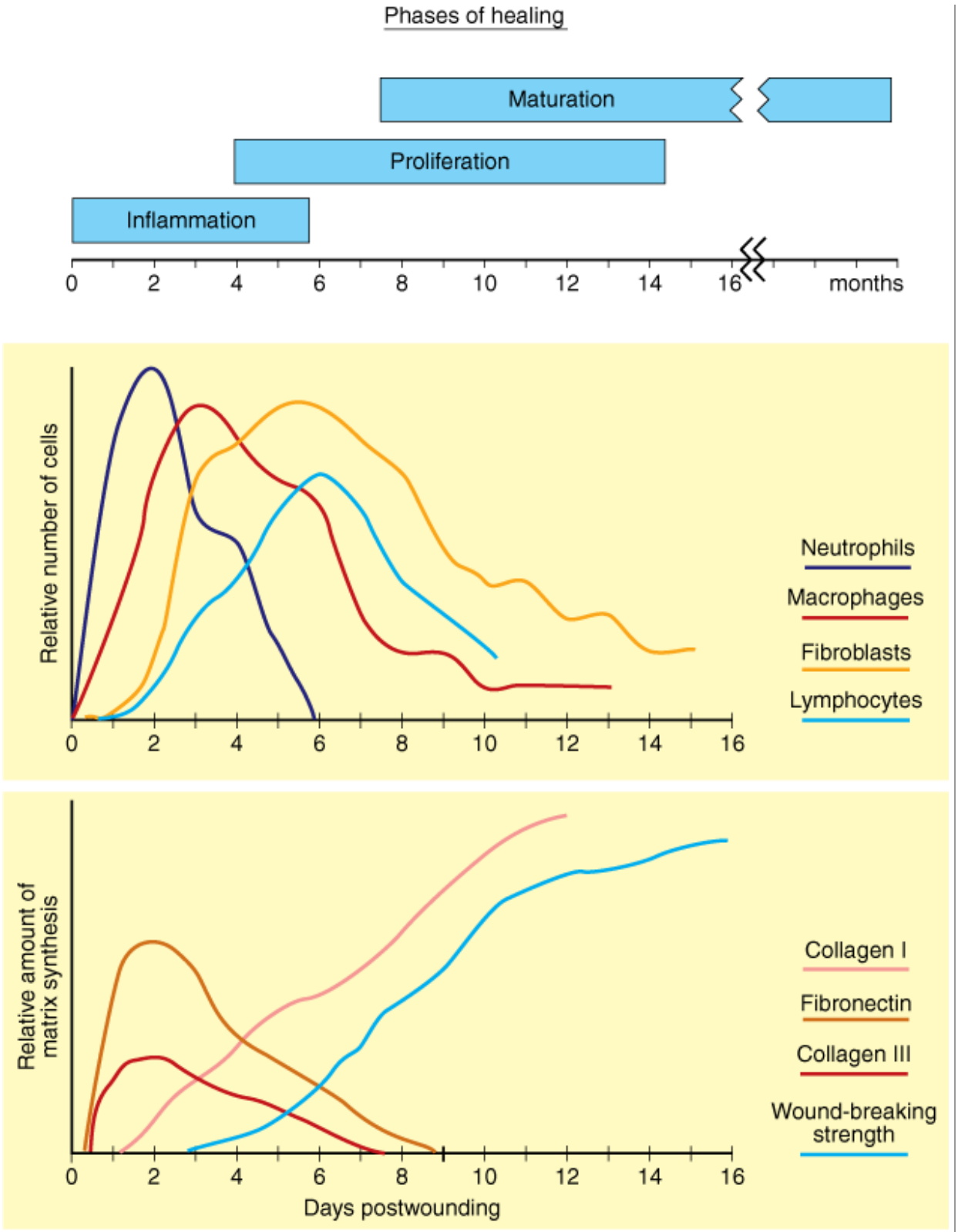
After attending an impressive lecture by Lister in 1876, Robert Wood Johnson left the meeting and began 10 years of research that would ultimately result in the production of an antiseptic dressing in the form of cotton gauze impregnated with iodoform. Since then, several other materials have been used to impregnate cotton gauze to achieve antisepsis.

Polymeric dressings were developed in the 1960s and 1970s. These polymeric dressings can be custom made to specific parameters, such as permeability to gases (occlusive vs. semiocclusive), varying degrees of absorbency, and different physical forms. Due to the ability to customize, the available range of materials that aid in wound care has grown exponentially to include an ever-expanding variety. Currently, the practice of wound healing encompasses manipulation and/or use of, among others, inflammatory cytokines, growth factors, and bioengineered tissue. It is the combination of all these modalities that enables optimal wound healing.

PHASES OF WOUND HEALING

As noted by John Hunter (1728–1793), a keen observer of biologic phenomena, ". . . the injury alone has in all cases a tendency to produce the disposition and the means of a cure."[2] Normal wound healing follows a predictable pattern that can be divided into overlapping phases defined by characteristic cellular populations and biochemical activities: (a) hemostasis and inflammation, (b) proliferation, and (c) maturation and remodeling. An approximate timeline of these events is depicted in Fig. 9-1. This sequence of events is fluid and overlapping, and in most circumstances spans the time from injury to resolution of acute wounds. All wounds need to progress through this series of cellular and biochemical events that characterizes the phases of healing to successfully re-establish tissue integrity.

Fig. 9-1.



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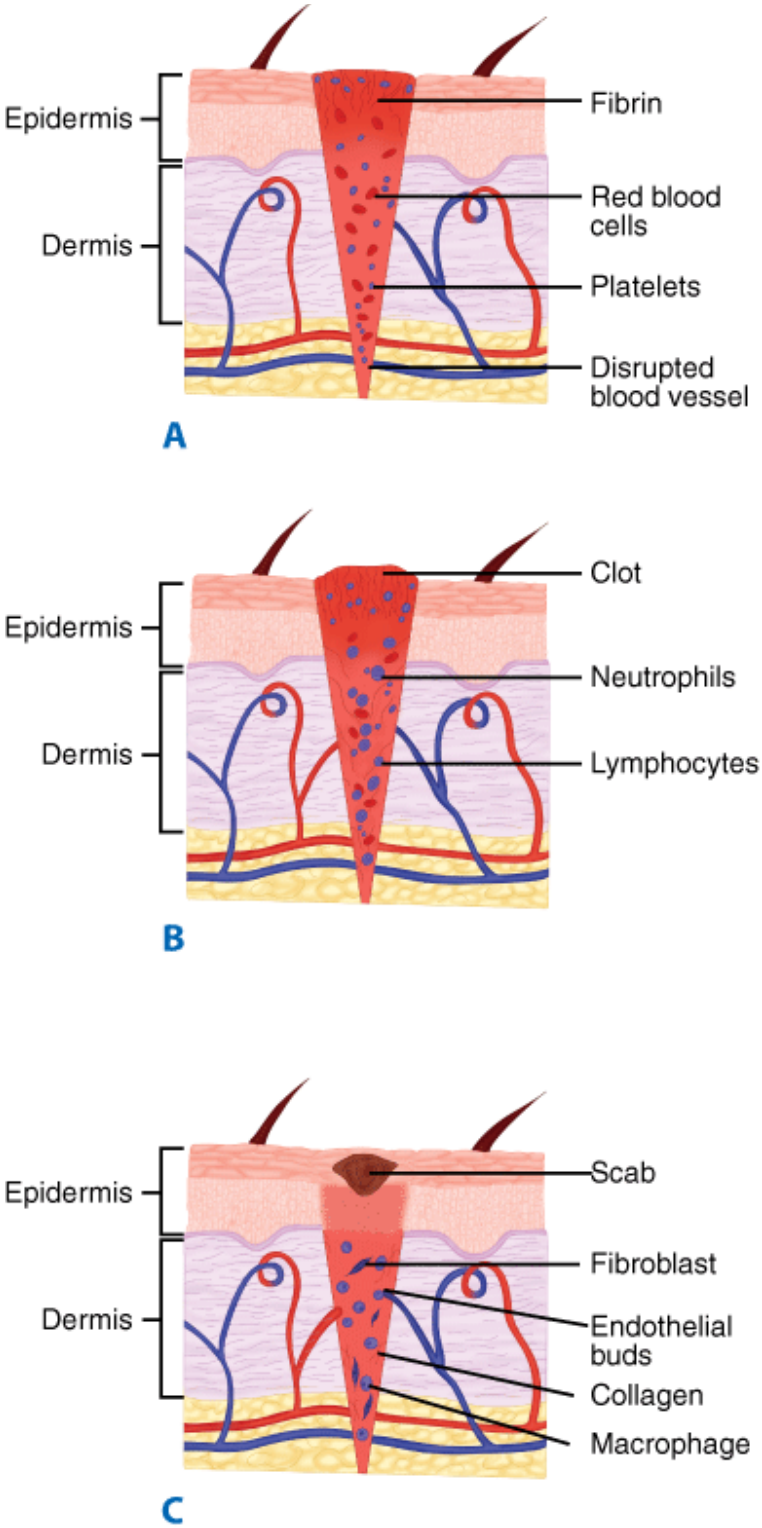
The cellular, biochemical, and mechanical phases of wound healing.

Hemostasis and Inflammation

Hemostasis precedes and initiates inflammation, with the ensuing release of chemotactic factors from the wound site (Fig. 9-

2A). Wounding by definition disrupts tissue integrity, leading to division of blood vessels and direct exposure of extracellular matrix to platelets. Exposure of subendothelial collagen to platelets results in platelet aggregation, degranulation, and activation of the coagulation cascade. Platelet α-granules release a number of wound-active substances, such as platelet-derived growth factor (PDGF), transforming growth factor beta (TGFβ), platelet-activating factor, fibronectin, and serotonin. In addition to achieving hemostasis, the fibrin clot serves as scaffolding for the migration into the wound of inflammatory cells such as polymorphonuclear leukocytes (PMNs, neutrophils) and monocytes.

Fig. 9-2.



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The phases of wound healing viewed histologically. **A.** The hemostatic/inflammatory phase. **B.** Latter inflammatory phases reflecting infiltration by mononuclear cells and lymphocytes. **C.** The proliferative phase, with associated angiogenesis and collagen synthesis.

Cellular infiltration after injury follows a characteristic, predetermined sequence (see Fig. 9-1). PMNs are the first infiltrating cells to enter the wound site, peaking at 24 to 48 hours. Increased vascular permeability, local prostaglandin release, and

the presence of chemotactic substances, such as complement factors, interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), TGFβ, platelet factor 4, or bacterial products, all stimulate neutrophil migration.

The postulated primary role of neutrophils is phagocytosis of bacteria and tissue debris. PMNs are also a major source of cytokines early during inflammation, especially TNF-α,[3] which may have a significant influence on subsequent angiogenesis and collagen synthesis (see Fig. 9-2B). PMNs also release proteases such as collagenases, which participate in matrix and ground substance degradation in the early phase of wound healing. Other than their role in limiting infections, these cells do not appear to play a role in collagen deposition or acquisition of mechanical wound strength. On the contrary, neutrophil factors have been implicated in delaying the epithelial closure of wounds.[4]

The second population of inflammatory cells that invades the wound consists of macrophages, which are recognized as being essential to successful healing.[5] Derived from circulating monocytes, macrophages achieve significant numbers in the wound by 48 to 96 hours postinjury and remain present until wound healing is complete.

Macrophages, like neutrophils, participate in wound débridement via phagocytosis and contribute to microbial stasis via oxygen radical and nitric oxide synthesis (see Fig. 9-2C). The macrophage's most pivotal function is activation and recruitment of other cells via mediators such as cytokines and growth factors, as well as directly by cell–cell interaction and intercellular adhesion molecules. By releasing such mediators as TGFβ, vascular endothelial growth factor (VEGF), insulin-like growth factor, epithelial growth factor, and lactate, macrophages regulate cell proliferation, matrix synthesis, and angiogenesis.[6,7] Macrophages also play a significant role in regulating angiogenesis and matrix deposition and remodeling (Table 9-1).

Table 9-1 Macrophage Activities during Wound Healing

Activity	**Mediators**
Phagocytosis	Reactive oxygen species
	Nitric oxide
Débridement	Collagenase, elastase
Cell recruitment and activation	Growth factors: PDGF, TGFβ, EGF, IGF
	Cytokines: TNF-α, IL-1, IL-6
	Fibronectin
Matrix synthesis	Growth factors: TGFβ, EGF, PDGF
	Cytokines: TNF-α, IL-1, IFN-γ
	Enzymes: arginase, collagenase
	Prostaglandins
	Nitric oxide
Angiogenesis	Growth factors: FGF, VEGF
	Cytokines: TNF-α
	Nitric oxide

EGF = epithelial growth factor; FGF = fibroblast growth factor; IGF = insulin-like growth factor; IFN-γ = interferon-γ; IL = interleukin; PDGF = platelet-derived growth factor; TGFβ = transforming growth factor beta; TNF-α = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor.

T lymphocytes comprise another population of inflammatory/immune cells that routinely invades the wound. Less numerous

than macrophages, T-lymphocyte numbers peak at about 1 week postinjury and truly bridge the transition from the inflammatory to the proliferative phase of healing. Although known to be essential to wound healing, the lymphocytes' role in wound healing is not fully defined.[8] A significant body of data supports the hypothesis that T lymphocytes play an active role in the modulation of the wound environment. Depletion of most wound T lymphocytes decreases wound strength and collagen content,[9] whereas selective depletion of the $CD8^+$ suppressor subset of T lymphocytes enhances wound healing. However, depletion of the $CD4^+$ helper subset has no effect.[10] Lymphocytes also exert a downregulating effect on fibroblast collagen synthesis by cell-associated interferon-γ, TNF-α, and IL-1. This effect is lost if the cells are physically separated, suggesting that extracellular matrix synthesis is regulated not only via soluble factors but also by direct cell–cell contact between lymphocytes and fibroblasts.[11]

Proliferation

The proliferative phase is the second phase of wound healing and roughly spans days 4 through 12 (see Fig. 9-2C). It is during this phase that tissue continuity is re-established. Fibroblasts and endothelial cells are the last cell populations to infiltrate the healing wound, and the strongest chemotactic factor for fibroblasts is PDGF.[12,13] Upon entering the wound environment, recruited fibroblasts first need to proliferate, and then become activated, to carry out their primary function of matrix synthesis remodeling. This activation is mediated mainly by the cytokines and growth factors released from wound macrophages.

Fibroblasts isolated from wounds synthesize more collagen than nonwound fibroblasts, they proliferate less, and they actively carry out matrix contraction. Although it is clear that the cytokine-rich wound environment plays a significant role in this phenotypic alteration and activation, the exact mediators are only partially characterized.[14,15] Additionally, lactate, which accumulates in significant amounts in the wound environment over time (~10 mmol), is a potent regulator of collagen synthesis through a mechanism involving adenosine 5'-diphosphate–ribosylation.[16,17]

Endothelial cells also proliferate extensively during this phase of healing. These cells participate in the formation of new capillaries (angiogenesis), a process essential to successful wound healing. Endothelial cells migrate from intact venules close to the wound. Their migration, replication, and new capillary tubule formation are under the influence of such cytokines and growth factors as TNF-α, TGFβ, and VEGF. Although many cells produce VEGF, macrophages represent a major source in the healing wound, and VEGF receptors are located specifically on endothelial cells.[18,19]

Matrix Synthesis

BIOCHEMISTRY OF COLLAGEN

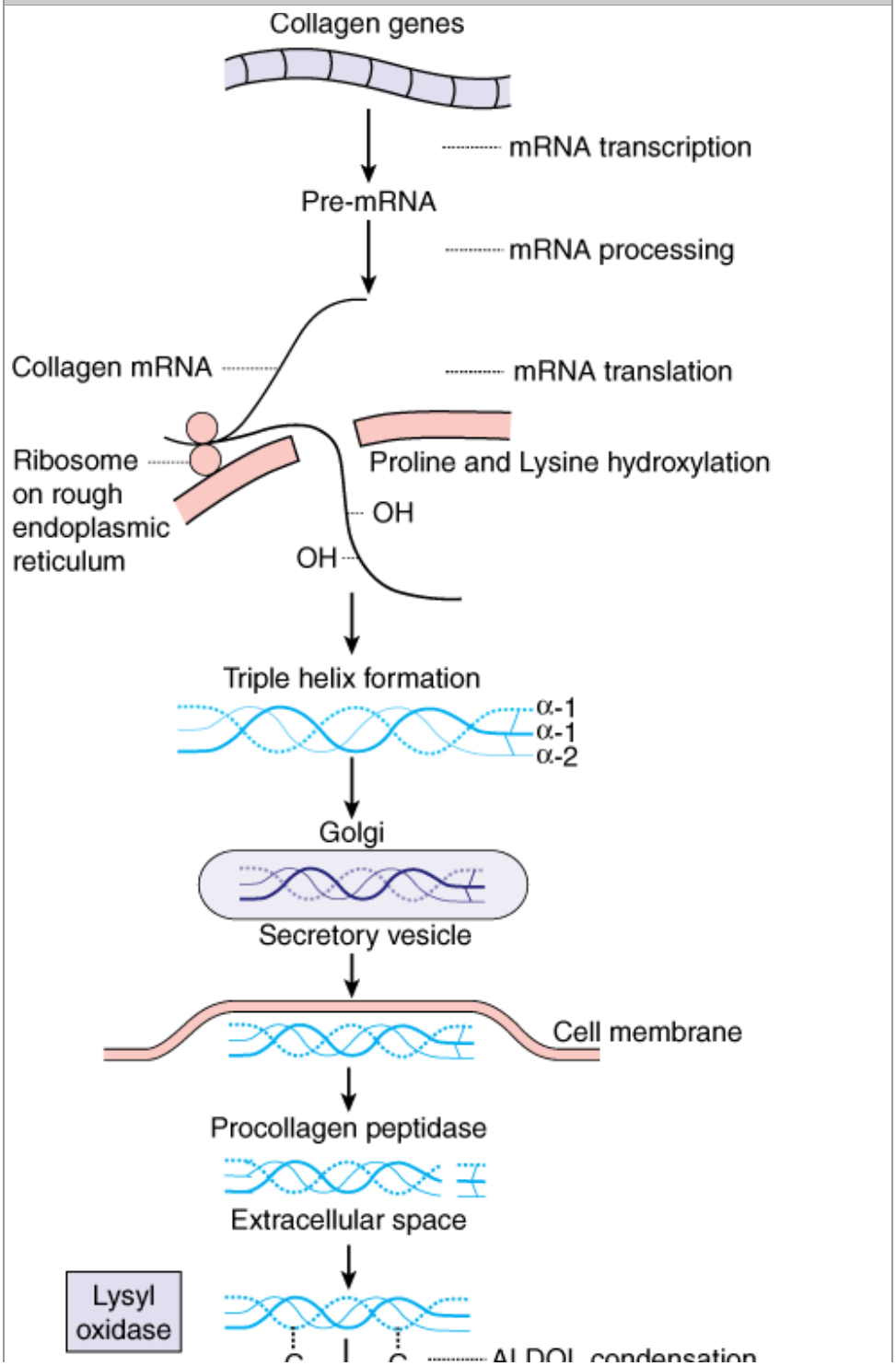
Collagen, the most abundant protein in the body, plays a critical role in the successful completion of adult wound healing. Its deposition, maturation, and subsequent remodeling are essential to the functional integrity of the wound.

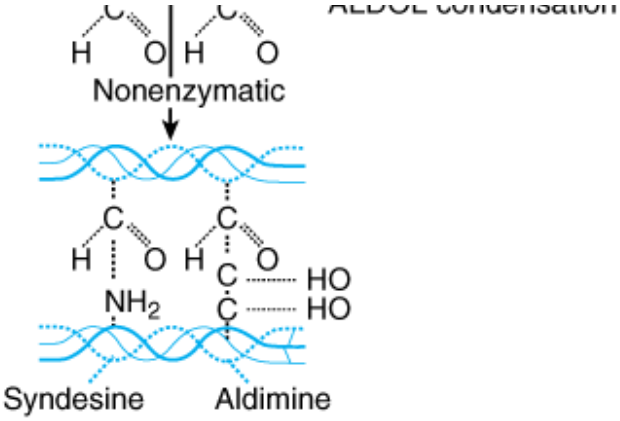
Although there are at least 18 types of collagen described, the main ones of interest to wound repair are types I and III. Type I collagen is the major component of extracellular matrix in skin. Type III, which is also normally present in skin, becomes more prominent and important during the repair process.

Biochemically, each chain of collagen is composed of a glycine residue in every third position. The second position in the triplet is made up of proline or lysine during the translation process. The polypeptide chain that is translated from messenger RNA (mRNA) contains approximately 1000 amino acid residues and is called *protocollagen*. Release of protocollagen into the endoplasmic reticulum results in the hydroxylation of proline to hydroxyproline and of lysine to hydroxylysine by specific

hydroxylases (Fig. 9-3). Prolyl hydroxylase requires oxygen and iron as cofactors, α-ketoglutarate as cosubstrate, and ascorbic acid (vitamin C) as an electron donor. In the endoplasmic reticulum, the protocollagen chain is also glycosylated by the linking of galactose and glucose at specific hydroxylysine residues. These steps of hydroxylation and glycosylation alter the hydrogen bonding forces within the chain, imposing steric changes that force the protocollagen chain to assume an α-helical configuration. Three α-helical chains entwine to form a right-handed superhelical structure called *procollagen*. At both ends, this structure contains nonhelical peptide domains called *registration peptides*. Although initially joined by weak, ionic bonds, the procollagen molecule becomes much stronger by the covalent cross-linking of lysine residues.

Fig. 9-3.





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The steps of collagen synthesis. mRNA = messenger RNA.

Extracellularly, the nonhelical registration peptides are cleaved by a procollagen peptidase, and the procollagen strands undergo further polymerization and cross-linking. The resulting collagen monomer is further polymerized and cross-linked by the formation of intra- and intermolecular covalent bonds.

Collagen synthesis, as well as posttranslational modifications, is highly dependent on systemic factors such as an adequate oxygen supply, the presence of sufficient nutrients (amino acids and carbohydrates) and cofactors (vitamins and trace metals), and the local wound environment (vascular supply and lack of infection). Addressing these factors and reversing nutritional deficiencies can optimize collagen synthesis and deposition.

PROTEOGLYCAN SYNTHESIS

Glycosaminoglycans comprise a large portion of the "ground substance" that makes up granulation tissue. Rarely found free, they couple with proteins to form *proteoglycans*. The polysaccharide chain is made up of repeating disaccharide units composed of glucuronic or iduronic acid and a hexosamine, which is usually sulfated. The disaccharide composition of proteoglycans varies from about 10 units in the case of heparan sulfate to as much as 2000 units in the case of hyaluronic acid.

The major glycosaminoglycans present in wounds are dermatan and chondroitin sulfate. Fibroblasts synthesize these compounds, increasing their concentration greatly during the first 3 weeks of healing. The interaction between collagen and proteoglycans is being actively studied. It is thought that the assembly of collagen subunits into fibrils and fibers is dependent on the lattice provided by the sulfated proteoglycans. Furthermore, it appears that the extent of sulfation is critical in determining the configuration of the collagen fibrils. As scar collagen is deposited, the proteoglycans are incorporated into the collagen scaffolding. However, with scar maturation and collagen remodeling, the content of proteoglycans gradually diminishes.

Maturation and Remodeling

The maturation and remodeling of the scar begins during the fibroplastic phase, and is characterized by a reorganization of previously synthesized collagen. Collagen is broken down by matrix metalloproteinases, and the net wound collagen content is the result of a balance between collagenolysis and collagen synthesis. There is a net shift toward collagen synthesis and eventually the re-establishment of extracellular matrix composed of a relatively acellular collagen-rich scar.

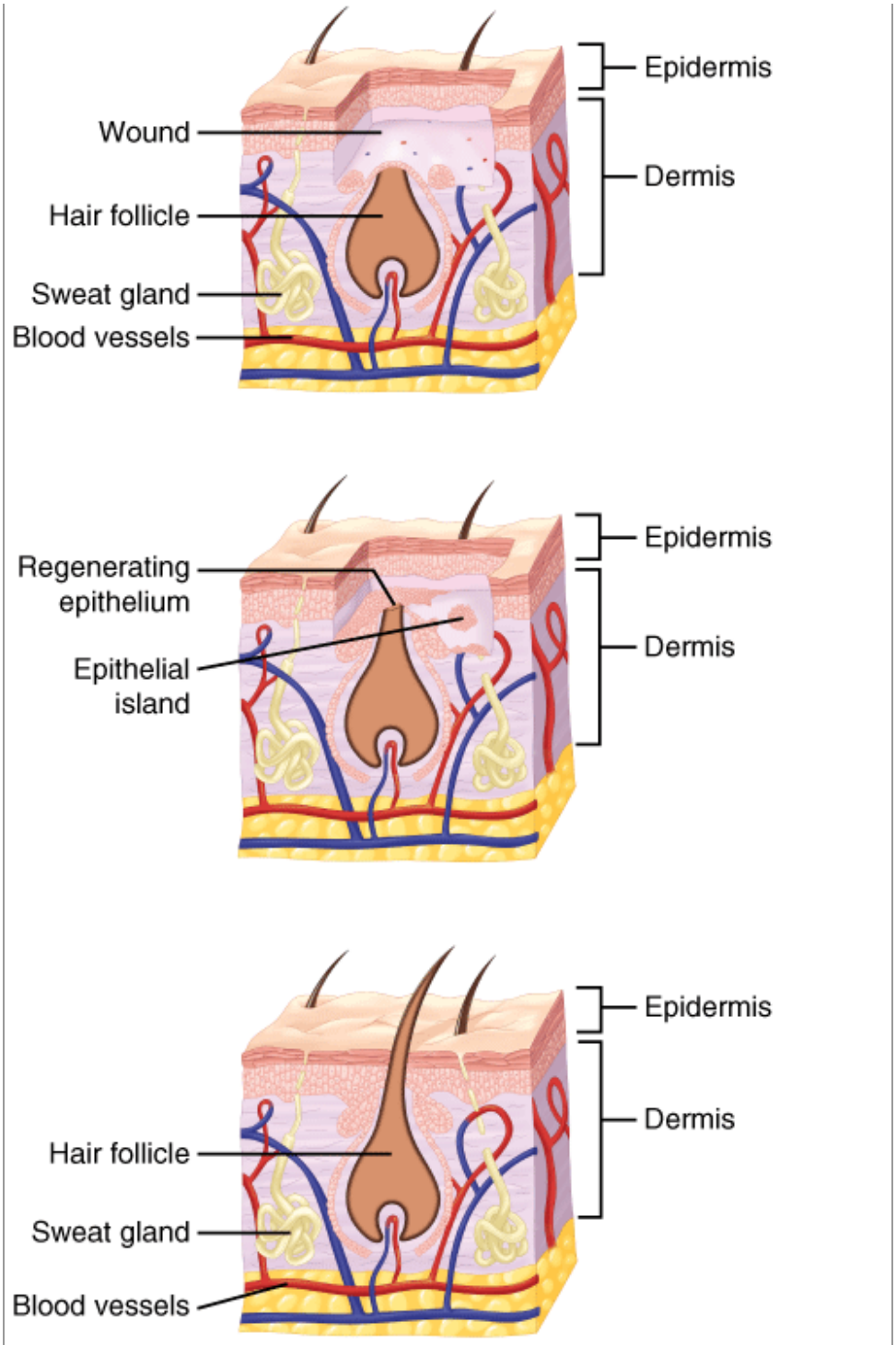
Wound strength and mechanical integrity in the fresh wound are determined by both the quantity and quality of the newly deposited collagen. The deposition of matrix at the wound site follows a characteristic pattern: Fibronectin and collagen type III constitute the early matrix scaffolding, glycosaminoglycans and proteoglycans represent the next significant matrix components, and collagen type I is the final matrix. By several weeks postinjury the amount of collagen in the wound reaches a plateau, but the tensile strength continues to increase for several more months.[20] Fibril formation and fibril cross-linking result in decreased collagen solubility, increased strength, and increased resistance to enzymatic degradation of the collagen matrix. Scar remodeling continues for many (6 to 12) months postinjury, gradually resulting in a mature, avascular, and acellular scar. The mechanical strength of the scar never achieves that of the uninjured tissue.

There is a constant turnover of collagen in the extracellular matrix, both in the healing wound, as well as during normal tissue homeostasis. Collagenolysis is the result of collagenase activity, a class of matrix metalloproteinases that require activation. Both collagen synthesis and lysis are strictly controlled by cytokines and growth factors. Some factors affect both aspects of collagen remodeling. For example, TGFβ increases new collagen transcription and also decreases collagen breakdown by stimulating synthesis of tissue inhibitors of metalloproteinase.[21] This balance of collagen deposition and degradation is the ultimate determinant of wound strength and integrity.

Epithelialization

While tissue integrity and strength are being re-established, the external barrier must also be restored. This process is characterized primarily by proliferation and migration of epithelial cells adjacent to the wound (Fig. 9-4). The process begins within 1 day of injury and is seen as thickening of the epidermis at the wound edge. Marginal basal cells at the edge of the wound lose their firm attachment to the underlying dermis, enlarge, and begin to migrate across the surface of the provisional matrix. Fixed basal cells in a zone near the cut edge undergo a series of rapid mitotic divisions, and these cells appear to migrate by moving over one another in a leapfrog fashion until the defect is covered.[22] Once the defect is bridged, the migrating epithelial cells lose their flattened appearance, become more columnar in shape, and increase their mitotic activity. Layering of the epithelium is re-established, and the surface layer eventually keratinizes.[23]

Fig. 9-4.



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The healing by epithelialization of superficial cutaneous wounds.

Re-epithelialization is complete in less than 48 hours in the case of approximated incised wounds, but may take substantially longer in the case of larger wounds, in which there is a significant epidermal/dermal defect. If only the epithelium and superficial dermis are damaged, such as occurs in split-thickness skin graft donor sites or in superficial second-degree burns, then repair consists primarily of re-epithelialization with minimal or no fibroplasia and granulation tissue formation. The stimuli for re-epithelialization remain incompletely defined; however, it appears that the process is mediated by a

combination of a loss of contact inhibition; exposure to constituents of the extracellular matrix, particularly fibronectin; and cytokines produced by immune mononuclear cells.[24,25] In particular, epithelial growth factor, TGFβ, basic fibroblast growth factor, PDGF, and insulin-like growth factor I have been shown to promote epithelialization.

Role of Growth Factors in Normal Healing

Growth factors and cytokines are polypeptides produced in normal and wounded tissue that stimulate cellular migration, proliferation, and function. They often are named for the cells from which they were first derived (e.g., platelet-derived growth factor, PDGF) or for their initially identified function (e.g., fibroblast growth factor). These names are often misleading, because growth factors have been demonstrated to have multiple functions. Most growth factors are extremely potent and produce significant effects in nanomolar concentrations.

They may act in an autocrine manner (in which the growth factor acts on the cell producing it), a paracrine manner (by release into the extracellular environment, where it acts on the immediately neighboring cells), or in an endocrine manner (in which the effect of the substance is distant to the site of release, and the substance is carried to the effector site through the bloodstream). The timing of release may be as important as concentration in determining the effectiveness of growth factors. As these polypeptides exert their effects by cell-surface receptor binding, the appropriate receptor on the responding cells must be present at the time of release for the biologic effect to occur. Table 9-2 summarizes the principal growth factors found in healing wounds and their known effects on cells participating in the healing process. Growth factors have divergent actions on different cells; they can be chemoattractive to one cell type while stimulating replication of a different cell type. Little is known about the ratio of growth factor concentrations, which may be as important as the absolute concentration of individual growth factors.

Table 9-2 Growth Factors Participating in Wound Healing

Growth Factor	Wound Cell Origin	Cellular and Biologic Effects
PDGF	Platelets, macrophages, monocytes, smooth muscle cells, endothelial cells	Chemotaxis: fibroblasts, smooth muscle, monocytes, neutrophils
		Mitogenesis: fibroblasts, smooth muscle cells
		Stimulation of angiogenesis
		Stimulation of collagen synthesis
FGF	Fibroblasts, endothelial cells, smooth muscle cells, chondrocytes	Stimulation of angiogenesis (by stimulation of endothelial cell proliferation and migration)
		Mitogenesis: mesoderm and neuroectoderm
		Stimulates fibroblasts, keratinocytes, chondrocytes, myoblasts
Keratinocyte growth factor	Keratinocytes, fibroblasts	Significant homology with FGF; stimulates keratinocytes
EGF	Platelets, macrophages, monocytes (also identified in salivary glands, duodenal glands, kidney, and lacrimal glands)	Stimulates proliferation and migration of all epithelial cell types
TGFα	Keratinocytes, platelets, macrophages	Homology with EGF; binds to EGF receptor
		Mitogenic and chemotactic for epidermal and endothelial cells
β		

TGF (three isoforms: β_1, β_2, β_3)	Platelets, T lymphocytes, macrophages, monocytes, neutrophils	Stimulates angiogenesis
		TGFβ_1 stimulates wound matrix production (fibronectin, collagen glycosaminoglycans); regulation of inflammation
		TGFβ_3 inhibits scar formation
Insulin-like growth factors (IGF-I, IGF-II)	Platelets (IGF-I in high concentrations in liver; IGF-II in high concentrations in fetal growth); likely the effector of growth hormone action	Promote protein/extracellular matrix synthesisIncrease membrane glucose transport
Vascular endothelial growth factor	Macrophages, fibroblasts, keratinocytes	Similar to PDGF
		Mitogen for endothelial cells (not fibroblasts)
		Stimulates angiogenesis
Granulocyte-macrophage colony-stimulating factor	Macrophage/monocytes, endothelial cells, fibroblasts	Stimulates macrophage differentiation/proliferation

EGF = epidermal growth factor; FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; TGF = transforming growth factor.

Growth factors act on cells via surface receptor binding. Various receptor types have been described, such as ion channels, G-protein linked, or enzyme linked. The response elicited in the cell is usually one of phosphorylation or dephosphorylation of second-messenger molecules through the action of phosphatases or kinases, resulting in activation or deactivation of proteins in the cytosol or nucleus of the target cell. Phosphorylation of nuclear proteins is followed by the initiation of transcription of target genes.[26] The signal is stopped by internalization of the receptor-ligand complex.

Wound Contraction

All wounds undergo some degree of contraction. For wounds that do not have surgically approximated edges, the area of the wound will be decreased by this action (healing by secondary intention); the shortening of the scar itself results in contracture. The myofibroblast has been postulated as being the major cell responsible for contraction, and it differs from the normal fibroblast in that it possesses a cytoskeletal structure. Typically this cell contains α-smooth muscle actin in thick bundles called *stress fibers*, giving myofibroblasts contractile capability.[27] The α-smooth muscle actin is undetectable until day 6, and then is increasingly expressed for the next 15 days of wound healing.[28] After 4 weeks this expression fades, and the cells are believed to undergo apoptosis.[29] A puzzling point is that the identification of myofibroblasts in the wound does not correspond directly to the initiation of wound contraction, which starts almost immediately after injury.

Fibroblasts placed in a collagen lattice in vitro actively move in the lattice and contract it without expressing stress fibers. It is postulated that the movement of cells with concomitant reorganization of the cytoskeleton is responsible for contraction.[30]

HERITABLE DISEASES OF CONNECTIVE TISSUE

Heritable diseases of connective tissue consist of a group of generalized, genetically determined, primary disorders of one of the elements of connective tissue: collagen, elastin, or mucopolysaccharide. Five major types, Ehlers-Danlos syndrome (EDS), Marfan syndrome, osteogenesis imperfecta (OI), epidermolysis bullosa (EB), and acrodermatitis enteropathica (AE), are discussed, as each presents unique challenges to the surgeon.

Ehlers-Danlos Syndrome

EDS is a group of 10 disorders that present as a defect in collagen formation. Characteristics include thin, friable skin with prominent veins, easy bruising, poor wound healing, abnormal scar formation, recurrent hernias, and hyperextensible joints. GI problems include bleeding, hiatal hernia, intestinal diverticulae, and rectal prolapse. Small blood vessels are fragile, making suturing difficult during surgery. Large vessels may develop aneurysms, varicosities, arteriovenous fistulas, or may spontaneously rupture.[31–33] EDS must be considered in every child with recurrent hernias and coagulopathy, especially when accompanied by platelet abnormalities and low coagulation factor levels. Inguinal hernias in these children resemble those seen in adults. Great care should be taken to avoid tearing the skin and fascia. The transversalis fascia is thin, and the internal ring is greatly dilated. An adult-type repair with the use of mesh or felt may result in a lower incidence of recurrence.[34] Table 9-3 presents a description of EDS subtypes.

Table 9-3 Clinical, Genetic, and Biochemical Aspects of Ehlers-Danlos Subtypes

Type	Clinical Features	Inheritance	Biochemical Defect
I	Skin: soft, hyperextensible, easy bruising, fragile, atrophic scars; hypermobile joints; varicose veins; premature births	AD	Not known
II	Similar to type I, except less severe	AD	Not known
III	Skin: soft, not hyperextensible, normal scars; small and large joint hypermobility	AD	Not known
IV	Skin: thin, translucent, visible veins, normal scarring, no hyperextensibility; no joint hypermobility; arterial, bowel, and uterine rupture	AD	Type III collagen defect
V	Similar to type II	XLR	Not known
VI	Skin: hyperextensible, fragile, easy bruising; hypermobile joints; hypotonia; kyphoscoliosis	AR	Lysyl hydroxylase deficiency
VII	Skin: soft, mild hyperextensibility, no increased fragility; extremely lax joints with dislocations	AD	Type I collagen gene defect
VIII	Skin: soft, hyperextensible, easy bruising, abnormal scars with purple discoloration; hypermobile joints; generalized periodontitis	AD	Not known
IX	Skin: soft, lax; bladder diverticula and rupture; limited pronation and supination; broad clavicle; occipital horns	XLR	Lysyl oxidase defect with abnormal copper use
X	Similar to type II with abnormal clotting studies	AR	Fibronectin defect

AD = autosomal dominant; AR = autosomal recessive; XLR = X-linked recessive.

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Marfan Syndrome

Patients with Marfan syndrome generally have tall stature, arachnodactyly, lax ligaments, myopia, scoliosis, pectus excavatum, and aneurysm of the ascending aorta. The genetic defect is in an extracellular protein, fibrillin, which is associated with elastic fibers. Patients who suffer from this syndrome also are prone to hernias. Surgical repair of a dissecting aneurysm is difficult, as the soft connective tissue fails to hold sutures. Skin may be hyperextensible, but shows no delay in wound healing.[35,36]

Osteogenesis Imperfecta

Characteristics of OI are brittle bones, osteopenia, low muscle mass, hernias, and ligament and joint laxity. OI is a result of a mutation in type I collagen. There are four major OI subtypes with mild to lethal manifestations. Patients experience dermal thinning and increased bruisability. Scarring is normal, and the skin is not hyperextensible. Surgery can be successful but difficult in these patients, as their bones fracture easily under minimal stress.[31,34] Table 9-4 lists the various features associated with the clinical subtypes of OI.

Table 9-4 Osteogenesis Imperfecta: Clinical and Genetic Features

Type	Clinical Features	Inheritance
I	Mild bone fragility, blue sclera	Dominant
II	"Prenatal lethal"; crumpled long bones, thin ribs, dark blue sclera	Dominant
III	Progressively deforming; multiple fractures; early loss of ambulation	Dominant/recessive
IV	Mild to moderate bone fragility; normal or gray sclera; mild short stature	Dominant

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Epidermolysis Bullosa

EB is classified into three major subtypes: EB simplex, junctional EB, and dystrophic EB. The genetic defect involves impairment in tissue adhesion within the epidermis, basement membrane, or dermis, resulting in tissue separation and blistering with minimal trauma. Characteristic features of EB are blistering and ulceration. Management of nonhealing wounds in patients with EB is a challenge, as their nutritional status is compromised because of oral erosions and esophageal obstruction. Surgical interventions include esophageal dilation and gastrostomy tube placement. Dermal incisions must be meticulously placed to avoid further trauma to skin.[34,37] The skin requires nonadhesive pads covered by "bulky" dressing to avoid blistering.

Acrodermatitis Enteropathica

AE is an autosomal recessive disease of children that causes an inability to absorb sufficient zinc from breast milk or food. The AE mutation affects zinc uptake in the intestine by preventing zinc from binding to the cell surface and its translocation into the cell. Zinc deficiency is associated with impaired granulation tissue formation, as zinc is a necessary cofactor for DNA polymerase and reverse transcriptase, and its deficiency may impair healing due to inhibition of cell proliferation.

AE is characterized by impaired wound healing as well as erythematous pustular dermatitis involving the extremities and the areas around the bodily orifices. Diagnosis is confirmed by the presence of an abnormally low blood zinc level (>100 μg/dL). Oral supplementation with 100 to 400 mg zinc sulfate orally per day is curative for impaired healing.[38,39]

HEALING IN SPECIFIC TISSUES

Gastrointestinal Tract

Healing of full-thickness injury to the GI tract remains an unresolved clinical issue. Healing of full-thickness GI wounds begins with a surgical or mechanical reapposition of the bowel ends, which is most often the initial step in the repair process. Sutures or staples are principally used, although various other means, such as buttons, plastic tubes, and various wrappings, have been attempted with variable success. Failure of healing results in dehiscence, leaks, and fistulas, which carry significant morbidity and mortality. Conversely, excessive healing can be just as troublesome, resulting in stricture formation

and stenosis of the lumen. Repair of the GI tract is vital to restoring the integrity of the luminal structure, and to the resumption of motor, absorptive, and barrier functions.

The gross anatomic features of the GI tract are remarkably constant throughout most of its length. Within the lumen, the epithelium is supported by the lamina propria and underlying muscularis mucosa. The submucosa lies radially and circumferentially outside of these layers, is comprised of abundant collagenous and elastic fibers, and supports neural and vascular structures. Further toward the peritoneal surface of the bowel are the inner and outer muscle layers and, ultimately, a peritoneal extension, the serosa. The submucosa is the layer that imparts the greatest tensile strength and greatest suture-holding capacity, a characteristic that should be kept in mind during surgical repair of the GI tract. Additionally, serosal healing is essential for quickly achieving a watertight seal from the luminal side of the bowel. The importance of the serosa is underscored by the significantly higher rates of anastomotic failure observed clinically in segments of bowel that are extraperitoneal and lack serosa (i.e., the esophagus and rectum).

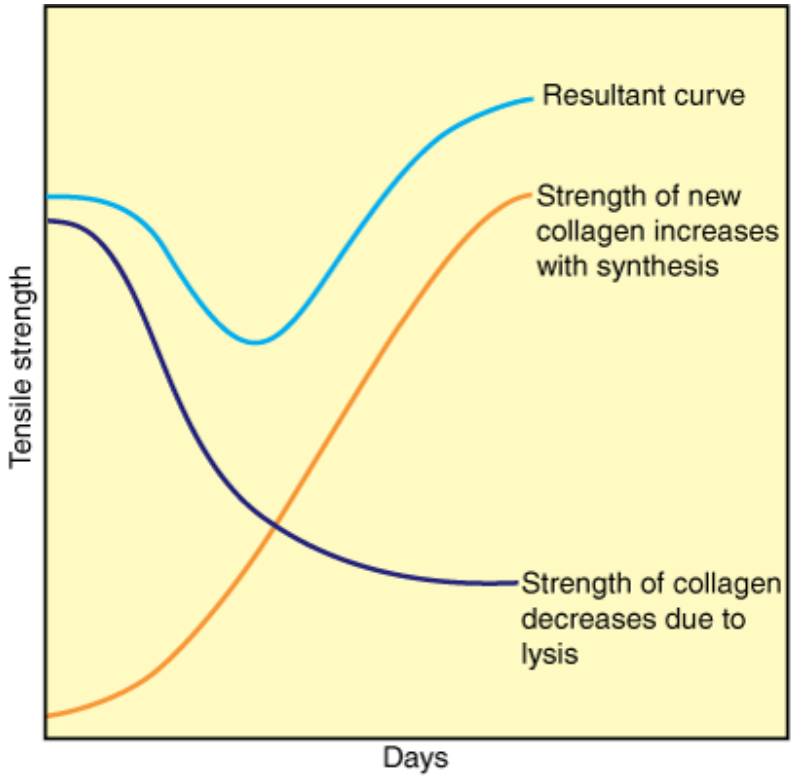
Injuries to all parts of the GI tract undergo the same sequence of healing as cutaneous wounds. However, there are some significant differences (Table 9-5). Mesothelial (serosal) and mucosal healing can occur without scarring. The early integrity of the anastomosis is dependent on formation of a fibrin seal on the serosal side, which achieves watertightness, and on the suture-holding capacity of the intestinal wall, particularly the submucosal layer. There is a significant decrease in marginal strength during the first week due to an early and marked collagenolysis. The lysis of collagen is carried out by collagenase derived from neutrophils, macrophages, and intraluminal bacteria. Collagenase activity occurs early in the healing process, and during the first 3 to 5 days collagen breakdown far exceeds collagen synthesis. The integrity of the anastomosis represents equilibrium between collagen lysis, which occurs early, and collagen synthesis, which takes a few days to initiate (Fig. 9-5). Collagenase is expressed postinjury in all segments of the GI tract, but it is much more marked in the colon compared to the small bowel. Collagen synthesis in the GI tract is carried out by both fibroblasts and smooth muscle cells. Colon fibroblasts produce greater amounts of collagen than skin fibroblasts, reflecting different phenotypic features, as well as different responses to cytokines and growth factors among these different fibroblast populations. Ultimate anastomotic strength is not always related to the absolute amount of collagen, and the structure and arrangement of the collagen matrix may be more important.[40]

Table 9-5 Comparison of Wound Healing in the Gastrointestinal Tract and Skin

		GI Tract	**Skin**
Wound environment	pH	Varies throughout GI tract in accordance with local exocrine secretions.	Usually constant except during sepsis or local infection.
	Microorganisms	Aerobic and anaerobic, especially in the colon and rectum; problematic if they contaminate the peritoneal cavity.	Skin commensals rarely cause problems; infection usually results from exogenous contamination or hematogenous spread.
	Shear stress	Intraluminal bulk transit and peristalsis exert distracting forces on the anastomosis.	Skeletal movements may stress the suture line but pain usually acts as a protective mechanism preventing excess movement.
	Tissue oxygenation	Dependent on intact vascular supply and neocapillary formation.	Circulatory transport of oxygen as well as diffusion.
Collagen	Cell type	Fibroblasts and smooth muscle cells.	Fibroblasts.

synthesis			
	Lathyrogens	D-Penicillamine has no effect on collagen cross-linking.	Significant inhibition of cross-linking with decreased wound strength.
	Steroids	Contradictory evidence exists concerning their negative effect on GI healing; increased abscess in the anastomotic line may play a significant role.	Significant decrease in collagen accumulation.
Collagenase activity	—	Increased presence throughout GI tract after transection and reanastomosis; during sepsis excess enzyme may promote dehiscence by decreasing suture-holding capacity of tissue.	Not as significant a role in cutaneous wounds.
Wound strength	—	Rapid recovery to preoperative level.	Less rapid than GI tissue.
Scar formation	Age	Definite scarring seen in fetal wound sites.	Usually heals without scar formation in the fetus.

Fig. 9-5.



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Diagrammatic representation of the concept of GI wound healing as a fine balance between collagen synthesis and collagenolysis. The "weak" period when collagenolysis exceeds collagen synthesis can be prolonged or exacerbated by any factors that upset the equilibrium.

(Reproduced with permission from Hunt TK, Van Winkle W Jr: Wound healing: normal repair, in Dunphy JE (ed): *Fundamentals of Wound Management in Surgery.* New York: Chirurgecom, Inc., 1976, p. 29.)

TECHNICAL CONSIDERATIONS

Traditional teaching holds that in order for an anastomosis to heal without complications it must be tension-free, have an

adequate blood supply, receive adequate nutrition, and be free of sepsis. Although sound principles for all wound healing, there are several considerations unique to anastomotic healing. From a technical viewpoint, the ideal method of suturing two ends of bowel together has not yet been identified. Although debate exists concerning methods of creating an anastomosis, clinically there has been no convincing evidence that a given technique has any advantage over another (i.e., hand-sutured vs. stapled, continuous vs. interrupted sutures, absorbable vs. nonabsorbable sutures, or single- vs. two-layer closure). A recent meta-analysis revealed that stapled ileo-colic anastomoses have fewer leak rates than hand-constructed ones, but no data on colo-colic or small bowel anastomoses have been offered yet.[41] It is known, however, that hand-sutured everting anastomoses are at greater risk of leakage and cause greater adhesion formation, but have a lower incidence of stenosis. As no overall definite superiority of any one method exists, it is recommended that surgeons be familiar with several techniques and apply them as circumstances dictate.

Bone

After any type of injury to bone, several changes take place at the site of injury to restore structural and functional integrity. Most of the phases of healing resemble those observed in dermal healing, but some notable individual characteristics apply to bone injuries. The initial stage of hematoma formation consists of an accumulation of blood at the fracture site, which also contains devitalized soft tissue, dead bone, and necrotic marrow. The next stage accomplishes the liquefaction and degradation of nonviable products at the fracture site. The normal bone adjacent to the injury site can then undergo revascularization, with new blood vessels growing into the fracture site. This is similar to the formation of granulation tissue in soft tissue. The symptoms associated with this stage are characteristic of inflammation, with clinical evidence of swelling and erythema.

Three to 4 days after injury, soft tissue forms a bridge between the fractured bone segments in the next stage (soft callus stage). This soft tissue is deposited where neovascularization has taken place and serves as an internal splint, preventing damage to the newly laid blood vessels and achieving a fibrocartilaginous union. The soft callus is formed externally along the bone shaft and internally within the marrow cavity. Clinically, this phase is characterized by the end of pain and inflammatory signs.

The next phase (hard callus stage) consists of mineralization of the soft callus and conversion to bone. This may take up to 2 to 3 months and leads to complete bony union. The bone is now considered strong enough to allow weightbearing and will appear healed on radiographs. This stage is followed by the remodeling phase, in which the excessive callus is reabsorbed and the marrow cavity is recanalized. This remodeling allows for the correct transmission of forces and restores the contours of the bone.

As in dermal healing, the process of osseous union is mediated by soluble growth factors and cytokines. The most extensively studied group is the bone morphogenic proteins, which belong to the TGFβ superfamily. By stimulating the differentiation of mesenchymal cells into chondroblasts and osteoblasts, bone morphogenic proteins directly affect bone and cartilage repair. Other growth factors, such as PDGF, TGFβ, TNF-α, and basic fibroblast growth factor, also participate in bony repair by mediating the inflammatory and proliferative phases of healing.

Cartilage

Cartilage consists of cells (chondrocytes) surrounded by an extracellular matrix made up of several proteoglycans, collagen fibers, and water. Unlike bone, cartilage is very avascular and depends on diffusion for transmittal of nutrients across the matrix. Additionally, the hypervascular perichondrium contributes substantially to the nutrition of the cartilage. Therefore,

injuries to cartilage may be associated with permanent defects due to the meager and tenuous blood supply.

The healing response of cartilage depends on the depth of injury. In a superficial injury, there is disruption of the proteoglycan matrix and injury to the chondrocytes. There is no inflammatory response, but an increase in synthesis of proteoglycan and collagen dependent entirely on the chondrocyte. Unfortunately, the healing power of cartilage is often inadequate and overall regeneration is incomplete. Therefore, superficial cartilage injuries are slow to heal and often result in persistent structural defects.

In contrast to superficial injuries, deep injuries involve the underlying bone and soft tissue. This leads to the exposure of vascular channels of the surrounding damaged tissue that may help in the formation of granulation tissue. Hemorrhage allows for the initiation of the inflammatory response and the subsequent mediator activation of cellular function for repair. As the granulation tissue is laid down, fibroblasts migrate toward the wound and synthesize fibrous tissue that undergoes chondrification. Gradually, hyaline cartilage is formed, which restores the structural and functional integrity of the injured site.

Tendon

Tendons and ligaments are specialized structures that link muscle and bone, and bone and bone, respectively. They consist of parallel bundles of collagen interspersed with spindle cells. Tendons and ligaments can be subjected to a variety of injuries, such as laceration, rupture, and contusion. Due to the mobility of the underlying bone or muscles, the damaged ends usually separate. Tendon and ligament healing progresses in a similar fashion as in other areas of the body (i.e., through hematoma formation, organization, laying down of reparative tissue, and scar formation). Matrix is characterized by accumulation of type I and III collagen along with increased water, DNA, and glycosaminoglycan content. As the collagen fibers are organized, transmission of forces across the damaged portion can occur. Restoration of the mechanical integrity may never be equal to that of the undamaged tendon.

Tendon vasculature has a clear effect on healing. Hypovascular tendons tend to heal with less motion and more scar formation than tendons with better blood supply. The specialized cells, tenocytes, are metabolically very active and retain a large regenerative potential, even in the absence of vascularity. Cells on the tendon surface are identical to those within the sheath and play a role in tendon healing as well.

Nerve

Nerve injuries are very common, with an estimated 200,000 repairs performed every year in the United States. Peripheral nerves are a complex arrangement of axons, nonneuronal cells, and extracellular elements. There are three types of nerve injuries: neurapraxia (focal demyelination), axonotmesis (interruption of axonal continuity but preservation of Schwann cell basal lamina), and neurotmesis (complete transection). After all types of injury, the nerve ends progress through a predictable pattern of changes involving three crucial steps: (a) survival of axonal cell bodies, (b) regeneration of axons that grow across the transected nerve to reach the distal stump, and (c) migration and connection of the regenerating nerve ends to the appropriate nerve ends or organ targets.

Phagocytes remove the degenerating axons and myelin sheath from the distal stump (wallerian degeneration). Regenerating axonal sprouts extend from the proximal stump and probe the distal stump and the surrounding tissues. Schwann cells ensheathe and help in remyelinating the regenerating axons. Functional units are formed when the regenerating axons connect with the appropriate end targets. Several factors play a role in nerve healing, such as growth factors, cell adhesion

molecules, and nonneuronal cells and receptors. Growth factors include nerve growth factor, brain-derived neurotropic factor, basic and acidic fibroblastic growth factors, and neuroleukin. Cell-adhesion molecules involved in nerve healing include nerve-adhesion molecule, neuron-glia adhesion molecule, myelin adhesion glycoprotein, and N-cadherin. This complex interplay of growth factors and adhesion molecules helps in nerve regeneration.

Fetal Wound Healing

The main characteristic that distinguishes the healing of fetal wounds from that of adult wounds is the apparent lack of scar formation. Understanding how fetal wounds achieve integrity without evidence of scarring holds promise for the possible manipulation of unwanted fibrosis or excessive scar formation in adults. Although early fetal healing is characterized by the absence of scarring and resembles tissue regeneration, there is a phase of transition during gestational life when a more adult-like healing pattern emerges. This so-called "transition wound" occurs at the beginning of the third trimester, and during this period there is scarless healing; however, there is a loss of the ability to regenerate skin appendages.[42] Eventually a classic, adult-patterned healing with scar formation occurs exclusively, although overall healing continues to be faster than in adults.

There are a number of characteristics that may influence the differences between fetal and adult wounds. These include wound environment, inflammatory responses, differential growth factor profiles, and wound matrix.

WOUND ENVIRONMENT

The fetus is bathed in a sterile, temperature-stable fluid environment, though this alone does not explain the observed differences. Experiments have demonstrated that scarless healing may occur outside of the amniotic fluid environment, and, conversely, scars can form in utero.[43,44]

INFLAMMATION

The extent and robustness of the inflammatory response correlates directly with the amount of scar formation in all healing wounds. Reduced fetal inflammation due to the immaturity of the fetal immune system may partially explain the lack of scarring observed. Not only is the fetus neutropenic, but fetal wounds also contain lower numbers of PMNs and macrophages.[45]

GROWTH FACTORS

Fetal wounds are notable for the absence of TGFβ, which may have a significant role in scarring. Conversely, blocking TGFβ1 or TGFβ2 using neutralizing antibodies considerably reduces scar formation in adult wounds. Exogenous application of TGFβ3 downregulates TGFβ1 and TGFβ2 levels at the wound site with a resultant reduction in scarring.[46] Thus, the balance between the concentration and/or activity of TGFβ isoforms may be important for regulating scar production.

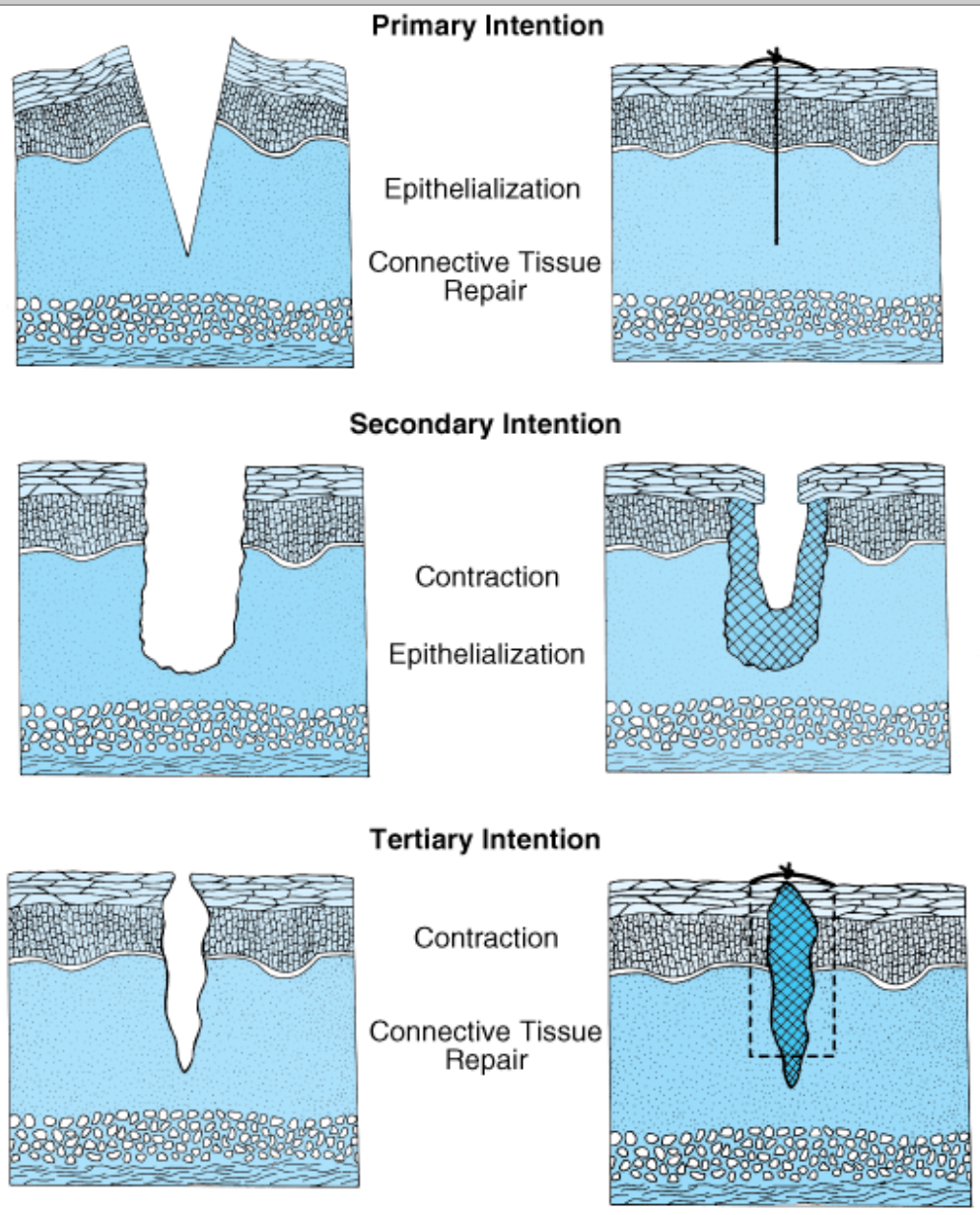
WOUND MATRIX

The fetal wound is characterized by excessive and extended hyaluronic acid production, a high molecular weight glycosaminoglycan that is produced primarily by fibroblasts. Although adult wounds also produce hyaluronic acid, its synthesis is sustained only in the fetal wound. Components of amniotic fluid, most specifically fetal urine, have a unique ability to stimulate hyaluronic acid production.[47] Fetal fibroblasts produce more collagen than adult fibroblasts, and the increased level of hyaluronic acid may aid in the orderly organization of collagen. As a result of these findings, hyaluronic acid is used topically to enhance healing and to inhibit postoperative adhesion formation.[48]

CLASSIFICATION OF WOUNDS

Wounds are classified as either acute or chronic. Acute wounds heal in a predictable manner and time frame. The process occurs with few, if any, complications, and the end result is a well-healed wound. Surgical wounds can heal in several ways. An incised wound that is clean and closed by sutures is said to heal by primary intention. Often, because of bacterial contamination or tissue loss, a wound will be left open to heal by granulation tissue formation and contraction; this constitutes healing by secondary intention. Delayed primary closure, or healing by tertiary intention, represents a combination of the first two, consisting of the placement of sutures, allowing the wound to stay open for a few days, and the subsequent closure of the sutures (Fig. 9-6).

Fig. 9-6.



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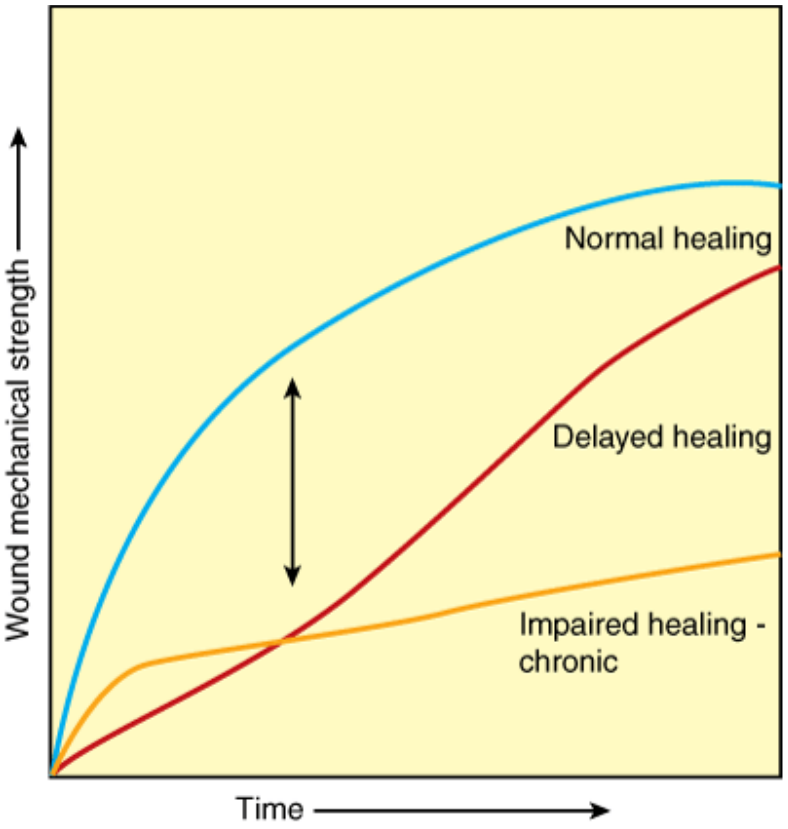
Different clinical approaches to the closure and healing of acute wounds.

The healing spectrum of acute wounds is broad (Fig. 9-7). In examining the acquisition of mechanical integrity and strength during healing, the normal process is characterized by a constant and continual increase that reaches a plateau at some point postinjury. Wounds with delayed healing are characterized by decreased wound-breaking strength in comparison to wounds that heal at a normal rate; however, they eventually achieve the same integrity and strength as wounds that heal normally. Conditions such as nutritional deficiencies, infections, or severe trauma cause delayed healing, which reverts to normal with correction of the underlying pathophysiology. Impaired healing is characterized by a failure to achieve mechanical strength equivalent to normally healed wounds. Patients with compromised immune systems, such as those with diabetes, chronic steroid usage, or tissues damaged by radiotherapy, are prone to this type of impaired healing. The surgeon must be aware of these situations and exercise great care in the placement of incision and suture selection, postoperative care, and adjunctive therapy to maximize the chances of healing without supervening complications.

Fig. 9-7.



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The acquisition of wound mechanical strength over time in normal, delayed, and impaired healing.

Normal healing is affected by both systemic and local factors (Table 9-6). The clinician must be familiar with these factors and should attempt to counteract their deleterious effects. Complications occurring in wounds with higher risk can lead to failure of healing or the development of chronic, nonhealing wounds.

Table 9-6 Factors Affecting Wound Healing

Systemic
Age
Nutrition
Trauma
Metabolic diseases
Immunosuppression
Connective tissue disorders
Smoking
Local
Mechanical injury
Infection
Edema
Ischemia/necrotic tissue
Topical agents
Ionizing radiation
Low oxygen tension
Foreign bodies

Factors Affecting Wound Healing

ADVANCED AGE

Most surgeons believe that aging produces intrinsic physiologic changes that result in delayed or impaired wound healing. Clinical experience with elderly patients tends to support this belief. Studies of hospitalized surgical patients show a direct correlation between older age and poor wound healing outcomes such as dehiscence and incisional hernia.[49,50] However, these statistics fail to take into account underlying illnesses or diseases as a possible source of impaired wound healing in the elderly. The increased incidence of cardiovascular disease, metabolic diseases (diabetes mellitus, malnutrition, and vitamin deficiencies), cancer, and the widespread use of drugs that impair wound healing may all contribute to the higher incidence of wound problems in the elderly. However, more recent clinical experience suggests that major operative interventions can be accomplished safely in the elderly.

The results of animal studies regarding the effects of aging on wound healing have yielded contradictory results. In healthy human volunteers there was a significant delay of 1.9 days in the epithelialization of superficial skin defects in those older than 70 years of age when compared to younger volunteers.[51] In the same volunteers, using a micro-model of fibroplasia, no difference in DNA or hydroxyproline wound accumulation could be demonstrated between the young and elderly groups; however, the young volunteers had a significantly higher amount of total α-amino nitrogen in their wounds, a reflection of total protein content of the wound. Thus, although wound collagen synthesis does not seem to be impaired with advanced age, noncollagenous protein accumulation at wounded sites is decreased with aging, which may impair the mechanical properties of scarring in elderly patients.

HYPOXIA, ANEMIA, AND HYPOPERFUSION

Low oxygen tension has a profoundly deleterious effect on all aspects of wound healing. Fibroplasia, although stimulated

initially by the hypoxic wound environment, is significantly impaired by local hypoxia. Optimal collagen synthesis requires oxygen as a cofactor, particularly for the hydroxylation steps. Increasing subcutaneous oxygen tension levels by increasing the fraction of inspired oxygen (FiO_2) of inspired air for brief periods during and immediately after surgery results in enhanced collagen deposition and in decreased rates of wound infection after elective surgery.[52–54]

Major factors affecting local oxygen delivery include hypoperfusion either for systemic reasons (low volume or cardiac failure) or due to local causes (arterial insufficiency, local vasoconstriction, or excessive tension on tissues). The level of vasoconstriction of the subcutaneous capillary bed is exquisitely responsive to fluid status, temperature, and hyperactive sympathetic tone as is often induced by postoperative pain. Correction of these factors can have a remarkable influence on wound outcome, particularly on decreasing wound infection rates.[53–55] Mild to moderate normovolemic anemia does not appear to adversely affect wound oxygen tension and collagen synthesis, unless the hematocrit falls below 15%.[55]

STEROIDS AND CHEMOTHERAPEUTIC DRUGS

Large doses or chronic usage of glucocorticoids reduce collagen synthesis and wound strength.[56] The major effect of steroids is to inhibit the inflammatory phase of wound healing (angiogenesis, neutrophil and macrophage migration, and fibroblast proliferation) and the release of lysosomal enzymes. The stronger the anti-inflammatory effect of the steroid compound used, the greater the inhibitory effect on wound healing. Steroids used after the first 3 to 4 days postinjury do not affect wound healing as severely as when they are used in the immediate postoperative period. Therefore, if possible, their use should be delayed or, alternatively, forms with lesser anti-inflammatory effects should be administered.

In addition to their effect on collagen synthesis, steroids also inhibit epithelialization and contraction and contribute to increased rates of wound infection, regardless of the time of administration.[56] Steroid-delayed healing of cutaneous wounds can be stimulated to epithelialize by topical application of vitamin A.[56,57] Collagen synthesis of steroid-treated wounds also can be stimulated by vitamin A.

All chemotherapeutic antimetabolite drugs adversely affect wound healing by inhibiting early cell proliferation and wound DNA and protein synthesis, all of which are critical to successful repair. Delay in the use of such drugs for about 2 weeks postinjury appears to lessen the wound healing impairment.[58] Extravasation of most chemotherapeutic agents is associated with tissue necrosis, marked ulceration, and protracted healing at the affected site.[59]

METABOLIC DISORDERS

Diabetes mellitus is the best known of the metabolic disorders contributing to increased rates of wound infection and failure.[60] Uncontrolled diabetes results in reduced inflammation, angiogenesis, and collagen synthesis. Additionally, the large- and small-vessel disease that is the hallmark of advanced diabetes contributes to local hypoxemia. Defects in granulocyte function, capillary ingrowth, and fibroblast proliferation all have been described in diabetes. Obesity, insulin resistance, hyperglycemia, and diabetic renal failure contribute significantly and independently to the impaired wound healing observed in diabetics.[61] In wound studies on experimental diabetic animals, insulin restores collagen synthesis and granulation tissue formation to normal levels if given during the early phases of healing.[62] In clean, noninfected, and well-perfused experimental wounds in human diabetic volunteers, type I diabetes mellitus was noted to decrease wound collagen accumulation in the wound, independent of the degree of glycemic control. Type II diabetic patients showed no effect on collagen accretion when compared to healthy, age-matched controls.[63] Furthermore, the diabetic wound appears to be lacking in sufficient growth factor levels, which signal normal healing. It remains unclear whether decreased collagen synthesis or an increased breakdown due to an abnormally high proteolytic wound environment is responsible.

Careful preoperative correction of blood sugar levels improves the outcome of wounds in diabetic patients. Increasing the inspired oxygen tension, judicious use of antibiotics, and correction of other coexisting metabolic abnormalities all can result in improved wound healing.

Uremia also has been associated with disordered wound healing. Experimentally, uremic animals demonstrate decreased wound collagen synthesis and breaking strength. The contribution of uremia alone to this impairment, rather than that of associated malnutrition, is difficult to assess.[61] The clinical use of dialysis to correct the metabolic abnormalities and nutritional restoration should impact greatly on the wound outcome of such patients.

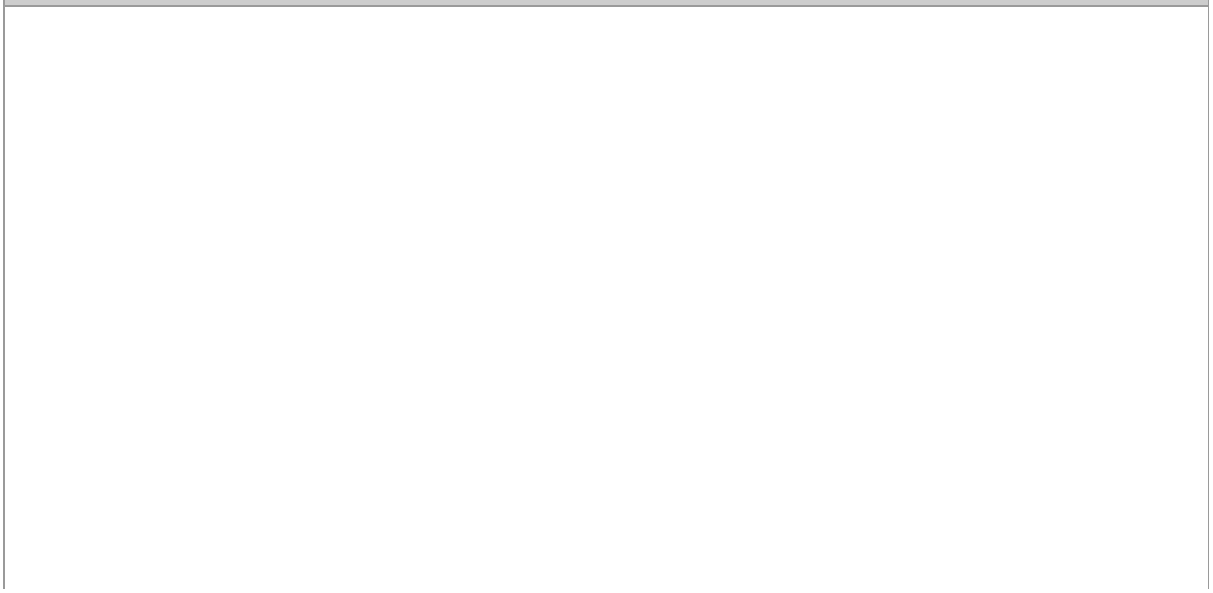
NUTRITION

The importance of nutrition in the recovery from traumatic or surgical injury has been recognized by clinicians since the time of Hippocrates. Poor nutritional intake or lack of individual nutrients significantly alters many aspects of wound healing. The clinician must pay close attention to the nutritional status of patients with wounds, as wound failure or wound infections may be no more than a reflection of poor nutrition. Although the full interaction of nutrition and wound healing is still not fully understood, efforts are being made to develop wound-specific nutritional interventions and the pharmacologic use of individual nutrients as modulators of wound outcomes.

Experimental rodents fed either a 0 or 4% protein diet have impaired collagen deposition with a secondary decrease in skin and fascial wound-breaking strength and increased wound infection rates. Induction of energy-deficient states by providing only 50% of the normal caloric requirement leads to decreased granulation tissue formation and matrix protein deposition in rats. Acute fasting in rats markedly impairs collagen synthesis while decreasing procollagen mRNA.[64]

Clinically, it is extremely rare to encounter pure energy or protein malnutrition, and the vast majority of patients exhibit combined protein-energy malnutrition. Such patients have diminished hydroxyproline accumulation (an index of collagen deposition) into subcutaneously implanted polytetrafluoroethylene tubes when compared to normally nourished patients (Fig. 9-8). Furthermore, malnutrition correlates clinically with enhanced rates of wound complications and increased wound failure after diverse surgical procedures. This reflects impaired healing response as well as reduced cell-mediated immunity, phagocytosis, and intracellular killing of bacteria by macrophages and neutrophils during protein-calorie malnutrition.[64]

Fig. 9-8.



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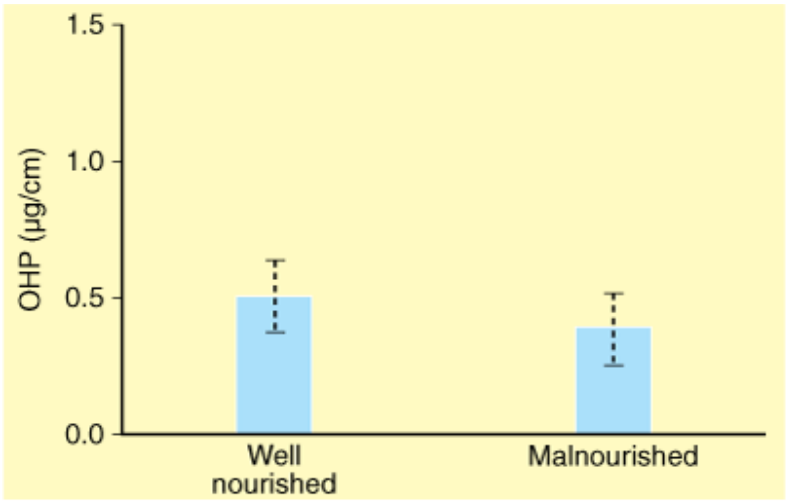

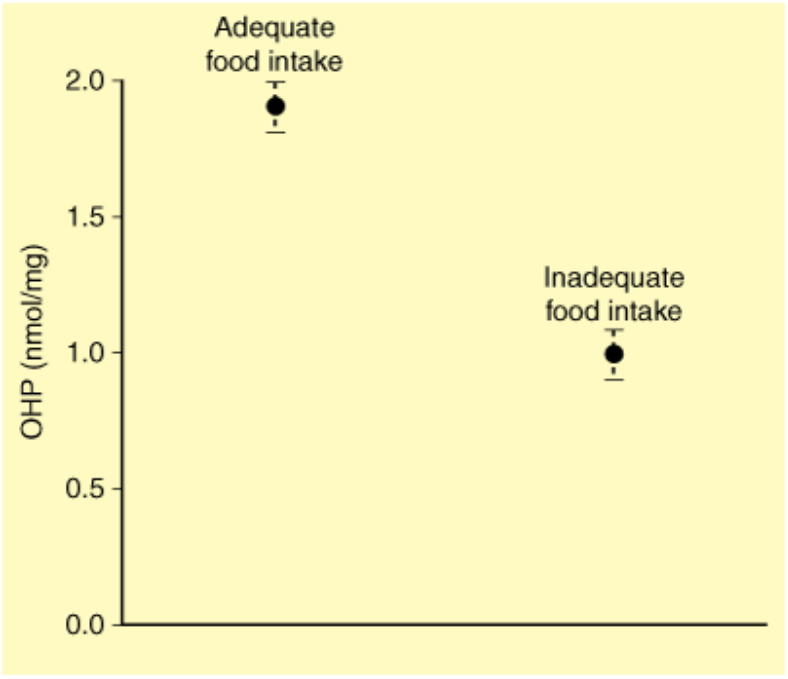

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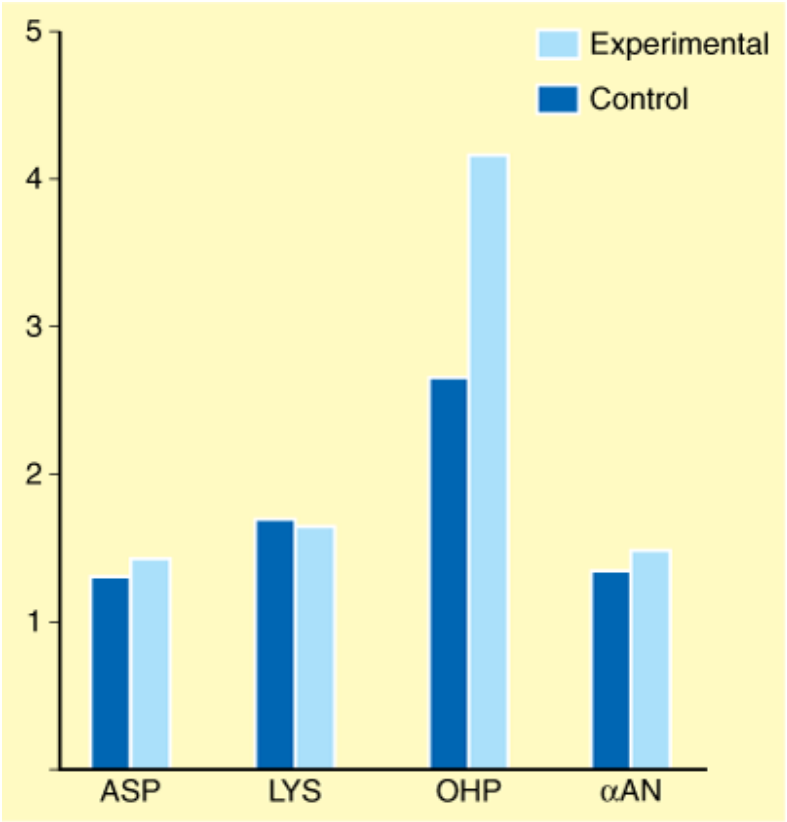
Effect of malnutrition on collagen deposition in experimental human wounds. OHP = hydroxyproline.

Two additional nutrition-related factors warrant discussion. First, the degree of nutritional impairment need not be long-standing in humans, as opposed to the experimental situation. Thus, patients with brief preoperative illnesses or reduced nutrient intake in the period immediately preceding the injury or operative intervention will demonstrate impaired fibroplasias.[65,66] Second, brief and not necessarily intensive nutritional intervention, either via the parenteral or enteral route, can reverse or prevent the decreased collagen deposition noted with malnutrition or with postoperative starvation.[67]

The possible role of single amino acids in enhanced wound healing has been studied for the last several decades. Arginine appears most active in terms of enhancing wound fibroplasia. Arginine deficiency results in decreased wound-breaking strength and wound collagen accumulation in chow-fed rats. Rats that are given 1% arginine HCl supplementation, and are therefore not arginine-deficient, have enhanced wound-breaking strength and collagen synthesis when compared to chow-

fed controls.[68] Studies have been carried out in healthy human volunteers to examine the effect of arginine supplementation on collagen accumulation. Young, healthy, human volunteers (aged 25 to 35 years) were found to have significantly increased wound collagen deposition after oral supplementation with either 30 g of arginine aspartate (17 g of free arginine) or 30 g of arginine HCl (24.8 g of free arginine) daily for 14 days.[69] In a study of healthy older humans (aged 67 to 82 years), daily supplements of 30 g of arginine aspartate for 14 days resulted in significantly enhanced collagen and total protein deposition at the wound site when compared to controls given placebos. There was no enhanced DNA synthesis present in the wounds of the arginine-supplemented subjects, suggesting that the effect of arginine is not mediated by an inflammatory mode of action.[70] In this study, arginine supplementation had no effect on the rate of epithelialization of a superficial skin defect. This further suggests that the main effect of arginine on wound healing is to enhance wound collagen deposition. Recently, a dietary supplemental regimen of arginine, β-hydroxy-β-methylbutyrate, and glutamine was found to significantly and specifically enhance collagen deposition in elderly, healthy human volunteers when compared to an isocaloric, isonitrogenous supplement (Fig. 9-9).[71] As increases in breaking strength during the first weeks of healing are directly related to new collagen synthesis, arginine supplementation may result in an improvement in wound strength as a consequence of enhanced collagen deposition.

Fig. 9-9.



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Ratios of 14-day to 7-day values for aspartate (ASP), hydroxyproline (OHP), lysine (LYS), and α-amino nitrogen (αAN) in volunteers given dietary supplements of arginine, β-hydroxy-β-methylbutyrate, and glutamine. *$P < .05$.

(From Williams JZ, et al,[71] with permission.)

The vitamins most closely involved with wound healing are vitamin C and vitamin A. Scurvy, or vitamin C deficiency, leads to

a defect in wound healing, particularly via a failure in collagen synthesis and cross-linking. Biochemically, vitamin C is required for the conversion of proline and lysine to hydroxyproline and hydroxylysine, respectively. Vitamin C deficiency has also been associated with an increased incidence of wound infection, and if wound infection does occur, it tends to be more severe. These effects are believed to be due to an associated impairment in neutrophil function, decreased complement activity, and decreased walling-off of bacteria secondary to insufficient collagen deposition. The recommended dietary allowance is 60 mg daily. This provides a considerable safety margin for most healthy nonsmokers. In severely injured or extensively burned patients this requirement may increase to as high as 2 g daily. There is no evidence that excess vitamin C is toxic; however, there is no evidence that supertherapeutic doses of vitamin C are of any benefit.[72]

Vitamin A deficiency impairs wound healing, whereas supplemental vitamin A benefits wound healing in nondeficient humans and animals. Vitamin A increases the inflammatory response in wound healing, probably by increasing the lability of lysosomal membranes. There is an increased influx of macrophages, with an increase in their activation and increased collagen synthesis. Vitamin A directly increases collagen production and epidermal growth factor receptors when it is added in vitro to cultured fibroblasts. As mentioned in the section Steroids and Chemotherapeutic Drugs, supplemental vitamin A can reverse the inhibitory effects of corticosteroids on wound healing. Vitamin A also can restore wound healing that has been impaired by diabetes, tumor formation, cyclophosphamide, and radiation. Serious injury or stress leads to increased vitamin A requirements. In the severely injured patient, supplemental doses of vitamin A have been recommended. Doses ranging from 25,000 to 100,000 IU per day have been advocated.

The connections between specific minerals and trace elements and deficits in wound healing are complex. Frequently, deficiencies are multiple and include macronutrient deficiencies. As with some of the vitamins described above, the specific trace element may function as a cofactor or part of an enzyme that is essential for homeostasis and wound healing. Clinically, preventing deficiencies is often easier to accomplish than diagnosing them.

Zinc is the most well-known element in wound healing and has been used empirically in dermatologic conditions for centuries. It is essential for wound healing in animals and humans. There are more than 150 known enzymes for which zinc is either an integral part or an essential cofactor, and many of these enzymes are critical to wound healing.[73] With zinc deficiency there is decreased fibroblast proliferation, decreased collagen synthesis, impaired overall wound strength, and delayed epithelialization. These defects are reversed by zinc supplementation. To date, no study has shown improved wound healing with zinc supplementation in patients who are not zinc deficient.[74]

INFECTIONS

Wound infections continue to represent a major medical problem, both in terms of how they affect the outcome of surgical procedures (surgical site infections), and for their impact on the length of hospital stay and medical costs.[75] Many otherwise successful surgical operations fail because of the development of wound infections. The occurrence of infections is of major concern when implants are used, and their occurrence may lead to the removal of the prosthetic material, thus subjecting the patient to further operations and severe risk of morbidity and mortality. Infections can weaken an abdominal closure or hernia repair and result in wound dehiscence or recurrence of the hernia. Cosmetically, infections can lead to disfiguring, unsightly, or delayed closures.

Exhaustive studies have been undertaken that examine the appropriate prophylactic treatment of operative wounds. Bacterial contaminants normally present on skin are prevented from entry into deep tissues by intact epithelium. Surgery breaches the intact epithelium, allowing bacteria access to these tissues and the bloodstream. Antibiotic prophylaxis is most

effective when adequate concentrations of antibiotic are present in the tissues at the time of incision, and assurance of adequate preoperative antibiotic dosing and timing has become a significant hospital performance measure.[76] Addition of antibiotics after operative contamination has occurred is clearly ineffective in preventing postoperative wound infections.

Studies that compare operations performed with and without antibiotic prophylaxis demonstrate that class II, III, and IV procedures (see below) treated with appropriate prophylactic antibiotics have only one third the wound infection rate of previously reported untreated series.[77] More recently, repeat dosing of antibiotics has been shown to be essential in decreasing postoperative wound infections in operations with durations exceeding the biochemical half-life ($t_{1/2}$) of the antibiotic or in which there is large-volume blood loss and fluid replacement.[78,79] In lengthy cases, those in which prosthetic implants are used, or when unexpected contamination is encountered, additional doses of antibiotic may be administered for 24 hours postoperatively.

Selection of antibiotics for use in prophylaxis should be tailored to the type of surgery to be performed, operative contaminants that might be encountered during the procedure, and the profile of resistant organisms present at the institution where the surgery is performed. The continuing widespread appearance of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci has significantly restricted the selection of these agents for routine use. An example of surgery-specific treatment guidelines is provided in Table 9-7.[78]

Table 9-7 Antimicrobial Prophylaxis for Surgery

Nature of Operation	Common Pathogens	Recommended Antimicrobials	Adult Dosage before Surgery[a]
Cardiac	*Staphylococcus aureus*, *S. epidermidis*	Cefazolin *or*	1–2 g IV[c]
		Cefuroxime *or*	1.5 g IV[c]
		Vancomycin[b]	1 g IV
GI, esophageal, gastroduodenal	Enteric gram-negative bacilli, gram-positive cocci	High risk[d] only: cefazolin	1–2 g IV
Biliary tract	Enteric gram-negative bacilli, enterococci, clostridia	High risk[e] only: cefazolin	1–2 g IV
Colorectal	Enteric gram-negative bacilli, anaerobes, enterococci	Oral: neomycin + erythromycin base[f] *or* metronidazole[f]	—
Appendectomy, nonperforated[h]	—	Parenteral: cefoxitin[g] *or*	1–2 g IV
		Cefazolin +	1–2 g IV
		Metronidazole[g] *or*	0.5 g IV
		Ampicillin/sulbactam	3 g IV
Genitourinary[i]	—	High risk only: ciprofloxacin	500 mg PO or 400 mg IV
Gynecologic and obstetric	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Cefoxitin[g] *or* cefazolin[g] *or*	1–2 g IV
Vaginal, abdominal, or laparoscopic hysterectomy		Ampicillin/sulbactam[g]	3 g IV

Cesarean section	Same as for hysterectomy	Cefazolin[g]	1–2 g IV after cord clamping
Abortion	Same as for hysterectomy	First trimester, high risk[j]:aqueous penicillin G *or*	2 million units IV
		Doxycycline	300 mg PO[k]
		Second trimester: cefazolin[g]	1–2 g IV
Head and neck surgery	Anaerobes, enteric gram-negative bacilli, *S. aureus*	Clindamycin +	600–900 mg IV
Incisions through oral or pharyngeal mucosa		Gentamicin *or*	1.5 mg/kg IV
		Cefazolin	1–2 g IV
Neurosurgery	*S. aureus*, *S. epidermidis*	Cefazolin *or*	1–2 g IV
		Vancomycin[b]	1 g IV
Ophthalmic	*S. epidermidis*, *S. aureus*, streptococci, enteric gram-negative bacilli, *Pseudomonas* spp.	Gentamicin, tobramycin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin *or*	Multiple drops topically over 2 to 24 h
		Neomycin, gramicidin, polymyxin B or cefazolin	100 mg subconjunctivally
Orthopedic	*S aureus*, *S. epidermidis*	Cefazolin[l] *or*	1–2 g IV
		Cefuroxime[l] *or*	1.5 g IV
		Vancomycin[b,l]	1 g IV
Thoracic (noncardiac)	*S. aureus*, *S. epidermidis*, streptococci, enteric gram-negative bacilli	Cefazolin *or*	1–2 g IV
		Cefuroxime *or*	1.5 g IV
		Vancomycin[b]	1 g IV
Vascular	*S. aureus*, *S. epidermidis*, enteric gram-negative bacilli	Cefazolin *or*	1–2 g IV
Arterial surgery involving a prosthesis, the abdominal aorta, or a groin incision		Vancomycin[b]	1 g IV
Lower extremity amputation for ischemia	*S. aureus*, *S. epidermidis*, enteric gram-negative bacilli, clostridia	Cefazolin *or*	1–2 g IV
		Vancomycin[b]	1 g IV

[a]Parenteral prophylactic antimicrobials can be given as a single IV dose begun 60 min or less before the operation. For prolonged operations, (>4 h) or those with major blood loss, additional intraoperative doses should be given at intervals 1–2 times the half-life of the drug for the duration of the procedure in a patient with normal renal function. If vancomycin or a fluoroquinolone is used, the infusion should be started 60–120 min before the initial incision to minimize the possibility of an infusion reaction close to the time of induction of anesthesia and to have adequate tissue levels at the time of incision.

[b]Vancomycin is used in hospitals in which methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. epidermidis* are a frequent cause of postoperative wound infection, for patients previously colonized with MRSA, or for those who are allergic to penicillin or cephalosporins. Rapid 1C administration may cause hypotension, which could be especially dangerous during induction of anesthesia.

Even when the drug is given over 60 min, hypertension may occur; treatment with diphenhydramine (Benadryl and others) and further slowing of the infusion rate may be helpful. Some experts would give 15 mg/kg of vancomycin to patients

weighing more than 75 kg up to a maximum of 1.5 g with a slower infusion rate (90 min for 1.5 g). To provide coverage against gram-negative bacteria, most Medical Letter consultants would also include cefazolin or cefuroxime in the prophylaxis regimen for patients not allergic to cephalosporins. Ciprofloxacin, levofloxacin, gentamicin, or aztreonam, each one in combination with vancomycin, can be used in patients who cannot tolerate a cephalosporin.

[c]Some consultants recommend an additional dose when patients are removed from bypass during open-heart surgery.

[d]Morbid obesity, esophageal obstruction, decreased gastric acidity, or gastrointestinal motility.

[e]Age >70 y, acute cholecystitis, nonfunctioning gallbladder, obstructive jaundice, or common duct stones.

[f]After appropriate diet and catharsis, 1 g of neomycin plus 1 g of erythromycin at 1 P.M., 2 P.M., and 11 P.M. or 2 g of neomycin plus 2 g of metronidazole at 7 P.M. and 11 P.M. the day before an 8 A.M. operation.

[g]For patients allergic to penicillin and cephalosporins, clindamycin with either gentamicin, ciprofloxacin, levofloxacin, or aztreonam is a reasonable alternative.

[h]For a ruptured viscous, therapy is often continued for about 5 days. Ruptured viscous in postoperative setting (dehiscence) requires antibacterial to include coverage of nosocomial pathogens.

[i]Urine culture positive or unavailable, preoperative catheter, transrectal prostatic biopsy, placement of prosthetic material.

[j]Patients with previous pelvic inflammatory disease, previous gonorrhea, or multiple sex partners.

[k]Divide into 100 mg 1 h before the abortion and 200 mg one half hour after.

[l]If a tourniquet is to be used in the procedure, the entire dose of antibiotic must be infused before its inflation.

Source: Reproduced with permission from Antimicrobial Prophylaxis for Surgery. *Treatment Guidelines from The Medical Letter* 4:84, 2006. The Medical Letter®, Inc. New Rochelle, New York.

Patients with prosthetic heart valves or any implanted vascular or orthopedic prostheses should receive antibiotic prophylaxis before any procedure in which significant bacteremia is anticipated. Dental procedures require prophylaxis with broad-spectrum penicillins or amoxicillin, whereas urologic instrumentation should be pretreated with a second-generation cephalosporin. Patients with prostheses who undergo GI surgery should receive anaerobic coverage combined with a cephalosporin.

The incidence of wound infection is about 5 to 10% nationwide and has not changed during the last few decades. Quantitatively, it has been shown that if the wound is contaminated with $>10^5$ microorganisms, the risk of wound infection is markedly increased, but this threshold may be much lower in the presence of foreign materials. The source of pathogens for the infection is usually the endogenous flora of the patient's skin, mucous membranes, or from hollow organs. The most common organisms responsible for wound infections, in order of frequency, are *Staphylococcus* species, coagulase-negative *Streptococcus*, enterococci, and *Escherichia coli*. The incidence of wound infection bears a direct relationship to the degree of contamination that occurs during the operation from the disease process itself (clean—class I, clean contaminated—class II, contaminated—class III, and dirty—class IV). Many factors contribute to the development of postoperative wound infections. Most surgical wound infections become apparent within 7 to 10 days postoperatively, although a small number manifest only years after the original operative intervention. With the hospital stay becoming shorter and shorter, many infections are detected in the outpatient setting, leading to underreporting of the true incidence of wound infections. There has been much debate about the actual definition of wound infection. The narrowest definition would include wounds that drain purulent material, with bacteria identified on culture. The more broad definition would include all wounds draining pus, whether or not the bacteriologic studies are positive; wounds that are opened by the surgeon; and wounds that the surgeon considers infected.[80]

Anatomically, wound infections can be classified as superficial or suprafascial and deep, involving fascia, muscle, or the abdominal cavity. About three fourths of all wound infections are superficial, involving skin and subcutaneous tissue only. Clinical diagnosis is easy when a postoperative wound looks edematous and erythematous and is tender. Often the presentation is more subtle, and development of postoperative fever (usually low-grade), development of a mild and unexplained leukocytosis, or the presence of undue incisional pain should direct attention to the wound. Inspection of the wound is most useful in detecting subtle edema around the suture or staple line, manifested as a waxy appearance of the skin, which characterizes the early phase of infection. If a wound infection is suspected, several stitches or staples around the most suspicious area should be removed with insertion of a cotton-tipped applicator into the subcutaneous area to open a small segment of the incision. This causes minimal if any discomfort to the patient. Presence of pus mandates further opening of the subcutaneous and skin layers to the full extent of the infected pocket. Samples should be taken for aerobic and anaerobic cultures, with very few patients requiring antibiotic therapy. Patients who are immunosuppressed (diabetics and those on steroids or chemotherapeutic agents), who have evidence of tissue penetration or systemic toxicity, or who have had prosthetic devices inserted (vascular grafts, heart valves, artificial joints, or mesh) should be treated with systemic antibiotics.[80]

Deep wound infections arise immediately adjacent to the fascia, either above or below it, and often have an intra-abdominal component. Most intra-abdominal infections do not, however, communicate with the wound. Deep infections present with fever and leukocytosis. The incision may drain pus spontaneously or the intra-abdominal extension may be recognized after the drainage of what was thought to be a superficial wound infection, but pus draining between the fascial sutures will be noted. Sometimes wound dehiscence will occur. The most dangerous of the deep infections is necrotizing fasciitis. It results in high mortality, particularly in the elderly. This is an invasive process that involves the fascia and leads to secondary skin necrosis. Pathophysiologically, it is a septic thrombosis of the vessels between the skin and the deep layers. The skin demonstrates hemorrhagic bullae and subsequent frank necrosis, with surrounding areas of inflammation and edema. The fascial necrosis is usually wider than the skin involvement or than the surgeon estimates on clinical grounds. The patient is toxic, has high fever, tachycardia, and marked hypovolemia, which if uncorrected, progresses to cardiovascular collapse. Bacteriologically, this is a mixed infection, and samples should be obtained for Gram's stain smears and cultures to aid in diagnosis and treatment. As soon as bacteriologic studies have been sent, high-dose penicillin treatment needs to be started (20 to 40 million U/d IV). Cardiovascular resuscitation with electrolyte solutions, blood, and/or plasma is carried out as expeditiously as possible before induction of anesthesia. The aim of surgical treatment is thorough removal of all necrosed skin and fascia. If viable skin overlies necrotic fascia, multiple longitudinal skin incisions can be made to allow for excision of the devitalized fascia. Although removal of all necrotic tissue is the goal of the first surgical intervention, the distinction between necrotic and simply edematous tissue often is difficult. Careful inspection every 12 to 24 hours will reveal any new necrotic areas, and these need further débridement and excision. When all necrotic tissue has been removed and the infection has been controlled, the wounds may be covered with homo- or xenografts until definitive reconstruction and autografting can take place.

The mere presence of bacteria in an open wound, either acute or chronic, does not constitute an infection, because large numbers of bacteria can be present in the normal situation. Second, the bacteria grown may not be representative of the bacteria causing the actual wound infection. There seems to be confusion as to what exactly constitutes wound infection. For purposes of clarity, contamination, colonization, and infection should be differentiated. *Contamination* is the presence of bacteria without multiplication, *colonization* is multiplication without host response, and *infection* is the presence of host response in reaction to deposition and multiplication of bacteria. The presence of a host response helps to differentiate

between infection and colonization as seen in chronic wounds. The host response that helps in diagnosing wound infection comprises cellulitis, abnormal discharge, delayed healing, change in pain, abnormal granulation tissue, bridging, and abnormal color and odor.

As discussed previously in the section Hemostasis and Inflammation, neutrophils play a major role in preventing wound infections. Chronic granulomatous disease (CGD) comprises a genetically heterogeneous group of diseases in which the reduced nicotinamide adenine dinucleotide phosphate–dependent oxide enzyme is deficient. This defect impairs the intracellular killing of microorganisms, leaving the patient liable to infection by bacteria and fungi. Afflicted patients have recurrent infections and form granulomas, which can lead to obstruction of the gastric antrum and genitourinary tracts and poor wound healing. Surgeons become involved when the patient develops infectious or obstructive complications.

The nitroblue tetrazolium reduction test is used to diagnose CGD. Normal neutrophils can reduce this compound, whereas neutrophils from affected patients do not, facilitating the diagnosis via a colorimetric test. Clinically, patients develop recurrent infections such as pneumonia, lymphadenitis, hepatic abscess, and osteomyelitis. Organisms most commonly responsible are *Staphylococcus aureus*, *Aspergillus*, *Klebsiella*, *Serratia*, or *Candida*. When CGD patients require surgery, a preoperative pulmonary function test should be considered because such patients are predisposed to obstructive and restrictive lung disease. Wound complications, mainly infection, are common. Sutures should be removed as late as possible because the wounds heal slowly. Abscess drains should be left in place for a prolonged period until the infection is completely resolved.[81]

Chronic Wounds

Chronic wounds are defined as wounds that have failed to proceed through the orderly process that produces satisfactory anatomic and functional integrity or that have proceeded through the repair process without producing an adequate anatomic and functional result. The majority of wounds that have not healed in 3 months are considered chronic. *Skin ulcers*, which usually occur in traumatized or vascularly compromised soft tissue, are also considered chronic in nature, and proportionately are the major component of chronic wounds. In addition to the factors discussed in the preceding section that can delay wound healing, other causative mechanisms may also play a role in the etiology of chronic wounds. Repeated trauma, poor perfusion or oxygenation, and/or excessive inflammation contribute to the causation and the perpetuation of the chronicity of wounds.

Unresponsiveness to normal regulatory signals also has been implicated as a predictive factor of chronic wounds. This may come about as a failure of normal growth factor synthesis,[82] and thus an increased breakdown of growth factors within a wound environment that is markedly proteolytic because of overexpression of protease activity or a failure of the normal antiprotease inhibitor mechanisms.[83] Fibroblasts from chronic wounds also have been found to have decreased proliferative potential, perhaps because of senescence[84] or decreased expression of growth factor receptors.[85] Chronic wounds occur due to various etiologic factors, and several of the most common are discussed in the following sections.

Malignant transformation of chronic ulcers can occur in any long-standing wound (Marjolin ulcer). Any wound that does not heal for a prolonged period of time is prone to malignant transformation. Malignant wounds are differentiated clinically from nonmalignant wounds by the presence of overturned wound edges. In patients with suspected malignant transformations, biopsy of the wound edges must be performed to rule out malignancy. Cancers arising de novo in chronic wounds include both squamous and basal cell carcinomas.

ISCHEMIC ARTERIAL ULCERS

Ischemic arterial ulcers occur due to a lack of blood supply and are painful at presentation. They usually are associated with other symptoms of peripheral vascular disease, such as intermittent claudication, rest pain, night pain, and color changes. These wounds commonly are present at the most distal portions of the extremities, such as the interdigital clefts, although more proximal locations are also encountered. On examination, there may be diminished or absent pulses with decreased ankle-brachial index and poor formation of granulation tissue. Other signs of peripheral ischemia, such as dryness of skin, hair loss, scaling, and pallor can be present. The wound itself usually is shallow with smooth margins, and a pale base and surrounding skin may be present. The management of these wounds is two-pronged and includes revascularization and wound care.[86] Nonhealing of these wounds is the norm unless successful revascularization is performed. After establishing adequate blood supply, most such wounds progress to heal satisfactorily.

A strategy of prevention is extremely important in the approach to patients with limb ischemia. In bedridden patients, especially those who are sedated (in the intensive care unit), demented, or with peripheral neural compromise (neuropathy or paraplegia), pressure ulcers develop rapidly and often unnecessarily. Removal of restrictive stockings (in patients with critical ischemia), frequent repositioning, and surveillance is vital to preventing these ulcers.[87]

VENOUS STASIS ULCERS

Although there is unanimous agreement that venous ulcers are due to venous stasis and hydrostatic back pressure, there is less consensus as to what are the exact pathophysiologic pathways that lead to ulceration and impaired healing. On the microvascular level, there is alteration and distention of the dermal capillaries with leakage of fibrinogen into the tissues; polymerization of fibrinogen into fibrin cuffs leads to perivascular cuffing that can impede oxygen exchange, thus contributing to ulceration. These same fibrin cuffs and the leakage of macromolecules such as fibrinogen and alpha$_2$-macroglobulin trap growth factors and impede wound healing. Another hypothesis suggests that neutrophils adhere to the capillary endothelium and cause plugging with diminished dermal blood flow. Venous hypertension and capillary damage lead to extravasation of hemoglobin. The products of this breakdown are irritating and cause pruritus and skin damage. The resulting brownish pigmentation of skin combined with the loss of subcutaneous fat produces characteristic changes called *lipodermatosclerosis*. Regardless of the pathophysiologic mechanisms, the clinically characteristic picture is that of an ulcer that fails to re-epithelialize despite the presence of adequate granulation tissue.

Venous stasis occurs due to the incompetence of either the superficial or deep venous systems. Chronic venous ulcers usually are due to the incompetence of the deep venous system and are commonly painless. Stasis ulcers tend to occur at the sites of incompetent perforators, the most common being above the medial malleolus, over Cockett's perforator. Upon examination, the typical location combined with a history of venous incompetence and other skin changes is diagnostic. The wound usually is shallow, with irregular margins and pigmented surrounding skin.

The cornerstone of treatment of venous ulcers is compression therapy, although the best method to achieve it remains controversial. Compression can be accomplished via rigid or flexible means. The most commonly used method is the rigid, zinc oxide–impregnated, nonelastic bandage. Others have proposed a four-layered bandage approach as a more optimal method of obtaining graduated compression.[88] Wound care in these patients focuses on maintaining a moist wound environment, which can be achieved with hydrocolloids. Other, more modern approaches include use of vasoactive substances and growth factor application, as well as the use of skin substitutes. Most venous ulcers can be healed with perseverance and by addressing the venous hypertension.[88] Unfortunately, recurrences are frequent in spite of preventative

measures, largely because of patients' lack of compliance.[89,90]

DIABETIC WOUNDS

Ten to 15% of diabetic patients run the risk of developing ulcers. There are approximately 50,000 to 60,000 amputations performed in diabetic patients each year in the United States. The major contributors to the formation of diabetic ulcers include neuropathy, foot deformity, and ischemia. It is estimated that 60 to 70% of diabetic ulcers are due to neuropathy, 15 to 20% are due to ischemia, and another 15 to 20% are due to a combination of both. The neuropathy is both sensory and motor, and is secondary to persistently elevated glucose levels. The loss of sensory function allows unrecognized injury to occur from ill-fitting shoes, foreign bodies, or other trauma. The motor neuropathy or Charcot foot leads to collapse or dislocation of the interphalangeal or metatarsophalangeal joints, causing pressure on areas with little protection. There is also severe micro- and macrovascular circulatory impairment.

Once ulceration occurs, the chances of healing are poor. The treatment of diabetic wounds involves local and systemic measures.[91] Achievement of adequate blood sugar levels is very important. Most diabetic wounds are infected, and eradication of the infectious source is paramount to the success of healing. Treatment should address the possible presence of osteomyelitis, and should employ antibiotics that achieve adequate levels both in soft tissue and bone. Wide débridement of all necrotic or infected tissue is another cornerstone of treatment. Off-loading of the ulcerated area by using specialized orthotic shoes or casts allows for ambulation while protecting the fragile wound environment. Topical application of PDGF and granulocyte-macrophage colony-stimulating factor has met with limited but significant success in achieving closure.[92] The application of engineered skin allograft substitutes, although expensive, has also shown some significant success.[93] Prevention and, specifically, foot care play an important role in the management of diabetics.[94]

DECUBITUS OR PRESSURE ULCERS

The incidence of pressure ulcers ranges from 2.7 to 9% in the acute care setting, in comparison to 2.4 to 23% in long-term care facilities. A pressure ulcer is a localized area of tissue necrosis that develops when a soft tissue is compressed between a bony prominence and an external surface. Excessive pressure causes capillary collapse and impedes the delivery of nutrients to body tissues. Pressure ulcer formation is accelerated in the presence of friction, shear forces, and moisture. Other contributory factors in the pathogenesis of pressure ulcers include immobility, altered activity levels, altered mental status, chronic conditions, and altered nutritional status. The four stages of pressure ulcer formation are as follows: stage I, nonblanchable erythema of intact skin; stage II, partial-thickness skin loss involving epidermis or dermis, or both; stage III, full-thickness skin loss, but not through the fascia; and stage IV, full-thickness skin loss with extensive involvement of muscle and bone.

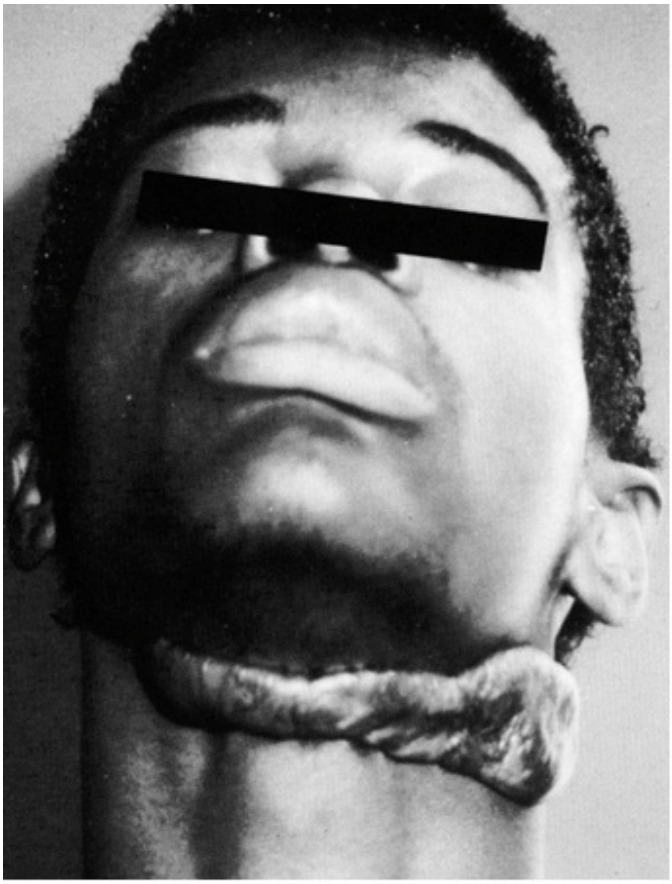
The treatment of established pressure ulcers is most successful when carried out in a multidisciplinary manner by involving wound care teams consisting of physicians, nurses, dietitians, physical therapists, and nutritionists. Care of the ulcer itself comprises débridement of all necrotic tissue, maintenance of a favorable moist wound environment that will facilitate healing, relief of pressure, and addressing host issues such as nutritional, metabolic, and circulatory status. Débridement is most efficiently carried out surgically, but enzymatic proteolytic preparations and hydrotherapy also are used. The wound bed should be kept moist by employing dressings that absorb secretions but do not desiccate the wound.[95] Operative repair, usually involving flap rotation, has been found to be useful in obtaining closure. Unfortunately, recurrence rates are extremely high, owing to the population at risk and the inability to fully address the causative mechanisms.[96,97]

EXCESS HEALING

Clinically, excess healing can be as significant as wound failure. It is likely that more operative interventions are required for correction of the morbidity associated with excessive healing than are required for wound failure. The clinical manifestations of exuberant healing are protean and differ in the skin (mutilating or debilitating scars, burn contractions), tendons (frozen repairs), the GI tract (strictures or stenoses), solid organs (cirrhosis, pulmonary fibrosis), or the peritoneal cavity (adhesive disease).

Hypertrophic scars (HTSs) and keloids represent an overabundance of fibroplasia in the dermal healing process. HTSs rise above the skin level but stay within the confines of the original wound and often regress over time. Keloids rise above the skin level as well, but extend beyond the border of the original wound and rarely regress spontaneously (Fig. 9-10). Both HTSs and keloids occur after trauma to the skin, and may be tender, pruritic, and cause a burning sensation. Keloids are 15 times more common in darker-pigmented ethnicities, with individuals of African, Spanish, and Asian ethnicities being especially susceptible. Men and women are equally affected. Genetically, the predilection to keloid formation appears to be autosomal dominant, with incomplete penetration and variable expression.[98,99]

Fig. 9-10.



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Recurrent keloid on the neck of a 17-year-old patient that had been revised several times.

[Reproduced with permission from Murray JC, Pinnell SR: Keloids and excessive dermal scarring, in Cohen IK, Diegelmann RF, Lindblad WJ (eds): *Wound Healing: Biochemical and Clinical Aspects.* Philadelphia: WB Saunders, 1993.]

HTSs usually develop within 4 weeks after trauma. The risk of HTSs increases if epithelialization takes longer than 21 days,

independent of site, age, and race. Rarely elevated more than 4 mm above the skin level, HTSs stay within the boundaries of the wound. They usually occur across areas of tension and flexor surfaces, which tend to be at right angles to joints or skin creases. The lesions are initially erythematous and raised, and over time may evolve into pale, flatter scars.

Keloids can result from surgery, burns, skin inflammation, acne, chickenpox, zoster, folliculitis, lacerations, abrasions, tattoos, vaccinations, injections, insect bites, ear piercing, or may arise spontaneously. Keloids tend to occur 3 months to years after the initial insult, and even minor injuries can result in large lesions. They vary in size from a few millimeters to large, pedunculated lesions with a soft to rubbery or hard consistency. Although they project above surrounding skin, they rarely extend into underlying subcutaneous tissues. Certain body sites have a higher incidence of keloid formation, including the skin of the earlobe as well as the deltoid, presternal, and upper back regions. They rarely occur on eyelids, genitalia, palms, soles, or across joints. Keloids rarely involute spontaneously, whereas surgical intervention can lead to recurrence, often with a worse result.

Histologically, both HTSs and keloids demonstrate increased thickness of the epidermis with an absence of rete ridges. There is an abundance of collagen and glycoprotein deposition. Normal skin has distinct collagen bundles, mostly parallel to the epithelial surface, with random connections between bundles by fine fibrillar strands of collagen. In HTSs, the collagen bundles are flatter, more random, and the fibers are in a wavy pattern. In keloids, the collagen bundles are virtually nonexistent, and the fibers are connected haphazardly in loose sheets with a random orientation to the epithelium. The collagen fibers are larger and thicker and myofibroblasts are generally absent.[100]

Keloidal fibroblasts have normal proliferation parameters, but synthesize collagen at a rate 20 times greater than that observed in normal dermal fibroblasts, and 3 times higher than fibroblasts derived from HTSs. Abnormal amounts of extracellular matrix, such as fibronectin, elastin, and proteoglycans, also are produced. The synthesis of fibronectin, which promotes clot generation, granulation tissue formation, and re-epithelialization, decreases during the normal healing process; however, production continues at high levels for months to years in HTSs and keloids. This perturbed synthetic activity is mediated by altered growth factor expression. TGFβ expression is higher in HTSs, and both HTS- and keloid-derived fibroblasts respond to lower concentrations of TGFβ than do normal dermal fibroblasts. HTSs also express increased levels of insulin-like growth factor I, which reduces collagenase mRNA activity and increases mRNA for types I and II procollagen.

The underlying mechanisms that cause HTSs and keloids are not known. The immune system appears to be involved in the formation of both HTSs and keloids, although the exact relationship is unknown. Much is inferred from the presence of various immune cells in HTSs and keloids. For example, in both HTSs and keloids, keratinocytes express human leukocyte antigen-2 and intercellular adhesion molecule-1 receptors, which are absent in normal scar keratinocytes. Keloids also have increased deposition of immunoglobulin G (IgG), IgA, and IgM, and their formation correlates with serum levels of IgE. Antinuclear antibodies against fibroblasts, epithelial cells, and endothelial cells are found in keloids, but not HTSs. HTSs have higher T-lymphocyte and Langerhans cell contents. There also is a larger number of mast cells present in both HTSs and keloids compared to normal scars. Other mechanisms that may cause abnormal scarring include mechanical tension (although keloids often occur in areas of minimal tension) and prolonged irritation and/or inflammation that may lead to the generation of abnormal concentrations of profibrotic cytokines.

Treatment goals include restoration of function to the area, relief of symptoms, and prevention of recurrence. Many patients seek intervention due to cosmetic concerns. Because the underlying mechanisms causing keloids and HTSs remain unknown, many different modalities of treatment have been used without consistent success.

Excision alone of keloids is subject to a high recurrence rate, ranging from 45 to 100%. There are fewer recurrences when surgical excision is combined with other modalities such as intralesional corticosteroid injection, topical application of silicone sheets, or the use of radiation or pressure. Surgery is recommended for debulking large lesions or as second-line therapy when other modalities have failed. Silicone application is relatively painless and should be maintained for 24 hours a day for about 3 months to prevent rebound hypertrophy. It may be secured with tape or worn beneath a pressure garment. The mechanism of action is not understood, but increased hydration of the skin, which decreases capillary activity, inflammation, hyperemia, and collagen deposition, may be involved. Silicone is more effective than other occlusive dressings and is an especially good treatment for children and others who cannot tolerate the pain involved in other modalities.[101]

Intralesional corticosteroid injections decrease fibroblast proliferation, collagen and glycosaminoglycan synthesis, the inflammatory process, and TGFβ levels. When used alone, however, there is a variable rate of response and recurrence, therefore steroids are recommended as first-line treatment for keloids and second-line treatment for HTSs if topical therapies have failed. Intralesional injections are more effective on younger scars. They may soften, flatten, and give symptomatic relief to keloids, but they cannot make the lesions disappear nor can they narrow wide HTSs. Success is enhanced when used in combination with surgical excision. Serial injections every 2 to 3 weeks are required. Complications include skin atrophy, hypopigmentation, telangiectasias, necrosis, and ulceration.

Although radiation destroys fibroblasts, it has variable, unreliable results and produces poor results with 10 to 100% recurrence when used alone. It is more effective when combined with surgical excision. The timing, duration, and dosage for radiation therapy are still controversial, but doses ranging from 1500 to 2000 rads appear effective. Given the risks of hyperpigmentation, pruritus, erythema, paresthesias, pain, and possible secondary malignancies, radiation should be reserved for adults with scars resistant to other modalities.

Pressure aids collagen maturation, flattens scars, and improves thinning and pliability. It reduces the number of cells in a given area, possibly by creating ischemia, which decreases tissue metabolism and increases collagenase activity. External compression is used to treat HTSs, especially after burns. Therapy must begin early, and a pressure between 24 and 30 mmHg must be achieved in order to exceed capillary pressure, yet preserve peripheral blood circulation. Garments should be worn for 23 to 24 hours a day for up to 1 or more years to avoid rebound hypertrophy. Scars older than 6 to 12 months respond poorly.

Topical retinoids also have been used as treatment for both HTSs and keloids, with reported responses of 50 to 100%. Intralesional injections of interferon-γ, a cytokine released by T lymphocytes, reduce collagen types I, II, and III by decreasing mRNA and possibly by reducing levels of TGFβ. This treatment is experimental, and complications are frequent and dose-dependent. Intralesional injections of chemotherapeutic agents such as 5-fluorouracil have been used both alone and in combination with steroids. The use of bleomycin has been reported to achieve some success in older scars resistant to steroids.

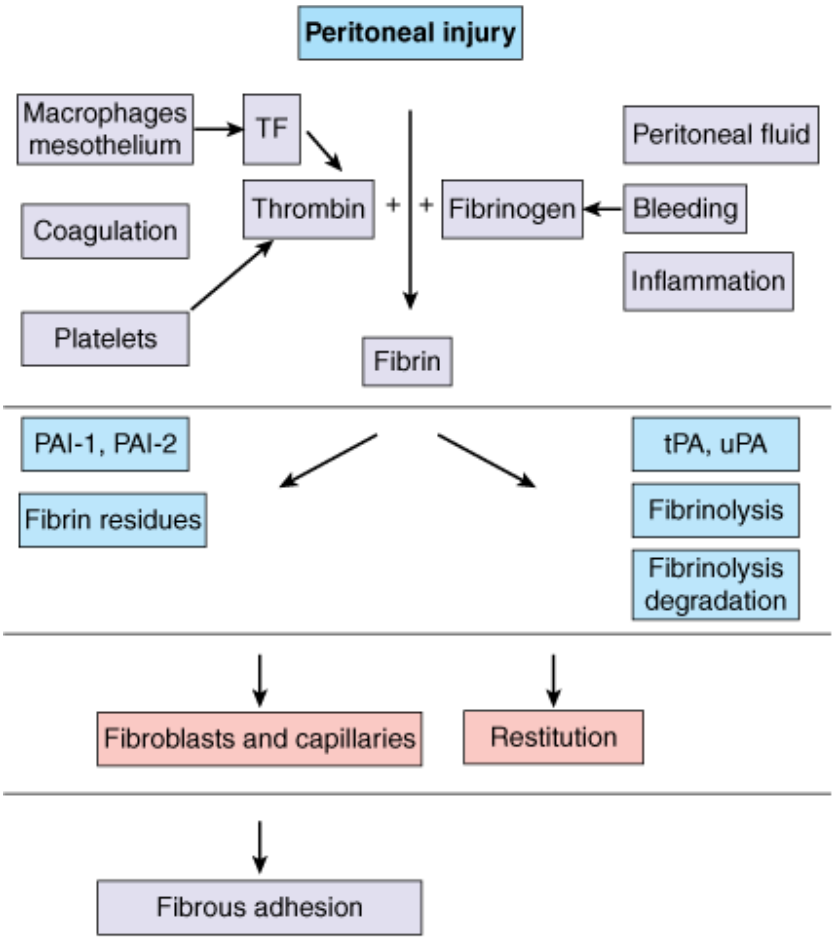
Peritoneal Scarring

Peritoneal adhesions are fibrous bands of tissues formed between organs that are normally separated and/or between organs and the internal body wall. Most intra-abdominal adhesions are a result of peritoneal injury, either by a prior surgical procedure or due to intra-abdominal infection. Postmortem examinations demonstrate adhesions in 67% of patients with prior surgical procedures and in 28% with a history of intra-abdominal infection. Intra-abdominal adhesions are the most common cause (65 to 75%) of small bowel obstruction, especially in the ileum. Operations in the lower abdomen have a

higher chance of producing small bowel obstruction. After rectal surgery, left colectomy, or total colectomy, there is an 11% chance of developing small bowel obstruction within 1 year, and this rate increases to 30% by 10 years. Adhesions also are a leading cause of secondary infertility in women and can cause substantial abdominal and pelvic pain. Adhesions account for 2% of all surgical admissions and 3% of all laparotomies in general surgery.[102]

Adhesions form when the peritoneal surface is damaged due to surgery, thermal or ischemic injury, inflammation, or foreign body reaction. The injury disrupts the protective mesothelial cell layer lining the peritoneal cavity and the underlying connective tissue. The injury elicits an inflammatory response consisting of hyperemia, fluid exudation, release and activation of white blood cells and platelets in the peritoneal cavity, activation of inflammatory cytokines, and the onset of the coagulation and complement cascades. Fibrin deposition occurs between the damaged but opposed serosal surfaces. These filmy adhesions often are transient and degraded by proteases of the fibrinolytic system, with restoration of the normal peritoneal surface. If insufficient fibrinolytic activity is present, permanent fibrous adhesions will form by collagen deposition within 1 week of the injury (Fig. 9-11).

Fig. 9-11.



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Fibrin formation and degradation in peritoneal tissue repair and adhesion formation. PAI-1, -2 = types 1 and 2 plasminogen activator inhibitor; TF = tissue factor; tPA = tissue plasminogen activator; uPA = urokinase plasminogen activator.

Extensive research has been done on the effect of surgery and peritonitis on the fibrinolytic and inflammatory cascades

within the peritoneal cavity. During normal repair, fibrin is principally degraded by the fibrinolytic protease plasmin, which is derived from inactive plasminogen through the action of two plasminogen activators: tissue-type plasminogen activator and urokinase-type plasminogen activator. Fibrinolytic activity in peritoneal fluid is reduced after abdominal surgery due to initial decreases in tissue-type plasminogen activator levels and later to increases in plasminogen activator inhibitor 1, which are induced by various cytokines, including TNF-α, IL-1, and IL-6.[103]

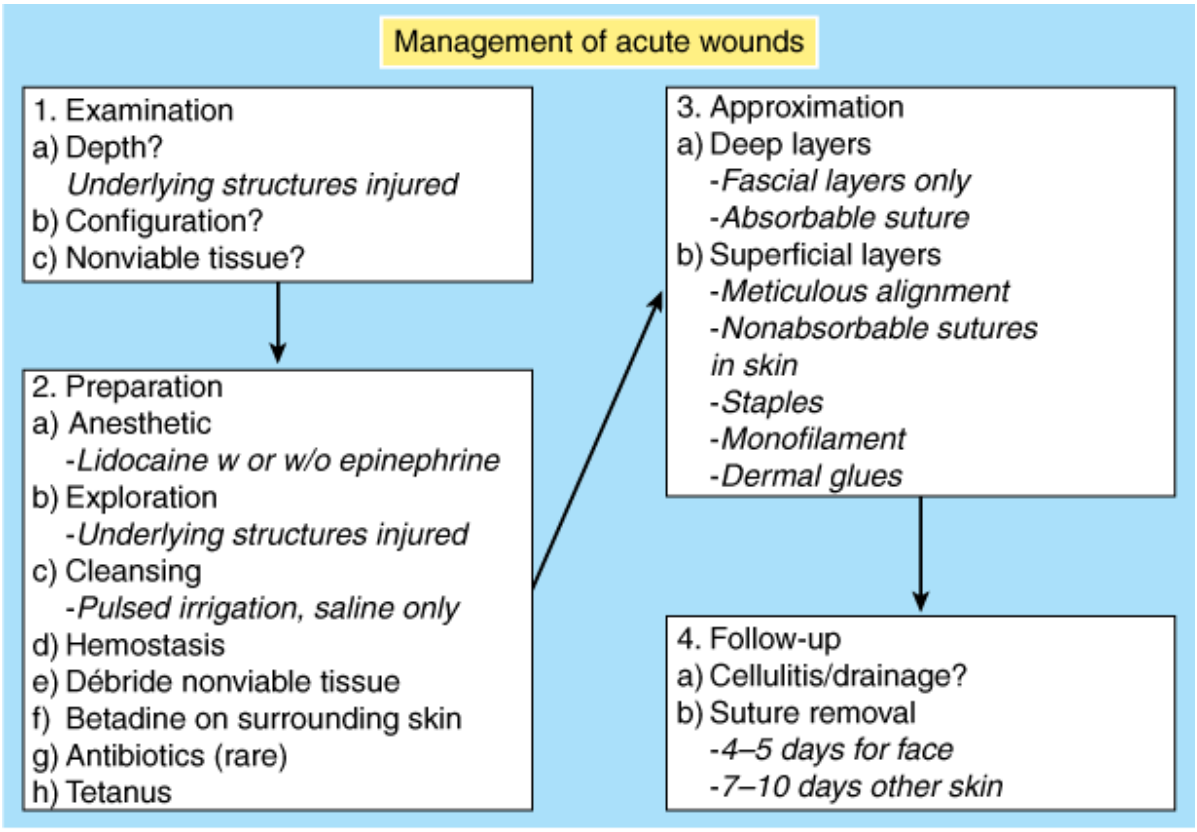
There are two major strategies for adhesion prevention or reduction. Surgical trauma is minimized within the peritoneum by careful tissue handling, avoiding desiccation and ischemia, and spare use of cautery, laser, and retractors. Fewer adhesions form with laparoscopic surgical techniques due to reduced tissue trauma. The second major advance in adhesion prevention has been the introduction of barrier membranes and gels, which separate and create barriers between damaged surfaces, allowing for adhesion-free healing. Modified oxidized regenerated cellulose and hyaluronic acid membranes or solutions have been shown to reduce adhesions in gynecologic patients, and have been investigated for their ability to prevent adhesion formation in patients undergoing bowel surgery.[104,105] Wrapping of the bowel suture area or placement in the proximity of the anastomoses with these substances is, however, contraindicated due to an elevated risk of leak.[106]

TREATMENT OF WOUNDS

Local Care

See Fig. 9-12. Management of acute wounds begins with obtaining a careful history of the events surrounding the injury. The history is followed by a meticulous examination of the wound. Examination should assess the depth and configuration of the wound, the extent of nonviable tissue, and the presence of foreign bodies and other contaminants. Examination of the wound may require irrigation and débridement of the edges of the wound, and is facilitated by use of local anesthesia. Antibiotic administration and tetanus prophylaxis may be needed, and planning the type and timing of wound repair should take place.

Fig. 9-12.



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Algorithm for management of acute wounds.

After completion of the history, examination, and administration of tetanus prophylaxis, the wound should be meticulously anesthetized. Lidocaine (0.5 to 1%) or bupivacaine (0.25 to 0.5%) combined with a 1:100,000 to 1:200,000 dilution of epinephrine provides satisfactory anesthesia and hemostasis. Epinephrine should not be used in wounds of the fingers, toes, ears, nose, or penis due to the risk of tissue necrosis secondary to terminal arteriole vasospasm in these structures. Injection of these anesthetics can result in significant initial patient discomfort, and this can be minimized by slow injection, infiltration of the subcutaneous tissues, and buffering the solution with sodium bicarbonate. Care must be observed in calculating the maximum dosages of lidocaine or bupivacaine to avoid toxicity-related side effects.

Irrigation to visualize all areas of the wound and remove foreign material is best accomplished with normal saline (without additives). High-pressure wound irrigation is more effective in achieving complete débridement of foreign material and nonviable tissues. Iodine, povidone-iodine, hydrogen peroxide, and organically based antibacterial preparations have all been shown to impair wound healing due to injury to wound neutrophils and macrophages, and thus should not be used. All hematomas present within wounds should be carefully evacuated and any remaining bleeding sources controlled with ligature or cautery. If the injury has resulted in the formation of a marginally viable flap of skin or tissue, these should be resected or revascularized before further wound repair and closure.

After the wound has been anesthetized, explored, irrigated, and débrided, the area surrounding the wound should be cleaned, inspected, and the surrounding hair clipped. The area surrounding the wound should be prepared with povidone-iodine or similar solution and draped with sterile towels. Having ensured hemostasis and adequate débridement of nonviable tissues and removal of any remaining foreign bodies, irregular, macerated, or beveled wound edges should be débrided in

order to provide a fresh edge for reapproximation. Although plastic surgical techniques such as W- or Z-plasty are seldom recommended for acute wounds, great care must be taken to realign wound edges properly. This is particularly important for wounds that cross the vermilion border, eyebrow, or hairline. Initial sutures that realign the edges of these different tissue types will speed and greatly enhance the aesthetic outcome of the wound repair.

In general, the smallest suture required to hold the various layers of the wound in approximation should be selected in order to minimize suture-related inflammation. Nonabsorbable or slowly absorbing monofilament sutures are most suitable for approximating deep fascial layers, particularly in the abdominal wall. Subcutaneous tissues should be closed with braided absorbable sutures, with care to avoid placement of sutures in fat. Although traditional teaching in wound closure has emphasized multiple-layer closures, additional layers of suture closure are associated with increased risk of wound infection, especially when placed in fat. Drains may be placed in areas at risk of forming fluid collections.

In areas of significant tissue loss, rotation of adjacent musculocutaneous flaps may be required to provide sufficient tissue mass for closure. These musculocutaneous flaps may be based on intrinsic blood supply, or may be moved from distant sites as free flaps and anastomosed into the local vascular bed. In areas with significant superficial tissue loss, split-thickness skin grafting (placed in a delayed manner to assure an adequate tissue bed) may be required and will speed formation of an intact epithelial barrier to fluid loss and infection. Split-thickness skin grafts are readily obtained using manual or mechanical dermatomes, and the grafts may be "meshed" in order to increase the surface area of their coverage. It is essential to ensure hemostasis of the underlying tissue bed before placement of split-thickness skin grafts, as the presence of a hematoma below the graft will prevent the graft from taking, resulting in sloughing of the graft. In acute, contaminated wounds with skin loss, use of porcine xenografts or cadaveric allografts is prudent until the danger of infection passes.

After closing deep tissues and replacing significant tissue deficits, skin edges should be reapproximated for cosmesis and to aid in rapid wound healing. Skin edges may be quickly reapproximated with stainless steel staples or nonabsorbable monofilament sutures. Care must be taken to remove these from the wound before epithelialization of the skin tracts where sutures or staples penetrate the dermal layer. Failure to remove the sutures or staples by 7 to 10 days after repair will result in a cosmetically inferior wound. When wound cosmesis is important, the above problems may be avoided by placement of buried dermal sutures using absorbable braided sutures. This method of wound closure allows for a precise reapproximation of wound edges, and may be enhanced by application of wound closure tapes to the surface of the wound. Intradermal absorbable sutures do not require removal. Use of skin tapes alone is only recommended for closure of the smallest superficial wounds. Larger wounds generate sufficient lateral tension that the epithelial edges either separate or curl upward under the tapes, resulting in inadequate epithelial apposition and poor cosmesis.

The development of octyl-cyanoacrylate tissue glues has shown new promise for the management of simple, linear wounds with viable skin edges. These new glues are less prone to brittleness and have superior burst-strength characteristics. Studies have shown them to be suitable for use in contaminated situations without significant risk of infection. When used in the above types of wounds, these glues appear to provide superb cosmetic results and result in significantly less trauma than sutured repair, particularly when used in pediatric patients.

Antibiotics

Antibiotics should be used only when there is an obvious wound infection. Most wounds are contaminated or colonized with bacteria. The presence of a host response constitutes an infection and justifies the use of antibiotics. Signs of infection to look for include erythema, cellulitis, swelling, and purulent discharge. Indiscriminate use of antibiotics should be avoided to

prevent emergence of multidrug-resistant bacteria.

Antibiotic treatment of acute wounds must be based on organisms suspected to be found within the infected wound and the patient's overall immune status. When a single specific organism is suspected, treatment may be commenced using a single antibiotic. Conversely, when multiple organisms are suspected, as with enteric contamination or when a patient's immune function is impaired by diabetes, chronic disease, or medication, treatment should commence with a broad-spectrum antibiotic or several agents in combination. Last, the location of the wound and the quality of tissue perfusion to that region will significantly impact wound performance after injury. Antibiotics can also be delivered topically as part of irrigations or dressings, although their efficacy is questionable.

Dressings

The main purpose of wound dressings is to provide the ideal environment for wound healing. The dressing should facilitate the major changes taking place during healing to produce an optimally healed wound. Although the ideal dressing is still not a clinical reality, technological advances are promising (Table 9-8).

Table 9-8 Desired Characteristics of Wound Dressings
Promote wound healing (maintain moist environment)
Conformability
Pain control
Odor control
Nonallergenic and nonirritating
Permeability to gas
Safety
Nontraumatic removal
Cost-effectiveness
Convenience

Covering a wound with a dressing mimics the barrier role of epithelium and prevents further damage. In addition, application of compression provides hemostasis and limits edema. Occlusion of a wound with dressing material helps healing by controlling the level of hydration and oxygen tension within the wound. It also allows transfer of gases and water vapor from the wound surface to the atmosphere. Occlusion affects both the dermis and epidermis, and it has been shown that exposed wounds are more inflamed and develop more necrosis than covered wounds. Occlusion also helps in dermal collagen synthesis and epithelial cell migration and limits tissue desiccation. As it may enhance bacterial growth, occlusion is contraindicated in infected and highly exudative wounds.

Dressings can be classified as primary or secondary. A primary dressing is placed directly on the wound and may provide absorption of fluids and prevent desiccation, infection, and adhesion of a secondary dressing. A secondary dressing is one that is placed on the primary dressing for further protection, absorption, compression, and occlusion. Many types of dressings exist and are designed to achieve certain clinically desired endpoints.

ABSORBENT DRESSINGS

Accumulation of wound fluid can lead to maceration and bacterial overgrowth. Ideally, the dressing should absorb without

getting soaked through, as this would permit bacteria from the outside to enter the wound. The dressing must be designed to match the exudative properties of the wound and may include cotton, wool, and sponge.

NONADHERENT DRESSINGS

Nonadherent dressings are impregnated with paraffin, petroleum jelly, or water-soluble jelly for use as nonadherent coverage. A secondary dressing must be placed on top to seal the edges and prevent desiccation and infection.

OCCLUSIVE AND SEMIOCCLUSIVE DRESSINGS

Occlusive and semiocclusive dressings provide a good environment for clean, minimally exudative wounds. These film dressings are waterproof and impervious to microbes, but permeable to water vapor and oxygen.

HYDROPHILIC AND HYDROPHOBIC DRESSINGS

Hydrophilic and hydrophobic dressings are components of a composite dressing. Hydrophilic dressing aids in absorption, whereas a hydrophobic dressing is waterproof and prevents absorption.

HYDROCOLLOID AND HYDROGEL DRESSINGS

Hydrocolloid and hydrogel dressings attempt to combine the benefits of occlusion and absorbency. Hydrocolloids and hydrogels form complex structures with water, and fluid absorption occurs with particle swelling, which aids in atraumatic removal of the dressing. Absorption of exudates by the hydrocolloid dressing leaves a yellowish-brown gelatinous mass after dressing removal that can be washed off. Hydrogel is a cross-linked polymer that has high water content. Hydrogels allow a high rate of evaporation without compromising wound hydration, which makes them useful in burn treatment.

ALGINATES

Alginates are derived from brown algae and contain long chains of polysaccharides containing mannuronic and glucuronic acid. The ratios of these sugars vary with the species of algae used, as well as the season of harvest. Processed as the calcium form, alginates turn into soluble sodium alginate through ion exchange in the presence of wound exudates. The polymers gel, swell, and absorb a great deal of fluid. Alginates are being used when there is skin loss, in open surgical wounds with medium exudation, and on full-thickness chronic wounds.

ABSORBABLE MATERIALS

Absorbable materials are mainly used within wounds as hemostats and include collagen, gelatin, oxidized cellulose, and oxidized regenerated cellulose.

MEDICATED DRESSINGS

Medicated dressings have long been used as a drug-delivery system. Agents delivered in the dressings include benzoyl peroxide, zinc oxide, neomycin, and bacitracin-zinc. These agents have been shown to increase epithelialization by 28%.

The type of dressing to be used depends on the amount of wound drainage. A nondraining wound can be covered with a semiocclusive dressing. Drainage of less than 1 to 2 mL/d may require a semiocclusive or absorbent nonadherent dressing. Moderately draining wounds (3 to 5 mL/d) can be dressed with a nonadherent primary layer plus an absorbent secondary layer plus an occlusive dressing to protect normal tissue. Heavily draining wounds (>5 mL/d) require a similar dressing to moderately draining wounds, but with the addition of a highly absorbent secondary layer.

MECHANICAL DEVICES

Mechanical therapy augments and improves on certain functions of dressings, in particular the absorption of exudates and control of odor. The vacuum-assisted closure system assists in wound closure by applying localized negative pressure to the surface and margins of the wound. The negative pressure therapy is applied to a special foam dressing cut to the dimensions of the wound and positioned in the wound cavity or over a flap or graft. The continuous negative pressure is very effective in removing exudates from the wound. This form of therapy has been found to be effective for chronic open wounds (diabetic ulcers and stages 3 and 4 pressure ulcers), acute and traumatic wounds,[107] flaps and grafts, and subacute wounds (i.e., dehisced incisions), although more randomized trials need to be carried out to confirm efficacy.

Skin Replacements

All wounds require coverage in order to prevent evaporative losses and infection and to provide an environment that promotes healing. Both acute and chronic wounds may demand use of skin replacement, and several options are available.

CONVENTIONAL SKIN GRAFTS

Skin grafts have long been used to treat both acute and chronic wounds. Split- or partial-thickness grafts consist of the epidermis plus part of the dermis, whereas full-thickness grafts retain the entire epidermis and dermis. Autologous grafts (autografts) are transplants from one site on the body to another; allogeneic grafts (allografts, homografts) are transplants from a living nonidentical donor or cadaver to the host; and xenogeneic grafts (heterografts) are taken from another species (e.g., porcine). Split-thickness grafts require less blood supply to restore skin function. The dermal component of full-thickness grafts lends mechanical strength and resists wound contraction better, resulting in improved cosmesis. Allogeneic and xenogeneic grafts require the availability of tissue, are subject to rejection, and may contain pathogens.

The use of skin grafts or bioengineered skin substitutes and other innovative treatments (e.g., topically applied growth factors, systemic agents, and gene therapy) cannot be effective unless the wound bed is adequately prepared. This may include débridement to remove necrotic or fibrinous tissue, control of edema, revascularization of the wound bed, decreasing the bacterial burden, and minimizing or eliminating exudate. Temporary placement of allografts or xenografts may be used to prepare the wound bed.

SKIN SUBSTITUTES

Originally devised to provide coverage of extensive wounds with limited availability of autografts, skin substitutes also have gained acceptance as natural dressings. Manufactured by tissue engineering, they combine novel materials with living cells to provide functional skin substitutes, providing a bridge between dressings and skin grafts.

Skin substitutes have theoretical advantages of being readily available, not requiring painful harvest, and they may be applied freely or with surgical suturing. In addition, they promote healing, either by stimulating host cytokine generation or by providing cells that may also produce growth factors locally. Their disadvantages include limited survival, high cost, and the need for multiple applications (Table 9-9). Allografting, albeit with a very thin graft, may at times be required to accomplish complete coverage.

Table 9-9 Desired Features of Tissue-Engineered Skin
Rapid re-establishment of functional skin (epidermis/dermis)
Receptive to body's own cells (e.g., rapid "take" and integration)

Graftable by a single, simple procedure
Graftable on chronic or acute wounds
Engraftment without use of extraordinary clinical intervention (i.e., immunosuppression)

A variety of skin substitutes are available, each with its own set of advantages and disadvantages; however, the ideal skin substitute has yet to be developed (Table 9-10). The development of newer composite substitutes, which provide both the dermal and epidermal components essential for permanent skin replacement, may represent an advance toward that goal. The acellular (e.g., native collagen or synthetic material) component acts as a scaffold, promotes cell migration and growth, and activates tissue regeneration and remodeling. The cellular elements re-establish lost tissue and associated function, synthesize extracellular matrix components, produce essential mediators such as cytokines and growth factors, and promote proliferation and migration.

Table 9-10 Advantages and Disadvantages of Various Bioengineered Skin Substitutes

Skin Substitute	Advantages	Disadvantages
Cultured allogeneic keratinocyte graft	No biopsy needed	Unstable
	"Off the shelf" availability	Does not prevent wound contracture
	Provides wound coverage	Inadequate cosmesis
	Promotes healing	Possibility of disease transmission
		Fragile
Bioengineered dermal replacement	Prevents contracture	Limited ability to drive re-epithelialization
	Good prep for graft application	Largely serves as temporary dressing
Cultured bilayer skin equivalent	More closely mimics normal anatomy	Cost
	Does not need secondary procedure	Short shelf life
	Easily handled	True engraftment questionable
	Can be sutured, meshed, etc.	

Cultured epithelial autografts (CEAs) represent expanded autologous or homologous keratinocytes. CEAs are expanded from a biopsy of the patient's own skin, will not be rejected, and can stimulate re-epithelialization as well as the growth of underlying connective tissue. Keratinocytes harvested from a biopsy roughly the size of a postage stamp are cultured with fibroblasts and growth factors and grown into sheets that can cover large areas and give the appearance of normal skin. Until the epithelial sheets are sufficiently expanded, the wound must be covered with an occlusive dressing or a temporary allograft or xenograft. The dermis regenerates very slowly, if at all, for full-thickness wounds, because the sheets are very fragile, difficult to work with, are susceptible to infection, and do not resist contracture well, leading to poor cosmetic results.

CEAs are available from cadavers, unrelated adult donors, or from neonatal foreskins. Fresh or cryopreserved cultured allogeneic keratinocytes can be left in place long enough to be superseded by multiplying endogenous skin cells because, unlike allografts containing epidermal Langerhans cells, they do not express major histocompatibility antigens. Cryopreserved CEAs are readily available "off the shelf," and provide growth factors that may aid healing. However, like autologous keratinocyte sheets, the grafts lack the strength provided by a dermal component and pose a risk of disease transmission.

Viable fibroblasts can be grown on bioabsorbable or nonbioabsorbable meshes to yield living dermal tissue that can act as a scaffold for epidermal growth. Fibroblasts stimulated by growth factors can produce type I collagen and glycosaminoglycans

(e.g., chondroitin sulfates), which adhere to the wound surface to permit epithelial cell migration, as well as adhesive ligands (e.g., the matrix protein fibronectin), which promote cell adhesion. This approach has the virtue of being less time-consuming and expensive than culturing keratinocyte sheets. There are a number of commercially available, bioengineered dermal replacements approved for use in burn treatment as well as other indications.

Bioengineered skin substitutes have evolved from keratinocyte monolayers to dermal equivalents to split-thickness products with a pseudoepidermis and, most recently, to products containing both epidermal and dermal components that resemble the three-dimensional structure and function of normal skin (see Table 9-10). Indicated for use with standard compression therapy in the treatment of venous insufficiency ulcers and for the treatment of neuropathic diabetic foot ulcers, these bilayered skin equivalents also are being used in a variety of wound care settings.

GROWTH FACTOR THERAPY

As discussed previously in the section Chronic Wounds, it is believed that nonhealing wounds result from insufficient or inadequate growth factors in the wound environment. A simplistic solution would be to flood the wound with single or multiple growth factors in order to "jump-start" healing and re-epithelialization. Although there is a large body of work demonstrating the effects of growth factors in animals, translation of these data into clinical practice has met with limited success. Growth factors for clinical use may be either recombinant or homologous/autologous. Autologous growth factors are harvested from the patient's own platelets, yielding an unpredictable combination and concentration of factors, which are then applied to the wound. This approach allows treatment with patient-specific factors at an apparently physiologic ratio of growth factor concentrations. Recombinant molecular biologic means permit the purification of high concentrations of individual growth factors. Current Food and Drug Administration–approved formulations, as well as those used experimentally, deliver concentrations approximately 10^3 times higher than those observed physiologically.

At present, only platelet-derived growth factor BB (PDGF-BB) is currently approved by the Food and Drug Administration for treatment of diabetic foot ulcers.[92] Application of recombinant human PDGF-BB in a gel suspension to these wounds increases the incidence of total healing and decreases healing time. Several other growth factors have been tested clinically and show some promise, but currently none are approved for use. A great deal more needs to be discovered about the concentration, temporal release, and receptor cell population before growth factor therapy is to make a consistent impact on wound healing.

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KEY POINTS

1. The following alterations are critical for malignant cancer growth: self-sufficiency of growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, potential for limitless replication, angiogenesis, and invasion and metastasis.

2. Understanding cancer biology is essential to successfully implement personalized cancer therapy.

3. Modern cancer therapy is multidisciplinary, involving coordinated care by surgeons, medical oncologists, radiation oncologists, reconstructive surgeons, pathologists, radiologists, and primary care physicians.

ONCOLOGY AND SURGICAL PRACTICE

As the population ages, oncology is becoming a larger portion of surgical practice. The surgeon often is responsible for the initial diagnosis and management of solid tumors. Knowledge of cancer epidemiology, etiology, staging, and natural history is required for initial patient assessment, as well as to determination of the optimal surgical therapy.

Modern cancer therapy is multidisciplinary, involving the coordinated care of patients by surgeons, medical oncologists, radiation oncologists, reconstructive surgeons, pathologists, radiologists, and primary care physicians. *Primary* (or *definitive*) *surgical therapy* refers to en bloc resection of tumor with adequate margins of normal tissues and regional lymph nodes as necessary. *Adjuvant therapy* refers to radiation therapy and systemic therapies, including chemotherapy, immunotherapy, hormonal therapy, and, increasingly, biologic therapy. The primary goal of surgical and radiation therapy is local and regional control. On the other hand, the primary goal of systemic therapy is systemic control by treatment of distant foci of subclinical disease to prevent distant recurrence. Surgeons must be familiar with adjuvant therapies to coordinate multidisciplinary care and to determine the best sequence of therapy.

Recent advances in molecular biology are revolutionizing medicine. Nowhere has basic biology had a greater and more immediate impact than in oncology. New information is being translated rapidly into clinical use, with the development of new prognostic and predictive markers and new biologic therapies. It is therefore essential that surgeons understand the principles of molecular oncology to appropriately interpret these new contributions and incorporate them into practice.

EPIDEMIOLOGY

Basic Principles of Cancer Epidemiology

The term *incidence* refers to the number of new cases occurring; incidence usually is expressed as the number of new cases per 100,000 persons per year. *Mortality* refers to the number of deaths occurring and is expressed as the number of deaths per 100,000 persons per year. Incidence and mortality data are usually available through cancer registries. Mortality data are also available as public records in many countries where deaths are registered as vital statistics, often with the cause of death. In areas where cancer registries do not exist, mortality data are used to extrapolate incidence rates. However, these numbers are likely to be less accurate than registry data, because the relationship between incidence and cause-specific death is likely to vary significantly among countries owing to the variation in health care delivery.

The incidence of cancer varies by geography. This is due in part to genetic differences and in part to differences in environmental and dietary exposures. Epidemiologic studies that monitor trends in cancer incidence and mortality have tremendously enhanced our understanding of the etiology of cancer. Furthermore, analysis of trends in cancer incidence and mortality allows us to monitor the effects of different preventive and screening measures, as well as the evolution of therapies for specific cancers.

The two types of epidemiologic studies that are conducted most often to investigate the etiology of cancer and the effect of prevention modalities are cohort studies and case-control studies. Cohort studies follow a group of people who initially do not have a disease over time and measure the rate of development of a disease. In cohort studies, a group that is exposed to a certain environmental factor or intervention usually is compared to a group that has not been exposed (e.g., smokers vs. nonsmokers). Case-control studies compare a group of patients affected with a disease to a group of individuals without the disease for a given exposure. The results are expressed in terms of an odds ratio, or relative risk. A relative risk <1 indicates a protective effect of the exposure, whereas a relative risk >1 indicates an increased risk of developing the disease with exposure.

Cancer Incidence and Mortality in the United States

In the year 2008, an estimated 1.44 million new cancer cases were diagnosed in the United States.[1] In addition, over a million cases of basal and squamous cell carcinomas of the skin, 54,020 cases of melanoma in situ, and 67,770 cases of carcinoma in situ of the breast were predicted.[1] Furthermore, an estimated 565,650 people were expected to die of cancer in the United States in the same year.[1] The estimated new cancer cases and deaths by cancer type are shown in Table 10-1.[1] The most common causes of cancer death in men are cancers of the lung and bronchus, prostate, and colon and rectum; in women, the most common cancers are of the lung and bronchus, breast, and colon and rectum (Fig. 10-1).[1]

Table 10-1 Estimated New Cancer Cases and Deaths, United States, 2007[a]

	Estimated New Cases Both Sexes	Estimated Deaths Both Sexes
All cancers	**1,444,920**	**559,650**
Oral cavity and pharynx	**34,360**	**7550**
Digestive system	**271,250**	**134,710**
Esophagus	15,560	13,940
Stomach	21,260	11,210
Small intestine	5640	1090
Colon and rectum	112,340	52,180
Anus, anal canal, and anorectum	4650	690
Liver and intrahepatic bile duct	19,160	16,780
Gallbladder and other biliary	9250	3250
Pancreas	37,170	33,370
Other digestive organs	4800	2200
Respiratory system	**229,400**	**164,840**
Larynx	11,300	3660
Lung and bronchus	213,380	160,390
Other respiratory organs	4720	790
Bones and joints	**2370**	**1330**
Soft tissue (including heart)	**9220**	**3560**
Skin (excluding basal and squamous)	**65,050**	**10,850**
Melanoma	59,940	8110
Other nonepithelial	5110	2740
Breast	**180,510**	**40,910**
Genital system	**306,380**	**55,740**
Uterine cervix	11,150	3670
Uterine corpus	39,080	7400
Ovary	22,430	15,280
Vulva	3490	880
Vagina and other genital, female	2140	790
Prostate	218,890	27,050
Testis	7920	380
Penis and other genital, male	1280	290
Urinary system	**120,400**	**27,340**
Urinary bladder	67,160	13,750
Kidney and renal pelvis	51,190	12,890
Ureter and other urinary organs	2050	700
Eye and orbit	**2340**	**220**
Brain and other nervous system	**20,500**	**12,740**
Endocrine system	**35,520**	**2320**
Thyroid	33,550	1530
Other endocrine	1970	790
Lymphoma	**71,380**	**19,730**

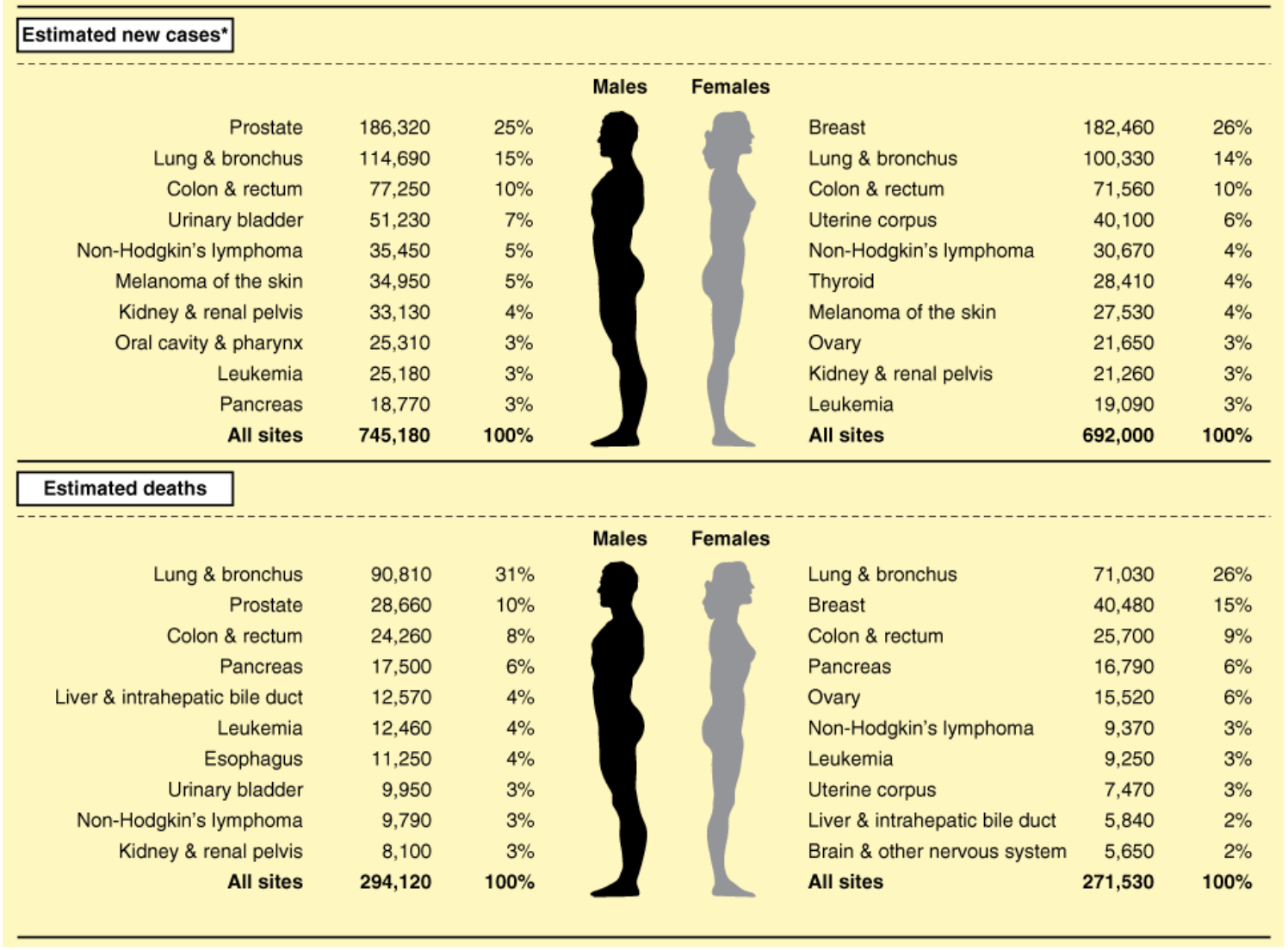
Multiple myeloma	**19,900**	**10,790**
Leukemia	**44,240**	**21,790**
Other and unspecified primary sites[b]	**32,100**	**45,230**

[a]Excludes basal and squamous cell skin cancers and in situ carcinomas except those of urinary bladder.

[b]More deaths than cases suggest lack of specificity in recording underlying causes of death on death certificate.

Source: Modified with permission from Jemal et al.[1]

Fig. 10-1.



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Ten leading cancer types with the estimated new cancer cases and deaths by sex in the United States, 2007. *Excludes basal and squamous cell skin cancers and in situ carcinomas except those of the urinary bladder. Estimates are rounded to the nearest 10.

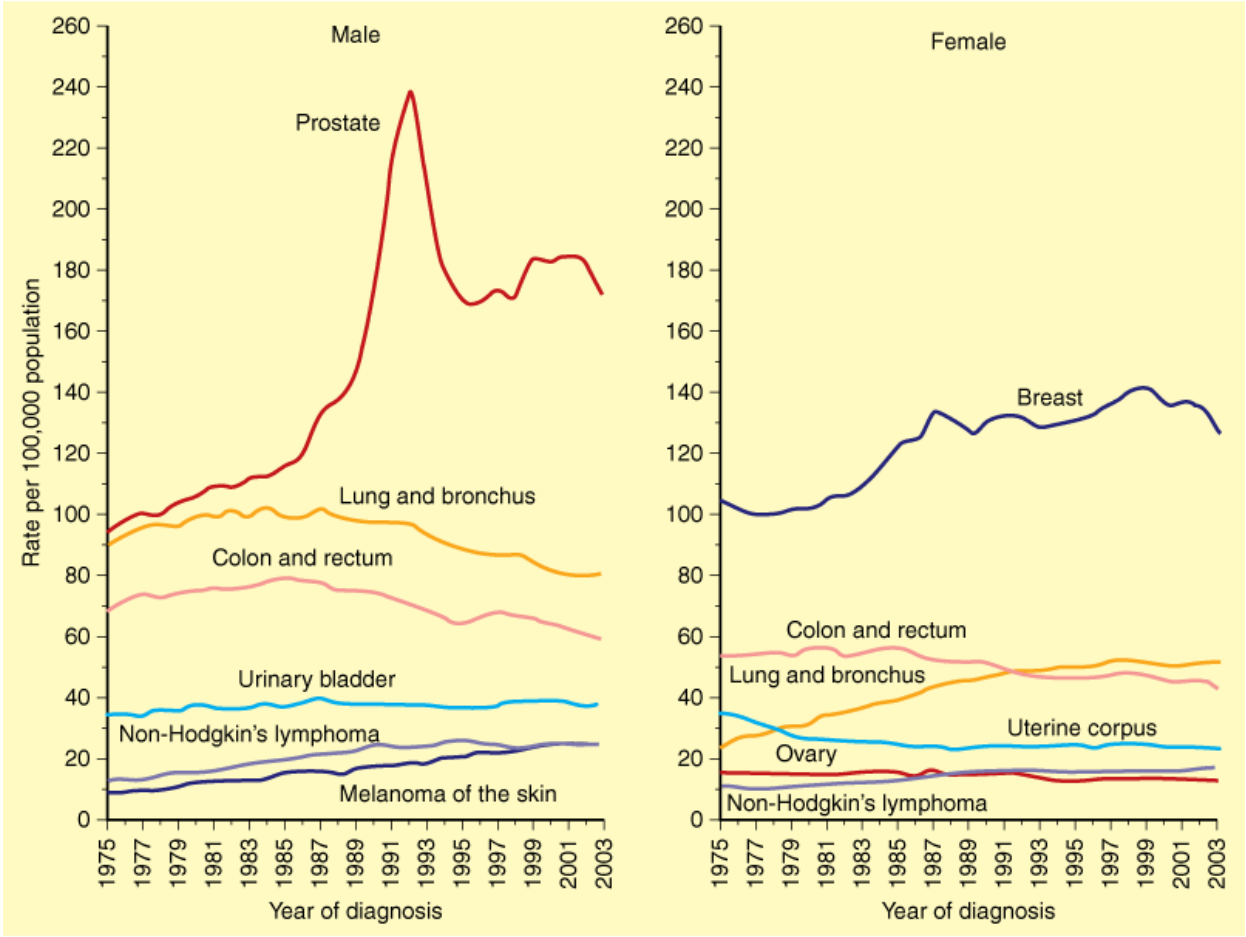
(Modified with permission from Jemal et al.[1])

Trends in Cancer Incidence and Mortality

Cancer deaths accounted for 23% of all deaths in the United States in 2005, second only to deaths from heart disease.[1] As the life expectancy of the human population increases because of reductions in other causes of death such as infections and cardiovascular disease, cancer is becoming the leading cause of death. Cancer is the leading cause of death among women aged 40 to 79 years and among men aged 60 to 79 years.[1]

Cancer incidence stabilized in males between 1995 and 2003 but has increased by 0.3% per year in females during the period from 1987 to 2003.[1] The annual age-adjusted cancer incidence rates among males and females for selected cancer types are shown in Fig. 10-2.[1] Prostate cancer rates rapidly increased and decreased between 1995 and 1998, but stabilized from 1998 to 2004. These trends are thought to be attributable to increased use of prostate-specific antigen (PSA) screening.[1] Age-adjusted incidence rate of breast cancer started to decrease from 2001 to 2004.[2] This decrease in breast cancer incidence has at least temporally been associated with the first report of the Women's Health Initiative, which documented an increased risk of coronary artery disease and breast cancer with the use of hormone replacement therapy; this was followed by a drop in the use of hormone replacement therapy by postmenopausal women in the United States.[2]

Fig. 10-2.



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Annual age-adjusted cancer incidence rates among males and females for selected cancer types, United States, 1975 to 2003. Rates are age adjusted to the U.S. standard population.

(Modified with permission from Jemal et al.[1])

From 1993 to 2003, for all cancer types combined, cancer death rates decreased by 1.6% per year in males and by 0.8% per year in females. The 5-year survival rates for selected cancers are listed in Table 10-2.[1] Mortality for cancer at all four major sites has continued to decrease except for female lung cancer, for which rates increased by 0.3% per year from 1995 to 2003. The decrease in lung cancer death rates in men is thought to be due to a decrease in tobacco use, whereas the decreases in death rates from breast, colorectal cancer, and prostate cancer reflect advances in early detection and treatment.

Table 10-2 Five-Year Relative Survival Rates Adjusted to Normal Life Expectancy by Year of Diagnosis, United States, 1975–2002

	Relative 5-Year Survival Rates (%)		
Cancer Type	**1975–1977**	**1984–1986**	**1996–2002**
All cancers	50	53	66
Brain	24	29	34

Breast (female)	75	79	89
Uterine cervix	70	68	73
Colon	51	59	65
Uterine corpus	87	83	84
Esophagus	5	10	16
Hodgkin's disease	73	79	86
Kidney	51	56	66
Larynx	66	66	65
Leukemia	35	42	49
Liver	4	6	10
Lung and bronchus	13	13	16
Melanoma of the skin	82	86	92
Multiple myeloma	26	29	33
Non-Hodgkin's lymphoma	48	53	63
Oral cavity	53	55	60
Ovary	37	40	45
Pancreas	2	3	5
Prostate	69	76	100
Rectum	49	57	66
Stomach	16	18	24
Testis	83	93	96
Thyroid	93	94	97
Urinary bladder	73	78	82

Source: Modified with permission from Jemal et al.[1]

Global Statistics on Cancer Incidence

It has been estimated that there were a total of 10.9 million new cancer cases around the world in 2002.[3] Lung cancer is the leading cancer in the world, accounting for 1.35 million new cases and 1.15 million deaths per year.[3] Breast cancer is now the second most common cancer (1.15 million cases per year) and the fifth most common cause of cancer death, after gastric cancer (934,000 cases, 700,000 deaths), colorectal cancer (1.03 million cases, 529,000 deaths), and liver cancer (626,000 cases, 598,000 deaths).[3]

STOMACH CANCER

The incidence of stomach cancer varies significantly among different regions of the world. The age-adjusted incidence is highest in Japan (62.1 per 100,000 men, 26.1 per 100,000 women). In comparison, the rates are much lower in North America (7.4 per 100,000 men, 3.4 per 100,000 women) and in northern and western Africa (4.4 to 3.4 per 100,000 men, 2.5 to 3.6 per 100,000 women).[3] The difference in risk by country is presumed to be primarily due to differences in dietary factors. The risk is increased by high consumption of preserved salted foods such as meats and pickles, and decreased by high intake of fruits and vegetables.[3] There also is some international variation in the incidence of infection with *Helicobacter pylori,* which is known to play a major role in gastric cancer development.[3] Fortunately, a steady decline is being observed in the incidence and mortality rates of gastric cancer. This may be related to improvements in preservation and storage of foods as well as due to changes in the prevalence of *H. pylori.*[3]

BREAST CANCER

The incidence of breast cancer is high in all of the most highly developed regions except Japan, including the United States and Canada, Australia, and Northern and Western Europe, ranging from 82.5 to 99.4 per 100,000 women per year.[3]

In comparison, the rates are relatively low (<30 per 100,000 women) in most of Africa (except South Africa) and Asia. The lowest incidence is in Central Africa (16.5 per 100,000). Although breast cancer has been linked to cancer susceptibility genes, mutations in these genes account for only 5 to 10% of breast tumors, which suggests that the wide geographic variations in breast cancer incidence are not due to geographic variations in the prevalence of these genes. Most of the differences, therefore, are attributed to differences in reproductive factors, diet, alcohol, obesity, physical activity, and other environmental differences. Indeed, breast cancer risk increases significantly in females who have migrated from Asia to America.[3] Overall, the incidence of breast cancer is rising in most countries.

COLON AND RECTAL CANCER

There is a 25-fold variation in colon cancer incidence worldwide.[3] The incidence of colon and rectal cancer is higher in developed countries than in developing countries. The incidence rates are highest in North America, Australia and New Zealand, and Western Europe, and especially in Japanese men.[3] In contrast, the incidence is relatively low in North Africa, South America, and eastern, southeastern, and western Asia. These geographic differences are thought to reflect environmental exposures and are presumed to be related mainly to dietary differences in consumption of animal fat, meat, and fiber.[3]

LIVER CANCER

In contrast to colon cancers, 82% of liver cancers occur in developing countries.[2] The incidence of liver cancer is especially high in China (37.9 per 100,000 men), whereas it is relatively low in North and South America and Europe (2.6 to 6.2 per 100,000 men).[2] Worldwide, the major risk factors for liver cancer are infection with hepatitis B and C viruses and consumption of foods contaminated with aflatoxin. Hepatitis B immunization in children has recently been shown to reduce the incidence of liver cancer.[3]

PROSTATE CANCER

The incidence of prostate cancer is dramatically higher in North America (119.9 per 100,000 men) than in China, Japan, and the rest of Asia (1.6 to 12.6 per 100,000).[3] A considerable part of the international differences in prostate cancer incidence is thought to reflect differences in diagnostic practices. As previously mentioned, the introduction of PSA screening has led to a significant increase in the diagnosis of prostate cancer in the United States (see Fig. 10-2).[1]

Global Statistics on Cancer Mortality

The mortality rates for different cancers also vary significantly among countries. This is attributable not only to variations in incidence but also to variations in survival after a cancer diagnosis. The survival rates are influenced by treatment patterns as well as by variations in cancer screening practices, which affect the stage of cancer at diagnosis. For example, the 5-year survival rate for stomach cancer is much higher in Japan, where the cancer incidence is high enough to warrant mass screening, which is presumed to lead to earlier diagnosis. In the case of prostate cancer, on the other hand, the mortality rates diverge much less than the incidence rates among countries. Survival rates for prostate cancer are much higher in North America than in developing countries.[3] It is possible that the extensive screening practices in the United States allow discovery of cancers at an earlier, more curable stage; however, it is also possible that this screening leads to discovery of more latent, less biologically aggressive cancers, which may not have caused death even if they had not been identified.

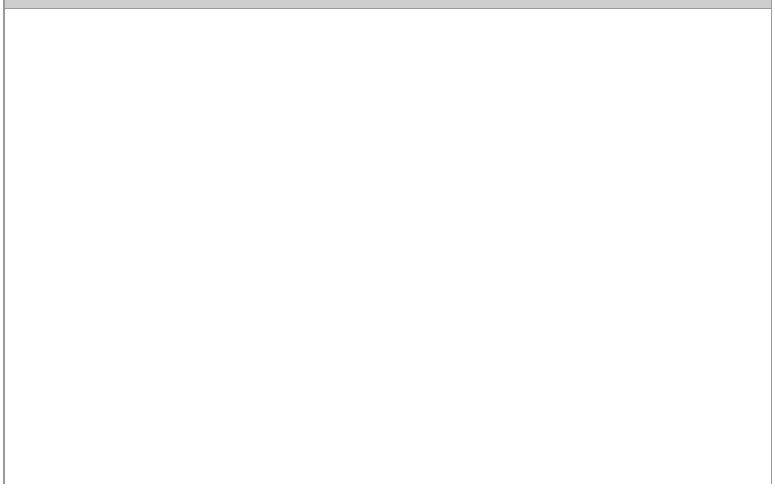
In summary, the incidence rates of many common cancers vary widely by geography. This is due in part to genetic differences, including racial and ethnic differences. It is due also in part to differences in environmental and dietary exposures, factors that can potentially be altered. Therefore, establishment of regional and international databases is critical to improving our understanding of the etiology of cancer and will ultimately assist in the initiation of targeted strategies for global cancer prevention. Furthermore, the monitoring of cancer mortality rates and 5-year cancer-specific survival rates will identify regions where there are inequities of health care, so that access to health care can be facilitated and guidelines for treatment can be established.

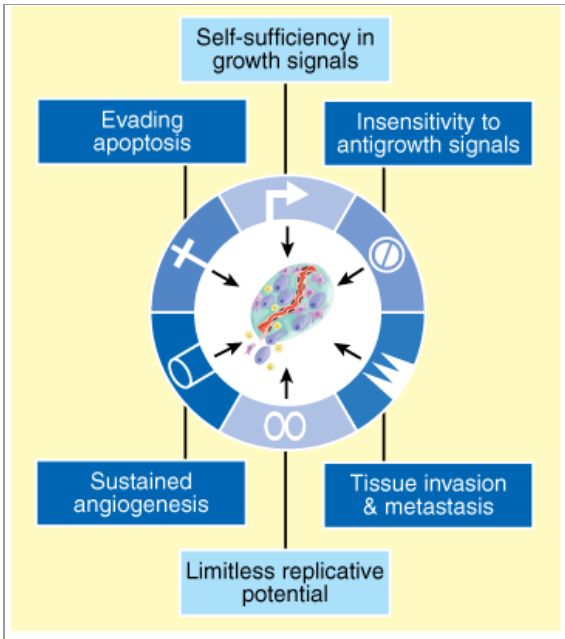
CANCER BIOLOGY

Hallmarks of Cancer

Although there are >100 types of cancer, it has been proposed that there are six essential alterations in cell physiology that dictate malignant growth: self-sufficiency of growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis (programmed cell death), potential for limitless replication, angiogenesis, and invasion and metastasis (Fig. 10-3).[4]

Fig. 10-3.





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Acquired capabilities of cancer.

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Cell Proliferation and Transformation

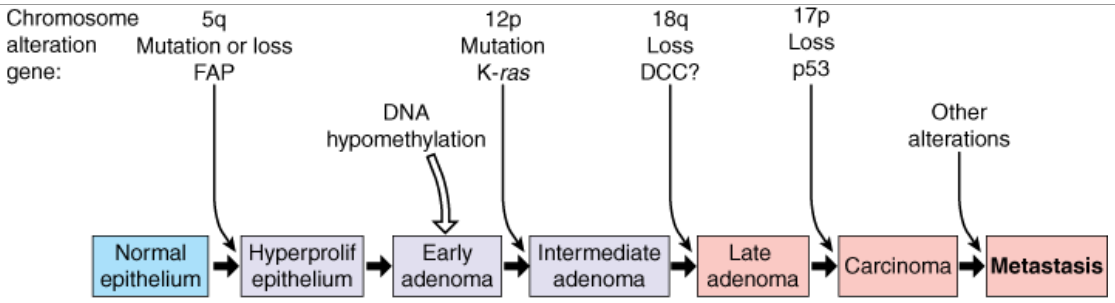
In normal cells, cell growth and proliferation are under strict control. In cancer cells, cells become unresponsive to normal growth controls, which leads to uncontrolled growth and proliferation. Human cells require several genetic changes for neoplastic transformation. Cell type–specific differences also exist for tumorigenic transformation. Abnormally proliferating, transformed cells outgrow normal cells in the culture dish (i.e., in vitro) and commonly display several abnormal characteristics.[5] These include loss of contact inhibition (i.e., cells continue to proliferate after a confluent monolayer is formed); an altered appearance and poor adherence to other cells or to the substratum; loss of anchorage dependence for growth; immortalization; and gain of tumorigenicity (i.e., the ability to give rise to tumors when injected into an appropriate host).

Cancer Initiation

Tumorigenesis is proposed to have three steps: initiation, promotion, and progression. Initiating events such as gain of function of genes known as *oncogenes* or loss of function of genes known as *tumor-suppressor genes* may lead a single cell to acquire a distinct growth advantage. Although tumors usually arise from a single cell or clone, it is thought that sometimes not a single cell but rather a large number of cells in a target organ may have undergone the initiating genetic event; thus many normal-appearing cells may have an elevated malignant potential. This is referred to as a *field effect.* The initiating events are usually genetic and occur as deletions of tumor-suppressor genes or amplification of oncogenes. Subsequent events can lead to accumulations of additional deleterious mutations in the clone.

Cancer is thought to be a disease of clonal progression as tumors arise from a single cell and accumulate mutations that confer on the tumor an increasingly aggressive behavior. Most tumors go through a progression from benign lesions to in situ tumors to invasive cancers (e.g., atypical ductal hyperplasia to ductal carcinoma in situ to invasive ductal carcinoma of the breast). Fearon and Vogelstein proposed the model for colorectal tumorigenesis presented in Fig. 10-4.[6] Colorectal tumors arise from the mutational activation of oncogenes coupled with mutational inactivation of tumor-suppressor genes, the latter being the predominant change.[6] Mutations in at least four or five genes are required for formation of a malignant tumor, whereas fewer changes suffice for formation of a benign tumor. Although genetic mutations often occur in a preferred sequence, a tumor's biologic properties are determined by the total accumulation of its genetic changes.

Fig. 10-4.



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A genetic model for colorectal tumorigenesis. Tumorigenesis proceeds through a series of genetic alterations involving oncogenes and tumor-suppressor genes. In general, the three stages of adenomas represent tumors of increasing size, dysplasia, and villous content. Individuals with familial adenomatous polyposis (FAP) inherit a mutation on chromosome arm 5q. In tumors arising in individuals without polyposis, the same region may be lost or mutated at a relatively early stage of tumorigenesis. A *ras* gene mutation (usually K-*ras*) occurs in one cell of a pre-existing small adenoma which, through clonal expansion, produces a larger and more dysplastic tumor. The chromosome arms most frequently deleted include 5q, 17p, and 18q. Allelic deletions of chromosome arms 17p and 18q usually occur at a later stage of tumorigenesis than do deletions of chromosome arm 5q or *ras* gene mutations. The order of these changes varies, however, and accumulation of these changes, rather than their order of appearance, seems most important. Tumors continue to progress once carcinomas have formed, and the accumulated chromosomal alterations correlate with the ability of the carcinomas to metastasize and cause death. DCC = deleted in colorectal cancer gene.

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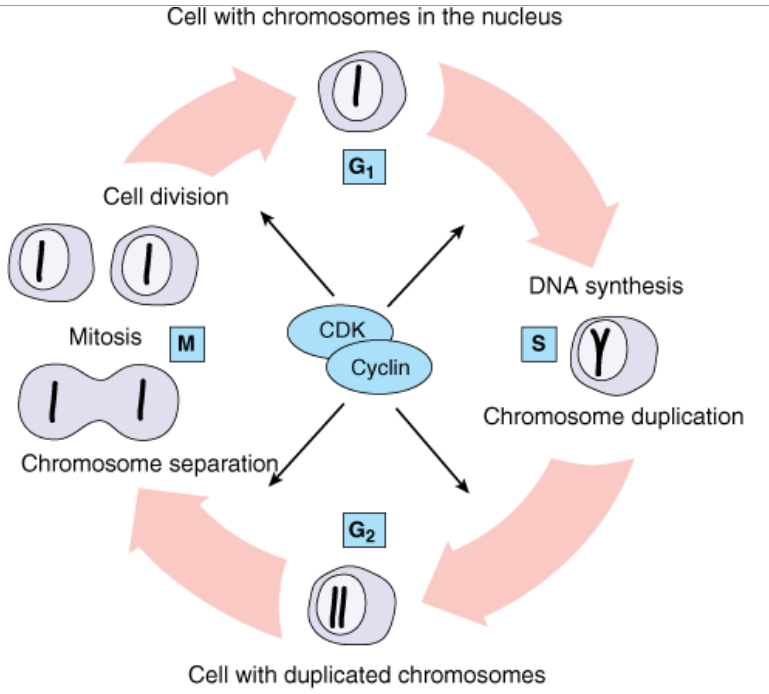
Gene expression is a multistep process that starts from transcription of a gene into messenger RNA (mRNA) and then translation of this sequence into the functional protein. There are several controls at each level. In addition to alterations at the genome level (e.g., amplifications of a gene), alterations at the transcription level (e.g., methylation of the DNA leading to transcriptional silencing) or at the level of mRNA processing, mRNA stability, mRNA translation, or protein stability all can alter the levels of critical proteins and thus contribute to tumorigenesis. Alternatively, changes in the genomic sequence can lead to a mutated product with altered function.

Cell-Cycle Dysregulation in Cancer

The proliferative advantage of tumor cells is a result of their ability to bypass quiescence. Cancer cells often show alterations in signal transduction pathways that lead to proliferation in response to external signals. Mutations or alterations in the expression of cell-cycle proteins, growth factors, growth factor receptors, intracellular signal transduction proteins, and nuclear transcription factors all can lead to disturbance of the basic regulatory mechanisms that control the cell cycle, allowing unregulated cell growth and proliferation.

The cell cycle is divided into four phases (Fig. 10-5).[7] During the synthetic or S phase, the cell generates a single copy of its genetic material, whereas in the mitotic or M phase, the cellular components are partitioned between two daughter cells. The G_1 and G_2 phases represent gap phases during which the cells prepare themselves for completion of the S and M phases, respectively. When cells cease proliferation, they exit the cell cycle and enter the quiescent state referred to as G_0. In human tumor cell-cycle regulators like INK4A, INK4B, and KIP1 are frequently mutated or altered in expression. These alterations underscore the importance of cell-cycle regulation in the prevention of human cancers.

Fig. 10-5.



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Schematic representation of the phases of the cell cycle. Mitogenic growth factors can drive a quiescent cell from G_0 into the cell cycle. Once the cell cycle passes beyond the restriction point, mitogens are no longer required for progression into and through S phase. The DNA is replicated in S phase, and the chromosomes are condensed and segregated in mitosis. In early G_1 phase, certain signals can drive a cell to exit the cell cycle and enter a quiescent phase. Cell-cycle checkpoints have been identified in G_1, S, G_2, and M phases. CDK = cyclin-dependent kinase.

(Adapted from Kastan et al.[7])

Oncogenes

Normal cellular genes that contribute to cancer when abnormal are called *oncogenes.* The normal counterpart of such a gene is referred to as a *proto-oncogene.* Oncogenes are usually designated by three-letter abbreviations, such as *myc* or *ras.* Oncogenes are further designated by the prefix "v-" for virus or "c-" for cell or chromosome, corresponding to the origin of the oncogene when it was first detected. Proto-oncogenes can be activated (show increased activity) or overexpressed (expressed at increased protein levels) by translocation (e.g., *abl*), promoter insertion (e.g., c-*myc*), mutation (e.g., *ras*), or amplification (e.g., *HER-2/neu*). More than 100 oncogenes have been identified.

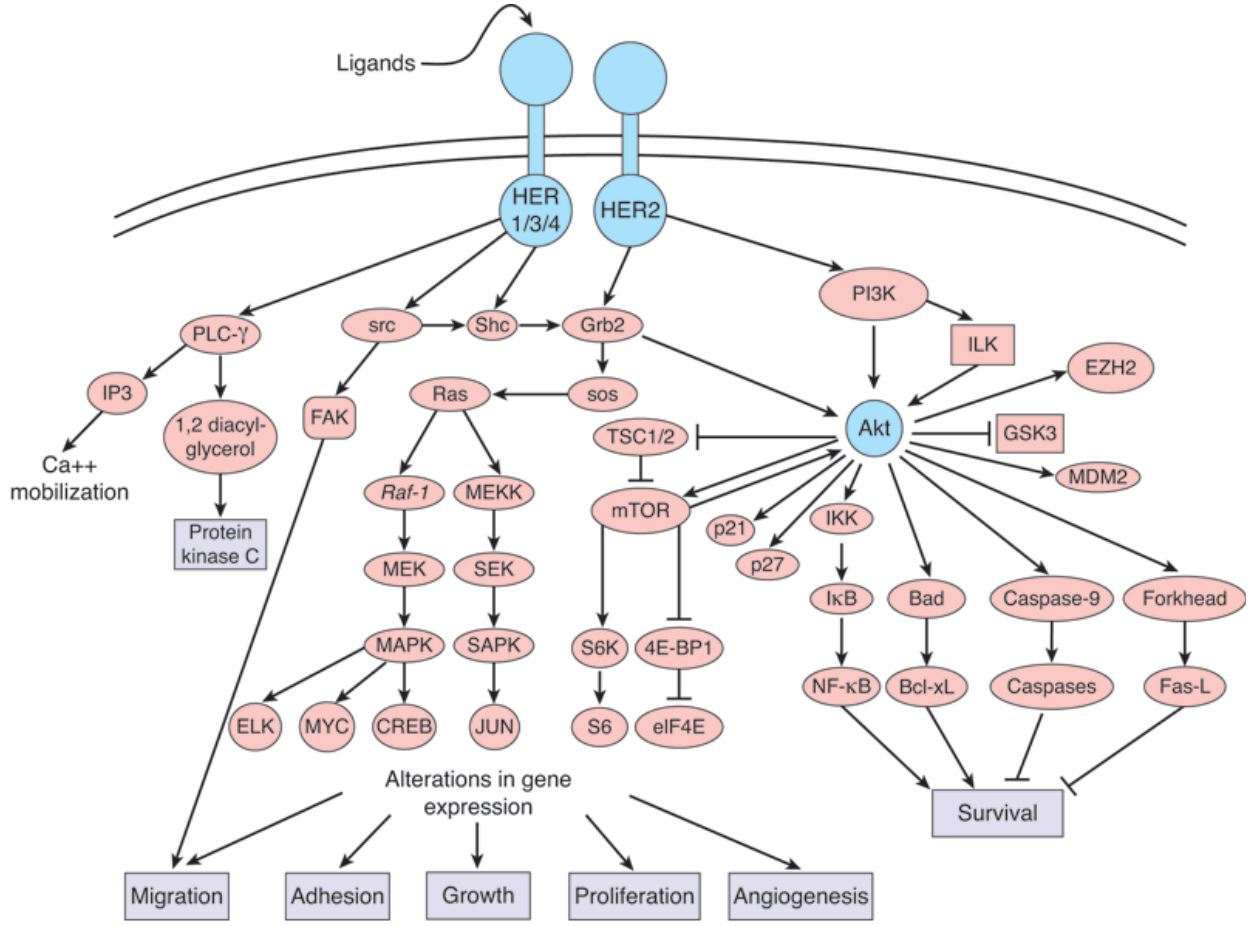
Oncogenes may be growth factors (e.g., platelet-derived growth factor), growth factor receptors (e.g., HER2), intracellular signal transduction molecules (e.g., *ras*), nuclear transcription factors (e.g., c-*myc*), or other molecules involved in the regulation of cell growth and proliferation. Growth factors are ubiquitous proteins that are produced and secreted by cells locally and that stimulate cell proliferation by binding specific cell-surface receptors on the same cells (autocrine stimulation) or on neighboring cells (paracrine stimulation). Persistent overexpression of growth factors can lead to uncontrolled autostimulation and neoplastic transformation. Alternatively, growth factor receptors can be aberrantly activated (turned on) through mutations or overexpressed (continually presenting cells with growth-stimulatory signals, even in the absence of growth factors), which leads cells to respond as if growth factor levels are altered. The growth-stimulating effect of growth factors and other mitogens is mediated through postreceptor signal transduction molecules. These molecules mediate the passage of growth signals from the outside to the inside of the cell and then to the cell nucleus, initiating the cell cycle and DNA transcription. Aberrant activation or expression of cell-signaling molecules, cell-cycle molecules, or transcription factors may play an important role in neoplastic transformation. Two of the best-studied oncogenes, *HER2* and *ras,* are discussed here.

HER2

Protein tyrosine kinases account for a large portion of known oncogenes. HER2, also known as *neu* or c-*erb*B-2, is a member of the epidermal growth factor receptor (EGFR) family and is one of the best-characterized tyrosine kinases. Unlike other receptor tyrosine kinases, HER-2/*neu* does not have a direct soluble ligand. It plays a key role in signaling, however, because it is the preferred partner in heterodimer formation with all the other EGFR family members (EGFR/c-*erb*B-1, HER2/c-*erb*B-3, and HER3/c-*erb*B-4), which bind at least 30 ligands, including epidermal growth factor (EGF), transforming growth factor α (TGFα), heparin-binding EGF-like growth factor, amphiregulin, and heregulin.[8] Heterodimerization with HER2 potentiates recycling of receptors rather than degradation, enhances signal potency and duration, increases affinity for ligands, and increases catalytic activity.[8]

HER2 can interact with different members of the HER family and activate mitogenic and antiapoptotic pathways (Fig. 10-6).[9] The specificity and potency of the intracellular signals are affected by the identity of the ligand, the composition of the receptors, and the phosphotyrosine-binding proteins associated with the erbB molecules. The Ras- and Shc-activated mitogen-activated protein kinase (MAPK) pathway is a target of all erbB ligands, which increase the transcriptional activity of early-response genes such as c-*myc,* c-*fos,* and c-*jun.*[10] MAPK-independent pathways such as the phosphoinositide-3 kinase (PI3K) pathway also are activated by most erbB dimers, although the potency and kinetics of activation may differ. Stimulation of the PI3K pathway through *HER2* signaling also can lead to activation of survival molecule Akt, which suppresses apoptosis through multiple mechanisms.

Fig. 10-6.



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Selected HER2 signaling pathways. HER2 can interact with different members of the HER family and activate mitogenic and antiapoptotic pathways. 4E-BP1= eIF4E binding protein 1; CREB = cyclic adenosine monophosphate element binding; eIF4E = eukaryotic initiation factor 4E; EZH = enhancer of zeste homolog; FAK = focal adhesion kinase; Fas-L = Fas ligand; GSK3 = glycogen synthase kinase-3; HER = human epidermal growth receptor; IKK = IκB kinase; ILK= integrin-linked kinase; IP3 = inositol triphosphate; IκB = inhibitor of NF-κB; MAPK = mitogen-activated protein kinase; MDM2 = mouse double minute 2 homologue; MEK = mitogen-activated protein/extracellular signal regulated kinase kinase; MEKK = MEK kinase; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor κB; PI3K = phosphoinositide-3 kinase; PLC-γ = phospholipase Cγ; SAPK = stress-activated protein kinase; SEK = SAPK/extracellular signal regulated kinase kinase; TSC = tuberous sclerosis complex.

(Modified with permission from Meric-Bernstam et al.[9])

The mutant rat *neu* gene was first recognized as an oncogene in neuroblastomas from carcinogen-treated rats.[11] The HER2 gene is frequently amplified and the protein overexpressed in many cancers, including breast, ovarian, lung, gastric, and oral cancers. Overexpression of HER2 results in ligand-independent activation of HER2 kinase, which leads to mitogenic signaling. HER2 overexpression is associated with increased cell proliferation and anchorage-independent growth as well as resistance to proapoptotic stimuli. Further, overexpression of HER2 increases cell migration and upregulates the activities of matrix metalloproteinases (MMPs) and in vitro invasiveness. In animal models, HER2 increases tumorigenicity, angiogenesis, and metastasis. These results all suggest that HER2 plays a key role in cancer biology.

RAS

The *ras* family of genes encodes small guanosine triphosphate (GTP)–binding proteins that regulate several cellular processes. The H- and K-*ras* genes were

first identified as the cellular counterparts of the oncogenes of the Harvey and Kirsten rat sarcoma viruses, whereas N-*ras* was isolated from a neuroblastoma.[12] The N-, H-, and K-*ras* genes are located on chromosomes 1, 11, and 12, respectively, and encode for 21-kDa proteins that are nearly identical in amino acid sequence but appear not to be redundant in function.[12]

ras cycles between active GTP-bound and inactive guanosine diphosphate–bound states. Various extracellular stimuli can promote ras activation, including various receptor and nonreceptor tyrosine kinases, G protein–coupled receptors, and integrins.[13] Guanine nucleotide exchange factors stimulate formation of ras-GTP. ras has an intrinsic ability to hydrolyze GTP, but this hydrolysis is slow. Guanosine triphosphatase–activating proteins (GAPs) stimulate hydrolysis of the bound GTP to return ras to its inactive form. Mutations of ras at amino acid positions 12, 13, or 61 may render ras insensitive to GAPs, which results in mutant proteins that are persistently activated. Approximately 20% of all tumors have activating mutations in one of the ras genes.[14] The frequency of ras mutations varies widely by cancer type (e.g., 90% of pancreatic cancers, but <5% of breast cancers).[12,14] Tumors that lack *ras* mutations, however, may undergo activation of the *ras* signaling pathway by other mechanisms, such as growth factor receptor activation, loss of GAP, or activation of *ras* effectors.[14]

The Ras proteins require posttranslational modification by farnesyltransferase. After association with the intracellular membrane via its farnesyl group, GTP-bound Ras then binds and activates several downstream pathways. The best-characterized downstream signaling pathway is that initiated by the serine-threonine kinase Raf. Activated Raf phosphorylates and activates MAPK1 and MAPK2 (MEK1 and MEK2).[14] MEK1 and MEK2 phosphorylate and activate the MAPKs extracellular signal regulated kinases 1 and 2 (ERK1 and ERK2). ERK phosphorylates the ETS (E26 transformation-specific) family of transcriptional factors; this leads to expression of cell-cycle regulatory proteins such as D-type cyclins, which enables the cell to progress through the G_1 phase of the cell cycle. Constitutive activation of Raf is common in some tumors such as non–small cell lung cancer, renal cell carcinoma, and hepatocellular cancer.[15] B-raf itself can have activating mutations in melanoma, sporadic colorectal cancer, and papillary thyroid cancer.[15] A second pathway activated by Ras is PI3K, an important mediator of the survival signaling. A third pathway is the Ras-related Ral proteins, which along with the PI3K/Akt pathway contribute to inhibition of the forkhead transcription factors that promote cell-cycle arrest by inducing p27. Further, Ras also associates with phospholipase Cε, which links Ras to activation of protein kinase C and calcium mobilization. Together, the Ras signaling pathways promote malignant transformation by increasing proliferation, which is accomplished by inducing cell-cycle regulators such as cyclin D1, which suppresses cell-cycle inhibitors like p27, and enhancing survival signaling through the PI3K/Akt pathway.

Alterations in Apoptosis in Cancer Cells

Apoptosis is a genetically regulated program to dispose of cells. Cancer cells must avoid apoptosis if tumors are to arise. The growth of a tumor mass is dependent not only on an increase in proliferation of tumor cells but also on a decrease in their apoptotic rate. Apoptosis is distinguished from necrosis because it leads to several characteristic changes. In early apoptosis, the changes in membrane composition lead to extracellular exposure of phosphatidylserine residues, which avidly bind annexin, a characteristic that is used to discriminate apoptotic cells in laboratory studies. Late in apoptosis there are characteristic changes in nuclear morphology, such as chromatin condensation, nuclear fragmentation, and DNA laddering, as well as membrane blebbing. Apoptotic cells are then engulfed and degraded by phagocytic cells. The effectors of apoptosis are a family of proteases called *caspases* (cysteine-dependent and aspartate-directed proteases). The initiator caspases (e.g., 8, 9, and 10), which are upstream, cleave the downstream executioner caspases (e.g., 3, 6, and 7) that carry out the destructive functions of apoptosis.

Two principal molecular pathways signal apoptosis by cleaving the initiator caspases with the potential for crosstalk: the mitochondrial pathway and the death receptor pathway. In the mitochondrial (or intrinsic) pathway, death results from the release of cytochrome c from the mitochondria. Cytochrome c, procaspase 9, and apoptotic protease activating factor 1 (Apaf-1) form an enzyme complex, referred to as the *apoptosome,* that activates the effector caspases. In addition to these proteins, the mitochondria contain other proapoptotic proteins such as SMAC/DIABLO. The mitochondrial pathway can be stimulated by many factors, including DNA damage, reactive oxygen species, or the withdrawal of survival factors. The permeability of the mitochondrial membrane determines whether the apoptotic pathway will proceed. The Bcl-2 family of regulatory proteins includes proapoptotic proteins (e.g., Bax, Bad, and Bak) and antiapoptotic proteins (e.g., Bcl-2 and Bcl-xL). The activity of the Bcl-2 proteins is centered on the mitochondria, where they regulate membrane permeability. Growth factors promote survival signaling through the PI3K/Akt pathway, which phosphorylates and inactivates proapoptotic Bad. In contrast, growth factor withdrawal may promote apoptosis through signaling by unphosphorylated Bad. The heat shock proteins, including Hsp70 and Hsp27, are also involved in inhibition of downstream apoptotic pathways by blocking formation of the apoptosome complex and inhibiting release of cytochrome c from the mitochondria.[16]

The second principal apoptotic pathway is the death receptor pathway, sometimes referred to as the *extrinsic pathway.* Cell-surface death receptors include Fas/APO1/CD95, tumor necrosis factor receptor 1, and KILL-ER/DR5, which bind their ligands Fas-L, tumor necrosis factor (TNF), and TNF-related apoptosis-inducing ligand (TRAIL), respectively. When the receptors are bound by their ligands, they form a death-inducing signaling complex (DISC). At the DISC, procaspase 8 and procaspase 10 are cleaved, yielding active initiator caspases.[17] The death receptor pathway may be regulated at the cell surface by the expression of "decoy" receptors for Fas (DcR3) and TRAIL (TRID and TRUNDD). The decoy receptors are closely related to the death receptors but lack a functional death domain; therefore, they bind death ligands but do not transmit a death signal. Another regulatory group is the FADD-like interleukin-1 protease-inhibitory proteins (FLIPs). FLIPs have homology to caspase 8; they bind to the DISC and inhibit the activation of caspase 8. Finally, inhibitors of

apoptosis proteins (IAPs) block caspase 3 activation and have the ability to regulate both the death receptor and the mitochondrial pathway.

In human cancers, aberrations in the apoptotic program include increased expression of Fas and TRAIL decoy receptors; increased expression of antiapoptotic Bcl-2; increased expression of the IAP-related protein survivin; increased expression of c-FLIP; mutations or downregulation of proapoptotic Bax, caspase 8, APAF1, XAF1, and death receptors CD95, TRAIL-R1, and TRAIL-R2; alterations of the p53 pathway; overexpression of growth factors and growth factor receptors; and activation of the PI3K/Akt survival pathway.[17]

Autophagy in Cancer Cells

Autophagy (self-eating) is a major cellular pathway for protein and organelle turnover. This process helps maintain a balance between anabolism and catabolism for normal cell growth and development. Inability to activate autophagy in response to nutrient deprivation, or constitutive activation of autophagy in response to stress, can lead to cell death; thus autophagy is sometimes referred to as a second form of programmed cell death. Autophagy plays an essential role during starvation, cellular differentiation, cell death, and aging. Autophagy is also involved in the elimination of cancer cells by triggering a nonapoptotic cell death program, which suggests a negative role in tumor development. Mouse models that are heterozygotes for the beclin 1 gene, an important gene for autophagy, have altered autophagic response and show a high incidence of spontaneous tumors, which establishes a role for autophagy in tumor suppression.[18] This also suggests that mutations in other genes operating in this pathway may contribute to tumor formation through deregulation of autophagy. However, autophagy also acts as a stress response mechanism to protect cancer cells from low nutrient supply or therapeutic insults. Studies on the molecular determinants of autophagy are ongoing to determine whether autophagy can be modulated for therapeutic purposes.

Cancer Invasion

A feature of malignant cells is their ability to invade the surrounding normal tissue. Tumors in which the malignant cells appear to lie exclusively above the basement membrane are referred to as *in situ cancer,* whereas tumors in which the malignant cells are demonstrated to breach the basement membrane, penetrating into surrounding stroma, are termed *invasive cancer.* The ability to invade involves changes in adhesion, initiation of motility, and proteolysis of the extracellular matrix (ECM).

Cell-to-cell adhesion in normal cells involves interactions between cell-surface proteins. Calcium adhesion molecules of the cadherin family (E-cadherin, P-cadherin, and N-cadherin) are thought to enhance the cells' ability to bind to one another and suppress invasion. Migration occurs when cancer cells penetrate and attach to the basal matrix of the tissue being invaded; this allows the cancer cell to pull itself forward within the tissue. Attachment to glycoproteins of the ECM such as fibronectin, laminin, and collagen is mediated by tumor cell integrin receptors. Integrins are a family of glycoproteins that form heterodimeric receptors for ECM molecules. The integrins can form at least 25 distinct pairings of their α and β subunits, and each pairing is specific for a unique set of ligands. In addition to regulating cell adhesion to the ECM, integrins relay molecular signals regarding the cellular environment that influence shape, survival, proliferation, gene transcription, and migration.

Factors that are thought to play a role in cancer cell motility include autocrine motility factor, autotaxin, scatter factor (also known as *hepatocyte growth factor*), TGFα, EGF, and insulin-like growth factors.

Serine, cysteine, and aspartic proteinases and MMPs have all been implicated in cancer invasion. Urokinase and tissue plasminogen activators (uPA and tPA) are serine proteases that convert plasminogen into plasmin. Plasmin, in return, can degrade several ECM components. Plasmin also may activate MMPs. uPA has been more closely correlated with tissue invasion and metastasis than tPA. Plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) are produced in tissues and counteract the activity of plasminogen activators.

MMPs comprise a family of metal-dependent endopeptidases. Upon activation, MMPs degrade a variety of ECM components. Although MMPs often are referred to by their common names, which reflect the ECM component for which they have specificity, a sequential numbering system has been adopted for standardization. For example, collagenase-1 is now referred to as *MMP-1.* The MMPs are further classified as secreted and membrane-type MMPs. Most of the MMPs are synthesized as inactive zymogens (pro-MMP) and are activated by proteolytic removal of the propeptide domain outside the cell by other active MMPs or serine proteinases.

MMPs are upregulated in almost every type of cancer. Some of the MMPs are expressed by cancer cells, whereas others are expressed by the tumor stromal cells. Experimental models have demonstrated that MMPs promote cancer progression by increasing cancer cell growth, migration, invasion, angiogenesis, and metastasis. MMPs exert these effects by cleaving not only structural components of the ECM but also growth factor–binding proteins, growth factor precursors, cell adhesion molecules, and other proteinases. The activity of MMPs is regulated by their endogenous inhibitors and tissue inhibitors of MMPs (TIMP-1, TIMP-2, TIMP-3, and TIMP-4).

Angiogenesis

Angiogenesis is the establishment of new blood vessels from a pre-existing vascular bed. This neovascularization is essential for tumor growth and metastasis. Tumors develop an angiogenic phenotype as a result of accumulated genetic alterations and in response to local selection pressures such as hypoxia. Many of

the common oncogenes and tumor-suppressor genes have been shown to play a role in inducing angiogenesis, including *ras,* HER2, and mutations in p53.

In response to the angiogenic switch, pericytes retract and the endothelium secretes several growth factors such as basic fibroblast growth factor, platelet-derived growth factor (PDGF), and insulin-like growth factor. The basement membrane and stroma around the capillary are proteolytically degraded, a process that is mediated in most part by uPA. The endothelium then migrates through the degraded matrix, initially as a solid cord and later forming lumina. Finally, sprouting tips anastomose to form a vascular network surrounded by a basement membrane.

Angiogenesis is mediated by factors produced by various cells, including tumor cells, endothelial cells, stromal cells, and inflammatory cells. The first proangiogenic factor was identified by Folkman and colleagues in 1971.[19] Since then, several other factors have been shown to be proangiogenic or antiangiogenic. Of the angiogenic stimulators, the best studied are the vascular endothelial growth factors (VEGFs). The VEGF family consists of six growth factors (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor) and three receptors (VEGFR1 or Flt-1, VEGFR2 or KDR/FLK-1, and VEGFR3 or Flt-4).[20] Neuropilin 1 and 2 also may act as receptors for VEGF.[21] VEGF is induced by hypoxia and by different growth factors and cytokines, including EGF, PDGF, TNF-α, TGFβ, and interleukin-1β. VEGF has various functions, including increasing vascular permeability, inducing endothelial cell proliferation and tube formation, and inducing endothelial cell synthesis of proteolytic enzymes such as uPA, PAI-1, urokinase plasminogen activator receptor, and MMP-1. Furthermore, VEGF may mediate blood flow by its effects on the vasodilator nitric oxide and act as an endothelial survival factor, thus protecting the integrity of the vasculature. The proliferation of new lymphatic vessels, lymphangiogenesis, is also thought to be controlled by the VEGF family. Signaling in lymphatic cells is thought to be modulated by VEGFR3.[22] Experimental studies with VEGF-C and VEGF-D have shown that they can induce tumor lymphangiogenesis and direct metastasis via the lymphatic vessels and lymph nodes.[22,23]

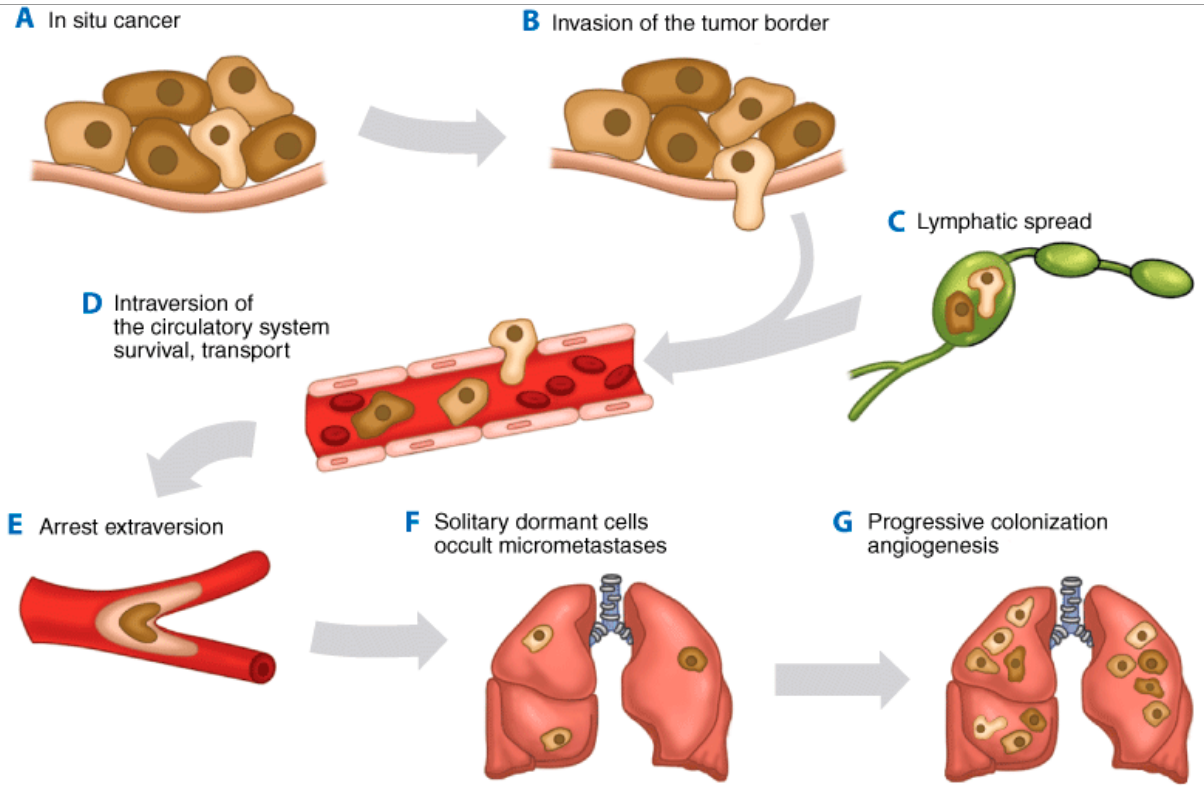
PDGFs A, B, C, and D also play important roles in angiogenesis. PDGFs can not only enhance endothelial cell proliferation directly but also upregulate VEGF expression in vascular smooth muscle cells, promoting endothelial cell survival via a paracrine effect.[20] The angiopoietins angiopoietin-1 and angiopoietin-2 (Ang-1 and Ang-2), in return, are thought to regulate blood vessel maturation. Ang-1 and Ang-2 both bind angiopoietin-1 receptor (also known as tyrosine-protein kinase receptor TIE-2), but only the binding of Ang-1 activates signal transduction; thus Ang-2 is an Ang-1 antagonist. Ang-1, via the Tie-2 receptor, induces remodeling and stabilization of blood vessels. Upregulation of Ang-2 by hypoxic induction of VEGF inhibits Ang-1–induced Tie-2 signaling, which results in destabilization of vessels and makes endothelial cells responsive to angiogenic signals, thus promoting angiogenesis in the presence of VEGF. Therefore the balance between these factors determines the angiogenetic capacity of a tumor.

Tumor angiogenesis is regulated by several factors in a coordinated fashion. In addition to upregulation of proangiogenic molecules, angiogenesis also can be encouraged by suppression of naturally occurring inhibitors. Such inhibitors of angiogenesis include thrombospondin 1 and angiostatin. Angiogenesis is a prerequisite not only for primary tumor growth but also for metastasis. Angiogenesis in the primary tumor, as determined by microvessel density, has been demonstrated to be an independent predictor of distant metastatic disease and survival in several cancers. Expression of angiogenic factors such as VEGFs has had prognostic value in many studies. These findings further emphasize the importance of angiogenesis in cancer biology.

Metastasis

Metastases arise from the spread of cancer cells from the primary site and the formation of new tumors in distant sites. The metastatic process consists of a series of steps that need to be completed successfully (Fig. 10-7).[24] First, the primary cancer must develop access to the circulation through either the blood circulatory system or the lymphatic system. After the cancer cells are shed into the circulation, they must survive. Next, the circulating cells lodge in a new organ and extravasate into the new tissue. Next, the cells need to initiate growth in the new tissue and eventually establish vascularization to sustain the new tumor. Overall, metastasis is an inefficient process, although the initial steps of hematogenous metastasis (the arrest of tumor cells in the organ and extravasation) are believed to be performed efficiently. Only a small subset of cancer cells is then able to initiate micrometastases, and an even smaller portion go on to grow into macrometastases.

Fig. 10-7.



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A schematic representation of the metastatic process. **A.** The metastatic process begins with an in situ cancer surrounded by an intact basement membrane. **B.** Invasion requires reversible changes in cell-cell and cell–extracellular matrix adherence, destruction of proteins in the matrix and stroma, and motility. **C.** Metastasizing cells can enter the circulation via the lymphatics. **D.** They can also directly enter the circulation. **E.** Intravascular survival of the tumor cells and extravasation of the circulatory system follow. **F.** Metastatic single cells can colonize sites and remain dormant for years as occult micrometastases. **G.** Subsequent progression and neovascularization leads to clinically detectable metastases and progressively growing, angiogenic metastases.

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Metastases can sometimes arise several years after the treatment of primary tumors. For example, although most breast cancer recurrences occur within the first 10 years after the initial treatment and recurrences are rare after 20 years, breast cancer recurrences have been reported decades after the original tumor. This phenomenon is referred to as *dormancy,* and it remains one of the biggest challenges in cancer biology. Persistence of solitary cancer cells in a secondary site such as the liver or bone marrow is one possible contributor to dormancy.[25] Another explanation of dormancy is that cells remain viable in a quiescent state and then become reactivated by a physiologically perturbing event. Interestingly, primary tumor removal has been proposed to be a potentially perturbing factor.[26] An alternate explanation is that cells establish preangiogenic metastases in which they continue to proliferate but that the proliferative rate is balanced by the apoptotic rate. Therefore, when these small metastases acquire the ability to become vascularized, substantial tumor growth can be achieved at the metastatic site, leading to clinical detection.

Several types of tumors metastasize in an organ-specific pattern. One explanation for this is mechanical and is based on the different circulatory drainage patterns of the tumors. When different tumor types and their preferred metastasis sites were compared, 66% of organ-specific metastases were explained on the basis of blood flow alone. The other explanation for preferential metastasis is what is referred to as the *"seed and soil" theory,* the dependence of the seed (the cancer cell) on the soil (the secondary organ). According to this theory, once cells have reached a secondary organ, their growth efficiency in that organ is based on the compatibility of the cancer cell's biology with its new microenvironment. For example, breast cancer cells may grow more efficiently in bone than in some other organs because of favorable molecular interactions that occur in the bone microenvironment. The ability of cancer cells to grow in a specific site likely depends on features inherent to the cancer cell, features inherent to the organ, and the interplay between the cancer cell and its microenvironment.[27]

Many of the oncogenes discovered to date, such as HER2 and *ras*, are thought to potentiate not only malignant transformation but also one or more of the steps required in the metastatic process. Experimental models have suggested a role for several molecules, including RhoC, osteopontin and interleukin-11, and Twist, in tumor metastasis. Metastasis also may involve the loss of metastasis-suppressor genes. Laboratory work involving cancer cell lines that have been selected to have a higher metastatic potential have led to the realization that these more highly metastatic cells have a different gene expression profile

than their less metastatic parental counterparts. This in turn has led to the currently held belief that the ability of a primary tumor to metastasize may be predictable by analysis of its gene expression profile. Indeed, several studies have recently focused on identifying a gene expression profile or a "molecular signature" that is associated with metastasis. It has been shown that such a gene expression profile can be used to predict the probability that the patient will remain free of distant metastasis.[28] This suggests that the metastatic potential of a tumor is already predetermined by the genetic alterations that the cancer cells acquire early in tumorigenesis. Notably, this hypothesis differs from the multistep tumorigenesis theory in that the ability to metastasize is considered an inherent quality of the tumor from the beginning. It is assumed that metastasis develops not from a few rare cells in the primary tumor that acquire the ability to metastasize but that all cells in tumors with such molecular signatures develop the ability to metastasize. The reality probably lies in between in that some early genetic changes detectable in the entire tumor can give tumors an advantage in the metastatic process, whereas additional genetic changes can give a clone of cells additional advantages, thus allowing them to succeed in metastasis.

Cancer Stem Cells

Stem cells are cells that have the ability to perpetuate themselves through self-renewal and to generate mature cells of a particular tissue through differentiation.[29] It has recently been proposed that stem cells themselves may be the target of transformation. It was first documented for leukemia and multiple myeloma that only a small subset of cancer cells is capable of extensive proliferation. It has subsequently also been shown for many solid cancers that only a small proportion of cells is clonogenic in culture and in vivo. In leukemia and multiple myeloma only a small subset of cancer cells is capable of extensive proliferation. Similarly, in many solid tumor types only a small proportion of cells is clonogenic in culture and in vivo. If indeed tumor growth and metastasis are driven by a small population of cancer stem cells, this may alter our current approaches to cancer therapy. Currently available drugs can shrink metastatic tumors but often cannot eradicate them. The failure of these treatments usually is attributed to the acquisition of drug resistance by the cancer cells; however, the cancer stem cell hypothesis raises the possibility that existing therapies may simply fail to kill cancer stem cells effectively. Therapeutic approaches targeting stem cells specifically are under study.

CANCER ETIOLOGY

Cancer Genetics

One widely held opinion is that cancer is a genetic disease that arises from an accumulation of mutations that leads to the selection of cells with increasingly aggressive behavior. These mutations may lead either to a gain of function by oncogenes or to a loss of function by tumor-suppressor genes. Most mutations in cancer are somatic and are found only in the cancer cells. Most of our information on human cancer genes has been gained from hereditary cancers. In the case of hereditary cancers, the individual carries a particular germline mutation in every cell. In the past decade, >30 genes for autosomal dominant hereditary cancers have been identified (Table 10-3).[30] A few of these hereditary cancer genes are oncogenes, but most are tumor-suppressor genes. Although hereditary cancer syndromes are rare, somatic mutations that occur in sporadic cancer have been found to disrupt the cellular pathways altered in hereditary cancer syndromes, which suggests that these pathways are critical to normal cell growth, cell cycle, and proliferation.

Table 10-3 Genes Associated with Hereditary Cancer

Gene	Location	Syndrome	Cancer Sites and Associated Traits
APC	17q21	Familial adenomatous polyposis (FAP)	Colorectal adenomas and carcinomas, duodenal and gastric tumors, desmoids, medulloblastomas, osteomas
BMPRIA	10q21-q22	Juvenile polyposis coli	Juvenile polyps of the GI tract, GI and colorectal malignancy
BRCA1	17q21	Breast-ovarian syndrome	Breast cancer, ovarian cancer, colon cancer, prostate cancer
BRCA2	13q12.3	Breast-ovarian syndrome	Breast cancer, ovarian cancer, colon cancer, prostate cancer, cancer of the gallbladder and bile duct, pancreatic cancer, gastric cancer, melanoma
p16;CDK4	9p21; 12q14	Familial melanoma	Melanoma, pancreatic cancer, dysplastic nevi, atypical moles
CDH1	16q22	Hereditary diffuse gastric cancer	Gastric cancer
hCHK2	22q12.1	Li-Fraumeni syndrome and hereditary breast cancer	Breast cancer, soft tissue sarcoma, brain tumors
hMLH1; hMSH2; hMSH6;PMS1; hPMS2	3p21; 2p22-21; 2p16; 2q31-33; 7p22	Hereditary nonpolyposis colorectal cancer	Colorectal cancer, endometrial cancer, transitional cell carcinoma of the ureter and renal pelvis, and carcinomas of the stomach, small bowel, ovary, and pancreas
MEN1	11q13	Multiple endocrine neoplasia type 1	Pancreatic islet cell cancer, parathyroid hyperplasia, pituitary adenomas
MET	7q31	Hereditary papillary renal cell carcinoma	Renal cancer
NF1	17q11	Neurofibromatosis type 1	Neurofibroma, neurofibrosarcoma, acute myelogenous leukemia, brain tumors

NF2	22q12	Neurofibromatosis type 2	Acoustic neuromas, meningiomas, gliomas, ependymomas
PTC	9q22.3	Nevoid basal cell carcinoma	Basal cell carcinoma
PTEN	10q23.3	Cowden disease	Breast cancer, thyroid cancer, endometrial cancer
rb	13q14	Retinoblastoma	Retinoblastoma, sarcomas, melanoma, and malignant neoplasms of brain and meninges
RET	10q11.2	Multiple endocrine neoplasia type 2	Medullary thyroid cancer, pheochromocytoma, parathyroid hyperplasia
SDHB; SDHC; SDHD	1p363.1-p35; 11q23; 1q21	Hereditary paraganglioma and pheochromocytoma	Paraganglioma, pheochromocytoma
SMAD4/DPC4	18q21.1	Juvenile polyposis coli	Juvenile polyps of the GI tract, GI and colorectal malignancy
STK11	19p13.3	Peutz-Jeghers syndrome	GI tract carcinoma, breast carcinoma, testicular cancer, pancreatic cancer, benign pigmentation of the skin and mucosa
p53	17p13	Li-Fraumeni syndrome	Breast cancer, soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, Wilms' tumor, phyllodes tumor of the breast, pancreatic cancer, leukemia, neuroblastoma
TSC1; TSC2	9q34; 16p13	Tuberous sclerosis	Multiple hamartomas, renal cell carcinoma, astrocytoma
VHL	3p25	von Hippel-Lindau disease	Renal cell carcinoma, hemangioblastomas of retina and central nervous system, pheochromocytoma
WT	11p13	Wilms' tumor	Wilms' tumor, aniridia, genitourinary abnormalities, mental retardation

Source: Modified with permission from Marsh DJ, Zori RT: Genetic insights into familial cancers – update and recent discoveries. *Cancer Lett* 181:125, 2002. Copyright Elsevier.

The following factors may suggest the presence of a hereditary cancer[31]:

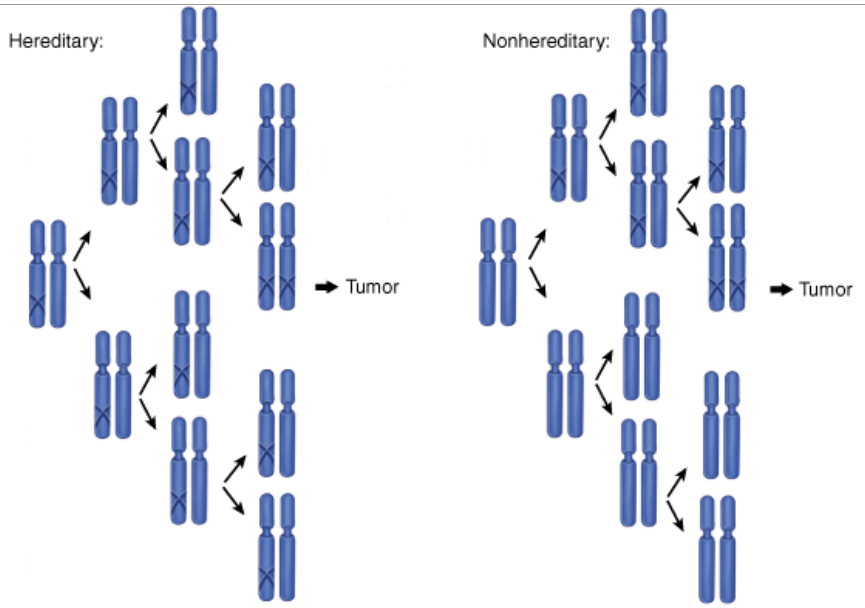
1. Tumor development at a much younger age than usual
2. Presence of bilateral disease
3. Presence of multiple primary malignancies
4. Presentation of a cancer in the less affected sex (e.g., male breast cancer)
5. Clustering of the same cancer type in relatives
6. Occurrence of cancer in association with other conditions such as mental retardation or pathognomonic skin lesions

It is crucial that all surgeons caring for cancer patients be aware of hereditary cancer syndromes, because a patient's genetic background has significant implications for patient counseling, planning of surgical therapy, and cancer screening and prevention. Some of the more commonly encountered hereditary cancer syndromes are discussed here.

RB1 GENE AND HEREDITARY RETINOBLASTOMA

The retinoblastoma gene *rb1* was the first tumor suppressor to be cloned. The *rb1* gene product, the Rb protein, is a regulator of transcription that controls the cell cycle, differentiation, and apoptosis in normal development.[32] Retinoblastoma has long been known to occur in hereditary and nonhereditary forms. Interestingly, although most children with an affected parent develop bilateral retinoblastoma, some develop unilateral retinoblastoma. Furthermore, some children with an affected parent are not affected themselves but then have an affected child, which indicates that they are *rb1* mutation carriers. These findings led to the theory that a single mutation is not sufficient for tumorigenesis. Dr. Alfred Knudson hypothesized that hereditary retinoblastoma involves two mutations, of which one is germline and one somatic, whereas nonhereditary retinoblastoma is due to two somatic mutations (Fig. 10-8).[33] Thus both hereditary and nonhereditary forms of retinoblastoma involve the same number of mutations, a hypothesis known as *Knudson's "two-hit" hypothesis.* A "hit" may be a point mutation, a chromosomal deletion referred to as *allelic loss,* or a loss of heterozygosity, or silencing of an existing gene.

Fig. 10-8.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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"Two-hit" tumor formation in both hereditary and nonhereditary cancers. A "one-hit" clone is a precursor to the tumor in nonhereditary cancers, whereas all cells are one-hit clones in hereditary cancer.

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Retinoblastoma is a pediatric retinal tumor. Most of these tumors are detected within the first 7 years of life. Bilateral disease usually is diagnosed earlier, at an average age of 12 months. There is a higher incidence of second extraocular primary tumors, especially sarcomas, malignant melanomas, and malignant neoplasms of the brain and meninges in patients with germline mutations. In addition to hereditary retinoblastoma, Rb protein is commonly inactivated directly by mutation in many sporadic tumors.[34] Moreover, other molecules in the Rb pathway, such as p16 and cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), have been identified in a number of sporadic tumors, which suggests that the Rb pathway is critical in malignant transformation.

P53 AND LI-FRAUMENI SYNDROME

Li-Fraumeni syndrome (LFS) was first defined on the basis of observed clustering of malignancies, including early-onset breast cancer, soft tissue sarcomas, brain tumors, adrenocortical tumors, and leukemia.[35] Criteria for classic LFS in an individual (the proband) include (a) a bone or soft tissue sarcoma when younger than 45 years, (b) a first-degree relative with cancer before age 45 years, and (c) another first- or second-degree relative with either a sarcoma diagnosed at any age or any cancer diagnosed before age 45 years.[36] Approximately 70% of LFS families have been shown to have germline mutations in the tumor-suppressor gene p53.[37] Breast carcinoma, soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, Wilms' tumor, and phyllodes tumor of the breast are strongly associated; pancreatic cancer is moderately associated; and leukemia and neuroblastoma are weakly associated with germline p53 mutations.[38] Mutations of p53 have not been detected in approximately 30% of LFS families, and it is hypothesized that genetic alterations in other proteins interacting with p53 function may play a role in these families.

Of the known genes in human cancer, p53 is the most commonly mutated. The p53 protein regulates cell-cycle progression as well as apoptotic cell death as part of stress response pathways after exposure to ionizing or ultraviolet (UV) irradiation, chemotherapy, acidosis, growth factor deprivation, or hypoxia. When cells are exposed to stressors, p53 acts as a transcription factor for genes that induce cell-cycle arrest or apoptosis. A majority of p53 mutations are found within a central DNA recognition motif and disrupt DNA binding by p53. Families with germline missense mutations in the DNA-binding domain show a more highly penetrant phenotype than families with other p53 mutations.[39] Furthermore, proband cancers are linked with significantly younger age at diagnosis in patients with missense mutations in the DNA-binding domain.[39]

HCHK2, LI-FRAUMENI SYNDROME, AND HEREDITARY BREAST CANCER

Germline mutations in the *hCHK2* gene have recently been identified as another susceptibility gene for LFS. The *hCHK2* gene encodes for the human homologue of the yeast Cds1 and the RAD53 G_2 checkpoint, whose activation by DNA damage prevents entry into mitosis. CHK2 directly phosphorylates p53, which suggests that CHK2 may be involved in p53 regulation after DNA damage. CHK2 also regulates *BRCA1* function after DNA damage. The protein truncation mutation *1100delC* in exon 10 identified in LFS and breast cancer abolishes the kinase function of CHK2. Another reported mutation in *hCHK2* is a missense mutation (R145W) that destabilizes the protein, shortening its half-life.[40]

Although some investigators found *hCHK2* mutations in classic LFS families, others have reported that the phenotypes of CHK2 families are not typical for LFS and involve no sarcomas or childhood cancers. The CHK2 mutation originally reported in LFS (1100delC) is found in 1.4% of population controls but is found at an increased frequency (3.1%) among breast cancer patients with a family history of the cancer.[41] Patients with bilateral breast cancers are six times more likely to have the mutation than patients with unilateral breast cancer. Thus *hCHK2* mutations may play a role in families with hereditary breast cancer as well as in families with LFS, but the extent of this is unclear. Mutations of *hCHK2* are rare in sporadic breast tumors.

BRCA1, BRCA2, AND HEREDITARY BREAST-OVARIAN CANCER SYNDROME

It is estimated that 5 to 10% of breast cancers are hereditary. Of women with early-onset breast cancer (aged 40 years or younger), nearly 10% have a germline mutation in one of the breast cancer genes *BRCA1* or *BRCA2.*[42] Mutation carriers are more prevalent among women who have a first- or second-degree relative with premenopausal breast cancer or ovarian cancer at any age. The likelihood of a *BRCA* mutation is higher in patients who belong to a population in which founder mutations may be prevalent, such as in the Ashkenazi Jewish population. For a female *BRCA1* mutation carrier, the cumulative risks of developing breast cancer and ovarian cancer by age 70 have been estimated to be 87 and 44%, respectively.[43] The cumulative risks of breast cancer and ovarian cancer by age 70 in families with *BRCA2* mutation have been estimated to be 84 and 27%, respectively.[44] Although male breast cancer can occur with either *BRCA1* or *BRCA2* mutation, the majority of families (76%) with both male and female breast cancer have mutations in *BRCA2.*[44] Besides breast and ovarian cancer, *BRCA1* and *BRCA2* mutations may be associated with increased risks for several other cancers. *BRCA1* mutations confer a fourfold increased risk for colon cancer and threefold increased risk for prostate cancer.[43] *BRCA2* mutations confer a fivefold increased risk for prostate cancer, sevenfold in men younger than 65 years.[45] Furthermore, *BRCA2* mutations confer a fivefold increased risk for gallbladder and bile duct cancers, fourfold increased risk for pancreatic cancer, and threefold increased risk for gastric cancer and malignant melanoma.[45]

BRCA1 was the first breast cancer susceptibility gene identified and has been mapped to 17q21. *BRCA2,* mapped to 13q12.3, was reported shortly afterward. *BRCA1* and *BRCA2* encode for large nuclear proteins, 208 kDa and 384 kDa, respectively, that have been implicated in processes fundamental to all cells, including DNA repair and recombination, checkpoint control of the cell cycle, and transcription.[46] Although early studies suggested that the two proteins function together as a complex, subsequent data demonstrated that they have distinct functions.[47,48] In fact, breast cancers arising from *BRCA1* or *BRCA2* mutations are different at the molecular level and have been found to have distinct gene expression profiles.[49]*BRCA1*-associated tumors are more likely to be estrogen receptor negative, whereas *BRCA2*-associated tumors are more likely to be estrogen receptor positive. Currently, studies are ongoing to determine whether *BRCA1* and *BRCA2* status can be used to guide systemic therapy choices for breast cancer.

APC GENE AND FAMILIAL ADENOMATOUS POLYPOSIS

Patients affected with familial adenomatous polyposis (FAP) characteristically develop hundreds to thousands of polyps in the colon and rectum. The polyps usually appear in adolescence and, if left untreated, progress to colorectal cancer. FAP is associated with benign extracolonic manifestations that may be useful in identifying new cases, including congenital hypertrophy of the retinal pigment epithelium, epidermoid cysts, and osteomas. In addition to colorectal cancer, patients with FAP are at risk for upper intestinal neoplasms (gastric and duodenal polyps, duodenal and periampullary cancer), hepatobiliary tumors (hepatoblastoma, pancreatic cancer, and cholangiocarcinoma), thyroid carcinomas, desmoid tumors, and medulloblastomas.

The product of the adenomatous polyposis coli tumor-suppressor gene (*APC*) is widely expressed in many tissues and plays an important role in cell-cell interactions, cell adhesion, regulation of β-catenin, and maintenance of cytoskeletal microtubules. Alterations in *APC* lead to dysregulation of several physiologic processes that govern colonic epithelial cell homeostasis, including cell-cycle progression, migration, differentiation, and apoptosis. Mutations in the *APC* gene have been identified in FAP and in 80% of sporadic colorectal cancers.[50] Furthermore, *APC* mutations are the earliest known genetic alterations in colorectal cancer progression, which emphasizes its importance in cancer initiation. The germline mutations in *APC* may arise from point mutations, insertions, or deletions that lead to a premature stop codon and a truncated, functionally inactive protein. The risk of developing specific manifestations of FAP is correlated with the position of the FAP mutations, a phenomenon referred to as *genotype-phenotype correlation.* For example, desmoids usually are associated with mutations between codons 1403 and 1578.[51,52] Mutations in the extreme 5' or 3' ends of *APC,* or in the alternatively spliced region of exon 9, are associated with an attenuated version of FAP. Better understanding of the genotype-phenotype correlations may assist in patient counseling and therapeutic planning.

MISMATCH REPAIR GENES AND HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

Hereditary nonpolyposis colorectal cancer (HNPCC), also referred to as *Lynch syndrome,* is an autosomal dominant hereditary cancer syndrome that predisposes to a wide spectrum of cancers, including colorectal cancer without polyposis. Some have proposed that HNPCC consists of at least two syndromes: Lynch syndrome 1, which entails hereditary predisposition for colorectal cancer with early age of onset (approximately age 44 years) and an excess of synchronous and metachronous colonic cancers; and Lynch syndrome 2, featuring a similar colonic phenotype accompanied by a high risk for carcinoma of the endometrium, transitional cell carcinoma of the ureter and renal pelvis, and carcinomas of the stomach, small bowel, ovary, and pancreas.[53] The diagnostic criteria for HNPCC are referred to as the *Amsterdam criteria,* or the *3-2-1-0 rule.* The classic Amsterdam criteria were revised to include other HNPCC-related cancers (Table 10-4).[54] These criteria are met when three or more family members have histologically verified, HNPCC-associated cancers (one of whom is a

first-degree relative of the other two), two or more generations are involved, at least one individual was diagnosed before age 50 years, and no individuals have FAP.[54]

Table 10-4 Revised Criteria for Hereditary Nonpolyposis Colon Cancer (HNPCC) (Amsterdam Criteria II)
Three or more relatives with an HNPCC-associated cancer (colorectal cancer, endometrial cancer, cancer of the small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two
At least two successive generations affected
At least one case diagnosed before age 50 y
Familial adenomatous polyposis excluded
Tumors verified by pathologic examination

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During DNA replication, DNA polymerases may introduce single nucleotide mismatches or small insertion or deletion loops. These errors are corrected through a process referred to as *mismatch repair.* When mismatch repair genes are inactivated, DNA mutations in other genes that are critical to cell growth and proliferation accumulate rapidly. In HNPCC, germline mutations have been identified in several genes that play a key role in DNA nucleotide mismatch repair: *hMLH1* (human mutL homologue 1), *hMSH2* (human mutS homologue 2), *hMSH6,* and *hPMS1* and *hPMS2* (human postmeiotic segregation 1 and 2), of which *hMLH1* and *hMSH2* are the most common.[55–60] The hallmark of HNPCC is microsatellite instability, which occurs on the basis of unrepaired mismatches and small insertion or deletion loops. Microsatellite instability can be tested by comparing the DNA of a patient's tumor with DNA from adjacent normal epithelium, amplifying the DNA with polymerase chain reaction (PCR) using a standard set of markers, comparing the amplified genomic DNA sequences, and classifying the degree of microsatellite instability as high, low, or stable. Such microsatellite instability testing may help select patients who are more likely to have germline mutations.

PTEN AND COWDEN DISEASE

Somatic deletions or mutations in the tumor-suppressor gene *PTEN* (phosphatase and tensin homologue deleted on chromosome 10) have been observed in a number of glioma and breast, prostate, and renal carcinoma cell lines and several primary tumor specimens.[61] *PTEN* also is referred to as the *gene mutated in multiple advanced cancers 1 (MMAC1). PTEN* was identified as the susceptibility gene for the autosomal dominant syndrome Cowden disease (CD) or multiple hamartoma syndrome.[62] Trichilemmomas, benign tumors of the hair follicle infundibulum, and mucocutaneous papillomatosis are pathognomonic of CD. Other common features include thyroid adenomas and multinodular goiters, breast fibroadenomas, and hamartomatous GI polyps. The diagnosis of CD is made when an individual or family has a combination of pathognomonic major and/or minor criteria proposed by the International Cowden Consortium (Table 10-5).[63] CD is associated with an increased risk of breast and thyroid cancers. Breast cancer develops in 25 to 50% of affected women.[63]

Table 10-5 Cowden Disease Diagnostic Criteria
Pathognomonic criteria
Mucocutaneous lesions
Facial trichilemmomas
Acral keratoses
Papillomatous lesions
Mucosal lesions
Major criteria
Breast cancer
Thyroid cancer, especially follicular thyroid carcinoma type
Macrocephaly (≥97th percentile)
Lhermitte-Duclos disease
Endometrial carcinoma
Minor criteria
Other thyroid lesions (e.g., goiter)
Mental retardation (intelligence quotient ≤75)
GI hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas

Genitourinary tumors (e.g., uterine fibroids) or malformation
Operational diagnosis in an individual
Mucocutaneous lesions alone if there are:
Six or more facial papules, of which three or more must be trichilemmoma, or
Cutaneous facial papules and oral mucosal papillomatosis, or
Oral mucosal papillomatosis and acral keratoses, or
Palmoplantar keratoses, six or more
Two major criteria, but one must be macrocephaly or Lhermitte-Duclos disease
One major and three minor criteria
Four minor criteria

Source: Modified with permission from Eng C: Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet* 37:828, 2000. With permission from the BMJ Publishing Group.

PTEN encodes a 403-amino-acid protein, tyrosine phosphatase. *PTEN* negatively controls the PI3K signaling pathway for the regulation of cell growth and survival by dephosphorylating phosphoinositol 3,4,5-triphosphate; thus mutation of *PTEN* leads to constitutive activation of the PI3K/Akt signaling pathway. The "hot spot" for *PTEN* mutations has been identified in exon 5. Forty-three percent of CD mutations have been identified in this exon, which contains the tyrosine phosphatase core domain. This suggests that the *PTEN* catalytic activity is vital for its biologic function.

P16 AND HEREDITARY MALIGNANT MELANOMA

The gene *P*16, also known as INK4A, CDKN1, CDKN2A, and MTS1, is a tumor suppressor that acts by binding CDK4 and CDK6 and inhibiting the catalytic activity of the CDK4-CDK6/cyclin D complex that is required for phosphorylation of Rb and subsequent cell-cycle progression. Studies suggest that germline mutations in p16 can be found in 20% of melanoma-prone families.[64] Mutations in p16 that alter its ability to inhibit the catalytic activity of the CDK4-CDK6/cyclin D complex not only increase the risk of melanoma by 75-fold but also increase the risk of pancreatic cancer by 22-fold.[65] Interestingly, p16 mutations that do not appear to alter its function increase the risk of melanoma by 38-fold and do not increase the risk of pancreatic cancer.[65] Genetic evaluation of primary tumors has revealed that p16 is inactivated through point mutation, promoter methylation, or deletion in a significant portion of sporadic tumors, including cancers of the pancreas, esophagus, head and neck, stomach, breast, and colon, as well as melanomas.

E-CADHERIN AND HEREDITARY DIFFUSE GASTRIC CANCER

E-cadherin is a cell adhesion molecule that plays an important role in normal architecture and function of epithelial cells. The adhesive function of E-cadherin is dependent on interaction of its cytoplasmic domain with β- and ϒ-catenins and may be regulated by phosphorylation of β-catenin.

Hereditary diffuse gastric carcinoma is an autosomal dominant cancer syndrome that results from germline mutations in the E-cadherin gene, *CDH1.* Carriers of *CDH1* mutations have a 70 to 80% chance of developing gastric cancer.[66] Furthermore, mutations of *CDH1* have been described in sporadic cancers of the ovary, endometrium, breast, and thyroid. However, frequent mutations have been identified in only two particular tumors: diffuse gastric carcinomas and lobular breast carcinomas. Invasive lobular breast carcinomas often show inactivating mutations in combination with a loss of heterozygosity of the wild-type *CDH1* allele.[67] Interestingly, in gastric carcinomas the predominant mutations are exon skipping causing in-frame deletions, whereas most mutations identified in lobular breast cancers are premature stop codons; this suggests a genotype-phenotype correlation.

RET PROTO-ONCOGENE AND MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

The *RET* (rearranged during transfection) gene encodes for a transmembrane receptor tyrosine kinase that plays a role in proliferation, migration, and differentiation of cells derived from the neural crest. Gain-of-function mutations in the *RET* gene are associated with medullary thyroid carcinoma in isolation or multiple endocrine neoplasia type 2 (MEN2) syndromes. MEN2A is associated with medullary thyroid carcinoma and pheochromocytoma (in 50%) or parathyroid adenoma (in 20%), whereas MEN2B is associated with medullary thyroid carcinoma, marfanoid habitus, mucosal neuromas, and ganglioneuromatosis.[68] *RET* mutations lead to uncontrolled growth of the thyroid C cells, and in familial medullary cancer, C-cell hyperplasia progresses to bilateral, multicentric medullary thyroid cancer. Mutations in the *RET* gene have also been identified in half of sporadic medullary thyroid cancers. The activating *RET* mutations in medullary thyroid cancer are being pursued as a therapeutic target.

TISSUE SPECIFICITY OF HEREDITARY CANCER

In spite of our increasing understanding of hereditary cancer genes, the tissue specificity of the hereditary cancers remains poorly understood. For example, although mutations in genes such as *rb* and p53 are encountered frequently in sporadic cancers arising in a variety of tissues, it is unclear why germline mutations in these genes would lead to tumors predominantly in selected tissues. However, mutations in tumor-suppressor genes alone are insufficient to produce tumors, and usually the development of cancer involves accumulation of multiple genetic alterations. The rate at which these changes occur in different tissues after inactivation of different tumor-suppressor genes may account for some of the tissue distribution seen with hereditary cancer syndromes.

GENETIC MODIFIERS OF RISK

Individuals carrying identical germline mutations vary in regard to cancer penetrance (whether cancer will develop or not) and cancer phenotype (the tissues involved). It is thought that this variability may be due to environmental influences or, if genetic, to genetic modifiers of risk. Similarly, genetic modifiers of risk also can play a role in determining whether an individual will develop cancer after exposure to carcinogens.

Chemical Carcinogens

The first report indicating that cancer could be caused by environmental factors was by John Hill, who in 1761 noted the association between nasal cancer and excessive use of tobacco snuff.[69] Currently, approximately 60 to 90% of cancers are thought to be due to environmental factors. Any agent that can contribute to tumor formation is referred to as a *carcinogen* and can be a chemical, physical, or viral agent. Chemicals are classified into three groups based on how they contribute to tumor formation. The first group of chemical agents, the genotoxins, can initiate carcinogenesis by causing a mutation. The second group, the cocarcinogens, by themselves cannot cause cancer but potentiate carcinogenesis by enhancing the potency of genotoxins. The third group, tumor promoters, enhances tumor formation when given after exposure to genotoxins.

The International Agency for Research on Cancer (IARC) maintains a registry of human carcinogens that is available through the World Wide Web (http://www.iarc.fr). The compounds are categorized into five groups based on an analysis of epidemiologic studies, animal models, and short-term mutagenesis tests. Group 1 contains what are considered to be proven human carcinogens, based on formal epidemiologic studies among workers who were exposed for long periods (several years) to the chemicals. Group 2A contains what are considered to be probable human carcinogens. Suggestive epidemiologic evidence exists for compounds in this group, but the data are insufficient to establish causality. There is evidence of carcinogenicity, however, from animal studies carried out under conditions relevant to human exposure. Group 2B contains what are considered to be possible carcinogens, because these substances are associated with a clear statistically and biologically significant increase in the incidence of malignant tumors in more than one animal species or strain. Group 3 agents are not classifiable as to carcinogenicity in humans. Group 4 agents are probably not carcinogenic to humans. Selected substances that have been classified as proven carcinogens (group 1) by the IARC are listed in Table 10-6.[70]

Table 10-6 Selected IARC Group 1 Chemical Carcinogens[a]

Chemical	Predominant Tumor Type[b]
Aflatoxins	Liver cancer
Arsenic	Skin cancer
Benzene	Leukemia
Benzidine	Bladder cancer
Beryllium	Lung cancer
Cadmium	Lung cancer
Chinese-style salted fish	Nasopharyngeal carcinoma
Chlorambucil	Leukemia
Chromium [VI] compounds	Lung cancer
Coal tar	Skin cancer, scrotal cancer
Cyclophosphamide	Bladder cancer, leukemia
Diethylstilbestrol (DES)	Vaginal and cervical clear cell adenocarcinomas
Ethylene oxide	Leukemia, lymphoma
Estrogen replacement therapy	Endometrial cancer, breast cancer
Nickel	Lung cancer, nasal cancer
Tamoxifen[c]	Endometrial cancer
Vinyl chloride	Angiosarcoma of the liver, hepatocellular carcinoma, brain tumors, lung cancer, malignancies of lymphatic and hematopoietic system
TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin)	Soft tissue sarcoma
Tobacco products, smokeless	Oral cancer
Tobacco smoke	Lung cancer, oral cancer, pharyngeal cancer, laryngeal cancer, esophageal cancer (squamous cell), pancreatic cancer, bladder cancer, liver cancer, renal cell carcinoma, cervical cancer, leukemia

[a]Based on information in the IARC monographs.[70]

[b]Only tumor types for which causal relationships are established are listed. Other cancer types may be linked to the agents with a lower frequency or with insufficient data to prove causality.

[c]Tamoxifen has been shown to prevent contralateral breast cancer.

IARC = International Agency for Research on Cancer.

Physical Carcinogens

Physical carcinogenesis can occur through induction of inflammation and cell proliferation over a period of time or through exposure to physical agents that induce DNA damage. Foreign bodies can cause chronic irritation that can expose cells to carcinogenesis due to other environmental agents. In animal models, for example, subcutaneous implantation of a foreign body can lead to the development of tumors that have been attributed to chronic irritation from the foreign objects. In humans, clinical scenarios associated with chronic irritation and inflammation such as chronic nonhealing wounds, burns, and inflammatory bowel syndrome have all been associated with an increased risk of cancer. *H. pylori* infection is associated with gastritis and gastric cancer, and thus its carcinogenicity may be considered physical carcinogenesis. Infection with the liver fluke *Opisthorchis viverrini* similarly leads to local inflammation and cholangiocarcinoma.

The induction of lung and mesothelial cancers by asbestos fibers and nonfibrous particles such as silica are other examples of foreign body–induced physical carcinogenesis.[71] Animal experiments have demonstrated that the dimensions and durability of the asbestos and other fibrous minerals are the key determinants of their carcinogenicity.[72] Short fibers can be inactivated by phagocytosis, whereas long fibers (>10 μm) are cleared less effectively and are encompassed by proliferating epithelial cells. The long fibers support cell proliferation and have been shown to preferentially induce tumors. Asbestos-associated biologic effects also may be mediated through reactive oxygen and nitrogen species. Furthermore, an interaction occurs between asbestos and silica and components of cigarette smoke. Polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke are metabolized by epithelial cells and form DNA adducts. If PAH is coated on asbestos, PAH uptake is increased.[71] Both PAH and asbestos impair lung clearance, potentially increasing uptake further. Therefore, physical carcinogens may be synergistic with chemical carcinogens.

Radiation is the best-known agent of physical carcinogenesis and is classified as ionizing radiation (x-rays, gamma rays, and alpha and beta particles) or nonionizing radiation (UV). The carcinogenic potential of ionizing radiation was recognized soon after Wilhelm Conrad Roentgen's discovery of x-rays in 1895. Within the next 20 years, a large number of radiation-related skin cancers were reported. Long-term follow-up of survivors of the atomic bombing of Hiroshima and Nagasaki revealed that virtually all tissues exposed to radiation are at risk for cancer.

Radiation can induce a spectrum of DNA lesions that includes damage to the nucleotide bases and cross-linking, and DNA single- and double-strand breaks (DSBs). Misrepaired DSBs are the principal lesions of importance in the induction of chromosomal abnormalities and gene mutations. DSBs in irradiated cells are repaired primarily by a nonhomologous end-joining process, which is error prone; thus DSBs facilitate the production of chromosomal rearrangements and other large-scale changes such as chromosomal deletions. It is thought that radiation may initiate cancer by inactivating tumor-suppressor genes. Activation of oncogenes appears to play a lesser role in radiation carcinogenesis.

Although it has been assumed that the initial genetic events induced by radiation constitute direct mutagenesis from radiation, other indirect effects may contribute to carcinogenesis. For example, radiation induces genomic instability in cells that persists for at least 30 generations after irradiation. Therefore, even if cells do not acquire mutations at initial irradiation, they remain at risk for developing new mutations for several generations. Moreover, even cells that have not been directly irradiated appear to be at risk, a phenomenon referred to as the *bystander effect.*

Nonionizing UV radiation is a potent DNA-damaging agent and is known to induce skin cancer in experimental animals. Most nonmelanoma human skin cancers are thought to be induced by repeated exposure to sunlight, which leads to a series of mutations that allow the cells to escape normal growth control. Patients with inherited xeroderma pigmentosum lack one or more DNA repair pathways, which confers susceptibility to UV-induced cancers, especially on sun-exposed body parts. Patients with ataxia telangiectasia mutated syndrome also have a radiation-sensitive phenotype.

Viral Carcinogens

One of the first observations that cancer may be caused by transmissible agents was by Peyton Rous in 1910 when he demonstrated that cell-free extracts from sarcomas in chickens could transmit sarcomas to other animals injected with these extracts.[73] This was subsequently discovered to represent viral transmission of cancer by the Rous sarcoma virus. At present, several human viruses are known to have oncogenic properties, and several have been causally linked to human cancers (Table 10-7).[74] It is estimated that 15% of all human tumors worldwide are caused by viruses.[75]

Table 10-7 Selected Viral Carcinogens[a]

Virus	Predominant Tumor Type[b]
Epstein-Barr virus	Burkitt's lymphoma

	Hodgkin's disease
	Immunosuppression-related lymphoma
	Sinonasal angiocentric T-cell lymphoma
	Nasopharyngeal carcinoma
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma
HIV type 1	Kaposi's sarcoma
	Non-Hodgkin's lymphoma
Human papillomavirus 16 and 18	Cervical cancer
	Anal cancer
Human T-cell lymphotropic viruses	Adult T-cell leukemia/lymphoma

[a]Based on information in the International Agency for Research on Cancer monographs.[74]

[b]Only tumor types for which causal relationships are established are listed. Other cancer types may be linked to the agents with a lower frequency or with insufficient data to prove causality.

Viruses may cause or increase the risk of malignancy through several mechanisms, including direct transformation, expression of oncogenes that interfere with cell-cycle checkpoints or DNA repair, expression of cytokines or other growth factors, and alteration of the immune system. Oncogenic viruses may be RNA or DNA viruses. Oncogenic RNA viruses are retroviruses and contain a reverse transcriptase. After the viral infection, the single-stranded RNA viral genome is transcribed into a double-stranded DNA copy, which is then integrated into the chromosomal DNA of the cell. Retroviral infection of the cell is permanent; thus integrated DNA sequences remain in the host chromosome. Oncogenic transforming retroviruses carry oncogenes derived from cellular genes. These cellular genes, referred to as *proto-oncogenes,* usually are involved in mitogenic signaling and growth control, and include protein kinases, G proteins, growth factors, and transcription factors (Table 10-8).[75]

Table 10-8 Cellular Oncogenes in Retroviruses

Oncogene	Virus Name	Origin	Protein Product
abl	Abelson murine leukemia virus	Mouse	Tyrosine kinase
fes	ST feline sarcoma virus	Cat	Tyrosine kinase
fps	Fujinami sarcoma virus	Chicken	Tyrosine kinase
src	Rous sarcoma virus	Chicken	Tyrosine kinase
erbB	Avian erythroblastosis virus	Chicken	Epidermal growth factor receptor
fms	McDonough feline sarcoma virus	Cat	Colony-stimulating factor receptor
kit	Hardy-Zuckerman 4 feline sarcoma virus	Cat	Stem cell factor receptor
mil	Avian myelocytoma virus	Chicken	Serine/threonine kinase
mos	Moloney murine sarcoma virus	Mouse	Serine/threonine kinase
raf	Murine sarcoma virus 3611	Mouse	Serine/threonine kinase
sis	Simian sarcoma virus	Monkey	Platelet-derived growth factor
H-ras	Harvey murine sarcoma virus	Rat	GDP/GTP binding
K-ras	Kirsten murine sarcoma virus	Rat	GDP/GTP binding
erbA	Avian erythroblastosis virus	Chicken	Transcription factor (thyroid hormone receptor)
ets	Avian myeloblastosis virus E26	Chicken	Transcription factor
fos	FBJ osteosarcoma virus	Mouse	Transcription factor (AP1 component)
jun	Avian sarcoma virus 17	Chicken	Transcription factor (AP1 component)
myb	Avian myeloblastosis virus	Chicken	Transcription factor
myc	MC29 myelocytoma virus	Chicken	Transcription factor (NF-κB family)

AP1 = activator protein 1; FBJ = Finkel-Biskis-Jinkins; GDP = guanosine diphosphate; GTP = guanosine triphosphate; NF-κB = nuclear factor κB.

Source: Modified with permission from Butel JS: Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. *Carcinogenesis* 21:405, 2000. By permission of Oxford University Press.

Integration of the provirus upstream of a proto-oncogene may produce chimeric virus-cell transcripts and recombination during the next round of replication that could lead to incorporation of the cellular gene into the viral genome.[75] On the other hand, many retroviruses do not possess oncogenes but can cause tumors in animals regardless. This occurs by integration of the provirus near a normal cellular proto-oncogene and activation of the expression of these genes

by the strong promoter and enhancer sequences in the integrated viral sequence.

Unlike the oncogenes of the RNA viruses, those of the DNA tumor viruses are viral, not cellular, in origin. These genes are required for viral replication using the host cell machinery. In permissive hosts, infection with an oncogenic DNA virus may result in a productive lytic infection, which leads to cell death and the release of newly formed viruses. In nonpermissive cells, the viral DNA can be integrated into the cellular chromosomal DNA, and some of the early viral genes can be synthesized persistently, which leads to transformation of cells to a neoplastic state. The binding of viral oncoproteins to cellular tumor-suppressor proteins p53 and Rb is fundamental to the carcinogenesis induced by most DNA viruses, although some target different cellular proteins.

Like other types of carcinogenesis, viral carcinogenesis is a multistep process. Some retroviruses contain two cellular oncogenes, rather than one, in their genome and are more rapidly tumorigenic than single-gene transforming retroviruses, which emphasizes the cooperation between transforming genes. Furthermore, some viruses encode genes that suppress or delay apoptosis.

Although immunocompromised individuals are at elevated risk, most patients infected with oncogenic viruses do not develop cancer. When cancer does develop, it usually occurs several years after the viral infection. It is estimated, for example, that the risk of hepatocellular carcinoma (HCC) among individuals infected with hepatitis C virus is 1 to 3% after 30 years.[76] There may be synergy between various environmental factors and viruses in carcinogenesis.

Recognition of a viral origin for some tumors has lead to the pursuit of vaccination as a preventive strategy. The use of childhood hepatitis B vaccination has already translated into a decrease in liver cancer incidence in the Far East.[3] Recently, vaccines against human papillomavirus have shown very promising results in preventing the development of cervical intraepithelial neoplasia and are now being pursued for primary prevention of cervical carcinoma.[77]

CANCER RISK ASSESSMENT

Cancer risk assessment is an important part of the initial evaluation of any patient. A patient's cancer risk not only is an important determinant of cancer screening recommendations but also may alter how aggressively an indeterminant finding will be pursued for diagnosis. A "probably benign" mammographic lesion, for example, defined as one with <2% probability of malignancy (American College of Radiology category III) is usually managed with a 6-month follow-up mammogram in a patient at baseline cancer risk, but obtaining a tissue diagnosis may be preferable in a patient at high risk for breast cancer.[78]

Cancer risk assessment starts with taking a complete history that includes history of environmental exposures to potential carcinogens and a detailed family history. Risk assessment for breast cancer, for example, includes obtaining a family history to determine whether another member of the family is known to carry a breast cancer susceptibility gene; whether there is familial clustering of breast cancer, ovarian cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, brain tumors, dermatologic manifestations, leukemia, or lymphoma; and whether the patient is from a population at increased risk, such as individuals of Ashkenazi Jewish descent. Patients who have a family history suggestive of a cancer susceptibility syndrome such as hereditary breast-ovarian syndrome, LFS, or CD would benefit from genetic counseling and possibly genetic testing.

Patients who do not seem to have a strong hereditary component of risk can be evaluated on the basis of their age, race, personal history, and exposures. One of the most commonly used models for risk assessment in breast cancer is the Gail model.[79] Gail and colleagues analyzed the data from 2852 breast cancer cases and 3146 controls from the Breast Cancer Detection and Demonstration Project, a mammography screening project conducted in the 1970s, and developed a model for projecting breast cancer incidence. The model uses risk factors such as an individual's age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, number of previous breast biopsies, and whether the biopsy results revealed atypical ductal hyperplasia (Table 10-9).[79] This model has led to the development of a breast cancer risk assessment tool, which is available on the World Wide Web.[80] This tool incorporates the risk factors used in the Gail model, as well as race and ethnicity, and allows a health professional to project a woman's individualized estimated risk for invasive breast cancer over a 5-year period and over her lifetime (to age 90 years). Notably, these risk projections assume that the woman is undergoing regular clinical breast examinations and screening mammograms. Also of note is that this program underestimates the risk for women who have already had a diagnosis of invasive or noninvasive breast cancer and does not take into account specific genetic predispositions such as mutations in *BRCA1* or *BRCA2.* However, risk assessment tools such as this have been validated and are now in widespread clinical use. Similar models are in development or are being validated for other cancers. For example, a lung cancer risk prediction model, which includes age, sex, asbestos exposure history, and smoking history, has been found to predict risk of lung cancer.[81]

Table 10-9 Assessment of Risk for Invasive Breast Cancer

Risk Factor	Relative Risk (%)
Age at menarche (years)	
>14	1.00
12–13	1.10
<12	1.21
Age at first live birth (years)	
Patients with no first-degree relatives with cancer	

<20	1.00
20–24	1.24
25–29 or nulliparous	1.55
≥30	1.93
Patients with one first degree-relative with cancer	
<20	1.00
20–24	2.64
25–29 or nulliparous	2.76
≥30	2.83
Patients with ≥2 first-degree relatives with cancer	
<20	6.80
20–24	5.78
25–29 or nulliparous	4.91
≥30	4.17
Breast biopsies (number)	
Patients aged <50 y at counseling	
0	1.00
1	1.70
≥2	2.88
Patients aged ≥50 y at counseling	
0	1.00
1	1.27
≥2	1.62
Atypical hyperplasia	
No biopsies	1.00
At least 1 biopsy, no atypical hyperplasia	0.93
No atypical hyperplasia, hyperplasia status unknown for at least 1 biopsy	1.00
Atypical hyperplasia in at least 1 biopsy	1.82

Source: Modified with permission from from Gail MH et al: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 81:1879, 1989. By permission of Oxford University Press.

CANCER SCREENING

Early detection is the key to success in cancer therapy. Screening for common cancers using relatively noninvasive tests is expected to lead to early diagnosis, allow more conservative surgical therapies with decreased morbidity, and potentially improve surgical cure rates and overall survival rates. Key factors that influence screening guidelines are how prevalent the cancer is in the population, what risk is associated with the screening measure, and whether early diagnosis actually affects outcome. The value of a widespread screening measure is likely to go up with the prevalence of the cancer in a population, which often determines the age cutoffs for screening and explains why screening is done only for common cancers. The risks associated with the screening measure are a significant consideration, especially with more invasive screening measures such as colonoscopy. The consequences of a false-positive screening test result also need to be considered. For example, when 1000 screening mammograms are taken, only 2 to 4 new cases of cancer will be identified; this number is slightly higher (6 to 10 prevalent cancers per 1000 mammograms) for initial screening mammograms.[82] However, as many as 10% of screening mammograms may be potentially suggestive of an abnormality, which requires further imaging (i.e., a 10% recall rate). Of those women with abnormal mammogram findings, only 5 to 10% will be determined to have a breast cancer. Among women for whom biopsy is recommended, 25 to 40% will have a breast cancer. A false-positive screening result is likely to induce significant emotional distress in patients, leads to unnecessary biopsies, and has cost implications for the health care system.

The 2009 American Cancer Society guidelines for the early detection of cancer are listed in Table 10-10.[83] These guidelines are updated periodically to incorporate emerging technologies and new data on the efficacy of screening measures. Besides the American Cancer Society, several other professional bodies make recommendations for screening. Although the screening guidelines differ somewhat, most organizations do not emphasize one screening strategy as superior to another, but all emphasize the importance of age-appropriate screening.

Table 10-10 American Cancer Society Recommendations for Early Detection of Cancer in Average-Risk, Asymptomatic Individuals

Cancer Site	Population	Test or Procedure	Frequency
Breast	Women aged ≥20 y	Breast self-examination	Monthly, starting at age 20
		Clinical breast examination	Every 3 y, ages 20–39
			Annual, starting at age 40
		Mammography	Annual, starting at age 40
Colorectal	Men and women aged ≥50 y	Fecal occult blood test (FOBT) or fecal immunochemical test (FIT)	Annual, starting at age 50
		or	
		Flexible sigmoidoscopy	Every 5 y, starting at age 50
		or	
		FOBT and flexible sigmoidoscopy	Annual FOBT (or FIT) and flexible sigmoidoscopy every 5 y, starting at age 50
		or	
		Double-contrast barium enema (DCBE) *or*	DCBE every 5 y, starting at age 50
		Colonoscopy	Colonoscopy every 10 y, starting at age 50
Prostate	Men aged ≥50 y	Digital rectal examination (DRE) and prostate-specific antigen (PSA) test	Offer PSA test and DRE annually, starting at age 50, for men who have life expectancy of at least 10 y
Cervix	Women aged ≥18 y	Pap test	Cervical cancer screening beginning 3 y after first vaginal intercourse, but no later than age 21 y; screening every year with conventional Pap tests or every 2 y using liquid-based Pap tests; at or after age 30 y, women who have had three normal test results in a row may get screened every 2 to 3 y with cervical cytologic analysis alone or every 3 y with a human papillomavirus DNA test plus cervical cytologic analysis.
Endometrial	Women at menopause	—	At the time of menopause, women at average risk should be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians.
Cancer-related checkup	Men and women aged ≥20 y	On the occasion of a periodic health examination, the cancer-related checkup should include examination of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, as well as health counseling about tobacco use, sun exposure, diet and nutrition, risk factors, sexual practices, and environmental and occupational exposures.	

Source: Modified with permission from Smith et al.[83]

Screening guidelines are developed for the general baseline-risk population. These guidelines need to be modified for patients who are at high risk. For example, more intensive colorectal cancer screening is recommended for individuals at increased risk because of a history of adenomatous polyps, a personal history of colorectal cancer, a family history of either colorectal cancer or colorectal adenomas diagnosed in a first-degree relative before age 60 years, a personal history of inflammatory bowel disease of significant duration, or a family history or genetic test result indicating FAP or HNPCC. For some diseases, in higher risk populations, both the screening modality and the screening intensity may be altered. For example, breast magnetic resonance imaging is recommended as an adjunct to mammography for breast cancer screening in BRCA mutation carriers, first-degree relatives of carriers, and women with a lifetime breast cancer risk of 20 to 25% or higher.[84]

CANCER DIAGNOSIS

The definitive diagnosis of solid tumors usually is obtained by performing a biopsy of the lesion. Biopsy findings determine the tumor histology and grade and thus assist in definitive therapeutic planning. When a biopsy has been performed at an outside institution, the slides should be reviewed to confirm the outside diagnosis.

Biopsy specimens of mucosal lesions usually are obtained endoscopically (e.g., via colonoscope, bronchoscope, or cystoscope). Lesions that are easily palpable, such as those of the skin, can either be excised or sampled by punch biopsy. Deep-seated lesions can be localized with computed tomographic (CT) scan or ultrasound guidance for biopsy.

A sample of a lesion can be obtained with a needle or with an open incisional or excisional biopsy. Fine-needle aspiration is easy and relatively safe, but has

the disadvantage of not giving information on tissue architecture. For example, fine-needle aspiration biopsy of a breast mass can make the diagnosis of malignancy but cannot differentiate between an invasive and noninvasive tumor. Therefore core-needle biopsy is more advantageous when the histologic findings will affect the recommended therapy. Core biopsy, like fine-needle aspiration, is relatively safe and can be performed either by direct palpation (e.g., a breast mass or a soft tissue mass) or can be guided by an imaging study (e.g., stereotactic core biopsy of the breast). Core biopsies, like fine-needle aspirations, have the disadvantage of introducing sampling error. For example, 19 to 44% of patients with a diagnosis of atypical ductal hyperplasia based on core biopsy findings of a mammographic abnormality are found to have carcinoma upon excision of the lesion.[85] It is crucial to ensure that the histologic findings are consistent with the clinical scenario and to know the appropriate interpretation of each histologic finding. A needle biopsy for which the report is inconsistent with the clinical scenario should be either repeated or followed by an open biopsy.

Open biopsies have the advantage of providing more tissue for histologic evaluation and the disadvantage of being an operative procedure. Incisional biopsies are reserved for very large lesions in which a definitive diagnosis cannot be made by needle biopsy. Excisional biopsies are performed for lesions for which either core biopsy is not possible or the results are nondiagnostic. Excisional biopsies should be performed with curative intent, that is, by obtaining adequate tissue around the lesion to ensure negative surgical margins. Marking of the orientation of the margins by sutures or clips by the surgeon and inking of the specimen margins by the pathologist will allow for determination of the surgical margins and will guide surgical re-excision if one or more of the margins are positive for microscopic tumor or are close. The biopsy incision should be oriented to allow for excision of the biopsy scar if repeat operation is necessary. Furthermore, the biopsy incision should directly overlie the area to be removed rather than tunneling from another site, which runs the risk of contaminating a larger field. Finally, meticulous hemostasis during a biopsy is essential, because a hematoma can lead to contamination of the tissue planes and can make subsequent follow-up with physical examinations much more challenging.

CANCER STAGING

Cancer staging is a system used to describe the anatomic extent of a malignant process in an individual patient. Staging systems may incorporate relevant clinical prognostic factors such as tumor size, location, extent, grade, and dissemination to regional lymph nodes or distant sites. Accurate staging is essential in designing an appropriate treatment regimen for an individual patient. Staging of the lymph node basin is considered a standard part of primary surgical therapy for most surgical procedures and is discussed later in this chapter. Cancer patients who are considered to be at high risk for distant metastasis usually undergo a preoperative staging work-up. This involves a set of imaging studies of sites of preferential metastasis for a given cancer type. For example, for a patient with breast cancer, a staging work-up would include a chest radiograph, bone scan, and liver ultrasound or CT scan of the abdomen to evaluate for lung, bone, and liver metastases, respectively. A distant staging work-up usually is performed only for patients likely to have metastasis based on the characteristics of the primary tumor; for example, a staging work-up for a patient with ductal carcinoma in situ of the breast or a small invasive breast tumor is likely to be low yield and not cost effective.

Recently there also is interest in using molecular imaging with positron emission tomography (PET) scanning, or PET/CT, for cancer staging. Most commonly PET scanning is performed with fluorine 18 incorporated into fluorodeoxyglucose (FDG). FDG PET assesses the rate of glycolysis. FDG uptake is increased in most malignant tissues but also in benign pathologic conditions such as inflammatory disorders, trauma, infection, and granulomatous disease. It may be especially useful in the staging and management of lymphoma, lung cancer, and colorectal cancer. The role of PET in evaluating many other cancers is evolving, and additional molecular tracers, such as 3'-deoxy-3'-^{18}F-fluorothymidine, used to assess proliferation, are being actively pursued.

Standardization of staging systems is essential to allow comparison of results from different studies from different institutions and worldwide. The staging systems proposed by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (International Union Against Cancer, or UICC) are among the most widely accepted staging systems. Both the AJCC and the UICC have adopted a shared tumor, node, and metastasis (TNM) staging system that defines the cancer in terms of the anatomic extent of disease and is based on assessment of three components: the size of the primary tumor (T), the presence (or absence) and extent of nodal metastases (N), and the presence (or absence) and extent of distant metastases (M).

The TNM staging applies only to tumors that have been microscopically confirmed to be malignant. Standard TNM staging (clinical and pathologic) is completed at initial diagnosis. Clinical staging (cTNM or TNM) is based on information gained up until the initial definitive treatment. Pathologic staging (pTNM) includes clinical information and information obtained from pathologic examination of the resected primary tumor and regional lymph nodes. Other classifications, such as retreatment staging (rTNM) or autopsy staging (aTNM), should be clearly identified as such.

The clinical measurement of tumor size (T) is the one judged to be the most accurate for each individual case based on physical examination and imaging studies. For example, in breast cancer the size of the tumor could be obtained from a physical examination, mammogram, or ultrasound, and the tumor size is based only on the invasive component.

If even one lymph node is involved by tumor, the N component is at least N1. For many solid tumor types, simply the absence or presence of lymph node involvement is recorded, and the tumor is categorized either as N0 or N1. For other tumor types, the number of lymph nodes involved, the size of the lymph nodes or the lymph node metastasis, or the regional lymph node basin involved also has been shown to have prognostic value. In these cancers, the designations N1, N2, N3, and N4 suggest an increasing abnormality of lymph nodes based on size, characteristics, and location. NX indicates that the lymph

nodes cannot be fully assessed.

Cases in which there is no distant metastasis are designated M0, cases in which one or more distant metastases are detected are designated M1, and cases in which the presence of distant metastasis cannot be assessed are designated MX. In clinical practice, negative findings on clinical history and examination are sufficient to designate a case as M0. However, in clinical trials, routine follow-up staging work-ups often are performed to standardize the detection of distant metastases.

The practice of dividing cancer cases into groups according to stage is based on the observation that the survival rates are higher for localized (lower-stage) tumors than for tumors that have extended beyond the organ of origin. Therefore, staging assists in selection of therapy, estimation of prognosis, evaluation of treatments, and exchange of information among treatment centers. Notably, the AJCC regularly updates its staging system to incorporate advances in prognostic technology to improve the predictive accuracy of the TNM system. Therefore it is important to know which revision of a staging system is being used when evaluating studies.

TUMOR MARKERS

Prognostic and Predictive Tissue Markers

Tumor markers are substances that can be detected in higher than normal amounts in the serum, urine, or tissues of patients with certain types of cancer. Tumors markers are produced either by the cancer cells themselves or by the body in a response to the cancer.

Over the past decade, there has been an especially high interest in identifying tissue tumor markers that can be used as prognostic or predictive markers. Although the terms *prognostic marker* and *predictive marker* are sometimes used interchangeably, the term *prognostic marker* generally is used to describe molecular markers that predict disease-free survival, disease-specific survival, and overall survival, whereas the term *predictive marker* often is used in the context of predicting response to certain therapies.

The goal is to identify prognostic markers that can give information on prognosis independent of other clinical characteristics and therefore can provide information to supplement the projections based on clinical presentation. This would allow practitioners to further classify patients as being at higher or lower risk within clinical subgroups and to identify patients who may benefit most from adjuvant therapy. For example, ideal prognostic tumor markers would be able to help determine which patients with node-negative breast cancer are at higher risk of relapse so that adjuvant systemic therapy could be given only to that group. However, although a large number of studies have identified potential novel prognostic markers, most have not been tested with enough vigor to be shown to be of clinical utility. In the 2007 American Society of Clinical Oncology (ASCO) guidelines, it was decided that level of uPA/PAI-1 measured by enzyme-linked immunosorbent assay could be used to determine prognosis in cases of newly diagnosed node-negative breast cancer.[86] In contrast, the data for many other markers, including DNA content, proportion of tumor cells in S phase, Ki-67, cyclin E, p27, p21, thymidine kinase, topoisomerase II, HER2, p53, and cathepsin D, were felt to be insufficient to support their use in the management of breast cancer patients.[86] Similarly, in the 2006 ASCO GI tumor guidelines, the data were felt to be insufficient to recommend the routine use of p53, *ras*, thymidine synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase, microsatellite instability, 18q loss of heterozygosity, or deleted-in-colon-cancer protein in the management of patients with colorectal cancer.[87]

Predictive markers are markers that can prospectively identify patients who will benefit from a certain therapy. For example in breast cancer, estrogen receptor (ER) and HER2 assessment can identify patients who can benefit from antiestrogen therapies (e.g., tamoxifen) and anti-HER2 targeted therapies (e.g., trastuzumab), respectively, and the 2007 ASCO guidelines recommend that these markers be routinely assessed.[86] High-throughput techniques such as transcriptional profiling allow for assessment of the relative mRNA levels of thousands of genes simultaneously in a given tumor using microarray technology. With the advent of such molecular profiling technologies, researchers have focused on identifying expression profiles that are prognostic for different cancer types. For breast cancer, although many such multiparameter tests are under development, few have reached the large-scale validation stage (Table 10-11).[88] In 2007, ASCO guidelines suggested that one of these, the Onco*type* DX assay, can be used to predict recurrence in women with node-negative, ER-positive breast cancer who are treated with tamoxifen.[86] Onco*type* DX is a quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) test that used paraffin-fixed tissue. A 21-gene recurrence score (RS) is generated based on the expression of 16 cancer genes and 5 reference genes. The levels of expression are used to derive an RS that ranges from 0 to 100, using a prospectively defined mathematical algorithm. This novel quantitative approach to the evaluation of the best-known molecular pathways in breast cancer has produced impressive results. Use of this multigene assay to predict recurrence was validated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, in which ER-positive, node-negative patients had received tamoxifen. Of the 2617 patients on the trial who had received tamoxifen, paraffin block tumor tissue samples were available for 675 of them and RT-PCR was successfully completed for 668.[89] By multivariate Cox proportional analysis, RS was found to be independently associated with recurrence risk, with a hazard ratio of 3.21 (95% confidence interval of 2.23 to 4.65, P <.001). The RS was indeed able to stratify patients by freedom from distant recurrence (Figs. 10-9, 10-10).[89] The ongoing Trial Assessing Individualized Options for Treatment for breast cancer (TAILORx) is evaluating the utility of Onco*type* DX for predicting prognosis in patients with ER-positive, node-negative tumors and will focus on women with intermediate RS scores in whom the role of chemotherapy is unclear. Several other multigene predictors for breast cancer are under development, including MammaPrint, a gene expression profiling platform assessing a 70-gene transcriptional signature.[90] This assay was approved by the Food and Drug Administration (FDA) in February 2007. The usefulness of this assay in making

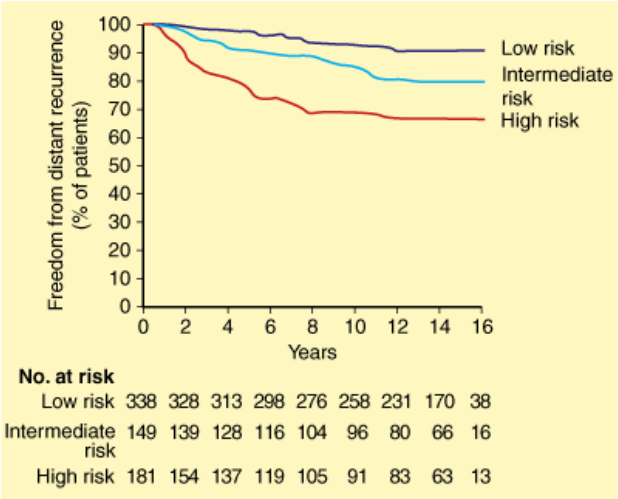
therapy-related decisions is being tested prospectively in a large-scale study, the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial.

Table 10-11 Sensitivity and Specificity of Some Common Tumor Markers

Marker	Cancer	Sensitivity (%)	Specificity (%)
Prostate-specific antigen (4 μg/L)	Prostate	57–93	55–68
Carcinoembryonic antigen	Colorectal	40–47	90
	Breast	45	81
	Recurrent disease	84	100
Alpha-fetoprotein	Hepatocellular	98	65
Cancer antigen 19-9	Pancreatic	78–90	95
Cancer antigen 27-29	Breast	62	83
Cancer antigen 15-3	Breast	57	87

Source: Adapted with permission from Way et al.[88]

Fig. 10-9.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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Likelihood of distant recurrence, according to recurrence score categories. Freedom from distant recurrence according to risk group, based on recurrence scores derived from tumor levels of expression of 21 genes.

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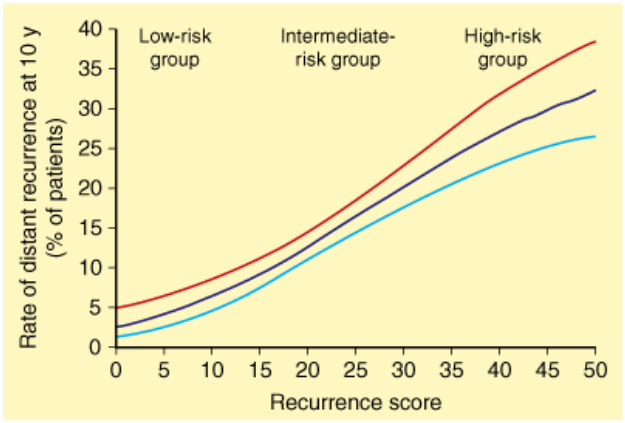
Fig. 10-10.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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Distant recurrence as a continuous function of the recurrence score derived from tumor levels of expression of 21 genes.

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Multigene profiles to predict prognosis are in development or in validation phases for many other solid tumor types, including lung cancer, ovarian cancer, pancreatic cancer, colorectal cancer, and melanoma. Gene signatures and sequence alterations also are being studied for their ability to predict response to specific chemotherapy regimens or targeted therapies. Many of these multigene marker sets will likely be incorporated into clinical practice in the years to come.

Serum Markers

Serum markers are under active investigation because they may allow early diagnosis of a new cancer or may be used to follow cancer response to therapy or monitor for recurrence. Unfortunately, identification of serum markers of clinical value has been challenging. Many of the tumor markers proposed so far have had low sensitivities and specificities (see Table 10-11).[88] Tumor marker levels may not be elevated in all patients with cancer, especially in the early stages, when a serum marker would be most useful for diagnosis. Therefore when a tumor marker is used to monitor recurrence, it is important to be certain that the level of the tumor marker was elevated before primary therapy. Moreover, tumor marker levels can be elevated in benign conditions. Many tumor markers are not specific for a certain type of cancer and can be elevated with more than one type of tumor. Because there may be significant laboratory variability, it is important to obtain serial results from the same laboratory. In spite of these many clinical limitations, several serum markers are in clinical use. A few of the commonly measured serum tumor markers are discussed in the following sections.

PROSTATE-SPECIFIC ANTIGEN

Prostate-specific antigen (PSA) is potentially the best serum marker now available. PSA is an androgen-regulated serine protease produced by the prostate epithelium. PSA is normally present in low concentrations in the blood of all adult males. PSA levels may be elevated in the blood of men with benign prostate conditions such as prostatitis and benign prostatic hyperplasia, as well as in men with prostate cancer. PSA levels have been shown to be useful in evaluating the effectiveness of prostate cancer treatment and monitoring for recurrence after therapy. In monitoring for recurrence, a trend of increasing levels is considered more significant than a single absolute elevated value.

Although PSA is widely used for prostate cancer screening in the United States, and the American Urologic Association and the American Cancer Society both recommend yearly PSA testing for men aged 50 years and older with a life expectancy of >10 years, the specific level indicating a need to initiate a work-up, the interval at which to measure PSA levels, and the utility of PSA screening all remain controversial.[91] Therefore it is advised that before PSA screening is initiated a discussion take place with the patient about the potential benefits, limitations, and harms associated with testing. Results of a large multicenter study suggested that a total serum PSA level of 4 ng/mL should be used as a threshold for performing a prostate biopsy, but 20 to 50% of clinically significant prostate cancers occur in men with total serum PSA levels of <4 ng/mL.[92] Others have suggested that biennial PSA screening is sufficient to detect almost all prostate cancers while they are curable and that the screening interval can be altered on the basis of PSA level. Finally, although the use of serum PSA screening does lead to earlier prostate cancer detection, it remains to be demonstrated that this translates into a survival benefit. The efficacy of PSA as a screening tool is being evaluated in randomized controlled trials, and it is hoped that these will answer this question.

CARCINOEMBRYONIC ANTIGEN

Carcinoembryonic antigen (CEA) is a glycoprotein found in the embryonic endodermal epithelium. Elevated CEA levels have been detected in patients with primary colorectal cancer as well as in patients with breast, lung, ovarian, prostate, liver, and pancreatic cancer. Levels of CEA also may be elevated in benign conditions such as diverticulitis, peptic ulcer disease, bronchitis, liver abscess, and alcoholic cirrhosis, especially in smokers and in elderly persons.

CEA measurement is most commonly used in the management of colorectal cancer. However, the appropriate use of CEA testing in patients with colorectal cancer has been debated. Use of CEA level as a screening test for colorectal cancer is not recommended. CEA levels may be useful if obtained preoperatively and postoperatively in patients with a diagnosis of colorectal cancer. Preoperative elevation of CEA level is an indicator of poor prognosis. However, the 2007 ASCO clinical practice guidelines state that the data are insufficient to support the use of CEA to determine whether to give a patient adjuvant therapy; the data are stronger for the use of CEA for monitoring for postoperative recurrence.[86] CEA measurement is the most cost-effective approach for detecting metastasis, with 64% of recurrences being detected first by an elevation in CEA level. Therefore, in cases in which the patient would be a candidate for resection of recurrent colorectal cancer or systemic therapy, the 2006 ASCO guidelines recommend that postoperative CEA testing be performed every 3 months in patients with stage II or III disease for at least 3 years.[87] CEA is the marker of choice for monitoring metastatic colorectal cancer during systemic therapy.[87]

There is also interest in using CEA levels for monitoring patients with breast cancer. However, the 2007 ASCO guidelines state that the routine use of CEA for screening, diagnosis, staging, or surveillance of breast cancer is not recommended because available data are insufficient.[86] For monitoring patients during active therapy, CEA can be used in conjunction with diagnostic imaging and history and physical examination.[86] In the absence of measurable disease, an increase in CEA level may be taken to indicate treatment failure. However, caution is advised when interpreting rising levels in the first 4 to 6 weeks of therapy.[86]

ALPHA-FETOPROTEIN

Alpha-fetoprotein (AFP) is a glycoprotein normally produced by a developing fetus. AFP levels decrease soon after birth in healthy adults. An elevated level of AFP suggests the presence of either primary liver cancer or a germ cell tumor of the ovary or testicle. Rarely, other types of cancer such as gastric cancer are associated with an elevated AFP level. Benign conditions that can cause elevations of AFP include cirrhosis, hepatic necrosis, acute hepatitis, chronic active hepatitis, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and pregnancy.[93]

The sensitivity of an elevated AFP level for detecting HCC is approximately 60%. AFP is considered to be sensitive and specific enough to be used for screening for HCC in high-risk populations. Current consensus recommendations are to screen healthy hepatitis B virus carriers with annual or semiannual measurement of AFP level and to screen carriers with cirrhosis or chronic hepatitis and patients with cirrhosis of any etiology with twice-yearly measurement of AFP level and liver ultrasonography.[94] Although AFP testing has been used widely for a long time, its efficacy in early diagnosis of HCC is limited. With improvements in imaging technology, a larger proportion of patients diagnosed with HCC are now AFP seronegative.

CANCER ANTIGEN 19-9

Cancer antigen 19-9 (CA 19-9) is a tumor-related antigen that was originally defined by a monoclonal antibody produced by a hybridoma prepared from murine spleen cells immunized with a human colorectal cancer cell line.[87] The data are insufficient to recommend use of CA 19-9 for screening, diagnosis, surveillance, or monitoring of therapy for colon cancer.[87] Based on the 2006 ASCO guidelines, there are also insufficient data to recommend use of CA 19-9 for screening, diagnosis, or determination of the operability of pancreatic cancer.[87] However, for patients with locally advanced or metastatic cancer receiving active therapy, CA 19-9 can be measured at the start of therapy and every 1 to 3 months while therapy is given; elevations in serial CA 19-9 levels may indicate progressive disease and should be confirmed by additional studies.[87]

CANCER ANTIGEN 15-3

Cancer antigen 15-3 (CA 15-3) is an epitope of a large membrane glycoprotein encoded by the *MUC1* gene that tumor cells shed into the bloodstream. The CA 15-3 epitope is recognized by two monoclonal antibodies in a sandwich radioimmunoassay. CA 15-3 levels are most useful in following the course of treatment in women diagnosed with advanced breast cancer. CA 15-3 levels are infrequently elevated in early breast cancer. CA 15-3 levels can be increased in benign conditions such as chronic hepatitis, tuberculosis, sarcoidosis, pelvic inflammatory disease, endometriosis, systemic lupus erythematosus, pregnancy, and lactation, and in other types of cancer such as lung, ovarian, endometrial, and GI cancers.

The sensitivity of CA 15-3 is higher for metastatic disease, and in these cases studies have shown sensitivity to be between 54 and 87%, with specificity as high as 96%. This has led to interest in using CA 15-3 for monitoring patients with advanced breast cancer for recurrence. Elevated CA 15-3 levels have been reported before relapse in 54% of patients, with a lead time of 4.2 months. Therefore, detection of elevated CA 15-3 levels during follow-up should prompt evaluation for recurrent disease. However, 6 to 8% of patients without recurrence will have elevated CA 15-3 levels that require evaluation. Moreover, monitoring with the use of CA 15-3 levels has shown no demonstrated impact on survival. Therefore, the 2007 ASCO guidelines state that the routine use of CA 15-3 for screening, diagnosis, staging, or surveillance of breast cancer is not recommended because available data are insufficient.[86] For monitoring patients during active therapy, CA 15-3 can be used in conjunction with diagnostic imaging and history and physical examination.[86] In the absence of measurable disease, an increase may be interpreted to indicate treatment failure. However, caution is advised when interpreting rising levels in the first 4 to 6 weeks of therapy.[86]

CANCER ANTIGEN 27-29

The MUC-1 gene product in the serum may be quantitated by using radioimmunoassay with a monoclonal antibody against the cancer antigen 27-29 (CA 27-29). CA 27-29 levels can be elevated in breast cancer as well as in cancers of the colon, stomach, kidney, lung, ovary, pancreas, uterus, and liver. First-trimester pregnancy, endometriosis, benign breast disease, kidney disease, and liver disease also may be associated with elevated CA 27-29 levels.

CA 27-29 has been reported to have a sensitivity of 57%, a specificity of 98%, a positive predictive value of 83%, and a negative predictive value of 93% in detecting breast cancer recurrences.[95] Although CA 27-29 has been found to predict recurrence an average of 5.3 months before other symptoms or tests, testing of CA 27-29 levels has not been demonstrated to affect disease-free and overall survival rates.[95,96] Therefore, the 2007 ASCO guidelines state that, as with CA 15-3, the routine use of CA 27-29 for screening, diagnosis, staging, or surveillance of breast cancer is not recommended because available data are insufficient.[86] CA 27-29 levels can be used together with diagnostic imaging and history and physical examination to monitor patients during active therapy.[86] When no measurable disease is present, an increase in level may be considered to indicate treatment failure. However, rising levels in the first 4 to 6 weeks of therapy should be interpreted with caution.[86]

CIRCULATING TUMOR CELLS

Circulating tumor cells (CTCs) are cells present in the blood that possess antigenic or genetic characteristics of a specific tumor type.[86] One CTC detection methodology is capture and quantitation of CTCs with immunomagnetic beads coated with antibody specific for cell-surface, epithelial, or cancer antigens. Another methodology used to detect cancer cells in the peripheral blood is RT-PCR. It has been suggested that measurement of CTCs can be an effective tool for selecting patients who have a high risk of relapse and for monitoring efficacy of cancer therapy.

CTCs have probably been most extensively studied in breast cancer, with over 400 publications to date.[86] The most promising data come from the use of CTC measures in metastatic breast cancer. In a prospective multicenter trial, the number of CTCs (≥5 CTCs vs. <5 CTCs per 7.5 mL of whole blood) before treatment of metastatic breast cancer was an independent predictor of progression-free and overall survival rates.[97] The presence of >5 CTCs after the first course of therapy predicted lack of response to treatment. This technology, known as *CellSearch,* has been approved by the FDA for clinical use. However, there are no data to prove that the use of CTC testing leads to improved survival or improved quality of life; thus the ASCO 2007 guideline update does not recommend the use of CTC measurement in any clinical setting.[86] The clinical utility of measuring CTC response to initial therapy is now being tested prospectively in a multicenter clinical trial. The use of CTC levels as a tool in treating many other types of tumor is also under active investigation, again with no level I evidence for clinical utility.

The prognostic implications of detection of CTCs by RT-PCR have been intensively studied for melanoma. In the recent multicenter Sunbelt Melanoma Trial, serial RT-PCR was performed on peripheral blood samples using four markers—tyrosinase, melanoma antigen reacting to T cell (MART-1), melanoma antigen 3 (MAGE3), and gp 100—to detect occult melanoma cells in the bloodstream.[98] Although there were no differences in survival between patients in whom at least one marker was detected and those in whom no markers were detected, the disease-free survival and distant disease-free survival were worse for patients in whom more than one marker was detected at any time during follow-up.[98] The detection of occult cancer cells with RT-PCR remains investigational, however, and is not used to direct therapy for melanoma and other cancer types at this time.

Bone Marrow Micrometastases

Micrometastatic disease in the bone marrow, also referred to as *minimal residual disease,* also is being investigated as a potential prognostic marker. Bone marrow micrometastatic disease usually is detected by staining bone marrow aspirates with monoclonal antibodies to cytokeratin, but other methodologies such as flow cytometry and RT-PCR are being explored. Breast cancer patients with bone marrow micrometastasis have larger tumors, tumors with a higher histologic grade, more lymph node metastases, and more hormone receptor–negative tumors than patients without bone marrow micrometastasis. In 4700 patients with stage I, II, or III breast cancer, micrometastasis was a significant prognostic factor associated with poor overall survival, breast cancer–specific survival, disease-free survival, and distant disease-free survival during a 10-year observation period.[99] At this time the routine use of bone marrow testing is not recommended.[86] Ongoing clinical trials are evaluating the role of routine assessment of bone marrow status in the care of patients with early and advanced breast cancer. The utility of assessment of bone marrow micrometastasis is also being evaluated in other tumor types, including gastric, esophageal, colorectal, lung, cervical, and ovarian cancer.[100]

SURGICAL APPROACHES TO CANCER THERAPY

Multidisciplinary Approach to Cancer

Although surgery is an effective therapy for most solid tumors, patients who die from cancer usually die of metastatic disease. Therefore, to improve patient survival rates, a multimodality approach including systemic therapy and radiation therapy is key for most tumors. It is important that surgeons involved in cancer care not only know the techniques for performing a cancer operation but also know the alternatives to surgery and be well versed in reconstructive options. It is also crucial that the surgeon be familiar with the indications for and complications of preoperative and postoperative chemotherapy and radiation therapy. Although the surgeon will not be delivering these other therapies, as the first physician to see a patient with a cancer diagnosis, he or she is ultimately responsible for initiating the appropriate consultations. For this reason, the surgeon often is responsible for determining the most appropriate

adjuvant therapy for a given patient as well as the best sequence for therapy. In most instances, a multidisciplinary approach beginning at the patient's initial presentation is likely to yield the best result.

Surgical Management of Primary Tumors

The goal of surgical therapy for cancer is to achieve oncologic cure. A curative operation presupposes that the tumor is confined to the organ of origin or to the organ and the regional lymph node basin. Patients in whom the primary tumor is not resectable with negative surgical margins are considered to have inoperable disease. The operability of primary tumors is best determined before surgery with appropriate imaging studies that can define the extent of local-regional disease. For example, a preoperative thin-section CT scan is obtained to determine resectability of pancreatic cancer, which is based on the absence of extrapancreatic disease, the absence of tumor extension to the superior mesenteric artery and celiac axis, and a patent superior mesenteric vein–portal vein confluence.[101] Disease involving multiple distant metastases is deemed inoperable because it is usually not curable with surgery of the primary tumor. Therefore patients who are at high risk of having distant metastasis should undergo a staging work-up before surgery for the primary tumor. On occasion, primary tumors are resected in these patients for palliative reasons, such as improving the quality of life by alleviating pain, infection, or bleeding. An example of this is toilet mastectomies for large ulcerated breast tumors. Patients with limited metastases from a primary tumor on occasion are considered surgical candidates if the natural history of isolated distant metastases for that cancer type is favorable or the potential complications associated with leaving the primary tumor intact are significant.

In the past it was presumed that the more radical the surgery, the better the oncologic outcome would be. Over the past 20 years, this has been recognized as not necessarily being true, which has led to more conservative operations, with wide local excisions replacing compartmental resections of sarcomas, and partial mastectomies, skin-sparing mastectomies, and breast-conserving therapies replacing radical mastectomies for breast cancer. The uniform goal for all successful oncologic operations seems to be achieving widely negative margins with no evidence of macroscopic or microscopic tumor at the surgical margins. The importance of negative surgical margins for local tumor control and/or survival has been documented for many tumor types, including sarcoma, breast cancer, pancreatic cancer, and rectal cancer. Thus it is clear that every effort should be made to achieve microscopically negative surgical margins. Inking of the margins, orientation of the specimen by the surgeon, and immediate gross evaluation of the margins by a pathologist using frozen-section analysis when necessary may assist in achieving negative margins at the first operation. In the end, although radiation therapy and systemic therapy can assist in decreasing local recurrence rates in the setting of positive margins, adjuvant therapy cannot substitute for adequate surgery.

Although it is clear that the surgical gold standard is negative surgical margins, the appropriate surgical margins for optimal local control are controversial for many cancer types. In contrast, in melanoma the optimal margin width for any tumor depth has been defined, owing to the systematic study of this question in randomized clinical trials.[102,103] Although such randomized studies may not be possible for all tumor types, it is important to determine optimum surgical margins for each cancer type so that adjuvant radiation and systemic therapy can be offered to patients deemed to be at increased risk for local treatment failure.

Surgical Management of the Regional Lymph Node Basin

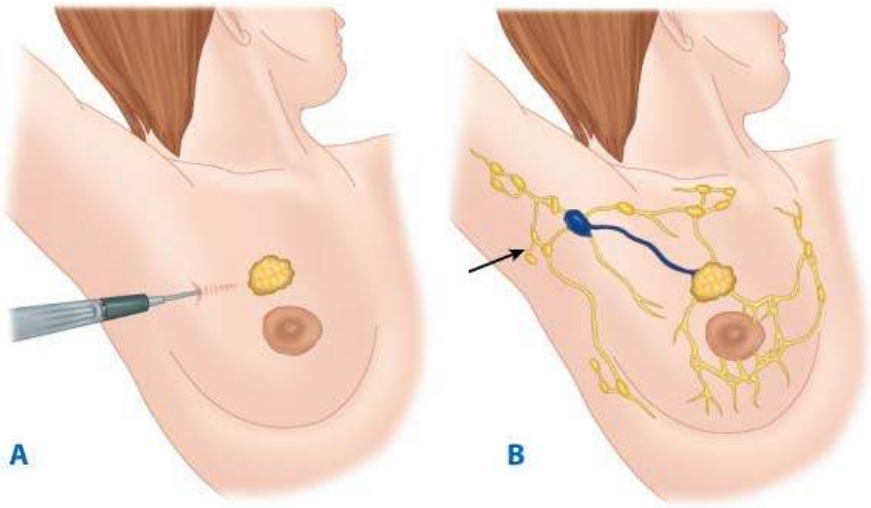
Most neoplasms have the ability to metastasize via the lymphatics. Therefore, most oncologic operations have been designed to remove the primary tumor and draining lymphatics en bloc. This type of operative approach usually is undertaken when the lymph nodes draining the primary tumor site lie adjacent to the tumor bed, as is the case for colorectal cancers and gastric cancers. For tumors in which the regional lymph node basin is not immediately adjacent to the tumor (e.g., melanomas), lymph node surgery can be performed through a separate incision. Unlike most carcinomas, soft tissue sarcomas rarely metastasize to the lymph nodes (<5%); therefore lymph node surgery usually is not necessary.

It is generally accepted that a formal lymphadenectomy is likely to minimize the risk of regional recurrence of most cancers. For example, the introduction of total mesorectal excision of rectal cancer has been associated with a large decline in local-regional recurrence, and this procedure has become the new standard of operative management.[104] On the other hand, there have been two opposing views regarding the role of lymphadenectomy in survival of cancer patients. The traditional Halsted view states that lymphadenectomy is important for staging and survival. The opposing view counters that cancer is systemic at inception and that lymphadenectomy, although useful for staging, does not affect survival. For most cancers, involvement of the lymph nodes is one of the most significant prognostic factors. Interestingly, removal of a larger number of lymph nodes has been found to be associated with an improved overall survial rate for many tumors, including breast cancer, colon cancer, and lung cancer. Although this seems to support the Halsted theory that more extensive lymphadenectomy yielding of nodes reduces the risk of regional recurrence, there may be alternative explanations for the same finding. For example, the surgeon who performs a more extensive lymphadenectomy may obtain wider margins around the tumor or even provide better overall care, such as ensuring that patients receive the appropriate adjuvant therapy or undergo a more thorough staging work-up. Alternatively, the pathologist may perform a more thorough examination, identifying more nodes and more accurately staging the nodes. The effect of appropriate staging on survival is twofold. Patients with nodal metastases may be offered adjuvant therapy, which improves their survival chances. Further, the improved staging can improve perceived survival rates through a "Will Rogers effect"; that is, identification of metastases that had formerly been silent and unidentified leads to stage migration and thus to a perceived improvement in chances of survival. Clearly the impact of lymphadenectomy on survival will not be easily resolved. Because minimizing regional

recurrences as much as possible is a goal of cancer treatment, the standard of care remains lymphadenectomy for most tumors.

A relatively new development in the surgical management of the clinically negative regional lymph node basin is the introduction of lymphatic mapping technology (Fig. 10-11).[105] Lymphatic mapping and sentinel lymph node biopsy were first reported in 1977 by Cabanas for penile cancer.[106] Now, sentinel node biopsy is the standard of care for the management of melanoma and breast cancer. Moreover, the utility of sentinel node biopsy in other cancer types is being explored.

Fig. 10-11.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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Lymphatic mapping and sentinel lymph node biopsy for breast cancer. **A.** Peritumoral injection of blue dye. **B.** Blue dye draining into the sentinel lymph node.

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The first node to receive drainage from the tumor site is termed the sentinel node. This node is the node most likely to contain metastases, if metastases to that regional lymph node basin are present. The goal of lymphatic mapping and sentinel lymph node biopsy is to identify and remove the lymph node most likely to contain metastases in the least invasive fashion. The practice of sentinel lymph node biopsy followed by selective regional lymph node dissection for patients with a positive sentinel lymph node avoids the morbidity of lymph node dissections in patients with negative nodes. An additional advantage of the sentinel lymph node technique is that it directs attention to a single node, which allows more careful analysis of the lymph node most likely to have a positive yield and increases the accuracy of nodal staging. Two criteria are used to assess the efficacy of a sentinel lymph node biopsy: the sentinel lymph node identification rate and the false-negative rate. The sentinel lymph node identification rate is the proportion of patients in whom a sentinel lymph node was identified and removed among all patients undergoing an attempted sentinel lymph node biopsy. The false-negative rate is the proportion of patients with regional lymph node metastases in whom the sentinel lymph node was found to be negative. False-negative biopsy results may be due to identifying the wrong node or to missing the sentinel node (i.e., surgical error) or they may be due to the cancer cells' establishing metastases not in the first node encountered but in a second-echelon node (i.e., biologic variation). Alternatively, false-negative biopsy results may be due to inadequate histologic evaluation of the lymph node. The false-negative rates for sentinel lymph node biopsy in study series range between 0 and 11%. Both increases in the identification rate and decreases in the false-negative rate have been observed as surgeons gain experience with the technique.

Lymphatic mapping is performed by using isosulfan blue dye, technetium-labeled sulfur colloid or albumin, or a combination of both techniques to detect sentinel nodes. The combination of blue dye and technetium has been reported to improve the capability of detecting sentinel lymph nodes. The nodal drainage pattern usually is determined with a preoperative lymphoscintigram, and the "hot" and/or blue nodes are identified with the assistance of a gamma probe and careful nodal basin exploration. Careful manual palpation is a crucial part of the procedure to minimize the false-negative rate.

The nodes are evaluated with serial sectioning, hematoxylin and eosin staining, and immunohistochemical analysis with S-100 protein and homatropine methylbromide staining for melanoma and cytokeratin staining for breast cancer. Studies also are ongoing to evaluate the use of molecular techniques such as RT-PCR to rapidly assess the sentinel node status in the intraoperative setting. In a recent prospective trial, an RT-PCR assay for mammaglobin and cytokeratin 19 mRNA (GeneSearch) was found to have a sensitivity of 98.1% for detection of breast cancer metastases larger than 2 mm and 77.8% for metastases larger than 0.2 mm,[107] and it has been approved for use by the FDA. Ongoing studies are addressing how best to incorporate this and other similar technologies into clinical practice.

Another area of active investigation is the prognostic value of minimal nodal involvement. For example, in breast cancer, nodes with isolated tumor cell deposits of <0.2 mm (also called *nanometastasis*) are considered to be N0 by the sixth edition of the AJCC staging manual. However, some retrospective studies have suggested that even this amount of nodal disease burden has negative prognostic implications.[108] Molecular ultrastaging with RT-PCR for patients with node-negative disease was assessed in a prospective multicenter trial and was found not to be prognostic in malignant melanoma.[98] However, a recent meta-analysis of 22 studies enrolling 4019 patients found that PCR positivity was associated with worse overall and disease-free survival.[109] Further study of the utility of ultrastaging of nodes in breast cancer, melanoma, and several other tumor types is ongoing.

Surgical Management of Distant Metastases

The treatment of a patient with distant metastases depends on the number and sites of metastases, the cancer type, the rate of tumor growth, the previous treatments delivered and the responses to these treatments, and the patient's age, physical condition, and desires. Although once a tumor has metastasized it usually is not curable with surgical therapy, such therapy has resulted in cure in selected cases with isolated metastases to the liver, lung, or brain.

Patient selection is the key to the success of surgical therapy for distant metastases. The cancer type is a major determinant in surgical decision making. A liver metastasis from a colon cancer is more likely to be an isolated and thus resectable lesion than a liver metastasis from a pancreatic carcinoma. The growth rate of the tumor also plays an important role and can be determined in part by the disease-free interval and the time between treatment of the primary tumor and detection of the distant recurrence. Patients with longer disease-free intervals have a higher survival rate after surgical metastasectomy than those with a short disease-free interval. Similarly, patients who have synchronous metastases (metastases diagnosed at the initial cancer diagnosis) do worse after metastasectomy than patients who develop metachronous metastases (metastasis diagnosed after a disease-free interval). The natural history of metastatic disease is so poor for some tumors (e.g., pancreatic cancer) that there is no role at this time for surgical metastasectomy. In cancers with a more favorable outlook, observation for several weeks or months, potentially with initial treatment with systemic therapy, can allow the surgeon to monitor for metastases at other sites.

In curative surgery for distant metastases, as with surgery for primary tumors, the goal is to resect the metastases with negative margins. In patients with hepatic metastases that are unresectable because their location near intrahepatic blood vessels precludes a margin-negative resection, or because they are multifocal or hepatic function is inadequate, tumor ablation with cryotherapy or radiofrequency ablation is an alternative.[110,111] Curative resections or ablative procedures should be attempted only if the lesions are accessible and the procedure can be performed safely.

CHEMOTHERAPY

Clinical Use of Chemotherapy

In patients with documented distant metastatic disease, chemotherapy is usually the primary modality of therapy. The goal of therapy in this setting is to decrease the tumor burden, thus prolonging survival. It is rare to achieve cure with chemotherapy for metastatic disease for most solid tumors. Chemotherapy administered to a patient who is at high risk for distant recurrence but has no evidence of distant disease is referred to as *adjuvant chemotherapy.*

The goal of adjuvant chemotherapy is eradication of micrometastatic disease, with the intent of decreasing relapse rates and improving survival rates.

Adjuvant therapy can be administered after surgery (postoperative chemotherapy) or before surgery (preoperative chemotherapy, neoadjuvant chemotherapy, or induction therapy). A portion or all of the planned adjuvant chemotherapy can be administered before the surgical removal of the primary tumor. Preoperative chemotherapy has three potential advantages. The first is that preoperative regression of tumor can facilitate resection of tumors that were initially inoperable or allow more conservative surgery for patients whose cancer was operable to begin with. In the NSABP B-18 project, for example, women were randomly assigned to receive adjuvant doxorubicin and cyclophosphamide preoperatively or postoperatively. More patients treated before surgery than after surgery underwent breast-conserving surgery (68 vs. 60%).[112] The second advantage of preoperative chemotherapy is the treatment of micrometastases without the delay of postoperative recovery. The third advantage is the ability to assess a cancer's response to treatment clinically, after a number of courses of chemotherapy, and pathologically, after surgical resection. This is especially important if alternative treatment regimens are available to be offered to patients whose disease responded inadequately. Molecular characterization of the residual disease may also give insight into mechanisms of chemoresistance and possible therapeutic targets.

There are some potential disadvantages to preoperative chemotherapy, however. Although disease progression while the patient is receiving preoperative chemotherapy is rare in chemotherapy-sensitive tumors such as breast cancer, it is more frequent in relatively chemotherapy-resistant tumors such as sarcomas.[113] Thus, patient selection is critical to ensure that the opportunity to treat disease surgically is not lost by giving preoperative chemotherapy. Often, rates of postoperative wound infection, flap necrosis, and delays in postoperative adjuvant therapy do not differ between patients who are treated with preoperative chemotherapy and patients who are treated with surgery first. However, preoperative chemotherapy can introduce special challenges to tumor localization, margin analysis, lymphatic mapping, and pathologic staging.

Response to chemotherapy is monitored clinically with imaging studies as well as physical examinations. Response usually is defined as complete response,

partial response, stable disease, or progression. Response generally is assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[114] Objective tumor response assessment is critical, because tumor response is used as a prospective endpoint in clinical trials and tumor response is a guide to clinicians regarding continuation of current therapy.

Principles of Chemotherapy

Chemotherapy destroys cells by first-order kinetics, which means that with the administration of a drug a constant percentage of cells is killed, not a constant number of cells. If a patient with 10^{12} tumor cells is treated with a dose that results in 99.9% cell kill (3-log cell kill), the tumor burden will be reduced from 10^{12} to 10^{9} cells (or 1 kg to 1 g). If the patient is re-treated with the same drug, which theoretically could result in another 3-log cell kill, the cells would decrease in number from 10^{9} to 10^{6} (1 g to 1 mg) rather than being eliminated totally.

Chemotherapeutic agents can be classified according to the phase of the cell cycle during which they are effective. Cell-cycle phase–nonspecific agents (e.g., alkylating agents) have a linear dose-response curve, such that the fraction of cells killed increases with the dose of the drug.[115] In contrast, the cell-cycle phase–specific drugs have a plateau with respect to cell killing ability, and cell kill will not increase with further increases in drug dose.

Anticancer Agents

ALKYLATING AGENTS

Alkylating agents are cell-cycle–nonspecific agents, that is, they are able to kill cells in any phase of the cell cycle. They act by cross-linking the two strands of the DNA helix or by causing other direct damage to the DNA. The damage to the DNA prevents cell division and, if severe enough, leads to apoptosis. The alkylating agents are composed of three main subgroups: classic alkylators, nitrosoureas, and miscellaneous DNA-binding agents (Table 10-12).

Table 10-12 Classification of Chemotherapeutic Agents
Alkylating agents
Classic alkylating agents
Busulfan
Chlorambucil
Cyclophosphamide
Ifosfamide
Mechlorethamine (nitrogen mustard)
Melphalan
Mitomycin C
Triethylene thiophosphoramide (thiotepa)
Nitrosoureas
Carmustine (BCNU)
Lomustine (CCNU)
Semustine (MeCCNU)
Streptozocin
Miscellaneous DNA-binding agents
Carboplatin
Cisplatin
Dacarbazine (DTIC)
Hexamethylmelamine
Procarbazine
Antitumor antibiotics
Bleomycin
Dactinomycin (actinomycin D)
Daunorubicin
Doxorubicin
Idarubicin
Plicamycin (mithramycin)
Antimetabolites
Folate analogues

Methotrexate
Purine analogues
Azathioprine
Mercaptopurine
Thioguanine
Cladribine (2-chlorodeoxyadenosine)
Fludarabine
Pentostatin
Pyrimidine analogues
Capecitabine
Cytarabine
Floxuridine
Gemcitabine
Ribonucleotide reductase inhibitors
Hydroxyurea
Plant alkaloids
Vinca alkaloids
Vinblastine
Vincristine
Vindesine
Vinorelbine
Epipodophyllotoxins
Etoposide
Teniposide
Taxanes
Paclitaxel
Docetaxel
Miscellaneous agents
Asparaginase
Estramustine
Mitotane

ANTITUMOR ANTIBIOTICS

Antitumor antibiotics are the products of fermentation of microbial organisms. Like the alkylating agents, these agents are cell-cycle nonspecific. Antitumor antibiotics damage the cell by interfering with DNA or RNA synthesis, although the exact mechanism of action may differ by agent.

ANTIMETABOLITES

Antimetabolites are generally cell-cycle–specific agents that have their major activity during the S phase of the cell cycle and have little effect on cells in G_0. These drugs are most effective, therefore, in tumors that have a high growth fraction. Antimetabolites are structural analogues of naturally occurring metabolites involved in DNA and RNA synthesis. Therefore, they interfere with normal synthesis of nucleic acids by substituting for purines or pyrimidines in the metabolic pathway to inhibit critical enzymes in nucleic acid synthesis. The antimetabolites include folate antagonists, purine antagonists, and pyrimidine antagonists (see Table 10-12).

PLANT ALKALOIDS

Plant alkaloids are derived from plants such as the periwinkle plant, *Vinca rosea* (e.g., vincristine, a vinca alkaloid), or the root of American mandrake, *Podophyllum peltatum* (e.g., etoposide, a podophyllotoxin).[115] Vinca alkaloids affect the cell by binding to tubulin in the S phase. This blocks microtubule polymerization, which results in impaired mitotic spindle formation in the M phase. Taxanes such as paclitaxel, on the other hand, cause excess polymerization and stability of microtubules, which blocks the cell cycle in mitosis. The epipodophyllotoxins act to inhibit a DNA enzyme called *topoisomerase II* by stabilizing the DNA–topoisomerase II complex. This results in an inability to synthesize DNA, and thus the cell cycle is stopped in the G_1 phase.[115]

Combination Chemotherapy

Combination chemotherapy may provide greater efficacy than single-agent therapy by three mechanisms: (a) it provides maximum cell kill within the range of toxicity for each drug that can be tolerated by the host, (b) it offers a broader range of coverage of resistant cell lines in a heterogeneous population, and (c) it prevents or delays the emergence of drug-resistant cell lines.[115] When combination regimens are devised, drugs known to be active as single agents usually are selected. Drugs with different mechanisms of action are combined to allow for additive or synergistic effects. Combining cell-cycle–specific and cell-cycle–nonspecific agents may be especially advantageous. Drugs with differing dose-limiting toxic effects are combined to allow for each drug to be given at therapeutic doses. Drugs with different patterns of resistance are combined whenever possible to minimize cross-resistance. The treatment-free interval between cycles is kept to the shortest possible time that will allow for recovery of the most sensitive normal tissue.

Drug Resistance

Several tumor factors influence tumor cell kill. Tumors are heterogeneous, and, according to the Goldie-Coldman hypothesis, tumor cells are genetically unstable and tend to mutate to form different cell clones. This has been used as an argument for giving chemotherapy as soon as possible in treatment to reduce the likelihood that resistant clones will emerge. Tumor size is another important variable. The larger the tumor, the greater the heterogeneity. Moreover, according to the gompertzian model, cancer cells initially grow rapidly (exponential growth phase), then the growth slows down owing to hypoxia and decreased nutrient supply. Because of the larger proportion of cells dividing, smaller tumors may be more chemosensitive.

Multiple mechanisms of chemotherapy resistance have been identified (Table 10-13).[116] Cells may exhibit reduced sensitivity to drugs by virtue of their cell-cycle distribution. For example, cells in the G_0 phase are resistant to drugs active in the S phase. This phenomenon of "kinetic resistance" usually is temporary, and if the drug level can be maintained, all cells will eventually pass through the vulnerable phase of the cell cycle.[115] Alternatively, tumor cells may exhibit "pharmacologic resistance," in which the failure to kill cells is due to insufficient drug concentration. This may occur when tumor cells are located in sites where effective drug concentrations are difficult to achieve (such as the central nervous system) or can be due to enhanced metabolism of the drug after its administration, decreased conversion of the drug to its active form, or decrease in the intracellular drug level caused by increased removal of the drug from the cell associated with enhanced expression of P-glycoprotein, the protein product of multidrug resistance gene 1. Other mechanisms of resistance include decreased affinity of the target enzyme for the drug, altered amount of the target enzyme, or enhanced repair of the drug-induced defect.

Table 10-13 General Mechanisms of Drug Resistance
Cellular and biochemical mechanisms
Decreased drug accumulation
Decreased drug influx
Increased drug efflux
Altered intracellular trafficking of drug
Decreased drug activation
Increased inactivation of drug or toxic intermediate
Increased repair of drug-induced damage to:
DNA
Protein
Membranes
Alteration of drug targets (quantitatively or qualitatively)
Alteration of cofactor or metabolite levels
Alteration of gene expression
DNA mutation, amplification, or deletion
Altered transcription, posttranscription processing, or translation
Altered stability of macromolecules
Mechanisms relevant in vivo
Pharmacologic and anatomic drug barriers (tumor sanctuaries)
Host-drug interactions
Increased drug inactivation by normal tissues
Decreased drug activation by normal tissues
Relative increase in normal tissue drug sensitivity (toxicity)
Host-tumor interactions

Source: Modified with permission from Morrow et al.[116]

For drug-sensitive cancers, another factor limiting optimal killing is improper dosing. A dose reduction of 20% because of drug toxicity can lead to a decline in

the cure rate by as much as 50%.[115] On the other hand, a twofold increase in dose can be associated with a tenfold (1 log) increase in tumor cell kill.

Drug Toxicity

Tumors are more susceptible than normal tissue to chemotherapeutic agents, in part because they have a higher proportion of dividing cells. Normal tissues with a high growth fraction, such as the bone marrow, oral and intestinal mucosa, and hair follicles, are also sensitive to chemotherapeutic effects. Therefore, treatment with chemotherapeutic agents can produce toxic effects such as bone marrow suppression, stomatitis, ulceration of the GI tract, and alopecia. Toxic effects usually are graded from 0 to 4 on the basis of World Health Organization standard criteria.[117] Significant drug toxicity may necessitate a dosage reduction. A toxic effect requiring a dose modification or change in dose intensity is referred to as a dose-limiting toxic effect. Because maintaining dose intensity is important to preserve as high a tumor cell kill as possible, several supportive strategies have been developed, such as administration of colony-stimulating factors and erythropoietin to treat poor bone marrow reserve and administration of cytoprotectants such as mesna and amifostine to prevent renal dysfunction.

Administration of Chemotherapy

Chemotherapy usually is administered systemically (IV, IM, SC, or PO). Systemic administration treats micrometastases at widespread sites and prevents systemic recurrence. However, it increases the drug's toxicity to a wide range of organs throughout the body. One method to minimize systemic toxicity while enhancing target organ delivery of chemotherapy is regional administration of chemotherapy. Many of these approaches require surgical access, such as intrahepatic delivery of chemotherapy for hepatic carcinomas or metastatic colorectal cancer using a hepatic artery infusion pump, limb perfusion for extremity melanoma and sarcoma, and intraperitoneal hyperthermic perfusion for pseudomyxoma peritonei.

HORMONAL THERAPY

Some tumors, most notably breast and prostate cancers, originate from tissues whose growth is under hormonal control. The first attempts at hormonal therapy were through surgical ablation of the organ producing the hormones involved, such as oophorectomy for breast cancer. Currently, hormonal anticancer agents include androgens, antiandrogens, antiestrogens, estrogens, glucocorticoids, gonadotropin inhibitors, progestins, aromatase inhibitors, and somatostatin analogues. Hormones or hormone-like agents can be administered to inhibit tumor growth by blocking or antagonizing the naturally occurring substance, such as with the estrogen antagonist tamoxifen. Other substances that block the synthesis of the natural hormone can be administered as alternatives. Aromatase inhibitors, for example, block the peripheral conversion of endogenous androgens to estrogens in postmenopausal women.

Hormonal therapy provides a highly tumor-specific form of therapy in sensitive tissues. In breast cancer, estrogen and progesterone receptor status is used to predict the success of hormonal therapy. Recently, several other biologic variables have been found to have an impact on the success of hormonal therapy, and these variables are likely to be incorporated into clinical practice in the near future.

TARGETED THERAPY

Over the past decade, increased understanding of cancer biology has fostered the emerging field of molecular therapeutics. The basic principle of molecular therapeutics is to exploit the molecular differences between normal cells and cancer cells to develop targeted therapies. Thus targeted therapies usually are directed at the processes involved in tumor growth rather than directly targeting the tumor cells. The ideal molecular target would be exclusively expressed in the cancer cells, be the driving force of the proliferation of the cancer cells, and be critical to their survival. A large number of molecular targets are currently being explored, both preclinically and in clinical trials. The major groups of targeted therapy agents are inhibitors of growth factor receptors, inhibitors of intracellular signal transduction, cell-cycle inhibitors, apoptosis-based therapies, and antiangiogenic compounds.

Protein kinases have come to the forefront as attractive therapeutic targets with the success of imatinib mesylate (Gleevec) in treating chronic myelogenous leukemia and GI stromal tumors, and trastuzumab (Herceptin) in treating breast cancer; these drugs work by targeting bcr-*abl*, c-*kit*, and HER2, respectively. Sequencing of the human genome has revealed approximately 500 protein kinases. Several tyrosine kinases have been shown to have oncogenic properties (see Table 10-8), and many other protein kinases have been shown to be aberrantly activated in cancer cells.[75] Therefore, protein kinases involved in these aberrantly activated pathways are being aggressively pursued in molecular therapeutics. Potential targets like HER2 can be targeted via different strategies, such as transcriptional downregulation, targeting of mRNA, RNA inhibition, antisense strategies, direct inhibition of protein activity, and induction of immunity against the protein. Most of the compounds in development are monoclonal antibodies like trastuzumab or small-molecule kinase inhibitors like imatinib. Some of the kinases proposed as molecular targets are listed in Table 10-14. Some other agents, such as sunitinib, are multitargeted kinase inhibitors. Selected FDA-approved targeted therapies are listed in Table 10-14.

Table 10-14 Selected FDA-Approved Targeted Therapies

Generic Name	Trade Name	Company	Target	FDA Approval Date	Initial Indication
Trastuzumab	Herceptin	Genentech	HER2	9/1998	Breast cancer

Imatinib	Gleevec	Novartis	c-kit, bcr-abl, PDGFR	5/2001, 12/2002	CML, GIST
Cetuximab	Erbitux	ImClone Systems	EGFR	2/2004	Colorectal cancer
Bevacizumab	Avastin	Genentech	VEGF	2/2004	Colorectal cancer, lung cancer
Erlotinib	Tarceva	Genentech, OSI Pharmaceuticals	EGFR	11/2004	Non–small cell lung cancer
Sorafenib	Nexavar	Bayer	Raf, PDGF, VEGFR, c-kit	12/2005	RCC
Sunitinib	Sutent	Pfizer	VEGFR PDGFR c-kit, Flt-3, RET	1/2006	GIST, RCC
Dasatinib	Sprycel	Bristol-Myers Squibb	bcr-abl, src family, c-kit, EPHA2, PDGFR-β	6/2006	CML
Lapatinib	Tykerb	GlaxoSmithKline	EGFR and HER2	3/2007	Breast cancer
Temsirolimus	Torisel	Wyeth	mTOR	5/2007	RCC

CML = chronic myelogenous leukemia; EGFR = epidermal growth factor receptor; EPHA2 = ephrin A2; FDA = Food and Drug Administration; Flt-3 = fms-related tyrosine kinase 3; GIST = GI stromal tumor; HER2 = human epidermal growth factor receptor 2; mTOR = mammalian target of rapamycin; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; RCC = renal cell carcinoma; RET = rearranged during transfection; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

Development of molecularly targeted agents for clinical use presents several unique challenges. Once an appropriate compound is identified and confirmed to have activity in preclinical testing, predictive markers for activity in the preclinical setting must be defined. Expression of a target may not be sufficient to predict response, because the pathway of interest may not be activated or critical to the cancer's survival. Although in traditional phase I trials the goal is to identify the maximum tolerated dosage, the maximum dosage of biologic agents may not be necessary to achieve the desired biologic effect. Thus assays to verify modulation of the target need to be developed to determine at what dosage the desired effect is achieved. When phase II and III clinical trials are initiated, biomarker modulation studies should be integrated into the trial to determine whether clinical response correlates with target modulation and thus to identify additional parameters that impact response. Rational dose selection and limitation of study populations to patients most likely to respond to the molecular therapy as determined by predictive markers are most likely to lead to successful clinical translation of a product. Finally, most biologic agents are cytostatic, not cytotoxic. Thus rational combination therapy mixing new biologic agents with either established chemotherapeutic agents that have synergy or with other biologic agents is more likely to lead to cancer cures.

IMMUNOTHERAPY

The aim of immunotherapy is to induce or potentiate inherent antitumor immunity that can destroy cancer cells. Central to the process of antitumor immunity is the ability of the immune system to recognize tumor-associated antigens present on human cancers and to direct cytotoxic responses through humoral or T-cell–mediated immunity. Overall, T-cell–mediated immunity appears to have the greater potential of the two for eradicating tumor cells. T cells recognize antigens on the surfaces of target cells as small peptides presented by class I and class II MHC molecules.

Several antitumor strategies are under investigation. One approach to antitumor immunity is nonspecific immunotherapy, which stimulates the immune system as a whole through administration of bacterial agents or their products, such as bacille Calmette-Guérin. This approach is thought to activate the effectors of antitumor response such as natural killer cells and macrophages, as well as polyclonal lymphocytes.[118] Another approach to nonspecific immunotherapy is systemic administration of cytokines such as interleukin-2, interferon-α, and interferon-γ. Interleukin-2 stimulates proliferation of cytotoxic T lymphocytes and maturation of effectors such as natural killer cells into lymphokine-activated killer cells. Interferons, on the other hand, exert antitumor effects directly by inhibiting tumor cell proliferation and indirectly by activating host immune cells, including macrophages, dendritic cells, and natural killer cells, and by enhancing human leukocyte antigen (HLA) class I expression on tumor cells.[118]

Antigen-specific immunotherapy can be active, as is achieved through antitumor vaccines, or passive. In passive immunotherapy, antibodies to specific tumor-associated antigens can be produced by hybridoma technique and then administered to patients whose cancers express these antigens, inducing antibody-dependent cellular cytotoxicity.

The early attempts at vaccination against cancers used allogeneic cultured cancer cells, including irradiated cells, cell lysates, and shed antigens isolated from tissue culture supernatants. An alternate strategy is the use of autologous tumor vaccines. These have the potential advantage of being more likely to contain antigens relevant for the individual patient but have the disadvantage of requiring a large amount of tumor tissue for preparation, which restricts eligibility of patients for this modality. Strategies to enhance immunogenicity of tumor cells include the introduction of genes encoding cytokines or chemokines, and fusion of the tumor cells to allogeneic MHC class II–bearing cells.[119] Alternatively, heat shock proteins derived from a patient's tumor can be used, because heat shock protein peptide complexes are readily taken up by dendritic cells for presentation to T cells.[119]

Identification of tumor antigens has made it possible to perform antigen-specific vaccination. For example in the case of melanoma, several antigens have been identified that can be recognized by both $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells, including MART-1, gp 100, MAGE1, tyrosinase, TRP-1, TRP-2, and NY-ESO-1.[120] Antigens tested usually are overexpressed or mutated in cancer cells. Tissue specificity and immunogenicity are important determinants in

choosing an appropriate target. Vaccines directed at defined tumor antigens aim to combine selected tumor antigens and appropriate routes for delivering these antigens to the immune system to optimize antitumor immunity.[121] Several different vaccination approaches are under study, including tumor cell–based vaccines, peptide-based vaccines, recombinant virus–based vaccines, DNA-based vaccines, and dendritic cell vaccines.

In adoptive transfer, antigen-specific effector cells (i.e., cytotoxic T lymphocytes) or antigen-nonspecific effector cells (i.e., natural killer cells) can be transferred to a patient. These effector cells can be obtained from the tumor (tumor-infiltrating lymphocytes) or the peripheral blood.

Clinical experience in patients with metastatic disease has shown objective tumor responses to a variety of immunotherapeutic modalities. It is thought, however, that the immune system is overwhelmed with the tumor burden in this setting, and thus adjuvant therapy may be preferable, with immunotherapy reserved for decreasing tumor recurrences. Trials to date suggest that immunotherapy is a potentially useful approach in the adjuvant setting. How to best select patients for this approach and how to integrate immunotherapy with other therapies are not well understood for most cancer types.

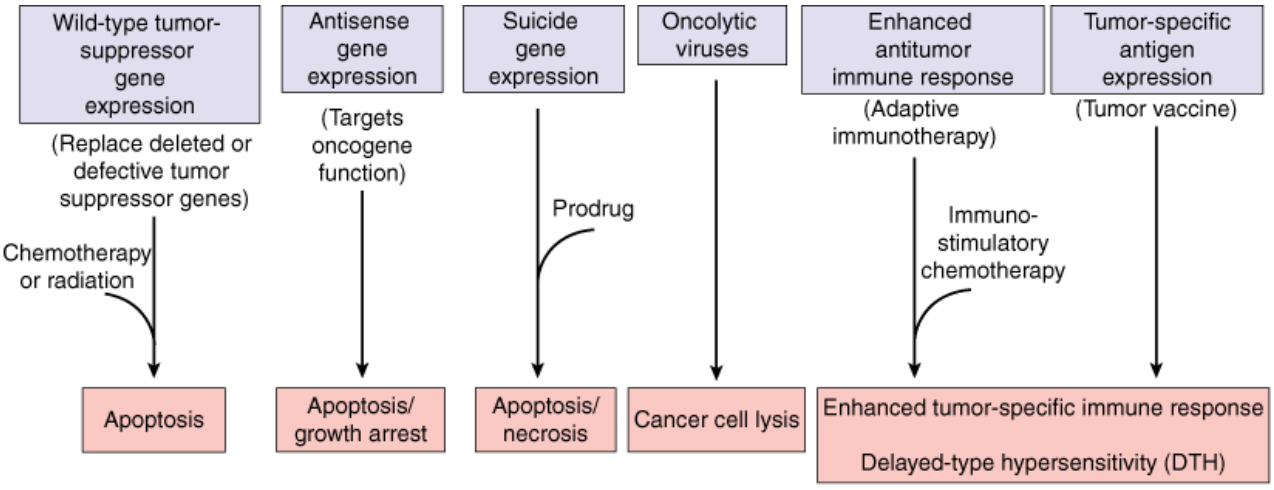
Tolerance to self-antigens expressed in tumors is a limitation in generating antitumor responses.[122] Recently, several pathways that modulate tolerance and approaches to manipulating these pathways have been identified: pathways that activate professional antigen-presenting cells such as Toll-like receptors, growth factors, and the CD40 pathway; cytokines to enhance immunoactivation; and pathways that inhibit T-cell inhibitory signals or Tregs.[122]

A new strategy being actively explored involves the use of cytotoxic T-lymphocyte antigen 4 (CTLA-4). CTLA-4 exists on the surfaces of T cells and has a homeostatic immunosuppressive function, downregulating the response of T cells to stimuli.[123] Two fully human monoclonal anti-CTLA-4 antibodies, ipilimumab and tremelimumab, are in clinical development. Anti-CTLA-4 antibodies are under study for use in melanoma as well as several other cancer types as single agents, in combination with interleukin-2, chemotherapy, or peptide vaccines.[123]

GENE THERAPY

Gene therapy is being pursued as a possible approach to modifying the genetic program of cancer cells as well as treating metabolic diseases. The field of cancer gene therapy uses a variety of strategies, ranging from replacement of mutated or deleted tumor-suppressor genes to enhancement of immune responses to cancer cells (Fig. 10-12).[124] Indeed, in preclinical models, approaches such as replacement of tumor-suppressor genes leads to growth arrest or apoptosis. However, the translation of these findings into clinically useful tools presents special challenges.

Fig. 10-12.



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Different strategies for gene therapy.

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One of the main difficulties in getting gene therapy technology from the laboratory to the clinic is the lack of a perfect delivery system. An ideal vector would be administered through a noninvasive route and would transduce all of the cancer cells and none of the normal cells. Furthermore, the ideal vector would have a high degree of activity, that is, it would produce an adequate amount of the desired gene product to achieve target cell kill. Unlike genetic diseases in which delivery of the gene of interest into only a portion of the cells may be sufficient to achieve clinical effect, cancer requires either that the therapeutic gene be delivered to all of the cancer cells or that a therapeutic effect be achieved on nontransfected cells as well as transfected cells through a bystander effect. On the other hand, treatment of a metabolic disease requires prolonged gene expression, whereas transient expression may be sufficient for cancer therapy.

Several vector systems are under study for gene therapy, however none is considered ideal. One of the promising approaches to increase the number of tumor cells transduced is the use of a replication-competent virus such as a parvovirus, human reovirus, or vesicular stomatitis virus that selectively replicates within malignant cells and lyses them more efficiently than it does normal cells. Another strategy for killing tumor cells with suicide genes exploits tumor-specific expression elements, such as the MUC-1, PSA, CEA, or VEGF promoters, that can be used to achieve tissue-specific or tumor-specific expression of the desired gene.

Because the goal in cancer therapy is to eradicate systemic disease, optimization of delivery systems is the key to success for gene therapy strategies. Gene therapy is likely to be most successful when combined with standard therapies, but it will provide the advantage of customization of therapy based on the molecular status of an individual's tumor.

RADIATION THERAPY

Physical Basis of Radiation Therapy

Ionizing radiation is energy strong enough to remove an orbital electron from an atom. This radiation can be electromagnetic, such as a high-energy photon, or particulate, such as an electron, proton, neutron, or alpha particle. Radiation therapy is delivered primarily as high-energy photons (gamma rays and x-rays) and charged particles (electrons). Gamma rays are photons that are released from the nucleus of a radioactive atom. X-rays are photons that are created electronically, such as with a clinical linear accelerator. Currently, high-energy radiation is delivered to tumors primarily with linear accelerators. X-rays traverse the tissue, depositing the maximum dose beneath the surface, and thus spare the skin. Electrons are used to treat superficial skin lesions, superficial tumors, or surgical beds to a depth of 5 cm. Gamma rays typically are produced by radioactive sources used in brachytherapy.

The dose of radiation absorbed correlates with the energy of the beam. The basic unit is the amount of energy absorbed per unit of mass (joules per kilogram) and is known as a *gray (Gy).* One gray is equivalent to 100 rads, the unit of radiation measurement used in the past.

Biologic Basis of Radiation Therapy

Radiation deposition results in DNA damage manifested by single- and double-strand breaks in the sugar phosphate backbone of the DNA molecule.[125] Cross-linking between the DNA strands and chromosomal proteins also occurs. The mechanism of DNA damage differs by the type of radiation delivered. Electromagnetic radiation is indirectly ionizing through short-lived hydroxyl radicals produced primarily by the ionization of cellular hydrogen peroxide (H_2O_2).[125] Protons and other heavy particles are directly ionizing and directly damage DNA.

Radiation damage is manifested primarily by the loss of cellular reproductive integrity. Most cell types do not show signs of radiation damage until they attempt to divide, so slowly proliferating tumors may persist for months and appear viable. Some cell types, however, undergo apoptosis.

The extent of DNA damage after radiation exposure is dependent on several factors. The most important of these is cellular oxygen. Hypoxic cells are significantly less radiosensitive than aerated cells. Because the presence of oxygen is thought to prolong the half-life of free radicals produced by the interaction of x-rays and cellular H_2O_2, indirectly ionizing radiation is less efficacious in tumors with areas of hypoxia.[125] In contrast, radiation damage from directly ionizing radiation is independent of cellular oxygen levels.

The extent of DNA damage from indirectly ionizing radiation is dependent on the phase of the cell cycle. The most radiation-sensitive phases are G_2 and M, whereas G_1 and late S phases are less sensitive. Thus irradiation of a population of tumor cells results in killing of a greater proportion of cells in G_2 and M phases. However, delivery of radiation in divided doses, a concept referred to as *fractionation,* allows the surviving G_1 and S phase cells to progress to more sensitive phases, a process referred to as *reassortment.* In contrast to DNA damage after indirectly ionizing radiation, that after exposure to directly ionizing radiation is less dependent on the cell-cycle phase.[126]

Several chemicals can modify the effects of ionizing radiation. These include hypoxic cell sensitizers such as metronidazole and misonidazole, which mimic oxygen and increase cell kill of hypoxic cells.[125] A second category of radiation sensitizers are the thymidine analogues iododeoxyuridine and bromodeoxyuridine. These molecules are incorporated into the DNA in place of thymidine and render the cells more susceptible to radiation damage; however, they are associated with considerable acute toxicity. Several other chemotherapeutic agents sensitize cells to radiation through various mechanisms, including 5-fluorouracil, actinomycin D, gemcitabine, paclitaxel, topotecan, doxorubicin, and vinorelbine.[125]

Radiation Therapy Planning

Radiation therapy is delivered in a homogeneous dose to a well-defined region that includes tumor and/or surrounding tissue at risk for subclinical disease. The first step in planning is to define the target to be irradiated as well as the dose-limiting organs in the vicinity.[127] Treatment planning includes evaluation of alternative treatment techniques, which is done through a process referred to as *simulation.* Once the beam distribution that will best achieve homogeneous delivery to the target volume and minimize the dose to the normal tissue is determined, immobilization devices and markings or tattoos on the patient's skin are used to ensure that each daily treatment is given in the same way. Conventional fractionation is 1.8 to 2 Gy/d, administered 5 days each week for 3 to 7 weeks.

Radiation therapy may be used as the primary modality for palliation in certain patients with metastatic disease, primarily patients with bony metastases. In these cases, radiation is recommended for symptomatic metastases only. However, lytic metastases in weight-bearing bones such as the femur, tibia, or humerus also are considered for irradiation. Another circumstance in which radiation therapy might be appropriate is spinal cord compression due to metastases to the vertebral body that extend posteriorly to the spinal canal.

The goal of adjuvant radiation therapy is to decrease local-regional recurrence rates. Adjuvant radiation therapy can be given before surgery, after surgery, or, in selected cases, during surgery. Preoperative radiation therapy has several advantages. It may minimize seeding of the tumor during surgery and it allows for smaller treatment fields because the operative bed has not been contaminated with tumor cells. Also, radiation therapy for inoperable tumors may achieve adequate reduction to make them operable. The disadvantages of preoperative therapy are an increased risk of postoperative wound healing problems and the difficulty in planning subsequent radiation therapy in patients who have positive surgical margins. If radiation therapy is given postoperatively, it is usually given 3 to 4 weeks after surgery to allow for wound healing. The advantage of postoperative radiation therapy is that the surgical specimen can be evaluated histologically and radiation therapy can be reserved for patients who are most likely to benefit from it. Further, the radiation therapy can be modified on the basis of margin status. The disadvantages of postoperative radiation therapy are that the volume of normal tissue requiring irradiation may be larger owing to surgical contamination of the tissue planes and that the tumor may be less sensitive to radiation owing to poor oxygenation. Postlaparotomy adhesions may decrease the mobility of the small bowel loops, increasing the risk for radiation injury in abdominal or pelvic irradiation. Given the potential advantages and disadvantages of both approaches, the roles of preoperative and postoperative radiation therapy are being actively evaluated and compared for many cancer types.

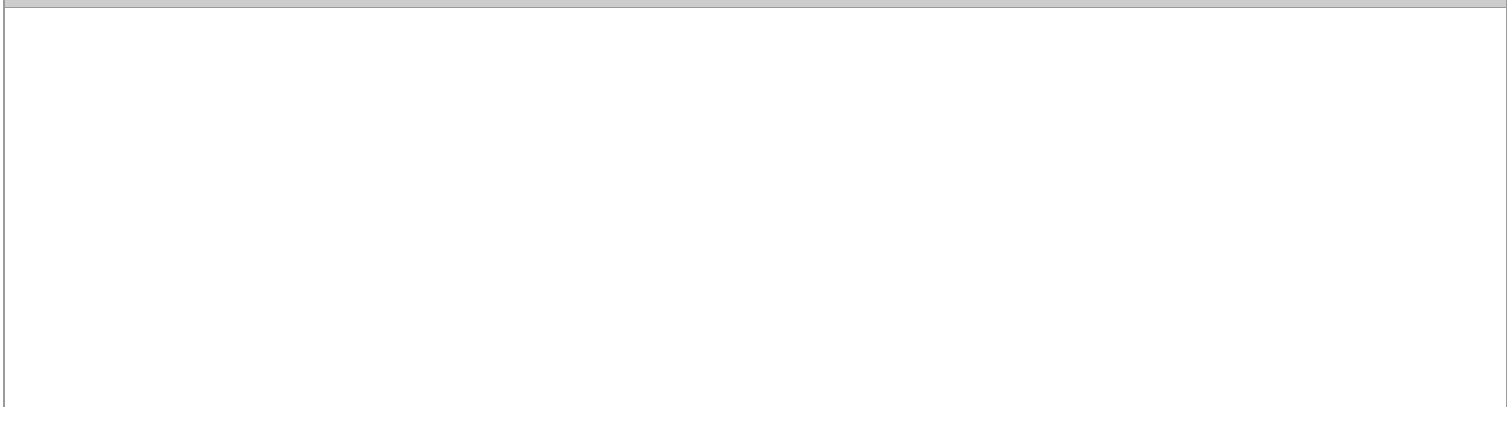
Another mode of postoperative radiation therapy is brachytherapy. In brachytherapy, unlike in external beam therapy, the radiation source is in contact with the tissue being irradiated. The radiation source may be cesium, gold, iridium, or radium. Brachytherapy is administered via temporary or permanent delivery implants such as needles, seeds, or catheters. Temporary brachytherapy catheters are placed either during open surgery or percutaneously soon after surgery. The implants are loaded interstitially, and treatment usually is given postoperatively for a short duration, such as 1 to 3 days. Although brachytherapy has the advantage of patient convenience owing to the shorter treatment duration, it has the disadvantages of leaving scars at the catheter insertion site and requiring special facilities for inpatient brachytherapy. Another short delivery approach is intraoperative radiotherapy (IORT), often used in combination with external beam therapy. The oncologic consequences of the limited treatment volume and duration associated with brachytherapy and IORT are not well understood. Accelerated partial breast irradiation with interstitial brachytherapy, intracavitary brachytherapy (MammoSite), IORT, and three-dimensional conformal external beam radiotherapy is being compared with whole breast irradiation in an intergroup phase III trial (NSABP B-39/Radiation Therapy Oncology Group 0413). Several additional studies of adjuvant IORT also are ongoing internationally.

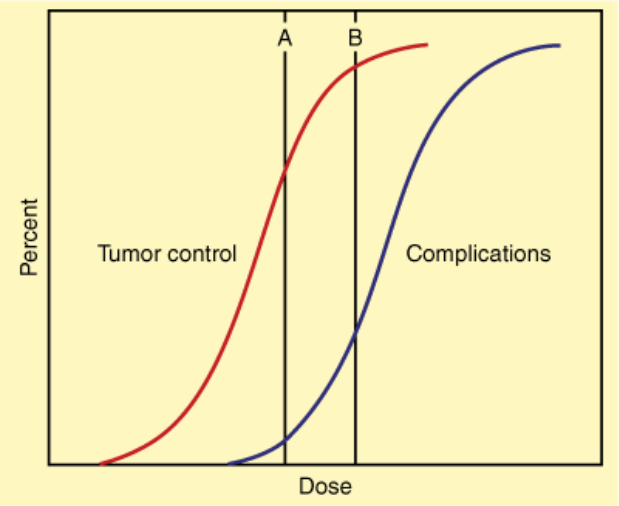
Chemotherapy can be given before or concurrently with radiation. Chemotherapy before radiation has the advantage of reducing the tumor burden, which facilitates radiation therapy. On the other hand, some chemotherapy regimens, when given concurrently with radiation, may sensitize the cells to radiation therapy.

Side Effects

Both tumor and normal tissue have radiation dose–response relationships that can be plotted as a sigmoidal curve (Fig. 10-13).[127] A minimum dose of radiation must be given before any response is seen. The response to radiation then increases slowly with an increase in dose. At a certain dose level the curves become exponential, with increases in tumor response and normal tissue toxicity with each incremental dose increase. The side effects of radiation therapy can be acute, occurring during or 2 to 3 weeks after therapy, or chronic, occurring weeks to years after therapy. The side effects depend on the tissue included in the target volume. Some of the major acute and chronic sequelae of radiation are summarized in Table 10-15.[127,128] In addition to these effects, a small increase in the risk for secondary malignancies is attributable to radiation therapy.

Fig. 10-13.





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The probability of tumor control and of complications at different radiation doses. *A.* At lower doses, the probability of complications is low, with a moderate chance of tumor control. *B.* Increasing the dose may gain a higher chance of tumor control at the price of significantly higher complication risks.

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Table 10-15 Local Effects of Radiation

Organ	Acute Changes	Chronic Changes
Skin	Erythema, wet or dry desquamation, epilation	Telangiectasia, subcutaneous fibrosis, ulceration
GI tract	Nausea, diarrhea, edema, ulceration, hepatitis	Stricture, ulceration, perforation, hematochezia
Kidney	—	Nephropathy, renal insufficiency
Bladder	Dysuria	Hematuria, ulceration, perforation
Gonads	Sterility	Atrophy, ovarian failure
Hematopoietic tissue	Lymphopenia, neutropenia, thrombocytopenia	Pancytopenia
Bone	Epiphyseal growth arrest	Necrosis
Lung	Pneumonitis	Pulmonary fibrosis
Heart	—	Pericarditis, vascular damage
Upper aerodigestive tract	Mucositis, xerostomia, anosmia	Xerostomia, dental caries
Eye	Conjunctivitis	Cataract, keratitis, optic nerve atrophy
Nervous system	Cerebral edema	Necrosis, myelitis

Source: Modified with permission from Daly et al.[128]

CANCER PREVENTION

The truth of the old axiom "An ounce of prevention is worth a pound of cure" is being increasingly recognized in oncology. Cancer prevention can be divided into three categories: (a) primary prevention (i.e., prevention of initial cancers in healthy individuals), (b) secondary prevention (i.e., prevention of cancer in individuals with premalignant conditions), and (c) tertiary prevention (i.e., prevention of second primary cancers in patients cured of their initial disease).

The systemic or local administration of therapeutic agents to prevent the development of cancer, called *chemoprevention,* is being actively explored for several cancer types. In breast cancer, the NSABP Breast Cancer Prevention Trial demonstrated that tamoxifen administration reduces the risk of breast cancer by one half and reduces the risk of estrogen receptor–positive tumors by 69% in high-risk patients.[129] Therefore, tamoxifen has been approved by the FDA for breast cancer chemoprevention. The subsequent NSABP P-2 trial demonstrated that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and is associated with a lower risk of thromboembolic events and cataracts but a non–statistically significant higher risk of noninvasive breast cancer; these findings led the FDA to approve raloxifene for prevention as well. Several other agents are also under investigation.[130] Celecoxib has been shown to reduce polyp number and polyp burden in patients with familial adenomatous polyposis (FAP), which led to its approval by the FDA for these patients. In head and neck cancer, 13-*cis*-retinoic acid has been shown both to reverse oral leukoplakia and to reduce second primary tumor development.[131,132] Thus, the chemoprevention trials completed so far have demonstrated success in primary, secondary, and tertiary prevention. Although the successes of these

chemoprevention studies are impressive, much remains to be done over the next few years to improve patient selection and decrease therapy-related toxic effects. It is important for surgeons to be aware of these preventive options, because they are likely to be involved in the diagnosis of premalignant and malignant conditions and will be the ones to counsel patients about their chemopreventive options.

In selected circumstances, the risk of cancer is high enough to justify surgical prevention. These high-risk settings include hereditary cancer syndromes such as hereditary breast-ovarian cancer syndrome, hereditary diffuse gastric cancer, multiple endocrine neoplasia type 2, FAP, and hereditary nonpolyposis colorectal cancer, as well as some nonhereditary conditions such as chronic ulcerative colitis. Most prophylactic surgeries are large ablative surgeries (e.g., bilateral risk-reducing mastectomy or total proctocolectomy). Therefore, it is important that the patient be completely informed about potential surgical complications as well as long-term lifestyle consequences. Further, the conservative options of close surveillance and chemoprevention need to be discussed. The patient's cancer risk needs to be assessed accurately and implications for survival discussed. Ultimately, the decision to proceed with surgical prevention should be individualized and made with caution.

TRENDS AND EVOLVING TECHNOLOGIES IN ONCOLOGY

Cancer Screening and Diagnosis

It is clear that the practice of oncology will change dramatically over the next few decades, because our understanding of the molecular basis of cancer and available technologies are evolving rapidly. One of the critical changes expected is earlier detection of cancers. With improvements in available imaging modalities and development of newer functional imaging techniques, it is likely that many tumors will be detected at earlier, more curable stages in the near future.

Another area of rapid development is the identification of serum markers. High-throughput technologies such as matrix-assisted laser desorption ionization time-of-flight mass spectroscopy and liquid chromatography ion-spray tandem mass spectroscopy have revolutionized the field of proteomics and are now being used to compare the serum protein profiles of patients with cancer with those of individuals without cancer. Identification of unique proteins as well as unique proteomic profiles for most cancer types is being pursued actively by many researchers and, if successful, could dramatically enhance our ability to detect cancers early.[133]

Surgical Therapy

The current trend in surgery is toward more conservative resections. With earlier identification of tumors, more conservative surgeries may be possible. The goal, however, is always to remove the tumor en bloc with wide negative margins. Another interesting area being explored is the destruction of tumors by techniques such as radiofrequency ablation, cryoablation, and heat-producing technologies like lasers, microwaves, or focused ultrasound. Pilot studies have demonstrated that radiofrequency ablation is effective for destruction of small primary breast cancers. Although this approach remains experimental and potentially of limited applicability because of the need for expertise in breast imaging, with the development of imaging technologies that can accurately map the extent of cancer cells, these types of noninvasive interventions are likely to come to the forefront. However, use of these techniques will be limited to treatment of cancers not involving hollow viscera.

The debate over how to manage the regional lymph node basins for certain cancer types continues. With an increasing understanding of the metastatic process, surgeons may be able to stratify patients on the basis of the likelihood that their disease will spread metastatically, based on the gene expression profile of their primary tumors, and offer regional therapy accordingly.

Systemic Therapy

The current trend in systemic therapy is toward individualized therapy. It is now presumed that all cancers of a certain cell origin are the same; thus all patients are offered the same systemic therapy. Not all patients respond to these therapies, however, which emphasizes the biologic variability within the tumor groups. Therefore, the intent is to determine the underlying biology of each tumor to tailor therapy accordingly. The transcriptional and proteomic profiling approaches are being used to identify molecular signatures that correlate with response to certain agents. It is likely that in the near future tumors can be tested and treatments individualized. Patients who will respond to conventional therapies can be treated with these regimens, whereas patients who will not respond will not, which spares them the toxicity. Instead, the latter patients can be offered novel therapies. Furthermore, with emerging biologic therapies, it is likely that patients may be given a combination of biologic therapies that specifically target the alterations in their own tumors. Patients can be genotyped for critical alleles that may affect drug metabolism and thus may influence the efficacy as well as the side effect of the drugs given. Finally, stratification of patients by gene expression profile for prognosis may assist in determining which patients are at higher risk of relapse, so that patients whose tumors have less aggressive biologic characteristics can be spared further therapy.

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KEY POINTS

1. The field of transplantation has made tremendous advances in the last 30 years, due mainly to refinements of surgical technique and development of effective immunosuppression medications.

2. Although immunosuppression drugs are essential for transplant, they are associated with significant short- and long-term morbidity.

3. Kidney transplantation now represents the treatment of choice for almost all patients with end-stage renal disease.

4. Liver transplantation is the viable option at present for patients with end-stage organ failure.

5. Pancreas transplantation and in the future islet cell transplantation represent the most reliable way to achieve euglycemia in the poorly controlled diabetic patient.

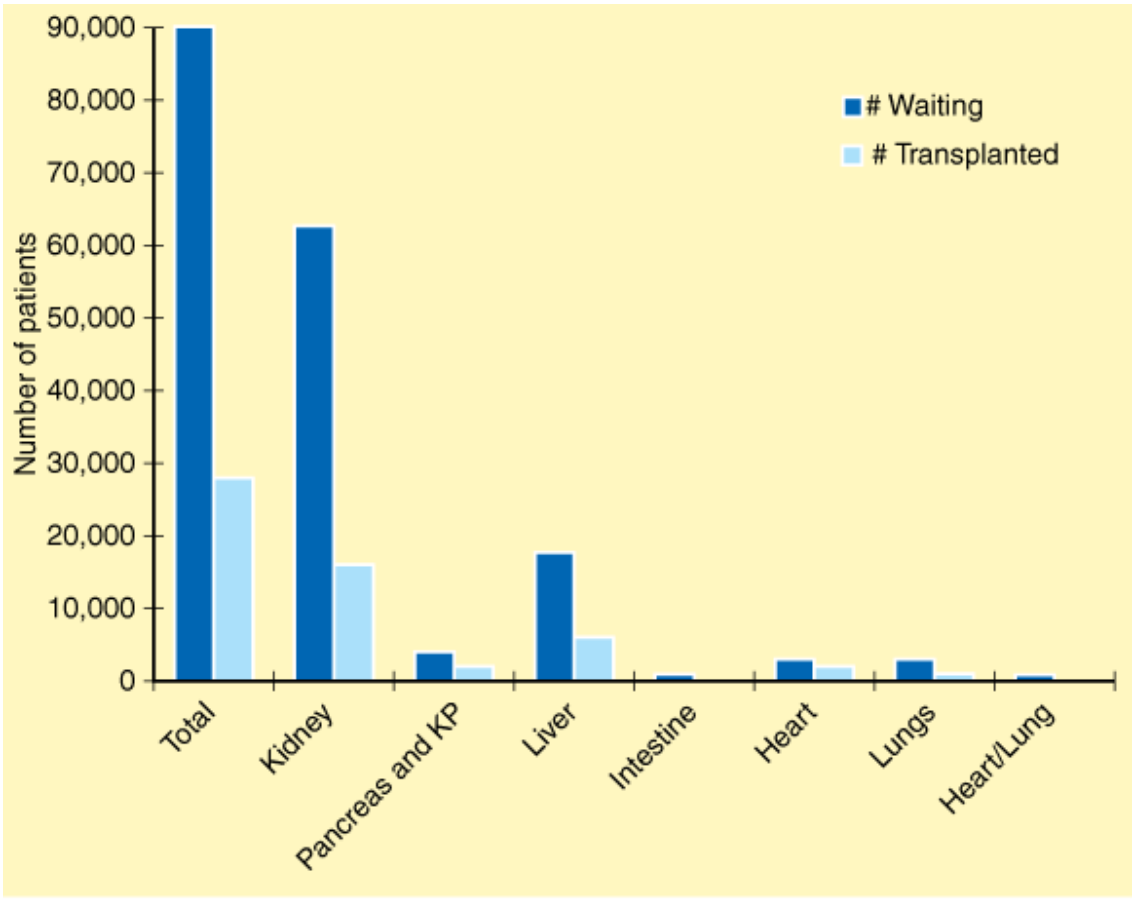
6. Opportunistic infections can be significantly lowered by the use of appropriate prophylaxis agents.

BACKGROUND

Although references to transplantation have existed in the scientific literature for centuries, the field of modern transplantation did not come into being until the latter half of the twentieth century. Thus, given its short history, it is truly remarkable how far this area of medicine has advanced. From an experimental procedure just 50 years ago, transplantation has evolved to become the treatment of choice for end-stage organ failure resulting from almost any of a wide variety of causes. Transplantation of the kidney, liver, pancreas, intestine, heart, and lung has now become commonplace in all parts of the world.

In fact, transplantation is now so widely accepted and successful that the main problem facing the field today is not surgical technique, rejection, or management of complications, but rather supply of organs. An increasing number of diseases and patients are now potentially treatable with transplants; however, this increase, coupled with the decrease in contraindications to transplants, has meant an increasing number of patients are now awaiting organ replacement therapy. The number of transplants performed yearly has increased over the last decade, but has not kept pace with the steadily growing waiting list. As a result, the gap is ever widening between the number of transplants performed and the number of waiting patients (Fig. 11-1).

Fig. 11-1.



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Patients on waiting list and number of organ transplants for 2005. (U.S. data from Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients Annual Report, http://www.ustransplant.org). KP = kidney and pancreas.

Transplantation statistics in the United States are tracked by the United Network for Organ Sharing (UNOS). By the end of 2007, roughly 98,000 patients were awaiting a transplant, while the number of transplants performed in that year was approximately 28,000.

DEFINITIONS

Transplantation is the act of transferring an organ, tissue, or cell from one place to another. Broadly speaking, transplants are divided into three categories based on the similarity between the donor and the recipient: autotransplants, allotransplants, and xenotransplants. *Autotransplants* involve the transfer of tissue or organs from one part of an individual to another part of the same individual. They are the most common type of transplants and include skin grafts, vein grafts for bypasses, bone and cartilage transplants, and nerve transplants. Because the donor and the recipient are the same person and no immunologic disparity exists, no immunosuppression is required. *Allotransplants* involve transfer from one individual to a different individual of the same species—the most common scenario for most solid organ transplants performed today. Immunosuppression is required for allograft recipients to prevent rejection. Finally, *xenotransplants* involve transfer across species barriers. Currently, xenotransplants are largely relegated to the laboratory, given the complex, potent immunologic barriers to success.

This chapter deals mainly with allotransplantation. The first part discusses immunobiology, mechanisms of the rejection

process, and medications currently used to achieve immunosuppression. The second part focuses on the various transplants, including kidney, pancreas, islet cell, liver, intestine, heart, and lungs. Clinical indications, surgical care, and posttransplant follow-up of these abdominal and thoracic organ recipients are described.

HISTORY

Attempts at transplantation have been documented since ancient times, but they are largely of only historic interest. They had no lasting impact on the field of modern transplantation, which did not originate until the latter half of the twentieth century. Important events in the first half of the twentieth century included the development of the surgical techniques for vascular anastomosis by Alexis Carrel; the first human-to-human kidney transplants by Yu Yu Voronoy in the 1930s (which were unsuccessful because of failure to address the immunologic barriers); and the studies of skin transplantation in animal models by Sir Peter Medawar in the 1940s.[1–3] Medawar's work was especially crucial: It provided scientific evidence for the role of the immune system in the failure of allografts to function long term, through a process later termed *rejection*. His work and observations formed the basis for modern transplant immunobiology.

The first human kidney transplant with long-term success was performed in Boston by Joseph Murray in 1954.[4] Because it was a living-donor transplant between identical twin brothers, the recipient required no immunosuppression and lived for more than 20 years, eventually dying of coronary artery disease. Soon, other centers performed similar transplants, which then led to attempts at kidney transplants between nonidentical individuals, using total body radiation and agents such as 6-mercaptopurine for immunosuppression. By the late 1950s to early 1960s, the combination of azathioprine (AZA) with corticosteroids allowed kidney allotransplantation to advance out of the realm of experimental therapy.[5,6]

Along with AZA and corticosteroids, the development of antilymphocyte serum (antibodies against human lymphoid tissue) gave clinicians reliable, adequate immunosuppression, allowing the birth of extrarenal transplants.[7] In 1963, the first liver transplant was performed by Thomas Starzl in Denver. The first pancreas transplant was performed in 1966 in Minneapolis by William Kelly and Richard Lillehei. Christiaan Barnard performed the first heart transplant in 1967 in Cape Town, South Africa. The 1970s saw other firsts with intestine, lung, and islet transplants.

Kidney transplants flourished during the 1970s, but extrarenal transplants remained largely experimental. One major reason was that rejection remained a major obstacle to the success of these transplanted organs. A dramatic change occurred, however, with the introduction in the early 1980s of cyclosporine. At that time, it was the most specific immunosuppressive agent available. It improved graft survival after kidney transplants by 30% and allowed extrarenal transplants to develop as viable therapies. Since that time, and especially in the 1990s, many new agents have been developed and approved for use in clinical transplantation; scores of others are currently being tested in clinical trials. These agents have allowed for progressively more specific targeting of the immune system pathways involved in the rejection process. As a result, rejection rates have substantially declined for all types of transplants, and graft survival rates have increased.

A large part of the recent success of transplants is due to the developments in clinical immunosuppression. But other discoveries also have played a role. More powerful immunosuppression has often meant more risk of infection with opportunistic viral, fungal, and bacterial pathogens. The development of powerful and effective antimicrobial, antifungal, and antiviral therapy (in parallel with immunosuppressive agents) has been crucial to successful solid organ transplantation.

Surgical innovations, beyond the first successful attempts at the various transplants, have continued. In the late 1980s and early 1990s, the development of deceased-donor split-liver transplant techniques and of living-donor liver transplants expanded the donor pool and helped alleviate the significant shortage of donors. The development of laparoscopic donor

nephrectomy enabled faster recovery of living kidney donors, thereby increasing their numbers. The 1990s ushered in innovations with thoracic, pancreatic, and cellular transplants.

TRANSPLANT IMMUNOBIOLOGY

The technical advances and techniques that made transplants possible were described almost a hundred years ago. Yet it was only after a basic understanding of transplant immunobiology was obtained that the obstacle of rejection could be overcome, thus making clinical transplants possible. The success of transplants today is due in large part to control of the rejection process, thanks to an ever-deepening understanding of the immune process triggered by a transplant.[8]

The immune system is important not only in graft rejection, but also in the body's defense system against viral, bacterial, fungal, and other pathogens. It also helps prevent tumor growth and helps the body respond to shock and trauma. As with the body's reaction to an infection, graft rejection is triggered when specific cells of the transplant recipient, namely T and B lymphocytes, recognize foreign antigens.

TRANSPLANT ANTIGENS

The main antigens involved in triggering rejection are coded for by a group of genes known as the *major histocompatibility complex* (MHC). These antigens, and hence genes, define the "foreign" nature of one individual to another within the same species. In humans, the MHC complex is known as the *human leukocyte antigen* (HLA) system. It comprises a series of genes located on chromosome 6. The HLA antigens are grouped into two classes, which differ in their structure and cellular distribution. Class I molecules (named HLA-A, -B, and -C) are found on the membrane of all nucleated cells. Class II molecules (named HLA-DR, -DP, and -DQ) generally are expressed by antigen-presenting cells (APCs) such as B lymphocytes, monocytes, and dendritic cells.

In a nontransplant setting, the function of the HLA gene product is to present antigens as fragments of foreign proteins that can be recognized by T lymphocytes. In the transplant setting, HLA molecules can initiate rejection and graft damage via either humoral or cellular mechanisms. Humoral rejection occurs if the recipient has circulating antibodies specific to the donor's HLA. These antibodies may be from prior exposure (i.e., blood transfusion, previous transplant, or pregnancy), or posttransplant, the recipient may develop antibodies specific to the donor's HLA. The antibodies then bind to the donor's recognized foreign antigens, activating the complement cascade and leading to cell lysis. The blood group antigens of the ABO system, although not part of the HLA system, may also trigger this form of humoral rejection.

Cellular rejection is the more common type of rejection after organ transplants. Mediated by T lymphocytes, it results from their activation and proliferation after exposure to donor MHC molecules.

ALLORECOGNITION AND DESTRUCTION

The recognition of foreign HLA antigens by the recipient T cells is referred to as *allorecognition*.[9] This process may occur by either a direct or an indirect pathway. In the direct pathway, the recipient's T cells directly interact with donor HLA molecules, leading to the generation of activated cytotoxic T cells. In the indirect pathway, the recipient's own APCs first process the donor's antigens (which may be shed from the parenchymal cells of the graft into the recipient's circulation, or alternatively may be encountered by the recipient's APCs in the graft itself); then the recipient's APCs present the donor's antigens to the recipient T cells, leading to the activation of those T cells.

Regardless of the method of presentation of foreign MHC, the subsequent steps are similar. Binding of the T cell to the

foreign molecule occurs at the T-cell receptor (TCR)-CD3 complex on the surface of the lymphocyte. This binding leads to transduction of a signal to the cell, named *signal 1*. This signal by itself, however, is not sufficient to result in T-cell activation. Full activation requires transduction of a second signal that is not antigen dependent. Signal 2 is provided by the binding of accessory molecules on the T cell to corresponding molecules (ligands) on the APC. An example is CD25 on the T lymphocytes binding with its ligand B7 on the surface of the APC. Transmission of signal 1 and 2 to the cell nucleus leads to interleukin-2 (IL-2) gene expression and to production of this important cytokine. IL-2 then permits the entire cascade of T-cell activation to proceed, leading to proliferation and differentiation of these cells into cells capable of causing damage to the graft.

T-cell activation is key in initiating the rejection process, but B-cell activation and antibody production also play a role. Foreign antigens are acquired by immunoglobulin (Ig) receptors on the surface of B cells. These antigens are then processed similarly to the way that APCs process the donor's antigens. The antigen-presenting B cells can then interact with activated helper T cells. This interaction leads to B-cell proliferation, differentiation into plasma cells, and to antibody production.

CLINICAL REJECTION

Graft rejection is a complex process involving several components, including T lymphocytes, B lymphocytes, macrophages, and cytokines, with resultant local inflammatory injury and graft damage.[10–12] Rejection can be classified into four types, based on timing and pathogenesis: *hyperacute*, *acceleratedacute*, *acute*, and *chronic*.

Hyperacute

This type of rejection, which usually occurs within minutes after the transplanted organ is reperfused, is due to the presence of preformed antibodies in the recipient, antibodies that are specific to the donor. These antibodies may be directed against the donor's HLA antigens or they may be anti-ABO blood group antibodies. Either way, they bind to the vascular endothelium in the graft and activate the complement cascade, leading to platelet activation and to diffuse intravascular coagulation. The result is a swollen, darkened graft, which undergoes ischemic necrosis. This type of rejection generally is not reversible, so prevention is key.

Prevention is best done by making sure the graft is ABO-compatible and by performing a pretransplant cross-match. The cross-match is an in vitro test that involves mixing the donor's cells with the recipient's serum to look for evidence of donor cell destruction by recipient antibodies. A positive cross-match indicates the presence of preformed antibodies in the recipient that are specific to the donor, thus a high risk of hyperacute rejection if the transplant is performed.

Accelerated Acute

This type of rejection, seen within the first few days posttransplant, involves both cellular and antibody-mediated injury. It is more common when a recipient has been sensitized by previous exposure to antigens present in the donor, resulting in an immunologic memory response.

Acute

This used to be the most common type of rejection, but with modern immunosuppression, it is becoming less and less common. Acute rejection usually is seen within days to a few months posttransplant. It is predominantly a cell-mediated process, with lymphocytes being the main cells involved. Biopsy of the affected organ demonstrates a cellular infiltrate, with membrane damage and apoptosis of graft cells. The process may be associated with systemic symptoms such as fever,

chills, malaise, and arthralgias. However, with current immunosuppressive drugs, most acute rejection episodes are generally asymptomatic. They usually manifest with abnormal laboratory values (e.g., elevated creatinine in kidney transplant recipients, and elevated transaminase levels in liver transplant recipients).

Acute rejection episodes may also be mediated by a humoral, rather than cellular, immune response. B cells may generate antidonor antibodies, which can damage the graft. Establishing the diagnosis may be difficult, as biopsy may not demonstrate a significant cellular infiltrate; special immunologic stains may be necessary.

Chronic

This form of rejection occurs months to years posttransplant. Now that short-term graft survival rates have improved so markedly, chronic rejection is an increasingly common problem. Histologically, the process is characterized by atrophy, fibrosis, and arteriosclerosis. Both immune and nonimmune mechanisms are likely involved. Clinically, graft function slowly deteriorates over months to years posttransplant.

CLINICAL IMMUNOSUPPRESSION

The success of modern transplantation is in large part due to the successful development of effective immunosuppressive agents. Without these agents, only transplants between genetically identical individuals would be possible. In the 1960s, just two immunosuppressive agents were available, but more than 15 agents are now approved in the United States by the Food and Drug Administration (FDA) for clinical immunosuppression, with scores of others in various stages of clinical trials (Table 11-1). Thus the therapeutic armamentarium for transplant patients has broadened significantly, with a variety of drug combinations and protocols. Characteristics of some common immunosuppressive agents are shown in Table 11-2.

Table 11-1 Immunosuppressive Drugs by Grouping
Immunophilin binders
Calcineurin inhibitors
Cyclosporine
Tacrolimus
Noninhibitors of calcineurin
Sirolimus
Antimetabolites
Inhibitors of de novo purine synthesis
Azathioprine
Mycophenolate mofetil
Inhibitors of de novo pyrimidine synthesis
Leflunomide
Biologic immunosuppression
Polyclonal antibodies
ATGAM
Antithymocyte immunoglobulin
Monoclonal antibodies
Muromonab-CD3

IL-2R (humanized)
Belatacept
Alemtuzumab
Rituximab
Others
Corticosteroids
JAK-3 inhibitor
Protein kinase C inhibitor (e.g., AEB)

ATGAM = antithymocyte globulin; IL-2R = interleukin-2R; JAK-3 = Janus kinase-3.

Table 11-2 Summary of the Main Immunosuppressive Drugs

Drug	Mechanism of Action	Adverse Effects	Clinical Uses	Dosage
Cyclosporine (CSA)	Binds to cyclophilin	Nephrotoxicity	Improved bioavailability of microemulsion form	Oral dose is 8–10 mg/kg per day (given in two divided doses)
	Inhibits calcineurin and IL-2 synthesis	Tremor		
		Hypertension	Used as mainstay of maintenance protocols	
		Hirsutism		
Tacrolimus (FK506)	Binds to FKBP	Nephrotoxicity	Improved patient and graft survival in (liver) primary and rescue therapy	IV 0.05–0.1 mg/kg per day
	Inhibits calcineurin and IL-2 synthesis	Hypertension		PO 0.15–0.3 mg/kg per day (given q12h)
		Neurotoxicity		
		GI toxicity (nausea, diarrhea)	Used as mainstay of maintenance, like CSA	
Mycophenolate mofetil	Antimetabolite	Leukopenia	Effective for primary and rescue therapy (kidney transplants)	1 g bid PO (may need 1.5 g in black recipients)
	Inhibits enzyme necessary for de novo purine synthesis	GI toxicity		
			May replace azathioprine	
Sirolimus	Inhibits lymphocyte effects driven by IL-2 receptor	Thrombocytopenia	May allow early withdrawal of steroids and decreased calcineurin doses	2–4 mg/d, adjusted to trough drug levels
		Increased serum cholesterol/LDL		
		Vasculitis (animal studies)		
Corticosteroids	Multiple actions	Cushingoid state	Used in induction, maintenance, and treatment of acute rejection	Varies from mg to several grams/d
	Anti-inflammatory	Glucose intolerance		Maintenance doses, 5–10 mg/d
	Inhibits lymphokine production	Osteoporosis		
Azathioprine	Antimetabolite	Thrombocytopenia	Used in maintenance protocols	1–3 mg/kg per day for maintenance
	Interferes with DNA and RNA synthesis	Neutropenia		
		Liver dysfunction		

FKBP = FK506-binding protein; IL = interleukin; LDL = low-density lipoprotein.

Immunosuppressive drugs generally are used in combination with others rather than alone. *Induction immunosuppression* refers to the drugs administered immediately posttransplant to induce immunosuppression. *Maintenance immunosuppression* refers to the drugs administered to maintain immunosuppression once recipients have recovered from the operative procedure.

Individual drugs can be categorized as either biologic or nonbiologic agents. *Biologic agents* consist of antibody preparations directed at various cells or receptors involved in the rejection process; they generally are used in induction (rather than maintenance) protocols. *Nonbiologic agents* form the mainstay of maintenance protocols.

Nonbiologic Agents

CORTICOSTEROIDS

Historically, corticosteroids represent the first family of drugs used for clinical immunosuppression. Today steroids remain an integral component of most immunosuppressive protocols, and often are the first-line agents in the treatment of acute rejection. Despite their proven benefit, steroids have significant side effects, especially with long-term use. Hence, there has been considerable interest recently in withdrawing steroids from long-term maintenance protocols. The newer immunosuppressive agents may make doing so possible.

Steroids have both anti-inflammatory and immunosuppressive properties as the two are closely related. Their effects on the immune system are complex. Although they have been used clinically for years, their exact mechanism of action is not fully understood. Primarily, they inhibit the production of T-cell lymphokines, which are needed to amplify macrophage and lymphocyte responses. Steroids also have a number of other immunosuppressive effects that are not as specific. For example, they cause lymphopenia secondary to the redistribution of lymphocytes from the vascular compartment back to lymphoid tissue, inhibit migration of monocytes, and function as anti-inflammatory agents by blocking various permeability-increasing agents and vasodilators.

Steroids in high doses are the first-line choice of many clinicians for the initial treatment of acute cellular rejection. Steroids also are an integral part of most maintenance immunosuppressive regimens. High-dose IV steroids usually are administered immediately posttransplant as induction therapy, followed by relatively high-dose oral steroids (e.g., prednisone at 30 mg/d in adults), tapering to the maintenance dose of 5 to 15 mg/d over 3 to 6 months.

Adverse effects of steroid therapy are numerous and contribute significantly to morbidity in transplant recipients.[13] Individual response varies markedly, but many of the side effects are dose dependent. Common side effects include mild cushingoid facies and habitus, acne, increased appetite, mood changes, hypertension, proximal muscle weakness, glucose intolerance, and impaired wound healing. Less common are posterior subcapsular cataracts, glaucoma, and aseptic necrosis of the femoral heads. High-dose steroid use, such as bolus therapy for treatment of acute rejection, increases the risk of opportunistic infections, osteoporosis, and in children, growth retardation. These serious side effects have fueled the current interest in withdrawing patients from steroids within a few months posttransplant, or avoiding steroids altogether. Promising results with steroid withdrawal and avoidance protocols have been reported with the different organ types.[14,15]

Most recent studies have concentrated on complete steroid avoidance or rapid steroid discontinuation (usually within 1 week posttransplant) rather than steroid withdrawal after 3 to 6 months posttransplant. Success rates as measured by acute rejection rates generally have been better with the former approaches. Additionally, many of the steroid-related side effects

occur early, and so much of the benefit of steroid-free regimens may be lost with a withdrawal regimen. Rapid discontinuation or complete avoidance of steroids has been associated with equivalent or superior results with regard to acute rejection rates compared to steroid maintenance groups, but with significantly less steroid-related and infectious complications.

AZATHIOPRINE

An antimetabolite, AZA is a derivative of 6-mercaptopurine, the active agent. It was first introduced for clinical immunosuppression in 1962; in combination with corticosteroids, it became the standard agent worldwide for the next two decades. Until the introduction of cyclosporine, it was the most widely used immunosuppressive drug, but now has become an adjunctive component of immunosuppressive drug regimens. With the introduction of newer agents such as mycophenolate mofetil (MMF), the use of AZA has decreased significantly, and may be discontinued altogether in the near future.

AZA acts late in the immune process, affecting the cell cycle by interfering with DNA synthesis, thus suppressing proliferation of activated B and T lymphocytes. AZA is valuable in preventing the onset of acute rejection, but is not effective in the treatment of rejection episodes themselves.

The most significant side effect of AZA is bone marrow suppression. All three hematopoietic cell lines can be affected, leading to leukopenia, thrombocytopenia, and anemia. Suppression often is dose related; it usually is reversible with dose reduction or temporary cessation of the drug. Other significant side effects include hepatotoxicity, GI disturbances (nausea and vomiting), pancreatitis, and alopecia.

CYCLOSPORINE

The introduction of cyclosporine in the early 1980s dramatically altered the field of transplantation.[16–18] It significantly improved results after kidney transplants, but its greatest impact was on extrarenal transplants. When it was introduced, cyclosporine was the most specific immunosuppressive agent available. Compared with steroids or AZA, it much more selectively inhibits the immune response. Currently, cyclosporine plays a central role in maintenance immunosuppression in many types of organ transplants.

Cyclosporine binds with its cytoplasmic receptor protein, cyclophilin, which subsequently inhibits the activity of calcineurin. Doing so impairs expression of several critical T-cell activation genes, the most important being for IL-2. As a result, T-cell activation is suppressed. The metabolism of cyclosporine is via the cytochrome P-450 system, therefore several drug interactions are possible. Inducers of P-450 such as phenytoin decrease blood levels; drugs such as erythromycin, cimetidine, ketoconazole, and fluconazole increase them.

Adverse effects of cyclosporine can be classified as renal or nonrenal. Nephrotoxicity is the most important and troubling adverse effect of cyclosporine. Cyclosporine has a vasoconstrictor effect on the renal vasculature. This vasoconstriction (likely a transient, reversible, and dose-dependent phenomenon) may cause early posttransplant graft dysfunction or may exaggerate existing poor graft function. Also, long-term cyclosporine use may result in interstitial fibrosis of the renal parenchyma, coupled with arteriolar lesions. The exact mechanism is unknown, but renal failure may eventually result.

A number of nonrenal side effects may also be seen with the use of cyclosporine. Cosmetic complications, most commonly hirsutism and gingival hyperplasia, may result in considerable distress, possibly leading to noncompliant behavior. Several neurologic complications, including headaches, tremor, and seizures, also have been reported. Other nonrenal side effects

include hyperlipidemia, hepatotoxicity, and hyperuricemia.

TACROLIMUS

Tacrolimus (FK506) is a metabolite of the soil fungus *Streptomyces tsukubaensis*, found in Japan. Released in the United States in April 1994 for use in liver transplantation, it is currently used in a fashion similar to cyclosporine. Tacrolimus, like cyclosporine, is a calcineurin inhibitor and has a very similar mechanism of action. Cyclosporine acts by binding cyclophilins, while tacrolimus acts by binding FK506-binding proteins (FKBPs). The tacrolimus-FKBP complex inhibits the enzyme calcineurin, which is essential for activating transcription factors in response to the rise in intracellular calcium seen with stimulation of the TCR. The net effect of tacrolimus is to inhibit T-cell function by preventing synthesis of IL-2 and other important cytokines. The main difference between tacrolimus and cyclosporine, other than the actual immunophilin each binds to, is in relative potency: Tacrolimus is 100 times more potent than cyclosporine on a molar basis. Similarly to cyclosporine, tacrolimus primarily is metabolized by the P-450 enzyme system of the liver; therefore similar drug interactions occur.

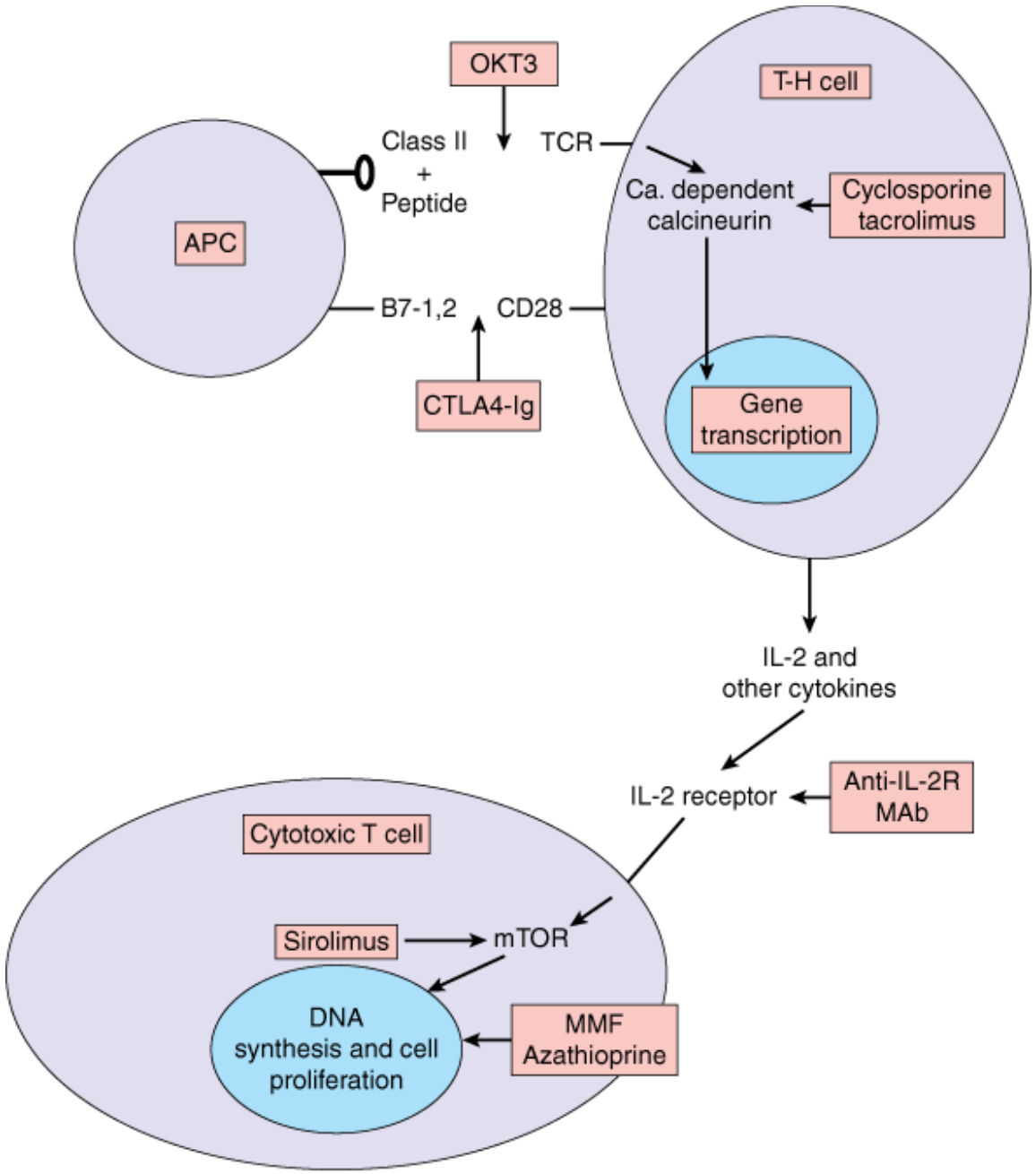
Adverse effects of tacrolimus and cyclosporine are similar. The most common problems include nephrotoxicity, neurotoxicity, impaired glucose metabolism, hypertension, infection, and GI disturbances. Nephrotoxicity is dose related and reversible with dose reduction. Neurotoxicity seen with tacrolimus ranges from mild symptoms (tremors, insomnia, and headaches) to more severe events (seizures and coma); it usually is related to high levels and resolves with dose reduction. These side effects are most common early posttransplant and subsequently tend to decrease in incidence.

The hyperglycemic effect of tacrolimus does not appear to be dose related. Its cause is unknown. However, in most studies, its incidence is significantly higher with tacrolimus than with cyclosporine. Other common side effects involve the GI tract, ranging from mild cramps to severe diarrhea. Hypertension, hypercholesterolemia, and hypomagnesemia occur with equal frequency with tacrolimus. As with other immunosuppressive drugs, infection and malignancy remain the most serious, long-term adverse events.

SIROLIMUS

A macrolide antibiotic derived from a soil actinomycete originally found on Easter Island (Rapa Nui), sirolimus (previously known as *rapamycin*) is structurally similar to tacrolimus and binds to the same immunophilin (FKBP). Unlike tacrolimus, it does not affect calcineurin activity, and therefore does not block the calcium-dependent activation of cytokine genes. Rather, the active complex binds so-called *target of rapamycin proteins* (Fig. 11-2), resulting in inhibition of P7056 kinase (an enzyme linked to cell division). The net result is to prevent progression from the G_1 to the S phase of the cell cycle, halting cell division.

Fig. 11-2.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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Sites of action of immunosuppressive drugs. APC = antigen-presenting cell; CTLA4-Ig = cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; IL = interleukin; MMF = mycophenolate mofetil; MAb = monoclonal antibody; mTOR = mammalian target of rapamycin; T-H Cell = helper T cell.

To date, sirolimus has been used in a variety of combinations and situations. It may be used in conjunction with one of the calcineurin inhibitors. In such combinations, sirolimus usually is used to help withdraw or avoid the use of steroids completely in maintenance immunosuppressive regimens. It also has been used as an alternative to tacrolimus or cyclosporine, as part of a calcineurin-sparing protocol.[19] The advantage of this type of protocol is that it may not be associated with long-term nephrotoxicity (as may be seen with the calcineurin agents). Hence, sirolimus may prove to be better for long-term preservation of renal function in transplant recipients.

The major side effects of sirolimus include neutropenia, thrombocytopenia, and a significant elevation of the serum

triglyceride and cholesterol levels. It also has been associated with impaired wound healing, leading to a higher incidence of wound-related complications.

MYCOPHENOLATE MOFETIL

MMF was approved in May 1995 by the FDA for use in the prevention of acute rejection after kidney transplants. It since has been rapidly incorporated into routine clinical practice at many centers as part of maintenance regimens.[20] A semisynthetic derivative of mycophenolate acid, it is isolated from the mold *Penicillium glaucum*. It works by inhibiting inosine monophosphate dehydrogenase, which is a crucial, rate-limiting enzyme in de novo synthesis of purines. Specifically, this enzyme catalyzes the formation of guanosine nucleotides from inosine. Many cells have a salvage pathway and therefore can bypass this need for guanosine nucleotide synthesis by the de novo pathway. Activated lymphocytes, however, do not possess this salvage pathway and require de novo synthesis for clonal expansion. The net result is a selective, reversible antiproliferative effect on T and B lymphocytes.

MMF differs from cyclosporine, tacrolimus, and sirolimus in that it does not affect cytokine production or the events immediately after antigen recognition. Rather, MMF works further distally in the chain of activation events to prevent proliferation of the stimulated T cell (see Fig. 11-2). Like AZA, it is an antimetabolite; unlike AZA, its impact is selective: It only affects lymphocytes, not neutrophils or platelets. In several clinical trials, it has proven to be more effective than AZA, and has largely replaced it.

The incidence and types of adverse events with MMF are similar to those seen with AZA. Notable exceptions are GI side effects (diarrhea, gastritis, and vomiting), which are more common with MMF. Clinically, significant leukopenia also is more common, affecting about one third of recipients. Dose reduction or temporary drug cessation usually is adequate to treat leukopenia (Table 11-3).

Table 11-3 Side Effects and Drug Interactions of the Main Immunosuppressive Drugs

	Common Side Effects	**Other Medications That Increase Blood Levels**	**Other Medications That Decrease Blood Levels**	**Other Medications That Potentiate Toxicity**
Cyclosporine (CSA)	Hypertension, nephrotoxicity, hirsutism, neurotoxicity, gingival hyperplasia	Verapamil, clarithromycin, doxycycline, azithromycin, erythromycin, fluconazole, itraconazole, ketoconazole	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin	Nephrotoxicity: Acyclovir, ganciclovir, aminoglycosides, NSAIDs
Tacrolimus (FK506)	Hypertension, nephrotoxicity, hyperglycemia, neurotoxicity	Verapamil, clarithromycin, doxycycline, azithromycin, erythromycin, fluconazole, itraconazole, ketoconazole	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin	Nephrotoxicity: Acyclovir, ganciclovir, aminoglycosides, NSAIDs
Sirolimus	Thrombocytopenia and nutropenia, elevated cholesterol, extremity edema, impaired wound healing	—	—	—
Mycophenolate mofetil	Leukopenia, thrombocytopenia, GI upset	—	Cholestyramine, antacids	—
Corticosteroids	Hyperglycemia, osteoporosis,	—	—	—

	cataracts, myopathy, weight gain			
Azathioprine	Leukopenia, anemia, thrombocytopenia, GI upset	—	—	Bone marrow suppression: Allopurinol, sulfonamides

Biologic Immunosuppression

Polyclonal antibodies directed against lymphocytes have been used in clinical transplantation since the 1960s. Monoclonal antibody (mAb) techniques were later developed and, in turn, allowed for the development of biologic agents such as muromonab-CD3 (OKT3), which were targeted to specific subsets of cells. A number of different mAbs are currently under development or have entered the phase of clinical testing for use in transplantation. Many are directed against functional secreted molecules of the immune system or their receptors, rather than against actual groups of cells.

POLYCLONAL ANTIBODIES

Polyclonal antibodies are produced by immunizing animals such as horses or rabbits with human lymphoid tissue, allowing for an immune response, removing the resultant immune sera, and purifying the sera in an effort to remove unwanted antibodies. These lymphocyte-depleting antibodies are potent suppressors of the T-cell mediated immune response and selectively prevent the activation of B-cells by a range of stimuli. Polyclonal antibodies have been successfully used as induction agents to prevent rejection and to treat acute rejection episodes.

Antithymocyte Globulin

Antithymocyte globulin (ATGAM) is a purified gamma globulin solution obtained by immunization of horses with human thymocytes. It contains antibodies to a wide variety of human T-cell surface antigens, including the MHC antigens. ATGAM generally must be infused via a central vein because infusion into a peripheral vein often is associated with thrombophlebitis. To avoid allergic reactions, patients should be premedicated with methylprednisolone and diphenhydramine hydrochloride. Even so, side effects may be significant because of the large amount of foreign protein. Symptoms of cytokine release syndrome include fever, chills, arthralgia, thrombocytopenia, leukopenia, and a serum sickness-like illness.

Thymoglobulin

Antithymocyte immunoglobulin (Thymoglobulin) is a polyclonal antibody obtained by immunizing rabbits with human thymocytes. It has been approved by the FDA to prevent and treat rejection in solid organ transplant recipients. Multicenter randomized studies comparing antithymocyte immunoglobulin (Thymoglobulin) vs. ATGAM as induction therapy have shown that at 1-year posttransplant, there was less incidence and severity of rejection in antithymocyte immunoglobulin treated patients.[21] Five-year follow-up studies have shown that this is sustained long term. Safety profile comparison shows a higher incidence of leukopenia with antithymocyte immunoglobulin, although the rate of cytomegalovirus (CMV) infection seems to be lower. Some data suggest that antithymocyte immunoglobulin may be associated with an increased risk of posttransplant lymphoproliferative disorder (PTLD) compared with no induction, but more studies are needed for confirmation.[22] Comparison studies with muromonab-CD3 showed that muromonab-CD3 reversed a slightly higher number of rejection episodes than antithymocyte immunoglobulin in renal transplant recipients, but that both were efficient treatments; first-time use of antithymocyte immunoglobulin was associated with fewer side effects than muromonab-CD3.

MONOCLONAL ANTIBODIES

mAbs have emerged as a new class of immunosuppressive agents, which appear to be effective in both the treatment and prevention of acute rejection and are well tolerated in renal transplant recipients.[23] mAbs are produced by the hybridization of murine antibody-secreting B-lymphocytes with a nonsecreting myeloma cell line. The highly specific nature of these drugs makes them less toxic than the oral, long-term maintenance agents such as corticosteroids and calcineurin inhibitors. Muromonab-CD3 remains a commonly used mAb but some of the new mAbs already have confirmed their efficacy in clinical phase III trials and are part of well-established immunosuppressive regimens. These include anti-CD25 mAbs (basiliximab and daclizumab). Other recently developed mAbs, like humanized anti-CD52 mAb alemtuzumab (Campath-1H), anti-CD20 (rituximab), anti–lymphocyte function-associated antigen-1 (anti–LFA-1), anti–intercellular adhesion molecule-1 (anti–ICAM-1) and anti–tumor necrosis factor alpha (TNF-α) (infliximab) currently are being tested and show encouraging immunosuppressive potential.

Muromonab-CD3

This MoAb is directed against the CD3 antigen complex found on all mature human T cells. The CD3 complex is an integral part of the TCR. Inactivation of CD3 by muromonab-CD3 causes the TCR to be lost from the cell surface. The T cells are then ineffective, and are rapidly cleared from the circulation and deposited into the reticuloendothelial system.

The standard dose is 5 mg/d, given IV. Smaller doses may be just as effective. Efficacy can be measured by monitoring $CD3^+$ cells in the circulation. If the drug is effective, the percentage of $CD3^+$ cells should fall to and stay below 5%. Failure to reach this level indicates an inadequate dose or the presence of antibodies directed against muromonab-CD3.

Muromonab-CD3 is highly effective and versatile. Most commonly, it is used to treat severe acute rejection episodes (i.e., those resistant to steroids). Muromonab-CD3 also has been used as prophylaxis against rejection, as induction therapy, and as primary rejection treatment.

Significant, even life-threatening adverse effects may be seen with muromonab-CD3, most commonly with the first few doses. Because muromonab-CD3 is a T-cell mitogen, most of these symptoms are thought to be mediated by T-cell release of cytokines via CD3 binding. The most common symptoms are fever, chills, and headaches. Muromonab-CD3's most serious side effect is a rapidly developing, noncardiogenic pulmonary edema. The risk of this side effect significantly increases if the patient is fluid-overloaded before beginning muromonab-CD3 treatment. Other serious side effects include encephalopathy, aseptic meningitis, and nephrotoxicity. Use of muromonab-CD3, especially multiple courses, significantly increases the risk of infection (e.g., CMV) and of neoplasms (e.g., PTLD). To reduce the side effects and the antigenicity of murine muromonab-CD3, a nonmitogenic "humanized" variant has been developed. Both in vitro and in vivo studies have found that the humanized variant of muromonab-CD3 does not activate human T cells, but retains significant immunosuppressive properties. The drug was well tolerated with minimal first-dose reactions (including lack of IL-2 release); induction of antibodies against muromonab-CD3 was not observed. Because it is less immunogenic, its half-life is much longer than that of conventional muromonab-CD3.

Anti-CD25 Monoclonal Antibodies (Basiliximab and Daclizumab)

The alpha subunit of the IL-2 receptor, also known as *Tac* or *CD25* is found exclusively on activated T cells. Blockade of this component by mAbs selectively prevents IL-2–induced T-cell activation. This selectivity makes the anti-CD25 mAbs powerful antirejection agents with no significant added risks of infection, malignancy, or other major side effects. There are two types

of anti-CD25 mAbs: chimeric (approximately 75% human and 25% murine protein) and humanized (approximately 90% human and 10% murine). Basiliximab (Simulect) and daclizumab (Zenapax) are currently the two anti-CD25 mAbs approved for clinical use. They are used as part of induction immunosuppression in renal transplantation, in association with calcineurin inhibitors, corticosteroids, and MMF. A randomized, double-blind, placebo-controlled phase III trial was done comparing daclizumab vs. no induction in renal patients receiving their first cadaveric kidney transplant who received triple immunosuppression of cyclosporine, AZA, and prednisolone.[24] In the daclizumab group, fewer patients developed rejection during the first 6 months after transplantation, time to develop rejection was longer, and the numbers of rejection episodes were lower. Moreover, infusion of the antibody was not associated with any adverse reactions. There also was no difference in infection or cancer rates between the two groups. A comparable study also has been published using basiliximab in renal transplantation.[25]

Anti-CD52 Monoclonal Antibody Alemtuzumab (Campath-1h)

Alemtuzumab (Campath-1H) is a humanized rat mAb (rat Ig G2b) directed against the CD-52 antigen. It is a powerful cytolytic agent and has been used therapeutically in bone marrow transplantation, several autoimmune diseases, and organ transplantation.[26] The CD52 antigen is expressed on T and B lymphocytes, monocytes, macrophages, and eosinophils, as well as on the lining of the male reproductive tract. It is one of the most abundant antigens on the surface of lymphocytes, accounting for approximately 5% of the surface antigens. This probably explains, in part, the profound and long-lasting lymphopenia produced after the administration of one or two doses of the antibody; these depressed lymphocyte levels may take months to years to return to normal levels. For example, two doses of alemtuzumab, 40 mg in total, given over 2 days in patients receiving a kidney transplant produce profound lymphopenia. Although B-lymphocyte counts return to normal levels within 3 to 12 months, $CD4^+$ and $CD8^+$ lymphocyte counts remain significantly depressed for as long as 3 years. After binding to its target, alemtuzumab causes cell death through several mechanisms, including complement-mediated cytolysis, antibody-mediated cytotoxicity, and apoptosis.

The most extensive experience with the use of alemtuzumab in solid organ transplantation has been in renal transplantation. It has been used in induction and maintenance therapy and treatment of acute rejection. Randomized trials comparing alemtuzumab with antithymocyte immunoglobulin found that there was no difference in patient or graft survival, acute rejection rates, or renal function; nor were there any differences in infections or incidence of diabetes or hyperlipidemia. As with all antibody treatments, there is an initial reaction with alemtuzumab administration. However, it is relatively modest and suppressed with an IV bolus injection of 1 g of methylprednisolone before administration of the antibody. Because of the long-lasting T-cell depletion, there is still concern regarding the risk of infection. An interesting observation is the occurrence of autoimmune disorders in the form of autoimmune hypothyroidism and autoimmune hemolytic anemia in rare patients treated with alemtuzumab. There is a need for large, prospective randomized control trials and long-term follow-up to establish the true role of alemtuzumab especially with respect to safety.

Anti-CD20 (Rituximab)

CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), is a protein which is located on pre-B and mature B lymphocytes. The antigen is expressed on most B-cell non-Hodgkin's lymphomas but is not found on stem cells, pro-B cells, normal plasma cells, or other normal tissues. It regulates an early step in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. Rituximab, a chimeric murine/human mAb, approved in the United States only for the treatment of refractory or relapsed B-cell lymphomas, reacts with the CD20 antigen.[27] In transplant recipients, it is used for treatment of posttransplant lymphoproliferative disease, to anecdotally reduce preformed

anti-HLA and anti-ABO antibodies, and for the prevention and treatment of acute humoral rejection. A need for controlled clinical trials clearly is needed to determine the best clinical situation in which to use this agent.

Monoclonal Antibodies to Adhesion Molecules

Adhesion molecules play a dual role in graft injury posttransplant. Initial ischemic reperfusion injury is characterized by a cellular infiltrate in the graft. This migration of cells into the graft is regulated by the endothelium, which recruits the infiltrating cells by expressing adhesion molecules on its surface. Adhesion molecules, such as the LFA-1: ICAM-1 receptor ligand pair also participate in subsequent antigen-dependent T-cell activation. When the TCR comes into contact with its target antigen, LFA-1 binds to ICAM-1 on the antigen-presenting cell (APC) surface. This binding then potentiates T-cell activation by stabilizing TCR binding to its target and transmitting amplifying signals to the cytoplasm. Therefore, mAb directed against adhesion molecules could simultaneously interrupt both the effect of ischemic injury and the alloresponse. This potential dual effect currently is being evaluated in laboratory and clinical studies.

Comparisons of the mAb directed against the alpha chain of LFA-1 (odulimomab) with antithymocyte immunoglobulin as induction therapy found, at 3 and 12 months after transplantation, similar rate and severity of rejection episodes as well as incidence of infection. An anti–LFA-1 mAb (efalizumab) was found capable of inhibiting lymphocyte adhesion, circulation, and activation. Another potential benefit of anti-LFA mAbs observed in both animal models and human beings is that they can diminish the ischemia-reperfusion injury associated with delayed graft function. The anti-CD4 mAb (priliximab) already has shown immunosuppressive potential in some therapeutic pilot studies. However, in another clinical trial, this mAb, although well tolerated, was associated with a high acute rejection rate (50% of patients developed an acute rejection episode within the first 3 months), probably because of poor drug bioavailability or possibly because of anti-murine antibody development. Due to these conflicting results, anti-CD4 mAbs are not recommended for clinical use at this time. Costimulatory blockade with anti-CD154 mAb prolongs allograft survival in nonhuman primates; but in clinical transplantation, the rejection rate has been unacceptably high and can have serious side effects, particularly thromboembolism, mediated probably by platelet activation leading to enhanced aggregation.

Belatacept: The best-characterized pathway of T-cell costimulation includes CD28, its homologue cytotoxic T-lymphocyte-associated protein 4 (CTLA4), and their ligands CD80 and CD86. CTLA4-Ig (abatacept) is a fusion protein consisting of the extra cellular domain of CTLA4 and the Fc domain of IgG. Two amino acid substitutions to this protein resulted in the development of LEA29Y or belatacept, a high-avidity molecule with slower dissociation rates.[28,29] A phase II, randomized multicenter study was done based on costimulation blockade with belatacept in renal transplantation. Renal transplant recipients were randomly assigned to receive an intensive or a less intensive regimen of belatacept or cyclosporine. All patients received induction therapy with basiliximab, MMF, and corticosteroids. The study showed that the rate of acute rejection was similar among the groups: 6% for intensive belatacept, 6% for less intensive belatacept, and 8% for cyclosporine. Subclinical rejection at routine biopsy in 6 months was more common with less intensive belatacept (20%) than with intensive belatacept (9%) or cyclosporine (11%). At 12 months, glomerular filtration rate was significantly higher with both intensive and less intensive belatacept than those treated with cyclosporine (66.3, 62.1, and 53.5 mL/min per 1.73 m^2 , respectively), and chronic allograft nephropathy was less common with both regimens of belatacept than with cyclosporine (29%, 20%, and 44%, respectively). Lipid levels and blood pressure values were similar or slightly lower in the belatacept groups. The frequency of infection was similar in all three groups, around 75%. Cancers occurred in two patients treated with intensive belatacept (one breast cancer and one PTLD) and in two patients treated with cyclosporine (one skin cancer and one thyroid cancer). However, PTLD developed in two additional patients treated with the intensive regimen 2 and 13 months

after replacement of belatacept with conventional immunosuppressive agents. As belatacept interacts with the CD28 pathway, there were no reports of thrombotic complications seen with intervention in the CD40: CD154 pathway. Belatacept did not appear to affect the number or activity of T regulatory cells and clinical monitoring of lymphocytes did not reveal any depleting effects. These findings suggest that belatacept acts by depleting initial T-cell activation rather than selective depletion or complement-mediated lysis. Although these results are exciting, they are preliminary, and the long-term implications can only be known with larger studies and longer-term observation.

New Agents

1. AEB: This is a new oral compound that effectively blocks early T-cell activation by selective inhibition of protein kinase C. Therefore, it has a different mechanism of action from that of calcineurin inhibitors, and early studies suggest it is not associated with the nephrotoxicity seen with calcineurin inhibitors. This agent is currently in phase II testing.

2. ISA247: This is a novel semisynthetic analogue of cyclosporine that is structurally similar to it except for a modification of a functional group. This agent has not been associated with the nephrotoxicity seen with cyclosporine and currently is in phase II testing.

3. Janus kinase-3 (JAK-3) inhibitors: JAKs are cytoplasmic tyrosine kinases that participate in the signaling of a broad range of cell surface receptors, particularly members of the cytokine receptor superfamily. JAK-3 is found primarily on hematopoietic cells and blocking this may provide a significant degree of selectivity in immunosuppression. It is currently in phase II trials.

ORGAN PROCUREMENT AND PRESERVATION

The biggest problem facing transplant centers today is the shortage of organ donors. Mechanisms that might increase the number of available organs include: (a) Optimizing the current donor pool (e.g., the use of multiple organ donors or marginal donors); (b) increasing the number of living-donor transplants (e.g., the use of living unrelated donors); (c) using unconventional and controversial donor sources (e.g., using deceased donors without cardiac activity or anencephalic donors); and (d) performing xenotransplants. The largest potential increase in the number of available organs would result from improving donation rates from suitable deceased donors. By recent estimates, over 10,000 brain-dead donors are potentially available in the United States annually. Currently, however, only about one half of them are actually used. The single most important reason for the lack of deceased-donor organ retrieval is the inability to obtain consent from the surviving next-of-kin. The need for public education is crucial, including more effective educational campaigns to increase awareness of the importance of organ transplants.

Deceased Donors

Most extrarenal transplants performed today, and roughly one half of all renal transplants, are from deceased donors. These donors are deceased individuals who meet the criteria for brain death, but whose organs are being perfused by life-support measures, allowing adequate time for referral to an organ procurement organization. A member of that organization can then ascertain whether donation is possible, and if so, approach the potential donor's family and possibly obtain consent to procure suitable organs.

Crucial to the concept of deceased-donor organ donation is the concept of brain death. Brain death means that all brain and brain stem function has irreversibly ceased, while circulatory and ventilatory functions are maintained temporarily. The clinical diagnosis of brain death rests on three criteria: (a) irreversibility of the neurologic insult; (b) absence of clinical evidence of cerebral function; and most important, (c) absence of clinical evidence of brain stem function. When testing for

From Lycan / Dr. MV

brain death, hypothermia, medication side effects, drug overdose, and intoxication must be excluded. Brain death can be diagnosed by routine neurologic examinations (including cold caloric and apnea testing on two separate occasions at least 6 hours apart), coupled with prior establishment of the underlying diagnosis. Confirmatory tests must verify the absence of intracranial blood flow on brain flow studies or the presence of an isoelectric electroencephalogram reading.

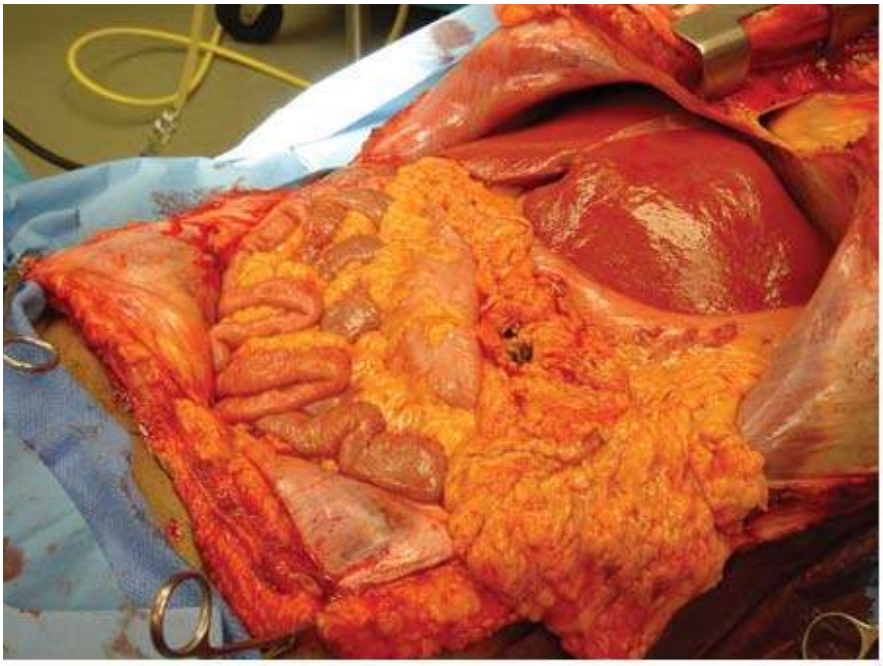
Once the diagnosis of brain death has been established, the process of organ donation can be initiated.[30,31] The focus then switches from the treatment of elevated intracranial pressure (ICP) to preserving organ function and optimizing peripheral oxygen delivery.[32] It is important to keep in mind that management of the deceased organ donor is an active process, requiring aggressive monitoring and intervention to ensure that perfusion to the organs of interest is not compromised. For all organ donors, core temperature, systemic arterial blood pressure, arterial oxygen saturation, and urine output must be determined routinely and frequently. Arterial blood gases, serum electrolytes, blood urea nitrogen, serum creatinine, liver enzymes, hemoglobin, and coagulation tests also need to be monitored regularly. Hemodynamic instability can be marked after brain death, with wide swings between the extremes of hypotension and hypertension. Hypotension is usually secondary to hypovolemia, due to a combination of vasomotor collapse after brain death and the effects of treatment protocols to decrease ICP. Hypertension may also be seen, often secondary to raised ICP. It can be treated with short-acting vasodilatory agents or with rapidly reversible beta blockers.

Other key factors in donor management include respiratory maintenance, good renal perfusion with brisk urine output, and avoidance of hypothermia.

Surgical technique: The technique of multiple organ procurement (kidney, liver, pancreas, small bowel) was first described by Starzl and his colleagues in 1984.[33] Most centers have now added their own modifications to these pioneering techniques and differ primarily on their degree of in vivo dissection. Some centers perform extensive dissection of the organs to be recovered before flushing the organs with preservative solution. Other centers prefer to flush the organs early, remove the abdominal contents "en-bloc," and perform the separation and dissection of the individual organs on the back table.[34] Each technique has its potential advantages and disadvantages. Regardless of personal technique and preference, it is paramount that the transplant surgeon develops a systematic approach to safely procure the liver, pancreas, and kidneys even in the unstable donor.

The basic steps involve a long incision to provide wide exposure of all thoracic and abdominal organs (Fig. 11-3). Complete mobilization of the distal small bowel, right colon, and duodenum is performed to allow for identification of the distal aorta, iliac bifurcation, and the distal inferior vena cava (IVC). The infrarenal aorta will serve as the site for insertion of the cannula that will allow for flushing of the organs with cold preservative solution (Fig. 11-4). The supraceliac aorta is encircled followed by limited dissection of the hepatic hilum and the pancreas. The portal system can be cannulated via the inferior mesenteric vein and the organs can then be flushed with preservative solution and topically cooled with slush. The thoracic organs, liver, pancreas, and kidneys are then removed individually.

Fig. 11-3.



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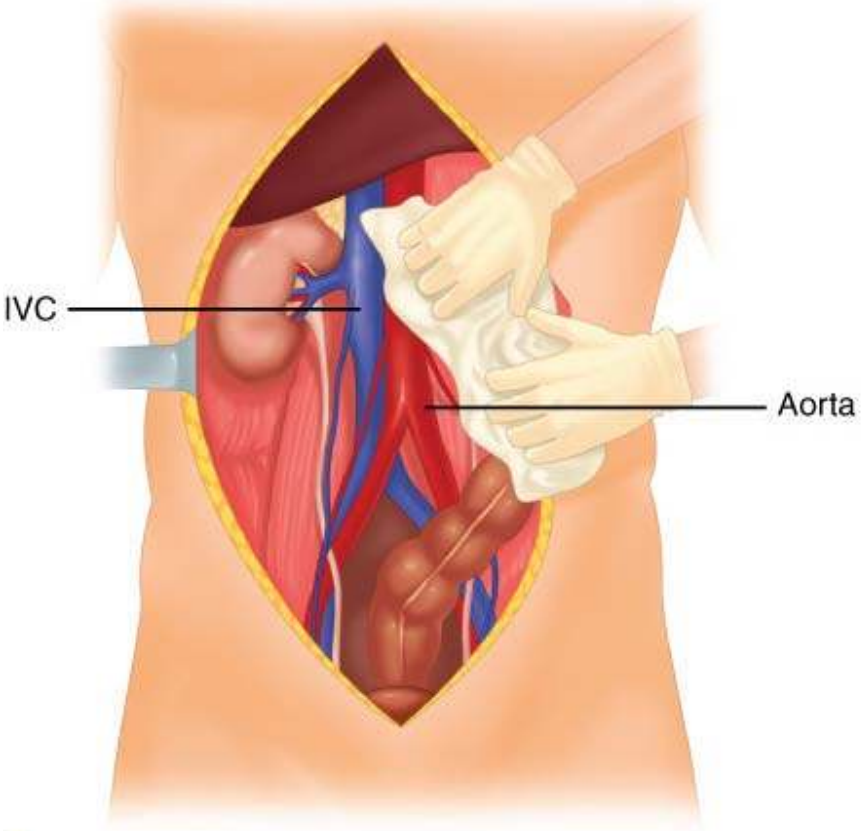
Incision for multiorgan abdominal procurement with wide exposure of all abdominal organs.

Fig. 11-4.



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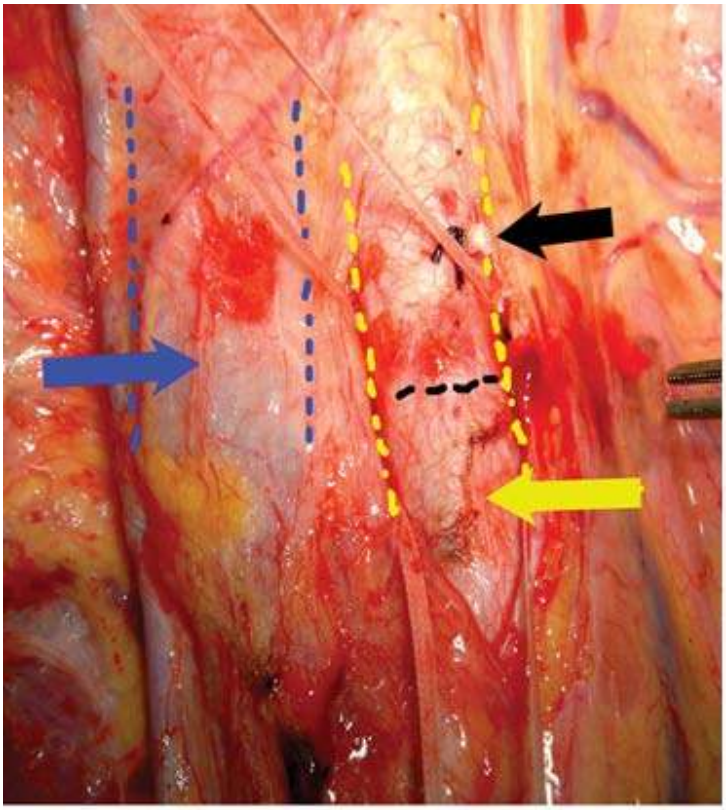

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A and **B.** With the small bowel and right colon completely mobilized, the infrarenal aorta can be isolated for insertion of the cannula that will allow the organs to be flushed with cold preservative solution. Black arrow = aorta; blue arrow = inferior vena cava (IVC); yellow arrow = cannula insertion site.

Donation after cardiac death: The non–heart-beating donor (NHBD), also referred to as the *donation after cardiac death* donor, is one type of expanded criteria donor that is increasingly being used by transplant centers to successfully boost the number of deceased donors and decrease the dire shortage of transplantable organs.[35] NHBD death is characterized by irreversible absence of circulation, in contrast to heart-beating donor death, defined by irreversible cessation of all brain functions. Organ ischemia is minimized in the brain-dead donor because circulatory arrest typically occurs concurrently with perfusion of preservation solution and rapid core cooling. NHBDs are less than ideal because the organs suffer ischemia during the prolonged periods between circulatory dysfunction, circulatory arrest, and subsequent perfusion and cooling. Furthermore, the surgical procedure for NHBD organ recovery is demanding and rushed.

It is important to differentiate controlled from uncontrolled NHBDs. Uncontrolled NHBDs sustain circulatory arrest and either fail to respond to cardiopulmonary resuscitation and/or are declared dead on arrival to the hospital. Uncontrolled NHBD death is unplanned, so the organs suffer protracted ischemia before recovery. Although kidneys tolerate a short period of the resultant warm ischemia, transplantation of extrarenal organs from uncontrolled NHBDs carries a much greater risk. In contrast, controlled NHBDs undergo circulatory arrest following planned withdrawal of life support, most often in the operating room, with a donor surgical team readily available. Controlled NHBDs suffer terminal illness, usually a severe neurologic injury without the possibility of meaningful recovery or survival. Controlled NHBDs provide organs that are exposed to significantly less ischemic damage than those of uncontrolled NHBDs and, in general, offer superior posttransplant

function when compared with uncontrolled NHBDs.

Living Donors

Living-donor transplantation is unique in that surgeons are operating on a healthy individual (i.e., a living donor) who has no medical disorders and does not require an operation. The use of living donors is an integral and important part of the field of transplantation today. The first transplants ever performed used living donors. Today, living donors are commonly used for every type of transplant except heart transplants. The number of such transplants continues to increase on a yearly basis. But living-donor transplants pose a unique set of medical, ethical, financial, and psychosocial problems that must be dealt with by the transplant team.

The use of living donors offers numerous advantages. Primary is the availability of a life-saving organ. A certain percentage of transplant candidates die while waiting for a deceased-donor organ as a direct result of a complication, or of progression of their underlying disease. For such ill candidates, the advantage of a living donor is obvious. In certain parts of the world, such as the Far East, where deceased-donor transplants are not accepted by the public, the advantage and need of the living donor is obvious. Even in countries where deceased-donor transplants are accepted, a living-donor transplant may significantly shorten the waiting time for potential recipients. A shorter waiting time generally implies a healthier candidate—one whose body has not been ravaged by prolonged end-stage organ failure. Moreover, living-donor transplants are planned (rather than emergency) procedures, allowing for better preoperative preparation of the potential recipient. Receiving an organ from a closely matched relative may also have immunologic benefits. Lastly, long-term results may be superior with living-donor transplants, which is certainly the case with kidney transplants.

The disadvantages of a living-donor transplant for the potential recipient are minimal. With some organ transplants (e.g., living-donor liver or lung), the procedure may be more technically complex, resulting in an increased incidence of surgical complications. However, this disadvantage is offset by the numerous advantages.

The major disadvantage of living-donor transplants is to the donor. Medically, there is no possibility of benefit for the donor, only potential for harm. The risk of death associated with donation depends on the organ being removed. For nephrectomy, the mortality risk is estimated to be less than 0.05%. However, for partial hepatectomy, it is about 0.5%. Risks for surgical and medical complications also depend on the procedure being performed. In addition, long-term complications or problems may be associated with partial loss of organ function through donation. The guiding principle of all living-donor transplants should be the minimization of risk to the donor. What risk there is must be carefully explained to the potential donor, and written informed consent should be obtained.

The kidney, the first organ to be used for living-donor transplants, is the most common type of organ donated by living donors today. Living-donor liver transplants are not as common, but have been performed for almost 15 years now. Initially, they involved adult donors and pediatric recipients, but now an adult donor for an adult recipient is more common. Living-donor transplants with organs besides the kidney and liver are fairly uncommon, but are performed at various centers. Living-donor pancreas transplants involve a distal pancreatectomy, with the graft consisting of the body and tail of the pancreas; vascular inflow and outflow are provided by the splenic artery and splenic vein. Living-donor intestinal transplants usually involve removal of about 200 cm of the donor's ileum, with inflow and outflow provided by the ileocolic vessels. Living-donor lung transplants involve removal of one lobe of one lung from each of two donors; both grafts are then transplanted into the recipient.

Preservation

Organ preservation methods have played an important role in the success of cadaver-donor transplants. They have resulted in improved graft function immediately posttransplant and have diminished the incidence of primary nonfunction of organs. By prolonging the allowable cold ischemia times, they have also allowed for better organ allocation and for safer transplants.[36,37]

The most common methods involve the use of hypothermia and pharmacologic inhibition to slow down metabolic processes in the organ once it has been removed from the deceased donor. Hypothermia very effectively slows down enzymatic reactions and metabolic activity, allowing the cell to make its limited energy reserves last much longer. A temperature decrease from 37° to 4°C (98.6° to 39.2°F) (the temperature of most preservation solutions) slows metabolism about 12-fold. However, in the absence of any energy inflow into the cell, degradative reactions begin to provide the cell with an energy source. The result can be destruction of important structural elements and, eventually, structural damage to the cells and the organ. So, although hypothermia greatly slows enzymatic reactions, they continue nonetheless, leading to accumulation of potentially detrimental end products within the cell. Hypothermia also contributes to the development of cellular swelling because the membrane ion pumps are slow to function.

Cold storage solutions have been developed to improve organ preservation by ameliorating some of the detrimental effects of hypothermia alone. Essentially, these solutions suppress hypothermia-induced cellular swelling and minimize the loss of potassium from the cell. Agents that do not readily permeate the cell membrane and that have an electrolyte composition resembling the intracellular environment (low sodium, high potassium) are used, thus preventing the loss of cellular potassium.

The most commonly used fluid worldwide is the University of Wisconsin solution.[38] It contains lactobionate, raffinose, and hydroxyethyl starch. Lactobionate is impermeable and prevents intracellular swelling; it also lowers the concentration of intracellular calcineurin and free iron, which may be beneficial in reducing reperfusion injury. Hydroxyethyl starch, a synthetic colloid, may help decrease hypothermia-induced cell swelling of endothelial cells and reduce interstitial edema. Another solution that is now being used commonly is histidine-tryptophan-ketoglutarate solution.[39]

Although cold preservation has improved cadaver-donor transplant results, the amount of time that an organ can be safely preserved is limited. After that, the incidence of organ nonfunction starts to increase. With kidneys, exceeding the preservation time limit results in delayed graft function, requiring dialysis support for the recipient until function improves. With livers, the result is primary nonfunction, requiring an urgent retransplant. How long an organ can be safely preserved depends on the type of organ and on the condition of the donor. With kidneys, cold ischemic times should be kept below 36 to 40 hours; after that, delayed graft function significantly increases. With pancreata, more than 24 hours of ischemia increases problems due to pancreatitis and duodenal leaks. With livers, more than 16 hours of ischemia increases the risk for primary nonfunction and biliary complications. Hearts and lungs tolerate preservation poorly; ideally, ischemia times should be below 6 hours. With marginal donors, all of these times should be adjusted further downward.

KIDNEY TRANSPLANTATION

A kidney transplant now represents the treatment of choice for patients with end-stage renal disease (ESRD). It offers the greatest potential for restoring a healthy, productive life in most such patients. Compared with dialysis, it is associated with better patient survival and superior quality of life, and is more cost effective.[40,41] Currently, there are nearly 70,000 patients in the United States awaiting a kidney transplant. Because of the success of the procedure, the waiting list has grown dramatically since the 1990s. Unfortunately, the number of available organs has not kept pace, resulting in longer waiting

times for recipients.

History

The history of kidney transplantation is in many ways the history of transplantation itself. The kidney was the first organ to be transplanted regularly, and it remains the most common organ transplanted today. The first clinical deceased-donor kidney transplant was performed in 1933 by Voronoy, a Ukrainian surgeon, with unsuccessful results secondary to rejection. In the 1950s, this immunologic barrier was circumvented by performing the kidney transplants between identical twins. The era of modern kidney transplantation began with the introduction of AZA to suppress the immune system. With the demonstration of the synergistic effect with glucocorticoids, renal transplantation was established as a viable option for the treatment of ESRD. Polyclonal antilymphocyte agents, such as antilymphocyte globulin, were soon developed, significantly contributing to the treatment of acute rejection. The introduction of cyclosporine in the 1980s significantly improved graft and patient survival rates, allowing for a dramatic increase in the number of kidney transplants.

Preoperative Evaluation

Very few absolute contraindications to kidney transplants exist. Therefore, most patients with ESRD should be considered as potential transplant candidates. However, the surgery and general anesthesia impose a significant cardiovascular stress. Subsequent lifelong immunosuppression also is associated with some risk. Pretransplant evaluation should identify any factors that would contraindicate a transplant or any risk factors that could be minimized pretransplant.[42]

The preoperative evaluation can be divided into four parts: medical, surgical, immunologic, and psychosocial. The purpose of the medical evaluation is to identify risk factors for the surgical procedure. Mortality posttransplant usually is due to underlying cardiovascular disease, so a detailed cardiac evaluation is necessary. Any history of congestive heart failure, angina, myocardial infarction, or stroke should be elicited. Patients with symptoms suggestive of cardiovascular disease or with significant risk factors (e.g., diabetes, age over 50, previous myocardial infarction) should undergo further cardiac evaluation with stress testing or angiography. Any problems identified should be treated appropriately (medically or surgically) before proceeding with the transplant.

Untreated malignancy and active infection are absolute contraindications to a transplant, because of the requisite lifelong immunosuppression. After curative treatment of malignancy, an interval of 2 to 5 years is recommended pretransplant. This recommendation is influenced by the type of malignancy, with longer observation periods for neoplasms such as melanoma or breast cancer and shorter periods for carcinoma in situ or low-grade malignancies such as basal cell carcinoma of the skin. Chronic infections such as osteomyelitis or endocarditis must be fully treated and a suitable waiting period must occur to ensure lack of recrudescence.

The medical evaluation also should concentrate on GI problems such as peptic ulcer disease, symptomatic cholelithiasis, and hepatitis. Patients who demonstrate serologic evidence of hepatitis C or B, but without evidence of active hepatic inflammation or cirrhosis, are acceptable transplant candidates. A biopsy may be helpful to determine the extent of the underlying liver disease. These patients are at increased risk for progression of their underlying liver disease after receiving immunosuppression, but exhibit excellent long-term survival rates and improved quality of life posttransplant, as compared with patients undergoing chronic dialysis.

The surgical evaluation should identify vascular or urologic abnormalities that may contraindicate or complicate a transplant. Evidence of vascular disease that is revealed by the history (claudication or rest pain) or the physical examination

(diminished or absent pulse or bruit) should be evaluated further by Doppler studies or angiography. Severe aortoiliac disease may make a transplant technically impossible; an option in such patients is a revascularization procedure such as aortobifemoral graft placement pretransplant. Areas of significant arterial stenosis proximal to the planned site of implantation may need preoperative balloon angioplasty. Urologic evaluation should exclude chronic infection in the native kidney, which may require nephrectomy pretransplant. Other indications for nephrectomy include huge polycystic kidneys, significant vesicoureteral reflux, or uncontrollable renovascular hypertension. Children especially require a complete urologic examination to evaluate reflux and bladder outlet obstruction.

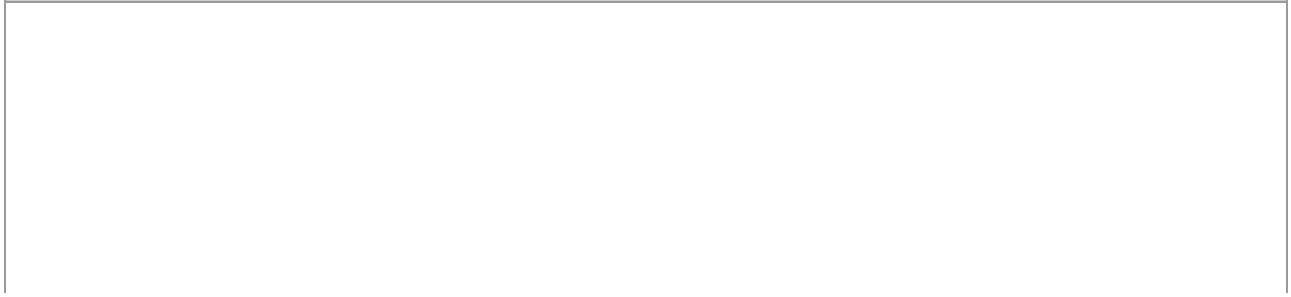
The immunologic evaluation involves determining blood type, tissue type (HLA-A, -B, or -DR antigens), and presence of any cytotoxic antibodies against HLA antigens (because of prior transplants, blood transfusions, or pregnancies). If a living-donor transplant is planned, a cross-match should be performed early on during the initial evaluation.

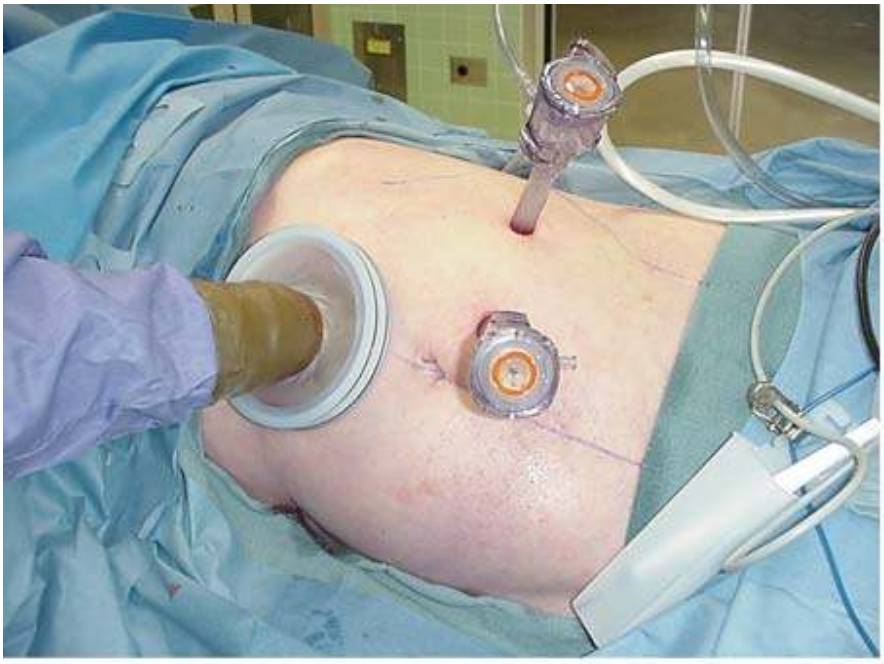
The psychosocial evaluation is necessary to ensure that transplant candidates understand the nature of the transplant procedure and its attendant risk. They must be capable of rigorously adhering to the medical regimen posttransplant. Patients who have not been compliant with their medical regimen in the past must demonstrate a willingness and capability to do so before they undergo the transplant.

Living-donor kidney transplant: One important aspect of the preoperative evaluation is the search for and evaluation of potential living donors. Living-donor kidney recipients enjoy improved long-term success, avoid a prolonged wait, and are able to plan the timing of their transplant in advance. Moreover, they have a significantly decreased incidence of acute tubular necrosis (ATN) and increased potential for HLA matching. As a result, living-donor transplants generally have better short- and long-term results, as compared with deceased-donor transplants. Of course, the risks to the living donor must be acceptably low. The donor must be fully aware of potential risks and must freely give informed consent. The search for a living donor should not be restricted to immediate family members. Results with living, unrelated donors are comparable to those with living, related (non–HLA-identical) donors.[43]

Potential living donors are first evaluated to ensure that they have normal renal function with two equally functioning kidneys and that they do not have any significant risk factors for developing renal disease (e.g., hypertension or diabetes). The anatomy of their kidneys and the vasculature can be determined by using various radiologic imaging techniques, including an IV pyelogram, arteriogram, or computed tomographic (CT) angiogram. Which kidney is removed depends on the anatomy. If there is any minor abnormality in one kidney, that kidney should be removed. If both kidneys are the same, the left kidney is preferred because of the longer left renal vein. Nephrectomy can be performed through a flank incision, by an anterior retroperitoneal approach, or by a laparoscopic technique. With the laparoscopic technique, an intraperitoneal approach is used. This involves mobilization of the colon, isolation of the ureter and renal vessels, mobilization of the kidney, division of the renal vessels, and removal of the kidney (Fig. 11-5).

Fig. 11-5.





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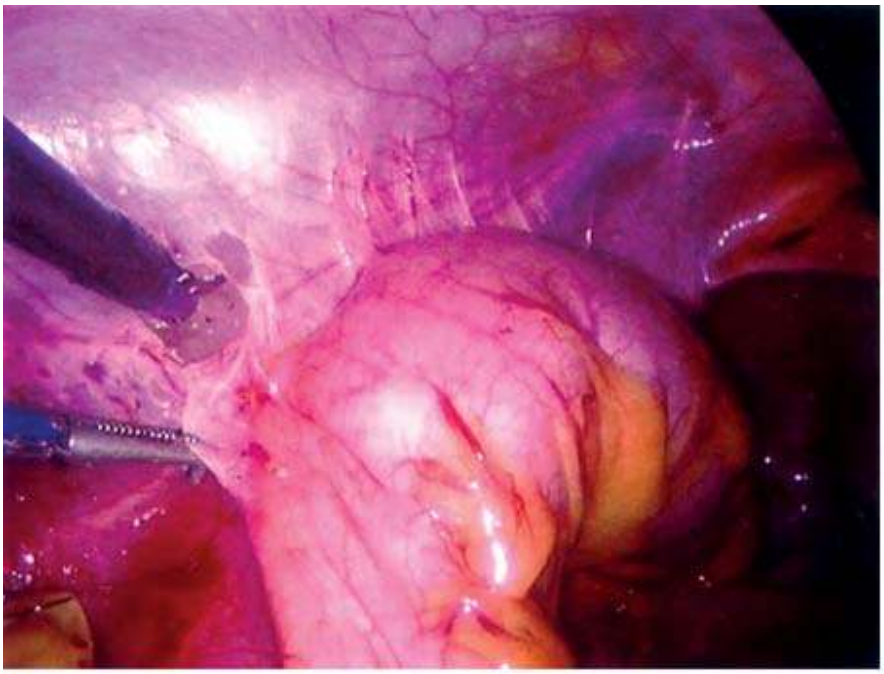

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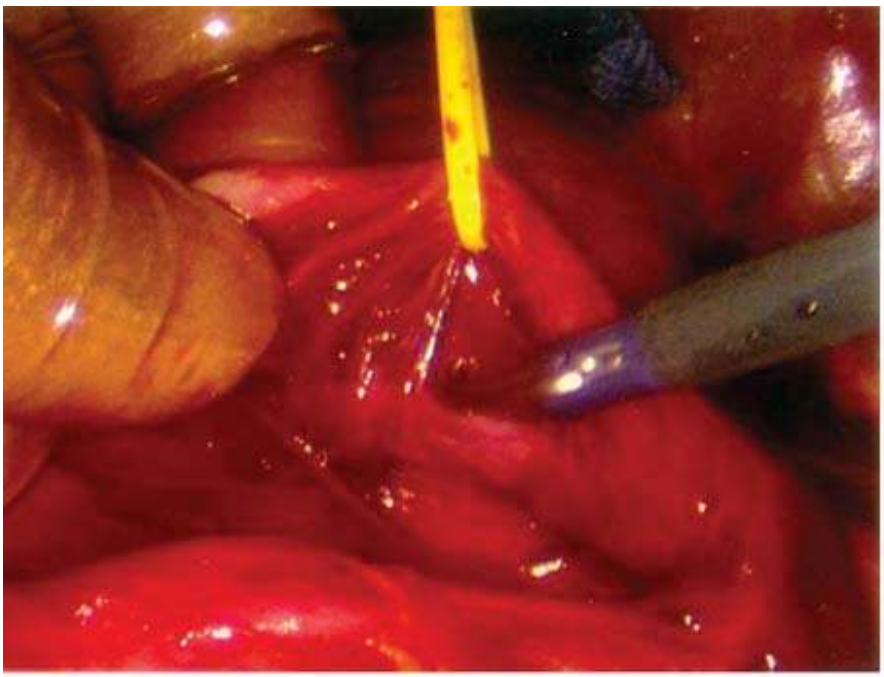

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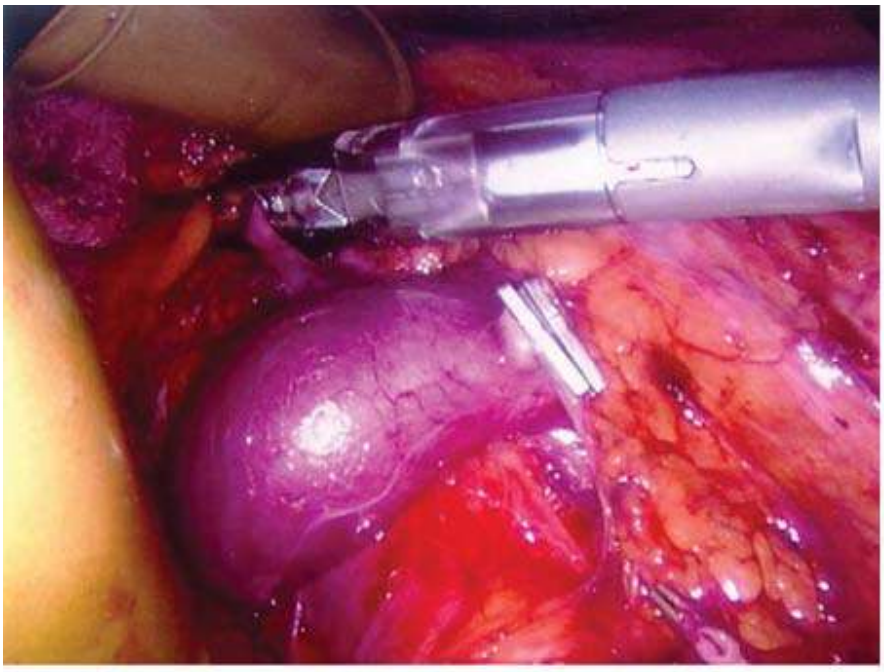

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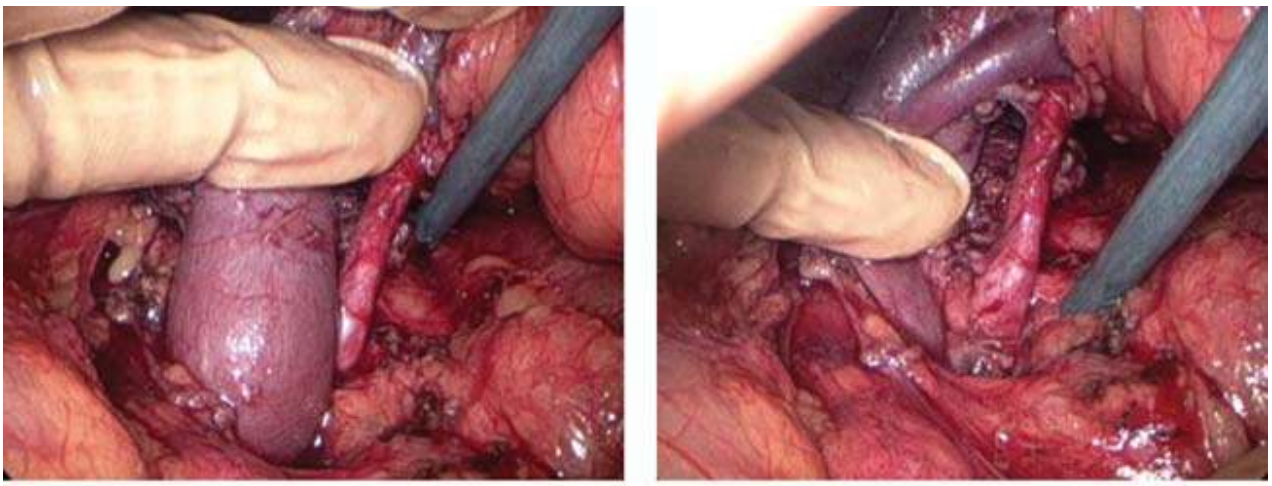

E

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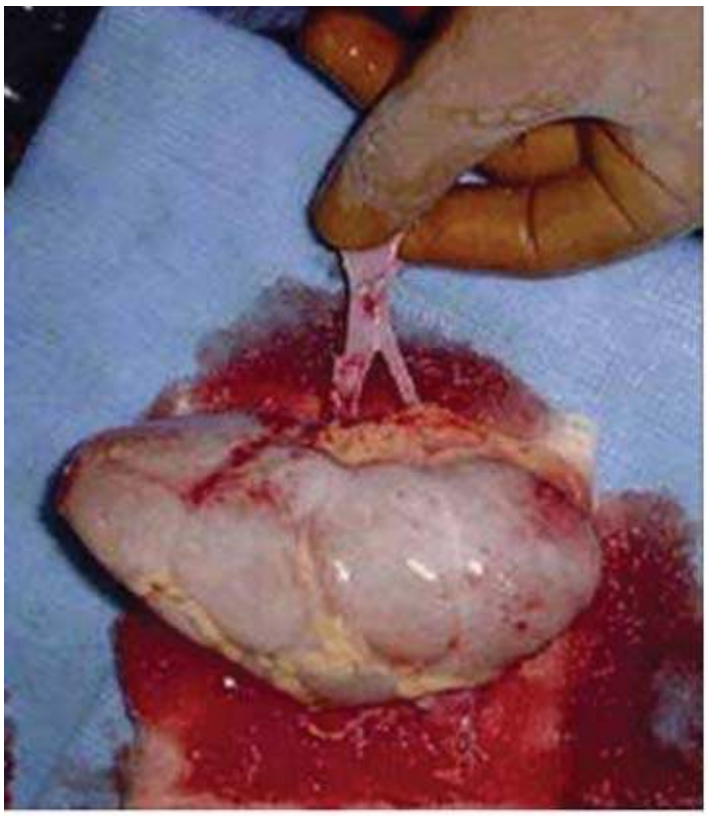

F

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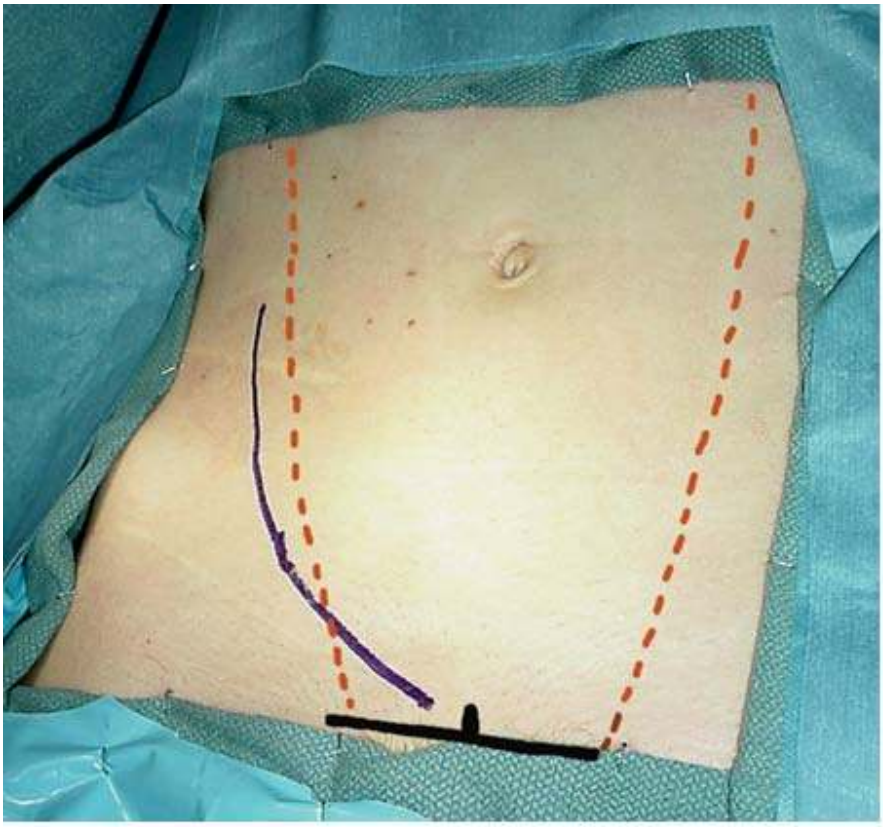
A through **F.** Hand-assisted laparoscopic donor nephrectomy for living-donor kidney transplant.

Recipient Surgical Procedure

The surgical technique for kidney transplantation has changed very little from the original pelvic operation described in the 1950s. The transplanted kidney is usually placed in a heterotopic position, with no need for native nephrectomy except in

select circumstances. Retroperitoneal placement is preferred, to allow for easy access for percutaneous renal biopsy. Usually, the right iliac fossa is chosen because of the more superficial location of the iliac vein on this side (Figs. 11-6 and 11-7). However, the left iliac fossa should be used if the recipient may be a candidate for a future pancreas transplant, if it is a second transplant, or if there is significant arterial disease on the right side.

Fig. 11-6.



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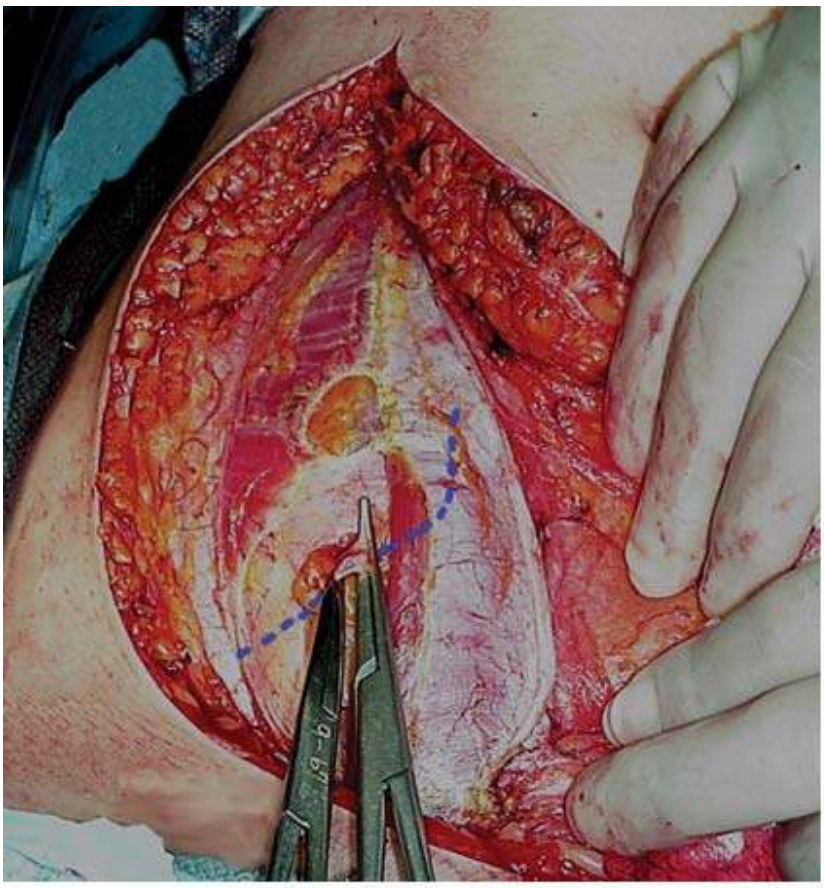
Placement of incision for heterotopic kidney transplant in the right iliac fossa. The incision starts just above the pubic bone in the midline, curves up laterally, and then passes superiorly along the edge of the rectus muscle.

Fig. 11-7.



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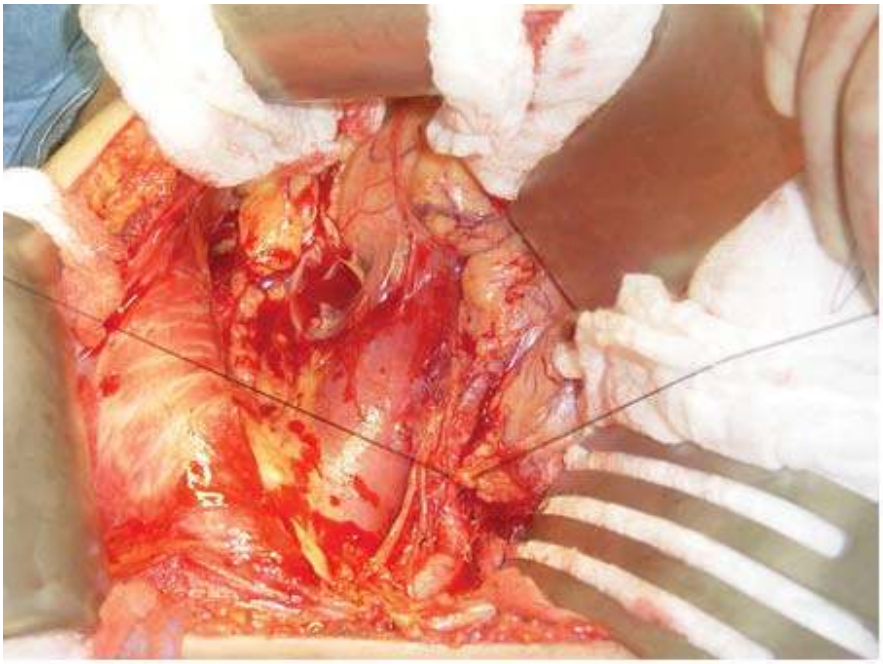
The incision is deepened along the lateral edge of the rectus muscle, identifying and dividing the epigastric vessels.

With the standard approach, the dissection is extraperitoneal. The iliac vessels are identified and assessed for suitability for anastomosis. The internal iliac artery can be used as the inflow vessel, with an end-to-end anastomosis, or the external iliac artery can be used with an end-to-side anastomosis. To minimize the risk of lymphocele formation after surgery, only a modest length of artery is dissected free and the lymphatics overlying the artery are ligated (Figs. 11-8 and 11-9). The donor renal vein is anastomosed end to side to the external iliac vein and the artery in a similar fashion to the iliac artery (Fig. 11-10).

Fig. 11-8.



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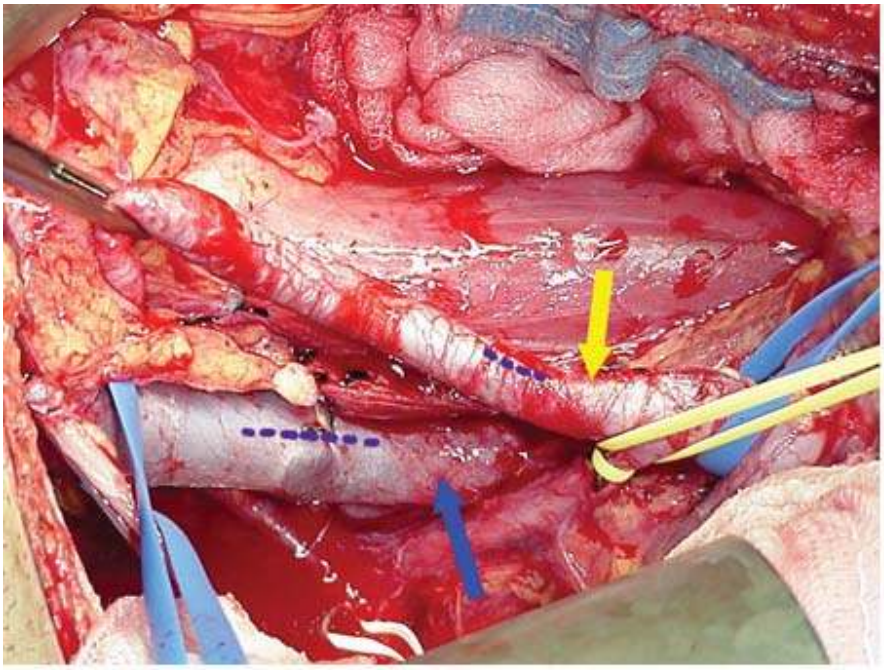
The peritoneum is reflected medially to expose the retroperitoneal space.

Fig. 11-9.



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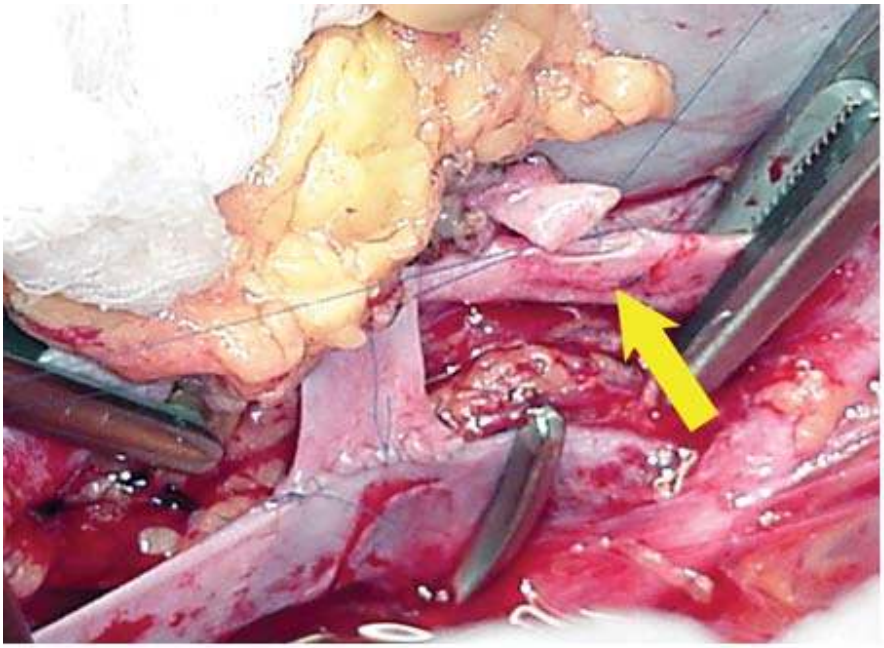
The external iliac vessels are isolated in preparation for anastomosis to the renal vessels. Yellow arrow = external iliac artery; blue arrow = external iliac vein; dotted lines = planned site of arteriotomy and venotomy.

Fig. 11-10.



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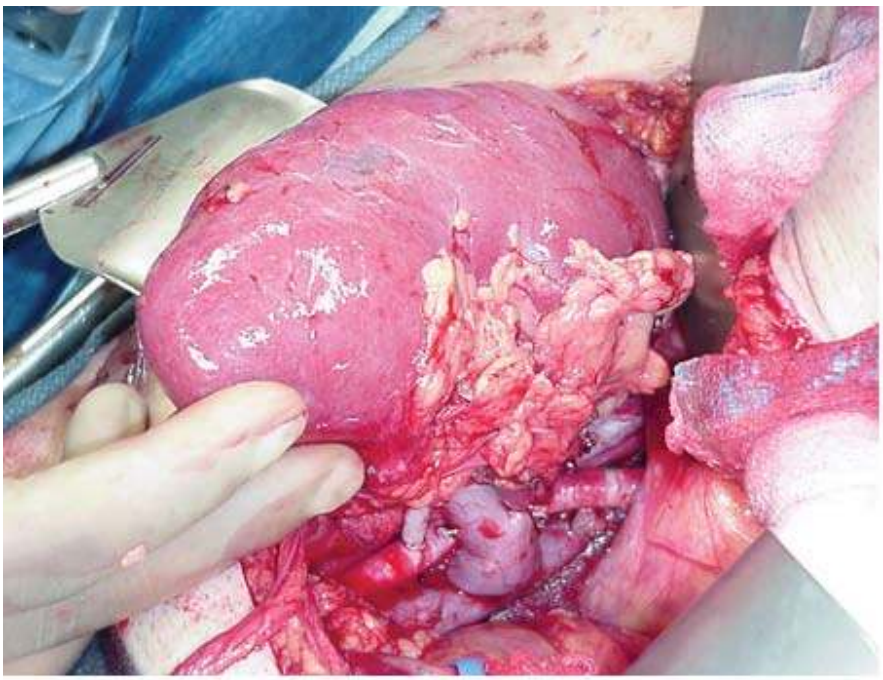
An end-to-side anastomosis of the renal artery to the external iliac artery is performed. Yellow arrow = external iliac artery.

After the vascular anastomosis is completed and the kidney perfused (Fig. 11-11), urinary continuity can be restored by a number of well-described techniques. The important principles are to attach the ureter to the bladder mucosa in a tension-free manner and to cover the distal 1 cm of the ureter with a submucosal tunnel, thus protecting against reflux during voiding (Figs. 11-11 and 11-12).

Fig. 11-11.



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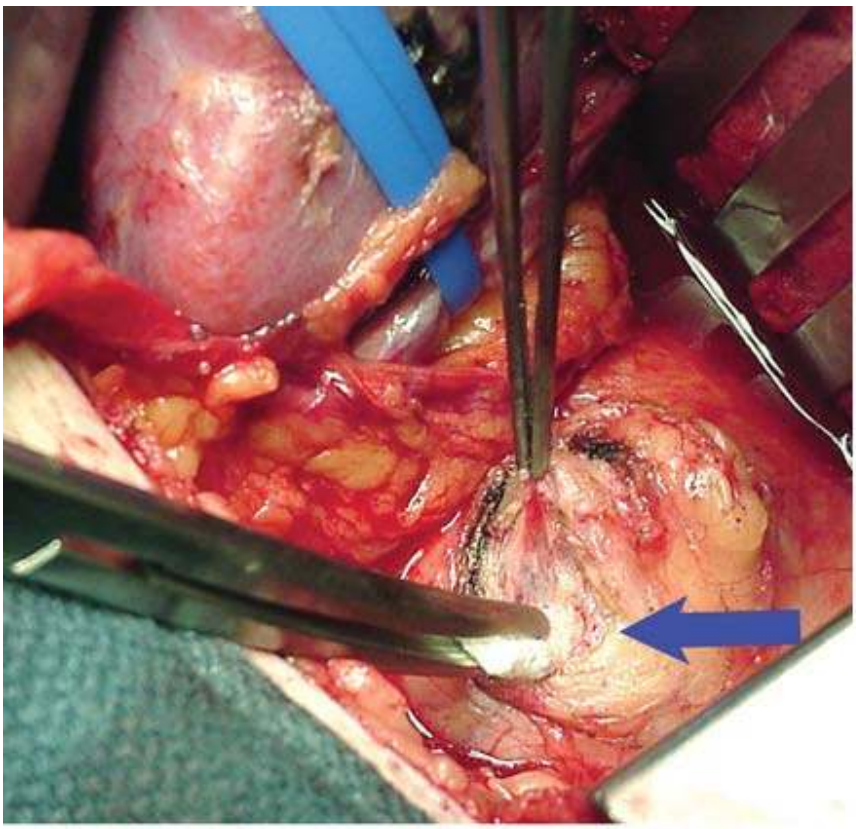
The clamps are removed, allowing the kidney to reperfuse.

Fig. 11-12.



A

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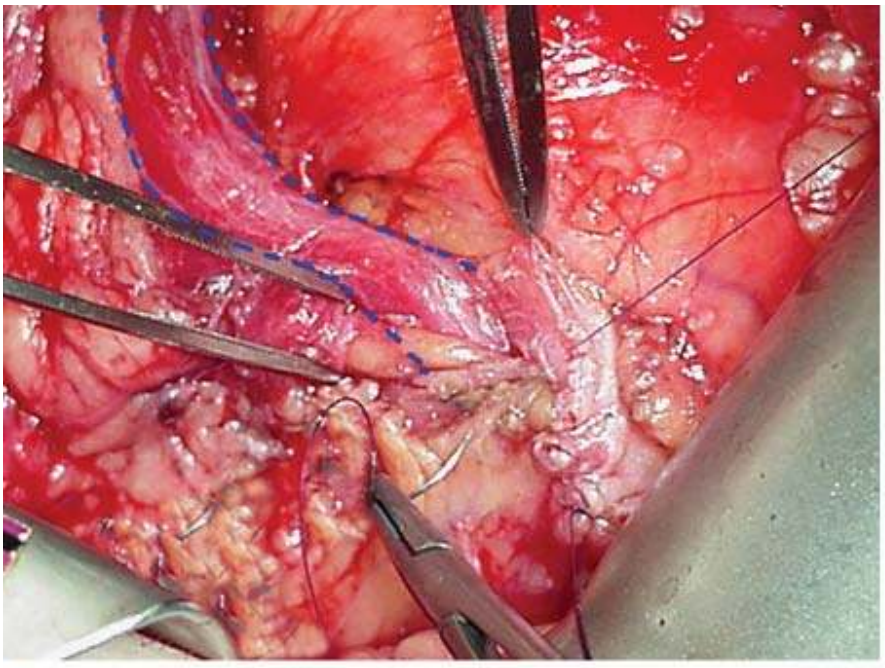

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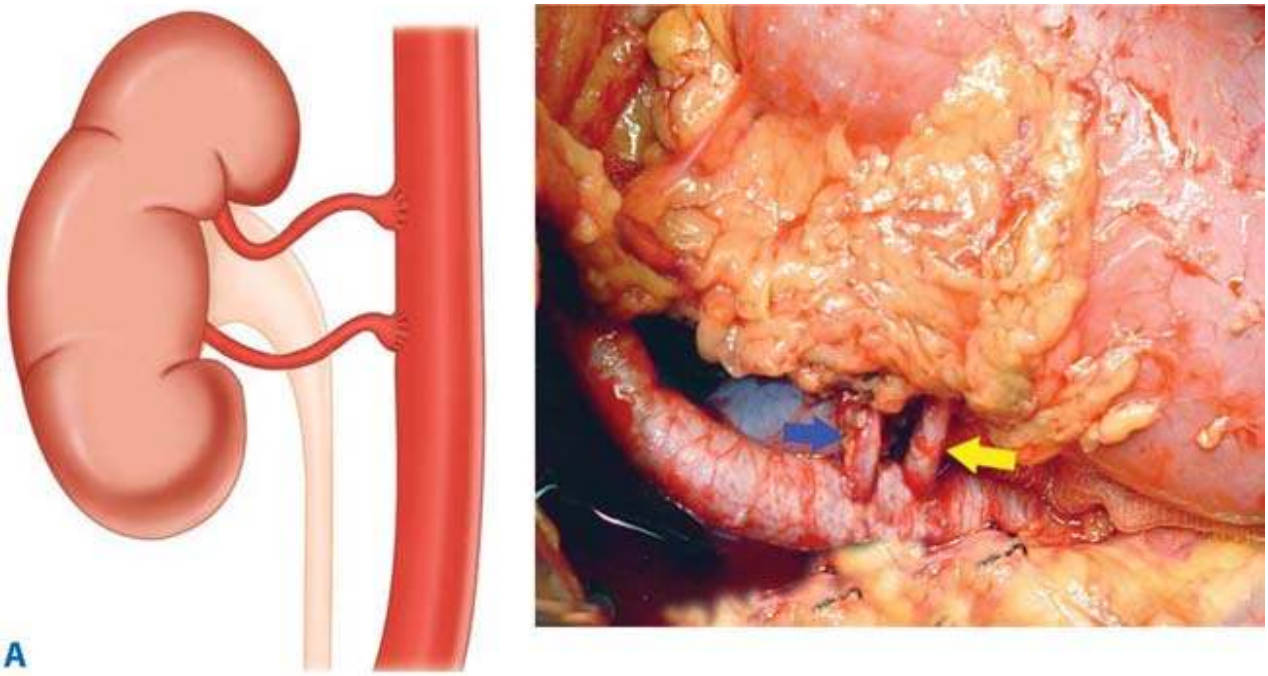
A. Preparation of the bladder for the ureter anastomosis by division of the detrusor muscle (*arrow*). **B.** Completion of the ureter (*dashed lines*) to bladder anastomosis with closure of the detrusor muscle over the distal ureter to create an

antireflux tunnel.

In approximately 10 to 15% of cases, there are multiple arteries to the kidney. Several options are possible for reconstruction in these cases, including implantation of the multiple vessels individually in the recipient (Fig. 11-13A) or back table reconstruction onto the main donor renal artery to allow for one arterial anastomosis in the recipient (Fig. 11-13B).

Fig. 11-13.



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B

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Options for multiple renal arteries, including (**A**) implantation of both arteries separately onto recipient iliac vessel (*blue and yellow arrows*) or (**B**) bench preparation of multiple vessels with end-to-side anastomosis to main donor renal artery.

Intraoperative care of kidney transplant recipients is not unlike that of other patients undergoing major surgical procedures. To decrease the incidence of ATN posttransplant, a liberal hydration policy is used intraoperatively. Adequate perfusion of the transplanted kidney is important to ensure postoperative diuresis. Central venous pressure (CVP) should be maintained around 10 mmHg, and systolic blood pressure should be greater than 120 mmHg. Maintaining adequate CVP is especially important in smaller, pediatric recipients because reperfusion of an adult-sized kidney graft may divert a significant amount of their own blood volume. Administering mannitol and furosemide just before reperfusion usually is helpful in maximizing perfusion to the kidney graft.

Early Postoperative Care

The immediate postoperative care of all recipients involves (a) stabilizing the major organ systems (e.g., cardiovascular, pulmonary, and renal); (b) evaluating graft function; (c) achieving adequate immunosuppression; and (d) monitoring and treating complications directly and indirectly related to the transplant. Initially, hemodynamic stability is assessed, as with all postsurgical patients. Blood pressure, heart rate, and urine output are measured. CVP monitoring may be useful in guiding fluid replacement therapy. Achieving hemodynamic stability is important for the recipient's overall status, but it also is necessary to optimize graft function; hemodynamically unstable recipients experience poor perfusion of their kidney graft.

Careful attention to fluid and electrolyte management is crucial. In general, recipients should be kept euvolemic or slightly hypervolemic. If initial graft function is good, fluid replacement can be regulated by hourly replacement of urine. Half-normal saline is a good solution to use for urine replacement. Aggressive replacement of electrolytes, including calcium, magnesium, and potassium, may be necessary, especially for recipients undergoing brisk diuresis. Those with ATN and fluid overload or hyperkalemia may need fluid restriction and even hemodialysis. Magnesium levels should be kept above 2 mEq/L to prevent seizures, and phosphate levels kept between 2 and 5 mEq/L for proper support of the respiratory and alimentary tracts. Marked hyperglycemia, which may be secondary to steroids, should be treated with insulin.

Hypotension is unusual early after a kidney transplant. When it occurs, it is usually related to hypovolemia. The treatment is to optimize preload and afterload and, only if necessary, to use inotropic agents such as dopamine. Systemic hypertension is more common early posttransplant. If hypertension is catecholamine-mediated or an effect of immunosuppressive agents, it usually responds well to treatment with calcium channel blockers. However, if it is secondary to fluid overload, and if the recipient has poor kidney function, dialysis may be necessary.

A critical aspect of postoperative care is the repeated evaluation of graft function, which in fact begins intraoperatively, soon after the kidney is reperfused. Signs of good kidney function include appropriate color and texture along with evidence of urine production. Postoperatively, urine output is the most readily available and easily measured indicator of graft function. Urine volume may range from none (anuria) to large quantities (polyuria). When using posttransplant urine volume to monitor graft function, the clinician should have knowledge of the recipient's pretransplant urine volume. If an individual was relatively anuric pretransplant, but then has normal urine output posttransplant, graft function is evident. However, if urine volume was significantly high pretransplant, normal urine output posttransplant does not necessarily mean good graft function; the urine may be from the native kidneys rather than from the graft. Laboratory values of obvious use in assessing graft function include serum blood urea nitrogen and creatinine levels.

Recipients can be divided into three groups (by initial graft function as indicated by their urine output and serum creatinine)

as those with (a) immediate graft function, characterized by a brisk diuresis posttransplant and rapidly falling serum creatinine level; (b) slow graft function, characterized by a moderate degree of kidney dysfunction posttransplant, with modest amounts of urine and a slowly falling creatinine level, but no need for dialysis at any time posttransplant; and (c) delayed graft function, which represents the far end of the spectrum of posttransplant graft dysfunction and is defined by the need for dialysis posttransplant.[44]

Decreased or minimal urine output is a frequent concern posttransplant. Most commonly, it is due to an alteration in volume status. Other causes include a blocked urinary catheter, vascular thrombosis, a urinary leak or obstruction, early acute rejection, drug toxicity, or delayed graft function (Table 11-4). Early diagnosis is important, and begins with an assessment of the recipient's volume status. The urinary catheter is checked to exclude the presence of occlusion with clots or debris. Other diagnostic tests that may be warranted, depending on the suspected cause, include a Doppler ultrasound, nuclear medicine scan, or a biopsy.

Table 11-4 Causes of Increased Serum Creatinine Early after Kidney Transplant

Cause	Characteristics	Diagnosis	Treatment
Hypovolemia	• Decreased CVP	• Check Hgb and CVP	• Rehydrate with appropriate fluids
	• Decreasing urine output		
	• Low blood pressure		
	• Low Hgb if due to bleeding		
Vascular thrombosis	• Sudden drop in urine output	• Ultrasound with Doppler	• Re-explore for thrombectomy or nephrectomy
	• Dark hematuria		
	• Tender, swollen graft		
Bladder outlet obstruction	• Clots in urinary catheter	• Distended bladder on examination or by ultrasound	• Irrigate or change bladder catheter
	• Sudden drop in urine output		
Ureter obstruction	—	• Euvolemic	• Do percutaneous nephrostogram
		• Ultrasound showing hydroureter	• Drainage of lymphocele (if it is the cause of ureter obstruction)
		• Possible lymphocele on ultrasound	
Drug toxicity	• High CSA or FK506 level	• Check drug levels	• Decrease dosage of drugs
Acute rejection	• May have risk factors such as low drug levels, high PRA	• Kidney biopsy	• Administer bolus steroid or antilymphocyte treatment
			• Begin plasmapheresis (and IVIG if humoral rejection)

CSA = cyclosporin A; CVP = central venous pressure; Hgb = hemoglobin; IVIG = intravenous immunoglobulin; PRA = panel reactive antibody.

Complications

Monitoring for potential surgical and medical complications is important. Early diagnosis and appropriate intervention can minimize the detrimental impact on the graft and recipient. Potential complications that may occur early after surgery include

hemorrhage, vascular complications, urologic complications, lymphocele, and several others.

HEMORRHAGE

Bleeding is uncommon after a kidney transplant; usually it occurs from unligated vessels in the graft hilum or from the retroperitoneum of the recipient. A falling hematocrit level, hypotension, or tachycardia should raise the possibility of bleeding. Surgical exploration seldom is required because bleeding often tamponades. However, ongoing transfusion requirements, hemodynamic instability, and compression of the kidney by hematoma are all indications for surgical re-exploration.

VASCULAR COMPLICATIONS

Vascular complications can involve the donor vessels (renal artery thrombosis or stenosis, renal vein thrombosis), the recipient vessels [iliac artery thrombosis, pseudoaneurysms, and deep venous thrombosis (DVT)], or both. Renal artery thrombosis usually occurs early posttransplant; it is uncommon, with an incidence of less than 1%. However, it is a devastating complication, usually resulting in graft loss. Typically, it occurs secondary to a technical problem such as intimal dissection or torsion of the vessels. Risk factors for thrombosis include hypotension, multiple renal arteries, unidentified injury to the intima of the artery, hyperacute rejection, unrelenting acute rejection, and a hypercoagulable state. Under these circumstances there is a sudden cessation of urine output. Diagnosis is made easily with color flow Doppler studies. Urgent thrombectomy is indicated, but most such grafts cannot be salvaged and require removal. Stenosis of the renal artery is a late complication and presents with evidence of graft dysfunction or hypertension. First-line treatment is with interventional radiologic techniques; surgery is reserved for stenosis that does not respond to this therapy.

Renal vein thrombosis is not as common as its arterial counterpart, but again, graft loss is the usual end result. Causes include angulation or torsion of the vein, compression by hematomas or lymphoceles, anastomotic stenosis, and extension of an underlying DVT. Again, Doppler studies are the best diagnostic test. Urgent thrombectomy rarely is successful, and nephrectomy is usually required. Venous thromboembolic complications that affect the recipient vessels [DVT and pulmonary embolism (PE)] are not uncommon. The incidence of DVT is close to 5%; the incidence of PE 1%. Identified risk factors include recipient age over 40, hypercoagulable states, diabetes, and a history of DVT. For recipients with these risk factors, prophylaxis with low-dose heparin is recommended.

UROLOGIC COMPLICATIONS

Urinary tract complications, manifesting as leakage or obstruction, generally occur in 2 to 10% of kidney recipients. The underlying cause often is related to poor blood supply and ischemia of the transplant ureter. Leakage most commonly occurs from the anastomotic site. Causes other than ischemia include undue tension created by a short ureter, and direct surgical injury. Presentation is usually early (before the fifth posttransplant week); symptoms include fever, pain, swelling at the graft site, increased creatinine level, decreased urine output, and cutaneous urinary drainage. Diagnosis can be confirmed initially with a hippurate renal scan, although a percutaneous nephrostogram is required for precise definition. Early surgical exploration with ureteral reimplantation usually is indicated, although small leaks may be managed by percutaneous nephrostomy and stent placement with good results.

Ureteral obstruction may develop early or late. Early obstruction may be due to edema, blood clots, hematomas, or torsion of the ureter. Late obstruction generally is due to scarring and fibrosis from chronic ischemia. Patients develop an elevated serum creatinine level. An ultrasound to look for hydronephrosis is a good initial test. Percutaneous transluminal dilatation, followed by placement of an internal or external stent, is a good initial treatment. If repeated dilatations and stenting are

required, surgical intervention (e.g., ureteral reimplantation or ureteropyelostomy using the native ureter) should be undertaken.

LYMPHOCELE

The reported incidence of lymphoceles (fluid collections of lymph that generally result from cut lymphatic vessels in the recipient) is 0.6 to 18%. Lymphoceles usually do not occur until at least 2 weeks posttransplant. Symptoms are generally related to the mass effect and compression of nearby structures (e.g., ureter, iliac vein, allograft renal artery), and patients develop hypertension, unilateral leg swelling on the side of the transplant, and elevated serum creatinine. Ultrasound is used to confirm a fluid collection, although percutaneous aspiration may be necessary to exclude presence of other collections such as urinomas, hematomas, or abscesses. The standard surgical treatment is creation of a peritoneal window to allow for drainage of the lymphatic fluid into the peritoneal cavity, where it can be absorbed. Either a laparoscopic or an open approach may be used. Another option is percutaneous insertion of a drainage catheter, with or without sclerotherapy; however, it is associated with some risk of recurrence or infection.

OTHER COMPLICATIONS

A wide variety of medical complications can be seen after a kidney transplant. Infections are probably the most common, but the incidence has declined significantly in recent years due to improvements in prophylaxis regimens. Common sites for infection include the urinary tract, the pulmonary system, and the wound. Noninfectious medical complications affecting the cardiac, GI, and neurologic systems also have been well described posttransplant.[45] Such complications are often related to the administration of immunosuppressive drugs.

Late Posttransplant Care

The goal of late posttransplant care of the kidney transplant recipient is to optimize immunosuppression, carefully monitor graft function, and screen and monitor for complications that are directly or indirectly related to immunosuppressive medications. Optimizing immunosuppression entails fitting it to the individual recipient's needs. Recipients at low risk for rejection should have their immunosuppression lowered to minimize side effects and complications. Careful attention should be paid to compliance; it often is easy for recipients to become less attentive to their medications as they progress through the posttransplant period. Monitoring kidney function may help detect noncompliance, but also is important to detect late rejection episodes, recurrence of disease, or late technical problems (such as renal artery stenosis or ureteric stricture). Other potential problems in these recipients include hypercholesterolemia, hypertriglyceridemia, and increased blood pressure, which may or may not be related to the immunosuppressive drugs. Screening for malignancy (especially skin, colorectal, breast, cervical, and prostate) is important, although the incidence of many of these malignancies is equivalent to those seen in the general population. Patients should be immunized, ideally pretransplant, for *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, as this is important to minimize infectious complications due to these pathogens.

Results

Posttransplant outcomes have steadily improved over the past 3 decades due to improvements in immunosuppression, organ retrieval techniques, perioperative care, and treatment of infectious posttransplant complications.[46–48] Since the late 1980s, the use of modern immunosuppressive drugs has been a primary factor, especially in those previously considered to be at high risk, such as diabetic, pediatric, and older recipients.

Most centers now report patient survival rates exceeding 95% during the first posttransplant year for all kidney recipients (Table 11-5). Living-donor transplants still have an advantage over deceased-donor transplants, but even this difference is diminishing with modern immunosuppression. The survival advantage after a transplant, as compared with dialysis, is probably greatest for diabetic patients. Without a transplant, their overall survival is 26% at 5 years; with a transplant, it jumps to about 80%. The major cause of death in all kidney recipients is cardiovascular (myocardial infarction or stroke); sepsis accounts for less than 3%, while malignancy accounts for 2%.

Table 11-5 Patient Survival Rates (%) after the Various Transplants

Time Posttransplant	3 Mo	1 Y	3 Y	5 Y	10 Y
Kidney					
Deceased donor	97.9	94.7	88.1	80.7	60.7
Living donor	99.2	98.0	94.5	90.4	76.4
SPK	97.7	95.1	90.8	85.8	69.2
PAK	98.3	95.5	89.9	83.6	60.7
PTA	97.9	94.9	91.6	90.2	66.9
Liver					
Deceased donor	93.2	86.9	79.0	73.4	59.4
Living donor	95.8	91.2	82.9	76.8	76.2
Intestine	93.2	87.5	62.2	50.2	40.6
Heart	92.5	88.1	80.2	73.7	53.4
Lung	93.2	84.9	66.4	51.6	25.6
Heart-lung	77.8	66.7	53.8	43.6	27.3

PAK = pancreas after kidney; PTA = pancreas transplant alone; SPK = simultaneous pancreas-kidney.

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The incidence of acute rejection has declined steadily since the early 1990s. Most centers now report acute rejection rates of 10 to 20% at 1 year posttransplant. This decline has been a major factor in the improvement in graft survival rates, which are now about 75 to 80% at 5 years and 60 to 65% at 10 years posttransplant for all kidney recipients[49] (Table 11-6). Currently, the most common cause of graft loss is recipient death (usually from cardiovascular causes) with a functioning graft. The second most common cause is chronic allograft nephropathy. Characterized by a slow, unrelenting deterioration of graft function, it likely has multiple causes (both immunologic and nonimmunologic).[50,51] The graft failure rate due to surgical technique has remained at about 2%.

Table 11-6 Graft Survival Rates (%) after the Various Transplants

Time Posttransplant	3 Mo	1 Y	3 Y	5 Y	10 Y
Kidney					
Deceased donor	94.3	89.5	78.6	67.1	40.8
Living donor	97.2	95.1	88.4	80.3	56.5
SPK (pancreas)	89.2	85.2	79.3	71.1	54.5
PAK	86.7	78.7	67.3	56.4	27.6

PTA	87.5	72.8	58.4	53.4	25.9
Liver					
Deceased donor	89.6	82.4	73.6	67.4	53.0
Living donor	90.0	84.0	76.0	68.8	66.5
Intestine	88.3	78.5	50.6	40.1	27.9
Heart	92.0	87.5	79.4	72.6	51.5
Lung	92.5	83.3	64.4	48.9	23.4
Heart-lung	75.2	64.1	53.1	41.5	26.5

PAK = pancreas after kidney; PTA = pancreas transplant alone; SPK = simultaneous pancreas-kidney.

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PANCREAS TRANSPLANTATION

Diabetes mellitus is a very common medical condition with immense medical, social, and financial costs. In North America, it is the leading cause of kidney failure, blindness, nontraumatic amputations, and impotence. The discovery of insulin in 1922 by Banting and Best changed diabetes from a lethal disease to a chronic illness. However, even though exogenous insulin can prevent the acute metabolic complications and decrease the incidence of secondary complications associated with diabetes, it cannot provide a homeostatic environment comparable to that afforded by a functioning pancreas. Only a functioning pancreas can provide immediate insulin responses to the moment-to-moment changes in glucose levels.

A successful pancreas transplant can establish normoglycemia and insulin independence in diabetic recipients, with glucose control similar to that seen with a functioning native pancreas. A pancreas transplant also has the potential to halt progression of some secondary complications of diabetes. No current method of exogenous insulin administration can produce a euglycemic, insulin-independent state akin to that achievable with a technically successful pancreas graft. In addition to improved metabolic control and beneficial effects on secondary complications, a pancreas transplant can substantially enhance quality of life, more than that achieved by exogenous insulin administration. Indeed, the modern management of diabetes by exogenous insulin may be as burdensome as dialysis is for kidney failure, as it consists of four blood glucose determinations daily, coupled with four insulin injections or a constantly present needle. A successful pancreas transplant obviates the need for such constant invasive monitoring.

Currently, the main drawback of a pancreas transplant is the need for immunosuppression. Pancreas transplants are now preferentially performed in diabetic patients with kidney failure who also are candidates for a kidney transplant, as they already require immunosuppression to prevent kidney rejection. However, a pancreas transplant alone (PTA) is appropriate for nonuremic diabetics if their day-to-day quality of life is so poor (e.g., labile serum glucose with ketoacidosis and/or hypoglycemic episodes, or progression of severe diabetic retinopathy, nephropathy, neuropathy, and/or enteropathy) that chronic immunosuppression is justified to achieve insulin independence.[52] As immunosuppressive agents become safer, it is likely that PTA will become increasingly common.

History

The first human pancreas transplant was performed in 1966; however, the procedure was not performed with any frequency until many years later. During the 1970s, a small number of institutions performed a few pancreas transplants, and their success rates were low, mainly because of problems with rejection. A dramatic improvement in outcome occurred in the

1980s, after advances in surgical techniques and the introduction of cyclosporine for immunosuppression. In the United States, the inception of UNOS in 1987 facilitated nationwide organ procurement and allocation. A steady growth in the application of pancreas transplants soon followed. By the mid-1990s, more than 1000 pancreas transplants were being performed annually in the United States, with improved results paralleling the introduction of even newer immunosuppressive drugs such as tacrolimus and MMF.

Results also improved because of refinements in surgical technique. By the mid-1970s, the following three techniques were in use: enteric drainage (ED), urinary drainage (first into the ureter, and later modified by direct implantation into the bladder), and duct injection. During the 1980s, bladder drainage (BD) was shown to be safe, and it became the predominant technique in all pancreas recipient categories, as it facilitated allograft monitoring via measurement of urine amylase levels. The 1990s saw a shift back to ED, especially in patients who underwent a simultaneous kidney transplant. In such recipients, the serum creatinine level could be used as a surrogate marker for pancreas rejection when both organs came from the same donor.

Preoperative Evaluation

The preoperative evaluation for pancreas transplant recipients does not differ substantially from that for diabetic kidney transplant recipients. Examination of the cardiovascular system is most important because significant coronary artery disease may be present without angina.[53] Noninvasive testing may not identify coronary artery disease, so coronary angiography is routinely performed. Detailed neurologic, ophthalmologic, metabolic, and kidney function testing may be needed to assess the degree of progression of secondary complications. Any contraindications to a transplant, such as active malignancy or infection, must be ruled out. A thorough evaluation of the peripheral vascular system is essential, given the high incidence of peripheral vascular disease in diabetics. The patency of the iliac system needs to be determined, because the iliac vessels will serve as the inflow source for the pancreas.

Once a patient is determined to be a good candidate for a pancreas transplant, with no obvious contraindications, it is important to decide which type of pancreas transplant is best for that individual. First, the degree of kidney dysfunction and the need for a kidney transplant must be determined. Patients with stable kidney function (creatinine less than 2 mg/dL and minimal protein in the urine) are candidates for a PTA. However, patients with moderate kidney insufficiency will likely require a kidney transplant as well; further deterioration of kidney function often occurs once calcineurin inhibitors are started for immunosuppression.

For patients requiring both a kidney and a pancreas transplant, various options are available. The two transplants can be performed either simultaneously or sequentially. A living donor or a deceased donor can be used, or both. Which option is best for the individual patient depends on the degree of kidney dysfunction, the availability of donors, and personal preference. The following options are currently possible:

- Deceased-donor, simultaneous pancreas-kidney transplant (SPK): The most common option worldwide, deceased-donor SPK transplants have well-documented, long-term survival results for both the kidney and the pancreas grafts. The recipient has the advantage of undergoing both transplants at the same time, and therefore may potentially become dialysis free and insulin independent at the same time. There is also an immunologic advantage, as acute rejection rates are significantly lower for SPK (vs. PTA) recipients.
- Living-donor kidney transplant, followed weeks to months later by a deceased-donor pancreas transplant [pancreas after kidney (PAK) transplant]: If a living donor is available for the kidney transplant, then this is a good option for uremic diabetic patients. It offers the possibility of performing the kidney transplant as soon as the living-donor evaluation is complete, rendering the recipient dialysis free within a short period. A living-donor (vs. deceased-donor) kidney transplant has superior long-term results. By performing the two operations sequentially instead of

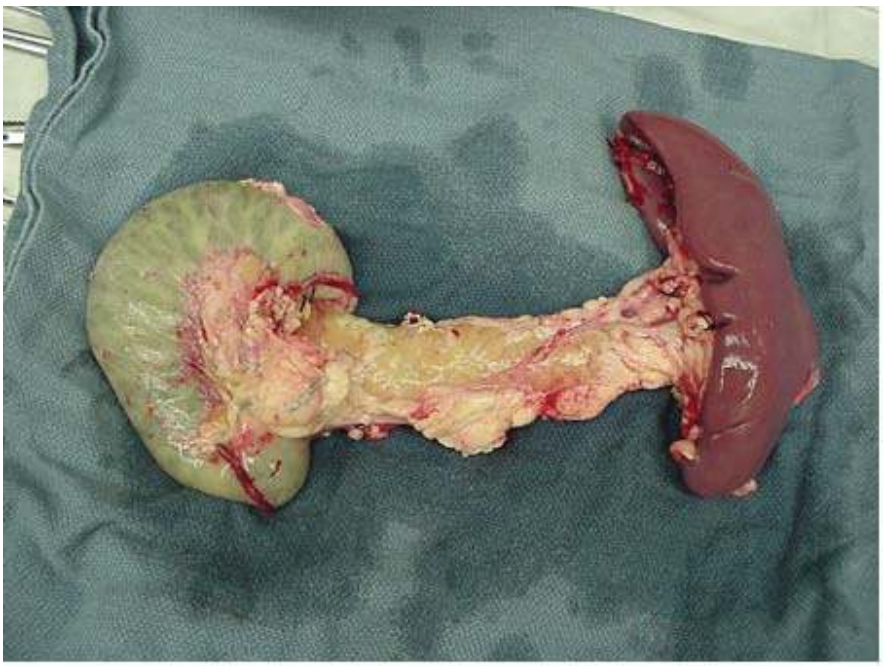
simultaneously, the overall surgical complication rate may be decreased, perhaps because by the time of the pancreas transplant, the effects of uremia have resolved and patients are in better metabolic and nutritional condition.[54] The disadvantage is that the long-term pancreas graft survival rates for PAK recipients are still somewhat inferior to those of individuals receiving SPK transplants.

- Simultaneous deceased-donor pancreas and living-donor kidney transplant: Candidates with a suitable living donor for the kidney transplant who have not yet progressed to dialysis can be placed on the deceased-donor pancreas transplant waiting list. When a deceased-donor pancreas becomes available, the living donor for the kidney is called in at the same time, and both procedures are performed simultaneously. Advantages include use of a living donor for the kidney, shorter waiting times, and a single operation.[55] Technically, this option may be more difficult to organize, as it requires using two full surgical teams and two full operating rooms, and at times the donor and the recipient will need to be called in from different locations. It also may create difficult timing issues for the living donor, who must come in quickly for an emergent operation.
- Living-donor, SPK transplant: If a single individual is suitable to donate both a kidney and a hemipancreas, then this may be a potential option. It is especially useful for candidates with a high level of preformed antibodies, or those who have difficulty acquiring a deceased-donor organ. The main disadvantage of this approach is to the living donor, who has to undergo a surgical procedure of substantial magnitude with its attendant risks and morbidity.

Surgical Procedure

The initial preparation of the donor pancreas is a crucial component of a successful transplant. Direct physical examination of the pancreas often is the best or only way to confirm its suitability (Fig. 11-14). If it is sclerotic, calcific, or markedly discolored, it should not be used. Before implantation, a surgical procedure is undertaken to remove the spleen and any excess duodenum, and to ligate blood vessels at the root of the mesentery (Fig. 11-15A-C). The inflow vessels to the graft are the splenic and superior mesenteric arteries; outflow is via the portal vein. Arterial reconstruction is performed before implanting the graft in the recipient. The donor superior mesenteric and splenic arteries are connected, most commonly using a reversed segment of donor iliac artery as a Y-graft (Figs. 11-15D and 11-16); doing so allows for a single arterial anastomosis in the recipient.

Fig. 11-14.



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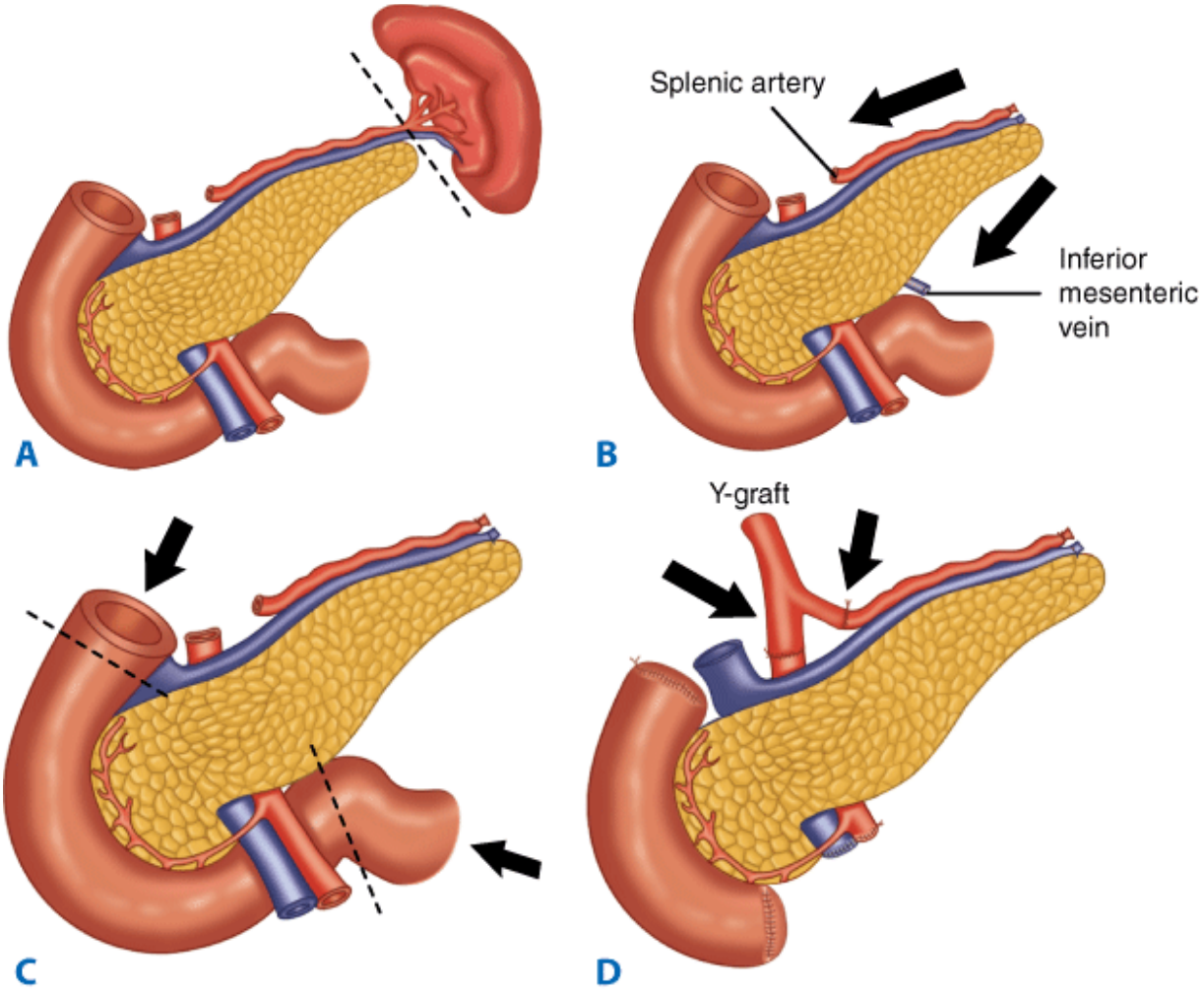
Pancreas graft before bench preparation with spleen attached.

Fig. 11-15.



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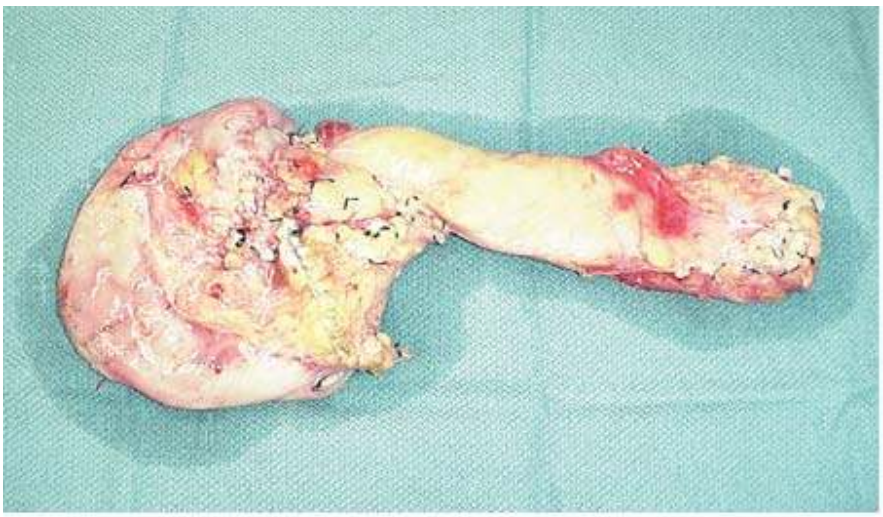
Bench preparation of pancreas graft. Steps include (**A**) removal of the spleen; (**B**) removal of tissue along the superior and inferior aspect of the tail of the pancreas; (**C**) trimming of excess duodenum; and (**D**) ligation of vessels at the root of the mesentery and placement of arterial Y-graft.

Fig. 11-16.



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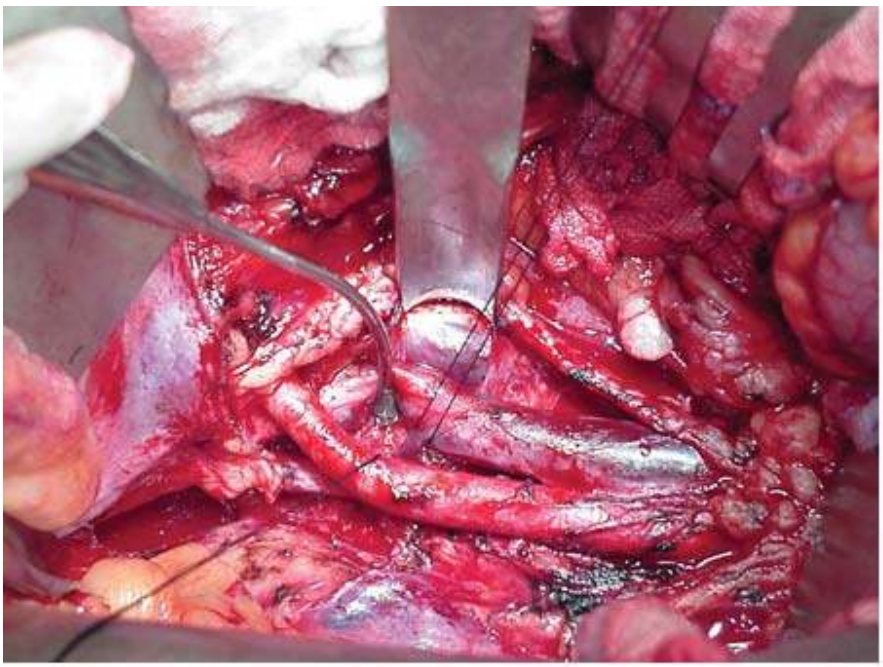
Final appearance of benched pancreas before implantation in the recipient.

The pancreas graft is then implanted via an anastomosis of the aforementioned arterial graft to the recipient common iliac artery or distal aorta, and, via a venous anastomosis of the donor portal vein to the recipient iliac vein (for systemic drainage, Fig. 11-17), or to the superior mesenteric vein (for portal drainage).[56] If both a kidney and a pancreas are transplanted, they are placed in an intraperitoneal position, with the kidney usually in the left iliac fossa and the pancreas in the right iliac fossa (Fig. 11-18). If the pancreas is drained via the portal route, then it usually sits higher in the mid-abdomen (Fig. 11-19).

Fig. 11-17.



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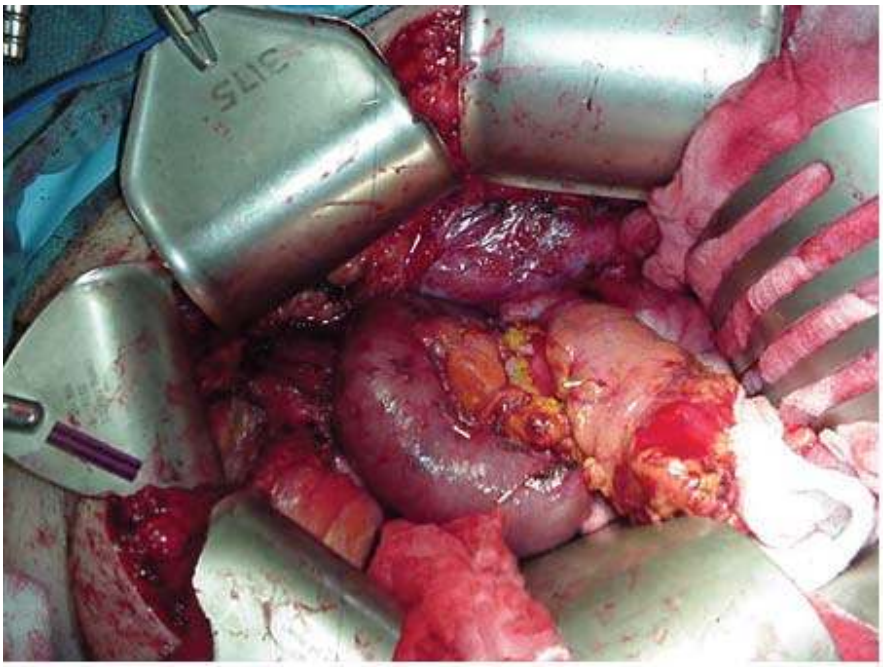
Preparation of iliac vessels for implantation of the pancreas with ligation and division of all hypogastric veins.

Fig. 11-18.



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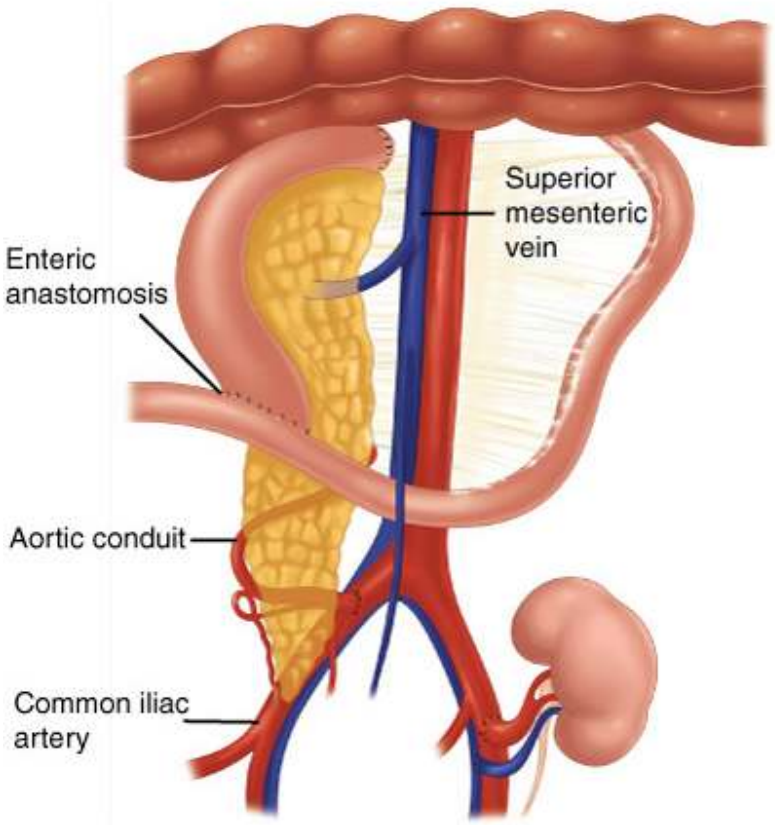
Reperfused pancreas allograft after completion of the vascular anastomosis.

Fig. 11-19.



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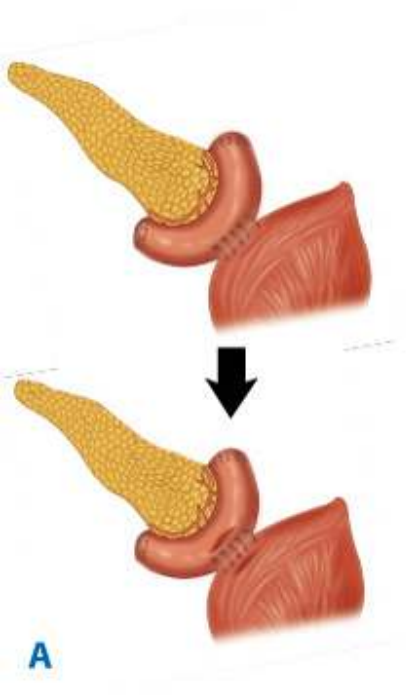
Combined kidney and pancreas transplant with portal enteric drainage of pancreas graft. The pancreas transplant is situated higher in the abdomen and is oriented pointing toward the head of the recipient.

Once the pancreas is revascularized, a drainage procedure must be performed to handle the pancreatic exocrine secretions. Options include anastomosing the donor duodenum to the recipient bladder (Fig. 11-20) or to the small bowel, with the small bowel either in continuity or connected to a Roux-en-Y limb. Some centers always use ED, others always use BD, and others tailor the approach according to the recipient category. Both ED and BD now have a relatively low surgical risk. The main advantage of BD is the ability to directly measure enzyme activity in the pancreatic graft exocrine secretions by measuring the amount of amylase in the urine. A decrease in urine amylase is a sensitive marker for rejection, even though it is not entirely specific. Urine amylase always decreases before hyperglycemia ensues. A rise in serum amylase may precede a decrease in urine amylase, but serum amylase by itself is less sensitive (it does not always rise, but urine amylase always decreases), and is no more specific for the diagnosis of rejection. The leak rate is the same whether the pancreas is drained to the bladder or to the bowel, but the consequences of a bladder leak are much less severe than those associated with a bowel leak. The disadvantages of BD include complications such as dehydration and acidosis (from loss of alkalotic pancreatic secretions in the urine), and local problems with the bladder such as infection, hematuria, stones, and urethritis. Because of these chronic complications, between 10 and 20% of bladder-drained graft recipients are ultimately converted to ED.

Fig. 11-20.



A

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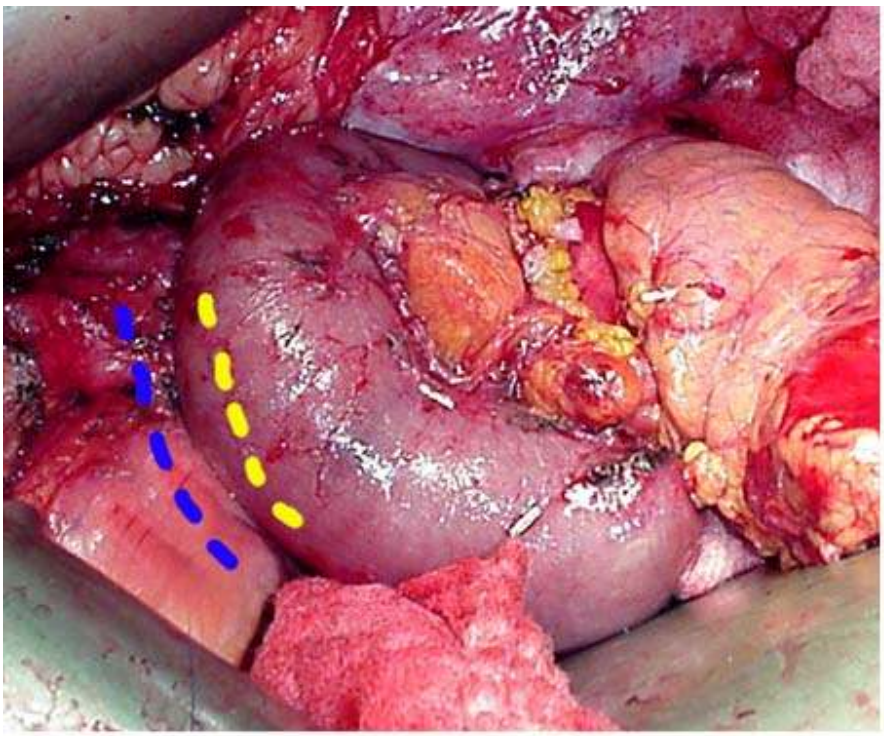

B

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A and **B.** Drainage of the exocrine secretions by anastomosis of the recipient bladder to the donor duodenum in a two-layer fashion.

ED is more physiologic and has fewer long-term complications. However, the ability to monitor for rejection is decreased,

given the absence of urinary amylase. Rejection in SPK transplant recipients almost always affects both the kidney and the pancreas; therefore, the serum creatinine level can be used as a marker for rejection of the pancreas. Hence, most centers now use ED for SPK transplants. If the kidney and the pancreas are from different donors, or if a PTA is performed, then BD is preferred, so rejection of the pancreas can be detected earlier.

Postoperative Care

In general, pancreas recipients do not require intensive care monitoring in the postoperative period. Laboratory values—serum glucose, hemoglobin, electrolytes, and amylase—are monitored daily. The serum glucose level is monitored even more frequently if normoglycemia is not immediately achieved. Nasogastric suction and IV fluids are continued for the first several days until bowel function returns. In the early postoperative period, regular insulin is infused to maintain plasma glucose levels less than 150 mg/dL, because chronic hyperglycemia may be detrimental to β-cells. In recipients who undergo BD, a Foley catheter is left in place for 10 to 14 days. At most centers, some form of prophylaxis is instituted against bacterial, fungal, and viral infections. In addition, many centers routinely institute some form of prophylaxis against thrombosis of the allograft; options include low-dose heparin, low molecular weight heparin, or oral antiplatelet agents for the first week posttransplant.

Complications

One crucial aspect of posttransplant care is monitoring for rejection and complications (both surgical and medical). Rejection episodes may be identified by an increase in serum creatinine (in SPK recipients), a decrease in urinary amylase (in recipients with BD), an increase in serum amylase, or by an increase in serum glucose levels. Complications are, unfortunately, common after pancreas transplants. The pancreas graft is susceptible to a unique set of complications because of its exocrine secretions and low blood flow. However, the incidence of graft-related complications has decreased significantly since the early 1990s due to better preservation techniques, better surgical methods, improved prophylaxis regimens, and improved immunosuppression.[57] Potential complications are described below.

THROMBOSIS

The incidence of thrombosis is approximately 6% for pancreas transplants reported to the UNOS registry. Low-dose heparin, dextran, or antiplatelet agents are administered routinely in the early postoperative period at many centers, although these agents slightly increase the risk of postoperative bleeding. Arterial or venous thrombosis is most common within the first several days posttransplant, heralded by an increase in blood glucose levels, an increase in insulin requirements, or a decrease in urine amylase levels. Venous thrombosis also is characteristically accompanied by hematuria, tenderness and swelling of the graft, and ipsilateral lower extremity edema. Treatment consists of graft removal.

HEMORRHAGE

Postoperative bleeding may be minimized by meticulous intraoperative control of bleeding sites. Hemorrhage may be exacerbated by anticoagulants and antiplatelet drugs, but their benefits seem to outweigh the risks. Bleeding is a much less significant cause (<1%) of graft loss than is thrombosis, according to UNOS registry data. Significant bleeding is treated by immediate re-exploration.

PANCREATITIS

Most cases of graft pancreatitis occur early, tend to be self limited, and are probably due to ischemic preservation injury.

Clinical manifestations may include graft tenderness and fever, in addition to hyperamylasemia. Treatment consists of IV fluid replacement and keeping the recipient fasting. Later episodes of graft pancreatitis may be caused by reflux into the allograft duct (in recipients who undergo BD) or by cytomegalovirus (CMV) infection. Reflux is treated by urinary catheter drainage, and occasionally by conversion to ED. CMV infections are treated with appropriate antiviral agents.

UROLOGIC COMPLICATIONS

Urologic complications are almost exclusively limited to recipients with BD. Hematuria is not uncommon in the first several months posttransplant, but usually it is transient and self limiting. Bladder calculi may develop because exposed sutures or staples along the duodenocystostomy serve as a nidus for stone formation. Recurrent urinary tract infections commonly occur concurrently. Treatment consists of cystoscopy with removal of the sutures or staples. Urinary leaks, most commonly from the proximal duodenal cuff or from the duodenal anastomosis to the bladder, typically occur during the first several weeks posttransplant. Small leaks can be successfully managed by prolonged (at least 2 weeks) urinary catheter drainage; larger leaks require surgical intervention.

Other urinary complications include chronic, refractory, metabolic acidosis because of bicarbonate loss, persistent and recurrent urinary tract infections, and urethritis. Along with recurrent hematuria, these complications are the major indications for converting recipients from BD to ED. Because 10 to 20% of recipients with initial BD will require conversion to ED, a recent trend has been to perform ED at the time of the transplant. ED is associated with significantly fewer urinary tract infections and urologic complications, but it obviates the use of urinary amylase determinations.

INFECTIONS

Infections remain a significant problem after pancreas transplants.[58] Most common are superficial wound infections and intra-abdominal infections, often related to graft complications such as leaks. Thanks to appropriate perioperative antimicrobial regimens (for prophylaxis against gram-positive bacteria, gram-negative bacteria, and yeast) the incidence of significant infections has decreased. Still, it remains about 10% and is associated with significant morbidity and mortality. Thus, if serious intra-abdominal infections occur (whether or not associated with the above complications), re-exploration and graft removal must be strongly considered, along with concurrent reduction in immunosuppression.

Results

The International Pancreas Transplant Registry (IPTR) maintains data on pancreas transplants. Analyses of IPTR data have been published yearly since the mid-1980s. The results (particularly as measured by long-term insulin independence) have continually improved over time. Patient survival rates are not significantly different between the three main recipient categories and are greater than 90% at 3 years posttransplant. Most deaths are due to pre-existing cardiovascular disease; the mortality risk of a pancreas transplant per se is extremely low (e.g., patient survival at 1 year for PTA recipients is >95%). Pancreas graft survival rates at 1 year remain higher in the SPK (~90%) than in the PAK (~85%) and PTA (~80%) categories, according to IPTR data. The differences are due in part to the decreased ability to monitor for rejection episodes in enteric-drained, solitary pancreas transplant recipients. With improving immunosuppressive protocols and the decreasing incidence of acute rejection, the difference between the three categories has been steadily decreasing since the late 1990s.[59,60]

ISLET CELL TRANSPLANTATION

The pancreas consists of two separate functional systems (endocrine and exocrine), but it is only the endocrine component

that is of use in the transplant process. However, many of the complications seen with whole-organ pancreas transplants are due to the exocrine component. Therefore, the concept of transplanting simply the cells responsible for the production of insulin is very logical and attractive.

Islet cell transplantation involves extracting islets of Langerhans from a donor's pancreas and then injecting them into a diabetic recipient. These islet cells then engraft into the recipient and secrete insulin, providing excellent moment-to-moment control of blood glucose, as is seen with a whole-organ pancreas transplant. Compared with exogenous insulin injections, an islet cell transplant offers advantages similar to those of a whole-organ pancreas transplant. A successful islet transplant provides perfect glucose homeostasis, freeing the diabetic patient from the burden of frequent glucose monitoring and insulin injections. It potentially prevents secondary complications of diabetes and significantly improves quality of life.

Unlike a whole-organ pancreas transplant, an islet cell transplant is not a major surgical procedure. It generally can be performed as an outpatient procedure, with minimal recovery time for the recipient. It avoids a major surgical procedure, with its associated mortality and morbidity. Given this significantly lower surgical risk, islet cell transplants could theoretically have much wider application than whole-organ transplants.

Typically, a pancreas is procured from a suitable deceased donor. Isolating the islets is a complex process, which generally involves digesting the pancreas with a collagenase solution to separate the islet cells. The islets may then be purified (i.e., separated from the acinar cells). The purified islets can then be injected into the recipient, most commonly into the portal vein. The islet cells then engraft in the hepatic parenchyma and secrete insulin, which drains into the circulation. Potential complications associated with the injection include portal hypertension, hepatic abscesses, and bacteremia.

One major disadvantage of an islet cell transplant (similar to that of a whole-organ transplant) is the need for long-term immunosuppression. This disadvantage has limited the use of islet cell transplants to patients with kidney failure who require immunosuppression because of a kidney transplant.

This immunologic problem is compounded by the fact that islet cell rejection can be difficult to monitor and diagnose. One possible method of avoiding the need for immunosuppression is to surround the islets with a semipermeable membrane, a process called *microencapsulation*. This process would allow small molecules such as oxygen and glucose to reach the islet cells and would allow insulin to reach the systemic circulation. But microencapsulation would prevent immune cells and large molecules such as antibodies from reaching the islet cells. The islet cells would then survive and function well inside the membranes, while being protected from immunologic damage.

Islet cell transplants have been a possibility for many years, but the results have generally been poor. In 1995, a report of the International Islet Transplant Registry indicated that of 270 recipients, only 5% were insulin independent at 1 year posttransplant. Recently, however, significantly improved results have been reported by using steroid-free immunosuppression and islet injections from multiple donors. These recent successes have stimulated a flurry of islet transplant activity at centers across the world. As results are likely to continue to improve, it is possible that islet cell transplants may come to replace whole-organ pancreas transplants.

LIVER TRANSPLANTATION

The field of liver transplantation has undergone remarkable advances in the last 2 decades. An essentially experimental procedure in the early 1980s, a liver transplant is now the treatment of choice for patients with acute and chronic liver failure. Patient survival at 1 year posttransplant has increased from 30% in the early 1980s to more than 85% at present. The major reasons for this dramatic increase include refined surgical and preservation techniques, better immunosuppressive

protocols, more effective treatment of infections, and improved care during the critical perioperative period. However, a liver transplant remains a major undertaking, with the potential for complications affecting every major organ system.

History

The history of liver transplantation began with experimental transplants performed in dogs in the late 1950s. The first liver transplant attempted in humans was in 1963 by Thomas Starzl. The recipient was a 3-year-old boy with biliary atresia who unfortunately died of hemorrhage. The first successful liver transplant was in 1967, again by Starzl. Yet, for the next 10 years, liver transplants remained essentially experimental, with survival rates well below 50%. Still, advances in the surgical procedure and in anesthetic management continued to be made during that time.

The major breakthrough for the field came in the early 1980s, with the introduction and clinical use of the immunosuppressive agent cyclosporine. Patient survival dramatically improved, and liver transplantation was soon being recognized as a viable therapeutic option. Results continued to improve through the 1980s, due to ongoing improvements in immunosuppression, critical care management, surgical technique, and preservation solutions. The late 1980s and 1990s saw a dramatic increase in the number of liver transplants, and an even greater increase in the number of patients waiting for a transplant. This, in turn, increased waiting times as well as mortality rates for those waiting.

The longer waiting time and higher mortality rates for patients on the deceased-donor liver transplant waiting list led to the development of innovative surgical techniques such as split-liver transplants and living-donor liver transplants. Initially, these new techniques were mainly applied to pediatric patients because of the difficulty associated with finding appropriate size-matched organs for them. However, as the number of adults on the waiting list grew, these techniques began to be applied for adult recipients as well. The use of living-donor liver transplants progressed at an even more rapid pace in countries such as Japan, where the concept of deceased-donor organ donation was not widely accepted.

Preoperative Evaluation

A liver transplant is indicated for liver failure, whether acute or chronic. Liver failure is signaled by a number of clinical symptoms [e.g., ascites, variceal bleeding, hepatic encephalopathy (HE), and malnutrition], and by biochemical liver test results that suggest impaired hepatic synthetic function (e.g., hypoalbuminemia, hyperbilirubinemia, and coagulopathy). The cause of liver failure often influences its presentation. For example, patients with acute liver failure generally have HE and coagulopathy, whereas patients with chronic liver disease most commonly have ascites, GI bleeding, and malnutrition.

Diseases Treatable by Transplant

A host of diseases are potentially treatable by a liver transplant (Table 11-7). Broadly, they can be categorized as acute or chronic, and then subdivided by the cause of the liver disease. Chronic liver diseases account for the majority of liver transplants today. The most common cause in North America is chronic hepatitis, usually due to hepatitis C and less commonly to hepatitis B. Chronic alcohol abuse accelerates the process, especially with hepatitis C. Progression from chronic infection to cirrhosis is generally slow, usually occurring over a period of 10 to 20 years. Chronic hepatitis may also result from autoimmune causes, primarily in women. It can present either acutely over months or insidiously over years. Alcohol often plays a role in end-stage liver disease secondary to hepatitis C, but it may also lead to liver failure in the absence of viral infection. In fact, alcohol is the most common cause of end-stage liver disease in the United States. Such patients generally are suitable candidates for a transplant as long as an adequate period of sobriety can be documented.

Table 11-7 Diseases Amenable to Treatment by a Liver Transplant
Cholestatic liver diseases
Primary biliary cirrhosis
Primary sclerosing cholangitis
Biliary atresia
Alagille syndrome
Chronic hepatitis
Hepatitis B
Hepatitis C
Autoimmune hepatitis
Alcohol liver disease
Metabolic diseases
Hemochromatosis
Wilson's disease
Alpha1-antitrypsin deficiency
Tyrosinemia
Cystic fibrosis
Hepatic malignancy
Hepatocellular carcinoma
Neuroendocrine tumor metastatic to liver
Fulminant hepatic failure
Others
Cryptogenic cirrhosis
Polycystic liver disease
Budd-Chiari syndrome
Amyloidosis

Cholestatic disorders also account for a significant percentage of transplant candidates with chronic liver disease. In adults, the most common causes are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). PBC, a destructive disorder of interlobular bile ducts, can progress to cirrhosis and liver failure over several decades. It most commonly affects middle-aged women. PSC, a disease characterized by inflammatory injury of the bile duct, occurs mostly in young men, 70% of whom have inflammatory bowel disease. In children, biliary atresia is the most common cholestatic disorder. It is a destructive, inflammatory condition of the bile ducts, and if left untreated, it usually results in death within the first 1 to 2 years of life.

A variety of metabolic diseases can result in progressive, chronic liver injury and cirrhosis, including hereditary hemochromatosis (an autosomal recessive disorder characterized by chronic iron accumulation, which may result in cirrhosis, cardiomyopathy, and endocrine disorders including diabetes), alpha1-antitrypsin deficiency (which may result in cirrhosis at any age, most commonly in the first or second decade of life), and Wilson's disease [an autosomal recessive disorder of copper excretion, which may present as either fulminant hepatic failure (FHF) or chronic hepatitis and cirrhosis].

Hepatocellular carcinoma (HCC) may be a complication of cirrhosis from any cause, most commonly with hepatitis B, hepatitis C, hemochromatosis, and tyrosinemia. HCC patients may have stable liver disease, but are often not candidates for hepatic resection because of the underlying cirrhosis. The desire to remove the malignancy and replace the remaining liver parenchyma (both to improve liver function and remove the diseased parenchyma at risk for further carcinogenesis) led clinicians to consider the use of orthotopic liver transplantation (OLT). Long-term patient survival in early series of OLT for HCC, however, only reached 30 to 40%. It was not until patient selection strategies evolved that OLT became a more effective treatment. In a landmark 1996 study by Mazzaferro and colleagues at the University of Milan,[61] characteristics of patients with HCC that were good candidates for OLT were described. These characteristics, now commonly referred to as the *Milan criteria*, included (a) a single lesion <5 cm or 1 to 3 tumors, each <3 cm; and (b) absence of vascular or lymphatic invasion. Patients meeting these criteria achieved an impressive 85% 4-year overall patient survival, while those patients that exceeded the Milan criteria had only 50% 4-year survival. As with surgical resection, vascular invasion appears to be the most important predictor of mortality among patients undergoing OLT for HCC. Also, the fibrolamellar subtype appears to have no better prognosis than nonfibrolamellar subtypes of HCC. Liver transplantation is now a well-accepted treatment option for patients with HCC. Attention has now focused on whether there may be tumor sizes and categories that may be just outside the Milan criteria that could benefit from transplant. A host of other diseases may lead to chronic liver failure and are potentially amenable to treatment with a transplant, including Budd-Chiari syndrome (obstruction of the hepatic veins secondary to thrombus, which leads to hepatic congestion, ascites, and eventually liver damage) and polycystic liver disease (in which a large number of cysts, depending on their size, can lead to debilitating symptoms).

Acute liver disease, more commonly termed *fulminant hepatic failure*, is defined as the development of HE and profound coagulopathy shortly after the onset of symptoms, such as jaundice, in patients without pre-existing liver disease. The most common causes include acetaminophen overdose, acute hepatitis B infection, various drugs and hepatotoxins, and Wilson's disease; often, however, no cause is identified. Treatment consists of appropriate critical care support, giving patients time for spontaneous recovery. The prognosis for spontaneous recovery depends on the patient's age (those younger than 10 and older than 40 years have a poor prognosis), the underlying cause, and the severity of liver injury (as indicated by degree of HE, coagulopathy, and kidney dysfunction; Table 11-8). A subset of patients may have delayed onset of hepatic decompensation that occurs 8 weeks to 6 months after the onset of symptoms. This condition is often referred to as *subacute hepatic failure*; these patients rarely recover without a transplant.

Table 11-8 Indications for a Liver Transplant in Patients with Acute Liver Failure
Acetaminophen toxicity
pH <7.30
Prothrombin time >100 s (INR >6.5)
Serum creatinine >300 μmol/L (>3.4 mg/dL)
No acetaminophen toxicity
Prothrombin time >100 s (INR >6.5)
age <10 or >40 y
Non-A, non-B hepatitis
Duration of jaundice before onset of encephalopathy >7 d
Serum creatinine >300 μmol/L (>3.4 mg/dL)

INR = International Normalized Ratio.

Indications for Transplant

The presence of chronic liver disease alone with established cirrhosis is not an indication for a transplant. Some patients have well-compensated cirrhosis with a low expectant mortality. Patients with decompensated cirrhosis, however, have a poor prognosis without transplant. The signs and symptoms of decompensated cirrhosis include:

- HE: In its early stages, HE may begin with subtle sleep disturbances, depression, and emotional lability. Increasing severity of HE is indicated by increasing somnolence, altered speech, and in extreme cases, coma. Physical examination shows the typical flapping tremor of asterixis. Blood tests often reveal an elevated serum ammonia level. HE may occur spontaneously, but more commonly is triggered by a precipitating factor such as spontaneous bacterial peritonitis (SBP), GI bleeding, use of sedatives, constipation, or excessive dietary protein intake.
- Ascites: Ascites generally is associated with portal hypertension. The initial approach to the management of ascites is sodium restriction and diuretics. If this approach is not successful, patients may require repeated large-volume (4 to 6 L) paracentesis. A better option to diuretic-resistant ascites requiring frequent paracentesis is transjugular intrahepatic portosystemic shunting (TIPS). A potential complication of TIPS is progression of liver failure or disabling encephalopathy. Patients with signs of far-advanced liver disease, such as hyperbilirubinemia, HE, and renal dysfunction, generally are not good candidates for TIPS.
- SBP: This complication of chronic liver failure generally signals advanced disease. It often tends to be recurrent. Anaerobic gram-negative bacteria account for 60% of the cultured organisms; gram-positive cocci account for the remainder. Diagnosis is confirmed if percutaneous sampling of the abdominal fluid shows a neutrophil count of greater than 250 cells/mL. Treatment with a third-generation cephalosporin is generally effective.
- Portal hypertensive bleeding: The likelihood of patients with cirrhosis developing varices ranges from 35 to 80%. About one third of those with varices will experience bleeding. The risk of recurrent bleeding approaches 70% by 2 years after the index bleeding episode. Each episode of bleeding is associated with a 30% mortality rate. Thus, urgent treatment of the acute episode and steps to prevent rebleeding are essential. Endoscopy is indicated to diagnose and treat the acute bleed with either band ligation or sclerotherapy. Other therapies include vasoactive drugs such as octreotide or vasopressin, balloon tamponade, TIPS, and emergency surgical procedures (such as a portosystemic shunt or transection of the esophagus). Generally, patients whose endoscopic procedure fails should undergo emergency TIPS, if feasible, to control bleeding. Beta blockers have been shown to be of value in preventing the first bleeding episode in patients with varices and in preventing rebleeding.
- Hepatorenal syndrome (HRS): In patients with advanced liver disease and ascites, HRS is characterized by oliguria (<500 mL of urine/d) in association with low urine sodium (<10 mEq/L). It is a functional disorder; the kidneys have no structural abnormalities, and the urine sediment is normal. The differential diagnosis includes ATN, drug nephrotoxicity, and chronic intrinsic renal disease. HRS may be precipitated by volume depletion from diuresis, SBP, or agents such as NSAIDs. Patients may require dialysis support, but the only effective treatment is a liver transplant.
- Others: Other signs and symptoms of decompensated cirrhosis include severe weakness and fatigue, which may sometimes be the primary symptoms. Such weakness can be debilitating, leading to the inability to work or even to carry out daily functions. It may be associated with malnutrition and muscle wasting, which at times may be quite severe. Biochemical abnormalities, advanced liver disease, and loss of synthetic function are associated with a low serum albumin, a high serum bilirubin, and a rise in the serum International Normalized Ratio (INR).

Generally, FHF patients are more acutely ill than chronic liver failure patients, and thus require more intensive care pretransplant. FHF patients have more severe hepatic parenchymal dysfunction, as manifested by coagulopathy, hypoglycemia, and lactic acidosis. Infectious complications also are more common, as is the incidence of kidney failure and neurologic complications, especially cerebral edema.

Coagulopathy usually is secondary to the impaired hepatic synthesis of clotting factors. Necrosis, as a result of disseminated intravascular coagulation (DIC), may also be associated with FHF. Close attention should be given to the serum glucose level, which is more likely to be decreased in FHF patients. IV glucose should be administered at a sufficient rate to maintain euglycemia.

The prevalence of bacterial infection in FHF patients is very high, a reflection of the loss of the immunologic functions of the liver. The respiratory and urinary systems are the most common sources. In addition, almost one third of FHF patients develop some form of fungal infection, usually secondary to *Candida* species. Sepsis is generally a contraindication to a liver transplant; if it is unrecognized pretransplant, the outcome posttransplant is poor.

Multiple organ dysfunction syndrome, characterized by respiratory distress, kidney failure, increased cardiac output, and decreased systemic vascular resistance, is a well-described complication of FHF. It may be due to impaired clearance of vasoactive substances by the liver. Mechanical ventilation and dialysis support may become necessary pretransplant. Hemodynamic abnormalities may manifest as hypotension and worsening tissue oxygenation.

Cerebral edema is substantially more common in FHF patients. As many as 80% of the patients who die secondary to FHF have evidence of cerebral edema. The pathogenesis is unclear, but it may be due to potential neurotoxins that are normally cleared by the liver. Establishing the diagnosis may be problematic; patients often are sedated and ventilated, making clinical examination difficult. Radiologic imaging is neither sensitive nor specific. Several centers have tried intracranial pressure (ICP) monitoring; therapy (e.g., mannitol, hyperventilation, and thiopental) can then be directed to achieve an adequate cerebral perfusion pressure (above 50 mmHg). ICP monitoring also helps predict the likelihood of neurologic recovery posttransplant. Sustained cerebral perfusion pressures of less than 40 mmHg have been associated with postoperative neurologic death. Disadvantages of ICP monitoring include the risks of performing it in patients with severe coagulopathy; it is also a possible source of infection and may precipitate an intracranial hemorrhage.

The indications for a liver transplant are numerous (and increasing), with the number of absolute contraindications few (and decreasing with time). There are no specific age limits for recipients; their mean age is steadily increasing. Patients must have adequate cardiac and pulmonary function. Coronary artery disease is uncommon in liver transplant candidates, but those with cirrhosis may develop significant hypoxia and pulmonary hypertension. Those with severe hypoxemia or with right atrial pressures greater than 60 mmHg rarely survive a liver transplant. Other contraindications, as with other types of transplants, include uncontrolled systemic infection and malignancy. HCC patients with metastatic disease, obvious vascular invasion, or significant tumor burden are not suitable transplant candidates. Patients with other types of extrahepatic malignancy should be deferred for at least 2 years after completing curative therapy before a transplant is attempted.

Currently, the most common contraindication to a liver transplant is ongoing substance abuse. Before considering patients for a transplant, most centers require a documented period of abstinence, demonstration of compliant behavior, and willingness to pursue a chemical dependency program.

Once the indications for a transplant and the absence of contraindications have been established, a careful search for underlying medical disorders of the cardiovascular, pulmonary, neurologic, genitourinary, and GI systems must be made. Serologic evaluation to screen for the presence of underlying viral infections is important. Unique to patients with chronic liver disease, the pretransplant evaluation must assess for any evidence of hepatopulmonary syndrome, pulmonary hypertension, and HRS.

Hepatopulmonary syndrome is characterized by impaired gas exchange, resulting from intrapulmonary arteriovenous shunts. These shunts may lead to severe hypoxemia, especially when patients are in the upright position (orthodeoxia). A transplant may be contraindicated if intrapulmonary shunting is severe, as manifested by hypoxemia that is only partially improved with high inspired oxygen concentrations.

Pulmonary hypertension is seen in a small proportion of patients with established cirrhosis. Its exact cause is unknown.

Diagnosing pulmonary hypertension pretransplant is critical, because major surgical procedures in the presence of nonreversible pulmonary hypertension are associated with a very high risk of mortality.

The development of hepatorenal syndrome indicates rapid hepatic deterioration. It is a clear indication for a liver transplant. Patients with hepatorenal syndrome or with kidney failure from any cause have worse outcomes posttransplant, as compared to patients with no kidney dysfunction. Therefore, all attempts must be made to avoid or reverse any kidney dysfunction pretransplant. Once the cause of kidney dysfunction is established, appropriate therapy should be initiated, including optimization of volume status with invasive monitoring techniques, large-volume paracentesis, cessation of nephrotoxic drugs, nonpressor doses of dopamine, or judicious use of diuretics, as indicated. If such therapy is unsuccessful, dialysis support may be required until a liver transplant becomes available.

Waiting list mortality can be quite accurately predicted in chronic liver failure patients by calculating their MELD (model for end-stage liver disease)[62] score. The formula for calculation of this is:

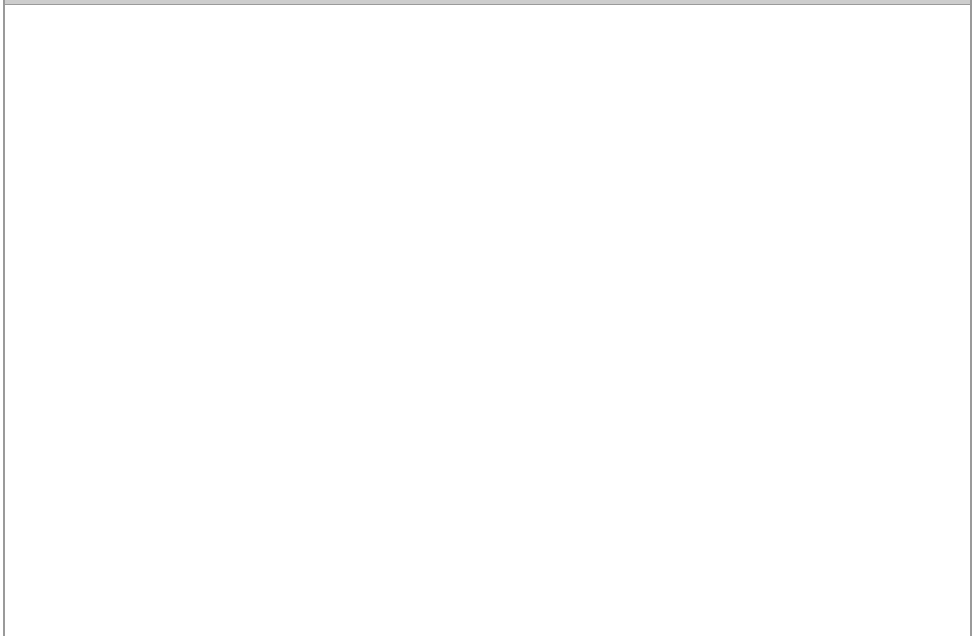
$$\text{MELD score} = 3.8 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{INR}) + 9.6 \log_e(\text{creatinine mg/dL})$$

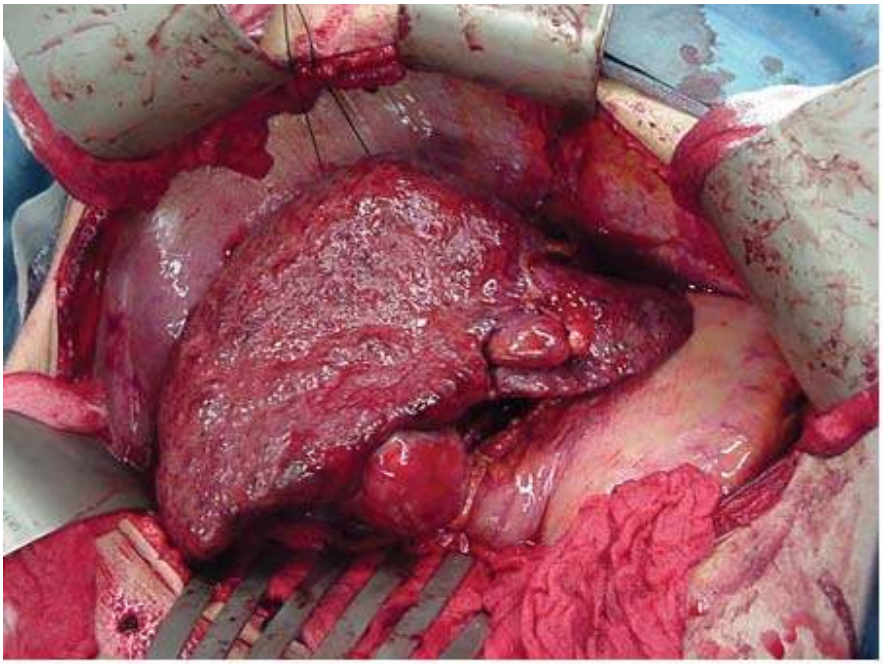
A higher MELD score indicates a sicker patient, with a higher risk for mortality. In the United States, this scoring system has proven to be a useful method to determine the allocation of livers, with priority given to the sickest individuals. The calculated score does not take into account special situations such as HCC, which have a definite impact on waiting list mortality, but scoring exceptions are applied to these situations to allow for timely transplants.

Surgical Procedure

The surgical procedure is divided into three phases: preanhepatic, anhepatic, and postanhepatic. The preanhepatic phase involves mobilizing the recipient's diseased liver in preparation for its removal (Fig. 11-21). The basic steps include isolating the supra- and infrahepatic vena cava, portal vein, and hepatic artery, and dividing the bile duct (Fig. 11-22). Given existing coagulopathy and portal hypertension, the recipient hepatectomy may be the most difficult aspect of the transplant procedure. The anesthesia team must be prepared to deal with excessive blood loss.

Fig. 11-21.





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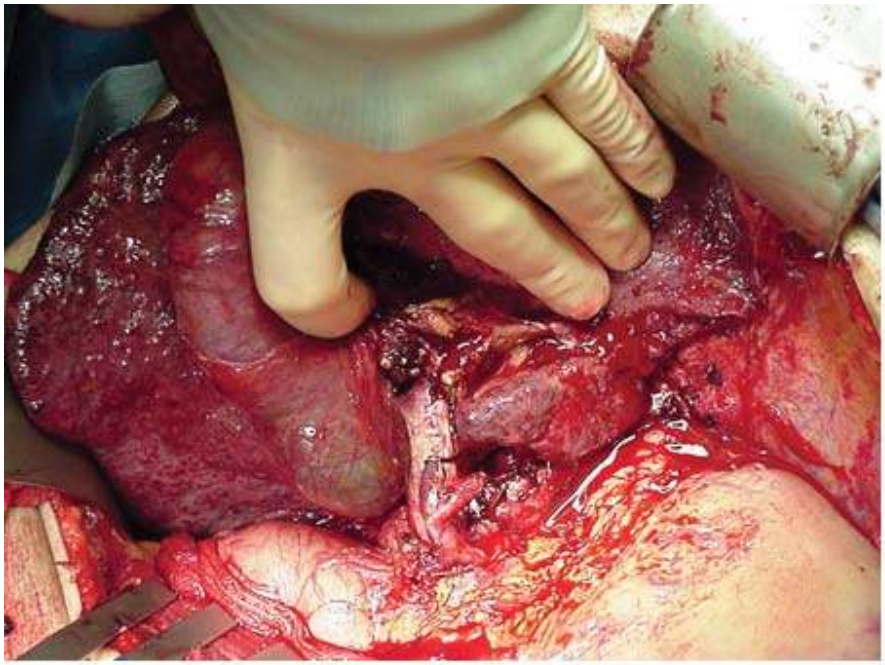
Cirrhotic liver mobilized in preparation for complete hepatectomy.

Fig. 11-22.



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Isolation and division of the hilar structures to diseased liver-hepatic artery, portal vein, and common bile duct.

Once the above structures have been isolated, vascular clamps are applied. The recipient's liver is removed, thus beginning the anhepatic phase. This phase is characterized by decreased venous return to the heart because of occlusion of the IVC

and portal vein. Some centers routinely use a venovenous bypass (VVB) system during this time, in which blood is drawn from the lower body and bowels via a cannula in the common femoral vein and portal vein, and returned through a central venous cannula in the upper body. Potential advantages of bypass include improved hemodynamic stability, reduction of bleeding from an engorged portal system, and avoidance of elevated venous pressure in the renal veins. However, many centers do not routinely use VVB. VVB does have potential complications such as air embolism, thromboembolism, hypothermia, and trauma to vessels. Some centers use VVB selectively, reserving it for patients who demonstrate hemodynamic instability with a trial of caval clamping. Few randomized trials have measured specific clinical outcomes with or without VVB.

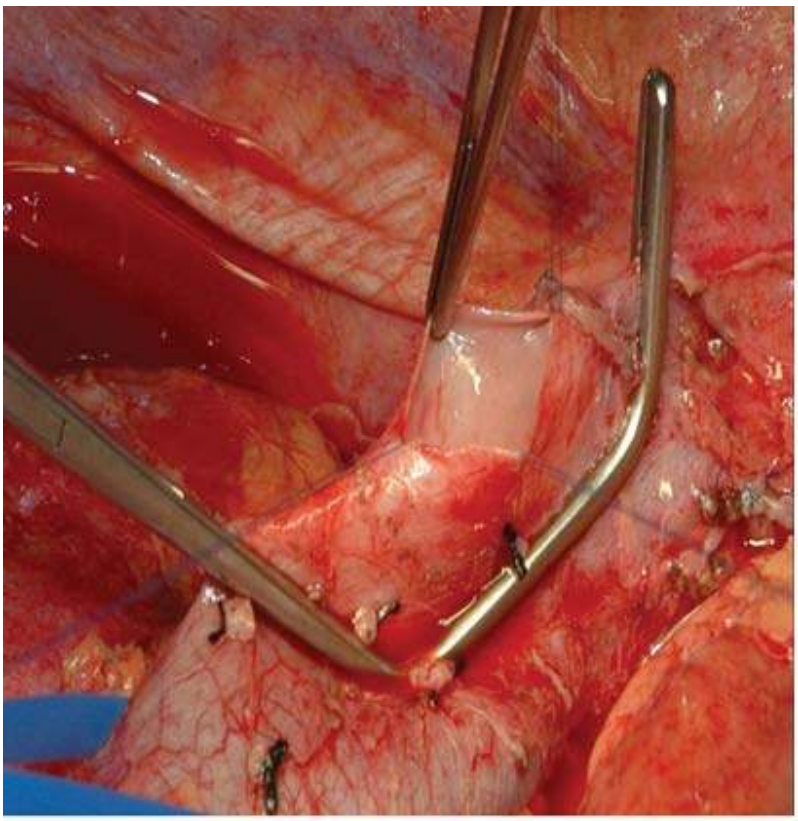
With the recipient liver removed, the donor liver is anastomosed to the appropriate structures to place it in an orthotopic position. The suprahepatic caval anastomosis is performed first, followed by the infrahepatic cava and the portal vein. The portal and caval clamps may be removed at this time. The new liver is then allowed to reperfuse. Either before or after this step, the hepatic artery may be anastomosed.

With the clamps removed and the new liver reperfused, the postanhepatic phase begins, often characterized by marked changes in the recipient's status. The most dramatic changes in hemodynamic parameters usually occur on reperfusion, namely hypotension and the potential for serious cardiac arrhythmias. Severe coagulopathy may also develop because of the release of natural anticoagulants from the ischemic liver or because of active fibrinolysis. Both ε-aminocaproic acid and aprotinin have been used prophylactically to prevent fibrinolysis and decrease transfusion requirements. Electrolyte abnormalities, most commonly hyperkalemia and hypercalcemia, often are seen after reperfusion, but they usually are transient and respond well to treatment with calcium chloride and sodium bicarbonate. After reperfusion, the final anastomosis is performed, establishing biliary drainage. The recipient's remaining common bile duct (choledochoduodenostomy) or a loop of bowel (choledochojejunostomy) may be used.

Variations on the Standard Procedure

Several variations of the standard operation have been described. With the "piggyback technique," the recipient's IVC is preserved, the infrahepatic donor cava is oversewn, and the suprahepatic cava is anastomosed to the confluence of the recipient hepatic veins. Alternatively, a side-to-side caval anastomosis can be performed between the back of the donor cava and the front of the recipient cava (Fig. 11-23). With these techniques, the recipient's vena cava does not have to be completely cross-clamped during anastomosis, thus allowing blood from the lower body to return to the heart uninterrupted, without the need for VVB. The piggyback technique has many advantages, including improved hemodynamic stability, improved kidney perfusion, and avoidance of the complications possible with VVB. However, no randomized studies have demonstrated the superiority of one technique over the other.

Fig. 11-23.



A

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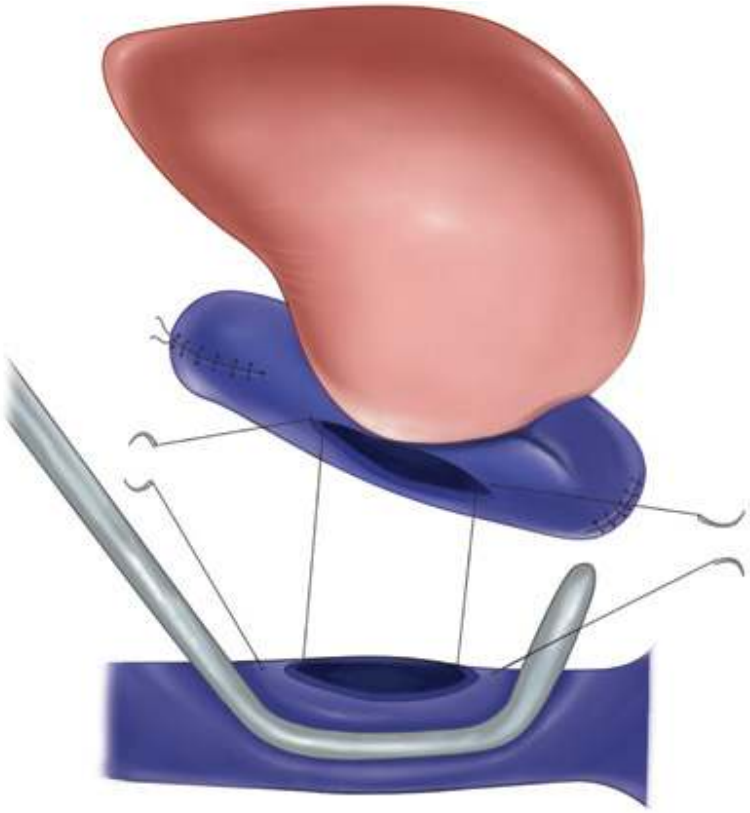

B

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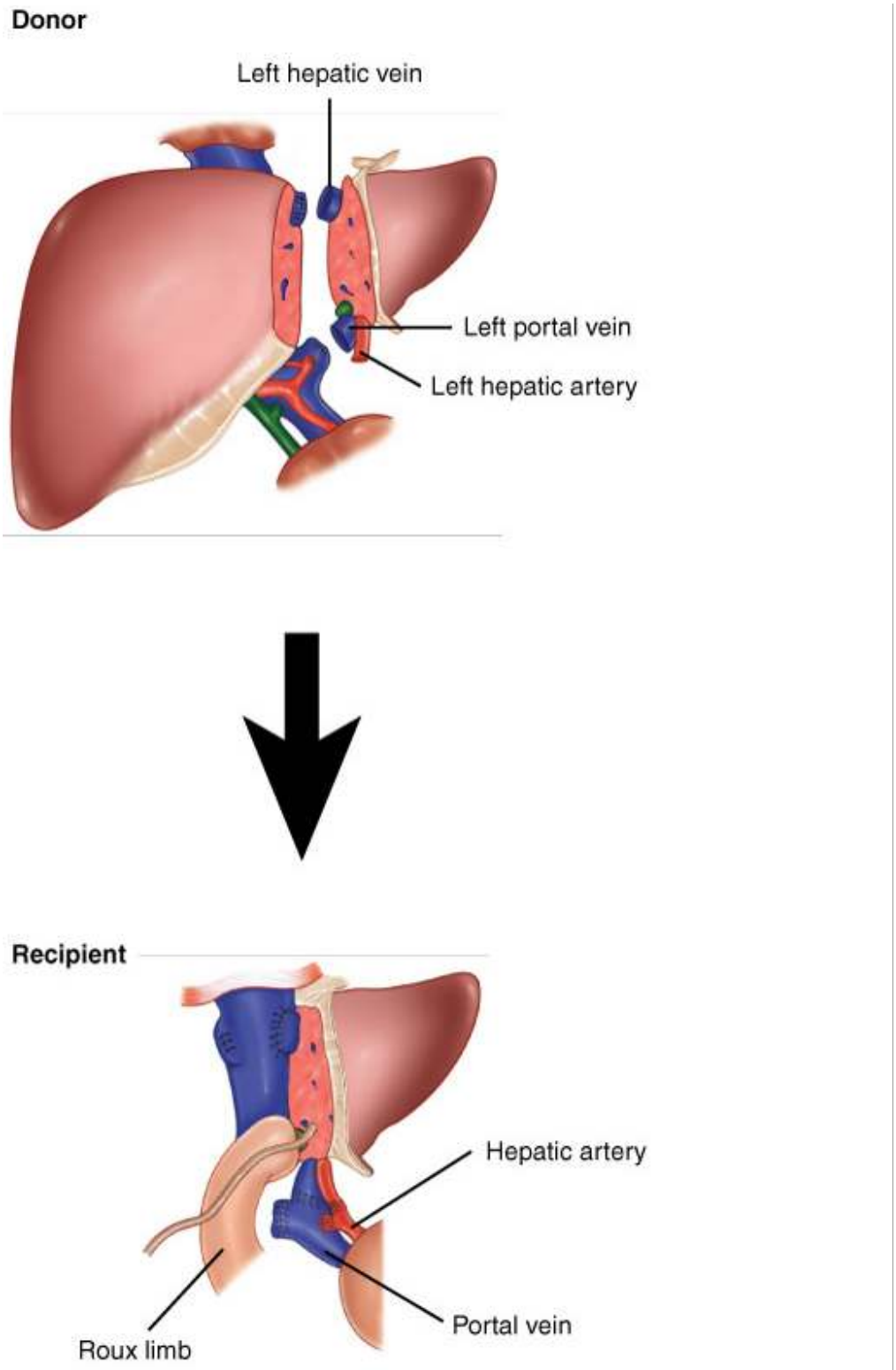
A and **B.** With the native liver removed and the cava preserved, the new liver is "piggybacked" onto the cava with a side-to-side caval anastomosis.

Another important variation of the standard operation is a partial transplant, either a living-donor transplant or a deceased-donor split-liver transplant. Both have developed in response to the donor shortage and are gaining in popularity. Usually, in living-donor liver transplants for pediatric recipients, the left lateral segment or left lobe is used; for adult recipients, the right lobe is usually used. Split-liver transplants from deceased donors involve dividing the donor liver into two segments, each of which is subsequently transplanted (see Fig. 11-10).

Living-Donor Liver Transplant

Living-donor liver transplants have been performed for almost 15 years. Initially, they involved adult donors and pediatric recipients. In such cases, the left lateral segment of the donor's liver is resected (Fig. 11-24). Inflow to the graft occurs via the donor's left hepatic artery and left portal vein; outflow is via the left hepatic vein. For adult recipients, a larger piece of the liver is required; usually the right lobe is chosen (Fig. 11-25). The liver has a remarkable ability to regenerate, and the remnant piece in the donor will achieve close to the original liver volume within 4 to 6 weeks after donation. The risks for living liver donors are higher than those for living kidney donors. The risks also generally are higher for right lobe donors than for left lateral segment donors.

Fig. 11-24.



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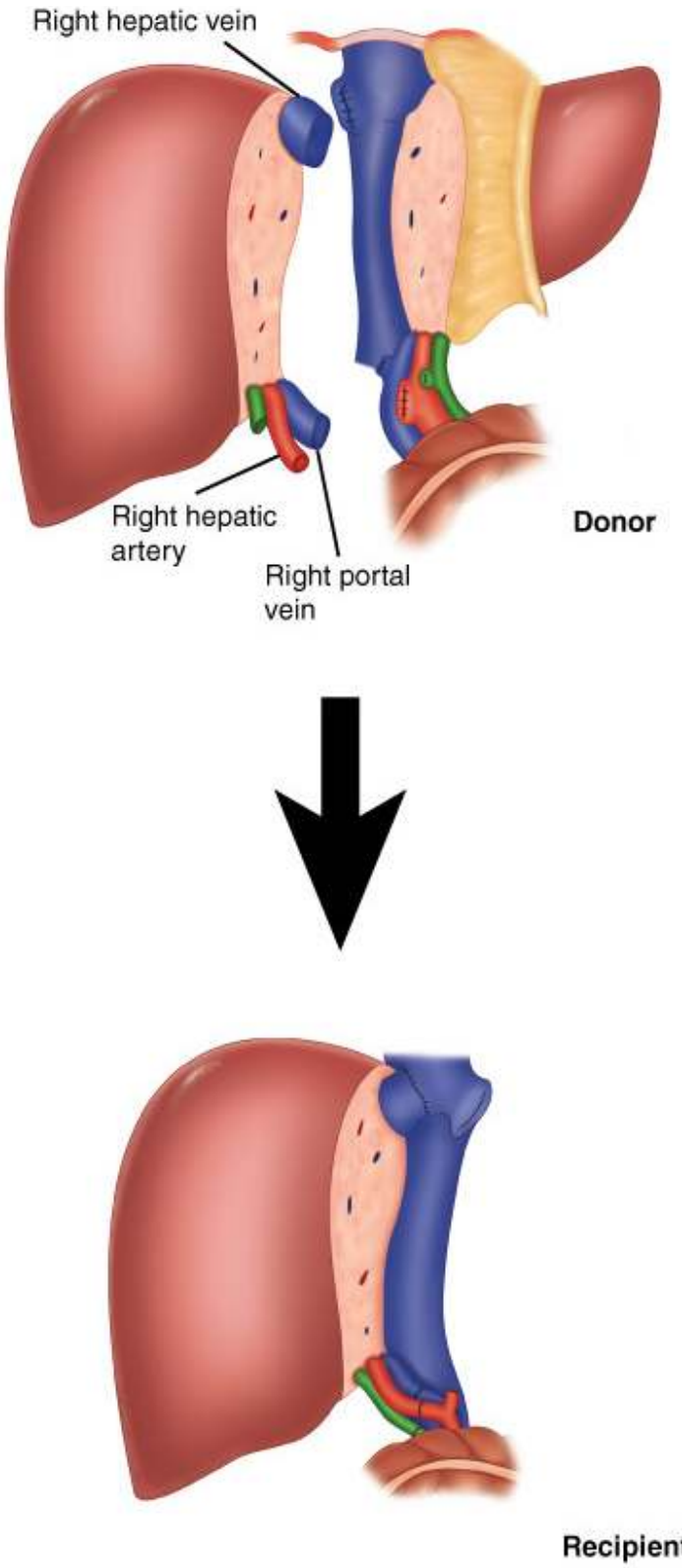
Donor and recipient procedure for living-donor liver transplant into a pediatric recipient.

Fig. 11-25.



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Donor and recipient procedure for living-donor liver transplant into an adult recipient.

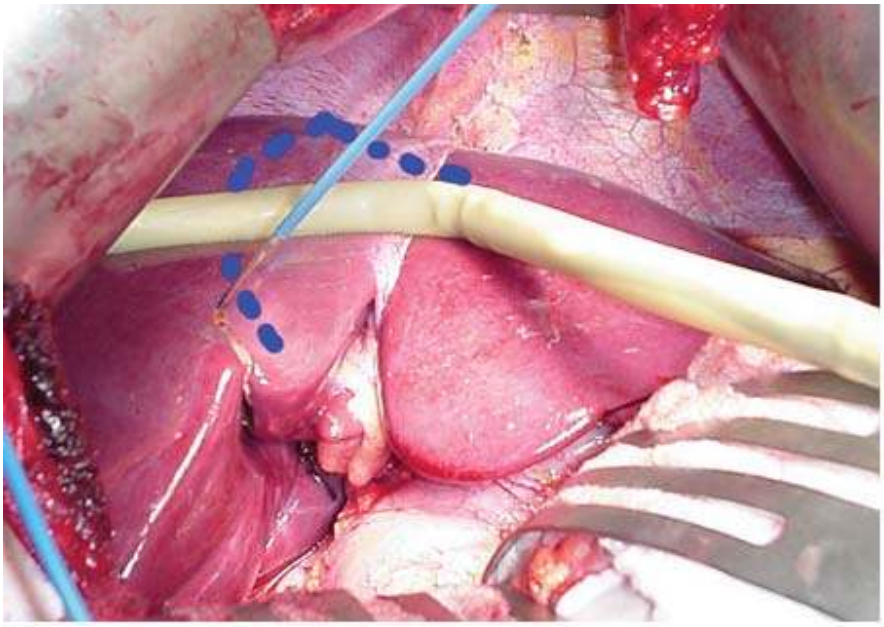
The greatest advantage of a living-donor liver transplant is that it avoids the often lengthy waiting period experienced with deceased-donor organ transplants. Over 17,000 people are now waiting for liver transplants in the United States, but only

5500 transplants are performed every year.[63] Roughly 15 to 25% of the candidates will die of their liver disease before having the chance to undergo a transplant. For those who do receive a transplant from a deceased donor, the waiting time can be significant, resulting in severe debilitation. With a living-donor liver transplant, this waiting time can be avoided, allowing the transplant to be performed before the recipient's health deteriorates further.

A partial hepatectomy in an otherwise healthy donor is a significant undertaking, so all potential donors must be carefully evaluated. Detailed medical screening must ensure that the donor is medically healthy; radiologic evaluation must ensure that the anatomy of the donor's liver is suitable and a psychosocial evaluation must ensure that the donor is mentally fit and not being coerced in any way. The decision to donate should be made entirely by the potential donor after careful consideration of the risks and of the potential complications.

If the recipient is a child, the lateral segment of the donor's liver (about 25% of the total liver) is removed.[64] If the recipient is an adult, a larger portion of the liver needs to be removed. Usually the right lobe of the liver, which comprises ~60% of the total liver, is used. The operative procedure involves isolating the blood vessels supplying the portion of the liver to be removed, transecting the hepatic parenchyma, and then removing the portion to be transplanted (Figs. 11-26, 11-27, and 11-28).

Fig. 11-26.



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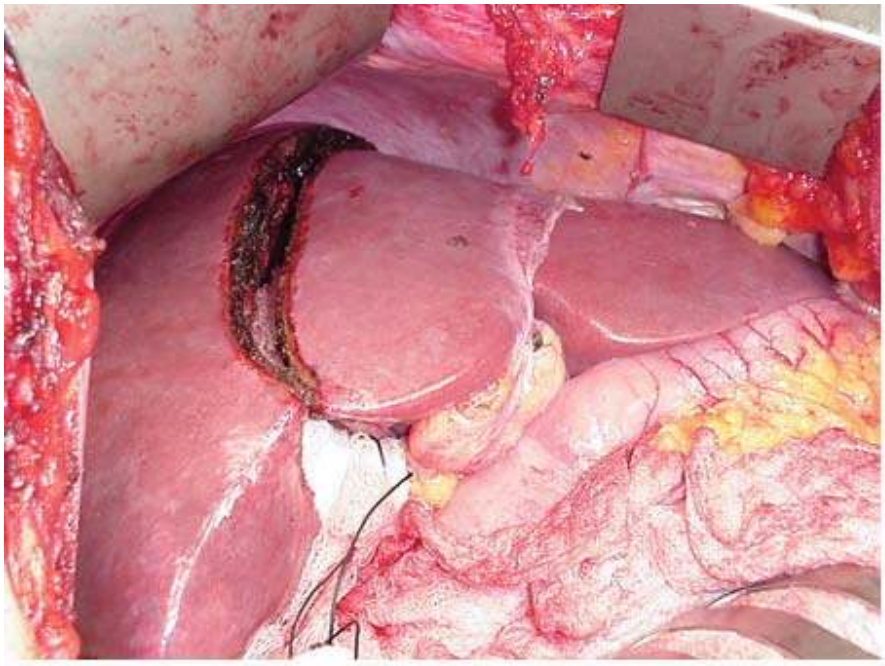
Intraoperative ultrasound can be used to trace the course of the middle hepatic vein and choose the line of transaction, staying just to the right or the left of the vein. Dotted blue lines = middle and left hepatic veins.

Fig. 11-27.



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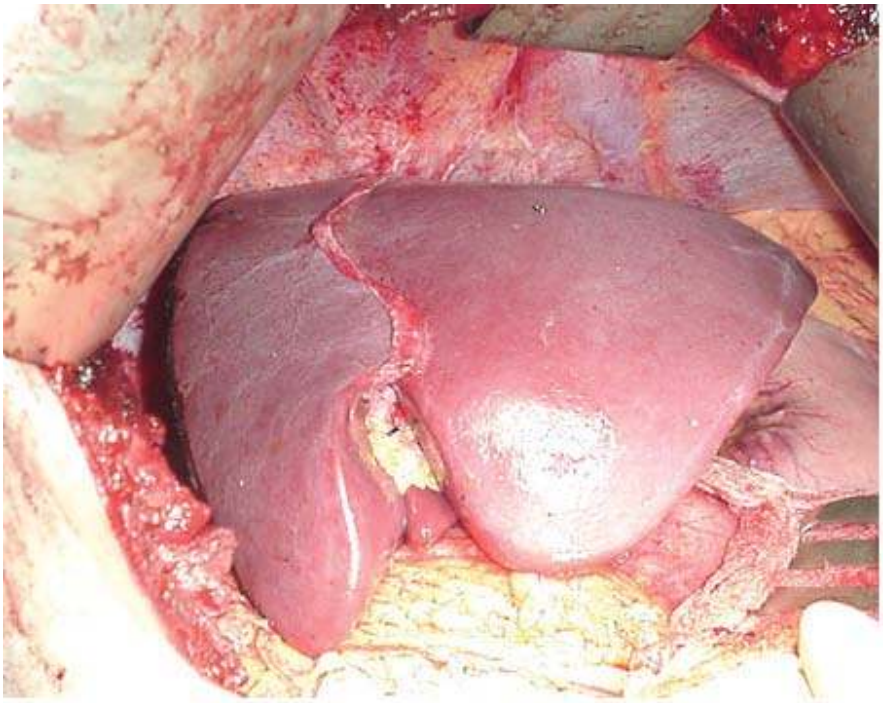
The donor liver after completion of the parenchymal transaction and before division of the vascular structures.

Fig. 11-28.



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The remnant left lobe in the donor after removal of the right lobe.

The overall incidence of complications in the donor after living-donor liver donation ranges from 20 to 30%. There is also a small risk (<0.5%) of death.[65] Bile duct problems are the most worrisome complication after donor surgery. Bile may leak from the cut surface of the liver or from the site where the bile duct is divided. That site may later become strictured. Generally, bile leaks resolve spontaneously with simple drainage. Strictures and sometimes bile leaks may require endoscopic retrograde cholangiopancreatography and stenting. If the above measures fail, a reoperation may be required. Intra-abdominal infections developing in donors usually are related to a biliary problem. Other complications after donor surgery may include incisional problems such as infections and hernias. The risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) is the same as for other major abdominal procedures.

The recipient operation with living-donor liver transplants is not greatly different from whole-organ, deceased-donor liver transplants. The hepatectomy is performed in a similar fashion; the vena cava should be preserved in all such cases because the graft generally will only have a single hepatic vein for outflow. This is then anastomosed directly to the recipient's preserved vena cava (Fig. 11-29). Outflow problems tend to be more common with partial vs. whole transplants, especially with right lobe transplants. Various methods have been described to improve the outflow of the graft, such as including the middle hepatic vein with the graft, reimplanting accessory hepatic veins, and reimplanting large tributaries that drain the right lobe into the middle hepatic vein.[66–69] Inflow to the graft can be re-established by anastomosing the donor organ hepatic artery and portal vein branch to the corresponding structures in the recipient (Fig. 11-30).

Fig. 11-29.

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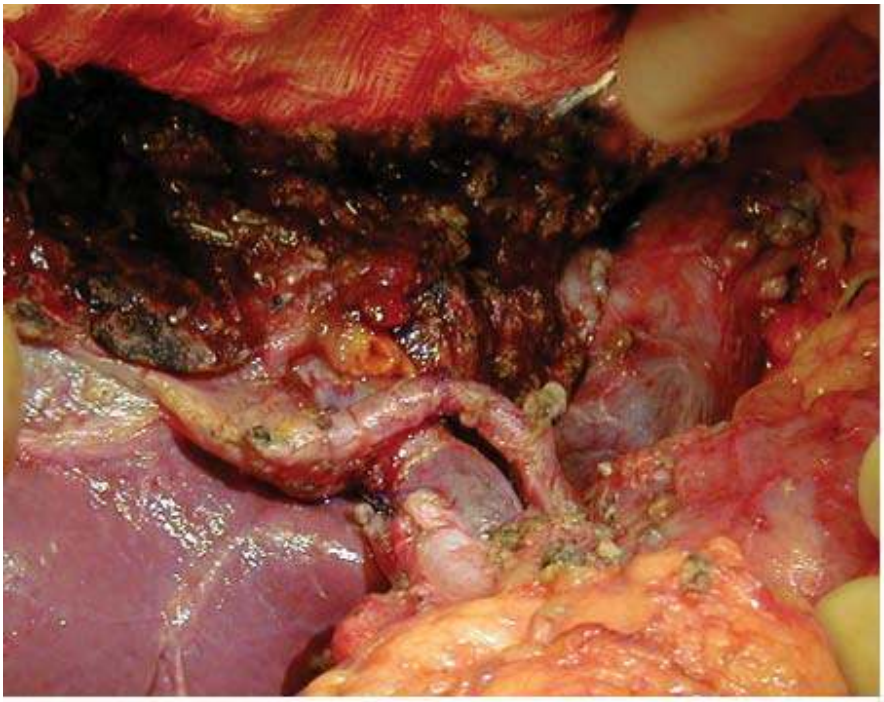
The recipient procedure begins with completion of the outflow by anastomosis of the right hepatic vein to the recipient inferior vena cava.

Fig. 11-30.



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The inflow to the right lobe graft is completed by anastomosis of the right hepatic artery and right portal vein to the corresponding structures in the recipient. Finally, the biliary system is reconstructed.

Split-Liver Transplants

Another method to increase the number of liver transplants is to split the liver from a deceased donor into two grafts, which are then transplanted into two recipients.[70] Thus, a whole adult liver from such a donor can be divided into two functioning grafts. The vast majority of split-liver transplants have been between one adult and one pediatric recipient. Usually, the liver is split into a smaller portion (the left lateral segment, which can be transplanted into a pediatric recipient) and a larger portion (the extended right lobe, which can be transplanted into a normal-sized adult recipient) (Fig. 11-31). The benefits for pediatric recipients have been tremendous, including an expansion of the donor pool and a significant decrease in waiting times and mortality rates.

Fig. 11-31.

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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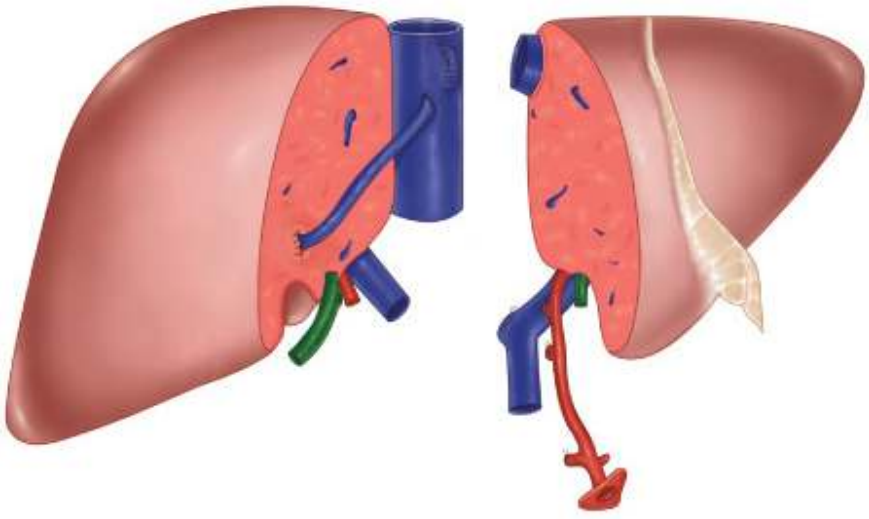
Split liver transplant from a deceased donor for transplant into an adult and pediatric recipient.

Splitting the liver as described in the paragraph above has no negative impact on the adult waiting list; however, it does not improve it. Adults now account for the majority of patients awaiting a transplant, and therefore the majority of patients dying on the waiting list. So, if split-liver transplants are to have a significant impact on waiting list time and mortality, they must be performed so the resulting two grafts can be used in two adult recipients.[55,71] The concern is that the smaller of the two pieces would not be of sufficient size to sustain life in a normal-sized adult. However, with appropriate donor and recipient selection criteria, a small percentage of livers from deceased donors could be split and transplanted into two adult recipients (Fig. 11-32).

Fig. 11-32.



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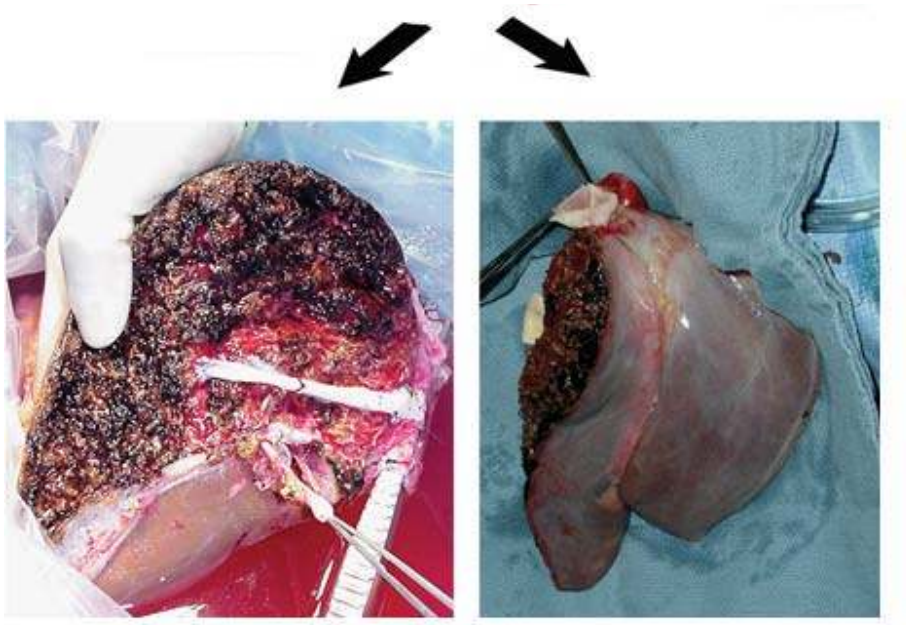

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Deceased-donor, split-liver transplant into a right lobe and left lobe for transplant into two adult recipients.

Postoperative Care

The immediate postoperative care for liver recipients involves (a) stabilizing the major organ systems (e.g., cardiovascular, pulmonary, and renal); (b) evaluating graft function and achieving adequate immunosuppression; and (c) monitoring and treating complications directly and indirectly related to the transplant.[72,73] This initial care should generally be performed in an intensive care unit (ICU) setting because recipients usually require mechanical ventilatory support for the first 12 to 24 hours. The goal is to maintain adequate oxygen saturation, acid-base equilibrium, and stable hemodynamics. Continuous hemodynamic monitoring is important to ensure adequate perfusion of the graft and vital organs. Hemodynamic instability occurring early posttransplant usually is due to fluid imbalance, but the presence of ongoing bleeding must first be excluded. Instability also may be secondary to the myocardial dysfunction that often is seen early in the reperfusion phase, but which may persist into the early postoperative period. Such dysfunction is characterized by decreased compliance and contractility of the ventricles. The usual treatment is to optimize preload and afterload, and to use inotropic agents such as dopamine or dobutamine if necessary.

Fluid management, electrolyte status, and kidney function require frequent evaluation. Most liver recipients have an increased extravascular volume but a reduced intravascular volume. Attention should be given to the potassium, calcium, magnesium, phosphate, and glucose levels. Potassium may be elevated because of poor kidney function, a residual perfusion effect, or medications. Diuretics may be required to remove excess fluid acquired intraoperatively, but they may result in hypokalemia. Magnesium levels should be kept above 2 mEq/L to prevent seizures, and phosphate levels between 2 and 5 mEq/L for proper support of the respiratory and alimentary tracts. Marked hyperglycemia, which may be secondary to steroids, should be treated with insulin. Hypoglycemia is often an indication of poor hepatic function.

A crucial aspect of postoperative care is to repeatedly evaluate graft function. In fact, doing so begins intraoperatively, soon after the liver is reperfused. Signs of hepatic function include good texture and good color of the graft, evidence of bile production, and restoration of hemodynamic stability. Postoperatively, hepatic function can be assessed using clinical signs

and laboratory values. Patients who rapidly awaken from anesthesia and whose mental status progressively improves likely have a well-functioning graft. Laboratory indicators of good graft function include normalization of the coagulation profile, resolution of hypoglycemia and hyperbilirubinemia, and clearance of serum lactate. Adequate urine production and good output of bile through the biliary tube (if present) are also indicators of good graft function. Serum transaminase levels will usually rise during the first 48 to 72 hours posttransplant secondary to preservation injury, and then should fall rapidly over the next 24 to 48 hours.

Another important aspect of postoperative care is to monitor for any surgical and medical complications. The incidence of complications tends to be high after liver transplants, especially in patients who were severely debilitated pretransplant. Surgical complications related directly to the operation include postoperative hemorrhage and anastomotic problems.

Postoperative bleeding is common. Usually multifactorial, it may be compounded by an underlying coagulopathy resulting from deficits in coagulation, fibrinolysis, and platelet function. Blood loss should be monitored via the abdominal drains; hemoglobin levels and CVP should be measured serially. If bleeding persists despite correction of coagulation deficiencies, an exploratory laparotomy should be performed.

The incidence of vascular complications after liver transplants ranges from 8 to 12%. Thrombosis is the most common early event, with stenosis and pseudoaneurysm formation occurring later. Hepatic artery thrombosis (HAT) has a reported incidence of about 3 to 5% in adults and about 5 to 10% in children. The incidence tends to be higher in partial liver transplant recipients. After HAT, liver recipients may be asymptomatic or may develop severe liver failure secondary to extensive necrosis. Doppler ultrasound evaluation is the initial investigative method of choice, with more than 90% sensitivity and specificity. If HAT is suggested by radiologic imaging, urgent re-exploration is indicated, with thrombectomy and revision of the anastomosis. If hepatic necrosis is extensive, a retransplant is indicated. However, HAT also may present in a less dramatic fashion. Thrombosis may render the common bile duct ischemic, resulting in a localized or diffuse bile leak from the anastomosis or in a more chronic, diffuse biliary stricture.

Thrombosis of the portal vein is less common. Signs include liver dysfunction, tense ascites, and variceal bleeding. Doppler evaluation should be used to establish the diagnosis. If thrombosis is diagnosed early, operative thrombectomy and revision of the anastomosis may be successful. If thrombosis occurs late, liver function is usually preserved due to the presence of collaterals; a retransplant is then unnecessary and attention is directed toward relieving the left-sided portal hypertension.

Biliary complications remain a significant problem after liver transplants, affecting 10 to 35% of all recipients. A higher incidence generally is seen after partial liver transplants, in which bile leaks may occur from the anastomoses or from the cut surface of the liver. Biliary complications manifest either as leaks or as obstructions. Leaks tend to occur early postoperatively and often require surgical repair; obstructions usually occur later and can be managed with radiologic or endoscopic techniques. Clinical symptoms of a bile leak include fever, abdominal pain, and peritoneal irritation. Ultrasound may demonstrate a fluid collection; however, cholangiography is required for diagnosis. Some leaks may be successfully managed by endoscopic placement of a biliary stent. If the leak does not respond to stent placement or if the liver recipient is systemically ill, a laparotomy is warranted. Biliary strictures occur later postoperatively and manifest as cholangitis or cholestasis, or both. Initial treatment involves balloon dilatation or stent placement across the stricture site, or both. If these initial options fail, surgical revision is required.

One devastating complication posttransplant is primary nonfunction of the hepatic allograft, with an attendant mortality rate of greater than 80% without a retransplant. By definition, primary nonfunction results from poor or no hepatic function from

the time of the transplant procedure. The incidence in most centers is about 3 to 5%. Factors associated with primary nonfunction include advanced donor age, increased fat content of the donor liver, prolonged donor hospitalization before organ procurement, prolonged cold ischemia time, and partial liver donation. IV prostaglandin E1 may have some useful effects and can be administered to recipients with suspected primary nonfunction. Ultimately, however, they should be listed for an urgent retransplant.

Medical complications (both infectious and noninfectious) are common posttransplant, especially in patients who were debilitated pretransplant. Almost any organ system may be involved. The neurologic, respiratory, and renal systems are commonly affected. Neurologic complications generally manifest as a decreased level of consciousness, seizures, or focal neurologic deficits. The most common cause of a decreased level of consciousness is sedation from drugs that have accumulated in the bloodstream over a period of days. Another cause is a poorly functioning or nonfunctioning graft with resulting liver failure and hepatic encephalopathy (HE). Central pontine myelinolysis, which may result from marked fluctuations in serum sodium levels and osmolality, is an uncommon cause of a patient not regaining consciousness posttransplant. Recipients who developed FHF, especially those with severe HE and evidence of cerebral edema preoperatively, invariably have a period of diminished consciousness posttransplant. Postoperative seizures usually occur de novo and tend to be of the generalized tonic-clonic variety. Causes can include electrolyte abnormalities, effects of drugs such as cyclosporine and tacrolimus, structural abnormalities such as intracranial hemorrhage and cerebral infarctions, and infectious processes such as encephalitis or brain abscesses.

The pulmonary system is one of the most common sites of complications posttransplant. Infectious and noninfectious pulmonary complications can occur in up to 75% of liver recipients. Noninfectious complications such as pulmonary edema, pleural effusion, atelectasis, and acute respiratory distress syndrome predominate during the first week, and generally manifest with respiratory distress and hypoxemia. The lungs are a very common site of posttransplant infections, which predominate after the first posttransplant week. Organisms may be bacterial, fungal, or viral, with different pathogens predominating at different times posttransplant. Early infections posttransplant generally are secondary to gram-negative organisms or fungi. Risk factors include mechanical ventilation, atelectasis, and aspiration.

Some degree of kidney dysfunction is very common posttransplant, affecting almost all liver recipients. About 10% develop kidney failure severe enough to require dialysis. Postoperative kidney problems that may have been present pretransplant are most commonly due to HRS or ATN. Usually, such problems will improve posttransplant, but recipients with severe pretransplant kidney dysfunction are at greater risk for persistent kidney impairment posttransplant, and some patients will require renal transplantation. Other causes of postoperative renal dysfunction include systemic hypovolemia, drug nephrotoxicity, or pre-existing kidney disease.

Infectious complications after liver transplant are common and can be devastating. Early infections (within the first month posttransplant) usually are related to surgical complications, initial graft function, or pre-existing comorbid conditions. Risk factors include prolonged surgery, large-volume blood transfusions, primary nonfunction requiring a retransplant, and reoperations for bleeding or bile leaks. The most common early infections are intra-abdominal and wound infections. Intra-abdominal infections should always lead the surgeon to consider the possibility of a bile leak. If an intra-abdominal infection is suspected, a CT scan should be performed, with aspiration and culture of any fluid collections that are identified. The biliary tree should be evaluated to exclude the presence of a bile leak. Patients with FHF are at high risk for fungal infections, usually secondary to *Candida* or *Aspergillus* species. Common sites include the abdomen, lungs, and central nervous system.

Late postoperative infections (generally occurring after the first month posttransplant) are usually a reflection of the

recipient's overall immunosuppressed state. Immunosuppressive drugs depress cell-mediated immunity, leading to opportunistic infections with viral, fungal, and parasitic pathogens. The risk increases with the level and length of immunosuppression, especially when acute rejection episodes are treated with bolus high-dose steroids or antilymphocyte agents. Viral infections generally are not seen until after the first month posttransplant. CMV is the most common pathogen involved. Its presentation ranges from asymptomatic infection to tissue-invasive disease. Epstein-Barr virus (EBV), another member of the herpesvirus family, also may be seen posttransplant. A wide spectrum of clinical presentations is possible, including an asymptomatic rise in antibody titers, a mononucleosis syndrome, hepatitis, and posttransplant lymphoproliferative disorder (PTLD). The most severe form of infection, PTLD can present as a localized tumor of the lymph nodes or GI tract, or rarely as a rapidly progressive, diffuse, often fatal lymphomatous infiltration.

Other aspects of postoperative care, especially in the later posttransplant period, involve careful monitoring of the recipient for any evidence of graft rejection, complications related to immunosuppression, and recurrence of the original disease.[74] After the recipient is discharged from the hospital, use of routine blood tests, including liver function tests, are important to monitor for acute rejection. The incidence of acute rejection is now about 20 to 30%; most episodes are asymptomatic and occur relatively early posttransplant. Most commonly, the serum bilirubin or transaminase levels are elevated. A percutaneous liver biopsy is then performed to confirm the diagnosis. Treatment is with high-dose corticosteroids; however, if there is no significant response, antilymphocyte therapy should be initiated. Mild acute rejection episodes often can be treated simply by temporarily increasing the baseline immunosuppression. This is especially useful in hepatitis C–positive patients in whom bolus immunosuppression represents a risk factor for recurrence of disease.

Immunosuppressive drugs are important to prevent rejection, but they are associated with a host of potential complications that recipients should be regularly evaluated for, including nephrotoxicity (especially prevalent with use of calcineurin inhibitors), cardiovascular and metabolic complications (such as hypertension, hyperlipidemia, diabetes, osteoporosis, and obesity), and malignancy (often related to long-term suppression of the immune system).

Disease recurrence is a significantly more important problem after liver transplants than with other solid organ transplants. Recurrence of hepatitis C is almost universal after transplants for this condition. Fortunately, only a minority of recipients experience aggressive recurrence leading to cirrhosis and liver failure. Ribavirin and α-interferon therapy should be considered in recipients with evidence of significant recurrence, as indicated by liver biopsy findings. Recurrence of hepatitis B has been significantly decreased by the routine use of hepatitis B immune globulin and the antiviral agent lamivudine posttransplant, but recurrence may still be seen with resistant viral strains. Other diseases that may recur posttransplant are PSC, primary hepatic malignancy, and autoimmune hepatitis.

Pediatric Liver Transplants

Liver transplants have become a well-established procedure to treat liver failure in pediatric patients. As a result of refinements in surgical technique, the advent of new immunosuppressive agents, and improvements in critical care, patient survival at 1 year has improved from 20% in the 1970s to 90% currently. In several ways, liver transplants for pediatric patients are quite similar to those for adults; however, several features make pediatric patients unique.

The clinical indications for a pediatric liver transplant are similar to those already mentioned for adults. Endpoints that require a transplant include evidence of portal hypertension as manifested by variceal bleeding and ascites, significant jaundice, intractable pruritus, encephalopathy, failing synthetic function (e.g., hypoalbuminemia or coagulopathy), poor quality of life, and failure to thrive (as manifested by poor weight gain or poor height increase).

Biliary atresia is the most common indication for a pediatric liver transplant. The incidence of biliary atresia is about one in 10,000 infant births. Once the diagnosis is established, a portoenterostomy, or Kasai procedure, is indicated to drain microscopic ducts within the porta hepatis. Successful bile flow can be achieved in 40 to 60% of patients whose Kasai procedure takes place early in their life. However, even with a Kasai procedure, 75% of children with biliary atresia eventually require a liver transplant because of progressive cholestasis followed by cirrhosis. Other cholestatic disorders that may eventually require a transplant include sclerosing cholangitis, familial cholestasis syndromes, and paucity of intrahepatic bile ducts (as seen with Alagille syndrome).

Metabolic disorders probably account for the next largest group of disorders that may require a liver transplant. Such disorders may directly result in liver failure or may have mainly extrahepatic manifestations. Alpha1-antitrypsin deficiency is the most common metabolic disorder that may require a liver transplant. Such patients may present with jaundice in the neonatal period, but this usually resolves. Subsequently, they may present in late childhood or early adolescence with cirrhosis and portal hypertension. Another metabolic disorder resulting in liver failure is tyrosinemia, a hereditary disorder characterized by deficiency of an enzyme that degrades the metabolic products of tyrosine, resulting in cirrhosis and a greatly increased risk for HCC. Still another is Wilson's disease, an autosomal recessive disorder characterized by copper accumulation in the liver, central nervous system, kidneys, eyes, and other organs, that may present as fulminant, subfulminant, or chronic liver failure. Metabolic disorders that do not affect liver function, but are treatable by a liver transplant, include urea cycle defects, most commonly ornithine transcarbamoylase deficiency (which may result in profound neurologic damage if not corrected early). Primary oxalosis, which results in kidney failure due to hyperoxaluria, can be treated by a kidney transplant to correct the kidney failure and by a liver transplant to correct the enzymatic defect so renal failure does not recur.

FHF may be seen in children from similar causes as seen in adults. Of note, younger children (<10 years old) with FHF have a poor prognosis for spontaneous recovery of liver function without a transplant. Other conditions that may require a transplant include chronic hepatitis (usually due to autoimmune or viral causes), and malignancy (most commonly a hepatoblastoma).

The surgical procedure for children does not differ significantly from that used in adults. The recipient's size is a more important variable in pediatric transplants, and it has an impact on both the donor and the recipient operations. For pediatric patients (especially infants and small children), the chance of finding a size-matched graft from a deceased donor may be very small, as the vast majority of such donors are adults. With adult grafts for pediatric patients, options include reduced-size liver transplants, in which a portion of the liver, such as the right lobe or extended right lobe, is resected and discarded; split-liver transplants in which a whole liver is divided into two functional grafts; and living-donor liver transplants in which a portion, usually the left lateral segment, is resected from a living donor. Graft implantation may be more demanding in pediatric patients, given the small caliber and delicate nature of the vessels. Use of VVB usually is not technically possible because of the small size of the vessels. For that reason, and given the increasing use of partial transplants, vena cava–sparing procedures are generally performed in children.

Surgical complications, especially those related to the vascular anastomoses, tend to be more frequent in pediatric recipients. HAT is three to four times more common in children. Factors associated with this increased risk include small recipient weight (less than 10 kg), use of just the left lateral segment (rather than the whole liver), and complex arterial reconstructions.

Patient survival rates have improved dramatically for pediatric liver recipients since the early 1990s. Most centers now report

patient survival of close to 90% at 1 year posttransplant. Even for small recipients, patient survival rates at 1 year are 80 to 85%. Also, pediatric recipients enjoy close to normal growth and development posttransplant. Usually, growth accelerates immediately posttransplant.

Results

Patient and graft survival rates after liver transplants have improved significantly since the mid-1990s, with most centers now reporting graft survival rates of 85 to 90% at 1 year. The main factors affecting short-term (within the first year posttransplant) patient and graft survival are the medical condition of the patient at the time of transplant and the development of early postoperative surgical complications. Severely debilitated patients with numerous comorbid conditions such as kidney dysfunction, coagulopathy, and malnutrition, have a significantly higher risk of early posttransplant mortality. Such patients are more likely to develop surgical and medical complications (especially infections) and are unable to tolerate them. The U.S. data show that for 2006, patient survival at 1 year after deceased-donor liver transplant was 87%, while graft survival was 82%.

Long-term survival rates (after the first year posttransplant) depend more on the cause of the underlying liver disease and on the presence or absence in the recipient of risk factors for other medical problems (especially cardiovascular disease). Generally, from 1 to 10 years posttransplant, survival curves decline slowly. Roughly half of the deaths in this time period are due to events not related to the underlying liver disease (e.g., myocardial infarctions, cerebrovascular accidents, and trauma). The other half of the deaths, however, are related to complications either of the underlying liver disease (e.g., recurrence) or of immunosuppression (e.g., infection or malignancy).

The original cause of liver failure has an impact on long-term survival rates as well. PBC in adults and biliary atresia in children generally are associated with a better long-term outcome, because recurrence of these diseases in the transplanted liver is rare. However, recipients with HCC or hepatitis C usually have poorer long-term outcomes, because these diseases often recur posttransplant.

INTESTINAL TRANSPLANTATION

Intestinal transplants have been performed in the laboratory for years. The first human intestinal transplant was performed in 1966, but it remained essentially an experimental procedure, producing dismal results well into the 1980s. Newer immunosuppressive drugs have played a significant role in the success with the procedure since the mid-1990s. However, intestinal transplants remain the least frequently performed of all transplants, with the highest rejection rates and the lowest graft survival rates.

There are several reasons why the number of intestinal transplants has not increased dramatically. As with kidney failure patients, a medical alternative exists for patients with intestinal failure, namely, long-term total parenteral nutrition (TPN). Unlike kidney failure patients, however, patients with intestinal failure have no survival advantage with a transplant vs. medical therapy. Immunologically, the small intestine is the most difficult organ to transplant. It is populated with highly immunocompetent cells, perhaps explaining the reason for the high rejection rates and the need for higher levels of immunosuppression. Moreover, monitoring for rejection in intestinal transplant recipients is difficult, as there is no good blood or urine laboratory test to indicate it. Lastly, the intestinal lumen is filled with potential infective pathogens that can gain access to the recipient's circulation if there is any breakdown of the mucosal barrier (which can occur during an acute rejection episode).

Preoperative Evaluation

Currently an intestinal transplant is indicated for irreversible intestinal failure that is not successfully managed by TPN (because of malnutrition and failure to thrive) or that has life-threatening complications (e.g., hepatic dysfunction, repeated episodes of sepsis secondary to central access, loss of central venous access sites).[75] Currently, patients who are stable while receiving TPN without such complications generally are not considered to be suitable transplant candidates because their estimated annual survival rate is higher with TPN.

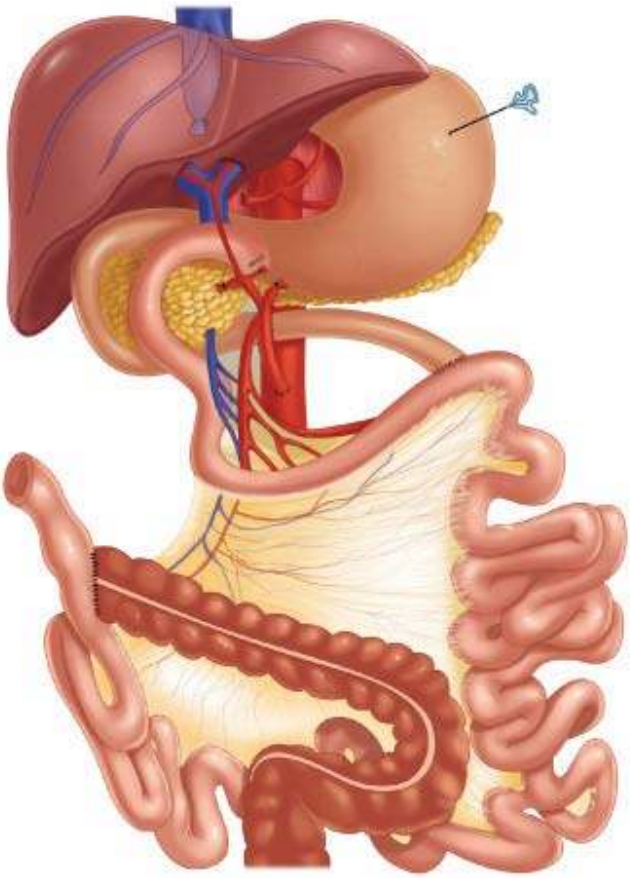
The causes of intestinal failure are different in adult than in pediatric patients. Most commonly, though, the underlying disease results in extensive resection of the small bowel with resultant short bowel syndrome.[76] The development of short bowel syndrome depends not only on the length of bowel resected, but also on the location of the resection, on the presence or absence of the ileocecal valve, and on the presence or absence of the colon. As a rough guideline, most patients can tolerate resection of 50% of their intestine with subsequent adaptation, avoiding the need for long-term parenteral nutritional support. Loss of greater than 75% of the intestine, however, usually necessitates some type of parenteral nutritional support. The most common causes of intestinal failure in children are necrotizing enterocolitis, gastroschisis, and volvulus. In adults, Crohn's disease, massive resection of ischemic bowel due to mesenteric vascular thrombosis, and trauma are the most common causes.

The pretransplant evaluation does not differ greatly from that for other transplants. Absolute contraindications such as malignancy and active infection must be ruled out, and hepatic function should be evaluated carefully. If there is evidence of significant liver dysfunction and cirrhosis, a combined liver and intestinal transplant is indicated. The serologic status of the potential recipient also should be evaluated carefully—especially regarding CMV status. Transplant candidates who are CMV-seronegative should not receive an organ from a donor who is seropositive, because of a very high incidence of highly morbid and occasionally lethal invasive CMV disease posttransplant in such recipients.

Surgical Procedure

The operative procedure varies, depending on whether or not a liver transplant also is performed.[77,78] In the case of an isolated intestinal transplant, the graft may be from a living or deceased donor. With a living donor, about 200 cm of the distal small bowel is used; inflow to the graft is via the ileocolic artery, and outflow via the ileocolic vein. With a deceased donor, the graft is based on the superior mesenteric artery for inflow and on the superior mesenteric vein for outflow. For a combined liver and intestinal transplant, the graft usually is procured intact with an aortic conduit that contains both the celiac and superior mesenteric arteries. The common bile duct can be maintained intact in the hepatoduodenal ligament along with the first part of the duodenum and a small rim of the head of the pancreas (Fig. 11-33). Doing so avoids a biliary reconstruction in the recipient.

Fig. 11-33.



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Combined liver, pancreas, and intestine transplant.

The recipient operation varies, depending on the graft being implanted. Generally, arterial inflow to the graft is achieved using the recipient's infrarenal aorta to perform an end-to-side anastomosis. Venous drainage of the graft can be performed to the systemic or portal circulation. Systemic drainage will lead to certain metabolic abnormalities, but there is no firm evidence to suggest that such abnormalities are of any obvious detriment to the recipient. GI continuity can be achieved by a number of different methods. A stoma is useful for ready endoscopic access to the transplanted bowel to perform a biopsy, which is the only reliable method to monitor for and diagnose acute rejection.

Postoperative Care

The early posttransplant care for intestinal transplant patients is in many ways similar to that of other transplant recipients. Initial care should take place in an ICU so that fluid, electrolytes, and blood product replacement can be carefully monitored. Broad-spectrum antibiotics are routinely administered, given the high risk for infectious complications.

A number of different immunosuppressive protocols have been described. Many involve some form of induction therapy, followed by tacrolimus-based maintenance immunosuppression. Regardless of the protocol, intestinal transplants clearly have a high risk of rejection. Therefore, careful monitoring for rejection is imperative and involves endoscopy with biopsy of the graft mucosa. Acute rejection episodes often are associated with infections. Rejection results in damage to the intestinal mucosa, leading to impaired barrier function and bacterial translocation. Therefore, advanced rejection can be very difficult to treat as concurrent infection invariably is present.

Short-term results after intestinal transplantation have improved dramatically, mainly due to improvements in surgical technique and in immunosuppression.[79,80] Nonetheless, intestinal transplants still are associated with a high complication rate. Potential complications include enteric leaks with generalized peritonitis or localized intra-abdominal abscesses, graft thrombosis, respiratory infections, and life-threatening hemorrhage. Long-term results also have improved, but remain inferior to other types of abdominal transplants.

HEART AND LUNG TRANSPLANTATION

Heart transplantation is a well-established therapy for end-stage heart failure, and is performed in age groups from neonates to senior citizens.[81] About 3500 heart transplants are performed each year, with roughly 10% taking place in pediatric recipients. The major limitation, as with almost all other types of transplants, is the inability to meet the demand with sufficient numbers of suitable donor organs.

Lung transplantation is a newer field than heart transplantation, and far fewer lung transplants (about 1000) are performed each year. Results have improved since the early 1990s, mainly due to improvements in immunosuppression and refinements in surgical techniques, in particular with modification of the airway anastomosis.[82] A combined heart-lung transplant usually is reserved for patients who have pulmonary hypertension and obvious right-sided heart failure.[83]

Preoperative Evaluation

A heart transplant generally is indicated in the presence of end-stage heart failure. The most common cause is ischemic or dilated cardiomyopathy, followed by intractable angina, valvular disease, congenital heart disease, life-threatening recurrent ventricular arrhythmias, and isolated intracardiac tumors.

Contraindications to a heart transplant are similar to those for other types of transplants, including active malignancy or infection, numerous or advanced comorbid conditions, and obvious noncompliance with medical care recommendations. Specific to heart transplantation is the need to exclude the presence of severe, nonreversible pulmonary hypertension, which could cause acute right-sided heart failure posttransplant.

Isolated lung transplants are performed for a number of indications, including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, and pulmonary hypertension (without right-sided heart failure).[84–86] Patients with chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis generally are treated with a single-lung transplant; those with cystic fibrosis or pulmonary hypertension (without right-sided heart failure) usually require a bilateral single-lung transplant. Patients with pulmonary hypertension with significant right-sided heart failure, or those with Eisenmenger's syndrome, usually require a combined heart-lung transplant.

Surgical Procedure

DONOR SELECTION

As with other organ transplants, donor selection criteria are important to ensure posttransplant success. The vast majority of lung transplants are performed with organs from deceased donors. A small number of lung transplants have used living-donor organs; in such cases, two living donors each contribute a lobe of a lung, and both lobes are then implanted into the appropriate hemithorax of a single recipient.

Numerous tests can be done to try to assess the suitability of hearts and lungs from deceased donors. Ultimately, however, physical examination at the time of procurement is likely the best method. The blood group, height, and weight of the donor

must be compatible with the potential recipient. A heart donor should have a normal echocardiogram and must not currently require high doses of inotropes to maintain blood pressure. The presence of significant coronary artery disease can be excluded using coronary angiography if necessary.

Lung donor criteria usually are more restrictive than heart donor criteria, but have been liberalized over the past several years. The best tests of lung donor suitability are arterial blood gas analysis, chest roentgenogram, bronchoscopy, and physical examination of the lungs at the time of procurement. Bronchoscopy is especially important, and any findings of significant secretions or evidence of bacterial or fungal infection in the donor should preclude the recovery of the lungs.

RECIPIENT OPERATION

A heart transplant is an orthotopic procedure. Therefore the first step of the procedure for heart or heart-lung recipients is removal of their corresponding thoracic organs. The recipient's aorta and vena cava are cannulated, an aortic cross-clamp is applied, and the diseased heart is excised along the atrioventricular groove. The recipient is maintained on cardiopulmonary bypass during this time. The new heart is then placed in an orthotopic position, with anastomoses performed in the following order: left atrium, right atrium, pulmonary artery, and aorta. Several variations to the original technique have been described, such as performing the aortic anastomosis before the pulmonary artery anastomosis to allow reperfusion of the heart and to minimize the ischemic time. Another variation is to perform selective anastomoses of the inferior and superior vena cava (rather than just of the right atrium); doing so is believed to allow for better geometry of the right atrium and to decrease the incidence of posttransplant atrial arrhythmias.

In heart-lung transplants, the new organs are implanted en bloc. Right and left pneumonectomies are carried out, with isolation and division of the trachea just above the carina. Anastomoses are then performed between the donor and recipient trachea, right atrium, and aorta.

Single-lung transplants are performed through a standard posterolateral thoracotomy. The superior and inferior pulmonary veins, pulmonary artery, and main stem bronchus are dissected. The pulmonary artery is then clamped to assess the recipient's hemodynamic status; cardiopulmonary bypass is used if necessary, although most recipients do not require bypass support. The bronchus and appropriate vascular structures are then clamped and the pneumonectomy completed. The bronchial anastomosis is performed first, followed by the pulmonary arterial and left atrial anastomoses. A telescoped bronchial anastomosis reduces the incidence of complications, most notably leaks. A pedicle of vascularized omentum also can be wrapped around the anastomosis for further reinforcement. Bilateral single-lung transplants are performed in a similar fashion, each side sequentially.

Postoperative Care

The immediate postoperative care does not differ significantly from any other major cardiac or pulmonary procedure. However, heart or lung recipients are at greater risk for infections than their nontransplant counterparts, and require appropriate precautions and prophylaxis regimens. As with other transplant recipients, maintenance immunosuppressive therapy is started immediately posttransplant.

After heart or heart-lung transplants, cardiac output is sustained by establishing a heart rate of 90 to 110 beats per minute, using either temporary epicardial atrial pacing or low-dose isoproterenol. For recipients who may suffer transient right-sided heart failure, adequate preload is important. Use of an oximetric Swan-Ganz catheter can be helpful to monitor pulmonary artery pressure and measure cardiac output. Urine output and arterial blood gases must be carefully monitored. Hypotension and a low cardiac output usually respond to an infusion of volume and to minor adjustments in inotropic support.

Cardiac tamponade can occur in heart recipients. It should be suspected in those who become hypotensive with concurrent increases in CVP and whose mediastinal chest tube output decreases suddenly. Serious ventricular failure posttransplant is unusual and can be related to poor donor organ selection, poor graft preservation, long ischemic time, or rarely, hyperacute rejection. Inotropes and pulmonary vasodilators can be used to manage ventricular failure; if it seems likely that the graft will recover, an intra-aortic balloon pump or a ventricular assist device can be added. In the case of a very severe rejection episode, the only option is to list the recipient for a retransplant.

Lung or heart recipients are initially cared for in the ICU.[87] Attempts should be made to wean them early from the ventilator. Acute failure of a transplanted lung may be seen early posttransplant. Reasons include the inherent difficulty of lung preservation, unrecognized injury or trauma to the donor lung, and reperfusion edema. Lung graft failure can manifest as hypoxemia, infiltrates on radiographic examination, or copious secretions in the presence of reperfusion edema. Care of such recipients involves active diuresis and high levels of positive end-expiratory pressure to maintain small airway patency. They should be kept intubated as necessary and extubated as the acute injury resolves. The diagnosis of a failing lung graft should be made using transbronchial biopsy (to exclude the presence of rejection) and bronchoalveolar lavage (to exclude the presence of early infection). Extracorporeal membrane oxygenation can be used as a last resort to maintain function while a diagnosis is being established and appropriate therapy initiated.

Complications can be surgical or medical, and may occur early or late posttransplant. Many of the complications, especially those occurring late, are medical in nature and are similar to those seen after other types of transplants. Generally, they are related to the medications and to the immunosuppressed state. Examples include hypertension, hyperglycemia, osteoporosis, and malignancy. Certain complications, such as airway problems, are unique to lung and heart recipients. Rejection, both acute and chronic, can occur, but manifests in very different ways as compared with abdominal organ transplants.

Early attempts at lung transplantation were severely hampered by a high incidence of airway complications. This anastomosis is at high risk for problems because of the poor blood supply. However, increased experience and refinements in surgical technique have dramatically reduced airway complications. Nonetheless, about 10 to 15% of lung recipients develop some airway complication, often resulting in significant morbidity and occasional mortality. Airway complications can occur after heart-lung or lung transplants, but are much less common after heart-lung transplants because a good blood supply is maintained to the tracheal anastomosis. After solitary and double-lung transplants, the bronchial anastomosis is at much greater risk for partial dehiscence, airway stenosis, or both. Hypotension, poor lung preservation, rejection, and infection can compromise blood flow to the anastomoses. The result can be ischemic necrosis and poor healing of the airway, leading to partial or total dehiscence or chronic narrowing of the bronchus.

Postoperative surveillance of the bronchial anastomosis is important. In the operating room, bronchoscopy is performed to establish the baseline appearance of the anastomosis. Frequent routine bronchoscopy is useful to survey the anastomosis for early signs of dehiscence, as well as to monitor for rejection and infection. Dehiscence usually occurs within 3 to 6 weeks posttransplant. Early signs on bronchoscopy include abnormal appearance of the mucosa at the suture line, loosened sutures or knots within the airway, and herniation of tissue into the airway in case of an omental wrap. If the recipient is clinically stable and the area of dehiscence is small, conservative treatment with antibiotics and serial evaluation via bronchoscopy is appropriate. Development of a bronchopleural or bronchovascular fistula requires reoperation.

Chronic airway stenosis may develop after initial healing. It may be managed in a variety of ways, including repeated dilations of the airway with a rigid bronchoscope, use of a metallic stent, or laser photocoagulation to débride granulation tissue.

Lung or heart organ transplant recipients are susceptible to bacterial, fungal, and viral infections. Infections are particularly problematic in lung recipients, with as many as 15 to 20% likely to develop some type of significant infectious disease. Fungal infections due to *Candida* and *Aspergillus* are generally more serious than bacterial infections.[88] Most *Aspergillus* infections, which are caused by the inhalation of aerosolized fungal spores, generally occur within the first 3 months posttransplant. Among lung transplant recipients who have underlying cystic fibrosis, infections due to *Pseudomonas aeruginosa* are common. The most morbid viral infection is caused by CMV.

Rejection can be acute or chronic. Acute rejection tends to be characterized by the presence of an inflammatory infiltrate (mostly lymphocytes) in the organ parenchyma, and usually is seen early posttransplant. Chronic rejection tends to be a later phenomenon; it is characterized by obliteration of small vessels and fibrosis.[89,90] For both lung or heart recipients, rejection usually does not have clinical symptoms until the rejection episode is advanced. Therefore, routine monitoring with transbronchial biopsy (for lung recipients) and with endomyocardial biopsy (for heart recipients) is important for early diagnosis. For heart-lung recipients, rejection of the lungs may occur without rejection of the heart, so biopsy of both organs may be necessary.

Fortunately, most acute rejection episodes can be effectively reversed. Much more difficult to treat is the process of chronic rejection, which has been a major obstacle to long-term survival. In heart recipients, chronic rejection manifests as graft arteriosclerosis, which is seen in 30 to 40% of recipients by 3 years posttransplant, and in 40 to 60% of recipients by 5 years. In lung transplant recipients, chronic rejection manifests as bronchiolitis obliterans, characterized clinically by a decreased forced expiratory volume in 1 second and histologically by inflammation and fibrosis of small airways.

INFECTION AND MALIGNANCY

Immunosuppressive therapy has played an essential role in the success of clinical transplants. However, it is a double-edged sword, because suppression of the immune system prevents or decreases the risk of rejection while concomitantly predisposing the transplant recipient to a wide variety of complications, including infections and malignancies.[91] Infections in transplant recipients may be caused by so-called *opportunistic microbes*, organisms that would not be harmful to a normal, nonimmunosuppressed host, as well as more common pathogens.

Infections

Transplant recipients exhibit an increased risk for infectious complications posttransplant, which can lead to significant morbidity and mortality. Numerous risk factors include long-standing end-stage organ failure (which can lead to an immunosuppressed state even before any immunosuppressive drugs are begun), impaired tissue healing, and poor vascular flow due to coexisting illnesses such as diabetes. The transplant surgery itself, which may involve opening nonsterile viscera such as the bladder or bowel, and the posttransplant need for powerful immunosuppressive agents further increase the risk for infections.

The spectrum of possible infections in transplant recipients is wide. Infections may occur early or late posttransplant. They may be related directly to the surgical procedure, to some complication that develops afterward, or to the recipient's overall immunosuppressed state (i.e., opportunistic). Infections are classified by the type of pathogen involved into bacterial, viral, or fungal infections. However, more than one type of pathogen may be involved in several different types of infections (e.g., pneumonia may be caused by a viral, bacterial, or fungal pathogen). Moreover, a number of different pathogens may be involved in a single infection (e.g., an intra-abdominal abscess can be due to several different bacterial and fungal pathogens).

Infections also can be classified by the primary method of treatment into surgical or medical infections. Surgical infections require some surgical intervention as an integral part of their treatment. They generally occur soon after the transplant operation and usually are related directly to it, or to some complication occurring as a result of it. Surgical infections are less likely to be related to the recipient's overall immunosuppressed state, though obviously this plays some role. Typical examples of surgical infections include generalized peritonitis, intra-abdominal abscesses, and wound infections. In contrast, medical infections generally do not require an invasive intervention for treatment, but rather are primarily treated with antiviral, antibacterial, or antifungal agents. They tend to occur later posttransplant and usually are related to the recipient's overall immunosuppressive state. Typical examples of medical infections include those secondary to CMV, polyomavirus-induced nephropathy, pneumonias, and EBV-related problems.

Risk factors for posttransplant infections are classified into those present in the recipient pretransplant, those related to the donor, those related to the recipient intraoperatively, and those that occur posttransplant. Pretransplant latent infections can reactivate or worsen early posttransplant, once high-dose immunosuppression is initiated. Pretransplant immunity, or lack of immunity, to certain viral pathogens can be an especially important risk factor for posttransplant infections. For example, recipients seronegative for CMV or EBV have a high incidence of posttransplant infections with these viruses, especially if their donor was seropositive. The recipient's overall medical status may be a factor in posttransplant infections. Poor nutritional status, advanced peripheral vascular disease, frequent hospitalizations pretransplant, and recipient obesity are all well-described risk factors for posttransplant infectious complications, especially involving the wound. Donor factors may also play an important role. Although transmission of bacterial infections from the donor are uncommon, viruses such as CMV, EBV, hepatitis B or C, and HIV can certainly be transmitted to any recipient who has not had previous exposure to them.

Intraoperative risk factors for infections include a longer operative procedure with significant bleeding, prolonged cold and warm ischemia of the graft, and certain types of transplants (e.g., pancreas and intestinal transplants are associated with a significantly higher risk of infections vs. kidney transplants). Posttransplant risk factors for infection are generally related either to the development of posttransplant complications or to the level of immunosuppression. Leaks from anastomoses with spillage of contaminated fluid (e.g., bile, urine, and enteric contents) will lead to a localized and possibly generalized infection. The level of immunosuppression is an important risk factor posttransplant, especially for opportunistic infections. The higher the level of immunosuppression, the greater the risk. Long induction protocols involving powerful antilymphocyte agents or bolus antirejection treatment, particularly several treatments in sequence, have been clearly identified as risk factors for a variety of infections.

The most common surgical infections, especially in liver and pancreas transplant recipients, are intra-abdominal infections. They are also the most likely to be life threatening. They may range from diffuse peritonitis to localized abscesses. Their presentation, management, and clinical course will in part depend on their underlying cause, their location, and on the recipient's overall medical condition.

The incidence of intra-abdominal infections in transplant recipients has steadily decreased over time. Nonetheless, intra-abdominal infections continue to be a major problem. Among pancreas recipients, they are the second most common technical reason for graft loss (after vascular thrombosis). Leaks from anastomoses with spillage of contaminated fluid are probably the most significant risk factor for intra-abdominal infections. Other risk factors include increased donor age (especially in pancreas transplants), recipient obesity, donor obesity, and prolonged pretransplant dialysis, especially peritoneal dialysis.

The clinical presentation of intra-abdominal infections will depend on their severity and location. Generalized peritonitis usually is associated with some catastrophic event such as biliary disruption or graft duodenal leak with spillage of enteric contents or urine into the peritoneal cavity. It may also occur as a result of perforation of some other viscus, unrelated to the transplant (e.g., perforated gastric ulcer or perforated cecum). Generalized peritonitis is diagnosed clinically; the physical examination is the most helpful tool. Such patients appear ill, with tachycardia, elevated temperature, falling blood pressure, and diffuse tenderness with guarding on palpation of the abdomen, although immunosuppression may mask many of the usual signs and symptoms. A plain film or CT scan of the abdomen usually is not necessary, but may demonstrate free air. Treatment involves prompt return of the recipient to the operating room to determine the reason for the peritonitis; the next step often will depend on the degree of contamination.

Fortunately, most intra-abdominal infections do not fall into the generalized peritonitis category. Instead, most of them consist of localized fluid collections in and around the graft. Patients usually develop symptoms such as fever, nausea, vomiting, and abdominal distention, with localized pain and guarding over the region of the fluid collection. A CT scan with contrast is the best diagnostic tool in this clinical situation. In pancreas recipients, about one half of these localized abscesses are monomicrobial; common isolates include enterococcus, *Escherichia coli*, *Klebsiella*, and *Pseudomonas* species. The other one half of such abscesses tend to be polymicrobial, containing two or more bacteria or both bacterial and fungal species. The most common fungal species isolated is *C. albicans*, but recently *C. krusei* and *C. glabrata* have been increasing in incidence. Treatment of localized intra-abdominal infections involves adequate drainage and administration of appropriate antibacterial or antifungal agents. These infections often can be drained percutaneously under radiologic guidance, at least as an initial approach. However, if the infected fluid is not adequately drained or if the recipient does not improve clinically, a laparotomy should be performed to achieve adequate drainage of all infected fluid.

Medical infections posttransplant tend to be more varied compared to surgical infections, and can involve bacterial, viral, or fungal pathogens. Bacterial infections primarily occur in the first few weeks posttransplant. The major sites are the incisional wound, respiratory tract, urinary tract, and bloodstream. Administration of perioperative systemic antibiotics decreases the risk and incidence of some infections. Viral infections in transplant recipients often involve the herpesvirus group; CMV is clinically the most important.[92–94] CMV establishes latent infection in its host and persists throughout life, and infection has been correlated with the overall degree of immunosuppression. CMV infection usually occurred 4 to 12 weeks posttransplant or after treatment of rejection; with routine use of antiviral prophylaxis posttransplant, however, the peak incidence of the disease has been pushed out later to 3 to 6 months posttransplant. A wide spectrum of disease manifestations may be seen during CMV infection. The infection may be subclinical, or it may present with a mild flu-like syndrome. Leukopenia, myalgia, and malaise are usual. CMV may also present as tissue-invasive disease, resulting in interstitial pneumonitis, hepatitis, or GI ulcerations. CMV-seronegative recipients of organs from CMV-seropositive donors are at highest risk. The incidence of CMV disease is reduced by use of prophylactic ganciclovir for 12 weeks posttransplant. Symptomatic disease generally is treated with IV ganciclovir or oral valganciclovir, and reduction in immunosuppression if possible.

Fungal infections are most commonly caused by *Candida* species; *Aspergillus*, *Cryptococcus*, *Blastomyces*, *Mucor*, *Rhizopus*, and other species account for a much smaller percentage of fungal infections, but are more serious.[95] Among patients who develop invasive *Candida* or *Aspergillus* infections, the mortality rate usually exceeds 20%. The standard treatment of serious posttransplant fungal infections has been with amphotericin B, along with overall reduction in immunosuppression. However, newer antifungal agents that are less toxic are showing promise.

Malignancy

Transplant recipients are at increased risk for developing certain types of de novo malignancies, including nonmelanomatous skin cancers (three- to sevenfold increased risk), lymphoproliferative disease (two- to threefold increased risk), gynecologic and urologic cancers, and Kaposi's sarcoma. The risk ranges from 1% among renal allograft recipients to approximately 5 to 6% among recipients of small bowel and multivisceral transplants.[96]

SKIN CANCERS

The most common malignancies in transplant recipients are skin cancers.[97] They tend to be located on sun-exposed areas and are usually squamous or basal cell carcinomas. Often they are multiple and have an increased predilection to metastasize. Human papillomavirus DNA has been detected in these tumors, suggesting that immunosuppression may have a permissive effect on viral proliferation. Diagnosis and treatment are the same as for the general population. Patients are encouraged to use sunscreen liberally and avoid significant sun exposure.

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER

Lymphomas constitute the largest group of noncutaneous neoplasms in transplant recipients.[98–100] The vast majority (>95%) of these lymphomas consist of a spectrum of B-cell proliferation disorders associated with EBV, known collectively as *posttransplant lymphoproliferative disorder* (PTLD). Risk factors include a high degree of immunosuppression, anti–T-cell antibody therapy, and primary EBV infection posttransplant. A wide variety of clinical manifestations may be seen. Symptoms may be systemic and include fever, fatigue, weight loss, or progressive encephalopathy. Lymphadenopathy may be localized, diffuse, or absent. Intrathoracic PTLD may present with well-circumscribed pulmonary nodules, with or without mediastinal adenopathy. Abdominal pain, rectal bleeding, or bowel perforation may occur with intra-abdominal involvement. Allograft involvement may occur and cause organ dysfunction. Central nervous system involvement is much more common (~15 to 20%), as compared with lymphomas in the nontransplant patient population.

Diagnosis is confirmed by histologic examination of tissue specimens, including in situ DNA hybridization studies to detect the EBV genome. Treatment includes reduction of immunosuppression, surgical extirpative therapy, chemotherapy, and newer agents such as monoclonal antibodies targeted to B cells (anti-CD20 mAb), the latter limited to patients whose tumors express the CD20 cell surface marker. Often a combination of these modalities is used. Mortality can exceed 50% with aggressive tumors.

OTHER MALIGNANCIES

A variety of other malignancies occur with increased incidence in transplant recipients. Conventional treatment is appropriate for most malignancies posttransplant. Immunosuppression should be reduced, particularly if bone marrow suppressive chemotherapeutic agents are administered. However, allograft function should be maintained for those organs that are critical to survival, such as the heart, liver, and lung. For other types of transplants with alternative therapies to fall back on if necessary (e.g., hemodialysis for kidney transplants, exogenous insulin for pancreas or islet cell transplants, and TPN for intestinal transplants), the risks of ongoing immunosuppression must be weighed against the benefits of organ function compared to the alternative therapies.

THE FUTURE OF TRANSPLANTATION

Dramatic advances have been made in the field of transplantation since the late 1970s, but it remains fraught with problems. A major disadvantage is the need for long-term, indeed lifelong, immunosuppression. Associated with immunosuppression is an increased risk for malignancies and infections, as well as a host of other potential side effects not related to the immune

system. That is why tolerance, or the ability to maintain the allograft without the need for long-term immunosuppression, remains the goal for all transplant recipients. *Tolerance* is defined as a state of donor-specific hyporeactivity in the absence of immunosuppressive medications (i.e., the recipient's immune system does not attack the transplanted organ, but is intact and able to mount a response to an organ from a different donor). Many different therapeutic approaches have been tested to induce tolerance; however, none have yet shown significant promise.

Perhaps even greater than the problems of long-term immunosuppression is the significant discrepancy between the demand for, and the supply of, organs. The increase in the number of transplants being performed has not kept pace with the increase in the number of patients being placed on the waiting list. The result has been longer waiting times and sicker patients once the transplant finally takes place, if it does at all. Several methods have been proposed to increase the number of transplants being performed. The increasing use of living donors has led to an increase in the number of transplants. However, further increasing the living-donor pool by including higher-risk procedures and higher-risk donors will quickly reach a limit if donor morbidity and donor mortality increase. The use of expanded criteria donors, especially donation after cardiac death donors, has also contributed to a significant increase in the number of organs available. In the future, the use of xenografts may prove to be the solution to the organ shortage problem, but difficult immunologic hurdles remain. Mechanical devices may represent another solution and would also have the advantage of not requiring immunosuppression.[101,102] However, completely implantable, long-lasting biomechanical devices offer their own set of unique problems, which may be worse than those associated with long-term immunosuppression.

Xenotransplantation

Clinical xenotransplants (i.e., transplants of organs between different species) have offered great hope for solving the problem of the expanding waiting list, but the primary hurdle is the formidable immunologic barrier between species.[103] Other problems include the potential risk of transmission of infections (zoonoses) and the ethical problems involved with using animals for widespread human transplants.

It generally is accepted that successful xenotransplants for human beings would probably involve the use of the pig, which would likely be much more readily accepted by the general population than, for example, a primate donor.[104] Pigs also would be easier to raise on a large-scale basis and likely would be less expensive to manage, compared to primates.

The immunologic barrier in pig-to-human xenotransplants is complex, but generally involves three components. The first is hyperacute rejection (HAR), which is mediated by the presence of natural xenoantibodies in humans. These antibodies bind to antigens found mainly on vascular endothelial cells of porcine donor organs, leading to complement activation, intravascular coagulation, and rapid graft ischemia soon after the transplant. After HAR, the next barrier is delayed xenograft rejection, which occurs later than HAR, but is likely still mediated by the presence of xenoreactive antibodies combined with platelet aggregation and activation of the coagulation cascade. The third barrier is a process similar to classic T-cell–mediated acute rejection in allografts. Many different options are being tested to overcome these barriers, including the genetic engineering of pigs to express human genes, use of agents to inhibit platelet aggregation and complement activation, and administration of powerful immunosuppressive drugs.[105]

Besides the immunologic issues, the potential infectious risks also need to be more clearly defined.[106] The risks associated with the transmission of porcine viruses into human transplant recipients and then potentially into the entire human population are not fully known and must be studied in detail.

Other Therapies

Xenotransplantation is not the only therapeutic approach currently being investigated for organ replacement therapy. Other possible approaches include cellular transplants, organogenesis, and artificial and bioartificial devices.[107,108]

Cellular transplants involve the injection of cells that have the potential to replace cells in an organ that has been damaged by disease, thereby augmenting the function of that organ. An example of a cellular transplant would be the injection of stem cells or isolated hepatocytes into a failing liver. Such a procedure would most likely work best in patients with enzymatic or genetic defects. For patients with well-established chronic liver disease with cirrhosis, a cellular transplant would have limitations, because the underlying problem of portal hypertension would not be addressed. Another example of a cellular transplant would be the transplantation of stem cells or primitive muscle cells into a damaged heart. After healing, the cells could potentially function as cardiac muscle cells, thereby augmenting cardiac function. Considerable research already has been done in this area. Cellular transplants show promise, but overall have several limitations. Primary is the inability of cellular transplants to improve the function of structurally complex organs such as the kidney, which consists of several different cell types, all arranged in a specific pattern to allow for proper function.

One potential approach to overcoming this limitation is organogenesis, which essentially involves growing organs de novo from primitive cells or stem cells. However, this form of therapy is still in the theoretical phase and is unlikely to be a clinically viable option in the near future.

Much further along in the clinical realm of organ replacement therapies is the use of bioartificial and artificial mechanical devices. Considerable investigative work has been undertaken to develop a bioreactor using artificial elements and hepatocytes to treat liver failure as a bridge to liver transplantation. However, consistent results have yet to be achieved in the clinical setting. The heart model is in the most advanced stage of development. Various implantable assist devices are already in routine clinical use. Currently, these are usually temporary devices that serve as a bridge to a transplant. Several different models of a totally implantable artificial heart are also currently under development and have been used occasionally. Thromboembolic complications and infections remain the primary problems with these devices.

The future of transplantation is certainly exciting. Continued active research will focus on newer immunosuppressive drugs, tolerance, xenotransplants, cellular transplants, and artificial devices. Most transplant centers in the next decade will probably offer some combination of these new therapies to potential transplant recipients.

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KEY POINTS

1. Patient harm due to medical mistakes can be catastrophic and, in some cases, result in high-profile consequences not only for the patient, but also for the surgeon and institution.

2. Patient safety is a science that promotes the use of evidence-based medicine and commonsense improvements in an attempt to minimize the impact of human error on the routine delivery of services.

3. The structure-process-outcome framework within the context of an organization's culture helps to clarify how risks and hazards embedded within the organization's structure may potentially lead to error and injure or harm patients.

4. Poor communication contributes to approximately 70% of the sentinel events reported to the Joint Commission on Accreditation of Healthcare Organizations.

5. Operating room briefings are team discussions of critical issues and potential hazards that can improve the safety of the operation and have been shown to improve operating room culture and decrease operating room delays.

6. National Quality Forum surgical "never events" include retained surgical items, wrong-site surgery, and death on the day of surgery of a normal healthy patient (ASA Class 1).

7. Patient rapport is the most important determinant of malpractice claims against a surgeon.

BACKGROUND

Patient harm due to medical mistakes can be catastrophic and, in some cases, result in high-profile consequences not only for the patient, but also for the surgeon and institution. A single error can even destroy a surgeon's career. Yet, medical mistakes are common to every physician, and errors themselves are unavoidably linked to human nature. Only recently has the science of the delivery of health care matured to recognize the contribution of vulnerable hospital systems in addition to individual responsibility in causing error.

Patient safety is a science that promotes the use of evidence-based medicine and commonsense improvements in an attempt to minimize the impact of human error on the routine delivery of services. Wrong-site/wrong-procedure surgeries, retained sponges, unchecked blood transfusions, mismatched organ transplants, and overlooked allergies are all examples of potentially catastrophic events that can be prevented by implementing safer hospital systems. This chapter provides an overview of the modern day field of patient safety by reviewing key measures of safety and quality, components of culture, interventions and tools, and risk management strategies in surgery.

THE SCIENCE OF PATIENT SAFETY

Medicine is considered a high-risk system with a high error rate, but these two characteristics are not always correlated. Other high-risk industries have managed to maintain an impeccably low error rate. For example, one of the highest risk

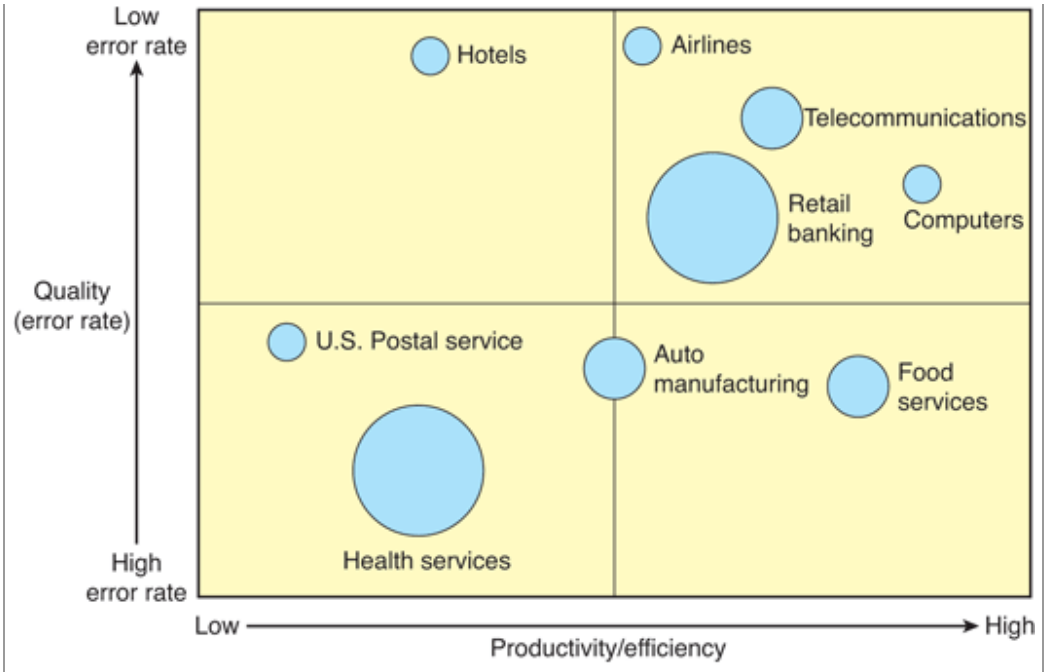
systems in existence today, the U.S. Navy's nuclear submarine program, has an unmatched safety record. The nuclear fleet has achieved this safety record despite the large number of plants in operation, the added complexity of the reactors being mobile instead of fixed in one location, the secrecy of its operations, and the hazards of engaging in demanding exercises with both friendly and hostile surface ships, submarines, and aircraft.

Much of the credit is due to the culture of the nuclear submarine program, with its insistence on individual ownership, responsibility, attention to detail, professionalism, moral integrity, and mutual respect. These characteristics have created the cultural context necessary for high quality communications under high-risk and high stress conditions. Each reactor operator is aware of what is going on at all times and is responsible for understanding the implications and possible consequences of any action. Communication flows freely between crewmen and officers, and information about any mistakes that occur are dispersed rapidly through the entire system so that other workers can learn how to prevent similar mistakes in the future.[1]

High Reliability Organizations

The nuclear submarine program is an excellent example of an organization that has achieved the distinction of being considered a "high reliability organization." High reliability organization theory, which was developed by a group of social scientists at the University of California at Berkeley, recognizes that there are certain high-risk industries and organizations that have achieved very low accident and error rates compared to what would be expected given the inherent risks involved in their daily operations (Fig. 12-1). Other examples of industries or organizations that are regarded as having achieved high reliability status include aircraft carrier flight decks, nuclear power plants, and the Federal Aviation Administration's air traffic control system. In fact, one reason why nuclear power plants have such an excellent reliability record may be that their operators are often former naval submarine officers whose previous experience and training within one highly reliable organization are easily transferable to other organizations.[1]

Fig. 12-1.



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Cross-industry comparison of size, productivity, and efficiency.

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One of the assumptions underlying the science of high reliability organizations is the following observation made by Weick in 1987: Humans who operate and manage complex systems are themselves not sufficiently complex to sense and anticipate the problems generated by the system.[2] This introduces another important idea undergirding the science of patient safety: the concept of normal accident theory. Instead of attributing accidents to individual error, this theory states that accidents are intrinsic to high-volume activities and even inevitable in some settings; that is, they are "normal" and should be expected to occur. Accidents should not be used merely to identify and punish the person at fault. As Reason states, even the "best people can make the worst errors as a result of latent conditions."[2]

Health care, naval submarines, airlines, and other industries can all be classified as "high-risk systems," which was defined by Perrow in 1984.[1] High-risk systems:

- Have the potential to create a catastrophe, loosely defined as an event leading to loss of human or animal life, despoiling of the environment, or some other situation that gives rise to the sense of "dread"
- Are complex, in that they have large numbers of highly interdependent subsystems with many possible combinations that are nonlinear and poorly understood
- Are tightly coupled, so that any perturbation in the system is transmitted rapidly between subsystems with little attenuation.

However, high reliability organization theory suggests that proper oversight of people, processes, and technology can handle complex and hazardous activities and keep error rates acceptably low.[2] Studies of multiple high reliability organizations have revealed that they share the following common characteristics[2]:

- People are supportive of one another.
- People trust one another.
- People have friendly, open relationships emphasizing credibility and attentiveness.

- The work environment is resilient and emphasizes creativity and goal achievement, providing strong feelings of credibility and personal trust.

Developing these characteristics is an important step toward achieving a low error rate in any organization.

The Institute of Medicine Report

Although health care as a whole can be considered a high-risk system, the industry is far from joining the ranks of nuclear submarines and the Federal Aviation Administration as a high reliability organization. This fact was brought to light in the Institute of Medicine's report "To Err Is Human: Building a Safer Health System," which was published in 2000.[3] A landmark document in raising awareness of the magnitude of the problem of medical mistakes, the report is the most frequently cited document in the medical literature in recent years.[4] The Institute of Medicine (IOM) report shocked the health care community by concluding that between 44,000 and 98,000 deaths and over 1 million injuries occurred each year in American hospitals due to medical error. In fact, the number of deaths attributed to medical error is the aviation equivalent of one jumbo jet crash per day. As this report was disseminated, awareness about medical errors increased, and physicians and other health providers began speaking openly about mistakes and the difficulties they face when dealing with them.

The IOM report brought much-needed attention to the field of patient safety. In addition, it standardized the language used to describe errors in medicine, defining important terms for future research and quality improvement (Table 12-1). Following the publication of the IOM report, interest in patient safety research and programs increased exponentially. In an effort to improve patient safety, health services researchers began to collaborate with scientists from other disciplines, such as human factors engineering, psychology, and informatics to develop innovative solutions to longstanding safety problems. The discussion around patient safety also became more personalized by highlighting the stories of individual patients who had died from medical errors. Most importantly, the report transformed the conversation about patient safety from blaming individuals for errors to improving the systems that allow them to take place (Case 12-1).[5]

Table 12-1 Types of Medical Error
Adverse event
• Injury caused by medical management rather than the underlying condition of the patient
• Prolongs hospitalization, produces a disability at discharge, or both
• Classified as preventable or unpreventable
Negligence
• Care that falls below a recognized standard of care
• Standard of care is considered to be care a reasonable physician of similar knowledge, training, and experience would use in similar circumstances
Near miss
• An error that does not result in patient harm
• Analysis of near misses provides the opportunity to identify and remedy system failures before the occurrence of harm
Sentinel event
• An unexpected occurrence involving death or serious physical or psychological injury
• The injury involves loss of limb or function
• This type of event requires immediate investigation and response
• Other examples

• Hemolytic transfusion reaction involving administration of blood or blood products having major blood group incompatibilities
• Wrong-site, wrong-procedure, or wrong-patient surgery
• A medication error or other treatment-related error resulting in death
• Unintentional retention of a foreign body in a patient after surgery

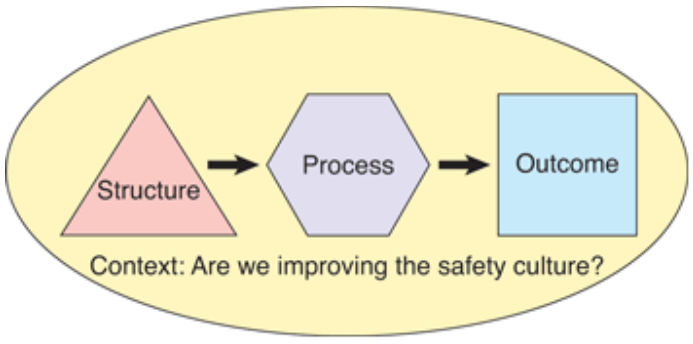
From Woreta et al,[45] with permission.

Case 12-1 Systems Change Resulting from Medical Error
Libby Zion was an 18-year-old woman who died after being admitted to the New York Hospital with fever and agitation on the evening of October 4, 1984. Her father, Sidney Zion, a lawyer and columnist for the *N.Y. Daily News*, was convinced that his daughter's death was due to inadequate staffing and overworked physicians at the hospital and was determined to bring about changes to prevent other patients from suffering as a result of the teaching hospital system. Due to his efforts to publicize the circumstances surrounding his daughter's death, Manhattan District Attorney Robert Morgenthau agreed to let a grand jury consider murder charges. Although the hospital was not indicted, in May 1986, a grand jury issued a report strongly criticizing "the supervision of interns and junior residents at a hospital in NY County."
As a result, New York State Health Commissioner David Axelrod convened a panel of experts headed by Bertrand M. Bell, a primary care physician at Albert Einstein College of Medicine who had long been critical of the lack of supervision of physicians-in-training, to evaluate the training and supervision of doctors in New York State. The Bell Commission recommended that residents work no more than 80 hours per week and no more than 24 consecutive hours per shift, and that a senior physician needed to be physically present in the hospital at all times. These recommendations were adopted by New York State in 1989. In 2003, the Accreditation Council on Graduate Medical Education followed by mandating that all residency training programs adhere to the reduced work hour schedule.

The Conceptual Model

The Donabedian model of measuring quality identifies three main types of improvements: changes to structure, process, and outcome (Fig. 12-2). *Structure* refers to the physical and organizational tools, equipment, and policies that improve safety. Structural measures ask, "Do the right tools, equipment, and policies exist?" *Process* is the application of these tools, equipment, and policies/procedures to patients (good practices and evidence-based medicine). Process measures ask, "Are the right tools, policies, and equipment being used?" *Outcome* is the result on patients. Outcome measures ask, "How often are patients harmed?" In this model, structure (how care is organized) plus process (what we do) influences patient outcomes (the results achieved).[7]

Fig. 12-2.



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Donebedian model for measuring quality.

(From Makary et al,[6] with permission.)

The structure, process, and outcome components of quality measurement all occur within the context of an organization's overall *culture*. The local culture impacts all aspects of the delivery of care because it affects how front-line personnel understand and deliver safe patient care. In fact, culture (collective attitudes and beliefs of caregivers) is increasingly being recognized to be the fourth measurable component to the structure-process-outcome model. This recent recognition is based on growing evidence that local culture is linked to a variety of important clinical outcomes.[7] This structure-process-outcome framework within the context of an organization's culture helps to clarify how risks and hazards embedded within the organization's structure may potentially lead to error and injure or harm patients. For any new patient safety initiative to be deemed successful, any change in structure or process must lead to a corresponding positive change in patient outcomes.[8]

CREATING A CULTURE OF SAFETY

Culture is to an organization what personality is to the individual—a hidden, yet unifying theme that provides meaning, direction, and mobilization.[2] Organizations with effective safety cultures share a constant commitment to safety as a top-level priority, a commitment that permeates the entire organization. These organizations frequently share the following characteristics[9] :

- An acknowledgment of the high-risk, error-prone nature of an organization's activities
- A nonpunitive environment where individuals are able to report errors or close calls without fear of punishment or retaliation
- An expectation of collaboration across ranks to seek solutions to vulnerabilities
- A willingness on the part of the organization to direct resources to address safety concerns

Traditional surgical culture stands almost in direct opposition to the values upheld by organizations with effective safety cultures for several reasons. Surgeons are less likely to acknowledge their propensity to make mistakes or to admit these mistakes to others.[10] Surgeons tend to minimize the effects of stress on their ability to make decisions, and often claim that their decision making is equally effective in emergency and normal situations.[11] The surgical culture, especially in the operating room (OR), is traditionally rife with hierarchy. Intimidation of other OR personal by surgeons was historically accepted as the norm. This can prevent nurses and other OR staff from pointing out potential errors or mistakes by surgeons. In the intensive care unit (ICU), when compared to physicians, nurses reported that they had more difficulty speaking up, disagreements were not appropriately resolved, and decisions were made without adequate input.[12] In addition, the field of medicine strongly values professional autonomy, which frequently promotes individualism over cooperation, often to the detriment of patient care.[13] Finally, patient safety, although often viewed as important, is seldom promoted from an organizational priority to an organizational value. Organizations often do not feel the need to devote resources to overhauling their patient safety systems as long as they perceive their existing processes to be adequate. It often takes a high-profile sentinel event to motivate leaders to commit the necessary time and resources to improving patient safety within their organization, as exemplified by the Dana-Farber Institute in the aftermath of Betsy Lehman's death (Case 12-2).

Case 12-2 High-Profile Sentinel Event

On December 3, 1994, Betsy Lehman, a *Boston Globe* health columnist, died as a result of receiving four times the intended dose of chemotherapy for breast cancer. Remarkably, 2 days later, Maureen Bateman, a teacher being treated for cancer, also received a chemotherapy overdose and suffered irreversible heart damage. After investigating the medication

errors, the prescribing doctor, three druggists, and 15 nurses were disciplined by state regulators. The hospital was sued by the two women's families and by one of the doctors disciplined.
As a result of this widely publicized event, the Dana-Farber Cancer Institute invested more than $11 million to overhaul their safety programs, including providing new training for their employees and giving doctors more time to meet with patients. The hospital adopted a full disclosure policy so that patients would be informed anytime a mistake had affected their care. Dana-Farber also started a patient committee providing advice and feedback on ways to improve care at the hospital.

Assessing an Organization's Safety Culture

Efforts to foster cultural change within an organization with regard to patient safety have been limited by the inability to measure the impact of any given intervention. However, previous studies have shown that employee attitudes about culture have been associated with error reduction behaviors in aviation and with patient outcomes in ICUs. The Safety Attitudes Questionnaire (SAQ) is a validated survey instrument that can be used to measure culture in a health care setting.[6] Adapted from two safety tools used in aviation, the Flight Management Attitudes Questionnaire and its predecessor, the Cockpit Management Attitudes Questionnaire, the SAQ consists of a series of questions measuring six domains: teamwork climate, safety climate, job satisfaction, perception of management, stress recognition, and working conditions.

The safety climate scale portion of the questionnaire consists of the following seven items:

- I am encouraged by my colleagues to report any patient safety concerns I may have.
- The culture in this clinical area makes it easy to learn from the mistakes of others.
- Medical errors are handled appropriately in this clinical area.
- I know the proper channels to direct questions regarding patient safety in this clinical area.
- I receive appropriate feedback about my performance.
- I would feel safe being treated here as a patient.
- In this clinical area, it is difficult to discuss mistakes.

Although perceptions of teamwork climate can differ as a function of one's role in the OR, perceptions of safety climate are relatively consistent across OR providers in a given hospital. Validated in over 500 hospitals, the SAQ is used to establish benchmark safety culture scores by health care worker type, department, and hospital. Thus, hospitals can compare their local culture between departments at their institution, among different types of health care workers within a department, and throughout the institution. Scores also are compared to national and global scores of all other participating centers seeking to compare their safety climate to national means. In addition, scores are used to evaluate the effectiveness of safety interventions by comparing the SAQ safety climate scores postimplementation to baseline scores.

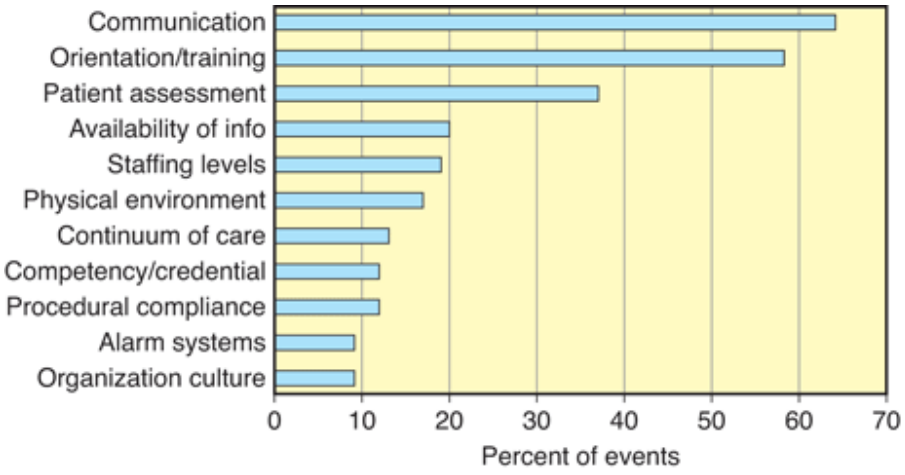
Strong teamwork is at the core of any effective organization and is a key element to ensuring patient safety in the OR. Teamwork is dependent on other elements such as an organization's underlying culture and patterns of communication. The ability for junior team members and other nonsurgeon professionals, including anesthesiologists, to "speak up" about patient safety concerns is one of the most important elements in relation to creating a culture of patient safety.

TEAMWORK AND COMMUNICATION

According to the Joint Commission, communication breakdown is the most common root cause of sentinel events such as wrong-site surgery (Fig. 12-3). Poor communication contributed to nearly 70% of sentinel events reported to the Joint Commission on Accreditation of Healthcare Organizations in 2006.[14] Good communication is an essential component of

teamwork and should be emphasized in any organization wishing to create a culture of patient safety. It especially is important in the OR, one of the most complex work environments in health care.

Fig. 12-3.



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Root causes of sentinel events 1995–2002.

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One of the best research reports ever written on the subject of breakdowns in communication was the 9/11 Commission Report.[15] The report cites Roberta Wohlsetter regarding Pearl Harbor, in which she observed that it is "much easier after the event to sort the relevant from the irrelevant signals. After the event, of course, a signal is always crystal clear; we can now see what disaster it was signaling since the disaster has occurred. But before the event it is obscure and pregnant with conflicting meanings." The circumstances leading up to 9/11 reinforce the difficulty that faces any organization charged with managing complex situations, large amounts of data, and multiple constituents. One of the criticisms of the intelligence agencies laid out in the report is that they "did not have the capability to link the collective knowledge of agents in the field to national priorities." In the same report, the authors "sympathize with the working-level officers, drowning in information and trying to decide what is important or what needs to be done when no particular action has been requested of them." In essence, much of the intelligence leading up to 9/11 could have been used to divert the attack on the United States had communications between the various agencies and individual officers clearly prioritized the threat posed by al Qaeda. In other words, the intelligence gathered actually contained the critical information needed to thwart an attack but was not prioritized sufficiently to alert the recipient of its significance until it was too late.

Similarly, within the realm of patient care, there are enormous amounts of information being exchanged between health care providers on a daily basis. Much of this information, if prioritized correctly, has the potential to prevent unintended medical errors and serious harm to patients. The importance of good communication in preventing medical error is undeniable; however, it is difficult to achieve. The traditional surgical hierarchy combined with an atmosphere of intimidation can prevent OR personnel from sharing important patient data and expressing safety concerns. Members of the team may be hesitant to raise a safety concern if they do not feel comfortable speaking up. In addition, nurses who do not feel empowered to voice their concerns have increased job dissatisfaction—a root problem in the national nursing shortage. One perioperative field study showed a 30% rate of communication failure in the OR, with 36% of these breakdowns having a substantial impact on

patient safety.[16]

In addition to overcoming the cultural barrier to better teamwork and communication in the OR, Christian and associates' prospective study of patient safety in the OR demonstrated that the standard workflow of a typical OR itself presents many opportunities for the loss or degradation of critical information.[17] Handoffs of patient care from the OR to other locations or providers are particularly prone to information loss, which has previously been demonstrated in other clinical settings. Handoffs and auxiliary tasks, such as the surgical count, frequently take place during critical portions of the case and place competing demands on provider attention from primary patient-centered activities. Communication between the surgeon and pathologist also are vulnerable, as the communication often occurs through secondary messengers such as nurses or technicians. This information loss can lead to delays, overuse of staff and resources, uncertainty in clinical decision making and planning, and oversights in patient preparation.

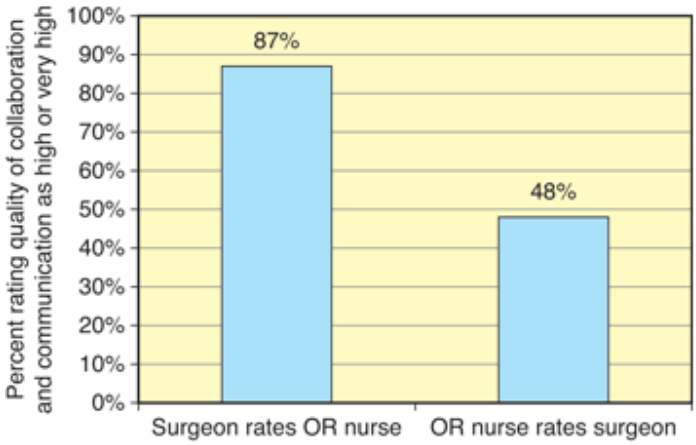
Measuring Teamwork

Research in commercial aviation has demonstrated a strong correlation between better teamwork and improved safety performance. Cockpit crew members' reluctance to question a captain's judgment has been identified as a root cause of aviation accidents. Attitudes about teamwork are associated with error-reduction behaviors in aviation, with patient outcomes in ICUs, and with nurse turnover in the OR. Good teamwork is associated with higher job satisfaction ratings and less sick time taken from work.

The SAQ can be used to measure teamwork, identify disconnects between or within disciplines, provide benchmarks for departments of surgery or hospitals seeking to measure their teamwork climate, and evaluate interventions aimed at improving patient safety.[18] The SAQ teamwork scores are responsive to interventions that aim to improve teamwork among operating teams, such as the implementation of ICU checklists, executive walk rounds, and preoperative briefing team discussions. The communication and collaboration sections of the SAQ reflect OR caregiver views on teamwork and can be used to distinguish meaningful interventions from impractical and ineffective programs to improve teamwork among OR professionals.

In a survey of operating room personnel across 60 hospitals, the SAQ identified substantial differences in the perception of teamwork in the OR depending on one's role. Physicians frequently rated the teamwork of others as good, while nurses at the same institutions perceived teamwork as poor (Fig. 12-4). Similar discrepancies about perceptions of collaboration between physicians and nurses have been found in ICUs. These discrepancies can be attributed to differences in the communication skills that are valued by surgeons and nurses, respectively. For example, nurses describe good collaboration as having their input respected, while physicians describe good collaboration as having nurses who can anticipate their needs and follow instructions. Efforts to improve the communication that takes place between physicians and nurses can directly improve the perception of teamwork and collaboration by the OR team (Table 12-2). Empowering well-respected surgeons to promote principles of teamwork and communication can go a long way toward transforming attitudinal and behavioral changes in fellow physicians as well as other members of the surgical team. Surgeons are increasingly encouraging the respectful and timely voicing of concerns of OR personnel related to patient safety.

Fig. 12-4.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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Differences in teamwork perceptions between surgeons and operating room (OR) nurses.

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Table 12-2 Percentage of Operating Room Caregivers Reporting a High or Very High Level of Collaboration with Other Members of the Operating Room Team

Caregiver Position Performing Rating	**Caregiver Position Being Rated**			
	Surgeon	**Anesthesiologist**	**Nurse**	**CRNA**
Surgeon	85	84	88	87
Anesthesiologist	70	**96**	89	92
Nurse	**48**	63	81	68
CRNA	58	75	76	93

The best teamwork scores were recorded by anesthesiologists when they rated their teamwork with other anesthesiologists ("high" or "very high" 96% of the time). The lowest teamwork ratings were recorded by nurses when they rated their teamwork with surgeons ("high" or "very high" 48% of the time).

CRNA = certified registered nurse anesthetist.

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COMMUNICATION TOOLS

Other high reliability organizations such as aviation frequently use tools such as prompts, checks, standard operating protocols, and communication interventions such as team briefings and debriefings. These tools identify and mitigate hazards and allow an organization to complete tasks more efficiently. They also foster a culture of open communication and speaking up if a team member senses a safety concern, a principle that has been mastered in the landmark business practices of the Toyota Production System. Safety checks and standardized team discussions serve as prompts to help "engineer out" human error, providing quality assurance and improving information flow. They also can prevent errors related to omissions, which are more likely to occur when there is information overload, multiple steps in a process, repetitions in steps, planned departures from routine processes, and when there are other interruptions and distractions present while the process is being executed. These same interventions have been shown to improve patient safety in ORs and ICUs.[19,20]

Operating Room Briefings

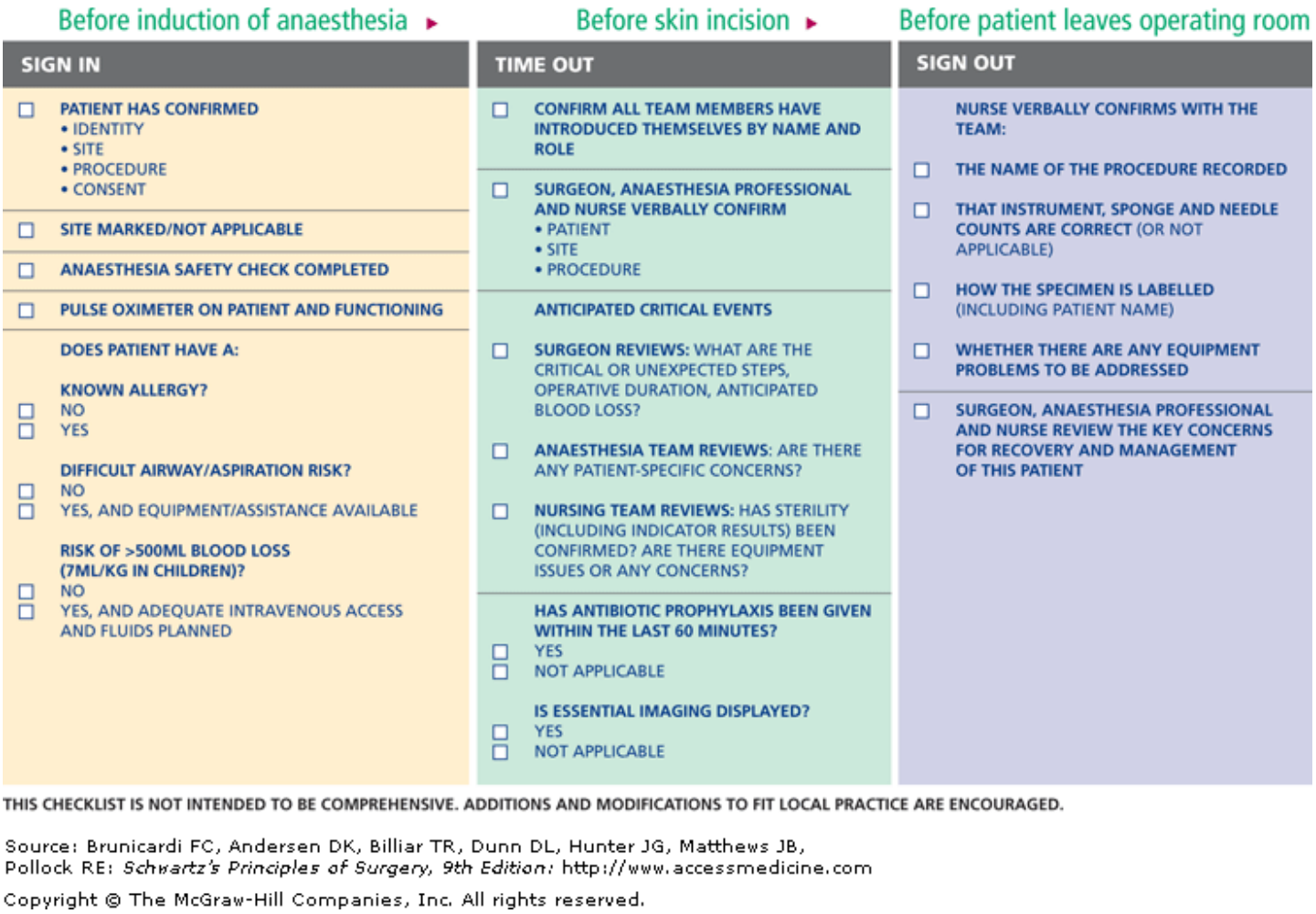
Preoperative briefings and checklists, when used appropriately, help to facilitate transfer of information between team members (Table 12-3). A briefing, or checklist, is any preprocedure discussion of requirements, needs, and special issues of the procedure. Briefings often are locally adapted to the specific needs of the specialty (orthopaedic surgery, transplantation, etc.). They have been associated with an improved safety culture, including increased awareness of wrong-site/wrong-procedure errors, early reporting of equipment problems, and reduced operational costs. OR briefings are increasingly being used to ensure evidence-based measures, such as the appropriate administration of preoperative antibiotics and deep vein thrombosis (DVT) prophylaxis, are used. It is well recognized that a team discussion of critical issues and potential hazards improves the safety of the operation when all members of the OR team are interested in providing optimal patient care. The use of briefings also is associated with fewer unexpected delays. In one study, 30.9% of OR personnel reported a delay before the institution of OR briefings, and only 23.3% reported delays postbriefing.[21] Briefings allow personnel to discuss potential problems, before they become a "near miss" or cause actual harm, by creating an open atmosphere that empowers all team members, whether circulating nurse, medical student, or senior resident, to feel empowered to address any concerns with the attending surgeon.

Table 12-3 Five-Point Operating Room Briefing
What are the **names and roles** of the team members?
Is the correct patient/procedure confirmed? [Joint Commission Universal Protocol (**TIME-OUT**)]
Have **antibiotics** been given? (if appropriate)
What are the **critical steps** of the procedure?
What are the **potential problems** for the case?

From Makary et al,[20] with permission. Copyright Elsevier.

The World Health Organization (WHO) has recently developed a comprehensive perioperative checklist as a primary intervention of the "Safe Surgery Saves Lives" program—an effort to reduce surgical deaths across the globe (Fig. 12-5).[22] The WHO checklist includes prompts to ensure that infection prevention measures are followed, potential airway complications are precluded (e.g., anesthesia has necessary equipment and assistance for a patient with a difficult airway), and the groundwork for effective surgical teamwork is established (e.g., proper introductions of all OR personnel). Aspects of the Joint Commission's preprocedure "Universal Protocol" (or "time-out") also are included in the checklist (e.g., checks to ensure operation performed on correct patient and correct site).

Fig. 12-5.



World Health Organization surgical safety checklist.

[Reproduced with permission from World Health Organization Safe Surgery Saves Lives: http://www.who.int/patientsafety/safesurgery/en/ (accessed April 15, 2009).]

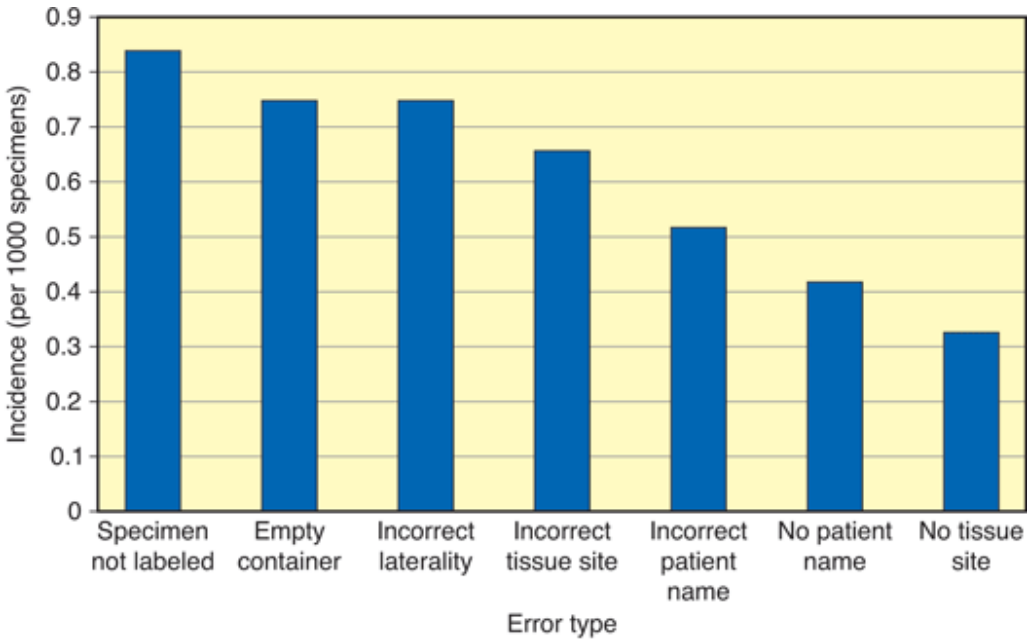
Operating Room Debriefings

Postprocedural debriefings improve patient safety by allowing for discussion and reflection on causes for errors and critical incidents that occurred during the case. The use of debriefings promotes a culture of learning from experience, and any errors or critical incidents are regarded as learning opportunities rather than cause for punishment. During the debriefing conversation, the team also can discuss what went well during the case, and designate a point person to follow up on any proposed actions that result from the discussion. In addition, most debriefings include a verification of the sponge, needle, and instrument counts, and confirm correct labeling of the surgical specimen.

Errors in surgical specimen labeling have not received as much attention as incorrect sponge or instrument counts as an indicator of the quality of communication in the OR. However, an error in verbal communication and transcription during the handoff process increases the risk of mislabeling a surgical specimen before its arrival in a pathology laboratory and can occur as a consequence of poor teamwork and communication. In one study, this type of identification error occurred in 4.3 per 1000 surgical specimens, which implies an annualized rate of occurrence of 182 mislabeled specimens per year (Fig. 12-6).[23] Errors involving specimen identification can result in delays in care, the need for an additional biopsy or therapy, failure to use appropriate therapy, or therapy administered to the wrong body site, side, or patient. These system failures can lead to significant harm to the patient, costs to the institution, and distrust by a community. Given the frequency of occurrence

and the feasibility and validity of measuring them, mislabeled surgical specimens may serve as a useful indicator of patient safety in surgical patients, and should be included in any postprocedural debriefing checklist.

Fig. 12-6.



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Incidence of identification errors observed per 1000 specimens (n = 21,351).

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Sign Outs

The 9/11 Commission Report cited the lack of prioritization as the key lethal defect in communications among government agencies. Similarly, health care is another setting where information frequently passes to covering providers without prioritizing potential concerns. In other words, sign outs represent a major vulnerable process of care which, if performed inadequately, can lead to catastrophic events.

The term *sign out* can refer to either the verbal or written communication of patient information being provided to familiarize oncoming or covering physicians about the patients who will be under their care. When performed well, sign outs help to ensure the transfer of pertinent information during these handoffs in patient care, such as when taking a patient from the OR to the recovery room, or when a patient is being transferred from one physician to another during shift changes. However, previous studies have shown the handoff process to be variable, unstructured, and prone to error. Common categories of communication failure during sign outs include content omissions, such as failure to mention active medical problems or current medications and treatments, and failures in the actual communication process, such as a lack of face-to-face communication or leaving illegible or unclear notes (Case 12-3).[24] These failures led to confusion and uncertainty by the covering physician during patient care decisions, resulting in the delivery of inefficient and suboptimal care.

Case 12-3 Inadequate Sign Out Leading to Medical Error

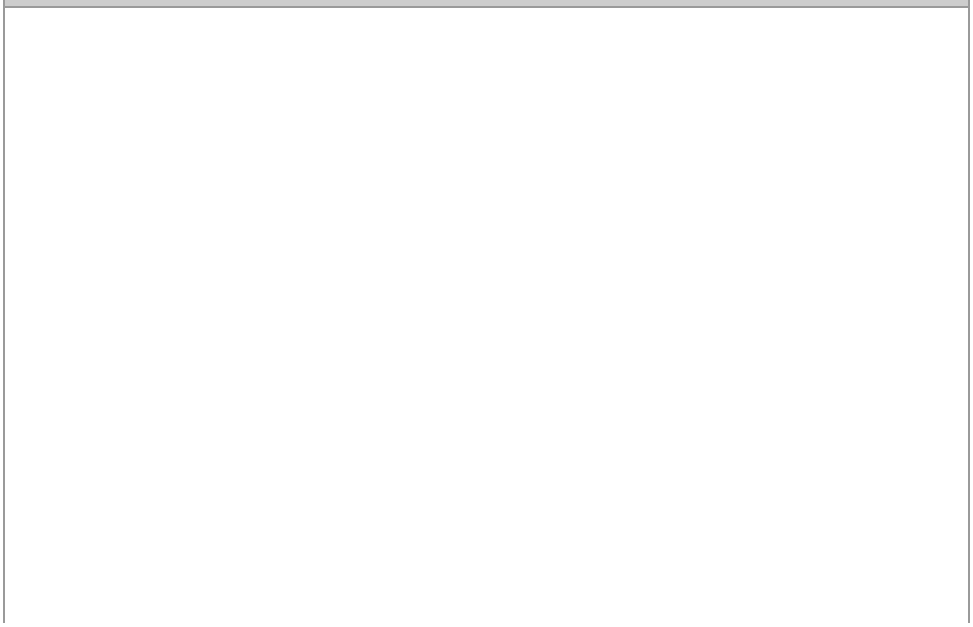
Josie King was an 18-month-old child who was admitted to Johns Hopkins Hospital in January of 2001 for first- and second-degree burns. She spent 10 days in the pediatric intensive care unit and was well on her way to recovery. She was transferred to an intermediate care floor with the expectation that she would be sent home in a few days.
The following week, her central line was removed, but nurses would not allow Josie to drink anything by mouth. Around 1 P.M. the next day, a nurse came to Josie's bedside with a syringe of methadone. Although Josie's mother told the nurse that there was no order for narcotics, the nurse insisted that the orders had been changed and administered the drug. Josie's heart stopped, and her eyes became fixed. She was moved to the pediatric intensive care unit and placed on life support. Two days later, on February 22, 2001, she died from severe dehydration.
After her death, Josie's parents, Sorrel and Jay King, were motivated to work with leaders at Johns Hopkins to ensure that no other family would have to endure the death of a child due to medical error. They later funded the Josie King Patient Safety Program and an academic scholarship in the field of safety.

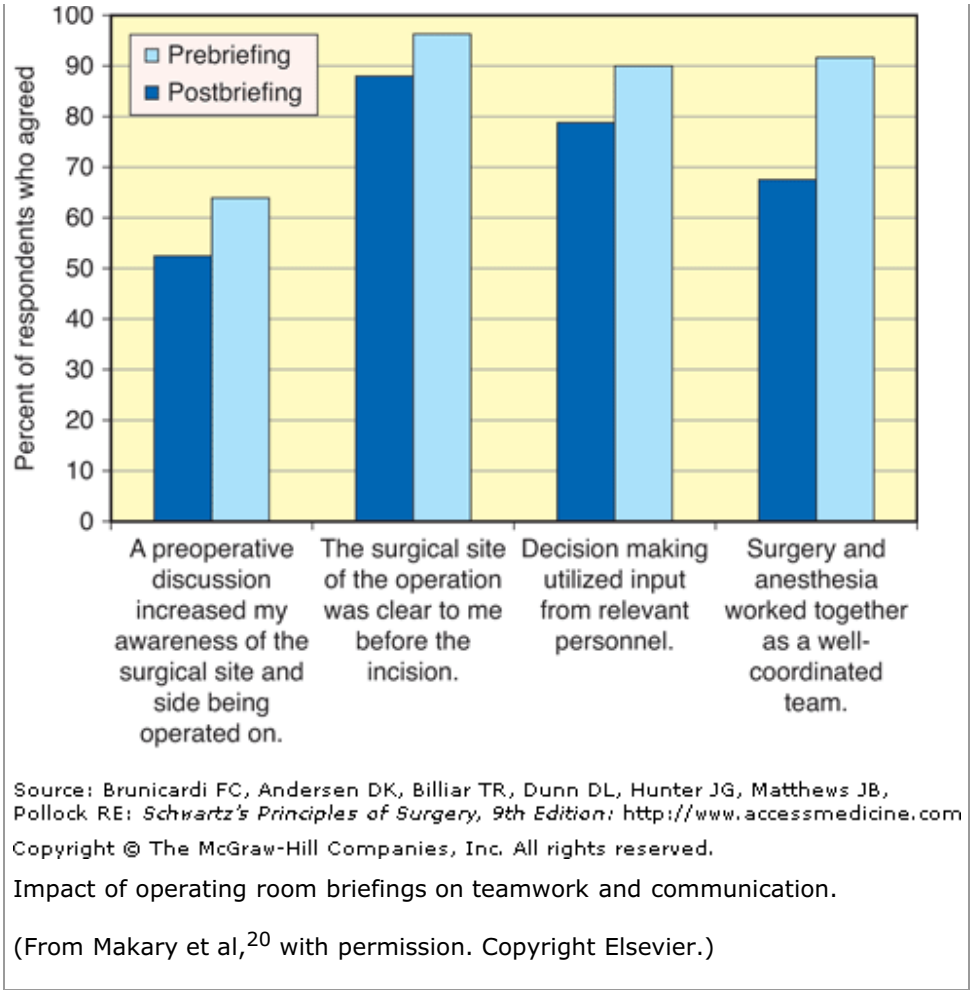
The use of more structured verbal communication such as the Situational Debriefing Model, otherwise known as *SBAR* (*s*ituation, *b*ackground, *a*ssessment, and *r*ecommendation), used by the U.S. Navy, can be applied to health care to improve the communication of critical information in a timely and orderly fashion.[24] In addition, all sign outs should begin with the statement "In this patient, I am most concerned about . . ." to signal to the health care provider on the receiving end the most important safety concerns regarding that specific patient.

Implementation

Tools such as checklists, sign outs, briefings, and debriefings improve communication between health care providers and create a safer patient environment (Fig. 12-7). Although their use in health care is still highly variable, specialties that have incorporated these tools, such as intensive care and anesthesia, have made impressive strides in patient safety, and the endorsement of many prominent surgeon champions is enabling the rapid diffusion of these communication tools nationally. Currently, communication breakdowns, information loss, hand off, multiple competing tasks, and high workload are considered "annoying but accepted features" of the perioperative environment by the physicians and nurses who encounter them on a daily basis.[17] As physician attitudes toward errors, stress, and teamwork in medicine become more favorable toward the common goals of reducing error and improving teamwork and communication, medicine will likely achieve many of the milestones in safety that high-reliability industries such as aviation have already accomplished.

Fig. 12-7.





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Impact of operating room briefings on teamwork and communication.

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MEASURING QUALITY IN SURGERY

Despite the newfound focus on patient safety in surgery and the number of initiatives being undertaken by many organizations to improve their safety culture, there are few tools to actually measure whether these efforts actually are effective in reducing the number of errors. Several agencies and private groups have developed criteria to evaluate quality and safety within hospitals.

Agency for Healthcare Research and Quality Patient Safety Indicators

The Agency for Healthcare Research and Quality (AHRQ) was created in 1989 as a Public Health Service agency in the Department of Health and Human Services. Its mission is to improve the quality, safety, efficiency, and effectiveness of health care for all Americans. Nearly 80% of the AHRQ's budget is awarded as grants and contracts to researchers at universities and other research institutions across the country. The AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes; quality; and cost, use, and access. The information helps health care decision makers—patients and clinicians, health system leaders, purchasers, and policymakers—make more informed decisions and improve the quality of health care services.[25]

The AHRQ has advocated the use of quality indicators to measure health care quality using readily available hospital inpatient administrative data. The Patient Safety Indicators (PSIs), which were released in March 2003, are a tool to help health system leaders identify potential adverse events occurring during hospitalization. Developed after a comprehensive literature review, analysis of ICD-9-CM codes, review by a clinician panel, implementation of risk adjustment, and empirical

analyses, these 27 indicators provide information on potential inhospital complications and adverse events following surgeries, procedures, and childbirth (Table 12-4).

Table 12-4 Agency for Healthcare Research and Quality Patient Safety Indicators
Provider-level patient safety indicators
• Complications of anesthesia
• Death in low mortality diagnosis-related groups
• Decubitus ulcer
• Failure to rescue
• Foreign body left in during procedure
• Iatrogenic pneumothorax
• Selected infections due to medical care
• Postoperative hip fracture
• Postoperative hemorrhage or hematoma
• Postoperative physiologic and metabolic derangements
• Postoperative respiratory failure
• Postoperative pulmonary embolism or deep vein thrombosis
• Postoperative sepsis
• Postoperative wound dehiscence in abdominopelvic surgical patients
• Accidental puncture and laceration
• Transfusion reaction
• Birth trauma—injury to neonate
• Obstetric trauma—vaginal delivery with instrument
• Obstetric trauma—vaginal delivery without instrument
• Obstetric trauma—cesarean delivery
Area-level patient safety indicators
• Foreign body left in during procedure
• Iatrogenic pneumothorax
• Selected infections due to medical care
• Postoperative wound dehiscence in abdominopelvic surgical patients
• Accidental puncture and laceration
• Transfusion reaction
• Postoperative hemorrhage or hematoma

From Agency for Healthcare Research and Quality,[26] with permission.

Provider-level indicators provide a measure of the potentially preventable complication for patients who received their initial care and the complication of care within the same hospitalization, and they include only those cases where a secondary diagnosis code flags a potentially preventable complication. Area-level indicators capture all cases of the potentially preventable complication that occur in a given area (e.g., metropolitan area or county), either during hospitalization or resulting in subsequent hospitalization.[26]

Administrative data are readily available, inexpensive, computer readable, typically continuous, and cover large populations. Their potential in patient safety research is increasingly recognized. Currently, PSIs are considered indicators, not definitive measures, of patient safety concerns. They can identify potential safety problems that merit further investigation. They also can be used to better prioritize and evaluate local and national initiatives, and even as benchmarks for tracking progress in patient safety. In the future, further growth in electronic health data will make administrative data based tools like the PSIs more useful.[27]

The Surgical Care Improvement Project Measures

The Surgical Care Improvement Project (SCIP) was established in 2003 by a national partnership of organizations committed to improving surgical care by reducing the occurrence of surgical complications. The steering committee is comprised of groups such as the Centers for Medicare and Medicaid Services, the American Hospital Association, Centers for Disease Control and Prevention (CDC), Institute for Healthcare Improvement, Joint Commission on Accreditation of Healthcare Organizations, and others. The organization has a stated goal of reducing the incidence of preventable surgical complications by 25% nationally by the year 2010.[28]

The incidence of postoperative complications ranges from 6% for patients undergoing noncardiac surgery to more than 30% for patients undergoing high-risk surgery. Common postoperative complications include surgical site infections (SSIs) and postoperative sepsis, cardiovascular complications including myocardial infarction, respiratory complications including postoperative pneumonia and failure to wean, and thromboembolic complications. Patients who experience postoperative complications have increased hospital length of stay (3 to 11 days longer than those without complications), increased hospital costs (ranging from $1398 for an infectious complication to $18,310 for a thromboembolic event), and increased mortality (median patient survival decreases by 69%).[28]

Despite well-established evidence that many of these adverse events are preventable, the failure to comply with standards of care known to prevent these complications results in unnecessary harm to a large number of patients. SCIP has identified three broad areas within surgery where potential complications have a high incidence and high cost and there is a significant opportunity for prevention: SSIs, venous thromboembolism, and adverse cardiac events. The SCIP measures aim to reduce the incidence of these events during the perioperative period by advocating the use of proven process and outcome measures by participating hospitals and providers. These process and outcome measures are detailed in Table 12-5.

Table 12-5 The Surgical Care Improvement Project Measures
Process of care performance measures
Infection
• Prophylactic antibiotic received within 1 h before surgical incision
• Prophylactic antibiotic selection for surgical patients
• Prophylactic antibiotics discontinued within 24 h after surgery end time (48 h for cardiac patients)
• Cardiac surgery patients with controlled 6 A.M. postoperative serum glucose
• Surgery patients with appropriate hair removal
• Colorectal surgery patients with immediate postoperative normothermia
Venous thromboembolism
• Surgery patients with recommended venous thromboembolism prophylaxis ordered
• Surgery patients who received appropriate venous thromboembolism prophylaxis within 24 h before surgery to 24 h after

surgery
Cardiac events
• Surgery patients on a beta blocker prior to arrival who received a beta blocker during the perioperative period
Proposed outcome measures
Infection
• Postoperative wound infection diagnosed during index hospitalization
Venous thromboembolism
• Intra- or postoperative pulmonary embolism diagnosed during index hospitalization and within 30 d of surgery
• Intra- or postoperative deep vein thrombosis diagnosed during index hospitalization and within 30 d of surgery
Cardiac events
• Intra- or postoperative acute myocardial infarction diagnosed during index hospitalization and within 30 d of surgery
Global measures
• Mortality within 30 d of surgery
• Readmission within 30 d of surgery

From Surgical Care Improvement Project,[29] with permission.

SSIs account for 14 to 16% of all hospital-acquired infections and are a common complication of care, occurring in 2 to 5% of patients after clean extra-abdominal operations and up to 20% of patients undergoing intra-abdominal procedures. By implementing steps to reduce SSIs, hospitals could recognize a savings of $3152 and reduction in extended length of stay by 7 days on each patient developing an infection.[29]

Adverse cardiac events occur in 2 to 5% of patients undergoing noncardiac surgery and as many as 34% of patients undergoing vascular surgery. Certain perioperative cardiac events, such as myocardial infarction, are associated with a mortality rate of 40 to 70% per event, prolonged hospitalization, and higher costs. Current studies suggest that appropriately administered beta blockers reduce perioperative ischemia, especially in patients considered to be at risk. It has been found that nearly half of the fatal cardiac events could be preventable with beta blocker therapy.[29]

DVT occurs after approximately 25% of all major surgical procedures performed without prophylaxis, and pulmonary embolism (PE) in 7% of surgeries conducted without prophylaxis. More than 50% of major orthopedic procedures are complicated by DVT, and up to 30% by PE, if prophylactic treatment is not instituted. Despite the well-established efficacy and safety of preventive measures, studies show that prophylaxis often is underused or used inappropriately. Both low-dose unfractionated heparin and low molecular weight heparin have similar efficacy in DVT and PE prevention. Prophylaxis using low-dose unfractionated heparin has been shown to reduce the incidence of fatal PEs by 50%.[29]

The SCIP effort provides an infrastructure and guidelines for data collection and quality improvement activities on a national scale. By achieving high levels of compliance with evidence-based practices to reduce SSIs, venous thromboembolism events, and perioperative cardiac complications, the potential number of lives saved in the Medicare patient population alone exceeds 13,000 annually.[28] Although SCIP still faces challenges with regard to implementing the proposed outcome measures at the local level, the SCIP process measures have been shown to effectively reduce perioperative complications and will continue to shape the national effort to improve the delivery of surgical care in the United States.

National Surgical Quality Improvement Program[30]

The National Surgical Quality Improvement Program (NSQIP) is a measurement program that allows hospitals to sample their rates of postoperative events and compare them to similar hospitals. Created by the Veterans Health Administration (VA) in 1991, NSQIP has been credited with measuring and improving morbidity and mortality outcomes at the VA, reducing 30-day mortality rate after major surgery by 31%, and 30-day postoperative morbidity by 45% in its first decade. Beta testing at 18 non-VA sites from 2001 to 2004 demonstrated the feasibility and utility of the program in the private sector. The program was subsequently expanded to the private sector in 2004 when the American College of Surgeons endorsed the program and encouraged hospital participation to measure and evaluate outcomes on a large scale. Currently, over 200 U.S. hospitals participate in the program.

NSQIP uses a risk-adjusted ratio of the observed to expected outcome (focusing primarily on 30-day morbidity and mortality) to compare the performance of participating hospitals with their peers. The data the program has compiled also can be used to conduct observational studies using prospectively collected information on more than 1.5 million patients and operations. The expansion of NSQIP to the private sector has helped shift the focus from merely preventing the provider errors and sentinel events highlighted by the IOM publication "To Err Is Human" to the larger goal of preventing all adverse postoperative outcomes to improve patient safety.

Several insights about patient safety have arisen as a result of NSQIP. First, safety is indistinguishable from overall quality of surgical care and should not be addressed independent of surgical quality. Defining quality in terms of keeping a patient safe from adverse outcomes allows the NSQIP data to be used to assess and improve quality of care by making improvements in patient safety. In other words, prevention of errors is synonymous with the reduction of adverse outcomes and can be used as a reliable quality measure. Second, during an episode of surgical care, adverse outcomes, and hence, patient safety, are primarily determined by the quality of the systems of care. Errors in hospitals with higher than expected observed to expected outcomes ratios are more likely to be from system errors than from provider incompetence, underscoring the importance of adequate communication, coordination, and team work in achieving quality surgical care. Finally, reliable comparative outcomes data are imperative for the identification of system problems and the assurance of patient safety from adverse outcomes. Risk-adjusted rates of adverse outcomes must be compared with similarly risk-adjusted rates at peer institutions to appreciate more subtle system errors that lead to adverse outcomes to prompt changes in the quality of an institution's processes and structures.

The Leapfrog Group

One of the largest efforts to standardize evidence-based medicine in the United States is being led by The Leapfrog Group, an alliance of large public and private health care purchasers representing more than 37 million individuals across the United States. This health care consortium was founded in 2000 with the aim to exert their combined leverage toward improving nationwide standards of health care quality, optimizing patient outcomes, and ultimately lowering health care costs. The Leapfrog Group's strategy to achieve these goals is through providing patient referral, financial incentives, and public recognition for hospitals that practice or implement evidence-based, health care standards. These include hospital use of computerized physician order entry systems, compliance with 24-hour ICU physician staffing, evaluation using a 30-point composite Leapfrog Safe Practices Score, and evidence-based hospital referral (EBHR) standards for five high-risk operations.[31]

Leapfrog encourages the use of evidence-based health care standards through the administration of an ongoing, voluntary, web-based hospital quality and safety survey. This survey is conducted in 33 regions that cover over one half of the U.S. population and 58% of all hospital beds in the country. Currently, more than 1300 hospitals participate in the survey.

Leapfrog asks for information on eight high-risk conditions or procedures, including the following surgical procedures: coronary artery bypass graft, percutaneous coronary intervention, AAA repair, pancreatic resection, and esophagectomy. These procedures were chosen because evidence exists that adherence to certain process measures can dramatically improve the outcomes of these procedures. In addition, more than 100 studies also have demonstrated that better results are obtained at high-volume hospitals when undergoing cardiovascular surgery, major cancer resections, and other high-risk procedures. Hospitals fulfilling the EBHR Safety Standard are expected to meet the hospital and surgeon volume criteria shown in Table 12-6. Hospitals that do not meet these criteria but adhere to the Leapfrog-endorsed process measures for coronary artery bypass graft surgery, percutaneous coronary intervention, AAA repair, and care for high-risk neonates, receive partial credit toward fulfilling the EBHR Safety Standard. Leapfrog purchasers work to recognize and reward hospitals that provide care for their enrollees who meet EBHR standards.[32]

Table 12-6 Recommended Annual Volumes: Hospitals and Surgeons	
1. Coronary artery bypass graft	≥450/100
2. Percutaneous coronary intervention	≥400/75
3. Abdominal aortic aneurysm repair	≥50/22
4. Aortic valve replacement	≥120/22
5. Pancreatic resection	≥11/2
6. Esophagectomy	≥13/2
7. Bariatric surgery	>100/20

From The Leapfrog Group,[32] with permission.

In a recent study, Brooke and associates analyzed whether achieving Leapfrog's established evidence-based standards for abdominal aortic aneurysm (AAA) repair, including meeting targets for case volume and perioperative beta blocker usage, correlated with improved patient outcomes over time.[31] After controlling for differences in hospital and patient characteristics, hospitals that implemented a policy for perioperative beta blocker usage had an estimated 51% reduction in mortality following open AAA repair cases, as compared to control hospitals. Among 111 California hospitals in which endovascular AAA repair was performed, inhospital mortality was reduced by an estimated 61% over time among hospitals meeting Leapfrog case volume standards when compared to control hospitals, although this result was not statistically significant. These results suggest that hospital compliance with Leapfrog standards for elective AAA repair are an effective means to help improve inhospital mortality outcomes over time, and support further efforts aimed at standardizing patient referral to hospitals that comply with other evidence-based medicine standards for other surgical procedures.

World Health Organization "Safe Surgery Saves Lives" Initiative

In October 2004, the WHO launched a global initiative to strengthen health care safety and monitoring systems by creating the World Alliance for Patient Safety. As part of the group's efforts to improve patient safety, the alliance implemented a series of safety campaigns that brought together experts in specific problem areas through individual Global Patient Safety Challenges. The second Global Patient Safety Challenge focuses on improving the safety of surgical care. The main goal of the campaign, called *Safe Surgery Saves Lives*, is to reduce surgical deaths and complications through the universal adaptation of a comprehensive perioperative surgical safety checklist in ORs worldwide. In addition, the WHO has defined a set of uniform measures for national and international surveillance of surgical care to better assess the quantity and quality

of surgical care being delivered worldwide (Table 12-7).[22] At the population level, metrics include the number of surgeon, anesthesia, and nurse providers per capita, the number of ORs per capita, and overall surgical case volumes and mortality rates. At the hospital level, metrics include safety improvement structures and a surgical "Apgar score," a validated method of prognosticating patient outcomes based on intraoperative events (i.e., hypotension, tachycardia, blood loss).[33]

Table 12-7 World Health Organization Basic Surgical Vital Statistics
• Number of operating theatres per capita
• Number of trained surgeons and trained anesthesia professionals per capita
• Number of operations performed in operating theatres within per capita
• Number of deaths on the day of surgery
• Number of inhospital deaths following surgery

From World Health Organization,[22] with permission.

National Quality Forum

The National Quality Forum (NQF) is a coalition of health care organizations that has worked to develop and implement a national strategy for health care quality measurement and reporting. The mission of the NQF is to improve the quality of American health care by setting national priorities and goals for performance improvement, endorsing national consensus standards for measuring and publicly reporting on performance, and promoting the attainment of national goals through education and outreach programs.

One of the major contributions of the NQF is the development of a list of Serious Reportable Events, which is frequently referred to as "*never events*."[34] According to the NQF, "never events" are errors in medical care that are clearly identifiable, preventable, and serious in their consequences for patients, and that indicate a real problem in the safety and credibility of a health care facility. Examples of "never events" include surgery performed on the wrong body part; a foreign body left in a patient after surgery; a mismatched blood transfusion; a major medication error; a severe "pressure ulcer" acquired in the hospital; and preventable postoperative deaths (Table 12-8). Criteria for inclusion as a "never event" are listed below. The event must be:

- Unambiguous (i.e., the event must be clearly identifiable and measurable, and thus feasible to include in a reporting system);
- Usually preventable, with the recognition that some events are not always avoidable, given the complexity of health care;
- Serious, resulting in death or loss of a body part, disability, or more than transient loss of a body function; and
- Any one of the following:
  - Adverse and/or,
  - Indicative of a problem in a health care facility's safety systems and/or,
  - Important for public credibility or public accountability.

Table 12-8 Surgical "Never Events"
• Surgery performed on the wrong body part
• Surgery performed on the wrong patient

• Wrong surgical procedure performed on a patient
• Unintended retention of a foreign object in a patient after surgery or other procedure
• Intraoperative or immediately postoperative death in an ASA Class I patient

ASA = American Society of Anesthesiologists.

From National Quality Forum,[34] with permission.

These events are not a reasonable medical risk of undergoing surgery that the patient must accept, but medical errors that should never happen (Case 12-4). The occurrence of any of these events signals that an organization's patient safety culture or processes have defects that need to be evaluated and corrected to prevent the event from happening again (Table 12-9).

Case 12-4 Surgical "Never-Event"
In 2002, Mike Hurewitz, a reporter for *The Times Union* of Albany, suddenly began vomiting blood 3 days after donating part of his liver to his brother while recovering on a hospital floor in which 34 patients were being cared for by one first-year resident. He aspirated and died immediately with no other physician available to assist the overworked first-year resident.
Recognized for its advances in the field of liver transplantation, at the time, Mount Sinai Hospital was performing more adult-to-adult live-donor operations than any other hospital in the country. But the program was shut down by this event. Mount Sinai was held accountable for inadequate care and was banned from performing any live-donor adult liver transplants for more than 1 year. Of the 92 complaints investigated by the state, 75 were filed against the liver transplant unit, with 62 involving patient deaths. The state concluded that most of the 33 serious violations exhibited by the hospital occurred within the liver transplant unit.
As a result of the investigation, Mount Sinai revamped many of the procedures within its transplant unit. Among the changes, first-year residents no longer staffed the transplant service, two health care practitioners physically present in the hospital oversaw the transplant unit at all times, and any page coming from the transplant unit had to be answered within 5 minutes of the initial call. In addition, nurses monitored patients' vital signs more closely after surgery, transplant surgeons were required to make postoperative visits to both organ donor and recipient, and each registered nurse was assigned to four patients, rather than six or seven. The death also led New York to become the first state to develop guidelines for treating live organ donors. Finally, Mike Hurewitz's widow became a patient safety advocate, urging stricter controls on live donor programs.

Table 12-9 Four Patient Events That Advanced the Modern Field of Patient Safety

Patient	Institution	Year	Event	Root Cause	Outcome
Libby Zion	New York Hospital, New York, NY	1984	Missed allergy to Demerol	Physician fatigue	Bell Commission shortened resident work hours
Betsy Lehman	Dana-Farber Cancer Institute, Boston, MA	1994	Chemotherapy overdose	Lack of medication checks and triggers	Fired doctor, three pharmacists, 15 nurses; overhauled safety program
Josie King	Johns Hopkins Hospital, Baltimore, MD	2001	Severe dehydration	Poor communication	Increased safety research funding
Mike Hurewitz	Mt. Sinai Hospital, New York, NY	2002	Inadequate postoperative care	Inadequate supervision	Transplant program shut down until better patient safety safeguards implemented

"NEVER EVENTS" IN SURGERY

Retained Surgical Items[35]

A retained surgical item refers to any surgical item that is found to be inside a patient after he or she has left the OR, thus requiring a second operation to remove the item. Estimates of retained foreign bodies in surgical procedures range from one case per 8000 to 18,000 operations, corresponding to one case or more each year for a typical large hospital or approximately 1500 cases per year in the United States.[36] This estimate is based on an analysis of malpractice claims and is likely to underestimate the true incidence. The risk of having a retained surgical item increases during emergency surgery, when there are unplanned changes in procedure (due to new diagnoses encountered in the OR), and in patients with higher body-mass index (Table 12-10).[36]

Table 12-10 Risk Factors for Retained Surgical Sponges
• Emergency surgery
• Unplanned changes in procedure
• Patient with higher body-mass index
• Multiple surgeons involved in same operation
• Multiple procedures performed on same patient
• Involvement of multiple operating room nurses/staff members
• Case duration covers multiple nursing "shifts"

The most common retained surgical item is a surgical sponge, but other items, such as surgical instruments and needles, can also be inadvertently left inside a patient after an operation. Retained surgical sponges are commonly discovered as an incidental finding on a routine postoperative radiograph, but also have been discovered in patients presenting with a mass or abdominal pain. Patients with sponges that were originally left in an intracavitary position (such as inside the chest or abdomen) also can present with complications such as erosion through the skin, fistula formation, bowel obstruction, hematuria, or the development of a new, tumor-like lesion.

Retained surgical needles usually are discovered incidentally, and reports of retained needles are uncommon. Retained surgical needles have not been reported to cause injury in the same way that nonsurgical needles (e.g., sewing needles, hypodermic needles) have been reported to perforate bowel or lodge in vessels and migrate. However, there have been reports of chronic pelvic pain and ocular irritation caused by retained surgical needles. A study of plain abdominal radiographs in pigs has demonstrated that medium to large size needles can easily be detected. The decision to remove these retained needles depends on whether they are symptomatic and the preference of the patient. Needles smaller than 13 mm have been found to be undetectable on plain radiograph in several studies, have not been shown to cause injury to vessels or visceral organs, and can probably be left alone.

Although the actual incidence of retained surgical instruments is unknown, they are known to be retained with far less frequency than surgical sponges. However, most of the cases that do occur are sensationalized by the lay media and draw significant attention from the general public. The initial presentation of a retained surgical instrument is pain in the surgical site or the sensation of a mass of fullness after a surgical procedure that led to the discovery of a metallic object on a radiographic study. Commonly retained instruments include the malleable and "FISH" instrument that are used when closing abdominal surgery.

A retained surgical foreign body should be included in the differential diagnosis of any postoperative patient who presents with pain, infection, a palpable mass, or a radiopaque structure on imaging. The diagnosis can usually be made using a

From Lycan / Dr. MV

computed tomographic (CT) scan, and this is often the only test that will be needed. If a retained surgical item is identified in the setting of an acute clinical presentation, the treatment usually is removal of the item. However, if the attempt to remove the retained surgical item can potentially cause more harm than the item itself, as in the case of a needle or a small part of a surgical item, then removal is occasionally not recommended. Retained surgical sponges should always be removed.

The American College of Surgeons and the Association of Perioperative Registered Nurses, in addition to the Joint Commission, have issued guidelines to try to prevent the occurrence of retained surgical items. Current recommendations include the use of standard counting procedures, performing a thorough wound exploration before closing a surgical site, and using only x-ray detectable items in the surgical wound. These organizations also strongly endorse the completion of a postoperative debriefing after every operation. An x-ray at the completion of an operation is encouraged if there is any concern for a foreign body based on any confusion regarding the counts by even a single member of the OR team, or in the presence of a risk factor.

Surgical Counts

The benefit of performing surgical counts to prevent the occurrence of retained surgical items is controversial. The increased risk of a retained surgical item during emergency surgery in the study by Gawande and colleagues appeared to be related to bypassing the surgical count in many of these cases, suggesting that the performance of a surgical count can be useful in reducing the incidence of this sentinel event.[36] However, the "falsely correct count," in which a count is performed and declared correct when it is actually incorrect, occurred in 21 to 100% of cases in which a retained surgical item was found.[35] This type of count was the most common circumstance encountered in all retained surgical item cases, which suggests that performing a surgical count in and of itself does not prevent this error from taking place. The counting protocol also imposes significant demands on the nursing staff and distracts them from focusing on other primarily patient-centered tasks.[17]

A retained surgical item can occur even in the presence of a known incorrect count. This event is usually a result of poor communication in which a surgeon will dismiss the incorrect count and/or fail to obtain a radiograph before the patient leaves the OR. Having stronger institutional policies in place in case of an incorrect count (such as requiring a mandatory radiograph while the patient is still in the OR) can avoid conflict among caregivers and mitigate the likelihood of a retained surgical item occurring as a result of a known incorrect count.

Although there is no single tool to prevent all errors, the development of multiple lines of defense to prevent retained surgical items and universally standardizing and adhering to OR safety protocols by all members of the surgical team will help reduce the incidence of this never event.[37] Surgeons should take the lead in the prevention of retained surgical items by avoiding the use of small or nonradiologically detectable sponges in large cavities, performing a thorough wound inspection before closing any surgical incision, and by having a vested interest in the counting procedure performed by nursing staff to keep track of sponges, needles, instruments, and any other potential retained surgical item. The value of routine radiography in the setting of emergency cases or when multiple major procedures involving multiple surgical teams are being performed to prevent a retained surgical item is becoming more apparent.

The widely accepted legal doctrine when a foreign body is erroneously left in a patient is that the mere presence of the item in the plaintiff's body indicates that the patient did not receive proper surgical care. Proof of negligence is not required in these cases because the doctrine of *Res ipsa loquitur*, or "the thing speaks for itself," applies. The characteristics of the surgeon, their style, bedside manner, honesty, and confidence demonstrated in the management of the case can go a long way in averting a lawsuit or mitigating damages.

Wrong-Site Surgery

Wrong-site surgery is any surgical procedure performed on the wrong patient, wrong body part, wrong side of the body, or wrong level of a correctly identified anatomic site. It is difficult to determine the true incidence of wrong-site surgery for several reasons. First, there is no standard definition for what constitutes wrong-site surgery among various health care organizations. Another factor is that wrong-site surgery is underreported by health care providers. Finally, the total number of potential opportunities for each type of wrong-site error is unknown. However, various studies show incidences ranging from one in 112,994 cases to one in 15,500 cases.[38] The Washington University School of Medicine suggests a rate of one in 17,000 operations, which adds up to approximately 4000 wrong-site surgeries in the United States each year. If these numbers are correct, wrong-site surgery is the third most frequent life-threatening medical error in the United States.[39]

Despite the difficulty in determining the overall incidence of wrong-site surgery, several states now require mandatory reporting of all wrong-site surgery events, including near misses. These data provide some insight into the number of actual errors compared to the number of potential opportunities to perform wrong-site surgery. Of the 427 reports of wrong-site surgery submitted from June 2004 through December 2006 to the Pennsylvania Patient Safety Reporting System, more than 40% of the errors actually reached the patient, and nearly 20% involved completion of a wrong-site procedure.[38]

The risk of performing wrong-site surgery increases when there are multiple surgeons involved in the same operation or multiple procedures are performed on the same patient, especially if the procedures are scheduled or performed on different areas of the body.[39] Time pressure, emergency surgery, abnormal patient anatomy, and morbid obesity are also thought to be risk factors.[39] Communication errors are the root cause in more than 70% of the wrong-site surgeries reported to the Joint Commission.[38] Other risk factors include receiving an incomplete preoperative assessment because documents are either unavailable or not reviewed for other reasons; having inadequate procedures in place to verify the correct surgical site; or having an organizational culture that lacks teamwork or reveres the surgeon as someone whose judgment should never be questioned.[38]

There is a one in four chance that surgeons who work on symmetric anatomic structures will be involved in a wrong-site error sometime during their careers.[39] No surgical specialty is immune. The specialties most commonly involved in reporting wrong-site surgeries according to the Joint Commission are orthopedic/podiatric surgery (41%), general surgery (20%), neurosurgery (14%), urology (11%), and maxillofacial, cardiovascular, otolaryngology, and ophthalmology (14%).[38] Most errors involved symmetric anatomic structures: lower extremities (30%), head/neck (24%), and genital/urinary/pelvic/groin (21%).[38] Although orthopedic surgery is the most frequently involved, this may be due to the higher volume of cases performed as well as the increased opportunity for lateralization errors inherent in the specialty. In addition, because the American Academy of Orthopaedic Surgeons has historically tried as a professional organization to reduce wrong-site operations, orthopedic surgeons may be more likely to report these events when they do occur.[39]

The Joint Commission Universal Protocol to Ensure Correct Surgery

The movement to eliminate wrong-site surgery began among professional orthopedic societies in the mid-1990s, when both the Canadian Orthopaedic Association and the American Academy of Orthopaedic Surgeons issued position statements and embarked on educational campaigns to prevent the occurrence of wrong-site surgery within their specialty.[39] Other organizations that issued position statements advocating for the elimination of wrong-site surgery include the North American Spine Society, the American Academy of Ophthalmology, the Association of Perioperative Registered Nurses, and the American College of Surgeons. After issuing a review of wrong-site surgery in their Sentinel Event Alert in 1998, the Joint

Commission made the elimination of wrong-site surgery one of their first National Patient Safety Goals in 2003 and adopted a universal protocol for preventing wrong-site, wrong-procedure, and wrong-person surgery in 2004. The protocol has been endorsed by more than 50 professional associations and organizations.

A preoperative "time-out" or "pause for the cause" to confirm the patient, procedure, and site to be operated on before incision was recommended by the Joint Commission and is now mandatory for all ORs in the United States. Elements of the protocol include the following:

- Verifying the patient's identity
- Marking the surgical site
- Using a preoperative site verification process such as a checklist
- Confirming the availability of appropriate documents and studies before the start of a procedure
- Taking a brief time-out immediately before skin incision, in which all members of the surgical team actively communicate and provide oral verification of the patient's identity, surgical site, surgical procedure, administration of preoperative medications, and presence of appropriate medical records, imaging studies, and equipment
- Monitoring compliance with protocol recommendations

Focusing on individual process components of the universal protocol, such as surgical site marking or the time-out, is not enough to prevent wrong-site surgery. Over a 30-month period in Pennsylvania, 21 wrong-side errors occurred despite the proper use of time-out procedures, with 12 of these errors resulting in complete wrong-side procedures. During the same period, correct site markings failed to prevent another 16 wrong-site surgeries, of which six were not recognized until after the procedure had been completed.[39]

Site verification begins with the initial patient encounter by the surgeon, continues throughout the preoperative verification process and during multiple critical points in the OR, and requires the active participation of the entire operating team, especially the surgeon and anesthesia provider. Based on a recent review of malpractice claims, two thirds of wrong-site operations could have been prevented by a site-verification protocol.[40]

Despite the proliferation of wrong-site protocols in the last decade, the effectiveness of surgical site verification is difficult to measure. As discussed earlier in this section, the incidence of wrong-site surgery is too rare to measure as a rate. Interestingly, the number of sentinel events reported to the Joint Commission has not changed significantly since the widespread implementation of the Universal Protocol in 2004.[39] This could be due to an increase in reporting rather than an actual increase in the incidence of wrong-site surgery. The number of sentinel events reported does not actually indicate whether or not surgical site verification protocols are effective in reducing the likelihood that a patient will be harmed when undergoing surgery.

The legal treatment of wrong-site surgery is similar to that of surgical items erroneously left in a patient: The mere fact that wrong-site surgery occurred indicates that the patient did not receive proper surgical care. Proof of negligence is not required in these cases because the doctrine of *Res ipsa loquitur*, or "the thing speaks for itself," applies. A malpractice claim may lead to a settlement or award on verdict in the 6- or 7-figure range in 2005 U.S. dollars.[39]

Ultimately, the occurrence of retained surgical items or wrong-site surgery is a reflection of the quality of professional communication between caregivers and the degree of teamwork among the members of the operating team. In addition to standardizing procedures like the surgical count, instituting mandatory postoperative radiographs in the presence of a known miscount, and reforming the processes of patient identification and site verification, to successfully minimize the risk of wrong-site surgery, organizations should also strive to create a culture of safety, create independent and redundant checks

for key processes, and create a system in which caregivers can learn from their mistakes (Table 12-11).[41]

Table 12-11 Best Practices for Operating Room Safety
• Conduct the Joint Commission Universal Protocol ("time-out") to prevent wrong-site surgery.
• Perform an operating room briefing (checklist) to identify and mitigate hazards early.
• Promote a culture of speaking up about safety concerns.
• Use a screening x-ray to detect foreign bodies in high-risk cases.
• Begin patient sign-outs with the most likely immediate safety hazard.

From Michaels et al,[41] with permission.

RISK MANAGEMENT

Between one half and two thirds of hospitalwide adverse events are attributable to surgical care. Most surgical errors occur in the OR and are technical in nature, including direct manual errors (such as transection of the ureter during hysterectomy) as well as judgment and knowledge errors leading to performance of an inappropriate, inadequate, or untimely procedure (i.e., performing a simple cholecystectomy for invasive adenocarcinoma of the gallbladder, or failing to intervene promptly in a patient with a leaking aortic aneurysm). Surgical complications and adverse outcomes have previously been linked to lack of surgeon specialization, low hospital volume, communication breakdowns, fatigue, surgical residents and trainees, and numerous other factors.[42]

However, poor surgical outcomes are not necessarily correlated with a surgeon's level of experience in performing a certain procedure. In one study, three fourths of the technical errors that occurred in a review of malpractice claims data involved fully trained and experienced surgeons operating within their area of expertise, and 84% occurred in routine operations that do not require advanced training beyond a standard surgical training program. Rather than surgeon expertise, these errors likely occurred due to situations complicated by patient comorbidity, complex anatomy, repeat surgery, or equipment problems (Table 12-12). Because these errors occurred during routine operations, previous suggestions to limit the performance of high-complexity operations using selective referral, regionalization, or limitation of privileging may not actually be effective in reducing the incidence of technical error among surgical patients.[42]

Table 12-12 Common Causes of Lawsuits in Surgery
• Positional nerve injury
• Common bile duct injury
• Failure to diagnose or delayed diagnosis
• Failure to treat, delayed treatment, or wrong treatment
• Inadequate documentation
• Inappropriate surgical indication
• Failure to call a specialist
• Cases resulting in amputation/limb loss

In any event, although there has been much emphasis on reducing the prevalence of surgical technical errors as a way of improving surgical care, the occurrence of a technical error in the OR may not be the most important indicator of whether or

not a surgeon will be sued by a patient. Recent studies point to the importance of a surgeon's communication skills in averting malpractice litigation. In the American College of Surgeons' Closed Claims Study, although intraoperative organ injuries occurred in 40% of patients, reviewers felt that a surgical technical misadventure was the most deficient component of care in only 12% of patients. In fact, communication and practice pattern violations were the most common deficiency in care identified for one third of the patients in the Closed Claims Study who received the expected standard of surgical care.[43]

The Importance of Communication in Managing Risk

The manner and tone in which a physician communicates is potentially more important to avoiding a malpractice claim than the actual content of the dialogue. For example, a physician relating to a patient in a "negative" manner (e.g., using a harsh or impatient tone of voice) may trigger litigious feelings when there is a bad result, whereas a physician relating in a "positive" manner may not. Expressions of dominance, in which the voice tone is generally deep, loud, moderately fast, unaccented, and clearly articulated, may communicate a lack of empathy and understanding for the patient, whereas concern or anxiety in the surgeon's voice is often positively related to expressing concern and empathy. General and orthopedic surgeons whose tone of voice was judged to be more dominant were more likely to have been sued than those who sounded less dominant.[44]

When significant medical errors do occur, physicians have an ethical and professional responsibility to immediately disclose them to patients. Failure to disclose errors to patients undermines the public confidence in medicine and can create legal liability related to fraud. Physicians' fear of litigation represents a major barrier to error disclosure. However, when handled appropriately, immediate disclosure of errors frequently leads to improved patient rapport, satisfaction, and fewer malpractice claims.[45] In fact, rapport is the most important factor in determining whether a lawsuit is filed against a physician.

In 1987, the Department of Veterans Affairs Hospital in Lexington, Kentucky, implemented the nation's first formal apology and medical error full disclosure program, which called for the hospital and its doctors to work with patients and their families to settle a case. As a result, the hospital improved from having one of the highest malpractice claims totals in the VA system to being ranked among the lowest quartile of a comparative group of similar hospitals for settlement and litigation costs over a 7-year period. Its average payout in 2005 was $16,000 per settlement, vs. the national VA average of $98,000 per settlement, and only two lawsuits went to trial during a 10-year period. As a result of the success of this program, the Department of Veteran Affairs expanded the program to all VA hospitals nationwide in October 2005. This model also was replicated at the University of Michigan Health System with similar results. Its full-disclosure program cut the number of pending lawsuits by one half and reduced litigation costs per case from $65,000 to $35,000, thus saving the hospital approximately $2 million in defense litigation bills each year. In addition, University of Michigan doctors, patients, and lawyers are happier with this system. The cultural shift toward honesty and openness also has led to the improvement of systems and processes to reduce medical errors, especially repeat medical errors.[46]

With regard to risk management, the importance of good communication by surgeons and other care providers cannot be overemphasized. Whether alerting other members of the care team about a patient's needs, openly discussing any concerns the patient and/or family might have, or disclosing the cause of a medical error, open communication with all parties involved can reduce anger and mistrust of the medical system, the frequency, morbidity, and mortality of preventable adverse events, and the likelihood of litigation.

COMPLICATIONS

Despite the increased focus on improving patient safety and minimizing medical errors, it is impossible to eliminate human error entirely. Individual errors can cause minor or major complications during or after a surgical procedure. Although these types of errors may not be publicized as much as wrong-site surgery or a retained surgical item, they can still lead to surgical complications that prolong the course of illness, lengthen hospital stay, and increase morbidity and mortality rates.

Complications in Minor Procedures

CENTRAL VENOUS ACCESS CATHETERS

Complications of central venous access catheters are common. Steps to decrease complications include the following:

- Ensure that central venous access is indicated.
- Experienced (credentialed) personnel should insert the catheter, or should supervise the insertion.
- Use proper positioning and sterile technique. Controversy exists as to whether or not placing the patient in the Trendelenburg position facilitates access.
- Central venous catheters should be exchanged only for specific indications (not as a matter of routine) and should be removed as soon as possible.

Common complications of central venous access include:

Pneumothorax

Occurrence rates from both subclavian and internal jugular vein approaches are 1 to 6%. Pneumothorax rates appear to be higher among the inexperienced but occur with experienced operators as well. If the patient is stable, and the pneumothorax is small (<15%), close expectant observation may be adequate. If the patient is symptomatic, a thoracostomy tube should be placed. Occasionally, pneumothorax will occur as late as 48 to 72 hours after central venous access attempts. This usually creates sufficient compromise that a tube thoracostomy is required. Prevention requires proper positioning of the patient and correct technique. A postprocedure chest x-ray is mandatory to confirm the presence or absence of a pneumothorax, regardless of whether a pneumothorax is suspected.

Arrhythmias

Arrhythmias result from myocardial irritability secondary to guidewire placement, and usually resolve when the catheter or guidewire is withdrawn from the right heart. Prevention requires electrocardiogram (EKG) monitoring whenever possible during catheter insertion.

Arterial Puncture

The inadvertent puncture or laceration of an adjacent artery with bleeding can occur, but the majority will resolve with direct pressure on or near the arterial injury site. Rarely will angiography, stent placement, or surgery be required to repair the puncture site, but close observation and a chest x-ray are indicated. Prevention requires careful attention to insertion technique.

Lost Guidewire

A guidewire or catheter that migrates into the vascular space completely can be readily retrieved with interventional angiography techniques. A prompt chest x-ray and close monitoring of the patient until retrieval is indicated.

Air Embolus

Although estimated to occur in only 0.2 to 1% of patients, an air embolism can be dramatic and fatal. Treatment may prove futile if the air bolus is larger than 50 mL. Auscultation over the precordium may reveal a "crunching" noise, but a portable chest x-ray is required for diagnosis. If an embolus is suspected, the patient should immediately be placed into a left lateral decubitus Trendelenburg position, so the entrapped air can be stabilized within the right ventricle. Aspiration via a central venous line accessing the heart may decrease the volume of gas in the right side of the heart, and minimize the amount traversing into the pulmonary circulation. Subsequent recovery of intracardiac and intrapulmonary air may require open surgical or angiographic techniques. Prevention requires careful attention to technique.

Pulmonary Artery Rupture

Flow-directed, pulmonary artery ("Swan-Ganz") catheters can cause pulmonary artery rupture due to excessive advancement of the catheter into the pulmonary circulation. There usually is a sentinel bleed noted when a pulmonary artery catheter balloon is inflated, and then the patient begins to have uncontrolled hemoptysis. Reinflation of the catheter balloon is the initial step in management, followed by immediate airway intubation with mechanical ventilation, an urgent portable chest x-ray, and notification of the OR that an emergent thoracotomy may be required. If there is no further bleeding after the balloon is reinflated, the x-ray shows no significant consolidation of lung fields from ongoing bleeding and the patient is easily ventilated, then a conservative nonoperative approach may be considered. This approach might include observation alone if the patient has no signs of bleeding or hemodynamic compromise; however, more typically a pulmonary angiogram with angioembolization or vascular stenting is required. Hemodynamically unstable patients rarely survive because of the time needed to perform the thoracotomy and identify the branch of the pulmonary artery that has ruptured.

Central Venous Line Infection

The Centers for Disease Control and Prevention (CDC) reports mortality rates of 12 to 25% when a central venous line infection becomes systemic, and this carries a cost of approximately $25,000 per episode.[47–50] The CDC does not recommend routine central line changes, but when the clinical suspicion is high, the site of venous access must be changed. Additionally, nearly 15% of hospitalized patients will acquire central venous line sepsis. In many instances, once an infection is recognized as central line sepsis, removing the line is adequate. *Staphylococcus aureus* infections, however, present a unique problem because of the potential for metastatic seeding of bacterial emboli. The required treatment is 4 to 6 weeks of tailored antibiotic therapy.

ARTERIAL LINES

Arterial lines are placed to facilitate arterial blood gas sampling and hemodynamic monitoring. They are often left in place to make routine blood sampling easier, but this practice leads to higher complication rates.

Arterial access requires a sterile Seldinger technique, and a variety of arteries are used, such as the radial, femoral, brachial, axillary, dorsal pedis, or superficial temporal arteries. Although complications occur less than 1% of the time, they can be catastrophic. Complications include thrombosis, bleeding, hematoma, arterial spasm (nonthrombotic pulselessness), and infection. Thrombosis or embolization of an extremity arterial catheter can result in the loss of a digit, hand, or foot, and the risk is nearly the same for both femoral and radial cannulation. Thrombosis with distal tissue ischemia is treated with anticoagulation, but occasionally surgical intervention is required to re-establish adequate inflow. Pseudoaneurysms and arteriovenous fistulae can also occur.

ENDOSCOPY AND BRONCHOSCOPY

The principal risk of GI endoscopy is perforation. Perforations occur in 1:10,000 patients with endoscopy alone, but have a higher incidence rate when biopsies are performed (up to 10%). This increased risk is due to complications of intubating a GI diverticulum (either esophageal or colonic), or from the presence of weakened or inflamed tissue in the intestinal wall (e.g., diverticulitis, glucocorticoid use, or inflammatory bowel disease).

Patients will usually complain of diffuse abdominal pain shortly after the procedure, and then will quickly progress with worsening abdominal discomfort on examination. In obtunded or elderly patients, a change in clinical status may take several hours, and occasionally as long as 24 to 48 hours, to become manifest. Radiologic studies to look for free intraperitoneal air, retroperitoneal air, or a pneumothorax are diagnostic. A delay in diagnosis results in ongoing contamination and sepsis.

Open or laparoscopic exploration locates the perforation, and allows repair and local decontamination of the surrounding tissues. The patient who may be a candidate for nonoperative management is one in which perforation arises during an elective, bowel-prepped, endoscopy, and yet the patient does not have significant pain or clinical signs of infection. The patient may be closely observed in a monitored setting, on strict dietary restriction and broad-spectrum antibiotics.

The complications of bronchoscopy include bronchial plugging, hypoxemia, pneumothorax, lobar collapse, and bleeding. When diagnosed in a timely fashion, they are rarely life threatening. Bleeding usually resolves and rarely requires surgery, but may require repeat endoscopy for thermocoagulation or fibrin glue application. The presence of a pneumothorax necessitates placement of a thoracostomy tube when significant deoxygenation occurs or the pulmonary mechanics are compromised. Lobar collapse or mucous plugging responds to aggressive pulmonary toilet, but occasionally requires repeat bronchoscopy.

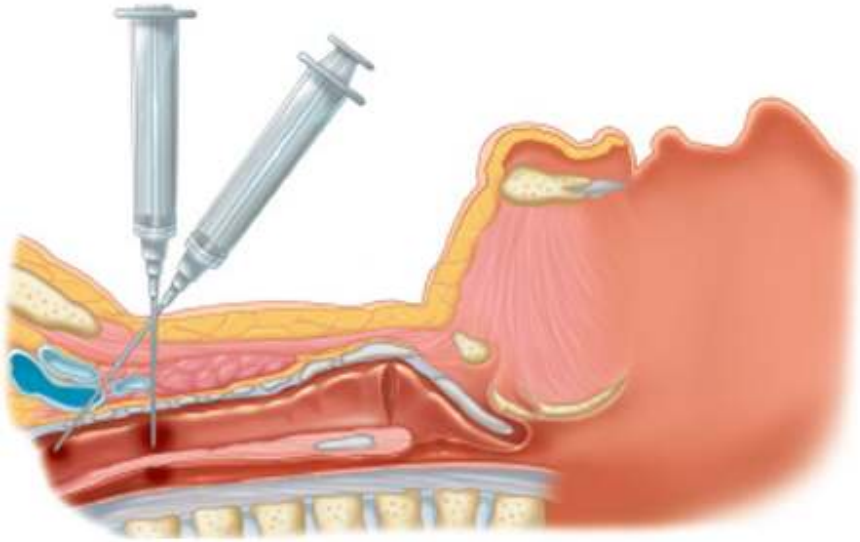
TRACHEOSTOMY

Tracheostomy facilitates weaning from a ventilator, decreases length of ICU or hospital stay, and improves pulmonary toilet. Tracheostomies are now performed open, percutaneously, with or without bronchoscopy, and with or without Doppler guidance, and yet complications still arise.

Recent studies do not support obtaining a routine posttracheostomy chest x-ray after either percutaneous or open tracheostomy.[51,52] However, significant lobar collapse can occur from copious tracheal secretions or mechanical obstruction.

The most dramatic complication of tracheostomy is tracheo-innominate artery fistula (TIAF) (Fig. 12-8).[53,54] This occurs rarely (~0.3%), but carries a 50 to 80% mortality rate. TIAFs can occur as early as 2 days or as late as 2 months after tracheostomy. The prototypical patient is a thin woman with a long, gracile neck. The patient may have a sentinel bleed, which occurs in 50% of TIAF cases, followed by a most spectacular bleed. Should a TIAF be suspected, the patient should be transported immediately to the OR for fiberoptic evaluation. If needed, remove the tracheostomy, and place a finger through the tracheostomy site to apply direct pressure anteriorly for compression of the innominate artery.

Fig. 12-8.



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This illustration depicts improper positioning (attitude) of the percutaneous needle. It is possible to access the innominate artery via the trachea, thus placing the patient at risk for early tracheo-innominate artery fistula.

PERCUTANEOUS ENDOGASTROSTOMY

A misplaced percutaneous endogastrostomy (PEG) may create intra-abdominal sepsis with peritonitis and/or an abdominal wall abscess with necrotizing fasciitis. As in other minor procedures, the initial placement technique must be fastidious to avoid complications. Transillumination of the abdomen may decrease the risk for error. Inadvertent colotomies, intraperitoneal leakage of tube feeds with peritonitis, and abdominal wall abscesses require surgery to correct the complications and to replace the PEG with an alternate feeding tube, usually a jejunostomy.

A dislodged or prematurely removed PEG tube must be replaced within 8 hours of dislodgment, because the gastrostomy site closes rapidly. A contrast x-ray should be performed to confirm the tube's intragastric position before feeding.

TUBE THORACOSTOMY

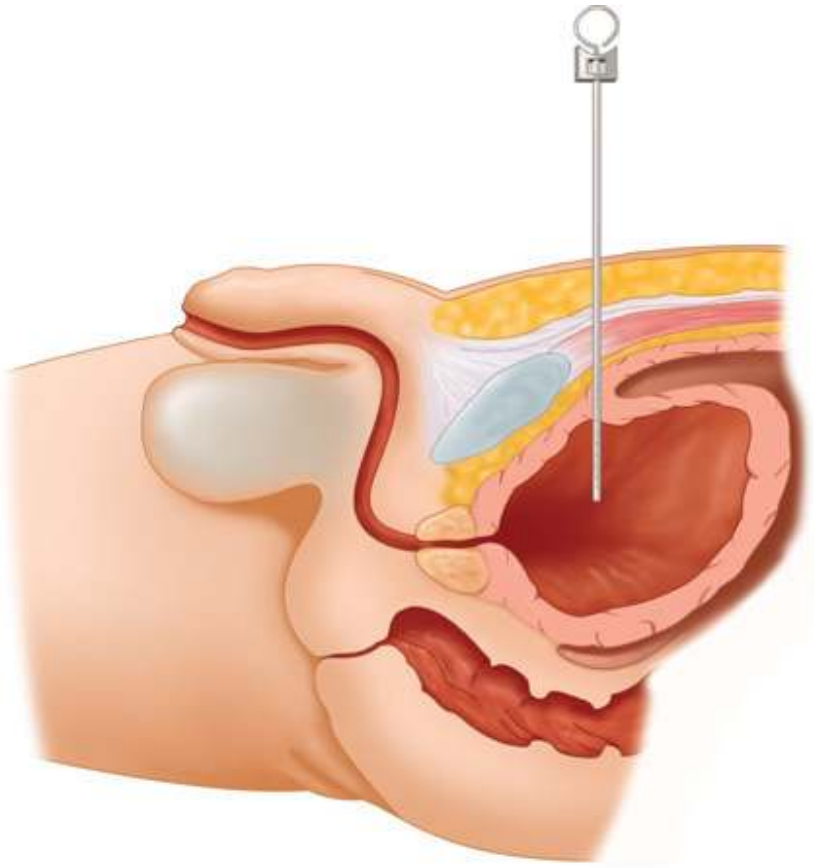
Tube thoracostomy (chest tube insertion) is performed for pneumothorax, hemothorax, pleural effusions, or empyema. A chest tube can be easily placed with a combination of local analgesia and light conscious sedation. Common complications include inadequate analgesia or sedation, incomplete penetration of the pleura with formation of a subcutaneous track for the tube, lacerations to the lung or diaphragm, intraperitoneal placement of the tube through the diaphragm, and bleeding related to these various lacerations or injury to pleural adhesions. Additional problems include slippage of the tube out of position or mechanical problems related to the drainage system. All of these complications can be avoided with proper initial insertion techniques, plus a daily review of the drainage system and follow-up radiographs. Tube removal can create a residual pneumothorax if the patient does not maintain positive intrapleural pressure by Valsalva's maneuver during tube removal and dressing application.

DIAGNOSTIC PERITONEAL LAVAGE

Diagnostic peritoneal lavage is performed in the emergent trauma setting for the hemodynamically unstable patient with neurologic impairment and an uncertain etiology for blood loss, when an abdominal trauma ultrasound is not available or is unreliable. Nasogastric and bladder catheter decompression is mandatory before diagnostic peritoneal lavage to avoid injury

during the procedure (Fig. 12-9). The small or large bowel, or the major vessels of the retroperitoneum also can be punctured inadvertently, and these injuries require surgical exploration and repair.

Fig. 12-9.



A

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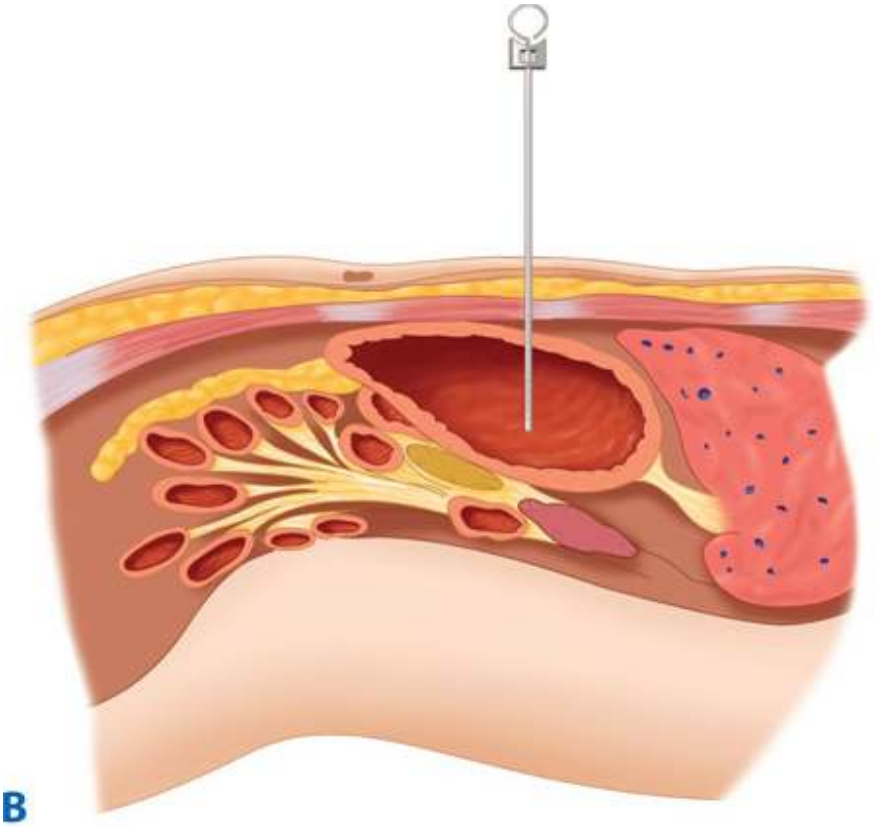

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The illustration depicts improper positioning of the diagnostic peritoneal lavage catheter, with overdistention of the urinary bladder (**A**) and the stomach (**B**). This error in technique clearly demonstrates the importance of decompressing hollow viscus before embarking on a diagnostic peritoneal lavage.

COMPLICATIONS OF ANGIOGRAPHY

Intramural dissection of a cannulated artery can lead to complications such as ischemic stroke from a carotid artery dissection or occlusion, mesenteric ischemia from dissection of the superior mesenteric artery, or a more innocuous finding of "blue toe syndrome" from a dissected artery in a peripheral limb. Invasive or noninvasive imaging studies confirm the suspected problem. The severity of the ischemia and the extent of the dissection determine if anticoagulation therapy or urgent surgical exploration is indicated.

Bleeding from the vascular access site usually is obvious, but may not be visible when the blood loss is tracking into the retroperitoneal tissue planes after femoral artery cannulation. These patients can present with hemorrhagic shock; an abdominopelvic CT scan delineates the extent of bleeding into the retroperitoneum. The initial management is direct compression at the access site and clinical observation with resuscitation as indicated. Urgent surgical exploration may be required to control the bleeding site.

Renal complications of angiography occur in 1 to 2% of patients. Contrast nephropathy is a temporary and preventable complication of radiologic studies such as CT, angiography, and/or venography. Some studies suggest a benefit of *N*-acetylcysteine for this condition. For the patient with impaired renal function or dehydration before contrast studies, twice-daily dosing 24 hours before and on the day of the radiographic study is suggested. Nonionic contrast also may be of benefit in higher-risk patients. IV hydration before and after the procedure is the most efficient method for preventing contrast

nephropathy.

COMPLICATIONS OF BIOPSIES

Lymph node biopsies have direct and indirect complications that include bleeding, infection, lymph leakage, and seromas. Measures to prevent direct complications include proper surgical hemostasis, proper skin preparation, and a single preoperative dose of antibiotic to cover skin flora 30 to 60 minutes before incision. Bleeding at a biopsy site usually can be controlled with direct pressure. Infection at a biopsy site will appear 5 to 10 days postoperatively, and may require opening of the wound to drain the infection. Seromas or lymphatic leaks resolve with aspiration of seromas and the application of pressure dressings, but may require repeated treatments.

Organ System Complications

NEUROLOGIC SYSTEM

Neurologic complications that occur after surgery include motor or sensory deficits and mental status changes. Peripheral motor and sensory deficits are often due to neurapraxia secondary to improper positioning and/or padding during operations. Treatment is largely clinical observation, and the majority will resolve spontaneously within 1 to 3 months.

Direct injury to nerves during a surgical intervention is a well-known complication of several specific operations, including superficial parotidectomy (facial nerve), carotid endarterectomy (hypoglossal nerve), prostatectomy (nervi erigentes), and inguinal herniorrhaphy (ilioinguinal nerve). The nerve injury may simply be a stretch injury, or an unintentionally severed nerve. In addition to loss of function, severed nerves can result in a painful neuroma that may require subsequent surgery.

Mental status changes in the postoperative patient can have numerous causes (Table 12-13). Mental status changes must be carefully documented and continually assessed. CT scanning should be used early to detect intracranial causes.

Table 12-13 Common Causes of Mental Status Changes

Electrolyte Imbalance	Toxins	Trauma	Metabolic	Medications
Sodium	Ethanol	Closed head injury	Thyrotoxicosis	Aspirin
Magnesium	Methanol	Pain	Adrenal insufficiency	Beta blockers
Calcium	Venoms and poisons	Shock	Hypoxemia	Narcotics
Inflammation	Ethylene glycol	Psychiatric	Acidosis	Antiemetics
Sepsis	Carbon monoxide	Dementia	Severe anemia	MAOIs
AIDS		Depression	Hyperammonemia	TCAs
Cerebral abscess		ICU psychosis	Poor glycemic control	Amphetamines
Meningitis		Schizophrenia	Hypothermia	Antiarrhythmics
Fever/hyperpyrexia			Hyperthermia	Corticosteroids, anabolic steroids

ICU = intensive care unit; MAOI = monoamine oxidase inhibitor; TCA = tricyclic antidepressant.

Atherosclerotic disease increases the risk for intraoperative and postoperative stroke (cerebrovascular accident). Postoperatively, hypotension and hypoxemia are the most likely causes of a cerebrovascular accident. Management is largely supportive once the diagnosis is made, and includes adequate intravascular volume replacement plus optimal oxygen delivery. Neurologic consultation should be obtained so that decisions regarding thrombolysis or anticoagulation can be made in a timely fashion.

EYES, EARS, AND NOSE

Corneal abrasions are unusual, but are due to inadequate protection of the eyes during anesthesia. Overlooked contact lenses in a trauma patient may cause conjunctivitis.

Persistent epistaxis can occur after nasogastric tube placement or removal, and nasal packing is the best treatment option if prolonged persistent direct pressure on the external nares fails. Anterior and posterior nasal gauze packing with balloon tamponade, angioembolization, and fibrin glue placement may be required in refractory cases. The use of antibiotics for posterior packing is controversial, but the incidence of toxic shock syndrome is documented at approximately 17:100,000 cases.

External otitis and otitis media occasionally occur postoperatively. Patients complain of ear pain or decreased hearing, and treatment includes topical antibiotics and nasal decongestion for symptomatic improvement.

Ototoxicity due to aminoglycoside administration occurs in up to 10% of patients, and is often irreversible. Recent data show that iron chelating agents and alpha-tocopherol may be protective against ototoxicity. Vancomycin-related ototoxicity occurs about 3% of the time when used alone, and as often as 6% when used with other ototoxic agents, but is self limiting.[55,56]

VASCULAR PROBLEMS OF THE NECK

Complications of carotid endarterectomy include central or regional neurologic deficits or bleeding with an expanding neck hematoma. An acute change in mental status or the presence of localized neurologic deficit may require an immediate return to the OR to correct an iatrogenic occlusion. An expanding hematoma may warrant emergent airway intubation and subsequent transfer to the OR for control of hemorrhage. Intraoperative anticoagulation with heparin during carotid surgery makes bleeding a postoperative risk. Other complications can arise, such as arteriovenous fistulae, pseudoaneurysms, and infection, all of which are treated surgically.

Intraoperative hypotension during manipulation of the carotid bifurcation can occur, and is related to increased tone from baroreceptors that reflexly cause bradycardia. Should hypotension occur when manipulating the carotid bifurcation, an injection of 1% lidocaine solution around this structure should attenuate this reflexive response.

The most common late complication following carotid endarterectomy is myocardial infarction. The possibility of a postoperative myocardial infarction should be considered as a cause of labile blood pressure and arrhythmias in high-risk patients.

THYROID AND PARATHYROID GLANDS

Surgery of the thyroid and parathyroid glands can result in hypocalcemia in the immediate postoperative period. Manifestations include EKG changes (shortened P-R interval), muscle spasm (tetany, Chvostek's sign, and Trousseau's sign), paresthesias, and laryngospasm. Treatment includes calcium gluconate infusion, and if tetany ensues, chemical paralysis with intubation. Maintenance treatment is thyroid hormone replacement (after thyroidectomy) in addition to calcium carbonate and vitamin D.

Recurrent laryngeal nerve (RLN) injury occurs in less than 5% of patients. Of those with injury, approximately 10% are permanent. As the thyroid gland is dissected from lateral to medial, the dissection near the inferior thyroid artery is a common area for RLN injury. At the conclusion of the operation, direct laryngoscopy confirms normal vocal cord apposition. The cord on the affected side will be in the paramedian position. If bilateral RLN has occurred, the chance of a successful

extubation is poor. The cords are found to be in the midline, and an early sign of respiratory distress is stridor with labored breathing. If paralysis of the cords is not permanent, function may return 1 to 2 months after injury. Permanent RLN injury can be treated by various techniques to stent the cords in a position of function.

Superior laryngeal nerve injury is less debilitating, as the common symptom is loss of projection of the voice. The glottic aperture is asymmetrical on direct laryngoscopy and management is limited to clinical observation.

RESPIRATORY SYSTEM

Surgical complications that put the respiratory system in jeopardy are not always confined to technical errors. Malnutrition, inadequate pain control, inadequate mechanical ventilation, inadequate pulmonary toilet, and aspiration can cause serious pulmonary problems.

Pneumothorax can occur from central line insertion during anesthesia or from a diaphragmatic injury during an abdominal procedure. Hypotension, hypoxemia, and tracheal deviation away from the affected side may be present. A tension pneumothorax can cause complete cardiovascular collapse. Treatment is by needle thoracostomy, followed by tube thoracostomy. A large-bore needle is placed either in the midclavicular line in the second rib interspace, or where the chest tube will be inserted, the fifth intercostal space in the anterior axillary line.

Hemothorax due to trauma or intrathoracic disease should be evacuated completely. A delay in evacuation of the hemothorax leaves the patient at risk for empyema and entrapped lung. If evacuation is incomplete with tube thoracostomy, video-assisted thoracoscopy or open evacuation and pleurodesis may be required.

Pulmonary atelectasis results in a loss of functional residual capacity (FRC) of the lung, and can predispose to pneumonia. Poor pain control in the postoperative period contributes to poor inspiratory effort and collapse of the lower lobes in particular. An increase in FRC by 700 mL or more can be accomplished by sitting patients up to greater than 45°. For mechanically ventilated patients, simply placing the head of the bed at 30 to 45° in elevation improves pulmonary outcomes. The prevention of atelectasis is facilitated by delivering adequate tidal volumes (8 to 10 mL/kg), preventing the abdominal domain from impinging on the thoracic cavity, and by sitting the patient up as much as possible. This includes having the ventilated patient out of bed and sitting in a chair if possible.

Aspiration complications include pneumonitis and pneumonia. The treatment of pneumonitis is similar to that for acute lung injury (ALI) (see below in this section), and includes oxygenation with general supportive care. Antibiotics are usually contraindicated unless known organisms are detected with bacteriologic analysis. Hospitalized patients who develop aspiration pneumonia carry a mortality rate as high as 70 to 80%. Early, aggressive, and repeated bronchoscopy for suctioning of aspirated material from the tracheobronchial tree will help to minimize the inflammatory reaction of pneumonitis and facilitate improved pulmonary toilet.

Patients with inadequate pulmonary toilet are at increased risk for bronchial plugging and lobar collapse. Patients with copious and tenacious secretions develop these plugs most often, but foreign bodies in the bronchus can be the cause of lobar collapse as well. The diagnosis of bronchial plugging is based on chest x-ray and clinical suspicion when there is acute pulmonary decompensation with increased work of breathing and hypoxemia. Fiberoptic bronchoscopy can be useful to clear mucous plugs and secretions.

Pneumonia is the second most common nosocomial infection and is the most common infection in ventilated patients. Ventilator-associated pneumonia (VAP) occurs in 15 to 40% of ventilated ICU patients, and accrues at a daily probability rate

of 5% per day, up to 70% at 30 days. The 30-day mortality rate of nosocomial pneumonia can be as high as 40%, and depends on the microorganisms involved and the timeliness of initiating appropriate treatment.

Once the diagnosis of pneumonia is suspected (an abnormal chest x-ray, fever, productive cough with purulent sputum, and no other obvious fever sources), it is invariably necessary to initially begin treatment with broad-spectrum antibiotics until proper identification, colony count [≥100,000 colony-forming units (CFU)], and sensitivity of the microorganisms are determined.[57] The spectrum of antibiotic coverage should be narrowed as soon as the culture sensitivities are determined. Double-coverage antibiotic strategy for the two pathogens, *Pseudomonas* and *Acinetobacter* spp., may be appropriate if the local prevalence of these particularly virulent organisms is high. One of the most helpful tools in treating pneumonia and other infections is the tracking of a medical center's antibiogram every 6 to 12 months.[58]

Epidural analgesia decreases the risk of perioperative pneumonia. This method of pain control improves pulmonary toilet and the early return of bowel function; both have a significant impact on the potential for aspiration and for acquiring pneumonia. The routine use of epidural analgesia has a lower incidence of pneumonia than patient-controlled analgesia.[59]

ALI is a diagnosis applied to patients with similar findings to those with acute respiratory distress syndrome (ARDS). These should be considered a spectrum of the same disease process, with the difference being in the degree of oxygenation deficits of patients. The pathology, pathophysiology, and the mechanism of lung injury for ALI are the same as for ARDS, except that the arterial oxygen to inspired oxygen (partial pressure of arterial oxygen:fraction of inspired oxygen) ratio is >200 for ALI and <200 for ARDS. Both types of patients will require some form of positive pressure ventilatory assistance to improve the oxygenation deficits, while simultaneously treating the primary etiology of the initiating disease.

The definition of ARDS includes five criteria (Table 12-14). The recent multicenter ARDS Research Network (ARDSnet) research trial demonstrated improved clinical outcomes for ARDS patients ventilated at tidal volumes of only 5 to 7 mL/kg.[60] It is important to note that these ventilator setting recommendations are for patients with ARDS, and not for patients requiring ventilatory support for a variety of other reasons. The beneficial effects of positive end-expiratory pressure (PEEP) for ARDS were confirmed in this study as well. The maintenance of PEEP during ventilatory support is determined based on blood gas analysis, pulmonary mechanics, and requirements for supplemental oxygen. As gas exchange improves with resolving ARDS, the initial step in decreasing ventilatory support should be to decrease the levels of supplemental oxygen first, and then to slowly bring the PEEP levels back down to minimal levels.[61] This is done to minimize the potential for recurrent alveolar collapse and a worsening gas exchange.

Table 12-14 Inclusion Criteria for the Acute Respiratory Distress Syndrome
Acute onset
Predisposing condition
Pa_{O_2}:Fi_{O_2} <200 (regardless of positive end-expiratory pressure)
Bilateral infiltrates
Pulmonary artery occlusion pressure <18 mmHg
No clinical evidence of right heart failure

Fi_{O_2} = fraction of inspired oxygen; Pa_{O_2} = partial pressure of arterial oxygen.

Not all patients can be weaned easily from mechanical ventilation. When the respiratory muscle energy demands are not

balanced, or there is an ongoing active disease state external to the lungs, patients may require prolonged ventilatory support. Protocol-driven ventilator weaning strategies are successful and have become part of the standard of care. The use of a weaning protocol for patients on mechanical ventilation greater than 48 hours reduces the incidence of VAP and the overall length of time on mechanical ventilation, when compared with nonprotocol managed ventilator weaning. Unfortunately, there is still no reliable way of predicting which patient will be successfully extubated after a weaning program, and the decision for extubation is based on a combination of clinical parameters and measured pulmonary mechanics.[62] The Tobin Index (frequency:tidal volume ratio), also known as the *rapid shallow breathing index*, is perhaps the best negative predictive instrument.[63] If the result equals less than 105, then there is nearly a 70% chance the patient will pass extubation. If the score is greater than 105, the patient has an approximately 80% chance of failing extubation. Other parameters such as the negative inspiratory force, minute ventilation, and respiratory rate are used, but individually have no better predictive value than the rapid shallow breathing index.[64]

Malnutrition and poor nutritional support may adversely affect the respiratory system. The respiratory quotient (RQ), or respiratory exchange ratio, is the ratio of the rate of carbon dioxide (CO_2) produced to the rate of oxygen uptake (RQ = $V_{CO_2}/\dot{V}_{O_2}$). Lipids, carbohydrates, and protein have differing effects on CO_2 production. Patients consuming a diet consisting mostly of carbohydrates would have an RQ of 1 or greater. The RQ for a diet mostly of lipids would be closer to 0.7, and that for a diet of mostly protein would be closer to 0.8. Ideally, an RQ of 0.75 to 0.85 suggests adequate balance and composition of nutrient intake. An excess of carbohydrate may negatively affect ventilator weaning because of the abnormal RQ due to higher CO_2 production and altered pulmonary gas exchange.

Although not without risk, tracheostomy will decrease the pulmonary dead space and provides for improved pulmonary toilet. When performed before the tenth day of ventilatory support, tracheostomy may decrease the incidence of VAP, the overall length of ventilator time, and the number of ICU patient days.

The occurrence of pulmonary embolism (PE) is probably underdiagnosed. Its etiology stems from DVT. The diagnosis of PE is made when a high degree of clinical suspicion for PE leads to imaging techniques such as ventilation:perfusion nuclear scans or CT pulmonary angiogram. Clinical findings include elevated central venous pressure, hypoxemia, shortness of breath, hypocarbia secondary to tachypnea, and right heart strain noted on EKG. Ventilation:perfusion nuclear scans are often indeterminate in patients who have an abnormal chest x-ray. The pulmonary angiogram remains the gold standard for diagnosing PE, but spiral CT angiogram has become an alternative method because of its relative ease of use and reasonable rates of diagnostic accuracy. For cases without clinical contraindications to therapeutic anticoagulation, patients should be empirically started on heparin infusion until the imaging studies are completed if the suspicion of a PE is strong.

Sequential compression devices on the lower extremities and low-dose subcutaneous heparin administration are routinely used to prevent DVT, and, by inference, the risk of PE. Neurosurgical and orthopedic patients have higher rates of PE, as do obese patients and those at prolonged bed rest.

When anticoagulation is contraindicated, or when a known clot exists in the inferior vena cava (IVC), therapy for PE includes insertion of an IVC filter. The Greenfield filter has been most widely studied, and it has a failure rate of less than 4%. Newer devices include those with nitinol wire that expands with body temperature and retrievable filters. Patients with spinal cord injury and multiple long-bone or pelvic fractures frequently receive IVC filters, and there appears to be a low long-term complication rate with their use.

CARDIAC SYSTEM

Arrhythmias are often seen preoperatively in elderly patients, but may occur postoperatively in any age group. Atrial fibrillation is the most common arrhythmia[65] and occurs between postoperative days 3 to 5 in high-risk patients. This is typically when patients begin to mobilize their interstitial fluid into the vascular fluid space. Contemporary evidence suggests that rate control is more important than rhythm control for atrial fibrillation.[66,67] The first-line treatment includes beta blockade and/or calcium channel blockade. Beta blockade must be used judiciously, because hypotension, as well as withdrawal from beta blockade with rebound hypertension, is possible. Calcium channel blockers are an option if beta blockers are not tolerated by the patient, but caution must be exercised in those with a history of congestive heart failure. Although digoxin is still a faithful standby medication, it has limitations due to the need for optimal dosing levels. Cardioversion may be required if patients become hemodynamically unstable and the rhythm cannot be controlled.

Ventricular arrhythmias and other tachyarrhythmias may occur in surgical patients as well. Similar to atrial rhythm problems, these are best controlled with beta blockade, but the use of other antiarrhythmics or cardioversion may be required if patients become hemodynamically unstable. Formal cardiac electrophysiology studies may be needed to clarify the etiology of the arrhythmias so that medical or surgical treatment can be tailored.

Cardiac ischemia is a cause of postoperative mortality. Acute myocardial infarction (AMI) can present insidiously or it can be more dramatic with the classic presentation of shortness of breath, severe angina, and sudden cardiogenic shock. The work-up to rule out an AMI includes an EKG and cardiac enzyme measurements. The patient should be transferred to a monitored (telemetry) floor as soon as a bed is available. *M*orphine, supplemental *O*xygen, *N*itroglycerine, and *A*spirin (MONA) are the initial therapeutic maneuvers for those who are being investigated for AMI.

Hypertension in the immediate postoperative period may be merely a failure of adequate pain control, but other causes include hypoxia, volume overload, and rebound hypertension from failure to resume beta blockade and/or clonidine. Perioperative hypertension carries significant morbidity and aggressive control is warranted. Twenty to 50% of patients with chronic atherosclerotic disease present with hypertension, and causes of perioperative hypertension include cerebrovascular disease, renal artery stenosis, aorto-occlusive disease, and rarely, pheochromocytoma. Routine perioperative cardiac protection with beta blockade is the standard of care for patients with a history of cardiovascular disease.

GASTROINTESTINAL SYSTEM

Surgery of the esophagus is potentially complicated because of its anatomic location and blood supply. The two primary types of esophageal resection performed are the transhiatal resection and the transthoracic (Ivor-Lewis) resection.[68] The transhiatal resection has the advantage that a formal thoracotomy incision is avoided. The dissection of the esophagus is blind, however, and an anastomotic leak occurs more than with other resections. However, when a leak does occur, simple opening of the cervical incision and draining the leak is all that is usually required.

The transthoracic Ivor-Lewis resection includes an esophageal anastomosis performed in the chest near the level of the azygos vein. These resections tend not to leak as often, but when they do, they can be difficult to control. The reported mortality is about 50% with an anastomotic leak, and the overall mortality is about 5%, which is similar to transhiatal resection. Nutritional support strategies must be considered for esophageal resection patients to maximize the potential for survival.

Nissen fundoplication is an operation that is fraught with possibilities for error. Bleeding is always a potential hazard, so dissection of the short gastric vessels must be done with care. Laparoscopic port site bleeding, injury to the aorta, and liver lacerations can also contribute to significant blood loss. The fundoplication may be too tightly wrapped or become unwrapped

postoperatively. Postoperative edema and patient noncompliance will produce symptoms of odynophagia and dysphagia.

Postoperative ileus is related to dysfunction of the neural reflex axis of the intestine. Excessive narcotic use may delay return of bowel function. Epidural anesthesia results in better pain control, and there is an earlier return of bowel function, and a shorter length of hospital stay. The limited use of nasogastric tubes and the initiation of early postoperative feeding are associated with an earlier return of bowel function.

Numerous studies have shown a decreased length of stay and improved pain control when bowel surgery is performed laparoscopically. In one study, however, patients with open colon resection were fed at the same time as the laparoscopically treated patients and had no difference in hospital length of stay.[69]

Pharmacologic agents commonly used to stimulate bowel function include metoclopramide and erythromycin. Metoclopramide's action is limited to the stomach, and it may help primarily with gastroparesis. Erythromycin is a motilin agonist that works throughout the stomach and bowel. Several studies demonstrate significant benefit from the administration of erythromycin in those suffering from an ileus.[70]

Small bowel obstruction occurs in less than 1% of early postoperative patients. When it does occur, adhesions are usually the cause. Internal and external hernias, technical errors, and infections or abscesses are also causative. No one can accurately predict which patients will form obstructive postoperative adhesions, because all patients who undergo surgery form adhesions to some extent, and there is little that can limit this natural healing process. Hyaluronidase is a mucolytic enzyme that degrades connective tissue, and the use of a methylcellulose form of hyaluronidase, Seprafilm, has been shown to result in a 50% decrease in adhesion formation in some patients.[71,72] This should translate into a lower occurrence of postoperative bowel obstruction, but this has yet to be proven.

Fistulae are the abnormal communication of one structure to an adjacent structure or compartment, and are associated with extensive morbidity and mortality. Common causes for fistula formation are summarized in the pneumonic FRIENDS (*F*oreign body, *R*adiation, *I*schemia/Inflammation/Infection, *E*pithelialization of a tract, *N*eoplasia, *D*istal obstruction, and *S*teroid use). The cause of the fistula must be recognized early, and treatment may include nonoperative management with observation and nutritional support, or a delayed operative management strategy that also includes nutritional support and wound care.

GI bleeding can occur perioperatively (Table 12-15). Technical errors such as a poorly tied suture, a nonhemostatic staple line, or a missed injury can all lead to postoperative intestinal bleeding.[73,74] The source of bleeding is in the upper GI tract about 85% of the time, and is usually detected and treated endoscopically. Surgical control of intestinal bleeding is required in up to 40% of patients.[75]

Table 12-15 Common Causes of Upper and Lower Gastrointestinal Hemorrhage

Upper GI Bleed	**Lower GI Bleed**
Erosive esophagitis	Angiodysplasia
Gastric varices	Radiation proctitis
Esophageal varices	Hemangioma
Dieulafoy's lesion	Diverticulosis
Aortoduodenal fistula	Neoplastic diseases
Mallory-Weiss tear	Trauma
Peptic ulcer disease	Vasculitis

Trauma	Hemorrhoids
Neoplastic disease	Aortoenteric fistula
	Intussusception
	Ischemic colitis
	Inflammatory bowel disease
	Postprocedure bleeding

When patients in the ICU have a major bleed from stress gastritis, the mortality risk is as high as 50%. It is important to keep the gastric pH greater than 4 to decrease the overall risk for stress gastritis, particularly in patients mechanically ventilated for 48 hours or greater and patients who are coagulopathic.[76] Proton pump inhibitors, H_2 receptor antagonists, and intragastric antacid installation are all effective measures.

HEPATOBILIARY-PANCREATIC SYSTEM

Complications involving the hepatobiliary tree are usually due to technical errors. Laparoscopic cholecystectomy has become the standard of care for cholecystectomy, but common bile duct injury remains a nemesis of this approach. Intraoperative cholangiography has not been shown to decrease the incidence of common bile duct injuries, because the injury to the bile duct usually occurs before the cholangiogram.[77,78] Early recognition of an injury is important, because delayed bile duct leaks often require a more complex repair.

Ischemic injury due to devascularization of the common bile duct has a delayed presentation days to weeks after an operation. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrates a stenotic, smooth common bile duct. Liver function studies are elevated. The recommended treatment is a Roux-en-Y hepaticojejunostomy.

A bile leak due to an unrecognized injury to the ducts may present after cholecystectomy as a biloma. These patients may present with abdominal pain and hyperbilirubinemia. The diagnosis of a biliary leak can be confirmed by CT scan, ERCP, or radionuclide scan. Once a leak is confirmed, a retrograde biliary stent and external drainage is the treatment of choice.

Hyperbilirubinemia in the surgical patient can be a complex problem. Cholestasis makes up the majority of causes for hyperbilirubinemia, but other mechanisms of hyperbilirubinemia include reabsorption of blood (e.g., hematoma from trauma), decreased bile excretion (e.g., sepsis), increased unconjugated bilirubin due to hemolysis, hyperthyroidism, and impaired excretion due to congenital abnormalities or acquired disease. Errors in surgery that cause hyperbilirubinemia largely involve missed or iatrogenic injuries.

The presence of cirrhosis predisposes to postoperative complications. Abdominal or hepatobiliary surgery is problematic in the cirrhotic patient. Ascites leak in the postoperative period can be an issue when any abdominal operation has been performed. Maintaining proper intravascular oncotic pressure in the immediate postoperative period can be difficult, and resuscitation should be maintained with crystalloid solutions. Prevention of renal failure and the management of the hepatorenal syndrome can be difficult, as the demands of fluid resuscitation and altered glomerular filtration become competitive. Spironolactone with other diuretic agents may be helpful in the postoperative care. These patients often have a labile course and bleeding complications due to coagulopathy are common. The operative mortality in cirrhotic patients is 10% for Child class A, 30% for Child class B, and 82% for Child class C patients.[79]

Pyogenic liver abscess occurs in less than 0.5% of adult admissions, due to retained necrotic liver tissue, occult intestinal perforations, benign or malignant hepatobiliary obstruction, and hepatic arterial occlusion. The treatment is long-term

antibiotics with percutaneous drainage of large abscesses.

Pancreatitis can occur following injection of contrast during cholangiography and ERCP. These episodes range from a mild elevation in amylase and lipase with abdominal pain, to a fulminant course of pancreatitis with necrosis requiring surgical débridement. Traumatic injuries to the pancreas during surgical procedures on the kidneys, GI tract, or spleen comprise the most common causes. Treatment involves serial CT scans and percutaneous drainage to manage infected fluid and abscess collections. A pancreatic fistula may respond to antisecretory therapy with a somatostatin analogue, Octreotide. Management of these fistulae initially includes ERCP with or without pancreatic stenting, percutaneous drainage of any fistula fluid collections, total parenteral nutrition (TPN) with bowel rest, and repeated CT scans. The majority of pancreatic fistulae will eventually heal spontaneously.

RENAL SYSTEM

Renal failure can be classified as prerenal failure, intrinsic renal failure, and postrenal failure. Postrenal failure, or obstructive renal failure, should always be considered when low urine output (oliguria) or anuria occurs. The most common cause is a misplaced or clogged urinary catheter. Other, less common causes to consider are unintentional ligation or transection of ureters during a difficult surgical dissection (e.g., colon resection for diverticular disease), or a large retroperitoneal hematoma (e.g., ruptured aortic aneurysm).

Oliguria is evaluated by flushing the Foley catheter using sterile technique. When this fails to produce the desired response, it is reasonable to administer an IV fluid challenge with a crystalloid fluid bolus of 500 to 1000 mL. However, the immediate postoperative patient must be examined and have recent vital signs recorded with total intake and output tabulated, as well as urinary electrolytes measured (Table 12-16). A hemoglobin and hematocrit level should be checked immediately. Patients in compensated shock from acute blood loss may manifest anemia and end-organ malperfusion as oliguria.

Table 12-16 Urinary Electrolytes Associated with Acute Renal Failure and Their Possible Etiologies

	FE_{Na}	**Osmolarity**	**UR_{Na}**	**Etiology**
Prerenal	<1	>500	<20	CHF, cirrhosis
Intrinsic failure	>1	<350	>40	Sepsis, shock

CHF = congestive heart failure; FE_{Na} = fractional excretion of sodium; UR_{Na} = urinary excretion of sodium.

Acute tubular necrosis (ATN) carries a mortality risk of 25 to 50% due to the many complications that can cause, or result from, this insult. When ATN is due to poor inflow (prerenal failure), the remedy begins with IV administration of crystalloid or colloid fluids as needed. If cardiac insufficiency is the problem, the optimization of vascular volume is achieved first, followed by inotropic agents, as needed. Intrinsic renal failure and subsequent ATN are often the result of direct renal toxins. Aminoglycosides, vancomycin, and furosemide, among other commonly used agents, contribute directly to nephrotoxicity. Contrast-induced nephropathy usually leads to a subtle or transient rise in creatinine. In patients who are volume depleted or have poor cardiac function, contrast nephropathy may permanently impair renal function.[80–83]

The treatment of renal failure due to myoglobinuria in severe trauma patients has shifted away from the use of sodium bicarbonate for alkalinizing the urine, to merely maintaining brisk urine output of 100 mL/h with crystalloid fluid infusion. Mannitol and furosemide are not recommended as long as the IV fluid achieves the goal rate of urinary output.

MUSCULOSKELETAL SYSTEM

A compartment syndrome can develop in any compartment of the body. Compartment syndrome of the extremities generally occurs after a closed fracture. The injury alone may predispose the patient to compartment syndrome, but aggressive fluid resuscitation can exacerbate the problem. Pain with passive motion is the hallmark of compartment syndrome, and the anterior compartment of the leg is usually the first compartment to be involved. Confirmation of the diagnosis is obtained by direct pressure measurement of the individual compartments. If the pressures are greater than 20 to 25 mmHg in any of the compartments, then a four-compartment fasciotomy is considered. Compartment syndrome can be due to ischemia-reperfusion injury, after an ischemic time of 4 to 6 hours. Renal failure (due to myoglobinuria), foot drop, tissue loss, and a permanent loss of function are possible results of untreated compartment syndrome.

Decubitus ulcers are preventable complications of prolonged bedrest due to traumatic paralysis, dementia, chemical paralysis, or coma. Ischemic changes in the microcirculation of the skin can be significant after 2 hours of sustained pressure. Routine skin care and turning of the patient helps ensure a reduction in skin ulceration. This can be labor intensive and special mattresses and beds are available to help with this ubiquitous problem. The treatment of a decubitus ulcer in the noncoagulopathic patient is surgical débridement. Once the wound bed has a viable granulation base without an excess of fibrinous debris, a vacuum-assisted closure dressing can be applied. Wet to moist dressings with frequent dressing changes is the alternative, and is labor intensive. Expensive topical enzyme preparations are also available. If the wounds fail to respond to these measures, soft tissue coverage by flap is considered.

Contractures are the result of muscle disuse. Whether from trauma, amputation, or from vascular insufficiency, contractures can be prevented by physical therapy and splinting. If not attended to early, contractures will prolong rehabilitation and may lead to further wounds and wound healing issues. Depending on the functional status of the patient, contracture releases may be required for long-term care.

HEMATOLOGIC SYSTEM

The transfusion guideline of maintaining the hematocrit level in all patients at greater than 30% is no longer valid. Only those patients with symptomatic anemia, or those who have significant cardiac disease, or the critically ill patient who requires increased oxygen-carrying capacity to adequately perfuse end organs, requires higher levels of hemoglobin. Other than these select patients, the decision to transfuse should generally not occur until the hemoglobin level reaches 7 mg/dL or the hematocrit reaches 21%.

Transfusion reactions are common complications of blood transfusion. These can be attenuated with a leukocyte filter, but not completely prevented. The manifestations of a transfusion reaction include simple fever, pruritus, chills, muscle rigidity, and renal failure due to myoglobinuria secondary to hemolysis. Discontinuing the transfusion and returning the blood products to the blood bank is an important first step, but administration of antihistamine and possibly steroids may be required to control the reaction symptoms. Severe transfusion reactions are rare but can be fatal.

Infectious complications in blood transfusion range from cytomegalovirus transmission, which is benign in the nontransplant patient, to HIV infection, to passage of the hepatitis viruses, which can lead to subsequent hepatocellular carcinoma. Although the efficiency of infectious agent screening in blood products has improved, universal precautions should be rigidly maintained for all patients (Table 12-17).

Table 12-17 Rate of Viral Transmission in Blood Product Transfusions[a]

HIV	1:1.9 million
HBV[b]	1:137,000
HCV	1:1 million

[a]Post–nucleic acid amplification technology (1999). Earlier rates were erroneously reported higher due to lack of contemporary technology.

[b]HBV is reported with pre–nucleic acid amplification technology. Statistical information is unavailable in post–nucleic acid amplification technology at this writing.

Note that bacterial transmission is 50 to 250 times higher than viral transmission per transfusion.

HBV = hepatitis B virus; HCV = hepatitis C virus.

Patients on warfarin (Coumadin) who require surgery can have anticoagulation reversal by administration of fresh-frozen plasma. Each unit of fresh-frozen plasma contains 200 to 250 mL of plasma and includes one unit of coagulation factor per milliliter of plasma.

Thrombocytopenia may require platelet transfusion for a platelet count less than 20,000/mL when invasive procedures are performed, or when platelet counts are low and ongoing bleeding from raw surface areas persists. One unit of platelets will increase the platelet count by 5000 to 7500 per mL in adults. It is important to delineate the cause of the low platelet count. Usually there is a self-limiting or reversible condition such as sepsis. Rarely, it is due to heparin-induced thrombocytopenia I and II. Complications of heparin-induced thrombocytopenia II can be serious because of the diffuse thrombogenic nature of the disorder. Simple precautions to limit this hypercoagulable state include saline solution flushes instead of heparin solutions, and to limit the use of heparin-coated catheters. The treatment is anticoagulation with synthetic agents such as argatroban.

For patients with uncontrollable bleeding due to disseminated intravascular coagulopathy, an expensive but useful drug is factor VIIa.[84–86] Largely used in hepatic trauma and obstetric emergencies, this agent may mean the difference between life or death in some circumstances. The combination of ongoing, nonsurgical bleeding and renal failure can sometimes be successfully treated with desmopressin.

In addition to classic hemophilia, other inherited coagulation factor deficiencies can be difficult to manage in surgery. When required, transfusion of appropriate replacement products is coordinated with the regional blood bank center before surgery. Other blood dyscrasias seen by surgeons include hypercoagulopathic patients. Those who carry congenital anomalies such as the most common, Factor V Leiden deficiency, as well as protein C and S deficiencies, are likely to form thromboses if inadequately anticoagulated.

ABDOMINAL COMPARTMENT SYNDROME

Abdominal compartment syndrome (ACS) and intra-abdominal hypertension represent the same problem. Multisystem trauma, thermal burns, retroperitoneal injuries, and surgery related to the retroperitoneum are the major initial causative factors that may lead to ACS. Ruptured AAA, major pancreatic injury and resection, or multiple intestinal injuries are also examples of clinical situations in which a large volume of IV fluid resuscitation puts these patients at risk for intra-abdominal hypertension. Manifestations of ACS typically include progressive abdominal distention followed by increased peak airway ventilator pressures, oliguria followed by anuria, and an insidious development of intracranial hypertension.[87] These findings are related to elevation of the diaphragm and inadequate venous return from the vena cava or renal veins secondary to the

transmitted pressure on the venous system.

Measurement of abdominal pressures is easily accomplished by transducing bladder pressures from the urinary catheter after instilling 100 mL of sterile saline into the urinary bladder.[88] A pressure greater than 20 mmHg constitutes intra-abdominal hypertension, but the diagnosis of ACS requires intra-abdominal pressure greater than 25 to 30 mmHg, with at least one of the following: compromised respiratory mechanics and ventilation, oliguria or anuria, or increasing intracranial pressures.[89–91]

The treatment of ACS is to open any recent abdominal incision to release the abdominal fascia, or to open the fascia directly if no abdominal incision is present. Immediate improvement in mechanical ventilation pressures, intracranial pressures, and renal output is usually noted. When expectant management for ACS is considered in the OR, the abdominal fascia should be left open and covered under sterile conditions with plans made for a second-look operation and delayed fascial closure. Patients with intra-abdominal hypertension should be monitored closely with repeated examinations and measurements of bladder pressure, so that any further deterioration is detected and operative management can be initiated. Left untreated, ACS may lead to multiple system end-organ dysfunction or failure, and has a high mortality.

Abdominal wall closure should be attempted every 48 to 72 hours until the fascia can be reapproximated. If the abdomen cannot be closed within 5 to 7 days following release of the abdominal fascia, a large incisional hernia is the net result.

Wounds, Drains, and Infection

WOUND (SURGICAL SITE) INFECTION

There exist no prospective, randomized, double-blind, controlled studies that demonstrate that antibiotics used beyond 24 hours in the perioperative period prevent infections. There is a general trend toward providing a single preoperative dose, as antibiotic prophylaxis may not impart any benefit at all beyond the initial dosing. Irrigation of the operative field and the surgical wound with saline solution has shown benefit in controlling wound inoculum.[92] Irrigation with an antibiotic-based solution has not demonstrated significant benefit in controlling postoperative infection.

Antibacterial-impregnated polyvinyl placed over the operative wound area for the duration of the surgical procedure has not been shown to decrease the rate of wound infection.[93–97] Although skin preparation with 70% isopropyl alcohol has the best bactericidal effect, it is flammable, and could be hazardous when electrocautery is used. The contemporary formulas of chlorhexidine gluconate with isopropyl alcohol or povidone-iodine and iodophor with alcohol are more advantageous.[98–100]

There is a difference between wound colonization and infection. Overtreating colonization is just as injurious as undertreating infection (Table 12-18). The strict definition of wound (soft tissue) infection is more than 10^5 CFU per gram of tissue. This warrants expeditious and proper antibiotic/antifungal treatment.[58,101] Often, however, clinical signs raise enough suspicion that the patient is treated before a confirmatory culture is undertaken. The clinical signs of wound infection include *rubor*, *tumor*, *calor*, and *dolor* (redness, swelling, heat, and pain), and once the diagnosis of wound infection has been established, the most definitive treatment remains open drainage of the wound to facilitate wound dressing care. The use of antibiotics for wound infection treatment should be limited.[102–105]

Table 12-18 Common Causes of Leukocytosis
Infection
Systemic inflammatory response syndrome
Glucocorticoid administration

Splenectomy
Leukemia
Medications
Physiologic stress
Increases in interleukin-1 and tumor necrosis factor

One type of wound dressing/drainage system that is gaining popularity is the vacuum-assisted closure dressing. The principle of the system is to decrease local wound edema and to promote healing through the application of a sterile dressing that is then covered and placed under controlled suction for a period of 2 to 4 days at a time. Although costly, the benefits are frequently dramatic and may offset the costs of nursing care, frequent dressing changes, and operative wound débridement.

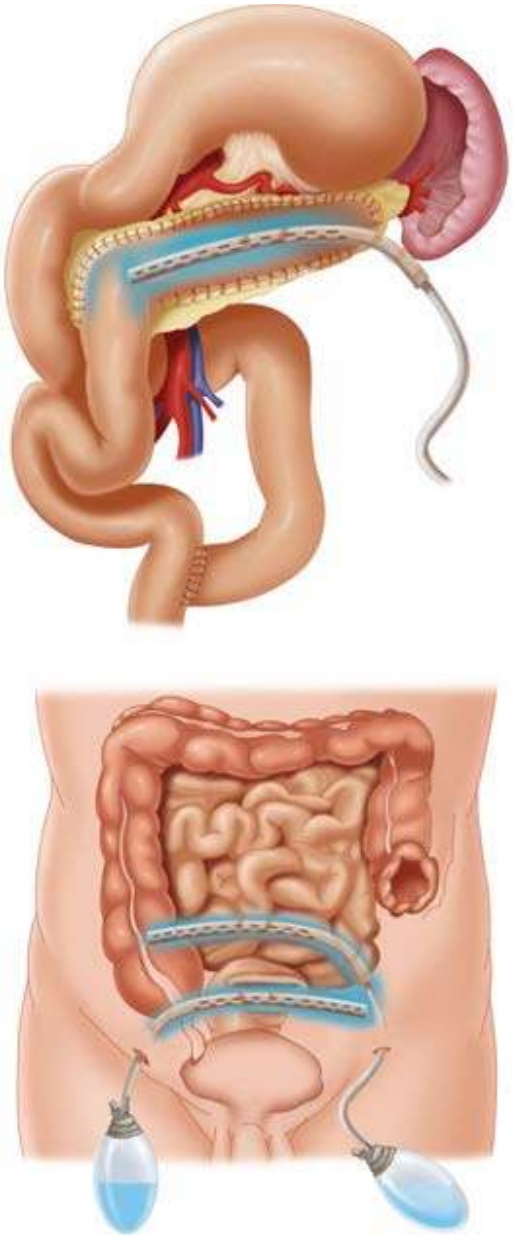
DRAIN MANAGEMENT

The four indications for applying a surgical drain are:

- To collapse surgical dead space in areas of redundant tissue (e.g., neck and axilla)
- To provide focused drainage of an abscess or grossly infected surgical site
- To provide early warning notice of a surgical leak (either bowel contents, secretions, urine, air, or blood)—the so-called *sentinel drain*
- To control an established fistula leak

Open drains are often used for large contaminated wounds such as perirectal or perianal fistulas and subcutaneous abscess cavities. They prevent premature closure of an abscess cavity in a contaminated wound, but do not address the fact that bacteria are free to travel in either direction along the drain tract. More commonly, surgical sites are drained by closed suction drainage systems, but data do not support closed suction drainage to "protect an anastomosis," or to "control a leak" when placed at the time of surgery. Closed suction devices can exert a negative pressure of 70 to 170 mmHg at the level of the drain, therefore the presence of this excess suction may call into question whether an anastomosis breaks down on its own, or if the drain creates a suction injury that promotes leakage (Fig. 12-10).[106]

Fig. 12-10.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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This illustration demonstrates typical intraoperative placement of closed suction devices in pancreatic or small bowel surgery, where there may be an anastomosis. At negative pressures of 70 to 170 mmHg, these devices may actually encourage anastomotic leaks and not prevent them, or become clogged by them.

On the other hand, CT- or ultrasound-guided placement of percutaneous drains is now the standard of care for abscesses, loculated infections, and other isolated fluid collections such as pancreatic leaks. The risk of surgery is far greater than the placement of an image-guided drain, and the risk can often be reduced in these instances by a brief course of antibiotics.

The use of antibiotics when drains are placed should be examined from a cost-benefit perspective. Antibiotics are rarely necessary when a wound is drained widely. Twenty-four to 48 hours of antibiotic use after drain placement is prophylactic, and after this period only specific treatment of positive cultures should be performed, to avoid increased drug resistance and superinfection.

URINARY CATHETERS

Several complications of urinary (Foley) catheters can occur that lead to an increased length of hospital stay and morbidity. It is recommended that the catheter be inserted its full length up to the hub, and that urine flow is established before the balloon is inflated, because misplacement of the catheter in the urethra with premature inflation of the balloon can lead to tears and disruption of the urethra.

Enlarged prostatic tissue can make catheter insertion difficult, and a catheter coudé may be required. If this attempt is also unsuccessful, then a urologic consultation for endoscopic placement of the catheter may be required to prevent harm to the urethra. For patients with urethral strictures, filiform-tipped catheters and followers may be used, but these can potentially cause bladder injury. If endoscopic attempts fail, the patient may require a percutaneously placed suprapubic catheter to obtain decompression of the bladder. Follow-up investigations of these patients are recommended so definitive care of the urethral abnormalities can be pursued.

The most frequent nosocomial infection is urinary tract infection (UTI). These infections are classified into complicated and uncomplicated forms. The uncomplicated type is a UTI that can be treated with trimethoprim-sulfamethoxazole for 3 days. The complicated UTI usually involves the hospitalized patient with an indwelling catheter whose UTI is diagnosed as part of a fever work-up. The interpretation of urine culture results of less than 100,000 CFU/mL is controversial. Before treating such a patient, one should change the catheter and then repeat the culture to see if the catheter was simply colonized with organisms. On the other hand, an argument can be made that, until the foreign body (catheter) is removed, the bladder will continue to be the nidus of infection, and antibiotics should be started. Cultures with more than 100,000 CFU/mL should be treated with the appropriate antibiotics and the catheter removed as soon as possible. Undertreatment or misdiagnosis of a UTI can lead to urosepsis and septic shock.

Recommendations are mixed on the proper way to treat *Candida albicans* fungal bladder infections. Continuous bladder washings with fungicidal solution for 72 hours have been recommended, but this is not always effective. Replacement of the urinary catheter and a course of fluconazole are appropriate treatments, but some infectious disease specialists claim that *C. albicans* in the urine may serve as an indication of fungal infection elsewhere in the body. If this is the case, then screening cultures for other sources of fungal infection should be performed whenever a fungal UTI is found.

EMPYEMA

One of the most debilitating infections is an empyema, or infection of the pleural space. Frequently, an overwhelming pneumonia is the source of an empyema, but a retained hemothorax, systemic sepsis, esophageal perforation from any cause, and infections with a predilection for the lung (e.g., tuberculosis) are potential etiologies as well. The diagnosis is confirmed by chest x-ray or CT scan, followed by aspiration of pleural fluid for bacteriologic analysis. Gram's stain, lactate dehydrogenase, protein, pH, and cell count are obtained, and broad-spectrum antibiotics are initiated while the laboratory studies are performed. Once the specific organisms are confirmed, anti-infective agents are tailored appropriately. Placement of a thoracostomy tube is needed to evacuate and drain the infected pleural fluid, but depending on the specific nidus of infection, video-assisted thoracoscopy may also be helpful for irrigation and drainage of the infection.

ABDOMINAL ABSCESSES

Postsurgical intra-abdominal abscesses can present with vague complaints of intermittent abdominal pain, fever, leukocytosis, and a change in bowel habits. Depending on the type and timing of the original procedure, the clinical

assessment of these complaints is sometimes difficult, and a CT scan is usually required. When a fluid collection within the peritoneal cavity is found on CT scan, antibiotics and percutaneous drainage of the collection is the treatment of choice. There should still be a determination as to what the cause of the infection was, so tailored antibiotic therapy can be initiated. Initial antibiotic treatment is usually with broad-spectrum antibiotics such as piperacillin-tazobactam or imipenem. Should the patient exhibit signs of peritonitis and/or have free air on x-ray or CT scan, then re-exploration should be considered.

For patients who present primarily (i.e., not postoperatively) with the clinical and radiologic findings of an abscess but are clinically stable, the etiology of the abscess must be determined. A plan for drainage of the abscess and decisions about further diagnostic studies with consideration of the timing of any definitive surgery all need to be balanced. This can be a complex set of decisions, depending on the etiology (e.g., appendicitis or diverticulitis); but if the patient exhibits signs of peritonitis, urgent surgical exploration should be performed.

NECROTIZING FASCIITIS

Postoperative infections that progress to the fulminant soft tissue infection known as *necrotizing fasciitis* are uncommon. Group A streptococcal (M types 1, 3, 12, and 28) soft tissue infections, as well as infections with *Clostridium perfringens* and *C. septicum* carry a mortality of 30 to 70%. Septic shock can be present and patients can become hypotensive less than 6 hours following inoculation. Manifestations of a group A *Streptococcus pyogenes* infection in its most severe form include hypotension, renal insufficiency, coagulopathy, hepatic insufficiency, ARDS, tissue necrosis, and erythematous rash.

These findings constitute a surgical emergency and the mainstay of treatment remains wide débridement of the necrotic tissue to the level of bleeding, viable tissue. A gray serous fluid at the level of the necrotic tissue is usually noted, and as the infection spreads, thrombosed blood vessels are noted along the tissue planes involved with the infection. Typically, the patient requires serial trips to the OR for wide débridement until the infection is under control. Antibiotics are an important adjunct to surgical débridement and broad-spectrum coverage should be used because these infections may be polymicrobial (i.e., so-called *mixed-synergistic infections*). *S. pyogenes* is eradicated with penicillin, and it should still be used as the initial drug of choice.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME, SEPSIS, AND MULTIPLE-ORGAN DYSFUNCTION SYNDROME

The systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS) carry significant mortality risks (Table 12-19). Specific criteria have been established for the diagnosis of SIRS (Table 12-20), but two criteria are not required for the diagnosis of SIRS: lowered blood pressure and blood cultures positive for infection. SIRS is the result of proinflammatory cytokines related to tissue malperfusion or injury. The dominant cytokines implicated in this process include interleukin-1, interleukin-6, and tissue necrosis factor. Other mediators include nitric oxide, inducible macrophage-type nitric oxide synthase, and prostaglandin I_2.

Table 12-19 Mortality Associated with Patients Exhibiting Two or More Criteria for Systemic Inflammatory Response Syndrome (SIRS)

Prognosis	Mortality (%)
2 SIRS criteria	5
3 SIRS criteria	10
4 SIRS criteria	15–20

Table 12-20 Inclusion Criteria for the Systemic Inflammatory Response Syndrome
Temperature >38°C or <36°C (>100.4°F or <96.8°F)
Heart rate >90 beats/min
Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg
White blood cell count <4000 or >12,000 cells/mm^3 or >10% immature forms

$PaCO_2$ = partial pressure of arterial carbon dioxide.

Sepsis is categorized as sepsis, severe sepsis, and septic shock. An oversimplification of sepsis would be to define it as SIRS plus infection. Severe sepsis is defined as sepsis plus signs of cellular hypoperfusion or end-organ dysfunction. Septic shock would then be sepsis associated with hypotension after adequate fluid resuscitation.

MODS is the culmination of septic shock and multiple end-organ failure.[107] Usually there is an inciting event (e.g., perforated sigmoid diverticulitis), and as the patient undergoes resuscitation, he or she develops cardiac hypokinesis and oliguric or anuric renal failure, followed by the development of ARDS and eventually septic shock with death.

Management of SIRS/MODS includes aggressive global resuscitation and support of end-organ perfusion, correction of the inciting etiology, control of infectious complications, and management of iatrogenic complications.[108–110] Drotrecogin α, or recombinant activated protein C, appears to specifically counteract the cytokine cascade of SIRS/MODS, but its use is still limited.[111,112] Other adjuncts for supportive therapy include tight glucose control, low tidal volumes in ARDS, vasopressin in septic shock, and steroid replacement therapy.

Nutritional and Metabolic Support Complications

NUTRITION-RELATED COMPLICATIONS

A basic principle is to use enteral feeding whenever possible, but complications can intervene such as aspiration, ileus, and to a lesser extent, sinusitis. There is no difference in aspiration rates when a small-caliber feeding tube is placed transpylorically into the duodenum or if it remains in the stomach. Patients who are fed via nasogastric tubes are at risk for aspiration pneumonia, because these relatively large-bore tubes stent open the esophagus, creating the possibility of gastric reflux. The use of enteric and gastric feeding tubes obviates complications of TPN, such as pneumothorax, line sepsis, upper extremity DVT, and the related expense. There is growing evidence to support the initiation of enteral feeding in the early postoperative period, before the return of bowel function, where it is usually well tolerated.

In patients who have had any type of nasal intubation that are having high, unexplained fevers, sinusitis must be entertained as a diagnosis. CT scan of the sinuses is warranted, followed by aspiration of sinus contents so the organism(s) are appropriately treated.

Patients who have not been enterally fed for prolonged periods secondary to multiple operations, those who have had enteral feeds interrupted for any other reason, or those with poor enteral access are at risk for the refeeding syndrome, which is characterized by severe hypophosphatemia and respiratory failure. Slow progression of the enteral feeding administration rate can avoid this complication.

Common TPN problems are mostly related to electrolyte abnormalities that may develop. These electrolyte errors include

deficits or excesses in sodium, potassium, calcium, magnesium, and phosphate. Acid-base abnormalities can also occur with the improper administration of acetate or bicarbonate solutions.

The most common cause for hypernatremia in hospitalized patients is underresuscitation, and conversely, hyponatremia is most often caused by fluid overload. Treatment for hyponatremia is fluid restriction in mild or moderate cases and the administration of hypertonic saline for severe cases. An overly rapid correction of the sodium abnormality may result in central pontine myelinolysis, which results in a severe neurologic deficit. Treatment for hyponatremic patients includes fluid restriction to correct the free water deficit by 50% in the first 24 hours. An overcorrection of hyponatremia can result in severe cerebral edema, a neurologic deficit, or seizures.

GLYCEMIC CONTROL

In 2001, Van den Berghe and colleagues demonstrated that tight glycemic control by insulin infusion is associated with a 50% reduction in mortality in the critical care setting.[113] This prospective, randomized, controlled trial of 1500 patients had two study arms: the intensive-control arm, where the serum glucose was maintained between 80 and 110 mg/dL with insulin infusion; and the control arm, where patients received an insulin infusion only if blood glucose was greater than 215 mg/dL, but serum glucose was then maintained at 180 to 200 mg/dL.

The tight glycemic control group had an average serum glucose level of 103 mg/dL, and the average glucose level in the control group was 153 mg/dL. Hypoglycemic episodes (glucose <40 mg/dL) occurred in 39 patients in the tightly controlled group, while the control group had episodes in 6 patients. The overall mortality was reduced from 8% to 4.6%, but the mortality of those patients whose ICU stay lasted longer than 5 days was reduced from 20% to 10%. Secondary findings included an improvement in overall morbidity, a decreased percentage of ventilator days, less renal impairment, and a lower incidence of bloodstream infections. These finding have been corroborated by subsequent similar studies, and the principal benefit appears to be a greatly reduced incidence of nosocomial infections and sepsis. It is not known whether the benefits are due to strict euglycemia, to the anabolic properties of insulin, or both, but the maintenance of strict euglycemia appears to be a powerful therapeutic strategy.[113–115]

METABOLISM-RELATED COMPLICATIONS

"Stress dose steroids" have been advocated for the perioperative treatment of patients on corticosteroid therapy, but recent studies strongly discourage the use of supraphysiologic doses of steroids when patients are on low or maintenance doses (e.g., 5 to 15 mg) of prednisone daily. Parenteral glucocorticoid treatment need only replicate physiologic replacement steroids in the perioperative period. When patients are on steroid replacement doses equal to or greater than 20 mg per day of prednisone, it may be appropriate to administer additional glucocorticoid doses for no more than two perioperative days.[116–118]

Adrenal insufficiency may be present in patients with a baseline serum cortisol less than 20 µg/dL. A rapid provocative test with synthetic adrenocorticotropic hormone may confirm the diagnosis. After a baseline serum cortisol level is drawn, 250 µg of cosyntropin is administered. At exactly 30 and 60 minutes following the dose of cosyntropin, serum cortisol levels are obtained. There should be an incremental increase in the cortisol level of between 7 and 10 µg/dL for each half hour. If the patient is below these levels, a diagnosis of adrenal insufficiency is made, and glucocorticoid and mineralocorticoid administration is then warranted. Mixed results are common, but the complication of performing major surgery on an adrenally insufficient patient is sudden or profound hypotension.[108]

Thyroid hormone abnormalities usually consist of previously undiagnosed thyroid abnormalities. Hypothyroidism and the so-

called *sick-euthyroid syndrome* are more commonly recognized in the critical care setting. When surgical patients are not progressing satisfactorily in the perioperative period, screening for thyroid abnormalities should be performed. If the results show mild to moderate hypothyroidism, then thyroid replacement should begin immediately and thyroid function studies monitored closely. All patients should be reassessed after the acute illness has subsided regarding the need for chronic thyroid replacement therapy.

Problems with Thermoregulation

HYPOTHERMIA

Hypothermia is defined as a core temperature less than 35°C (95°F), and is divided into subsets of mild [35 to 32°C, (95 to 89.6°F)], moderate [32 to 28°C (89.6 to 82.4°F)], and severe [<28°C, (<82.4°F)] hypothermia. Shivering, the body's attempt to reverse the effects of hypothermia, occurs between 37 and 31°C (98.6 and 87.8°F), but ceases at temperatures below 31°C (87.8°F). Patients who are moderately hypothermic are at higher risk for complications than are those who are more profoundly hypothermic.

Hypothermia creates a coagulopathy that is related to platelet and clotting cascade enzyme dysfunction. This triad of metabolic acidosis, coagulopathy, and hypothermia is commonly found in long operative cases, and in patients with blood dyscrasias. The enzymes that contribute to the clotting cascade and platelet activity are most efficient at normal body temperatures; therefore all measures must be used to reduce heat loss intraoperatively.[119]

The most common cardiac abnormality is the development of arrhythmias when body temperature drops below 35°C (95°F). Bradycardia occurs with temperatures below 30°C (86°F). It is well known that hypothermia may induce CO_2 retention resulting in respiratory acidosis. Renal dysfunction of hypothermia manifests itself as a paradoxic polyuria, and is related to an increased glomerular filtration rate, as peripheral vascular constriction creates central shunting of blood. This is potentially perplexing in patients that are undergoing resuscitation for hemodynamic instability, because the brisk urine output provides a false sense of an adequate intravascular fluid volume.

Neurologic dysfunction is inconsistent in hypothermia, but a deterioration in reasoning and decision-making skills progresses as body temperature falls, and profound coma (and a flat electroencephalogram) occurs as the temperature drops below 30°C (86°F). The diagnosis of hypothermia is important, so accurate measurement techniques are required to get a true core temperature.

Methods used to warm patients include warm air circulation over the patient, and heated IV fluids, and more aggressive measures such as bilateral chest tubes with warm solution lavage, intraperitoneal rewarming lavage, and extracorporeal membrane oxygenation. A rate of temperature rise of 2 to 4°C/h (3.6 to 7.2°F/h) is considered adequate, but the most common complication for nonbypass rewarming is arrhythmia with ventricular arrest.

HYPERTHERMIA

Hyperthermia is a core temperature greater than 38.6°C (101.5°F), and has a host of etiologies (Table 12-21).[120] Hyperthermia can be environmentally induced (e.g., summer heat with inability to dissipate heat or control exposure), iatrogenically induced (e.g., heat lamps and medications), endocrine in origin (e.g., thyrotoxicosis), or neurologically induced (i.e., hypothalamic).

Table 12-21 Common Causes of Elevated Temperature in Surgical Patients

Hyperthermia	Hyperpyrexia
Environmental	Sepsis
Malignant hyperthermia	Infection
Neuroleptic malignant syndrome	Drug reaction
Thyrotoxicosis	Transfusion reaction
Pheochromocytoma	Collagen disorders
Carcinoid syndrome	Factitious syndrome
Iatrogenic	Neoplastic disorders
Central/hypothalamic responses	
Pulmonary embolism	
Adrenal insufficiency	

Malignant hyperthermia occurs after exposure to agents such as succinylcholine and some halothane-based inhalational anesthetics. The presentation is dramatic, with rapid onset of increased temperature, rigors, and myoglobinuria related to myonecrosis. Medications must be discontinued immediately and dantrolene administered (2.5 mg/kg every 5 minutes) until symptoms subside. Aggressive cooling methods are also implemented, such as an alcohol bath, or packing in ice. In cases of severe malignant hyperthermia, the mortality rate is nearly 30%.

Thyrotoxicosis can occur after surgery, due to undiagnosed Graves' disease. Hyperthermia [>40°C, (104°F)], anxiety, copious diaphoresis, congestive heart failure (present in about one fourth of episodes), tachycardia (most commonly atrial fibrillation), and hypokalemia (up to 50% of patients) are hallmarks of the disease. The treatment of thyrotoxicosis includes glucocorticoids, propylthiouracil, beta blockade, and iodide (Lugol's solution) delivered in an emergent fashion. As the name suggests, these patients are usually toxic and require supportive measures as well. Acetaminophen, cooling modalities noted in the paragraph above, and vasoactive agents often are indicated.

ISSUES IN CARING FOR OBESE PATIENTS AND PATIENTS AT THE EXTREMES OF AGE

Surgery in the obese patient has multiple risks, and it is important to optimize these patients before surgery to minimize these risks. Optimization begins preoperatively with teaching about dietary modifications, exercise, and pulmonary toilet issues. Obese patients often have eccentric left ventricular hypertrophy, right ventricular hypertrophy, and congestive heart failure. Sleep studies and patient history may also reveal significant sleep apnea and gastroesophageal reflux disease. Glycemic control is often poor and contributes significantly to infection and diabetes. The obese patient has a decrease in antithrombin III levels, and a higher risk of DVT and PE. Measures to optimize physiologic function in obese patients include keeping the head of the bed elevated at all times. This can improve the FRC of the lungs by almost a liter, thereby decreasing complications associated with atelectasis and pneumonia. Proper glycemic control via a tight insulin sliding scale is also recommended. Finally, the risk of DVT may be attenuated by immediate use of prophylactic doses of low molecular weight heparin and early ambulation.

Issues for surgery in the very young and the very old have many similarities when it comes to potential errors and complications. Perhaps the most notable similarity is the lack of physiologic reserve. The elderly may have end-organ insufficiency, while the young can have underdeveloped or anomalous organ function that may not yet have become manifest. Similarly, the immune responses at the extremes of age are often compromised. This makes diagnosing an

infection difficult; elderly adults may not be capable of mounting a febrile response, and young children can often resolve fevers overnight, and the cause may remain undiagnosed.

Other alterations in these groups include the amount and distribution of total body water and total body fat. This is important to consider because some medications are predominantly distributed to fat stores, and this deposition may lead to altered drug clearance. Similarly, total body water is decreased and serum concentrations of medications may be higher than anticipated. In both groups there is a lower lean body mass, which may potentiate the adverse effects of some anesthetic agents. Metabolism of various analgesic and anesthetic agents can be protracted, leading to postoperative problems such as prolonged intubation and the need for the administration of reversal agents.

Other issues that can lead to complex decision making include those related to communication. Whether due to neurologic impairments, agitation, confusion, or an inability to comprehend a language, these factors associated with the extremes of age increase the potential for medical errors. Open and direct communication with the supporting family members is critical for optimal outcomes in these patient groups.

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KEY POINTS

1. The delivery of modern critical care is predicated on the ability to monitor a large number of physiologic variables and formulate evidenced-based therapeutic strategies to manage these variables.

2. Technologic advances in monitoring have at least a theoretical risk of exceeding our ability to understand the clinical implications of the derived information. This could result in the use of monitoring data to make inappropriate clinical decisions. Therefore, the implementation of any new monitoring technology must take into account the relevance and accuracy of the data obtained, the risks to the patient, as well as the evidence supporting any intervention directed at correcting the detected abnormality.

3. The routine use of invasive monitoring devices, specifically the pulmonary artery catheter, must be questioned in light of the available evidence that does not demonstrate a clear benefit to its widespread use in various populations of critically ill patients.

4. The future of physiologic monitoring will be dominated by the application of noninvasive and highly accurate devices that guide evidenced-based therapy.

BACKGROUND

The Latin verb *monere*, which means "to warn, or advise" is the origin for the English word *monitor*. In contemporary medical practice, patients undergo monitoring to detect pathologic variations in physiologic parameters, providing advanced warning of impending deterioration in the status of one or more organ systems. The intended goal of this endeavor is that by using this knowledge, the clinician takes appropriate actions in a timely fashion to prevent or ameliorate the physiologic derangement. Furthermore, physiologic monitoring is used not only to warn, but also to titrate therapeutic interventions, such as fluid resuscitation or the infusion of vasoactive or inotropic drugs. Monitoring tools also can be valuable for diagnostic evaluation and assessment of prognosis. The intensive care unit (ICU) and operating room are the two locations where the most advanced monitoring capabilities are routinely used in the care of critically ill patients.

In the broadest sense, physiologic monitoring encompasses a spectrum of endeavors, ranging in complexity from the routine and intermittent measurement of the classic vital signs (i.e., temperature, pulse, arterial blood pressure, and respiratory rate) to the continuous recording of the oxidation state of cytochrome oxidase, the terminal element in the mitochondrial electron transport chain. The ability to assess clinically relevant parameters of tissue and organ status and use this knowledge to improve patient outcomes represents the "holy grail" of critical care medicine. Unfortunately, consensus is often lacking regarding the most appropriate parameters to monitor to achieve this goal. Furthermore, making an inappropriate therapeutic decision due to inaccurate physiologic data or misinterpretation of good data can lead to a worse outcome than having no data at all. Of the highest importance is the integration of physiologic data obtained from monitoring

into a coherent and evidenced-based treatment plan. Current technologies available to assist the clinician in this endeavor are summarized in this chapter, as well as a brief look at emerging techniques that may soon enter into clinical practice.

In essence, the goal of hemodynamic monitoring is to ensure that the flow of oxygenated blood through the microcirculation is sufficient to support aerobic metabolism at the cellular level. Mammalian cells cannot store oxygen (O_2) for subsequent use in oxidative metabolism, although a relatively tiny amount is stored in muscle tissue as oxidized myoglobin. Thus aerobic synthesis of adenosine triphosphate, the energy "currency" of cells, requires the continuous delivery of O_2 by diffusion from hemoglobin (Hgb) in red blood cells to the oxidative machinery within mitochondria. Delivery of O_2 to mitochondria may be insufficient for several reasons.

For example, cardiac output, Hgb, or the O_2 content of arterial blood can each be inadequate for independent reasons. Alternatively, despite adequate cardiac output, perfusion of capillary networks can be impaired as a consequence of dysregulation of arteriolar tone, microvascular thrombosis, or obstruction of nutritive vessels by sequestered leukocytes or platelets. Hemodynamic monitoring that does not take into account all of these factors will portray an incomplete and perhaps misleading picture of cellular physiology.

Under normal conditions when the supply of O_2 is plentiful, aerobic metabolism is determined by factors other than the availability of O_2. These factors include the hormonal milieu and mechanical workload of contractile tissue. However, in pathologic circumstances when O_2 availability is inadequate, O_2 utilization ($\dot{V}O_2$) becomes dependent upon O_2 delivery ($\dot{D}O_2$). The relationship of $\dot{V}O_2$ to $\dot{D}O_2$ over a broad range of $\dot{D}O_2$ values is commonly represented as two intersecting straight lines. In the region of higher $\dot{D}O_2$ values, the slope of the line is approximately equal to zero, indicating that $\dot{V}O_2$ is largely independent of $\dot{D}O_2$. In contrast, in the region of low $\dot{D}O_2$ values, the slope of the line is nonzero and positive, indicating that $\dot{V}O_2$ is supply dependent. The region where the two lines intersect is called the point of critical O_2 delivery ($\dot{D}O_{2crit}$), and represents the transition from supply-independent to supply-dependent O_2 uptake. Below this critical threshold of O_2 delivery (approximately 4.5 mL/kg per minute), increased O_2 extraction cannot compensate for the delivery deficit; hence, O_2 consumption begins to decrease.[1] The slope of the supply-dependent region of the plot reflects the maximal O_2 extraction capability of the vascular bed being evaluated.

The dual-line representation for depicting $\dot{D}O_2$-$\dot{V}O_2$ relationships has proven useful and informative. Nevertheless, other approaches for depicting $\dot{D}O_2$-$\dot{V}O_2$ relationships may be equally or even more relevant. For example, some investigators believe that experimentally derived $\dot{D}O_2$-$\dot{V}O_2$ data are optimally characterized by using the classic Michaelis-Menten relationship for describing the kinetics of an enzymatic reaction, a view that is prompted by the recognition that the oxygen-consuming reaction in mitochondria is catalyzed by an enzyme, cytochrome oxidase.[2]

ARTERIAL BLOOD PRESSURE

The pressure exerted by blood in the systemic arterial system, commonly referred to as *blood pressure*, is a cardinal parameter measured as part of the hemodynamic monitoring of patients. Extremes in blood pressure are either intrinsically deleterious or are indicative of a serious perturbation in normal physiology. In the past, blood pressure served as a proxy for cardiac output; the term *shock* was used more or less as a synonym for arterial hypotension. Although it is now known that arterial blood pressure is a complex function of both cardiac output and vascular input impedance, clinicians, especially inexperienced ones, tend to assume that the presence of a normal blood pressure is evidence that cardiac output and tissue perfusion are adequate. This assumption is frequently incorrect and is the reason why some critically ill patients may benefit from forms of hemodynamic monitoring in addition to measurement of arterial pressure.

Blood pressure can be determined directly by measuring the pressure within the arterial lumen or indirectly using a cuff around an extremity. When the equipment is properly set up and calibrated, direct intra-arterial monitoring of blood pressure provides accurate and continuous data. Additionally, intra-arterial catheters provide a convenient way to obtain samples of blood for measurements of arterial blood gases and other laboratory studies. Despite these advantages, intra-arterial catheters are invasive devices and occasionally are associated with serious complications. Noninvasive monitoring of blood pressure is desirable in many circumstances.

Noninvasive Measurement of Arterial Blood Pressure

Both manual and automated means for the noninvasive determination of blood pressure use an inflatable cuff to increase pressure around an extremity. If the cuff is too narrow (relative to the extremity), the measured pressure will be artifactually elevated. Therefore, the width of the cuff should be approximately 40% of its circumference.

In addition to using a cuff to cause vascular compression and thereby cessation of blood flow, noninvasive means for measuring blood pressure also require some means for detecting the presence or absence of arterial pulsations. Several methods exist for this purpose. The time-honored approach is the auscultation of the Korotkoff sounds, which are heard over an artery distal to the cuff as the cuff is deflated from a pressure higher than systolic pressure to one less than diastolic pressure. *Systolic pressure* is defined as the pressure in the cuff when tapping sounds are first audible. *Diastolic pressure* is the pressure in the cuff when audible pulsations first disappear.

Another means for pulse detection when measuring blood pressure noninvasively depends upon the detection of oscillations in the pressure within the bladder of the cuff. This approach is simple, and unlike auscultation, can be performed even in a noisy environment (e.g., a busy emergency room). Unfortunately, this approach is neither accurate nor reliable. Other methods, however, can be used to reliably detect the reappearance of a pulse distal to the cuff and thereby estimate systolic blood pressure. Two excellent and widely available approaches for pulse detection are use of a Doppler stethoscope (reappearance of the pulse produces an audible amplified signal) or a pulse oximeter (reappearance of the pulse is indicated by flashing of a light-emitting diode).

A number of automated devices are capable of repetitively measuring blood pressure noninvasively. Some of these devices measure pressure oscillations in the inflatable bladder encircling the extremity to detect arterial pulsations as pressure in the cuff is gradually lowered from greater than systolic to less than diastolic pressure.[3] Another automated noninvasive device uses a piezoelectric crystal positioned over the brachial artery as a pulse detector.[3] According to one clinical study of these approaches, the most accurate is oscillometry combined with stepped deflation of the sphygmomanometric cuff. Using this approach and comparing the results of oscillometry to those obtained by invasive intra-arterial monitoring, errors in the measurement of mean blood pressure greater than 10 or 20 mmHg occur in 0% and 8.5% of readings, respectively.[3]

Another noninvasive approach for measuring blood pressure relies on a technique called *photoplethysmography*. This method is capable of providing continuous information because systolic and diastolic blood pressures are recorded on a beat-to-beat basis. Photoplethysmography uses the transmission of infrared light to estimate the amount of Hgb (directly related to the volume of blood) in a finger placed under a servo-controlled inflatable cuff. A feedback loop controlled by a microprocessor continually adjusts the pressure in the cuff to maintain the blood volume of the finger constant. Under these conditions, the pressure in the cuff reflects the pressure in the digital artery. Although results obtained using photoplethysmography generally agree closely with those obtained by invasive monitoring of blood pressure, the difference between the two methods occasionally can be large (20 to 40 mmHg) in some patients.[4] This problem limits the usefulness of

photoplethysmography as a stand-alone method for monitoring arterial blood pressure, particularly in high-risk situations. However, if initial photoplethysmographic readings are corrected by comparison with measurements obtained noninvasively by an oscillometric device, then photoplethysmography is sufficiently accurate to be used for continuous monitoring in most situations.[4]

Invasive Monitoring of Arterial Blood Pressure

Direct monitoring of arterial pressure in critically ill patients may be performed by using fluid-filled tubing to connect an intra-arterial catheter to an external strain-gauge transducer. The signal generated by the transducer is electronically amplified and displayed as a continuous waveform by an oscilloscope. Digital values for systolic and diastolic pressure also are displayed. Mean pressure, calculated by electronically averaging the amplitude of the pressure waveform, also can be displayed.

The fidelity of the catheter-tubing-transducer system is determined by numerous factors, including the compliance of the tubing, the surface area of the transducer diaphragm, and the compliance of the diaphragm. If the system is underdamped, then the inertia of the system, which is a function of the mass of the fluid in the tubing and the mass of the diaphragm, causes overshoot of the points of maximum positive and negative displacement of the diaphragm during systole and diastole, respectively. Thus in an underdamped system, systolic pressure will be overestimated and diastolic pressure will be underestimated. In an overdamped system, displacement of the diaphragm fails to track the rapidly changing pressure waveform, and systolic pressure will be underestimated and diastolic pressure will be overestimated. It is important to note that even in an underdamped or overdamped system, mean pressure will be accurately recorded, provided the system has been properly calibrated. For these reasons, when using direct measurement of intra-arterial pressure to monitor patients, clinicians should make clinical decisions based on the measured mean arterial blood pressure.

The degree of ringing (i.e., overshoot and undershoot) in a minimally damped system is determined by its resonant frequency. Ideally, the resonant frequency of the system should be at least five times greater than the highest frequency component of the pressure waveform. The resonant frequency can be too low for optimal performance if the connector tubing is too compliant or there are air bubbles in the fluid column between the arterial pressure source and the diaphragm of the transducer. For arterial pressure monitoring, the optimal resonance frequency is higher than is practically obtainable. Therefore, to prevent excessive ringing, some degree of damping is essential. To determine if the combination of resonance frequency and damping is adequate, one can pressurize the system to approximately 300 mmHg by pulling the tab that controls the valve between the monitoring system and the high-pressure bag of flush solution. When the valve is abruptly closed by allowing the tab to snap back into its normal position, a sharp pressure transient will be introduced into the system. The resulting pressure tracing can be observed on a strip chart recording. Damping is optimal if at least two oscillations are observed, and there is at least a threefold decrease in the amplitude of successive oscillations.

The radial artery at the wrist is the site most commonly used for intra-arterial pressure monitoring. It is important to recognize, however, that measured arterial pressure is determined in part by the site where the pressure is monitored. Central (i.e., aortic) and peripheral (e.g., radial artery) pressures typically are different as a result of the impedance and inductance of the arterial tree. Systolic pressures typically are higher and diastolic pressures are lower in the periphery, whereas mean pressure is approximately the same in the aorta and more distal sites.

Distal ischemia is an uncommon complication of intra-arterial catheterization. The incidence of thrombosis is increased when larger-caliber catheters are used and when catheters are left in place for an extended period of time. The incidence of

thrombosis can be minimized by using a 20-gauge (or smaller) catheter in the radial artery and removing the catheter as soon as feasible. The risk of distal ischemic injury can be reduced by ensuring that adequate collateral flow is present before catheter insertion. At the wrist, adequate collateral flow can be documented by performing a modified version of the Allen test, wherein the artery to be cannulated is digitally compressed while using a Doppler stethoscope to listen for perfusion in the palmar arch vessels.

Another potential complication of intra-arterial monitoring is retrograde embolization of air bubbles or thrombi into the intracranial circulation. In order to minimize the risk of this rare but potentially devastating complication, great care should be taken to avoid flushing arterial lines when air is present in the system, and only small volumes of fluid (less than 5 mL) should be used for this purpose. Catheter-related infections can occur with any intravascular monitoring device. However, catheter-related bloodstream infection is a relatively uncommon complication of intra-arterial lines used for monitoring, occurring in 0.4 to 0.7% of catheterizations.[5] The incidence increases with longer duration of arterial catheterization.

ELECTROCARDIOGRAPHIC MONITORING

The electrocardiogram (ECG) records the electrical activity associated with cardiac contraction by detecting voltages on the body surface. A standard 3-lead ECG is obtained by placing electrodes that correspond to the left arm (LA), right arm (RA), and left leg (LL). The limb leads are defined as lead I (LA-RA), lead II (LL-RA), and lead III (LL-LA). The ECG waveforms can be continuously displayed on a monitor, and the devices can be set to sound an alarm if an abnormality of rate or rhythm is detected. Continuous ECG monitoring is widely available and applied to critically ill and perioperative patients. Monitoring of the ECG waveform is essential in patients with acute coronary syndromes or blunt myocardial injury, because dysrhythmias are the most common lethal complication. In patients with shock or sepsis, dysrhythmias can occur as a consequence of inadequate myocardial O_2 delivery or as a complication of vasoactive or inotropic drugs used to support blood pressure and cardiac output. Dysrhythmias can be detected by continuously monitoring the ECG tracing, and timely intervention may prevent serious complications. With appropriate computing hardware and software, continuous ST-segment analysis also can be performed to detect ischemia or infarction. This approach has proven useful to detect silent myocardial ischemia in patients undergoing weaning from mechanical ventilation.[6,7]

Additional information can be obtained from a 12-lead ECG, which is essential for patients with potential myocardial ischemia or to rule out cardiac complications in other acutely ill patients. Continuous monitoring of the 12-lead ECG now is available and is proving to be beneficial in certain patient populations. In a study of 185 vascular surgical patients, continuous 12-lead ECG monitoring was able to detect transient myocardial ischemic episodes in 20.5% of the patients.[7] This study demonstrated that the precordial lead V_4, which is not routinely monitored on a standard 3-lead ECG, is the most sensitive for detecting perioperative ischemia and infarction. To detect 95% of the ischemic episodes, two or more precordial leads were necessary. Thus, continuous 12-lead ECG monitoring may provide greater sensitivity than 3-lead ECG for the detection of perioperative myocardial ischemia, and is likely to become standard for monitoring high-risk surgical patients.

CARDIAC OUTPUT AND RELATED PARAMETERS

Bedside catheterization of the pulmonary artery was introduced into clinical practice in the 1970s. Although the pulmonary artery catheter (PAC) initially was used primarily to manage patients with cardiogenic shock and other acute cardiac diseases, indications for this form of invasive hemodynamic monitoring gradually expanded to encompass a wide variety of clinical conditions. Clearly, many clinicians believe that information valuable for the management of critically ill patients is afforded by having a PAC in place. However, unambiguous data in support of this view are scarce, and several studies

suggest that bedside pulmonary artery catheterization may not benefit most critically ill patients, and in fact lead to some serous complications, as is discussed in Effect of Pulmonary Artery Catheterization on Outcome below.

Determinants of Cardiac Performance

PRELOAD

Starling's law of the heart states that the force of muscle contraction depends on the initial length of the cardiac fibers. Using terminology that derives from early experiments using isolated cardiac muscle preparations, preload is the stretch of ventricular myocardial tissue just before the next contraction. Preload is determined by end-diastolic volume (EDV). For the right ventricle, central venous pressure (CVP) approximates right ventricular (RV) end-diastolic pressure (EDP). For the left ventricle, pulmonary artery occlusion pressure (PAOP), which is measured by transiently inflating a balloon at the end of a pressure monitoring catheter positioned in a small branch of the pulmonary artery, approximates left ventricular EDP. The presence of atrioventricular valvular stenosis will alter this relationship.

Clinicians frequently use EDP as a surrogate for EDV, but EDP is determined not only by volume but also by the diastolic compliance of the ventricular chamber. Ventricular compliance is altered by various pathologic conditions and pharmacologic agents. Furthermore, the relationship between EDP and true preload is not linear, but rather is exponential.

AFTERLOAD

Afterload is another term derived from in vitro experiments using isolated strips of cardiac muscle, and is defined as the force resisting fiber shortening once systole begins. Several factors comprise the in vivo correlate of ventricular afterload, including ventricular intracavitary pressure, wall thickness, chamber radius, and chamber geometry. Because these factors are difficult to assess clinically, afterload is commonly approximated by calculating systemic vascular resistance, defined as mean arterial pressure (MAP) divided by cardiac output.

CONTRACTILITY

Contractility is defined as the inotropic state of the myocardium. Contractility is said to increase when the force of ventricular contraction increases at constant preload and afterload. Clinically, contractility is difficult to quantify, because virtually all of the available measures are dependent to a certain degree on preload and afterload. If pressure-volume loops are constructed for each cardiac cycle, small changes in preload and/or afterload will result in shifts of the point defining the end of diastole. These end-diastolic points on the pressure-versus-volume diagram describe a straight line, known as the *isovolumic pressure line*. A steeper slope of this line indicates greater contractility.

Placement of the Pulmonary Artery Catheter

In its simplest form, the PAC has four channels. One channel terminates in a balloon at the tip of the catheter. The proximal end of this channel is connected to a syringe to permit inflation of the balloon with air. Before insertion of the PAC, the integrity of the balloon should be verified by inflating it. To minimize the risk of vascular or ventricular perforation by the relatively inflexible catheter, it is important to verify that the inflated balloon extends just beyond the tip of the device. A second channel in the catheter contains wires that are connected to a thermistor located near the tip of the catheter. At the proximal end of the PAC, the wires terminate in a fitting that permits connection to appropriate hardware for the calculation of cardiac output using the thermodilution technique (see Measurement of Cardiac Output by Thermodilution below). The final two channels are used for pressure monitoring and the injection of the thermal indicator for determinations of cardiac output.

One of these channels terminates at the tip of the catheter; the other terminates 20 cm proximal to the tip.

Placement of a PAC requires access to the central venous circulation. Such access can be obtained at a variety of sites, including the antecubital, femoral, jugular, and subclavian veins. Percutaneous placement through either the jugular or subclavian vein generally is preferred. Right internal jugular vein cannulation carries the lowest risk of complications, and the path of the catheter from this site into the right atrium is straight. In the event of inadvertent arterial puncture, local pressure is significantly more effective in controlling bleeding from the carotid artery as compared to the subclavian artery. Nevertheless, it is more difficult to keep occlusive dressings in place on the neck than in the subclavian fossa. Furthermore, the anatomic landmarks in the subclavian position are quite constant, even in patients with anasarca or massive obesity; the subclavian vein is always attached to the deep (concave) surface of the clavicle. In contrast, the appropriate landmarks to guide jugular venous cannulation are sometimes difficult to discern in obese or very edematous patients. However, ultrasonic guidance has been shown to facilitate bedside jugular venipuncture.[8]

Cannulation of the vein normally is performed percutaneously, using the Seldinger technique. A small-bore needle is inserted through the skin and subcutaneous tissue into the vein. After documenting return of venous blood, a guidewire with a flexible tip is inserted through the needle into the vein and the needle is withdrawn. A dilator/introducer sheath is passed over the wire, and the wire and the dilator are removed. The introducer sheath is equipped with a side port, which can be used for administering fluid. The introducer sheath also is equipped with a diaphragm that permits insertion of the PAC while preventing the backflow of venous blood. The proximal terminus of the distal port of the PAC is connected through low-compliance tubing to a strain-gauge transducer, and the tubing-catheter system is flushed with fluid. While constantly observing the pressure tracing on an oscilloscope, the PAC is advanced with the balloon deflated until respiratory excursions are observed. The balloon is then inflated, and the catheter advanced further, while monitoring pressures sequentially in the right atrium and right ventricle en route to the pulmonary artery. The pressure waveforms for the right atrium, right ventricle, and pulmonary artery are each characteristic and easy to recognize. The catheter is advanced out the pulmonary artery until a damped tracing indicative of the "wedged" position is obtained. The balloon is then deflated, taking care to ensure that a normal pulmonary arterial tracing is again observed on the monitor; leaving the balloon inflated can increase the risk of pulmonary infarction or perforation of the pulmonary artery. Unnecessary measurements of the PAOP are discouraged as rupture of the pulmonary artery may occur.

Hemodynamic Measurements

Even in its simplest embodiment, the PAC is capable of providing clinicians with a remarkable amount of information about the hemodynamic status of patients. Additional information may be obtained if various modifications of the standard PAC are used. By combining data obtained through use of the PAC with results obtained by other means (i.e., blood Hgb concentration and oxyhemoglobin saturation), derived estimates of systemic O_2 transport and utilization can be calculated. Direct and derived parameters obtainable by bedside pulmonary arterial catheterization are summarized in Table 13-1. The equations used to calculate the derived parameters are summarized in Table 13-2. The approximate normal ranges for a number of these hemodynamic parameters (in adults) are shown in Table 13-3.

Table 13-1 Directly Measured and Derived Hemodynamic Data Obtainable by Bedside Pulmonary Artery Catheterization

Standard PAC	PAC with Additional Feature(s)	Derived Parameters
CVP	$S\bar{v}O_2$ (continuous)	SV (or SVI)

PAP	Q_T or Q_T* (continuous)	SVR (or SVRI)
PAOP	RVEF	PVR (or PVRI)
$S\bar{v}O_2$ (intermittent)		RVEDV
Q_T or Q_T* (intermittent)		$\dot{D}O_2$
		$\dot{V}O_2$
		ER
		Q_S/Q_T

CVP = mean central venous pressure; $\dot{D}O_2$ = systemic oxygen delivery; ER = systemic oxygen extraction ratio; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion (wedge) pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; Q_S/Q_T = fractional pulmonary venous admixture (shunt fraction); Q_T = cardiac output; Q_T* = cardiac output indexed to body surface area (cardiac index); RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; SV = stroke volume; SVI = stroke volume index; $S\bar{v}O_2$ = fractional mixed venous (pulmonary artery) hemoglobin saturation; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; $\dot{V}O_2$ = systemic oxygen utilization.

Table 13-2 Formulas for Calculation of Hemodynamic Parameters that Can Be Derived by Using Data Obtained by Pulmonary Artery Catheterization
Q_T* ($L \cdot min^{-1} \cdot m^{-2}$) = Q_T/BSA, where BSA is body surface area (m^2)
SV (mL) = Q_T/HR, where HR is heart rate (min^{-1})
SVR ($dyne \cdot sec \cdot cm^{-5}$) = [(MAP – CVP) x 80]/$Q_T$, where MAP is mean arterial pressure (mmHg)
SVRI ($dyne \cdot sec \cdot cm^{-5} \cdot m^{-2}$) = [(MAP – CVP) x 80]/$Q_T$*
PVR ($dyne \cdot sec \cdot cm^{-5}$) = [(PAP – PAOP) x 80]/QT, where PPA is mean pulmonary artery pressure
PVRI ($dyne \cdot sec \cdot cm^{-5} \cdot m^{-2}$) = [(PAP – PAOP) x 80]/$Q_T$*
RVEDV (mL) = SV/RVEF
$\dot{D}O_2$ ($mL \cdot min^{-1} \cdot m^{-2}$) = Q_T* x CaO_2 x 10, where CaO_2 is arterial oxygen content (mL/dL)
$\dot{V}O_2$ ($mL \cdot min^{-1} \cdot m^{-2}$) = Q_T* x (CaO_2 – $C\bar{v}O_2$) x 10, where $C\bar{v}O_2$ is mixed venous oxygen content (mL/dL)
CaO_2 = (1.36 x Hgb x SaO_2) + (0.003 + PaO_2), where Hgb is hemoglobin concentration (g/dL), SaO_2 is fractional arterial hemoglobin saturation, and PaO_2 is the partial pressure of oxygen in arterial blood

$C\bar{v}O_2$ = (1.36 x Hgb x $S\bar{v}O_2$) + (0.003 + $P\bar{v}$ O_2), where $P\bar{v}O_2$ is the partial pressure of oxygen in pulmonary arterial (mixed venous) blood
Q_S/Q_T = (CcO_2 – CaO_2)/(CcO_2 – $C\bar{v}O_2$), where CcO_2 (mL/dL) is the content of oxygen in pulmonary end capillary blood
CcO_2 = (1.36 x Hgb) + (0.003 + PAO_2), where PAO_2 is the alveolar partial pressure of oxygen
PAO_2 = [FiO_2 x (P_B – P_{H2O})] – $PaCO_2$/RQ, where FiO_2 is the fractional concentration of inspired oxygen, P_B is the barometric pressure (mmHg), P_{H2O} is the water vapor pressure (usually 47 mmHg), $PaCO_2$ is the partial pressure of carbon dioxide in arterial blood (mmHg), and RQ is respiratory quotient (usually assumed to be 0.8)

$C\bar{v}O_2$ = central venous oxygen pressure; CVP = mean central venous pressure; $\dot{D}O_2$ = systemic oxygen delivery; PAOP = pulmonary artery occlusion (wedge) pressure; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; Q_S/Q_T = fractional pulmonary venous admixture (shunt fraction); Q_T = cardiac output; Q_T* = cardiac output indexed to body surface area (cardiac index); RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; SV = stroke volume; SVI = stroke volume index; $S\bar{v}O_2$ = fractional mixed venous (pulmonary artery) hemoglobin saturation; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; $\dot{V}O_2$ = systemic oxygen utilization.

Table 13-3 Approximate Normal Ranges for Selected Hemodynamic Parameters in Adults

Parameter	**Normal Range**
CVP	0–6 mmHg
Right ventricular systolic pressure	20–30 mmHg
Right ventricular diastolic pressure	0–6 mmHg
PAOP	6–12 mmHg
Systolic arterial pressure	100–130 mmHg
Diastolic arterial pressure	60–90 mmHg
MAP	75–100 mmHg
Q_T	4–6 L/min
Q_T*	2.5–3.5 $L \cdot min^{-1} \cdot m^{-2}$
SV	40–80 mL
SVR	800–1400 $dyne \cdot sec \cdot cm^{-5}$
SVRI	1500–2400 $dyne \cdot sec \cdot cm^{-5} \cdot m^{-2}$
PVR	100–150 $dyne \cdot sec \cdot cm^{-5}$
PVRI	200–400 $dyne \cdot sec \cdot cm^{-5} \cdot m^{-2}$
Cao_2	16–22 mL/dL

$C\bar{v}O_2$	~15 mL/dL
$\dot{D}O_2$	400–660 $mL \cdot min^{-1} \cdot m^{-2}$
$\dot{V}O_2$	115–165 $mL \cdot min^{-1} \cdot m^{-2}$

CaO_2 = arterial oxygen content; $C\bar{v}O_2$ = central venous oxygen pressure; CVP = mean central venous pressure; $\dot{D}O_2$ = systemic oxygen delivery; MAP = mean arterial pressure; PAOP = pulmonary artery occlusion (wedge) pressure; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; Q_T = cardiac output; Q_T* = cardiac output indexed to body surface area (cardiac index); SV = stroke volume; SVI = stroke volume index; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; $\dot{V}O_2$ = systemic oxygen utilization.

Measurement of Cardiac Output by Thermodilution

Before the development of the PAC, determining cardiac output (Q_T) at the bedside required careful measurements of O_2 consumption (Fick method) or spectrophotometric determination of indocyanine green dye dilution curves. Measurements of Q_T using the thermodilution technique are simple and reasonably accurate. The measurements can be performed repetitively, and the principle is straightforward. If a bolus of an indicator is rapidly and thoroughly mixed with a moving fluid upstream from a detector, then the concentration of the indicator at the detector will increase sharply and then exponentially diminish back to zero. The area under the resulting time-concentration curve is a function of the volume of indicator injected and the flow rate of the moving stream of fluid. Larger volumes of indicator result in greater areas under the curve, and faster flow rates of the mixing fluid result in smaller areas under the curve. When Q_T is measured by thermodilution, the indicator is heat and the detector is a temperature-sensing thermistor at the distal end of the PAC. The relationship used for calculating Q_T is called the *Stewart-Hamilton equation*:

$$Q_T = [V \times (T_B - T_I) \times K_1 \times K_2] \div \int T_B(t)dt$$

where V is the volume of the indicator injected, T_B is the temperature of blood (i.e., core body temperature), T_I is the temperature of the indicator, K_1 is a constant that is the function of the specific heats of blood and the indicator, K_2 is an empirically derived constant that accounts for several factors (the dead space volume of the catheter, heat lost from the indicator as it traverses the catheter, and the injection rate of the indicator), and $\int T_B(t)dt$ is the area under the time-temperature curve. In clinical practice, the Stewart-Hamilton equation is solved by a microprocessor.

Determination of cardiac output by the thermodilution method is generally quite accurate, although it tends to systematically overestimate Q_T at low values. Changes in blood temperature and Q_T during the respiratory cycle can influence the measurement. Therefore, results generally should be recorded as the mean of two or three determinations obtained at random points in the respiratory cycle. Using cold injectate widens the difference between T_B and T_I and thereby increases signal-to-noise ratio. Nevertheless, most authorities recommend using room temperature injectate (normal saline or 5% dextrose in water) to minimize errors resulting from warming of the fluid as it transferred from its reservoir to a syringe for injection.

Technologic innovations have been introduced that permit continuous measurement of Q_T by thermodilution. In this approach, thermal transients are not generated by injecting a bolus of a cold indicator, but rather by heating the blood with a tiny filament located on the PAC upstream from the thermistor. By correlating the amount of current supplied to the heating

element with the downstream temperature of the blood, it is possible to estimate the average blood flow across the filament and thereby calculate Q_T. Based upon the results of several studies, continuous determinations of Q_T using this approach agree well with data generated by conventional measurements using bolus injections of a cold indicator.[9] Information is lacking regarding the clinical value of being able to monitor Q_T continuously.

Mixed Venous Oximetry

The Fick equation can be written as $Q_T = \dot{V}O_2/(CaO_2 - C\bar{v}O_2)$, where CaO_2 is the content of O_2 in arterial blood and $C\bar{v}O_2$ is the content of O_2 in mixed venous blood. The Fick equation can be rearranged as follows: $C\bar{v}O_2 = CaO_2 - \dot{V}O_2/Q_T$. If the small contribution of dissolved O_2 to $C\bar{v}O_2$ and CaO_2 is ignored, the rearranged equation can be rewritten as $S\bar{v}O_2 = SaO_2 - \dot{V}O_2/(Q_T \times Hgb \times 1.36)$, where $S\bar{v}O_2$ is the fractional saturation of Hgb in mixed venous blood, SaO_2 is the fractional saturation of Hgb in arterial blood, and Hgb is the concentration of Hgb in blood. Thus, it can be seen that $S\bar{v}O_2$ is a function of $\dot{V}O_2$ (i.e., metabolic rate), Q_T, SaO_2, and Hgb. Accordingly, subnormal values of $S\bar{v}O_2$ can be caused by a decrease in Q_T (due, for example, to heart failure or hypovolemia), a decrease in SaO_2 (due, for example, to intrinsic pulmonary disease), a decrease in Hgb (i.e., anemia), or an increase in metabolic rate (due, for example, to seizures or fever). With a conventional PAC, measurements of $S\bar{v}O_2$ require aspirating a sample of blood from the distal (i.e., pulmonary arterial) port of the catheter and injecting the sample into a blood gas analyzer. Therefore for practical purposes, measurements of $S\bar{v}O_2$ can be performed only intermittently.

By adding a fifth channel to the PAC, it has become possible to monitor $S\bar{v}O_2$ continuously. The fifth channel contains two fiber-optic bundles, which are used to transmit and receive light of the appropriate wavelengths to permit measurements of Hgb saturation by reflectance spectrophotometry. A clinical study of the Abbott Oximetrix PAC has documented that the device provides measurements of $S\bar{v}O_2$ that agree quite closely with those obtained by conventional analyses of blood aspirated from the pulmonary artery.[10] Despite the theoretical value of being able to monitor $S\bar{v}O_2$ continuously, data are lacking to show that this capability favorably improves outcome. Indeed, in several studies, the ability to monitor $S\bar{v}O_2$ was not shown to affect the management of critically ill patients.[11,12] Moreover, in another large study, titrating the resuscitation of critically ill patients to maintain $S\bar{v}O_2$ greater than 69% (i.e., in the normal range) failed to improve mortality or change length of ICU stay.[13] In a recent prospective, observational study of 3265 patients undergoing cardiac surgery with either a standard PAC or a PAC with continuous $S\bar{v}O_2$ monitoring, the oximetric catheter was associated with fewer arterial blood gases and thermodilution cardiac output determinations, but no difference in patient outcome.[14] Because PACs that permit continuous monitoring of $S\bar{v}O_2$ are much more expensive than conventional PACs, the routine use of these devices cannot be recommended.

The saturation of O_2 in the right atrium or superior vena cava ($ScvO_2$) correlates closely with $S\bar{v}O_2$ over a wide range of conditions,[15] although the correlation between $ScvO_2$ and $S\bar{v}O_2$ has recently been questioned.[16] Since measurement of $ScvO_2$ requires placement of a central venous catheter (CVC) rather than a PAC, it is somewhat less invasive and easier to carry out. By using a CVC equipped to permit fiber-optic monitoring of $ScvO_2$, it may be possible to titrate the resuscitation of patients with shock using a less invasive device than the PAC.[15,17]

Right Ventricular Ejection Fraction

Ejection fraction (EF) is calculated as (EDV – ESV)/EDV, where ESV is end-systolic volume. EF is an ejection-phase measure of myocardial contractility. By equipping a PAC with a thermistor with a short time constant, the thermodilution method can be used to estimate RVEF. Measurements of RVEF by thermodilution agree reasonably well with those obtained by other

means, although values obtained by thermodilution typically are lower than those obtained by radionuclide cardiography.[18] Stroke volume (SV) is calculated as EDV – ESV. Left ventricular stroke volume (LVSV) also equals Q_T/HR, where HR is heart rate. Because LVSV is equal to RVSV, it is possible to estimate right ventricular end-diastolic volume by measuring RVEF, Q_T, and HR.

Several studies have attempted to assess the clinical value of RVEF measurements using these catheters. In one study, use of an RVEF catheter did not alter therapy in 93% of patients with sepsis, hemorrhagic shock, or acute respiratory distress syndrome (ARDS), but was useful in cases of abdominal compartment syndrome (ACS) with high PAOP despite low preload.[19] In a series of 46 trauma patients who required more than 10 L of fluid in the first 24 hours of resuscitation, there was a better correlation between RV volume and Q_T than there was with PAOP.[20] However, data are lacking to show that outcomes are improved by making measurements of RVEF in addition to Q_T and other parameters measured by the conventional PAC.

Effect of Pulmonary Artery Catheterization on Outcome

In 1996, Connors and colleagues reported surprising results in a major observational study evaluating the value of pulmonary artery catheterization in critically ill patients.[21] They took advantage of an enormous data set, which had been previously (and prospectively) collected for another purpose at five major teaching hospitals in the United States. These researchers compared two groups of patients: those who did and those who did not undergo placement of a PAC during their first 24 hours of ICU care. The investigators recognized that the value of their intended analysis was completely dependent on the robustness of their methodology for case-matching, because sicker patients (i.e., those at greater risk of mortality based upon the severity of their illness) were presumably more likely to undergo pulmonary artery catheterization. Accordingly, the authors used sophisticated statistical methods for generating a cohort of study (i.e., PAC) patients, each one having a paired control matched carefully for severity of illness. A critical assessment of their published findings supports the view that the cases and their controls were indeed remarkably well matched with respect to a large number of pertinent clinical parameters. Connors and associates concluded that placement of a PAC during the first 24 hours of stay in an ICU is associated with a significant increase in the risk of mortality, even when statistical methods are used to account for severity of illness.

Although the report by Connors and coworkers generated an enormous amount of controversy in the medical community, the results reported actually confirmed the results of two prior similar observational studies. The first of these studies used as a database 3263 patients with acute myocardial infarction treated in central Massachusetts in 1975, 1978, 1981, and 1984 as part of the Worcester Heart Attack Study.[22] For all patients, hospital mortality was significantly greater for patients treated using a PAC, even when multivariate statistical methods were used to control for key potential confounding factors such as age, peak circulating creatine kinase concentration, and presence or absence of new Q waves on the ECG. The second large observational study of patients with acute myocardial infarction also found that hospital mortality was significantly greater for patients managed with the assistance of a PAC, even when the presence or absence of "pump failure" was considered in the statistical analysis.[23] In neither of these reports did the authors conclude that placement of a PAC was truly the cause of worsened survival after myocardial infarction.

The available prospective, randomized controlled trials of PACization are summarized in Table 13-4. The study by Pearson and associates was underpowered with only 226 patients enrolled.[24] In addition, the attending anesthesiologists were permitted to exclude patients from the CVP group at their discretion; thus randomization was compromised. The study by

Tuman and coworkers was large (1094 patients were enrolled), but different anesthesiologists were assigned to the different groups.[25] Furthermore, 39 patients in the CVP group underwent placement of a PAC because of hemodynamic complications. All of the individual single-institution studies of vascular surgery patients were relatively underpowered, and all excluded at least certain categories of patients (e.g., those with a history of recent myocardial infarction).[26,27]

Table 13-4 Summary of Randomized, Prospective Clinical Trials Comparing Pulmonary Artery Catheter with Central Venous Pressure Monitoring

Author	Study Population	Groups	Outcomes
Pearson, et al[24]	"Low-risk" patients undergoing cardiac or vascular surgery	CVP catheter (group 1); PAC (group 2); PAC with continuous $Sv\text{-}o_2$, readout (group 3)	No differences among groups for mortality or length of ICU stay; significant differences in costs (group 1 < group 2 < group 3)
Tuman, et al[25]	Cardiac surgical patients	PAC; CVP	No differences between groups for mortality, length of ICU stay, or significant noncardiac complications
Bender, et al[26]	Vascular surgery patients	PAC; CVP	No differences between groups for mortality, length of ICU stay, or length of hospital stay
Valentine, et al[27]	Aortic surgery patients	PAC + hemodynamic optimization in ICU night before surgery; CVP	No difference between groups for mortality or length of ICU stay; significantly higher incidence of postoperative complications in PAC group
Sandham, et al[28]	"High-risk" major surgery	PAC; CVP	No differences between groups for mortality, length of ICU stay; increased incidence of pulmonary embolism in PAC group
Harvey, et al[29]	Medical and surgical ICU patients	PAC vs. no PAC, with option for alternative CO measuring device in non-PAC group	No difference in hospital mortality between the two groups, increased incidence of complications in the PAC group
Binanay, et al[31]	Patients with CHF	PAC vs. no PAC	No difference in hospital mortality between the two groups, increased incidence of adverse events in the PAC group
Wheeler, et al[32]	Patients with ALI	PAC vs. CVC with a fluid and inotropic management protocol	No difference in ICU or hospital mortality, or incidence of organ failure between the two groups; increased incidence of adverse events in the PAC group

ALI = acute lung injury; CHF = congestive heart failure; CO = cardiac output; CVC = central venous catheter; CVP = central venous pressure; ICU = intensive care unit; PAC = pulmonary artery catheter; $Sv\text{-}o_2$ = fractional mixed venous (pulmonary artery) hemoglobin saturation.

In the largest randomized controlled trial of the PAC, Sandham and associates randomized 1994 American Society of Anesthesiologists class III and IV patients undergoing major thoracic, abdominal, or orthopedic surgery to placement of a PAC or CVP catheter.[28] In the patients assigned to receive a PAC, physiologic, goal-directed therapy was implemented by protocol. There were no differences in mortality at 30 days, 6 months, or 12 months between the two groups, and ICU length of stay was similar. There was a significantly higher rate of pulmonary emboli in the PAC group (0.9 vs. 0%). This study has been criticized because most of the patients enrolled were not in the highest risk category.

In the "PAC-Man" trial, a multicenter, randomized trial in 65 United Kingdom hospitals, more than 1000 ICU patients were managed with or without a PAC.[29] The specifics of the clinical management were then left up to the treating clinicians. There

was no difference in hospital mortality between the two groups (with PAC 68% vs. without PAC 66%, *P* = .39). However, a 9.5% complication rate was associated with the insertion or use of the PAC, although none of these complications was fatal. Clearly, these were critically ill patients, as noted by the high hospital mortality rates. Supporters of the PAC may cite methodology problems with this study, such as loose inclusion criteria and the lack of a defined treatment protocol.

A recent meta-analysis of 13 randomized studies of the PAC that included more than 5000 patients was recently published.[30] A broad spectrum of critically ill patients was included in these heterogeneous trials, and the hemodynamic goals and treatment strategies varied. Although the use of the PAC was associated with an increased use of inotropes and vasodilators, there were no differences in mortality or hospital length of stay between the patients managed with a PAC and those managed without a PAC.

Next, the ESCAPE trial (which was one of the studies included in the previous meta-analysis)[31] evaluated 433 patients with severe or recurrent congestive heart failure admitted to the ICU. Patients were randomized to management by clinical assessment and a PAC or clinical assessment without a PAC. The goal in both groups was resolution of congestive heart failure, with additional PAC targets of a pulmonary capillary occlusion pressure of 15 mmHg and a right atrial pressure of 8 mmHg. There was no formal treatment protocol, but inotropic support was discouraged. Substantial reduction in symptoms, jugular venous pressure, and edema was noted in both groups. There was no significant difference in the primary endpoint of days alive and out of the hospital during the first 6 months, or hospital mortality (PAC 10%; vs. without PAC 9%). Adverse events were more common among patients in the PAC group (21.9% vs. 11.5%; *P* = .04).

Finally, the Fluids and Catheters Treatment Trial (FACTT) conducted by the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network was recently published.[32] The risks and benefits of PAC compared with CVCs were evaluated in 1000 patients with acute lung injury. Patients were randomly assigned to receive either a PAC or a CVC to guide management for 7 days via an explicit protocol. Patients also were randomly assigned to a conservative or liberal fluid strategy in a 2 x 2 factorial design (outcomes based on the fluid management strategy were published separately). Mortality during the first 60 days was similar in the PAC and CVC groups (27% and 26%; *P* = .69). The duration of mechanical ventilation and ICU length of stay also were not influenced by the type of catheter used. The type of catheter used did not affect the incidence of shock, respiratory or renal failure, ventilator settings, or requirement for hemodialysis or vasopressors. There was a 1% rate of crossover from CVC-guided therapy to PAC-guided therapy. The catheter used did not affect the administration of fluids or diuretics, and the fluid balance was similar in the two groups. The PAC group had approximately twice as many catheter-related adverse events (mainly arrhythmias).

Few subjects in critical care medicine generate more emotional responses among experts in the field than the use of the PAC. Some experts may be able to use the PAC to titrate vasoactive drugs and IV fluids for specific patients in ways that improve their outcomes. But, as these studies indicate, it is impossible to verify that use of the PAC saves lives when it is evaluated over a large population of patients. Certainly, given the current state of knowledge, routine use of the PAC cannot be justified. Whether very selective use of the device in a few relatively uncommon clinical situations is warranted or valuable remains a controversial issue. Consequently, a marked decline in the use of the PAC from 5.66 per 1000 medical admissions in 1993 to 1.99 per 1000 medical admissions in 2004 has been seen.[33] These significant reductions in the use of the PAC were noted for a variety of patients, including those admitted with myocardial infarction, surgical patients, and for patients with septicemia. Based upon the results and exclusion criteria in these prospective randomized trials, reasonable criteria for perioperative monitoring without use of a PAC are presented in Table 13-5.

Table 13-5 Suggested Criteria for Perioperative Monitoring Without Use of a Pulmonary Artery Catheter in Patients Undergoing Cardiac or Major Vascular Surgical Procedures
No anticipated need for suprarenal or supraceliac aortic cross-clamping
No history of myocardial infarction during 3 mo before operation
No history of poorly compensated congestive heart failure
No history of coronary artery bypass graft surgery during 6 wk before operation
No history of ongoing symptomatic mitral or aortic valvular heart disease
No history of ongoing unstable angina pectoris

One of the reasons for using a PAC to monitor critically ill patients is to optimize cardiac output and systemic O_2 delivery. Defining what constitutes the optimum cardiac output, however, has proven to be difficult. Based upon an extensive observational database and comparisons of the hemodynamic and O_2 transport values recorded in survivors and nonsurvivors, Bland and colleagues proposed that "goal-directed" hemodynamic resuscitation should aim to achieve a Q_T greater than 4.5 L/min per square meter and $\dot{D}O_2$ greater than 600 mL/min per square meter.[34] Prompted by these observational findings, a number of investigators have conducted randomized trials designed to evaluate the effect on outcome of goal-directed as compared to conventional hemodynamic resuscitation. Some studies provide support for the notion that interventions designed to achieve supraphysiologic goals for $\dot{D}O_2$, $\dot{V}O_2$, and Q_T improve outcome.[35–37] However, other published studies do not support this view, and a meta-analysis concluded that interventions designed to achieve supraphysiologic goals for O_2 transport do not significantly reduce mortality rates in critically ill patients.[19,38,39] At this time, supraphysiologic resuscitation of patients in shock cannot be endorsed.

There is no simple explanation for the apparent lack of effectiveness of pulmonary artery catheterization. Connors has offered several suggestions.[40] First, even though bedside pulmonary artery catheterization is quite safe, the procedure is associated with a finite incidence of serious complications, including ventricular arrhythmias, catheter-related sepsis, central venous thrombosis, pulmonary arterial perforation, and as noted above, pulmonary embolism.[28,40] The adverse effects of these complications on outcome may equal or even outweigh any benefits associated with using a PAC to guide therapy. Second, the data generated by the PAC may be inaccurate, leading to inappropriate therapeutic interventions. Third, the measurements, even if accurate, are often misinterpreted in practice. A study by Iberti and associates showed that 47% of 496 clinicians were unable to accurately interpret a straightforward recording of a tracing obtained with a PAC, and 44% could not correctly identify the determinants of systemic $\dot{D}O_2$.[41] A more recent study has confirmed that even well-trained intensivists are capable of misinterpreting results provided by pulmonary artery catheterization.[42] Furthermore, the current state of understanding is primitive when it comes to deciding what is the best management for certain hemodynamic disturbances, particularly those associated with sepsis or septic shock. Taking all of this into consideration, it may be that interventions prompted by measurements obtained with a PAC are actually harmful to patients. As a result, the marginal benefit now available by placing a PAC may be quite small. Less invasive modalities are available that can provide clinically useful hemodynamic information.

It may be true that aggressive hemodynamic resuscitation of patients, guided by various forms of monitoring, is valuable only during certain critical periods, such as the first few hours after presentation with septic shock or during surgery. For example, Rivers and colleagues reported that survival of patients with septic shock is significantly improved when resuscitation in the emergency department is guided by a protocol that seeks to keep $ScvO_2$ greater than 70%.[17] Similarly, a study using an ultrasound-based device (see Doppler Ultrasonography below) to assess cardiac filling and SV showed that

maximizing SV intraoperatively results in fewer postoperative complications and shorter hospital length of stay.[43]

Minimally Invasive Alternatives to the Pulmonary Artery Catheter

Because of the cost, risks, and questionable benefit associated with bedside pulmonary artery catheterization, there has been interest for many years in the development of practical means for less invasive monitoring of hemodynamic parameters. Several approaches have been developed, which have achieved variable degrees of success. None of these methods render the standard thermodilution technique of the PAC obsolete. However, these strategies may contribute to improvements in the hemodynamic monitoring of critically ill patients.

DOPPLER ULTRASONOGRAPHY

When ultrasonic sound waves are reflected by moving erythrocytes in the bloodstream, the frequency of the reflected signal is increased or decreased, depending on whether the cells are moving toward or away from the ultrasonic source. This change in frequency is called the *Doppler shift*, and its magnitude is determined by the velocity of the moving red blood cells. Therefore, measurements of the Doppler shift can be used to calculate red blood cell velocity. With knowledge of both the cross-sectional area of a vessel and the mean red blood cell velocity of the blood flowing through it, one can calculate blood flow rate. If the vessel in question is the aorta, then Q_T can be calculated as:

$$QT = HR \times A \times \int V(t)dt$$

where A is the cross-sectional area of the aorta and $\int V(t)dt$ is the red blood cell velocity integrated over the cardiac cycle.

Two approaches have been developed for using Doppler ultrasonography to estimate Q_T. The first approach uses an ultrasonic transducer, which is manually positioned in the suprasternal notch and focused on the root of the aorta. Aortic cross-sectional area can be estimated using a nomogram, which factors in age, height, and weight, back calculated if an independent measure of Q_T is available, or by using two-dimensional transthoracic or transesophageal ultrasonography. Although this approach is completely noninvasive, it requires a highly skilled operator to obtain meaningful results, and is labor intensive. Moreover, unless Q_T measured using thermodilution is used to back-calculate aortic diameter, accuracy using the suprasternal notch approach is not acceptable.[44] Accordingly, the method is useful only for obtaining very intermittent estimates of Q_T, and has not been widely adopted by clinicians.

A more promising, albeit more invasive, approach has been introduced. In this method blood flow velocity is continuously monitored in the descending thoracic aorta using a continuous-wave Doppler transducer introduced into the esophagus in sedated or anesthetized patients. The probe is advanced into the esophagus to about 35 cm from the incisors (in adults) and connected to a monitor, which continuously displays the blood flow velocity profile in the descending aorta as well as the calculated Q_T. To maximize the accuracy of the device, the probe position must be adjusted to obtain the peak velocity in the aorta. To transform blood flow in the descending aorta into Q_T, a correction factor is applied that is based on the assumption that only 70% of the flow at the root of the aorta is still present in the descending thoracic aorta. Aortic cross-sectional area is estimated using a nomogram based on the patient's age, weight, and height. Results using these methods appear to be reasonably accurate across a broad spectrum of patients. In a multicenter study, good correlation was found between esophageal Doppler and thermodilution ($r = 0.95$), with a small systematic underestimation (bias 0.24 L/min) using esophageal Doppler.[45] The ultrasonic device also calculates a derived parameter termed *flow time corrected* (FTc), which is the systolic flow time in the descending aorta corrected for HR. FTc is a function of preload, contractility, and vascular input impedance. Although it is not a pure measure of preload, Doppler-based estimates of SV and FTc have been used successfully to guide volume resuscitation in high-risk surgical patients undergoing major operations.[43]

IMPEDANCE CARDIOGRAPHY

The impedance to flow of alternating electrical current in regions of the body is commonly called *bioimpedance*. In the thorax, changes in the volume and velocity of blood in the thoracic aorta lead to detectable changes in bioimpedance. The first derivative of the oscillating component of thoracic bioimpedance (dZ/dt) is linearly related to aortic blood flow. On the basis of this relationship, empirically derived formulas have been developed to estimate SV, and subsequently Q_T, noninvasively. This methodology is called *impedance cardiography*. The approach is attractive because it is noninvasive, provides a continuous readout of Q_T, and does not require extensive training for use. Despite these advantages, studies suggest that measurements of Q_T obtained by impedance cardiography are not sufficiently reliable to be used for clinical decision making and have poor correlation with standard methods such as thermodilution and ventricular angiography.[46,47] Impedance cardiography also has been proposed as a way to estimate LVEF, but the results obtained show poor agreement with those obtained by radionuclide ventriculography.[48,49] Based upon these data, impedance cardiography cannot be recommended at the present time for hemodynamic monitoring of critically ill patients.

PULSE CONTOUR ANALYSIS

Another method for determining cardiac output is an approach called *pulse contour analysis* for estimating SV on a beat-to-beat basis. The mechanical properties of the arterial tree and SV determine the shape of the arterial pulse waveform. The pulse contour method of estimating Q_T uses the arterial pressure waveform as an input for a model of the systemic circulation to determine beat-to-beat flow through the circulatory system. The parameters of resistance, compliance, and impedance are initially estimated based on the patient's age and sex, and can be subsequently refined by using a reference standard measurement of Q_T. The reference standard estimation of Q_T is obtained periodically using the indicator dilution approach by injecting the indicator into a CVC and detecting the transient increase in indicator concentration in the blood using an arterial catheter.

Measurements of Q_T based on pulse contour monitoring are comparable in accuracy to standard PAC-thermodilution methods, but it uses an approach that is less invasive since arterial and central venous, but not transcardiac, catheterization is needed.[50] Using on-line pressure waveform analysis, the computerized algorithms can calculate SV, Q_T, systemic vascular resistance, and an estimate of myocardial contractility, the rate of rise of the arterial systolic pressure (dP/dT). The use of pulse contour analysis has been applied using noninvasive photoplethysmographic measurements of arterial pressure. However, the accuracy of this technique has been questioned and its clinical use remains to be determined.[51]

PARTIAL CARBON DIOXIDE REBREATHING

Partial carbon dioxide (CO_2) rebreathing uses the Fick principle to estimate Q_T noninvasively. By intermittently altering the dead space within the ventilator circuit via a rebreathing valve, changes in CO_2 production (V_{CO_2}) and end-tidal CO_2 ($ETCO_2$) are used to determine cardiac output using a modified Fick equation ($Q_T = \Delta V_{CO_2}/\Delta ETCO_2$). Commercially available devices use this Fick principle to calculate Q_T using intermittent partial CO_2 rebreathing through a disposable rebreathing loop. These devices consist of a CO_2 sensor based on infrared light absorption, an airflow sensor, and a pulse oximeter. Changes in intrapulmonary shunt and hemodynamic instability impair the accuracy of Q_T estimated by partial CO_2 rebreathing. Continuous in-line pulse oximetry and inspired fraction of inspired O_2 (FiO_2) are used to estimate shunt fraction to correct Q_T.

Some studies of the partial CO_2 rebreathing approach suggest that this technique is not as accurate as thermodilution, the [50,52]

gold standard for measuring Q_T. However, other studies suggest that the partial CO_2 rebreathing method for determination of Q_T compares favorably to measurements made using a PAC in critically ill patients.[53]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) has made the transition from operating room to ICU. TEE requires that the patient be sedated and usually intubated for airway protection. Using this powerful technology, global assessments of LV and RV function can be made, including determinations of ventricular volume, EF, and Q_T. Segmental wall motion abnormalities, pericardial effusions, and tamponade can be readily identified with TEE. Doppler techniques allow estimation of atrial filling pressures. The technique is somewhat cumbersome and requires considerable training and skill to obtain reliable results.

Assessing Preload Responsiveness

Although pulse contour analysis or partial CO_2 rebreathing may be able to provide estimates of SV and Q_T, these approaches alone can offer little or no information about the adequacy of preload. Thus, if Q_T is low, some other means must be used to estimate preload. Most clinicians assess the adequacy of cardiac preload by determining CVP or PAOP. However, neither CVP nor PAOP correlate well with the true parameter of interest, left ventricular end-diastolic volume (LVEDV).[54] Extremely high or low CVP or PAOP results are informative, but readings in a large middle zone (i.e., 5 to 20 mmHg) are not very useful. Furthermore, changes in CVP or PAOP fail to correlate well with changes in SV.[55] Echocardiography can be used to estimate LVEDV, but this approach is dependent on the skill and training of the individual using it, and isolated measurements of LVEDV fail to predict the hemodynamic response to alterations in preload.[56]

When intrathoracic pressure increases during the application of positive airway pressure in mechanically ventilated patients, venous return decreases, and as a consequence, LVSV also decreases. Therefore, pulse pressure variation (PPV) during a positive pressure episode can be used to predict the responsiveness of cardiac output to changes in preload.[57] PPV is defined as the difference between the maximal pulse pressure and the minimum pulse pressure divided by the average of these two pressures. This approach has been validated by comparing PPV, CVP, PAOP, and systolic pressure variation as predictors of preload responsiveness in a cohort of critically ill patients. Patients were classified as being "preload responsive" if their cardiac index increased by at least 15% after rapid infusion of a standard volume of IV fluid.[58] Receiver-operating characteristic curves demonstrated that PPV was the best predictor of preload responsiveness. Although atrial arrhythmias can interfere with the usefulness of this technique, PPV remains a useful approach for assessing preload responsiveness in most patients because of its simplicity and reliability.[56]

Tissue Capnometry

Global indices of Q_T, $\dot{D}O_2$, or $\dot{V}O_2$ provide little useful information regarding the adequacy of cellular oxygenation and mitochondrial function. On theoretical grounds, measuring tissue pH to assess the adequacy of perfusion is an attractive concept. As a consequence of the stoichiometry of the reactions responsible for the substrate level phosphorylation of adenosine diphosphate to form adenosine triphosphate, anaerobiosis is associated with the net accumulation of protons. Accordingly, knowing that tissue pH is not in the acid range should be enough information to conclude that global perfusion as well as arterial O_2 content are sufficient to meet the metabolic demands of the cells, even without knowledge of the actual values for tissue blood flow or O_2 delivery. The detection of tissue acidosis should alert the clinician to the possibility that perfusion is inadequate. Thus, tonometric measurements of tissue P_{CO_2} in the stomach or sigmoid colon could be used to estimate mucosal pH (pH_i) and thereby monitor visceral perfusion in critically ill patients.

Unfortunately, the notion of using tonometric estimates of GI mucosal pH_i for monitoring perfusion is predicated on a number of assumptions, some of which may be partially or completely invalid. Furthermore, currently available methods for performing measurements of gastric mucosal P_{CO_2} in the clinical setting remain rather cumbersome and expensive. It is perhaps for these reasons that gastric tonometry for monitoring critically ill patients has primarily been used as a research tool.

Tonometric determination of mucosal CO_2 tension, $P_{CO_{2muc}}$, can be used to calculate pH_i by using the Henderson-Hasselbalch equation as follows:

$$pH_i = \log ([HCO_3^-]_{muc}/0.03 \times P_{CO_{2muc}})$$

where $[HCO_3^-]_{muc}$ is the concentration of bicarbonate anion in the mucosa. Whereas $P_{CO_{2muc}}$ can be measured with reasonable accuracy and precision using tonometric methods, $[HCO_3^-]_{muc}$ cannot be measured directly, but must be estimated by assuming that the concentration of bicarbonate anion in arterial blood, $[HCO_3^-]_{art}$, is approximately equal to $[HCO_3^-]_{muc}$. Under normal conditions, the assumption that $[HCO_3^-]_{art} \cong [HCO_3^-]_{muc}$ is probably valid. Under pathologic conditions, however, the assumption that $[HCO_3^-]_{art} \cong [HCO_3^-]_{muc}$ is almost certainly invalid. For example, when blood flow to the ileal mucosa is very low, HCO_3^- in the tissue is titrated by hydrogen ions produced as a result of anaerobic metabolism, and replenishment of tissue HCO_3^- stores from arterial blood is impeded by stagnant perfusion. Thus under such conditions, $[HCO_3^-]_{muc}$ is less than $[HCO_3^-]_{art}$, and tonometric estimates of pH_i based on the Henderson-Hasselbalch equation underestimate the degree of tissue acidosis present.[59]

There is another inherent problem in using pH_i as an index of perfusion. As noted above, pH_i calculated using the Henderson-Hasselbalch equation is a function of both $P_{CO_{2muc}}$ and $[HCO_3^-]_{art}$. Under steady-state conditions, the first of these parameters, $P_{CO_{2muc}}$, reflects the balance between inflow of CO_2 into the interstitial space and outflow of CO_2 from the interstitial space. CO_2 can enter the interstitial compartment via three mechanisms: diffusion of CO_2 from arterial blood, production as a result of aerobic metabolism of carbon-containing fuels, and production as a result of titration of HCO_3^- by protons liberated during anaerobic metabolism. CO_2 leaves the interstitial compartment by diffusing into venous blood. If blood flow to the mucosa decreases, then $P_{CO_{2muc}}$ increases as a result of decreased extraction of CO_2 into venous blood. If mucosal perfusion decreases sufficiently, (i.e., to less than the anaerobic threshold for the tissue), then $P_{CO_{2muc}}$ also increases as a result of increased production due to titration of HCO_3^-.[52] Clearly, therefore, an increase in $P_{CO_{2muc}}$ *can* reflect a decrease in mucosal perfusion. However, as documented experimentally by Salzman and colleagues, an increase in $P_{CO_{2muc}}$ also can be caused by arterial hypercarbia, leading to increased diffusion of CO_2 from arterial blood into the interstitium.[60] Similarly, changes in $[HCO_3^-]_{art}$ can occur as a result of factors unrelated to either tissue perfusion or the adequacy of aerobic metabolism (e.g., diabetic ketoacidosis, iatrogenic alkalinization due to administration of sodium bicarbonate solution). For these reasons, tonometrically derived estimates of pH_i are not a reliable way to assess mucosal perfusion.

Although P_{CO_2} and pH are affected by changes in perfusion in all tissues, efforts to monitor these parameters in patients using tonometric methods have focused on the mucosa of the GI tract, particularly the stomach, for both practical and theoretical reasons. From a practical standpoint, the stomach is already commonly intubated in clinical practice for purposes of decompression and drainage or feeding. However, there are theoretical reasons why monitoring GI mucosal perfusion might be more desirable than monitoring perfusion in other sites. First, when global perfusion is compromised, blood flow to the splanchnic viscera decreases to a greater extent than does perfusion to the body as a whole.[61] Thus, the finding of compromised splanchnic perfusion may be an indicator of impending adverse changes in blood flow to other organs. Second,

the gut has been hypothesized to be the "motor" of the multiple organ dysfunction syndrome (MODS), and in experimental models, intestinal mucosal acidosis, whether due to inadequate perfusion or other causes, has been associated with hyperpermeability to hydrophilic solutes.[62] Therefore, ensuring adequate splanchnic perfusion might be expected to minimize derangements in gut barrier function and, on this basis, improve outcome for patients.

The stomach, however, may not be an ideal location for monitoring tissue P_{CO_2}. First, CO_2 can be formed in the lumen of the stomach when hydrogen ions secreted by parietal cells in the mucosa titrate luminal bicarbonate anions, which are present either as a result of backwash of duodenal secretions or secretion by gastric mucosal cells. Measurements of gastric P_{CO_2} and pH_i can be confounded by gastric acid secretion.[63] Consequently, accurate measurements of gastric P_{CO_2} and pH_i depend on pharmacologic blockade of luminal proton secretion using histamine receptor antagonists or proton pump inhibitors. The need for using pharmacologic therapy adds to the cost and complexity of the monitoring strategy. Second, enteral feeding can interfere with measurements of gastric mucosal P_{CO_2}, necessitating temporary cessation of the administration of nutritional support or the placement of a postpyloric tube.[64]

Despite the problems noted above, measurements of gastric pH_i and/or mucosal-arterial P_{CO_2} gap have been proven to be a remarkably reliable predictor of outcome in a wide variety of critically ill individuals, including general medical ICU patients, victims of multiple trauma, patients with sepsis, and patients undergoing major surgical procedures.[65–67] In studies using endoscopic measurements of gastric mucosal blood flow by laser Doppler flowmetry, the development of gastric mucosal acidosis has been shown to correlate with mucosal hypoperfusion.[68] Moreover, in a landmark prospective, randomized, multicentric clinical trial of monitoring in medical ICU patients, titrating resuscitation to a gastric pH_i endpoint rather than conventional hemodynamic indices resulted in a higher 30-day survival rate.[69] In another study, trauma patients were randomized to resuscitation titrated to a gastric pH_i greater than 7.30, or to resuscitation titrated to achieve systemic $\dot{D}O_2$ or $\dot{V}O_2$ goals.[70] Although survival was not significantly different in the two arms of the study, failure to normalize gastric pH_i within 24 hours was associated with a high mortality rate (54%), whereas normalization of pH_i was associated with a significantly lower mortality rate (7%).

There is also interest in measuring tissue capnometry in less invasive sites. Results from some preliminary clinical studies support the view that the monitoring of tissue P_{CO_2} in the sublingual mucosa may provide valuable clinical information. Increased sublingual P_{CO_2} (Psl_{CO_2}) was associated with decreases in arterial blood pressure and Q_T in patients with shock due to hemorrhage or sepsis.[71] In a study of critically ill patients with septic or cardiogenic shock, the Psl_{CO_2}-Pa_{CO_2} gradient was found to be a good prognostic indicator, being 9.2 ± 5.0 mmHg in the survivors and 17.8 ± 11.5 mmHg in nonsurvivors.[72] This study also demonstrated that sublingual capnography was superior to gastric tonometry in predicting patient survival. The Psl_{CO_2}-Pa_{CO_2} gradient also correlated with the mixed venous-arterial P_{CO_2} gradient, but failed to correlate with blood lactate level, mixed venous O_2 saturation (Sv_{-O_2}), or systemic $\dot{D}O_2$. These latter findings suggest that the Psl_{CO_2}-Pa_{CO_2} gradient may be a better marker of tissue hypoxia than are these other parameters.

Near Infrared Spectroscopic Measurement of Tissue Hemoglobin Oxygen Saturation

Near infrared spectroscopy (NIRS) allows continuous, noninvasive measurement of tissue Hgb O_2 saturation (StO_2) using near infrared wavelengths of light (700–1000 nm). This technology is based on Beer's law, which states that the transmission of light through a solution with a dissolved solute decreases exponentially as the concentration of the solute increases. In mammalian tissue, three compounds change their absorption pattern when oxygenated: cytochrome a,a_3, myoglobin, and Hgb. Because of the distinct absorption spectra of oxyhemoglobin and deoxyhemoglobin, Beer's law can be

used to detect their relative concentrations within tissue. Thus, the relative concentrations of the types of Hgb can be determined by measuring the change in light intensity as it passes through the tissue. Because about 20% of blood volume is intra-arterial and the StO_2 measurements are taken without regard to systole or diastole, spectroscopic measurements are primarily indicative of the venous oxyhemoglobin concentration.

NIRS has been evaluated to assess the severity of traumatic shock in animal models and in trauma patients. Studies have shown that peripheral muscle StO_2, as determined by NIRS, is as accurate as other endpoints of resuscitation [i.e., base deficit (BD), mixed venous O_2 saturation] in a porcine model of hemorrhagic shock.[73] Continuously-measured StO_2 has been evaluated in blunt trauma patients as a predictor of the development of multiple organ dysfunction syndrome (MODS) and mortality.[74] At seven level 1 trauma centers, 383 patients were prospectively studied. StO_2 was monitored for 24 hours after admission along with vital signs and other endpoints of resuscitation such as BD. Minimum StO_2 (using a minimum StO_2 ≤75% as a cutoff) had a similar sensitivity and specificity in predicting the development of MODS as BD ≥6 mEq/L. StO_2 and BD were also comparable in predicting mortality. Thus, NIRS-derived muscle StO_2 measurements perform similarly to BD in identifying poor perfusion and predicting the development of MODS or death after severe torso trauma, yet have the additional advantages of being continuous and noninvasive. Ongoing prospective studies will help determine the clinical use of continuous monitoring of StO_2 in clinical scenarios such as trauma, hemorrhagic shock, sepsis, etc.

RESPIRATORY MONITORING

The ability to monitor various parameters of respiratory function is of utmost importance in critically ill patients. Many of these patients require mechanical ventilation. Monitoring of their respiratory physiology is necessary to assess the adequacy of oxygenation and ventilation, guide weaning and liberation from mechanical ventilation, and detect adverse events associated with respiratory failure and mechanical ventilation. These parameters include gas exchange, neuromuscular activity, respiratory mechanics, and patient effort.

Arterial Blood Gases

The standard for respiratory monitoring has been to carry out intermittent measurements of arterial blood gases. Blood gas analysis provides useful information when caring for patients with respiratory failure. However, even in the absence of respiratory failure or the need for mechanical ventilation, blood gas determinations also can be valuable to detect alterations in acid-base balance due to low Q_T, sepsis, renal failure, severe trauma, medication or drug overdose, or altered mental status. Arterial blood can be analyzed for pH, P_{O_2}, P_{CO_2}, HCO_3^- concentration, and calculated BD. When indicated, carboxyhemoglobin and methemoglobin levels also can be measured. In recent years, efforts have been made to decrease the unnecessary use of arterial blood gas analysis. Serial arterial blood gas determinations are not necessary for routine weaning from mechanical ventilation in the majority of postoperative patients.

Most bedside blood gas analyses still involve removal of an aliquot of blood from the patient, although continuous bedside arterial blood gas determinations are now possible without sampling via an indwelling arterial catheter that contains a biosensor. In studies comparing the accuracy of continuous arterial blood gas and pH monitoring with a conventional laboratory blood gas analyzer, excellent agreement between the two methods has been demonstrated.[75] Continuous monitoring can reduce the volume of blood loss due to phlebotomy and dramatically decrease the time necessary to obtain blood gas results. Continuous monitoring, however, is expensive and is not widely used.

Determinants of Oxygen Delivery

The primary goal of the cardiovascular and respiratory systems is to deliver oxygenated blood to the tissues. $\dot{D}O_2$ is dependent to a greater degree on the O_2 saturation of Hgb in arterial blood (SaO_2) than on the partial pressure of O_2 in arterial blood (PaO_2). $\dot{D}O_2$ also is dependent on Q_T and Hgb. Dissolved O_2 in blood, which is proportional to the PaO_2, makes only a negligible contribution to $\dot{D}O_2$, as is apparent from the equation:

$$\dot{D}O_2 = Q_T \times [(Hgb \times SaO_2 \times 1.36) + (PaO_2 \times 0.0031)]$$

SaO_2 in mechanically ventilated patients depends on the mean airway pressure, the fraction of inspired O_2 (FiO_2), and $Sv\text{-}O_2$. Thus, when SaO_2 is low, the clinician has only a limited number of ways to improve this parameter. The clinician can increase mean airway pressure by increasing positive end-expiratory pressure (PEEP) or inspiratory time. FiO_2 can be increased to a maximum of 1.0 by decreasing the amount of room air mixed with the O_2 supplied to the ventilator. $Sv\text{-}O_2$ can be increased by increasing Hgb or Q_T or decreasing O_2 use (e.g., by administering a muscle relaxant and sedation).

Peak and Plateau Airway Pressure

Airway pressures are routinely monitored in mechanically ventilated patients. The peak airway pressure measured at the end of inspiration (P_{peak}) is a function of the tidal volume, the resistance of the airways, lung/chest wall compliance, and peak inspiratory flow. The airway pressure measured at the end of inspiration when the inhaled volume is held in the lungs by briefly closing the expiratory valve is termed *the plateau airway pressure* ($P_{plateau}$). As a static parameter, plateau airway pressure is independent of the airway resistance and peak airway flow, and is related to the lung/chest wall compliance and delivered tidal volume. Mechanical ventilators monitor P_{peak} with each breath and can be set to trigger an alarm if the P_{peak} exceeds a predetermined threshold. $P_{plateau}$ is not measured routinely with each delivered tidal volume, but rather is measured intermittently by setting the ventilator to close the exhalation circuit briefly at the end of inspiration and record the airway pressure when airflow is zero.

If both P_{peak} and $P_{plateau}$ are increased (and tidal volume is not excessive), then the problem is a decrease in the compliance in the lung/chest wall unit. Common causes of this problem include pneumothorax, hemothorax, lobar atelectasis, pulmonary edema, pneumonia, acute respiratory distress syndrome (ARDS), active contraction of the chest wall or diaphragmatic muscles, abdominal distention, and intrinsic PEEP, such as occurs in patients with bronchospasm and insufficient expiratory times. When P_{peak} is increased but $P_{plateau}$ is relatively normal, the primary problem is an increase in airway resistance, such as occurs with bronchospasm, use of a small-caliber endotracheal tube, or kinking or obstruction of the endotracheal tube. A low P_{peak} also should trigger an alarm, as it suggests a discontinuity in the airway circuit involving the patient and the ventilator.

Ventilator-induced lung injury is now an established clinical entity of great relevance to the care of critically ill patients. Excessive airway pressure and tidal volume adversely affect pulmonary and possibly systemic responses to critical illness. Subjecting the lung parenchyma to excessive pressure, known as *barotrauma*, can result in parenchymal lung injury, diffuse alveolar damage similar to ARDS, and pneumothorax, and can impair venous return and therefore limit cardiac output. Lung-protective ventilation strategies have been developed to prevent the development of ventilator-induced lung injury and improve patient outcomes. In a large, multicenter randomized trial of patients with ARDS from a variety of etiologies, limiting plateau airway pressure to less than 30 cm H_2O and tidal volume to less than 6 mL/kg of ideal body weight reduced 28-day mortality by 22% relative to a ventilator strategy that used a tidal volume of 12 mL/kg.[76] For this reason, monitoring of plateau pressure and using a low tidal volume strategy in patients with ARDS is now the standard of care.

Pulse Oximetry

The pulse oximeter is a microprocessor-based device that integrates oximetry and plethysmography to provide continuous noninvasive monitoring of the O_2 saturation of arterial blood (Sa_{O_2}). It is considered one of the most important and useful technologic advances in patient monitoring. Continuous, noninvasive monitoring of arterial O_2 saturation is possible using light-emitting diodes and sensors placed on the skin. Pulse oximetry uses two wavelengths of light (i.e., 660 nm and 940 nm) to analyze the pulsatile component of blood flow between the light source and sensor. Because oxyhemoglobin and deoxyhemoglobin have different absorption spectra, differential absorption of light at these two wavelengths can be used to calculate the fraction of O_2 saturation of Hgb. Under normal circumstances, the contributions of carboxyhemoglobin and methemoglobin are minimal. However, if carboxyhemoglobin levels are elevated, the pulse oximeter will incorrectly interpret carboxyhemoglobin as oxyhemoglobin and the arterial saturation displayed will be falsely elevated. When the concentration of methemoglobin is markedly increased, the Sa_{O_2} will be displayed as 85%, regardless of the true arterial saturation.[77] The accuracy of pulse oximetry begins to decline at Sa_{O_2} values less than 92%, and tends to be unreliable for values less than 85%.[78]

Several studies have assessed the frequency of arterial O_2 desaturation in hospitalized patients and its effect on outcome. For example, in a study of general medical patients, Bowton and associates found that patients who had an episode of hypoxemia (Sa_{O_2} <90% for 5 minutes) in the first 24 hours of hospital admission had a mortality rate three times higher than that of patients who did not have an episode of arterial desaturation.[79] Because of its clinical relevance, ease of use, noninvasive nature, and cost-effectiveness, pulse oximetry has become a routine monitoring strategy in patients with respiratory disease, intubated patients, and those undergoing surgical intervention under sedation or general anesthesia. Pulse oximetry is especially useful in the titration of Fi_{O_2} and PEEP for patients receiving mechanical ventilation, and during weaning from mechanical ventilation. The widespread use of pulse oximetry has decreased the need for arterial blood gas determinations in critically ill patients.

Capnometry

Capnometry is the measurement of CO_2 in the airway throughout the respiratory cycle. Capnometry is most commonly measured by infrared light absorption. CO_2 absorbs infrared light at a peak wavelength of approximately 4.27 μm. Capnometry works by passing infrared light through a sample chamber to a detector on the opposite side. More infrared light passing through the sample chamber (i.e., less CO_2) causes a larger signal in the detector relative to the infrared light passing through a reference cell. Capnometric determination of the partial pressure of CO_2 in end-tidal exhaled gas (P_{ETCO_2}) is used as a surrogate for the partial pressure of CO_2 in arterial blood (Pa_{CO_2}) during mechanical ventilation. In healthy subjects, P_{ETCO_2} is about 1 to 5 mmHg less than Pa_{CO_2}.[80] Thus, P_{ETCO_2} can be used to estimate Pa_{CO_2} without the need for blood gas determination. However, changes in P_{ETCO_2} may not correlate with changes in Pa_{CO_2} during a number of pathologic conditions (see below).

Capnography allows the confirmation of endotracheal intubation and continuous assessment of ventilation, integrity of the airway, operation of the ventilator, and cardiopulmonary function. Capnometers are configured with either an in-line sensor or a sidestream sensor. The sidestream systems are lighter and easy to use, but the thin tubing that samples the gas from the ventilator circuit can become clogged with secretions or condensed water, preventing accurate measurements. The in-line devices are bulky and heavier, but are less likely to become clogged. Continuous monitoring with capnography has become routine during surgery under general anesthesia and for some intensive care patients. A number of situations can be promptly detected with continuous capnography. A sudden reduction in P_{ETCO_2} suggests either obstruction of the sampling tubing with water or secretions, or a catastrophic event such as loss of the airway, airway disconnection or obstruction,

ventilator malfunction, or a marked decrease in Q_T. If the airway is connected and patent and the ventilator is functioning properly, then a sudden decrease in P_{ETCO_2} should prompt efforts to rule out cardiac arrest, massive pulmonary embolism, or cardiogenic shock. P_{ETCO_2} can be persistently low during hyperventilation or with an increase in dead space such as occurs with pulmonary embolization (even in the absence of a change in Q_T). Causes of an increase in P_{ETCO_2} include reduced minute ventilation or increased metabolic rate.

RENAL MONITORING

Urine Output

Bladder catheterization with an indwelling catheter allows the monitoring of urine output, usually recorded hourly by the nursing staff. With a patent Foley catheter, urine output is a gross indicator of renal perfusion. The generally accepted normal urine output is 0.5 mL/kg per hour for adults and 1 to 2 mL/kg per hour for neonates and infants. Oliguria may reflect inadequate renal artery perfusion due to hypotension, hypovolemia, or low Q_T. Low urine flow also can be a sign of intrinsic renal dysfunction. It is important to recognize that normal urine output does not exclude the possibility of impending renal failure.

Bladder Pressure

The triad of oliguria, elevated peak airway pressures, and elevated intra-abdominal pressure is known as the *abdominal compartment syndrome* (ACS). This syndrome, first described in patients after repair of ruptured abdominal aortic aneurysm, is associated with interstitial edema of the abdominal organs, resulting in elevated intra-abdominal pressure. When intra-abdominal pressure exceeds venous or capillary pressures, perfusion of the kidneys and other intra-abdominal viscera is impaired. Oliguria is a cardinal sign. Although the diagnosis of ACS is a clinical one, measuring intra-abdominal pressure is useful to confirm the diagnosis. Ideally, a catheter inserted into the peritoneal cavity could measure intra-abdominal pressure to substantiate the diagnosis. In practice, transurethral bladder pressure measurement reflects intra-abdominal pressure and is most often used to confirm the presence of ACS. After instilling 50 to 100 mL of sterile saline into the bladder via a Foley catheter, the tubing is connected to a transducing system to measure bladder pressure. Most authorities recommend that a bladder pressure greater than 20 to 25 mmHg confirms the diagnosis of ACS.[81] Less commonly, gastric or inferior vena cava pressures can be monitored with appropriate catheters to detect elevated intra-abdominal pressures.

NEUROLOGIC MONITORING

Intracranial Pressure

Because the brain is rigidly confined within the bony skull, cerebral edema or mass lesions increase intracranial pressure (ICP). Monitoring of ICP is currently recommended in patients with severe traumatic brain injury (TBI), defined as a Glasgow Coma Scale (GCS) score ≤8 with an abnormal CT scan, and in patients with severe TBI and a normal CT scan if two or more of the following are present: age greater than 40 years, unilateral or bilateral motor posturing, or systolic blood pressure less than 90 mmHg.[82] ICP monitoring also is indicated in patients with acute subarachnoid hemorrhage with coma or neurologic deterioration, intracranial hemorrhage with intraventricular blood, ischemic middle cerebral artery stroke, fulminant hepatic failure with coma and cerebral edema on CT scan, and global cerebral ischemia or anoxia with cerebral edema on CT scan. The goal of ICP monitoring is to ensure that cerebral perfusion pressure (CPP) is adequate to support perfusion of the brain. CPP is equal to the difference between MAP and ICP: CPP = MAP − ICP.

One type of ICP measuring device, the ventriculostomy catheter, consists of a fluid-filled catheter inserted into a cerebral ventricle and connected to an external pressure transducer. This device permits measurement of ICP, but also allows drainage of cerebrospinal fluid (CSF) as a means to lower ICP and sample CSF for laboratory studies. Other devices locate the pressure transducer within the central nervous system and are used only to monitor ICP. These devices can be placed in the intraventricular, parenchymal, subdural, or epidural spaces. Ventriculostomy catheters are the accepted standard for monitoring ICP in patients with TBI due to their accuracy, ability to drain CSF, and low complication rate. The associated complications include infection (5%), hemorrhage (1.4%), catheter malfunction or obstruction (6.3 to 10.5%), and malposition with injury to cerebral tissue.[83]

The purpose of ICP monitoring is to detect and treat abnormal elevations of ICP that may be detrimental to cerebral perfusion and function. In TBI patients, ICP greater than 20 mmHg is associated with unfavorable outcomes.[84] However, few studies have shown that treatment of elevated ICP improves clinical outcomes in human trauma patients. In a randomized, controlled, double-blind trial, Eisenberg and colleagues demonstrated that maintaining ICP less than 25 mmHg in patients without craniectomy and less than 15 mmHg in patients with craniectomy is associated with improved outcome.[85] In patients with low CPP, therapeutic strategies to correct CPP can be directed at increasing MAP or decreasing ICP. Although it often has been recommended that CPP be maintained above 70 mmHg, the evidence to support this recommendation is not overly compelling.[86] Furthermore, a retrospective cohort study of patients with severe TBI found that ICP/CPP-targeted neurointensive care was associated with prolonged mechanical ventilation and increased therapeutic interventions, without evidence for improved outcome in patients who survive beyond 24 h.[87]

Electroencephalogram and Evoked Potentials

Electroencephalography offers the capacity to monitor global neurologic electrical activity, while evoked potential monitoring can assess pathways not detected by the conventional electroencephalogram (EEG). Continuous EEG (CEEG) monitoring in the ICU permits ongoing evaluation of cerebral cortical activity. It is especially useful in obtunded and comatose patients. CEEG also is useful for monitoring of therapy for status epilepticus and detecting early changes associated with cerebral ischemia. CEEG can be used to adjust the level of sedation, especially if high-dose barbiturate therapy is being used to manage elevated ICP. Somatosensory and brain stem evoked potentials are less affected by the administration of sedatives than is the EEG. Evoked potentials are useful for localizing brain stem lesions or proving the absence of such structural lesions in cases of metabolic or toxic coma. They also can provide prognostic data in posttraumatic coma.

A recent advance in EEG monitoring is the use of the bispectral index (BIS) to titrate the level of sedative medications. Although sedative drugs usually are titrated to the clinical neurologic examination, the BIS device has been used in the operating room to continuously monitor the depth of anesthesia. The BIS is an empiric measurement statistically derived from a database of more than 5000 EEGs.[88] The BIS is derived from bifrontal EEG recordings and analyzed for burst suppression ratio, relative alpha:beta ratio, and bicoherence. Using a multivariate regression model, a linear numeric index (BIS) is calculated, ranging from 0 (isoelectric EEG) to 100 (fully awake). Its use has been associated with lower consumption of anesthetics during surgery and earlier awakening and faster recovery from anesthesia.[89] The BIS also has been validated as a useful approach for monitoring the level of sedation for ICU patients, using the revised Sedation-Agitation Scale as a gold standard.[90]

Transcranial Doppler Ultrasonography

This modality provides a noninvasive method for evaluating cerebral hemodynamics. Transcranial Doppler (TCD)

measurements of middle and anterior cerebral artery blood flow velocity are useful for the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. Qureshi and associates demonstrated that an increase in the middle cerebral artery mean flow velocity as assessed by TCD is an independent predictor of symptomatic vasospasm in a prospective study of patients with aneurysmal subarachnoid hemorrhage.[91] In addition, while some have proposed using TCD to estimate ICP, studies have shown that TCD is not a reliable method for estimating ICP and CPP, and currently cannot be endorsed for this purpose.[92] TCD also is useful to confirm the clinical examination for determining brain death in patients with confounding factors such as the presence of central nervous system depressants or metabolic encephalopathy.

Jugular Venous Oximetry

When the arterial O_2 content, Hgb concentration, and the oxyhemoglobin dissociation curve are constant, changes in jugular venous O_2 saturation (Sjo_2) reflect changes in the difference between cerebral O_2 delivery and demand. Generally, a decrease in Sjo_2 reflects cerebral hypoperfusion, whereas an increase in Sjo_2 indicates the presence of hyperemia. Sjo_2 monitoring cannot detect decreases in regional cerebral blood flow if overall perfusion is normal or above normal. This technique requires the placement of a catheter in the jugular bulb, usually via the internal jugular vein. Catheters that permit intermittent aspiration of jugular venous blood for analysis or continuous oximetry catheters are available.

Low Sjo_2 is associated with poor outcomes after TBI.[93] Nevertheless, the value of monitoring Sjo_2 remains unproven. If it is used, it should not be the sole monitoring technique, but rather should be used in conjunction with ICP and CPP monitoring. By monitoring ICP, CPP, and Sjo_2, early intervention with volume, vasopressors, and hyperventilation has been shown to prevent ischemic events in patients with TBI.[94]

Transcranial Near Infrared Spectroscopy

Transcranial NIRS is a noninvasive continuous monitoring method to determine cerebral oxygenation. It uses technology similar to that of pulse oximetry to determine the concentrations of oxy- and deoxyhemoglobin with near infrared light and sensors, and takes advantage of the relative transparency of the skull to light in the near infrared region of the spectrum. McCormick and associates demonstrated that cerebral desaturation can occur more than 2 hours before any clinical deterioration in neurologic status.[95] Nevertheless, this form of monitoring remains largely a research tool at the present time.

Brain Tissue Oxygen Tension

Although the standard of care for patients with severe TBI includes ICP and CPP monitoring, this strategy does not always prevent secondary brain injury. Growing evidence suggests that monitoring local brain tissue O_2 tension ($PbtO_2$) may be a useful adjunct to ICP monitoring in these patients. Normal values for $PbtO_2$ are 20 to 40 mmHg, and critical levels are 8 to 10 mmHg. A recent clinical study sought to determine whether the addition of a $PbtO_2$ monitor to guide therapy in severe TBI was associated with improved patient outcomes.[96] Twenty-eight patients with severe TBI (GCS score ≤8) were enrolled in an observational study at a level I trauma center. These patients received invasive ICP and $PbtO_2$ monitoring and were compared with 25 historical controls matched for age, injuries, and admission GCS score that had undergone ICP monitoring alone. Goals of therapy in both groups included maintaining an ICP <20 mmHg and a CPP >60 mmHg. Among patients with $PbtO_2$ monitoring, therapy also was directed at maintaining $PbtO_2$ >25 mmHg. The groups had similar mean daily ICP and CPP levels. The mortality rate in the historical controls treated with standard ICP and CPP management was 44%. Mortality was significantly lower in the patients who had therapy guided by $PbtO_2$ monitoring in addition to ICP and CPP (25%; P <.05). The benefits of PbtO monitoring may include the early detection of brain tissue ischemia despite normal ICP and CPP.

In addition, $PbtO_2$-guided management may reduce potential adverse effects associated with therapies to maintain ICP and CPP.

CONCLUSIONS

Modern intensive care is predicated by the need and ability to continuously monitor a wide range of physiologic parameters. This capability has dramatically improved the care of critically ill patients and advanced the development of the specialty of critical care medicine. In some cases, the technologic ability to measure such variables has surpassed our understanding of the significance or the knowledge of the appropriate intervention to ameliorate such pathophysiologic changes. In addition, the development of less invasive monitoring methods has been promoted by the recognition of complications associated with invasive monitoring devices. The future portends the continued development of noninvasive monitoring devices along with their application in an evidenced-based strategy to guide rational therapy.

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KEY POINTS

1. Minimally invasive surgery describes a philosophical approach to surgery in which access trauma is minimized without compromising the quality of the surgical procedure.

2. Minimally invasive surgery is dependent upon videoscopic, ultrasonographic, radiologic, and magnetic resonance imaging.

3. The carbon dioxide pneumoperitoneum used for laparoscopy induces some unique pathophysiologic consequences.

4. Training for laparoscopy requires practice outside of the operating room in a simulation laboratory and/or in animal models.

5. Laparoscopy during pregnancy is best performed in the second trimester and is safe if appropriate monitoring is performed.

6. Laparoscopic surgery for cancer is also appropriate if good tissue handling techniques are maintained.

7. Robotic surgery has been most valuable in the pelvis for performance of minimally invasive prostatectomy and gynecologic and fertility procedures.

8. Natural orifice transluminal endoscopic surgery represents a new opportunity to develop truly scar-free surgery.

MINIMALLY INVASIVE SURGERY, ROBOTICS, AND NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY: INTRODUCTION

Minimally invasive surgery describes an area of surgery that crosses all traditional disciplines, from general surgery to neurosurgery. It is not a discipline unto itself, but more a philosophy of surgery, a way of thinking. Minimally invasive surgery is a means of performing major operations through small incisions, often using miniaturized, high-tech imaging systems, to minimize the trauma of surgical exposure. Some believe that the term *minimal access surgery* more accurately describes the small incisions generally necessary to gain access to surgical sites in high-tech surgery, but John Wickham's term *minimally invasive surgery* (MIS) is widely used because it describes the paradox of postmodern high-tech surgery—small holes, big operations—and the "minimalness" of the access and invasiveness of the procedures, captured in three words.

Robotic surgery today is practiced using a single platform (Intuitive, Inc., Sunnyvale, CA) and should better be termed *computer enhanced surgery* as the term *robotics* assumes autonomous action that is not a feature of the da Vinci robotic system. Instead, the da Vinci robot couples an ergonomic workstation that features stereoptic video imaging and intuitive micromanipulators (surgeon side) with a set of arms delivering specialized laparoscopic instruments enhanced with more degrees of freedom than is allowed by laparoscopic surgery alone (patient side). A computer between the surgeon side and patient side removes surgical tremor and scales motion to allow precise microsurgery, helpful for microdissection and difficult anastomoses.

Natural orifice transluminal endoscopic surgery (NOTES) is a recent extension of interventional endoscopy. Using the mouth, the anus, the vagina, and the urethra (natural orifices), flexible endoscopes are passed through the wall of the esophagus, stomach, colon, bladder, or vagina entering the mediastinum, the pleural space, or the peritoneal cavity. The advantage of this method of minimal access is principally the elimination of the scar associated with laparoscopy or thoracoscopy. Other advantages are yet to be elucidated, including pain reduction, need for hospitalization, and cost savings.

HISTORICAL BACKGROUND

Although the term *minimally invasive surgery* is relatively recent, the history of its component parts is nearly 100 years old. What is considered the newest and most popular variety of MIS, laparoscopy, is, in fact, the oldest. Primitive laparoscopy, placing a cystoscope within an inflated abdomen, was first performed by Kelling in 1901.[1] Illumination of the abdomen required hot elements at the tip of the scope and was dangerous. In the late 1950s, Hopkins described the rod lens, a method of transmitting light through a solid quartz rod with no heat and little light loss.[1] Around the same time, thin quartz fibers were discovered to be capable of trapping light internally and conducting it around corners, opening the field of fiber-optics and allowing the rapid development of flexible endoscopes.[2,3] In the 1970s, the application of flexible endoscopy grew faster than that of rigid endoscopy except in a few fields such as gynecology and orthopedics.[4] By the mid-1970s, rigid and flexible endoscopes made a rapid transition from diagnostic instruments to therapeutic ones. The explosion of video-assisted surgery in the past 20 years was a result of the development of compact, high-resolution, charge-coupled devices (CCDs) that could be mounted on the internal end of flexible endoscopes or on the external end of a Hopkins telescope. Coupled with bright light sources, fiber-optic cables, and high-resolution video monitors, the videoendoscope has changed our understanding of surgical anatomy and reshaped surgical practice.

Flexible endoscopic imaging started in the 1960s with the first bundling of many quartz fibers into bundles, one for illumination and one for imaging. The earliest upper endoscopes revolutionized the diagnosis and treatment of gastroesophageal reflux, peptic ulcer disease, and made possible early detection of upper and lower GI cancer at a stage that could be cured. The first endoscopic surgical procedure was the colonoscopic polypectomy, developed by Shinya and Wolfe, two surgeons from New York City. The percutaneous endoscopic gastrostomy (PEG) invented by Gauderer and Ponsky may have been the first NOTES procedure, reported in 1981.[5] Endoscopic pancreatic pseudocyst drainage is thought to be the next NOTES procedure developed; however, there was little energy and money put into the development of NOTES until a number of gastroenterologists claimed the ability to remove the gallbladder with a flexible endoscope, using a transgastric technique. With this pronouncement, the surgical community "woke up" and seized the momentum for NOTES research and development.

Although optical imaging produced the majority of MIS procedures, other (traditionally radiologic) imaging technologies allowed the development of innovative procedures in the 1970s. Fluoroscopic imaging allowed the adoption of percutaneous vascular procedures, the most revolutionary of which was balloon angioplasty. Balloon-based procedures spread into all fields of medicine used to open up clogged lumens with minimal access. Stents were then developed that were used in many disciplines to keep the newly ballooned segment open. The culmination of fluoroscopic balloon and stent proficiency is exemplified by the transvenous intrahepatic portosystemic shunt and by the aortic stent graft, which has nearly replaced open elective abdominal aortic aneurysm repair.

MIS procedures using ultrasound imaging have been limited to fairly crude exercises, such as fragmenting kidney stones and freezing liver tumors, because of the relatively low resolution of ultrasound devices. Newer, high-resolution ultrasound methods with high-frequency crystals may act as a guide while performing minimally invasive resections of individual layers of the intestinal wall.

Axial imaging, such as computed tomography (CT), has allowed the development of an area of MIS that often is not recognized because it requires only a CT scanner and a long needle. CT-guided drainage of abdominal fluid collections and percutaneous biopsy of abnormal tissues are minimally invasive means of performing procedures that previously required a celiotomy. CT-guided percutaneous radiofrequency (RF) ablation has emerged as a useful treatment for primary and metastatic liver tumors. This procedure also is performed laparoscopically under ultrasound guidance.[6]

A powerful, noninvasive method of imaging that will allow the development of the least invasive—and potentially noninvasive—surgery is magnetic resonance imaging (MRI).

MRI is an extremely valuable diagnostic tool, but it is only slowly coming to be of therapeutic value. One obstacle to the use of MRI for MIS is that image production and refreshment of the image as a procedure progresses are slow. Another is that all instrumentation must be nonmetallic when working with the powerful magnets of an MRI scanner. Moreover, MRI magnets are bulky and limit the surgeon's access to the patient. Open magnets have been developed that allow the surgeon to stand between two large MRI coils, obtaining access to the portion of the patient being scanned. The advantage of MRI, in addition to the superb images produced, is that there is no

radiation exposure to patient or surgeon. Some neurosurgeons are accumulating experience using MRI to perform frameless stereotactic surgery.

Robotic surgery has been dreamed about for some time, and many "Rube Goldberg" devices have been developed over the years to provide mechanical assistance for the surgeon. The first computer-assisted robot, the "RoboDoc" was designed to accurately drill femoral shaft bone for wobble-free placement of hip prostheses. Although the name was appealing, the robot proved no better than a skilled orthopedic surgeon and was a good deal slower. Following this, the first and only two commercially successful robots for laparoscopic surgery were in development in California. Computer Motion, founded by Yulun Wang in Santa Barbara, used National Science Foundation funds to create a mechanical arm, the Aesop robot, which held and moved the laparoscope with voice, foot, or hand control. In Northern California, a master-slave system first developed for surgery on the multinational space station by Philip Green was purchased by Fred Moll and Lonnie Smith, then re-engineered with the surgeon in mind to create a remarkably intuitive computer-enhanced surgical platform. The company, Intuitive Surgical, was aptly named, and their primary product, the da Vinci robot, is the only major "robotic" surgical device currently on the market. Although eschewed by many experienced laparoscopists, the da Vinci achieved a toehold among many skilled surgeons who found that the robot could facilitate MIS procedures that were difficult with standard laparoscopic procedures.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF MINIMALLY INVASIVE SURGERY

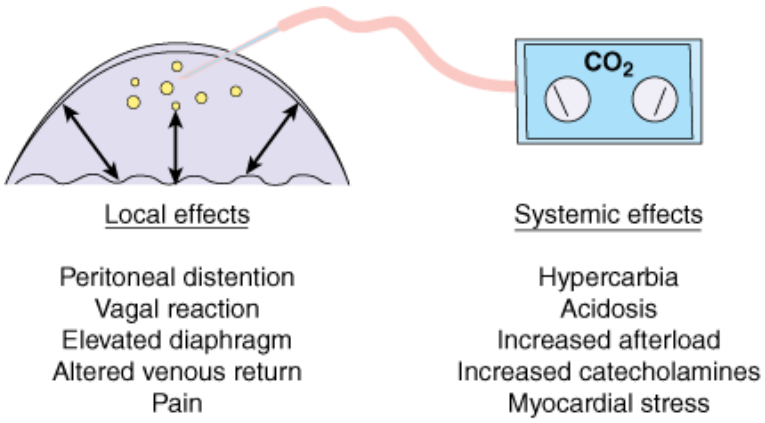
Even with the least invasive of the MIS procedures, physiologic changes occur. Many minimally invasive procedures require minimal or no sedation, and there are few adverse consequences to the cardiovascular, endocrinologic, or immunologic systems. The least invasive of such procedures include stereotactic biopsy of breast lesions and flexible GI endoscopy. Minimally invasive procedures that require general anesthesia have a greater physiologic impact because of the anesthetic agent, the incision (even if small), and the induced pneumoperitoneum.

Laparoscopy

The unique feature of laparoscopic surgery is the need to lift the abdominal wall from the abdominal organs. Two methods have been devised for achieving this.[7] The first, used by most surgeons, is a pneumoperitoneum. Throughout the early twentieth century, intraperitoneal visualization was achieved by inflating the abdominal cavity with air, using a sphygmomanometer bulb.[8] The problem with using air insufflation is that nitrogen is poorly soluble in blood and is slowly absorbed across the peritoneal surfaces. Air pneumoperitoneum was believed to be more painful than nitrous oxide (N_2O) pneumoperitoneum, but less painful than carbon dioxide (CO_2) pneumoperitoneum. Subsequently, carbon dioxide and N_2O were used for inflating the abdomen. N_2O had the advantage of being physiologically inert and rapidly absorbed. It also provided better analgesia for laparoscopy performed under local anesthesia when compared with CO_2 or air.[9] Despite initial concerns that N_2O would not suppress combustion, controlled clinical trials have established its safety within the peritoneal cavity.[10] In addition, N_2O has been shown to reduce the intraoperative end-tidal CO_2 and minute ventilation required to maintain homeostasis when compared to CO_2 pneumoperitoneum.[10] The effect of N_2O on tumor biology and the development of port site metastasis are unknown. As such, caution should be exercised when performing laparoscopic cancer surgery with this agent. Finally, the safety of N_2O pneumoperitoneum in pregnancy has yet to be elucidated.

The physiologic effects of CO_2 pneumoperitoneum can be divided into two areas: (a) gas-specific effects and (b) pressure-specific effects (Fig. 14-1). CO_2 is rapidly absorbed across the peritoneal membrane into the circulation. In the circulation, CO_2 creates a respiratory acidosis by the generation of carbonic acid.[11] Body buffers, the largest reserve of which lies in bone, absorb CO_2 (up to 120 L) and minimize the development of hypercarbia or respiratory acidosis during brief endoscopic procedures.[11] Once the body buffers are saturated, respiratory acidosis develops rapidly, and the respiratory system assumes the burden of keeping up with the absorption of CO_2 and its release from these buffers.

Fig. 14-1.



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Carbon dioxide gas insufflated into the peritoneal cavity has both local and systemic effects that cause a complex set of hemodynamic and metabolic alterations.

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In patients with normal respiratory function, this is not difficult; the anesthesiologist increases the ventilatory rate or vital capacity on the ventilator. If the respiratory rate required exceeds 20 breaths per minute, there may be less efficient gas exchange and increasing hypercarbia.[12] Conversely, if vital capacity is increased substantially, there is a greater opportunity for barotrauma and greater respiratory motion-induced disruption of the upper abdominal operative field. In some situations, it is advisable to evacuate the pneumoperitoneum or reduce the intra-abdominal pressure to allow time for the anesthesiologist to adjust for hypercarbia.[13] Although mild respiratory acidosis probably is an insignificant problem, more severe respiratory acidosis leading to cardiac arrhythmias has been reported.[14] Hypercarbia also causes tachycardia and increased systemic vascular resistance, which elevates blood pressure and increases myocardial oxygen demand.[11,14]

The pressure effects of the pneumoperitoneum on cardiovascular physiology also have been studied. In the hypovolemic individual, excessive pressure on the inferior vena cava and a reverse Trendelenburg position with loss of lower extremity muscle tone may cause decreased venous return and decreased cardiac output.[11,15] This is not seen in the normovolemic patient. The most common arrhythmia created by laparoscopy is bradycardia. A rapid stretch of the peritoneal membrane often causes a vagovagal response with bradycardia and, occasionally, hypotension.[16] The appropriate management of this event is desufflation of the abdomen, administration of vagolytic agents (e.g., atropine), and adequate volume replacement.[17]

With the increased intra-abdominal pressure compressing the inferior vena cava, there is diminished venous return from the lower extremities. This has been well documented in the patient placed in the reverse Trendelenburg position for upper abdominal operations. Venous engorgement and decreased venous return promote venous thrombosis.[18,19] Many series of advanced laparoscopic procedures in which deep venous thrombosis (DVT) prophylaxis was not used demonstrate the frequency of pulmonary embolus. This usually is an avoidable complication with the use of sequential compression stockings, subcutaneous heparin, or low molecular weight heparin.[20] In short-duration laparoscopic procedures, such as appendectomy, hernia repair, or cholecystectomy, the risk of DVT may not be sufficient to warrant extensive DVT prophylaxis.

The increased pressure of the pneumoperitoneum is transmitted directly across the paralyzed diaphragm to the thoracic cavity, creating increased central venous pressure and increased filling pressures of the right and left sides of the heart. If the intra-abdominal pressures are kept under 20 mmHg, the cardiac output usually is well maintained.[19–21] The direct effect of the pneumoperitoneum on increasing intrathoracic pressure increases peak inspiratory pressure, pressure across the chest wall, and also, the likelihood of barotrauma. Despite these concerns, disruption of blebs and consequent pneumothoraces are rare after uncomplicated laparoscopic surgery.[21] Pneumothoraces occurring with laparoscopic esophageal surgery may be very significant. The pathophysiology and management are

discussed at the end of this section. Increased intra-abdominal pressure decreases renal blood flow, glomerular filtration rate, and urine output. These effects may be mediated by direct pressure on the kidney and the renal vein.[22,23] The secondary effect of decreased renal blood flow is to increase plasma renin release, thereby increasing sodium retention. Increased circulating antidiuretic hormone levels also are found during the pneumoperitoneum, increasing free water reabsorption in the distal tubules.[24] Although the effects of the pneumoperitoneum on renal blood flow are immediately reversible, the hormonally mediated changes such as elevated antidiuretic hormone levels decrease urine output for up to 1 hour after the procedure has ended. Intraoperative oliguria is common during laparoscopy, but the urine output is not a reflection of intravascular volume status; IV fluid administration during an uncomplicated laparoscopic procedure should not be linked to urine output. Because insensible fluid losses through the open abdomen are eliminated with laparoscopy, the need for supplemental fluid during a laparoscopic surgical procedure should only keep up with venous pooling in the lower limbs, third-space losses into the bowel, and blood loss, which is generally less than occurs with an equivalent open operation.

The hemodynamic and metabolic consequences of pneumoperitoneum are well tolerated by healthy individuals for a prolonged period and by most individuals for at least a short period. Difficulties can occur when a patient with compromised cardiovascular function is subjected to a long laparoscopic procedure. It is during these procedures that alternative approaches should be considered or insufflation pressure reduced. Alternative gases that have been suggested for laparoscopy include the inert gases helium, neon, and argon. These gases are appealing because they cause no metabolic effects, but are poorly soluble in blood (unlike CO_2 and N_2O) and are prone to create gas emboli if the gas has direct access to the venous system.[19] Gas emboli are rare but serious complications of laparoscopic surgery.[20,25] They should be suspected if hypotension develops during insufflation. Diagnosis may be made by listening (with an esophageal stethoscope) for the characteristic "mill wheel" murmur. The treatment of gas embolism is to place the patient in a left lateral decubitus position with the head down to trap the gas in the apex of the right ventricle.[20] A rapidly placed central venous catheter then can be used to aspirate the gas out of the right ventricle.

In some situations, minimally invasive abdominal surgery should be performed without insufflation. This has led to the development of an abdominal lift device that can be placed through a 10- to 12-mm trocar at the umbilicus.[26] These devices have the advantage of creating little physiologic derangement, but they are bulky and intrusive. The exposure and working room offered by lift devices also are inferior to those accomplished by pneumoperitoneum. Lifting the anterior abdominal wall causes a "pinching in" of the lateral flank walls, displacing the bowel medially and anteriorly into the operative field. A pneumoperitoneum, with its well-distributed intra-abdominal pressure, provides better exposure. Abdominal lift devices also cause more postoperative pain, but they do allow the performance of MIS with standard (nonlaparoscopic) surgical instruments.

Endocrine responses to laparoscopic surgery are not always intuitive. Serum cortisol levels after laparoscopic operations are often higher than after the equivalent operation performed through an open incision.[27] The greatest difference between the endocrine response of open and laparoscopic surgery is the more rapid equilibration of most stress-mediated hormone levels after laparoscopic surgery. Immune suppression also is less after laparoscopy than after open surgery. There is a trend toward more rapid normalization of cytokine levels after a laparoscopic procedure than after the equivalent procedure performed by celiotomy.[28]

Transhiatal mobilization of the distal esophagus is commonly performed as a component of many laparoscopic upper abdominal procedures. If there is compromise of the mediastinal pleura with resultant CO_2 pneumothorax, the defect should be enlarged so as to prevent a tension pneumothorax. Even with such a strategy, tension pneumothorax may develop, as mediastinal structures may seal the hole during inspiration, allowing the chest to fill during expiration. In addition to enlargement of the hole, a thoracostomy tube (chest tube) should be placed across the breach into the abdomen with intra-abdominal pressures reduced below 8 mmHg, or a standard chest tube may be placed. When a pneumothorax occurs with laparoscopic Nissen fundoplication or Heller myotomy, it is preferable to place an 18 F red rubber catheter with multiple side holes cut out of the distal end across the defect. At the end of the procedure, the distal end of the tube is pulled out a 10-mm port site (as the port is removed), and the pneumothorax is evacuated to a primitive water seal using a bowl of sterile water or saline. During laparoscopic esophagectomy, it is preferable to leave a standard chest tube, as residual intra-abdominal fluid will tend to be siphoned through the defect postoperatively, if the tube is removed at the end of the case.

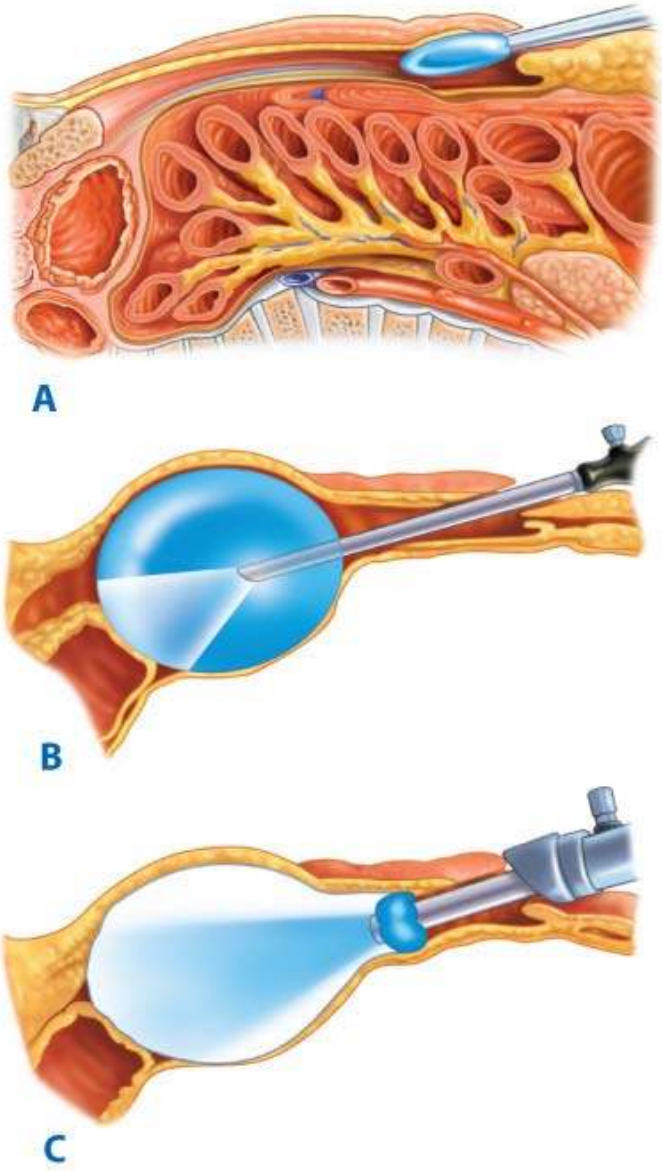
Thoracoscopy

The physiology of thoracic MIS (thoracoscopy) is different from that of laparoscopy. Because of the bony confines of the thorax, it is unnecessary to use positive pressure when working in the thorax.[29] The disadvantages of positive pressure in the chest include decreased venous return, mediastinal shift, and the need to keep a firm seal at all trocar sites. Without positive pressure, it is necessary to place a double-lumen endotracheal tube so that the ipsilateral lung can be deflated when the operation starts. By collapsing the ipsilateral lung, working space within the thorax is obtained. Because insufflation is unnecessary in thoracoscopic surgery, it can be beneficial to use standard instruments via extended port sites in conjunction with thoracoscopic instruments. This approach is particularly useful when performing advanced procedures such as thoracoscopic anatomic pulmonary resection.

Extracavitary Minimally Invasive Surgery

Many MIS procedures create working spaces in extrathoracic and extraperitoneal locations. Laparoscopic inguinal hernia repair usually is performed in the anterior extraperitoneal Retzius space.[30,31] Laparoscopic nephrectomy often is performed with retroperitoneal laparoscopy. Endoscopic retroperitoneal approaches to pancreatic necrosectomy have seen some limited use.[32] Lower extremity vascular procedures and plastic surgical endoscopic procedures require the development of working space in unconventional planes, often at the level of the fascia, sometimes below the fascia, and occasionally in nonanatomic regions.[33] Some of these techniques use insufflation of gas, but many use balloon inflation to develop the space, followed by low-pressure gas insufflation or lift devices to maintain the space (Fig. 14-2). These techniques produce fewer and less severe adverse physiologic consequences than does the pneumoperitoneum, but the insufflation of carbon dioxide into extraperitoneal locations can spread widely, causing subcutaneous emphysema and metabolic acidosis.

Fig. 14-2.



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Balloons are used to create extra-anatomic working spaces. In this example (**A** through **C**), a balloon is introduced into the space between the posterior rectus sheath and the rectus abdominal muscle. The balloon is inflated in the preperitoneal space to create working room for extraperitoneal endoscopic hernia repair.

Anesthesia

Proper anesthesia management during laparoscopic surgery requires a thorough knowledge of the pathophysiology of the CO_2 pneumoperitoneum.[17] The laparoscopic surgeon can influence cardiovascular performance by reducing or removing the CO_2 pneumoperitoneum. Insensible fluid losses are negligible, and therefore, IV fluid administration should not exceed that necessary to maintain circulating volume. MIS procedures are often outpatient procedures, so short-acting anesthetic agents are preferable. Because the factors that require hospitalization after laparoscopic procedures include the management of nausea, pain, and urinary retention, the anesthesiologist should minimize the use of agents that provoke these conditions and maximize the use of medications that prevent such problems. Critical to the anesthesia management of these patients is the use of nonnarcotic analgesics (e.g., ketorolac) when hemostasis allows it, and the liberal use of antiemetic agents, including ondansetron and steroids.

The Minimally Invasive Team

From the beginning, the tremendous success of MIS was founded on the understanding that a team approach was necessary. The many laparoscopic procedures performed daily range from basic to advanced complexity, and require that the surgical team have an intimate understanding of the operative conduct (Table 14-1). Minimally invasive procedures require complicated and fragile equipment that demands constant maintenance. In addition, multiple intraoperative adjustments to the equipment, camera, insufflator, monitors, and patient/surgeon position are made during these procedures. As such, a coordinated team approach is mandated to ensure patient safety and excellent outcomes. More and more, flexible endoscopes are used to guide or provide quality control for laparoscopic procedures. As NOTES evolves, hybrid procedures (laparoscopy and endoscopy) and sophisticated NOTES technology will require a nursing staff capable of maintaining flexible endoscopes and understanding the operation of sophisticated endoscopic technology.

Table 14-1 Laparoscopic Surgical Procedures

Basic	**Advanced**
Appendectomy	Nissen fundoplication
Cholecystectomy	Heller myotomy
Hernia repair	Gastrectomy
	Esophagectomy
	Enteral access
	Bile duct exploration
	Colectomy
	Splenectomy
	Adrenalectomy
	Nephrectomy
	Lymph node dissection
	Robotics
	Stereo imaging
	Telemedicine
	Laparoscopy-assisted procedures
	Hepatectomy
	Pancreatectomy
	Prostatectomy
	Hysterectomy

A typical MIS team may consist of a laparoscopic surgeon and an operating room (OR) nurse with an interest in laparoscopic and endoscopic surgery. Adding dedicated assistants and circulating staff with an intimate knowledge of the equipment will add to and enhance the team nucleus. Studies have demonstrated that having a designated laparoscopic team increases the efficiency and safety of laparoscopic surgery, which is translated into a benefit for patient and hospital.[34]

Room Setup and the Minimally Invasive Suite

Nearly all MIS, whether using fluoroscopic, ultrasound, or optical imaging, incorporates a video monitor as a guide. Occasionally, two images are necessary to adequately guide the operation, as in procedures such as endoscopic retrograde cholangiopancreatography, laparoscopic common bile duct exploration, and laparoscopic ultrasonography. When two images are necessary, the images should be displayed on two adjacent video monitors or projected on a single screen with a picture-in-picture effect. The video monitor(s) should be set across the operating table from the surgeon. The patient should be interposed between the surgeon and the video monitor; ideally, the operative field also lies between the surgeon and the monitor. In pelviscopic surgery it is best to place the video monitor at the patient's feet, and in laparoscopic cholecystectomy, the monitor is placed at the 10 o'clock position (relative to the patient) while the

surgeon stands on the patient's left at the 4 o'clock position. The insufflating and patient-monitoring equipment ideally also is placed across the table from the surgeon, so that the insufflating pressure and the patient's vital signs and end-tidal CO_2 tension can be monitored.

The development of the minimally invasive surgical suite has been a tremendous contribution to the field of laparoscopy in that it has facilitated the performance of advanced procedures and techniques (Fig. 14-3). By having the core equipment (monitors, insufflators, and imaging equipment) located within mobile, ceiling-mounted consoles, the surgery team is able to accommodate and make small adjustments rapidly and continuously throughout the procedure. The specifically designed minimally invasive surgical suite serves to decrease equipment and cable disorganization, ease the movements of operative personnel around the room, improve ergonomics, and facilitate the use of advanced imaging equipment such as laparoscopic ultrasound.[35] Although having a minimally invasive surgical suite available is very useful, it is not essential to successfully carry out advanced laparoscopic procedures.

Fig. 14-3.

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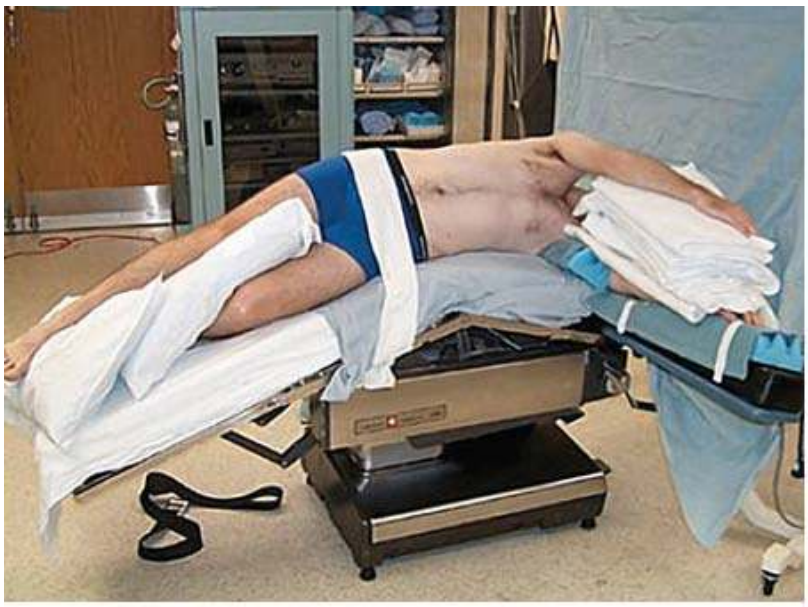
An example of a typical minimally invasive surgery suite. All core equipment is located on easily movable consoles.

Patient Positioning

Patients usually are placed in the supine position for laparoscopic surgery. When the operative field is the gastroesophageal junction or the left lobe of the liver, it is easiest to operate from between the legs. The legs may be elevated in Allen stirrups or abducted on leg boards to achieve this position. When pelvic procedures are performed, it usually is necessary to place the legs in Allen stirrups to gain access to the perineum. A lateral decubitus position with the table flexed provides the best access to the retroperitoneum when performing nephrectomy or adrenalectomy. For laparoscopic splenectomy, a 45°-tilt of the patient provides excellent access to the lesser sac and the lateral peritoneal attachments to the spleen. For thoracoscopic surgery, the patient is placed in the lateral position with table flexion to open the intercostal spaces and the distance between the iliac crest and costal margin (Fig. 14-4).

Fig. 14-4.



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Proper padding and protection of pressure points is an essential consideration in laparoscopic and thoracoscopic approaches. In preparation for thoracoscopy, this patient is placed in left lateral decubitus position with the table flexed, which serves to open the intercostal spaces and increase the distance between the iliac crest and the inferior costal margin.

When the patient's knees are to be bent for extended periods or the patient is going to be placed in a reverse Trendelenburg position for more than a few minutes, DVT prophylaxis should be used. Sequential compression of the lower extremities during prolonged (>90 minutes) laparoscopic procedures increases venous return and provides inhibition of thromboplastin activation.

General Principles of Access

The most natural ports of access for MIS and NOTES are the anatomic portals of entry and exit. The nares, mouth, urethra, and anus are used to access the respiratory, GI, and urinary systems. The advantage of using these points of access is that no incision is required. The disadvantages lie in the long distances between the orifice and the region of interest. For NOTES procedures, the vagina may serve as another point of access, entering the abdomen via the posterior cul–de-sac of the pelvis. Similarly, the peritoneal cavity may be reached through the side wall of the stomach or colon.

Access to the vascular system may be accomplished under local anesthesia by cutting down and exposing the desired vessel, usually in the groin. Increasingly, vascular access is obtained with percutaneous techniques using a small incision, a needle, and a guidewire, over which are passed a variety of different sized access devices. This approach, known as the *Seldinger technique*, is most frequently used by general surgeons for placement of Hickman catheters, but also is used to gain access to the arterial and venous system for performance of minimally invasive procedures. Guidewire-assisted, Seldinger-type techniques also are helpful for gaining access to the gut for procedures such as PEG, for gaining access to the biliary system through the liver, and for gaining access to the upper urinary tract.

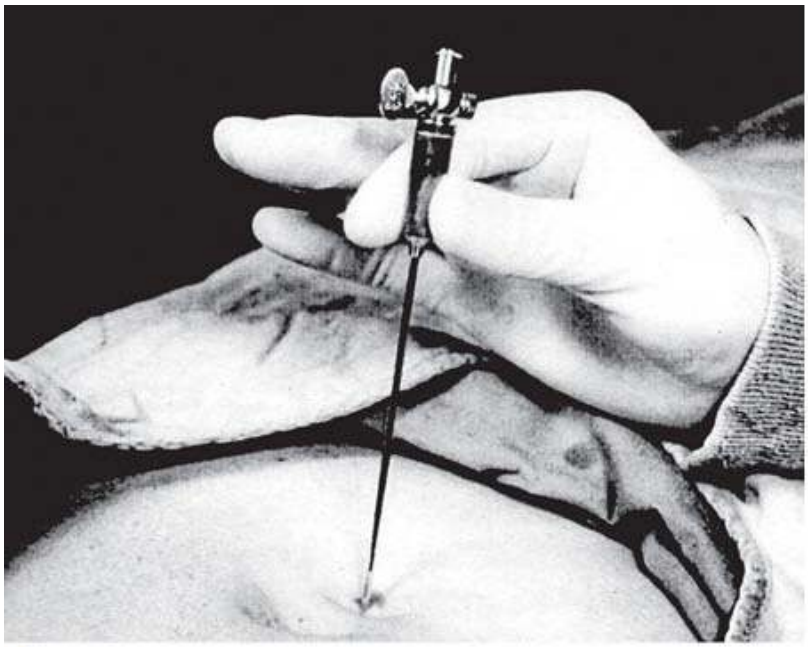
In thoracoscopic surgery, the access technique is similar to that used for placement of a chest tube. In these procedures general anesthesia and single lung ventilation are essential. A small incision is made over the top of a rib and, under direct vision, carried down through the pleura. The lung is collapsed, and a trocar is inserted across the chest wall to allow access with a telescope. Once the lung is completely collapsed, subsequent access may be obtained with direct puncture, viewing all entry sites through the videoendoscope. Because insufflation of the chest is unnecessary, simple ports that keep the small incisions open are all that is required to allow repeated access to the thorax.

Laparoscopic Access

The requirements for laparoscopy are more involved, because the creation of a pneumoperitoneum requires that instruments of access (trocars) contain valves to maintain abdominal inflation.

Two methods are used for establishing abdominal access during laparoscopic procedures.[36,37] The first, direct puncture laparoscopy, begins with the elevation of the relaxed abdominal wall with two towel clips or a well-placed hand. A small incision is made in the umbilicus, and a specialized spring-loaded (Veress) needle is placed in the abdominal cavity (Fig. 14-5). With the Veress needle, two distinct pops are felt as the surgeon passes the needle through the abdominal wall fascia and the peritoneum. The umbilicus usually is selected as the preferred point of access because, in this location, the abdominal wall is quite thin, even in obese patients. The abdomen is inflated with a pressure-limited insufflator. CO_2 gas usually is used, with maximal pressures in the range of 14 to 15 mmHg. During the process of insufflation, it is essential that the surgeon observe the pressure and flow readings on the monitor to confirm an intraperitoneal location of the Veress needle tip (Fig. 14-6). Laparoscopic surgery can be performed under local anesthesia, but general anesthesia is preferable. Under local anesthesia, N_2O is used as the insufflating agent, and insufflation is stopped after 2 L of gas is insufflated or when a pressure of 10 mmHg is reached.

Fig. 14-5.



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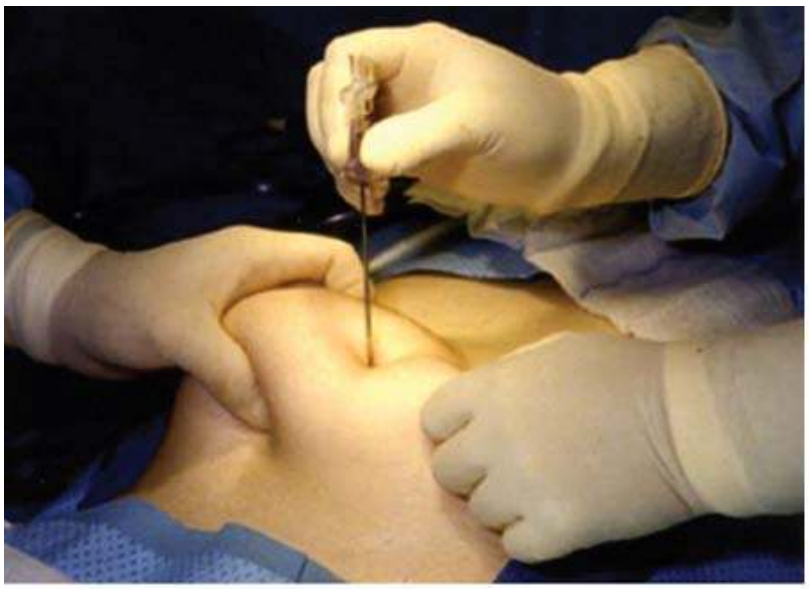

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A. Insufflation of the abdomen is accomplished with a Veress needle held at its serrated collar with a thumb and forefinger. **B.** Because linea alba is fused to the umbilicus, the abdominal wall is grasped with fingers or penetrating towel clip to elevate the abdominal wall away from the underlying structures.

Fig. 14-6.

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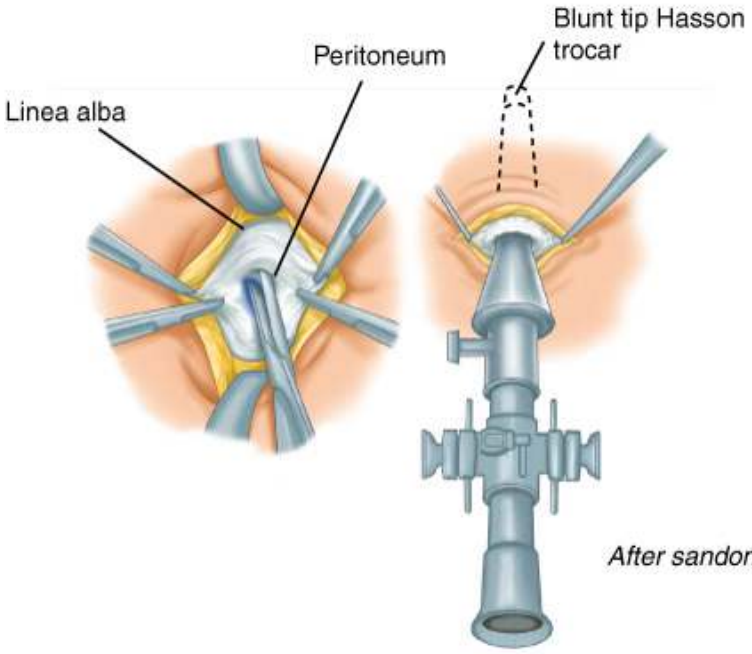
It is essential to be able to interpret the insufflator pressure readings and flow rates. These readings indicate proper intraperitoneal placement of the Veress needle.

After peritoneal insufflation, direct access to the abdomen is obtained with a 5- or 10-mm trocar. The critical issues for safe direct-puncture laparoscopy include the use of a vented stylet for the trocar, or a trocar with a safety shield or dilating tip. The trocar must be

pointed away from the sacral promontory and the great vessels.[38] Patient position should be surveyed before trocar placement to ensure a proper trajectory. For performance of laparoscopic cholecystectomy, the trocar is angled toward the right upper quadrant.

Occasionally, the direct peritoneal access (Hasson) technique is advisable.[39] With this technique, the surgeon makes a small incision just below the umbilicus and under direct vision locates the abdominal fascia. Two Kocher clamps are placed on the fascia, and with curved Mayo scissors, a small incision is made through the fascia and underlying peritoneum. A finger is placed into the abdomen to make sure that there is no adherent bowel. A sturdy suture is placed on each side of the fascia and secured to the wings of a specialized trocar, which is then passed directly into the abdominal cavity (Fig. 14-7). Rapid insufflation can make up for some of the time lost with the initial dissection. This technique is preferable for the abdomen of patients who have undergone previous operations in which small bowel may be adherent to the undersurface of the abdominal wound. The close adherence of bowel to the peritoneum in the previously operated abdomen does not eliminate the possibility of intestinal injury but should make great vessel injury extremely unlikely. Because of the difficulties in visualizing the abdominal region immediately adjacent to the primary trocar, it is recommended that the telescope be passed through a secondary trocar to inspect the site of initial abdominal access.[37] Secondary punctures are made with 5- and 10-mm trocars. For safe access to the abdominal cavity, it is critical to visualize all sites of trocar entry.[38,39] At the completion of the operation, all trocars are removed under direct vision, and the insertion sites are inspected for bleeding. If bleeding occurs, direct pressure with an instrument from another trocar site or balloon tamponade with a Foley catheter placed through the trocar site generally stops the bleeding within 3 to 5 minutes. When this is not successful, a full-thickness abdominal wall suture has been used successfully to tamponade trocar site bleeding.

Fig. 14-7.



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The open laparoscopy technique involves identification and incision of the peritoneum, followed by the placement of a specialized trocar with a conical sleeve to maintain a gas seal. Specialized wings on the trocar are attached to sutures placed through the fascia to prevent loss of the gas seal.

It is generally agreed that 5-mm trocars need no site suturing. Ten-millimeter trocars placed off the midline and above the transverse mesocolon do not require repair. Conversely, if the fascia has been dilated to allow the passage of the gallbladder or other organ, it should be repaired at the fascial level with interrupted sutures. The port site may be closed with suture delivery systems similar to crochet needles enabling mass closure of the abdominal wall. This is especially helpful in obese patients where direct fascial closure may

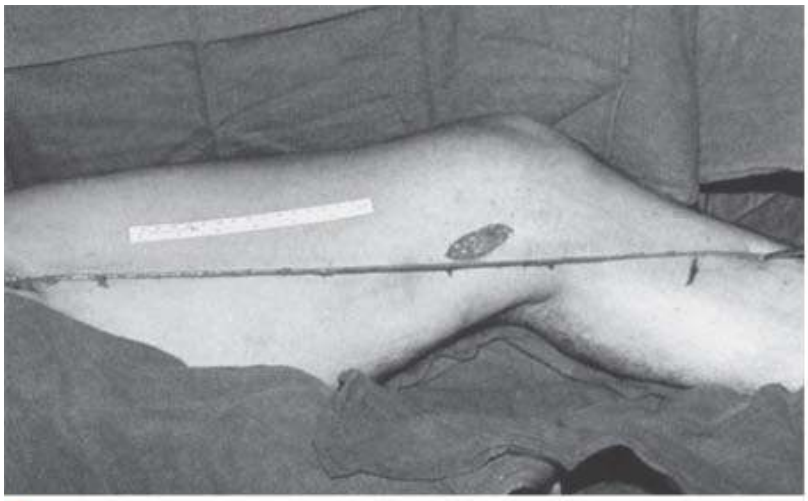
be challenging, through a small skin incision. Failure to close lower abdominal trocar sites that are 10 mm in diameter or larger can lead to an incarcerated hernia.

Access for Subcutaneous and Extraperitoneal Surgery

There are two methods for gaining access to nonanatomic spaces. For retroperitoneal locations, balloon dissection is effective. This access technique is appropriate for the extraperitoneal repair of inguinal hernias and for retroperitoneal surgery for adrenalectomy, nephrectomy, lumbar discectomy, pancreatic necrosectomy, or para-aortic lymph node dissection.[40,41] The initial access to the extraperitoneal space is performed in a way similar to direct puncture laparoscopy, except that the last layer (the peritoneum) is not traversed. Once the transversalis fascia has been punctured, a specialized trocar with a balloon on the end is introduced. The balloon is inflated in the extraperitoneal space to create a working chamber. The balloon then is deflated and a Hasson trocar is placed. An insufflation pressure of 10 mmHg usually is adequate to keep the extraperitoneal space open for dissection and will limit subcutaneous emphysema. Higher gas pressures force CO_2 into the soft tissues and may contribute to hypercarbia. Extraperitoneal endosurgery provides less working space than laparoscopy but eliminates the possibility of intestinal injury, intestinal adhesion, herniation at the trocar sites, and ileus. These issues are important for laparoscopic hernia repair because extraperitoneal approaches prevent the small bowel from sticking to the prosthetic mesh.[31]

Subcutaneous surgery has been most widely used in cardiac, vascular, and plastic surgery.[33] In cardiac surgery, subcutaneous access has been used for saphenous vein harvesting, and in vascular surgery for ligation of subfascial perforating veins (Linton procedure). With minimally invasive techniques, the entire saphenous vein above the knee may be harvested through a single incision[42,43] (Fig. 14-8). Once the saphenous vein is located, a long retractor that holds a 5-mm laparoscope allows the coaxial dissection of the vein and coagulation or clipping of each side branch. A small incision above the knee also can be used to ligate perforating veins in the lower leg.

Fig. 14-8.



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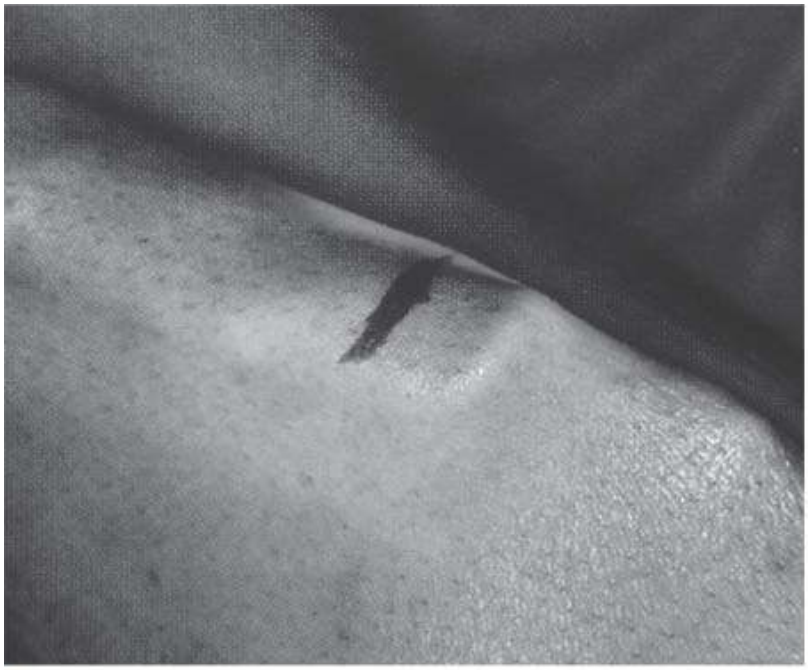

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A. With two small incisions, virtually the entire saphenous vein can be harvested for bypass grafting. **B.** The lighted retractor in the subcutaneous space during saphenous vein harvest is seen illuminating the skin.

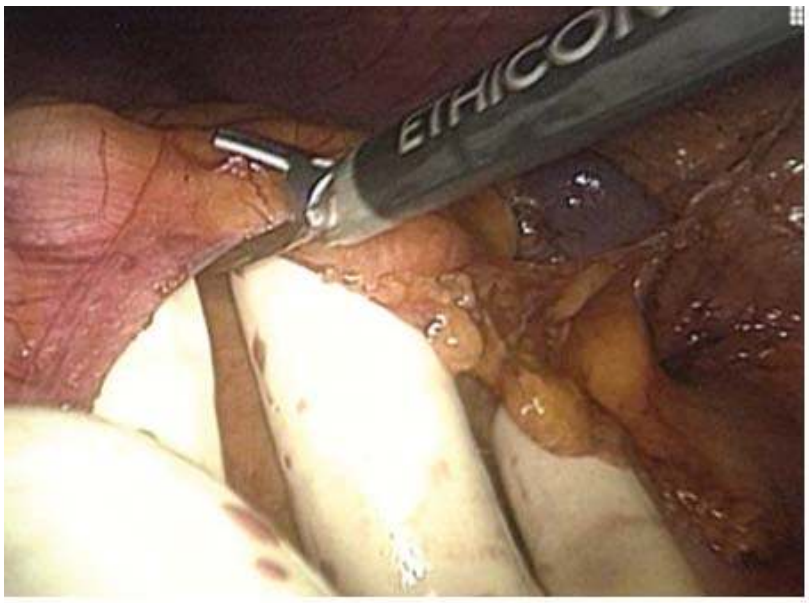
[Reproduced with permission from Jones GE, Eaves FE III, Howell RL et al: Harvest of muscle, nerve, fascia, and vein, in Bostwick J III, Eaves FE III, Nahai F (eds): *Endoscopic Plastic Surgery.* St Louis: Quality Medical Publishing, Inc., 1995, p 542.]

Subcutaneous access also is used for plastic surgery procedures.[43] Minimally invasive approaches are especially well suited to cosmetic surgery, in which attempts are made to hide the incision. It is easier to hide several 5-mm incisions than one long incision. The technique of blunt dissection along fascial planes combined with lighted retractors and endoscope-holding retractors is most successful for extensive subcutaneous surgery. Some prefer gas insufflation of these soft tissue planes. The primary disadvantage of soft tissue insufflation is that subcutaneous emphysema can be created.

Hand-Assisted Laparoscopic Access

Hand-assisted laparoscopic surgery is thought to combine the tactile advantages of open surgery with the minimal access of laparoscopy and thoracoscopy. This approach commonly is used to assist with difficult cases before conversion to celiotomy is necessary. Additionally, hand-assisted laparoscopic surgery is used to help surgeons negotiate the steep learning curve associated with advanced laparoscopic procedures.[44] This technology uses a "port" for the hand that preserves the pneumoperitoneum and enables endoscopic visualization in combination with the use of minimally invasive instruments (Fig. 14-9). Formal investigation of this modality has been limited primarily to case reports and small series, and has focused primarily on solid organ and colon surgery.

Fig. 14-9.



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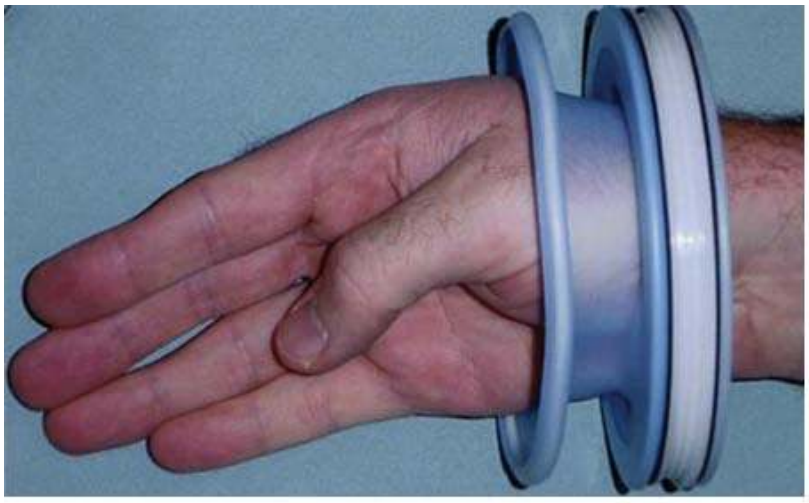

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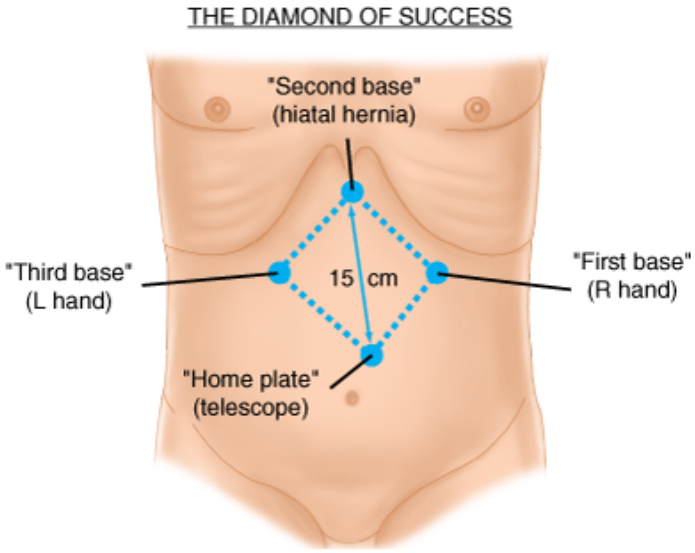
This is an example of hand-assisted laparoscopic surgery during left colectomy. The surgeon uses a hand to provide retraction and counter tension during mobilization of the colon from its retroperitoneal attachments, as well as during division of the mesocolon. This technique is particularly useful in the region of the transverse colon.

Intraperitoneal, intrathoracic, and retroperitoneal access for robotic surgery adheres to the principles of laparoscopic and thoracoscopic access; however, the port size for the primary puncture is 12 mm to allow placement of the stereo laparoscope.

Port Placement

Trocars for the surgeon's left and right hand should be placed at least 10 cm apart. For most operations, it is possible to orient the telescope between these two trocars and slightly back from them. The ideal trocar orientation creates an equilateral triangle between the surgeon's right hand, left hand, and the telescope, with 10 to 15 cm on each leg. If one imagines the target of the operation (e.g., the gallbladder or gastroesophageal junction) oriented at the apex of a second equilateral triangle built on the first, these four points of reference create a diamond (Fig. 14-10). The surgeon stands behind the telescope, which provides optimal ergonomic orientation but frequently requires that a camera operator (or mechanical camera holder) reach between the surgeon's hands to guide the telescope.

Fig. 14-10.



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The diamond configuration created by placing the telescope between the left and the right hand, recessed from the target by about 15 cm. The distance between the left and the right hand is also ideally 10 to 15 cm. In this "baseball diamond" configuration, the surgical target occupies the second base position.

The position of the operating table should permit the surgeon to work with both elbows in at the sides, with arms bent 90° at the elbow.[45] It usually is necessary to alter the operating table position with left or right tilt with the patient in the Trendelenburg or reverse Trendelenburg position, depending on the operative field.[46,47]

Imaging Systems

Two methods of videoendoscopic imaging are widely used. Both methods use a camera with a CCD, which is an array of photosensitive sensor elements (pixels) that convert the incoming light intensity to an electric charge. The electric charge is subsequently converted into a black-and-white image.[48]

With videoendoscopy, the CCD chip is placed on the internal end of a long, flexible endoscope. With older flexible endoscopes, thin quartz fibers are packed together in a bundle, and the CCD camera is mounted on the external end of the endoscope. Most standard GI endoscopes have the CCD chip at the distal end, but small, delicate choledochoscopes and nephroscopes are equipped with fiber-optic bundles.[49] Distally mounted CCD chips were developed for laparoscopy as well but have not become popular.

Video cameras come in two basic designs. Nearly all laparoscopic cameras contain a red, green, and blue input, and are identical to the color cameras used for television production.[48] An additional feature of many video cameras is digital enhancement. Digital enhancement detects edges, areas where there are drastic color or light changes between two adjacent pixels.[50] By enhancing this difference, the image appears sharper and surgical resolution is improved. New laparoscopic cameras contain a high-definition (HD) chip which increases the lines of resolution from 480 to 1080 lines. To enjoy the benefit of the clarity of HD video imaging, HD monitors also are necessary. Although this technology will inevitably replace more standard video imaging, it is not clear that the safety or efficiency of laparoscopic surgery is benefited by HD video imaging.

Priorities in a video imaging system for MIS are illumination first, resolution second, and color third. Without the first two attributes, video surgery is unsafe. Illumination and resolution are as dependent on the telescope, light source, and light cable as on the video camera used. Imaging for laparoscopy, thoracoscopy, and subcutaneous surgery uses a rigid metal telescope, usually 30 cm in length. Longer telescopes are available for obese patients and for reaching the mediastinum and deep in the pelvis from a periumbilical entry site. The standard telescope contains a series of quartz optical rods and focusing lenses.[51] Telescopes vary in size from 2 to 12 mm in

diameter. Because light transmission is dependent on the cross-sectional area of the quartz rod, when the diameter of a rod/lens system is doubled, the illumination is quadrupled. Little illumination is needed in highly reflective, small spaces such as the knee, and a very small telescope will suffice. When working in the abdominal cavity, especially if blood is present, the full illumination of a 10-mm telescope usually is necessary.

Rigid telescopes may have a flat or angled end. The flat end provides a straight view (0°), and the angled end provides an oblique view (30 or 45°).[48] Angled telescopes allow greater flexibility in viewing a wider operative field through a single trocar site (Fig. 14-11); rotating an angled telescope changes the field of view. The use of an angled telescope has distinct advantages for most videoendoscopic procedures, particularly in visualizing the common bile duct during laparoscopic cholecystectomy or visualizing the posterior esophagus or the tip of the spleen during laparoscopic fundoplication.

Fig. 14-11.

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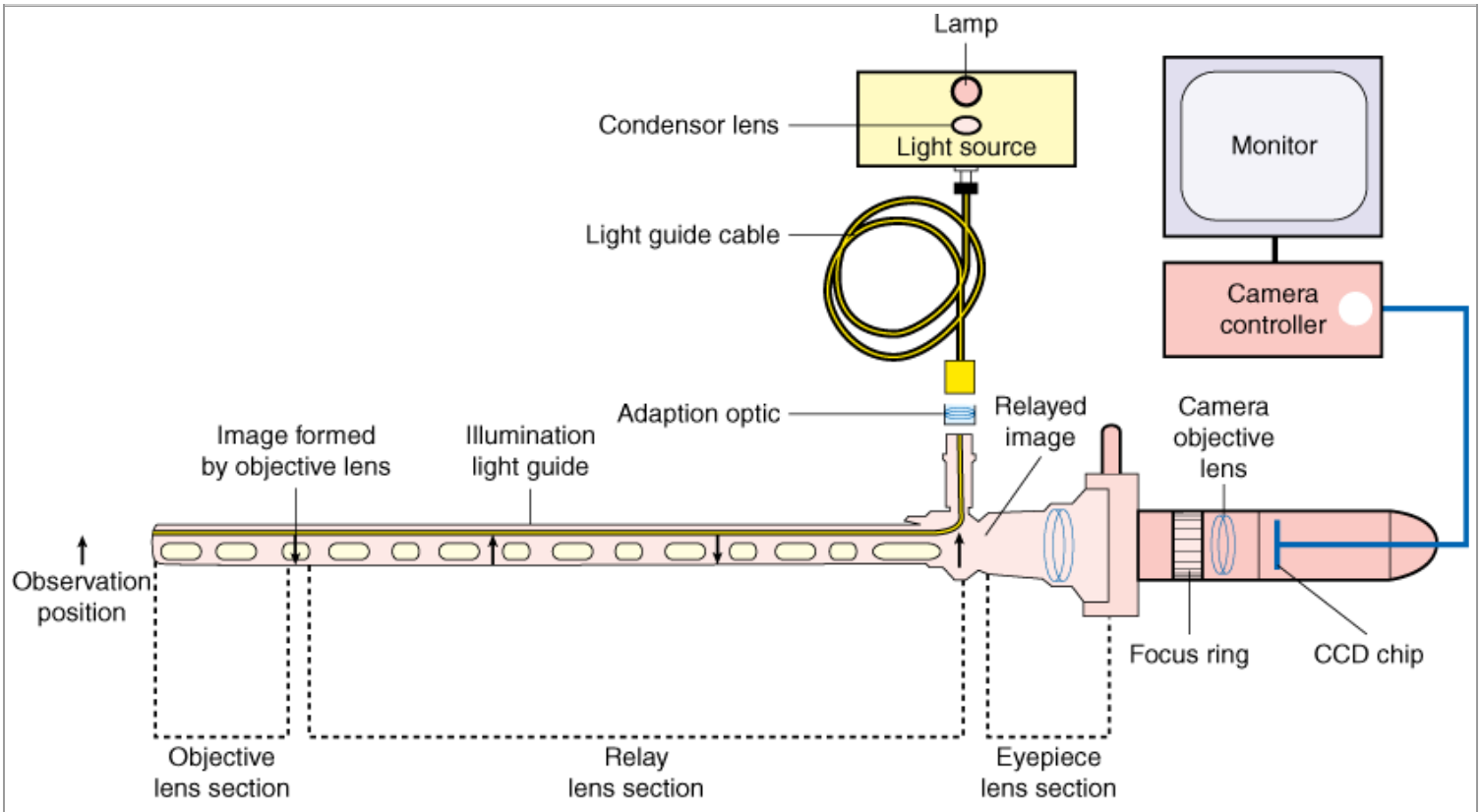
The laparoscope tips come in a variety of angled configurations. All laparoscopes have a 70° field of view. A 30°-angled scope enables the surgeon to view this field at a 30° angle to the long axis of the scope.

Light is delivered to the endoscope through a fiber-optic light cable. These light cables are highly inefficient, losing >90% of the light delivered from the light source. Extremely bright light sources (300 watts) are necessary to provide adequate illumination for laparoscopic surgery.

The quality of the videoendoscopic image is only as good as the weakest component in the imaging chain (Fig. 14-12). Therefore, it is important to use a video monitor that has a resolution equal to or greater than the camera being used.[51] *Resolution* is the ability of the optical system to distinguish between line pairs. The larger the number of line pairs per millimeter, the sharper and more detailed the image. Most high-resolution monitors have up to 700 horizontal lines. High-definition television can deliver up to eight times more resolution than standard monitors; when combined with digital enhancement, a very sharp and well-defined image can be achieved.[48,51] A heads-up display is a high-resolution liquid crystal monitor that is built into eyewear worn by the surgeon.[52] This technology allows the surgeon to view the endoscopic image and operative field simultaneously. The proposed advantages of heads-up display include a high-resolution monocular image, which affords the surgeon mobility and reduces vertigo and eyestrain. However, this technology has not yet been widely adopted.

Fig. 14-12.



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The Hopkins rod lens telescope includes a series of optical rods that effectively transmit light to the eyepiece. The video camera is placed on the eyepiece to provide the working image. The image is only as clear as the weakest link in the image chain. CCD = charge-coupled device.

(Reproduced with permission from Prescher et al.[48])

Interest in three-dimensional (3-D) laparoscopy has waxed and waned. 3-D laparoscopy provides the additional depth of field that is lost with two-dimensional endosurgery and improves performance of novice laparoscopists performing complex tasks of dexterity, including suturing and knot tying.[53] The advantages of 3-D systems are less obvious to experienced laparoscopists. Additionally, because 3-D systems require the flickering of two similar images, which are resolved with special glasses, the images' edges become fuzzy and resolution is lost. The optical accommodation necessary to rectify these slightly differing images is tiring and may induce headaches when one uses these systems for a long period of time. The da Vinci robot uses a specialized laparoscope with two optical bundles on opposite sides of the telescope. A specialized binocular eyepiece receives input from two CCD chips, each capturing the image from one of the two quartz rod lens systems, thereby creating true 3-D imaging without using the "tricks" that have made 3-D laparoscopy so disappointing.

Energy Sources for Endoscopic and Endoluminal Surgery

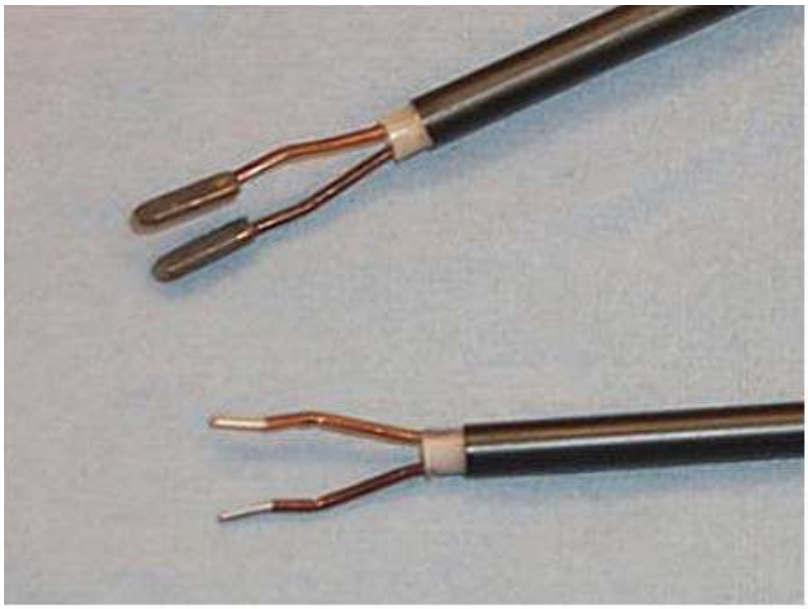
Many MIS procedures use conventional energy sources, but the benefits of bloodless surgery to maintain optimal visualization has spawned new ways of applying energy. The most common energy source is RF electrosurgery using an alternating current with a frequency of 500,000 cycles/s (Hz). Tissue heating progresses through the well-known phases of coagulation [60°C (140°F)], vaporization and desiccation [100°C (212°F)], and carbonization [>200°C (392°F)].[54]

The two most common methods of delivering RF electrosurgery are with monopolar and bipolar electrodes. With monopolar electrosurgery, a remote ground plate on the patient's leg or back receives the flow of electrons that originate at a point source, the surgical electrode. A fine-tipped electrode causes a high current density at the site of application and rapid tissue heating. Monopolar electrosurgery is inexpensive and easy to modulate to achieve different tissue effects.[55] A short-duration, high-voltage discharge of

current (coagulation current) provides extremely rapid tissue heating. Lower-voltage, higher-wattage current (cutting current) is better for tissue desiccation and vaporization. When the surgeon desires tissue division with the least amount of thermal injury and least coagulation necrosis, a cutting current is used.

With bipolar electrosurgery, the electrons flow between two adjacent electrodes. The tissue between the two electrodes is heated and desiccated. There is little opportunity for tissue cutting when bipolar current is used, but the ability to coapt the electrodes across a vessel provides the best method of small-vessel coagulation without thermal injury to adjacent tissues[56] (Fig. 14-13).

Fig. 14-13.



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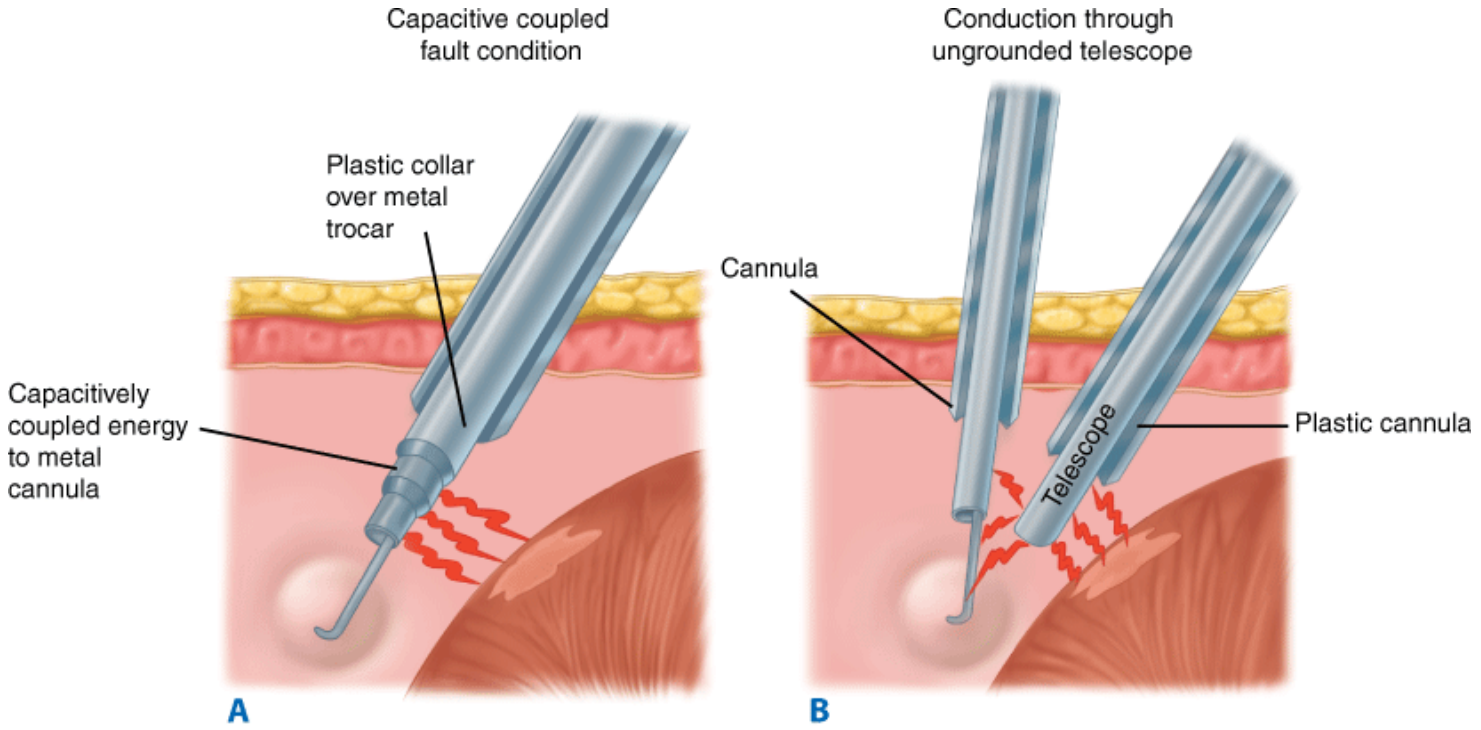
An example of bipolar coagulation devices. The flow of electrons passes from one electrode to the other, and the intervening tissue is heated and desiccated.

To avoid thermal injury to adjacent structures, the laparoscopic field of view must include all uninsulated portions of the electrosurgical electrode. In addition, the integrity of the insulation must be maintained and assured. Capacitive coupling occurs when a plastic trocar insulates the abdominal wall from the current; in turn, the current is bled off of a metal sleeve or laparoscope into the viscera[54] (Fig. 14–14A). This may result in thermal necrosis and a delayed fecal fistula. Another potential mechanism for unrecognized visceral injury may occur with the direct coupling of current to the laparoscope and adjacent bowel[54] (Fig. 14-14B).

Fig. 14-14.



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A. Capacitive coupling occurs as a result of high current density bleeding from a port sleeve or laparoscope into adjacent bowel. **B.** Direct coupling occurs when current is transmitted directly from the electrode to a metal instrument or laparoscope, and then into adjacent tissue.

(Reproduced with permission from Odell.[54])

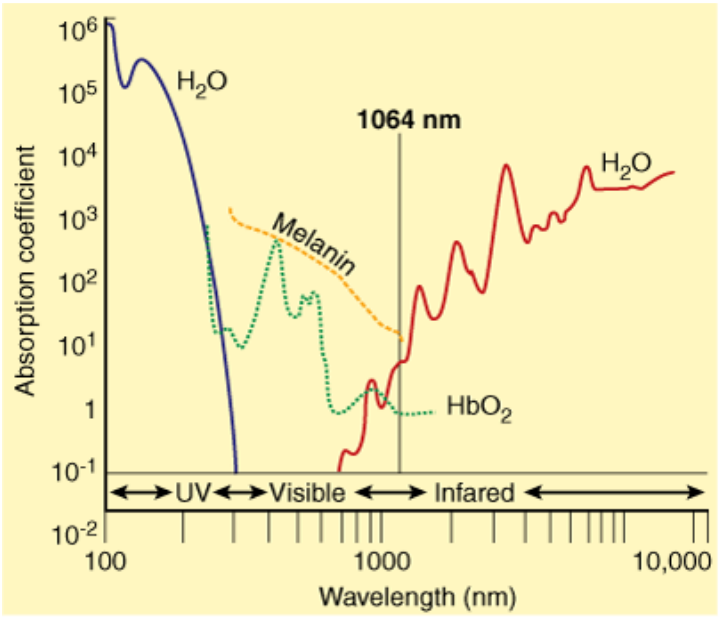
Another method of delivering RF electrosurgery is argon beam coagulation. This is a type of monopolar electrosurgery in which a uniform field of electrons is distributed across a tissue surface by the use of a jet of argon gas. The argon gas jet distributes electrons more evenly across the surface than does spray electrofulguration. This technology has its greatest application for coagulation of diffusely bleeding surfaces such as the cut edge of liver or spleen. It is of less value in laparoscopic procedures because the increased intra-abdominal pressures created by the argon gas jet can increase the chances of a gas embolus. It is paramount to vent the ports and closely monitor insufflation pressure when using this source of energy within the context of laparoscopy.

With endoscopic endoluminal surgery, RF alternating current in the form of a monopolar circuit represents the mainstay for procedures such as snare polypectomy, sphincterotomy, lower esophageal sphincter ablation, and "hot" biopsy.[57,58] A grounding ("return") electrode is necessary for this form of energy. Bipolar electrocoagulation is used primarily for thermal hemostasis. The electrosurgical generator is activated by a foot pedal so the endoscopist may keep both hands free during the endoscopic procedure.

Gas, liquid, and solid-state lasers have been available for medical application since the mid-1960s.[59] The CO_2 laser (wavelength 10.6 μm) is most appropriately used for cutting and superficial ablation of tissues. It is most helpful in locations unreachable with a scalpel such as excision of vocal cord granulomas. The CO_2 laser beam must be delivered with a series of mirrors and is therefore somewhat cumbersome to use. The next most popular laser is the neodymium yttrium-aluminum garnet (Nd:YAG) laser. Nd:YAG laser light is 1.064 μm (1064 nm) in wavelength. It is in the near-infrared portion of the spectrum, and, like CO_2 laser light, is invisible to the naked eye. A unique feature of the Nd:YAG laser is that 1064-nm light is poorly absorbed by most tissue pigments and therefore travels deep into tissue.[60] Deep tissue penetration provides deep tissue heating (Fig. 14-15). For this reason, the Nd:YAG laser is capable of the greatest amount of tissue destruction with a single application.[59] Such capabilities make it the ideal laser for destruction of large fungating tumors of the rectosigmoid, tracheobronchial tree, or esophagus. A disadvantage is that the deep tissue heating may cause perforation of

a hollow viscus.

Fig. 14-15.



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This graph shows the absorption of light by various tissue compounds (water, melanin, and oxyhemoglobin) as a function of the wavelength of the light. The nadir of the oxyhemoglobin and melanin curves is close to 1064 nm, the wavelength of the neodymium yttrium-aluminum garnet laser.

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When it is desirable to coagulate flat lesions in the cecum, a different laser should be chosen. The frequency-doubled Nd:YAG laser, also known as the *KTP laser* (potassium thionyl phosphate crystal is used to double the Nd:YAG frequency), provides 532-nm light. This is in the green portion of the spectrum, and at this wavelength, selective absorption by red pigments in tissue (such as hemangiomas and arteriovenous malformations) is optimal. The depth of tissue heating is intermediate, between those of the CO_2 and the Nd:YAG lasers. Coagulation (without vaporization) of superficial vascular lesions can be obtained without intestinal perforation.[60]

In flexible GI endoscopy, the CO_2 and Nd:YAG lasers have largely been replaced by heater probes and endoluminal stents. The heater probe is a metal ball that is heated to a temperature [60 to 100°C (140 to 212°F)] that allows coagulation of bleeding lesions without perforation.

Photodynamic therapy is a palliative treatment for obstructing cancers of the GI tract.[61] Patients are given an IV dose of porfimer sodium, which is a photosensitizing agent that is taken up by malignant cells. Two days after administration, the drug is endoscopically activated using a laser. The activated porfimer sodium generates oxygen free radicals, which kill the tumor cells. The tumor is later endoscopically débrided. The use of this modality for definitive treatment of early cancers is in experimental phases and has yet to become established.

A unique application of laser technology provides extremely rapid discharge ($<10^{-6}$ s) of large amounts of energy ($>10^3$ volts). These high-energy lasers, of which the pulsed dye laser has seen the most clinical use, allow the conversion of light energy to mechanical disruptive energy in the form of a shock wave. Such energy can be delivered through a quartz fiber, and with rapid repetitive discharges, can provide sufficient shock-wave energy to fragment kidney stones and gallstones.[62] Shock waves also may be created with miniature electric spark-plug discharge systems known as *electrohydraulic lithotriptors*. These devices also are inserted through thin probes for endoscopic application. Lasers have the advantage of pigment selectivity, but electrohydraulic lithotriptors are more popular because they

are substantially less expensive and are more compact.

Methods of producing shock waves or heat with ultrasonic energy are also of interest. Extracorporeal shockwave lithotripsy creates focused shock waves that intensify as the focal point of the discharge is approached. When the focal point is within the body, large amounts of energy are capable of fragmenting stones. Slightly different configurations of this energy can be used to provide focused internal heating of tissues. Potential applications of this technology include the ability to noninvasively produce sufficient internal heating to destroy tissue without an incision.

A third means of using ultrasonic energy is to create rapidly oscillating instruments that are capable of heating tissue with friction; this technology represents a major step forward in energy technology.[63] An example of its application is the laparoscopic coagulation shears device (Harmonic Scalpel), which is capable of coagulating and dividing blood vessels by first occluding them and then providing sufficient heat to weld the blood vessel walls together and to divide the vessel. This nonelectric method of coagulating and dividing tissue with a minimal amount of collateral damage has facilitated the performance of numerous endosurgical procedures.[64] It is especially useful in the control of bleeding from medium-sized vessels that are too big to manage with monopolar electrocautery and require bipolar desiccation followed by cutting.

Instrumentation

Hand instruments for MIS usually are duplications of conventional surgical instruments made longer, thinner, and smaller at the tip. It is important to remember that when grasping tissue with laparoscopic instruments, a greater force is applied over a smaller surface area, which increases the risk for perforation or injury.[65]

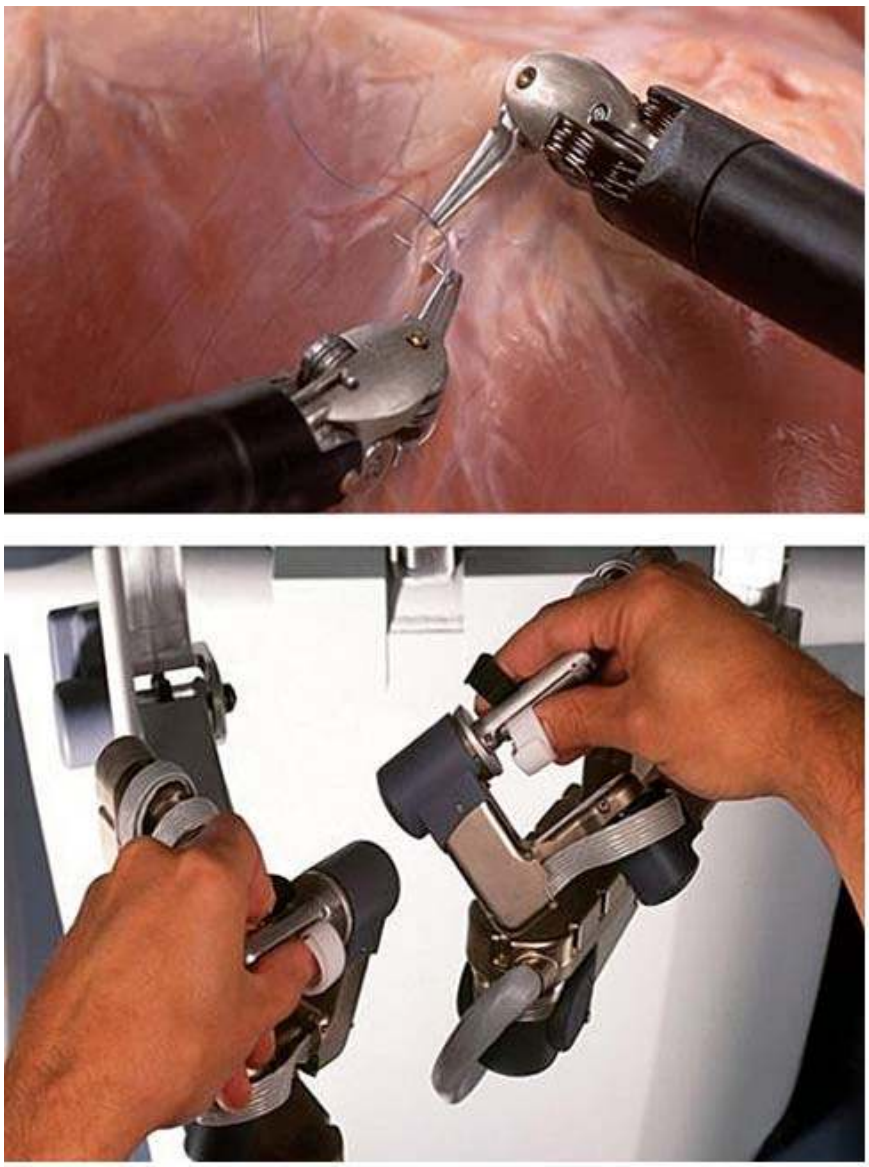
Certain conventional instruments such as scissors are easy to reproduce with a diameter of 3 to 5 mm and a length of 20 to 45 cm, but other instruments such as forceps and clamps cannot provide remote access. Different configurations of graspers were developed to replace the various configurations of surgical forceps and clamps. Standard hand instruments are 5 mm in diameter and 30 cm in length, but smaller and shorter hand instruments are now available for pediatric surgery, for microlaparoscopic surgery, and for arthroscopic procedures.[65] A unique laparoscopic hand instrument is the monopolar electrical hook. This device usually is configured with a suction and irrigation apparatus to eliminate smoke and blood from the operative field. The monopolar hook allows tenting of tissue over a bare metal wire with subsequent coagulation and division of the tissue.

Instrumentation for NOTES is still evolving, but many long micrograspers, microscissors, suturing devices, clip appliers, and visceral closure devices are evolving in design and application.

Robotic Surgery

The term *robot* defines a device that has been programmed to perform specific tasks in place of those usually performed by people. The devices that have earned the title "surgical robots" would be more aptly termed *computer-enhanced surgical devices*, as they are controlled entirely by the surgeon for the purpose of improving performance. The first computer-assisted surgical device was the laparoscopic camera holder (Aesop, Computer Motion, Goleta, Calif), which enabled the surgeon to maneuver the laparoscope either with a hand control, foot control, or voice activation (Fig. 14-16). Randomized studies with such camera holders demonstrated a reduction in operative time, steadier image, and a reduction in the number of required laparoscope cleanings.[66] This device had the advantage of eliminating the need for a human camera holder, which served to free valuable OR personnel for other duties. This technology has now been eclipsed by simpler systems using passive positioning of the camera with a mechanical arm, but the benefit of a steadier image and fewer members of the OR team remain.

Fig. 14-16.



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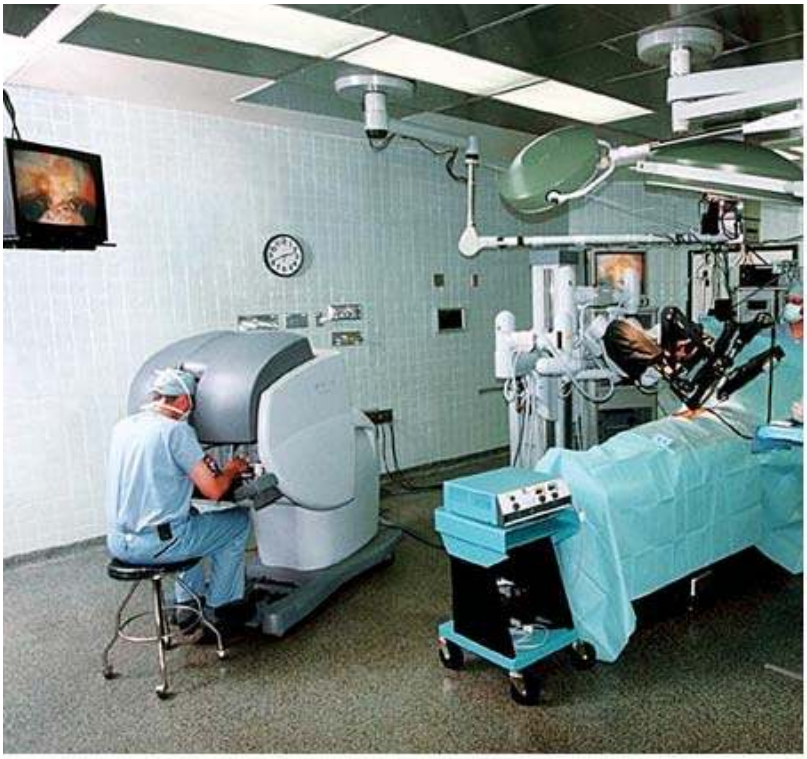
Robotic instruments and hand controls. The surgeon is in a sitting position and the arms and wrists are in an ergonomic and relaxed position.

The "Big Bang" in robotic surgery was the development of a *master-slave* surgical platform that returned the wrist to laparoscopic surgery and improved manual dexterity by developing an ergonomically comfortable work station, with 3-D imaging, tremor elimination, and scaling of movement (e.g., large, gross hand movements can be scaled down to allow suturing with microsurgical precision) (see Fig. 14-16). The surgeon is physically separated from the operating table, and the working arms of the device are placed over the patient (Fig. 14-17). An assistant remains at the bedside and changes the instruments as needed, providing retraction as needed to facilitate the procedure. This "robotic" platform (da Vinci, Intuitive Surgical, Sunnyvale, Calif) was initially greeted with some skepticism by expert laparoscopists, as it was difficult to prove additional value for operations performed with the da Vinci robot. Not only were the operations longer, and the equipment more expensive, but additional quality could not be demonstrated. Two randomized controlled trials compared robotic and conventional laparoscopic approaches to Nissen fundoplication.[67,68] In both these trials, the operative time was longer for robotic surgery, and there was no difference in ultimate outcome. Similar results were achieved for laparoscopic cholecystectomy.[69] Nevertheless, the increased dexterity provided by the da Vinci robot convinced many surgeons and health administrators that robotic platforms were worthy of investment, for marketing purposes if for no other reason.

Fig. 14-17.



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Room setup and position of surgeon and assistant for robotic surgery.

The success story for computer-enhanced surgery with the da Vinci started with cardiac surgery and migrated to the pelvis. Mitral valve surgery, performed with right thoracoscopic access became one of the more popular procedures performed with "the robot."[70]

The tidal wave of enthusiasm for robotic surgery came when most minimally invasive urologists declared robotic prostatectomy to be preferable to laparoscopic and open prostatectomy.[71] The great advantage—it would appear—of robotic prostatectomy is the ability to visualize and spare the pelvic nerves responsible for erectile function. In addition, the creation of the neocystourethrotomy, following prostatectomy, was greatly facilitated by needle holders and graspers with a wrist in them. Female pelvic surgery with the "robot" also is picking up steam. The magnified imaging provided makes this approach ideal for microsurgical tasks such as reanastomosis of the Fallopian tubes.

The final frontier for computer-enhanced surgery is the promise of telesurgery, in which the surgeon is a great distance from the patient (e.g., combat or space). This application has rarely been used, as the safety provided by having the surgeon at bedside cannot be sacrificed to prove the concept. However, remote laparoscopic cholecystectomy has been performed when a team of surgeons located in New York performed a cholecystectomy on a patient located in France.[72]

Endoluminal and Endovascular Surgery

The fields of vascular surgery, interventional radiology, neuroradiology, gastroenterology, general surgery, pulmonology, and urology all encounter clinical scenarios that require the urgent restoration of luminal patency of a "biologic cylinder." Based on this need, fundamental techniques have been pioneered that are applicable to all specialties and virtually every organ system. As a result, all minimally invasive surgical procedures, from coronary artery angioplasty to palliation of pancreatic malignancy, involve the use of access devices, catheters, guidewires, balloon dilators, stents, and other devices (e.g., lasers, atherectomy catheters) that are capable of opening up the occluded biologic cylinder[73] (Table 14-2). Endoluminal balloon dilators may be inserted through an endoscope, or they

From Lycan / Dr. MV

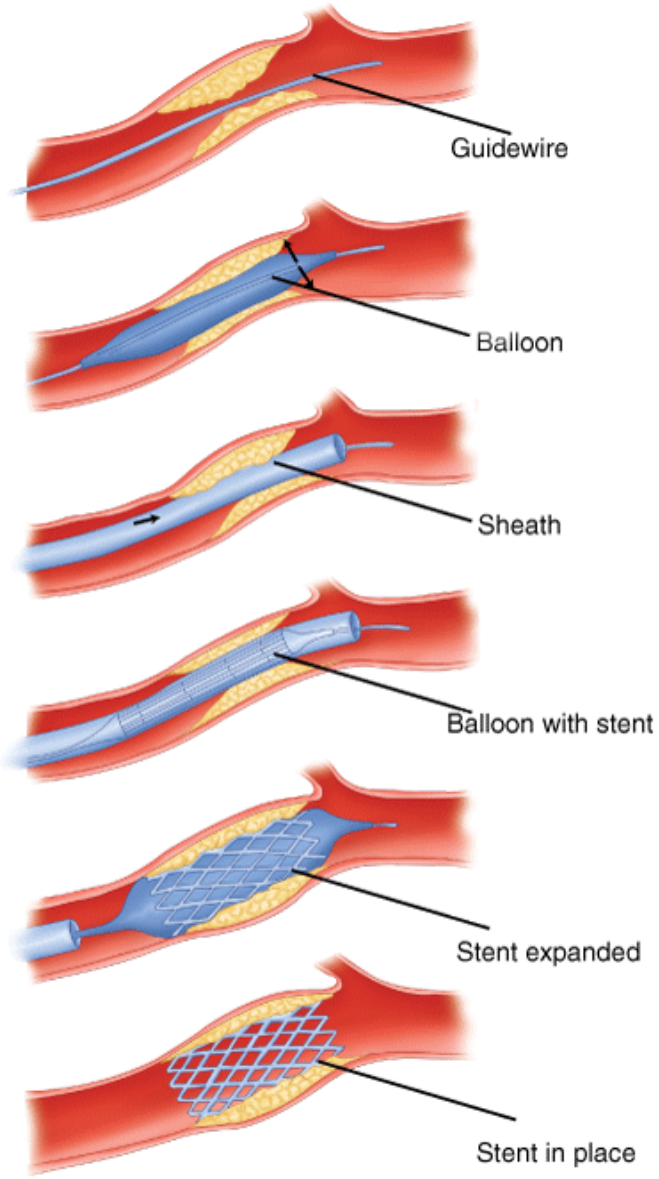
may be fluoroscopically guided. Balloon dilators all have low compliance—that is, the balloons do not stretch as the pressure within the balloon is increased. The high pressures achievable in the balloon create radial expansion of the narrowed vessel or orifice, usually disrupting the atherosclerotic plaque, the fibrotic stricture, or the muscular band (e.g., esophageal achalasia).[74]

Table 14-2 Modalities and Techniques of Restoring Luminal Patency

Modality	Technique
Core out	Photodynamic therapy
	Laser
	Coagulation
	Endoscopic biopsy forceps
	Chemical
	Ultrasound
Fracture	Ultrasound
	Endoscopic biopsy
	Balloon
Dilate	Balloon
	Bougie
	Angioplasty
	Endoscope
Bypass	Transvenous intrahepatic portosystemic shunt
	Surgical (synthetic or autologous conduit)
Stent	Self-expanding metal stent
	Plastic stent

Once the dilation has been attained, it is frequently beneficial to hold the lumen open with a stent.[75] Stenting is particularly valuable in treating malignant lesions and atherosclerotic occlusions or aneurysmal disease (Fig. 14-18). Stenting is also of value to seal leaky cylinders, including aortic dissections, traumatic vascular injuries, leaking GI anastomoses, and fistulas. Stenting usually is not applicable for long-term management of benign GI strictures except in patients with limited life expectancy [75–77] (Fig. 14-19).

Fig. 14-18.



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The deployment of a metal stent across an isolated vessel stenosis is illustrated.

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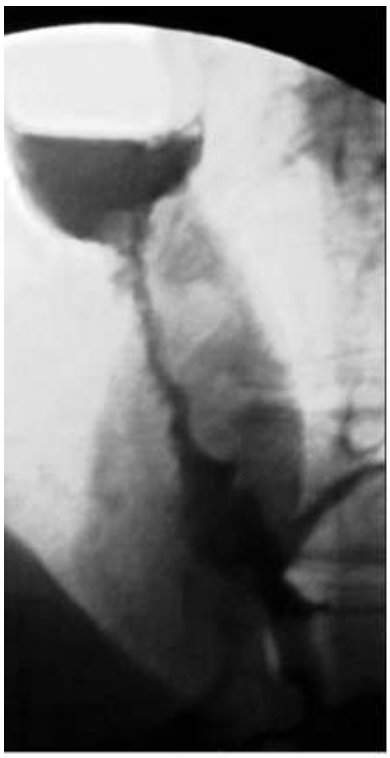
Fig. 14-19.



A

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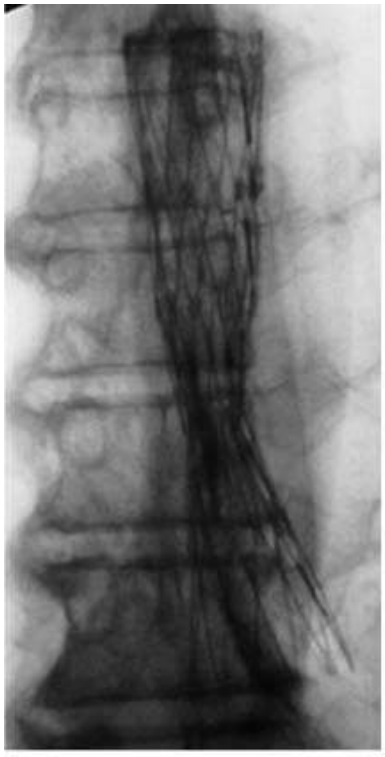

B

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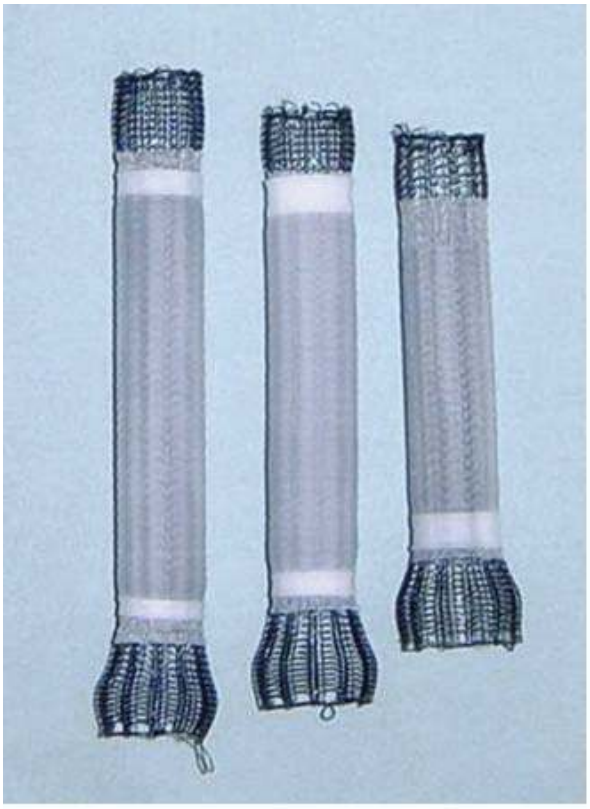
This is an esophagram in a patient with severe dysphagia secondary to advanced esophageal cancer (**A**) before and (**B**) after placement of a covered self-expanding metal stent.

A variety of stents are available that are divided into six basic categories: plastic stents, metal stents, drug-eluting stents (to decrease fibrovascular hyperplasia), covered metal stents, anchored stent grafts, and removable covered plastic stents[76] (Fig. 14-20). Plastic stents came first and are used widely as endoprostheses for temporary bypass of obstructions in the biliary or urinary systems. Metal stents generally are delivered over a balloon and expanded with the balloon to the desired size. These metal stents usually are made of titanium or nitinol, and are still used in coronary stenting. A chemotherapeutic agent was added to coronary stents several years ago to decrease endothelial proliferation. These drug-eluting stents provide greater long-term patency but require long-term anticoagulation with antiplatelet agents to prevent thrombosis.[78] Coated metal stents are use to prevent tissue ingrowth. Ingrowth may be an advantage in preventing stent migration, but such tissue ingrowth may occlude the lumen and cause obstruction anew. This is a particular problem when stents are used for palliation of GI malignant growth, and may be a problem for the long-term use of stents in vascular disease. Filling the interstices with Silastic or other materials may prevent tumor ingrowth but also makes stent migration more likely. In an effort to minimize stent migration, stents have been incorporated with hooks and barbs at the proximal end of the stent to anchor it to the wall of the vessel. Endovascular stenting of aortic aneurysms has nearly replaced open surgery for this condition. Lastly, self-expanding plastic stents have been developed as temporary devices to be used in the GI tract to close internal fistulas and bridge leaking anastomoses.

Fig. 14-20.



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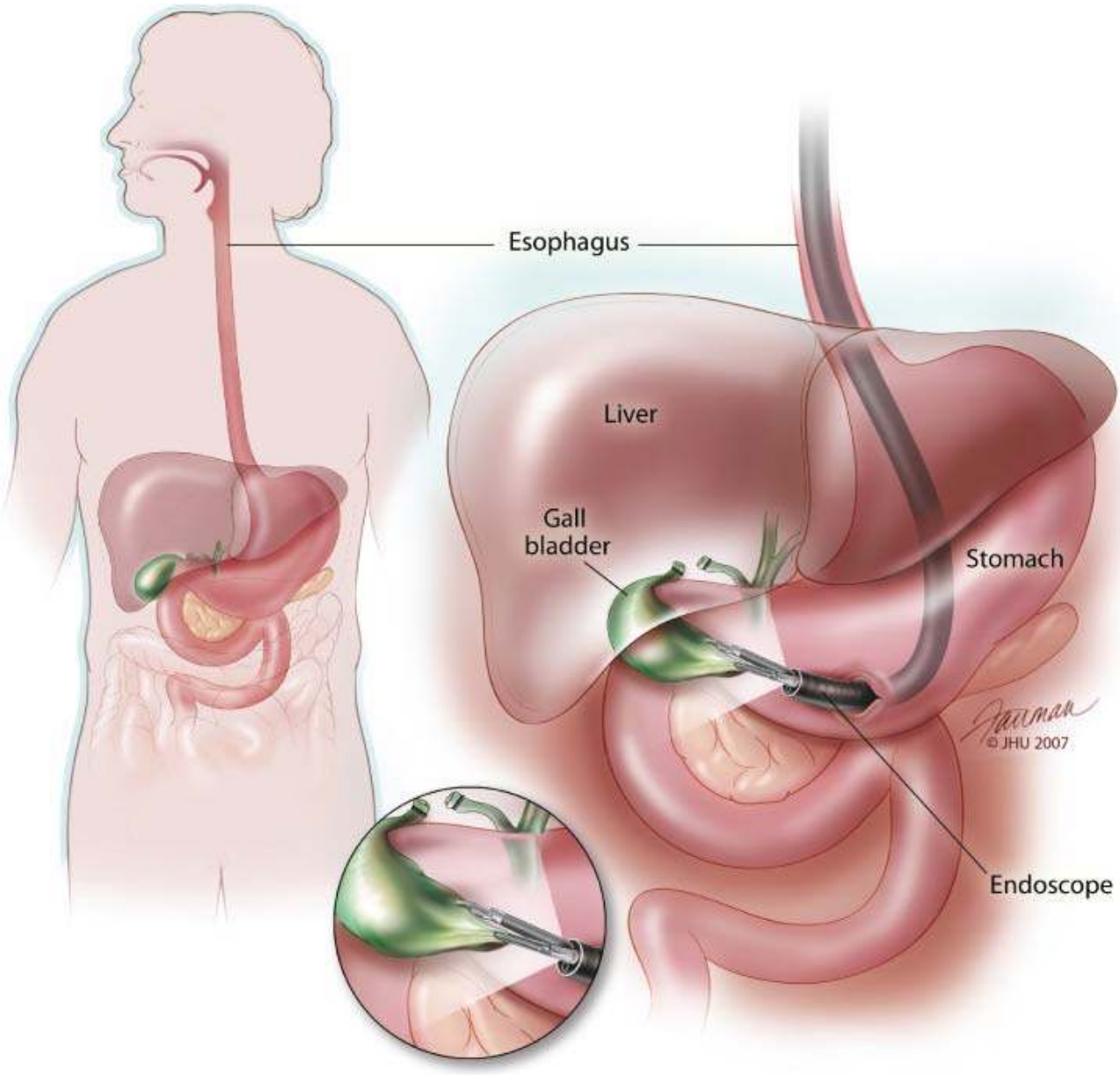
Covered self-expanding metal stents. These devices can be placed fluoroscopically or endoscopically.

Natural Orifice Transluminal Endoscopic Surgery

The "latest rage" in MIS is NOTES, the use of the flexible endoscope to enter the GI, urinary, or reproductive tracts, then traverse the wall of the structure to enter the peritoneal cavity, the mediastinum, or the chest. In truth, transluminal surgery has been performed in the stomach for a long time, either from the inside out (e.g. percutaneous, PEG, and transgastric pseudocyst drainage) or from the outside in (e.g., laparoscopic assisted intragastric tumor resection). The catalyzing event for NOTES was the demonstration that a porcine

gallbladder could be removed with a flexible endoscope passed through the wall of the stomach, then removed through the mouth, and the demonstration in a series of 10 human cases from India of the ability to perform transgastric appendectomy. Since that time, a great deal of money has been invested by endoscopic and MIS companies to help surgeons and gastroenterologists explore this new territory. To date, the most headline-grabbing procedures have been the transvaginal and transgastric removal of the gallbladder[79–81] (Fig. 14-21). To ensure safety, all cases thus far have involved laparoscopic assistance to aid in retraction, and ensure adequate closure of the stomach. As such, the benefits of NOTES cholecystectomy have not been demonstrated convincingly, but when all laparoscopic assistance has been eliminated, this approach will surely appeal to many. Additional procedures performed with NOTES might include staging of intra-abdominal malignancy, segmental colectomy, gastrojejunostomy, and a host of other procedures capable of exciting the curious mind. In addition, the rapid growth of endoscopic technology catalyzed by NOTES has already spun off new technologies capable of performing a wide variety of endoscopic surgical procedures from endoscopic mucosal resection to ablation of Barrett's esophagus, to creation of competent antireflux valves in patients with gastroesophageal reflux disease. Although some of these applications are still considered experimental, there is little doubt that when equivalent operations can be performed with less pain, fewer scars, and less disability, patients will flock to it. Surgeons should engage only when they can perform these procedures with the safety and efficacy demanded by our profession.

Fig. 14-21.



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Transgastric cholecystectomy using natural orifice transluminal endoscopic surgery technology and one to three laparoscopic ports has been performed occasionally in several locations around the world.

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SPECIAL CONSIDERATIONS

Pediatric Laparoscopy

The advantages of MIS in children may be more significant than in the adult population. MIS in the adolescent is little different from that in the adult, and standard instrumentation and trocar positions usually can be used. However, laparoscopy in the infant and young child requires specialized instrumentation. The instruments are shorter (15 to 20 cm), and many are 3 mm in diameter rather than 5 mm. Because the abdomen of the child is much smaller than that of the adult, a 5-mm telescope provides sufficient illumination for most operations. The development of 5-mm clippers and bipolar devices has obviated the need for 10-mm trocars in pediatric laparoscopy.[82] Because the abdominal wall is much thinner in infants, a pneumoperitoneum pressure of 8 mmHg can provide adequate exposure. DVT is

rare in children, so prophylaxis against thrombosis probably is unnecessary. A wide variety of pediatric surgical procedures are frequently performed with MIS access, from pull-through procedures for colonic aganglionosis (Hirschsprung's disease) to repair of congenital diaphragmatic hernias.[83]

Laparoscopy during Pregnancy

Concerns about the safety of laparoscopic cholecystectomy or appendectomy in the pregnant patient have been thoroughly investigated and are readily managed. Access to the abdomen in the pregnant patient should take into consideration the height of the uterine fundus, which reaches the umbilicus at 20 weeks. In order not to damage the uterus or its blood supply, most surgeons feel that the open (Hasson) approach should be used in favor of direct puncture laparoscopy. The patient should be positioned slightly on the left side to avoid compression of the vena cava by the uterus. Because pregnancy poses a risk for thromboembolism, sequential compression devices are essential for all procedures. Fetal acidosis induced by maternal hypercarbia also has been raised as a concern. The arterial pH of the fetus follows the pH of the mother linearly; and therefore, fetal acidosis may be prevented by avoiding a respiratory acidosis in the mother.[84] The pneumoperitoneum pressure induced by laparoscopy is not a safety issue either as it has been proved that midpregnancy uterine contractions provide a much greater pressure in utero than a pneumoperitoneum of 15 mmHg. Experience in >100 cases of laparoscopic cholecystectomy in pregnancy have been reported with uniformly good results.[85] The operation should be performed during the second trimester of pregnancy if possible. Protection of the fetus against intraoperative x-rays is imperative. Some believe it advisable to track fetal pulse rates with a transvaginal ultrasound probe; however, the significance of fetal tachycardia or bradycardia is a bit unclear in the second trimester of pregnancy. To be prudent, however, heart rate decelerations reversibly associated with pneumoperitoneum creation might signal the need to convert to open cholecystectomy or appendectomy.

Minimally Invasive Surgery and Cancer Treatment

MIS techniques have been used for many decades to provide palliation for the patient with an obstructive cancer. Laser treatment, intracavitary radiation, stenting, and dilation are outpatient techniques that can be used to re-establish the continuity of an obstructed esophagus, bile duct, ureter, or airway. MIS techniques also have been used in the staging of cancer. Mediastinoscopy is still used occasionally before thoracotomy to assess the status of the mediastinal lymph nodes. Laparoscopy also is used to assess the liver in patients being evaluated for pancreatic, gastric, or hepatic resection. New technology and greater surgical skills allow for accurate minimally invasive staging of cancer.[86] Occasionally, it is appropriate to perform palliative measures (e.g., laparoscopic gastrojejunostomy to bypass a pancreatic cancer) at the time of diagnostic laparoscopy if diagnostic findings preclude attempts at curative resection.

Initially controversial, the role of MIS to provide a safe curative treatment of cancer has proven to be no different from the principles of open surgery. All gross and microscopic tumor should be removed (an R0 resection), and an adequate lymphadenectomy should be performed to allow accurate staging. Generally, this number has been 10 to 15 lymph nodes, although there is still debate as to the value of more extensive lymphadenectomy. All of the major abdominal cancer operations have been performed with laparoscopy. Of the three major cancer resections of GI cancer (liver lobe, pancreatic head, and esophagus), only esophagectomy is routinely performed by a fair number of centers.[87,88] Laparoscopic hepatectomy has attracted a loyal following, and distal pancreatectomy frequently is performed with laparoscopic access. In Japan, laparoscopic-assisted gastrectomy has become quite popular for early gastric cancer, an epidemic in Japan far exceeding that of colon cancer in North America and Northern Europe. The most common cancer operation performed laparoscopically is segmental colectomy, which has proven itself safe and efficacious in a multicenter controlled randomized trial.[89]

Considerations in the Elderly and Infirm

Laparoscopic cholecystectomy has made possible the removal of a symptomatic gallbladder in many patients previously thought to be too elderly or too ill to undergo a laparotomy. Older patients are more likely to require conversion to celiotomy because of disease chronicity.[89]

Operations on these patients require close monitoring of anesthesia. The intraoperative management of these patients may be more

difficult with laparoscopic access than with open access. The advantage of MIS lies in what happens after the operation. Much of the morbidity of surgery in the elderly is a result of impaired mobility. In addition, pulmonary complications, urinary tract sepsis, DVT, pulmonary embolism, congestive heart failure, and myocardial infarction often are the result of improper fluid management and decreased mobility. By allowing rapid and early mobilization, laparoscopic surgery has made possible the safe performance of procedures in the elderly and infirm.

Cirrhosis and Portal Hypertension

Patients with hepatic insufficiency pose a significant challenge for any type of surgical intervention.[90] The ultimate surgical outcome in this population relates directly to the degree of underlying hepatic dysfunction.[91] Often, this group of patients has minimal reserve, and the stress of an operation will trigger complete hepatic failure or hepatorenal syndrome. These patients are at risk for major hemorrhage at all levels, including trocar insertion, operative dissection in a field of dilated veins, and secondary to an underlying coagulopathy. Additionally, ascitic leak from a port site may occur, leading to bacterial peritonitis. Therefore, a watertight port site closure should be carried out in all patients.

It is essential that the surgeon be aware of the severity of hepatic cirrhosis as judged by a MELD score (Model of Endstage Liver Disease) or Child's classification. Additionally, the presence of portal hypertension is a relative contraindication to laparoscopic surgery until the portal pressures are reduced with portal decompression. For example, if a patient has an incarcerated umbilical hernia and ascites, a preoperative paracentesis or transjugular intrahepatic portosystemic shunt procedure in conjunction with aggressive diuresis may be considered. Because these patients commonly are intravascularly depleted, insufflation pressures should be reduced to prevent a decrease in cardiac output and minimal amounts of Na^+ sparing IV fluids should be given.

Economics of Minimally Invasive Surgery

Minimally invasive surgical procedures reduce the costs of surgery most when length of hospital stay can be shortened and return to work is quickened. For example, shorter hospital stays can be demonstrated in laparoscopic cholecystectomy, Nissen fundoplication, splenectomy, and adrenalectomy. Procedures such as inguinal herniorrhaphy that are already performed as outpatient procedures are less likely to provide cost savings. Procedures that still require a 4- to 7-day hospitalization, such as laparoscopy-assisted colectomy, are less likely to deliver a lower bottom line than their open surgery counterparts. Nonetheless, with responsible use of disposable instrumentation and a commitment to the most effective use of the inpatient setting, most laparoscopic procedures can be made less expensive than their conventional equivalents.

Education and Skill Acquisition

Historically, surgeons in training (residents, registrars, and fellows) acquired their skills in minimally invasive techniques through a series of operative experiences of graded complexity. This training occurred on patients. Although such a paradigm did not compromise patient safety, learning in the OR is costly. In addition, the recent worldwide constraint placed on resident work hours makes it attractive to teach laparoscopic skills outside of the OR.

Skills labs started at nearly every surgical training center in the 1990s with a "box trainer," a rudimentary or sophisticated simulated abdominal cavity with a video camera, a monitor, trocars, laparoscopic instruments, and target models as simple as a pegboard and rubber rings, or a latex drain to practice suturing and knot tying. Virtual reality training devices present a unique opportunity to improve and enhance experiential learning in endoscopy and laparoscopy for all surgeons. This technology has the advantage of enabling objective measurement of psychomotor skills, which can be used to determine progress in skill acquisition, and ultimately, technical competency.[92] Several of these devices have been validated as a means of measuring proficiency in skill performance. More importantly, training on virtual reality platforms has proven to translate to improved operative performance in randomized trials.[93,94] In the near future, and today in some institutions, simulator training to the expert level will become a prerequisite for performance of laparoscopic procedures in the OR. The American College of Surgeons has taken a leadership position in accrediting these skills labs at American College of Surgeons–accredited educational institutes.

Telementoring

In response to the Institute of Medicine's call for the development of unique technologic solutions to deliver health care to rural and underserved areas, surgeons are beginning to explore the feasibility of telementoring. Teleconsultation or telementoring is two-way audio and visual communication between two geographically separated providers. This communication can take place in the office setting or directly in the OR when complex scenarios are encountered. Although local communication channels may limit its performance in rural areas, the technology is available and currently is being used, especially in states and provinces with large geographically remote populations[94] (Fig. 14-22).

Fig. 14-22.

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Teleconsultation and telementoring are carried out between two providers who are geographically separated. The console has a video camera, microphone, and flat screen display that can be positioned at the operating room table or in the clinic.

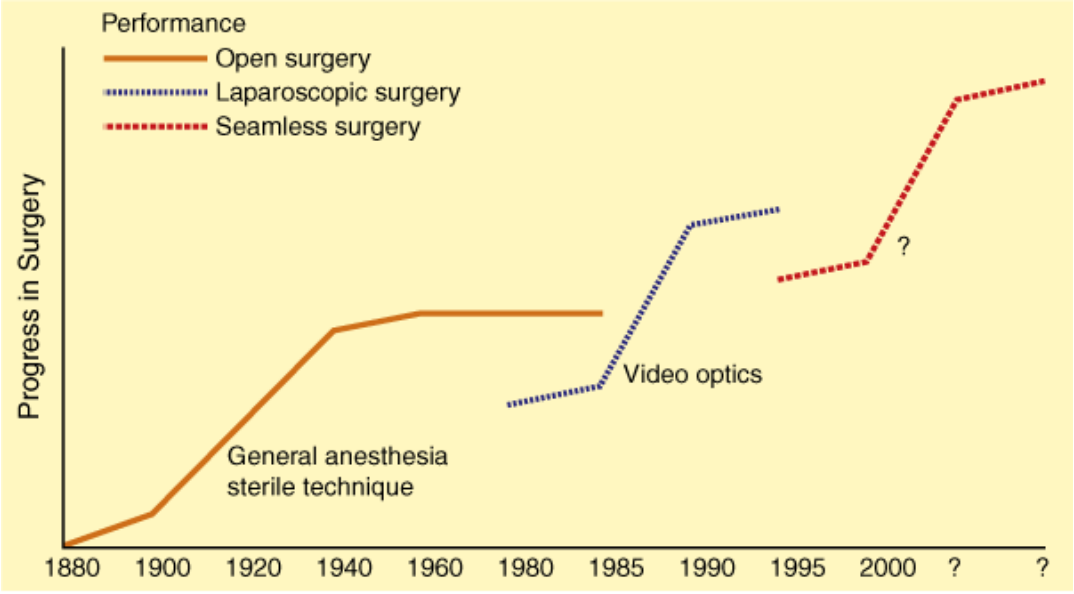
Innovation and Introduction of New Procedures

The revolution in minimally invasive general surgery, which occurred in 1990, created ethical challenges for the profession. The problem was this: If competence is gained from experience, how was the surgeon to climb the competence curve (otherwise known as the *learning curve*) without injuring patients? If it was indeed impossible to achieve competence without making mistakes along the way, how should one effectively communicate this to patients such that they understand the weight of their decisions? Even more fundamentally important is determining the path that should be followed before one recruits the first patient for a new procedure.

Although procedure development is fundamentally different than drug development (i.e., there is great individual variation in the performance of procedures, but no difference between one tablet and the next), adherence to a process similar to that used to develop a new drug is a reasonable path for a surgical innovator. At the outset, the surgeon must identify the problem that is not solved with current surgical procedures. For example, although the removal of a gallbladder through a Kocher incision is certainly effective, it creates

a great deal of disability, pain, and scarification. As a result of those issues, many patients with very symptomatic biliary colic delayed operation until life-threatening complications occurred. Clearly, there was a need for developing a less invasive approach (Fig. 14-23).

Fig. 14-23.



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The progress of general surgery can be reflected by a series of performance curves. General anesthesia and sterile technique allowed the development of maximally invasive open surgery over the last 125 years. Video optics allowed the development of minimally invasive surgery over the last 25 years. Noninvasive (seamless) surgery will result when a yet undiscovered transformational event allows surgery to occur without an incision, and perhaps without anesthesia.

Once the opportunity has been established, the next step involves a search through other disciplines for technologies and techniques that might be applied. Again, this is analogous to the drug industry, where secondary drug indications have often turned out to be more therapeutically important than the primary indication for drug development. The third step is in vivo studies in the most appropriate animal model. These types of studies are controversial because of the resistance to animal experimentation, and yet without such studies, many humans would be injured or killed during the developmental phase of medical drugs, devices, and techniques. These steps often are called the *preclinical phase of procedure development*.

The decision as to when such procedures are ready to come out of the lab is a difficult one. Put simply, the procedure should be reproducible, provide the desired effect, and not have serious side effects. Once these three criteria are reached, the time for human application has arrived. Before the surgeon discusses the new procedure with patients, it is important to achieve full institutional support. Involvement of the medical board, the chief of the medical staff, and the institutional review board is essential before commencing on a new procedure. These bodies are responsible for the use of safe, high-quality medical practices within their institution, and they will demand that great caution and all possible safeguards are in place before proceeding.

The dialogue with the patient who is to be first must be thorough, brutally honest, and well documented. The psychology that allows a patient to decide to be first is quite interesting, and may, under certain circumstances, require psychiatric evaluation. Certainly if a dying cancer patient has a chance with a new drug, this makes sense. Similarly, if the standard surgical procedure has a high attendant morbidity and the new procedure offers a substantially better outcome, the decision to be first is understandable. On the other hand, when the benefits of the new approach are small and the risks are largely unknown, a more complete psychological profile may be necessary before proceeding.

For new surgical procedures, it generally is wise to assemble the best possible operative team, including a surgeon experienced with the

old technique, and assistants who have participated in the earlier animal work. This initial team of experienced physicians and nurses should remain together until full competence with the procedure is attained. This may take 10 procedures, or it may take 50 procedures. The team will know that it has achieved competence when the majority of procedures take the same length of time, and the team is relaxed and sure of the flow of the operation. This will complete phase I of the procedure development.

In phase II, the efficacy of the procedure is tested in a nonrandomized fashion. Ideally, the outcome of new techniques must be as good or better than the procedure that is being replaced. This phase should occur at several medical centers to prove that good outcomes are achievable outside of the pioneering institution. These same requirements may be applied to the introduction of new technology into the OR. The value equation requires that the additional measurable procedure quality exceeds the additional measurable cost to the patient or health care system. In phase III, a randomized trial pits the new procedure against the old.

Once the competence curve has been climbed, it is appropriate for the team to engage in the education of others. During the ascension of the competence curve, other learners in the institution (i.e., surgical residents) may not have the opportunity to participate in the first case series. Although this may be difficult for them, the best interest of the patient must be put before the education of the resident.

The second stage of learning occurs when the new procedure has proven its value and a handful of experts exist, but the majority of surgeons have not been trained to perform the new procedure. In this setting, it is relatively unethical for surgeons to forge ahead with a new procedure in humans as if they had spent the same amount of time in intensive study that the first team did. The fact that one or several surgical teams were able to perform an operation does not ensure that all others with the same medical degrees can perform the operation with equal skill. It behooves the learners to contact the experts and request their assistance to ensure an optimal outcome at the new center. Although it is important that the learners contact the experts, it is equally important that the experts be willing to share their experience with their fellow professionals. As well, the experts should provide feedback to the learners as to whether they feel the learners are equipped to forge ahead on their own. If not, further observation and assistance from the experts are required. Although this approach may sound obvious, it is fraught with difficulties. In many situations ego, competitiveness, and monetary concerns have short-circuited this process and led to poor patient outcomes. To a large extent, MIS has recovered from the black eye it received early in development, when inadequately trained surgeons caused an excessive number of significant complications.

If innovative procedures and technologies are to be developed and applied without the mistakes of the past, surgeons must be honest when they answer these questions: Is this procedure safe? Would I consider undergoing this procedure if I developed a surgical indication? Is the procedure as good or better than the procedure it is replacing? Do I have the skills to apply this procedure safely and with equivalent results to the more experienced surgeon? If the answer to any of these questions is "no," or "I don't know," there is a professional obligation to seek another procedure or outside assistance before subjecting a patient to the new procedure.

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KEY POINTS

1. The advent of recombinant DNA technology, polymerase chain reaction techniques, and completion of the human genome have revolutionized the understanding of disease development and also radically transformed the practice of medicine and surgery.

2. Genes govern cell activity in different cell types, which ultimately leads to the health of the human organism. The cellular diversity is controlled by the *genome* and accomplished by tight regulation of gene expression in a given cell at a given time.

3. Human diseases arise from improper changes in the genome. The continuous understanding of how the genome functions will make it possible to tailor medicine on an individual basis. The goal of personalized genomic medicine is to attack the disease by choosing personalized treatments that work with the individual's genomic profile. Personalized genomic medicine will undoubtedly revolutionize the practice of modern medicine.

4. Improving the outlook for human diseases can only come from a better understanding of the molecular signaling mechanisms that cause these diseases and subsequent successful therapeutic regimens.

OVERVIEW OF MOLECULAR CELL BIOLOGY

One of the goals of modern biology is to analyze the molecular structure and gain a fuller understanding of how cells, tissues, organs, and entire organisms function, both in a normal state and under pathologic conditions. Significant progress has been made in molecular studies of metabolism pathways, gene expression, cellular signaling, and organ development in human beings. The advent of recombinant DNA technology, polymerase chain reaction (PCR) techniques, and completion of the Human Genome Project are positively affecting human society by not only broadening our knowledge and understanding of disease development but also by bringing about necessary changes in disease treatment.

Today's practicing surgeons are becoming increasingly aware that many modern surgical procedures rely on the information gained through molecular research. Genomic information, such as BRCA and *RET* proto-oncogene, is being used to help direct prophylactic procedures to remove potentially harmful tissues before they do damage to patients. Molecular engineering has led to cancer-specific gene therapy that could serve in the near future as a more effective adjunct to surgical debulking of tumors than radiation or chemotherapy, so surgeons will benefit from a clear introduction to how basic biochemical and biologic principles relate to the developing area of molecular biology.

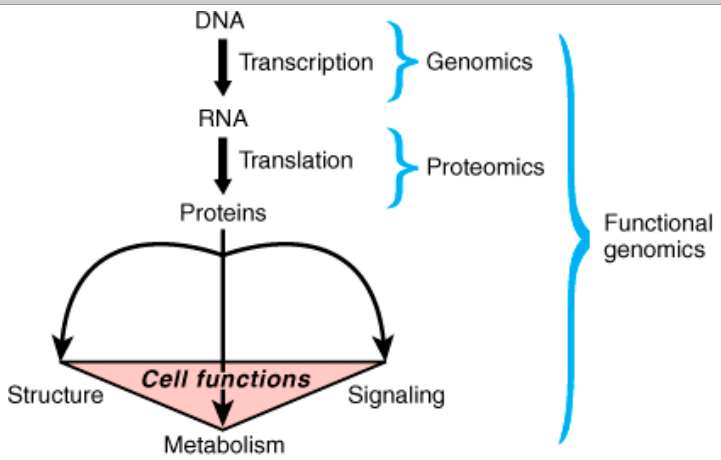
This chapter reviews the current information on modern molecular biology for the surgical community. It is written with the intent of serving two functions. The first is to introduce or update the readers about the general concepts of molecular cell biology, which are essential for comprehending the real power and potential of modern molecular technology. The second aim is to inform the reader about the modern molecular techniques that are commonly used for surgical research and to provide a fundamental introduction on the background of how these techniques are developed and applied to benefit patients.

Basic Concepts of Molecular Research

The modern era of molecular biology, which has been mainly concerned with how genes govern cell activity, began in 1953 when James D. Watson and Francis H. C. Crick made one of the greatest scientific discoveries by deducing the double-helical structure of deoxyribonucleic acid, or DNA.[1,2] The year 2003 marked the fiftieth anniversary of this great discovery. Before 1953, one of the most mysterious aspects of biology was how genetic material was precisely duplicated from one generation to the next. Although DNA had been implicated as genetic material, it was the base-paired structure of DNA that provided a logical interpretation of how a double helix could "unzip" to make copies of itself. This DNA synthesis, termed *replication*, immediately gave rise to the notion that a template was involved in the transfer of information between generations, and thus confirmed the suspicion that DNA carried an organism's hereditary information.

Within cells, DNA is packed into chromosomes. One important feature of DNA as genetic material is its ability to encode important information for all of a cell's functions (Fig. 15-1). Based on the principles of base complementarity, scientists also discovered how information in DNA is accurately transferred into the protein structure. DNA serves as a template for RNA synthesis, termed *transcription*, including messenger RNA (mRNA, or the protein-encoding RNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). mRNA carries the information from DNA to make proteins, termed *translation*, with the assistance of rRNA and tRNA. Each of these steps is precisely controlled in such a way that genes are properly expressed in each cell at a specific time and location. In recent years, new classes of noncoding RNAs, for example, microRNA (or miRNA) and Piwi-interacting RNA (or piRNA), have been identified that regulate gene expression through mRNA degradation. Consequently, the differential gene activity in a cell determines its actions, properties, and functions.

Fig. 15-1.



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The flow of genetic information from DNA to protein to cell functions. The process of transmission of genetic information from DNA to RNA is called *transcription*, and the process of transmission from RNA to protein is called *translation*. Proteins are the essential controlling components for cell structure, cell signaling, and metabolism. *Genomics* and *proteomics* are the study of the genetic composition of a living organism at the DNA and protein level, respectively. The study of the relationship between genes and their cellular functions is called *functional genomics*.

Molecular Approaches to Surgical Research

Rapid advances in molecular and cellular biology over the past half century have revolutionized the understanding of disease and will radically transform the practice of surgery. In the future, molecular techniques will be increasingly applied to surgical disease and will lead to new strategies for the selection and implementation of operative therapy. Surgeons should be familiar with the fundamental principles of molecular and cellular biology so that emerging scientific breakthroughs can be translated into improved care of the surgical patient.

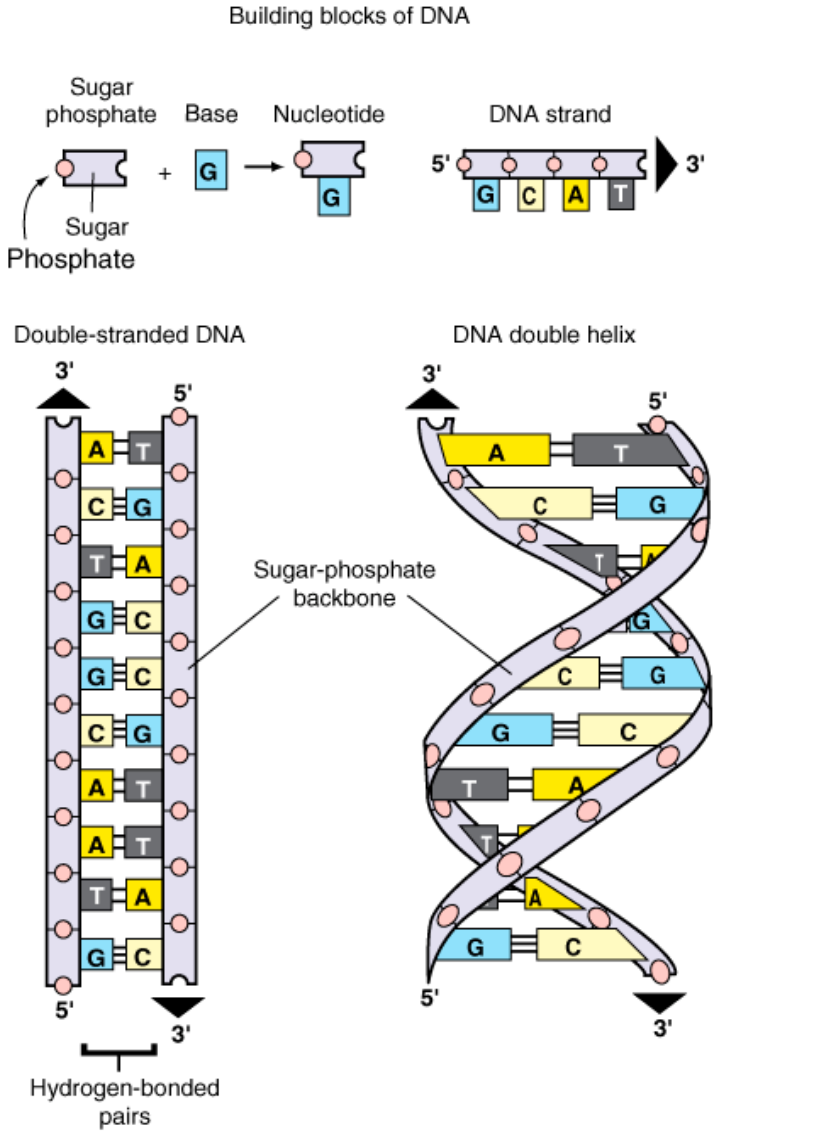
The greatest advances in the field of molecular biology have been in the areas of analysis and manipulation of DNA.[1] Since Watson and Crick's discovery of DNA structure, an intensive effort has been made to unlock the deepest biologic secrets of DNA. Among the avalanche of technical advances, one discovery in particular has drastically changed the world of molecular biology: the uncovering of the enzymatic and microbiologic techniques that produce recombinant DNA. Recombinant DNA technology involves the enzymatic manipulation of DNA and, subsequently, the cloning of DNA. DNA molecules are cloned for a variety of purposes including safeguarding DNA samples, facilitating sequencing, generating probes, and expressing recombinant proteins in one or more host organisms. DNA can be produced by a number of means, including restricted digestion of an existing vector, PCR, and cDNA synthesis. As DNA cloning techniques have developed over the last quarter century, researchers have moved from studying DNA to studying the functions of proteins, and from cell and animal models to molecular therapies in humans. Expression of recombinant proteins provides a method for analyzing gene regulation, structure, and function. In recent years the uses for recombinant proteins have expanded to include a variety of new applications, including gene therapy and biopharmaceuticals. The basic molecular approaches for modern surgical research include DNA cloning, cell manipulation, disease modeling in animals, and clinical trials in human patients.

FUNDAMENTALS OF MOLECULAR AND CELL BIOLOGY

DNA and Heredity

DNA forms a right-handed, double-helical structure that is composed of two antiparallel strands of unbranched polymeric deoxyribonucleotides linked by phosphodiester bonds between the 5' carbon of one deoxyribose moiety to the 3' carbon of the next (Fig. 15-2). DNA is composed of four types of deoxyribonucleotides: adenine (A), cytosine (C), guanine (G), and thymine (T). The nucleotides are joined together by phosphodiester bonds. In the double-helical structure deduced by Watson and Crick, the two strands of DNA are complementary to each other. Because of size, shape, and chemical composition, A always pairs with T, and C with G, through the formation of hydrogen bonds between complementary bases that stabilize the double helix.

Fig. 15-2.



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Schematic representation of a DNA molecule forming a double helix. DNA is made of four types of nucleotides, which are linked covalently into a DNA strand. A DNA molecule is composed of two DNA strands held together by hydrogen bonds between the pair bases. The arrowheads at the ends of the DNA strands indicate the polarities of the two strands, which run antiparallel to each other in the DNA molecule. The diagram at the bottom left of the figure shows the DNA molecule straightened out. In reality, the DNA molecule is twisted into a double helix, of which each turn of DNA is made up of 10.4 nucleotide pairs, as shown on the right.

(From Alberts et al,[1] with permission.)

Recognition of the hereditary transmission of genetic information is attributed to the Austrian monk, Gregor Mendel. His seminal work, ignored upon publication until its rediscovery in 1900, established the laws of segregation and of independent assortment. These two principles established the existence of paired elementary units of heredity and defined the statistical laws that govern them.[3] DNA was isolated in 1869, and a number of important observations of the inherited basis of certain diseases were made in the early part of the twentieth century. Although today it appears easy to understand how DNA replicates, before the 1950s, the idea of DNA as the primary genetic material was not appreciated. The modern era of molecular biology began in 1944 with the demonstration that DNA was the substance that carried genetic information. The first experimental evidence that DNA was genetic material came from simple transformation experiments conducted in the 1940s using *Streptococcus pneumoniae*. One strain of the bacteria could be converted into another by incubating it with DNA from the other, just as the treatment of the DNA with deoxyribonuclease would inactivate the transforming activity of the DNA. Similarly, in the early 1950s, before the discovery of the double-helical structure of DNA, the entry of viral DNA and not the protein into the host bacterium was believed to be necessary to initiate infection by the bacterial virus or bacteriophage. Key historical events concerning genetics are outlined in Table 15-1.

Table 15-1 Historical Events in Genetics and Molecular Biology

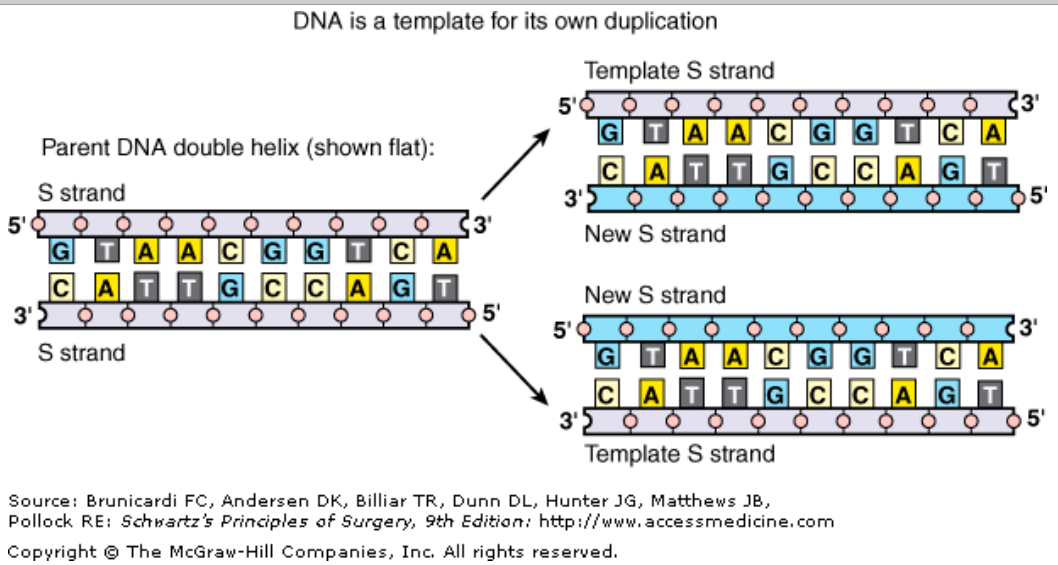
Year	Investigator	Event
1865	Mendel	Laws of genetics established
1869	Miescher	DNA isolated
1905	Garrod	Human inborn errors of metabolism
1913	Sturtevant	Linear map of genes
1927	Muller	X-rays cause inheritable genetic damage
1928	Griffith	Transformation discovered
1941	Beadle and Tatum	"One gene, one enzyme" concept
1944	Avery, MacLeod, McCarty	DNA as material of heredity
1950	McKlintock	Existence of transposons confirmed
1953	Watson and Crick	Double-helical structure of DNA
1957	Benzer and Kornberg	Recombination and DNA polymerase
1966	Nirenberg, Khorana, Holley	Genetic code determined
1970	Temin and Baltimore	Reverse transcriptase
1972	Cohen, Boyer, Berg	Recombinant DNA technology
1975	Southern	Transfer of DNA fragments from sizing gel to nitrocellulose (Southern blot)
1977	Sanger, Maxim, Gilbert	DNA sequencing methods
1982	—	GenBank database established
1985	Mullis	Polymerase chain reaction
1986	—	Automated DNA sequencing
1989	Collins	Cystic fibrosis gene identified by positional cloning and linkage analysis
1990	—	Human Genome Project initiated
1997	Roslin Institute	Mammalian cloning (Dolly)
2001	IHGSC and Celera Genomics	Draft versions of human genome sequence published
2003	—	Human Genome Project completed

IHGSC = International Human Genome Sequencing Consortium.

For cells to pass on the genetic material (DNA) to each progeny, the amount of DNA must be doubled. Watson and Crick recognized that the complementary base-pair structure of DNA implied the existence of a template-like mechanism for the copying of genetic material.[2] The transfer of DNA material from the mother cell to daughter cells takes place during somatic cell division (also called *mitosis*). Before a cell divides, DNA must be precisely duplicated. During replication, the two strands of DNA separate and each strand creates a new complementary strand by precise base-pair matching (Fig. 15-3). The two, new, double-stranded DNAs carry the same genetic information, which can then be

passed on to two daughter cells. Proofreading mechanisms ensure that the replication process occurs in a highly accurate manner. The fidelity of DNA replication is absolutely crucial to maintaining the integrity of the genome from generation to generation. However, mistakes can still occur during this process, resulting in *mutations*, which may lead to a change of the DNA's encoded protein and, consequently, a change of the cell's behavior. The reliable dependence of many features of modern organisms on subtle changes in genome is linked to Mendelian inheritance and also contributes to the processes of Darwinian evolution. In addition, massive changes, so-called *genetic instability*, can occur in the genome of somatic cells such as cancer cells.

Fig. 15-3.



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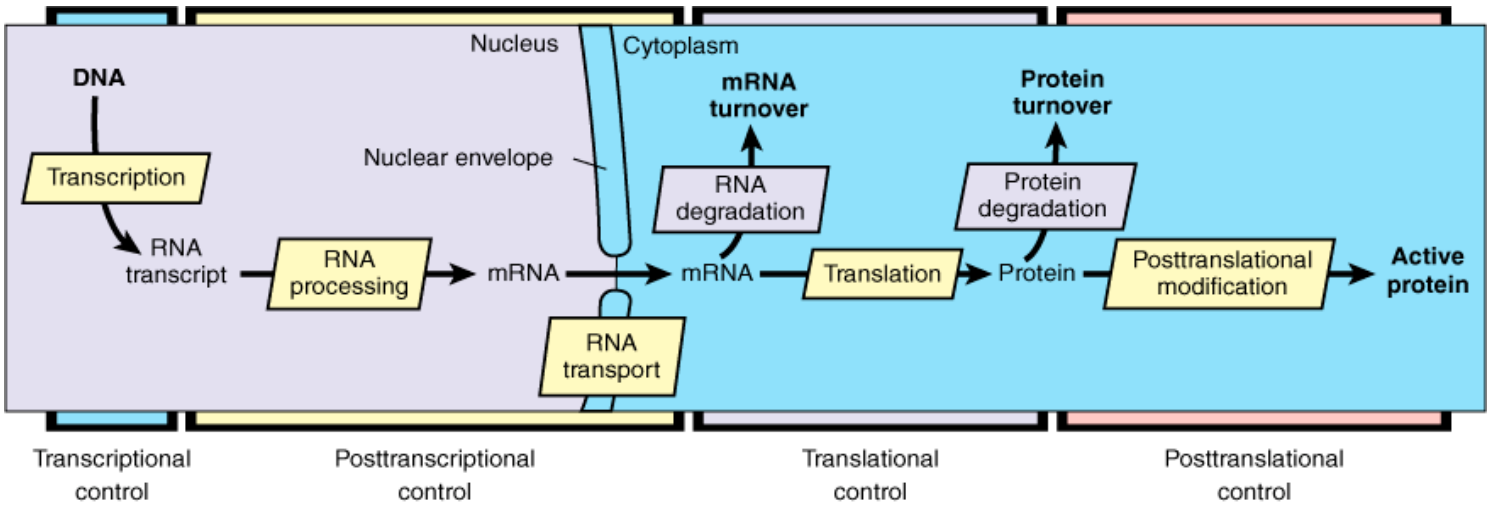
DNA replication. As the nucleotide A only pairs with T, and G with C, each strand of DNA can determine the nucleotide sequence in its complementary strand. In this way, double-helical DNA can be copied precisely.

(From Alberts et al,[1] with permission.)

Gene Regulation

Living cells have the necessary machinery to enzymatically transcribe DNA into RNA and translate the mRNA into protein. This machinery accomplishes the two major steps required for gene expression in all organisms: transcription and translation (Fig. 15-4). However, gene regulation is far more complex, particularly in eukaryotic organisms. For example, many gene transcripts must be spliced to remove the intervening sequences. The sequences that are spliced off are called *introns*, which appear to be useless, but in fact may carry some regulatory information. The sequences that are joined together, and are eventually translated into protein, are called *exons*. Additional regulation of gene expression includes modification of mRNA, control of mRNA stability, and its nuclear export into cytoplasm (where it is assembled into ribosomes for translation). After mRNA is translated into protein, the levels and functions of the proteins can be further regulated posttranslationally. However, the following sections will mainly focus on gene regulation at transcriptional and translational levels.

Fig. 15-4.



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Four major steps in the control of eukaryotic gene expression. Transcriptional and posttranscriptional control determine the level of messenger RNA (mRNA) that is available to make a protein, while translational and posttranslational control determine the final outcome of functional proteins. Note that posttranscriptional and posttranslational controls consist of several steps.

TRANSCRIPTION

Transcription is the enzymatic process of RNA synthesis from DNA.[4] In bacteria, a single RNA polymerase carries out all RNA synthesis, including that of mRNA, rRNA, and tRNA. Transcription often is coupled with translation in such a way that an mRNA molecule is completely accessible to ribosomes, and bacterial protein synthesis begins on an mRNA molecule even while it is still being synthesized. Therefore, a discussion of gene regulation with a look at the simpler prokaryotic system precedes that of the more complex transcription and posttranscriptional regulation of eukaryotic genes.

Transcription in Bacteria

Initiation of transcription in prokaryotes begins with the recognition of DNA sequences by RNA polymerase. First, the bacterial RNA polymerase catalyzes RNA synthesis through loose binding to any region in the double-stranded DNA and then through specific binding to the *promoter* region with the assistance of accessory proteins called σ factors (sigma factors). A promoter region is the DNA region upstream of the transcription initiation site. RNA polymerase binds tightly at the promoter sites and causes the double-stranded DNA structure to unwind. Consequently, few nucleotides can be base-paired with the DNA template to begin transcription. Once transcription begins, the σ factor is released. The growing RNA chain may begin to peel off as the chain elongates. This occurs in such a way that there are always about 10 to 12 nucleotides of the growing RNA chains that are base-paired with the DNA template.

The bacterial promoter contains a region of about 40 bases that include two conserved elements called *–35 region* and *–10 region*. The numbering system begins at the initiation site, which is designated +1 position, and counts backward (in negative numbers) on the promoter and forward on the transcribed region. Although both regions on different promoters are not the same sequences, they are fairly conserved and very similar. This conservation provides the accurate and rapid initiation of transcription for most bacterial genes. It is also common in bacteria that one promoter serves to transcribe a series of clustered genes, called an *operon*. A single transcribed mRNA contains a series of coding regions, each of which is later independently translated. In this way, the protein products are synthesized in a coordinated manner. Most of the time these proteins are involved in the same metabolic pathway, thus demonstrating that the control by one operon is an efficient system. After initiation of transcription, the polymerase moves along the DNA to elongate the chain of RNA, although at a certain point, it will stop. Each step of RNA synthesis, including initiation, elongation, and termination, will require the integral functions of RNA polymerase as well as the interactions of the polymerase with regulatory proteins.

Transcription in Eukaryotes

Transcription mechanisms in eukaryotes differ from those in prokaryotes. The unique features of eukaryotic transcription are as follows: (a)

Three separate RNA polymerases are involved in eukaryotes: RNA polymerase I transcribes the precursor of 5.8S, 18S, and 28S rRNAs; RNA polymerase II synthesizes the precursors of mRNA as well as microRNA; RNA polymerase III makes tRNAs and 5S rRNAs. (b) In eukaryotes, the initial transcript is often the precursor to final mRNAs, tRNAs, and rRNAs. The precursor is then modified and/or processed into its final functional form. RNA splicing is one type of processing to remove the noncoding introns (the region between coding exons) on an mRNA. (c) In contrast to bacterial DNA, eukaryotic DNA often is packaged with histone and nonhistone proteins into chromatins. Transcription will only occur when the chromatin structure changes in such a way that DNA is accessible to the polymerase. (d) RNA is made in the nucleus and transported into cytoplasm, where translation occurs. Therefore, unlike bacteria, eukaryotes undergo uncoupled transcription and translation.

Eukaryotic gene transcription also involves the recognition and binding of RNA polymerase to the promoter DNA. However, the interaction between the polymerase and DNA is far more complex in eukaryotes than in prokaryotes. Because the majority of studies have been focused on the regulation and functions of proteins, this chapter primarily focuses on how protein-encoding mRNA is made by RNA polymerase II.

TRANSLATION

DNA directs the synthesis of RNA; RNA in turn directs the synthesis of proteins. Proteins are variable-length polypeptide polymers composed of various combinations of 20 different amino acids and are the working molecules of the cell. The process of decoding information on mRNA to synthesize proteins is called *translation* (see Fig. 15-1). Translation takes place in ribosomes composed of rRNA and ribosomal proteins. The numerous discoveries made during the 1950s made it easy to understand how DNA replication and transcription involves base-pairing between DNA and DNA, or DNA and RNA. However, at that time it was still impossible to comprehend how mRNA transfers the information to the protein-synthesizing machinery. The genetic information on mRNA is composed of arranged sequences of four bases that are transferred to the linear arrangement of 20 amino acids on a protein. Amino acids are characterized by a central carbon unit linked to four side chains: an amino group ($-NH_2$), a carboxy group (–COOH), a hydrogen, and a variable (–R) group. The amino acid chain is assembled via peptide bonds between the amino group of one amino acid and the carboxy group of the next. Because of this decoding, the information carried on mRNA relies on tRNA. Translation involves all three RNAs. The precise transfer of information from mRNA to protein is governed by *genetic code*, the set of rules by which codons are translated into an amino acid (Table 15-2). A *codon*, a triplet of three bases, codes for one amino acid. In this case, random combinations of the four bases form 4 x 4 x 4, or 64 codes. Because 64 codes are more than enough for 20 amino acids, most amino acids are coded by more than one codon. The start codon is AUG, which also corresponds to methionine; therefore, almost all proteins begin with this amino acid. The sequence of nucleotide triplets that follows the start codon signal is termed the *reading frame*. The codons on mRNA are sequentially recognized by tRNA adaptor proteins. Specific enzymes termed *aminoacyl-tRNA synthetases* link a specific amino acid to a specific tRNA. The translation of mRNA to protein requires the ribosomal complex to move stepwise along the mRNA until the initiator methionine sequence is identified. In concert with various protein initiator factors, the methionyl-tRNA is positioned on the mRNA and protein synthesis begins. Each new amino acid is added sequentially by the appropriate tRNA in conjunction with proteins called *elongation factors*. Protein synthesis proceeds in the amino-to-carboxy-terminus direction.

Table 15-2 The Genetic Code

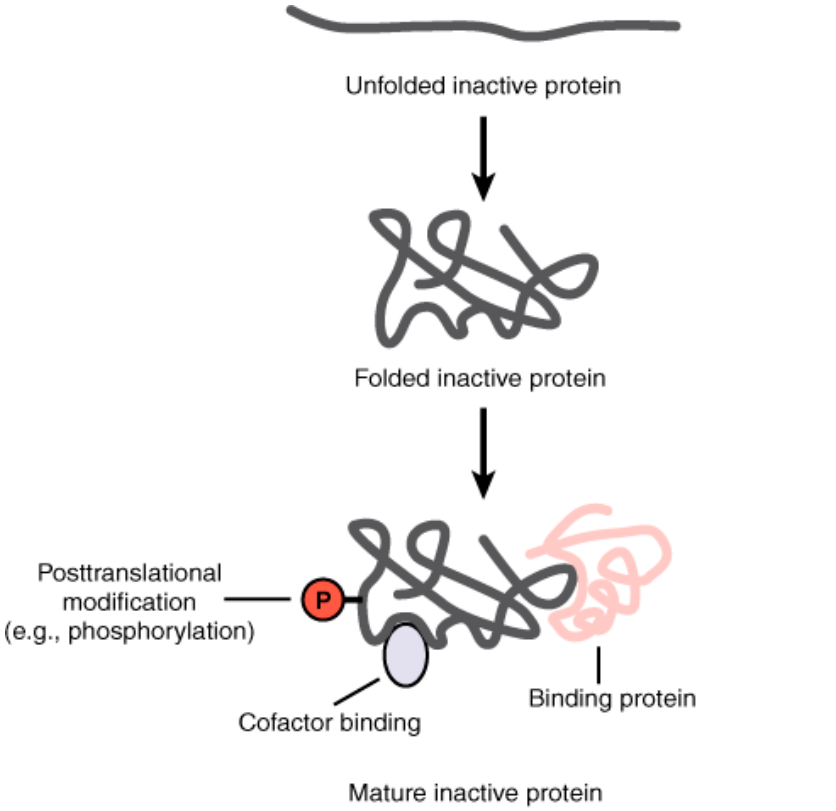
Second Base in Codon															
		U			***C***			***A***			***G***				
First Base in Codon		UUU	Phe	[F]	UCU	Ser	[S]	UAU	Tyr	[Y]	UGU	Cys	[C]	*U*	Third Base in Codon
	U	UUC	Phe	[F]	UCC	Ser	[S]	UAC	Tyr	[Y]	UGC	Cys	[C]	*C*	
		UUA	Leu	[L]	UCA	Ser	[S]	UAA	*STOP*	—	UGA	*STOP*	—	*A*	
		UUG	Leu	[L]	UCG	Ser	[S]	UAG	*STOP*	—	UGG	Trp	[W]	*G*	
		CUU	Leu	[L]	CCU	Pro	[P]	CAU	His	[H]	CGU	Arg	[R]	*U*	
		CUC	Leu	[L]	CCC	Pro	[P]	CAC	His	[H]	CGC	Arg	[R]	*C*	
	C	CUA	Leu	[L]	CCA	Pro	[P]	CAA	Gln	[Q]	CGA	Arg	[R]	*A*	
		CUG	Leu	[L]	CCG	Pro	[P]	CAG	Gln	[Q]	CGG	Arg	[R]	*G*	
		AUU	Ile	[I]	ACU	Thr	[T]	AAU	Asn	[N]	AGU	Ser	[S]	*U*	
		AUC	Ile	[I]	ACC	Thr	[T]	AAC	Asn	[N]	AGC	Ser	[S]	*C*	
	A	AUA	Ile	[I]	ACA	Thr	[T]	AAA	Lys	[K]	AGA	Arg	[R]	*A*	

		AUG	Met	[M]	ACG	Thr	[T]	AAG	Lys	[K]	AGG	Arg	[R]	*G*
		GUU	Val	[V]	GCU	Ala	[A]	GAU	Asp	[D]	GGU	Gly	[G]	*U*
		GUC	Val	[V]	GCC	Ala	[A]	GAC	Asp	[D]	GGC	Gly	[G]	*C*
	G	GUA	Val	[V]	GCA	Ala	[A]	GAA	Glu	[E]	GGA	Gly	[G]	*A*
		GUG	Val	[V]	GCG	Ala	[A]	GAG	Glu	[E]	GGG	Gly	[G]	*G*

A = adenine; C = cytosine; G = guanine; U = uracil; Ala = alanine; Arg = arginine; Asn = asparagine; Asp = aspartic acid; Cys = cysteine; Glu = glutamic acid; Gln = glutamine; Gly = glycine; His = histidine; Ile = isoleucine; Leu = leucine; Lys = lysine; Met = methionine; Phe = phenylalanine; Pro = proline; Ser = serine; Thr = threonine; Trp = tryptophan; Tyr = tyrosine; Val = valine. Letter in [ ] indicates single lettercode for amino acid.

The biologic versatility of proteins is astounding. Among many other functions, proteins serve as enzymes that catalyze critical biochemical reactions, carry signals to and from the extracellular environment, and mediate diverse signaling and regulatory functions in the intracellular environment. They also transport ions and various small molecules across plasma membranes. Proteins make up the key structural components of cells and the extracellular matrix and are responsible for cell motility. The unique functional properties of proteins are largely determined by their structure (Fig. 15-5).

Fig. 15-5.



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Maturation of a functional protein. Although the linear amino acid sequence of a protein often is shown, the function of a protein also is controlled by its correctly folded three-dimensional structure. In addition, many proteins also have covalent posttranslational modifications such as phosphorylation or noncovalent binding to a small molecule or a protein.

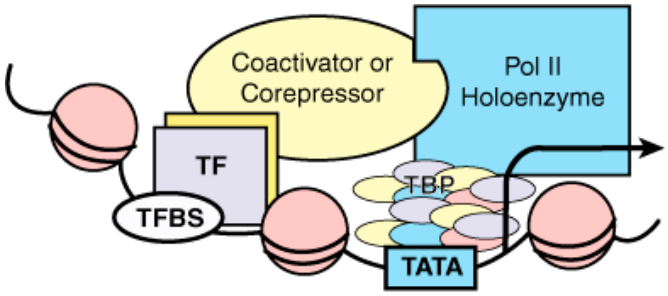
REGULATION OF GENE EXPRESSION

The human organism is made up of a myriad of different cell types that, despite their vastly different characteristics, contain the same genetic material. This cellular diversity is controlled by the *genome* and accomplished by tight regulation of gene expression. This leads to the synthesis and accumulation of different complements of RNA and, ultimately, to the proteins found in different cell types. For example, muscle and bone express different genes or the same genes at different times. Moreover, the choice of which genes are expressed in a given cell at a given time

depends on signals received from its environment. There are multiple levels at which gene expression can be controlled along the pathway from DNA to RNA to protein (see Fig. 15-4). *Transcriptional control* refers to the mechanism for regulating when and how often a gene is transcribed. Splicing of the primary RNA transcript (*RNA processing control*) and selection of completed mRNAs for nuclear export (*RNA transport control*) represent additional potential regulatory steps. The mRNAs in the cytoplasm can be selectively translated by ribosomes (*translational control*), or selectively stabilized or degraded (*mRNA degradation control*). Finally, the resulting proteins can undergo selective activation, inactivation, or compartmentalization (*protein activity control*).

Because a large number of genes are regulated at the transcriptional level, regulation of gene transcripts (i.e., mRNA) often is referred to as *gene regulation* in a narrow definition. Each of the steps during transcription is properly regulated in eukaryotic cells. Because genes are differentially regulated from one another, one gene can be differentially regulated in different cell types or at different developmental stages. Therefore, gene regulation at the level of transcription is largely context dependent. However, there is a common scheme that applies to transcription at the molecular level (Fig. 15-6). Each gene promoter possesses unique sequences called *TATA boxes* that can be recognized and bound by a large complex containing RNA polymerase II, forming the basal transcription machinery. Usually located upstream of the TATA box (but sometimes longer distances) are a number of regulatory sequences referred to as *enhancers* that are recognized by regulatory proteins called *transcription factors*. These transcription factors specifically bind to the enhancers, often in response to environmental or developmental cues, and cooperate with each other and with basal transcription factors to initiate transcription. Regulatory sequences that negatively regulate the initiation of transcription also are present on the promoter DNA. The transcription factors that bind to these sites are called *repressors*, in contrast to the *activators* that activate transcription. The molecular interactions between transcription factors and promoter DNA, as well as between the cooperative transcription factors, are highly regulated and context-dependent. Specifically, the recruitment of transcription factors to the promoter DNA occurs in response to physiologic signals. A number of structural motifs in these DNA-binding transcription factors facilitate this recognition and interaction. These include the helix-turn-helix, the homeodomain motif, the zinc finger, the leucine zipper, and the helix-loop-helix motifs.

Fig. 15-6.



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Transcriptional control by RNA polymerase. DNA is packaged into a chromatin structure. TATA = the common sequence on the promoter recognized by TBP and polymerase II holoenzyme; TBP = TATA-binding protein and associated factors; TF = hypothetical transcription factor; TFBS = transcription factor binding site; ball-shaped structures = nucleosomes. Coactivator or corepressor are factors linking the TF with the Pol II complex.

Human Genome

Genome is a collective term for all genes present in one organism. The human genome contains DNA sequences of 3 billion base-pairs, carried by 23 pairs of chromosomes. The human genome has an estimated 25,000 to 30,000 genes, and overall it is 99.9% identical in all people.[5,6] Approximately 3 million locations where single-base DNA differences exist have been identified and termed *single nucleotide polymorphisms* . Single nucleotide polymorphisms may be critical determinants of human variation in disease susceptibility and responses to environmental factors.

The completion of the human genome sequence in 2003 represented another great milestone in modern science. The human genome project created the field of *genomics*, which is the study of genetic material in detail (see Fig. 15-1). The medical field is building upon the knowledge, resources, and technologies emanating from the human genome to further the understanding of the relationship of the genes and their

mutations to human health and disease. This expansion of genomics into human health applications resulted in the field of genomic medicine.

The emergence of genomics as a science will transform the practice of medicine and surgery in this century. This breakthrough has allowed scientists the opportunity to gain remarkable insights into the lives of humans. Ultimately, the goal is to use this information to develop new ways to treat, cure, or even prevent the thousands of diseases that afflict humankind. In the twenty-first century, work will begin to incorporate the information embedded in the human genome sequence into surgical practices. By doing so, the genomic information can be used for diagnosing and predicting disease and disease susceptibility. Diagnostic tests can be designed to detect errant genes in patients suspected of having particular diseases or of being at risk for developing them. Furthermore, exploration into the function of each human gene is now possible, which will shed light on how faulty genes play a role in disease causation. This knowledge also makes possible the development of a new generation of therapeutics based on genes. Drug design is being revolutionized as researchers create new classes of medicines based on a reasoned approach to the use of information on gene sequence and protein structure function rather than the traditional trial-and-error method. Drugs targeted to specific sites in the body promise to have fewer side effects than many of today's medicines. Finally, other applications of genomics will involve the transfer of genes to replace defective versions or the use of gene therapy to enhance normal functions such as immunity.

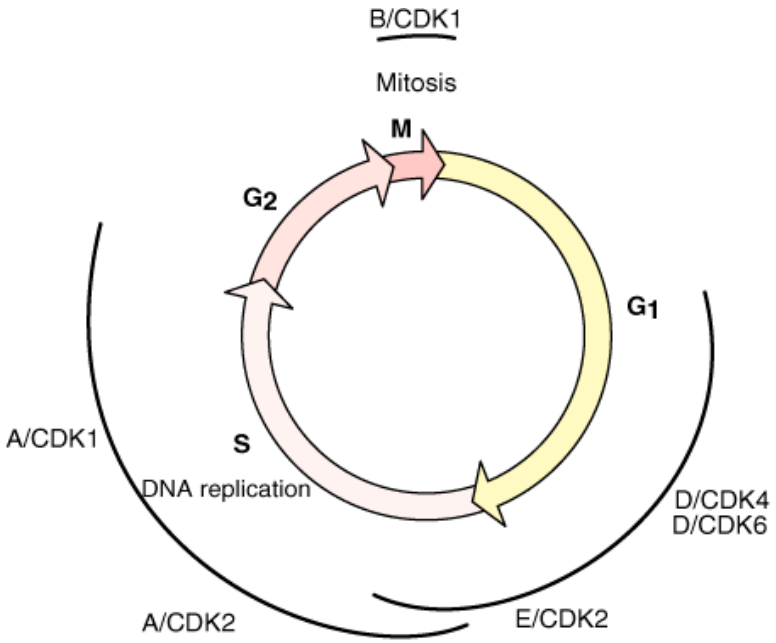
Proteomics refers to the study of the structure and expression of proteins as well as the interactions among proteins encoded by a human genome (see Fig. 15-1).[7] A number of Internet-based repositories for protein sequences exist, including Swiss-Prot (http://www.expasy.ch). These databases allow comparisons of newly identified proteins with previously characterized sequences to allow prediction of similarities, identification of splice variants, and prediction of membrane topology and posttranslational modifications. Tools for proteomic profiling include two-dimensional gel electrophoresis, time-of-flight mass spectrometry, matrix-assisted laser desorption/ionization, and protein microarrays. *Structural proteomics* aims to describe the three-dimensional structure of proteins that is critical to understanding function. *Functional genomics* seeks to assign a biochemical, physiologic, cell biologic, and/or developmental function to each predicted gene. An ever-increasing arsenal of approaches, including transgenic animals, RNA interference (RNAi), and various systematic mutational strategies, will allow dissection of functions associated with newly discovered genes. Although the potential of this field of study is vast, it is in its early stages.

It is anticipated that a genomic and proteomic approach to human disease will lead to a new understanding of pathogenesis that will aid in the development of effective strategies for early diagnosis and treatment.[8] For example, identification of altered protein expression in organs, cells, subcellular structures, or protein complexes may lead to development of new biomarkers for disease detection. Moreover, improved understanding of how protein structure determines function will allow rational identification of therapeutic targets, and thereby not only accelerate drug development, but also lead to new strategies to evaluate therapeutic efficacy and potential toxicity.[7]

Cell Cycle and Apoptosis

Every organism has many different cell types. Many cells grow, while some cells such as nerve cells and striated muscle cells do not. All growing cells have the ability to duplicate their genomic DNA and pass along identical copies of this genetic information to every daughter cell. Thus, the cell cycle is the fundamental mechanism to maintain tissue homeostasis. A cell cycle comprises four periods: G_1 (first gap phase before DNA synthesis), S (synthesis phase when DNA replication occurs), G_2 (the gap phase before mitosis), and M (mitosis, the phase when two daughter cells with identical DNA are generated) (Fig. 15-7). After a full cycle, the daughter cells enter G_1 again, and when they receive appropriate signals, undergo another cycle, and so on. The machinery that drives cell cycle progression is made up of a group of enzymes called *cyclin-dependent kinases* (CDK). Cyclin expression fluctuates during the cell cycle, and cyclins are essential for CDK activities and form complexes with CDK. The cyclin A/CDK1 and cyclin B/CDK1 drive the progression for the M phase, while cyclin A/CDK2 is the primary S phase complex. Early G_1 cyclin D/CDK4/6 or late G_1 cyclin E/CDK2 controls the G_1-S transition. There also are negative regulators for CDK termed *CDK inhibitors*, which inhibit the assembly or activity of the cyclin-CDK complex. Expression of cyclins and CDK inhibitors often are regulated by developmental and environmental factors.

Fig. 15-7.



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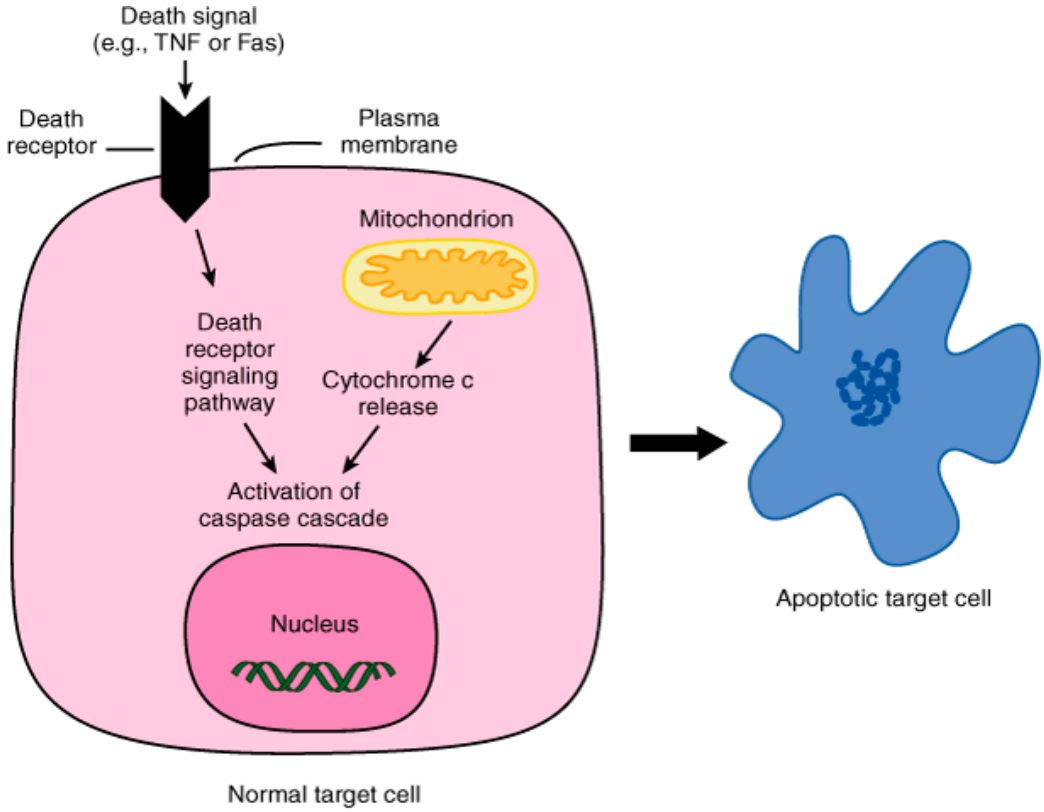
The cell cycle and its control system. M is the mitosis phase, when the nucleus and the cytoplasm divide; S is the phase when DNA is duplicated; G_1 is the gap between M and S; G_2 is the gap between S and M. A complex of cyclin and cyclin-dependent kinase (CDK) controls specific events of each phase. Without cyclin, CDK is inactive. Different cyclin/CDK complexes are shown around the cell cycle. A, B, D, and E stand for cyclin A, cyclin B, cyclin D, and cyclin E, respectively.

The cell cycle is connected with signal transduction pathways as well as gene expression. While the S and M phases rarely are subjected to changes imposed by extracellular signals, the G_1 and G_2 phases are the primary periods when cells decide whether to move on to the next phase or not. During the G_1 phase, cells receive green- or red-light signals, S phase entry or G_1 arrest, respectively. Growing cells proliferate only when supplied with appropriate mitogenic growth factors. Cells become committed to entry of the cell cycle only toward the end of G_1. Mitogenic signals stimulate the activity of early G_1 CDKs (e.g., cyclin D/CDK4) that inhibit the activity of pRb protein and activate the transcription factor called *E2F* to induce the expression of batteries of genes essential for G_1-S progression. Meanwhile, cells also receive antiproliferative signals such as those from tumor suppressors. These antiproliferative signals also act in the G_1 phase to stop cells' progress into the S phase by inducing CKI production. For example, when DNA is damaged, cells will repair the damage before entering the S phase. Therefore, G_1 contains one of the most important checkpoints for cell cycle progression. If the analogy is made that CDK is to a cell as an engine is to a car, then cyclins and CKI are the gas pedal and brake, respectively. Accelerated proliferation or improper cell cycle progression with damaged DNA would be disastrous. Genetic gain-of-function mutations in oncogenes (that often promote expression or activity of the cyclin/CDK complex) or loss-of-function mutations in tumor suppressor (that stimulate production of CKI) are causal factors for malignant transformation.

In addition to cell cycle control, cells use genetically programmed mechanisms to kill cells. This cellular process, called *apoptosis* or *programmed cell death*, is essential for the maintenance of tissue homeostasis (Fig. 15-8).

Fig. 15-8.



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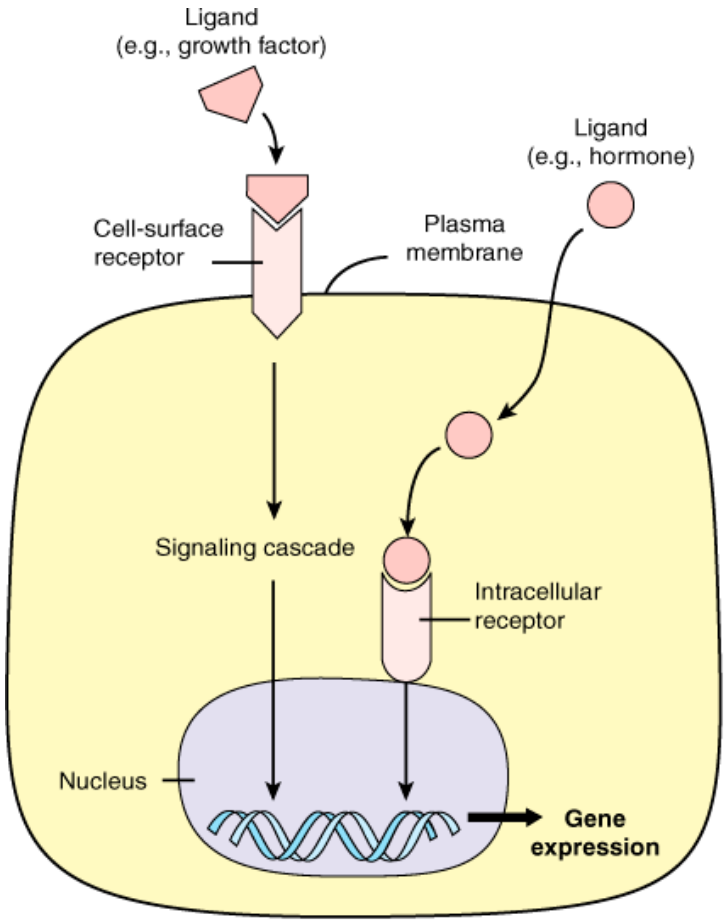
A simplified view of the apoptosis pathways. Extracellular death receptor pathways include the activation of Fas and tumor necrosis factor (TNF) receptors, and consequent activation of the caspase pathway. Intracellular death pathway indicates the release of cytochrome c from mitochondria, which also triggers the activation of the caspase cascade. During apoptosis, cells undergo DNA fragmentation, nuclear and cell membrane breakdown, and are eventually digested by other cells.

Normal tissues undergo proper apoptosis to remove unwanted cells, those that have completed their jobs or have been damaged or improperly proliferated. Apoptosis can be activated by many physiologic stimuli such as death receptor signals (e.g., Fas or cytokine tumor necrosis factor), growth factor deprivation, DNA damage, and stress signals. Two major pathways control the biochemical mechanisms governing apoptosis: the death receptor and mitochondrial. However, recent advances in apoptosis research suggest an interconnection of the two pathways. What is central to the apoptotic machinery is the activation of a cascade of proteinases called caspases. Similarly to CDK in the cell cycle, activities and expression of caspases are well controlled by positive and negative regulators. The complex machinery of apoptosis must be tightly controlled. Perturbations of this process can cause neoplastic transformation or other diseases.

Signal Transduction Pathways

Gene expression in a genome is controlled in a temporal and spatial manner, at least in part by signaling pathways.[9] A signaling pathway generally begins at the cell surface and, after a signaling relay by a cascade of intracellular effectors, ends up in the nucleus (Fig. 15-9). All cells have the ability to sense changes in their external environment. The bioactive substances to which cells can respond are many and include proteins, short peptides, amino acids, nucleotides/nucleosides, steroids, retinoids, fatty acids, and dissolved gases. Some of these substances are lipophilic and thereby can cross the plasma membrane by diffusion to bind to a specific target protein within the cytoplasm (intracellular receptor). Other substances bind directly with a transmembrane protein (cell-surface receptor). Binding of ligand to receptor initiates a series of biochemical reactions (*signal transduction*) typically involving protein-protein interactions and the transfer of high-energy phosphate groups, leading to various cellular end responses.

Fig. 15-9.



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Cell-surface and intracellular receptor pathways. Extracellular signaling pathway: Most growth factors and other hydrophilic signaling molecules are unable to move across the plasma membrane and directly activate cell-surface receptors such as G-protein coupled receptors and enzyme-linked receptors. The receptor serves as the receiver, and in turn activates the downstream signals in the cell. Intracellular signaling pathway: Hormones or other diffusible molecules enter the cell and bind to the intracellular receptor in the cytoplasm or in the nucleus. Either extracellular or intracellular signals often reach the nucleus to control gene expression.

Control and specificity through simple protein-protein interactions—referred to as *adhesive interactions*—is a common feature of signal transduction pathways in cells.[10] Signaling also involves catalytic activities of signaling molecules, such as protein kinases/phosphatases, that modify the structures of key signaling proteins. Upon binding and/or modification by upstream signaling molecules, downstream effectors undergo a conformational (allosteric) change and, consequently, a change in function. The signal that originates at the cell surface and is relayed by the cytoplasmic proteins often ultimately reaches the transcriptional apparatus in the nucleus. It alters the DNA binding and activities of transcription factors that directly turn genes on or off in response to the stimuli. Abnormal alterations in signaling activities and capacities in otherwise normal cells can lead to diseases such as cancer.

Advances in biology in the last two decades have dramatically expanded the view on how cells are wired with signaling pathways. In a given cell, many signaling pathways operate simultaneously and crosstalk with one another. A cell generally may react to a hormonal signal in a variety of ways: (a) by changing its metabolite or protein, (b) by generating an electric current, or (c) by contracting. Cells continually are subject to multiple input signals that simultaneously and sequentially activate multiple receptor and non–receptor-mediated signal transduction pathways, which form a signaling network. Although the regulators responsible for cell behavior are rapidly identified as a result of genomic and proteomic techniques, the specific functions of the individual proteins, how they assemble, and the networks that control cellular behavior remain to be defined. An increased understanding of cell regulatory pathways—and how they are disrupted in disease—will likely reveal common themes based on protein interaction domains that direct associations of proteins with other polypeptides, phospholipids, nucleic acids, and other regulatory molecules. Advances in the understanding of signaling networks will require methods of investigation that move beyond traditional "linear" approaches into medical informatics and computational biology. The bewildering biocomplexity of such networks mandates

multidisciplinary and transdisciplinary research collaboration. The vast amount of information that is rapidly emerging from genomic and proteomic data mining will require the development of new modeling methodologies within the emerging disciplines of medical mathematics and physics.

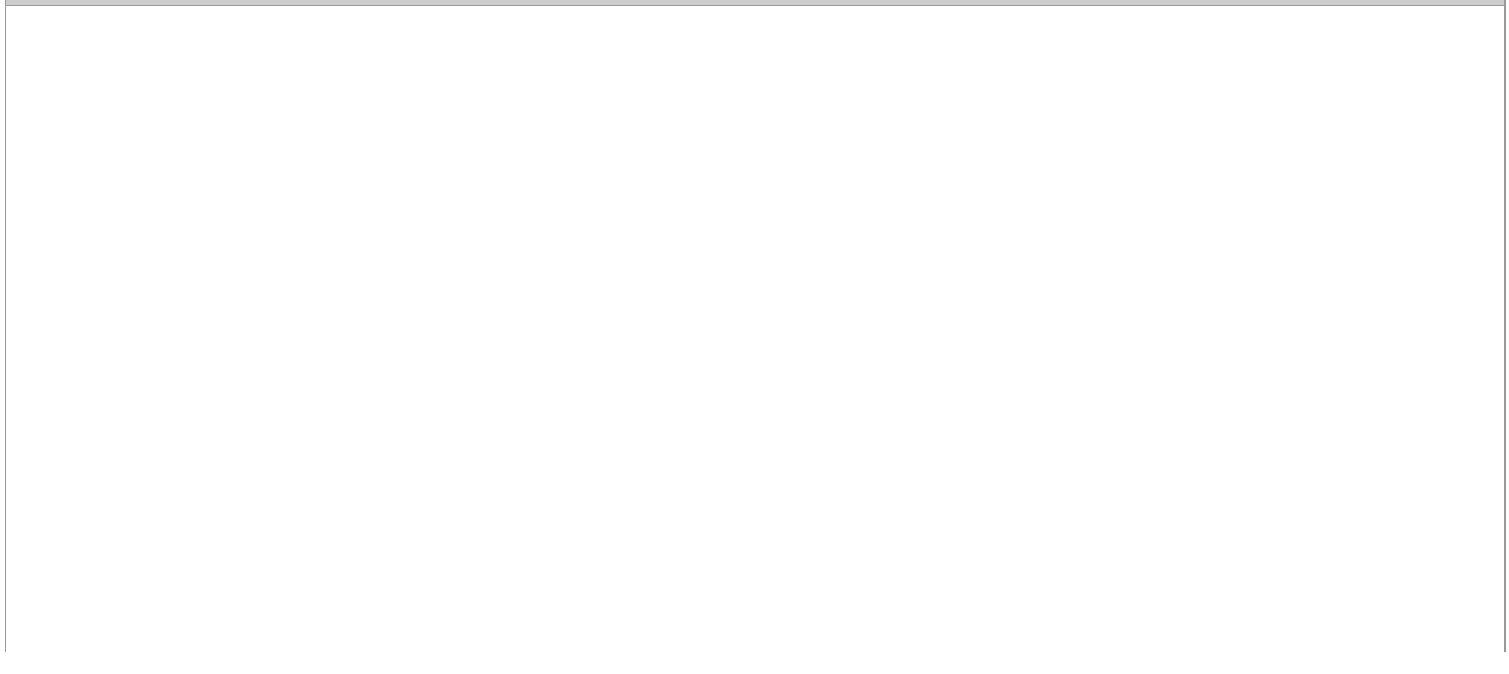
Signaling pathways often are grouped according to the properties of signaling receptors. Many hydrophobic signaling molecules are able to diffuse across plasma membranes and directly reach specific cytoplasmic targets. Steroid hormones, thyroid hormones, retinoids, and vitamin D are examples that exert their activity upon binding to structurally related receptor proteins that are members of the *nuclear hormone receptor superfamily*. Ligand binding induces a conformational change that enhances transcriptional activity of these receptors. Most extracellular signaling molecules interact with transmembrane protein receptors that couple ligand binding to intracellular signals, leading to biologic actions.

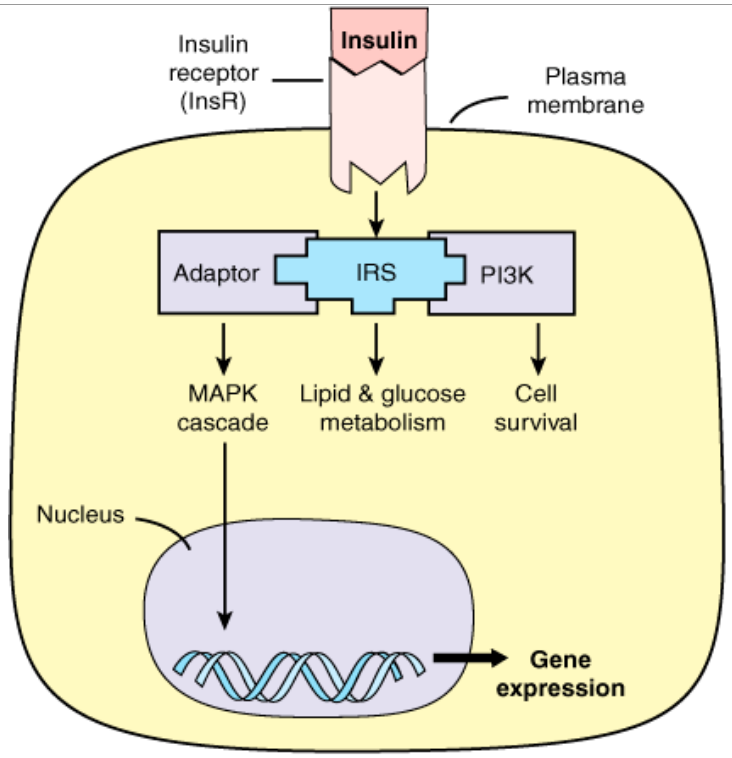
There are three major classes of cell-surface receptors: *transmitter-gated ion channels*, *seven-transmembrane G-protein coupled receptors (GPCRs)*, and *enzyme-linked receptors*. The superfamily of GPCRs is one of the largest families of proteins, representing over 800 genes of the human genome. Members of this superfamily share a characteristic seven-transmembrane configuration. The ligands for these receptors are diverse and include hormones, chemokines, neurotransmitters, proteinases, inflammatory mediators, and even sensory signals such as odorants and photons. Most GPCRs signal through *heterotrimeric G proteins*, which are guanine-nucleotide regulatory complexes. Thus the receptor serves as the receiver, the G protein serves as the transducer, and the enzyme serves as the effector arm. *Enzyme-linked receptors* possess an extracellular ligand-recognition domain and a cytosolic domain that either has intrinsic enzymatic activity or directly links with an enzyme. Structurally, these receptors usually have only one transmembrane-spanning domain. Of at least five forms of enzyme-linked receptors classified by the nature of the enzyme activity to which they are coupled, the growth factor receptors such as tyrosine kinase receptor or serine/threonine kinase receptors mediate diverse cellular events including cell growth, differentiation, metabolism, and survival/apoptosis. Dysregulation (particularly mutations) of these receptors is thought to underlie conditions of abnormal cellular proliferation in the context of cancer. The following sections will further review two examples of growth factor signaling pathways and their connection with human diseases.

INSULIN PATHWAY AND DIABETES[11]

The discovery of insulin in the early 1920s is one of the most dramatic events in the treatment of human disease. *Insulin* is a peptide hormone that is secreted by the β-cell of the pancreas. Insulin is required for the growth and metabolism of most mammalian cells, which contain cell-surface insulin receptors (InsR). Insulin binding to InsR activates the kinase activity of InsR. InsR then adds phosphoryl groups, a process referred to as *phosphorylation*, and subsequently activates its immediate intracellular effector, called *insulin receptor substrate* (IRS). IRS plays a central role in coordinating the signaling of insulin by activating distinct signaling pathways, the PI3K-Akt pathway and MAPK pathway, both of which possess multiple protein kinases that can control transcription, protein synthesis, and glycolysis (Fig. 15-10).

Fig. 15-10.





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Insulin-signaling pathway. Insulin is a peptide growth factor that binds to and activates the heterotetrameric receptor complex (InsR). InsR possesses protein tyrosine kinase activity and is able to phosphorylate the downstream insulin receptor substrate (IRS). Phosphorylated IRS serves as a scaffold and controls the activation of multiple downstream pathways for gene expression, cell survival, and glucose metabolism. Inactivation of the insulin pathway can lead to type 2 diabetes.

The primary physiologic role of insulin is in glucose homeostasis, which is accomplished through the stimulation of glucose uptake into insulin-sensitive tissues such as fat and skeletal muscle. Defects in insulin synthesis/secretion and/or responsiveness are major causal factors in diabetes, one of the leading causes of death and disability in the United States, affecting an estimated 16 million Americans. Type 2 diabetes accounts for about 90% of all cases of diabetes. Clustering of type 2 diabetes in certain families and ethnic populations points to a strong genetic background for the disease. More than 90% of affected individuals have insulin resistance, which develops when the body is no longer able to respond correctly to insulin circulating in the blood. Although relatively little is known about the biochemical basis of this metabolic disorder, it is clear that the insulin-signaling pathways malfunction in this disease. It is also known that genetic mutations in the InsR or IRS cause type 2 diabetes, although which one is not certain. The majority of type 2 diabetes cases may result from defects in downstream-signaling components in the insulin-signaling pathway. Type 2 diabetes also is associated with declining α-cell function, resulting in reduced insulin secretion; these pathways are under intense study. A full understanding of the basis of insulin resistance is crucial for the development of new therapies for type 2 diabetes. Furthermore, apart from type 2 diabetes, insulin resistance is a central feature of several other common human disorders, including atherosclerosis and coronary artery disease, hypertension, and obesity.

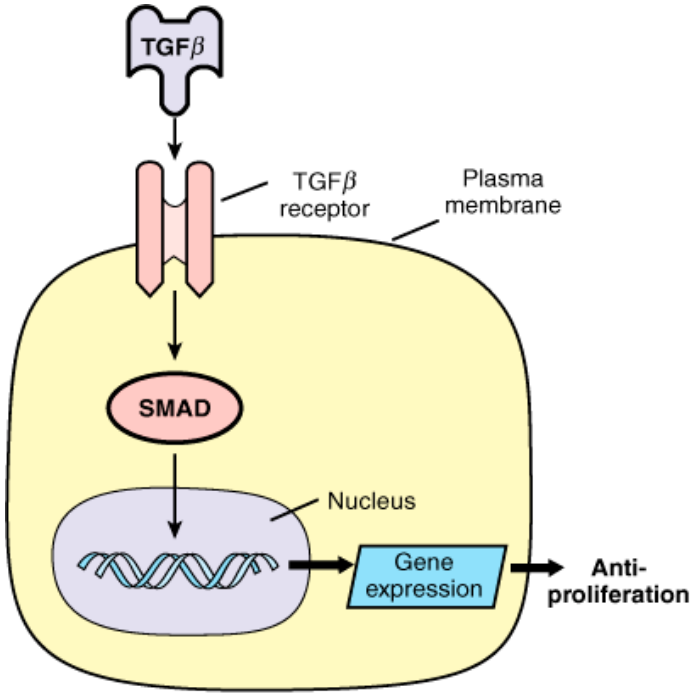
TRANSFORMING GROWTH FACTOR β (TGFβ) PATHWAY AND CANCERS[12]

Growth factor signaling controls cell growth, differentiation, and apoptosis. Although insulin and many mitogenic growth factors promote cell proliferation, some growth factors and hormones inhibit cell proliferation. Transforming growth factor β (TGFβ) is one of them. The balance between mitogens and TGFβ plays an important role in controlling the proper pace of cell cycle progression. The growth inhibition function of TGFβ signaling in epithelial cells plays a major role in maintaining tissue homeostasis.

The TGFβ superfamily comprises a large number of structurally related growth and differentiation factors that act through a receptor complex at the cell surface (Fig. 15-11). The complex consists of transmembrane serine/threonine kinases. The receptor signals through activation of heterotrimeric complexes of intracellular effectors called SMADs (which are contracted from homologous *Caenorhabditis elegans* Sma and *Drosophila* Mad, two evolutionarily conserved genes for TGFβ signaling). Upon phosphorylation by the receptors, SMAD complexes translocate

into the nucleus, where they bind to gene promoters and cooperate with specific transcription factors to regulate the expression of genes that control cell proliferation and differentiation. For example, TGFβ strongly induces the transcription of a gene called $p15^{INK4B}$ (a type of CKI) and, at the same time, reduces the expression of many oncogenes such as *c-Myc*. The outcome of the altered gene expression leads to the inhibition of cell cycle progression. Meanwhile, the strength and duration of TGFβ signaling is fine-tuned by a variety of positive or negative modulators, including protein phosphatases. Therefore, controlled activation of TGFβ signaling is an intrinsic mechanism for cells to ensure controlled proliferation.

Fig. 15-11.



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TGFβ signaling pathway. The TGFβ family has at least 29 members encoded in the human genome. They are also peptide growth factors. Each member binds to a heterotetrameric complex consisting of a distinct set of type I and type II receptors. TGFβ receptors are protein serine/threonine kinases and can phosphorylate the downstream substrates called *SMAD proteins*. Phosphorylated SMADs are directly transported into the nucleus, where they bind to the DNA and regulate gene expression that is responsible for inhibition of cell proliferation. Inactivation of the TGFβ pathway through genetic mutations in the TGFβ receptors or SMADs is frequent in human cancer, leading to the uncontrolled proliferation of cancer cells.

Resistance to TGFβ's anticancer action is one hallmark of human cancer cells. TGFβ receptors and SMADs are identified as tumor suppressors. The TGFβ signaling circuit can be disrupted in a variety of ways and in different types of human tumors. Some lose TGFβ responsiveness through downregulation or mutations of their TGFβ receptors. The cytoplasmic SMAD4 protein, which transduces signals from ligand-activated TGFβ receptors to downstream targets, may be eliminated through mutation of its encoding gene. The locus encoding cell cycle inhibitor $p15^{INK4B}$ may be deleted. Alternatively, the immediate downstream target of its actions, cyclin-dependent kinase 4 (CDK4), may become unresponsive to the inhibitory actions of $p15^{INK4B}$ because of mutations that block $p15^{INK4B}$ binding. The resulting cyclin D/CDK4 complexes constitutively inactivate tumor suppressor pRb by hyperphosphorylation. Finally, functional pRb, the end target of this pathway, may be lost through mutation of its gene. For example, in pancreatic and colorectal cancers, 100% of cells derived from these cancers carry genetic defects in the TGFβ signaling pathway. Therefore, the antiproliferative pathway converging onto pRb and the cell division cycle is, in one way or another, disrupted in a majority of human cancer cells. Besides cancer, dysregulation of TGFβ signaling also has been associated with other human diseases such as Marfan syndrome and thoracic aortic aneurysm.

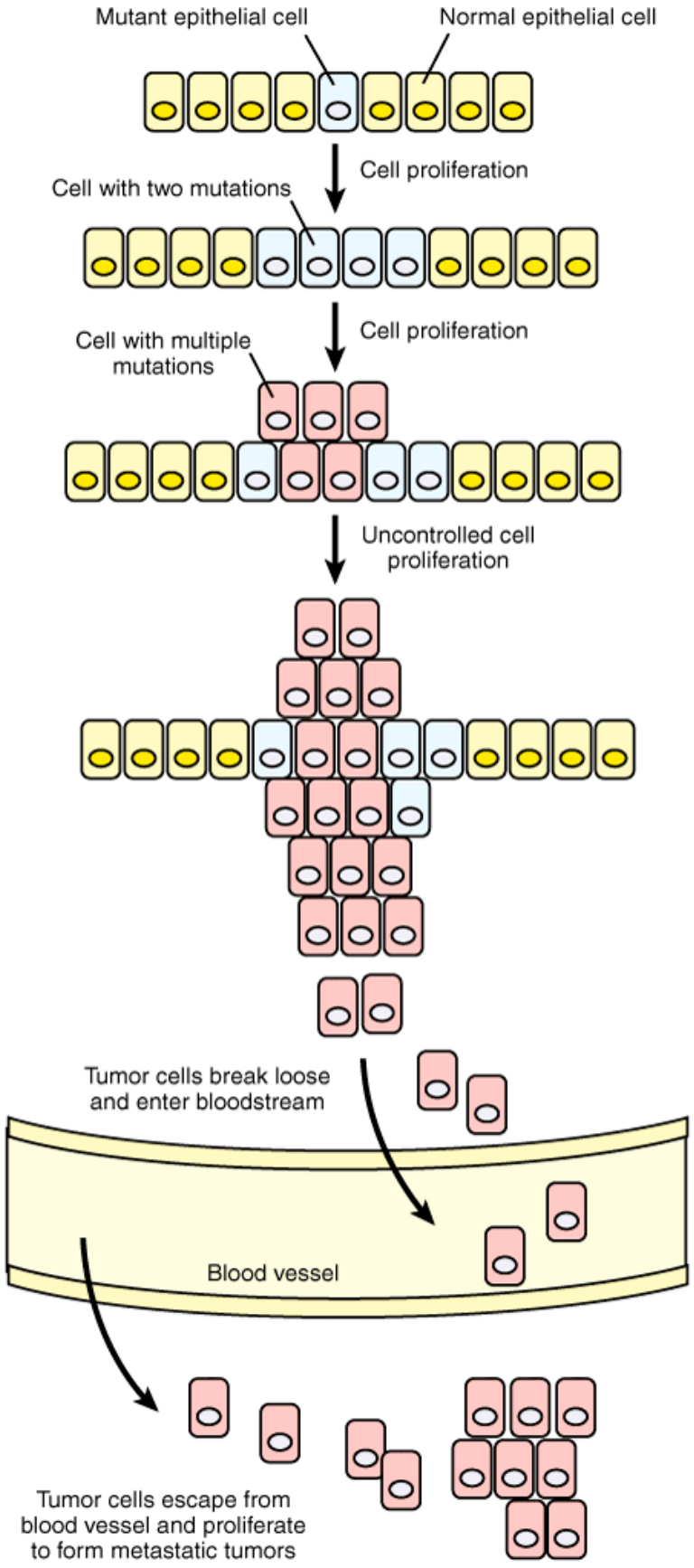
Gene Therapy and Molecular Drugs in Cancer

Modern advances in the use of molecular biology to manipulate genomes have greatly contributed to the understanding of the molecular basis

for how cells live, die, or differentiate. Given the fact that human diseases arise from improper changes in the genome, the continuous understanding of how the genome functions will make it possible to tailor medicine on an individual basis. Although significant hurdles remain, the course toward therapeutic application of molecular biology already has been mapped out by many proof-of-principle studies in the literature. In this section, cancer is used as an example to elaborate some therapeutic applications of molecular biology. Modern molecular medicine includes gene therapy and molecular drugs that target genes or gene products that wire human cells.

Cancer is a complex disease, involving uncontrolled growth and spread of tumor cells (Fig. 15-12). Cancer development depends on the acquisition and selection of specific characteristics that set the tumor cell apart from normal somatic cells. Cancer cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis. Many lines of evidence indicate that tumorigenesis in humans is a multistep process and that these steps reflect genetic alterations that drive the progressive transformation of normal human cells into highly malignant derivatives. The genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement. A succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells.

Fig. 15-12.



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Tumor clonal evolution and metastasis. A tumor develops from mutant cells with multiple genetic mutations. Through repeated alterations in the genome, mutant epithelial cells are able to develop into a cluster of cells (called a *tumor clone*) that proliferates in an uncontrollable

fashion. Further changes in the tumor cells can transform the tumor cells into a population of cells that can enter the blood vessels and repopulate in a new location.

Cancer research in the past 20 years has generated a rich and complex body of knowledge, revealing cancer to be a disease involving dynamic changes in the genome. The causes of cancer include genetic predisposition, environmental influences, infectious agents, and aging. These transform normal cells into cancerous ones by derailing a wide spectrum of regulatory pathways including signal transduction pathways, cell cycle machinery, or apoptotic pathways.[13] The early notion that cancer was caused by mutations in genes critical for the control of cell growth implied that genome stability is important for preventing oncogenesis. There are two classes of cancer genes in which alteration has been identified in human and animal cancer cells: oncogenes, with dominant gain-of-function mutations, and tumor suppressor genes, with recessive loss-of-function mutations. In normal cells, oncogenes promote cell growth by activating cell cycle progression, while tumor suppressors counteract oncogenes' functions. Therefore, the balance between oncogenes and tumor suppressors maintains a well-controlled state of cell growth.

During the development of most types of human cancer, cancer cells can break away from primary tumor masses, invade adjacent tissues, and hence travel to distant sites where they form new colonies. This spreading process of tumor cells, called *metastasis*, is the cause of 90% of human cancer deaths. Metastatic cancer cells that enter the bloodstream can reach virtually all tissues of the body. Bones are one of the most common places for these cells to settle and start growing again. Bone metastasis is one of the most frequent causes of pain in people with cancer. It also can cause bones to break and create other symptoms and problems for patients.

The progression in the knowledge of cancer biology has been accelerating in recent years. All of the scientific knowledge acquired through hard work and discovery has made it possible for cancer treatment and prevention. As a result of explosive new discoveries, some modern treatments were developed. The success of these therapies, together with traditional treatments such as surgical procedures, is further underscored by the fact that in 2002 the cancer rate was reduced in the United States. Current approaches to the treatment of cancer involve killing cancer cells with toxic chemicals, radiation, or surgery. Alternatively, several new biologic- and gene-based therapies are aimed at enhancing the body's natural defenses against invading cancers. Understanding the biology of cancer cells has led to the development of designer therapies for cancer prevention and treatment. Gene therapy, immune system modulation, genetically engineered antibodies, and molecularly designed chemical drugs are all promising fronts in the war against cancer.

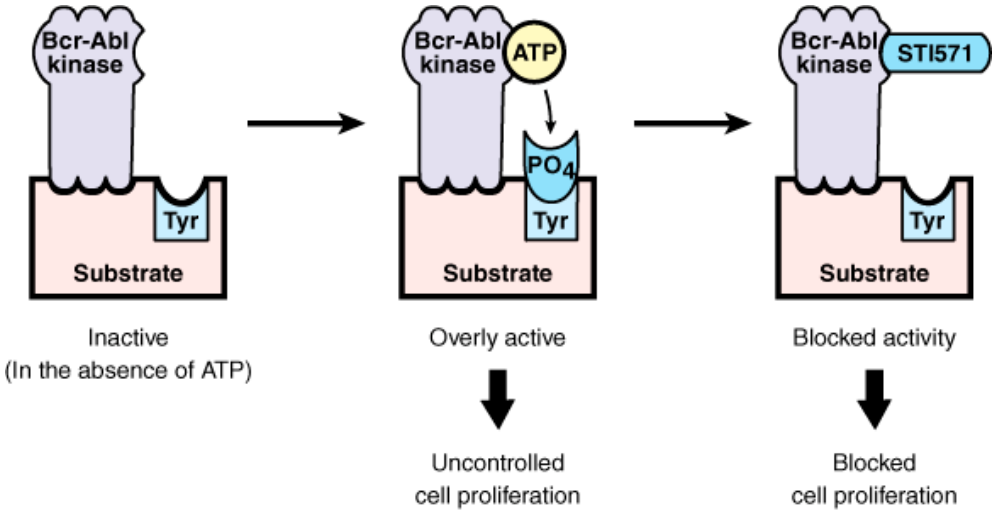
IMMUNOTHERAPY

The growth of the body is controlled by many natural signals through complex signaling pathways. Some of these natural agents have been used in cancer treatment and have been proven effective for fighting several cancers through the clinical trial process. These naturally occurring biologic agents, such as interferons, interleukins, and other cytokines, can now be produced in the laboratory. These agents, as well as the synthetic agents that mimic the natural signals, are given to patients to influence the natural immune response agents either by directly altering the cancer cell growth, or by acting indirectly to help healthy cells control the cancer. One of the most exciting applications of immunotherapy has come from the identification of certain tumor targets called *antigens* and the aiming of an antibody at these targets. This was first used as a means of localizing tumors in the body for diagnosis, and was more recently used to attack cancer cells. Trastuzumab (Herceptin) is an example of such a drug.[14] Trastuzumab is a monoclonal antibody that neutralizes the mitogenic activity of cell-surface growth factor receptor HER-2. Approximately 25% of breast cancers overexpress HER-2. These tumors tend to grow faster and generally are more likely to recur than tumors that do not overproduce HER-2. Trastuzumab is designed to attack cancer cells that overexpress HER-2. Trastuzumab slows or stops the growth of these cells and increases the survival of HER-2–positive breast cancer patients. Another significant example is the administration of interleukin-2 (IL-2) to patients with metastatic melanoma or kidney cancer, which has been shown to mediate the durable regression of metastatic cancer. IL-2, a cytokine produced by human helper T lymphocytes, has a wide range of immune regulatory effects, including the expansion of lymphocytes following activation by a specific antigen. IL-2 has no direct impact on cancer cells. The impact of IL-2 on cancers in vivo derives from its ability to expand lymphocytes with antitumor activity. The expanded lymphocytes somehow recognize the antigen on cancer cells. Thus, the molecular identification of cancer antigens has opened new possibilities for the development of effective immunotherapies for patients with cancer. Clinical studies using immunization with peptides derived from cancer antigens have shown that high levels of lymphocytes with antitumor activity can be produced in cancer-bearing patients. Highly avid antitumor lymphocytes can be isolated from immunized patients and grown in vitro for use in cell-transfer therapies.

CHEMOTHERAPY

The primary function of anticancer chemicals is to block different steps involved in cell growth and replication. These chemicals often block a critical chemical reaction in a signal transduction pathway or during DNA replication or gene expression. For example, STI571, also known as *Gleevec*, is one of the first molecularly targeted drugs based on the changes that cancer causes in cells.[15] STI571 offers promise for the treatment of chronic myeloid leukemia (CML) and may soon surpass interferon-γ as the standard treatment for the disease. In CML, STI571 is targeted at the Bcr-Abl kinase, an activated oncogene product in CML (Fig. 15-13). Bcr-Abl is an overly activated protein kinase resulting from a specific genetic abnormality generated by chromosomal translocation that is found in the cells of patients with CML. STI571-mediated inhibition of Bcr-Abl-kinase activity not only prevents cell growth of Bcr-Abl–transformed leukemic cells, but also induces apoptosis. Clinically, the drug quickly corrects the blood cell abnormalities caused by the leukemia in a majority of patients, achieving a complete disappearance of the leukemic blood cells and the return of normal blood cells. Additionally, the drug appears to have some effect on other cancers including certain brain tumors and GI stromal tumors, a very rare type of stomach cancer.

Fig. 15-13.



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Mechanism of STI571 as a molecular drug. Bcr-Abl is an overly activated oncogene product resulting from a specific genetic abnormality generated by chromosomal translocation that is found in cells of patients with chronic myeloid leukemia. Bcr-Abl is an activated protein kinase and thus requires adenosine triphosphate (ATP) to phosphorylate substrates, which in turn promote cell proliferation. STI571 is a small molecule that competes with the ATP-binding site and thus blocks the transfer of phosphoryl group to substrate. PO_4 = phosphate; Tyr = tyrosine.

GENE THERAPY

Gene therapy is an experimental treatment that involves genetically altering a patient's own tumor cells or lymphocytes (cells of the immune system, some of which can attack cancer cells). For years, the concept of gene therapy has held promise as a new, potentially potent weapon to attack cancer. Although a rapid progression in the understanding of the molecular and clinical aspects of gene therapy has been witnessed in the past decade, gene therapy treatment has not yet been shown to be superior to standard treatments in humans.

Several problems must be resolved to transform it into a clinically relevant form of therapy. The major issues that limit its translation to the clinic are improving the selectivity of tumor targeting, improving the delivery to the tumor, and the enhancement of the transduction rate of the cells of interest. In most gene therapy trials for malignant diseases, tumors can be accessed and directly injected (in situ gene therapy). The in situ gene therapy also offers a better distribution of the vector virus throughout the tumor. Finally, a combination of gene therapy strategies will be more effective than the use of a single gene therapy system. An important aspect of effective gene therapy involves the choice of appropriate genes for manipulation. Genes that promote the production of messenger chemicals or other immune-active substances can be transferred into the patient's cells. These include genes that inhibit cell cycle progression, induce apoptosis, enhance host immunity against cancer cells, block the ability of cancer cells to metastasize, and cause tumor cells to undergo suicide. Recent development of RNAi technology,

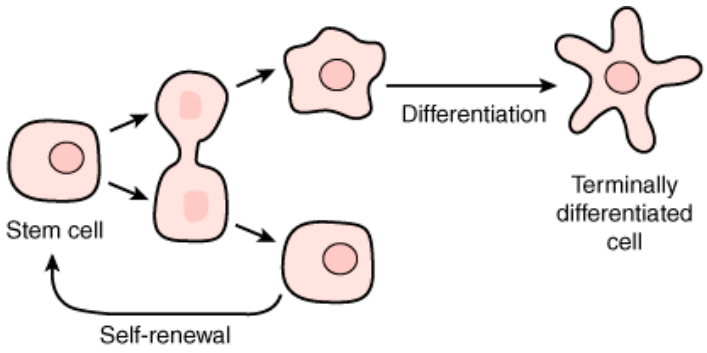
which uses a loss-of-function approach to block gene functions, ensures a new wave of hopes for gene therapy. Nonetheless, gene therapy is still experimental and is being studied in clinical trials for many different types of cancer. The mapping of genes responsible for human cancer is likely to provide new targets for gene therapy in the future. The preliminary results of gene therapy for cancer are encouraging, and as advancements are made in the understanding of the molecular biology of human cancer, the future of this rapidly developing field holds great potential for treating cancer.

It is noteworthy that the use of multiple therapeutic methods has proven more powerful than a single method. The use of chemotherapy after surgery to destroy the few remaining cancerous cells in the body is called *adjuvant* therapy. Adjuvant therapy was first tested and found to be effective in breast cancer. It was later adopted for use in other cancers. A major discovery in chemotherapy is the advantage of multiple chemotherapeutic agents (known as *combination* or *cocktail chemotherapy*) over single agents. Some types of fast-growing leukemias and lymphomas (tumors involving the cells of the bone marrow and lymph nodes) responded extremely well to combination chemotherapy, and clinical trials led to gradual improvement of the drug combinations used. Many of these tumors can be cured today by combination chemotherapy. As cancer cells carry multiple genetic defects, the use of combination chemotherapy, immunotherapy, and gene therapies may be more effective in treating cancers.

Stem Cell Research

Stem cell biology represents a cutting-edge scientific research field with potential clinical applications.[16] It may have an enormous impact on human health by offering hope for curing human diseases such as diabetes mellitus, Parkinson's disease, neurologic degeneration, and congenital heart disease. Stem cells are endowed with two remarkable properties (Fig. 15-14). First, stem cells can proliferate in an undifferentiated but pluripotent state, and as a result can self-renew. Second, they have the ability to differentiate into many specialized cell types. There are two groups of stem cells: embryonic stem (ES) cells and adult stem cells. Human ES cells are derived from early preimplantation embryos called *blastocysts* (5 days postfertilization), and are capable of generating all differentiated cell types in the body. Adult stem cells are present in and can be isolated from adult tissues. They often are tissue specific and only can generate the cell types comprising a particular tissue in the body; however, in some cases they can transdifferentiate into cell types found in other tissues. Hematopoietic stem cells are adult stem cells. They reside in bone marrow and are capable of generating all cell types of the blood and immune system.

Fig. 15-14.



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Stem cells. A stem cell is capable of self-renewal (unlimited cell cycle) and differentiation (becoming nondividing cells with specialized functions). Differentiating stem cells often undergo additional cell divisions before they become fully mature cells that carry out specific tissue functions.

Stem cells can be grown in culture and be induced to differentiate into a particular cell type, either in vitro or in vivo. With the recent and continually increasing improvement in culturing stem cells, scientists are beginning to understand the molecular mechanisms of stem cell self-renewal and differentiation in response to environmental cues. It is believed that discovery of the signals that control self-renewal vs. differentiation will be extremely important for the therapeutic use of stem cells in treating disease. It is possible that success in the study of the changes in signal transduction pathways in stem cells will lead to the development of therapies to specifically differentiate stem cells into a

particular cell type to replace diseased or damaged cells in the body. Recently, stem cell research has been transformed by the discovery from the Shinya Yamanaka group and the James Thomsen group, who have found that a simple genetic manipulation can reprogram adult differentiated cells into pluripotent cells.[17] This exciting discovery not only bypasses the ethical issues of using early embryos to generate ES cells, but also ensures a potentially limitless source of patient-specific stem cells for tissue engineering and transplantation medicine.

Personalized Genomic Medicine

Genes determine our susceptibility to diseases and direct our body's response to medicine. Because an individual's genes differ from those of another, the determination of each individual's genome has the potential to improve the predication, prevention, and treatment of disease. Sequencing of individual genomes holds the key to realize this revolution called *personalized genomic medicine*. Next generation sequencing such as 454 Life Sciences technology is promising to reduce the time and cost so that genome sequencing can be affordable in the health care system. The goal of personalized genomic medicine is to spot the gene variations in each individual and to attack the disease by choosing personalized treatments that work with the individual's genomic profile. Personalized genomic medicine will undoubtedly revolutionize the practice of modern medicine.

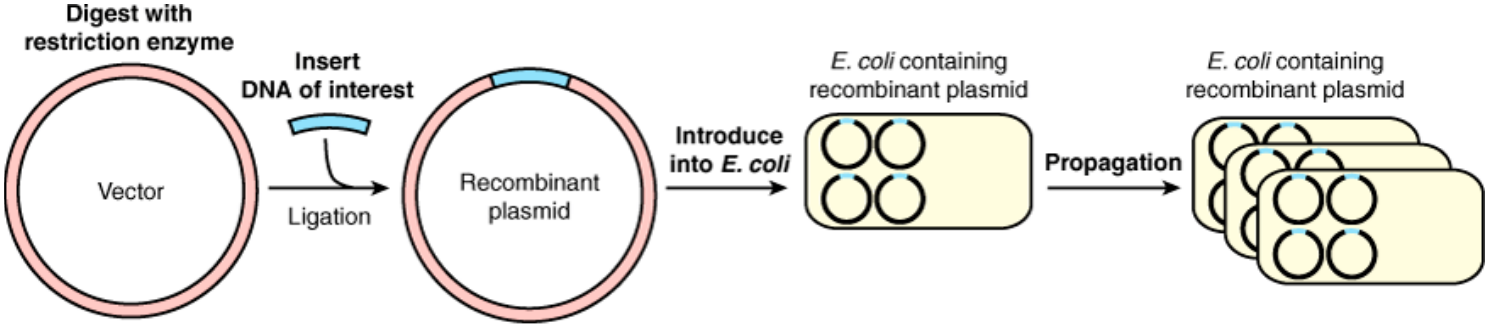
TECHNOLOGIES OF MOLECULAR AND CELL BIOLOGY

DNA Cloning

Since the advent of recombinant DNA technology three decades ago, hundreds of thousands of genes have been identified. Recombinant DNA technology is the technology that uses advanced enzymatic and microbiologic techniques to manipulate DNA.[18] Pure pieces of any DNA can be inserted into bacteriophage DNA or other carrier DNA such as plasmids to produce recombinant DNA in bacteria. In this way, DNA can be reconstructed, amplified, and used to manipulate the functions of individual cells or even organisms. This technology, often referred to as *DNA cloning*, is the basis of all other DNA analysis methods. It is only with the awesome power of recombinant DNA technology that the completion of the Human Genome Project was possible. It also has led to the identification of the entire gene complements of organisms such as viruses, bacteria, worms, flies, and plants.

Molecular cloning refers to the process of cloning a DNA fragment of interest into a DNA vector that ultimately is delivered into bacterial or mammalian cells or tissues[19,20] (Fig. 15-15). This represents a very basic technique that is widely used in almost all areas of biomedical research. DNA vectors often are called *plasmids*, which are extrachromosomal molecules of DNA that vary in size and can replicate and be transmitted from bacterial cell to cell. Plasmids can be propagated either in the cytoplasm, or after insertion, as part of the bacterial chromosome in *Escherichia coli*. The process of molecular cloning involves several steps of manipulation of DNA. First, the vector plasmid DNA is cleaved with a restriction enzyme to create compatible ends with the foreign DNA fragment to be cloned. The vector and the DNA fragment are then joined in vitro by a DNA ligase. Alternatively, DNA cloning can be simply done through the so-called *Gateway Technology* that allows for the rapid and efficient transfer of DNA fragments between different cloning vectors while maintaining reading frame and orientation, without the use of restriction endonucleases and DNA ligase. The technology, which is based on the site-specific recombination system of bacteriophage l, is simple, fast, robust and automatable, thus compatible for high-throughput DNA cloning.

Fig. 15-15.



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Generation of recombinant DNA. The vector is a circular DNA molecule that is capable of replicating in *Escherichia coli* cells. Insert DNA (often your favorite gene) is ligated to the vector after ends of both DNA are properly treated with restriction enzymes. Ligated DNA (i.e., the recombinant plasmid DNA) is then transformed into *E. coli* cells, where it replicates to produce recombinant progenies. *E. coli* cells carrying the recombinant plasmid can be propagated to yield large quantities of plasmid DNA.

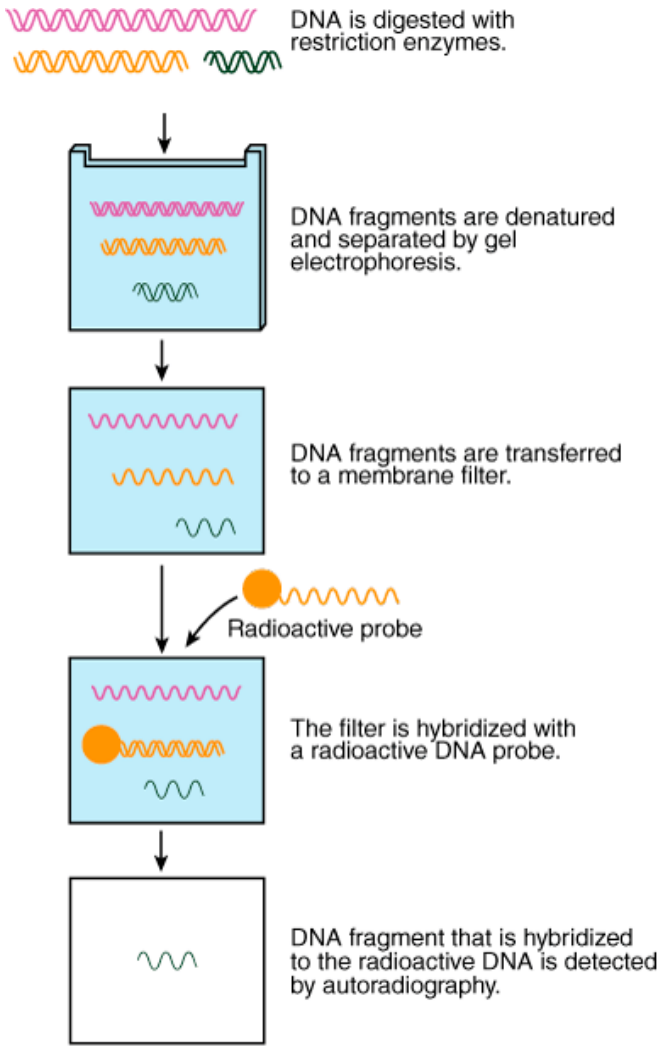
Finally, the ligation product or the Gateway reaction product is introduced into competent host bacteria; this procedure is called *transformation*, which can be done by either calcium/heat shock or electroporation. Precautions must be taken in every step of cloning to generate the desired DNA construct. The vector must be correctly prepared to maximize the creation of recombinants; for example, it must be enzymatically treated to prevent self-ligation. Host bacteria must be made sufficiently competent to permit the entry of recombinant plasmids into cells. The selection of desired recombinant plasmid-bearing *E. coli* normally is achieved by the property of drug resistance conferred by the plasmid vectors. The plasmids encoding markers provide specific resistance to (i.e., the ability to grow in the presence of) antibiotics such as ampicillin, kanamycin, and tetracycline. The foreign component in the plasmid vector can be a mammalian expression cassette, which can direct expression of foreign genes in mammalian cells. The resulting plasmid vector can be amplified in *E. coli* to prepare large quantities of DNA for its subsequent applications such as transfection, gene therapy, transgenics, and knockout mice.

Detection of Nucleic Acids and Proteins

SOUTHERN BLOT HYBRIDIZATION

Southern blotting refers to the technique of transferring DNA fragments from an electrophoresis gel to a membrane support, and the subsequent analysis of the fragments by hybridization with a radioactively labeled probe (Fig. 15-16).[21] Southern blotting is named after E. M. Southern, who in 1975 first described the technique of DNA analysis. It enables reliable and efficient analysis of size-fractionated DNA fragments in an immobilized membrane support. Southern blotting is composed of several steps. It normally begins with the digestion of the DNA samples with appropriate restriction enzymes and the separation of DNA samples in an agarose gel with appropriate DNA size markers. The DNA gel is stained with ethidium bromide and photographed with a ruler laid alongside the gel so that band positions can later be identified on the membrane. The DNA gel then is treated so the DNA fragments are denatured (i.e., strand separation). The DNA then is transferred onto a nitrocellulose membrane by capillary diffusion or under electricity. After immobilization, the DNA can be subjected to hybridization analysis, enabling bands with sequence similarity to a radioactively labeled probe to be identified.

Fig. 15-16.



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Southern blotting. Restriction enzymatic fragments of DNA are separated by agarose gel electrophoresis, transferred to a membrane filter, and then hybridized to a radioactive probe.

The development of Southern transfer and the associated hybridization techniques made it possible for the first time to obtain information about the physical organization of single and multicopy sequences in complex genomes. The later application of Southern blotting hybridization to the study of restriction fragment length polymorphisms opened up new possibilities such as genetic fingerprinting and prenatal diagnosis of genetic diseases.

NORTHERN BLOT HYBRIDIZATION

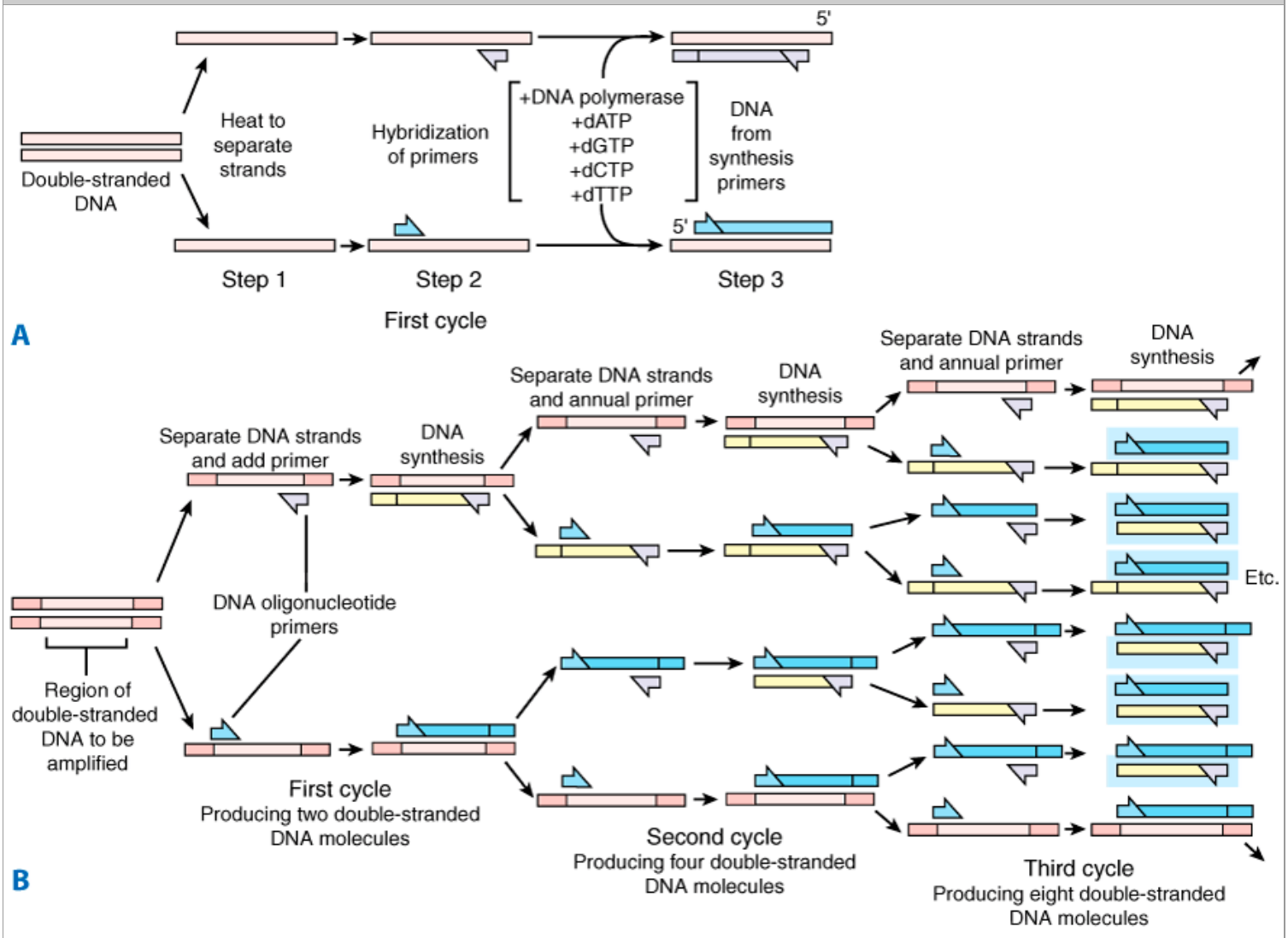
Northern blotting refers to the technique of size fractionation of RNA in a gel and the transferring of an RNA sample to a solid support (membrane) in such a manner that the relative positions of the RNA molecules are maintained. The resulting membrane then is hybridized with a labeled probe complementary to the mRNA of interest. Signals generated from detection of the membrane can be used to determine the size and abundance of the target RNA. In principle, Northern blot hybridization is similar to Southern blot hybridization (and hence its name), with the exception that RNA, not DNA, is on the membrane. Although reverse-transcriptase polymerase chain reaction has been used in many applications (described in Polymerase Chain Reaction below), Northern analysis is the only method that provides information regarding mRNA size and has remained a standard method for detection and quantitation of mRNA. The process of Northern hybridization involves several steps, as does Southern hybridization, including electrophoresis of RNA samples in an agarose-formaldehyde gel, transfer to a membrane support, and hybridization to a radioactively labeled DNA probe. Data from hybridization allow quantification of steady-state mRNA levels, and at the same time, provide information related to the presence, size, and integrity of discrete mRNA species. Thus, Northern blot analysis, also termed *RNA*

gel blot analysis, commonly is used in molecular biology studies relating to gene expression.

POLYMERASE CHAIN REACTION

PCR is an in vitro method for the polymerase-directed amplification of specific DNA sequences using two oligonucleotide primers that hybridize to opposite strands and flank the region of interest in the target DNA (Fig. 15-17).[22] One cycle of PCR reaction involves template denaturation, primer annealing, and the extension of the annealed primers by DNA polymerase. Because the primer extension products synthesized in one cycle can serve as a template in the next, the number of target DNA copies nearly doubles at each cycle. Thus, a repeated series of cycles result in the exponential accumulation of a specific fragment in which the termini are sharply defined by the 5' ends of the primers. The introduction of the thermostable DNA polymerase (e.g., Taq polymerase) transforms the PCR into a simple and robust reaction. The reaction components (e.g., template, primers, Taq polymerase, 2'-deoxynucleoside 5'-triphosphates, and buffer) could all be assembled and the amplification reaction carried out by simply cycling the temperatures within the reaction tube. The specificity and yield in amplifying a particular DNA fragment by PCR reaction is affected by the proper setting of the reaction parameters (e.g., enzyme, primer, and Mg^{2+} concentration, as well as the temperature cycling profile). Modifying various PCR parameters to optimize the specificity of amplification yields more homogenous products, even in rare template reactions.

Fig. 15-17.



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Amplification of DNA using the polymerase chain reaction technique. Knowledge of the DNA sequence to be amplified is used to design two synthetic DNA oligonucleotides, each complementary to the sequence on one strand of the DNA double helix at opposite ends of the region to

be amplified. These oligonucleotides serve as primers for in vitro DNA synthesis, which is performed by a DNA polymerase, and they determine the segment of the DNA that is amplified. **A.** PCR starts with a double-stranded DNA, and each cycle of the reaction begins with a brief heat treatment to separate the two strands (*Step 1*). After strand separation, cooling of the DNA in the presence of a large excess of the two primer DNA oligonucleotides allows these primers to hybridize to complementary sequences in the two DNA strands (*Step 2*). This mixture is then incubated with DNA polymerase and the four deoxyribonucleoside triphosphates so that DNA is synthesized, starting from the two primers (*Step 3*). The entire cycle is then begun again by a heat treatment to separate the newly synthesized DNA strands. **B.** As the procedure is performed over and over again, the newly synthesized fragments serve as templates in their turn, and, within a few cycles, the predominant DNA is identical to the sequence bracketed by and including the two primers in the original template. Of the DNA put into the original reaction, only the sequence bracketed by the two primers is amplified because there are no primers attached anywhere else. In the example illustrated in **B**, three cycles of reaction produce 16 DNA chains, eight of which (*boxed in brown*) are the same length as and correspond exactly to one or the other strand of the original bracketed sequence shown at the far left; the other strands contain extra DNA downstream of the original sequence, which is replicated in the first few cycles. After three more cycles, 240 of the 256 DNA chains correspond exactly to the original bracketed sequence, and after several more cycles, essentially all of the DNA strands have this unique length.

(From Alberts et al,[1] with permission.)

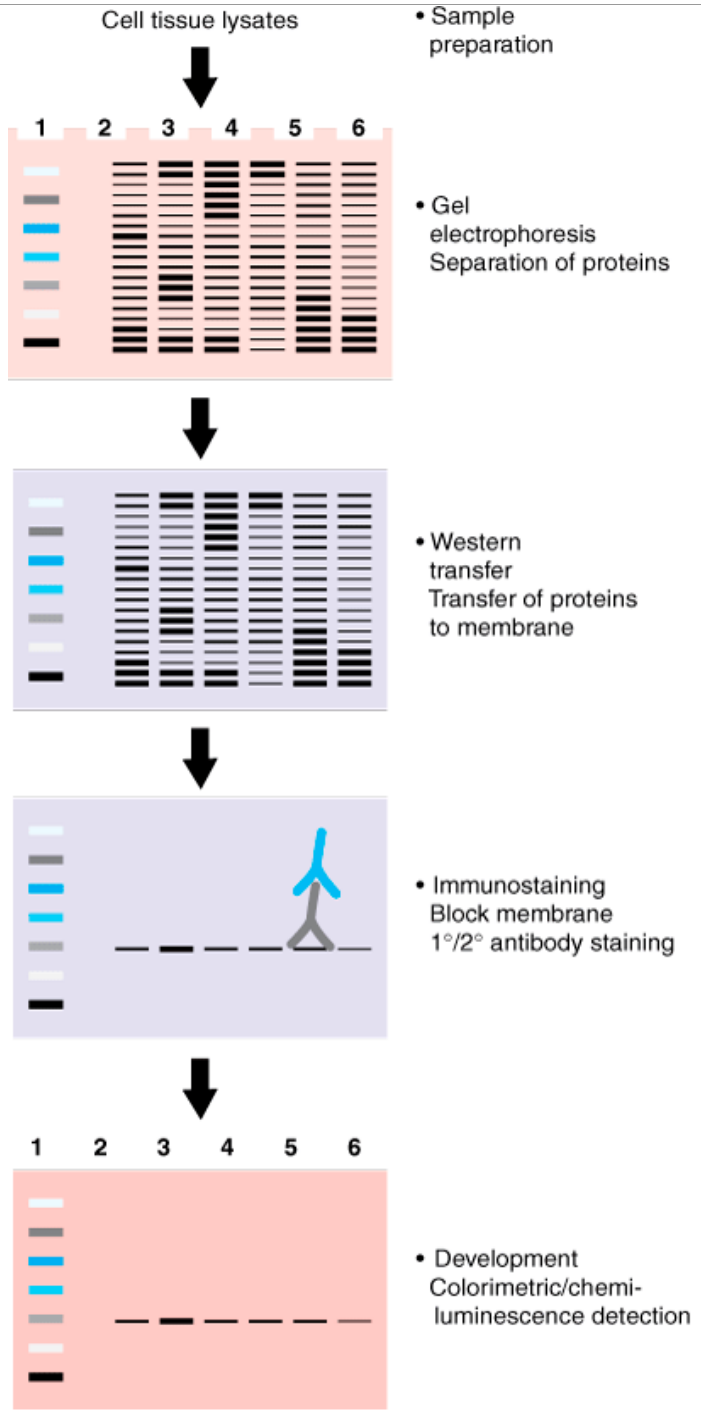
The emergence of the PCR technique has dramatically altered the approach to both fundamental and applied biologic problems. The capability of amplifying a specific DNA fragment from a gene or the whole genome greatly advances the study of the gene and its function. It is simple, yet robust, speedy, and most of all, flexible. As a recombinant DNA tool, it underlies almost all of molecular biology. This revolutionary technique enabled the modern methods for the isolation of genes, construction of a DNA vector, introduction of alterations into DNA, and quantitation of gene expression, making it a fundamental cornerstone of genetic and molecular analysis.

IMMUNOBLOTTING AND IMMUNOPRECIPITATION

Analyses of proteins are primarily carried out by antibody-directed immunologic techniques. For example, Western blotting, also called *immunoblotting*, is performed to detect protein levels in a population of cells or tissues, whereas immunoprecipitation is used to concentrate proteins from a larger pool. Using specific antibodies, microscopic analysis called *immunofluorescence* and *immunohistochemistry* is possible for the subcellular localization and expression of proteins in cells or tissues, respectively.

Immunoblotting refers to the process of identifying a protein from a mixture of proteins (Fig. 15-18). It consists of five steps: (a) sample preparation; (b) electrophoresis (separation of a protein mixture by sodium dodecyl sulfate-polyacrylamide gel electrophoresis); (c) transfer (the electrophoretic transfer of proteins from gel onto membrane support, (e.g., nitrocellulose, nylon, or polyvinylidene difluoride); (d) staining (the subsequent immunodetection of target proteins with specific antibody); and (e) development (colorimetric or chemiluminescent visualization of the antibody-recognized protein). Thus, immunoblotting combines the resolution of gel electrophoresis with the specificity of immunochemical detection. Immunoblotting is a powerful tool used to determine a number of important characteristics of proteins. For example, immunoblotting analysis will determine the presence and the quantity of a protein in a given cellular condition and its relative molecular weight. Immunoblotting also can be used to determine whether posttranslational modification such as phosphorylation has occurred on a protein. Importantly, through immunoblotting analysis, a comparison of the protein levels and modification states in normal vs. diseased tissues is possible.

Fig. 15-18.



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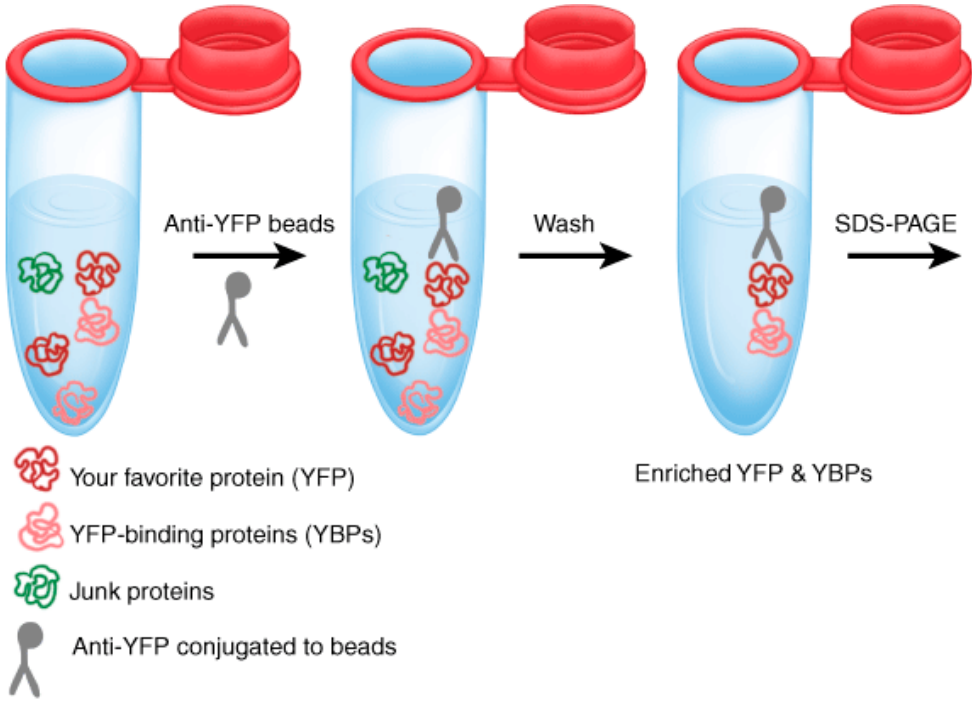
Immunoblotting. Proteins are prepared from cells or tissues, separated according to size by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and transferred to a membrane filter. Detection of a protein of interest can be done by sequential incubation with a primary antibody directed against the protein, and then with an enzyme-conjugated secondary antibody that recognizes the primary antibody. Visualization of the protein is carried out by using colorimetric or luminescent substrates for the conjugated enzyme.

Immunoprecipitation, another widely used immunochemical technique, is a method that uses antibody to enrich a protein of interest and any other proteins that are associated with it (Fig. 15-19). The principle of the technique lies in the property of a strong and specific affinity between antibodies and their antigens to locate and pull down target proteins in solution. Once the antibody-antigen (target protein) complexes are formed in the solution, they are collected and purified using small agarose beads with covalently attached protein A or protein G. Both protein A and protein G specifically interact with the antibodies, thus forming a large immobilized complex of antibody-antigen bound to beads.

The purified protein can then be analyzed by a number of biochemical methods. When immunoprecipitation is combined with immunoblotting, it can be used for the sensitive detection of proteins in low concentrations, which would otherwise be difficult to detect. Moreover, combined immunoprecipitation and immunoblotting analysis is very efficient in analyzing the protein-protein interactions or determining the posttranslational modifications of proteins. In addition, immunoprecipitated proteins can be used as preparative steps for assays such as intrinsic or associated enzymatic activities. The success of immunoprecipitation is influenced by two major factors: (a) the abundance of the protein in the original preparation and (b) the specificity and affinity of the antibody for this protein.

Fig. 15-19.



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Immunoprecipitation. Proteins prepared from cells or tissues can be enriched using an antibody directed against them. The antibody is first conjugated to agarose beads and then incubated with protein mixture. Owing to the specific high-affinity interaction between antibody and its antigen (the protein), the antigen-antibody complex can be collected on beads by centrifugation. The immunoprecipitated protein can then be analyzed by immunoblotting. Alternatively, if proteins are radiolabeled in cells or tissues, detection of immunoprecipitated proteins can be achieved by simple sodium dodecyl sulfate-polyacrylamide gel electrophoresis followed by autoradiography.

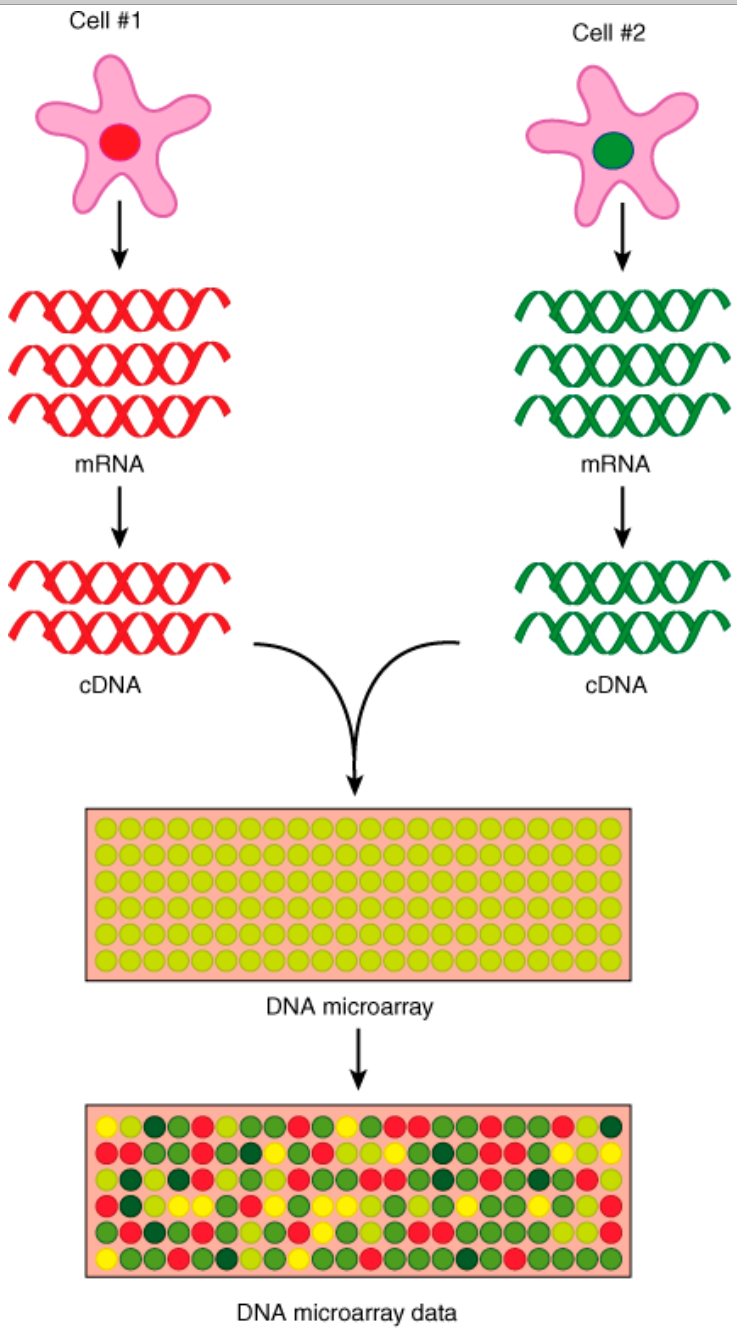
DNA MICROARRAY

Now that the human genome sequence is completed, the primary focus of biologists is rapidly shifting toward gaining an understanding of how genes function. One of the interesting findings about the human genome is that there are only approximately 25,000 to 30,000 protein-encoding genes. However, it is known that genes and their products function in a complicated and yet orchestrated fashion and that the surprisingly small number of genes from the genome sequence is sufficient to make a human being. Nonetheless, with the tens of thousands of genes present in the genome, traditional methods in molecular biology, which generally work on a one-gene-in-one-experiment basis, cannot generate the whole picture of genome function. In the past several years, a new technology called *DNA microarray* has attracted tremendous interest among biologists as well as clinicians. This technology promises to monitor the whole genome on a single chip so researchers can have a better picture of the interactions among thousands of genes simultaneously.

DNA microarray, also called *gene chip*, *DNA chip*, and *gene array*, refers to large sets of probes of known sequences orderly arranged on a small chip, enabling many hybridization reactions to be carried out in parallel in a small device (Fig. 15-20).[23] Like Southern and Northern hybridization, the underlying principle of this technology is the remarkable ability of nucleic acids to form a duplex between two strands with complementary base sequences. DNA microarray provides a medium for matching known and unknown DNA samples based on base-pairing rules, and automating the process of identifying the unknowns. Microarrays require specialized robotics and imaging equipment that spot the

samples on a glass or nylon substrate, carry out the hybridization, and analyze the data generated. DNA microarrays containing different sets of genes from a variety of organisms are now commercially available, allowing biologists to simply purchase the chips and perform hybridization and data collection. The massive scale of microarray experiments requires the aid of computers. They are used during the capturing of the image of the hybridized target, the conversion of the image into usable measures of the extent of hybridization, and the interpretation of the extent of hybridization into a meaningful measure of the amount of the complementary sequence in the target. Some data-analysis packages are available commercially or can be found in the core facility of certain institutions.

Fig. 15-20.



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DNA microarrays. DNA microarrays, also referred to as *gene chips*, have arrayed oligonucleotides or complementary DNAs (cDNAs) corresponding to tens or hundreds of distinct genes. DNA microarray is used to comparatively analyze gene expression in different cells or tissues. Messenger RNAs (mRNAs) extracted from different sources are converted into cDNAs, which are then labeled with different fluorescent dyes. The two fluorescent cDNA probes are mixed and hybridized to the same DNA microarrays. The ratio of dark brown to light brown

fluorescence at each spot on the chip represents the relative expression of levels of that gene between two different cells. In the example shown in the figure, cDNA from cell #1 is labeled with dark brown fluorescence and the cell #2 light brown fluorescence. On the microarray, dark brown spots demonstrate that the gene in cell sample #1 is expressed at a higher level than the corresponding gene in cell sample #2. The light brown spots indicate that the gene in cell sample #1 also is expressed at a higher level than the corresponding gene in cell sample #2. Beige spots represent equal expression of the gene in both cell samples.

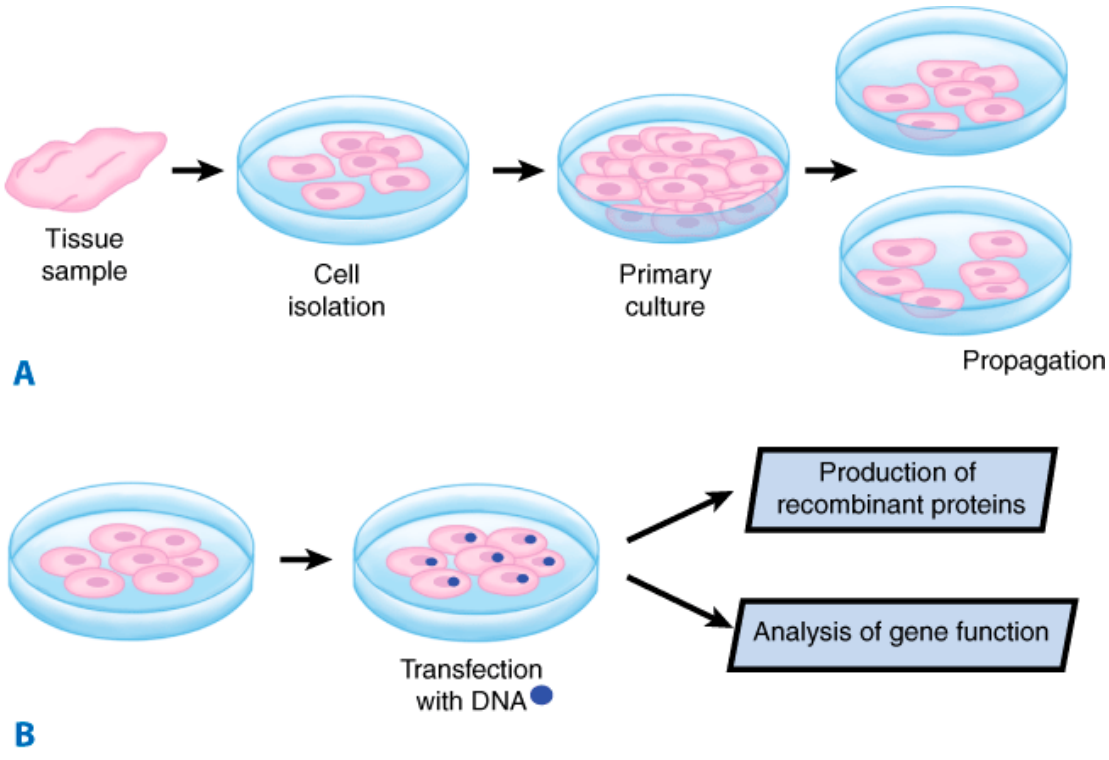
DNA microarray technology has produced many significant results in quite different areas of application. There are two major application forms for the technology: identification of sequence (gene/gene mutation) and determination of expression level (abundance) of genes. For example, analysis of genomic DNA detects amplifications and deletions found in human tumors. Differential gene expression analysis also has uncovered networks of genes differentially present in cancers that cannot be distinguished by conventional means. Significantly, recent advancements in next generation sequencing (e.g., Solexa and 454 technology) have demonstrated the precision and speed to analyze gene expression in any genome.

Cell Manipulations

CELL CULTURE

Cell culture has become one of the most powerful techniques, as cultured cells are being used in a diversity of biologic fields ranging from biochemistry to molecular and cellular biology.[24] Through their ability to be maintained in vitro, cells can be manipulated by the introduction of genes of interest (cell transfection) and be transferred into in vivo biologic receivers (cell transplantation) to study the biologic effect of the interested genes (Fig. 15-21). In general, cell culture procedures are simple and straightforward. In the laboratory, cells are cultured either as a monolayer (in which cells grow as one layer on culture dishes) or in suspension.

Fig. 15-21.



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Cell culture and transfection. **A.** Primary cells can be isolated from tissues and cultured in medium for a limited period of time. After genetic manipulations to overcome the cell aging process, primary cells can be immortalized into cell lines for long-term culture. **B.** DNA can be introduced into cells to produce recombinant gene products or to analyze the biologic functions of the gene.

It is important to know the wealth of information concerning cell culturing before attempting the procedure. For example, conditions of culture will depend on the cell types to be cultured (e.g., origins of the cells such as epithelial or fibroblasts, or primary vs. immortalized/transformed

cells). It also is necessary to use special culture medium that has been used to establish the cell line (if it is a cell line), including the type and concentration of serum used to maintain the growth of cells in vitro. If primary cells are derived from human patients or animals, some commercial resources have a variety of culture media available for testing. Generally, cells are manipulated in a sterile hood and the working surfaces are wiped with 80% ethyl alcohol solution. Cultured cells are maintained in a humidified carbon dioxide incubator at 37°C (98.6°F), and need to be examined daily under an inverted microscope to check for possible contamination and confluency (the area cells occupy on the dish). As a general rule, cells should be fed with fresh medium every 2 to 3 days and split when they reach confluency. Depending upon the growth rate of cells, the actual time and number of plates required to split cells in two varies from cell line to cell line. Splitting a monolayer requires the detachment of cells from plates by using a trypsin treatment, of which concentration and time period vary depending on cell lines. If cultured cells grow continuously in suspension, they are split or subcultured by dilution.

Because cell lines may change their properties when cultured, it is not possible to maintain cell lines in culture indefinitely. Therefore, it is essential to store cells at various time passages for future use. The common procedure is to use cryopreservation. The solution for cryopreservation is fetal calf serum containing 10% dimethyl sulfoxide or glycerol, stored in liquid nitrogen [−196°C (−320.8°F)]. Cells can be stored for many years using this method.

CELL TRANSFECTION

Cells are cultured for two reasons: to maintain and to manipulate them (see Fig. 15-21). The transfer of foreign macromolecules, such as nucleic acid, into living cells provides an efficient method for studying a variety of cellular processes and functions at the molecular level. DNA transfection has become an important tool for studying the regulation and function of genes. The cDNA to be expressed should be in a plasmid vector, behind an appropriate promoter working in mammalian cells (e.g., the constitutively active cytomegalovirus promoter or inducible promoter). Depending on the cell type, many ways of introducing DNA into mammalian cells have been developed. Commonly used approaches include calcium phosphate, electroporation, liposome-mediated transfection, the nonliposomal formulation, and the use of viral vectors. These methods have shown variable success when attempting to transfect a wide variety of cells. Transfection can be performed in the presence or absence of serum. It is suggested to test the transfection efficiency of cell lines of interest by comparing transfection with several different approaches. For a detailed transfection protocol, it is best to follow the manufacturer's instructions for the particular reagent. General considerations for a successful transfection depend on several parameters, such as the quality and quantity of DNA and cell culture (type of cell and growth phase). To minimize variations in both of these in transfection experiments, it is best to use cells that are healthy, proliferate well, and are plated at a constant density. After DNA is introduced into the cells, it is normally maintained epitopically in cells and will be diluted while host cells undergo cell division. Therefore, functional assays should be performed 24 to 72 hours after transfection, also termed *transient transfection*. In many applications, it is important to study the long-term effects of DNA in cells by stable transfection. Stable cell clones can be selected for DNA integration into the host cell genome, when plasmids carry an antibiotic-resistant marker. In the presence of antibiotics, only those cells that continuously carry the antibiotic-resistant marker (after generations of cell division) can survive. One application of stable transfection is the generation of transgenic or knockout mouse models, in which the transgene has to be integrated in the mouse genome. Stable cells also can be transplanted into host organs.

Genetic Manipulations

Understanding how genes control the growth and differentiation of the mammalian organism has been the most challenging topic of modern research. It is essential for us to understand how genetic mutations and chemicals lead to the pathologic condition of human bodies. The knowledge and ability to change the genetic program will inevitably make a great impact on society and have far-reaching effects on how we think of ourselves.

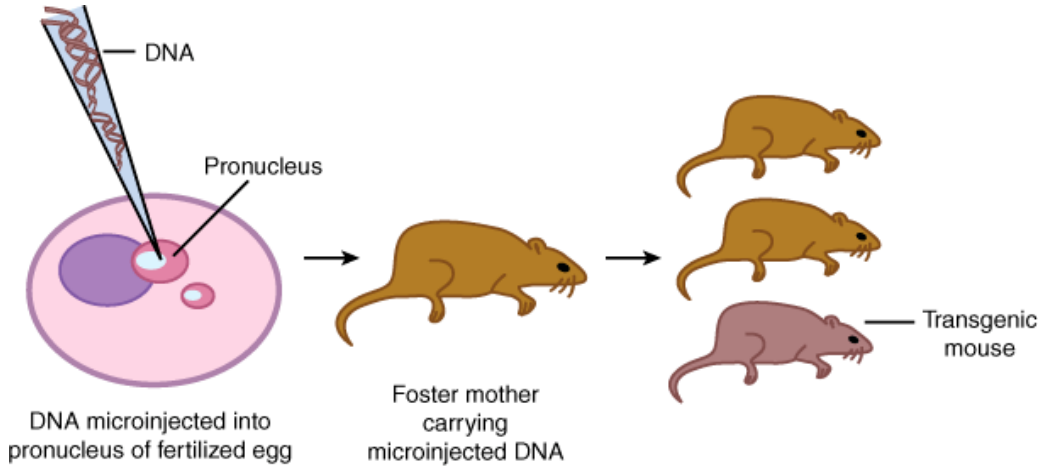
The mouse has become firmly established as the primary experimental model for studying how genes control mammalian development. Genetically altered mice are powerful model systems in which to study the function and regulation of genes.[25] The gene function can be studied by creating mutant mice through homologous recombination (gene knockout). A gene of interest also can be introduced into the mouse (transgenic mouse) to study its effect on development or diseases. As mouse models do not precisely represent human biology, genetic manipulations of human somatic or ES cells provide a great means for the understanding of the molecular networks in human cells. In all cases, the gene to be manipulated must first be cloned. Gene cloning has been made easy by recombinant DNA technology and the availability of human and mouse genomes (see the Human Genome section). The following section briefly describes the technologies and the principles behind

them.

TRANSGENIC MICE

During the past 20 years, DNA cloning and other techniques have allowed the introduction of new genetic material into the mouse germline. As early as 1980, the first genetic material was successfully introduced into the mouse germline by using pronuclear microinjection of DNA (Fig. 15-22). These animals, called *transgenic*, contain foreign DNA within their genomes. In simple terms, a transgenic mouse is created by the microinjection of DNA into the one-celled mouse embryo, allowing the efficient introduction of cloned genes into the developing mouse somatic tissues, as well as into the germline.

Fig. 15-22.



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Transgenic mouse technology. DNA is microinjected into a pronucleus of a fertilized egg, which is then transplanted into a foster mother. The microinjected egg develops offspring mice. Incorporation of the injected DNA into offspring is indicated by the different coat color of offspring mice.

Designs of a Transgene

The transgenic technique has proven to be extremely important for basic investigations of gene regulation, creation of animal models of human disease, and genetic engineering of livestock. The design of a transgene construct is a simple task. Like constructs used in cell transfection, a simple transgene construct consists of a protein-encoding gene and a promoter that precedes it. The most common applications for the use of transgenic mice are similar to those in the cell culture system: (a) to study the functions of proteins encoded by the transgene and (b) to analyze the tissue-specific and developmental-stage–specific activity of a gene promoter. Examples of the first application include overexpression of oncogenes, growth factors, hormones, and other key regulatory genes, as well as genes of viral origins. Overexpression of the transgene normally represents gain-of-function mutations. The tissue distribution or expression of a transgene is determined primarily by *cis*-acting promoter enhancer elements within or in the immediate vicinity of the genes themselves. Thus, controlled expression of the transgene can be made possible by using an inducible or tissue-specific promoter. Furthermore, transgenic mice carrying dominant negative mutations of a regulatory gene also have been generated. For example, a truncated growth factor receptor that can bind to the ligand, but loses its catalytic activity when expressed in mice, can block the growth factor binding to the endogenous protein. In this way, the transgenic mice exhibit a loss of function of phenotype, possibly resembling the knockout of the endogenous gene. The second application of the transgenic expression is to analyze the gene promoter of interest. The gene promoter of interest normally is fused to a reporter gene that encodes β-galactosidase (also called *LacZ*), luciferase, or green fluorescence protein. Chemical staining of LacZ activity or detection of chemiluminescence/fluorescence can easily visualize the expression of the reporter gene. The amount of the reporter gene activity represents the activity of the promoter, and thus, reporter activities are tightly correlated to expression of the gene in which the promoter is used to drive the reporter gene expression.

Production of Transgenic Mice

The success of generating transgenic mice is largely dependent upon the proper quality and concentration of the DNA supplied for

microinjection. For DNA to be microinjected into mouse embryos, it should be linearized by restriction digestion to increase the chance of proper transgene integration. Concentration of DNA should be accurately determined. Mice that develop from injected eggs often are termed *founder* mice.

Genotyping of Transgenic Mice

The screening of founder mice and the transgenic lines derived from the founders is accomplished by determining the integration of the injected gene into the genome. This normally is achieved by performing PCR or Southern blot analysis with a small amount of DNA extracted from the mouse tail. Once a given founder mouse is identified to be transgenic, it will be mated to begin establishing a transgenic line.

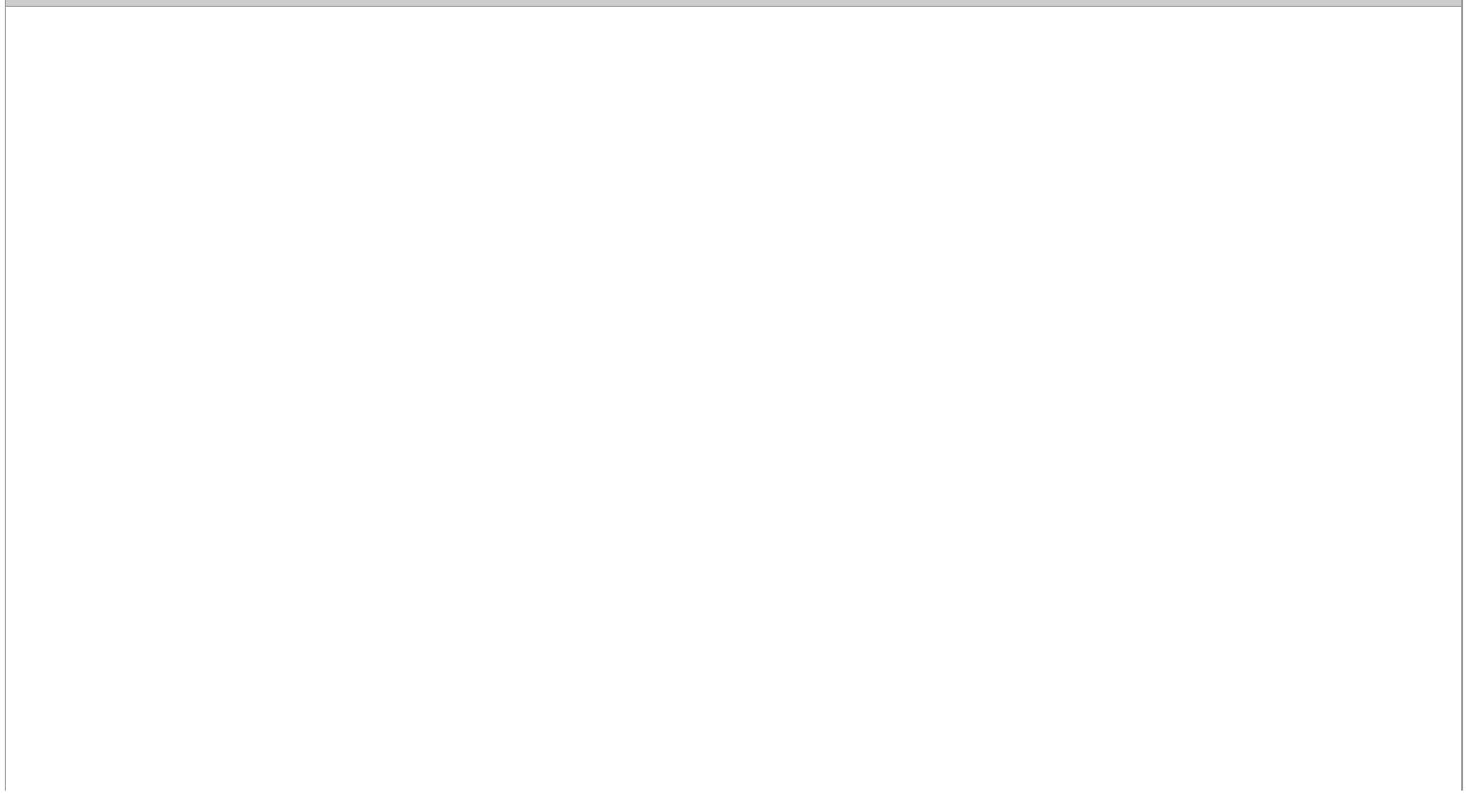
Analysis of Phenotype of Transgenic Mice

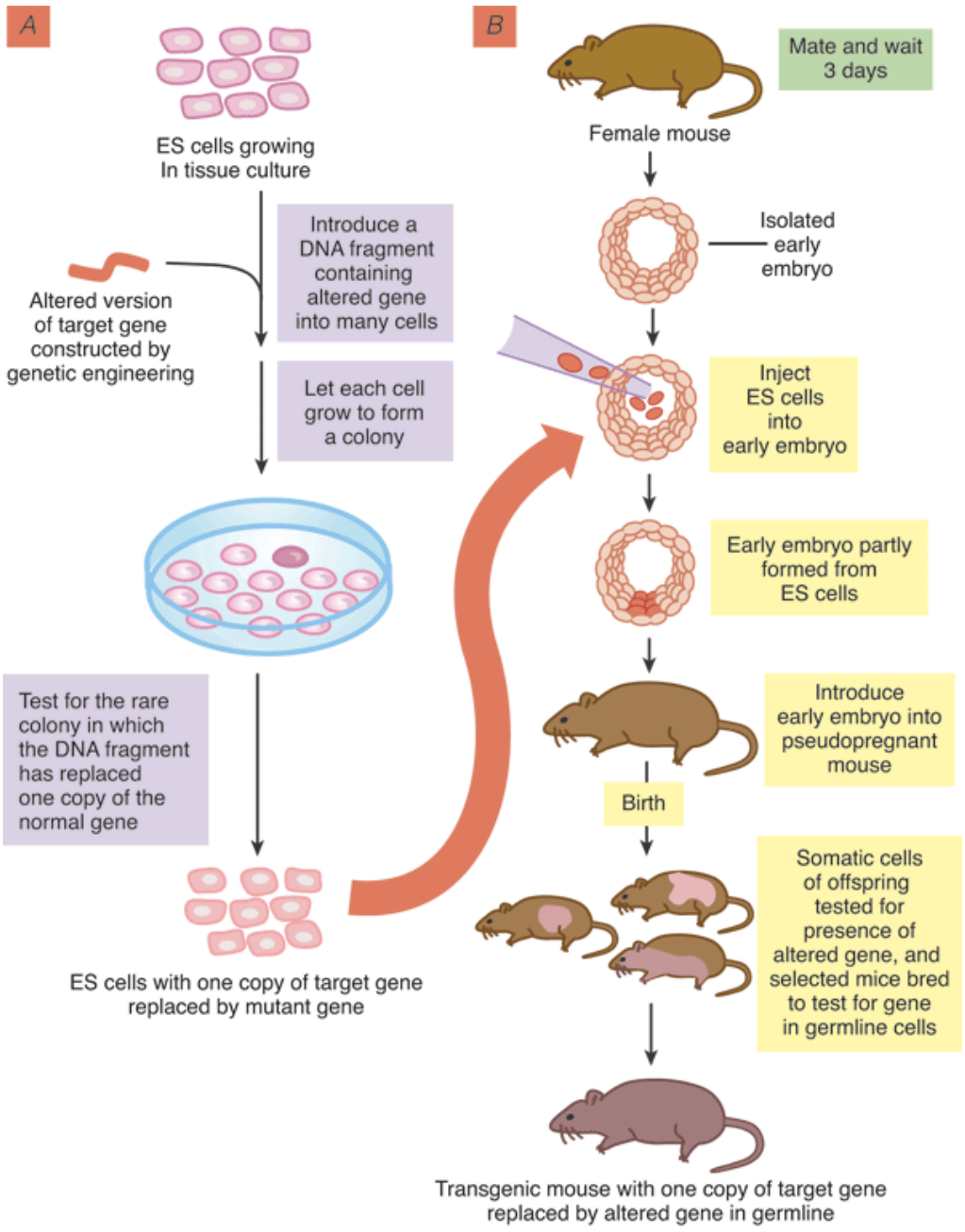
Phenotypes of transgenic mice are dictated by both the expression pattern and biologic functions of the transgene. Depending on the promoter and the transgene, phenotypes can be predictable or unpredictable. Elucidation of the functions of the transgene-encoded protein in vitro often offers some clue to what the protein might do in vivo. When a constitutively active promoter is used to drive the expression of transgenes, mice should express the gene in every tissue; however, this mouse model may not allow the identification and study of the earliest events in disease pathogenesis. Ideally, the use of tissue-specific or inducible promoter allows one to determine if the pathogenic protein leads to a reversible or irreversible disease process. For example, rat insulin promoter can target transgene expression exclusively in the α-cells of pancreatic islets. The phenotype of insulin promoter-mediated transgenic mice is projected to affect the function of human α-cells.

GENE KNOCKOUT IN MICE

The isolation and genetic manipulation of ES cells represents one of the most important milestones for modern genetic technologies. Several unique properties of these ES cells, such as the pluripotency to differentiate into different tissues in an embryo, make them an efficient vehicle for introducing genetic alterations into this species. Thus, this technology provides an important breakthrough, making it possible to genetically manipulate ES cells in a controlled way in the culture dish and then introduce the mutation into the germline (Fig. 15-23). This not only makes mouse genetics a powerful approach for addressing important gene functions but also identifies the mouse as a great system to model human disease.

Fig. 15-23.





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Knockout mouse technology. Summary of the procedures used for making gene replacements in mice. In the first step (**A**), an altered version of the gene is introduced into cultured embryonic stem (ES) cells. Only a few rare ES cells will have their corresponding normal genes replaced by the altered gene through a homologous recombination event. Although the procedure is often laborious, these rare cells can be identified and cultured to produce many descendants, each of which carries an altered gene in place of one of its two normal corresponding genes. In the next step of the procedure (**B**), these altered ES cells are injected into a very early mouse embryo; the cells are incorporated into the growing embryo, and a mouse produced by such an embryo will contain some somatic cells that carry the altered gene. Some of these mice also will contain germline cells that contain the altered gene. When bred with a normal mouse, some of the progeny of these mice will contain the altered gene in all of their cells. If two such mice are in turn bred (not shown), some of the progeny will contain two altered genes (one on each chromosome) in all of their cells. If the original gene alteration completely inactivates the function of the gene, these mice are known as *knockout mice*. When such mice are missing genes that function during development, they often die with specific defects long before they reach adulthood. These defects are carefully analyzed to help decipher the normal function of the missing gene.

(From Alberts et al,[1] with permission.)

Targeting Vector

The basic concept in building a target vector to knock out a gene is to use two segments of homologous sequence to a gene of interest that

flank a part of the gene essential for functions (e.g., the coding region). In the target vector, a positive selectable marker (e.g., the *neo* gene) is placed between the homology arms. Upon the homologous recombination between the arms of the vector and the corresponding genomic regions of the gene of interest in ES cells, the positive selectable marker will replace the essential segment of the target gene, thus creating a null allele. In addition, a negative selectable marker also can be used alone or in combination with the positive selectable marker, but must be placed outside of the homologous arms to enrich for homologous recombination. To create a conditional knockout (i.e., gene knockout in a spatiotemporal fashion), site-specific recombinases such as the popular cre-loxP system are used. If the consensus loxP sequences that are recognized by cre recombinases are properly designed into targeting loci, controlled expression of the recombinase as a transgene can result in the site-specific recombination at the right time and in the right place (i.e., cell type or tissue). This method is markedly useful to prevent developmental compensations and to introduce null mutations in the adult mouse that would otherwise be lethal. Overall, this cre-loxP system allows for spatial and temporal control over transgene expression and takes advantage of inducers with minimal pleiotropic effects.

Introduction of the Targeting Vector into ES Cells

ES cell lines can be obtained from other investigators, commercial sources, or established from blastocyst-stage embryos. To maintain ES cells at their full developmental potential, optimal growth conditions should be provided in culture. If culture conditions are inappropriate or inadequate, ES cells may acquire genetic lesions or alter their gene expression patterns, and consequently decrease their pluripotency. Excellent protocols are available in public domains or in mouse facilities in most institutions.

To alter the genome of ES cells, the targeting vector DNA then is transfected into ES cells. Electroporation is the most widely used and the most efficient transfection method for ES cells. Similar procedures for stable cell transfection are used for selecting ES cells that carry the targeting vector. High-quality, targeting-vector DNA free of contaminating chemicals is first linearized and then electroporated into ES cells. Stable ES cells are selected in the presence of a positive selectable antibiotic drug. After a certain period of time and depending on the type of antibiotics, all sensitive cells die and the resistant cells grow into individual colonies of the appropriate size for subcloning by picking. It is extremely important to minimize the time during which ES cells are in culture between selection and injection into blastocysts. Before injecting the ES cells, DNA is prepared from ES colonies to screen for positive ES cells that exhibit the correct integration or homologous recombination of the targeting vector. Positive ES colonies are then expanded and used for creation of chimeras.

Creation of the Chimera

A chimeric organism is one in which cells originate from more than one embryo. Here, chimeric mice are denoted as those that contain some tissues from the ES cells with an altered genome. When these ES cells give rise to the lineage of the germ layer, the germ cells carrying the altered genome can be passed on to the offspring, thus creating the germline transmission from ES cells. There are two methods for introducing ES cells into preimplantation-stage embryos: injection and aggregation. The injection of embryonic cells directly into the cavity of blastocysts is one of the fundamental methods for generating chimeras, but aggregation chimeras also have become an important alternative for transmitting the ES cell genome into mice. The mixture of recognizable markers (e.g., coat color) that are specific for the donor mouse and ES cells can be used to identify chimeric mice. However, most experimenters probably use existing mouse core facilities already established in some institutions, or contract a commercial vendor for the creation of a chimera.

Genotyping and Phenotyping of Knockout Animals

The next step is to analyze whether germline transmission of targeted mutation occurs in mice. DNA from a small amount of tissue from offspring of the chimera is extracted and subjected to genomic PCR or Southern blot DNA hybridization. Positive mice (i.e., those with properly integrated targeting vector into the genome) will be used for the propagation of more knockout mice for phenotype analysis. When the knockout genes are crucial for early embryogenesis, mice often die in utero, an occurrence called *embryonic lethality*. When this happens, only the phenotype of the homozygous (both alleles ablated) knockout mouse embryos and the phenotype of the heterozygous (only one allele ablated) adult mice can be studied. Because most are interested in the phenotype of adult mice, in particular when using mice as disease models, it is recommended to create the conditional knockout using the cre-loxP system so that the gene of interest can be knocked out at will.

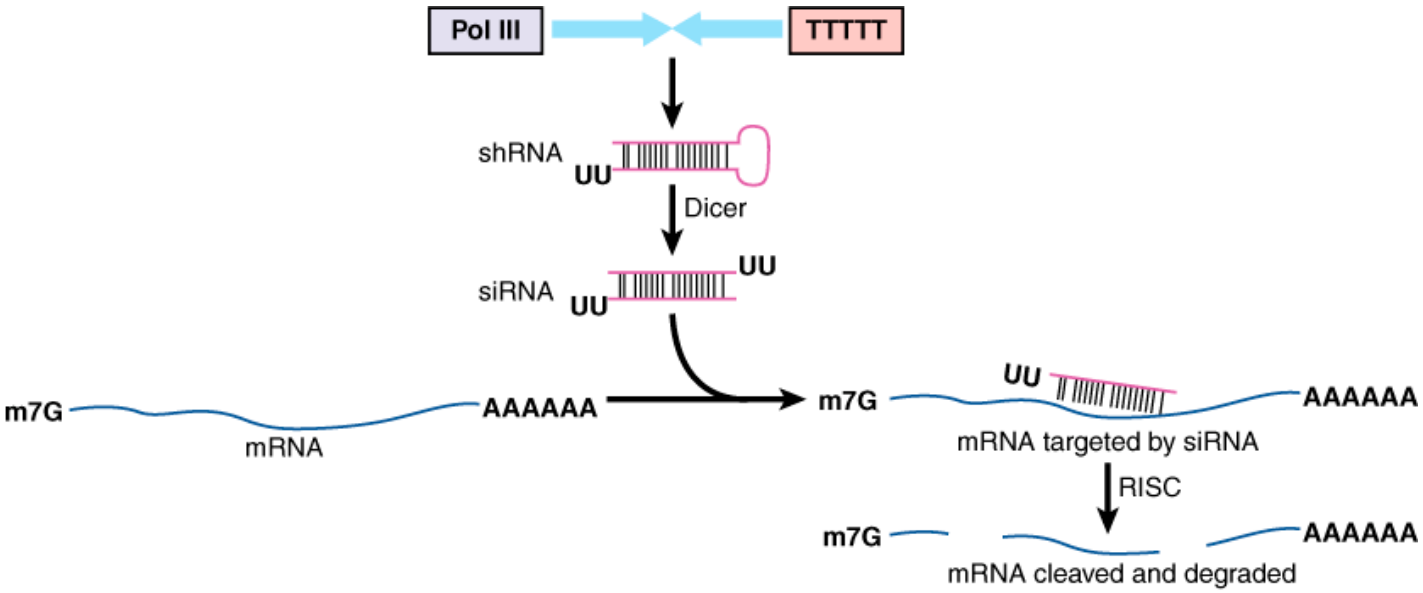
To date, more than 5000 genes have been disrupted by homologous recombination and transmitted through the germline. The phenotypic studies of these mice provide ample information on the functions of these genes in growth and differentiation of organisms, and during development of human diseases.

RNA INTERFERENCE

Although gene ablation in animal models provides an important means to understand the in vivo functions of genes of interest, animal models may not adequately represent human biology. Alternatively, gene targeting can be used to knock out genes in human cells, including human ES cells. A number of recent advances have made gene targeting in somatic cells as easy as in murine ES cells.[25] However, gene targeting (knocking out both alleles) in somatic cells is a time-consuming process.

Development of RNAi technology in the past few years has provided a more promising approach to understanding the biologic functions of human genes in human cells.[26] RNAi is an ancient natural mechanism by which small, double-stranded RNA (dsRNA) acts as a guide for an enzyme complex that destroys complementary RNA and downregulates gene expression in a sequence-specific manner. Although the mechanism by which dsRNA suppresses gene expression is not entirely understood, experimental data provide important insights. In nonmammalian systems such as *Drosophila*, it appears that longer dsRNA is processed into 21–23 nt dsRNA (called *small interfering RNA* or *siRNA*) by an enzyme called *Dicer* containing RNase III motifs. The siRNA apparently then acts as a guide sequence within a multicomponent nuclease complex to target complementary mRNA for degradation. Because long dsRNA induces a potent antiviral response pathway in mammalian cells, short siRNAs are used to perform gene silencing experiments in mammalian cells (Fig. 15-24).

Fig. 15-24.



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RNA inference in mammalian cells. Small interfering RNA (siRNA) can be produced from a polymerase III–driven expression vector. Such a vector first synthesizes a 19–29 nt double-stranded (ds)RNA stem and a loop (labeled as *shRNA* in the figure), and then the RNase complex called *Dicer* processes the hairpin RNA into a small dsRNA (labeled as *siRNA* in the figure). siRNA can be chemically synthesized and directly introduced into the target cell. In the cell, through RNA-induced silencing complex (RISC), siRNA recognizes and degrades target messenger RNAs (mRNAs).

For siRNA studies in mammalian cells, researchers have used two 21-mer RNAs with 19 complementary nucleotides and 3' terminal noncomplementary dimers of thymidine or uridine. The antisense siRNA strand is fully complementary to the mRNA target sequence. Target sequences for an siRNA are identified visually or by software.

The target 19 nucleotides should be compared to an appropriate genome database to eliminate any sequences with significant homology to other genes. Those sequences that appear to be specific to the gene of interest are the potential siRNA target sites. A few of these target sites are selected for siRNA design. The antisense siRNA strand is the reverse complement of the target sequence. The sense strand of the siRNA is the same sequence as the target mRNA sequence. A deoxythymidine dimer is routinely incorporated at the 3' end of the sense strand siRNA, although it is unknown whether this noncomplementary dinucleotide is important for the activity of siRNAs.

There are two ways to introduce siRNA to knock down gene expression in human cells:

1. RNA transfection: siRNA can be made chemically or using an in vitro transcription method. Like DNA oligos, chemically synthesized siRNA oligos can be commercially ordered. However, synthetic siRNA is expensive and several siRNAs may have to be tried before a particular gene is successfully silenced. In vitro transcription provides a more economic approach. Both short and long RNA can be synthesized using bacteriophage RNA polymerase T7, T3, or SP6. In the case of long dsRNAs, RNase such as recombinant Dicers will be used to process the long dsRNA into a mixture of 21–23 nt siRNA. siRNA oligos or mixtures can be transfected into a few characterized cell lines such as HeLa (human cervical carcinoma) and 293T cells (human kidney carcinoma). Transfection of siRNA directly into primary cells may be difficult.

2. DNA transfection: Expression vectors for expressing siRNA have been made using RNA polymerase III promoters such as U6 and H1. These promoters precisely transcribe a hairpin structure of dsRNA, which will be processed into siRNA in the cell (see Fig. 15-24). Therefore, properly-designed DNA oligos corresponding to the desired siRNA will be inserted downstream of the U6 or H1 promoter. There are two advantages of the siRNA expression vectors over siRNA oligos. First, it is easier to transfect DNA into cells. Second, stable populations of cells can be generated that maintain the long-term silencing of target genes. Furthermore, the siRNA expression cassette can be incorporated into a retroviral or adenoviral vector to provide a wide spectrum of applications in gene therapy.

There has been a fast and fruitful development of RNAi tools for in vitro and in vivo use in mammals. These novel approaches, together with future developments, will be crucial to put RNAi technology to use for effective disease therapy or to exert the awesome power of mammalian genetics. Therefore, the applications of RNAi to human health are enormous. siRNA can be applied as a new tool for sequence-specific regulation of gene expression in functional genomics and biomedical studies. With the availability of the human genome sequences, RNAi approaches hold tremendous promise for unleashing the dormant potential of sequenced genomes.

Practical applications of RNAi will possibly result in new therapeutic interventions. In 2002, the concept of using siRNA in battling infectious diseases and carcinogenesis was proven effective. These include notable successes in blocking replication of viruses, such as HIV, hepatitis B virus, and hepatitis C virus, in cultured cells using siRNA targeted at the viral genome or the human gene encoding viral receptors. RNAi has been shown to antagonize the effects of hepatitis C virus in mouse models. In cancers, silencing of oncogenes such as *c-Myc* or *Ras* can slow down the proliferation rate of cancer cells. Finally, siRNA also has potential applications for some dominant genetic disorders.

The twenty-first century, already heralded as the "century of the gene," carries great promise for alleviating suffering from disease and improving human health. On the whole, completion of the human genome blueprint, the promise of gene therapy, and the existence of stem cells has captured the imagination of the public and the biomedical community for good reason. Aside from their potential in curing human diseases, these emerging technologies also have provoked many political, economic, religious, and ethical discussions. As more is discerned about the technologic advances, more attention must also be paid to concerns for their inherent risks and social implications. Surgeons must take the opportunity to collaborate with basic scientists to develop the field of personalized genomic surgery this century.

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a silverchair information system

Note: Large images and tables on this page may necessitate printing in landscape mode.

KEY POINTS

1. The epidermis consists of five layers. The two most superficial layers (the stratum corneum and lucidum) contain nonviable keratinocytes.

2. Collagen III provides tensile strength to the dermis and epidermis.

3. Adult dermis contains a 4:1 ratio of type I:type III collagen.

4. Of the congenital skin disorders, only pseudoxanthoma elasticum and cutis laxia are responsive to surgical rejuvenation.

5. Hemangioma is the most common cutaneous lesion of infancy and a large majority spontaneously involute (resolve) past the first year of patient age.

6. Basal cell carcinoma (BCC) is the most common form of skin cancer and nodular BCC is the most frequent form of this tumor.

7. Breslow thickness is the most important prognostic variable predicting survival in those with cutaneous melanoma.

BACKGROUND

As the largest human organ, the skin is one of the most complex and physiologically underappreciated elements of our bodies. Beneath its uniform appearance, the skin demonstrates profound regional variation due to the highly structured organization of many different cell types and dermal elements. Although primarily valued as a protective barrier allowing interface with our surroundings, the structure and physiology of the skin is complex and fascinating. As an environmental buffer, the skin protects against a vast array of destructive forces: The structural integrity of the epidermis creates a semipermeable barrier to chemical absorption, prevents fluid loss, protects against penetration of solar radiation, rebuffs infectious agents, and dermal durability resists physical forces. In addition, the skin's ability to regulate body heat makes it the body's primary thermoregulatory organ. The relative ease of analyzing skin specimens has made the skin one of the best-studied tissues of the human body. Not only does this fascinating organ form the primary focus of the subspecialties of plastic surgery and dermatology, but it also has driven research in a broad number of fields, including immunology, transplantation, and would healing.

ANATOMY AND PHYSIOLOGY OF THE SKIN

Anatomically, the skin may be divided into three layers: the epidermis, basement membrane, and dermis.[1–3] With very little extracellular matrix (ECM), the epidermis is composed primarily of specialized cells that perform vital functions. Sandwiched between epidermal and dermal structures, the basement membrane anchors these layers together.[1–3] This membrane fulfills many biologic functions, including tissue organization, growth factor reservoir, support of cell monolayers during tissue development, and semipermeable selective barrier. In addition to its role in providing soft-tissue durability, the dermis is

primarily composed of a dense ECM that provides support for a complex network of nerves, vasculature, and adnexal structures.[3,4] The ECM is a collection of fibrous proteins and associated glycoproteins embedded in a hydrated ground substance of glycosaminoglycans and proteoglycans. These distinct molecules are organized into a highly ordered network that is closely associated with the cells that produce them. In addition to providing the architectural framework that imparts mechanical support and viscoelasticity, the ECM can regulate the neighboring cells, including their ability to migrate, proliferate, and survive injury.[2,4,5]

The Epidermis

Composed primarily of keratinocytes, the epidermis is a dynamic, multilayered composite of maturing cells. From internal to external-most layer, the epidermis is composed of the (a) stratum germinatum, (b) stratum spinosum, (c) stratum granulosum, (d) stratum lucidum, and finally, (e) the stratum corneum. Basal cells are a mitotically active, single-cell layer of the least-differentiated keratinocytes at the base of epidermal structure.[2,6] As basal cells multiply, they leave the basal lamina to begin their differentiation and upward migration. In the spinous layer, keratinocytes are linked together by tonofibrils and produce keratin. As these cells drift upward, they lose their mitotic ability. With entry into the granular layer, cells accumulate keratohyalin granules.[1,4,6] In the horny layer, keratinocytes age, lose their intercellular connections, and shed. From basal layer exit to shedding, keratinocyte transit time approximates 40 to 56 days.[2,3]

Melanocytes and other cellular components within the skin deter absorption of harmful radiation. Initially derived from precursor cells of the neural crest, melanocytes extend dendritic processes upward into epidermal tissues from their position beneath the basal cell layer.[5,7] They number approximately one for every 35 keratinocytes, and produce melanin from tyrosine and cysteine. Once the pigment is packaged into melanosomes within the melanocyte cell body, these pigment molecules are transported into the epidermis via dendritic processes.[6,7] As dendritic processes (apocopation) are sheared off, melanin is transferred to keratinocytes via phagocytosis. Despite differences in skin tone, the density of melanocytes is constant among individuals. It is the rate of melanin production, transfer to keratinocytes, and melanosome degradation that determine the degree of skin pigmentation.[5,6] Whereas people of North European ancestry have melanocytes that release relatively low amounts of melanin, those of African descent demonstrate the same overall quantity of melanocytes, but with much higher melanin production. Genetically activated factors as well as ultraviolet (UV) radiation, hormones such as estrogen, adrenocorticotropic hormone, and melanocyte-stimulating hormone, increase melanin production.[6,7]

Cutaneous melanocytes play a critical role in neutralizing the sun's harmful rays. UV-induced damage affects the function of tumor suppressor genes, directly causes cell death, and facilitates neoplastic transformation.[2–5] Although a majority of solar radiation that reaches the Earth is UVA (315 to 400 nm), the majority of skin damage is caused by UVB (240 to 315 nm). UVB is the major factor in sunburn injury, and is a known risk factor in the development of melanoma. Although UVB causes considerable DNA damage in the skin, UVA has only recently has been shown to damage DNA, proteins, and lipids.[8–11] In addition, UV-related damage can either be potentiated by or contribute to effects of other harmful agents such as ionizing radiation, viruses, or chemical carcinogens.[3–6]

As a durable barrier against external forces, the skin relies on a complex network of filaments to maintain cellular integrity. Intermediate filaments, called *keratins*, are found within the spindle layer and provide flexible scaffolding that enables the keratinocyte to resist external stress.[4,6] Various keratins are expressed according to keratinocyte maturation phase, and mitotically active keratinocytes mainly express keratins 5 and 14.[6,7] Point mutations affecting these genes may result in blistering diseases, such as epidermolysis bullosa, associated with spontaneous release of dermal-epidermal attachments.[4,7]

In addition to its role in resisting radiation, toxin absorption, and deforming forces, the skin is a critically immunoreactive barrier.[4,6] Following migration into epidermal structure from the bone marrow, Langerhans' cells act as the skin's macrophages. This specialized cell type expresses class II major histocompatibility antigens, and has antigen-presenting capabilities.[4,7] In addition to initiating rejection of foreign bodies, Langerhans' cells play a crucial role in immunosurveillance against viral infections and neoplasms of the skin.[2,7]

The Dermis

The dermis is mostly comprised of structural proteins, and to a smaller degree, cellular components.[2,4–6] Collagen, the main functional protein within the dermis, constitutes 70% of dermal dry weight and is responsible for its remarkable tensile strength.[4,5] Tropocollagen, a collagen precursor, consists of three polypeptide chains (hydroxyproline, hydroxylysine, and glycine) wrapped in a helix.[2,6] These long molecules are then cross-linked to one another to form collagen fibers. Of the seven structurally distinct collagens, the skin primarily contains type I. Fetal dermis contains mostly type III (reticulin fibers) collagen, but this only remains in the basement membrane zone and perivascular regions during postnatal development.[6,7] Elastic fibers are highly branched proteins capable of stretching to twice their resting length. In addition to resisting stretch forces, these fibers allow a return to baseline form after the skin responds to deforming stress.[4,6] Ground substance, consisting of various polysaccharide–polypeptide (glycosaminoglycans) complexes, is an amorphous material that occupies the remaining spaces. These glycosaminoglycans, secreted by fibroblasts, can hold up to 1000 times their own volume in water and constitute most of dermal volume.[6,7]

The blood supply to the dermis is based on an intricate network of blood vessels which provide vascular inflow to superficial structures, as well as regulate body temperature.[3–7] This is achieved with the help of vertical vascular channels that interconnect two horizontal plexuses, one within the papillary dermis, and the other at the dermal–subcutaneous junction.[4,6] Glomus bodies are tortuous arteriovenous shunts that allow a substantial increase in superficial blood flow when stimulated to open.[3,5]

Cutaneous sensation is achieved via activation of a complicated plexus of dermal autonomic fibers synapsed to sweat glands, erector pili, and vasculature control points.[6,7] These fibers also connect to corpuscular receptors that relay information from the skin back to the central nervous system. Meissner's, Ruffini's, and Pacini's corpuscles transmit information on local pressure, vibration, and touch.[4,6] In addition, "unspecialized" free nerve endings report temperature, touch, pain, and itch sensations.[4,6]

Cutaneous Adnexal Structures

The skin has three main adnexal structures: eccrine glands, pilosebaceous units, and apocrine glands.[4–7] The sweat-producing eccrine glands are located over the entire body but are concentrated on the palms, soles, axillae, and forehead.[3,4] Although pheromone-producing apocrine glands play a distinct role in lower mammalian life, these structures have not been shown to demonstrate significant activity in human populations.[5,7] However, large populations of apocrine glands are primarily found in the human axillae and anogenital region. It is these structures that predispose both regions to suppurative hydroadenitis.[4,6] Hair follicles are mitotically active germinal centers that produce hair, a cylinder of tightly packed cornified epithelial cells. Together with oil-secreting sebaceous glands, these two structures form a pilosebaceous unit.[3,4,7] In addition to the production of hair, hair follicles perform several vital functions. The hair follicle contains a reservoir of pluripotential stem cells critical in epidermal reproductivity.[2,7] These cells are capable of near limitless expansion to replace lost or injured cells, as well as restore epidermal continuity after wounding. For example, in skin graft harvest, residual hair follicles supply

new keratinocytes to regenerate the epidermis and restore skin integrity.[3,5]

INJURIES TO THE SKIN AND SUBCUTANEOUS TISSUE

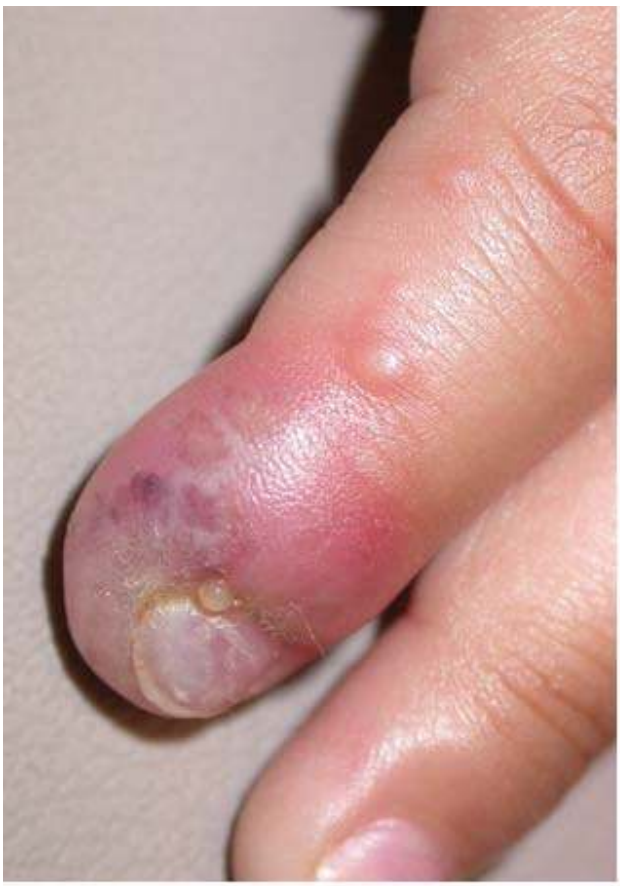
Each day, the skin and subcutaneous tissue face an endless supply of stimuli that threaten to break tissue integrity. Such lapses in continuity provide entry of microorganisms, allow injury to deeper tissue layers, and prompt local tissue inflammation. In addition to penetrating trauma, the environment offers a host of potentially injurious elements, such as caustic substances, extreme temperatures, prolonged or excessive pressure, and radiation.

Traumatic Injuries

Traumatic wounds may be caused by penetrating, blunt, and shear force, bite, and degloving injuries. Although clean lacerations may be closed primarily after irrigation, débridement, and careful evaluation, contaminated or infected wounds should be allowed to heal by secondary intention or delayed primary closure.[8–10] Débridement of nonviable tissue and aggressive irrigation of the wound are principles guiding the management of more complex wounds. Tangential abrasions should be approached similarly to second-degree burns, and degloving injuries considered third-degree or full-thickness burns.[8–10] Degloved skin may be partially salvaged by placing it back on the wound like a skin graft. In addition, replacement of clean, avulsed tissue can effectively provide wound coverage as a biologic dressing.[8–10] As the injured tissues declare their viability throughout the post-injury period, necrotic debris is removed. Areas of uncovered wound bed undergo delayed primary closure, are allowed to granulate in, or undergo definitive reconstruction.[8–10]

Bite wounds account for 4.5 million injuries each year, and prompt 2% of all emergency rooms visits.[8–10] These small puncture wounds may initially seem innocuous, but the impregnation of oral bacteria into deep, contained tissue layers can lead to significant morbidity if unrecognized (Fig. 16-1). The most common infectious organisms found with human bites are *Viridans streptococci*, *Staphylococcus aureus*, *Eikenella corrodens*, *Haemophilus influenzae*, and beta-lactamase-producing bacteria.[8–10] Dog bites account for the most frequent animal-related wound. Because the canine jaw can exert over 450 pounds of pressure per square inch,[9,10] dog bites often add a crushing element in addition to penetrating injury as well as an avulsion element. Although the dog bite injury may contaminate tissues with both aerobic and anaerobic organisms, the most commonly cultured bacteria include *Pasteurella multocida*, *Staphylococcus* species, alpha-hemolytic streptococci, *E. corrodens*, *Actinomyces*, and *Fusobacterium*.[8–10] The bite wound, whether from human or animal, is a contaminated wound and should not be closed primarily. Selected facial wounds may be closed primarily after very thorough cleansing and initiation of antibiotic therapy. Although there remains a potential risk of serious infection, this risk may be low enough on the face to weigh in favor of the improved long-term wound appearance after primary closure. The great majority of bite wounds should be approached via drainage, copious irrigation, débridement of necrotic material, antibiotic therapy, extremity immobilization, and elevation.[8–10]

Fig. 16-1.



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Digital infection following puncture or bite wounds often contain a variety of bacteria, and rapid spread of infection is possible in the absence of antibiotic therapy.

Exposure to Caustic Substances

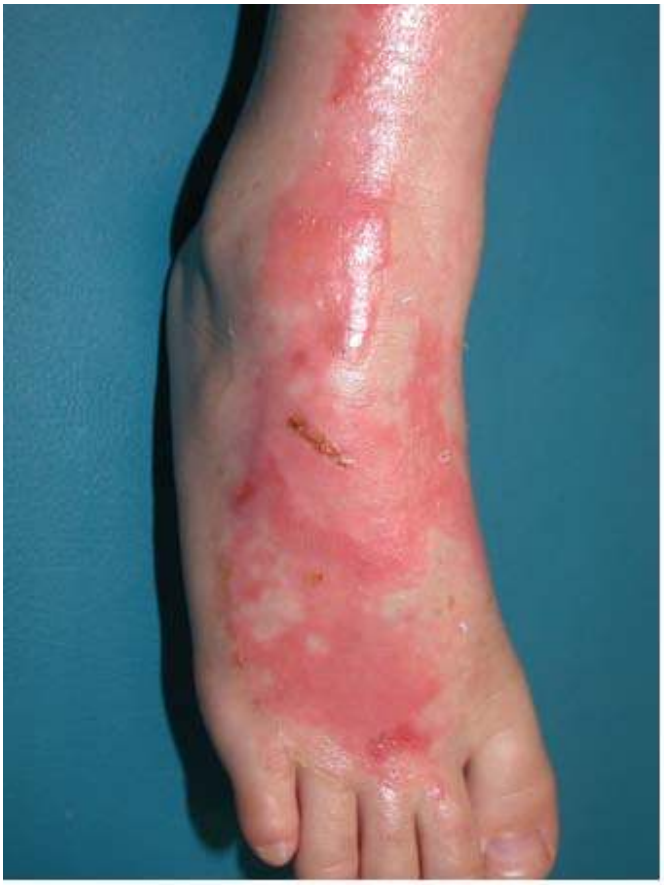
Injuries secondary to caustic substance exposure may be categorized as resulting from either acidic or alkali solutions. The effect of acid exposure on the skin is determined by the concentration, duration of contact, amount, and penetrability.[11–13] Deep tissue *coagulative* injury may result, damaging nerves, blood vessels, tendons, and bone.[12–15] The initial treatment should include copious skin irrigation for at least 30 minutes with either saline or water.[11–15] This dilutes active acid solution and helps return the skin to normal pH. Injuries associated with hydrofluoric acid present an additional treatment challenge. Fluoride ions continue to injure underlying tissue until they are neutralized with calcium, and absorb the body's calcium supply, which may prompt cardiac arrythmia.[12,14,15] Topical quaternary ammonium compounds are widely used, and topical calcium carbonate gel also effectively detoxifies fluoride ions.[14,15]

Alkaline agents often used as household cleaning agents are responsible for more than 15,000 skin burns in the United States annually.[12,13] After penetrating the skin, alkaline substances cause fat saponification that facilitates tissue penetration and increases tissue damage. In addition, the *liquefactive* injury produced by alkali burns provides a longer, more sustained period of injury.[12,13] Immediate irrigation of the affected area with continuous water flow should be maintained for at least 2 hours, or until symptomatic relief is achieved.

Intravenous fluid (IVF) extravasation—leakage of injectable fluids into interstitial space—is considered a chemical burn (Fig. 16-2). In contrast to many cutaneous injuries, this type of insult occurs from underneath the skin surface and is actually a

deep injury. Extravasation produces injury via chemical toxicity, osmotic toxicity, or from pressure effects in a closed environment.[12,13] This displacement may be the result of IV catheter movement or increased vascular permeability. The most common substances associated with these injuries are cationic solutions (e.g., potassium ion, calcium ion, bicarbonate), osmotically active chemicals (e.g., total parenteral nutrition or hypertonic dextrose solutions), and antibiotics or cytotoxic drugs.[12,13] The dorsum of the hand is the most common site of extravasation in the adult, which may result in extensor tendon exposure.

Fig. 16-2.



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Infiltration of IV fluid may produce significant soft-tissue injury. However, a great majority of these wounds respond well to conservative management, including frequent dressing change and continued wound care.

Patients undergoing chemotherapy have a 4.7% risk for developing extravasation, and children present an incidence as high as 58%.[16,17] Newborn babies are at particular risk due to the fragility and small caliber of their veins, their poor ability to verbalize pain, and the frequent use of pressurized IVF pumps used in their care. The most common IVF extravasations causing necrosis in the infant are high-concentration dextrose solutions, calcium, bicarbonate, and parenteral nutrition.[16,17] In the adult population, commonly extravasated drugs are chemotherapeutic agents, such as doxorubicin (Adriamycin) and paclitaxel.[18] The direct toxic effects of doxorubicin causes cellular death that is perpetuated by release of doxorubicin-DNA complexes from dead cells. This cellular death prevents release of cytokines and growth factors, which may ultimately result in wound healing failure.[18] Following extravasation, edema, erythema, and induration usually are present. Injury to underlying nerves, muscles, tendons, and blood vessels must be taken into account. Although a majority of such injuries are

successfully managed through a conservative approach, many treatment options are available.[16–18] In the severe infusion injury, vigorous liposuction with a small cannula may be used to introduce saline flush into the injured area. The flush is then allowed to egress via the small liposuction wounds.[16–18] Although patients more than 24 hours after extravasation injury have shown no benefit from flush-out, this technique has proved useful in the acute setting. Surgery should be limited to patients with necrotic tissue, pain, or damage of underlying structures.[16–18]

Hyper- and Hypothermic Injury

Skin exposed to temperature extremes is at significant risk of hypo- or hyperthermic injury. Depending upon the temperature, period, and method of exposure, hyperthermic burns may cause varying degrees of tissue injury affecting the skin at different levels of depth.[19] The central area of injury, the zone of coagulation, is exposed to the most direct heat transfer and typically becomes necrotic.[20,21] Surrounding the zone of coagulation is the zone of stasis, which has marginal tissue perfusion and questionable viability. The outermost area, the zone of hyperemia, is most similar to uninjured tissue and demonstrates increased blood flow due to the body's response to injury.[20,21] A more detailed discussion of burn wounds may be found in Chap. 8. Hypothermic injury (frostbite) results in the acute freezing of tissues and is the product of two factors: (a) duration of exposure, and (b) the temperature gradient at the skin surface.[22,23] Severe hypothermia primarily exerts its damaging effect by causing direct cellular injury to blood vessel walls and microvascular thrombosis. In addition, the skin's tensile strength decreases by 20% in a cold environment [12°C, (53.6°F)].[22,23] The treatment protocol for frostbite includes rapid rewarming, close observation, elevation and splinting, daily hydrotherapy, and serial débridements.[22,23]

Pressure Injury

Prolonged, excessive pressure often results in pressure ulcer formation. As pressure is applied to overlying tissues, cutaneous vascular flow is decreased, rendering local tissues functionally ischemic.[23–25] As little as 1 hour of 60 mmHg pressure produces histologically identifiable venous thrombosis, muscle degeneration, and tissue necrosis.[23–25] Although normal arteriole, capillary, and venule pressures are 32, 20, and 12 mmHg, respectively, sitting can produce pressures as high 300 mmHg at the ischial tuberosities.[23–25] Healthy individuals regularly shift their body weight, even while asleep. However, sacral pressure can build to 150 mmHg when lying on a standard hospital mattress.[24,25] Patients unable to sense pain or shift their body weight, such as paraplegics or bedridden individuals, may develop prolonged elevated tissue pressures and local necrosis. Because muscle tissue is more sensitive to ischemia than skin, necrosis usually extends to a deeper area than that apparent on superficial inspection.[24,25] The elements of pressure sore treatment include relief of pressure, wound care, and systemic enhancement, such as optimization of nutrition. Air flotation mattresses and gel seat cushions redistribute pressure, decrease the incidence of pressure ulcers, and are cost-effective in the care of patients at high risk.[24,25] In addition, many institutions provide nutritional support services to facilitate proper dietary intake. Surgical management should include débridement of all necrotic tissue followed by thorough irrigation. Shallow ulcers may be allowed to close by secondary intention, but deeper wounds with involvement of the underlying bone require surgical débridement and coverage.[24,25]

Radiation Exposure

Radiation injuries are frequently produced by a wide range of environmental elements, such as solar (UV) exposure, iatrogenic management, and industrial/occupational applications.[26,27] Solar or UV radiation is the most common form of radiation exposure. The UV spectrum is divided into UVA (400 to 315 nm), UVB (315 to 290 nm), and UVC (290 to 200

nm).[27–29] With regard to skin damage and development of skin cancers, significant wavelengths are in the UV spectrum. The ozone layer absorbs UVC wavelengths below 290 nm, allowing only UVA and UVB to reach the earth.[50,52] UVB is responsible for the acute sunburns and for the chronic skin damage leading to malignant degeneration, although it makes up less than 5% of the solar UV radiation that hits the earth.[27–29]

Ionizing radiation effectively blocks mitosis in rapidly dividing cell types,[26,28,29] and has become a mainstay in the treatment of various malignancies. The extent of cellular damage is dependent on radiation dose, exposure period, and the cell type being treated.[27–29] Acute radiation changes include erythema and basal epithelial cellular death in the area of direct application. With cellular repair, permanent hyperpigmentation is observed in healing areas. Four to 6 months following radiation application, chronic radiation changes are characterized by a loss of capillaries via thrombosis and fibrinoid necrosis of vessel walls.[27,29] Progressive fibrosis and hypovascularity may eventually lead to ulceration when poor vascular inflow results in poor tissue perfusion that progresses as the skin ages.[27–29]

INFECTIONS OF THE SKIN AND SUBCUTANEOUS TISSUE

Heralded by erythema, warmth, tenderness, and edema, cellulitis is a superficial, spreading infection of the skin and subcutaneous tissue. The most common organisms associated with cellulitis are group A streptococci and *S. aureus*.[30] Unless associated with significant patient morbidities, uncomplicated cellulitis usually can be managed with oral antibiotics on an outpatient basis.

Folliculitis, Furuncles, and Carbuncles

Folliculitis is an infection of the hair follicle. The causative organism is usually *Staphylococcus*, but gram-negative organisms may cause follicular inflammation as well. A furuncle (boil) begins as folliculitis, but may eventually progress to form a fluctuant nodule.[30,31] Whereas folliculitis usually resolves with adequate hygiene, soaking the furuncle in warm water hastens liquefaction and hastens spontaneous rupture. More involved, deep-seated infections that result in multiple draining cutaneous sinuses are called carbuncles. Along with furuncles, these lesions often require incision and drainage before healing can be initiated.[30,31]

Necrotizing Soft-Tissue Infections

Although many soft-tissue infections remain localized, some result in rapid, necrotizing spread and septic shock. The most common sites are the external genitalia, perineum, or abdominal wall (*Fournier gangrene*).[30–32] Currently, classification of these infections is based on (a) the tissue plane affected and extent of invasion, (b) the anatomic site, and (c) the causative pathogen(s).[30–32] Deep soft-tissue infections are classified as either necrotizing fasciitis or necrotizing myositis. Necrotizing fasciitis represents a rapid, extensive infection of the fascia deep to the adipose tissue. Necrotizing myositis primarily involves the muscles but typically spreads to adjacent soft tissues.[30–32] The most common organisms isolated from patients presenting with necrotizing soft-tissue infections include the gram-positive organisms: group A streptococci, enterococci, coagulase-negative staphylococci, *S. aureus*, *S. epidermidis*, and *Clostridium* species.[30–32] Gram-negative species frequently associated with necrotizing infections include *Escherichia coli*, *Enterobacter*, *Pseudomonas* species, *Proteus* species, *Serratia* species, and bacteroides.[30–32] Polymicrobial infections tend to be more common than single organism disease in these cases.[31,32]

Clinical risk factors for necrotizing soft-tissue infection include diabetes mellitus, malnutrition, obesity, chronic alcoholism, peripheral vascular disease, chronic lymphocytic leukemia, steroid use, renal failure, cirrhosis, and autoimmune deficiency

syndrome.[30–32] Appropriate management starts with prompt recognition, broad-spectrum IV antibiotics, aggressive surgical débridement, and intensive care unit support.[30–32] Débridement must be extensive, including all skin, subcutaneous tissue, and muscle, until there is no further evidence of infected tissue. Initial resection is followed by frequent returns to the operating room for additional débridement as required.[31,32] In addition, aggressive fluid replacement is typically needed to offset acute renal failure from ongoing sepsis.[31,32]

Hidradenitis Suppurativa

Hidradenitis suppurativa is a defect of the terminal follicular epithelium.[33,34] Because the follicular defect results in apocrine gland blockage, obstructed infection leads to abscess formation throughout affected axillary, inguinal, and perianal regions. Following spontaneous rupture of these localized collections, foul-smelling sinuses form and repeated infections create a wide area of inflamed, painful tissue.[33,34] Treatment of acute infections includes application of warm compresses, antibiotics, and open drainage. In cases of chronic hidradenitis, wide excision is required and closure may be achieved via skin graft or local flap placement.[33,34]

Actinomycosis

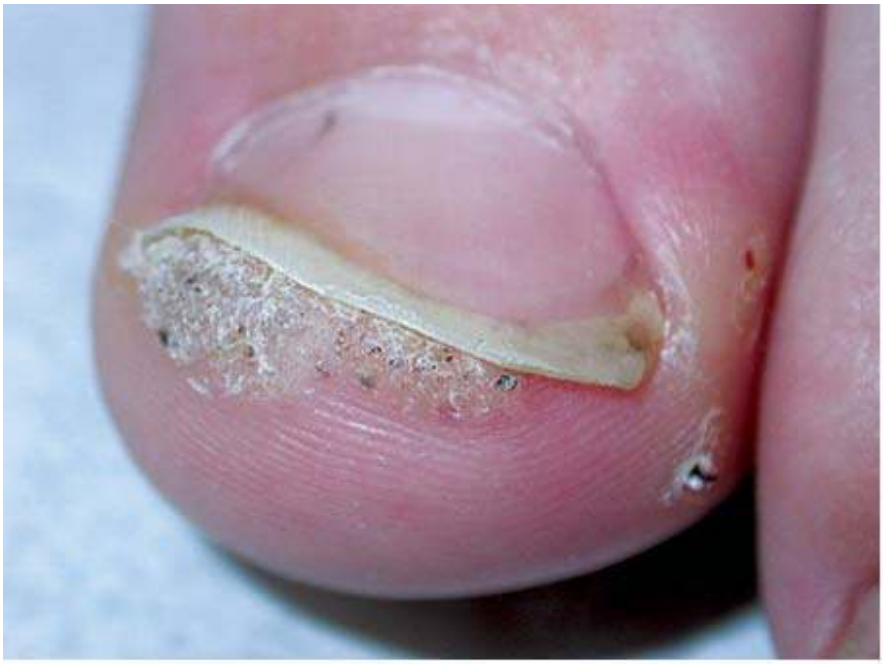
Actinomycosis is a granulomatous suppurative bacterial disease caused by *Actinomyces*. In addition to *Nocardia*, *Actinomadura*, and *Streptomyces*, *Actinomyces* infections may produce deep cutaneous infections that present as nodules and spread to form draining tracts within surrounding soft tissue.[35,36] Forty to 60% of the actinomycotic infections occur within the face or head.[35,36] Actinomycotic infection usually results following tooth extraction, odontogenic infection, or facial trauma.[35,36] Accurate diagnosis depends on careful histologic analysis, and the presence of sulfur granules within purulent specimen is pathognomonic.[35] Penicillin and sulfonamides are typically effective against these infections. However, areas of deep-seated infection, abscess, or chronic scarring may require surgical therapy.[35,36]

VIRAL INFECTIONS OF THE SKIN AND SUBCUTANEOUS TISSUE

Human Papillomavirus

Warts are epidermal growths resulting from human papillomavirus (HPV) infection. Different morphologic types have a tendency to occur at different areas of the body. The common wart (verruca vulgaris) is found on the fingers and toes and is rough and bulbous (Fig. 16-3). Plantar warts (verruca plantaris) occur on the soles and palms, and may resemble a common callus. Flat warts (verruca plana) are slightly raised and flat. This particular subtype tends to appear on the face, legs, and hands.[37–39] Venereal warts (condylomata acuminata) grow in the moist areas around the vulva, anus, and scrotum. Histologic examination demonstrates hyperkeratosis (hypertrophy of the horny layer), acanthosis (hypertrophy of the spinous layer), and papillomatosis.[37–39] A multitude of various therapies have been created to eradicate the papillomatous growth. Warts may be removed via application of chemicals, such as formalin, podophyllum, and phenol-nitric acid.[37–39] Curettage with electrodesiccation also can be used for scattered lesions. Treatment of extensive areas of skin requires surgical excision under general anesthesia.[37–39] Because of the infectious etiology, recurrences are common, and repeated excisions are often necessary. Some warts (especially HPV types 5, 8, and 10) are associated with squamous cell cancers, therefore lesions that grow rapidly, atypically, or ulcerate should be biopsied.[38,39]

Fig. 16-3.



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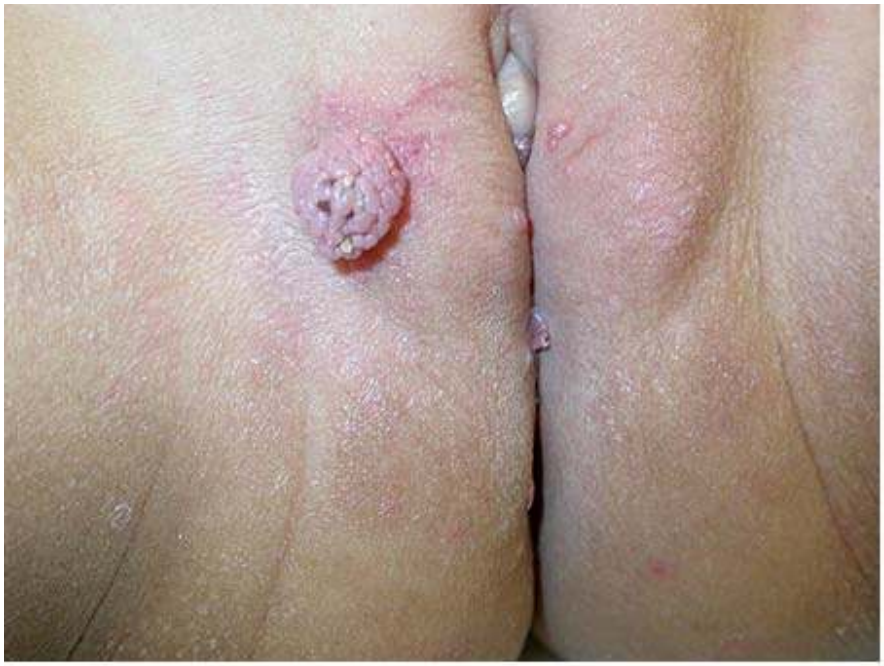
The common wart, caused by cutaneous infection with human papillomavirus, may affect all areas covered by epidermal tissues.

Condylomata acuminata is one of the most common sexually transmitted diseases, and largely results from HPV types 6 and 11 (Fig. 16-4).[37–39] Extensive growths, facilitated by concomitant HIV infection, are often multiple and can grow large in size (Buschke-Löwenstein tumor). In addition to local destruction or excision, adjuvant therapy with interferon, isotretinoin, or autologous tumor vaccine decreases recurrence rates.[38,39] Immune response modifiers, such as imiquimod, may also optimize long-term eradication of HPV-induced anogenital lesions.[37–39] Because larger lesions have a significant risk of malignant transformation, close observation of lesion return or atypical presentation should be advised.

Fig. 16-4.



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Human papillomavirus affecting digital and genitourinary sites often proves most problematic for the patient.

Human Immunodeficiency Virus

Patients with HIV commonly display a variety of skin manifestations. As a result of intrinsic wound-healing deficiencies and much lower resilience, these patients frequently develop chronic wounds.[40–42] In addition, the risk of postoperative soft-tissue complications directly increases with disease progression. The cause for delayed wound healing is unknown but is thought to be secondary to: (a) decreasing T-cell $CD4^+$ count, (b) opportunistic infection, (c) low serum albumin, and (d) poor nutrition.40–42 Overall, these effects are thought to result in poor collagen cross-linking and deposition producing a profound compromise in wound healing.[40–42]

INFLAMMATORY DISEASES OF THE SKIN AND SUBCUTANEOUS SOFT TISSUE

Pyoderma Gangrenosum

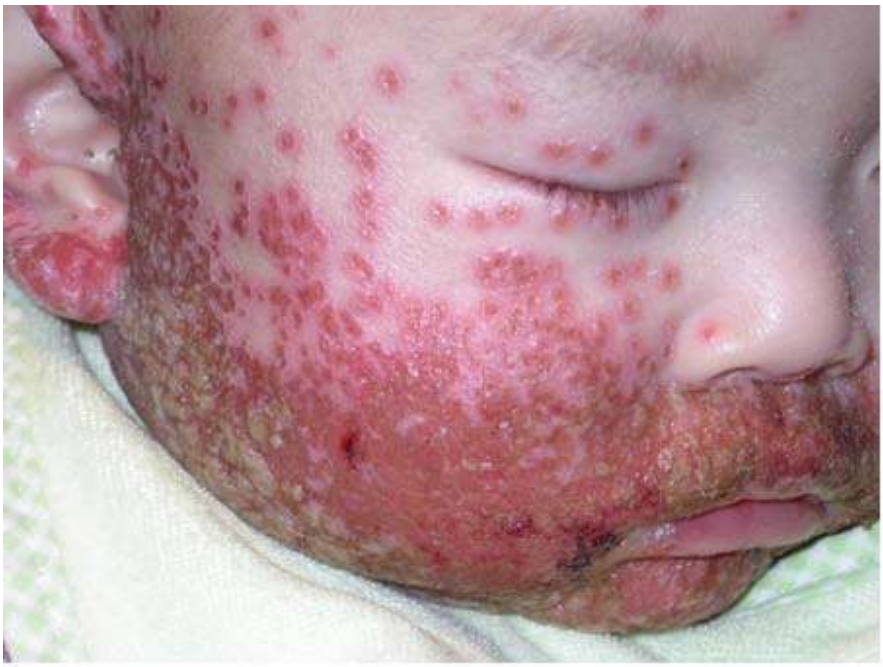
Pyoderma gangrenosum is a relatively uncommon destructive cutaneous lesion. Clinically, a rapidly enlarging, necrotic lesion with undermined border and surrounding erythema characterize this disease.[43–45] Linked to underlying systemic disease in 50% of cases, these lesions are commonly associated with inflammatory bowel disease, rheumatoid arthritis, hematologic malignancy, and monoclonal immunoglobulin A gammapathy.[43–45] Recognition of the underlying disease is of paramount importance. Management of pyoderma gangrenosum ulcerations without correction of underlying systemic disorders is fraught with complication. A majority of patients receive systemic steroids or cyclosporine.[43–45] Although medical management alone may slowly result in wound healing, many physicians advocate chemotherapy with aggressive wound care and skin graft coverage.[43–45]

Staphylococcal Scalded Skin Syndrome and Toxic Epidermal Necrolysis

Staphylococcal scalded skin syndrome (SSSS) and toxic epidermal necrolysis (TEN) create a similar clinical picture including

skin erythema, bullae formation, and wide areas of tissue loss (Fig. 16-5).[46,47] SSSS is caused by an exotoxin produced during staphylococcal infection of the nasopharynx or middle ear.[46,47] TEN is an immune response to certain drugs such as sulfonamides, phenytoin, barbiturates, and tetracycline.[46,47] Diagnosis is made via skin biopsy. Histologic analysis of SSSS reveals a cleavage plane in the granular layer of the epidermis.[46,47] In contrast, TEN results in structural defects at the dermoepidermal junction and is similar to a second-degree burn.[46,47] Treatment involves fluid and electrolyte replacement, as well as wound care similar to burn therapy. Whereas those with more than 30% of total body surface area involvement are classified as TEN, patients with less than 10% of epidermal detachment are categorized as Stevens-Johnson syndrome.[46,47] In Stevens-Johnson syndrome, respiratory and alimentary tract epithelial sloughing may result in intestinal malabsorption and pulmonary failure. Patients with significant soft-tissue loss should be treated in burn units with specially trained staff and critical equipment.[46,47] Although corticosteroid therapy has not been efficacious, temporary coverage via cadaveric, porcine skin, or semisynthetic biologic dressings (Biobrane) allows the underlying epidermis to regenerate spontaneously.[46,47]

Fig. 16-5.



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Staphylococcal scalded skin syndrome is associated with retained foreign objects colonized with toxin-secreting staphylococcus strains.

BENIGN TUMORS OF THE SKIN AND SUBCUTANEOUS TISSUE

Cysts (Epidermal, Dermoid, Trichilemmal)

Cutaneous cysts are categorized as either epidermal, dermoid, or trichilemmal.[48,49] Although surgeons often refer to cutaneous cysts as sebaceous cysts because they appear to contain sebum, this is a misnomer and the substance is actually keratin.[48,49] Epidermal cysts are the most common type of cutaneous cyst, and may present as a single, firm nodule anywhere on the body. Dermoid cysts are congenital lesions that result when epithelium is trapped during fetal midline

closure.[48,49] Although the eyebrow is the most frequent site of presentation, dermoid cysts are common anywhere from the nasal tip to the forehead.[48,49] Trichilemmal (pilar) cysts, the second most common cutaneous cyst, occur more often on the scalp of females.[48,49] When ruptured, these cysts have an intense, characteristic odor.

On clinical examination, it is difficult to distinguish one type of cyst from another: Each cyst presents as a subcutaneous, thin-walled nodule containing a white, creamy material.[48,49] Histologic examination reveals several key features. Cyst walls consist of an epidermal layer oriented with the basal layer superficial, and the more mature layers deep (i.e., with the epidermis growing into the center of the cyst).[48,49] The desquamated cells (keratin) collect in the center to form the cyst. Epidermal cysts have a mature epidermis complete with granular layer.[48,49] Dermoid cysts demonstrate squamous epithelium, eccrine glands, and pilosebaceous units. In addition, these particular cysts may develop bone, tooth, or nerve tissue on occasion.[48,49] Trichilemmal cyst walls do not contain a granular layer; however, these cysts contain a distinctive outer layer resembling the root sheath of a hair follicle (trichilemmoma).[48–50] Each of these cysts typically remain unnoticed and asymptomatic until they rupture, cause local inflammation, or become infected. Once infected, these cysts behave similar to abscesses, and incision and drainage is recommended. After resolution of inflammation, the cyst wall must be removed in its entirety or the cyst will recur.[48–50]

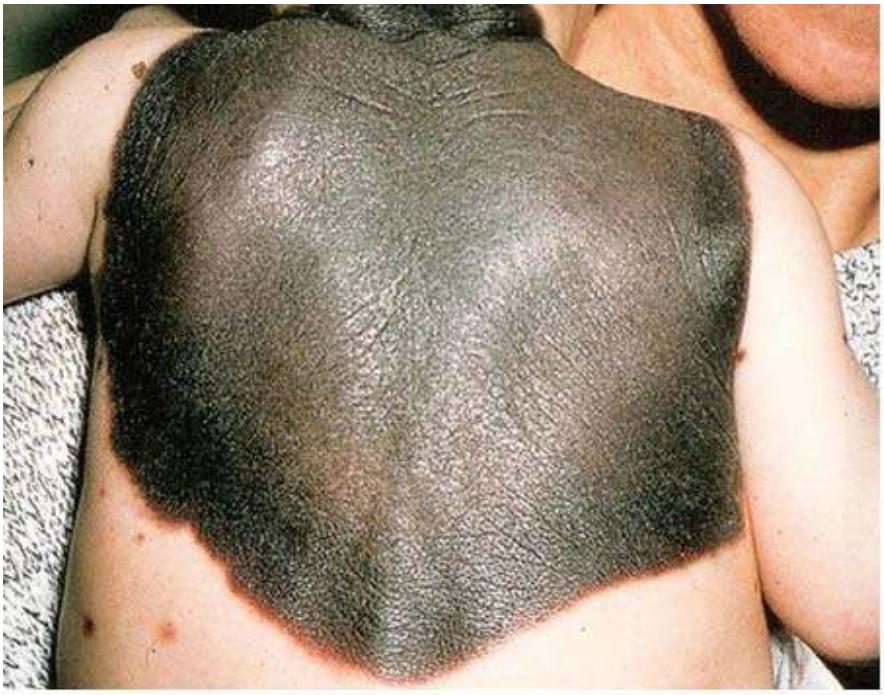
Keratoses (Seborrheic, Solar)

Seborrheic keratoses arise in sun-exposed areas of the body such as the face, forearms, and back of the hands.[51–53] Most notable in the older age groups, lesions appear light brown or yellow and have a velvety, greasy texture. Seborrheic keratoses are considered premalignant lesions, and squamous cell carcinoma (SCC) may develop over time.[52,53] Interestingly, sudden eruptions of multiple lesions may be associated with internal malignancies.[50,52] However, seborrheic keratoses are rarely mistaken for other lesions, so biopsy and treatment are seldom required.[50,52] Histologically, these lesions contain atypical-appearing keratinocytes and evidence of dermal solar damage.[50,52] Although malignancies that do develop rarely metastasize, lesion destruction is the treatment of choice. Treatments often include application of topical 5-fluorouracil, surgical excision, electrodesiccation, and dermabrasion.[50,52]

Nevi (Acquired and Congenital)

Depending on the location of nevus cells, acquired melanocytic nevi are classified as junctional, compound, or dermal.[54–57] This classification does not represent different types of nevi, but rather different stages in nevus maturation. Initially, nevus cells accumulate in the epidermis (junctional).[55–57] As they mature, nevus cells migrate partially into the dermis (compound) and finally rest completely within dermal tissues (dermal). Eventually most lesions undergo involution. Congenital nevi are relatively rare, and may be found in less than 1% of neonates.[54,56,57] These lesions are larger and often contain hair. Histologically, congenital and acquired nevi appear similar. Giant congenital lesions (giant hairy nevi) most often occur in a swim trunk distribution, chest, or back (Fig. 16-6).[54–57] Not only are these lesions cosmetically unpleasant, but congenital nevi may develop into malignant melanoma in 1 to 5% of cases.[54–57] Total excision of the nevus is the treatment of choice; however, the lesion is often so large that inadequate tissue for wound closure precludes complete resection. Instead, serial excisions with local tissue expansion/advancement are frequently required over several years.[54–57]

Fig. 16-6.



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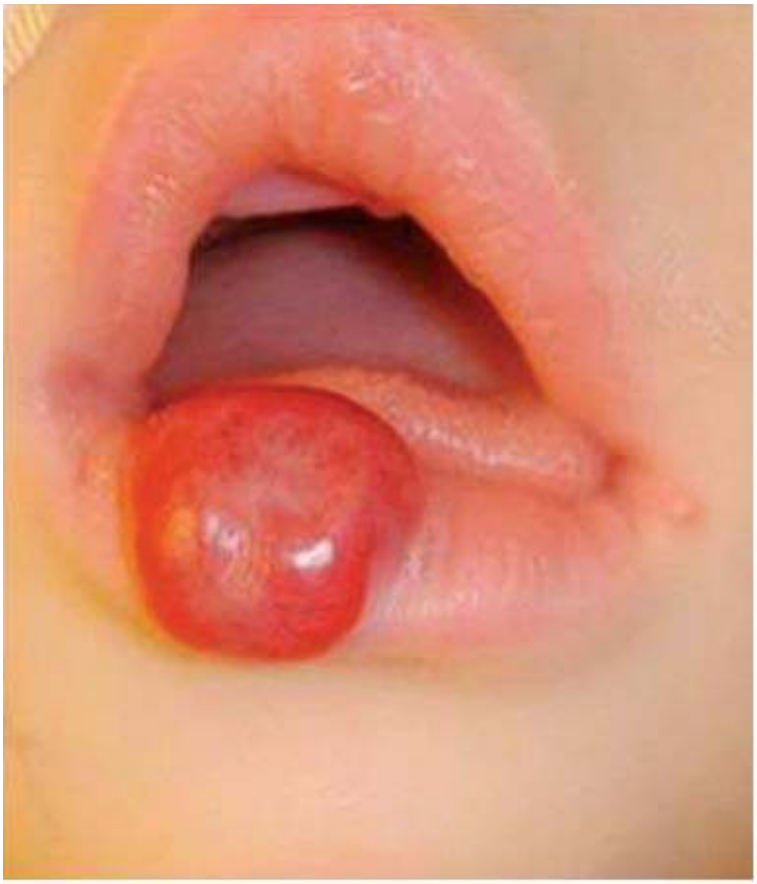
Although the giant nevus may be aesthetically concerning, these lesions present a roughly 5% risk of malignant transformation over one's lifetime.

Vascular Tumors of the Skin and Subcutaneous Tissue

Hemangiomas are benign vascular neoplasms that present soon after birth (Fig. 16-7). They initially undergo rapid cellular proliferation over the first year of life, then undergo slow involution throughout childhood.[58–60] Histologically, hemangiomas are composed of mitotically active endothelial cells surroundings several, confluent blood-filled spaces. Although these lesions may enlarge significantly in the first year of life, approximately 90% involute over time.[58–60] Acute treatment is limited to hemangiomata that interfere with function, such as airway, vision, and feeding. In addition, lesions resulting in systemic problems, such as thrombocytopenia or high-output cardiac failure, should prompt resection. The growth of rapidly enlarging lesions also can be halted with systemic prednisone or interferon alpha-2a treatment use.[58–60] In the absence of acute surgical indications or significant patient/parent concern, many lesions are allowed to spontaneously involute. However, hemangiomata that remain into adolescence or involute to leave an unsightly telangiectasia typically require surgical excision for optimal resolution.[58–60]

Fig. 16-7.



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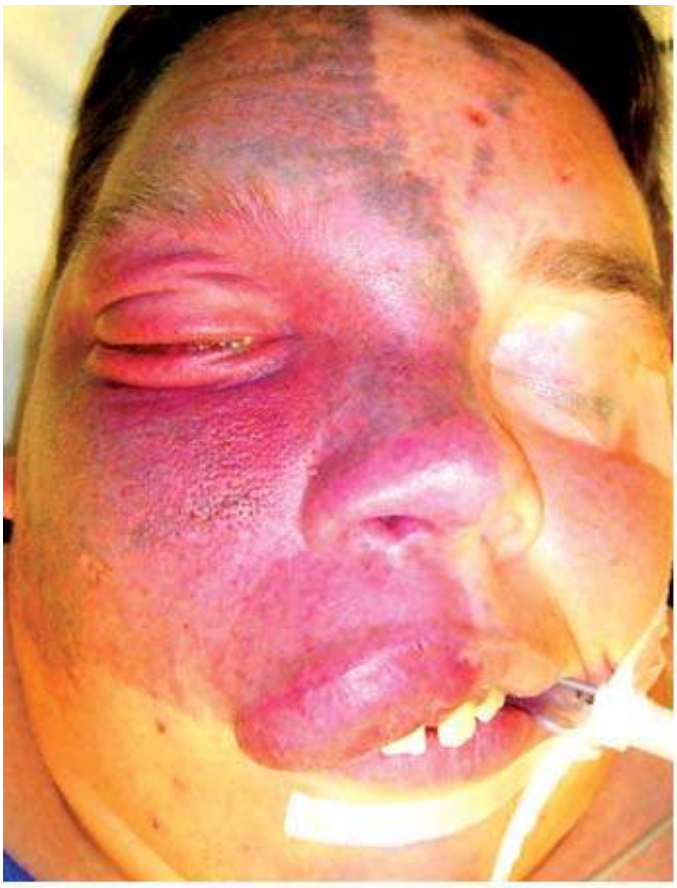
Hemangiomas most often present at approximately 2 to 4 weeks after birth, rapidly proliferate during infancy, reach a plateau phase, then involute over several years. Unless the hemangiomatous mass obstructs the airway, visual axis, or imposes psychological harm to a preschool age child, these tumors typically are allowed to spontaneously involute.

In contrast to neoplasms, vascular malformations are a result of structural abnormalities formed during fetal development.[61,62] Unlike hemangiomas, vascular malformations grow in proportion to the body and never involute. Histologically, they contain enlarged vascular spaces lined by nonproliferating endothelium.[61,62] Arteriovenous malformations are high-flow lesions that often present as subcutaneous masses associated with locally elevated temperature, dermal stain, thrill, and bruit. In addition, overlying ischemic ulcers, adjacent bone destruction, or local hypertrophy may occur.[61,62] Very large malformations may cause cardiac enlargement and congestive heart failure. Complications of arteriovenous malformations, such as pain, hemorrhage, ulceration, cardiac effects, or local tissue destruction, should prompt attempts at lesion destruction.[61,62] Therapy consists of surgical resection. Even when complete lesion resection is not possible, significant debulking may greatly diminish symptomatology. In addition, angiography with selective embolization just before surgery greatly facilitates operative removal.[61,62]

The capillary malformation, or port-wine stain, is a flat, dull-red lesion often located on the trigeminal (cranial nerve V) distribution on the face, trunk, or extremities (Fig. 16-8).[61,62] Presentation within the V1 or V2 facial regions should prompt concern of a possible link to more systemic syndromes such as Sturge-Weber syndrome (leptomeningeal angiomatosis, epilepsy, and glaucoma).[61,62] Histologically, these nevi are composed of ectatic capillaries lined by mature endothelium. Unsightly lesions may be treated with pulsed dye laser, covered with cosmetics, or surgically excised.[61,62]

Fig. 16-8.



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A capillary hemangioma (also known as a *port-wine stain*) present upon the midface may signify Churg-Strauss syndrome, and computed tomography of the brain is appropriate to rule out intracranial berry aneurysms.

Glomus tumor is an uncommon, benign neoplasm of the extremity. Representing less than 1.5% of all benign, soft-tissue extremity tumors, these lesions arise from dermal neuromyoarterial apparatus (glomus bodies).[63,64] Glomus tumor more commonly affects the hand, and presentation within the subungual region of the toe is rare. Diagnosis of these lesions is traditionally delayed, and atypical presentation on the foot or toes often leads to even greater diagnostic challenges. In addition to the severe pain, point tenderness and cold sensitivity are associated with these lesions and subungual glomus tumors typically appear as blue, subungual discolorations of 1 to 2 mm. Tumor excision is the treatment of choice.[63,64]

Soft-Tissue Tumors (Acrochordons, Dermatofibromas, Lipomas)

Lipomas are the most common subcutaneous neoplasm.[64] Although they are found most frequently on the trunk, these lesions may appear anywhere. Typically soft and fleshy on palpation, lipomas may grow to a large size and become substantially deforming. Histologic examination reveals a lobulated tumor composed of normal fat cells.[64] Although fears of malignant degeneration have prompted resection in the past, no report of such malignancy has been substantiated. To date, the lipoma is widely viewed as benign with essentially no risk of malignant devolvement.[64] Although observation is an option, surgical excision is required for tumor removal. Acrochordons (skin tags) are fleshy, pedunculated masses located on the preauricular areas, axillae, trunk, and eyelids.[65–67] They are composed of hyperplastic epidermis over a fibrous connective

tissue stalk. These lesions are usually small, and are frequently treated via "tying off" or with resection in the clinic.[65–67] Dermatofibromas are solitary, soft-tissue nodules usually approximating 1 to 2 cm in diameter, and are found primarily on the legs and flanks. Histologically, these lesions are composed of unencapsulated connective tissue whorls containing fibroblasts.[65–67] Although a majority of dermatofibromas can be diagnosed clinically, atypical presentation or course should prompt excisional biopsy to assess for malignancy. Although these tumors may be managed conservatively, operative removal is the treatment of choice.[66–68]

Neural Tumors (Neurofibromas, Neurilemomas, Granular Cell Tumors)

Benign, cutaneous neural tumors such as neurofibromas, neurilemomas, and granular cell tumors primarily arise from the nerve sheath.[65,68] Neurofibromas can be sporadic and solitary. However, a majority are associated with café au lait spots, Lisch nodules, and an autosomal dominant inheritance (von Recklinghausen's disease).[65,66] These lesions are firm, discrete nodules attached to a nerve. Histologically, proliferation of perineurial and endoneurial fibroblasts with Schwann cells embedded in collagen are noted. In contrast to direct nerve attachment as seen with neurofibromas, neurilemomas are solitary tumors arising from cells of the peripheral nerve sheath.[65,66] These lesions are discrete nodules that may induce local or radiating pain along the distribution of the nerve. Microscopically, the tumor contains Schwann cells with nuclei packed in palisading rows. Surgical resection is the management option of choice. Granular cell tumors are usually solitary lesions of the skin or, more commonly, the tongue.[65,66] They consist of granular cells derived from Schwann cells that often infiltrate the surrounding striated muscle. Based on the severity of symptomatology, operative resection is the primary therapy of choice.[65–68]

MALIGNANT TUMORS OF THE SKIN

Although malignancies arising from cells of the dermis or adnexal structures are relatively uncommon, the skin is frequently subject to epidermal tumors, such as basal cell carcinoma (BCC), SCC, and melanoma.[69–72] Each of these tumors has received exhaustive study, and several key factors associated with their development have been identified. Perhaps of greatest significance is that increased exposure to UV radiation is associated with an increased development of all skin cancer.[69–72] Clinical studies reveal that persons with outdoor occupations are at greater risk, as are those with fair complexions and people living in regions receiving higher per capita sunlight. In addition, albino individuals of dark-skinned races are prone to develop cutaneous neoplasms that are typically rare in nonalbino members of the same group. This observation suggests that melanin, and its ability to limit UV radiation tissue penetration, plays a large role in carcinogenesis protection.[69–72]

Skin cancer development also has been strongly linked to chemical carcinogens such as tar, arsenic, and nitrogen mustard. Radiation therapy directed at skin lesions increases the risk for local BCC and SCC.[69–72] As an ongoing area of intense research interest, certain subtypes of HPV have been linked to SCC.[69–72] Additionally, chronically irritated or nonhealing areas such as burn scars, sites of repeated bullous skin sloughing, and decubitus ulcers present an elevated risk of developing SCC.[69–72] Systemic immunologic dysfunction is also related to an increase in cutaneous malignancies. Immunosuppressed patients receiving chemotherapy, those with advanced HIV/AIDS, and immunosuppressed transplant recipients have an increased incidence of BCC, SCC, and melanoma.[69–72]

Basal Cell Carcinoma

Arising from the basal layer of the epidermis, BCC is the most common type of skin cancer. Based on gross and histologic

morphology, BCC has been divided into several subtypes: nodular, superficial spreading, micronodular, infiltrative, pigmented, and morpheaform.[69–72]

Nodulocystic or noduloulcerative type accounts for 70% of BCC tumors. Waxy and frequently cream colored, these lesions present with rolled, pearly borders surrounding a central ulcer. Although superficial basal cell tumors commonly occur on the trunk and form a red, scaling lesion, pigmented BCC lesions are tan to black in color. Morpheaform BCC often appears as a flat, plaque-like lesion.[69–72] This particular variant is considered relatively aggressive and should prompt early excision. A rare form of BCC is the basosquamous type, which contains elements of both basal cell and squamous cell cancer. These lesions may metastasize similar to SCC, and should be treated aggressively.[69–72]

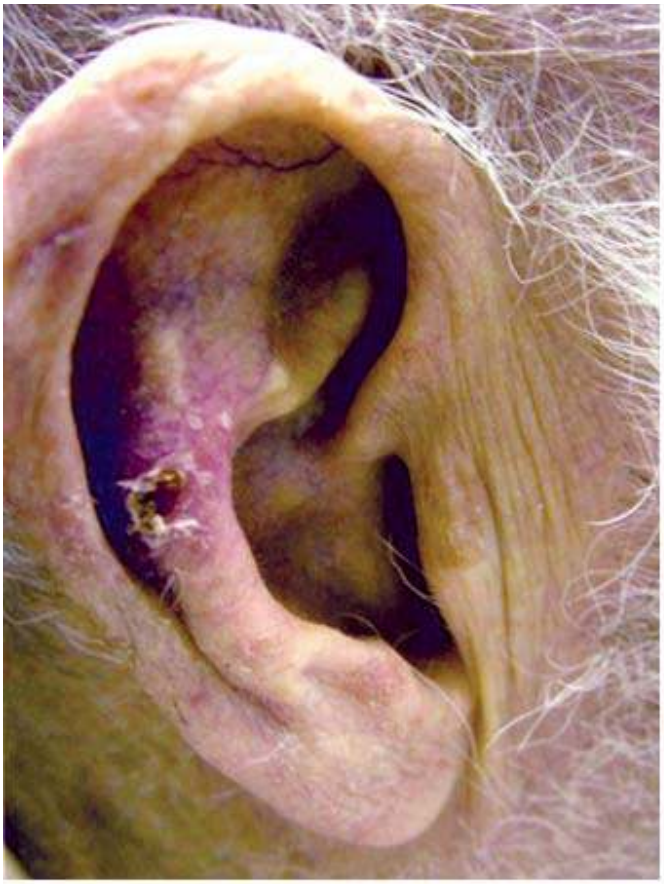
BCCs are slow growing, and metastasis is extremely rare.[69–72] Due to this slow developmental progression, patients often neglect these lesions for years and presentation with extensive local tissue destruction is common. The majority of small (less than 2 mm), nodular lesions may be treated via curettage, electrodesiccation, or laser vaporization.[69–72]

Although effective, these techniques destroy any potential tissue sample for confirmatory pathology diagnosis and tumor margin analysis. Surgical excision may be used to both effect complete tumor removal as well as allow proper laboratory evaluation. Basal cell tumors located at areas of great aesthetic value, such as the cheek, nose, or lip, may be best approached with Mohs' surgery.[69–72] Typically completed by specialized dermatology surgeons, Mohs' surgery uses minimal tissue resection and immediate microscopic analysis to confirm appropriate resection. Large tumors, those that invade surrounding structures, and aggressive histologic types (morpheaform, infiltrative, and basosquamous) are best treated by surgical excision with 0.5-cm to 1-cm margins.[69–72]

Squamous Cell Carcinoma

SCCs arise from epidermal keratinocytes (Fig. 16-9). While less common than BCC, SCC is more devastating due to an increased invasiveness and tendency to metastasize.[69–72] Before local invasion, in situ SCC lesions are termed *Bowen's disease*. In situ SCC tumors specific to the penis are referred to as *erythroplasia of Queyrat*.[67,68] Following tissue invasion, tumor thickness correlates well with malignant behavior. Tumor recurrence is more prevalent once SCC tumors grow more than 4 mm in thickness, and lesions that metastasize are typically at least 10 mm in diameter.[69–72] Tumor location is also of great prognostic importance. Although SCC tumors in areas with cumulative solar damage are less aggressive, and respond well to local excision, lesions arising in burn scars (Marjolin's ulcer), areas of chronic osteomyelitis, and areas of previous injury metastasize early.[69–72]

Fig. 16-9.



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Although basal cell carcinoma is the most common tumor involving the head and neck, squamous cell carcinoma (pictured here) occurs with high frequency on the nose, ears, and lower lip.

Although small lesions can be treated with curettage and electrodesiccation, most surgeons recommend surgical excision. Lesions should be excised with a 1-cm margin, and histologic confirmation of tumor-free borders is mandatory.[69–72] Tumors within areas of great aesthetic value, such as the cheek, nose, or lip, may be best approached with Mohs' surgery. This precise, specialized surgical technique uses minimal tissue resection and immediate microscopic analysis to confirm appropriate resection yet limit removal of valuable anatomy. The need for lymph node (LN) dissection in the setting of SCC remains a topic of debate. Regional LN excision is indicated for clinically palpable nodes.[69–72] However, SCC lesions arising in chronic wounds are more aggressive and regional lymph node metastases are observed more frequently. In this instance, lymphadenectomy before development of palpable nodes (prophylactic LN dissection) is indicated. Metastatic disease is a poor prognostic sign, and only 13% of patients typically survive 10 years.[69–72]

Mohs' Surgery for Squamous and Basal Cell Carcinomas

Basal and squamous cell lesions often present on sun-exposed portions of the body such as the head and face. Unfortunately, these areas are of great aesthetic value and significant tissue loss may significantly alter facial symmetry, contour, and continuity. Developed in 1936, Mohs' technique uses serial excision in small increments coupled with immediate microscopic analysis to ensure tumor removal, yet limit resection of aesthetically valuable tissue.[70–72] One distinct advantage of Mohs' technique is that all specimen margins are evaluated. In contrast, traditional histologic examination surveys selected portions on surgical margin. The major benefit of Mohs' technique is the ability to remove a tumor with

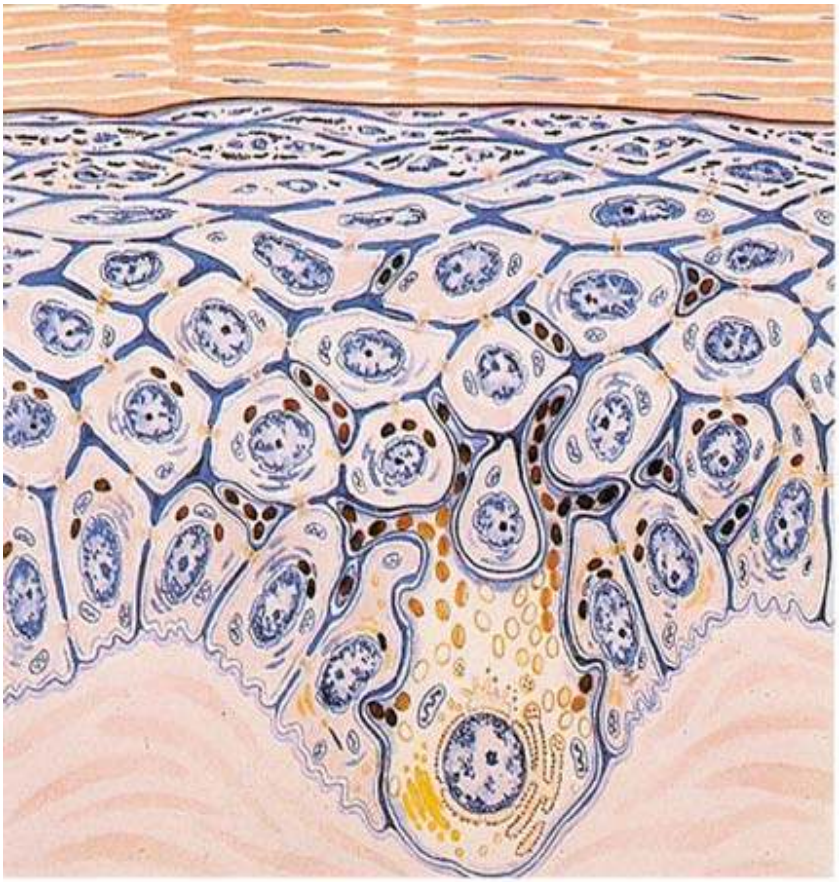
minimal sacrifice of uninvolved tissue.[70–72] Although this procedure is of particular value when managing tumors of the eyelid, nose, or cheek, one major drawback is procedure length. Total lesion excision may require multiple attempts at resection, and many procedures may be carried out over several days. Recurrence and metastases rates are comparable to those of wide local excision.[70–72]

Malignant Melanoma

The increasing rate of melanoma diagnoses is the highest of any cancer in the United States. The age-adjusted incidence of invasive melanoma in the United States increased from approximately 4 to 18 per 100,000 white males between 1973 and 1998.[73] With this increasing prevalence, it is critical that physicians recognize and appropriately manage these lesions early.

The pathogenesis of melanoma is complex and remains poorly understood to date. Melanoma may arise from transformed melanocytes anywhere that these cells have migrated during normal embryogenesis (Fig. 16-10).[73–76] Although nevi (freckles) are benign melanocytic neoplasms found on the skin of many people, dysplastic nevi contain a histologically identifiable focus of atypical melanocytes. These lesions are thought to represent an intermediate stage between benign nevus and true malignant melanoma.[73–76] Studies demonstrate increased relative risk of melanoma development based on increasing numbers of dysplastic nevi found on the patient. In addition, a strong genetic component has been described.[73–76] Up to 14% of malignant melanomas occur in a familial pattern, and family members of those with either dysplastic nevi or melanoma are at increased risk for tumor development.[73–76]

Fig. 16-10.



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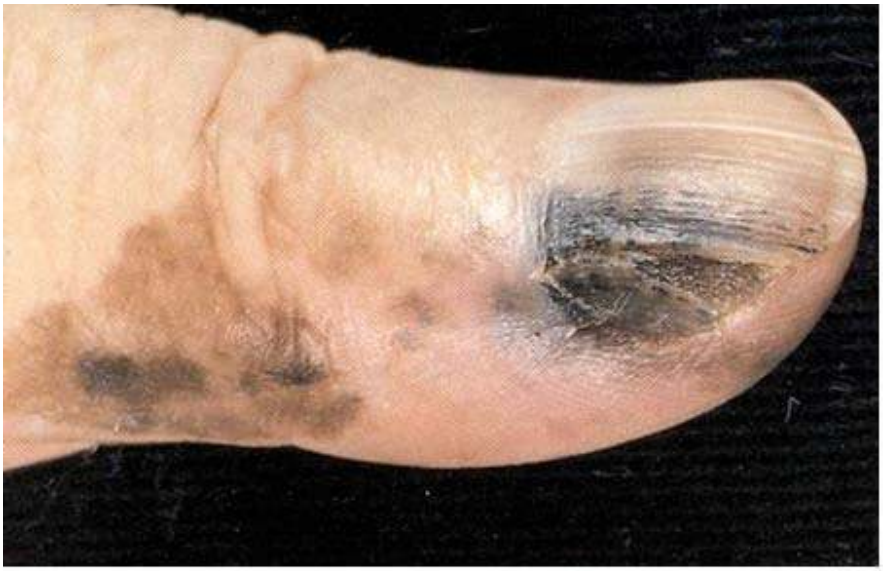
Following malignant transformation, invasive melanoma cells replicate, penetrate surrounding epidermal layers, and migrate to more distant tissues.

Once the melanocyte has transformed into the malignant phenotype, tumor growth occurs radially in the epidermal plane.[73–76] Even though microinvasion of the dermis may have occurred, metastases do not occur until these melanocytes form dermal nests. During the subsequent vertical growth phase, cells develop different cell-surface antigens and their malignant behavior becomes much more aggressive.[73–76] Study of these cell populations in culture medium demonstrates substantially lengthened cellular life span and increased malignant growth despite significantly poor nutrient medium.[73–76]

Although the eye and anus are notable sites, over 90% of melanomas are found on the skin (Fig. 16-11).[73–76] In addition, 4% of tumors are discovered as metastases without any identifiable primary site. Suspicious features suggestive of melanoma include any pigmented lesion with an irregular border, darkening coloration, ulceration, and raised surface.[73–76] Although many benign lesions may fit these descriptors, it is perhaps most critical to note recent changes in nevus appearance that may denote malignant transformation. In addition, approximately 5 to 10% of melanomas are nonpigmented.[73–76]

Fig. 16-11.



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Lateral view of a subungual melanoma demonstrating apparent proximal digital extension.

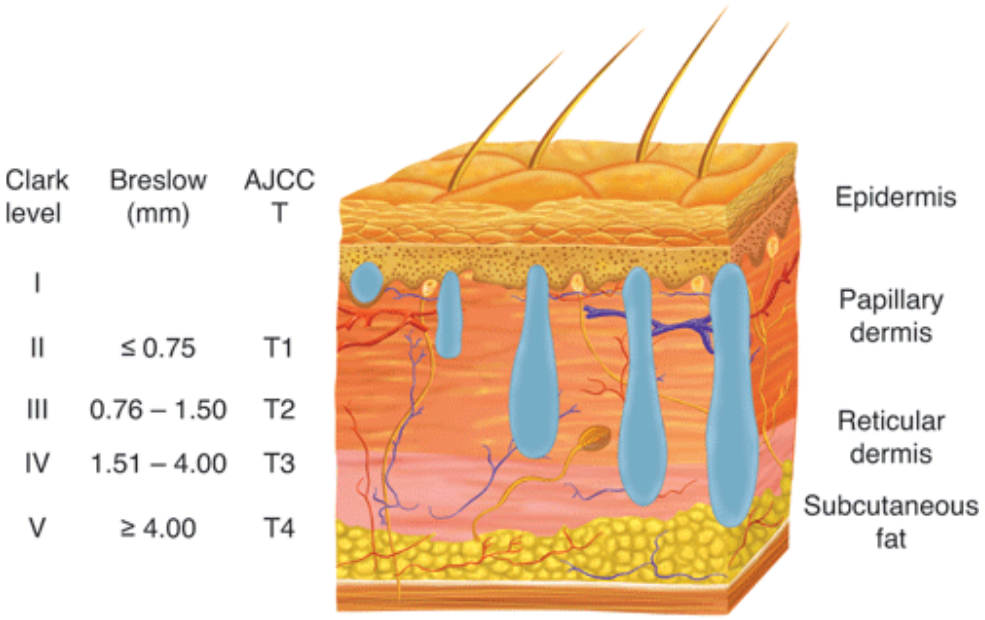
In order of decreasing frequency, the four types of melanoma are superficial spreading, nodular, lentigo maligna, and acral lentiginous.[73–76] The most common type, superficial spreading, accounts for up to 70% of melanomas. These lesions occur anywhere on the skin except the hands and feet. They are typically flat and measure 1 to 2 cm in diameter at diagnosis.[73–76] Before vertical extension, a prolonged radial growth phase is characteristic of these lesions. Typically of darker coloration and often raised, the nodular type accounts for 15 to 30% of melanomas.[73–76] These lesions are noted for their lack of radial growth; hence, all nodular melanomas are in the vertical growth phase at diagnosis. Although considered a more aggressive lesion, the prognosis for patients with nodular-type melanomas is similar to that for a patient with a superficial spreading

lesion of the same depth. Lentigo maligna accounts for 4 to 15% of melanomas, and occurs most frequently on the neck, face, and hands of the elderly.[73–76] Although they tend to be quite large at diagnosis, these lesions have the best prognosis because invasive growth occurs late. Less than 5% of lentigo maligna are estimated to evolve into melanoma.[74,75] Acral lentiginous melanoma is the least common subtype, and constitutes only 2 to 8% of melanomas in white populations. Although acral lentiginous melanoma among dark-skinned people is relatively rare, this type accounts for 29 to 72% of all melanomas in dark-skinned people (African Americans, Asians, and Hispanics).[74,75] Acral lentiginous melanoma most frequently is encountered on the palms, soles, and subungual regions. Most common on the great toe or thumb, subungual lesions appear as blue-black discolorations of the posterior nail fold. The additional presence of pigmentation in the proximal or lateral nail folds (Hutchinson's sign) is diagnostic of subungual melanoma.[73–76]

Several clinical features of melanoma have been identified as significant prognostic indicators. Independent of histologic type and depth of invasion, those with lesions of the extremities have a better prognosis than patients with melanomas of the head, neck, or trunk (10-year survival rate of 82% for localized disease of the extremity compared to a 68% survival rate with a lesion of the face).[73–76] Lesion ulceration carries a worse prognosis. The 10-year survival rate for patients with local disease (stage I) and an ulcerated melanoma was 50% compared to 78% for the same stage lesion without ulceration.[73–76] Early studies identified that the incidence of ulceration increases with increasing thickness, from 12.5% in melanomas less than 0.75 mm to 72.5% in melanomas greater than 4.0 mm.[74,76] Recent evidence suggests that tumors ulcerate as the result of increased angiogenesis.[73–76] Gender is also a substantial prognostic indicator. Numerous studies demonstrate that females have an improved survival compared to males.[74,75] Women tend to acquire melanomas in more favorable anatomic sites, and these lesions are less likely to contain ulceration. After correcting for thickness, age, and location, females continue to have a higher survival rate than men (10-year survival rate of 80% for women vs. 61% for men with stage I disease).[74–76] In general, there is no significant difference between different histologic tumor types in terms of prognosis, when matched for tumor thickness, gender, age, or other. Nodular melanomas have the same prognosis as superficial spreading types when lesions are matched for depth of invasion. Lentigo maligna types, however, have a better prognosis even after correcting for thickness, and acral lentiginous lesions have a worse prognosis. Even though the various types of melanoma have similar prognoses when controlled for the other prognostic factors, acral lentiginous melanoma has a shorter interval to recurrence.[74–76]

The most current staging system, from the American Joint Committee on Cancer (AJCC), contains the best method of interpreting clinical information in regard to prognosis of this disease (Fig. 16-12).[74–76] Historically, the vertical thickness of the primary tumor (Breslow thickness) and the anatomic depth of invasion (Clark level) have represented the dominant factors in the T classification. The T classification of lesions comes from the original observation by Clark that prognosis is directly related to the level of invasion of the skin by the melanoma. Whereas Clark used the histologic level [I, superficial to basement membrane (in situ); II, papillary dermis; III, papillary/reticular dermal junction; IV, reticular dermis; and V, subcutaneous fat], Breslow modified the approach to obtain a more reproducible measure of invasion by the use of an ocular micrometer. The lesions were measured from the granular layer of the epidermis or the base of the ulcer to the greatest depth of the tumor (I, 0.75 mm or less; II, 0.76 to 1.5 mm; III, 1.51 to 4.0 mm; IV, 4.0 mm or more).[74–76] These levels of invasion have been subsequently modified and incorporated in the AJCC staging system. The new staging system has largely replaced the Clark level with another histologic feature, ulceration, based on analysis of large databases available to the AJCC Melanoma Committee.[75,76]

Fig. 16-12.



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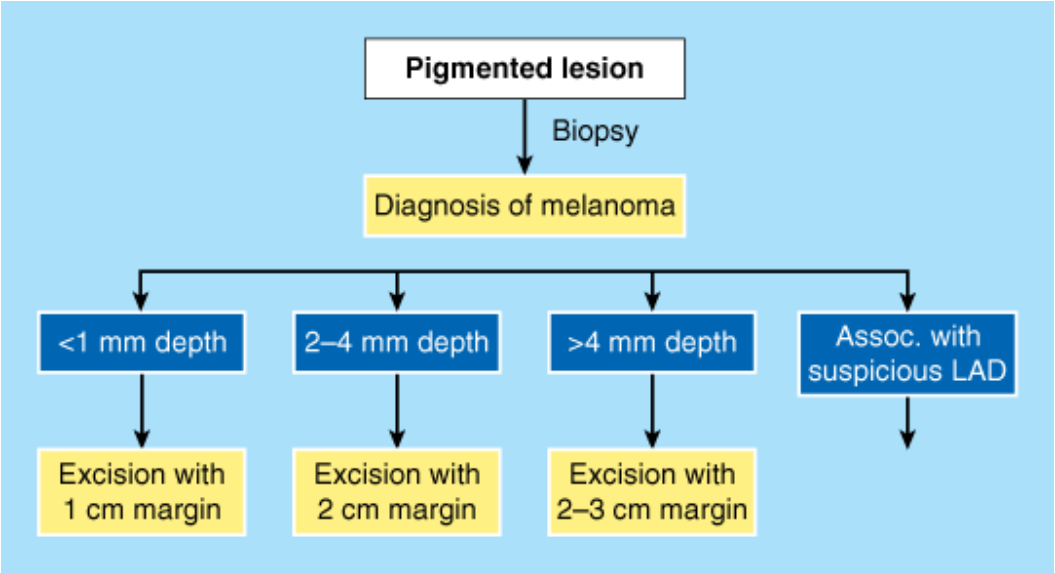
Although Breslow's thickness has traditionally been used to anticipate clinical outcomes based on the depth of melanoma invasion, more recent staging criteria advanced by the American Joint Committee on Cancer (AJCC) are today's standard of care.

Evidence of tumor in regional LNs is a poor prognostic sign associated with a precipitous drop in survival at 15-year follow-up.[77–81] Based on the tumor, node, and metastasis tumor staging system, this finding advances any classification from stage I or II to stage III. Identification of distant metastasis is the worst prognostic sign and is classified as stage IV disease. Although occasional survival for several years has been noted, median survival ranges from 2 to 7 months depending on the number and site of metastases.[77–81]

Diagnosis of melanoma typically requires excisional biopsy (Fig. 16-13). A 1-mm margin of normal skin is taken if the wound can be closed primarily.[73–76] If removal of the entire lesion creates too large a defect, then an incisional biopsy of a representative part is recommended. Biopsy incisions should be made with the expectation that a subsequent wide excision of the biopsy site may be done.

Fig. 16-13.



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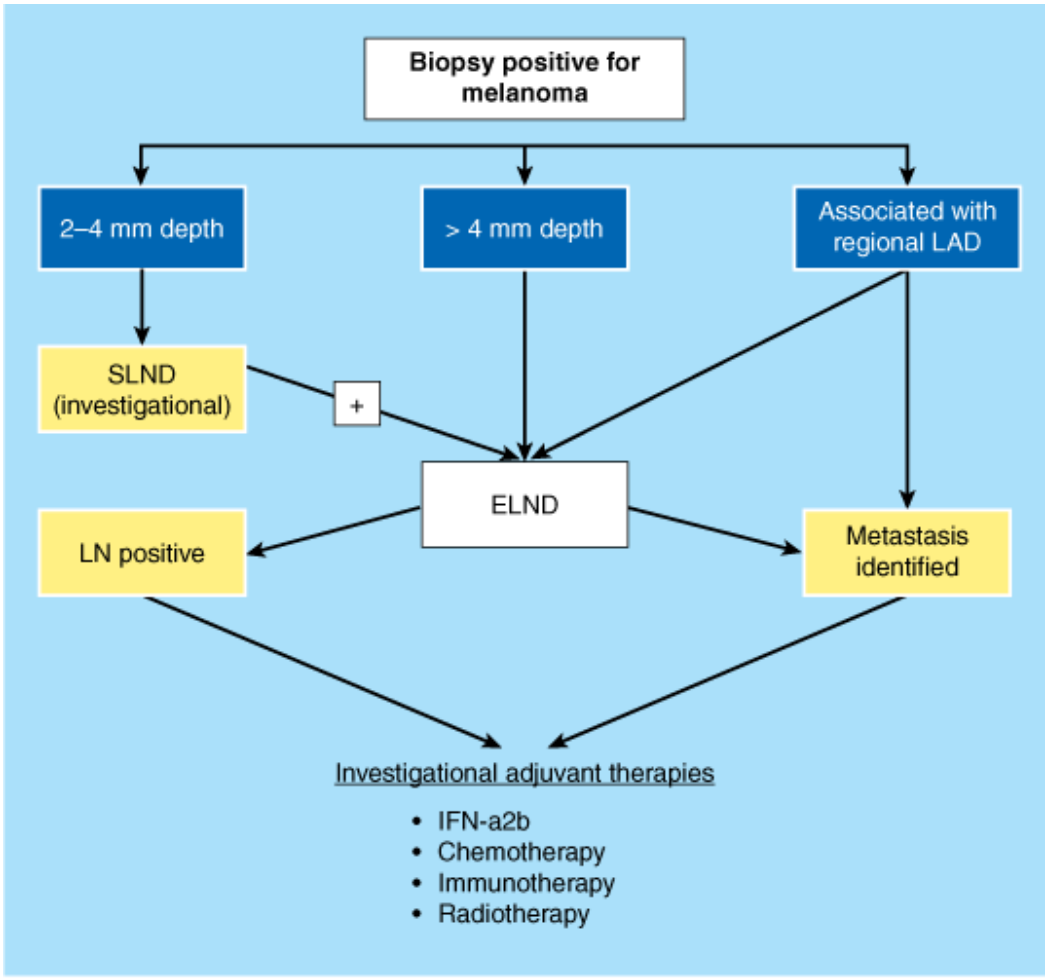
The diagnosis of melanoma should be made via excisional biopsy. Based on tumor depth, appropriate margins may be planned. Indications for lymph node evaluation continue to advance as our understanding of tumor behavior improves and outcome data become available. LAD = lymphadenopathy.

With diagnosis made, treatment of melanoma may range from simple excision to more complex lymphadenectomy or immunotherapy (see Fig. 16-13). Regardless of tumor depth or extension, surgical excision is the management of choice. Lesions 1 mm or less in thickness can be treated with a 1-cm margin.[73–76] For lesions 1 mm to 4 mm thick, a 2-cm margin is recommended. Lesions of greater than 4 mm may be treated with 3-cm margins.[73–76] The surrounding tissue should be removed down to the fascia to remove all lymphatic channels. If the deep fascia is not involved by the tumor, removing it does not affect recurrence or survival rates, so the fascia is left intact.[73–76]

Treatment of regional LNs that do not obviously contain tumor in patients without evidence of metastasis is an area of continued debate. In patients with thin lesions (less than 1 mm), the tumor cells are still localized in the surrounding tissue, and the cure rate is excellent with wide excision of the primary lesion; therefore treatment of regional LNs is not beneficial (Fig. 16-14).[73–76] With lesions deeper than 4 mm, it is highly likely that the tumor cells already have spread to the regional LNs and distant sites. Removal of the melanomatous LNs has no effect on survival.[73–76] Most of these patients die of metastatic disease before developing problems in regional nodes.

Fig. 16-14.



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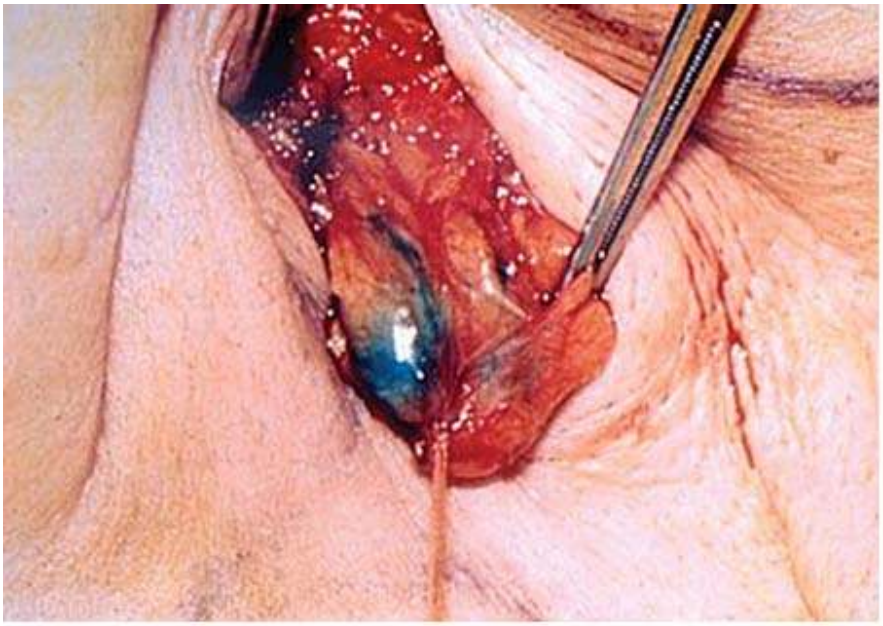
Melanoma treatment algorithm. The algorithmic approach to melanoma has taken many forms throughout the last several decades. However, as our diagnostic technology, therapeutic approaches, and ability to assess outcome improves, the current algorithm incorporates these advances. ELND = elective lymph node dissection; IFN-a2b = interferon alfa-2b; LAD = lymphadenopathy; LN = lymph node; SLND = sentinel lymph node dissection.

In patients with intermediate-thickness tumors (T2 and T3, 1 to 4.0 mm) and no clinical evidence of nodal or metastatic disease, the use of prophylactic dissection (elective LN dissection on clinically negative nodes) is controversial. To date, no prospective, randomized studies have demonstrated that elective LN dissection improves survival in patients with intermediate-thickness melanomas. However, 25 to 50% of LN specimens contain micrometastases in these cases and recurrence may be decreased with LN dissection.[77–81]

Sentinel lymphadenectomy for malignant melanoma is gaining acceptance (Fig. 16-15). The sentinel node may be preoperatively located with the use of a gamma camera, which identifies the radioisotope injected into the primary lesion.[77–81] Whereas preoperative identification may provide the surgeon greater reliability in localizing the LN, intraoperative mapping with 1% isosulfan blue dye injection may be equally effective.[77–81] Both techniques identify the lymphatic drainage from the primary lesion, and determine the first (sentinel) LN draining the tumor area.[77–81] If micrometastasis is identified in the removed node by frozen-section examination, a complete LN dissection is performed.[77–81] This method may be used to identify patients who would benefit from LN dissection, while sparing others an unnecessary operation.

Fig. 16-15.



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Intraoperative view of sentinel lymph node identification during distal melanoma excision.

All microscopically or clinically positive LNs should be removed by regional nodal dissection.[77–81] When groin LNs are removed, the deep (iliac) nodes must be removed along with the superficial (inguinal) nodes, or disease will recur in that region. For axillary dissections, the nodes medial to the pectoralis minor muscle also must be resected.[77–81] For lesions on the face, anterior scalp, and ear, a superficial parotidectomy to remove parotid nodes and a modified neck dissection is recommended.[77–81]

Once melanoma has spread to a distant site, median survival is 7 to 8 months and the 5-year survival rate is less than 5%.[77–81] Solitary lesions in the brain, GI tract, or skin that are symptomatic should be excised when possible. Although cure is extremely rare, the degree of palliation can be high and asymptomatic survival prolonged.[77–81] A decision to operate on metastatic lesions must be made after careful deliberation with the patient and the treating oncologist.

Locally recurrent, lymphatic-invading, or tumors unamenable to surgical excision present a significant management challenge. In-transit disease (local disease in lymphatics) develops in 5 to 8% of melanoma patients with a high-risk primary melanoma (>1.5 mm).[77–81] Hyperthermic regional perfusion with a chemotherapeutic agent (e.g., melphalan) is presently the treatment of choice. The goal of regional perfusion therapy is to increase the dosage of the chemotherapeutic agent to maximize tumor response while limiting systemic toxic effects.[77–81] Melphalan generally is heated to an elevated temperature [up to 41.5°C, (106.7°F)] and perfused for 60 to 90 minutes. Although difficult to perform and associated with complications (neutropenia, amputation, death), it does produce a high response rate (greater than 50%).[74,77–79] The introduction of tumor necrosis factor alpha or interferon-γ with melphalan results in the regression of more than 90% of cutaneous in-transit metastases.[75–77]

Although initially thought to be ineffective in the treatment of melanoma, the use of radiation therapy, regional and systemic chemotherapy, and immunotherapy are all under investigation. High-dose-per-fraction radiation produces a better response

rate than low-dose large-fraction therapy. As the treatment of choice for patients with symptomatic multiple brain metastases, radiation therapy produced measurable improvement in tumor size, symptomatology, or performance status in 70% of treated patients.[79–81]

Another promising area of nonsurgical melanoma treatment is the use of immunologic manipulation. Interferon alfa-2b is the only Food and Drug Administration–approved adjuvant treatment for AJCC stages IIB/III melanoma.[80,81] In these patients, both the relapse-free interval and overall survival were improved with use of INF-α.[80,81] Side effects were common and frequently severe; the majority of the patients required modification of the initial dosage and 24% discontinued treatment.80,81 Immunotherapy also continues to be a field of great promise. Vaccines have been developed with the hope of stimulating the body's own immune system against the tumor. Melanoma cells contain a number of distinctly different cell-surface antigens, and monoclonal antibodies have been raised against these antigens.[80,81] These antibodies have been used alone or linked to a radioisotope or cytotoxic agent in an effort to selectively kill tumor cells. All treatments are currently investigational. One defined-antigen vaccine has entered clinical testing; the ganglioside G_{M2}. Gangliosides are carbohydrate antigens found on the surface of melanomas as well as many other tumors.[80,81]

ADDITIONAL MALIGNANCIES OF THE SKIN

Merkel Cell Carcinoma (Primary Neuroendocrine Carcinoma of the Skin)

Once thought to be a variant of SCC, Merkel cell carcinomas are actually of neuroepithelial differentiation.[82,83] These tumors are associated with a synchronous or metasynchronous SCC 25% of the time. Due to their aggressive nature, wide local resection with 3-cm margins is recommended.[82,83] Local recurrence rates are high, and distant metastases occur in one third of patients. Prophylactic regional LN dissection and adjuvant radiation therapy are recommended. Overall, the prognosis is worse than for malignant melanoma.[82,83]

Kaposi's Sarcoma

Kaposi's sarcoma (KS) appears as rubbery bluish nodules that occur primarily on the extremities but may appear anywhere on the skin and viscera. These lesions are usually multifocal rather than metastatic.[84–88] Histologically, the lesions are composed of capillaries lined by atypical endothelial cells. Early lesions may resemble hemangiomas, while older lesions contain more spindle cells and resemble sarcomas.[84–86] Classically, KS is seen in people of Eastern Europe or sub-Saharan Africa. The lesions are locally aggressive but undergo periods of remission. A different variety of KS has been described for people with AIDS or with immunosuppression from chemotherapy.[84–86] For reasons not yet understood, AIDS-related KS occurs primarily in male homosexuals and not in IV drug abusers or hemophiliacs. In this form of the disease, the lesions spread rapidly to the nodes, and the GI and respiratory tract often are involved.[84–86] Development of AIDS-related KS is associated with concurrent infection with a herpes-like virus.[84–86] Treatment for all types of KS consists of radiation to the lesions. Combination chemotherapy is effective in controlling the disease, although most patients develop an opportunistic infection during or shortly after treatment. Surgical treatment is reserved for lesions that interfere with vital functions, such as bowel obstruction or airway compromise.[84–86]

Extramammary Paget's Disease

This tumor is histologically similar to the mammary type. It is a cutaneous lesion that appears as a pruritic red patch that does not resolve.[85] Biopsy demonstrates classic Paget's cells. Paget's disease is thought to be a cutaneous extension of an underlying adenocarcinoma, although an associated tumor cannot always be demonstrated.[85]

Angiosarcoma

Angiosarcomas may arise spontaneously, mostly on the scalp, face, and neck. They usually appear as a bruise that spontaneously bleeds or enlarges without trauma.[87,88] Tumors also may arise in areas of prior radiation therapy or in the setting of chronic lymphedema of the arm, such as after mastectomy (Stewart-Treves syndrome).[87,88] The angiosarcomas that arise in these areas of chronic change occur decades later. The tumors consist of anaplastic endothelial cells surrounding vascular channels. Although total excision of early lesions can provide occasional cure, the prognosis usually is poor, with 5-year survival rates of less than 20%. Chemotherapy and radiation therapy are used for palliation.[87,88]

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) accounts for 1 to 2% of all soft-tissue sarcomas, occurs most frequently in persons aged 20 to 50 years, and is more common in males.[88,89] The most common presenting location is on the trunk (50 to 60%), although the proximal extremities (20 to 30% of cases), as well as head and neck also are frequently affected (10 to 15%).[88,89] DFSP often appears as a pink, nodular lesion that may ulcerate and become infected. Histologically, the lesions contain atypical spindle cells, probably of fibroblast origin, located around a core of collagen tissue. Despite what appears to be complete lesion excision, local recurrence remains frequent and mortality associated with metastasis relatively high.[88,89] To date, the minimum resection margin needed to achieve local control remains undefined. Local recurrence rates of up to 50% have been reported after simple excision, and wide local excision with 3-cm margins is linked to a 20% recurrence rate. Most authorities seem to advocate a three-dimensional margin of 2 to 3 cm with resection of skin, subcutaneous tissue, and the underlying investing fascia.[88,89] The periosteum and a portion of the bone may also need to be resected to achieve negative deep surgical margins. In addition to achieving wide macroscopic resection, conformation of negative microscopic margins is especially critical. DFSP is considered to be a radiosensitive tumor, and radiotherapy following wide local excision has reached local control rates approximating 95% at 10 years.[88,89] Continued study of chemotherapy efficacy on DFSP also has produced optimistic results. Imatinib, a selective inhibitor of platelet-derived growth factor (PDGF) β-chain alpha and PDGF receptor beta protein-tyrosine kinase activity, alters the biologic effects of deregulated PDGF receptor signaling. Clinical trials have shown activity against localized and metastatic DFSP containing the t(17:22) translocation, suggesting that targeting the PDGF receptors may become a new therapeutic option for DFSP. Phase II clinical trials are underway.[88,89]

Fibrosarcoma

Fibrosarcomas are hard, irregular masses found in the subcutaneous fat.[88,89] The fibroblasts appear markedly anaplastic with disorganized growth. If they are not excised completely, metastases usually develop. The 5-year survival rate after excision is approximately 60%.[88,89]

Liposarcoma

Liposarcomas arise in the deep muscle planes, and, rarely, from the subcutaneous tissue.[88,89] They occur most commonly on the thigh. An enlarging lipoma should be excised and inspected to distinguish it from a liposarcoma. Wide excision is the treatment of choice, with radiation therapy reserved for metastatic disease.[88,89]

SYNDROMIC SKIN MALIGNANCIES

Several genetic syndromes are associated with an increased incidence of skin malignancy. Although many are related to development of a specific lesion, others appear to produce a more generic prevalence for neoplastic formation. Based on

their respective genetic defects, syndromes associated with BCC, SCC, and melanoma have all been identified and well described. Diseases linked with BCC include the basal cell nevus (Gorlin's) syndrome and nevus sebaceus of Jadassohn.[90–92] Basal cell nevus syndrome is an autosomal dominant disorder characterized by the growth of hundreds of BCCs during young adulthood. Palmar and plantar pits are a common physical finding and represent foci of neoplasms.[90–92] Treatment is limited to excision of only aggressive and symptomatic lesions. Nevus sebaceus of Jadassohn is a lesion containing several cutaneous tissue elements that develops during childhood.[90–92] This lesion is associated with a variety of neoplasms of the epidermis, but most commonly BCC. Diseases associated with SCC may have a causative role in the development of carcinoma. Skin diseases that cause chronic wounds, such as epidermolysis bullosus and lupus erythematosus, are associated with a high incidence of SCC.[90–92] Epidermodysplasia verruciformis is a rare autosomal recessive disease associated with infection with HPV. Large verrucous lesions develop early in life and often progress to invasive SCC in middle age.[90–92] Xeroderma pigmentosum is an autosomal recessive disease associated with a defect in cellular repair of DNA damage. The inability of the skin to correct DNA damage from UV radiation leaves these patients prone to cutaneous malignancies.[90–92] SCCs are most frequent, but BCCs, melanomas, and even acute leukemias are seen. Dysplastic nevi are considered precursors to melanoma. Familial dysplastic nevus syndrome is an autosomal dominant disorder.[90–92] Patients develop multiple dysplastic nevi, and longitudinal studies have demonstrated an almost 100% incidence of melanoma. Gene mapping of the defects found in familial dysplastic nevus syndrome has identified several candidate "melanoma" genes.[90–94] It remains to be determined whether these germline mutations also are found in sporadic cases of melanoma. Much like other familial malignancy syndromes, genetic analysis of the hereditary defect may shed much needed light on the molecular mechanisms that lead to malignant transformation. Much like familial polyposis coli and the association with colon cancer, familial dysplastic nevus syndrome is treated by close surveillance and frequent biopsy of all suspicious lesions. Similarly, the development of colon cancer can be arrested with total proctocolectomy; unfortunately, a similar solution is not possible in patients with familial dysplastic nevi.[90–94]

FUTURE DEVELOPMENTS IN SKIN SURGERY

The last decade has seen unprecedented advances in our understanding of the skin and its pathology as well as our ability to protect and replace it. Autologous skin grafts remain the best method to cover skin defects, but donor-site problems and limited availability of autologous skin remain problematic.[95–98] Tissue expansion with subcutaneous balloon implants produces new epidermis, and mobilization achieved via expansion remains a highly effective approach to wound coverage.[95–98] Still, optimal wound coverage lies in the development of engineered skin replacements. Current research is directed at identifying different materials and cells that can be used to replace both epidermis and dermis.

Several dermal replacements based on synthetic materials or cadaveric sources are in clinical use (Fig. 16-16). A bovine-collagen and shark-proteoglycan–based dermis (Integra) has been used primarily in burn patients for more than a decade.[95–98] This prosthetic dermis, available in ready-to-use form, can cover large surface areas. Vascularization of this dermis takes 2 to 3 weeks, and final epidermal coverage of the wound requires a thin skin graft.[95–98] The final result is functionally and aesthetically good, but the high cost has been problematic. Cadaveric dermis, with all of the cellular elements removed, is not antigenic and is not rejected by the recipient patient.[95–98] This human dermal matrix is commercially-available (AlloDerm) and functions much like Integra, with similar limitations of engraftment and high cost. Both forms of dermal replacements are more frequently used in delayed reconstruction of burn patients than in the acute setting.[95–98]

Fig. 16-16.

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The most recent generation of dermal matrix replacement tissues includes both cadaveric and xenographic materials. AlloDerm (pictured here) may be placed over various deeper tissues to provide a dermal scaffold onto which autologous skin may be grafted.

Another issue confounding surgeons is the lack of means to quickly provide numerous autologous skin cells for permanent skin replacement. The expansion of epidermis by the growth and maturation of keratinocytes in culture is readily performed.[95–98] A small skin biopsy specimen can produce enough autologous epithelium to cover the entire body surface. However, on the body, the cultured epidermis often blisters and sloughs as a consequence of slow restoration of the basement membrane. Improving the durability of these cells may one day negate autologous skin grafting technique or the requirement for cadaveric soft tissues. In addition, as more is learned about the protein factors that control wound healing and tissue growth, the replacement for damaged skin will eventually come from complete organogenesis of tissue.[95–98] Characterization of these growth factors on a structural and functional level is progressing rapidly. Factors have been isolated that cause specific mesenchymal cells to proliferate, migrate, and organize into structures such as capillaries or even rudimentary organoid tissue.[95–98]

CONCLUSION

Anatomically, the epidermal, basement membrane, and dermal layers of the skin each play a vital role in maintaining dermal/epidermal integrity. Multiple, complex mechanisms within these soft tissues protect us from injury as well as relay external information along a vast neural network. In addition to penetrating trauma, the environment offers a host of potentially injurious elements such as caustic substances, extreme temperatures, prolonged or excessive pressure, and radiation. Infections ranging from simple bacterial to necrotizing, life-threatening disease may also affect the skin and subcutaneous tissues. Perhaps of greatest public concern, a multitude of benign and malignant tumors threaten to disrupt, disfigure, and invade normal skin structure. Although the risks associated with many of these lesions are great, a broad variety of medical and surgical management options currently exist. Although contemporary medicine may not have an optimal answer for each threat the skin may face, continued research, advances in our understanding, and technical improvements in the field promise to enhance our ability to replace and protect the skin well into the future.

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KEY POINTS

1. The breast receives its principal blood supply from perforating branches of the internal mammary artery, lateral branches of the posterior intercostal arteries, and branches from the axillary artery, including the highest thoracic, lateral thoracic, and pectoral branches of the thoracoacromial artery.

2. The axillary lymph nodes usually receive >75% of the lymph drainage from the breast, and the rest flows through the lymph vessels that accompany the perforating branches of the internal mammary artery and enters the parasternal (internal mammary) group of lymph nodes.

3. Breast development and function are initiated by a variety of hormonal stimuli, with the major trophic effects being modulated by estrogen, progesterone, and prolactin.

4. Benign breast disorders and diseases are related to the normal processes of reproductive life and to involution, and there is a spectrum of breast conditions that ranges from normal to disorder to disease (aberrations of normal development and involution classification).

5. To calculate breast cancer risk using the Gail model, a woman's risk factors are translated into an overall risk score by multiplying her relative risks from several categories. This risk score is then compared with an adjusted population risk of breast cancer to determine the woman's individual risk. This model is not appropriate for use in women with a known *BRCA1* or *BRCA2* mutation or women with lobular or ductal carcinoma in situ.

6. Routine use of screening mammography in women ≥50 years of age reduces mortality from breast cancer by 33%.

7. Core-needle biopsy is the preferred method for diagnosis of palpable or nonpalpable breast abnormalities.

8. When a diagnosis of breast cancer is made, the surgeon should determine the clinical stage, histologic characteristics, and appropriate biomarker levels before initiating local therapy.

9. Sentinel node dissection is the preferred method for staging of the regional lymph nodes in women with clinically node-negative invasive breast cancer.

10. Local-regional and systemic therapy decisions for an individual patient with breast cancer are best made using a multidisciplinary treatment approach.

A BRIEF HISTORY OF BREAST CANCER THERAPY

Breast cancer, with its uncertain cause, has captured the attention of surgeons throughout the ages. Despite centuries of theoretical meandering and scientific inquiry, breast cancer remains one of the most dreaded of human diseases.[1–12] The story of efforts to cope with breast cancer is complex, and there is no successful conclusion as in diseases for which cause and cure are known. However, progress has been made in lessening the horrors that formerly devastated the body and psyche. Currently, 50% of American women will consult a surgeon regarding breast disease, 25% will undergo breast biopsy, and 12% will develop

some variant of breast cancer.

The Smith Surgical Papyrus (3000–2500 B.C.) is the earliest known document to refer to breast cancer. The cancer was in a man, but the description encompassed most of the common clinical features. In reference to this cancer, the author concluded, "There is no treatment."[1] There were few other historical references to breast cancer until the first century. In *De Medicina,* Celsus commented on the value of operations for early breast cancer: "None of these may be removed but the cacoethes (early cancer), the rest are irritated by every method of cure. The more violent the operations are, the more angry they grow."[2] In the second century, Galen inscribed his classical clinical observation: "We have often seen in the breast a tumor exactly resembling the animal the crab. Just as the crab has legs on both sides of his body, so in this disease the veins extending out from the unnatural growth take the shape of a crab's legs. We have often cured this disease in its early stages, but after it has reached a large size, no one has cured it. In all operations we attempt to excise the tumor in a circle where it borders on the healthy tissue."[3]

The galenic system of medicine ascribed cancers to an excess of black bile and concluded that excision of a local bodily outbreak could not cure the systemic imbalance. Theories espoused by Galen dominated medicine until the Renaissance. The majority of respected surgeons considered operative intervention to be a futile and ill-advised endeavor. However, beginning with Morgagni, surgical resections were more frequently undertaken, including some early attempts at mastectomy and axillary dissection. Le Dran repudiated Galen's humoral theory in the eighteenth century and stated that breast cancer was a local disease that spread by way of lymph vessels to axillary lymph nodes. When operating on a woman with breast cancer, he routinely removed any enlarged axillary lymph nodes.[5]

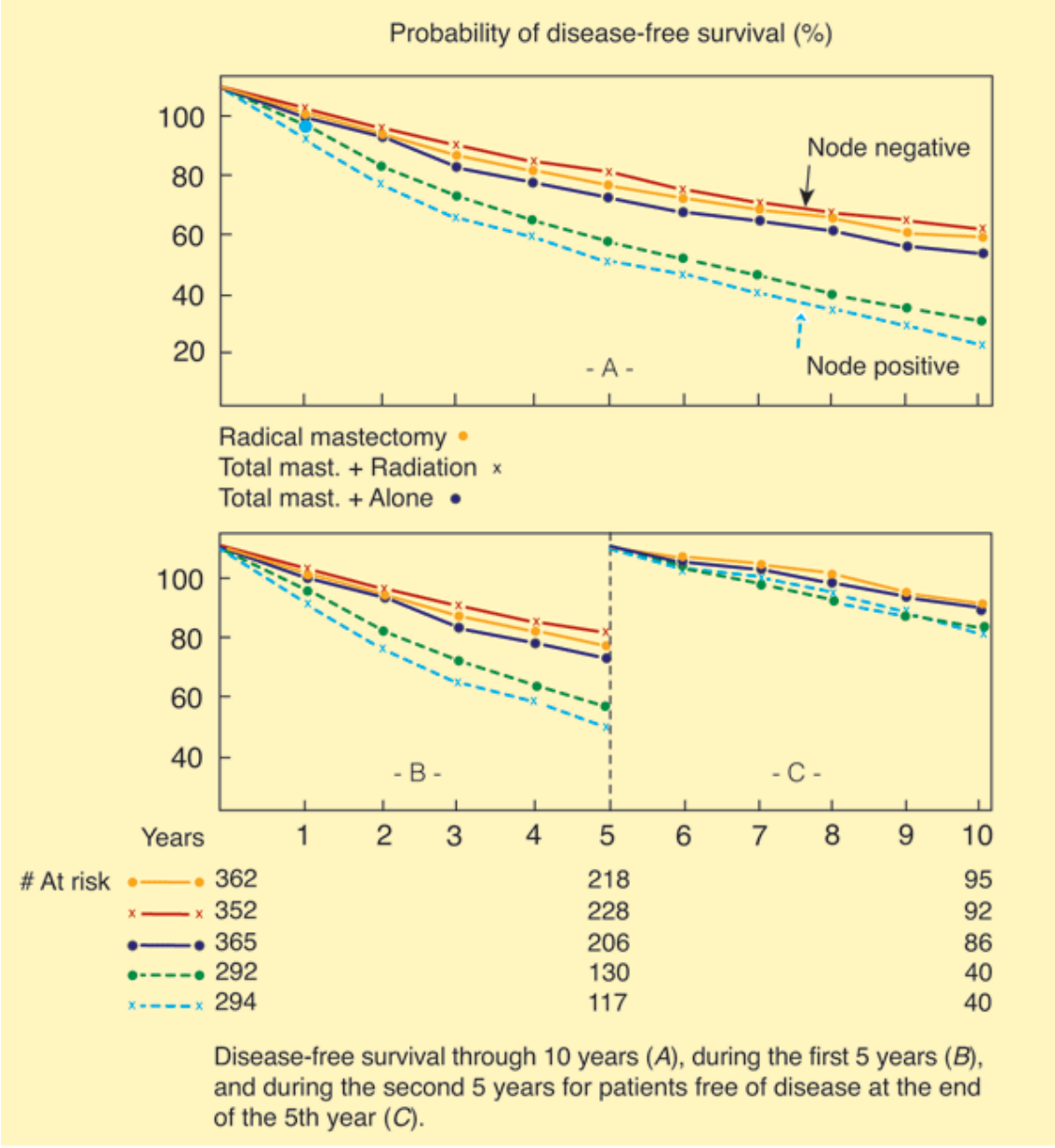
In the nineteenth century, Moore, of the Middlesex Hospital, London, emphasized complete resection of the breast for cancer and stated that palpable axillary lymph nodes also should be removed.[11] In a presentation before the British Medical Association in 1877, Banks supported Moore's concepts and advocated the resection of axillary lymph nodes even when palpable lymphadenopathy was not evident, recognizing that occult involvement of axillary lymph nodes was frequently present. In 1894, Halsted and Meyer reported their operations for treatment of breast cancer.[4] By demonstrating superior local-regional control rates after radical resection, these surgeons established radical mastectomy as state-of-the-art treatment for that era. Both Halsted and Meyer advocated complete dissection of axillary lymph node levels I to III. Both routinely resected the long thoracic nerve and the thoracodorsal neurovascular bundle with the axillary contents.

In 1943, Haagensen and Stout described the grave signs of breast cancer, which included (a) edema of the skin of the breast, (b) skin ulceration, (c) chest wall fixation, (d) an axillary lymph node >2.5 cm in diameter, and (e) fixed axillary lymph nodes. Women with two or more signs had a 42% local recurrence rate and only a 2% 5-year disease-free survival rate.6 Based on these findings, they declared that women with grave signs were beyond cure by radical surgery. Approximately 25% of women were excluded from surgery based on these criteria of inoperability. Today, with comprehensive mammography screening, only 10% of women are found to have such advanced breast cancers. In 1948, Patey and Dyson of the Middlesex Hospital, London, advocated a modified radical mastectomy for the management of advanced operable breast cancer, explaining, "Until an effective general agent for treatment of carcinoma of the breast is developed, a high proportion of these cases are doomed to die."[12] Their technique included removal of the breast and axillary lymph nodes with preservation of the pectoralis major muscle. They showed that removal of the pectoralis minor muscle allowed access to and clearance of axillary lymph node levels I to III. Subsequently, Madden advocated a modified radical mastectomy that preserved both the pectoralis major and pectoralis minor muscles, even though this approach prevented complete dissection of the apical (level III) axillary lymph nodes.[7]

In the 1970s, there was a transition from the Halsted radical mastectomy to the modified radical mastectomy as the surgical procedure most frequently used by American surgeons to treat breast cancer. This transition acknowledged that (a) extirpation of

the pectoralis major muscle was not essential for local-regional control in stage I and stage II breast cancer, and (b) neither the modified radical mastectomy nor the Halsted radical mastectomy consistently achieved local-regional control of stage III breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial conducted by Fisher and colleagues compared local and regional treatments of breast cancer. Life table estimates were obtained for 1665 women enrolled and followed for a mean of 120 months (Fig. 17-1). This study randomly divided clinically node-negative women into three treatment groups: (a) Halsted radical mastectomy; (b) total mastectomy plus radiation therapy; and (c) total mastectomy alone. Clinically node-positive women were treated with Halsted radical mastectomy or total mastectomy plus radiation therapy. This trial accrued patients between 1971 and 1974, an era that predated widespread availability of effective systemic therapy for breast cancer. Outcomes from this trial therefore reflect survival associated with local-regional therapy only. There were no differences in survival between the three groups of node-negative women or between the two groups of node-positive women (see Fig. 17-1A). Correspondingly, there were no differences in survival during the first and second 5-year follow-up periods (see Fig. 17-1B and 17-1C). These overall survival equivalence patterns have persisted at 25 years of follow-up.[13]

Fig. 17-1.



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Results of the National Surgical Adjuvant Breast and Bowel Project B-04 trial. Disease-free survival for women treated by radical mastectomy (*orange circles*), total mastectomy plus radiation (*x*'s), or total mastectomy alone (*blue circles*).

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Other prospective clinical trials that compared the Halsted radical mastectomy to the modified radical mastectomy were the Manchester trial, reported by Turner and colleagues, and the University of Alabama trial, reported by Maddox and colleagues.[8,9] In both studies, the type of surgical procedure did not influence recurrence rates for patients with stage I and stage II breast cancer. The criterion for accrual to the Alabama Breast Cancer Project (1975 to 1978) was a T1 to T3 breast cancer with no apparent distant metastases. Patients received a radical or a modified radical mastectomy. Node-positive patients received adjuvant cyclophosphamide (Cytoxan), methotrexate, and 5-fluorouracil chemotherapy or adjuvant melphalan. After a median follow-up period of 15 years, neither type of surgery nor type of chemotherapy was shown to affect local-regional, disease-free,

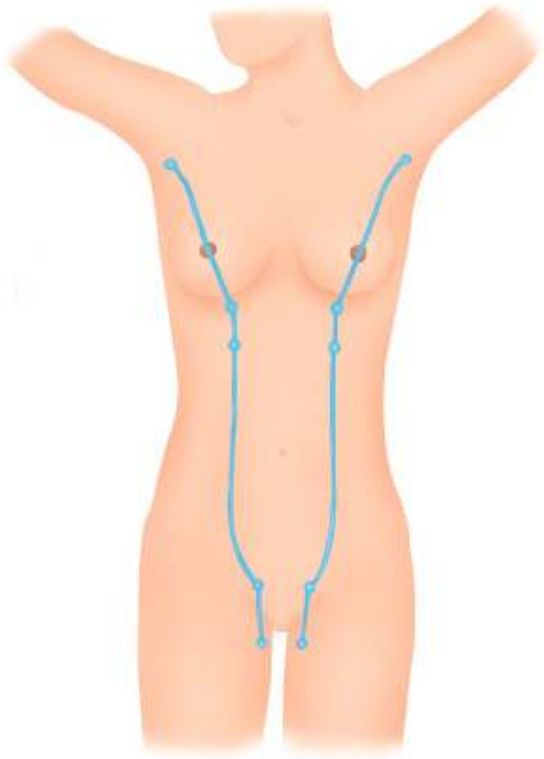
or overall survival.[8] Since the 1970s, considerable progress has been made in the integration of surgery, radiation therapy, and chemotherapy to control local-regional disease, enhance survival, and increase the possibility of breast conservation. Local-regional control is achieved for nearly 80% of women with advanced breast cancers.

EMBRYOLOGY AND FUNCTIONAL ANATOMY OF THE BREAST

Embryology

At the fifth or sixth week of fetal development, two ventral bands of thickened ectoderm (mammary ridges, milk lines) are evident in the embryo.[14] In most mammals, paired breasts develop along these ridges, which extend from the base of the forelimb (future axilla) to the region of the hind limb (inguinal area). These ridges are not prominent in the human embryo and disappear after a short time, except for small portions that may persist in the pectoral region. Accessory breasts (*polymastia*) or accessory nipples (*polythelia*) may occur along the milk line (Fig. 17-2) when normal regression fails. Each breast develops when an ingrowth of ectoderm forms a primary tissue bud in the mesenchyme. The primary bud, in turn, initiates the development of 15 to 20 secondary buds. Epithelial cords develop from the secondary buds and extend into the surrounding mesenchyme. Major (lactiferous) ducts develop, which open into a shallow mammary pit. During infancy, a proliferation of mesenchyme transforms the mammary pit into a nipple. If there is failure of a pit to elevate above skin level, an inverted nipple results. This congenital malformation occurs in 4% of infants. At birth, the breasts are identical in males and females, demonstrating only the presence of major ducts. Enlargement of the breast may be evident and a secretion, referred to as *witch's milk,* may be produced. These transitory events occur in response to maternal hormones that cross the placenta.

Fig. 17-2.



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The mammary milk line.

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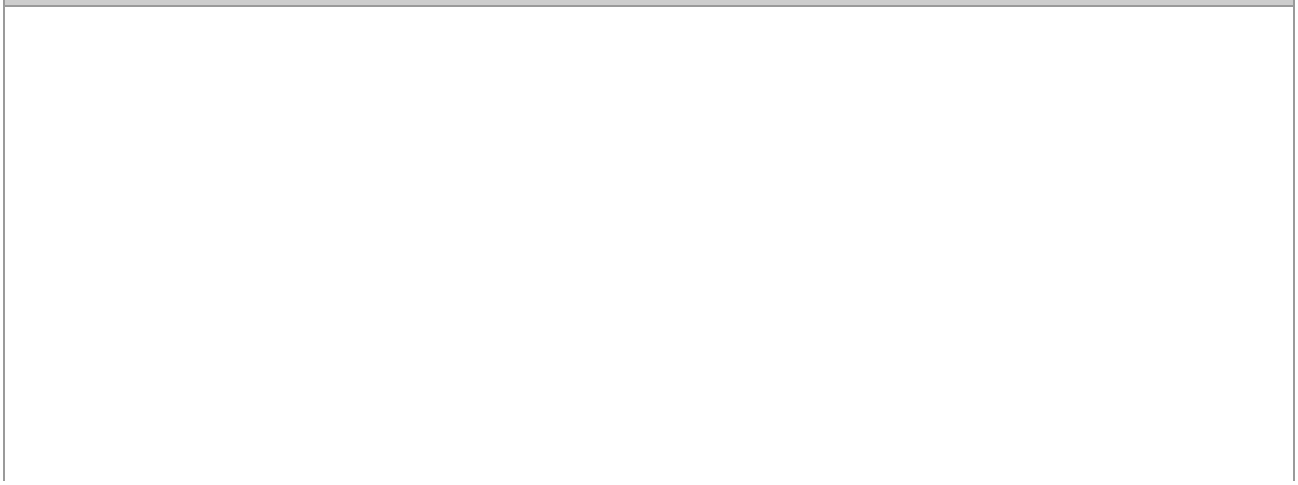
The breast remains undeveloped in the female until puberty, when it enlarges in response to ovarian estrogen and progesterone, which initiate proliferation of the epithelial and connective tissue elements. However, the breasts remain incompletely developed until pregnancy occurs. Absence of the breast (*amastia*) is rare and results from an arrest in mammary ridge development that occurs during the sixth fetal week. Poland's syndrome consists of hypoplasia or complete absence of the breast, costal cartilage and rib defects, hypoplasia of the subcutaneous tissues of the chest wall, and brachysyndactyly. Breast hypoplasia also may be iatrogenically induced before puberty by trauma, infection, or radiation therapy. *Symmastia* is a rare anomaly recognized as webbing between the breasts across the midline. Accessory nipples (polythelia) occur in <1% of infants and may be associated with abnormalities of the urinary tract (renal agenesis and cancer), abnormalities of the cardiovascular system (conduction disturbances, hypertension, congenital heart anomalies), and other conditions (pyloric stenosis, epilepsy, ear abnormalities, arthrogryposis). Supernumerary breasts may occur in any configuration along the mammary milk line but most frequently occur between the normal nipple location and the symphysis pubis. Turner's syndrome (ovarian agenesis and dysgenesis) and Fleischer's syndrome (displacement of the nipples and bilateral renal hypoplasia) may have polymastia as a component. Accessory axillary breast tissue is uncommon and usually is bilateral.

Functional Anatomy

The breast is composed of 15 to 20 lobes (Fig. 17-3), which are each composed of several lobules.[15] Fibrous bands of connective tissue travel through the breast (Cooper's suspensory ligaments), insert perpendicularly into the dermis, and provide structural support. The mature female breast extends from the level of the second or third rib to the inframammary fold at the sixth or seventh rib. It extends transversely from the lateral border of the sternum to the anterior axillary line. The deep or posterior surface of the breast rests on the fascia of the pectoralis major, serratus anterior, and external oblique abdominal muscles, and the upper extent of the rectus sheath. The retromammary bursa may be identified on the posterior aspect of the breast between the investing fascia of the breast and the fascia of the pectoralis major muscles. The axillary tail of Spence extends laterally across the anterior axillary fold. The upper outer quadrant of the breast contains a greater volume of tissue than do the other quadrants. The breast has a protuberant conical form. The base of the cone is roughly circular, measuring 10 to 12 cm in diameter. Considerable variations in the size, contour, and density of the breast are evident among individuals. The nulliparous breast has a hemispheric configuration with distinct flattening above the nipple. With the hormonal stimulation that accompanies pregnancy and lactation, the breast becomes larger and increases in volume and density, whereas with senescence, it assumes a flattened, flaccid, and more pendulous configuration with decreased volume.

Fig. 17-3.



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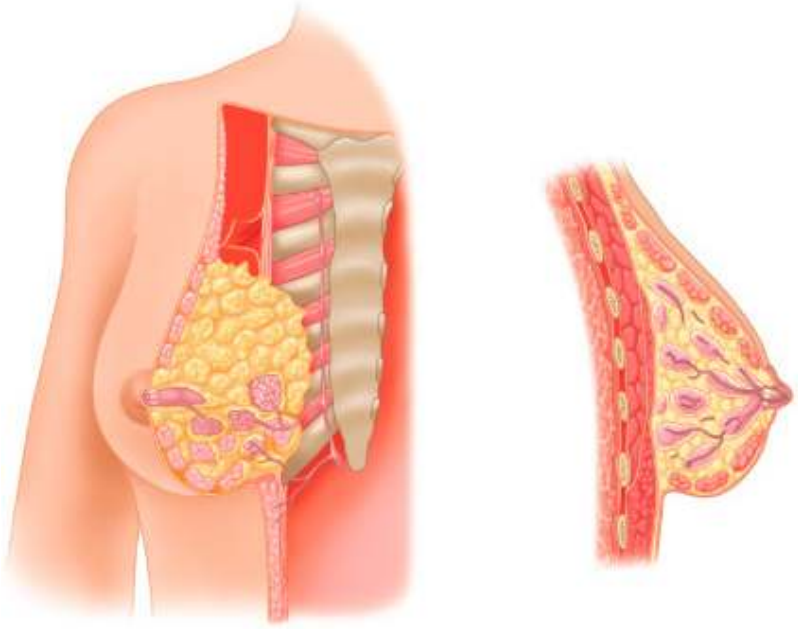

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Anatomy of the breast. Tangential and cross-sectional (sagittal) views of the breast and associated chest wall.

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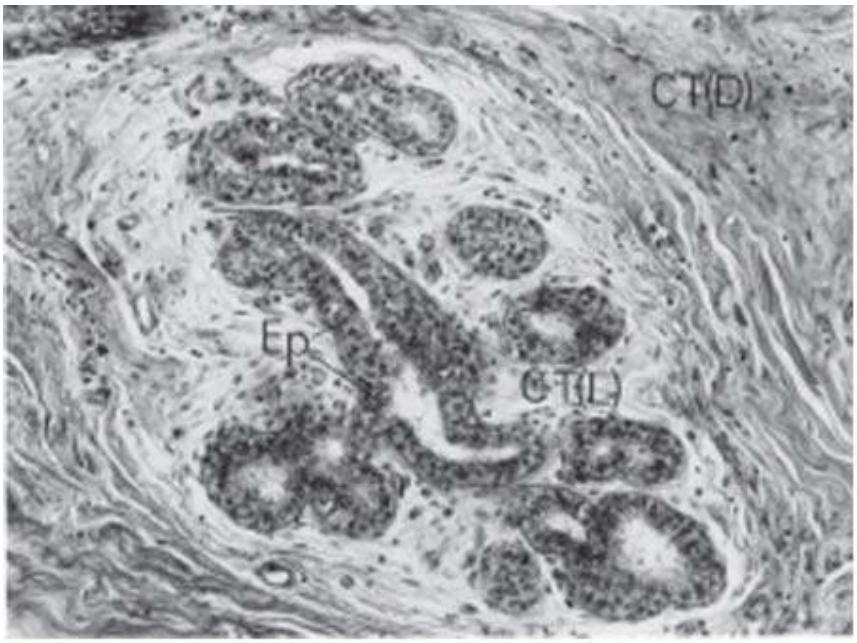
NIPPLE-AREOLA COMPLEX

The epidermis of the nipple-areola complex is pigmented and is variably corrugated. During puberty, the pigment becomes darker and the nipple assumes an elevated configuration. During pregnancy, the areola enlarges and pigmentation is further enhanced. The areola contains sebaceous glands, sweat glands, and accessory glands, which produce small elevations on the surface of the areola (Montgomery's tubercles). Smooth muscle bundle fibers, which lie circumferentially in the dense connective tissue and longitudinally along the major ducts, extend upward into the nipple, where they are responsible for the nipple erection that occurs with various sensory stimuli. The dermal papilla at the tip of the nipple contains numerous sensory nerve endings and Meissner's corpuscles. This rich sensory innervation is of functional importance, because the sucking of the infant initiates a chain of neurohumoral events that results in milk letdown.

INACTIVE AND ACTIVE BREAST

Each lobe of the breast terminates in a major (lactiferous) duct (2 to 4 mm in diameter), which opens through a constricted orifice (0.4 to 0.7 mm in diameter) into the ampulla of the nipple (see Fig. 17-3). Immediately below the nipple-areola complex, each major duct has a dilated portion (lactiferous sinus), which is lined with stratified squamous epithelium. Major ducts are lined with two layers of cuboidal cells, whereas minor ducts are lined with a single layer of columnar or cuboidal cells. Myoepithelial cells of ectodermal origin reside between the epithelial cells in the basal lamina and contain myofibrils. In the inactive breast, the epithelium is sparse and consists primarily of ductal epithelium (Fig. 17-4). In the early phase of the menstrual cycle, minor ducts are cord-like with small lumina. With estrogen stimulation at the time of ovulation, alveolar epithelium increases in height, duct lumina become more prominent, and some secretions accumulate. When the hormonal stimulation decreases, the alveolar epithelium regresses.

Fig. 17-4.



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Inactive human breast (x160). The epithelium (*Ep*), which is primarily ductal, is embedded in loose connective tissue [*CT(L)*]. Dense connective tissue [*CT(D)*] surrounds the lobule.

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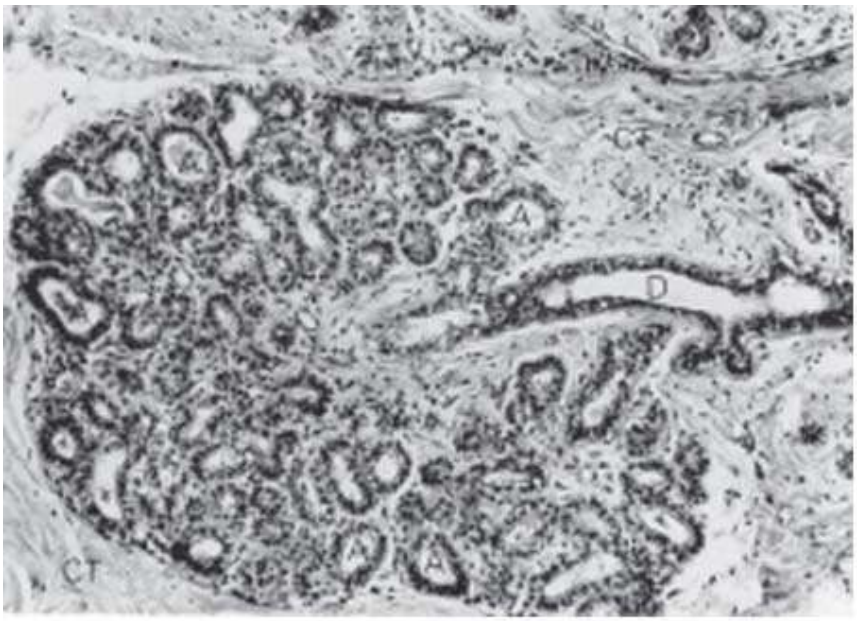
With pregnancy, the breast undergoes proliferative and developmental maturation. As the breast enlarges in response to hormonal stimulation, lymphocytes, plasma cells, and eosinophils accumulate within the connective tissues. The minor ducts branch and alveoli develop. Development of the alveoli is asymmetric, and variations in the degree of development may occur within a single lobule (Fig. 17-5). With parturition, enlargement of the breasts occurs via hypertrophy of alveolar epithelium and accumulation of secretory products in the lumina of the minor ducts. Alveolar epithelium contains abundant endoplasmic reticulum, large mitochondria, Golgi complexes, and dense lysosomes. Two distinct substances are produced by the alveolar epithelium: (a) the protein component of milk, which is synthesized in the endoplasmic reticulum (merocrine secretion); and (b) the lipid component of milk (apocrine secretion), which forms as free lipid droplets in the cytoplasm. Milk released in the first few days after parturition is called *colostrum* and has low lipid content but contains considerable quantities of antibodies. The lymphocytes and plasma cells that accumulate within the connective tissues of the breast are the source of the antibody component. With subsequent reduction in the number of these cells, the production of colostrum decreases and lipid-rich milk is released.

Fig. 17-5.



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Active human breast: pregnancy and lactation (x160). The alveolar epithelium becomes conspicuous during the early proliferative period. An alveolus (*A*) and a duct (*D*) are shown. The alveolus is surrounded by cellular connective tissue (*CT*).

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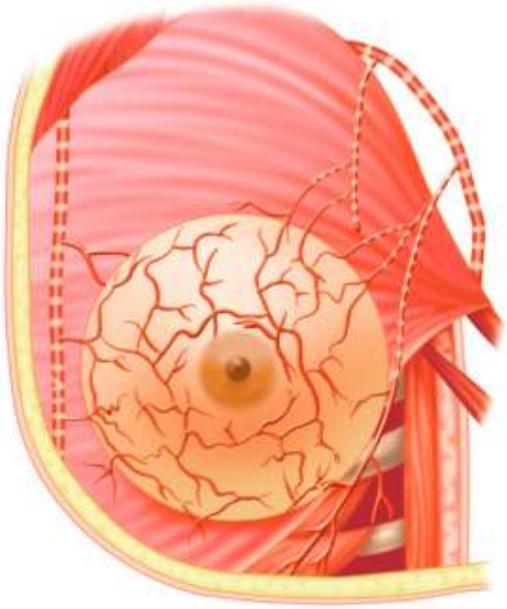
BLOOD SUPPLY, INNERVATION, AND LYMPHATICS

The breast receives its principal blood supply from (a) perforating branches of the internal mammary artery; (b) lateral branches of the posterior intercostal arteries; and (c) branches from the axillary artery, including the highest thoracic, lateral thoracic, and pectoral branches of the thoracoacromial artery (Fig. 17-6). The second, third, and fourth anterior intercostal perforators and branches of the internal mammary artery arborize in the breast as the medial mammary arteries. The lateral thoracic artery gives off branches to the serratus anterior, pectoralis major and pectoralis minor, and subscapularis muscles. It also gives rise to lateral mammary branches. The veins of the breast and chest wall follow the course of the arteries, with venous drainage being toward the axilla. The three principal groups of veins are (a) perforating branches of the internal thoracic vein, (b) perforating branches of the posterior intercostal veins, and (c) tributaries of the axillary vein. Batson's vertebral venous plexus, which invests the vertebrae and extends from the base of the skull to the sacrum, may provide a route for breast cancer metastases to the vertebrae, skull, pelvic bones, and central nervous system. Lymph vessels generally parallel the course of blood vessels.

Fig. 17-6.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com
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Arterial supply to the breast, axilla, and chest wall.

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Lateral cutaneous branches of the third through sixth intercostal nerves provide sensory innervation of the breast (lateral mammary branches) and of the anterolateral chest wall. These branches exit the intercostal spaces between slips of the serratus anterior muscle. Cutaneous branches that arise from the cervical plexus, specifically the anterior branches of the supraclavicular nerve, supply a limited area of skin over the upper portion of the breast. The intercostobrachial nerve is the lateral cutaneous branch of the second intercostal nerve and may be visualized during surgical dissection of the axilla. Resection of the intercostobrachial nerve causes loss of sensation over the medial aspect of the upper arm.

The boundaries for lymph drainage of the axilla are not well demarcated, and there is considerable variation in the position of the axillary lymph nodes. The six axillary lymph node groups recognized by surgeons (Figs. 17-7 and 17-8) are (a) the axillary vein group (lateral), which consists of four to six lymph nodes that lie medial or posterior to the vein and receive most of the lymph drainage from the upper extremity; (b) the external mammary group (anterior or pectoral group), which consists of five or six lymph nodes that lie along the lower border of the pectoralis minor muscle contiguous with the lateral thoracic vessels and receive most of the lymph drainage from the lateral aspect of the breast; (c) the scapular group (posterior or subscapular), which consists of five to seven lymph nodes that lie along the posterior wall of the axilla at the lateral border of the scapula contiguous with the subscapular vessels and receive lymph drainage principally from the lower posterior neck, the posterior trunk, and the posterior shoulder; (d) the central group, which consists of three or four sets of lymph nodes that are embedded in the fat of the axilla lying immediately posterior to the pectoralis minor muscle and receive lymph drainage both from the axillary vein, external mammary, and scapular groups of lymph nodes, and directly from the breast; (e) the subclavicular group (apical), which consists of six to twelve sets of lymph nodes that lie posterior and superior to the upper border of the pectoralis minor muscle and receive lymph drainage from all of the other groups of axillary lymph nodes; and (f) the interpectoral group (Rotter's nodes), which consists of one to four lymph nodes that are interposed between the pectoralis major and pectoralis minor muscles and receive lymph drainage directly from the breast. The lymph fluid that passes through the interpectoral group