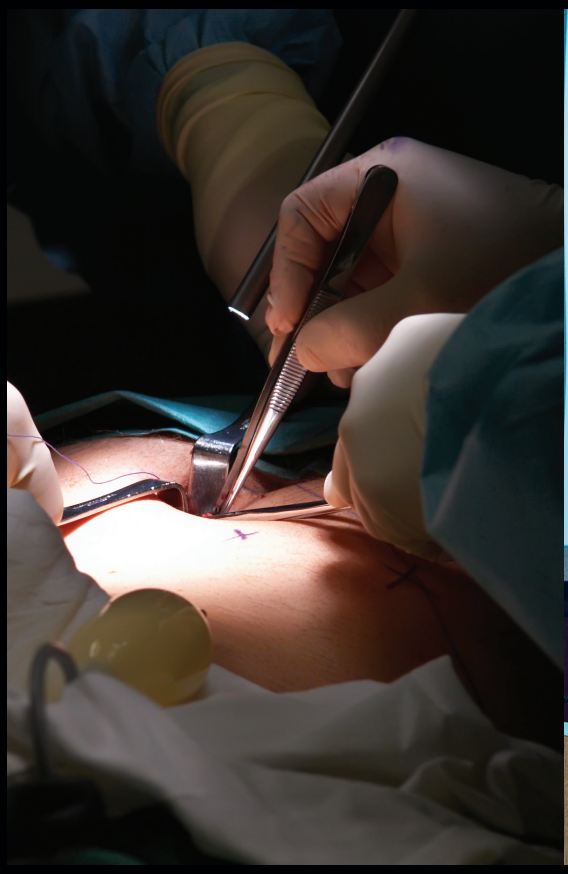
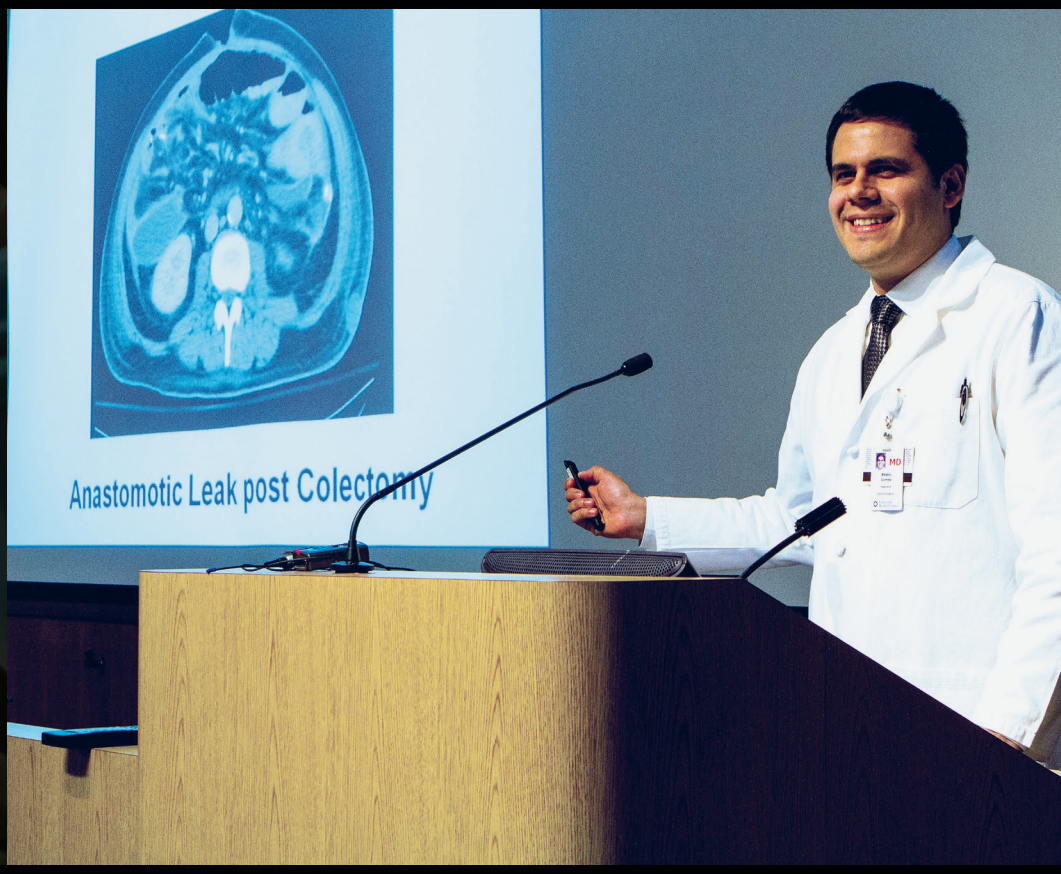
SECOND EDITION

COMPLICATIONS IN SURGERY AND TRAUMA





EDITED BY
STEPHEN M. COHN • MATTHEW O. DOLICH

CRC Press
Taylor & Francis Group

SECOND EDITION

COMPLICATIONS IN SURGERY AND TRAUMA

SECOND EDITION

COMPLICATIONS IN SURGERY AND TRAUMA

EDITED BY

STEPHEN M. COHN, MD, FACS
Professor of Surgery, University of Texas Health Science Center
San Antonio, TX, USA

MATTHEW O. DOLICH, MD, FACS
Professor of Surgery, University of California, Irvine Medical Center
Orange, CA, USA

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20131122

International Standard Book Number-13: 978-1-4822-0887-0 (eBook - PDF)

This text is dedicated:

The memory of my loving mother, Iris

To my supportive father, Leland, the real "Marcus Welby"...

To the memory of my loving mother

And to my wonderful children, Sam and Elizabeth

Lechaim (To Life!)

Steve Cohn

Dedicated to my family:

My parents, Carol and Barry

My wife, Bel

My children, Ally and Jake

Each of whom fills my world with love and support, every day.

Matt Dolich

Contents

Section III Abdomen

Section IV Endocrine

Section V Cardiothoracic

Section VI Vascular

Section VII Orthopaedic

Section VIII Neurologic

Section IX Burns and Wound Healing

Section X Genitourinary

Section XI Pediatric

Section XII Transplantation

Foreword

Most surgeons would prefer not to talk about surgical complications, much less write about them. If they are written about, unusual complications are frequently published as case reports. For this reason, I know of no single-author books on this topic; multiple-author works on surgical complications are the norm. This book is no exception. The multiple authors of its chapters have been chosen for their specific expertise in a given anatomic or physiologic field.

From the patient's viewpoint, a surgical complication is any unexpected event that occurs after surgical intervention and causes the patient pain or suffering. From the surgeon's viewpoint, many of the occurrences that patients would call complications are seen instead as sequelae. A sequela is an untoward occurrence that is out of the surgeon's control, such as phantom limb pain after amputation, the dumping syndrome after gastric resection, and the onset of diabetes after pancreatic resection. The list is almost endless. Surgeons should warn their patients about potential problems before performing the procedure and should convince patients that the need for operative intervention outweighs any problems that may result.

A classic example of such a problem is wound infection. Wound infection can be a sequela when the surgeon is forced to operate through an infected site. In fact, one wound classification system is based on the potential that infection may develop. More often, however, wound infections are true complications and can be prevented. Among the many available preventive techniques are nutritional support, prophylactic administration of antibiotics, skin preparation, sterility of the operative environment, and sterile technique. For example, before sterile technique was adopted, compound fractures resulted in amputation and a mortality rate of 50%–80% because of systemic infection, probably by streptococcus. The patients who survived frequently experienced the development of "laudable pus," which indicated a localized infection, probably due to staphylococcus. War wounds, whether clean contaminated or fully contaminated, were and still are treated with debridement and secondary closure. Appendicitis with rupture is still treated with secondary closure at many medical centers. Since 1900, long before the development of antibiotics, addressing clean wounds under sterile surgical conditions has been associated with low rates of wound infection.

The example given earlier, wound infection, cuts across all surgical disciplines and demonstrates the need for a system-oriented approach to minimizing complications. The occurrence and severity of complications are affected by factors related to patient, environment, hospital, nursing, and surgeon. It makes little difference whether one uses the "weakest link" or the "Swiss cheese" model to explain the occurrence of complications due to failure of the system if, during each case, the level of care is optimized and adequate communication between all personnel providing patient care is ensured.

A strong case can be made for the usefulness of the classic surgical mortality and morbidity conference in analyzing the system failures associated with a given complication. The mortality and morbidity discussion addresses approaches that can be used to obviate a surgical complication in the future. The use of a table can be helpful in placing complications related to system failure into such categories as errors in judgment, errors in technique, and delay in diagnosis, treatment, or both because of the disease progress. Such an analysis serves both educational and quantity-of-care goals.

The thrust of this book is to review and classify the complications related to surgery from the standpoints of prevention, recognition, and management so that their impact on the patient's recovery can be minimized. This book analyzes the complications associated with many types of surgical intervention and dissects the optimal manner of preventing each one. It also discusses diagnostic and therapeutic techniques that can be used to minimize the impact of such complications on the welfare of the patient. Therefore, it should be a standard reference for all surgeons, regardless of specialty.

J. Bradley Aust, MD, PhD (Deceased)
Department of Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Preface

This was not my patient…
I was not present for this case…
There is nothing different I would do the next time…
Let me have the surgical attending tell you why we did this…
I never saw this patient…
If you do enough operations you are bound to have this happen…
It was an act of God…
I did a perfect operation… the ungrateful patient died…

Anonymous Chief Resident

This text was conceived to provide important information regarding the incidence and management of complications encountered in the surgical care of patients. More importantly, the contributing authors have identified methods to prevent or avoid complications. To paraphrase Albert Einstein, "Geniuses learn from other people's mistakes."

This book is dedicated to all the surgeons who have paved the path for surgical success.

Stephen M. Cohn

Matthew O. Dolich

Contributors

Bassan J. Allan
Division of Trauma and Surgical Critical Care
The DeWitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Jayson D. Aydelotte
Department of Trauma–Acute Care Surgery
University Medical Center Brackenridge
Austin, Texas

Jonathan Barasch
Department of Medicine
Columbia University Medical Center
New York, New York

Erik Barquist
Osceola Regional Medical Center
and
University of South Florida
Kissimmee, Florida

Regan J. Berg
Division of Trauma Surgery and Surgical Critical Care
Los Angeles County Medical Center
University of Southern California
Los Angeles, California

Matthew Bindewald
Division of Plastic and Reconstructive Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

James G. Bittner IV
Division of General Surgery
Department of Surgery
School of Medicine
Virginia Commonwealth University
Richmond, Virginia

Joshua R. Blomberg
Department of Orthopedics and Rehabilitation
Miller School of Medicine
University of Miami
Miami, Florida

Susan E. Brien
Royal College of Physicians and Surgeons of Canada
and
Department of Surgery
University of Ottawa
Ottawa, Ontario, Canada

and

Centre de santé et de services sociaux de Gatineau
Gatineau, Quebec, Canada

Joseph R. Buck
Division of Trauma and Surgical Critical Care
Department of Surgery
St. John Hospital
Detroit, Michigan

Sayl Bunyan Al-Saedi
Department of General Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

George W. Burke
Division of Kidney and Pancreas Transplantation
The Dewitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Denise M. Carneiro-Pla
Department of Surgery
Medical University of South Carolina
Charleston, South Carolina

Linda Chen
Division of Kidney and Pancreas Transplantation
The Dewitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Gaetano Ciancio
Division of Kidney and Pancreas Transplantation
The Dewitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Mark Cockburn
Department of Surgery and Critical Care
Kendall Regional Medical Center
and
Mercy Hospital
Miami, Florida

Daniel T. DeArmond
Department of Cardiothoracic Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Johnny Delashaw
Department of Neurological Surgery
University of California, Irvine
Orange, California

Lawrence N. Diebel
Division of Trauma and Critical Care
Department of Surgery
Wayne State University School of Medicine
Detroit, Michigan

James C. Doherty
Division of Trauma Surgery
Advocate Christ Medical Center
Oak Lawn, Illinois

and

Department of Surgery
College of Medicine
University of Illinois at Chicago
Chicago, Illinois

Matthew O. Dolich
Division of Trauma, Burns, Critical Care, & Acute Care Surgery
University of California, Irvine
Orange, California

Joseph J. DuBose
Division of Trauma Acute Dare Surgery and Surgical Critical Care
R. Adams Cowley Shock Trauma Center
University of Maryland Medical System
Baltimore, Maryland

David J. Ebler
The DeWitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Akpofure Peter Ekeh
Division of Acute Care Surgery
Department of Surgery
Boonshoft School of Medicine
Wright State University
Dayton, Ohio

Obi Ekwenna
Miami Transplant Institute
Jackson Memorial Hospital
and
Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Monique Espinosa
Division of Trauma Anesthesiology
Miller School of Medicine
University of Miami
Miami, Florida

Mohamed Fahim
Department of Pain Management
Davis Memorial Hospital
Elkins, West Virginia

Ara J. Feinstein
Department of Surgery
Banner Good Samaritan Medical Center
College of Medicine
The University of Arizona, Phoenix
Phoenix, Arizona

Jonathan A. Fridell
Department of Surgery
School of Medicine
Indiana University
Indianapolis, Indiana

Nicole S. Gibran
Department of Surgery
University of Washington
Seattle, Washington

Enrique Ginzburg
Division of Trauma and Surgical Critical Care
The DeWitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Amy J. Goldberg
Division of Trauma/Surgical Critical Care
Department of Surgery
School of Medicine
Temple University
Philadelphia, Pennsylvania

Gerald Gollin
Division of Surgery and Pediatrics
Loma Linda University School of Medicine
Loma Linda, California

Andrew A. Gonzalez
Department of Surgery
College of Medicine
University of Illinois at Chicago
Chicago, Illinois

Andrea L. Goode
Department of Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Barth A. Green
Department of Neurological Surgery
and
The Miami Project to Cure Paralysis
School of Medicine
University of Miami
Miami, Florida

Navrose S. Grewal
TCS Medical Group
Lakewood, California

and

Division of Cardiothoracic Surgery
Irvine Medical Center
University of California, Irvine
Orange, California

Susan J. Gross
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine
Bronx, New York

John J. Hong
Department of Surgery
Lehigh Valley Health Network
Allentown, Pennsylvania

Gillian Hotz
Department of Neurosurgery
Miller School of Medicine
University of Miami
Miami, Florida

Frank P. Hsu
Department of Neurological Surgery
University of California, Irvine
Orange, California

John O. Hwabejire
Division of Trauma, Acute Care Surgery, and Surgical Critical Care
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Kenji Inaba
Division of Trauma Surgery and Surgical Critical Care
Los Angeles County Medical Center
University of Southern California
Los Angeles, California

George L. Irvin III
The DeWitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

F. Frank Isik
Department of Surgery
University of Washington
Seattle, Washington

Ismail Jatoi
Department of Surgical Oncology
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Scott B. Johnson
Department of Cardiothoracic Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Meghann L. Kaiser
Baptist Medical Center
Wake Forest University
Winston-Salem, North Carolina

David R. King
Division of Trauma, Acute Care Surgery, and Surgical Critical Care
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Joshua Kras
Department of Neurological Surgery
University of California, Irvine
Orange, California

Jane Kayle Lee
Division of Trauma Surgery
Advocate Christ Medical Center
Oak Lawn, Illinois

and

Department of Surgery
College of Medicine
University of Illinois at Chicago
Chicago, Illinois

David M. Levi
Transplant Center
Carolinas Medical Center
Charlotte, North Carolina

Deborah M. Little
Department Psychology & Behavioral Science
College of Medicine
Texas A&M University Health Sciences
and
Scott and White Healthcare
Temple, Texas

Shannon W. Longshore
Department of Surgery and Pediatrics
The Brody School of Medicine at East Carolina University
Greenville, North Carolina

Peter P. Lopez
Division of Trauma and Critical Care
Department of Surgery
Wayne State University School of Medicine
Detroit, Michigan

Jack Louro
Department of Anesthesiology, Perioperative Medicine and Pain Management
Jackson Memorial Hospital
University of Miami
Miami, Florida

Mark G. McKenney
Kendall Regional Medical Center
Miami, Florida

Andrew Michael
Department of Surgery
Lehigh Valley Health Network
Allentown, Pennsylvania

Nicholas Namias
Miller School of Medicine
University of Miami
Miami, Florida

Deepak Narayan
Section of Plastic Surgery
School of Medicine
Yale University
New Haven, Connecticut

Raja R. Narayan
University of California Irvine Medical Center
Orange, California

James V. O'Connor
Division of Trauma Acute Dare Surgery and Surgical Critical Care
R. Adams Cowley Shock Trauma Center
University of Maryland Medical System
Baltimore, Maryland

Adrian W. Ong
Department of Surgery
Reading Hospital
West Reading, Pennsylvania

and

Department of Surgery
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Matthew O'Rourke
Department of Pediatrics
Columbia University Medical Center
New York, New York

Jay D. Pal
Department of Cardiothoracic Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Hao Pan
Department of Cardiothoracic Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Abhijit S. Pathak
Division of Trauma/Surgical Critical Care
Department of Surgery
School of Medicine
Temple University
Philadelphia, Pennsylvania

J. Martin Perez
Department of Surgery
Rutgers New Jersey Medical School
and
Surgical Intensive Care Unit
Hackensack University Medical Center
Hackensack, New Jersey

Edgar J. Pierre
Department of Anesthesiology
Kendall Regional Medical Center
Miami, Florida

Louis R. Pizano
The DeWitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Mohan Ramalingam
Department of Surgery
Banner Good Samaritan Medical Center
Phoenix, Arizona

Junichiro Sageshima
Division of Kidney and Pancreas Transplantation
The Dewitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Kevin M. Schuster
Department of Surgery (Trauma)
Yale School of Medicine
Trauma, Surgical Critical Care and Surgical Emergencies
Yale Medical Group
New Haven, Connecticut

Christopher K. Senkowski
Department of Surgery
Mercer University
Memorial Health University Medical Center
Savannah, Georgia

Gennaro Selvaggi
Division of Transplantation
The DeWitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Amit A. Shah
Department of Anesthesiology
School of Medicine
Yale University
New Haven, Connecticut

Joseph H. Shin
Division of Plastic Surgery
Montefiore Medical Center
Albert Einstein School of Medicine
Bronx, New York

Raymond S. Sinatra
Department of Anesthesiology
School of Medicine
Yale University
New Haven, Connecticut

Meghan E. Sise
Department of Medicine
Columbia University Medical Center
New York, New York

Lars O. Sjoholm
Division of Trauma/Surgical Critical Care
Department of Surgery
School of Medicine
Temple University
Philadelphia, Pennsylvania

Brian R. Smith
Division of Gastrointestinal and Bariatric Surgery
University of California Irvine Medical Center
Orange, California
and
VA Long Beach Healthcare System
Long Beach, California

Kenneth D. Stahl
Division of Trauma and Surgical Critical Care
DeWitt Daughtry Family Department of Surgery
and
William Lehman Injury Research Center
Miller School of Medicine
University of Miami
Miami, Florida

John Stanton
The Bone and Joint Group
Clarksville, Tennesse

Mary Frances Stuever
Department of Surgery
Boonshoft School of Medicine
Wright State University
Dayton, Ohio

Lorena P. Suarez-Kelly
Department of Surgery
Mercer University
Memorial Health University Medical Center
Savannah, Georgia

Ethan A. Taub
Department of Surgery
Mount Sinai Hospital
University of Illinois College of Medicine at Chicago
Chicago, Illinois

Akin Tekin
Miami Transplant Institute
Jackson Memorial Hospital
and
Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Callie M. Thompson
Department of Surgery
University of Washington
Seattle, Washington

Chad M. Thorson
Division of Trauma and Surgical Critical Care Services
Miller School of Medicine
and
Jackson Memorial Hospital/Ryder Trauma Center
University of Miami
Miami, Florida

Kusum Tom
Department of Surgery
Temple University School of Medicine
Philadelphia, Pennsylvania

and

Department of Surgery
Allegheny General Hospital
Pittsburgh, Pennsylvania

Boulos Toursarkissian
Division of Vascular Surgery
Department of Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Andreas G. Tzakis
Transplant Center
Cleveland Clinic Florida
Westin, Florida

Robert M. Van Haren
Division of Trauma and Surgical Critical Care
The DeWitt Daughtry Family Department of Surgery
Miller School of Medicine
University of Miami
Miami, Florida

J. Esteban Varela
Section of Minimally Invasive Surgery
Department of Surgery
School of Medicine
Washington University
St. Louis, Missouri

Albert J. Varon
Division of Trauma Anesthesiology
Miller School of Medicine
University of Miami
Miami, Florida

Howard Wang
Division of Plastic and Reconstructive Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Michael Y. Wang
Department of Neurological Surgery
and
The Miami Project to Cure Paralysis
School of Medicine
University of Miami
Miami, Florida

Constance A. Young
Department of Obstetrics and Gynecology
Jacobi Medical Center
Bronx, New York

Gregory A. Zych
Department of Orthopedics and Rehabilitation
Miller School of Medicine
University of Miami
Miami, Florida

The Surgical Mortality and Morbidity Review

Introduction

We surgeons establish a delightfully rewarding, gratifying, and unique bond with our patients. For our medical colleagues, the stakes are totally different. Without much trepidation, we, the authors, would permit Helen Keller to take our blood pressure or even palpate our edematous ankles. Similarly, if our health maintenance organization (HMO) relegated our primary care to someone with limited intellectual capacity, we would risk a visit or two before complaining.

But when a surgeon suggests that we must go to sleep while he or she clamps our aorta or removes our cancerous tumor, we demand dazzling expertise and total commitment. We may not be able to accurately assess the former (the diplomas on the wall are not sufficient), but we can sense the latter. From our surgeon, we expect knowledge, experience, and technical proficiency; equally important, if things do not go well, we want our surgeon to hurt as much as we do. That is commitment!

What Is Hurt?

Physical pain is easy to describe and define. We have all stubbed a toe or bruised an elbow. Calibrating pain is more complex. We have all seen the rancher from Wyoming who brings his traumatically amputated lower limb to the surgeon by bus, and the businessman from New York City who requires morphine for a haircut. Vicarious hurt, on the other hand, may be unique to humans and is more difficult to explain.

In its simplest form, the morbidity and mortality conference examines misadventures; dissects the preoperative, intraoperative, and postoperative events related to them; and derives strategies to prevent their recurrence. The varieties of surgical error are comprehensively explored in this book. Some are "surgeon specific": we may commit an error in the patient's diagnosis, in our surgical technique, or in the perioperative management of the case. Occasionally, these errors are readily apparent: the appendix was normal or the anastomosis leaked. Some problems, however, are "system specific": the Monday morning anesthesiology conference typically runs later than 8:00 AM. On Mondays, when the rushed anesthesiologists exit their conference, their tardiness prompts an abbreviated preoperative assessment of the patient. The chart clearly states that the patient has diabetes or is being treated with drops for glaucoma, but the anesthesiologist misses this statement. That is a system-specific problem.

To the conscientious surgeon, any problem is always his or her fault. Whenever we, as surgeons, blame the hospital administrator because the ceiling collapsed or blame "patient disease" because our diabetic patient experienced a wound infection, that is a cop-out. We must always strive to eliminate all trouble for our patients. Every mishap is always avoidable, and every problem that does occur is our fault. This philosophy greatly simplifies the adjudication of the mortality and morbidity process. This philosophy also defines hurt. If you want to be God, you must accept responsibility. God controls everything. It follows logically that you receive credit for both the good and the bad. If the bad is your fault, it must hurt. Good surgeons hurt—a lot.

Who Is Responsible?

Ultimately, our goal is to make our patients and their families feel better. If we can accomplish this by virtue of our superior comprehension of some subcellular mechanism of disease or by means of some particular therapy, so much the better. We infuse a phosphodiesterase inhibitor to prevent cyclic-adenosine monophosphate degradation and thus to build the contractile strength of cardiomyocytes. We do this because we know that, with age and congestive failure, patients deplete their cardiac beta-adrenergic receptors, and thus we must resort to a different inotropic strategy. That is great! We can tuck our thumbs into our axillae and strut off to the next lucky patient with the full knowledge that this cardiac cripple is incredibly fortunate to have a surgeon with our degree of omniscience.

Conversely, after our patient tiptoes his or her way through the surgical intensive care unit minefield, some well-meaning cardiology fellow or surgical intensive care unit nurse tells the family that Uncle Andy "almost died" and "really has a bag for a heart." The family (and Uncle Andy) is justifiably delighted to be discharged eventually from the surgical intensive care unit (and the hospital). But, in reality, Uncle Andy arrives home on pins and needles, expecting to die at any moment,

for he is now obsessed with the knowledge of the horrible condition of his heart. That is a complication! We can have a civil discussion about who is responsible for this travesty of care, but we believe that it is the surgeon. From the moment that a surgical diagnosis is even suggested by the patient, his or her mother-in-law, or the medical consultant, the surgeon must enthusiastically accept responsibility for the pathophysio-psycho-social outcome of his or her surgical endeavors. Transfecting a responsive insulin receptor into an unsuspecting hepatocyte for the purpose of glorifying dysfunctional carbohydrate metabolism is nearly miraculous. Accomplishing this while sacrificing Uncle Andy's comprehension and adding to the confusion of the family is a travesty of surgical or medical skill. Our ultimate surgical goal is to make the family understand that Uncle Andy really does feel better.

Are Death and Disease Inevitable?

As conscientious, sensitive, thoughtful, compassionate surgeons, we must not accept the obvious answer to this question of whether death and disease are unavoidable [1]. The surgical mortality and morbidity conference is unique in medicine and probably in the civilized world. Short of bank robbery, few events are as independently attributable to their perpetrator as is a surgical procedure. The surgeon meets the patient and family. He or she describes the pathological problem and the proposed surgical solution. If trust and commitment are not immediately emblazoned into this initial interaction, the whole process is fortunate to achieve junior bush league status. If the diagnosis is omniscient, the surgical technique flawless, the perioperative care masterful, and the patient expeditiously returned to the position of a socially responsible contributor to society, but the patient or the family does not comprehend the process, then the surgeon has failed.

Open discussion of this glorious spectrum of therapeutic opportunities is the purpose of a constructively educational surgical mortality and morbidity conference. When we, as surgeons, welcome this amplitude of criticism, we confidently bare our souls in the knowledge that no matter how good we are, we welcome any sacrifice to be even better. And after every patient we are privileged to treat and after every mortality and morbidity conference, we should look ourselves in the mirror, acknowledging that we may not know what profession is second best but that we are incredibly fortunate to be members of the most gratifying, responsible, receptive, critical, rewarding, and fun guild that exists (H. Polk, S. Guandlick S, Personal communication, 2002).

Julie Heimbach, MD
Mayo Clinic, Rochester, Minnesota

Jyoti Arya, MD
University of Colorado, Denver, Colorado

Alden H. Harken, MD
University of California, San Francisco, and UCSF-East Bay Surgery Program
Oakland, California

Reference

1. Harken AH. Enough is enough. *Arch Surg* 1999; 134: 1061–1063.

The Surgical Mortality and Morbidity Review: Best Practices and Procedures

The mortality and morbidity conference is an exercise unique to surgeons among all the members of the medical profession. Our colleagues in the medical specialties do not organize such conferences and rarely publicly probe their practices for systematic or individual error. Because surgeons collect data on mortality and morbidity and discuss such events regularly, surgical practice is most frequently analyzed by quality assurance staff. The quality assurance mavens are simply being lazy. They would provide a much greater return, in terms of overall improvement in patient care, if they invested their effort among those, primarily nonsurgeons, who do not engage in regular analysis of potential error.

Sad to say, the mortality and morbidity conference in some institutions I have had the privilege to visit sometimes fails to meet the objective of identifying error so that it may be corrected. Failure most frequently is due to lack of any real discussion in depth about the details of complications and deaths. Cases of senior or powerful attending physicians are not brought up for discussion, or details of errors in such cases are glossed over. No one utters critical remarks; moderators shirk their responsibility to probe. The conference is a sham. Even worse, in some institutions, the mortality and morbidity conference is converted into a presentation of "interesting" cases—an exercise better reserved for Grand Rounds—and investigation of the potential for prevention of deaths and complications does not occur.

If a mortality and morbidity conference is to achieve its desired goal, all cases resulting in any deviation, however minor, from the desired and expected outcome must be identified and be eligible for discussion. There can be no exceptions. Additionally, the conference must be appropriately structured; attendance without exception must be required of all staff, residents, and students assigned to the service or department. The conference must be led by moderators who understand and accept that it is their duty to probe for errors and for the causes of untoward outcomes. The conference should be open to nurses and other members of the hospital staff interested in the presentations and discussions.

To enhance effective discussion and sharing of experience, both the number of cases eligible for review and the size of the audience participating in the discussion should be neither too large nor too small. Between 30 and 50 is about the right number for both parameters. If necessary, because of the great workload of the service or department, multiple mortality and morbidity conferences should be conducted by subunits. The conference should be conducted weekly, be limited to one hour in duration so that the attention of the audience does not wander, start on time, and end on time. The room in which the mortality and morbidity conference is held should be large enough to accommodate the audience comfortably. There should be facilities for displaying x-rays—about eight large films simultaneously—and equipment to project occasional pertinent slide or computer illustrations should also be available.

It is not necessary, in my view, to have a pathologist or radiologist in regular attendance. These specialists tend to spend too much time on demonstration of details that are of great interest within their medical niche but do not quickly advance the point of the mortality and morbidity conference: determination of the accuracy and effectiveness of the diagnosis or treatment in the case under discussion.

An agenda listing pertinent statistical and case information should be distributed at the entrance to the meeting room. No information identifiable with a specific patient should be included in the agenda. Material presented at mortality and morbidity conferences is usually protected by quality assurance privileges and regulations. Nonetheless, all copies of the agenda should be collected and destroyed at the end of the conference.

The agenda should include all material for a fixed time period; from eight o'clock Sunday morning to the same time on the following Sunday morning is a convenient interval. The agenda should list the following statistics: numbers of admissions, discharges, open operations, closed (e.g., laparoscopic) procedures, other procedures, complications, and deaths. This statistical information should be followed by a morbidity summary that separately lists each instance of an unexpected or untoward outcome in outline fashion (e.g., wound infection; 64F, colectomy, drained sixth pod). The sketchy information serves simply to remind the audience of the patient involved. The morbidity data are followed by a mortality summary in which each death is individually listed, also in shorthand fashion (e.g., 64F, colectomy; stroke fourth pod; pneumonia; died 10th pod; cause: MOF; no autopsy).

The assignment as moderator should be rotated among several of the most junior members of the staff. These persons are more likely to be up to date in their knowledge base. The moderator chooses from among the cases

listed on the agenda those for presentation and discussion, emphasizing cases with unexpected outcomes, teaching value, rarity, etc. The moderator must maintain control of the conference, insisting that presentations be succinct, discussions be pertinent, and no witch-hunting be practiced by the audience. Knowledgeable members of the staff should be called upon for comment, especially if it is likely they will dissent. Residents should be liable to be called upon at any time—a device that helps to keep them awake. The moderator should generate any required minutes or reports soon after the conference has been completed.

Presentations, as requested by the moderator, are made by the resident team involved. All members of the team should stand at the front of the room. Usually a student or intern quickly summarizes the clinical course up to the time of operation or other salient event. These presentations should be rehearsed so that they are short and succinct, no more than a minute or two in length, even for a complicated case. Because all cases are eligible for discussion, all will have to be prepared. Pertinent x-rays should be put up during the initial presentation for viewing by the audience; the x-rays must be sorted in advance because there is no time within an efficiently conducted mortality and morbidity conference for rummaging through an x-ray file.

The presentation is next taken up and completed, beginning with the operation and continuing through the postoperative course, by the most senior resident involved in the procedure. I advise residents to read *Forgive and Remember* by Bosk [1] and to identify and follow the 15 rules of successful resident behavior identified therein. If they do so, they will acknowledge their errors during their presentation, thus anticipating reaction from the audience and controlling the discussion at the mortality and morbidity conference. If they do not, their experience at mortality and morbidity will sometimes be unnecessarily unpleasant.

I made it a rule that if residents had not disagreed at the time with the attending physician about any decision or other matter, then they carried responsibility for the outcome and had to conduct the presentation and answer questions from the audience. On the other hand, if they had clearly established their position of dissent, all they had to do was say so; the attending physician then had to come forward to complete the presentation and handle the discussion.

After the completed presentation, the moderator may ask the members of the audience whether they have questions that might clarify details of the presentation. Then the moderator initiates discussion of alternatives and possible error. If their presentation has been conducted as it should be, the residents will have left no question unanswered and the conference will simply move on to the next case.

The mortality and morbidity conference should be the best teaching exercise conducted by a surgical service or department. The goal is to have an open, thorough, detailed discussion of untoward outcomes so that all may learn from these events with the aim of improving the excellence of patient care. Properly conducted, the mortality and morbidity conference will, at least sometimes, be an uncomfortable exercise for some participants because no one, save an intellectual masochist, relishes having his or her potential lapses discussed in public. But if properly conducted in a spirit of open intellectual inquiry, the mortality and morbidity conference will serve to enhance the professional knowledge and conduct of all participants and will help to avoid repetitive error. It is, therefore, "worth the price" of occasional embarrassment.

Robert E. Condon, MD, MSc, FACS
Department of Surgery
The Medical College of Wisconsin
Milwaukee, Wisconsin

and

The University of Washington Medical School
Seattle, Washington

Reference

1. Bosk CL. *Forgive and Remember: Managing Medical Failure*, 2nd edn. Chicago, IL: University of Chicago Press, 2003.

Section I

Introduction

1

Strategies for Reducing Variation in Surgical Outcomes

Raja R. Narayan and Brian R. Smith

CONTENTS

1.1 Introduction

For more than a decade, growing interest has emerged in improving patient safety as a significant priority in American medicine. This relatively new goal has taken on a complex form in recent years, with its origins dating back to the early 1970s. The modern version of improving patient safety and improving outcomes has been branded *quality*. Stakeholders in medicine have also defined themselves more transparently in recent years, including governments, insurers, and providers. With healthcare expenditures growing in an economically unsustainable fashion, all three major stakeholders have become increasingly invested in improving quality in an effort to decrease costs and model medicine into a more business-like entity with defined products and expected outcomes. However, the variability in outcomes in medicine has proven to be a formidable obstacle to overcome. Variability has been shown to exist between providers, between facilities, within facilities, and even geographically, making targets for reform elusive. To that end, application of similar expectations to those of the business world has revealed the monumental challenge that optimizing the "product" of medicine poses, and has underscored the realization that medicine is the most complex business model known.

Lessons from both the automobile and airline industries have previously demonstrated the detrimental effects of variability on product quality and cost. Translating those same lessons to medicine has revealed similar deleterious effects. One of the seminal studies that began to shed light on variability and outcomes was by O'Connor et al. (1998). This regional study by the Northern New England Cardiovascular Disease Study Group reported on the modes of death associated with coronary artery bypass grafting (CABG) and assessed the causes of outcome variability in patients receiving the procedure. There was wide variability among the five different facilities performing the procedure, with mortality rates ranging from 3% to 11%. The group was able to show that variation in outcomes could be traced to the occurrence of low-output heart failure, while other seminal complications were statistically similar across surgeons including hemorrhage, stroke, infection, and dysrhythmia. These findings ultimately allowed for process improvements targeting low-output failure regionwide as a means of lowering mortality after CABG. This was one of the earliest documented efforts at identifying and subsequently managing variability as a means of improving outcomes.

The national focus on quality and safety effectively began a few years later in 2000 with *To Err Is Human* and was followed shortly thereafter with *Crossing the Quality Chasm*, both published by the Institute of Medicine.[2,3] Between these two reports, it was noted that over 44,000 people die every year from preventable medical errors costing between $17 billion and $29 billion a year in additional care. These two reports gave the public and insurers a first glimpse at the true quality of the product that the healthcare community was producing. This was a wake-up call to the healthcare community that change was needed. Since that time, there has been growing pressure by insurers and more recently by government to initially encourage and more recently force the healthcare community to focus on improving quality. Providers, in the form of national organizations such as the American College of Surgeons (ACS), have now made quality part of their mission, as providers have begun to realize that failure to take the lead in improving quality will result in policymakers and/or insurers doing so for them.

The Centers for Medicare and Medicaid Services (CMS) have also begun scrutinizing variance as a barrier to quality by launching large hospital-wide initiatives to decrease the rates of postoperative complications.[4] In an effort to directly target items that are widely viewed as preventable markers of quality patient care, CMS began withholding payment for the following hospital-acquired secondary diagnoses as of October 1, 2008:

- Retained foreign bodies (such as laparotomy pads and surgical instruments)
- Pressure ulcers
- Catheter-associated urinary tract infections
- Catheter-based vascular infections
- Air embolism
- Mediastinitis
- Blood incompatibility for transfusions
- Falls

Most of these complications have strong evidence to suggest that they can be avoided. However, some of these "preventable" complications occur despite every precaution, especially in those hospitals that inherently care for more complicated patients. Insurance providers have followed suit and also begun linking adherence to evidence-based methods with reimbursement.[5] While some reluctance should exist in applying average solutions to highly variable patients, there is an inherent advantage to applying data-proven approaches to deal with common problems in surgical patients.

Beyond issues with insurance, variability has been identified as a key factor driving up the cost of medical care.[6] A recent article published in the lay press regarding variability helped clarify many of the problems that plague medicine. In 2009, Gawande wrote an article for *The New Yorker Magazine* entitled "The cost conundrum," which was one of the first to critically evaluate the effect of variability in medicine and its resultant effect on healthcare costs. In this article, Gawande was able to show that wide variability in costs at different institutions failed to result in improved outcomes. While not the first, this article was certainly the most mainstream and signaled a departure from the notion that spending more yields better care. The author went on to point out that centers accruing high cost tended to have wide variability related to the use of multiple repeated diagnostic and therapeutic procedures. At the same time, these facilities tended to have poorer patient outcomes overall. Therefore, in order to improve reimbursement rates, drive down medical costs, and foremost to improve patient care and outcomes, it becomes critical to identify the factors leading to variability.

1.2 Causes of Variability

Several proposals have been put forward to facilitate the conceptual equation that results in patient outcomes. One of the first was described by Iezzoni in 2003, where she noted that variance in patient outcome could be defined in a mathematical form.[7] She described an "algebra of effectiveness" such that

Patient factors + Effectiveness of care + Random events = Patient outcome

Birkmeyer and Dimick took Iezzoni's theorem one step further, applying the Donabedian quality-of-care framework to describe patient outcome as a result of various aspects of the healthcare structure and process[8] (Figure 1.1). They note that the structure includes variables that do not directly affect patient outcome but do change the process by which a patient is cared for. The structure first includes the surgeons' level of experience as determined by their skill with patient care by evaluating and correctly selecting surgical candidates, managing patients in the operating room, preventing complications in the postoperative period, as well as recognizing and treating complications that do occur. A litany of evidence supports the notion that the experience of the surgeon affects patient outcome as classically seen in seasonal variance with new residents every July.[9]

Birkmeyer and Dimick further note that the structure includes the volume of cases performed—surgeons operating in high-volume centers tend to have lower rates of mortality.[10,11] Paradoxically, it has been shown

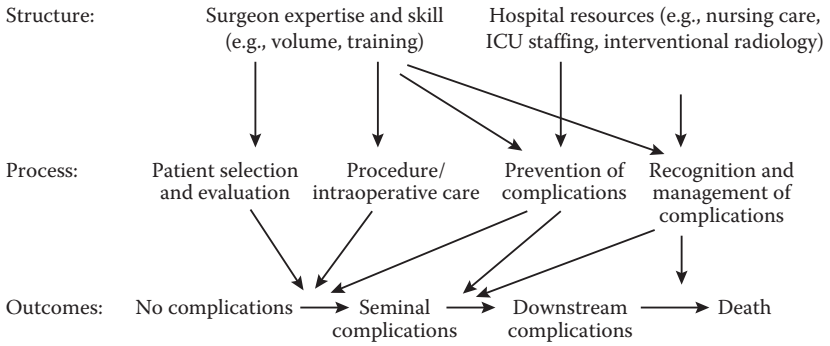


FIGURE 1.1
Birkmeyer and Dimick's application of the Donabedian quality-of-care framework to describe patient outcome as a function of the healthcare structure and process.

that low-volume surgeons operating in high-volume hospitals tend to have similar results as high-volume surgeons, suggesting that decreased mortality in high-volume centers speaks more of the institutional management of patients rather than that provided by the individual surgeon.[12]

1.2.1 Quality of Care

1.2.1.1 Structure of Care

Hospital resources play a large part in determining the structure of patient care. This includes the volume of nurses caring for a ward, the volume of ICU staff on hand to manage acute postoperative issues, and resources available for the care of the patient (i.e., interventional radiology, advanced imaging techniques, etc). The relationship between increased nurse staffing and decreased surgical mortality has been well-documented in the literature.[13–17] The same can be said for inadequate physician staffing in the ICU.[18,19] Beyond sheer staffing, Pronovost et al. showed that infrastructure within the ICU plays a large part in reducing mortality in the postoperative period.[20–22] The act of conducting daily rounds with an intensivist, for instance, was found to reduce inpatient mortality by a factor of 3. Additionally, the frequency of which an ICU is "closed" or without an available bed has been associated with increased mortality in patients undergoing unexpected surgeries. As such, Birkmeyer and Dimick place increased emphasis on the need to focus on the ICU to improve outcomes of surgical patients.[23]

While these measures have been employed to improve overall outcome, certain patient factors still influence their fate. In a study of Medicare patients, Silber et al. found that the rate of postoperative morbidity was most related to patient factors, whereas the rate of "failure-to-rescue" was determined by hospital factors.[24] "Failure-to-rescue," as described by Silber, is a measure of surgical quality defined as death after diagnosis of one or more specific complications noted as follows:

- Pressure ulcer
- Deep venous thrombosis
- Pulmonary embolism
- Aspiration
- Central line infection
- Malnutrition
- Postoperative infection
- Postoperative cardiac complications

Birkmeyer and Dimick also noted that failure to manage these seminal complications could often cause the patient to acquire downstream complications such as ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS), leading to death. It is thus critical to acknowledge factors in the structure of patient care that need to be improved to optimize overall patient outcome and prevent these types of complications.

1.2.1.2 Process of Care

The process of managing surgical patients provides numerous opportunities to improve communication and, ultimately, patient outcome. Recent studies have described the benefits of using checklists, similar to those used in the airline industry, to decrease rates of wrong-site surgeries and to improve morbidity and mortality overall.[25] A study by Haynes et al. employing intraoperative checklists in eight hospitals in eight different cities around the world found that mean morbidity decreased from 11% to 7% and mean mortality dropped from 1.5% to 0.8%. Both of these findings were statistically significant. Further, they showed that the rate of postoperative complications declined in three

different centers, ranging from wealthy to poorer countries, suggesting that perioperative checklists may confer patient benefit in a resource-independent fashion.

Emphasis has also been placed on improving teamwork among surgeons and ancillary staff to optimize the process of surgical patient care. McCafferty and Polk parallel team-building strategies also used in the aviation sector as applicable to the medical field.[26] They note that an effective team is one where all members feel free to communicate during preflight briefings to acquaint everyone with expected tasks and potential challenges. Unfortunately, many hospitals have yet to fully optimize teamwork for both surgeons and involved staff members. Makary et al. found vast discrepancies in opinion when surgeons and staff alike were surveyed on their perception of teamwork at their institution.[27] They discovered that while surgeons rated the quality of collaboration with other surgeons as "high" or "very high" 85% of the time, nurses rated their collaboration with surgeons highly only 48% of the time. To improve communication, some experts have suggested holding preoperative meetings similar to those used in aviation. Nundy et al. experimented with the implementation of preoperative briefings with the goal of decreasing intraoperative delays.[28] These meetings, averaging 2 min, reduced intraoperative delays from 31% to 25%. Furthermore, delays due to communication failure decreased by 80%, and overall communication failure dropped by 17%. Other techniques that have been embraced to varying degrees include surgical "check rides," where a surgeon is supervised intraoperatively by a senior surgeon providing advice as well as time-outs to diminish instances of wrong-site surgeries.

1.2.2 Patient Characteristics

Despite every precaution taken by the surgeon, patients may still develop complications due to inherent characteristics brought to the table by the patients themselves. The task for the surgeon then is to screen for these characteristics whenever possible and to take the appropriate steps in optimizing patients for surgery, or to pursue other avenues if surgery is relatively or absolutely contraindicated. Preoperative screening should thus assess for any preexisting cardiac, respiratory, hepatic, or renal disease, diabetes mellitus, or malnutrition and optimize the medical management of these conditions prior to surgery.[29,30] Recommendations for preoperative screening from the ACS, American College of Cardiology Foundation (ACC), American Heart Association (AHA), and the American Academy of Family Physicians (AAFP) are summarized in Table 1.1.

Tools have also been developed to help surgeons predict perioperative risk and hence counsel patients about their actual perioperative risks prior to surgery. Aust et al. utilized the Veterans Affairs National Surgical Quality Improvement Program (NSQIP) database to estimate the perioperative risk of mortality.[31] With this calculator, patients can be appropriately counseled regarding the likelihood of perioperative mortality after surgery. In particular, those patients with significant underlying comorbidities that have already been optimized can be counseled about predicted operative mortality that is procedure specific. Tools such as this permit truly informed consent and allow for input from the patients themselves in a patient-centric fashion. If a patient or family is told that they have a 75% likelihood of dying from surgery, for example, they may very well forego the pain and suffering involved. This calculator thus provides a tool the surgeon can use to potentially avoid high-risk and/or futile surgery, which is often at the compulsion of inadequately informed patients and/or family.

1.3 How to Measure Variability

Numerous mechanisms have evolved to measure variability. The first and certainly most noteworthy is the measurement of variance through systematic assessment of surgical quality. The only program developed by surgeons to do so as of this writing is NSQIP. This program originated in the Veterans' Administration Health System under the auspices of Shukri Khuri and was the first validated outcomes-based program to evaluate surgical quality among providers.[32] The program was later validated in non-VA hospitals and has been shown to remain valid in private sector hospitals too.[33] NSQIP contains a complex risk stratification system, which allows patient comorbidities to be accounted for when comparing outcomes. Such a comparative assessment of quality between various services and between hospitals permits identification of outliers of morbidity and mortality, both at the service and facility levels. Hospitals are categorized quarterly as performing below, at, or above the mean compared to similar participating institutions, and realization of these data has been shown to improve surgical outcomes.[34] However, participation in this program costs nearly $100,000 annually. In addition to the up-front cost to participate, hospitals must devote experienced clinical personnel, typically a nurse, to run the program full time and gather data through chart review. Nevertheless, Dimick et al. were able to demonstrate that the program can soon pay for itself in short order through improved patient outcomes and shorter lengths of hospital stay.[35]

Within a short period after adoption of NSQIP in the VA system, Khuri et al. were able to demonstrate a 40% decline in morbidity rates.[36] Since the widespread adoption of NSQIP, Henderson et al. have critically evaluated

TABLE 1.1

Recommendations for Preoperative Screening

Indication	Recommendations
Healthy patient	
≤40 years old	Hemoglobin, urinalysis for pregnancy in women of childbearing age
>40 years old	Hemoglobin, urinalysis for pregnancy in women of childbearing age, ECG, blood glucose if age ≥45 years or history of diabetes
Cardiovascular disease	ECG, CXR, hemoglobin, electrolytes, BUN, creatinine, glucose if age ≥45 years or history of diabetes
MI within 6 weeks, unstable angina, decompensated CHF, significant arrhythmia, severe valvular disease	Stress test, cardiology consultation, intraoperative ECG monitoring
Previous MI (>6 weeks ago), mild stable angina, compensated CHF, diabetes mellitus	Stress test if procedure high risk or patient has low functional capacity, consider assessing left ventricular function by echocardiogram
Rhythm other than normal sinus, abnormal ECG, history of stroke, age >70, low functional capacity	Stress test if procedure high risk or patient has low functional capacity
Pulmonary disease	CXR, hemoglobin, blood glucose if age ≥45 years, ECG if age >40 years, provide patient with instructions for incentive spirometry or deep-breathing exercises
Asthma	Pulmonary function testing or peak flow rate to assess status of disease
COPD	Consider pulmonary function testing and arterial blood gas to assess severity of disease
Cough	Determine etiology
Dyspnea	Determine etiology
Smoking	Counsel patient to cease smoking 4–8 weeks before procedure
Obesity	Provide patient with instructions for incentive spirometry or deep-breathing exercises
Abdominal or thoracic surgery	Provide patient with instructions for incentive spirometry or deep-breathing exercises
Hepatic disease	Elective surgery contraindicated in patients with Child–Pugh class C or MELD score >15
Renal disease	BUN, serum creatinine, urinalysis if UTI suspected, creatinine clearance, FeNa, ECG, and serum potassium for patient on dialysis
Malnutrition	Consider postponing surgery if serum albumin <3.2 g/dL or lymphocyte count <3000 per μL

Note: ECG, electrocardiogram; CXR, chest radiograph; BUN, blood urea nitrogen; MI, myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MELD, model for end-stage liver disease; UTI, urinary tract infection; FeNa, fractional excretion of sodium.

the design and statistical methodology of the program.[37] Unfortunately, NSQIP does not assess quality at the level of the individual surgeon, although factors determining surgical quality are often due to systems and teams of care. Nonetheless, NSQIP follows patients for 30 days from the date of surgery to evaluate for more than 20 different postoperative complications. In addition, reoperations as well as readmissions and lengths of stay are also captured in NSQIP. Hall et al. evaluated 118 NSQIP hospitals and showed that each hospital prevents 250–500 complications per year from participation in the program.[38] Additionally, 82% of participating hospitals had improvement in morbidity levels, while 66% experienced improvement in mortality levels. Sustained improvement in performance is shared within NSQIP for widespread dissemination to other facilities.

Fundamentally the program has shown that the association between complications and overall mortality tends to disappear when risk adjustment occurs. When risk stratification occurs, postoperative complications become more closely associated with patient factors rather than quality of care. Decreased variability may also be due to the fact that more monitoring occurs now after the implementation of NSQIP (i.e., Hawthorne effect). Currently, NSQIP remains the only surgeon-developed mechanism of quality assessment and mechanism for measuring and minimizing variability.

Another means of measuring variability is by ranking hospitals based on surgical mortality. Dimick et al. were able to show that adjusting hospital mortality for reliability through the use of the Bayes technique reduced apparent variation across mortality from CABG, abdominal aortic aneurysm (AAA) repair, and pancreatic resection.[39] They were also able to show that (1) reliability-adjusted mortality better forecasts future performance and (2) it is essential to adjust for statistical reliability when sample sizes are small. When evaluating variance in small sample sizes, it is difficult to

determine if variation is due to chance (good or bad luck) or due to true differences in quality. The Bayes technique reveals just how difficult it is to distinguish true variance in outcome as surveillance inherently causes improvement in outcome. Unfortunately, neither morbidity nor mortality has changed much through the institution of the Surgical Care Improvement Project (SCIP), which originated from this concept. It can therefore be surmised that evidence-based medicine must be the foundation of surgical care, as without it, disparities in quality rapidly arise while reimbursement falls off.

1.4 Strategies to Reduce Variability

1.4.1 Process Compliance in Perioperative Care

Steps have been taken by providers, policymakers, and even insurers to reduce variation in surgical outcomes. Several measures taken to institute national protocols for effective patient management have reported success in reducing this variation.

1.4.1.1 Leapfrog Group

Based on the concept of improvement through transparency, the Leapfrog Group is one of several organizations seeking to both improve health institutions and enable patients to make informed decisions when selecting a healthcare provider and/or facility.[40] Launched in 2000, the Leapfrog Group now reports on the quality of over 1300 hospitals nationwide, offering incentives and rewards to the best performing centers. Performance is measured by the Leapfrog Hospital Survey, which is updated monthly. Endorsed by the National Quality Forum (NQF), this survey has been shown to reduce the occurrence of preventable medical mistakes by assessing hospital performance. A study by Brooke et al. noted that compliance with Leapfrog-sponsored NQF safety practices was associated with increased detection of deep venous thrombi (DVT), surgical site infections (SSI), and postoperative cardiac events following six high-risk procedures.[41] They further noted that compliance decreased the likelihood of failure-to-rescue following diagnosis of SSI and even decreased the odds of mortality at 30 days postoperation.

1.4.1.2 Pay for Performance

Akin to the business world, the concept of tying pay to results or outcomes has begun to permeate into medicine. As one of the earliest models, the Leapfrog Group licenses a Leapfrog Hospital Recognition Program to insurance providers as a pay-for-performance program. The function of this program is to incentivize participating hospitals to maintain transparency and continue to further improve according to the Leapfrog standards. With the federal government rolling out pay-for-performance to all hospitals participating in Medicare in October 2012, this method of quality improvement has already come under due scrutiny. Pay-for-performance has noted varying degrees of success to date. Rosenthal et al. noted that incentive payments made through pay-for-performance seemed to be most effective in improving process compliance among mostly poor performers.[42] Recent data published by Sutton et al. found that pay-for-performance instituted in hospitals in the United Kingdom achieved reductions in mortality of statistical significance from pneumonia and of clinical significance from acute myocardial infarction and heart failure.[43] Similar studies in the United States looking only at Medicare patients, however, have been less optimistic.[44] Epstein noted in a recent editorial in the *New England Journal of Medicine* that key differences exist between American attempts with pay-for-performance and the success Sutton noted in England. He found that bonuses paid to the best performers were not only larger but also paid out to a greater proportion of participants. Participating English hospitals were also evaluated for the care rendered to all patients, not just those covered by Medicare as done in the analogous American studies. Perhaps most importantly, English hospitals agreed to invest awarded funds internally to take further steps to improve clinical care by hiring specialist nurses, instituting new data-collection systems linking performance feedback to clinical personnel, and participating in regular shared-learning events. Until American institutions are able to fully embrace such a unilateral approach to pay-for-performance, similar lackluster findings may continue.

1.4.1.3 SCIP and Surgical Site Infection Prevention

One of the national protocols supported by most pay-for-performance programs includes SCIP. Launched in 2006 by CMS and the Center for Disease Control and Prevention (CDC) as an improvement on the NQF, SCIP aimed to decrease the rate of postoperative complications by 25% by 2010 through 10 policies, noted in Table 1.2.[45] Compliance with SCIP has now become a nationally acknowledged measure for surgical quality. Initial studies found that SCIP effectively decreased the rate of SSIs by as much as 27%.[46] In fact, one multicenter study of 400,000 patients found that lower rates of SSIs could be noted upon compliance with at least 2 of the 10 SCIP policies.[47] More recent studies have been less positive, suggesting that the task of monitoring SSIs itself may have more to do with their decrease than SCIP. Hawn et al. found from a survey of the National Veterans Affairs'

TABLE 1.2

Measures of SCIP

Measure	Description
SCIP Inf-1	Prophylactic antibiotics given within 60 min before incision (120 min for vancomycin or fluoroquinolones)
SCIP Inf-2	Appropriate antibiotic selection
SCIP Inf-3	Discontinuation of prophylactic antibiotics within 24 h after surgery (48 h for cardiac cases)
SCIP Inf-4	Controlled (<200 mg/dL) 06:00 postoperative glucose in cardiac surgery patients
SCIP Inf-6	Appropriate hair removal by clippers or depilatory cream
SCIP Inf-9	Urinary catheter removed on POD 1–2 with day of surgery being day 0
SCIP Inf-10	Normothermia (postoperative temperature >96.8°F)
SCIP Card-2	Patients on beta-blocker therapy, prior to arrival, receive beta-blocker between 24 h before incision and discharge from PACU
SCIP VTE-1	Recommended venous thromboembolism prophylaxis ordered within hospital arrival to 24 h after anesthesia end-time
SCIP VTE-2	Patient received appropriate venous thromboembolism prophylaxis within 24 h prior to anesthesia start-time to 24 h after anesthesia end-time

Note: SCIP, surgical care improvement project; Inf, infection; Card, cardiac; VTE, venous thromboembolism; POD, postoperative day; PACU, postanesthesia care unit.

data that SSI rates after risk adjustment remained stable over the course of their 4-year study.[48] Barie also noted in his editorial to *Surgical Infections* that "baseline infection rates may have increased due to improved reporting," making it difficult to detect any true improvement.[49] Some argue that the recently noted shortcomings of SCIP could be blamed for its inability to account for increasing resistance of surgical pathogens to traditional antibiotics.[50] Edmiston et al. elaborated on several modifications to SCIP, suggesting instead a "SCIP-Plus" protocol with five additional policies to more effectively decrease the risk of SSIs, as shown in the following:

- Preadmission antiseptic shower with 4% chlorhexidine gluconate (CHG).
- Perioperative skin antisepsis with povidine iodide or 2% CHG.
- Use antimicrobial-coated devices wherever available.
- Preoperative surveillance for antibiotic-resistant *Staphylococcus aureus*.
- Routine intraoperative glove changes on a 2 h cycle to avoid contamination by microperforation.

To date, SCIP remains the mainstay metric used to assess surgical quality across healthcare providers. However, modifications and additions to the various measures mentioned earlier must occur in time to appropriately deal with the growing resistance to antibiotics. In practicing evidence-based medicine, it becomes essential to consistently update national protocols to remain on the cutting edge of the standard of care and maximize quality. In doing so, the structure and process through which patient care is administered can continuously be optimized to produce the best patient outcomes. Good science informs good management.

References

1. O'Connor GT, Birkmeyer JD, Dacey LJ, Quinton HB, Marrin CA, Birkmeyer NJ et al. Results of a regional study of modes of death associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. *Ann Thorac Surg* 1998;66(4):1323–1328.
2. Kohn LT, Corrigan JM, Donaldson MS, Institute of Medicine. *To Err Is Human*. Washington, DC: National Academy Press, 1999.
3. Committee on Quality of Health Care in America, Institute of Medicine. *Crossing the Quality Chasm*. Washington, DC: National Academy Press, 2001.

   This article was one of the seminal writings that initiated the thrust toward improved quality in health care and marked the beginning of quality reform as a national priority.
4. Centers for Medicare and Medicaid Services. Available at: http://www.cms.gov/ (accessed October 30, 2012).
5. Gold JA. The surgical care improvement project. *Wisc Med J* 2005;104:73–74.
6. Gawande A. The cost conundrum. *The New Yorker*. New York: Advance Publications, 2009.
7. Iezzoni LI. *Risk Adjustment for Measuring Healthcare Outcomes*, 3rd edn. Chicago, IL: Health Administration Press, 2003.
8. Birkmeyer JD, Dimick JB. Understanding and reducing variation in surgical mortality. *Annu Rev Med* 2009;60:405–415.

   This article described patient outcomes as a function of several aspects of the structure and process of health care. It goes on to describe several variables that factor into structure and process.
9. Englesbe MJ, Pelletier SJ, Magee JC, Gauger P, Schifftner T, Henderson WG et al. Seasonal variation in surgical outcomes as measured by the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP). *Ann Surg* 2007;246(3):456–462.
10. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel HA, Lucas FL, Batista I et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–1137.
11. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med* 2002;137:511–520.

12. Glasgow RE, Jackson HH, Neumayer L, Schifftner TL, Khuri SF, Henderson WG et al. Pancreatic resection in veterans affairs and selected university medical centers: Results of the patient safety in surgery study. *J Am Coll Surg* 2007;204(6):1252–1260.
13. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 2002; 288:1987–1993.
14. Sasichay-Akkadechanunt T, Scalzi CC, Jawad AF. The relationship between nurse staffing and patient outcomes. *J Nurs Admin* 2003;33:478–485.
15. Carayon P, Gürses AP. A human factors engineering conceptual framework of nursing workload and patient safety in intensive care units. *Intensive Crit Care Nurs* 2005;21:284–301.
16. Aiken LH, Clarke SP, Cheung RB, Sloane DM, Silber JH. Educational levels of hospital nurses and surgical patient mortality. *JAMA* 2003;290:1617–1623.
17. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 2002;288:1987–1993.
18. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: A systematic review. *JAMA* 2002;288:2151–2162.
19. Pronovost PJ, Needham DM, Waters H, Birkmeyer CM, Calinawan JR, Birkmeyer JD et al. Intensive care unit physician staffing: Financial modeling of the Leapfrog standard. *Crit Care Med* 2004;32:1247–1253.
20. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: A systematic review. *JAMA* 2002;288:2151–2162.
21. Pronovost PJ, Jenckes MW, Dorman T, Garrett E, Breslow MJ, Rosenfeld BA et al. Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. *JAMA* 1999; 281:1310–1317.
22. Pronovost PJ, Dang D, Dorman T, Lipsett PA, Garrett E, Jenckes M et al. Intensive care unit nurse staffing and the risk for complications after abdominal aortic surgery. *Eff Clin Pract* 2001;4:199–206.
23. Birkmeyer JD, Dimick JB. Potential benefits of the new Leapfrog standards: Effect of process and outcomes measures. *Surgery* 2004;135:569–575.
24. Silber JH, Williams SV, Krakauer H, Schwartz JS. Hospital and patient characteristics associated with death after surgery. A study of adverse occurrence and failure to rescue. *Med Care* 1992;310:615–629.
25. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med* 2009;360:491–499.
26. McCafferty MH, Polk HC, Jr. Patient safety and quality in surgery. *Surg Clin North Am* 2007;87(4):867–881, vii.
27. Makary MA, Sexton JB, Freischlag JA, Holzmueller CG, Millman EA, Rowen L et al. Operating room teamwork among physicians and nurses: Teamwork in the eye of the beholder. *J Am Coll Surg* 2006;202(5):746–752.
28. Nundy S, Mukherjee A, Sexton JB, Pronovost PJ, Knight A, Rowen LC et al. Impact of preoperative briefings on operating room delays: A preliminary report. *Arch Surg* 2008;143(11):1068–1072.
29. Roy M, Zarebczan B, Weber S. Evaluation of surgical risk, including cardiac and pulmonary risk assessment. In: Ashley SW, Cance WG, Jurkovich GJ, Pemberton JH, Napolitano LM, Soper NJ et al., eds. *ACS Surgery: Principles and Practice*. Hamilton, Ontario, Canada: Decker Publishing Inc. 2012.
30. King MS. Preoperative evaluation. *Am Fam Phys* 2000;62(2):387–396.
31. Aust JB, Henderson W, Khuri S, Page CP. The impact of operative complexity on patient risk factors. *Ann Surg* 2005;241(6):1024–1028.
32. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB et al. The Department of Veterans Affairs' NSQIP: The first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. *Ann Surg* 1998;228(4):491–507.

    This introduction to the National Surgical Quality Improvement Program (NSQIP) described the various aspects of the program and set the stage for its expansion from the Veterans' Affairs system to most other forums of health care.
33. Khuri SF, Henderson WG, Daley J, Jonasson O, Jones RS, Campbell DA Jr et al. Successful implementation of the Department of Veterans Affairs' National Surgical Quality Improvement Program in the private sector: The Patient Safety in Surgery study. *Ann Surg* 2008;248(2):329–336.
34. ACS NSQIP—Surgical Quality Improvement. Available at: http://site.acsnsqip.org/ (accessed November 11, 2012).

    The official NSQIP website offers details about its cost, the efficacy it has been able to demonstrate since its implementation, and how the program has been able to assist in improving patient outcomes.
35. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr. Hospital costs associated with surgical complications: A report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004;199(4):531–537.
36. Khuri SF, Daley J, Henderson WG. The comparative assessment and improvement of quality of surgical care in the Department of Veterans Affairs. *Arch Surg* 2002;137(1):20–27.
37. Henderson WG, Daley J. National Surgical Quality Improvement Program: Why is it what it is? *J Am Surg* 2009;198:S19–S27.
38. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program. *Ann Surg* 2009;250(3):363–376.
39. Dimick JB, Staigler DO, Birkmeyer JD. Ranking hospitals on surgical mortality: The importance of reliability adjustment. *Health Serv Res* 2010;45:1614–1629.
40. The Leapfrog Group. Available at: http://www.leapfroggroup.org/ (accessed November 1, 2012).

41. Brooke BS, Dominici F, Provonost PJ, Makary MA, Schneider E, Pawlik TM. Variations in surgical outcomes associated with hospital compliance with safety practices. *Surgery* 2012;151:651–659.
42. Rosenthal MB, Dudley RA. Pay-for-performance: Will the latest payment trend improve care? *JAMA* 2007;297:740–744.
43. Sutton M, Nikolova S, Boaden R, Lester H, McDonald R, Roland M. Reducing mortality with hospital pay for performance in England. *N Engl J Med* 2012; 367 (19):1821–1828.
44. Epstein AM. Will pay for performance improve quality of care? The answer is in the details. *N Engl J Med* 2012;367(19):1852–1853.
45. Surgical Care Improvement Project Core Measure Set. Available at: http://www.jointcommission.org/ (accessed November 22, 2012).

    The 10 policies of the Surgical Care Improvement Project (SCIP) as noted on the official website of the Joint Commission have become a national measure for surgical quality.
46. Dellinger EP, Hausmann SM, Bratzler DW, Johnson RM, Daniel DM, Bunt KM et al. Hospitals collaborate to decrease surgical site infections. *Am J Surg* 2005;190(1):9.
47. Stulberg JJ, Delaney CP, Neuhauser DV, Aron DC, Fu P, Koroukian SM. Adherence to surgical care improvement project measures and the association with postoperative infections. *JAMA* 2010;303(24):2479.
48. Hawn MT, Itani KMF, Vick CC, Holman WG. Has the surgical care improvement program improved outcomes? *Ann Surg* 2011;254:494–501.
49. Barie PS. SCIP to the Loo? *Surg Infect* 2011;12:161–162.
50. Edmiston CE, Spencer M, Lewis BD, Brown KR, Rossi PJ, Henen CR et al. Reducing the risk of surgical site infections: Did we really think SCIP was going to lead us to the promised land? *Surg Infect* 2011;12:169–177.

2

Optimizing Patient Safety in Surgery

Kenneth D. Stahl and Susan E. Brien

CONTENTS

2.1 Introduction

On May 16, 1769, at the commencement ceremony for the first graduating class of King's College of Medicine, George Washington's private physician, Dr. Samuel Bard, offered these thoughts to the first physicians educated in the New World: "It is to you, gentlemen, who are candidates for these medical degrees that I endeavor to explain the weighty duties of your chosen profession. Your labors must have no end for no less than life, and its greatest blessing of health, are the objects of your attention. As you have embraced this profession of profound responsibilities, you are accountable even for your missteps and errors. For no weeping family will receive consolation that you rashly trampled with the lives and safety of your fellow creatures and they have been robbed of life, not by the malignancy of their disease but by the ignorance or error of his physician."[1] Over these many years, everything has changed in medicine and surgery, except this philosophy.

The important issues of errors and adverse outcomes in patient care have received attention in recent years as healthcare professionals become more focused on patient safety. Patient safety is defined as the risks patients face, not from the "malignancy of their disease" or the severity of their injuries, but from the healthcare system itself. Although the exact number of errors in patient management remains difficult to quantify, the fact that errors in patient care occur and that some patients are seriously or fatally harmed by these mistakes is no longer in dispute.[2] Most studies of healthcare systems document an incidence of errors occurring in 3.5%–10% of hospitalized patients.[3,4] In a 2008 review of in-hospital errors, Healthcare Grades cites a 5.5% incidence of errors in surgical patients of which 29.1% resulted in fatalities.[5]

This indicates that there is an approximate fatality rate of 1% in the group of all hospitalized surgical patients due to avoidable adverse events. An equally important but not fatal category of error is wrong-site surgery. This type of adverse event accounts for 13.4% of sentinel events in the most recent statistics from the Joint Commission. These errors are preventable adverse outcomes.[6]

2.2 Errors in Trauma and Elective Surgery

There is a higher incidence of errors that occurs in surgical patients than in general medical patients, as there are more opportunities for errors with the multiple steps of surgical care. This is partly explained by the higher number of treatment events surgical patients undergo during and after an operation and the increased complexity of the tasks that surgeons perform.[7]

Furthermore, the incidence of errors increases with the complexity of the surgical procedures. In a recent study of errors in neurosurgical procedures, of 1108 elective neurosurgical operations reported over a 6-year period, 87% of patients incurred at least one error, 23% of the errors were major, and 79% were deemed preventable.[8]

In trauma patients, the rate of deaths due to error is two to four times higher than deaths due to errors in the general hospital population, and these incidents require special attention from surgeons.[9] This incremental risk is partly accounted for by time compression and acute physiological instability of trauma victims. Preventable deaths in Level I trauma centers due to human and system errors account for up to 10% of fatalities in patients with otherwise survivable injuries.[10–12] These unintended deaths equate to as many as 15,000 lost lives per year in the United States or two deaths every hour of the day.[13]

In trauma care, the three highest risk locations for occurrence of errors have been identified as the operating room,[14] the emergency department,[15,16] and intensive care units.[17] Furthermore, the situations that are most conducive to producing errors are the very environments in which trauma victims present, unstable patients, fatigued operators, incomplete histories, time-critical decisions, concurrent tasks, involvement of many disciplines, complex teams, transportation of unstable patients, and multiple hand-offs of patient management. These factors combine to create a "perfect storm" for medical errors.

Errors during treatment occur during all phases of care of the trauma patients: resuscitation phase, operative phase, and critical care phase. In a retrospective observational study of errors causing morbidity and mortality, Davis reports on 1295 trauma deaths at a Level I center in which he documented 1032 significant patient errors that were judged avoidable by two independent reviewers.[18] These errors contributed to 76 (5.6%) preventable or potentially preventable deaths. Of these fatal errors, 36% occurred in the resuscitative phase, 14% in the operative phase, and 50% in the critical care phase. Gruen studied avoidable deaths and identified 64 (2.5%) of 2594 deaths due to error at a Level I trauma center.[11] These incidents were also analyzed by phase of trauma management, showing a similar distribution of fatal patient errors. They documented that 34% of errors occurred in the ED (20% during initial assessment and resuscitation, 14% during the secondary survey and diagnostic tests), 8% during stabilization and interhospital transport, 11% during initial interventions (surgery and/or angiography), and 37% during the intensive care phase.

Elective surgery also carries risks to patients for adverse outcomes. Each of the complex phases of surgical management (Table 2.1) introduces unique risks for errors with slightly different etiologies. In a recent review, Krizek identified surgical errors and adverse events in 480 (45.8%) of 1047 patients. There were a total of 2138 incidents that included 164 (7.5%) diagnostic errors (of which 5.2% were judged to be serious), 230 (10.5%) errors that occurred during the surgical procedure (17.9% serious), and 693 (29.3%) that occurred during monitoring and daily care (17.1% serious).[19] The root causes of these errors involve a combination of surgical competency, technical skill, team performance, communication, and decision-making.[20]

TABLE 2.1

Phases of Surgical Care at Risk for Errors

1	Initial assessment and diagnosis of surgical disease
2	Patient selection for surgery
3	Timing and plan of surgical intervention
4	Immediate preoperative care
5	Technical aspects of surgical procedure
6	Postoperative care
7	Discharge and medication reconciliation

2.3 Human Error and Surgical Decisions

Although the nature of errors differs slightly in trauma and elective surgery, with both, incidents can occur on a system or an individual level. There are numerous reasons why adverse events occur, and in order to understand the nature of these errors it is important to study their origins on both of these levels. A useful construct of the individual human components of error in surgery is based on Rasmussen's "Skill, Knowledge & Rule" error model.[21] The skill component refers to actions that are automatic and are carried out based on stored patterns of preprogrammed sets of actions. These skills can be acquired with repetitive training and practice which are the basic functions of surgical residency programs. Failure to execute these skills correctly will invariably lead to procedural complications. Knowledge, another key element of residency training programs, is key to the surgical specialty, and failures on this level refer to either a lack of information or the inability to recall and access stored knowledge during surgical decision-making. The rule component references tasks that are completed using stored sets of conventions. These rules consist of familiar, rehearsed algorithms such as steps of a procedure or ATLS[22] management of injured patients. Failure to utilize these rule patterns correctly, or using the wrong rule pattern, leads to both procedural and cognitive errors.

In all three levels of this model, the main principle is to avoid management errors, and the surgeon needs to

make correct decisions and choose the correct "rules" during each critical phase of surgical care. The more urgent the decision and rushed the decision process, the more opportunity for error is introduced. Decision-making skills are central to all human intellectual activities and are among the most important nontechnical skills (NTSs) surgical trainees need to learn and surgeons need to master. It is not an exaggeration to suggest that decision-making is nearly synonymous with thinking.[23] Understanding how we process information and arrive at critical decisions, especially under time constraints, fatigue, and stress, crucial to making the right decisions when there is no room for error.[24]

Although our surgical training programs focus on acquiring knowledge and technical skills, decision-making skills are more difficult to teach and assess.[25] As the Rasmussen model indicates, decision-making skills need to be emphasized in order to enhance patient safety in surgery. Reviews of surgical complications show that 47%–80% of incidents are based on faulty decision-making capabilities.[18] Teaching decision-making skills with simulations, repetitive task rehearsals, and didactic lessons have been shown to enhance outcomes in the emergency room[25] and anesthetic care in the operating room.[26]

Making correct decisions while carrying out tasks that use rule-based cognitive mechanisms requires a greater degree of thought than rote, skill-based tasks. If confronted with an unfamiliar task, a surgeon requires a high degree of conscious thought in attempts to devise a novel solution or find an analogous scenario to a situation that has not been previously encountered. Any error in this process, if made during the surgical procedure, can lead to disastrous outcomes. A scenario in the operating room, the "pause phenomena," occurs when a surgeon transitions from an automatic mode during a time when the procedure is routine to a more effortful, attentive mode when confronted with a novel or complex surgical predicament. Accurate decisions during these times depend upon unimpeded concentration by the surgeon, and reducing errors requires curtailing distractions, such as extraneous operating room conversation, so as to achieve successful management.[27]

2.4 System-Level Errors

System errors can be understood with the well-known "Swiss cheese" analogy, coined by Reason.[28] This model postulates that multiple levels of protection from possible error exist within the system ranging from organization, supervisory, and preconditions for error, which represent "shields" against adverse occurrences. The final shield from error in this model is the individual, who represents not only the last option to catch and prevent a system-based error, but also a possible source of errors as described in the previous section. Weaknesses, or holes, in any of these "shields" represent either failures of the broad system to catch potential errors or actual fostering of errors by setting up preconditions where errors are likely to occur. By definition, any error that falls through holes in the system to the final level of the individual represents a failure of the system. Any event that originates at the individual level results from a cognitive or decision-making error on the part of the individual, and, importantly, has no additional barrier to catch these errors. This makes the individual the last chance to catch system errors and the only member of the system with no safety barrier beyond him or her to check his or her actions and catch a potential mistake. The last barrier, individual performance, is particularly important as it represents these two critical issues in patient safety.

It is apparent from these models of individual and system error that surgical care is a high-risk and labor-intensive profession. With this significant degree of complexity, adverse events and errors are inordinately intricate matters involving many levels of system and individual performance, all of which are intertwined in a complicated organization. Patient safety in surgery is, to a large extent, dependent on detailed internal systems working smoothly and efficiently together. Systems with this level of complexity require sophisticated design elements to prevent the multiplication of error or generation of errors within themselves.[29] A breakdown of individual or system function at any of these levels at best fails to catch errors, and at worst is the cause of these errors.

2.5 Conditions That Lead to Errors

In order to prevent errors and adverse outcomes, it is necessary to understand and anticipate the conditions that lead to errors.[30] There are known sets of conditions that, when understood, give surgeons advanced warning to be on guard against possible error.[31] These sets of circumstances are known as "error-producing conditions" and link traditional system analysis of errors with advanced human factor analysis of individual performance. The top error-producing conditions described in incident and accident investigations that are most important in surgical care are found in Table 2.2.

The most important condition that leads to error is fatigue, and this is well-documented in a study of pediatric intensive care units. The day-time mortality rate of

TABLE 2.2

Error-Producing Conditions	
1	Fatigue/physiological degradation
2	Faulty risk perception and stratification
3	High-risk/low-frequency event
4	Time pressure
5	Inadequate standardization
6	Poor information transfer
7	"One-way decision gates" and plan continuation

a cohort of 20,547 children admitted to 15 pediatric ICUs compared to night-time admission revealed that night admission carries an incremental risk of death from 1.1 to 4.5.[32] The associated physiological degradation of skills and judgment that accompanies fatigue requires no further emphasis than to extrapolate Dawson's often-cited laboratory study to the fatigued surgeon who performs with the same aptitude as a person who is legally drunk.[33] Fatigue acts as a force multiplier on both individuals and teams, exaggerating small missteps and making it much more difficult to catch misperceptions and fosters errors in communications and information exchange.[34]

The human brain goes into "sleep mode" as cortisol levels fall and melatonin levels rise, and the negative impact of fatigue in surgery has been documented in a retrospective cohort study of general and vascular surgical procedures. Operative cases starting at night demonstrated a strong effect on morbidity, and surgical start-time was the independent variable on mortality.[35] Data from this outcome study can be superimposed on data from studies of human cortisol[36] and melatonin[37] levels to derive a graphic depiction of surgical mortality versus surgeon circadian rhythm. Figure 2.1 shows this important relationship between human circadian physiology and surgical outcomes. Numerous studies can be found in the literature demonstrating diminished physician performance during periods of fatigue.[38] The relationship between diurnal variation of circadian physiology and surgical mortality should be respected during late-night emergency surgery by every surgeon and surgical team. This is a condition that requires extra attention and cooperation between the surgeon and team members to oversee each others' actions and guard against errors.

Faulty risk perception is another factor that contributes to adverse surgical outcome. The surgeon must guard against a failure to understand the extent of a patient's injuries or the risks a patient faces from underlying illness and concurrent diseases. The impact of chronic illnesses such as heart or renal dysfunction must be accounted for in order to develop an appropriate operative plan. Studies of emergency and trauma surgery show that errors of faulty risk stratification are frequent causes of death in patients with otherwise survivable conditions.[2–4,13,15]

Surgeons must also be aware of a type of error known as "plan continuation bias", which represents the unconscious human bias to pursue a course of action, a treatment plan, or procedure in spite of changing conditions. This is an extension of a failure to properly assess underlying risks and compounds those mistakes by continuing through "one-way decision gates" that prevent reassessment of assumptions and conditions. Surgeons are goal-directed and oriented toward

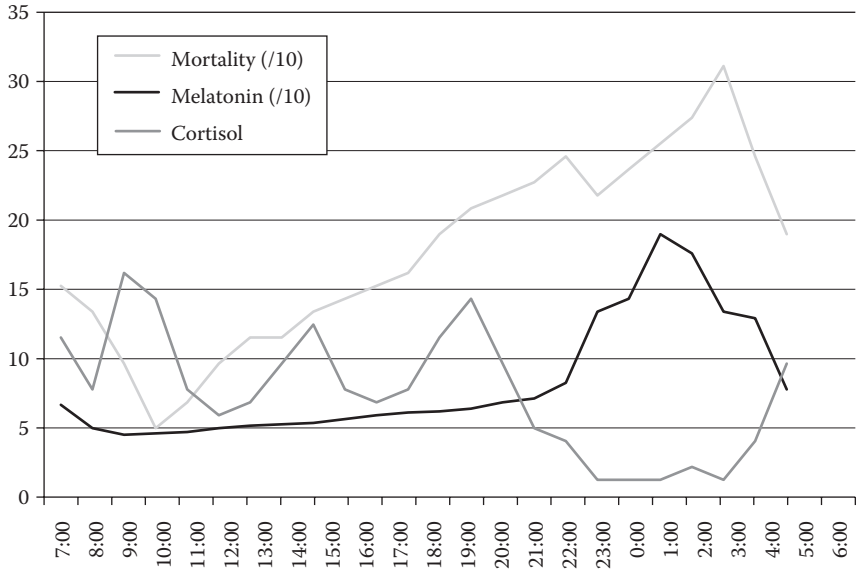


FIGURE 2.1
Surgical mortality[35] (/10) vs. serum cortisol[36] (μg/dL) vs. serum melatonin[37] (pg/mL/10).

completing a course of action, and the inability to recognize a point where modifications and/or changes in direction are needed leads to adverse events. This type of task fixation can be exacerbated by stress, fatigue, and time compression.[39]

Another condition that can contribute to adverse outcomes is frequent shift changes and duty hour limitations. Frequent handovers between care providers can lead to loss of the continuity of care and poor communication of critical patient care information.[40] Multiple studies have found that the odds of adverse events could decrease from an odds ratio of 5.2 to an odds ratio of 1.5 with standardization of communication and complete and timely handoffs of patient care.[41]

Errors occur in all aspects of surgical management where the relationships between human and system factors are so crucial. For surgeons to mitigate and manage errors, it is important to understand various sets of conditions that make error more likely, and with this information fully anticipate the chances of an error. The next step is using this information to change the conditions that induce error, determine behaviors that prevent or mitigate error, and train personnel in use of error avoidance tools.[19]

2.6 Types of Errors

The nature of surgical errors can best be characterized utilizing the Joint Commission standard nomenclature for the taxonomy of adverse outcomes. This framework has been adopted from Chang and categorizes errors into several root nodes[42]:

1. *Impact*—the outcome or effects of medical error and system failures on the patient, commonly referred to as the degree of harm to the patient, with the greatest degree of harm being patient death.
2. *Type*—the implied or visible processes that were faulty or failed. These types of errors include errors in diagnosis, operative or procedure management and treatment, prophylaxis, equipment failures, communication breakdowns, and errors in patient transfer.
3. *Domain*—the characteristics of the setting in which an incident occurred and the type of individuals involved. The setting includes initial assessment and resuscitation, secondary survey and testing areas, interhospital transfers, initial interventions such as angiography and CT scanning, ICU, general inpatient ward, and rehabilitation.
4. *Cause*—the factors and agents that led to an incident usually attributed to what the person who erred understood or thought at the time of the occurrence. Causal errors can be subdivided into three major divisions. The first division includes errors of perception where an incorrect intention is based on incorrect data input and the wrong action is performed. The second division encompasses errors of intention where the input data are correctly perceived, but an incorrect intention is formed, and the wrong action is performed. The third division includes execution error where the input data are correctly perceived and the correct intention is formed, but the wrong action is performed, that is, the action is not what was intended.

The most common error types (node 2) and domain (node 3) contributing to avoidable deaths in surgery fall into three major categories: (1) diagnosis, (2) treatment, and (3) prevention. In Gruen's analysis, 61% of fatal errors were errors of treatment, 20% were errors in prophylaxis and prevention, 13% were errors in diagnosis, 5% errors in transport and transfer, and 1% were associated with equipment failures.[11] Failures in airway management, missed injuries, and inadequate recognition or control of hemorrhage account for the majority of errors in the treatment node. These authors identified 16% of preventable deaths were due to failure of airway management and 28% due to failure to identify or control hemorrhage. Ivatury documents a similar distribution of event types in his study of fatal errors: 16% failure of airway management, 14.5% errors in diagnosis, 11.8% missed diagnosis, and 42.1% errors in critical care management.[10] Houshian identified 8.1% of patients in his Level I trauma center that had suffered an injury that was missed during the primary and secondary survey.[43]

2.7 Preventing and Mitigating Errors

There are proven safety models that can be adapted to patient safety that have been thoroughly researched and utilized by "High Reliability Organizations" (HROs). These organizations are characterized as high-risk, error-intolerant systems that are capable of repetitively carrying out potentially dangerous tasks with virtually no occurrence of adverse outcomes. Commercial aviation serves as the primary example of the HRO safety model as evidenced by Federal Aviation Authority statistics, indicating that the risk of a major commercial carrier accident ranges from 0.00 to 0.218/1,000,000 flight hours.[44] Compared to statistics quoted earlier in

this chapter that show a 1% risk of fatal surgical error, an individual must fly 24 h/day every day for 570 years before standing a 1% chance of being involved in a fatal commercial aviation accident.

This safety record is based, in part, on a thorough comprehension of the mechanisms of errors gleaned from collecting incident and error reports. In aviation, as in other HROs, avoiding error has become a compulsion and a cultural norm. Collected data on pertinent adverse events along with detailed analysis of these data and near-miss case studies have generated a body of knowledge known as *high reliability theory* that defines a number of organizational features known to reduce the risk and error hazards.[45,46] This profound understanding of error threats is derived from HRO system-wide culture and use of critical incident reporting (CIR) programs. The largest critical incident database is maintained by NASA for the FAA known as the aviation safety reporting system (ASRS).

HROs manage risks by being completely consumed with understanding and anticipating all possible chances for errors and thereby trapping small missteps before major adverse events have a chance of taking place. The critical importance of this concept of error trapping and recovery from minor adverse events has been demonstrated in numerous HRO safety models.[47] An important difference between health care and HROs systems exists. HROs are engineered with the expectation that individuals can and will make mistakes and that the system itself, unless properly configured, can fail to catch these mistakes. Healthcare professionals are expected not to make mistakes. A system to catch human and system error when it does occur has not been vigorously adopted by our medical system. In order to bring these principles into health care and use them to enhance patient safety, three tasks need to be emphasized: designing a system to prevent errors, designing procedures to make errors visible when they do occur so that they may be intercepted, and designing methods for minimizing the impact of adverse events when they are not detected or intercepted.[48]

In healthcare, there are obvious barriers to reporting errors and untoward outcomes, and many factors contribute to this reluctance.[49] One method that has improved reporting is by broadening the targets of incident reporting to include no harm events and near misses and ease the disincentive to reporting actual adverse outcomes. This has been shown to increase reporting by 3–300-fold.[50] Inclusion of these types of minor incidents and near incidents offers other advantages such as increasing the databases to allow more accurate quantitative analysis, lowering the reporting barrier, allowing recovery strategies to be included and used to generate proactive avoidance schemes, and reducing hindsight bias.[51] CIR systems in healthcare must be totally anonymous and nonpunitive.[52]

Healthcare incident reporting systems collect only 1.5%–10% of actual adverse events.[44] Encouraging use of CIR systems is gaining momentum in several specialties such as anesthesia,[53] emergency medicine,[54] and critical care.[55] Further progress has been made by The National Patient Safety Foundation that has commissioned the development and implementation of an Internet-based CIR system for use in critical care environments.[56] The findings from incident reporting systems must be used to close gaps in organizational and individual performances as well as examining policies and procedures that might be improved or done differently.[43]

2.8 Simulation and Nontechnical Skill Training

Simulation has been recognized by HROs as one of the essential safety tools to rehearse and train for error recognition and recovery as well as to enhance and practice safety skills. For decades, simulators have been used in the aviation industry and by the military and nuclear power plant operators for training and assessment of performance with excellent results.[57] Similarly, simulation and role-playing allow surgical teams to replicate the task environments and stresses of the operating room environment with no risk of adverse outcomes. Errors can be allowed to occur and their outcomes studied by replaying video recordings of the simulations that are used, so that participants can see the consequences of their decisions. Presentations of uncommon but critical scenarios that require immediate recognition and attention can be programmed into the simulator and practiced for both pattern recognition and technical management skills.[58] Much of the guidance for simulation scenarios is based on studying information captured by Critical Information Report systems,[59] the value of which is described in the previous section.

Simulation is also being used in many centers to train in cognitive and team functions in order to avoid errors.[60] Simulation as a method of training in specific trauma skills has been adopted for use in the Advanced Trauma Life Support (American College of Surgeons) and Advanced Trauma Operative Management[61] courses. Simulation has been shown to improve technical surgical skills in other specialties in randomized control studies.[62] With regard to surgical team training, studies demonstrate a significant improvement in scored and timed trauma team resuscitation outcomes after simulation practice sessions for multiple injured models.[63] The value of team building and team skills training with the use of simulation in pediatric trauma resuscitation has found a similar significant improvement in

multidisciplinary team function and successful injury recognition and resuscitation.[64]

HROs have also pioneered safety through simulation and didactic training in NTSs. NTSs are defined as cognitive, social, and personal resource skills that complement and enhance technical skills and as such contribute to safe and efficient task performance.[60] NTSs focus as much on individual interpersonal skills as on team dynamics, since it is the individual that is the basic building block from which teams and larger organizational groupings are formed.[65] Reader studied NTSs from analysis of ICU CIRs looking for nontechnical contributing factors to error.[66] From this, taxonomy of categories labeled "ANTS" (anesthesiologists' nontechnical skills) was used to retrospectively analyze studies of 2677 CIRs. They documented 5610 total contributory factors, of which 50% could be attributed to some form of NTS deficit. Their taxonomy of NTSs closely matches those that have become the foundation of HRO safety (Table 2.3).

These skills are interrelated and revolve around the central axis of teamwork and communication. Training in these skills acknowledges that surgical team composition is rarely fixed due to shift and rotation patterns and other organizational constraints. The flux of team composition mandates that each team member carry with him or her skills that apply regardless of the team makeup at any given period:

1. *Situational awareness (SA)* is simply the big picture; it is "the *accurate* perception of what is going on with you, your patient, your team members and the surrounding environment 5 minutes ago, now, and 5 minutes from now."[67] Building SA requires developing and maintaining an overall dynamic and temporal awareness of the clinical entirety based on perceiving all elements in the environment, understanding their interrelationship and implications of each, and using this understanding to think ahead, to predict, and anticipate the most likely eventualities. Prioritizing information and actions are important aspects of situational awareness. Making accurate and timely decisions and predicting how a situation will evolve allow surgeons and their team to see the clinical "big picture" and to be ready for any unexpected events. Although building and maintaining SA is largely an individual skill, it requires team participation in that team members must combine all of their perceptions and experiences in order to form a correct "big clinical picture." This must be shared through accurate and timely communication with the team, allowing all team members to modify and reassess their clinical impressions as moment to moment situations change.[68]
2. *Crew resource management (CRM)* is an educational program that has evolved over three decades of HRO safety studies. It is focused on teamwork concepts, increased knowledge of teamwork principles, and improved teamwork performance.[69] CRM encompasses skills such as clearly defining team roles and duties, managing distractions, prioritizing tasks, and avoiding task overload, all of which are integral components of a well-functioning trauma team.

   The by-products of CRM skills are individual and team situational awareness, judgment, safety, resource preservation, and competitive advantage. This important set of skills has been emphasized in the medical literature also to optimize and manage workload and task assignments, clinical task planning, and review and critique strategies.[70] Skills such as preprocedure briefs and "time-outs" and postprocedure debriefs are critical safety skills and are indispensible elements of communication in the operating room.[71,72]
3. *Decision-making skills* are central to all human intellectual activities and among the most important NTSs healthcare trainees need to master.[73] Understanding how we process information and arrive at critical decisions, especially under time constraints, fatigue, and stress, are crucial to making the right decisions when there is no room for error.[74] Incident data indicates that 47%–80% of accidents are based on faulty decision-making capabilities.[18] Teaching decision-making skills with simulations, repetitive task rehearsals, and didactic lessons has been shown to enhance outcomes in the emergency room[75] and anesthetic care in the operating room.[76]
4. *Effective communication* is crucial to mitigating error. Communication is the glue that holds teams together. The Joint Commission (2003) statistics have identified that 67% of the root cause of sentinel events are the result of errors in

TABLE 2.3

HRO Safety Skills

1	Situational awareness
2	Crew resource management
3	Information processing and decision-making
4	Communication skills
5	Teamwork and team skills
6	Leadership and supervision
7	Human factors

communication between team members.[77] Poor teamwork and communication lapses among members of healthcare teams have emerged as key factors in the occurrence of errors.

5. *Team skills* and understanding team dynamics are important aspects of avoiding errors in the management of the trauma patient.[78]

   HRO models of team training stresses that teams are made up of many people, but teamwork itself is an individual skill.[79] High-performing teams exhibit a sense of collective efficacy and recognize that they are dependent upon each other and believe that, working together, they can solve complex problems by optimizing their resources, engaging in self-correction, and compensating for each other by providing backup behaviors and reallocating functions as necessary. Effective teams recognize potential problems or dangerous circumstances and adjust their strategies accordingly.[80] Good teamwork establishes and maintains group and individual situational awareness, and share information, perceptions, and ideas to keep everyone ahead of the evolving clinical condition.

   In all aspects of healthcare, team care has been shown to reduce mortality, morbidity, and length of stay in patients.[81,82] Team training improves trauma and ICU team performance and recognition of life-threatening injuries with reduction in death, adverse outcomes, and lengths of stay.[58,59,79] Observational studies in the operating room have demonstrated that training clinicians in nontechnical and teamwork skills provides important safety nets.[83]

6. *Effective leadership and supervision* are crucial parts of team dynamics.[84] Leaders perform three key functions: provide strategic direction of care, monitor the performance of the team, and teach team members by providing instructions.[85,86] A leader's ability to get the best performance from all team members and encouraging each person on the team to share all information are traits of good leaders and supervisors.[87]
7. *Human factors (HF)* is the science of understanding and analyzing human physiology and how these factors impact performance. This has been dealt with in Section 2.5. Sleep and nap physiology, work attitude, caffeine use, interpersonal relationships, and work environment are all involved in the study and management of HF. These factors have been emphasized in both the HRO safety literature and medical literature.[88]

2.9 Conclusion

Surgeons and surgical teams must accept the fact that there are some patients who cannot be helped, but none who cannot be harmed. The potential for error exists continually and it is crucial for surgeons to constantly remind themselves and their teams that these conditions occur with every patient encounter. Sustaining this awareness and managing and detecting those risks, and then intervening in modest errors before they induce tragedy are essential strategies for the safety of surgical patients. Surgeons will never be able to protect every patient from the "malignancy of their disease," but surgeons can minimize patient risks as they treat the patients' illnesses and repair their injuries.

References

1. Bard S. A discourse on the duties of a physician. Delivered before the president and governors of King's College at the commencement. Carlisle, MA: Applewood Books, May 16, 1769:2–3.
2. Weingart SN, Wison RM, Gibberd RW et al. Epidemiology of medical error. *Br Med J*. 2000; 320:774–777.
3. Kohn LT, Corrigan JM, Donaldson MS. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press, 2000.
4. Aron D, Headrick L. Educating physicians prepared to improve care and safety is no accident: It requires a systematic approach. *Qual Saf Health Care*. 2002; 11:168–173.
5. HealthGrades Quality Study. *Fifth Annual Patient Safety in American Hospitals Study*. Golden, CO: Healthgrades, Inc., April 2008.
6. Joint Commission. Sentinel events statistics. March 31, 2010. Oakbrook Terrace, IL, http://www.jointcommission.org. Accessed 11/29/10.
7. Mendelsohn D, Bernstein M. Patient safety in surgery. *Israeli J Emerg. Med*. 2009;9(2):15–21.
8. Stone S, Bernstein M. Prospective error recording in surgery: An analysis of 1108 elective neurosurgical cases. *Neurosurgery*. 2007;60(6):1075–1080.
9. Institute of Medicine. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press, 2000.
10. Ivatury RR, Guilford KBS, Malhotra AK et al. Patient safety in trauma: Maximal impact management errors at a level I trauma center. *J Trauma*. 2008;64:265–272.
11. Gruen RL, Jurkovich GJ, McIntyre LK et al. Patterns of errors contributing to trauma mortality: Lessons learned from 2594 deaths. *Ann Surg*. 2006;244(3):371–380.
12. Teixeira PG, Inaba K, Hadjizacharia P et al. Preventable or potentially preventable mortality at a mature trauma center. *J Trauma*. 2007;63:1338–1347.

13. Miniño AM, Anderson RN, Fingerhut LA et al. *National Vital Statistics Reports*. 2006(54) No.10.
14. Healey MA, Shackford SR, Osler TM et al. Complications in surgical patients. *Arch Surg*. 2002;137(5):611–618.
15. Croskerry P, Wears RL. Safety errors in emergency medicine. In Markovchick VJ and Pons PT, eds. *Emergency Medicine Secrets*, 3rd edn. Philadelphia, PA: Hanley and Belfus, 2002, pp. 29–37.
16. Famularo G, Salvini P, Terranova A et al. Clinical errors in emergency medicine: Experience at the emergency department of an Italian teaching hospital. *Acad Emerg Med*. 2000;7:1278–1281.
17. Donchin Y, Gopher D, Olin M et al. A look into the nature and causes of human errors in the intensive care unit. *Crit Care Med*. 1995;23:294–300.
18. Davis JW, Hoyt DB, McArdle MS et al. An analysis of errors causing morbidity and mortality in a trauma system: A guide for quality improvement. *J Trauma*. 1992;32:660–666.
19. Krizek TJ. Surgical error: Ethical issues of adverse events. *Arch Surg*. 2000(11);135:1359–1366.
20. Sarker SK. Courses, counselors and cadavers: Reducing errors in the operating theatre. *Br Med J*. 2003;327:s109.
21. Rasmussen J. Skills, rules, knowledge: Signals, signs and symbols and other distinctions in human performance models. *IEEE Trans Systems Man Cybernetics*. 1983;13:257–267.
22. American College of Surgeons, Committee on Trauma, *Advanced Trauma Life Support*, 8th edn., Revised November 9, 2009.
23. Patel VL, Kaufman DR, Arocha JF. Emerging paradigms of cognition in medical decision-making. *J Biomed Inform*. 2002;35:52–75.
24. Croskerry P. The cognitive imperative: Thinking about how we think. *Acad Emerg Med*. 2000;7:1223–1231.
25. Andersen DK. How can educators use simulation applications to teach and assess surgical judgement? *Acad Med*. 2012;87:934–941.
26. Gaba DM, Howard SK, Fish KJ et al. Simulation-based training in anesthesia crisis resource management (ACRM): A decade of experience. *Simul Gaming*. 2001;32(2):175–193.
27. Moulton CA, Regehr G, Lingard L. Slowing down to stay out of trouble in the operating room: Remaining attentive in automaticity. *Acad Med*. 2010;85:1571–1577.
28. Reason J. Human error: Modes and management. *Br Med J*. 2000;320:768–770.
29. Merry MD, Brown JP. From a culture of safety to a culture of excellence. *J Innov Manage*. 2001;7(2):29–46.
30. Hollnagel E. *Barriers and Accident Prevention*. Hampshire, U.K.: Ashgate Publishing Limited, 2004.
31. Williams JC. A data based method for assessing and reducing human error to improve operational performance. In *Proceedings of IEEE Fourth Conference on Human Factors in Power Plants*, June 5–9, 1988, Monterey, CA, pp. 436–450.
32. Arias Y, Taylor DS, Marcin JP. Association between evening admissions and higher mortality rates in the pediatric intensive care unit. *Pediatrics*. 2004;113(6):530–534.
33. Dawson D, Reid K. Fatigue, alcohol and performance impairment. *Nature*. 1997;388:235.
34. Helmreich RL, Merritt AC. *Culture at Work: National, Organizational and Professional Influences*. Aldershot, U.K.: Ashgate, 1998.
35. Kelz R, Timothy T, Hosokawa P et al. Time-of-day effects on surgical outcomes in the private sector: A retrospective cohort study. *J Am Coll Surg*. 2009;209:434–445.
36. Chan S, Debono M. Replication of cortisol circadian rhythm: New advances in hydrocortisone replacement therapy. *Ther Adv Endocrinol Metab*. 2010;1(3):129–138.
37. Rajaratnam SW, Middleton B, Stone BM, Arendt J. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. *J Physiol*. 2004;561(Pt 1):339–351.
38. Weinger MB, Ancoli-Israel S. Sleep deprivation and clinical performance. *JAMA*. 2002;287(8):955–957.
39. Durden R., Going below minimums. *Aviation Safety*. 2008;(28):4–7.
40. Stahl K, Palileo A, Schulman C et al. Enhancing patient safety in the trauma/surgical intensive care unit. *J Trauma*. 2009;67:430–435.
41. Petersen LA, Orav FA, Teich JM et al. Using a computerized sign-out program to improve continuity of inpatient care and prevent adverse events. *Joint Comm J Qual Improv*. 1998;24:77–87.
42. Chang A, Schyve PM, Croteau RJ et al. The JCAHO patient safety event taxonomy: A standardized terminology and classification schema for near misses and adverse events. *Int J Qual Health Care*. 2005;17:95–105.
43. Houshian S, Larsen MS, Holm C. Missed injuries in a level I trauma center. *J Trauma*. 2002;52:715–719.
44. http://www.ntsb.gov/aviation/Stats.htm. Accessed November 25, 2012.
45. Shojania KG, Duncan BW, McDonald KM et al., eds. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Evidence Report/Technology Assessment No. 43*, AHRQ Publication No. 01-E058, Rockville, MD: Agency for Healthcare Research and Quality, 2001.
46. Reason J. Human error: Models and management. *Br Med J*. 2000;320:768–770.
47. Sundt TM, Brown JP, Uhlig PN. STS workforce on patient advocacy, communications, and safety, Focus on Patient Safety: Good News for the Practicing Surgeon. *Ann Thorac Surg*. 2005;79:11–15.
48. Nolan TW. System changes to improve patient safety. *Br Med J*. 2000;320:771–773.
49. Pietro DA, Shyavitz LJ, Smith RA et al. Detecting and reporting medical errors; Why the dilemma? *Br Med J*. 2000;320:794–798.
50. Battles J, Kaplan H, Van der Schaaf T, Shea C. The attributes of medical event reporting systems. *Arch Pathol Lab Med*. 1998;122:231–238.
51. Wald H, Shojania KG. Incident reporting. In Shojania KG, Duncan BW, McDonald KM et al., eds. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. AHRQ Publication No. 01-E058. Rockville, MD: Agency for Healthcare Research and Quality, 2001, pp. 362–372.
52. Geiduschek JM. Registry offers insight on preventing cardiac arrests in children. *ASA Newslett*. 1998;62:16–18.

53. Choy CY. Critical incident monitoring in anaesthesia. *Curr Opin Anaesthesiol*. 2008;21(2):183–186.
54. Kram R. Critical incident reporting system in emergency medicine. *Curr Opin Anaesthesiol*. 2008;21(2):240–244.
55. Pronovost PJ, Thompson DA, Holzmueller CG et al. Toward learning from patient safety reporting systems. *J Crit Care*. 2006;21(4):305–315.
56. Wu AW, Holzmueller CG, Lubomski LH et al. Development of the ICU Safety Reporting System. *J Patient Saf*. 2005;1:23–32.
57. Klinect JR, Wilhelm JA, Helmreich RL. Threat and error management: Data from line operations safety audits. In *Proceedings of the Tenth International Symposium on Aviation Psychology*. Columbus, OH: Ohio State University, 1999, pp. 683–688.
58. Gaba DM. Anesthesiology as a model for patient safety in healthcare. *Br Med J*. 2000;320:785–788.
59. Beckmann U, Gillies DM. Factors associated with reintubation in intensive care. *Chest*. 2001;120:538–542.
60. Gaba DM, Howard SK, Glanagan B et al. Assessment of clinical performance during simulated crisis using both technical and behavioral ratings. *Anesthesiology*. 1998;89:8–18.
61. Jacobs LM, Gross RI, Luk SS. Advanced trauma operative management: Surgical strategies for penetrating trauma. *Arch Surg*. 2006;141:1265–1266.
62. Peugnet F, Dubois P, Rouland JF. Virtual reality versus conventional training in retinal photocoagulation: A first clinical assessment. *Comp Aided Surg*. 1998;3:20–26.
63. Holcomb JB, Dumire RD, Cormmett JW et al. Evaluation of trauma team performance using an advanced human patient simulator for resuscitation training. *J Trauma*. 2002;52:1078–1086.
64. Falcone RA Jr, Daugherty M, Schweer L et al. Multidisciplinary pediatric trauma team training using high-fidelity trauma simulation. *J Pediatr Surg*. 2008; 43(6):1065–1071.
65. Flin R, O'Connor P, Crichton M. *Safety at the Sharp End: A Guide to Non-Technical Skills*. Surrey, U.K.: Ashgate Publishing Ltd., 2008.
66. Reader T, Flin R, Lauch K et al. Non-technical skills in the intensive care unit. *Br J Anaesth*. 2006;96:552–559.
67. Kern T. *Redefining Airmanship*. New York: McGraw-Hill Corp, 1997.
68. Banbury S, Dudefield H, Hormann J et al. FASA: Development and validation of a novel measure to assess the effectiveness of commercial airline pilot situation awareness training. *Int J Aviat Psychol*. 2007;17:131–152.
69. Salas E, Burke SC, Bowers CA et al. Team training in the skies: Does crew resource management (CRM) training work? *Human Factors*. 2001;43:641–674.
70. Risser DT, Rice MM, Salisbury ML et al. The potential for improved teamwork to reduce medical errors in the emergency department. The MedTeams Research Consortium. *Ann Emerg Med*. 1999;34:373–383.
71. Awad SS, Fagan SP, Bellows C et al. Bridging the communication gap in the operating room with medical team training. *Am J Surg*. 2005;190(5):770–774.
72. Lingard L, Epsin S, Whyte S et al. Communication failures in the operating room: An observational classification of recurrent types and effects. *Qual Saf Health Care*. 2004;13:330–334.
73. Patel VL, Kaufman DR, Arocha JF. Emerging paradigms of cognition in medical decision-making. *J Biomed Inform*. 2002;35:52–75.
74. Croskerry P. The cognitive imperative: Thinking about how we think. *Acad Emerg Med*. 2000;7:1223–1231.
75. Small SD, Wuerz RC, Simon R et al. Demonstration of high-fidelity simulation team training for emergency medicine. *Acad Emerg Med*. 1999;6:312–323.
76. Gaba DM, Howard SK, Fish KJ et al. Simulation-based training in anesthesia crisis resource management (ACRM): A decade of experience. *Simul Gaming*. 2001;32(2):175–193.
77. http://www.jcaho.org/accredited±organizations.htm. Accessed November 26, 2012.
78. Salas E, Cannon-Bowers J, Weaver J. Command and control teams: Principles for training and assessment. In Flin R, Arbuthnot K, eds. *Incident Command: Tales from the Hot Seat*. Aldershot, U.K.: Ashgate, 2002.
79. Hackman JR. Learning more by crossing levels: Evidence from airplanes, hospitals and orchestras. *J Org Behav*. 2003;24:905–922.
80. Baker DP, Salas E, Barach P. Medical teamwork and patient safety: The evidence-based relation. Literature Review. AHRQ Publication No. 05-0053, Rockville, MD: Agency for Healthcare Research and Quality, April 2005. http://www.ahrq.gov/qual/medteam/
81. Jeffcott SA, MacKenzie CF. Measuring team performance in healthcare: Review of research and implications for patient safety. *J Crit Care*. 2008;23:188–196.
82. Bellomo R, Goldsmith S, Uchino J et al. Prospective controlled trial of effect of medical emergency team on postoperative morbidity and mortality rates. *Crit Care Med*. 2004;32(4):916–921.
83. Healey AN, Undre S, Vincent CA. Defining the technical skills of teamwork in surgery. *Qual Saf Health Care*. 2006;15:231–234.
84. Day DV, Halpin SM. *Leadership Development: A review of Industry Best Practices*. Alexandria, VA: US Army Research Institute for the Behavioral and Social Sciences, 2001.
85. Klein KJ. *Teamwork in a Shock Trauma Unit: New Lessons in Leadership*. Knowledge@Wharton, 2004. http://knowledge.wharton.upenn.edu/article.cfm?articleid=1048. Accessed November 25, 2012.
86. Yun S, Faraj S, Sims HP. Contingent leadership and effectiveness of trauma resuscitation teams. *J Appl Psychol*. 2005;90:1288–1296.
87. Healy GB, Barker J, Madonna G. The surgeon as a leader. *Bull Am Coll Surg*. 2006;91:26–29.
88. Jha AK, Duncan BW, Bates DW. Fatigue, sleepiness and medical errors. In Shojania KG, Duncan BW, McDonald KM et al., eds. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. Evidence Report/Technology Assessment No. 43 AHRQ Publication No. 01-E058. Rockville, MD: Agency for Healthcare Research and Quality, 2001.

Section II

Critical Care

3

Assessment of Cardiac and Noncardiac Risk Factors

Edgar J. Pierre, Jack Louro, and Mark Cockburn

CONTENTS

3.1 Introduction

The purpose of preoperative evaluation is not simply to just give medical clearance but rather to perform an evaluation of the patient's current medical status while making recommendations concerning the evaluation, management, and risk of cardiac (or medical) problems over the entire perioperative period. Furthermore, a complete evaluation will provide a clinical risk profile that the patient, primary physician, anesthesiologist, and surgeon can use in making treatment decisions that may influence short-term and long-term outcomes. The overall goal of the preoperative evaluation is to assess medical problems in surgical patients in order to medically optimize these patients preoperatively, manage them intraoperatively, and to provide recommendations for postoperative care. Preoperative risk assessment is a critical part of this process and begins by identifying the major contributors to risk. There are two elements that determine the risk of complications for any given procedure: the risk associated with the type of surgery to be performed and the risk related to the individual patient's health status. This chapter will discuss the general principles of the preoperative evaluation to assess the major cardiac and noncardiac risk factors that can be used to guide decision-making by the surgical team.

3.2 Surgery-Associated Risk

One factor that greatly impacts the risk of complications, which must be considered preoperatively, is the type of operation the patient will undergo. There is a significant distinction between emergent and elective procedures in terms of evaluation and risks. Emergency surgery of any kind carries a higher risk of mortality and postoperative complications. Emergency surgery has at least twice the incidence of cardiac complications in comparison to elective surgery.[1] In cases of emergency surgery there is very limited ability to assess risk factors or intervene preoperatively.

In general, operative death is uncommon, occurring in only 0.3% of all operations. Average risk implies perioperative mortality of 1% or less. Significant risk implies 1%–10% and high risk is 10%–20%. Elective noncardiac procedures in the adult population carry an overall risk of cardiac complications of approximately 1.4% in unselected individuals.[2] In elective surgery, cardiac risk has a significant range related to the magnitude of the procedure. Superficial procedures such as endoscopic and ophthalmologic procedure are classified as low risk with cardiac complication risks of <1%, while major procedures such as an open aortic procedure has a cardiac complication risk above 5%. Cases associated with cardiac complication risks between 1% and 5%, such as orthopedic, are

considered intermediate risk. Establishing the risk of the surgery is paramount as patients with many cardiac risk factors undergoing a very low-risk procedure will need less testing than a patient with few risk factors undergoing a major surgery.[1]

3.3 Patient-Associated Risk

The second factor of the risk equation is determined by the patient's health. The American Society of Anesthesiology (ASA) classification of patients gives an impression of the patients' current clinical state that correlates with surgical outcomes. The classifications range from 1 to 5, with 1 being healthy and 5 having severe systemic illness requiring immediate intervention, and all intermediate levels identifying more significant systemic disease as the classification increases. ASA class 6 is a separate class reserved for brain-dead patients undergoing organ procurement for eventual transplantation. Between the various conditions that increase a patient's overall risk, there is a subset of conditions that is specifically associated with an increased risk of cardiac complications. The cardiac complications revolve mainly around perioperative ischemic injury, although they can include deadly arrhythmias, sudden cardiac death, or heart failure.[3,4] The risk of noncardiac complications is also significant, varies depending on the patient's comorbidities, and can involve any of the other organ systems.

3.3.1 Cardiac Risk Assessment

As modern medicine has progressed over the last few decades, patients of advanced age with more comorbidities are undergoing elective surgery. There has been a focus on evaluating these patients for risk associated with poor outcomes, specifically cardiac-related outcomes. Although the incidence of perioperative ischemia is low in the general population (<2%), certain groups such as patients of advanced age and with history of coronary artery disease (CAD) have a higher incidence approaching 5%.[5,6] Major organizations such as the American Heart Association (AHA) and European Society of Anesthesiology (ESA) have developed broad practice guidelines with risk stratification tools and testing algorithms for assessing a patient's risk. These guidelines are primarily evidence based, giving specific strength levels for the recommendations based on the available evidence. General principles and specific factors from these guidelines can help clinicians assess their patients' cardiac risk and need for further testing rather easily. Numerous risk indices have been developed over the past 25 years on the basis of multivariate analyses.[7–12]

The evaluation of cardiac risk always involves a thorough history and directed physical exam. The primary goal of any cardiac risk assessment is to evaluate for active cardiac conditions. The initial history, physical examination, and electrocardiogram (EKG) assessment should focus on the identification of these conditions. The active conditions that should delay elective surgery until they are addressed include unstable coronary syndromes, acute heart failure, and significant arrhythmias or valvular disease. Through appropriate questioning about chest pain, palpitations, orthostasis, or dyspnea along with adequate heart and lung auscultation for murmurs, rhythm irregularities, and respiratory rales, these conditions should be identified. A resting EKG can also help detect abnormalities specifically related to arrhythmias, ischemia, and conduction abnormalities. An EKG is indicated in certain groups of patients: (a) patients undergoing major vascular surgery; (b) patients with known CAD, peripheral artery disease, or cerebrovascular disease, undergoing intermediate-risk surgery; and (c) patients with clinical risk factors for CAD that will be undergoing intermediate or high-risk surgery. The identification of active cardiac conditions should prompt the surgical team to delay nonemergent surgery and obtain medical consultation to evaluate and medically optimize the patient prior to surgery.

Aside from assessing for active cardiac conditions, the next most crucial step to determine a patient's risk of cardiac complications is assessing their functional capacity. A high-risk patient with known CAD would not need further evaluation if he/she is able to exercise for 30 min daily without symptoms. On the other hand, a sedentary person with clinical factors suggesting the possibility of increased operative risk may benefit from further testing even in the absence of known CAD. Functional capacity can be expressed in metabolic equivalent (MET) levels. Multiples of the baseline-MET value can be used to express aerobic demands for specific activities. Perioperative cardiac and long-term risks are increased in patients unable to meet a 4-MET demand during most normal daily activities.[13,14] Energy expenditures for activities such as eating, dressing, walking around the house, and dishwashing range from 1 to 4 METs; climbing a flight of stairs, walking on level ground at 6.4 km/h, running a short distance, scrubbing floors, or playing a game of golf represent 4–10 METs. Fulfilling 10 METs consists of participating in strenuous sports like running, basketball, or sexual activity. For those patients with poor functional capacity, it is imperative to evaluate them carefully for their risk factors.

Cardiac risk indices are routinely used when assessing the preoperative patient. Cardiac risk is the most-feared and most-studied complication of surgery and is often an implicit request to determine the perioperative risk of cardiac complications. The cost of a perioperative

ischemic event has been found to be nearly $10,000 per ischemic injury.[15] As no patient (and no procedure) is risk-free, the internist should avoid statements like "avoid hypoxia, hypotension, and hypovolemia" or "cleared for surgery." The internist could provide more information to the surgical team by mentioning what the patient's risk level is, based on the patient's medical conditions along with specific recommendations for individual conditions the patient may have (e.g., "patient with chronic renal disease and severe anemia, consider erythropoietin perioperatively and blood conservation therapies intraoperatively"). The role of the anesthesiologist is to determine the risk factors (patient and surgical), identify the patient's risk for that procedure, and determine if further testing is indicated. The original Goldman risk index was based on a series of patients over the age of 40 undergoing noncardiac surgery. Nine preoperative factors were found to be associated with life-threatening cardiac complications and death. These were myocardial infarctions (MI) within 6 months, S3 gallop or jugular venous distension, age over 70, arrhythmias, aortic stenosis, poor general medical condition, emergency surgery, and major intraabdominal or intrathoracic surgery. More recently, Lee and colleagues[2] validated a much simpler index for patients undergoing nonurgent major noncardiac surgery known as the Revised Cardiac Risk Index. Their analysis identified six independent risk factors: ischemic heart disease, congestive heart failure, cerebral vascular disease, high-risk surgery, preoperative insulin treatment for diabetes mellitus, and preoperative creatinine >2 mg/dL. Rather than weighing each of these risk factors, they designated risk classes by the number of risk factors. Patients without any risk factors are assigned to the lowest risk class (I) and were found to have cardiac complication rates of 0.5% and 0.4% in the derivation and validation cohorts. In contrast, patients with three or more risk factors are assigned to the highest risk class (IV) and were found to have cardiac complication rates of 9.1% and 11%, respectively.

The American College of Cardiology (ACC) and the AHA task force for practice guidelines have devised a stepwise algorithm for determining the need for further cardiac workup.[1] Within the algorithm, all patients with poor functional capacity are evaluated for certain risk factors to determine the need for further testing. They divide these risk factors into major, intermediate, and minor. The major clinical predictors of increased perioperative cardiovascular risk fall within the active cardiac conditions previously mentioned, more specifically, a recent unstable coronary syndrome such as an acute MI (documented MI <7 days previously), recent MI (>7 days, but <1 month before surgery), unstable or severe angina, decompensated heart failure, significant arrhythmias (high-grade atrioventricular block, symptomatic arrhythmias in the presence of underlying heart disease, or supraventricular arrhythmias with uncontrolled ventricular rate), and severe valvular disease. Once active cardiac conditions are excluded, we must then look at the intermediate predictors of increased risk, as these are what will determine if the patient needs further testing prior to undergoing an elective procedure. These intermediate predictors of increased risk are more remote prior to MI (more than 1 month before planned surgery) or other evidence of CAD, compensated heart failure, renal insufficiency with preoperative creatinine greater than or equal to 2.0 mg/dL, and diabetes mellitus. Minor predictors are not used in the algorithm as risk factors altering management, but they are indicative of an increased likelihood of a patient having CAD. Minor predictors of risk are advanced age (>70 years), abnormal ECG, rhythm other than sinus, and uncontrolled systemic hypertension.

In patients undergoing intermediate or high-risk surgery with multiple intermediate risk predictors, it is reasonable to do noninvasive testing for ischemia if it will change the management prior to surgery. Noninvasive testing includes exercise or pharmacologic stress testing. In patients with unstable angina or other active cardiac conditions and many risk factors, it may even be reasonable to undergo cardiac catheterization as it may be clinically indicated independently from preoperative assessment. Studies have shown that exercise tolerance is as good as exercise stress testing in predicting perioperative complications in patients with stable CAD, which emphasizes the importance of determining functional capacity.[14]

The past medical history can bring up other factors that affect cardiac risk factor management. It is important to uncover any history of prior MI, heart failure, anemia, cardiac procedures, or implants such as prior stenting, implantable defibrillators (ICD), or pacemakers as these can give a more complete picture of a patient's cardiac risk factors as well as alter the perioperative management. Although there are not enough data on which to base firm recommendations, it appears reasonable to wait 4–6 weeks after MI to perform elective surgery. In patients with heart failure, precautions such as monitoring fluid balance and avoidance of certain medications that can exacerbate symptoms are key perioperative factors to consider.[16] Significant anemia should be treated in patients with CAD as it can precipitate myocardial ischemia.[17] If a patient has a stent previously placed, there is the need to continue perioperative antiplatelet therapy for a period of time depending on the type of stent, which may delay elective surgery. Recent interrogation and evaluation of implanted pacemakers and ICDs are also necessary to manage the patient's underlying cardiac condition, as devices may not be functioning properly and the patient may be dependent on the device's function.

3.3.2 Management of Patients at High Cardiac Risk

If preoperative evaluation suggests that a patient is at high risk for cardiac complications from surgery, one option to consider is elective cardiac revascularization prior to surgery. Evidence from retrospective studies suggests that the reduction in risk from revascularization is approximately equal to the risk from surgery itself. Therefore, the decision to refer a patient for coronary revascularization in the perioperative setting is identical to that in the nonoperative setting. It is not appropriate to propose surgery for coronary revascularization that would not otherwise have been indicated. Cardiac revascularization surgery is related with much higher risks of CHF and serious arrhythmias when compared to noncardiac surgery.[4,18–21] Patients undergoing elective noncardiac procedures who are found to have prognostic high-risk coronary disease and in whom long-term outcome would likely be improved by coronary artery bypass grafting (CABG) should generally undergo revascularization before a noncardiac elective surgical procedure of high or intermediate risk.[22] Data to support percutaneous transluminal coronary angioplasty (PTCA) are also sparse. There is a lack of controlled trials comparing perioperative cardiac outcome after noncardiac surgery for patients treated with preoperative PTCA versus medical therapy. Several small observational series have suggested that cardiac death is infrequent in patients who have undergone PTCA before noncardiac surgery.[22–26]

Several studies have also demonstrated a number of complications from angioplasty, including emergency CABG in some patients. There is uncertainty regarding how much time should pass between PTCA and noncardiac procedures. Delaying surgery for at least 1 week after balloon angioplasty to allow for healing of the vessel injury has theoretical benefits. If a coronary stent is used, a delay of at least 4–6 weeks should occur before noncardiac surgery to allow four full weeks of dual antiplatelet therapy and re-endothelialization of the stent to be completed, or nearly so.[27] Patients receiving drug-eluting stents should be on dual antiplatelet therapy and have elective surgery delayed for as much as one full year. There is some suggestion that patients undergoing noncardiac surgery soon after PTCA are at higher risk or cardiac complications, and elective surgery should generally be delayed for at least 2 weeks after PTCA, and longer if stents are placed.

Since 1996, perioperative beta-blockade has become the mainstay of medical therapy for noncardiac surgical patients. Randomized, placebo-controlled trials of beta-blocker administration in the perioperative period have been performed.[12,28,29] One trial demonstrated reduced perioperative cardiac events, and another demonstrated improved 6-month survival with perioperative beta-blocker usage. Current studies suggest that appropriately administered beta-blockers reduce perioperative ischemia and may reduce the risk of MI and death in high-risk patients. When possible, beta-blockers should be started days or weeks before elective surgery, with the dose titrated to achieve a resting heart rate between 50 and 60 beats per minute. Perioperative treatment with alpha-2 agonists may have similar effects on myocardial ischemia, infarction, and cardiac death. However, beta-blockade must be titrated to hemodynamic parameters and not given to every patient as a standardized dose, as it has been found to increase some risks, specifically that of stroke when hypotension occurs.[30] Further research in this area is needed. Although the optimal dosing schedule for beta-blockers is unknown, it is recommended that beta-blockers should be started before hospitalization or immediately upon hospitalization, and in the high cardiac risk patients they should be continued through the hospitalization and up to a month postoperatively.

3.3.3 Pulmonary Complication Risks

Pulmonary function is altered in patients undergoing surgery. Decreased functional residual capacity, productive coughs, atelectasis are all frequent causes of operative morbidity. Postoperative pulmonary complications (PPC) are defined as pneumonia, symptomatic atelectasis, respiratory failure with prolonged mechanical ventilation, bronchospasm, and exacerbation of chronic lung disease. The incidence of PPC is estimated to be between 2% and 3% in unselected populations.[31] The ASA recognizes advanced age and poor physical status of ASA classification >2 as risk factors. Other well-established risk factors of PPC are duration of anesthesia and surgery longer than 2 h and high-risk surgical sites such as thoracic and upper abdominal region. These risk factors logically follow from the physiologic changes of intubation and mechanical ventilation for prolonged periods which are known to adversely alter lung function.

Preoperative assessment of all patients requires asking about the history of lung disease or related symptoms such as cough or wheezing along with lung auscultation. Preoperative assessment of patients undergoing pulmonary resection is generally extensive. Patients with no history or symptoms of clinically significant lung disease and a normal lung exam require no further studies. Routine preoperative pulmonary function tests are not required, and routine preoperative chest x-ray has not shown to be helpful in improving patient outcomes.[32] In a meta-analysis of routine preoperative chest x-rays, even though over 20% of the exams were abnormal, only 3% changed management.[33] In asymptomatic patients without history of pulmonary disease, chest x-ray is not required and should not be done on a routine basis.

In patients with extensive lung disease undergoing lung resection, pulmonary function testing and other studies such as arterial blood gasses, gas transfer capacity, and functional tests determining VO_{2max} are commonly used for determining the extent of possible resection.

Smoking increases the risk of pulmonary complications even in the absence of chronic lung disease, and all patients undergoing elective surgery should be counseled on smoking cessation and improvement of perioperative risk. The risk declines if smoking is stopped at least 8 weeks before surgery; one study actually showed a higher risk among patients who stopped smoking for <8 weeks than those who never stopped. However, acute cessation of smoking for 24 h does reduce the quantity of methemoglobin and can improve oxygenation. Cessation between 24 h and 6 weeks is associated with an increased incidence of morbidity, presumably secondary to decreased mucociliary clearance.[34] Healthcare providers should avail themselves of every opportunity to discuss the importance of smoking cessation with all patients who smoke.

Patients with obstructive lung disease such as asthma or chronic obstructive pulmonary disease (COPD) can be a challenge. Patients with COPD are complex and have a higher risk of postoperative atelectasis, pneumonia, and death.[35] Determining the presence of symptoms such as wheezing and worsening dyspnea is extremely important in patients with asthma as well as those with COPD. The onset of these symptoms may indicate early bronchitis or a pulmonary infection. These patients should have surgery delayed until wheezing has stopped. Symptoms of dyspnea and reduced exercise tolerance identify those who are at increased risk, while the absence of such symptoms with moderate exercise is rarely associated with advanced disease. Asthmatics should be on appropriate medical therapy with bronchodilators, steroids, immunomodulators, or any combination of these and not currently having exacerbation of symptoms. Patients who were "unable to walk more than 100 yards," or "breathless while talking, dressing or unable to leave the house because of breathlessness" had a 53% incidence of complication compared with those having no abnormal dyspnea.[35]

Patients who have a history of sleep apnea and/or who are morbidly obese without systemic disease are acceptable for surgery, but hospitalization postoperatively is recommended. Sleep apnea suggests intermittent airway obstruction, and these patients may have a difficult airway. A thorough evaluation is frequently required to identify those patients in whom a fiberoptic intubation is necessary and in whom postoperative continuous positive airway pressure (CPAP) would be beneficial.

The management of patients with productive cough represents a difficult dilemma. Retrospective series did not demonstrate an increased risk of complications in patients with uncomplicated respiratory infections, whereas other studies did show a significant difference, especially if endotracheal intubation was involved.[36–40] For procedures that will be done under MAC/sedation without airway manipulation, there does not appear to be concern for infectious spread and causing pneumonia. For cases that will involve intubation, in patients with signs of significant untreated infection such as fever, chills, and copious secretions, it is reasonable to delay elective cases. However, risk–benefit ratio must be considered on an individual basis.

Perioperative interventions have been shown to reduce the incidence of pulmonary complications. Patients who stop smoking 2 months prior to surgery have significantly fewer pulmonary complications than those who continue to smoke or stop <8 weeks before admission. Incentive spirometry and chest physiotherapy in the postoperative period have been used for many years to reduce pulmonary morbidity, however the evidence is conflicting about their effectiveness.[41] Adequate analgesia and early mobilization are strongly recommended.

3.3.4 Noncardiopulmonary Perioperative Complications

Multiple organ systems can have altered function during the perioperative period. As the surgical stimulus initiates a stress response and alters cardiopulmonary function, this can lead to changes in organ perfusion and response throughout the body. Acute kidney injury (AKI), neurologic impairment, endocrine alterations, and coagulation abnormalities are some of the more commonly described noncardiopulmonary complications, and all have specific risk factors.

The fluid and hemodynamic shifts associated with general anesthesia and surgical procedures can tip a high-risk patient over the edge into outright renal failure. The overall risk of AKI, resulting in a rise in creatinine >2 mg/dL or need for dialysis is only 1% in the general surgical population[42]; however, this number increases significantly to 7.5% for patients requiring postoperative ICU admission and is an independent risk factor for postoperative mortality. Risk factors for AKI have been identified. These risk factors were collected from data of over 75,000 patients and include: male sex, existing renal insufficiency, intraperitoneal surgery, ascites, emergency surgery, age >55, CHF, hypertension, and diabetes requiring medication management or insulin. Having less than three of these risk factors results in <5% risk of AKI, whereas patients with more than five of the risk factors had >40% risk of AKI.[43] Many strategies have been looked at for prevention of postoperative AKI without much clarity in the general surgical population. Interventions that can reduce the risk of AKI

include maintaining adequate renal perfusion by maintaining intravascular volume and cardiac output perioperatively. Tight glucose control with the use of insulin in this period can also offer some advantages for AKI prevention. There is no clear evidence of pharmacologic interventions for prevention of AKI despite reports of the use of fenoldopam or dopamine for this purpose.[44]

Neurologic complications in the postoperative period are an underrecognized problem. With the increasing age of the surgical population, this problem is growing as age has been identified as one of the major risk factors not only for postoperative delirium and cognitive dysfunction but also for perioperative stroke. The incidence of stroke in cardiac, neurologic, and carotid procedures is significant, ranging from 2.2% to 5.2%. In procedures other than cardiac, neurosurgical, and carotid, stroke risk ranges from 0.05% to 7.4%. The risk of stroke is of serious concern as perioperative stroke carries a mortality risk of 26% in the general surgical population. The greatest risk factors for stroke include increasing age (especially in those over 70), previous stroke, and atrial fibrillation. In some studies, many of the risk factors for cardiac complications such as heart disease (e.g., valvular, CHF, CAD), diabetes, and renal impairment have also been found to increase the risk for stroke. Interestingly, carotid bruit or stenosis, which were believed to be associated with a higher risk of stroke, still remain controversial when looked at in studies. Some associations have been shown between hypotension, beta-blocker use, and the incidence of stroke, but direct correlation cannot be assumed. The type of surgery also imposes a risk with higher incidence noted in vascular, hip arthroplasty, and neck dissections for cancer as compared to the general surgical population.[45]

Postoperative delirium is associated with longer hospital stay and higher incidence of death; therefore, risk factor identification and aggressive preventive treatment are essential. As mentioned earlier, increasing age is a significant risk factor. Other risk factors include: male sex, existing dementia or depression, metabolic derangements, use of multiple psychoactive drugs, malnutrition, dehydration, and poor functional status. The best treatment for delirium is to prevent it from ever occurring in patients who are at increased risk. There are many events that can trigger delirium in the high-risk patients, which can be avoided. Postoperative anemia, hypovolemia, urinary catheters, physical restraints, and certain medications can trigger delirium and should be used cautiously in high-risk patients. Consideration may be given for utilization of low-dose antipsychotic medications such as haloperidol. Anesthetic management can play a role especially when it comes to pain control and drug selection.[46]

Surgical stress can impose alterations on the endocrine system. Amongst these stress responses, alterations in blood glucose can be quite common, especially with the increasing prevalence of diabetes. It has been demonstrated that poor perioperative control of blood glucose is one of the most significant factors leading to surgical site infections in the postoperative period.[47] Although the exact parameters for glucose levels are not clear, levels exceeding 200 mg/dL are considered unacceptably high in all types of patients. Surgery also imposes stress on the pituitary–adrenal system, which could render patients who may have some degree of adrenal suppression from exogenous glucocorticoids susceptible to postoperative adrenal insufficiency. Measures to assess these factors are simple as they entail a history of diabetes or recent treatment with steroids. Perioperative interventions like insulin infusions and glucose control could reduce the number of endocrine-related complications.

Alterations in the coagulation cascade are a common problem encountered during surgery. In patients with liver disease, genetic coagulopathies, or having had major trauma requiring massive resuscitation and transfusion, the risk of perioperative coagulopathy is extremely high, leading to significant hemorrhage and the requirement for factor replacement via platelets, fresh frozen plasma (FFP), cryoprecipitate, and other factors. These special patient populations should be identified early and efforts to normalize coagulation taken. On the other end of the spectrum, the incidence of deep venous thrombosis and venous thromboembolism (VTE) is high in the surgical population, being up to 20 times more likely than in the general population. The incidence of VTE is also used as a core measure of perioperative care as many modalities such as early ambulation, compression devices, and pharmacologic interventions (i.e., low-molecular weight heparin) have been shown to reduce the incidence. Certain risk factors have been associated with surgical patients that lead to increased VTE. Certain groups of patients such as those in chronic care facilities suffering from immobility, cancer, obesity, and those with prothrombotic genetic variations are at increased risk.[48] Certain types of surgery such as total hip or knee replacement have been associated with extremely high rates of VTE, higher than 40% without adequate prophylaxis.[49] Other types of surgery like general orthopedics, neurosurgical, and gynecologic are also associated with higher risk. Identifying the patients at high VTE risk is essential for implementing appropriate prophylaxis.

3.4 Conclusion

It is evident that a thorough preoperative evaluation of each and every patient is imperative. Good

communication is also an essential feature of preoperative evaluation. Findings and recommendations should always be discussed with the referring surgeon, ideally in person. Notes should be brief, focused, and specific. The goal of preoperative risk assessment is to stratify an individual patient's risk for a specific procedure, or to recommend diagnostic testing if this determination cannot yet be made. As no patient is completely free of risk, the phrase "medical clearance" is misleading and should be avoided. The patient should understand that the surgeon, primary care physician, and anesthesiologist are all working together as a team to optimize their care and that the final decision on whether or not to operate will be made between the surgeon and the patient. The most important part of the preoperative evaluation will be a complete medical history and thorough physical examination of the patient.

Cardiac and Noncardiac Surgical Complications

Complication	Incidence/ Risk	Comments	Reference
Cardiac			
MI/ischemia	1.1%–5.6%	Lowest incidence seen in unselected population excluding emergency surgery. Highest incidence seen in a study of populations >50 with coronary artery disease (CAD)	[2,5,6]
CHF	3.5% (20%*)	As determined by pulmonary edema and symptomatology in veteran population.	[3,18]
V tach/V fib	0.4% (1.2%*)	Higher incidence was found in cardiac surgery*	[3,19]
Supraventricular tachyarrhythmia	2%–6.1% (30%–60%*)	Low incidence in noncardiac surgery compared to cardiac surgery*	[4,20,21]
Severe bradyarrhythmia	0.4%	Requiring treatment	[21]
Noncardiac			
Pneumonia, respiratory failure, atelectasis, pneumothorax	2.7%	In nonselected patients undergoing noncardiac surgery	[31]
Atelectasis or pneumonia	5%–10%	In a population of COPD patients	[35]
Acute renal failure	1%	In patients with normal renal function	[42]

Note: * indicates cardiac surgery population.

Avoidance of Major Cardiac Complications

Complication	Avoidance	Reference	Comments
MI/ischemia	Postpone elective surgery in patients with active cardiac disease	[1]	
	Continue antiplatelet therapy in patients with stents	[1]	
	Continue beta-blockade in patients taking them to control HTN or angina	[1]	
	Beta-blockade titrated to control HR in patients with known CAD undergoing vascular or intermediate risk surgery	[1]	
	Stress testing and intervention in patients undergoing vascular surgery with three or more risk factors for CAD and <4 METs	[1]	
	Treat anemia (hematocrit <28) in patients with CAD	[17]	
Heart failure	Monitor for fluid overload and use diuretics as needed in HF patients	[16]	
	Avoid medications: NSAIDs, calcium channel blockers (CCB), antiarrhythmics	[16]	Vasoselective CCB, amiodarone, and dofetilide do not affect survival
	Continue/resume medications showing benefits in HF patients, such as ACE inhibitors and beta-blockers	[16]	
	Assessing heart function with hemodynamic parameters (Echo and pulmonary artery catheters)	[18]	Recommendations specific to cardiac surgery patients
	Use of intraaortic balloon pump, vasopressors/inotropes, ventricular assist devices as needed	[18]	Recommendations specific to cardiac surgery patients
Arrhythmias	Correct electrolyte abnormalities	[21]	Specifically hypomagnesemia
	Use of beta-blockers and adequate analgesia (i.e., epidural) to reduce adrenergic stimulation in select patients	[21]	
	Use of diltiazem or amiodarone perioperatively	[21]	
	Overdrive biatrial pacing	[21]	

References

1. Fleisher LA, Beckman JA, Brown KA et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Writing Committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). *Circulation*. 2007;116:1971–1996.
   Recent key guidelines for perioperative evaluation with step-by-step algorithm for risk stratification.
2. Lee TH, Marcantonio ER, Mangione CM et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.
   Key study identifying clinical risk factors and quantifying cardiac risk.
3. Kumar R, McKinney WP, Raj G et al. Adverse cardiac events after surgery: Assessing risk in a veteran population. *J Gen Intern Med*. 2001;16:507–518.
4. Goldman L. Supraventricular tachyarrhythmias in hospitalized adults after surgery. Clinical correlates in patients over 40 years of age after major noncardiac surgery. *Chest*.1978;73(4):450–454.
5. Devereaux PJ, Goldman L, Cook DJ et al. Perioperative cardiac events in patients undergoing noncardiac surgery: A review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ*. 2005;173(6):627–634.
6. Badner NH, Knill RL, Brown JE et al. Myocardial infarction after noncardiac surgery. *Anesthesiology*. 1998;88(3):572–578.
7. Goldman L, Caldera DL, Nussbaum SR et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977;297:845–850.
8. Ashton CM, Petersen NJ, Wray NP et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med*. 1993; 118:504–510.
9. Cooperman M, Pflug B, Martin EW, Jr., Evans WE. Cardiovascular risk factors in patients with peripheral vascular disease. *Surgery*. 1978;84:505–509.
10. Lette J, Waters D, Bernier H et al. Preoperative and long-term cardiac risk assessment. Predictive value of 23 clinical descriptors, 7 multivariate scoring systems, and quantitative dipyridamole imaging in 360 patients. *Ann Surg*. 1992;216:192–204.
11. Eagle KA, Coley CM, Newell JB et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med*. 1989;110:859–866.
12. Boersma E, Poldermans D, Bax JJ et al. Predictors of cardiac events after major vascular surgery. Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA*. 2001;285:1865–1873.
13. Reilly DF, McNeely MJ, Doerner D et al. Self-reported exercise tolerance and the risk of serious perioperative complications. *Arch Intern Med*. 1999;159:2185–2192.
14. Bartels C, Bechtel JF, Hossmann V, Horsch S. Cardiac risk stratification for high-risk vascular surgery. *Circulation*. 1997;95:2473–2475.
15. Mackey WC, Fleisher LA, Haider S et al. Perioperative myocardial ischemic injury in high-risk vascular surgery patients: Incidence and clinical significance in a prospective clinical trial. *J Vasc Surg*. 2006; 43:533–538.
16. Jessup M, Abraham WT, Casey DE et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977–2016.
17. Hogue CW, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. *Transfusion*. 1998;38:924–931.
18. Mebazaa A, Pitsis AA, Rudiger A et al. Clinical review: Practical recommendations on the management of perioperative heart failure in cardiac surgery. *Crit Care*. 2010;14(2):201.
19. Abedin Z, Soares J, Phillips DF, Sheldon WC. Ventricular tachyarrhythmias following surgery for myocardial revascularization. A follow-up study. *Chest*. 1977;72(4):426–428.
20. Heintz KM, Hollenberg SM. Perioperative cardiac issues: Postoperative arrhythmias. *Surg Clin N Am*. 2005;85:1103–1014.
21. Amar D. Perioperative atrial tachyarrhythmias. *Anesthesiology*. 2002;97:1618–1623.
22. Eagle KA, Guyton RA, Davidoff R et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery).*Circulation*. 2004;110(14):e340–e437.
23. Huber KC, Evans MA, Bresnahan JF et al. Outcome of noncardiac operations in patients with severe coronary artery disease successfully treated preoperatively with coronary angioplasty. *Mayo Clin Proc*. 1992;67:15–21.
24. Elmore JR, Hallett JW, Jr., Gibbons RJ et al. Myocardial revascularization before abdominal aortic aneurysmorrhaphy: Effect of coronary angioplasty. *Mayo Clin Proc*. 1993;68:637–641.
25. Allen JR, Helling TS, Hartzler GO. Operative procedures not involving the heart after percutaneous transluminal coronary angioplasty. *Surg Gynecol Obstet*. 1991;173:285–288.
26. Gottlieb A, Banoub M, Sprung J et al. Perioperative cardiovascular morbidity in patients with coronary artery disease undergoing vascular surgery after percutaneous transluminal coronary angioplasty. *J Cardiothorac Vasc Anesth*. 1998;12:501–506.
27. Posner KL, Van Norman GA, Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesth Analg*. 1999;89:553–560.

28. Wallace A, Layug B, Tateo I et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. *Anesthesiology*. 1998;88:7–17.
29. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med*. 1996;335:1713–1720.
30. Devereaux PJ, Yang H, Yusuf S et al. Effects of extended-release metoprolol succinate in patients undergoing noncardiac surgery (POISE trial): A randomised controlled trial. *Lancet*. 2008;371(9627):1839–1847.
    Large trial showing potential benefits and drawbacks to widespread beta-blocker use perioperatively.
31. McAlister FA, Bertsch K, Man J et al. Incidence of and risk factors for pulmonary complications after nonthoracic surgery. *Am J Respir Crit Care Med*. 2005; 171(5):514–517.
32. Cain HD, Stevens PM, Adaniya R. Preoperative pulmonary function and complications after cardiovascular surgery. *Chest*. 1979;76:130–135.
33. Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: Systematic review for the American College of Physicians. *Ann Intern Med*. 2006;144:581–595.
34. Warner MA, Offord KP, Warner ME et al. Role of preoperative cessation of smoking and other factors in postoperative pulmonary complications: A blinded prospective study of coronary artery bypass patients. *Mayo Clin Proc*. 1989;64:609–616.
35. Wong DH, Weber EC, Schell MJ et al. Factors associated with postoperative pulmonary complications in patients with severe chronic obstructive pulmonary disease. *Anesth Analg*. 1995;80:276–284.
36. Stein M, Cassara EL. Preoperative pulmonary evaluation and therapy for surgery patients. *JAMA* 1970; 211:787–790.
37. Pien LC, Grammer LC, Patterson R. Minimal complications in a surgical population with severe asthma receiving prophylactic corticosteroids. *J Allergy Clin Immunol*. 1988;82:696–700.
38. Schuurmans M, Diacon A, Bolliger C. Functional evaluation before lung resection. *Clin Chest Med*. 2002; 23:159–172.
39. Gerson MC, Hurst JM, Hertzberg VS et al. Prediction of cardiac and pulmonary complications related to elective abdominal and noncardiac thoracic surgery in geriatric patients. *Am J Med*. 1990;88:101–107.
40. Kocabas A, Kara K, Ozgur G et al. Value of preoperative spirometry to predict postoperative pulmonary complications. *Respir Med*. 1996;90:25–33.
41. Guimarães MM, El Dib R, Smith AF, Matos D. Incentive spirometry for prevention of postoperative pulmonary complications in upper abdominal surgery. *Cochrane Database Syst Rev*. 2009;(3):CD006058.
42. Kheterpal S, Tremper KK, Englesbe MJ et al. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. *Anesthesiology*. 2007;107(6):892–902.
43. Kheterpal S, Tremper KK, Heung M et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. *Anesthesiology*. 2009;110:505–515.
44. Brienza N, Giglio MT, Marucci M. Preventing acute kidney injury after noncardiac surgery. *Curr Opin Crit Care*. 2010;16(4):353–358.
45. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology*. 2011;115(4):879–890.
46. Chaput AJ, Bryson GL. Postoperative delirium: Risk factors and management: Continuing professional development. *Can J Anaesth*. 2012;59(3):304–320.
47. Ata A, Lee J, Bestle SL et al. Postoperative hyperglycemia and surgical site infection in general surgery patients. *Arch Surg*. 2010;145(9):858–864.
48. Heit JA, Silverstein MD, Mohr DN et al. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. *Arch Intern Med*. 2000;160:809–815.
49. Baser O. Prevalence and economic burden of venous thromboembolism after total hip arthroplasty or total knee arthroplasty. *Am J Manag Care*. 2011;17(1 Suppl):S6–S8.

4

Complications of Anesthesia

Monique Espinosa and Albert J. Varon

CONTENTS

4.1 Introduction

Over the past two decades, anesthesia-related deaths have decreased from 1 per 10,000 to about 1 in 250,000 anesthetics administered. According to the American Society of Anesthesiologists (ASA), a person is more likely to be struck by lightning than die from anesthesia-related complications. Advances in anesthesia care, patient monitoring, and training of anesthesia providers have made surgery much safer and lowered the risk of complications. Although complications due to anesthesia are uncommon, they must be recognized and appropriately managed. More importantly, measures should be taken to avoid preventable complications. This chapter will review the incidence, etiology, and prevention of anesthesia-related complications. Some complications have been included because of their frequency, while others, despite being exceedingly rare, have been included because of their severity. The complications are grouped into the following categories: complications of airway management, complications of the respiratory system, complications of the cardiovascular system, complications of the renal and hepatic systems, complications of the neurological system, complications of regional anesthesia, systemic and metabolic complications, and other complications.

The ASA Closed Claims database cited throughout this chapter is a standardized collection of case summaries derived from professional liability insurance companies' closed claims files [1]. This large database was developed by ASA in order to analyze complications and improve patient safety.

4.2 Complications of Airway Management

4.2.1 Sore Throat

Although it may not be considered a severe complication, sore throat is one of the most frequently occurring complications of general anesthesia. Sore throat is most commonly associated with tracheal intubation, but it has also been reported following use of a laryngeal mask airway (LMA) or mask ventilation. The incidence of sore throat after general anesthesia is variable in the literature, with some reports suggesting it is as high as 70% [2]. Given the fact that this complication can occur with or without tracheal intubation, its etiology remains unclear. Preventive measures that may decrease postoperative sore throat include use of an LMA instead of tracheal intubation, systemic or topical lidocaine administration, and monitoring of tracheal tube cuff pressure [2]. Sore throat following general anesthesia usually resolves within 24–48 h. Some clinicians offer treatment with analgesic lozenges.

4.2.2 Airway Trauma

4.2.2.1 Dental Injury

The incidence of dental injury in patients who require anesthesia services has been reported between 0.02% and 0.07% [3]. The etiology is often direct trauma during laryngoscopy, and poor dentition is a risk factor. Preventive strategies include careful laryngoscopy and use of properly placed soft bite blocks and mouth guards. Early recognition is paramount. If a tooth is dislodged, it must be retrieved as soon as possible to prevent aspiration. The tooth should be stored in moist gauze or in normal saline, and the anesthesiologist should consult a dentist or oral surgeon to evaluate whether reimplantation is feasible. Reimplantation must be performed within 1 h.

4.2.2.2 Laryngeal Trauma

Laryngeal complications associated with general anesthesia include vocal cord trauma, vocal cord paralysis, and arytenoid subluxation or dislocation. The incidence of vocal cord injury is approximately 6%, and the etiology is usually direct trauma. The best preventive measure is intubation by an experienced practitioner. Treatment is conservative. Patients should be informed that hoarseness might last up to 2 weeks. Hoarseness can also occur without direct trauma as a result of vocal cord paralysis. Paralysis is most often secondary to recurrent laryngeal nerve injury. This may occur due to malposition with overinflation of the tracheal tube cuff, which presses on the recurrent laryngeal nerve in the subglottic larynx. Unilateral vocal cord paralysis manifests as hoarseness. Bilateral cord paralysis can lead to respiratory obstruction. Preventive measures include avoiding overinflation of the tracheal tube cuff and placing the tracheal tube at least 15 mm below the vocal cords.

4.2.2.3 Tracheal Trauma

Tracheal stenosis and tracheomalacia are complications associated with prolonged tracheal intubation. Tracheal injury can occur secondary to brief perioperative tracheal intubation. The etiology of mucosal injury is usually tracheal tube cuff overinflation. Tracheal laceration or rupture is a rare but serious complication of endotracheal intubation. The incidence is <1% [4]. However, the risk is likely higher in cases of difficult intubation with repeated and blind attempts at tracheal intubation.

Treatment for tracheal laceration can range from conservative management to surgical repair, depending on the extent of injury and the patient's condition.

4.2.3 Laryngospasm

Laryngospasm is a protective reflex mediated by the vagus nerve causing spastic closure of the vocal cords with infolding of the arytenoids and aryepiglottic folds. The reflex is most likely to occur during stage II of anesthesia and can be precipitated by saliva, blood, or gastric contents coming in contact with the glottis during this perilous period. Laryngospasm is the most common cause of postobstructive pulmonary edema (POPE). The first step in the treatment of laryngospasm is the application of a jaw thrust. This maneuver elevates the hyoid bone and can open the aryepiglottic folds. If the jaw thrust is insufficient, positive airway pressure should be applied. Pharmacologic treatment with propofol or a small dose of succinylcholine may also be required.

4.3 Complications of the Respiratory System

4.3.1 Atelectasis

General anesthesia will lead to atelectasis, even in healthy patients. There are multiple factors that contribute to the etiology of atelectasis under general anesthesia. Proposed causes include compression atelectasis, gas resorption, and surfactant impairment [5].

The diaphragm is displaced cephalad in supine patients under general anesthesia. This increases the intrapleural pressure and can lead to alveolar collapse (compression atelectasis). Atelectasis can be worsened by body habitus, patient positioning (e.g., Trendelenburg), and surgical factors (e.g., retraction, packing). The best preventive measure against compression atelectasis is the use of positive end-expiratory pressure (PEEP). Ideally, PEEP should be initiated at the onset of anesthesia induction.

Gas resorption atelectasis is secondary to the increased oxygen concentration that patients receive during general anesthesia. Lung zones with low ventilation/perfusion ratios are most likely to be affected by gas resorption. When the alveolar oxygen tension is elevated, the rate at which oxygen moves from the alveoli to the blood is markedly increased. If the flow rate of gas into the blood exceeds the rate of inspired gas, the alveoli become smaller, and eventually collapse. Studies have shown that decreasing the inspired oxygen concentration during the induction of anesthesia may prevent atelectasis. This technique is difficult to incorporate into clinical practice, since it directly affects the permissible apnea time and increases the risk of hypoxia.

Surfactant impairment may be fostered by the administration of anesthetic agents, increased length of surgery, and decreased tidal volume [5].

Atelectasis decreases the ventilation/perfusion ratio and increases intrapulmonary shunt, leading to hypoxemia. Although in healthy patients atelectasis can be a relatively benign condition, this is much more threatening in patients with preexisting lung disease or decreased cardiopulmonary reserve. The treatment objective is to provide an increase in transpulmonary pressure that is sufficient to re-expand collapsed alveoli. Therapies used in the postoperative period include deep breathing, incentive spirometry, and continuous positive airway pressure (CPAP) [6]. In patients who are hypoxic, treatment with CPAP may decrease the incidence of postoperative tracheal intubation [7].

4.3.2 Bronchospasm

Intraoperative bronchospasm is often anticipated in patients with preexisting bronchospastic diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and bronchopulmonary dysplasia. Bronchospasm can also occur in patients without comorbidities. It can be triggered by direct respiratory stimuli including tracheal intubation, carinal irritation, and mainstem intubation, or it can be precipitated by indirect stimuli—surgical stimulation with inadequate anesthesia. Furthermore, bronchospasm can be a symptom of other pulmonary complications, such as aspiration or pulmonary edema, and intraoperative hypersensitivity reactions. A study reviewing 136,929 cases reported an overall incidence of bronchospasm of 1.6 per 1000 anesthetics [8]. The same study found increased incidence of bronchospasm in pediatric patients and in those with respiratory infection or obstructive lung disease.

Preoperative identification of patients at risk for bronchospasm is essential for the implementation of preventive strategies. Smokers must be counseled early on. Smoking cessation must be attained at least 8 weeks prior to surgery to decrease the risk of pulmonary complications. Patients with asthma or COPD should be medically optimized prior to elective surgery, and those with respiratory infections should receive appropriate therapy.

Several intraoperative measures can be taken to prevent perioperative bronchospasm. Regional anesthesia, which avoids airway instrumentation, should be considered whenever possible. Use of an LMA instead of a tracheal tube is associated with less bronchoconstriction [9]. When general anesthesia is required in patients at risk for bronchospasm, the trachea should be instrumented only after adequate neuromuscular

blockade and depth of anesthesia have been achieved. Deep extubation should be considered in selected cases (e.g., patients without risk for aspiration or difficult intubation).

The first step in the treatment of bronchospasm is usually to deepen the inhaled anesthetic, since this is easy to execute. Surgical stimulation should be paused, if possible, in the presence of significant bronchospasm. Mechanical causes of airway irritation should be excluded. The next step is to administer a nebulized beta-2 agonist (e.g., albuterol). Although neuromuscular blockade does not affect bronchial smooth muscle tone, it may facilitate ventilation by improving chest wall compliance. Treatment with intravenous corticosteroids may also be beneficial (e.g., methylprednisolone).

4.3.3 Aspiration

Aspiration accounts for 3% of claims in the ASA Closed Claims Project database [1]. A 1986 Scandinavian study reported an incidence of 0.7–4.7 in 10,000 general anesthetics [10]. More recent studies in the United States have also reported an incidence within this range. On the other hand, the incidence of aspiration has been reported to be higher in obstetric patients.

Risk factors for aspiration include pregnancy, esophageal disease, gastric disease, small bowel obstruction, ileus, trauma, diabetes, obesity, and recent food ingestion. Rapid sequence induction (RSI) and tracheal intubation should be used to decrease the risk of aspiration in such patients during general anesthesia. Although the effectiveness of cricoid pressure in preventing aspiration continues to be debated, cricoid pressure remains the mainstay for RSI due to its low risk/benefit ratio. Awake intubation is the technique of choice for securing the airway in patients at risk for aspiration who are also suspected of having difficult-to-manage airways. Pharmacologic agents are available to reduce the acidity or the volume of gastric contents, but do not prevent aspiration. Currently, the ASA Practice Guidelines do not recommend the routine use of any of these agents in healthy patients undergoing elective surgery.

When witnessed aspiration occurs, the treatment is immediate suctioning of the oropharynx or tracheal tube. The treatment of aspiration pneumonitis is supportive. Only patients with evidence of aspiration pneumonia should receive antibiotic therapy. Steroids have not been shown to improve outcome in this condition [11].

4.3.4 Postobstructive Pulmonary Edema

POPE, or "negative pressure" pulmonary edema, is the acute onset of pulmonary edema following upper airway obstruction. POPE Type I follows episodes of acute upper airway obstruction, such as laryngospasm, whereas POPE Type II follows relief of chronic upper airway obstruction (e.g., tonsillectomy, tumor resection). Although sufficiently powered studies are lacking, the incidence of POPE is thought to be as high as 1 in 1000 anesthetics [12]. Clinical presentation of POPE is characterized as acute respiratory distress following relief of the obstruction; however, onset can be delayed by as much as 24 h [13]. The most common etiology is laryngospasm [13]. Chest radiography can be useful in distinguishing POPE from aspiration pneumonitis since POPE has a faster onset of radiologic changes [13]. Echocardiogram is helpful to exclude cardiogenic causes of pulmonary edema. Treatment of POPE is supportive and includes CPAP or PEEP tailored to the severity of the respiratory distress or failure.

4.4 Complications of the Cardiovascular System

4.4.1 Myocardial Ischemia/Infarction

Cardiac complications are the most common cause of mortality after surgery and anesthesia [14]. The most recent guidelines set forth by the American College of Cardiology/American Heart Association (ACC/AHA) regarding perioperative cardiovascular evaluation and care for noncardiac surgery cite the Revised Cardiac Risk Index developed by Lee et al. in 1999 [15]. This prospective cohort study including 4315 patients identified six risk factors for major cardiac complications (ventricular fibrillation/cardiac arrest, complete heart block, acute myocardial infarction (MI), and pulmonary edema) in noncardiac surgery. The risk factors identified were high-risk surgery, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin-dependent diabetes, and elevated serum creatinine (>2.0 mg/dL). In this study, patients with 0, 1, 2, or >2 of these risk factors had incidences of major cardiac complications of 0.5%, 1.3%, 3.6%, and 9.1%, respectively.

In addition to patient risk factors, the risk of cardiac complications is significantly affected by the type of surgery. Aortic and peripheral vascular surgeries are considered high-risk, carrying a risk of cardiac death and MI >5%. Intraperitoneal, intrathoracic, carotid, head and neck, orthopedic, and prostate surgeries are classified as intermediate risk, with a 1%–5% risk. Low-risk procedures carry a risk of <1%. These procedures include endoscopy, superficial procedures, cataract surgery, breast surgery, and ambulatory surgery [16].

There is evidence to support both medical and interventional treatment modalities to reduce perioperative

cardiovascular risk. Here, we will only mention those interventions that are supported by Class I evidence. The first recommendation is that patients with active cardiac conditions be evaluated and treated as per the ACC/AHA guidelines prior to undergoing noncardiac surgery. Active cardiac conditions are unstable coronary syndromes (recent MI, and unstable or severe angina), decompensated congestive heart failure, significant arrhythmias, and severe valvular disease. Patients on beta-blockers should continue them in the perioperative period. Beta-blockers should be given to patients who will undergo vascular surgery and have known coronary artery disease. Statins should be continued in the perioperative period. Coronary revascularization before surgery is recommended in patients with stable angina who have significant left main coronary artery disease, three-vessel disease, or two-vessel disease with proximal left anterior descending coronary disease. Revascularization is also recommended for patients with high-risk unstable angina or non-ST-segment elevation MI, and for patients with acute ST-elevation MI (STEMI) [16].

4.4.2 Dysrhythmias

The incidence of perioperative dysrhythmia varies according to the definition used. The incidence of dysrhythmia, including bradycardia and tachycardia, in a large multicenter study of 17,201 patients was 70.2% [17]. However, the need for antidysrhythmic medication, use of electrical devices, or cardiopulmonary resuscitation, only occurred in 1.6% of these patients [18]. Dysrhythmias range from benign to lethal, and may result from direct mechanical irritation, electrolyte abnormalities, conduction abnormalities, or structural cardiac disease.

Continuous electrocardiogram monitoring during anesthesia is an ASA standard for basic anesthetic monitoring. Dysrhythmias should be identified, determined to be stable or unstable, and treated according to ACLS algorithms. Clinicians should also look for and treat reversible causes of dysrhythmia.

4.5 Complications of the Renal and Hepatic Systems

4.5.1 Postoperative Renal Dysfunction

The development of acute kidney injury results in a significant increase in morbidity and mortality, as well as in health care costs, since renal replacement therapy is expensive and not free of complications. Development of renal failure in the perioperative period is almost always the result of a combination of factors, and almost never the result of an anesthetic agent. Renal failure can be categorized into prerenal, renal, and postrenal etiologies. Prerenal causes are generally secondary to hypovolemia, or relative hypovolemia. Renal etiologies include ischemia and toxins. Postrenal causes are urinary tract obstructions, from the ureters to the urinary catheter.

The incidence of postoperative renal dysfunction depends highly on the type of surgery. Cardiac surgery, for instance, poses a significantly higher risk than other surgeries. Kheterpal et al. reviewed 65,043 noncardiac surgery cases and reported an incidence of 0.8% [19]. This study also identified the following as independent preoperative predictors of postoperative acute renal failure: age, emergent surgery, liver disease, elevated body mass index, high-risk surgery, peripheral vascular disease, and COPD.

Nonpharmacologic strategies, such as appropriate fluid administration, and avoidance of hypotension and nephrotoxins are the most effective preventive strategies for postoperative renal dysfunction. There is evidence against the use of diuretics as preventive therapy [20].

4.5.2 Postoperative Hepatic Dysfunction

Severe postoperative hepatic injury is a rare complication of anesthesia; however, it has been reported after the administration of halogenated agents. The most significant anesthesia-related risk factor is prior exposure to halothane. Nevertheless, halothane is no longer available for clinical use in the United States. There are case reports of hepatic dysfunction following anesthesia with the newer halogenated agents, including sevoflurane, but it is exceedingly rare.

Postoperative hepatic dysfunction can also occur due to ischemic hepatitis. This type of hepatic injury results from hepatic hypoperfusion, hypoxemia, or sepsis. Prevention strategies are nonspecific and include maintaining adequate systemic perfusion and oxygenation [21].

4.6 Complications of the Neurological System

4.6.1 Perioperative Stroke

The risk of perioperative stroke is highly dependent on the type of surgical procedure. For general surgery, the risk is between 0.2% and 0.7% [22], while for carotid endarterectomy, the risk is as high as 5.1% [23]. The risk variation inherent to the surgery makes it difficult to assess the risk of stroke secondary to general

anesthesia. There is conflicting evidence whether choice of anesthetic technique (general vs. regional) affects perioperative stroke in patients undergoing carotid endarterectomy. Most perioperative strokes in patients with carotid stenosis undergoing coronary artery bypass grafting (CABG) are embolic in nature [24] rather than secondary to anesthesia-induced hypotension.

Patient-related risk factors for perioperative stroke include age, female sex, hypertension, diabetes, renal insufficiency, COPD, peripheral vascular disease, cardiac disease, prior history of stroke or transient ischemic attack, carotid stenosis, and aortic atherosclerosis [25].

Despite the inherent risk of the surgery and patient-related risk factors, there are management strategies that can decrease the risk of perioperative stroke. Statins have been shown to be protective in patients undergoing CABG [26]. Maintenance of intraoperative blood pressure as close as possible to baseline is key. Perioperative glucose control is another important parameter that may affect outcome. A glucose range of 140–180 mg/dL is recommended for critically ill patients [27]. Patients on antiplatelet therapy should continue taking these medications throughout the perioperative period whenever possible. If not feasible, antiplatelet therapy should be resumed as early as possible in the postoperative period.

4.6.2 Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction (POCD) is of concern primarily in geriatric patients, but is also reported in middle-aged patients. POCD is loosely defined as problems with thinking and memory in the postoperative period. The mechanism of the cognitive dysfunction is unknown, and the incidence is largely dependent on the time elapsed since surgery. Johnson et al. [28] reported an incidence of 19.2%, 1 week after surgery in a group of 508 patients, compared to 4.1% in the control group. At 3 months postsurgery, the same group had a POCD incidence of 6.2%, which was not statistically significant compared to the control group.

The Mini-Mental State Examination (MMSE) is the most commonly used test of cognitive function, and is a valuable tool for establishing the baseline function in patients who may be at risk for POCD.

There are no evidence-based management strategies that have been proven to significantly impact the incidence of this complication. One hypothesis formulated in the literature has been whether general anesthesia is associated with higher incidence of POCD than regional anesthesia. Ramsussen et al. [29] randomized 438 patients over the age of 60 undergoing noncardiac surgery. While patients who received general anesthesia had more cognitive dysfunction 1 week after surgery, there was no difference at 3 months after surgery in comparison to patients who received regional anesthesia.

4.6.3 Perioperative Visual Loss

Perioperative visual loss (POVL) following nonocular surgery is an extremely rare complication; the incidence is 0.002%. It is of greater concern in patients undergoing cardiac surgery or spine surgery, where the combined incidence is 0.2%. [30] Although the most common etiology of POVL in these cases is ischemic optic neuropathy, its mechanism is not completely understood. Proposed risk factors include length of time in the prone position, large intraoperative blood loss, preoperative presence of anemia, obesity, tobacco use, and vascular comorbidity (e.g., hypertension, diabetes, peripheral vascular disease, coronary artery disease).

The ASA has developed a practice advisory for POVL associated with spine surgery [31]. Recommendations include informing patients in whom prolonged procedures, substantial blood loss, or both are anticipated that there is a small, unpredictable risk of POVL. Patients at risk should have continuous monitoring of their blood pressure and their hemoglobin or hematocrit values monitored periodically during surgery. When possible, patients should be positioned so that the head is level with or higher than the heart, and the head maintained in a neutral forward position. Direct pressure on the eyes should be avoided, and the eyes of prone-positioned patients assessed regularly and documented. Finally, consideration should be given to the use of staged spine procedures in high-risk patients. The Practice Advisory offered no recommendations for transfusion threshold or guidelines for the use of vasopressors in this setting.

In the event of POVL, the anesthesiologist and surgeon should promptly seek the consultation of an ophthalmologist.

4.6.4 Perioperative Nerve Injury

Anesthesia-related nerve injury accounted for 16% (4183 claims) of the claims in a 1999 analysis of the ASA Closed Claims Project database [32]. The most common nerve injury among these cases was the ulnar nerve (28%), followed by the brachial plexus (20%), and lumbosacral nerve roots (16%). Nerve injury can be secondary to pressure, stretch, ischemia, toxins, direct trauma, or other undetermined causes. Ulnar nerve and brachial plexus injury are more commonly seen in cases of general anesthesia, while lumbosacral root injury is associated with regional technique [32].

The ASA 2010 Practice Advisory for the Prevention of Perioperative Peripheral Neuropathies [33] lists several strategies that may prevent or reduce the incidence or severity of peripheral neuropathy that may be related to perioperative positioning. Arm abduction in supine patients should not exceed 90°. For supine patients with arms placed on arm boards, the arm should be

positioned in a neutral or supinated position in order to decrease pressure on the ulnar groove. When the patient's arms are tucked, the forearms should be in the neutral position. Positions that stretch the hamstring should not exceed beyond stretch that was comfortable in the awake patient (this increases the risk of sciatic nerve stretch). When patients are placed in the lithotomy position, pressure on the peroneal nerve near the fibular head from contact with a rigid support may increase the risk of neuropathy. Therefore, prolonged pressure on this site should be avoided. Protective padding of pressure points may help decrease the risk of injury. Vigilance with frequent assessment of patient positioning is essential to avoid complications.

4.6.5 Awareness

The incidence of intraoperative awareness during general anesthesia is 1–2 per 1000 cases [34]. Potential risk factors include previous episode of intraoperative awareness, history of difficult intubation or anticipated difficult intubation, substance use or abuse, chronic pain patients using high doses of opioids, ASA physical status of IV or V, and limited hemodynamic reserve. Other potential risk factors include cardiac surgery, cesarean delivery, trauma and emergency surgery, reduced anesthetic doses in the presence of paralysis, planned use of muscle relaxants during the maintenance of anesthesia, and planned use of nitrous oxide–opioid anesthesia [35].

The ASA has published a practice advisory listing strategies that may prevent or reduce the frequency of unintended intraoperative awareness [35]. The first step in prevention of awareness is to ensure proper function of the anesthesia machine and other equipment used to administer anesthetics, ideally with a checklist protocol. The decision to administer a benzodiazepine prophylactically and use of a brain function monitor should be made on a case-by-case basis for selected patients. However, recent studies have reported that the use of the bispectral index (BIS) monitor, as compared with the use of end-tidal anesthetic-agent concentration, does not reduce awareness during anesthesia [36,37]. Episodes of intraoperative awareness should be reported and documented, and the patient should be offered counseling or psychological support [35].

4.7 Complications of Regional Anesthesia

4.7.1 Postdural Puncture Headache

Postdural puncture headache (PDPH) is a well-known complication of either advertent or inadvertent puncture of the dura with a needle for spinal or epidural anesthesia. The classic presentation of PDPH is a frontal or occipital headache that is relieved by the supine position and exacerbated by sitting or standing up. One mechanism for PDPH is thought to be traction on the meninges, secondary to loss of cerebral spinal fluid volume. The incidence of inadvertent dural puncture during epidural placement is highly operator-dependent. Once dural puncture occurs, the incidence of PDPH is related to needle gauge and needle design. Larger and beveled (Quincke) needles are associated with a higher incidence of PDPH than smaller and pencil-point needles. Other risk factors for PDPH include female gender, pregnancy, younger age, and history of headache prior to the lumbar puncture.

Strategies to prevent PDPH include orienting needle bevel parallel to the longitudinal axis of the body, use of a needle with a noncutting edge, and having the procedure performed by an experienced and nonfatigued provider [38].

Conservative treatment for PDPH includes hydration and administration of caffeine. Epidural blood patch is the treatment for PDPH that fails conservative management, and its success rate is 70%–98% if performed more than 24 h after the dural puncture [39].

4.7.2 Neuraxial Hematoma

The risk of neuraxial hematoma is <1 in 150,000 for epidural anesthesia and <1 in 220,000 for spinal anesthesia. Risk factors that increase the risk of bleeding are age, abnormalities of the spinal cord or vertebral column, coagulopathy, difficult needle placement, and anticoagulation therapy. About one-third to one-fourth of neuraxial hematoma cases have been associated with anticoagulation therapy. Due to the rarity of this complication, prospective randomized controlled trials are lacking to help guide management of neuraxial anesthesia in patients who receive or will receive anticoagulation therapy. The American Society of Regional Anesthesia (ASRA) consensus statement regarding regional anesthesia and anticoagulation is based on case reports and known risk factors for surgical bleeding [40].

At this time, Class I evidence for preventive strategies is lacking. The complication of neuraxial hematoma may be prevented by appropriate patient selection, careful review of medication and coagulopathy history, and adherence to the ASRA Practice Advisory.

4.7.3 Complications of Peripheral Nerve Blocks

Complications of peripheral nerve blocks include hematoma, infection, nerve injury, and local anesthetic systemic toxicity. All of these complications occur infrequently, and their incidence is difficult to define.

Fredrickson et al. [41] performed a prospective study to determine the incidence of neurological complications following 1010 peripheral nerve blocks over a 3-year period. Nerve blocks performed included interscalene, supraclavicular, infraclavicular, sciatic, and femoral nerve blocks. The authors reported an incidence of all-cause neurological symptoms of 8.2% at 10 days, 3.7% at 1 month, and 0.6% at 6 months.

While use of ultrasound has improved the efficacy of peripheral nerve blocks, current studies lack the power to determine if its use has decreased complications such as nerve injury and anesthetic toxicity [42].

ASRA has a practice advisory on neurologic complications in regional anesthesia and pain medicine with recommendations based on expert opinion [43]. The practice advisory states that patients with prior history of nerve injury may be at increased risk for block-related injury. Abnormally painful paresthesia or pain on injection of local anesthetic should prompt stopping for repositioning of the needle. Although administration of general anesthesia or heavy sedation precludes patient recognition of an abnormal sensation, the impact on the actual occurrence of injury has not been determined. Absence of nerve function or progression of a deficit beyond the expected duration of anesthesia should lead to urgent neurological or neurosurgical consultation.

4.7.4 Local Anesthetic Systemic Toxicity

Local anesthetic systemic toxicity (LAST) affects the central nervous and cardiovascular systems. The clinical presentation at its worst presents with generalized seizure activity and/or cardiovascular collapse. Such a severe presentation is usually secondary to inadvertent intravascular injection. The incidence of LAST has significantly decreased over the past 20 years due to the advent of multiple safety steps. Intravascular test dosing with a local anesthetic containing a small dose of epinephrine (15 μg) is the most reliable method to rule out intravascular injection. Prevention has also improved due to the practice of incremental injections and adherence to maximum dosage recommendations [44].

Treatment of LAST requires airway assessment and intervention as needed to prevent hypoxia and acidosis. The next priority is seizure suppression. ACLS protocol should be initiated promptly if cardiac arrest occurs. Once these three priorities have been addressed, lipid emulsion therapy should be initiated to reverse signs and symptoms of toxicity [45]. Cardiopulmonary bypass should be considered for patients who do not respond to lipid emulsion and vasopressors. A website has been developed as a readily available source of information for the treatment of LAST (www.lipidrescue.org).

4.8 Systemic and Metabolic Complications

4.8.1 Malignant Hyperthermia

Malignant hyperthermia (MH) is a pharmacogenetic disorder with deregulation of skeletal muscle contraction triggered by volatile anesthetics or depolarizing neuromuscular blocking drugs in genetically susceptible patients. Even when promptly and appropriately treated, this disorder has a significant risk of morbidity and mortality.

The incidence of MH in the United States has recently increased (13.3 patients per million hospital discharges), and its mortality remains elevated [46]. Reports of incidence and prevalence vary in the literature, likely due to geographical differences.

Clinical signs of MH include masseter spasm, muscle rigidity, hypercarbia, tachycardia, elevated temperature, sweating, and cardiac dysrhythmias. The clinical presentation must be differentiated from other disorders with similar signs such as sepsis, thyroid storm, pheochromocytoma, and neuroleptic malignant syndrome. The only specific and effective drug available for the treatment of MH is dantrolene. It is important to immediately call for help, because preparation and administration of dantrolene is cumbersome. Triggering agents should be immediately discontinued, and the patient should be actively cooled. Severe metabolic acidosis can be treated with sodium bicarbonate. The Malignant Hyperthermia Association of the United States has made available a 24 h hotline for emergency consultation (1–800-MH-HYPER).

4.8.2 Latex Allergy

Latex allergic patients are at risk for inadvertent exposure to latex in the perioperative period and therefore at risk for anaphylactic reactions. The incidence of latex allergy among the general population is <1% [47]. However, there is a higher prevalence of latex allergy among health care workers, patients with spina bifida, and children with urogenital abnormalities.

Preventive measures are highly effective for evading this complication. This begins with obtaining a thorough medical history. There must be communication with the anesthesia, surgical, and nursing teams to ensure avoidance of latex-containing products and devices. Signs should be placed throughout the operating room as reminders, especially if there will be change of providers. The efficacy of interventional preventive measures such as pharmacologic prophylaxis or desensitization therapy is undetermined [48].

4.9 Other Complications

4.9.1 Corneal Abrasion

Eye injury occurred in 3% of the claims in the ASA Closed Claims Project database [1]. Of these, 35% were described as corneal abrasions. A study of 60,965 cases that reviewed eye injuries after nonocular surgery found corneal abrasion to be the most common injury, with 21 occurrences [49].

Risk factors for corneal abrasion include longer length of surgery, increased age, general anesthesia, surgery of the head and neck, and surgery in the lateral position [49]. Taping the eyelids closed and the use of soft contact lenses and ointments are effective at decreasing the risk of this complication. Corneal abrasions usually heal within 24 h. However, ulceration can develop, and ophthalmologic consultation is recommended.

4.9.2 Operating Room Fire

Three components must be present for fire to occur. These are fuel, an ignition source, and an oxidizer ("the fire triad"). Prevention of operating room fires is best achieved by isolation of the three components, although this is not always possible. Every surgery should be assessed for fire risk; high-risk surgeries are those in which an ignition source will be used near an oxidizer (e.g., laser surgery near an endotracheal tube).

The ASA Practice Advisory for the Prevention and Management of Operating Room Fires [50] recommends various preventive strategies. These include minimizing the presence of an oxidizer-enriched atmosphere in proximity to an ignition source, positioning surgical drapes in a manner that will minimize accumulation of oxidizers under the drapes and prevent flow into the surgical site, allowing flammable skin-prepping solutions to adequately dry before draping, and moistening gauze and sponges when used in proximity to an ignition source.

In the event of an operating room fire (airway fire or otherwise), the flow of airway gases should be stopped and all flammable materials should be removed from the patient. The fire should be extinguished with saline, water, or smothering. If attempts to extinguish the fire by the aforementioned methods fail, a carbon dioxide fire extinguisher should be used [50].

Complications of Anesthesia

Complications	Incidence	References	Comments
Sore throat	30%–70%	[2]	Range is for post-tracheal intubation
Dental injury	0.02%–0.07%	[3]	
Airway injury	7%	[1]	
Bronchospasm	1.6:1000	[8]	
Aspiration	0.7–4.7:10,000	[10]	
POPE	0.05%–0.1%	[12]	
MI/cardiac death	1%–5%	[16]	Combined incidence of cardiac death and nonfatal MI for intermediate-risk surgery[a]
Dysrhythmias	70%	[17,18]	Only 1.6% require intervention
Renal dysfunction	0.8%	[19]	For noncardiac surgery
Stroke	0.2%–0.7%	[22]	For general surgery
Cognitive dysfunction	19.2%	[28]	Incidence for middle-aged patients at 1 week after surgery
Visual loss	0.002%	[30]	0.2% for spine and cardiac surgery combined
Awareness	1–2:1000	[34]	
Postdural puncture headache	<2%–70%	[38]	Varies depending on needle size and type
Spinal hematoma	1:220,000	[40]	
Epidural hematoma	1:150,000	[40]	
Malignant hyperthermia	13.3:1,000,000	[46]	
Latex allergy	<1%	[47]	

[a] Intermediate risk surgery includes intraperitoneal, intrathoracic, carotid, head and neck, orthopedic, and prostate surgery. It excludes aortic, major vascular, and peripheral vascular surgery.

Preventive Measures for Anesthesia Complications

Complications	Preventive Measures	References
Sore throat	• LMA • Systemic or topical lidocaine • Monitor tracheal tube cuff pressure	[2]
Dental injury	• Careful laryngoscopy • Use of mouth guards and soft bite blocks	[3]
Airway injury	• Laryngoscopy by an experienced practitioner • Appropriate tracheal tube size and position • Avoid tracheal tube cuff overinflation	[4]
Laryngospasm	• Avoid extubation during stage II of anesthesia	[12]
Atelectasis	• Intraoperative use of PEEP • Lower inspired oxygen concentration • Incentive spirometry and CPAP	[5–7]
Bronchospasm	• Preoperative medical optimization • Avoid airway instrumentation when possible • Adequate depth of anesthesia before intubation • Deep extubation in selected cases	[8,9]
Aspiration	• Adherence to fasting guidelines • Rapid sequence induction • Consider awake intubation when difficult airway suspected	[10,11]
POPE	• Use of a bite block to prevent tracheal tube obstruction • Avoid extubation during stage II of anesthesia • Immediate relief of upper airway obstruction	[12,13]
Myocardial ischemia/ infarction	• Evaluate and treat patients with active cardiac conditions as per the ACC/AHA guidelines • Beta-blockers and statins should be continued in the perioperative period • Coronary revascularization in select cases (see text)	[16]
Dysrhythmias	• Avoid direct mechanical irritation by central catheters • Correct electrolyte abnormalities	[18]
Renal dysfunction	• Appropriate hydration • Avoid hypotension • Avoid nephrotoxins	[19,20]
Hepatic dysfunction	• Maintain adequate systemic perfusion and oxygenation	[21]
Stroke	• Maintain blood pressure close to baseline • Continuation of antiplatelet therapy whenever possible	[22,25]
Visual loss	• Monitor blood pressure continuously and hemoglobin or hematocrit during surgery in patients at risk • Position with head level at or above heart level • Avoid direct pressure on eyes • Consider staged procedures	[31]
Nerve injury	• Appropriate positioning and padding of pressure points	[33]
Awareness	• Check proper function of anesthesia equipment • Prophylactic administration of a benzodiazepine • Monitor end-tidal anesthetic concentration	[35]
Postdural puncture headache	• Experienced practitioner • Use of a pencil-point needle • Use of a smaller gauge needle	[38]
Neuraxial hematoma	• Appropriate patient selection • Careful review of medication and coagulopathy history • Adherence to ASRA recommendations regarding neuraxial anesthesia and anticoagulation	[40]
Local anesthetic systemic toxicity	• Follow dosage recommendations • Incremental injection • Test dosing with epinephrine	[44]
Malignant hyperthermia	• Avoid succinylcholine and volatile anesthetics in MH-susceptible patients	[46]
Latex allergy	• Avoid latex-containing products and devices • Effective communication • Post warning signs	[47,48]
Corneal abrasion	• Taping eyelids closed • Consider eye ointment/lubricant in long cases	[49]
Operating room fire	• Minimize oxidizers near the ignition source • Appropriate placement of surgical drapes • Moistening of potential fuel	[50]

References

1. Metzner J, Posner KL, Lam MS, et al. Closed claims' analysis. *Best Pract Res Clin Anaesthesiol* 2011;25:263–276.

   The authors analyze the ASA Closed Claims database providing anesthesia-related injury statistics and current trends.
2. Tanaka Y, Nakayama T, Nishimori M, et al. Lidocaine for preventing postoperative sore throat. *Cochrane Database Syst Rev* 2009;8:3.
3. Yasny JS. Perioperative dental considerations for the anesthesiologist. *Anesth Analg* 2009;108:1564–1573.
4. Chen EH, Logman ZM, Glass PS, et al. A case of tracheal injury after emergent endotracheal intubation: A review of the literature and causalities. *Anesth Analg* 2001;93(5):1270–1271.
5. Duggan M, Kavanagh, BP. Pulmonary atelectasis: A pathogenic perioperative entity. *Anesthesiology* 2005; 102:838–854.
6. Thomas JA, McIntosh JM. Are incentive spirometry, intermittent positive pressure breathing, and deep breathing exercises effective in the prevention of postoperative pulmonary complications after upper abdominal surgery? A systematic overview and meta-analysis. *Phys Ther* 1994;74:3–10.
7. Squadrone V, Coha M, Cerutti E, et al. Continuous positive airway pressure for treatment of postoperative hypoxemia. *JAMA* 2005;293:589–595.
8. Olsson GL. Bronchospasm during anaesthesia. A computer-aided incidence study of 136,929 patients. *Acta Anaesthesiol Scand* 2008;31:244–252.
9. Berry A, Brimacombe J, Keller C, et al. Pulmonary airway resistance with the endotracheal tube versus laryngeal mask airway in paralyzed anesthetized adult patients. *Anesthesiology* 1999;90:395–397.
10. Olsson GL, Hallen B, Hambraeus-Jonzon, K. Aspiration during anaesthesia: A computer-aided study of 185, 358 anaesthetics. *Acta Anaesthesiol Scand* 2008;30:84–92.
11. Beck-Schimmer B, Bonvini JM. Bronchoaspiration: Incidence, consequences and management. *Eur J Anaesthesiol* 2011;28:78–84.
12. Udeshi A, Cantie SM, Pierre E. Postobtructive pulmonary edema. *J Crit Care* 2010;25:538.e1–538.e5.
13. McConkey PP. Postobstructive pulmonary oedema—a case series and review. *Anaesth Intens Care* 2000; 28:72–76.
14. Mangano DT, Hollenberg M, Fegert G, et al. Perioperative myocardial ischemia in patients undergoing noncardiac surgery— I: Incidence and severity during the 4 day perioperative period. *J Am Coll Cardiol* 1991; 17:843–850.
15. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043–1049.
16. Fleisher LA, Beckman JA, Brown KA. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Writing Committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). *J Am Coll Cardiol* 2007;50:1707–1732.

   This article offers the most recent guidelines by the ACC/AHA for the perioperative cardiovascular evaluation of patients undergoing noncardiac surgery. Based on the most current evidence, experts provide recommendations for or against various diagnostic and therapeutic interventions.
17. Forrest JB, Cahalan MK, Rehder K, et al. Multicenter study of general anesthesia. II. Results. *Anesthesiology* 1990;72:262–268.
18. Atlee JL. Perioperative cardiac dysrhythmias: Diagnosis and management. *Anesthesiology* 1997;86:1397–1424.
19. Kheterpal S, Tremper KK, Englesbe MJ, et al. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. *Anesthesiology* 2007;107:892–902.

   This prospective, observational study, reviewed 65,043 cases at a tertiary care university hospital. The authors report incidence of acute renal failure in the noncardiac surgical population and identify independent preoperative risk factors for postoperative acute renal failure.
20. Kellum JA, Leblanc M, Gibney RTN, et al. Primary prevention of acute renal failure in the critically ill. *Curr Opin Crit Care* 2005;11:537–541.
21. Rothenberg DM, O'Connor CJ, Tuman KG. Anesthesia and the hepatobiliary system. In *Miller's Anesthesia*, 7th edn. Miller RD, ed. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 2135–2153.
22. Kam PCA and Calcroft RM. Peri-operative stroke in general surgical patients. *Anaesthesia* 1997;52:879–883.
23. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* 2003;34:2290–2301.
24. Likosky DS, Marrin CA, Caplan LR, et al. Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. *Stroke* 2003;34:2830–2834.
25. Selim M. Perioperative stroke. *N Engl J Med* 2007; 356:706–713.

   This review article provides a comprehensive discussion on perioperative stroke, including information on incidence, pathophysiology, risk stratification/modification, and management.
26. Aboyans V, Labrousse L, Lacroix P, et al. Predictive factors of stroke in patients undergoing coronary bypass grafting: Statins are protective. *Eur J Cardiothorac Surg*. 2006;30:300–304.
27. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;32:1119–1131.
28. Johnson T, Monk T, Rasmussen LS, et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology* 2002;96:1351–1357.
29. Rasmussen LS, Johnson T, Kuipers HM, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* 2003;47:260–266.

30. Newman NJ. Perioperative visual loss after nonocular surgeries. *Am J Ophthalmol* 2008;145:604–610.
31. Apfelbaum JL, Roth S, Connis RT, et al. Practice advisory for perioperative visual loss associated with spine surgery: An updated report by the American Society of Anesthesiologists task force on perioperative visual loss. *Anesthesiology* 2012;116:274–285.
32. Cheney FW, Domino KB, Caplan RA, et al. Nerve injury associated with anesthesia: A closed claims analysis. *Anesthesiology* 1999;90:1062–1069.
33. Apfelbaum JL, Connis RT, Caplan RA, et al. Practice advisory for the prevention of perioperative peripheral neuropathies: An updated report by the American Society of Anesthesiologists task force on prevention of perioperative peripheral neuropathies. *Anesthesiology* 2011;114:1–13.
34. Sebel PS, Bowdle TA, Ghoneim MM, et al. The incidence of awareness during anesthesia: A multicenter United States study. *Anesth Analg* 2004;99:833–839.
35. Apfelbaum JL, Arens JF, Cole DJ, et al. Practice advisory for intraoperative awareness and brain function monitoring: A report by the American Society of Anesthesiologists task force on intraoperative awareness. *Anesthesiology* 2006;104:847–864.
36. Avidan MS, Jacobsohn E, Glick D, et al. Prevention of intraoperative awareness in a high-risk surgical population. *N Engl J Med* 2011;365:591–600.
37. Mashour GA, Shanks A, Tremper KK, et al. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: A randomized comparative effectiveness trial. *Anesthesiology* 2012;117:717–725.
38. Turnbull D, Shepherd DB. Post-dural puncture headache: Pathogenesis, prevention and treatment. *Br J Anaesth* 2003;91:718–729.
39. Abouleish E, de la Vega S, Blendinger I, et al. Long-term follow-up of epidural blood patch. *Anesth Analg* 1975;54:459–463.
40. Horlocker TT, Wedel D, Rowlingson J, et al. Regional anesthesia in the patient receiving antithrombotic of thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition). *Reg Anesth Pain Med* 2010;35:64–101.
41. Fredrickson MJ, Kilfoyle DH. Neurological complication analysis of 1000 ultrasound guided peripheral nerve blocks for elective orthopaedic surgery: A prospective study. *Anaesthesia* 2009;64:836–844.
42. Abrahams MS, Aziz MF, Fu RF, et al. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: A systematic review and meta-analysis of randomized controlled trials. *Br J Anaesth* 2009;102:408–417.
43. Neal JM, Bernards CM, Hadzic A, et al. ASRA practice advisory on neurologic complications in regional anesthesia and pain medicine. *Reg Anesth Pain Med* 2008;33:404–415.
44. Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: Incidence and preventive measures. *Reg Anesth Pain Med* 2002;27:556–561.
45. Weinberg GL. Lipid emulsion infusion: Resuscitation for local anesthetic and other drug overdose. *Anesthesiology* 2012;117:180–187.
46. Rosero EB, Adesanya AO, Timaran CH, et al. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. *Anesthesiology* 2009;110:89–94.
47. Turjanmaa K, Makinen-Kiljunen S. Latex allergy: Prevalence, risk factors, and cross-reactivity. *Methods* 2002;27:10–14.
48. Holzman RS. Latex allergy an emerging operating room problem. *Anesth Analg* 1993;76:635–641.
49. Roth S, Thisted RA, Erickson JP, et al. Eye injuries after nonocular surgery: A study of 60 965 anesthetics from 1988 to 1992. *Anesthesiology* 1996;85:1020–1027.
50. Caplan RA, Barker SJ, Connis RT, et al. Practice advisory for the prevention and management of operating room fires: A report by the American Society of Anesthesiologists task force on operating room fires. *Anesthesiology* 2008;108:786–801.

5

Respiratory Failure after Surgery or Trauma

Joseph J. DuBose and James V. O'Connor

CONTENTS

Respiration is a complex physiologic process that involves coordinated functioning of the different components of the respiratory system. Acute dysfunction of one or more of these components may result in inability to meet the metabolic requirements of the tissues in terms of oxygen delivery or carbon dioxide removal. Such impairment is not infrequent after surgery, trauma, or both and may result from a multitude of causes. Recognition of the more common of these causes will allow the preoperative determination of which patients are at a high risk of respiratory dysfunction and may allow modification of risk factors.

In order to effectively manage pulmonary dysfunction, a thorough understanding of the principles of mechanical ventilation is crucial. An evidence-based approach to the most severe form of respiratory failure, acute respiratory distress syndrome (ARDS), is essential for a potentially successful outcome. Finally, some other causes of respiratory failure in this setting require physicians to maintain a high index of suspicion. Awareness of these conditions may allow earlier recognition and, therefore, earlier treatment.

This chapter emphasizes the definition and scope of the problem and provides the basics of mechanical ventilation as

applied to the management of acute respiratory failure, the evidence behind the current strategies used to treat ARDS, and some less common causes of respiratory failure that are unique to surgical and trauma patients.

5.1 Respiratory Failure

5.1.1 Definitions

Respiratory failure is defined as the failure of the respiratory system to oxygenate blood or remove carbon dioxide at levels that are commensurate with the metabolic requirements of the tissues. The development of acute severe hypoxemia in the presence of bilateral lung infiltrates and in the absence of evidence of cardiac dysfunction constitutes a severe form of acute respiratory failure. This condition is further characterized on the basis of the ratio of partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (the PF ratio). Accordingly, a PF ratio of <300 indicates acute lung injury (ALI), whereas a PF ratio of <200 indicates ARDS (Table 5.1) [1].

5.1.2 Classifications

Traditionally, respiratory failure is classified according to the resultant abnormalities in the results of blood gas analysis. It is termed *hypercarbic* if the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is >45 mmHg, *hypoxemic* if the PaO_2 is <55 mmHg at an FiO_2 of greater than or equal to 0.6, or *combined* if a mixed picture exists.

These categories are best understood by dividing the respiratory system into two functionally distinct portions. The *respiratory pump* consists of the central nervous system, the peripheral nervous system, the respiratory muscles, and the chest wall. It functions to deliver air from the atmosphere to the alveoli. Its dysfunction results in hypoventilation characterized predominantly by hypercarbia. Various degrees of associated hypoxemia occur. The alveoli compose the *gas exchange units*. Their dysfunction causes respiratory failure marked by hypoxemia, which results from collapse or flooding of the alveoli. Flooding of the alveoli occurs when the alveoli is filled with purulent material, blood, or fluid.

TABLE 5.1

Definition of ARDS and ALI

Acute onset
PaO_2/FiO_2 ratio <300 for ALI and <200 for ARDS. Bilateral chest infiltrates as demonstrated by chest radiograph. Pulmonary artery occlusion pressure 18 mmHg or less or the absence of clinical evidence of left atrial hypertension

The decreased compliance increases the work of breathing and causes dyspnea and tachypnea. Postoperative respiratory failure is often a multifactorial process that results in a combination of hypoxemia and hypercarbia.

5.1.3 Epidemiology

Common respiratory problems that develop after surgery and trauma include atelectasis, bronchospasm, exacerbation of underlying chronic lung disease, pneumonia, pulmonary embolism, ALI, and ARDS. Approximately 5% of patients undergoing surgical intervention will experience one or more of these conditions, and approximately 1% will experience respiratory failure severe enough to necessitate mechanical ventilation for more than 24 h [2]. The occurrence of these problems not only increases the length of stay in the hospital and in the intensive care unit (ICU), but also is responsible for 25% of postoperative deaths [3].

Trauma and burns are an important cause of respiratory failure, especially among patients <30 years old [4]. ARDS occurs among 12% of critically ill trauma patients who are admitted to ICUs and carries a mortality rate of 16%, whereas ALI occurs among 4% of such patients and carries an associated mortality rate of 9% [5]. Risk factors that predispose patients to the development of ARDS after trauma include long-bone fractures, pelvic fractures, head injury, direct chest trauma, tissue hypoxia, and massive blood transfusion [6].

5.1.4 Determination of Risk

Risk factors may primarily be patient-related, procedure-related, or a combination of the two. Patient-related risk factors include smoking, poor general health status, chronic obstructive pulmonary disease (COPD), and asthma. The relative risk of complications for smokers is 4.3, whereas that for nonsmokers is 1.4 [7]. Smoking cessation for at least 8 weeks preoperatively is required if a beneficial effect is to be observed. The presence of underlying COPD increases the relative risk of pulmonary complications from 2.7 to 4.7 and imposes a 5% risk of respiratory failure [8].

Procedure-related risk factors include the type of operative procedure performed, the type of anesthesia used, the nature of the neuromuscular agent employed, the duration of surgery, and the adequacy of pain relief. Upper abdominal and thoracic surgical procedures impair respiration by deranging pulmonary mechanics. Therefore, lesser degrees of dysfunction occur with minimally invasive procedures such as laparoscopic operations and video-assisted thoracoscopic surgery. The use of general anesthesia is associated with a loss of muscle tone in the diaphragm and intercostal muscles, cephalad movement of the diaphragm, a decrease

in transverse thoracic diameter, a drug-induced reduction in the respiratory drive, and an impaired response to CO_2. These effects cause a 20% reduction in functional residual capacity and also result in compressive atelectasis, increased shunt fraction, and impaired hypoxic pulmonary vasoconstriction [9]. The use of long-acting neuromuscular blocking agents (e.g., pancuronium) also contributes to impaired muscle function and an increased risk of complications. Prolonged surgical procedures also result in greater pulmonary dysfunction. Providing inadequate pain relief results in splinting with a reduction in deep breathing and a decrease in coughing. Both of these responses cause atelectasis and retained secretions, which promote respiratory dysfunction.

Preoperative education of patients about the techniques for lung expansion, deep-breathing exercises, and the use of incentive spirometry is beneficial. Options for adequate pain control, such as epidural analgesia and intercostal nerve blocks, can also be planned for patients who are at risk of complications.

5.2 Principles of Mechanical Ventilation

5.2.1 Overview

The goal of mechanical ventilation is clear: to maintain oxygenation and ventilation, thereby allowing time for the underlying disease to heal and for the patient to independently resume these functions. It provides the time required for other measures, normal healing, or both, to bring about healing without causing further damage to the lung. No ideal method of ventilation exists, but the features of commonly employed methods are outlined in Table 5.2.

TABLE 5.2

Key Features of the More Commonly Employed Methods of Ventilation

Assist-control: Relates to the control process of the breath. The assist portion is controlled by the patient; the control portion is controlled by the ventilator. The patient's triggering may be based on flow or pressure. Once initiated, the breath may be controlled by flow or pressure.
Intermittent mandatory ventilation/synchronized intermittent mandatory ventilation: The ventilator delivers a predetermined number of controlled breaths; the patient breathes spontaneously between mandatory breaths. The controlled breath may be controlled by flow or pressure. The spontaneous breaths may be augmented by pressure support.
Pressure support ventilation: The breath must be triggered by the patient; after initiation, inhalation is assisted by a predetermined amount of pressure. Inspiration ceases when the flow falls below a certain predetermined rate. Requires an intact respiratory drive; used for weaning.
Mandatory minute ventilation: In this method, the minimum minute ventilation is set by the clinician. The patient breathes spontaneously with or without pressure support. The difference between the spontaneous and set-minute ventilation is delivered as mandatory breaths with set tidal volume and flow. This method allows patients to take over a greater portion of their breathing efforts.
Volume-assured pressure ventilation: Used for patients who are breathing spontaneously. The minimal tidal volume is set. The patient initiates a pressure-supported breath. If the volume falls below the preset minimum, the ventilator completes the breath by delivering additional constant flow at increasing pressures.
Volume support: The patient initiates the breath with clinician-determined pressure support. The machine determines the generated tidal volume and adjusts this pressure support to maintain a minimal target tidal volume.
Pressure-regulated volume control: A form of controlled ventilation in which, at a preset rate, the machine regulates the inspiratory pressure to generate a target tidal volume.
Airway pressure release ventilation: Here, the upper and lower continuous airway pressures are set as are the pressure release time and the frequency of release.

5.2.2 Noninvasive Positive-Pressure Ventilation

Endotracheal intubation, a key component of positive-pressure mechanical ventilation, is associated with several complications such as upper airway trauma, nosocomial pneumonia, and sinusitis. The use of intubation prolongs hospital stay and increases the costs associated with ICU resource utilization. Noninvasive positive-pressure ventilation (NIPPV) combines pressure support and positive end-expiratory pressure (PEEP) delivered via a nasal or facial mask. Although initially studied as a means of avoiding intubation during exacerbations of COPD, NIPPV is now increasingly being applied in settings of interest to surgeons. These settings include perioperative acute respiratory failure due to obstructive sleep apnea in the morbidly obese, hypoxemic respiratory failure due to pneumonia, ARDS, trauma, and cardiogenic pulmonary edema. NIPPV improves oxygenation, reduces the need for endotracheal intubation, decreases septic complications, reduces the length of ICU stay, and lowers mortality rates [10].

Postoperative indications for NIPPV include a $PaCO_2$ higher than 50 mmHg, a PaO_2 lower than 60 mmHg, and respiratory muscle fatigue. Its use may preclude reintubation because of respiratory failure, which may occur in association with 5%–20% of planned extubations [11] and 40%–50% of unplanned extubations [12]. Its successful application requires the ability to protect the airway, a spontaneously breathing patient, intact dentition, absence of facial trauma, minimal secretions, and the absence of severe acid–base and gas derangements. Contraindications to NIPPV include respiratory arrest, inability to protect the airway, hemodynamic instability, excessive secretions, uncooperative or

agitated patients, inability to fit the mask, and upper airway or upper gastrointestinal surgery.

NIPPV is administered through an oronasal mask, with a change to a nasal mask if a prolonged duration of support is anticipated. Inspiratory support is begun at 8–10 cmH_2O and is increased as tolerated. Support is maintained at <20 cmH_2O so that discomfort due to sinus pain, gastric distention, or both, can be avoided. A trial-and-error method is used to identify the optimal degree of support. Expiratory support begins at 5 cmH_2O and is increased as necessary. With increases in expiratory pressure, the inspiratory pressures must be increased so that the pressure support can be kept constant. Supplemental oxygen is provided so that oxygen saturation can be maintained at >90%. Humidification improves patient tolerance and the ability to deal with secretions. A nasogastric tube is not routinely used because it breaks the seal. Complications include nasal bridge edema, erythema, and ulceration, as well as nasal congestion, sinus or ear pain, mucosal dryness, eye irritation, and gastric insufflation. Rarely, pneumothorax, hypotension, or aspiration may occur.

5.3 Acute Lung Injury and Adult Respiratory Distress Syndrome

ALI and ARDS are severe forms of respiratory dysfunction that may occur as the result of a multitude of causes. These causes either may involve mechanisms that bring about direct injury to pulmonary tissue or may represent the pulmonary response to a systemic insult that sets into motion a cascade of events culminating in inflammation. Common causes of direct injury to pulmonary tissue include aspiration, pneumonia, toxic inhalation, lung contusion, and near drowning. Common causes of indirect injury include severe sepsis, shock, multisystem trauma, burn injury, pancreatitis, cardiopulmonary bypass, and drug overdose. Of these, trauma, aspiration, and sepsis are the most common predisposing causes [13]. Among trauma patients, an injury severity scale (ISS) score of more than 25 and pulmonary contusion are the primary risk factors that predispose patients to the development of ARDS.

Clinically, the condition is characterized by impaired oxygenation, decreased pulmonary compliance, and normal or supranormal cardiac function. These features, which have been incorporated into the definition jointly developed by the American–European Consensus Conference [1], include a PF ratio of <300 for ALI and <200 for ARDS, bilateral pulmonary infiltrates, and the absence of evidence of left heart dysfunction, either clinically or on the basis of pulmonary artery catheter (PAC) measurements. Intrapulmonary shunting is a primary mechanism of the observed hypoxemia, whereas the combination of increased dead space fraction and reduced compliance results in an increase in the work of breathing. Together, these factors result in a form of respiratory failure characterized by hypoxemia, hypercarbia, and acidosis.

Histologically, ARDS is characterized by diffuse pulmonary inflammatory infiltrates, interstitial and alveolar edema, loss of type II pneumocytes, depletion of surfactant, deposition of hyaline membranes, and, in long-standing cases, fibrosis [14].

Although ARDS is the most common cause of pulmonary infiltrates associated with hypoxemia in the critically ill patient, it is not the only cause. The differential diagnosis includes acute interstitial pneumonia, acute eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia, diffuse alveolar hemorrhage, and acute hypersensitivity pneumonitis. These conditions should be suspected in the appropriate clinical setting, especially when acute pulmonary dysfunction with features of ARDS develops in the absence of an identifiable precipitating cause. Diagnosis is made by characteristic findings on bronchoscopy or is based on the appearance of the tissue during open lung biopsy. Treatment depends on the underlying cause and usually involves the administration of steroids.

Because ARDS is associated with high mortality and morbidity rates, the optimal management of the disease remains an elusive goal. However, important advances in our understanding of the pathophysiology of the disease process have led to an evidence-based approach.

5.3.1 Identification and Treatment of Underlying Disorders and Infections

Identification and possible control of the inciting event are important first steps in the treatment of ARDS. They remove the source of continued stimulation that generates the inflammatory cascade responsible for perpetuation and potentiation of the lung injury. The early identification of any associated or subsequent infection and its aggressive and appropriate treatment cannot be overemphasized.

5.3.2 Lung-Protective Ventilation Strategies

An important advancement in the management of ARDS has been the recognition of the beneficial effects of lung-protective ventilation strategies. The reduction in mortality rates was demonstrated in two clinical trials [15,16], whereas three other contemporaneous studies failed to demonstrate any benefit [17–19]. There are several possible explanations for the observed differences in outcome. First, the tidal volumes used in the control

arms of the studies that demonstrated a difference were, by current standards, excessive. These nonphysiologic tidal volumes may have resulted in excessive mortality in the control arm, thereby giving an impression of benefit from low tidal volumes. Second, in studies showing benefit, additional lung-protective strategies, such as a higher PEEP and lung-recruitment maneuvers, were employed. These strategies may have had an additive effect on limited tidal volumes with resultant benefit. Third, respiratory acidosis was aggressively controlled in the National Institutes of Health (NIH) trial with increases in respiratory rate for a pH lower than 7.30 and bicarbonate infusions for a pH lower than 7.2. Such an approach was not emphasized in the studies that did not show a benefit. Finally, in the NIH trial, the tidal volumes were based on predicted and not actual body weight. Despite these shortcomings, the ARDS Network trial represents the best evidence currently available and should be the benchmark against which future trials are compared.

Limitation of airway pressures is another key tenet. The plateau pressure is regularly monitored and maintained at or below 30 cmH_2O. Lung-recruitment maneuvers are recommended and should be regularly performed [20]. Several techniques of recruitment have been successfully employed, including sustained continuous positive airway pressure for 30–40 s, traditional sigh breaths, extended sighs, intermittent high levels of PEEP, and brief periods of super-PEEP. Higher than normal levels of PEEP are required for maintaining lung volume after a recruitment maneuver. Although these high levels of PEEP produce a short-term improvement in oxygenation, they have not been shown to provide long-term benefits.

5.3.3 Optimal Positive End–Expiratory Pressure for Patients with Adult Respiratory Distress Syndrome

Selection of the optimal level of PEEP is another key component in the management of ARDS. The elastic forces of the lung tissue and the surface tension within the alveoli determine the end-expiratory alveolar volume. Inadequate PEEP and altered surface tension, presumably due to reduced or altered production of surfactants, allow end-expiratory alveolar collapse. This condition results in shunting and persistent hypoxemia. Furthermore, the alveoli are once again recruited during the inspiratory phase of tidal ventilation. The resultant repetitive derecruitment and recruitment lead to potentiation of the lung injury. Using adequate levels of PEEP maintains alveolar volume at the end of expiration, prevents derecruitment, and yields an open lung pattern of ventilation. It additionally attenuates pulmonary edema and maintains an adequate functional residual capacity. At the other end of the spectrum, excessive PEEP is equally detrimental. At high levels of PEEP, cardiac output is diminished as a consequence of decreased venous return due to increased intrathoracic pressures and impaired distention of the right heart, which limits its filling. Also, the resultant alveolar distention compresses the pulmonary vasculature, thereby increasing the pulmonary vascular afterload. Hence, if maximal benefit is to be obtained, PEEP must be maintained at its lowest effective level.

Several techniques have been used for determining the optimal level of PEEP. It is recognized that the lower inflection point of the pressure–volume curve represents the beginning of recruitment. By using this measurement as the reference point, PEEP is maintained at 2 cmH_2O above the lower inflection point. Improved survival is seen when low tidal volumes are combined with a PEEP that has been titrated with this technique [15]. Alternatively, PEEP may be titrated above the closing pressure of the deflection limb or may be adjusted by decrements. In this technique, maximal levels of PEEP are applied at the beginning, usually 20–25 cmH_2O. Then, while PO_2 is monitored, PEEP is reduced in decrements of 2 cmH_2O until the minimum PEEP that results in maximal oxygenation has been determined. Yet another technique involves measuring the internal thoracic diameter in centimeters and multiplying this measurement by a factor of 0.8.

5.3.4 High-Frequency Ventilation

Recognition of the beneficial effects of strategies, with an emphasis on strategies that limit ventilator-associated ALI, has generated interest in alternative methods of ventilation. One such approach is the use of high-frequency ventilation, a technique that employs very high respiratory rates in conjunction with very small tidal volumes that are less than the anatomical dead space.

Although several methods of high-frequency ventilation exist (viz., high-frequency oscillatory ventilation [HFOV], high-frequency jet ventilation, and high-frequency positive-pressure ventilation), all employ a similar physiologic principle. In HFOV, oxygenation at a given FiO_2 is proportional to the mean airway pressure (P_{aw}) and the resultant lung volume. The P_{aw} is adjusted either by changing the resistance at the end of the bias flow circuit or by changing the rate of bias flow. Ventilation is controlled by changes in the amplitude of the oscillating membrane (DP). With this method of ventilation, the tidal volume and frequency are inversely related. Hence, the level of carbon dioxide can be reduced by increasing the DP, decreasing the frequency, or both. Because both inspiration and expiration are active events, the incidence of dynamic hyperinflation is reduced.

The efficacy of HFOV is probably the result of several mechanisms, such as bulk convection, penduluft, cardiogenic oscillations, asymmetric velocity profiles, augmented dispersion, and molecular diffusion. Theoretically, this method of ventilation may have several benefits in preventing VALI. First, the use of small tidal volumes with minimal variation around the mean airway pressure and mean lung volumes allows for more effective oxygenation and reduction of FiO_2. Second, HFOV can be adjusted to avoid atelectasis or overdistention. Finally, oxygenation and ventilation are decoupled.

Despite these potential benefits, HFOV is currently used most frequently in the setting of rescue therapy when conventional ventilation fails. Even under such circumstances, its use results in improved oxygenation; however, results are better if HFOV is begun early [21,22]. Recognizing the importance of lung recruitment is crucial and is best achieved by setting the mean airway pressure 4–8 cmH_2O greater than that being used for conventional ventilation. The pressure is then titrated to achieve adequate oxygenation. The patient is weaned from FiO_2 before the mean airway pressure is reduced.

5.3.5 Inhaled Nitric Oxide in the Management of Acute Respiratory Distress Syndrome

Nitric oxide (NO) is synthesized by numerous cell types from L-arginine and oxygen by a group of enzymes called nitric oxide synthetases. When nitric oxide is administered by the inhaled route (iNO), its high lipid solubility allows rapid diffusion across epithelial cells and access to the pulmonary vasculature. Because NO possesses a high affinity for hemoglobin, a portion of the iNO enters the pulmonary vasculature, where it is rapidly inactivated by binding to the hemoglobin in red cells. The remainder enters the smooth muscle cells of the pulmonary arterioles and causes vasodilatation. It modulates pulmonary vascular tone in healthy people and also functions as a pulmonary vasodilator in a variety of conditions that cause pulmonary hypertension.

When NO is inhaled, its distribution is limited to well-ventilated areas; hence, it does not reverse hypoxic pulmonary vasoconstriction. Furthermore, the resultant distribution of ventilation–perfusion is improved when blood is moved away from poorly ventilated areas to areas with better ventilation [23]; this movement improves oxygenation. Additional pulmonary effects include a reduction in the shunt fraction, relaxation of bronchial smooth muscles, a decrease in pulmonary capillary permeability because of a reduction in pulmonary venous tone, a decrease in oxidant injury, and a reduction in cytokine levels.

Initial studies [23] found that iNO produces a dose-related pulmonary vasodilatory response, with a decrease in pulmonary artery pressure, without substantial effects on the systemic circulation. They also found greater venous dilation than arterial dilation of the pulmonary system, with resultant reductions in pulmonary capillary pressure. These vascular changes result in acute improvements in oxygenation, a phenomenon associated with rebound on abrupt discontinuation of the drug. Several randomized controlled studies [24–26] have observed transient improvements in oxygenation; however, the effects have not been sustained. Furthermore, the improvement in oxygenation has not translated to improvements in mortality rates or in reductions in the number of ventilator-free days. Therefore, iNO improves the physiologic parameters but does not affect outcome.

There are several explanations for the lack of success with iNO. Until now, the dose of iNO has been titrated so that it maximizes oxygenation. At these doses, only small changes in pulmonary artery pressure have been seen. Higher doses that target the pulmonary artery pressure rather than oxygenation may be of benefit. Also, the benefit of improved oxygenation may have been overshadowed by the adverse effects of the toxic levels of oxygen and high levels of airway pressure. Furthermore, the studies were not adequately powered, the patients were a heterogeneous group, and the treatments were not standardized and were employed only for a brief period, which may not have permitted the underlying condition to improve.

Patients most likely to benefit from iNO include those with a high baseline pulmonary vascular tone, a high degree of initial venous admixture, and increased cardiac output. Efforts aimed at improving outcomes have focused on combination therapies involving iNO. Its use in combination with pulmonary vasoconstrictors such as almitrine [27] or norepinephrine [28] increases the PF ratio more than does the use of either agent alone. This outcome is probably the effect of a reduction in the shunt fraction that is the result of generalized pulmonary vasoconstriction with vasodilatation in the well-ventilated areas. Other combination therapies include the use of phosphodiesterase inhibitors [29], prone positioning, high-frequency ventilation, and partial liquid ventilation.

At the present time, iNO has no proven benefit on outcome. It does, however, produce short-term symptomatic relief. The subgroup of patients who may benefit from such improvement and from the combination of iNO with other treatment strategies needs to be further defined.

5.3.6 Prone-Position Ventilation

Placing patients in the prone position causes gravity-dependent fluid shifts from the dorsal to the ventral

aspects of the lungs, thereby increasing the area available for oxygenation. Such positioning also restores the functional residual capacity and decreases the vertical transpulmonary pressure gradient, thereby allowing the alveoli to maintain a more uniform size. Such positioning lessens the cyclic opening and closing of unstable alveolar units in the dependent regions and lessens overdistention at end-expiration in nondependent lung regions. Additionally, prone positioning alters chest wall compliance and decreases the shunt fraction, without any significant change in the hemodynamics. Like iNO, prone positioning improves oxygenation, but no improvement in outcome has been demonstrated.

A response to therapy is defined as an increase in PaO_2 of at least 10 mmHg or an increase in the PF ratio of at least 20. Factors predictive of success include worse oxygenation at baseline [30], shorter duration of ARDS [31], and higher baseline chest wall compliance [32]. The use of prone positioning in combination with other therapies, especially iNO, has produced even better response rates [33].

Prone-position ventilation may be associated with several complications, including loss of intravenous catheters, skin breakdown, loss or displacement of the endotracheal tube, and transient hemodynamic instability.

5.3.7 Steroids in Acute Respiratory Distress Syndrome

Steroids have been used to treat patients with ARDS in the hope of reducing the systemic response to the inciting event. Neither prophylactic use for high-risk patients nor steroid administration early in the course of the disease process has altered outcome [34,35]. Improved survival has, however, been observed with late use of steroid in the fibroproliferative stage of the disease [36]. The role of steroids remains ill-defined, and a NIH-sponsored study is currently underway to address the issue.

5.3.8 Immunomodulation in Adult Respiratory Distress Syndrome

It is now recognized that a local or systemic triggering event brings about a release of mediators (interleukin-8, tumor necrosis factor-α [TNF-α], lipid mediators, platelet-activating factors, etc.) that cause endothelial cell damage. The increased vascular permeability that results causes noncardiogenic pulmonary edema, hypoxemia, and impaired systemic oxygenation. Recognition of the central role played by inflammation has led to attempts at modulating the inflammatory process, and thereby influencing outcome. Options include nonsteroidal anti-inflammatory agents, steroids, antioxidants, pentoxyfylline, and ketoconazole.

Ibuprofen has been used as a nonsteroidal anti-inflammatory drug, without benefit [37]. Ketoconazole has similarly been used for its anti-inflammatory properties [38]. The phosphodiesterase inhibitors pentoxyfylline and lysinophylline also inhibit neutrophil activation, platelet activation, and release of TNF-α. No benefit has been observed with their use. One study [39] found that the antioxidants *N*-acetylcysteine and procysteine reduced the number of days of ALI and lowered the lung injury scores, but had no beneficial effect on mortality.

5.3.8.1 Extracorporeal Life Support

Extracorporeal life support (ECLS) has been an extremely successful treatment for neonates with respiratory distress. Early studies with adult patients failed to demonstrate that ECLS was more beneficial than conventional ventilation. These trials were flawed, however, with mortality rates higher than 90% in the control and treatment arms. This high mortality rate probably occurred because of extremely sick patients who could not be successfully treated. In addition, at that time, there was only limited experience with the use of the technique for adult patients, and the standard tidal volumes used were excessive by current standards. More recent trials have been more encouraging [40,41], and have demonstrated higher survival rates than those for historical control subjects.

ECLS is presently indicated for patients who cannot be oxygenated even at a FiO_2 of 100%, or for whom peak airway pressures higher than 40 cmH_2O are needed for maintaining oxygenation. For patients with adequate cardiac function, venovenous ECLS is sufficient, but for those with cardiac dysfunction, arteriovenous bypass is required.

5.3.8.2 Fluid Management

Judicious fluid management is an essential component of the management strategy for ARDS. The rationale for using a restrictive fluid strategy is to decrease the pulmonary vascular hydrostatic pressure, thereby limiting transudation across leaky capillaries. At the same time, however, adequate tissue perfusion must be maintained. Using a PAC may be helpful in achieving this fine balance. The pulmonary artery occlusion pressure is maintained at the lowest level that will result in adequate circulation volume and mean arterial pressures, and in cardiac output that meets the oxygen delivery needs of the tissues. For patients without PACs, surrogate markers include central venous pressure, urine output, and acid–base balance. Vasopressors may be used to maintain perfusion if fluid resuscitation is inadequate. There is, however, no role for their use in generating a supranormal oxygen delivery. Adopting a restrictive fluid

strategy with diuresis results in fewer days on mechanical ventilation and improved oxygenation, and is associated with better outcomes [42]. Great caution, however, should be taken in patients who have not yet achieved euvolemic states after injury. Restrictive fluid utilization policies or diuresis in patients with ongoing resuscitative needs is not advised.

5.3.8.3 Nutritional Support

Adequate nutritional support is essential for meeting the needs of increased metabolic demand and for synthesizing new lean body tissue. Diets low in carbohydrate and high in fat are preferred, because diets high in carbohydrate increase the respiratory quotient by producing carbon dioxide, which increases the ventilatory demand. Diets that include eicosapentaenoic acid and gamma-linoleic acid improve outcome [43], because these acids have anti-inflammatory, antioxidant, and vasodilatory properties that improve microvascular permeability and reduce the generation of proinflammatory eicosanoids.

5.4 Other Causes of Respiratory Failure after Trauma or Surgery

5.4.1 Rib Fractures

Chest wall trauma is most frequently the result of motor vehicle collisions; approximately 10% of patients with chest wall trauma have rib fractures [44]. When such fractures are present, the resultant pain limits the ability to breathe deeply or cough, causes retention of sputum and atelectasis, and reduces the functional residual capacity. All of these changes combine to cause reduced lung compliance and to produce ventilation–perfusion mismatch, with resultant hypoxemia. Adequate pain management is, therefore, crucial and may be achieved by one of several methods, such as systemic opioids, intercostal nerve blocks, epidural analgesia, intrathecal opioids, intrapleural analgesia, thoracic paravertebral blocks, transcutaneous nerve stimulation, and oral analgesic agents. Each technique has its own unique strengths, weaknesses, and contraindications and must be individualized for each patient. Epidural analgesia is preferable when its use is feasible because it has been shown to provide better pain control than intermittent intrapleural injections [45] or patient-controlled analgesia [46].

5.4.2 Pulmonary Contusion

Pulmonary contusion is common after blunt trauma to the chest; its incidence is 17% among patients who suffer multisystem trauma [47]. Pulmonary contusion most often follows mechanisms of injury that involve rapid deceleration, such as motor vehicle crashes and falls.

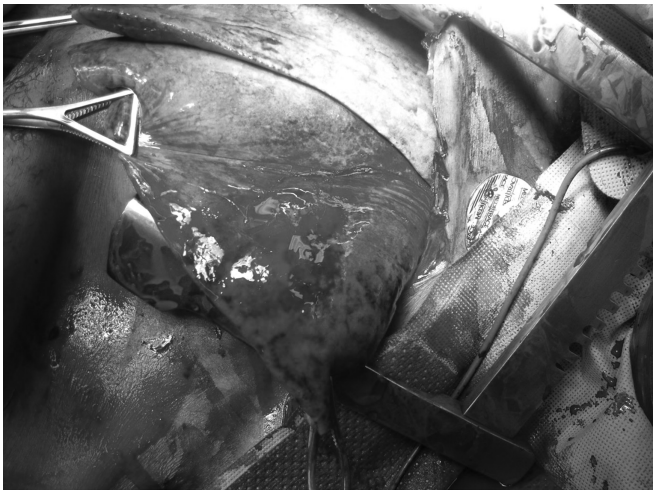


FIGURE 5.1
Pulmonary contusion intraoperative photo.

Injury to the lung parenchyma may be direct or indirect. Direct injury is commonly a result of either mechanical tearing of tissue or laceration from overlying injured ribs. Indirect injury results from shearing at the gas–liquid interface, differential rates of movement of the various intrathoracic tissues with varying densities, and the distention of contained air that occurs after a pressure wave passes. These effects result in pulmonary parenchymal injury that is proportional to the severity of the force applied (Figure 5.1). The resultant injury produces a ventilation–perfusion mismatch, increased intrapulmonary shunting, increased lung water, and reduced compliance. Clinically, these changes manifest themselves as hypoxemia, hypercarbia, and increased work of breathing. Generally, the severity of the injury worsens over the first 24–48 h, reaches a maximum at 72 h, and then resolves over the ensuing 7 days. Long-term consequences may develop as a reaction to blood in the lung tissue, the pulmonary effects of systemic inflammation, or the development of nosocomial pneumonia.

Results of initial chest radiography may be negative; however, infiltrates appear over a period of 4–6 h as the process evolves. Chest radiographs, however, underestimate the severity of the disease process. Computed tomography of the chest is much more accurate in delineating the extent of pulmonary contusion.

Treatment is essentially supportive and includes management of associated injuries, adequate pain control, aggressive pulmonary toilet, and intubation if indicated based on the patient's physiologic parameters and gas exchange. In cases of severe unilateral injuries, the patient may be placed in a kinematic bed, with the uninjured lung in the dependent position.

This positioning increases blood flow to the lung with better gas exchange capabilities, thereby improving oxygenation. Fluid management remains a challenging issue for this group of patients. Overzealous fluid resuscitation increases the lung water and decreases compliance and gas exchange; therefore, it may be detrimental. The uses of hypertonic saline and, more recently, hemoglobin substitutes have been suggested as alternatives for fluid management, but have not proven a panacea in management. Antibiotics are not indicated unless there is evidence of infection. Similarly, prophylactic steroids provide no clear benefit; rather, they increase the risk of infection.

5.4.3 Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a poorly defined, temporary condition that follows allogeneic blood transfusion. Although its true incidence is unknown, it is now being increasingly recognized [48].

TRALI is defined as a new episode of ALI that occurs during or within 6 h of a completed transfusion. It is characterized by hypoxemia with a PF ratio of 300 or less or arterial oxygen saturation below 90% on room air. The chest radiograph demonstrates bilateral infiltrates, and there is no evidence of left atrial hypertension (Figure 5.2). There is no temporal relationship to an alternative risk factor that would explain the development of ARDS. Although the exact pathophysiology remains unknown, the two most favored mechanisms are (1) an antigen–antibody reaction by antibodies contained in the transfused blood against the recipient's white blood cell components and (2) activation of pulmonary endothelial cells by the transfusion of neutrophils that have been previously primed. A number of potential additional risk factors, including the utilization of plasma from female donor sources, have been hypothesized as contributory.

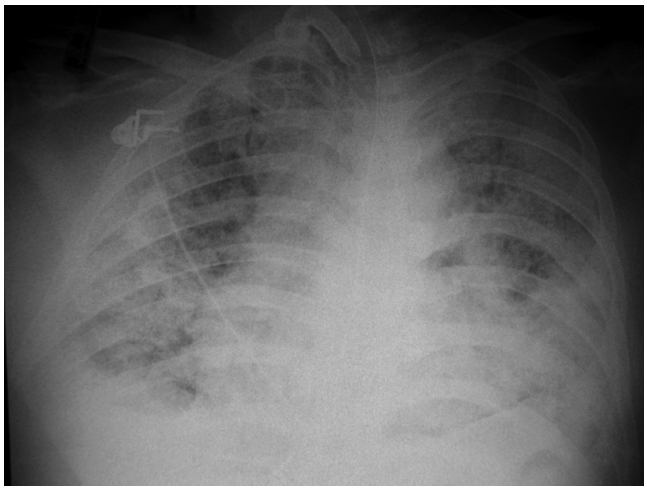


FIGURE 5.2
Plain radiography of trauma patient developing acute TRALI.

Clinically, the patient exhibits dyspnea, fever, hypotension, tachypnea, tachycardia, and a frothy endotracheal aspirate. Treatment is supportive. Prevention involves limiting the transfusion of blood products, minimizing the inappropriate use of blood products, using blood with a more recent storage date, and using washed cellular products.

5.4.4 Thoracic Compartment Syndrome

The concept of compartment syndrome is well recognized in orthopedic and trauma surgery. Initially described as occurring only in the extremity, the condition is now recognized to affect the abdomen and the thorax as well. It is a clinical syndrome diagnosed by compartment tissue pressures that exceed perfusion pressures; this pressure differential results in decreased capillary perfusion and compromised tissue viability.

Originally described by Riahi [49], thoracic compartment syndrome usually presents with increased airway pressures that occur when the chest is closed after thoracic or cardiac surgery, especially when cases are associated with coagulopathy and uncontrolled bleeding. On occasion, thoracic compartment syndrome may develop more slowly over a period of hours to days; in such cases, it causes reduced cardiac output, hypoperfusion, and worsening acidosis. The diagnosis is usually one of exclusion; hence, physicians must maintain a high index of suspicion.

Therapeutic options include leaving the chest cavity open and packed, or using skin flaps or synthetic materials to provide temporary closure of the chest cavity. Definitive closure can be attempted once the patient's hemodynamic condition stabilizes, and both the coagulopathy and the acidosis have been corrected. The average time to closure is usually 2–5 days. Diuretics may play an adjunctive role. Mediastinitis is a serious and potentially life-threatening complication.

5.4.5 Posttraumatic Retained Hemothorax and Posttraumatic Empyema

Retained blood within the chest following thoracostomy tube placement represents a significant risk for the development of posttraumatic empyema (Figure 5.3). Once thought to be rare, a recent multicenter trauma study found that among 20 busy trauma centers, the incidence of empyema was 26.8% [50]. Trauma patients who developed this complication had significantly longer hospital and intensive care unit stays. They also had longer ventilator requirements, reflective of the challenge infection within the pleural space places poses for the restoration of normal pulmonary mechanics and liberation from artificial respiration. Routine early

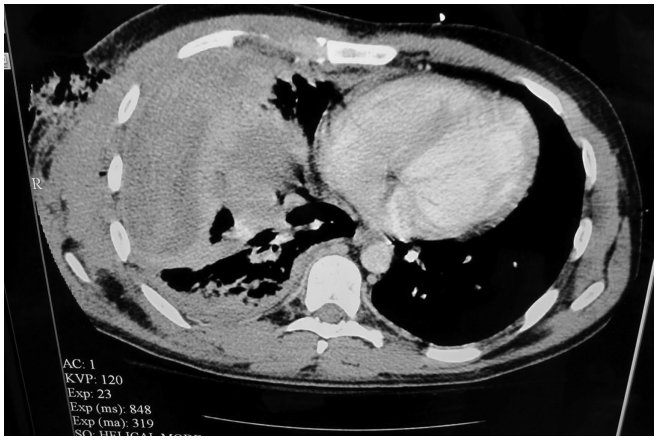


FIGURE 5.3
Chest computed tomography (CT) of delayed diagnosis of posttraumatic retained hemothorax. Operative findings and cultures confirmed the diagnosis of empyema.

removal of posttraumatic retained hemothorax, via video-assisted thoracoscopic methods, provides for the removal of potential infective culture material and mitigates the associated risk for subsequent empyema.

5.5 Conclusion

Respiratory failure is not uncommon following surgery or trauma. In this setting, it is often multifactorial due to a combination of patient- and procedure-related factors. Although preoperative risk reduction is ideal, aggressive postoperative pulmonary care may reduce the impact. In patients requiring mechanical ventilation to support lung function, the data derived from the ARDSNet trial probably represents the current standard of care. The lung protection strategies espoused there should be followed to minimize the occurrence of VALI. A multimodality approach to the most severe form of respiratory failure, ARDS, will most likely lead to a successful outcome. Other unusual causes of respiratory failure in this group of patients must be recognized.

Incidence of Pulmonary Complications Following Surgery or Trauma

Complication	Incidence
ARDS/ALI	4.1%–6.8% among trauma patients [13]
Pulmonary contusion due to trauma	17% after multisystem trauma [47]
Transfusion-related acute lung injury	1 per 5000 units blood product transfused [48]
Posttraumatic empyema (in patients with retained hemothorax)	26.8% [50]

Avoiding and Treating Complications Presented in This Chapter

ARDS/ALI
- Maintain fluid resuscitation strategies that avoid overresuscitation
- Aggressively identify and treat infections and complications
- Employ lung-protective ventilator strategies conducive with ARDSNet

Pulmonary contusion
- Avoid overresuscitation
- Supportive care

Transfusion-related acute lung injury
- Appropriate utilization of blood products in resuscitation
- Leukocyte reduction may assist
- Rapidly diagnose once occurs and provide diligent supportive care

Posttraumatic retained hemothorax/empyema
- Early identification and characterization of retained hemothorax by CT
- Aggressive evacuation of retained hemothorax volumes >300 mL on CT by early video-assisted thoracoscopy

References

1. Bernard GR, Artigas A, Brigham KL et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149(3 Pt 1): 818–824.

   All providers should be familiar with the report from the American–European Consensus Conference on ARDS. This group has provided significant contributions in the standardization of definitions, outcomes, and clinical trials of a challenging entity.
2. Pedersen T, Eliasen K, Henriksen E. A prospective study of risk factors and cardiopulmonary complications associated with anaesthesia and surgery: Risk indicators of cardiopulmonary morbidity. *Acta Anaesthesiol Scand* 1990;34:144–155.
3. Lawrence VA, Dhanda R, Hilsenbeck SG, Page CP. Risk of pulmonary complications after elective abdominal surgery. *Chest* 1996;110:744–750.
4. Behrendt CE. Acute respiratory failure in the United States: Incidence and 31-day survival. *Chest* 2000;118: 1100–1105.
5. Treggiari MM, Hudson LD, Martin DP, Weiss NS, Caldwell E, Rubenfeld G. Effect of acute lung injury and acute respiratory distress syndrome on outcome in critically ill trauma patients. *Crit Care Med* 2004;32: 327–331.
6. White TO, Jenkins PJ, Smith RD, Cartlidge CW, Robinson CM. The epidemiology of posttraumatic adult respiratory distress syndrome. *J Bone Joint Surg Am* 2004; 86-A:2366–2376.

7. Warner MA, Offord KP, Warner ME, Lennon RL, Conover MA, Jansson-Schumacher U. Role of pre-operative cessation of smoking and other factors in postoperative pulmonary complications: A blinded prospective study of coronary artery bypass patients. *Mayo Clin Proc* 1989;64:609–616.
8. Goldman L, Caldera DL, Nussbaum SR et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;297:845–850.
9. Sykes LA, Bowe EA. Cardiorespiratory effects of anesthesia. *Clin Chest Med* 1993;14:211–226.
10. Antonelli M, Conti G, Rocco M et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998;339: 429–435.
11. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112:186–192.
12. Chevron V, Menard JF, Richard JC, Girault C, Leroy J, Bonmarchand G. Unplanned extubation: Risk factors of development and predictive criteria for reintubation. *Crit Care Med* 1998;26:1049–1053.
13. Sloane PJ, Gee MH, Gottlieb JE et al. A multicenter registry of patients with acute respiratory distress syndrome. Physiology and outcome. *Am Rev Respir Dis* 1992;146:419–426.
14. Hasleton PS. Adult respiratory distress syndrome—An update. *Histopathology* 1999;34(4):285–294.
15. Amato MB, Barbas CS, Medeiros DM et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):1835–1846.
16. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? *Am J Respir Crit Care Med* 1994; 150(6 Pt 1):1722–1737.
17. Stewart TE, Meade MO, Cook DJ et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *N Engl J Med* 1998;338:355–361.
18. Brochard L, Roudot-Thoraval F, Roupie E et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume Reduction in ARDS. *Am J Respir Crit Care Med* 1998;158:1831–1838.
19. Brower RG, Shanholtz CB, Fessler HE et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999;27:1492–1498.

    This work demonstrated the value of low-tidal ventilation strategies in the management of ARDS. This trial remains a clinical standard.
20. Valente Barbas CS. Lung recruitment maneuvers in acute respiratory distress syndrome and facilitating resolution. *Crit Care Med* 2003;31(suppl 4):S265–S271.
21. Mehta S, Granton J, MacDonald RJ et al. High-frequency oscillatory ventilation in adults: The Toronto experience. *Chest* 2004;126:518–527.
22. Ferguson ND, Chiche JD, Kacmarek RM et al. Combining high-frequency oscillatory ventilation and recruitment maneuvers in adults with early acute respiratory distress syndrome: The Treatment with Oscillation and an Open Lung Strategy (TOOLS) trial pilot study. *Crit Care Med* 2005;33:479–486.
23. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399–405.
24. Michael JR, Barton RG, Saffle JR et al. Inhaled nitric oxide versus conventional therapy: Effect on oxygenation in ARDS. *Am J Respir Crit Care Med* 1998;157(5 Pt 1):1372–1380.
25. Troncy E, Collet JP, Shapiro S et al. Inhaled nitric oxide in acute respiratory distress syndrome: A pilot randomized controlled study. *Am J Respir Crit Care Med* 1998;157 (5 Pt 1):1483–1488.
26. Lundin S, Mang H, Smithies M, Stenqvist O, Frostell C. Inhalation of nitric oxide in acute lung injury: Results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. *Intensive Care Med* 1999;25:911–919.
27. Payen DM, Gatecel C, Plaisance P. Almitrine effect on nitric oxide inhalation in adult respiratory distress syndrome. *Lancet* 1993;341(8861):1664.
28. Papazian L, Bregeon F, Gaillat F et al. Does norepinephrine modify the effects of inhaled nitric oxide in septic patients with acute respiratory distress syndrome? *Anesthesiology* 1998;89:1089–1098.
29. Ziegler JW, Ivy DD, Wiggins JW, Kinsella JP, Clarke WR, Abman SH. Effects of dipyridamole and inhaled nitric oxide in pediatric patients with pulmonary hypertension. *Am J Respir Crit Care Med* 1998;158(5 Pt 1):1388–1395.
30. Vollman KM, Bander JJ. Improved oxygenation utilizing a prone positioner in patients with acute respiratory distress syndrome. *Intensive Care Med* 1996;22: 1105–1111.
31. Blanch L, Mancebo J, Perez M et al. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med* 1997;23:1033–1039.
32. Guerin C, Badet M, Rosselli S et al. Effects of prone position on alveolar recruitment and oxygenation in acute lung injury. *Intensive Care Med* 1999;25:1222–1230.
33. Johannigman JA, Davis K Jr, Miller SL et al. Prone positioning and inhaled nitric oxide: Synergistic therapies for acute respiratory distress syndrome. *J Trauma* 2001;50:589–596.
34. Weigelt JA, Norcross JF, Borman KR, Snyder WH III. Early steroid therapy for respiratory failure. *Arch Surg* 1985;120:536–540.
35. Bernard GR, Luce JM, Sprung CL et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med* 1987;317:1565–1570.
36. Hooper RG, Kearl RA. Established ARDS treated with a sustained course of adrenocortical steroids. *Chest* 1990;97:138–143.
37. Bernard GR, Wheeler AP, Russell JA et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997;336:912–918.

38. The ARDS Network. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2000;283:1995–2002.
39. Bernard GR, Wheeler AP, Arons MM et al. A trial of antioxidants N-acetylcysteine and procysteine in ARDS. The antioxidant in ARDS Study Group. *Chest* 1997;112:164–172.
40. Anderson H III, Steimle C, Shapiro M et al. Extracorporeal life support for adult cardiorespiratory failure. *Surgery* 1993;114:161–173.
41. Kolla S, Awad SS, Rich PB, Schreiner RJ, Hirschl RB, Bartlett RH. Extracorporeal life support for 100 adult patients with severe respiratory failure. *Ann Surg* 1997;226:544–566.
42. Martin GS, Mangialardi RJ, Wheeler AP, Dupont WD, Morris JA, Bernard GR. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2002;30:2175–2182.
43. Pacht ER, DeMichele SJ, Nelson JL, Hart J, Wennberg AK, Gadek JE. Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants reduces alveolar inflammatory mediators and protein influx in patients with acute respiratory distress syndrome. *Crit Care Med* 2003;31:491–500.
44. Mayberry JC, Trunkey DD. The fractured rib in chest wall trauma. *Chest Surg Clin N Am* 1997;7:239–261.
45. Luchette FA, Radafshar SM, Kaiser R, Flynn W,Hassett JM. Prospective evaluation of epidural versus intrapleural catheters for analgesia in chest wall trauma. *J Trauma* 1994;36:865–870.
46. Moon MR, Luchette FA, Gibson SW et al. Prospective, randomized comparison of epidural versus parenteral opioid analgesia in thoracic trauma. *Ann Surg* 1999;229:684–692.
47. Cohn SM, DuBose JJ. An update on recent advances in clinical management. *World J Surg* 2010;34(8):1959–1970.

    Pulmonary contusion remains a problematic component of trauma care. This update reviews this entity comprehensively.
48. Sillman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, Podloscky L, Clarke G, Ambruso DR. Transfusion-related acute lung injury: Epidemiology and prospective analysis of etiologic factors. *Blood* 2003;101:454–462.
49. Riahi M, Tomatis LA, Schlosser RJ, Bertolozzi E, Johnston DW. Cardiac compression due to closure of the median sternotomy in open heart surgery. *Chest* 1975;67:113–114.
50. DuBose J, Inaba K, Okoye O, Demetriades D, Scalea T, O'Connor J, Menaker J, Morales C, Shiflett T, Brown C, Copwood B; AAST Retained Hemothorax Study Group. Development of posttraumatic empyema in patients with retained hemothorax: Results of a prospective observational AAST Study. *J Trauma Acute Care Surg* 2012;73(3):752–757.

    This work represents the largest investigation of retained hemothorax to date. It demonstrates the independent predictors for successful utilization of VATS and thoracotomy. It also documents the high rates of empyema associated with posttraumatic retained hemothorax.

6

Complications of Acute Fluid Loss and Replacement

David R. King and John O. Hwabejire

CONTENTS

6.1 Introduction

Despite hundreds of years of science and experience,[1] complications from fluid loss and replacement continue to plague clinicians and surgeons. On any given day in the intensive care unit, one can overhear discussions concerning the fluid status of any particular patient. These discussions generally revolve around determining if a patient is "wet" or "dry" and whether the patient is better served by a fluid bolus or a loop diuretic. This schizophrenic discussion occurs daily in every hospital in the world and exemplifies our current and persisting poor understanding of fluid balance, loss, and resuscitation. Our poor understanding of fluid balance routinely contributes to complications of fluid loss and replacement. Sometimes, these complications occur as a natural progression of the disease process, and sometimes they are iatrogenic misadventures of the very best intentions.

6.2 Theoretical Basis of Fluid Distribution

6.2.1 Body Fluid Compartments

Three classically described fluid compartments exist: the plasma compartment, the interstitial compartment, and the intracellular compartment. Under normal conditions, the interstitial compartment is three times the volume of the intravascular compartment, and the intracellular compartment is three times the volume of the interstitial compartment. Consequently, the intracellular compartment is nine times the volume of the intravascular compartment. The intravascular compartment volume is preserved at the expense of the other compartments. Significant changes in the intravascular volume are poorly tolerated. A loss of 30%–40% of the intravascular volume will lead to severe hypovolemia and profound hypotension and hypoperfusion. Hypovolemic

cardiovascular collapse usually occurs after loss of 60% of the intravascular volume. In contrast, a mild 20%–30% sudden increase in intravascular volume may produce pulmonary edema.[2] The intravascular compartment is tightly regulated and is maintained at the expense of the interstitial and intracellular compartments when under duress.

6.2.2 Fluid Maintenance and Regulation in Disease States

The interstitial compartment is in dynamic equilibrium with the intravascular compartment, primarily regulated by albumin flux controlled by opening and closing of peptidoglycans within the interstitial space.[3] The obligation of albumin to the intravascular and interstitial compartments determines how water and sodium flux between the two. When the peptidoglycans have an open stoichiometry and favor interstitial albumin obligation, the interstitial compartment expands. When the stoichiometry of the peptidoglycans is closed, the albumin is released into the lymph where it is recirculated into the intravascular compartment (along with the obligated water and sodium), expanding the intravascular compartment. The opening and closing of the peptidoglycans are regulated by the patient's inflammatory state. When the inflammatory stimuli are profound, the interstitial compartment's capacitance becomes impressive, until the compartment is filled to several times its normal volume, while maintaining relatively low hydrostatic pressure.[2,4]

An understanding of the cycling of interstitial peptidoglycans, and subsequent albumin obligation, will help guide fluid therapy. The capillary endothelium also regulates albumin flux, but the degree of flux differs depending on each specific organ. For example, the capillary endothelium is much more permeable in the lung and the liver than it is in peripheral tissues such as muscle, skin, and subcutaneous fat.[5,6] For example, albumin flux within the capillaries of the lungs under normal circumstances is so high that the interstitial concentration is approximately 70%–80% of the serum concentration. Therefore, the relative albumin concentration gradient across the pulmonary capillary membrane is relatively minor. The permeability of the liver endothelium to albumin is only slightly less than that of the lung; the interstitial concentration is approximately 60% of the serum. In contrast, much less albumin fluxes through peripheral tissues, specifically muscle and fat, than through the liver or the lung; therefore, the interstitial concentration in muscle is approximately 20%–30% of the serum.

Unlike the capillary endothelium, the cell surface membrane is impermeable to proteins. The entry of proteins into cells is accomplished by active transport; therefore, oncotic pressure has a minimal effect at the cell surface membrane. The sodium pump is the active mechanism that operates at the cell surface, ejecting sodium from the cells while potassium is exchanged or diffuses passively to maintain charge equilibrium on both sides of the cell membrane. Bicarbonate molecules and chloride ions cross the cell membrane relatively easily, and because the membrane is permeable to water, this fluid crosses readily to maintain osmotic equilibrium.

There are two crucial differences between the capillary endothelium and the cell surface membrane. First, the capillary endothelium is a passive membrane that does not require energy; it functions for an extended period of time independently of an energy source, such as adenosine triphosphate (ATP). In contrast, the cell surface membrane actively requires energy. As the production of ATP is impaired during severe shock, the sodium pump begins to fail and the passive diffusion of sodium into the cells increases their osmotic pressure, and water immediately follows. This influx of water causes increased cellular edema.[6] The capillary endothelium is much more resilient to ischemic changes (such as those induced by hypovolemia) than is the cell membrane.

The second important difference between the capillary endothelium and the cell surface membrane is that large molecules dictate the oncotic pressure across the capillary endothelium, and the oncotic pressure plays little role at the cell membrane. Osmotic pressure is the gradient that causes water to move between the intracellular compartment and both the interstitial and intravascular compartments. Oncotic pressure and hydrostatic pressure across the capillary endothelium influence water movement between the intravascular and interstitial compartments. A firm understanding of these influences will guide fluid resuscitation.

6.3 Volume Expansion

6.3.1 Resuscitation with Crystalloid Solutions

Thirty minutes after a rapid 2 L bolus of lactated Ringer's infusion, this crystalloid solution has equilibrated into the intravascular and interstitial compartments. Because all components of a balanced salt solution freely cross the capillary endothelium, there is no restriction of movement between these compartments. The solution immediately crosses from one space to the other and is distributed between the two compartments in exact proportion to their starting volumes, which are primarily regulated by albumin and other large proteins. For example, if the starting volume of the

interstitial space is three times that of the intravascular volume, as is normally the case in a healthy person, then the balanced salt solution will be distributed in the same 1:3 ratio. If 2 L of solution is given, then 500 mL will remain in the intravascular compartment, and 1500 mL will move into the interstitial compartment. Because a balanced salt solution is iso-osmotic, no gradient in osmolarity is produced, and there is no net movement across the cell surface membrane, which responds only to osmotic pressures. The volume of the intracellular compartment is therefore unchanged. This effect is crucial, but it has never been adequately emphasized in the literature. This effect is also transient, however, until the renal excretion of the bolus of sodium and water occurs a short time later, restoring normovolemia.

In a condition of severe established ischemia or profound inflammatory state (not sudden, acute blood loss), the flux of albumin will change dramatically, ushered by open peptidoglycans and albumin obligation within the interstitial compartment. Under these circumstances, the ratio of an administered balanced salt solution within the intravascular and interstitial compartments will be directly proportional to the ratio of albumin within these compartments.

6.3.2 Resuscitation with Colloid Solutions

If a colloid solution such as 5% albumin is introduced into the intravascular volume during a nonischemic and noninflammatory state, the relative flux of the infused albumin solution will be proportional to the net albumin flux in the entire body, that is, approximately 25%–35% depending on the permeability. There is a reason that the net albumin leakage is much closer to the leakage of muscle, skin, and fat. The organs that are highly permeable to albumin (e.g., the liver and the lungs) make up a relatively small fraction of the body mass. The tissues that are not as permeable to albumin (e.g., muscle, skin, and fat) make up most of the body mass. As a result of this effect, an iso-oncotic solution administered into the intravascular compartment will leak in rough proportion to the total leakage of albumin in the body, that is, approximately 25%–35%. For example, if 2 L of a 5% albumin solution (colloid) is administered, the volume would be distributed as follows: 500 mL (25%) would leak into the interstitium, and 1500 mL would be retained in the intravascular volume. Because the albumin solution is iso-osmotic, there would be no net gradient into cells. Therefore, the cellular volume would not change. When the net effect of volume expansion resulting from the administration of 2 L of Ringer's lactate is compared with that resulting from the administration of 2 L of albumin, the results show that one-fourth of the balanced solution (500 mL) would remain in the vascular space and three-fourths of the colloid solution (1500 mL) would remain in the intravascular space. Therefore, the ratio of intravascular filling with a colloid solution to intravascular filling with a crystalloid solution is 3:1. Almost every study in which the effects of crystalloid and colloid solutions have been compared has found that this ratio of intravascular expansion is consistent at approximately 3:1. This ratio fits the proposed theoretical model; it is what is measured hemodynamically, and it is predictable. Unfortunately, analyzing the results of published studies is difficult because most studies of crystalloid and colloid solutions have been based on protocols that did not consider this physiologic reality. Achieving the same effect on intravascular volume expansion requires the administration of three times as much crystalloid solution as colloid solution, because only one-fourth of the balanced crystalloid solution will remain in the vascular space (the rest of the crystalloid solution will end up in the interstitial space). Administering a crystalloid solution therefore may induce significant interstitial edema.

The concept of leakage or intravascular retention of a crystalloid solution is based on studies of shock in animal models using incomplete or inadequate resuscitation. When a volume deficit is created and then replaced with inadequate volume, even though the volume is similar to what has been lost, one may conclude that fluid has leaked. In a stable replacement model that includes the theoretical considerations explained earlier, the volume of distribution will be considered. Once full equilibration has been achieved, the relative volumes of distribution should remain the same. Depending on the volume used and the deficit replaced, the effects of volume resuscitation can therefore be predicted and anticipated on the basis of these three basic axioms: (1) one-fourth of the amount of balanced salt solutions administered remains in the vascular space; (2) three-fourths of the amount of colloid solutions administered remains in the intravascular space; and (3) the ratio of intravascular filling with crystalloid solutions to that with colloid solutions is 3:1.

6.3.3 Resuscitation with Hypertonic Saline Solution

Hypertonic saline solution has been the topic of considerable discussion in recent years because of its potential for use as a prehospital fluid. When a 7.5% saline solution is administered, its hypertonic effect immediately exerts eight times the normal osmotic pressure of the body. Therefore, infusing this solution increases the osmotic pressure in the intravascular space, and this increase in pressure immediately pulls water from the intracellular space. Again because all of the ions that produce the osmotic gradient move freely across the capillary endothelium, there are no osmotic gradients across the capillary endothelium. Only the cell membrane restricts

them; therefore, the gradient is acutely generated only across the cell membrane.

The osmotic pressures created by 7.5% saline infusions can be hundreds of millimeters of mercury, even when relatively small volumes of 7.5% saline solution are infused. As a result, fluid is pulled to the intravascular space with extraordinary rapidity. Whereas colloid equilibrium typically develops within 10–30 min of infusion, development of hypertonic saline equilibrium requires <60 s. In fact, this latter type of equilibration occurs so rapidly that it cannot be measured by any available technique. The best evidence indicates that the equilibration occurs within approximately 3–5 s after administration of the solution. Therefore, when a hypertonic solution is given, the pull of fluid into the vascular space is effective instantaneously. The net effect, however, has a direct repercussion on the intravascular volume. Administering hypertonic solution forces equilibrium between the intracellular osmotic pressure and the intravascular osmotic pressure; because the saline solution is eight times more concentrated than the normal osmotic pressure, the solution pulls seven times its volume and dilutes itself by a factor of eight in the vascular space. For example, an intravenous infusion of 250 mL of a 7.5% saline solution pulls 1750 mL from the cellular space, thus resulting in an initial net increase in the intravascular volume of 2 L. Therefore, the volume of reexpansion achieved by the administration of 250 mL of 7.5% saline solution is equivalent to that achieved by the administration of 2 L of an isotonic salt solution. Once the 7.5% saline solution has forced 1750 mL of fluid into the vascular space (from the intracellular space), redistribution occurs between the intravascular space and the interstitial space. Again, the now balanced salt solution is distributed in proportion to the sizes of the spaces. Therefore, of the 2 L of fluid pulled from the cellular space, 500 mL ends up in the intravascular space and 1500 mL ends up in the interstitial space. The only difference is that the net deficit occurs at the expense of the cells; therefore, the cellular compartment now contains 1750 mL less fluid. In contrast, this compartment is unaffected by the administration of Ringer's lactate solution.

6.4 Volume Replacement after Acute Blood Loss

Over the last eight decades, there has been a significant shift in the approach to fluid resuscitation of the hemorrhaging trauma patient. Early investigators had suggested that survival was improved by infusion of large volumes of iso-osmotic crystalloids, and emphasis was placed on replenishing both the intravascular and interstitial fluid components.[7–9] However, this aggressive fluid resuscitation approach was challenged by data suggesting that patients who were treated as such did not have an improvement in outcome and were at increased risk of complications such as acute respiratory distress syndrome and abdominal compartment syndrome (ACS).[10–15] It is now known that aggressive resuscitation may potentiate organ and tissue injury resulting from the initial trauma and hemorrhage.[10] Therefore, the recommended approach to fluid replacement after acute blood loss includes early control of hemorrhage, low volume, carefully guided crystalloid resuscitation or avoidance of crystalloid whenever possible, early use of blood products to prevent coagulopathy, and hypotensive resuscitation in young patients with penetrating trauma.[10,16] This approach is referred to as "damage control" or hemostatic resuscitation.[16]

6.5 Goals of Fluid Replacement and End Points of Resuscitation

There appears to be a consensus among clinicians that heart rate, systemic arterial blood pressure, skin temperature, and urine flow (i.e., the primary end points of resuscitation used by clinicians before the era of invasive hemodynamic monitoring) provide relatively little information about the adequacy of oxygen delivery to tissues. Accordingly, reliance on these simple indices of perfusion may result in failure to recognize ongoing anaerobiosis (cryptic shock).

With the introduction of central venous and Swan–Ganz catheterization, clinicians sought to titrate resuscitation therapy to achieve "adequate" indices of ventricular preload, cardiac output, and systemic oxygen delivery. On the basis of extensive analyses of the hemodynamic profiles of survivors and nonsurvivors of critical illness, Shoemaker et al.[17] proposed that patients suffering from trauma and shock develop an oxygen "debt" and therefore require supranormal levels of oxygen delivery to reestablish homeostasis. Tuchschmidt et al.[18] later reported similar findings from a study of patients with sepsis. Subsequently, in three prospective, randomized trials,[19–21] Shoemaker and coworkers obtained evidence that survival is improved by titrating resuscitative measures to achieve the target values established in earlier observational studies (specifically, a cardiac index >4.5 L/min/m^2 of body area, a systemic oxygen delivery index >600 mL/min/m^2, and systemic oxygen consumption >170 mL/min/m^2). In another trial,[22] a significant improvement in survival rates was achieved when high-risk surgical patients were treated with dopexamine, an inotrope and vasodilator

that increases cardiac output during the perioperative period. No significant differences in systemic oxygen consumption or blood lactate concentration were found between patients who were and were not treated with dopexamine; this finding suggests that dopexamine has beneficial effects, independent of its hemodynamic actions. To complicate the picture, several subsequent clinical studies[23–26] have failed to demonstrate that survival rates improve when resuscitation therapy is titrated to achieve supranormal values for oxygen delivery or cardiac output.

Resuscitation therapy can also be adjusted to achieve certain biochemical end points, such as arterial base deficit or blood lactate concentration. These end points can be used, because tissue hypoperfusion leads to increased anaerobic metabolism. During anaerobic metabolism, large quantities of pyruvate are converted to lactate, and thus do not enter the tricarboxylic acid cycle. Meanwhile, because of the stoichiometry of substrate-level (rather than oxidative) phosphorylation of adenosine diphosphate to ATP, there is a net accumulation of protons.[27]

Accordingly, increases in arterial base deficit, blood lactate concentration, or both are evidence of an increase in the rate of anaerobic metabolism. Numerous studies[28–31] have documented that high concentrations of blood lactate portend an unfavorable outcome for patients with shock, but it has not been proven that survival is improved when therapy is titrated by using blood lactate concentration as an end point.

Base deficit is the amount of base (in millimoles) required to titrate 1 L of whole blood to a pH of 7.40 while the sample is maintained at 37°C, fully saturated with oxygen, and equilibrated with an atmosphere containing carbon dioxide at a PCO_2 of 40 mmHg. Base deficit is calculated by arterial blood gas analyzers that use a nomogram developed by Astrup et al.[32] Base deficit is more quickly and easily measured than is lactate concentration, and it has prognostic value for patients with shock.[33–36] Although titrating therapy to a base deficit end point is intuitively reasonable, whether it improves survival rates remains unproven.

Until recently, a randomized clinical trial of gastric tonometry,[37] a form of tissue capnometry, was the only source of published findings demonstrating that the use of a monitoring tool to guide resuscitation can improve the outcome of critically ill patients. However, Rivers et al.[38] published the results of a partially blinded, randomized trial of goal-directed therapy initiated in the emergency ward for patients with septic shock. An algorithm was developed to adjust central venous pressure (CVP) to 8–12 mmHg, mean arterial pressure to 65–90 mmHg, and central venous oxygen saturation to more than 70%. A central venous oximetry catheter was used to titrate resuscitative therapy in an attempt to balance systemic oxygen supply with oxygen demand. Unlike similar studies carried out in an ICU setting, this study initiated goal-directed therapy at an earlier point after injury. The findings showed that early institution of goal-directed hemodynamic support prevented cardiovascular collapse in high-risk patients, and reduced hospital mortality rates from 46.5% to 30.5% ($p = 0.009$).

Perhaps, the most rational way to titrate resuscitative therapy is to use a measure of the adequacy of regional tissue perfusion. Several highly complex approaches can achieve this goal, such as using near-infrared spectroscopy to assess the redox state of cytochrome a, a_3 (the terminal enzyme complex in the mitochondrial respiratory chain). However, tissue capnometry offers the promise of being inexpensive, reliable, and minimally invasive.

6.6 Complications of Fluid Losses in Surgical Patients

Many surgical complications are associated with fluid losses and electrolyte disturbances that result from conditions other than hemorrhage. These conditions may have a broader but less acute impact on all of the body fluid compartments, and may be associated with severe electrolyte derangements. Therefore, therapy must be directed at restoring homeostasis and minimizing iatrogenic complications.

Because sodium and water are the primary determinants of the adequacy of volume status, the surgeon must have a clear understanding of the interactions of these two important components of the internal milieu. Hyponatremia and hypernatremia are the most commonly encountered complications of fluid loss in surgical patients.

External losses or internal shifts of fluids are commonly associated with surgical patients and may initially be indicated by signs of inadequate volume and perfusion, without marked changes in plasma sodium concentrations. The most common cause of hyponatremia is inappropriate therapy, and the most common conditions associated with hypernatremia are excessive diuresis and unrecognized or miscalculated losses of free water. The plasma sodium concentration is an index of the relative proportions of sodium and water in the extracellular fluid (ECF). The constant redistribution of fluid across all body fluid compartments is ruled by the laws of tonicity. The combined depletion of sodium and water is a common occurrence among patients with volume depletion resulting from excessive fluid losses. In a similar fashion, the loss of gastrointestinal fluid, which may occur as the result of vomiting, diarrhea, fistulas, or prolonged nasogastric suction, is also typically

characterized by combined deficits of water and sodium. Third spacing or sequestration of fluid in patients with severe peritonitis, pancreatitis, or other local inflammatory conditions in the abdominal cavity is also associated with combined losses of sodium and water.

6.6.1 Hyponatremia

Hyponatremia occurs when there is an excess of total body water relative to total body sodium content. Hyponatremia may be associated with decreased, increased, or near-normal amounts of total body sodium. In general, hyponatremia occurs as a disorder of the kidneys' ability to dilute urine. The approach to therapy for the hyponatremic patient can be simplified by establishing first whether the patient's ECF is reduced (depletion) or increased (edema). Renal losses, which include diuretic excess, mineralocorticoid deficiency, salt-losing nephritis, renal tubular acidosis, and osmotic diuresis, are characterized by volume depletion and a urinary sodium concentration >20 mmol/L. When the urinary sodium concentration is <10 mmol/L, the hyponatremic state is usually the result of extrarenal losses, a common condition among surgical patients. Those with extrarenal losses usually have a history of vomiting or nasogastric suction, third spacing of fluid, pancreatitis, burns, or soft-tissue trauma. Both types of hyponatremic conditions (renal and extrarenal losses) respond to fluid replacement with isotonic solution.[39] Patients with normal or mildly diminished ECF, abnormally low sodium concentration, and no edema are not commonly seen by surgery services. Such patients often have a glucocorticoid deficiency or inappropriate antidiuretic hormone secretion. These conditions usually respond to water restriction. Finally, hyponatremia can occur in patients with edema and enhanced ECF; these patients typically have conditions associated with impaired renal perfusion, such as congestive heart failure, cirrhosis, or nephrotic syndrome. In these patients, a urinary sodium concentration of <10 mmol/L is common. If the urinary sodium concentration is >20 mmol/L in patients with edema, then a component of acute or chronic renal failure is also present.

6.6.2 Hypernatremia

The renal concentrating mechanism is the first defense against water depletion and hyperosmolality. When this mechanism is impaired, thirst becomes a very effective mechanism for preventing further increases in serum sodium concentration. Unfortunately, most clinical conditions experienced by surgical patients are also associated with an impairment in water intake. The most practical approach to treating the patient with an elevated serum sodium concentration relies on a basic assessment to determine whether the patient is experiencing hypernatremia with sodium and water losses, hypernatremia with mostly water losses, or hypernatremia with mostly increased sodium intake.

Again, identifying the site of sodium or water losses is crucial; for example, patients receiving diuretic therapy (osmotic or loop diuretics) or having postobstruction or intrinsic renal disease will produce isotonic or hypotonic urine; their urinary sodium concentration will be >20 mEq/L, and their total body sodium concentration will be low.[40] If the urinary sodium concentration is <10 mEq/L, the most likely cause of hypernatremia will be extrarenal losses (sweating, heat exposure, burns, diarrhea, or fistula). If most of the losses are free water, then the total body sodium concentration must be close to normal values. These patients' urinary sodium concentration will vary, and their clinical symptoms will resemble those of patients with diabetes insipidus syndromes, or those with insensible water losses that are purely respiratory and dermal. If hypernatremia is present and an increase in total body sodium concentration is suspected, the patient usually has primary hyperaldosteronism, Cushing's syndrome, or hypertonic dialysis; alternatively, the patient may chronically ingest large amounts of sodium bicarbonate or sodium chloride tablets. The urinary sodium concentration usually exceeds 20 mEq/L. Management consists of the replacement of free water and the initiation of diuretic therapy.

6.7 Complications of Fluid Replacement

Fluid replacement, especially when not judiciously used, has some potentially deleterious complications. There are risk factors that predispose patients to specific complications, but the most common etiology is aggressive fluid resuscitation. Some of these complications are more general and may occur with any type of fluid, whereas others tend to occur with specific fluids.

6.7.1 General Complications Associated with Fluid Resuscitation

ACS, defined as intra-abdominal pressure >20 mmHg with evidence of organ dysfunction or failure,[41] is one of the most feared complications of fluid replacement. It can occur following massive resuscitation with colloids, crystalloids, blood, and blood products, although it is most common with excessive crystalloid use. ACS is associated with increased morbidity and mortality,[42] as sustained elevation of intra-abdominal pressure can have negative physiologic effects on the functions of the cardiovascular, pulmonary, renal, hepatic, gastrointestinal, and central nervous systems.[41] Clinical conditions

that place patients at risk include trauma, burns, sepsis, damage control laparotomy, coagulopathy, massive transfusion, peritonitis, and abdominal surgery with tight fascial closures.[41] If conservative measures fail to reverse the rise in intra-abdominal pressure, then decompressive laparotomy is required. However, laparotomy has its inherent risks. Therefore, prevention by early identification of risk factors and judicious fluid replacement is a key component of management of ACS.

Similar to ACS, extremity compartment syndrome can also complicate overhydration, particularly in injured extremities.[43] Tissue perfusion is reduced, resulting in increased risk of nerve and muscle necrosis, rhabdomyolysis with possible renal failure, and Volkmann's ischemic contracture. While immediate fasciotomy can save the limb and prevent the subsequent complications, avoidance of excessive fluid resuscitation is the more important preventive strategy.

Acute pulmonary edema is another potential complication of fluid replacement. Patients with major trauma, burns, or sepsis who may already have some form of pulmonary vascular injury and increased lung permeability are more prone to developing postresuscitation pulmonary edema.[44] Bedside transpulmonary dilution-derived extravascular lung water measurement may serve as a guide to treatment.[45] However, adequate monitoring during fluid can prevent many of these cases.

6.7.2 Complications Associated with the Use of Albumin Solutions

A 2004 Cochrane report examined the use of albumin for treatment of critically ill patients.[46] The authors carried out a systematic review of 30 randomized controlled trials comparing the effects of administering albumin or plasma protein fraction with the effects of not administering this protein fraction or administering crystalloid solution to 1419 critically ill patients with hypovolemia, burns, or hypoalbuminemia. For each patient category, the risk of death in the albumin-treated group was higher than that in the comparison group. The relative risk of death after albumin administration was 1.46 (95% confidence interval, 0.97–2.22) for hypovolemic patients, 2.40 (1.11–5.19) for patients with burns, and 1.69 (1.07–2.67) for patients with hypoalbuminemia. More recently, a posthoc analysis of the saline versus albumin fluid evaluation (SAFE) study in patients with traumatic brain injury (TBI) concluded that patients with severe TBI who received albumin had a significantly higher mortality compared with those who received saline (41.8% vs. 22.2%; $p < 0.001$).[47] The Cochrane group concluded that in patients with trauma, burns, or following surgery, there is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of mortality compared to resuscitation with crystalloids.[48] Therefore, albumin has no role in the management of critically ill patients.

6.7.3 Complications Associated with the Use of Ringer's Lactate Solution

Ringer's lactate solution, widely used as a volume expander and resuscitation fluid, has been shown to have multiple immunologic and proinflammatory effects on neutrophils and other cells involved in host defense mechanisms. These effects are more pronounced when the racemic lactated Ringer solution is used.[10] Rhee et al. showed that, compared to blood or 7.5% hypertonic saline, Ringer's lactate caused the greatest increase in neutrophil activation in a swine model of hemorrhagic shock.[49] Neutrophil activation returned to baseline in the other two groups after resuscitation in the animals that received shed blood or 7.5% hypertonic saline solution. In another study by the same research group, they showed that fluid resuscitation with Ringer's lactate solution significantly increased apoptosis of cells in the small intestine and liver in a rat model of hemorrhagic shock.[50] In the clinical setting, patients who develop complications related to increased inflammatory response are those who have been massively resuscitated with Ringer's lactate after severe hemorrhagic shock.[10] Administration of small amounts of the racemic isoform, lactated Ringer solution in which D-lactate has been eliminated, or one in which lactate has been replaced with monocarboxylates like ketone bodies or pyruvate may reduce these complications.[10]

6.8 Conclusions

The use of intravenous fluids is one of the main pillars of resuscitative therapy for surgical patients. Many conditions, such as acute hemorrhage, burn injuries, and intra-abdominal inflammatory catastrophes, require appropriate fluid resuscitation. The clinician must be very familiar with the type and proper dosage of the many available solutions. Clear objectives and end points of resuscitation strategies must be determined in advance, and the possible side effects and complications need to be predicted and identified early in the course of treatment if the best possible outcome is to be achieved. Unfortunately, fluid therapy is not always seen as a pharmacologic intervention, but we must realize that fluids, like any other drug, may be indicated or contraindicated in specific situations.

Current trends in fluid resuscitation indicate a shift toward minimal use of large-volume crystalloids, limitation or avoidance of albumin in critically ill patients, early use of blood products in trauma patients to prevent

trauma-induced coagulopathy, use of vasopressors, early control of hemorrhage, and goal-directed fluid therapy. There is rarely a need for aggressive resuscitation. These are based on findings from recent studies that fluid resuscitation can induce new tissue injury or worsen existing injuries and should be used only when indicated.[55] In addition, careful monitoring during fluid therapy is required to prevent many of the associated complications.

Complications of Fluid Loss and Resuscitation

	Incidence
Complications of fluid loss	
Hyponatremia	11%[51] (in ICU patients)
Hypernatremia	26%[51] (in ICU patients)
Complications of fluid replacement	
ACS	4.2%[52] (mixed ICU patients)
Extremity compartment syndrome	1.2%–6%[53]
Acute pulmonary edema	1%–8%[54]
Increased mortality (albumin)	41.8%[47] (in TBI patients)
Cytotoxicity (Ringer's lactate)	?

Prevention of Complications Associated with Fluid Loss and Replacement

Hyponatremia
Avoid excessive administration of hypotonic fluids
Avoid excessive diuresis
Early identification and treatment of risk factors (e.g., third spacing of fluid, pancreatitis, burns, or soft-tissue trauma)
Hypernatremia
Avoid excessive diuresis (osmotic or loop diuretics)
Accurate estimation and replacement of free water loss
ACS
Early identification and treatment of risk factors (e.g., peritonitis, trauma, burns, sepsis)
Minimal use of crystalloids
Adequate monitoring during fluid resuscitation
Extremity compartment syndrome
Early identification of risk factors (injured extremities)
High index of suspicion
Judicious use of fluids
Adequate monitoring during fluid resuscitation
Acute pulmonary edema
Early identification and treatment of risk factors (e.g., major burns, trauma, sepsis)
Minimal use of crystalloids
Bedside monitoring using transpulmonary dilution-derived extravascular lung water measurement
Increased mortality from albumin use
Avoid using albumin in critically ill patients
Cytotoxicity from use of Ringer's lactate
Use only small volumes
Use isoforms without D-lactate
Use formulations in which lactate is replaced with monocarboxylates

References

1. Cosnett JE. The origins of intravenous fluid therapy. *Lancet* 1989; 333:768–771.
2. Tranbaugh RF, Lewis FR. Mechanisms and etiologic factors of pulmonary edema. *Surg Gynecol Obstet* 1984; 158:193–206.
3. Lucas, CE. The water of life: A century of confusion. *J Am Coll Surg* 2001; 192(1):86–93.
4. Manning RD Jr., Guyton AC. Dynamics of fluid distribution between the blood and interstitium during overhydration. *Am J Physiol* 1980; 238:H645–H651.
5. Baldwin AL, Thurston G. Mechanics of endothelial cell architecture and vascular permeability. *Crit Rev Biomed Eng* 2001; 29:247–278.
6. Tranbaugh RF, Elings VB, Christensen J, Lewis FR. Determinants of pulmonary interstitial fluid accumulation after trauma. *J Trauma* 1982; 22:820–826.
7. Shires GT, Carrico CJ, Baxter CR et al. Principles in treatment of severely injured patients. *Adv Surg* 1970; 4:255–324.
8. Shires GT, Coln D, Carrico J et al. Fluid therapy in hemorrhagic shock. *Arch Surg* 1964; 88:688–93.
9. Dillon J, Lunch LJ, Myers R et al. A bioassay of treatment of hemorrhagic shock. *Arch Surg* 1966; 93:537–55.
10. Alam HB, Rhee P. New developments in fluid resuscitation. *Surg Clin N Am* 2007; 87 (1):55–72.

    The authors, both trauma surgeons who have done extensive basic science research on resuscitation in large animal models of trauma and hemorrhagic shock, reviewed the evolution of fluid resuscitation in trauma patients, beginning from the Vietnam War till date. Their review indicated that resuscitation of the trauma patient has shifted from an aggressive approach, which has been shown to confer no survival benefit and may actually worsen outcome, to a more proactive, but low-volume approach consisting of early control of hemorrhage, early use of blood and blood products, limited use of crystalloids, and hypotensive resuscitation in select patients. This approach, referred to as "damage control resuscitation," is gaining wide acceptance as a result of clinical and laboratory evidence indicating improved outcome with its use.
11. Lobo SM, Lobo FR, Polachini CA et al. Prospective, randomized trial comparing fluids and dobutamine optimization of oxygen delivery in high-risk surgical patients. *Crit Care* 2006; 10:R72.
12. McKinley BA, Kozar RA, Cocanour CS et al. Normal versus supranormal oxygen delivery goals in shock resuscitation: The response is the same. *J Trauma* 2002;53:825–832.
13. Velmahos GC, Demetriades D, Shoemaker WC et al. Endpoints of resuscitation of critically injured patients: Normal or supranormal? A prospective randomized trial. *Ann Surg* 2000; 232:409–418.
14. Marr AB, Moore FA, Sailors RM et al. Preload optimization using "starling curve" generation during shock resuscitation: Can it be done? *Shock* 2004; 21:300–305.

15. Yu M, Levy MM, Smith P et al. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: A prospective, randomized, controlled study. *Crit Care Med* 1993; 21:830–838.
16. Alam HB, Velmahos GC. New trends in resuscitation. *Curr Probl Surg* 2011;48(8):531–564.

    Alam and Velmahos reviewed the current and future trends in resuscitation, as the search for the ideal resuscitative strategy continues. They explored the roles that crystalloids, colloids, and blood products have in current clinical practice in view of the available evidence and the gradual use of nonfluid resuscitation strategies such as inotropes and vasopressors. According to the authors, inotropes and vasopressors have a sound physiological basis for use in survivors of acute blood loss who develop the systemic inflammatory response syndrome. The rationale for future resuscitation strategies such as "fluidless, pharmacologic resuscitation," and use of preserved blood products were also discussed. The latter may find increased use in austere environments.
17. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Arch Surg* 1973; 106:630–636.
18. Tuchschmidt J, Fried J, Swinney R, Sharma OP. Early hemodynamic correlates of survival in patients with septic shock. *Crit Care Med* 1989; 17:719–723.
19. Fleming A, Bishop M, Shoemaker W et al. Prospective trial of supranormal values as goals of resuscitation in severe trauma. *Arch Surg* 1992; 127:1175–1179; discussion 1179–1181.
20. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; 94:1176–1186.
21. Bishop MH, Shoemaker WC, Appel PL et al. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation end points in severe trauma. *J Trauma* 1995; 38:780–787.
22. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993; 270:2699–2707.
23. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722.
24. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest* 1992; 102:216–220.
25. Yu M, Levy MM, Smith P, Takiguchi SA, Miyasaki A, Myers SA. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: A prospective, randomized, controlled study. *Crit Care Med* 1993; 21:830–838.
26. Gattinoni L, Brazzi L, Pelosi P et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med* 1995; 333:1025–1032.
27. Hochachka PW, Mommsen TP. Protons and anaerobiosis. *Science* 1983; 219:1391–1397.
28. Marecaux G, Pinsky MR, Dupont E et al. Blood lactate levels are better prognostic indicators than TNF and IL-6 levels in patients with septic shock. *Intensive Care Med* 1996; 22:404–408.
29. Bernardin G, Pradier C, Tiger F et al. Blood pressure and arterial lactate level are early indicators of short-term survival in human septic shock. *Intensive Care Med* 1996; 22:17–25.
30. Broder G, Weil MH. Excess lactate: An index of reversibility of shock in human patients. *Science* 1964; 143: 1457–1459.
31. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996; 171:221–226.
32. Astrup P, Engel K, Jorgensen K, Siggaard-Andersen O. Definitions and terminology in blood acid-base chemistry. *Ann N Y Acad Sci* 1966; 133:59–65.
33. Siegel JH, Rivkind AI, Dalal S et al. Early physiologic predictors of injury severity and death in blunt multiple trauma. *Arch Surg* 1990; 125:498–508.
34. Davis JW, Parks SN, Kaups KL et al. Admission base deficit predicts transfusion requirements and risk of complications. *J Trauma* 1996; 41:769–774.
35. Davis JW, Kaups KL, Parks SN. Base deficit is superior to pH in evaluating clearance of acidosis after traumatic shock. *J Trauma* 1998; 44:114–118.
36. Rutherford EJ, Morris JA Jr, Reed GW et al. Base deficit stratifies mortality and determines therapy. *J Trauma* 1992; 33:417–423.
37. Gutierrez G, Palizas F, Doglio G et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; 339:195–199.
38. Rivers E, Nguyen B, Havstad S et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377.
39. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the critically ill patient. *Curr Opin Crit Care* 2001; 7:204–211.
40. ChubbSA. Hyponatremia treatment guidelines 2007: Expert panel recommendations. *Clin Biochem Rev* 2009; 30(1):35–38.
41. Malbrain ML, Cheatham ML, Kirkpatrick A et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome, I: Definitions. *Intensive Care Med* 2006; 32(11):1722–1732.
42. Malbrain ML, Chiumello D, Pelosi P et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: A multiple-center epidemiologic study. *Crit Care Med* 2005; 33(2): 315–322.
43. Gestring M. Abdominal Compartment Syndrome, in *UpToDate* http://www.uptodate.com/contents/abdominal-compartment-syndrome. Accessed on February 13, 2013

44. Groeneveld ABJ, Polderman KH. Fluid resuscitation: The good, the bad and the ugly. *Crit Care Shock* 2005; 8:52–54.

Groeneveld and Polderman discussed the advantages of fluid resuscitation when appropriately used and the complications that can occur with aggressive resuscitation. The concept of goal-directed therapy, where fluid administration is tailored to specific hemodynamic and tissue perfusion end points, is believed by some authorities to be advantageous in patients who are hemodynamically unstable, trauma patients, and those who are critically ill. However, controversies still exist regarding whether goal-directed fluid resuscitation carries any benefits. Complications that can occur following aggressive fluid resuscitation include pulmonary edema, systemic edema, ACS, and extremity compartment syndrome. Fluid overload can also delay wound healing in the surgical patient and impair tolerance to enteric feeds.

45. Khan S, Trof RJ, Groeneveld ABJ. Transpulmonary dilution-derived extravascular lung water as a measure of lung edema. *Curr Opin Crit Care* 2007; 13:303–307.
46. Alderson P, Bunn F, Lefebvre C et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev* 2004; (4):CD001208.
47. Myburgh J, Cooper DJ, Finfer S et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007, 357:874–884.

This is posthoc analysis of the SAFE trial. In this study, patients with TBI who were resuscitated with albumin (n = 231) were compared with similar TBI patients treated with normal saline (n = 229). Outcome measures include mortality and functional neurological outcome. The analysis showed that those who got albumin had a significantly higher mortality (41.8%) when compared to those who had normal saline (22.2%). The results suggest that albumin should not be used in this group of critically ill patients, a point that has been supported by other studies.

48. Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2007; 13(6):CD000567.
49. Rhee P, Burris D, Kaufmann C et al. Lactated Ringer's solution resuscitation causes neutrophil activation after hemorrhagic shock. *J Trauma* 1998; 44:313–319.
50. Deb S, Martin B, Sun L et al. Resuscitation with lactated Ringer's solution in rats with hemorrhagic shock induces immediate apoptosis. *J Trauma* 1999; 46:582–588; discussion 588–589.
51. Stelfox, H.T., Ahmed SB, Khandwala F et al. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. *Crit Care* 2008; 12(6):R162.
52. Ball CG, Kirkpatrick AW, Mc Beth P. The secondary abdominal compartment syndrome: Not just another post-traumatic complication. *Can J Surg* 2008; 51(5):399–405.
53. Frink M, Hildebrand F, Krettek C et al. Compartment syndrome of the lower leg and foot. *Clin Orthop Relat Res* 2010; 468(4):940–950.
54. Gajic O, Gropper MA, Hubmayr RD. Pulmonary edema after transfusion: How to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. *Crit Care Med* 2006; 34 (5 Suppl): S109–S113.
55. Dulhunty JM, Boots RJ, Rudd MJ et al. Increased fluid resuscitation can lead to adverse outcomes in major-burn injured patients, but low mortality is achievable. *Burns* 2008; 34(8):1090–1097.

The authors examined 80 patients with major burns who were admitted to the intensive care unit within 48 h of injury. They showed that although early use of colloids (within the first 24 h) reduced the risk of renal failure and extremity compartment syndrome, fluid resuscitation that exceeded the standard Parkland formula was associated with adverse events. This study underscores the need for judicious use of fluids in critically ill surgical patients, most of whom are already susceptible to tissue injury from the primary illness.

7

Acute Renal Dysfunction

Meghan E. Sise, Matthew O'Rourke, and Jonathan Barasch

CONTENTS

Acute renal dysfunction is a common complication in hospitalized patients that is associated with significant morbidity and mortality. The Risk, Injury, Failure, Loss, End-Stage (RIFLE) renal disease classification system that is based on changes in the level of serum creatinine and urine output defines acute kidney injury (AKI) and allows severity grading, each level predicting increasing degrees of in-hospital mortality. However, there are significant limitations to the use of serum creatinine, and ongoing research has highlighted serum and urinary biomarkers that are expressed soon after kidney injury. There are multiple forms of AKI in hospitalized patients including prerenal, intrinsic renal, and postrenal causes of renal failure, and multiple conditions, including sepsis, hypovolemia, chronic kidney disease, and major trauma or surgery that confer significantly increased risk of the intrinsic form of AKI. Unfortunately, medical therapies to limit or reverse the intrinsic forms of AKI have thus far eluded researchers, and while the judicious use of fluids is appropriate in volume-depleted patients with renal failure, they may be dangerous in patients with renal failure who are volume overloaded or have pulmonary edema. Neither time of renal replacement therapy (RRT) initiation, nor modality, nor intensity seem to impact mortality or renal recovery. Intermittent hemodialysis is used for hemodynamically stable patients, whereas continuous RRT is typically used for patients who are unstable or in shock.

7.1 Introduction

Acute renal dysfunction is a commonly encountered clinical entity with profound implications. In the United States, one million patients each year are diagnosed with acute renal dysfunction, and the incidence is rising.[1,2] It is a rapidly progressive disease that predicts morbidity and mortality. Patients with acute renal dysfunction often require admission to the intensive care unit, dialysis initiation, and prolonged hospitalization. They encounter significant risk of in-hospital death and long-term development of chronic kidney disease (CKD).[3] Recent discoveries have shown that even small changes in kidney function are associated with significant morbidity and mortality, underscoring the significance of this condition.[4]

In 2004, the Acute Dialysis Quality Initiative Group published a consensus definition known as the RIFLE renal disease classification system of AKI. This scheme identified three grades of AKI severity (risk, injury, and failure) based on relative changes in serum creatinine (sCr) and absolute changes in urine output, and two AKI outcome classes (loss and end-stage) determined by the duration of RRT.[5] From this description, it is clear that the term "AKI" can encompass a spectrum of renal dysfunction: AKI is neither acute tubular necrosis (ATN) nor renal failure, but the term also includes less severe alterations in kidney function, including the rapidly reversible physiologic changes typical of prerenal azotemia. Despite their imprecision, RIFLE criteria have been validated as independent predictors of in-hospital mortality, with elevated risk of death found in all RIFLE grades, with risk increasing across grades.[6] These criteria have established a degree of uniformity required for research on the numerous unknowns that hinder the prevention and treatment of AKI.

7.2 Risk Factors

Question 1: Who is at risk for AKI?

While a combination of vascular, tubular, and inflammatory factors has been known to underlie most cases of AKI, several cohort studies have attempted to define risk factors for the development of AKI and to place cellular factors in the context of clinical presentations. Among critically ill patients, sepsis is the most common condition associated with AKI. Bagshaw et al. found that AKI occurred in 42% of septic patients admitted to intensive care units.[7] In a prospective cohort study, Uchino et al. studied 30,000 patients admitted to 54 intensive care units and found sepsis contributed to 47% of cases of AKI.[8] This study also highlighted another group at particular risk for AKI as 30% of critically ill patients who progressed to AKI had some degree of baseline CKD. This finding is supported by data from Hsu et al. who reported that CKD is a risk factor for AKI that is severe enough to require RRT during hospitalization.[9] CKD limits the kidney's capacity for intrinsic repair, and this may contribute to elevated rates of AKI demonstrated in patients with baseline renal dysfunction. Diminished capacity for renal repair appears to place older patients at risk for unresolving AKI as well.[10] Retrospective reviews of public and private health delivery systems data in the United States reveal consistently elevated rates of AKI in older patients.[2] Hypovolemia is also a risk factor for renal ischemia and thus AKI. Reduced effective intravascular volume (i.e., from cirrhosis or congestive heart failure), which causes renal vasoconstriction and ischemia, also predisposes to AKI from contrast or nephrotoxins.

Both patient and surgical characteristics can herald perioperative AKI. Preexisting conditions such as diabetes, CKD, cardiac disease, and advanced age can affect rates of perioperative AKI.[11] Surgical procedures that produce higher rates of AKI include cardiac surgery requiring cardiopulmonary bypass, major intraabdominal surgery, vascular surgery requiring aortic manipulation and/or cross clamping, and organ transplantation. Trauma patients are at risk for AKI, particularly those with rhabdomyolysis. In a review of 436 consecutive admissions to a level 1 trauma center, Gomes et al. found that 50% satisfied RIFLE criteria, with higher severity of trauma score more likely to result in AKI.[12]

Answer: AKI occurs in numerous clinical settings and therefore has a variety of risk factors. Conditions which confer significant risk of AKI include sepsis, baseline CKD, advanced age, hypovolemia, major surgery, and trauma.

7.3 Diagnosis

Question 2: What is the optimal diagnostic test to establish AKI?

Despite its prevalence, the timely and early recognition of AKI remains difficult due to the inadequacies of sCr, the current diagnostic standard, to definitively highlight AKI. RIFLE criteria require the identification of a change in sCr from baseline. This creates several problems: (1) baseline sCr may be unknown; (2) significant time may elapse after an injury until sCr reaches a diagnostic threshold; (3) the level of sCr may not accurately reflect the degree of renal injury, since the kinetics of sCr are influenced by age, gender, muscle mass, nutritional status, hemodynamics, fluid status, and medications.[13] These limitations have generated intense interest in the identification of biomarkers that allow for the early diagnosis of AKI and the differentiation of AKI from other processes that also elevate sCr. A variety of renal insults have been found to elevate several proteins found in urine and in serum including the urinary biomarkers neutrophil gelatinase–associated lipocalin, kidney injury molecule 1, interleukin 18, liver fatty acid binding protein, cystatinC, and the fractional excretion of sodium (FENa).[14] Studies have shown promise in predicting postoperative AKI[15,16]; however, larger studies in heterogeneous populations are needed to determine which urinary biomarker performs best in prospectively diagnosing AKI at patient presentation and in the early postoperative period. The largest studies to date have recruited patients undergoing triage and admission to the hospital from emergency departments and demonstrated a valuable role for neutrophil gelatinase–associated lipocalin in the diagnosis of the initiation of AKI, and neutrophil gelatinase–associated lipocalin and kidney injury molecule 1 in predicting morbidity and mortality during hospitalization.[17]

Answer: While standardized creatinine-based definitions of AKI now exist, novel biomarkers hold promise for expedient and accurate diagnosis.

Question 3: What is the best approach to differential diagnos of AKI?

AKI can be divided into prerenal, intrinsic renal, and postrenal causes (Figure 7.1).

Postrenal causes refer to obstruction of urinary flow, which may be partial or complete, unilateral or bilateral, and may occur at any location in the urinary tract, from the renal pelvis to the urethra. Common causes of urinary obstruction include preexisting bladder outlet obstruction from benign prostatic hypertrophy, which may be exacerbated by the use of narcotic analgesics or anticholinergic medications in the hospital; a high index of suspicion for obstruction is necessary in older men

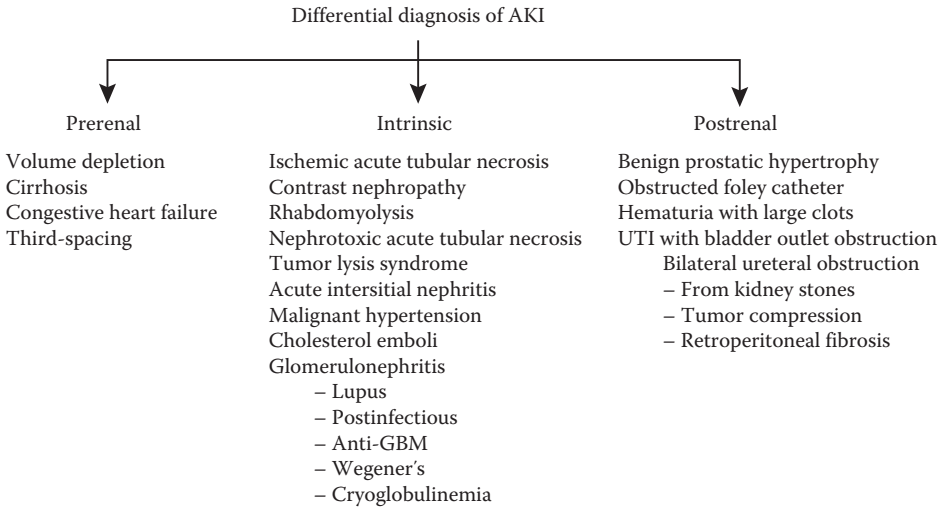


FIGURE 7.1
Categorization of acute kidney injury (AKI) according to the inciting stimulus. The *prerenal* form of AKI is characterized by a reduction in glomerular filtration as a result of liver or heart failure, or as a result of central hypotension due to volume depletion or third spacing. Hormonal dysregulation of the Na and water balance is a prominent feature of prerenal AKI. The *intrinsic* form of AKI is characterized by a reduction of glomerular filtration due to an injury to glomerular cells (glomerulonephritis), tubular cells (toxic, ischemic or sepsis related), or interstitial cells (allergic reactions). Prolonged kidney dysfunction is a prominent feature of Intrinsic AKI. The *postrenal* form of AKI is characterized by a reduction of glomerular filtration due to a mechanical or functional blockade of the urinary pathway. Surgical correction can ameliorate acute episodes of postrenal AKI. It is evident from this list that unrelated injuries reduce the glomerular filtration, emphasizing the lack of specificity in measurements of the serum creatinine. Nonetheless, characterization of AKI subtypes has both prognostic and therapeutic validity.

with unexplained AKI. Severe cystitis or obstruction of a urinary catheter may cause bladder outlet obstruction. An obstructing kidney stone may cause AKI in patients with single-functioning kidney or baseline CKD. Obstruction can be evaluated by renal ultrasonography demonstrating hydroureter or hydronephrosis; however, it should be noted that patients with early obstruction, significant volume depletion, or retroperitoneal fibrosis may have normal ultrasound findings despite urinary tract obstruction.[18] Normal urine output does not exclude partial urinary tract obstruction. Normal creatinine values do not exclude the diagnosis of unilateral kidney obstruction,[19] and in fact are likely to delay its diagnosis.

Distinguishing prerenal AKI from intrinsic AKI is more difficult; however, it is important given the significant increase in morbidity and mortality in the latter. Prerenal causes of AKI include volume depletion from dehydration, blood loss, and diuretics. Prerenal AKI can also result in volume overloaded or edematous states including congestive heart failure or cirrhosis, which are also associated with decreased renal blood flow. Urinary studies are helpful to distinguish prerenal causes from intrinsic renal causes. Prerenal causes are associated with low urine sodium (i.e., <20 mEq/L) and low FENa (<1%); these measures indicate intact sodium retention.[20] However, recently administered diuretics or CKD might elevate the urine sodium even in the setting of prerenal azotemia. Blood urea nitrogen (BUN) to creatinine ratio of >20:1 also suggests prerenal azotemia; however, this is neither sensitive nor specific. Sepsis, high-protein enteral feeding, corticosteroid use, and upper gastrointestinal bleeding can all elevate BUN out of proportion to the creatinine, and conversely, liver disease and poor nutritional status will depress the BUN, meaning that prerenal disease cannot be excluded by a normal BUN/creatinine ratio. It is important to note that fluid management cannot be determined based on serum or urinary findings alone, but must incorporate history and physical exam findings, since both volume depletion and congestive heart failure are "prerenal" causes of AKI, yet are managed very differently: intravenous fluids in the former group, and diuresis and possible inotropic support in the latter group.

Urinary biomarkers currently under investigation may be able to distinguish intrinsic renal failure from prerenal causes; because certain biomarkers are upregulated in response to tubular damage rather than quickly reversible prerenal azotemia; high urinary levels are expected in intrinsic renal failure but not prerenal azotemia.[21,22]

Answer: When evaluating AKI, a systematic approach which reviews prerenal, intrinsic renal, and postrenal causes must be considered. Urinary studies can help distinguish prerenal AKI from intrinsic AKI.

Question 4: What are common causes of intrinsic AKI seen on surgical services?

Causes of intrinsic renal failure commonly encountered on surgical service include ischemic and nephrotoxic ATN, contrast-induced nephropathy (CIN), and allergic interstitial nephritis. Postoperative AKI may occur in up to 25% of patients undergoing coronary artery bypass grafting.[23] Medications including vancomycin and aminoglycosides are important causes of nephrotoxic ATN.[24] Beta-lactam and sulfonamide antibiotics, fluoroquinolones, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with acute interstitial nephritis; in these cases of AKI, patients may also have other allergic symptoms, including rash, fever, and peripheral eosinophila.[25] NSAIDs such as ketorolac and ibuprofen can also cause ischemic ATN or renal cortical necrosis, and should be used with caution in elderly patients and avoided entirely in patients with CKD or cardiac disease.[26] CIN typically occurs in patients with other underlying risk factors including CKD, congestive heart failure, diabetes, and volume depletion, and is also related to the amount and type of contrast agent administered. Patients with normal renal function have negligible risk, and patients with moderate CKD have 9%–38% risk compared to a risk of 50% if baseline creatinine is >4–5.[27,28] Strategies for prophylaxis include discontinuing furosemide and angiotensin-converting enzyme inhibitors or angiotensin receptor blocking medications prior to contrast exposure. Patients should be hydrated with either normal saline or sodium bicarbonate at a rate of 1 mL/kg/h for 12 h prior to contrast and 12 h after contrast exposure. If a patient is known to have congestive heart failure, then the rate of IV fluid administration should be decreased to 0.5 mL/kg/h.[29] Once CIN is established, and urine output has decreased, it is wise to stop standing IV fluids to prevent worsening volume overload. Pigment-induced nephropathy, due to either rhabdomyolysis (myoglobin pigment) or massive hemolysis (hemoglobin pigment), results from direct tubular damage of pigments. Prophylaxis with judicious IV fluids are recommended to prevent AKI in patients with rhabdomyolysis or hemolysis.[30]

7.4 Management

Question 5: Does time of RRT initiation, modality, or intensity impact mortality?

RRT is the definitive treatment for complications of AKI (extracellular fluid volume overload, solute imbalance, and uremia) that are intractable to medical management. Nevertheless, the current literature offers incomplete guidance as to the optimal timing, method, and intensity of such therapy. While case–control and retrospective studies suggested "early" dialysis reduces mortality, two randomized clinical trials produced conflicting results. In 2002, a trial of 106 patients initiated "early" dialysis if urine output was <30 mL/h after 6 h but did not find a difference with regard to mortality or recovery of renal function in survivors.[31] A 2004 trial found a large reduction in mortality with early dialysis, defined by postoperative urine output (RR, 0.17; 95% CI, 0.05–0.61), but weak methods and a small sample size (N = 28) temper this conclusion.[32] The lone observational study in this area found that the risk of death in critically ill AKI patients decreased significantly by initiating RRT before levels of BUN were >76 mg/dL (adjusted hazard ratio, 0.54; CI, 0.34–0.86).[33] Based on this evidence, a 2008 systematic review concluded that the available literature does not permit a definitive statement as to the optimal timing of acute RRT initiation.[34]

Debate also persists regarding the preferred mode of dialysis. Available methods include intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT), and significant differences exist between these techniques. IHD is conventionally performed three times a week in 4 h sessions via venovenous access; because of more rapid fluid shifts, IHD requires hemodynamic stability. Using venovenous or arteriovenous access and reduced blood flow and ultrafiltration rates, CRRT is performed continuously and offers gradual solute and fluid clearance. Despite the theoretical advantage of more "physiologic" restoration of solute and fluid balance, CRRT has not been found to offer a survival benefit compared to IHD. While methodological concerns—such as patient selection—plague this literature, no recent randomized controlled trial has demonstrated a mortality advantage to CRRT.[35–39] Similarly, numerous meta-analyses have also concluded that CRRT does not appear to confer a survival advantage over IHD.[40,41] On the other hand, it is likely that sicker patients are offered CRRT, rather than IHD.

Six randomized trials have analyzed whether the dose of dialysate administered with CRRT impacts mortality. Two early studies produced preliminary evidence to suggest that increased CRRT intensity decreases mortality. Ronco et al. found that patients who received doses of 45 mL/kg/h or 35 mL/kg/h demonstrated reduced mortality compared to patients who received doses of 20 mL/kg/h (RR, 0.72; 95% CI, 0.54–0.94; and RR, 0.73; 95% CI, 0.56–0.96, respectively).[42] However, the preponderance of subsequent evidence has come to suggest that CRRT dose does not affect mortality. In 2002, Bouman et al. found no decrease in mortality among 106 patients who sustained higher hemofiltration volumes compared to lower volumes (48 vs. 20 mL/kg/h).[31] Similarly,

Tolwani et al. found no difference in mortality between 200 patients randomized to receive CRRT dose of 35 or 20 mL/kg/h.[43] In a multicenter 1100-patient randomized trial, Palevsky et al. did not note a mortality difference between patients receiving CRRT dose of 35 versus 20 mL/kg/h.[44] Bellomo et al. conducted a 1500-patient trial and found no mortality difference at 90 days between patients who received a dose of 40 mL/kg/h and those who received 25 mL/kg/h.[45] In addition, none of these studies reported a difference in rates of recovery of renal function following more intense CRRT treatment. Given this body of evidence, most authors recommend achieving flow rates of 20 mL/kg/h. Higher rates may be used in cases with clinically significant metabolic acidosis or hyperkalemia or severe catabolic disease.

Early studies implied that more frequent IHD might also reduce mortality among critically ill patients with AKI. Schiff et al. studied 160 patients and found reduced mortality among patients treated with daily IHD as compared to an alternating day schedule.[46] Another group found reduced mortality among 34 patients randomized to receive either IHD to maintain BUN levels <60 mg/dL and sCr levels <5 mg/dL as compared to conventional IHD schedule.[47] In spite of these early reports, a more recent, large randomized trial with 1100 patients failed to demonstrate a mortality benefit to daily IHD[44] in AKI.
Answer: Neither the exact timing of RRT initiation, nor the modality of dialysis, nor the intensity of the therapy above a minimum seem to impact mortality or renal recovery.
Question 6: What are potential pharmacologic treatments of AKI?

As AKI is characterized by a spectrum of volume responsiveness, initial therapeutic efforts may include a judicious trial of fluid repletion in the appropriate clinical setting, unless evidence of congestive heart failure or pulmonary edema is present. Diuretics are often utilized in an attempt to improve urine output in AKI. Numerous studies have found that diuretics do not decrease mortality or improve renal outcomes in established renal failure.[48,49] However, diuretics can be used for management of volume overload in a patient with AKI.

Various vasoactive substances have been trialed in AKI. Low or renal dose dopamine has been proposed to preferentially reduce renal vasoconstriction and thus was advocated as a technique to ameliorate renal dysfunction. Several recent meta-analyses have not documented reduced mortality or improved renal function with low-dose dopamine and have explicitly argued against its use.[50,51] Fenoldopam is a pure dopamine A-1 receptor agonist that increases blood flow to the renal cortex and outer medulla. Two meta-analyses, one in critically ill patients following cardiac surgery and one in critically ill patients with or at risk for AKI, found that fenoldopam reduced the need for RRT, decreased mortality, and reduced length of stay.[52] Heterogeneity among analyzed studies limits this conclusion; large randomized clinical trials are needed before widespread implementation is justified. Atrial natriuretic peptide (ANP) is produced by modified cardiac myocytes and increases glomerular filtration rate through afferent arteriolar vasodilation and efferent arteriolar vasoconstriction. ANP has been mainly studied in the setting of postcardiac surgery AKI. While systematic reviews found a reduced need for RRT in AKI patients, other meta-analyses have concluded that the lack of high-quality studies limits this conclusion.[53]

Another area of active research concerns the use of growth factors in the treatment of AKI. Noting that expression in animal models of insulin-like growth factor (IGF) decreased during ischemia and increased coincident with renal recovery, Hammerman et al. found that IGF administration ameliorated AKI in animal models.[54] Translation of this concept from animals to humans has however proven difficult. Similarly, while large doses of erythropoietin improved AKI in animal models, a randomized, placebo-controlled trial of erythropoietin revealed that prophylactic administration did not decrease rates of AKI in the intensive care setting.[55]
Answer: Medical therapies to limit or reverse AKI have thus far eluded researchers.

Types of AKI Commonly Encountered in Surgical Patients

Complications	Incidence	References
Postoperative ATN	Up to 25% after coronary artery bypass surgery	[23]
Contrast nephropathy	Ranges from 0% to 50% based on the presence of risk factors	[27, 28]
Septic AKI	42% of septic patients admitted to intensive care units	[7]
Rhabdomyolysis-induced AKI	15%–33% of patients with rhabdomyolysis	[30]
Vancomycin-induced AKI	5%–15% of patients treated with vancomycin	[24]
Gentamycin-induced AKI	10% of patients receiving aminoglycosides	[24]
NSAID-induced AKI	Although absolute risks are low, relative risk of AKI increased >2.5-fold in the elderly	[26]
Acute interstitial nephritis	May account for ~25% of unexplained renal failure in hospitalized patients	[25]

Types of AKI Encountered in Surgical Patients and Strategies to Avoid Complications

Complications	Strategies to Avoid Complications
Postoperative ATN	Keep MAP >65, avoid unnecessary nephrotoxins
Acute intersititial nephritis	Early identification of renal dysfunction in patients receiving medications associated with AIN and early discontinuation of the offending agent

Complications	Strategies to Avoid Complications
Contrast nephropathy	Discontinue Lasix and angiotensin-converting enzyme inhibitors. Hydration at 1 mL/kg/h for 12 h prior to contrast exposure and 12 h after contrast exposure (0.5 mL/kg/h in patients with CHF). Use of *N*-acetyl cysteine 1200 mg PO BID for 24 h prior and 24 h after contrast exposure
Septic AKI	Avoid hypotension, early goal-directed therapy and early institution of antibiotics
Vancomycin- or gentamycin-induced AKI	Use weight-based and glomerular filtration rate–based nomograms for vancomycin dosing. Consult hospital pharmacist. Follow drug levels. Identify that even small changes in renal function require adjustment of vancomycin dosing. Dose vancomycin by level in patients with AKI.
NSAID-induced AKI	Avoid use of NSAIDs in elderly patients and patients with CKD or cardiac disease

References

1. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16(11):3365–3370.
2. Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM, Go AS. Community-based incidence of acute renal failure. *Kidney Int*. 2007;72(2):208–212.
3. Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, Bidani AK. Acute kidney injury: A springboard for progression in chronic kidney disease. *Am J Physiol Renal Physiol*. 2010;298(5):F1078–1094.
4. Lassnigg A, Schmidlin D, Mouhieddine M et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. *J Am Soc Nephrol*. 2004;15(6):1597–1605.
5. Hoste EA, Clermont G, Kersten A et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit Care*. 2006;10(3):R73.
6. Abosaif NY, Tolba YA, Heap M, Russell J, El Nahas AM. The outcome of acute renal failure in the intensive care unit according to RIFLE: Model application, sensitivity, and predictability. *Am J Kidney Dis*. 2005;46(6):1038–1048.
7. Bagshaw SM, George C, Bellomo R, Committee ADM. Early acute kidney injury and sepsis: A multicentre evaluation. *Crit Care*. 2008;12(2):R47.
8. Uchino S, Kellum JA, Bellomo R et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA*. Aug 17 2005;294(7):813–818.
9. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int*. 2008;74(1):101–107.
10. Rosner MH. The pathogenesis of susceptibility to acute kidney injury in the elderly. *Curr Aging Sci*. 2009;2(2):158–164.
11. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol*. 2005;16(1):162–168.
12. Gomes E, Antunes R, Dias C, Araujo R, Costa-Pereira A. Acute kidney injury in severe trauma assessed by RIFLE criteria: A common feature without implications on mortality? *Scand J Trauma Resusc Emerg Med*. 2010; 18:1–6.
13. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol*. 2009;20(3):672–679.
14. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: A systematic review. *Kidney Int*. 2008;73(9):1008–1016.
15. Liu S, Che M, Xue S et al. Urinary L-FABP and its combination with urinary NGAL in early diagnosis of acute kidney injury after cardiac surgery in adult patients. *Biomarkers*. 2013; 18(1):95–101.
16. Portilla D, Dent C, Sugaya T et al. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int*. 2008;73(4):465–472.
17. Nickolas TL, Schmidt-Ott KM, Canetta P et al. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: A multicenter prospective cohort study. *J Am Coll Cardiol*. Jan 17 2012;59(3):246–255.
18. Webb JA. Ultrasonography in the diagnosis of renal obstruction. *BMJ*. 1990;301(6758):944–946.
19. Sise ME, Forster C, Singer E et al. Urine neutrophil gelatinase-associated lipocalin identifies unilateral and bilateral urinary tract obstruction. *Nephrol Dial Transplant*. 2011;26(12):4132–4135.
20. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. *Lancet*. 2005;365(9457):417–430.
21. Nickolas TL, O'Rourke MJ, Yang J et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med*. 2008;148(11):810–819.
22. Bagshaw SM, Bennett M, Devarajan P, Bellomo R. Urine biochemistry in septic and non-septic acute kidney injury: A prospective observational study. *J Crit Care*. 2013; 28(4):371–378.
23. Del Duca D, Iqbal S, Rahme E, Goldberg P, de Varennes B. Renal failure after cardiac surgery: Timing of cardiac catheterization and other perioperative risk factors. *Ann Thorac Surg*. 2007;84(4):1264–1271.
24. Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother*. 1990;25(4):679–687.
25. Farrington K, Levison DA, Greenwood RN, Cattell WR, Baker LR. Renal biopsy in patients with unexplained renal impairment and normal kidney size. *Q J Med*. 1989;70(263):221–233.
26. Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. *Am J Epidemiol*. 2006;164(9):881–889.

27. Parfrey PS, Griffiths SM, Barrett BJ et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med*. 1989;320(3):143–149.
28. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med*. 1990;89(5):615–620.
29. Asif A, Epstein M. Prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis*. 2004;44(1):12–24.
30. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine (Baltimore)*. 2005;84(6):377–385.
31. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. *Crit Care Med*. 2002;30(10):2205–2211.
32. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. *Hemodial Int*. 2004;8(4):320–325.
33. Liu KD, Himmelfarb J, Paganini E et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. *Clin J Am Soc Nephrol*. 2006;1(5):915–919.
34. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M, Alberta Kidney Disease Network. Renal replacement therapy in patients with acute renal failure: A systematic review. *JAMA*. Feb 2008;299(7):793–805.
35. Mehta RL, McDonald B, Gabbai FB et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int*. 2001;60(3):1154–1163.
36. Uehlinger DE, Jakob SM, Ferrari P et al. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant*. 2005; 20(8):1630–1637.
37. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis*. 2004;44(6):1000–1007.
38. Vinsonneau C, Camus C, Combes A et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet*. 2006;368(9533):379–385.
39. Cho KC, Himmelfarb J, Paganini E et al. Survival by dialysis modality in critically ill patients with acute kidney injury. *J Am Soc Nephrol*. 2006;17(11):3132–3138.
40. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: A meta-analysis. *Crit Care Med*. 2008;36(2):610–617.
41. Rabindranath K, Adams J, Macleod AM, Muirhead N. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *Cochrane Database Syst Rev*. 2007;(3):CD003773.
42. Ronco C, Bellomo R, Homel P et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet*. 2000;356(9223):26–30.
43. Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM. Standard versus high-dose CVVHDF for ICU-related acute renal failure. *J Am Soc Nephrol*. 2008;19(6):1233–1238.
44. Network VNARFT, Palevsky PM, Zhang JH et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):7–20.
45. Investigators RRTS, Bellomo R, Cass A et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. Oct 2009;361(17):1627–1638.
46. Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med*. 2002;346(5):305–310.
47. Gillum DM, Dixon BS, Yanover MJ et al. The role of intensive dialysis in acute renal failure. *Clin Nephrol*. 1986;25(5):249–255.
48. Bagshaw SM, Delaney A, Haase M, Ghali WA, Bellomo R. Loop diuretics in the management of acute renal failure: A systematic review and meta-analysis. *Crit Care Resusc*. 2007;9(1):60–68.
49. Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA*. 2002;288(20):2547–2553.
50. Holmes CL, Walley KR. Bad medicine: Low-dose dopamine in the ICU. *Chest*. 2003;123(4):1266–1275.
51. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: Low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med*. 2005;142(7):510–524.
52. Landoni G, Biondi-Zoccai GG, Tumlin JA et al. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: A meta-analysis of randomized clinical trials. *Am J Kidney Dis*. 2007; 49(1):56–68.
53. Nigwekar SU, Navaneethan SD, Parikh CR, Hix JK. Atrial natriuretic peptide for preventing and treating acute kidney injury. *Cochrane Database Syst Rev*. 2009;(4):CD006028.
54. Hammerman MR. Growth factors and apoptosis in acute renal injury. *Curr Opin Nephrol Hypertens*. 1998;7(4):419–424.
55. Endre ZH, Walker RJ, Pickering JW et al. Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). *Kidney Int*. 2010;77(11):1020–1030.

8

Complications of Nutritional Support

Jayson D. Aydelotte and Andrea L. Goode

CONTENTS

Nutritional support, through the enteral and parenteral routes, has become a hallmark breakthrough and veritable success of modern surgical care. The choice to provide nutritional support and the type of nutritional support has been the focus of many quality research initiatives as well as distinguished careers. While surgical nutrition has become a staple in every surgical practice in the United States, several complications remain serious issues, which play a role in the surgical nutrition decision-making process. These adverse events center around two major themes: complications related to the delivery device and complications related to the food itself.

8.1 Complications Associated with the Actual Nutrient Source

The complications associated with the actual nutrient source can also be subdivided into those associated with enteral nutrition (EN) versus total parenteral nutrition (TPN) and those associated with the type and amount of calories and macronutrients delivered, the so-called overfeeding complications. One large meta-analysis of prospective, random-assignment trials comparing EN and TPN outlines a common theme among many trials comparing these two nutrition delivery methods: a significant increase in overall infection, most notably central line infections, in the parenteral over the enteral groups. There were no differences in mortality.[1] It should be noted that most of these trials predated the use of antibiotic-coated catheters and central line management protocols that have significantly lowered the incidence of catheter-related bacteremia (see following sections). A recent large, prospective random-assignment trial in Belgium published in 2011 compared the *timing* of the initiation of TPN and its effect on outcome. The patients were assigned to two groups, one which started TPN within 48 h of admission and one which started TPN no sooner than 8 days after admission. The late group had a higher likelihood of being discharged from the ICU alive, lower ICU infections, lower percentage of requiring mechanical ventilation longer than 2 days, and lower health-care costs.[2] However, a more recent study performed in Switzerland found the *addition* of TPN to EN feeds to reach 100% of calculated caloric needs started 4 days after admission resulted in significantly reduced number of nosocomial infections in the subsequent 30 hospital days and a lower mean number of infections per patient.[3]

8.2 Overfeeding

Overfeeding is a catch-all term that really encompasses a variety of different studied clinical entities including caloric intake, protein to fat calories, and specific macronutrient effects on metabolism and outcome. One retrospective analysis of 200 patients receiving TPN discovered an increased risk of blood stream infection (BSI) in those patients who received 36 kcal/kg/day versus the group that received 31 kcal/kg/day despite adequate and similar blood glucose control in each group.[4] Similarly, a large prospective trial in surgical patients receiving TPN stratified patients into tertiles in regards to their amount of calculated caloric intake (<33.4%, 33.4%–64.6%, and >64.6%)

and overall complication rates. Those patients in the third tertile, those actually receiving closer to their calculated goals, had increased hospital mortality, increased ICU infections, increased ventilator-associated pneumonia, increased days of mechanical ventilation, and increased hospital and ICU length of stay.[5] But, neither of these studies illustrates exactly what to avoid in administering TPN. It is unclear just what is causing these increased complications in these studies. But they raise significant concerns and pave the way for future prospective randomized trials comparing volumes/amount of calories infused in the critically ill.

Liver dysfunction: One particular concern of overfeeding is liver dysfunction. Grau et al. prospectively studied the incidence of liver dysfunction of various degrees, including hepatic necrosis, in patients receiving TPN and in patients receiving EN. There was a statistically significant association of hepatic necrosis in those patients receiving TPN. Moreover, there was an increased incidence of liver dysfunction overall in those patients who received TPN, early feeding, and those who received calculated caloric energy requirements over 25 kcal/kg/day.[6]

Overall, there appears to be increased complications in those patients who (1) start TPN before 8 days of admission, (2) receive over 25 kcal/kg/day of calculated caloric requirements, and (3) receive TPN over EN when possible.

8.3 Delivery Device–Related Complications

Complications related to the delivery device of nutritional support are both well-represented in the literature at large and dramatic. It is difficult to find even the most junior surgery resident who does not have a dramatic story about a malpositioned feeding tube or central line. And while the literature does describe these dramatic cases, it is much more replete with information relative to things like hospital-associated complications (increased cost), complications specific to placement of devices, and central line associated blood stream infection (CLABSI).

8.4 TPN Access

8.4.1 Line Sepsis

CLABSI is perhaps the most recent focus of national health-care organizations relative to nutritional supplementation. The interest lies not so much on the actual delivery of TPN, but limiting the BSI associated with TPN delivery. CLABSI can be thought of as a consequence to two major physiologic concepts relative to the central line itself, its insertion/external cleanliness (extraluminal) and migration of pathogens down the inside of the catheter (intraluminal). Extraluminal-related CLABSI is thought to be responsible for the majority of infection surrounding short-term catheters, whereas intraluminal infection is related to long-term catheter use. CLABSI is best described in infections per catheter days. Prior to these major changes in focus surrounding CLABSI, the general range of infection was around 1.5 to about 7 infections per 1000 catheter days. After these sweeping changes, the rates have fallen to between 0.2 and 5.2 infections per 1000 catheter days.[7]

One particular study that both articulated these sweeping changes and demonstrated their effectiveness was performed prospectively and compared to historical controls in 108 ICUs in Michigan in 2004 and 2005. This study looked at the effectiveness of implementing five major foci of catheter-related care and compared the effectiveness of using this entire bundle, as opposed to examining each item, on the incidence of CLABSI during the study period. The five procedures were: ensuring good hand washing, using full barrier precautions during insertion of the catheter, cleaning skin with chlorhexidine (bathing the patients when they had the catheter in place), avoiding femoral line insertion if possible, and removing unnecessary catheters. The mean rate of catheter infection was 7.7/1000 at baseline and decreased to 1.4/1000 at 18 month follow-up.[8]

8.4.2 Enteral Access

Complications associated with enteral feeding tube access range from increased cost to devastating effects of tube dislodgment. The simplest tube placements can also prove to be costly and have serious complications. One study done in 2005 evaluated the placement of small bore feeding tubes by nurses in a tertiary care facility. A total of 1822 tubes were placed with a 93% success rate for intragastric placement and a 60% success rate for postpyloric feeding. About 18.6% of the patients required fluoroscopy to place the tube (mostly in the postpyloric position). Placement in the tracheobronchial tree occurred in 3.2%; 1.2% of patients had a pneumothorax and 0.5% died.[9]

Gastrostomy tube placement is another reliable means to provide enteral feeds. Several studies have been done to establish the safety and complication profile of different gastrostomy tube placement strategies. One study comparing percutaneous gastrostomy tube (PEG) placement versus laparoscopic gastric tube placement in 238 children identified immediate procedural complications requiring conversion to an open procedure in 1.5% and 2.9%, respectively. Postoperative complications including leak, hemorrhage, gastric separation, early tube dislodgment, gastrocolic fistula, and pyloric obstruction were 8.2% and

4.8%, respectively. The most serious complications surrounded PEG tube dislodgment in four patients.[10]

Late accidental dislodgment of percutaneously placed tubes is an underreported problem nationwide. In one study analysis of 563 PEG tubes placed in adults, 4.1% suffered early (7 day) dislodgment; lifetime accidental dislodgment in this group was 12.8%; the vast majority of these required Emergency Room visits and surgical consultation totaling an average of 1200$ per patient.[11]

In addition to tube dislodgment or misplacement, some surgeons have a concern over the changing physiologic performance of the stomach when fixed with a gastric (mostly PEG) tube. One major review of PEG complications lists the risk of aspiration during PEG placement to be between 0.3% and 1.0%.[12] Another study evaluated the risk of aspiration in 64 patients with PEG tubes and found 19% developed some sort of aspiration event during or shortly after the PEG placement as far out as 9 months after the procedure.[13]

One study comparing open, standard gastrostomy to PEG found a periprocedural complication rate for PEG to be 7.4%–30.2% for standard, open gastrostomy. All the major complications requiring laparotomy for repair were in the standard gastrostomy group.[14]

Some surgeons insist on having postpyloric feeding, and some disease processes/surgeries require jejunal feeding because of the anatomical situation (gastroesophagectomy). One study comparing nasojejunal (NJT) feedings, jejunostomy (JT) feedings, and TPN in patients undergoing pancreaticoduodenectomy found there was a prolonged course (12 vs. 8 days) of EN in the JT group versus the NJT group. Tube-related complications occurred most commonly in the NJT group (34% dislodgment). The JT group had a 6% relaparotomy rate because of leak or bowel obstruction at the site of insertion.[15] Another study done in 73 patients undergoing gastroesophagectomy who had JT placed at the time of surgery found that 25% had complications, 48% of which were major complications; 2.7% of patients required a relaparotomy for small bowel obstructions.[16]

Overall, the incidence of tube-related complications varies among the type of tube inserted and the method of insertion. The most common complications are misplacement, dislodgment, and bowel obstruction/injury from the tube placement itself.

Complications of Access

Central line blood stream infections/ TPN	0.2–5.0 infections/1000 catheter days	[6,7]
PEG tube early dislodgment	0.3%–8%	[9,11,13]
Misplaced postpyloric feeding access	40%	[8]
In tracheobronchial tree	3.2%	[8]
Major jejunostomy complications requiring laparotomy	2.7%–6%	[14,15]

References

1. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: A meta-analysis. Am J Clin *Nutr* 2001; 74:534–542.
2. Casaer MP, Mesotten D, Hermans G et al. Early versus late parenteral nutrition in critically ill adults. *New Engl J Med* 2011; 365:506–517.
3. Heidegger CP, Berger MM et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: A randomized controlled clinical trial. *Lancet* 2013; 381:9864: 385–393.
4. Dissanaike S, Shelton M, Warner K, O'Keefe GE. The risk for bloodstream infections is associated with increased parenteral caloric intake in patients receiving parenteral nutrition. *Crit Care* 2007; 11:R114.
5. Arabi YM, Haddad SH, Tamim HM et al. Near-target caloric intake in critically ill medical-surgical patients is associated with adverse outcomes. *J Parenter Enteral Nutr* 2010; 34:280–288.
6. Grau T, Bonet A, Rubio M et al. Liver dysfunction associated with artificial nutrition in critically ill patients. *Crit Care* 2007; 11:R10.
7. Miller SE, Maragakis LL. Central line-associated bloodstream infection prevention. *Curr Opin Infect Dis* 2012; 25:412–422.
8. Pronovost P, Needham D, Berenholtz S et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006; 355:2725–2732.
9. Aguilar-Nascimento JE, Kudsk KA. Clinical costs of feeding tube placement. *J Parenter Enteral Nutr* 2007; 31:269–273.
10. Akay B, Capizzani TR, Lee AM et al. Gastrostomy tube placement in infants and children: Is there a preferred technique? *J Pediatr Surg* 2010; 45:1147–1152.
11. Rosenberger LH, Newhook T, Schirmer B, Sawyer RG. Late accidental dislodgement of a percutaneous endoscopic gastrostomy tube: An underestimated burden on patients and the health care system. Surg Endosc 2011; 25:3307–3311.
12. Schrag SP, Sharma R, Jaik NP et al. Complications related to percutaneous endoscopic gastrostomy (PEG) tubes. A comprehensive clinical review. *J Gastrointest Liver Dis* 2007; 16:407–418.
13. Jarnagin WR, Quan-Yang D. The efficacy and limitations of percutaneous endoscopic gastrostomy. *Arch Surg* 1992; 127:262–264.
14. Dwyer KM, Watts DD, Thurber JS et al. Percutaneous endoscopic gastrostomy: The preferred method of elective feeding tube placement in trauma patients. *J Trauma* 2002; 52:26–32.
15. Gerritsen A, Besselink MG, Cieslak KP et al. Efficacy and complications of nasojejunal, jejunostomy and parenteral feeding after pancreaticoduodenectomy. *J Gastrointest Surg* 2012; 16:1144–1151.
16. Llaguna OH, Kim HJ, Deal AM et al. Utilization and morbidity associated with placement of a feeding jejunostomy at the time of gastroesophageal resection. *J Gastrointest Surg* 2011; 15:1663–1669.

9

Complications of Anticoagulants and Blood Transfusion

Ara J. Feinstein and Mohan Ramalingam

CONTENTS

Bleeding is a potential complication in any surgical or trauma patient. A major risk factor that increases the incidence of bleeding is anticoagulation. An analysis from the National Trauma Databank[1] showed prevalence of preinjury warfarin alone to be nearly 3%. As the population ages, the use of newer anticoagulant, antiplatelet, and fibrinolytic medications is also on the rise. Understanding the mechanisms of these commonly encountered drugs in clinical practice is essential to counteract their effects on the coagulation system and prevent ongoing bleeding. Bleeding complications may ultimately lead to transfusion. The indications for transfusion can be divided into two broad categories: to enhance the oxygen-carrying capability of blood by expanding the red blood cell (RBC) mass, or to replace clotting factors that are lost, consumed, or not produced.[2] Unfortunately, transfusion carries its own set of complications that can be serious and sometimes fatal.

9.1 Complications of Anticoagulants (Table 9.1)

9.1.1 Warfarin

Warfarin and its derivatives work by blocking the essential vitamin K-dependent carboxylation of coagulation factors II, VII, IX, and X, which results in a decrease in the activity of these factors in plasma. The duration of warfarin's anticoagulation is a function of the half-lives of the vitamin K-dependent coagulation factors, which range from 6 to 72 h, and thus the full effect of therapy can be delayed for up to 3 days.[3] Variations in pharmacokinetics as well as genetic polymorphisms can also account for clinically important differences in the way warfarin is metabolized,

TABLE 9.1

Summary of Anticoagulant Medications

Drug	Route	Mechanism of Action	Plasma T_{max}	$T_{1/2}$	Clearance	Preoperative Cessation	Monitoring	Specific Antidote
Warfarin	PO	Vitamin K antagonist	2–4 days	35–45 h	Renal/hepatic	5 days	INR	Vitamin K
UFH	SC/IV	Potentiates ATIII	Immediate	45 min	RE system/renal	4–6 h	PTT	Protamine
Enoxaparin (Lovenox)	SC	LMWH	4 h	5–7 h	Renal	12 h	Anti-Xa assay	None
Dabigatran (Pradaxa)	PO	Direct thrombin (II) inhibitor	2 h	12–17 h	Renal	2–4 days	Thrombin clotting time (TCT), ECT	None
Rivaroxaban (Xarelto)	PO	Direct factor Xa inhibitor	3–4 h	6–12 h	Hepatic/renal	24–36 h	Anti-Xa assay	None
Aspirin	PO	COX-I	1–2 h	30 min	Hepatic/renal	7 days	None[a]	None
Clopidogrel (Plavix)	PO	ADPr-I	45 min	6 h	Hepatic/renal	7 days	None[a]	None
Dipyridamole (Persantine)	PO	PDE-I	75 min	10 h	Hepatic	3 days	None[a]	None
Abciximab (ReoPro)	IV	GP 2a/3b inhibitor	Immediate	10 min	RE system	48 h	None[a]	None
Alteplase	IV	Fibrinolytic	Immediate	5 min	Hepatic	4 h	TCT, FDPs	Aminocaproic acid, tranexamic acid

[a] Laboratory-specific tests (e.g., thromboelastography) for platelet function exist but are not routinely employed to monitor drug dosing/effects.

and more than 700 commonly used drugs interact with warfarin, either inhibiting or accelerating its metabolism.[4]

To help monitor these multiple interacting processes, the INR (international normalized ratio) is used. A therapeutic range is commonly defined as 2.0–3.0 for most indications. The numbers themselves do not represent a linear correlation with factor activity. For example, at an INR of 2, factor activity level is ~40%, an INR of 3.5 correlates to ~30%, while at an INR of 5, factor activity is closer to <10%.[5]

While the most important side effect of warfarin is bleeding, the inhibitory effect on proteins C and S (shorter half-lives of 36 h and 42 h, respectively) causes a temporary procoagulant effect due to the longer half-lives of II, XI, and X. In rare cases, usually associated with a protein C deficiency, warfarin-induced skin necrosis may occur.

Patients on warfarin in need of procedures or who experience clinically significant bleeding are eligible for reversal of their anticoagulation with several approaches: (1) stop warfarin therapy, (2) administer vitamin K, and (3) administer FFP (fresh frozen plasma), or (4) PCC (prothrombin complex concentrate) with or without rFVIIa (recombinant factor VIIa).[6]

Patients should stop taking warfarin at least 5 days prior to elective surgery and have an INR corrected to <1.5 preoperatively.

Reversal with vitamin K takes anywhere from 6 to 48 h, depending on the route of administration and initial INR.[7] Reinitiation of warfarin therapy is ineffective for approximately 1 week due to still circulating vitamin K and active gamma-carboxylase enzyme molecules. Thus, heparin or low-molecular weight heparin (LMWH) may be required as a bridge.

For more significant bleeding, administration of 2–6 units of FFP will help reduce the INR to <1.5 within 24 h, but is limited by thawing time and volume overload.

PCCs have several advantages over FFP, including quicker reversal of INR, smaller volumes to achieve correction, no need for thawing, and a better safety profile. For life-threatening bleeding, a one-time administration of PCC, which contains either three (II, IX, and X) or four (II, VII, IX, and X) concentrated (25 times normal serum levels) factors together with vitamin K and occasionally rFVIIa, will promptly correct the coagulopathy.[8] Currently, only the three-factor PCC is available in the United States. PCC also contains proteins C, S, and heparin to prevent clotting factor activation in vitro.

Presently, evidence supporting the use of rFVIIa (at doses ranging from 10 to 90 μg/kg) for the treatment of warfarin-associated bleeding is confined to review articles although off-labeled use of rFVIIa has found its place in cardiac surgery, trauma, liver transplantation, and prostatectomy.[9] This analysis suggested no mortality reduction for any of the aforementioned conditions. In addition, there was an increased risk for arterial thromboembolism. rFVIIa may be effective in

controlling intracranial bleeding when administered within 3–4 h of onset, although improvements in neurological outcome and mortality remain unclear.[10]

9.1.2 Heparin

Heparin is comprised of various glycosaminoglycan molecules ranging in size from 10 to 20 kDa and acts by binding to and potentiating the inhibitory effect of AT-III (antithrombin III) on coagulation factors IIa and Xa more than 1000-fold. Heparin has a dose-dependent half-life, and the anticoagulant effect of heparin may be highly variable; so partial thromboplastin time (PTT) should be monitored closely, aiming for a therapeutic PTT between 1.5 and 2.5× the control. After achieving steady state, heparin has a half-life of ∼90 min, and clearance occurs via a dual mechanism. At therapeutic doses, clearance is predominantly through the reticuloendothelial system. At higher doses, renal clearance also occurs.[11] The clearance of heparin from plasma may be reduced in patients with cirrhosis or severe renal impairment.

Heparin should be held 4–6 h prior to procedures with a significant bleeding risk.

For more rapid correction, intravenous protamine sulfate can be used to reverse heparin. One milligram of protamine sulfate reverses approximately 100 U of heparin.[12] PTT or ACT (activated clotting time) can be checked to follow the reversal process.

Bleeding is the most frequently encountered adverse effect of heparin. In addition, heparin-induced thrombocytopenia (HIT) may also occur. This entity is an immunological response to heparin characterized by the occurrence of thrombocytopenia and venous and arterial thromboembolism. Two different forms of HIT are recognized: the first is a nonimmune-mediated reaction occurring within 4 days of initiating heparin where platelets drop to between 100,000 and 140,000 μL. Type II is an immune-mediated reaction occurring 5–7 days after initial exposure to heparin, and platelet counts drop by more than 50%. Despite thrombocytopenia, bleeding complications are rare with thrombotic events being much more common, including extensive arterial thrombi in 20%–50% of patients. Warfarin administration may potentiate the hypercoagulable state, frequently requiring alternative anticoagulation, usually a direct thrombin inhibitor.[13]

9.1.3 Low-Molecular-Weight Heparin

LMWH is comprised of depolymerized fragments of heparin, with an average molecular weight between 4 and 6 kDa and inhibits factor Xa by inducing a conformational change in AT-III. The advantages of LMWH include fewer bleeding complications at therapeutic doses compared to unfractionated heparin, less incidence of osteopenia, and less platelet interactions.[14] In addition, LMWH has predictable bioavailability and clearance, enabling weight-based dosing. This precludes the need for frequent laboratory monitoring and dose adjustments. As LMWH has a longer half-life, it is suitable for once daily dosing and long-term therapy. It should be noted that the anti-Xa laboratory assay does not actually measure the degree of anticoagulation in vivo but rather the concentration of circulating LMWH, which depends on the dosing and renal clearance.

LMWHs should be stopped 12 h prior to an elective procedure. Protamine may be partially effective as a reversal agent to neutralize ∼60% of the circulating drug.[15] In healthy volunteers given fondaparinux, rFVIIa normalized coagulation times and thrombin generation within 1.5 h, with sustained effect for 6 h.[16]

A crucial clinical point is that the administration of FFP will not correct the anticoagulant effect of either unfractionated heparin or LMWH and could actually enhance the heparins' anticoagulant effect as it contains antithrombin.[17]

9.1.4 Direct Factor Inhibitors

DTIs (direct thrombin inhibitors) work by inhibiting thrombin, whose procoagulant properties include cleaving fibrinogen, activating the coagulation factors V and VIII, inducing platelet aggregation, upregulating expression of tissue factor on cell surfaces, and activating factor XIII that cross-links and stabilizes the fibrin clot.

Lepirudin and Bivalirudin are derived from hirudin, an anticoagulant that was first derived from leeches. Bivalirudin reversibly binds to the active and secondary binding sites of thrombin and is approved for use in coronary procedures. Argatroban is a synthetic direct thrombin inhibitor that is also approved for treating HIT, and its clearance is primarily hepatic. Dabigatran, like argatroban, directly inhibits both free and clot-bound thrombin and is approved for treating nonvalvular atrial fibrillation.[18]

Most of the DTIs cause nonlinear prolongation of the PTT, and checking an ECT (ecarin clotting time) or TT (thrombin time) may be preferable to ensure minimal anticoagulant effect before a procedure.[19]

Indirect factor Xa inhibitors include rivaroxaban and pentasaccharides (e.g., fondaparinux), which are synthetic compounds that exert antithrombin-dependent, exclusive inhibition of factor Xa, somewhat similar to LMWH. They too do not require monitoring of coagulation parameters. They have been shown to be superior to LMWH in the prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement and are being introduced into clinical practice.[20] Rivaroxaban is

approved for nonvalvular atrial fibrillation and being investigated for use in acute coronary syndromes.[21]

Although these drugs have relatively short half-lives, no supported strategy is available for reversal of these direct factor inhibitors.

FFP is largely ineffective, as free circulating drug molecules will bind the prothrombin in the FFP. For this same reason, PCC has been shown to have an inadequate reversal of anticoagulation effect.[22] Dabigatran has a high volume of distribution and may be cleared with multiple rounds of dialysis.[23]

Anticoagulant effect of rivaroxaban can be reversed with PCC, and tranexamic acid has been shown to reduce blood loss.[19] Unfortunately due to high plasma protein binding rivaroxaban is nondialyzable.

9.1.5 Antiplatelet Agents

Aspirin is commonly used in the prevention and treatment of myocardial infarction, strokes, and occlusion of smaller caliber vascular grafts and stents. It acts by irreversibly acetylating the platelet-associated enzyme cyclooxygenase, thus inhibiting the formation of thromboxane A_2, a potent platelet aggregation agonist and mediator of vasoconstriction. Recovery is dependent on the interval needed to produce new functional platelets from the bone marrow. Approximately 7 days is usually required to restore adequate platelet function and effective hemostasis.[24]

Thienopyridine derivatives such as clopidogrel and ticlopidine act by blocking the ADP receptor on the platelet, which normally promotes platelet aggregation and secretion of vasoactive substances. The combination of clopidogrel and aspirin is shown to be superior over aspirin alone for patients after acute coronary events and coronary stent placement,[25] and it is not infrequent to see patients on both drugs for 6–24 months post myocardial stenting. Although the half-life of clopidogrel is 8 h, the bleeding risk remains prolonged until complete recovery in functional platelet numbers occurs, usually at 7 days postcessation.

Phosphodiesterase inhibitors such as dipyramidole and cilostazol exert their antiplatelet effect by inhibiting the phosphodiesterase enzymes that normally break down cAMP and cGMP, which mediate the inhibitory effect on platelet adhesion, granule release, and aggregation, normally induced by prostacyclin and nitric oxide. Additionally, dipyridamole blocks the thromboxane synthase as well as the thromboxane receptor. Dipyramidole is used to prevent thromboembolic complications associated with prosthetic heart valves and occasionally for prevention of transient ischemic attacks and bypass graft occlusion.[26]

Inhibitors of the glycoprotein receptor IIb/IIIa are potent inhibitors of platelet aggregation by competitively competing for fibrinogen and von Willebrand factor binding to platelets. They are used mainly in preventing coronary artery thrombosis post angioplasty, unstable angina, and cerebrovascular diseases, and can be found in oral as well as intravenous forms.[27] Although they have an extremely short half-life of 1–2 h, the bleeding time remains elevated due to a protracted effect on platelet function, and surgery should be delayed for 36–48 h.

There are no formal guidelines and limited data regarding reversing antiplatelet agents. Aside from discontinuing the antiplatelet medication, options include administering desmopressin (deamino-D-arginine vasopressin [dDAVP]) (IV 0.3 μg/kg), and transfusing platelets. Methylprednisolone (20 mg) and aprotinin may reduce clopidogrel-induced bleeding, and zero balance ultrafiltration may be used with debatable efficacy.[28] Additionally there is a potential off-label rescue role for rFVIIa in life-threatening hemorrhage that still merits further research.[29]

9.1.6 Fibrinolytics

Fibrinolytics are commonly employed for reestablishing circulatory flow in deep vein thrombosis, acute thrombosis of peripheral, mesenteric and coronary arteries, and for opening up arteriovenous grafts and venous catheter devices.

Fibrin represents the final end product of the coagulation cascade, and enzymatic degradation of fibrin is carried out by the fibrinolytic system, which provides feedback amplification and inhibition to prevent unrestrained coagulation. Conversion of plasminogen into the active protease plasmin cleaves cross-linked fibrin, resulting in the dissolution of the clot. Plasminogen activators facilitate this conversion of plasminogen into plasmin.

Commonly used drugs are recombinant endogenous plasminogen activators such as alteplase, urokinase, and activators derived from exogenous bacterial sources such as streptokinase and reteplase.

Cryoprecipitate may be used to replace fibrinogen stores, particularly when fibrinogen levels are <100 mg/dL, and FFP may be administered to replenish the coagulation factors.[30] Antifibrinolytic agents such as e-aminocaproic acid and tranexamic acid may also be utilized.

9.2 Complications of Transfusion

9.2.1 Immunologic Complications

Immunologic complications of blood transfusion are characterized as hemolytic (red-cell type) and nonhemolytic (non-red-cell type).

9.2.1.1 Hemolytic Reactions

Hemolytic reactions occur as a result of the interaction between the antibodies in the plasma of the recipient and the ABO antigens on the red blood cells of the donor. Compared with other reactions, severe hemolytic reactions are associated with the highest morbidity and mortality rates. These reactions are usually acute, appearing within minutes after beginning the transfusion.

These reactions are usually due to misidentifying blood types on the blood product or by giving a properly labeled product to the wrong patient. To avoid these errors, the American Association of Blood Banks recommends that two unique identifiers (e.g., name and hospital identification number) always be used when linking blood products and blood samples to the intended patient.[31]

Acute hemolytic reaction begins with the transfusion of as little as few milliliters of incompatible blood, and its severity is proportional to the volume of blood to which the recipient is exposed.[32] This type of reaction is characterized by pain at the infusion site, fever, chills, back and substernal pain, mental status changes, dyspnea, hypotension, facial flushing, cyanosis, and a bleeding diathesis.[2,32] During a surgical procedure, the only evidence of an acute hemolytic reaction may be hypertension and myoglobinuria. Renal impairment[33] and disseminated intravascular coagulation (DIC) may also be present.[34]

When acute hemolytic reaction is suspected, the transfusion should be stopped immediately. The free hemoglobin and haptoglobin concentrations in the patient's serum should be assessed, and a direct Coombs' test should be performed. The blood product in question should be returned to the blood bank for repeated type-and cross-match tests.[35]

Patients who are experiencing an acute hemolytic reaction characterized by urticaria or other allergic phenomena should receive diphenhydramine (Benadryl® 50 mg) intramuscularly or intravenously, immediately and every 6 h as needed. In addition, Ringer's lactate solution should be administered intravenously with 12.5–25 g of mannitol to ensure copious output of urine (100–200 mL/h). One to two ampules of sodium bicarbonate can be added to each liter of fluid to alkalinize the urine to a pH of at least 6.5. If shock occurs, hydrocortisone and additional fluids should be administered.[36]

Hemolytic reactions may also be delayed. These reactions are usually mild and appear 3–21 days after transfusion, and affect patients who have previously been exposed to blood products. Several days after transfusion, patients may experience hemolysis characterized by jaundice, hemoglobinuria, and decreased hematocrit, but as many as 35% of patients experience no symptoms.[37] Delayed hemolytic reactions are self-limiting, require no specific treatment, and do not affect the patient's compatibility in relation to future transfusions.[35]

Another type of hemolytic transfusion reaction relates specifically to pregnancy. In pregnant trauma patients, fetomaternal hemorrhage may cause a sufficient quantity of Rh-positive fetal blood to enter the circulation of an Rh-negative mother, leading to alloimmunization. This has no adverse health effects during the pregnancy in which it occurs, but results in a rapid, amplified immune response if further maternal exposure to the antigen occurs during a subsequent pregnancy. Maternal anti-Rh antibodies cross the placenta and bind to fetal antigens, causing erythrocyte destruction, which can lead to erythroblastosis fetalis, heart failure, hydrops fetalis, and intrauterine death.[38] Since transfused blood may cause a similar sensitization, transfusions of blood from blood banks should be avoided in women who may later choose to bear children.[39] Quantitative testing for fetal maternal hemorrhage and administration of anti-Rh antibody should be considered in any pregnant Rh-negative patient after events potentially associated with placental trauma and/or disruption of the fetomaternal interface.[40]

9.2.1.2 Nonhemolytic Reactions

Nonhemolytic reactions are more frequent and lead to the development of fever, urticaria, hives, or respiratory distress after the administration of blood. The incidence of these reactions is approximately 2%–10%.[41] They may be related to leukocytes or proteins, and the incidence of these reactions may be reduced by the use of packed RBC or filters that remove leukocytes from transfused blood.[36]

9.2.1.3 Febrile Reactions

Elevation in basal core temperature occurs in as many as 7% of transfusion recipients, but is usually self-limiting.[2] Prior transfusions predispose the patient to the development of fever-causing antibodies, which increases with repeated exposure to blood and blood products.

Febrile reactions are diagnosed by exclusion. The differential diagnosis includes red cell incompatibility, bacterial contamination, and unrelated disease process. When fever occurs during transfusion, the transfusion should be stopped and studies should be conducted to rule out hemolysis. If hemolysis is not a possibility, the patient may be given antipyretic agents.[42] Antihistamines are not effective in the treatment of febrile reaction; therefore, premedication is not indicated with future transfusions.[35]

9.2.1.4 Allergic Reactions

Two percent of transfusion reactions are classified as allergic reactions that result from the transfusion of antigen or immunoglobulin to which patient has preexisting antibodies.[34] A blood transfusion recipient can experience an

allergic reaction to either medications or food ingested by the donor. The reaction can vary in severity from urticaria to anaphylaxis. Furthermore, allergic reaction can develop as a result of the passive transfer of sensitizing antibodies. When the recipient subsequently encounters the allergen to which the donor has produced antibodies, the recipient can experience an allergic reaction to that allergen. Unlike delayed hemolytic or febrile reactions, an allergic reaction does not require prior exposure to blood. Symptoms range from urticaria and pruritus to a full anaphylactic response characterized by hypotension, cutaneous flushing, and bronchospasm. In this situation, the transfusion should be stopped, and epinephrine may be required to support hemodynamics and relieve bronchospasm.[42]

With future transfusions, the use of washed RBCs may decrease the incidence of anaphylactic reactions. Furthermore, the customary type and cross-match test should be supplemented with an assay for complement-activating activity.

9.2.1.5 Graft versus Host Disease

Graft versus host disease (GVHD) occurs after the infusion of immunocompetent cells into a recipient whose immune system is incapable of rejecting the foreign cells. Consequently, the infused immunocompetent cells initiate rejection of the normal host tissues. Acute GVHD also occurs in recipients of allogenic bone marrow transplants and in persons with primary immunodeficiencies who receive viable allogenic lymphocytes.[43] Blood products that place patients at risk of GVHD are whole blood, packed RBCs, fresh plasma, granulocytes, and platelets. GVHD has not been seen after transfusion of frozen blood, FFP, cryoprecipitate, or washed red cells. Irradiated blood products also may be given safely.[44]

GVHD usually occurs 2–30 days after transfusion.[45] Fever occurs first. After 24–48 h, a generalized erythroderma begins to appear on the face (frequently behind the ears), and then spreads to the trunk and extremities. Bullous formations can occur. Skin biopsy shows extensive lymphocytic infiltration. Other signs and symptoms include anorexia, nausea, vomiting, diarrhea, and hepatocellular dysfunction and pancytopenia. There have been no reports of the occurrence of GVHD among immunologically competent persons or among those lacking only humoral immunity.[46]

9.2.1.6 Posttransfusion Purpura

Posttransfusion purpura is a rare form of acute hemorrhagic thrombocytopenia that appears 1 week after transfusion and primarily affects multiparous women who lack the platelet-specific antigen (PLA) 1 (human platelet antigen [HPA] 1).[47] Thrombocytopenia (platelet counts <50,000) results in bleeding from the skin and mucous membranes. Additional transfusions, even with platelets, accentuate the thrombocytopenia, but plasmapheresis and exchange transfusion have resulted in some benefit. The syndrome spontaneously abates in several days to months.[35]

9.2.1.7 Transfusion-Associated Circulatory Overload and Transfusion-Related Acute Lung Injury

Transfusion-associated circulatory overload (TACO) results from the inability of the circulatory system to effectively handle the volume of transfusion. Risk factors for TACO include being at an extreme of age, cardiac or renal dysfunction, acute myocardial infarction, and individuals receiving plasma.[48] Prevention centers on identifying patients at risk, and treatment is supportive with diuresis when possible. Transfusion-related acute lung injury is an acute respiratory distress syndrome that develops within 4 h after transfusion of blood and is characterized by dyspnea and hypoxia due to noncardiogenic pulmonary edema. This injury has been estimated to occur once in approximately 5000 transfusions. This injury is most likely the result of several mechanisms leading to increased permeability of the pulmonary microcirculation. Reactive lipid products that arise during storage of blood products and donor antibodies from multiparous women have been recently implicated in the pathophysiology of transfusion-related acute lung injury.[49] As in other cases of acute respiratory distress syndrome, supportive therapy is indicated. At least 90% of the patients with transfusion-related acute lung injury recover.[50]

9.2.2 Immunomodulatory Complications

Numerous reports have suggested an increase in tumor recurrence and a decrease in survival for transfusion recipients who have colorectal, breast, cervical, lung, prostate, or head and neck tumors.[51]

Transfusions of RBCs are also associated with an increase in septic complications among patients undergoing surgical procedures for carcinoma of the colon[52] and among patients with multiple injuries.[53] Among patients undergoing hip replacement or spine surgery, the postoperative infection rate with allogenic blood transfusion appears to be 7–10 times higher than that associated with autologous blood or absence of transfusion.

9.2.3 Infectious Complications

The primary perceived risks associated with the transfusion of blood and blood products are related to the transmission of infectious diseases. Human immunodeficiency virus (HIV) and hepatitis B and C viruses are of particular concern to patients. Although these risks are steadily decreasing with new screening tests and better

TABLE 9.2
Infectious Risks of Blood Transfusion

Risk Factor	Estimated per Million Units	Frequency per Actual Unit	No. of Deaths per Million Units
Viral infection			
Hepatitis A	1	1/1,000,000	0
Hepatitis B	7–32	1/30,000–1/250,000	0–0.14
Hepatitis C	4–36	1/30,000–1/150,000	0.5–17
HIV	0.4–5	1/200,00–1/2,000,000	0.5–5
HTLV types I and II	0.5–4	1/250,00–1/2,000,000	0
Parvovirus B 19	100	1/10,000	0
Bacterial contamination			
Red cells	2	1/500,000	0.1–0.25
Platelets	83	1/12,000	21

Note: HTLV, human T lymphotropic virus.

antiviral processing, there are still documented cases.[54] Bacterial contamination of blood units is directly related to the length of storage. The organism most commonly implicated in bacterial contamination of red cells is *Yersinia enterocolitica*.[55] The risk of platelet-related sepsis is estimated to be far greater, especially with pooled platelet concentrates from multiple donors. The organisms most commonly implicated in death due to bacterial contamination of platelets are *Staphylococcus aureus, Klebsiella pneumonia, Serratia marcescens*, and *Staphylococcus epidermidis*.[56] To date, there is no widely accepted test method or device that can identify bacterially contaminated blood products. In any patient in whom fever develops within 6 h after platelet transfusion, the possibility of bacterial contamination should be examined, and empiric antibiotic therapy should be considered.

Estimates of the infectious risk per unit of blood are shown in Table 9.2.[50]

9.2.4 Complications of Massive Transfusion

Massive transfusion is arbitrarily defined as the replacement of a patient's total blood volume in <24 h, or as the acute administration of more than half the patient's estimated blood volume per hour.

In traumatic shock, the severity of metabolic acidosis and the rapidity of its correction are correlated with the likelihood of survival. The predominant cause of acidosis is inadequate tissue perfusion, and the occurrence of this complication indicates a need for further resuscitation. Stored red cells are acidic, but the metabolism of citrate produces alkalosis in vivo. Therefore, a pH imbalance to RBC transfusion itself is rare.

A growing body of evidence suggests that high ratios of FFP and platelets to RBCs improve survival in massively bleeding trauma patient.[57] The mechanisms are unclear, but this benefit may be in part due to diminished coagulopathy. This was first noted in the military experience with transfusing whole blood.[58]

Each unit of PRBCs contains approximately 3 g of citrate, which binds ionized calcium. Because citrate is commonly used as an anticoagulant for blood storage, rapid infusion of blood may induce hypocalcemia if excess citrate binds with serum calcium. During massive transfusion, calcium levels should be checked routinely. Hyperkalemia is an often discussed but rarely documented complication of blood transfusion.[59] Potassium escapes from RBCs during storage: the plasma potassium concentration can reach 70 mEq/L in a stored unit of packed RBCs. However, this is usually clinically insignificant, because each unit of packed red cells contains only 10–20 mL of plasma (1 mEq of potassium), and red cells resorb much of this leaked cation upon transfusion. Even so, death due to hyperkalemia has been associated with massive transfusion; therefore, the serum potassium concentration should be closely monitored.

Hypothermia can be avoided or at least minimized by warming all fluids, particularly blood, before they are infused. If transfusion-related hypothermia occurs, rapid infusion of warmed blood will help alleviate its deleterious effects.

When blood products are infused in too large a quantity or at too fast a rate, overload can occur. Elderly and neonatal patients are most sensitive to rapid volume shifts and constitute the largest groups in which this condition commonly develops. Also, patients with impaired cardiac function require careful monitoring so as to prevent circulatory overload during transfusion. In trauma patients, this may have deleterious effects on pulmonary function and elevate abdominal compartment, limb, and intracranial pressures. In mild cases of volume overload, decreasing the rate of transfusion or stopping it will allow equilibration. In more severe instances, aggressive diuresis should be provided.

9.2.5 Alternatives to Allogenic Transfusion

Several strategies exist to avoid blood transfusion altogether. Preoperative autologous donation was rarely used before the recognition that HIV could be transmitted via blood transfusion. Autologous donation should only be considered if the likelihood of transfusion exceeds 50%.[60]

Acute normovolemic hemodilution entails the removal of whole blood from a patient immediately before surgery and simultaneous replacement with acellular fluid such as crystalloid or colloid to maintain normovolemia. Blood is collected in standard blood bags containing anticoagulants, remains in the operating room, and is

reinfused after major loss of blood has ceased, or sooner if indicated. Intraoperative recovery of blood involves collection and reinfusion of autologous red cells lost by patient during the surgery. A cell-washing device can provide the equivalent of 10 units of banked blood per hour to a patient with massive bleeding. Relative contraindications include the potential for aspiration of malignant cells, the presence of infection, and presence of other contaminants as amniotic or ascitic fluid in the operative field. Because washing does not completely remove bacteria from the recovered blood, intraoperative recovery should not be used if the operative field has gross bacterial contamination.[50]

Avoiding Complications

Complications	Avoidance Strategies
Bleeding due to anticoagulants	1. Take a thorough history 2. Stop anticoagulants at appropriate time interval prior to elective surgery 3. Know reversal agents or strategies 4. Monitor anticoagulation when possible
Hemolytic transfusion reactions	1. Avoid blood transfusion with autologous donation, hemodilution, or intraoperative collection 2. Transfuse O-blood in the absence of typing 3. Follow procedures for verifying patient and blood type 4. Consider Rh testing in childbearing women
Nonhemolytic transfusion reactions	Use leukocyte-filtered blood products
TACO	Limit volume and rate of transfusion in those with extremes of age, cardiac or renal dysfunction, or acute myocardial infarction
TRALI	It may be beneficial to avoid transfusing FFP from multiparous women
Complications of massive transfusion	1. Match transfusion of RBCs to FFP and platelets 2. Warm products before transfusion 3. Check labs frequently 4. Do not transfuse blood products too quickly in high volumes, especially in the elderly, neonates, or patients with impaired cardiac function

References

1. Dossett LA, Riesel JN, Griffin MR, Cotton BA. Prevalence and implications of pre-injury warfarin use: An analysis of the National Trauma Databank. *Arch Surg*. 2011;146(5):565–570.
2. Rotondo MF. Physiology of transfusion therapy. In: Savage EB, Fishman SJ, Miller LD, eds. *Essentials of Basic Science in Surgery*. Philadelphia, PA: JB Lippincott, 1993, pp. 61–67.
3. Hirsh J, Dalen JE, Deykin D. Oral anticoagulants. *Chest*. 1995;108:231S–247S.
4. Hirsh J, Dalen JE, Anderson DR. Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest*. 1998;114(5 suppl):445S.
5. Gulati G, Hevelow M, George M, Behling E, Siegel J. International normalized ratio versus plasma levels of coagulation factors in patients on vitamin K antagonist therapy. *Arch Pathol Lab Med*. 2011;135(4):490–494.
6. Makris M et al. Warfarin anti-coagulation reversal: Management of the asymptomatic and bleeding patient. *J Thromb Thrombolysis*. 2010;29:171–181.
7. Taylor CT et al. Vitamin K to reverse excessive anticoagulation: A review of the literature. *Pharmacotherapy*. 1999;19(12): 1415–1425.
8. Franchini M, Lippi G. Prothrombin complex concentrates: An update. *Blood Transfus*. 2010;8(3):149–154.
9. Yank V et al. Systematic review: Benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med*. 2011;154(8): 529–540
10. Broderick J et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke*. 2007; 38(6):2001–2023.
11. Hirsh J et al. Heparin: Mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest*. 1995;108:258S–275S.
12. Shannon MT, Wilson BA, Shields KM. *Health Professional's Drug Guide 2011–2012*. Upper Saddle River, NJ: Pearson Health Science, 2012, pp. 1289–1290.
13. Arepally GMA, Ortel TL. Heparin-induced thrombocytopenia. *N Engl J Med*. 2006;355:809–817.
14. Weitz JI. Low molecular weight heparins. *N Engl J Med*. 1997;337:688–698.
15. Crowther M, Warkentin T. Bleeding risk and the management of bleeding complications in patients undergoing anti-coagulant therapy: Focus on new anticoagulant agents. *Blood*. 2008:111:4871–4879.

    Addresses management strategies for bleeding associated with established as well as newer anticoagulants.
16. Bijsterveld NR et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation*. 2002; 106:2550–2554.
17. Spiess BD. Treating heparin resistance with antithrombin or fresh frozen plasma. *Ann Thorac Surg*. 2008; 85(6): 2153–2160.
18. Fenton JW, Ofosu FA, Brezniak DV. Thrombin and antithrombotics. *Semin Thromb Hemost*. 1998;24:87.
19. Baumann L et al. New anti-coagulants: A concise review. *J Trauma*. 2012;73(4):983–992.

    A good summary of the newer oral anticoagulants and attached clinical trials.
20. Bauer KA et al. Fondaparinux, a synthetic pentasaccharide: The first in a new class of antithrombotic agents—The selective factor Xa inhibitors. *Cardiovasc Drug Rev*. 2002;20:37–52.

21. Mega JL, Braunwald E et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): A randomized double-blind, phase II trial. *Lancet*. 2009;374(9683):29–38.
22. Eerenberg ES et al. Reversal of rivaroxaban and dabigatran by PCC: A randomized, placebo-controlled crossover study in healthy subjects. *Circulation*. 2011; 12(4): 1573–1579.
23. Van Ryn et al. Dabigatran etexilate—A novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103:1116–1127.
24. Hirsh J et al. Aspirin and other platelet-active drugs. *Chest*. 1995;108:247S–257S.
25. Yusuf S et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345: 494–502.
26. Shannon MT, Wilson BA, Shields KM. Health professional's drug guide 2011–2012. *Pearson Health Sci*. 2012; 480–481.
27. Topol EJ et al. Randomized, double-blind, placebo-controlled, international trial of the oral IIb/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. *Circulation*. 2003;108:399–406.
28. Leonard YL et al. The effects of platelet inhibitors on blood use in cardiac surgery. *Perfusion*. 2002;17:33–37.
29. Ingerslev J, Vanek T, Culic S. Use of recombinant factor VIIa for emergency reversal of anticoagulation. *J Postgrad Med*. 2007;53(1):17–22.
30. O'Shaughnessy DF et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol*. 2004;126(1):11–28.
31. American Association of Blood Banks. *Standards for Blood Banks and Transfusion Services*, 15th edn. Bethesda, MD: American Association of Blood Banks, 1993, p. 23.
32. Greenwalt TJ. Pathogenesis and management of hemolytic transfusion reactions. *Semin Hematol*. 1981; 18(2):84–94.
33. Paller MS, Hoidal JR, Ferris TF. Oxygen free radicals in ischemic acute renal failure in the rat. *J Clin Invest*. 1984; 74:1156–1164.
34. Edelman B, Heyman MR. Blood component therapy for trauma patients. In: Stene JK, Grande CM, eds. *Trauma Anesthesia*. Baltimore, MD: Williams & Wilkins, 1991, pp. 133–176.
35. Phillips G, Rotondo M, Schwab CW. Transfusion therapy. In: Maull KI, Rodrigez A, Wiles CE III, eds. *Complications in Trauma and Critical Care*. Philadelphia, PA: WB Saunders, 1996, pp. 73–79.
36. Wilson RF, ed. *Handbook of Trauma: Pitfalls and Pearls*. Vol. 4. Philadelphia, PA: JB Lippincott, Williams & Wilkins, 1999, pp. 32–33.
37. Moore SB, Taswell HF, Pineda AA, Sonnenberg CL. Delayed hemolytic transfusion reaction: Evidence of the need for an improved pre-transfusion compatibility test. *Am J Clin Pathol*. 1980;74:94–97.
38. Griffey RT, Chen BC, Krehbiel NW. Performance in appropriate Rh testing and treatment with Rh immunoglobulin in the emergency department. *Ann Emerg Med*. 2012;59:285–293.

This retrospective study of Rh testing in pregnant patients showed a significant lack of appropriate testing and makes recommendations for performance improvement.

39. Ness PM. Transfusion medicine: An overview and update. *Clin Chem*. 2000;46:1270–1276.
40. Fung K, Eason E. Prevention of Rh alloimmunization. *J Obstet Gynaecol Can*. 2003;25(9):765–773.
41. Barnes A. Transfusion of universal donor and uncrossmatched blood. *Bibl Haematol*. 1980;(46):132–142.
42. Barton JC. Nonhemolytic, noninfectious transfusion reactions. *Semin Hematol*. 1981;18(2):95–121.
43. Dennis RC et al. Transfusion therapy. In: Civetta JM, Taylor RW, Kirby R, eds. *Critical Care*. Philadelphia, PA: Lippincott Williams & Wilkins, 1997, pp. 653–654.
44. Brubaker DB. Human posttransfusion graft-versus-host disease. *Vox Sang*. 1983;45(6):401–420.
45. Brubaker DB. Immunopathogenic mechanism of post-transfusion graft-vs-host disease. *Proc Soc Exp Biol Med*. 1993;202(2):122–147.
46. Hong M, Gatti RA, Good RA. Hazards and potential benefits of blood transfusion in immunologic deficiency. *Lancet*. 1968;2:388–389.
47. Nauck MS, Gierens H, Nauck MA, Marz W, Wieland H. Rapid genotyping of human platelet antigen 1 (HPA-1) with fluorophore-labelled hybridization probes on the LightCycler. *Br J Haematol*. 1999;105(3):803–810.
48. Alam A, Lin Y, Lima A, Hansen M, Callum JL. The prevention of transfusion-associated circulatory overload. *Transfus Med Rev*. 2013;27(2):105–112.
49. Schmidt AE, Adamski J. Pathology consultation on transfusion-related acute lung injury (TRALI). *Am J Clin Pathol*. 2012;138(4):498–503.
50. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First of two parts—blood transfusion. *N Eng J Med*. 1999;340(6):438–447.
51. Wu HS, Little AG. Perioperative blood transfusion and cancer recurrence. *J Clin Oncol*. 1988;6(8):1348–1354.
52. Tartter PI. Blood transfusion and infectious complications following colorectal cancer surgery. *Br J Surg*. 1988;75(8):789–792.
53. Nichols RL et al. Risk of infection after penetrating abdominal trauma. *N Eng J Med*. 1984;311 (17): 1065–1070.
54. Klein HG. Allogeneic transfusion risks in the surgical patient. *Am J Surg*. 1995;170(suppl 6A):21S–26S.
55. Schreider GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infection. The Retrovirus Epidemiology Donor Study. *N Engl J Med*. 1996;334(26):1685–1690.
56. Goldman M, Blajchman MA. Blood product-associated bacterial sepsis. *Transfus Med Rev*. 1991;5(1):73–83.
57. Godier A, Samama CM, Susen S. Plasma/platelets/red blood cell ratio in the management of the bleeding traumatized patient: Does it matter? *Curr Opin Anaesthesiol*. 2012;25(2):242–247.
58. Holcomb JB, Zarzabal LA, Michalek JE. Increased platelet: RBC ratios are associated with improved survival after massive transfusion. *J Trauma*. 2011;71(2 Suppl 3): S318–S328.

This large, multicenter retrospective study of transfusion in trauma patients showed that platelet:RBC ratios of 1:1 were associated with improved early and late survival, decreased hemorrhagic death, and a concomitant increase in multiple organ failure-related mortality.

59. Jameson LC, Popic PM, Harms BA. Hypercalcemic death during use of high capacity fluid warmer for massive transfusion. *Anesthesiology*. 1990;73(5):1050–1052.
60. Thomas MJ, Gillon J, Desmond MJ. Consensus conference on autologous transfusion. Preoperative autologous donation. *Transfusion*. 1996;36(7):633–639.

10

Complications of Antibiotic Therapy

Mohamed Fahim, Chad M. Thorson, and Nicholas Namias

CONTENTS

Antibiotics are frequently used as an adjunct to the surgical therapy of infections. All antibiotics are potentially harmful, and various benefit-to-risk factors must be considered whenever they are used.[1] Antimicrobial chemotherapy used in association with surgery may be complicated by failure of therapy or unwanted side effects. Most antibiotic-related adverse reactions are predictable and are often dose-dependent. Unpredictable reactions occur independently of the dose and route of administration and are due to drug intolerance, allergy, and other idiosyncratic responses.[2] Other reactions occur rarely and are unique to the compound administered; one such example is toxic epidermal necrolysis (Stevens–Johnson syndrome) induced by sulfonamides.[1]

The problems encountered in the use of antimicrobial chemotherapeutic agents can be conveniently divided into general complications (e.g., those associated with the route of administration, hypersensitivity reactions, failure of therapy, induction of resistance, antagonism, and effects on immune response) and specific complications related to each individual antimicrobial agent.

10.1 General Complications

10.1.1 Complications Associated with the Route of Administration

Oral administration of an antimicrobial agent may cause complications involving the gastrointestinal tract, such as nausea, vomiting, diarrhea, and gastritis. Parenteral administration of antimicrobial agents can result in reactions at the injection site, as well as local neurovascular reactions, including warmth, vasospasm, pallor, mottling, gangrene, numbness and cyanosis of the extremities, and neurovascular damage. Intravenous administration of antibiotics may cause thrombophlebitis. Intramuscular injection of antibiotics may result in direct mechanical trauma to major nerves.[3]

10.1.2 Hypersensitivity Reactions

10.1.2.1 Anaphylaxis

Anaphylaxis is the most severe reaction to antibiotics. It is most frequently encountered after parenteral injection of penicillin or one of its synthetic analogs. Clinically, the reaction may develop within minutes to hours of drug administration. Patients may experience primary vascular collapse with hypotension, as well as bronchospasm and laryngeal edema. Dermal manifestations include eruption and hives. Angioedema may also occur. The drug of choice for anaphylaxis is epinephrine, 1:1000, 0.3 mL intramuscular. Depending on the response, intravenous administration of epinephrine may be required. Progression of laryngeal edema may require immediate tracheostomy or cricothyroidotomy.[4]

10.1.2.2 Cutaneous Eruptions

Cutaneous eruptions, the most common manifestation of hypersensitivity to antibiotics, are due to delayed hypersensitivity mediated by the cellular immune system. When a dermal reaction appears, the best course of action is to discontinue the administration of the drug.

Penicillins and cephalosporins both possess the beta-lactam ring, but cross-reactivity probably occurs in no more than 1% of patients allergic to one of these types of antibiotics.[5]

10.1.2.3 Drug Fever

Drug fever is presumably a hypersensitivity reaction and may be the most difficult complication to diagnose because of its similarity to fever due to the infection. Drug fever may be associated with the use of any antimicrobial agent and may be accompanied by eosinophilia or cutaneous eruption. Drug fever can occur at any time, but usually has an onset of 7–10 days after the initiation of the drug, resolves with discontinuation of the drug, and recurs with reintroduction of the drug.[6]

10.1.3 Emergence of Resistance to Antimicrobial Agents

One of the most difficult problems in dealing with infectious diseases is microbial resistance to antimicrobial agents. Qualitative antibiotic susceptibility profile and the quantitative minimum inhibitory concentration (MIC) of clinically indicated antibiotics can guide the selection of the appropriate antibiotic. The MIC is the concentration of the antibiotic that inhibits the growth of a standardized concentration of bacteria. Armed with a qualitative result of "sensitive," the clinician can further refine the choice of antibiotic with the quantitative MIC and the knowledge from the package insert of the expected serum concentration. All other things being equal, the antibiotic that will achieve the highest ratio of serum concentration to MIC will be the least likely to fail and the least likely to become resistant. Acquired resistance arises from the microbe's acquisition of genetic material or its mutation. This occurs when the organism is exposed to the antibiotic. Excessive or unnecessary use of antibiotics increases the organism's exposure to the antibiotic and the likelihood of the development of resistance.[7]

Worldwide, many strains of *Staphylococcus aureus* are already resistant to all antibiotics except vancomycin. Methicillin-resistant *Staphylococcus aureus* (MRSA) was first detected in England[8] and constituted 46.7% of all *S. aureus* isolates collected in 1998 by the National Nosocomial Infections Surveillance (NNIS) Program of the Centers for Disease Control and Prevention.[9] The 2004 report from the NNIS showed methicillin resistance in *S. aureus* was up to 59.5% in nosocomial infections.[10]

Beta-lactamase production is also an important mechanism of resistance in Gram-negative organisms. There are now organisms whose beta-lactamase (ESBL) will hydrolyze the beta-lactam ring of multiple beta-lactam drugs.[11,12] The ESBLs have become predominant in much of Asia and the Middle East[13] and are becoming more common in North America.[14] Vancomycin-intermediate and vancomycin-resistant strains of *S. aureus* have been isolated, although they have not yet become widespread.[15] Resistance to vancomycin has also become common in the enterococci,[9,16] and there have been case reports of patients infected with vancomycin-dependent enterococci.[17]

10.1.4 *Clostridium difficile*–Associated Diarrhea/Pseudomembranous Colitis

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of

Clostridium spp. This was recognized early on with clindamycin, although currently it is recognized that all antibiotics pose a risk for the development of *Clostridium difficile*–associated diarrhea (CDAD). *C. difficile* produces toxins that can be assayed in the stool to make the diagnosis. CDAD and pseudomembranous colitis have evolved over the years to a virulent disease that can be lethal. Fulminant colitis is treated with colectomy.

Pseudomembranous colitis is diagnosed by proctoscopy, which reveals raised yellow-whitish plaques on mucosa that is often erythematous or edematous and sometimes friable. The most important treatment for pseudomembranous colitis is prompt withdrawal of the causative antibiotic, physiologic support, and treatment of the *C. difficile* superinfection. Among patients with prolonged diarrhea after discontinuation of antimicrobial therapy, several studies conducted[18,19] indicate that vancomycin or metronidazole given by mouth is effective in eliminating C. *difficile* from the colon and subsequently relieving diarrhea. Treatment failures can be treated with vancomycin given orally at a dosage of 500 mg every 6 h for 7–14 days. Other novel treatments are becoming available, including fidaxomicin, nitazoxanide, rifaximin, and monoclonal antibodies. Less exotic but successful in some cases is fecal transplant.[20,21]

Prevention is by avoidance of antibiotics. Prevention of transmission is by handwashing with soap and water. Alcohol hand gels do not kill the spores of *C. difficile*.[22]

10.1.5 Antagonism

Antibiotic antagonism implies that a combination of antibiotics yields a treatment effect less than the sum of the treatment effect of the two antibiotics. It is often referred to, but there is little support that it exists in a clinically meaningful way. One plausible, but not clinically proven, mechanism of significance in surgery would be the combination of two beta-lactam agents when one is an inducer of a chromosomal beta lactamase.[23]

10.2 Specific Antibiotics and Their Associated Complications

Detailed listings of all reactions to antibiotics can be found in their package inserts or on the respective drug's website. We present a broader overview of relevant clinical concerns.

10.2.1 Beta-Lactam Antibiotics

The beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, and the monobactam, aztreonam) can all cause the general adverse events listed earlier (anaphylaxis, cutaneous eruptions, drug fever, and the emergence of resistance). Patients tend to report that they have a "penicillin allergy," although this is frequently a rash not associated with a serious allergic reaction such as anaphylaxis. Adverse reactions to penicillins can include anaphylaxis, urticaria, hemolytic anemia, and serum sickness, all of which are rare. IgE-mediated rash, as well as nonallergic rash, is relatively common. GI complications include diarrhea in 2%–5% of patients, and enterocolitis in <1% of patients. Penicillins can rarely cause seizures. Any penicillin drug can cause interstitial nephritis (<1%).[24]

Beta-lactamase inhibitors used in combination drugs have been remarkably safe. Clavulanate has been known to cause dose-dependent diarrhea, but neither sulbactam nor tazobactam has caused any significant adverse effects.[24]

The surgeon is commonly faced with the dilemma of the "penicillin-allergic" patient who may need a cephalosporin for surgical prophylaxis. The greatest risk of cross-reactivity in a penicillin-allergic patient is with the administration of a first generation cephalosporin. The risk is reduced with a second-or-third generation cephalosporin (<1.5%). Options for the surgeon include the use of a non-beta-lactam antibiotic, use of a cephalosporin antibiotic, or performance of skin testing to aid the decision.[25]

Myriad adverse events have been reported for a remarkably safe class of drugs, the cephalosporins. Most of them are reported rarely or in <1%. The clinically relevant adverse events that occur with any meaningful frequency are diarrhea (1%–19%), nausea/vomiting (1%–6%), and transient transaminase elevation (1%–7%). Cefotetan can cause a hypoprothrombinemia in <1% of patients that is reversible with vitamin K. Ceftriaxone in high doses can lead to biliary sludge from crystallization in the biliary tree. Reports of this problem are in children receiving high doses of ceftriaxone.[26]

The carbapenem drugs share an adverse event profile with the other beta-lactams. All carbapenems have been associated with seizures.

The monobactam, aztreonam, is remarkably safe. Cross-reactivity to other beta-lactams does not occur.[27]

10.2.2 Aminoglycosides (Amikacin, Gentamicin, Tobramycin, Netilmicin, and Streptomycin)

All aminoglycosides have the potential to induce auditory, vestibular, and renal toxicity, and neuromuscular blockade. These events are most common among patients with a history of renal impairment, those receiving other ototoxic or nephrotoxic drugs, and those treated for periods longer than recommended or given doses higher than recommended.[28]

Damage to the vestibular system occurs more frequently with gentamicin administration, and cochlear damage is more common with amikacin therapy.[29,30] Prolonged neuromuscular blockade and respiratory paralysis have been reported with the use of aminoglycosides, especially in patients receiving anesthetics and neuromuscular blocking agents.[28,31] Other effects of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. Aminoglycoside-induced ototoxicity is usually irreversible.[28]

The most common clinical manifestation of gentamicin nephrotoxicity is nonoliguric renal failure with proteinuria, and increased concentrations of serum creatinine and blood urea. Renal function changes are usually reversible when administration of the drug is discontinued.[3] Although less common, an acute oliguric renal failure and a subsequent diuretic phase may occur.[32] Avoiding this and other forms of toxicity requires careful monitoring of serum concentrations of aminoglycosides, when feasible, to ensure that drug concentrations are adequate, but are not at potentially toxic levels. Extended interval dosing reduces the incidence of nephrotoxicity, but not ototoxicity.[33]

10.2.3 Tetracyclines (Doxycycline, Minocycline, and Tigecycline)

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow, gray, or brown).[28] Nausea, heartburn, epigastric pain, vomiting, and diarrhea are more commonly associated with tetracyclines than with most other orally administered antibiotics.[3] The newer agent, tigecycline, has been useful against some multidrug-resistant acinetobacter and MRSA. However, a systematic review reveals significantly worse outcomes with tigecycline as compared to other agents, and recommends it be used as a last resort for resistant infections.[34]

10.2.4 Fluoroquinolones

Quinolones have been reported to have myriad side effects, some so bad as to lead to withdrawal from the market. To varying degrees, the quinolones that remain on the market can cause alterations in blood glucose regulation, QTc interval prolongation, seizures, spontaneous tendon rupture, and phototoxicity. Like all antibiotics, they can also cause CDAD.[35]

10.2.5 Antifolate Agents (Trimethoprim–Sulfamethoxazole)

The most serious type of adverse reaction to sulfonamides (trimethoprim and sulfamethoxazole) is the Stevens–Johnson syndrome. This syndrome consists of erythema multiforme and ulceration of the mucous membranes of the mouth, eyes, and urethra, and it can sometimes be fatal.[36] Acute agranulocytosis can occur, although it is more commonly associated with the use of older sulfonamides.[3]

10.2.6 Miscellaneous

10.2.6.1 Vancomycin

During or soon after rapid infusion of vancomycin, patients sometimes experience anaphylactoid reactions such as hypotension, wheezing, dyspnea, urticaria, or pruritus.[28] Rapid infusion may also cause flushing of the upper body ("Red Man syndrome"),[37] or pain and spasms in the muscles of the chest and back. Although such events usually resolve within 20 min, they are infrequent if vancomycin is infused slowly over a 60 min period.[28] Ototoxicity has been reported in association with vancomycin. One study found that most patients who experienced ototoxicity had kidney dysfunction or were receiving an ototoxic drug such as aminoglycoside.[38] Nephrotoxicity has occurred among patients who were given vancomycin and aminoglycosides concomitantly, or who had preexisting kidney dysfunction.[39]

10.2.6.2 Clindamycin

Clindamycin is an old drug that has remained important in the surgical armamentarium because of its coverage of gram-positive cocci (useful for surgical prophylaxis in beta-lactam-allergic patients) and its coverage of oral anaerobes. It is associated with *C. difficile* colitis (discussed earlier), but all antibiotics are now known to be associated with *C. difficile* colitis. There is presently a resurgence in its use, because increasing proportions of acquired MRSA are susceptible to clindamycin.[40] Caution should be used, however, in the treatment of surgical site infections (SSI) with clindamycin. MRSA in SSI has been shown to be resistant to clindamycin in 91% of cases in one series.[41]

The most common inciting agent for emergency department visits for adverse antibiotic effects is clindamycin. Effects include rashes and fever. The most common side effect is diarrhea (non-*C. difficile*-related), in up to 20% of cases. CDAD is still a well-known complication of clindamycin.[42]

10.2.6.3 Linezolid

Myelosuppression, usually thrombocytopenia, but including red cell aplasia and pancytopenia have all occurred with linezolid use. Hematologic monitoring for patients on linezolid is recommended. Lactic acidosis can occur, and is thought to be due to interference

with mitochondrial protein synthesis. Neuropathies have also been reported, including optic nerve, peripheral nerves, and cranial nerves.[43]

10.2.6.4 Metronidazole

Metronidazole is generally well tolerated. The most common side effects are in the gastrointestinal system, most commonly nausea and epigastric distress. A metallic taste in the mouth is commonly reported as well. Neurologic side effects can occur, and may include neuropathy, headache, syncope, and are uncommon. There are significant interactions with food and other drugs, including disulfiram-like reactions, psychosis, and sudden death when combined with alcohol or disulfiram, increased drug levels of cyclosporine and tacrolimus, and increased warfarin levels.[44]

10.2.7 Antifungal Agents

10.2.7.1 Polyenes (Amphotericin B)

Before the advent of the lipid formulations of amphotericin B, the deoxycholate form of the drug was commonly referred to as amphoterrible B, because of the acute systemic reaction it caused, including fever and rigors, as well as dose-dependent renal failure. There is an expected reversible azotemia, with creatinine rising up to 2–3 g/dL. Treatment should continue despite this azotemia. The most important side effect of amphotericin B is dose-related nephrotoxicity, with the destruction of the renal tubules. This toxicity may be attenuated by the use of liposomal or lipid emulsion preparations. These effects are very much attenuated with the lipid preparations of the drug.[45]Although rare, anaphylaxis has been associated with both amphotericin–deoxycholate and liposomal amphotericin B.[46]

10.2.7.2 Azoles

Fluconazole and other azole agents are well tolerated, but can cause hepatic reactions, usually mild transient elevations in transaminases, in up to 10% of patients. Uniquely, voriconazole can cause a transient visual disturbance, which should not cause cessation of therapy.[45]

10.2.7.3 Echinocandins

The echinocandins, caspofungin, micafungin, and anidulafungin, are remarkably safe. They are neither hepatotoxic nor nephrotoxic. They may occasionally cause some histamine-related side effects.[45]

10.2.7.4 Colistin

Colistimethate has emerged as a drug of last resort for *Acinetobacter baumannii* infections for multidrug-resistant isolates. It has been used both intravenously and inhalationally. Intravenous administration is associated with reversible, dose-dependent nephrotoxicity. Neurologic side effects ranging from not uncommon paresthesias to rare neuromuscular blockade have been reported. Inhalational therapy is generally well tolerated.[47,48]

10.3 Surgical Site Infections

SSI are a complication of surgery, not of antibiotics. However, the role of antibiotics in the prevention and treatment of SSI merits mention in this chapter. Antibiotics of the appropriate spectrum administered in the hour prior to surgery can reduce the incidence of SSI. SSI can involve the superficial incision (no fascia or muscle), the deep incision (to include fascia or muscle), or the organ space.[49] Risk factors for SSI include the contamination category of the wound (clean contaminated or worse is a risk factor), the American Society of Anesthesiologists score of the patient, and the length of time it takes to complete the surgery, as well as other factors that refine the earlier-mentioned three major predictors.[50] Treatment of SSI follows basic surgical principles. Superficial SSI without cellulitis can be treated by simply opening the wound and allowing drainage; antibiotics do not have a role. The presence of cellulitis is an indication for antibiotic treatment. Deep SSI may require debridement of involved fascia or muscle, as well as antibiotics. Organ space infections are typically treated with drainage, most commonly percutaneous, and antibiotics. Nonantibiotic approaches to the prevention of SSI include maintenance of intraoperative euthermia, administration of a high fraction of inspired oxygen intraoperatively, adequate nutritional support preoperatively, appropriate antiseptic skin preparation, appropriate timing of preoperative shaving, and adequate glycemic control.[51] These are all surrounded in controversy as to their specifics. The practitioner will need to use judgment in this regard until such a time as funding becomes available to study them adequately.

10.4 Conclusion

In conclusion, despite the medical advances that have been made due to the development of antibiotics, significant complications can occur from their use. Practitioners must remain abreast of the literature regarding the potential complications of the prescribed therapy.

Antibiotic-Induced Side Effects

General Side Effects

Side Effect	Highest Incidence
Nausea, vomiting	Macrolides[4]
Diarrhea	Macrolides, ampicillin, amoxicillin-clavulanic acid[4]
C. difficile diarrhea	Beta-lactams[4,24]—May occur weeks after exposure
Anaphylaxis	Beta-lactams (0.01%)[4,24,52]
Cutaneous eruptions/ drug rash	Beta-lactams (4%–8%), Trimethoprim sulfamethoxazole (TMP–SMX)[4,24] —Most common manifestation of antibiotic hypersensitivity[4,5]
Drug fever	Beta-lactams[4,24]—10%–15% of unexplained fevers in hospitalized patients[4]
Seizures	Imipenem, ciprofloxacin[4]
Photosensitivity	Tetracycline[3]
Tendonitis, tendon rupture	Ciprofloxacin (<1%)
Hepatitis	Isoniazid[4]
Interstitial nephritis	Oxacillin[4]
Ototoxicity	Aminoglycosides (10%–22%)[53,54]
Nephrotoxicity	Aminoglycosides (7%–25%),[53] amphotericin (60%–80%)[55]
Myelosuppression	Linezolid[4]
Hepatotoxicity	Rifampin[4]
Erythema multiforme or Stevens–Johnson syndrome	TMP–SMX[4]
Prolonged QTc interval	Erythromycin, quinolones[4]—Occurs rapidly after administration, subsides with withdrawal
Hyperbilirubinemia	Ceftriaxone[4]—May cause kernicterus during pregnancy
Flushing	Vancomycin[4]
Metallic taste	Clarithromycin, metronidazole[4]

Common Side Effects by Drug Classes

Drug Class	Side Effects
Beta-lactams[24]	Diarrhea (2%–5%); enterocolitis (<1%); interstitial nephritis (<1%)
Aminoglycosides	Ototoxicity (10%–22%)[53,54]; nephrotoxicity (7%–25%)[53]; neurotoxicity (very rare)
Tetracyclines	Permanent tooth discoloration during development[28] GI symptoms (nausea/vomiting, heartburn, diarrhea)[3]
Fluoroquinolones[35,56]	QTc interval prolongation; seizures; phototoxicity
TMP–SMX[36]	Stevens–Johnson syndrome
Vancomycin	Anaphylactoid reaction (hypotension, wheezing, dyspnea, urticarial) with rapid administration (10%)[57]; nephrotoxicity[39]
Clindamycin[42]	Diarrhea (20%)
Linezolid[43]	Myelosuppression; neuropathies (optic, peripheral, cranial)
Metronidazole	GI symptoms (nausea, heartburn, metallic taste)[44] Disulfiram-like reaction with alcohol[58]
Amphotericin[46]	Nephrotoxicity (attenuated with liposomal preparation)
Azoles[45]	Elevated transaminases
Colistin[47,48]	Nephrotoxicity Neurotoxicity (paresthesia, neuromuscular blockade)

Avoidance of Antibiotic-Induced Side Effects

Side Effect	Prevention/Treatment of Side Effect
Nausea, vomiting	Take with meals, avoid alcoholic beverages
Diarrhea	Concomitant probiotic administration[59]
C. difficile diarrhea	Judicious use of antibiotics when clinically indicated
Anaphylaxis	Intramuscular epinephrine used for treatment
Seizures	Adjust imipenem dose for renal function
Photosensitivity	Avoid prolonged outdoor exposure while taking
Ototoxicity	Concomitant aspirin administration[60]
Nephrotoxicity	Adequate fluid hydration, avoid additional nephrotoxic drugs
Myelosuppression	Weekly hematologic monitoring and prompt discontinuation of linezolid at first sign of myelosuppression
Hepatotoxicity	Avoid additional hepatotoxic medications/ alcohol
Erythema multiforme or Stevens–Johnson syndrome	Drug avoidance
Prolonged QTc interval	Prompt discontinuation of drug
Flushing	Slow intravenous infusion

References

1. Gleckman RA, Borrego F. Adverse reactions to antibiotics. Clues for recognizing, understanding, and avoiding them. *Postgraduate Medicine* 1997;101:97–98, 101–104, 7–8.
2. Rieder MJ. Mechanisms of unpredictable adverse drug reactions. *Drug Safety: An International Journal of Medical Toxicology and Drug Experience* 1994;11:196–212.
3. Kucers A. *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, and Antiviral Drugs*, 5th edn. Oxford, U.K.: Butterworth-Heinemann, 1997.
4. Cunha BA. Antibiotic side effects. *The Medical Clinics of North America* 2001;85:149–185.
5. Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: A literature review. *The Journal of Emergency Medicine* 2012;42:612–620.
6. Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy* 2010;30:57–69.

7. Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiology and Molecular Biology Reviews* 2010;74:417–433.
8. Jevons MP, Coe AW, Parker MT. Methicillin resistance in staphylococci. *Lancet* 1963;1:904–907.
9. CDC. *National Nosocomial Infections Surveillance Antimicrobial Resistance Report*. Atlanta: Centers for Disease Control and Prevention, 1998.
10. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *American Journal of Infection Control* 2004;32:470–85.
11. Jacoby GA, Munoz-Price LS. The new beta-lactamases. *The New England Journal of Medicine* 2005;352:380–91.
    This is a well-illustrated and comprehensive review of one of the most important mechanisms of resistance.
12. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. *The New England Journal of Medicine* 2010;362:1804–1813.
13. El Kholy A, Baseem H, Hall GS, Procop GW, Longworth DL. Antimicrobial resistance in Cairo, Egypt 1999–2000: A survey of five hospitals. *The Journal of Antimicrobial Chemotherapy* 2003;51:625–630.
14. Nicasio AM, Kuti JL, Nicolau DP. The current state of multidrug-resistant gram-negative bacilli in North America. *Pharmacotherapy* 2008;28:235–249.
15. van Hal SJ, Paterson DL. Systematic review and meta-analysis of the significance of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates. *Antimicrobial Agents and Chemotherapy* 2011;55:405–410.
16. Calfee DP. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, and other Gram-positives in healthcare. *Current Opinion in Infectious Diseases* 2012;25:385–394.
17. Yowler CJ, Blinkhorn RJ, Fratianne RB. Vancomycin-dependent enterococcal strains: case report and review. *The Journal of Trauma* 2000;48:783–785.
18. Wenisch JM, Schmid D, Kuo HW et al. Prospective observational study comparing three different treatment regimes in patients with *Clostridium difficile* infection. *Antimicrobial Agents and Chemotherapy* 2012; 56:1974–1978.
19. Nelson RL, Kelsey P, Leeman H et al. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database of Systematic Reviews* 2011:CD004610. *This report provides an evidence base for treating one of the most important complications of antibiotic therapy*.
20. McCollum DL, Rodriguez JM. Detection, treatment, and prevention of *Clostridium difficile* infection. *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association* 2012;10:581–592.
21. Cocanour CS. Best strategies in recurrent or persistent *Clostridium difficile* infection. *Surgical Infections* 2011; 12:235–239.
22. Jabbar U, Leischner J, Kasper D et al. Effectiveness of alcohol-based hand rubs for removal of *Clostridium difficile* spores from hands. *Infection Control and Hospital Epidemiology: The Official Journal of the Society of Hospital Epidemiologists of America* 2010;31:565–570.
23. Acar JF. Antibiotic synergy and antagonism. *The Medical Clinics of North America* 2000;84:1391–1406.
24. Chambers H. Penicillin. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Churchill Livingtone Elsevier, 2010, pp. 309–22.
25. Weiss M, Jr NA. Beta lactam allergy. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 347–354.
26. Andres D, Craig W. Cephalosporins. In: Mandell G, Bennett J, Dolin. R, eds. *Principles and Practice of Infectious Diseases*. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 323–339.
27. Chambers H. Carbapenems and monobactams. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 341–346.
28. Physician Desk Reference. PDR Network, LLC, 2012. (Accessed December 4, 2012, at http://pdr.net.)
29. Appel GB, Neu HC. Gentamicin in 1978. *Annals of Internal Medicine* 1978;89:528–538.
30. Meyer RD. Amikacin. *Annals of Internal Medicine* 1981; 95:328–332.
31. Hall DR, McGibbon DH, Evans CC, Meadows GA. Gentamicin, tubocurarine, lignocaine and neuromuscular blockade. A case report. *British Journal of Anaesthesia* 1972;44:1329–1332.
32. Kahn T, Stein RM. Gentamicin and renal failure. *Lancet* 1972;1:498.
33. Pagkalis S, Mantadakis E, Mavros MN, Ammari C, Falagas ME. Pharmacological considerations for the proper clinical use of aminoglycosides. *Drugs* 2011; 71:2277–2294.
34. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: A systematic review and meta-analysis. *The Journal of Antimicrobial Chemotherapy* 2011; 66:1963–1971.
35. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *The Annals of Pharmacotherapy* 2007; 41:1859–1866. *This is an important read before prescribing fluoroquinolones*.
36. Downey A, Jackson C, Harun N, Cooper A. Toxic epidermal necrolysis: Review of pathogenesis and management. *Journal of the American Academy of Dermatology* 2012;66:995–1003.
    This is a good review of one of the most devastating complications of antibiotics.
37. Polk RE, Healy DP, Schwartz LB, Rock DT, Garson ML, Roller K. Vancomycin and the red-man syndrome: Pharmacodynamics of histamine release. *The Journal of Infectious Diseases* 1988;157:502–507.
38. Brummett RE, Fox KE, Jacobs F, Kempton JB, Stokes Z, Richmond AB. Augmented gentamicin ototoxicity induced by vancomycin in guinea pigs. *Archives of Otolaryngology—Head & Neck Surgery* 1990;116:61–64.
39. Schilling A, Neuner E, Rehm SJ. Vancomycin: A 50-something-year-old antibiotic we still don't understand. *Cleveland Clinic Journal of Medicine* 2011;78:465–471.

40. Hermos CR, Sandora TJ, Williams LE, Mosammaparast N, McAdam AJ. Changing epidemiology of methicillin-resistant *Staphylococcus aureus* colonization in paediatric intensive-care units. *Epidemiology and Infection* 2013;141:1983–1992.
41. Takesue Y, Watanabe A, Hanaki H et al. Nationwide surveillance of antimicrobial susceptibility patterns of pathogens isolated from surgical site infections (SSI) in Japan. *Journal of Infection and Chemotherapy: Official Journal of the Japan Society of Chemotherapy* 2012;18:816-826.
42. Sivapalasingam S, Steigibigel N. Macrolides, clindamycin, and ketolides. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Churchill Livingstone Elesevier, 2010, pp. 427–448.
43. Ager S, Gould K. Clinical update on linezolid in the treatment of Gram-positive bacterial infections. *Infection and Drug Resistance* 2012;5:87–102.
44. Salvatore M, Meyers B. Metronidazole. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 419–426.
45. Rex J, Stevens D. Systemic Antifungal agents. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 549–563.
46. Bates CM, Carey PB, Hind CR. Anaphylaxis due to liposomal amphotericin (AmBisome). *Genitourinary Medicine* 1995;71:414.
47. Kaye K, Kaye D. Polymixins (Polymixin B and Colistin). In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 469–470.
48. Yahav D, Farbman L, Leibovici L, Paul M. Colistin: New lessons on an old antibiotic. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* 2012; 18:18–29.
49. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: A modification of CDC definitions of surgical wound infections. *Infection Control and Hospital Epidemiology: The Official Journal of the Society of Hospital Epidemiologists of America* 1992;13:606–608.
50. Mu Y, Edwards JR, Horan TC, Berrios-Torres SI, Fridkin SK. Improving risk-adjusted measures of surgical site infection for the national healthcare safety network. *Infection Control and Hospital Epidemiology: The Official Journal of the Society of Hospital Epidemiologists of America* 2011;32:970–986.
51. Leaper D, Burman-Roy S, Palanca A et al. Prevention and treatment of surgical site infection: Summary of NICE guidance. *British Medical Journal* 2008;337:a1924.

    This is a concise and practical summary of the steps clinicians can take immediately to practice the state of the art in prevention of surgical site infection.
52. Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. *Bulletin of the World Health Organization* 1968;38:159–188.
53. Granowitz EV, Brown RB. Antibiotic adverse reactions and drug interactions. *Critical Care Clinics* 2008;24:421–442, xi.
54. Smith CR, Lipsky JJ, Laskin OL et al. Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. *The New England Journal of Medicine* 1980;302:1106–1109.
55. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. *Reviews of Infectious Diseases* 1990;12:308–329.
56. Hooper D, Strahilevitz J. Quinolones. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Churchill Livingstone Elsevier, 2010, pp. 487–510.
57. Newfield P, Roizen MF. Hazards of rapid administration of vancomycin. *Annals of Internal Medicine* 1979; 91:581.
58. Cina SJ, Russell RA, Conradi SE. Sudden death due to metronidazole/ethanol interaction. *The American Journal of Forensic Medicine and Pathology* 1996;17:343–346.
59. Butler CC, Duncan D, Hood K. Does taking probiotics routinely with antibiotics prevent antibiotic associated diarrhoea? *British Medical Journal* 2012;344:e682.
60. Sha SH, Qiu JH, Schacht J. Aspirin to prevent gentamicin-induced hearing loss. *The New England Journal of Medicine* 2006;354:1856–1857.

11

Complications of Hypovolemic and Septic Shock

Meghann L. Kaiser and Matthew O. Dolich

CONTENTS

11.1 Introduction

Shock may be broadly defined as hypoperfusion of end organs. It is important to differentiate shock from hypotension, since hypoperfusion can exist in the face of normal blood pressure, and low blood pressure does not necessarily imply inadequate blood supply. Simply conceived, the mammalian circulatory system may be thought of as the plumbing to a modern apartment complex. The water supply to an apartment (or number of apartments) may fail for any number of reasons, including leaking pipes, inadequate water pressure, pump failure, insufficient total water supply, misdirection of water, overuse, and clogged pipes, to name a few. Intuitively, each form of shock is best addressed after recognizing the underlying pathophysiology. Hypovolemic shock (often of hemorrhagic etiology in the setting of trauma and surgery) and septic shock together account for most nonneurologic deaths in the classic trimodal distribution of mortality following trauma.[1] The complications associated with these two forms of shock are the focus of this chapter.

Using the apartment complex plumbing model, understanding the initial insult of hemorrhagic shock is relatively straightforward in principle: a broken pipe, causing volume loss. Septic shock, by comparison, may be more complicated. At various stages of sepsis, blood vessels become leaky, blood supply may be shunted away from target organs, oxygen demand may outstrip supply, and pump failure may ensue, with each type of dysfunction contributing to another. On a cellular level, there is evidence to suggest that even the mitochondria—the "faucets" of the individual apartments—malfunction during septic shock. However, the downstream effects of both septic and hemorrhagic shock can be remarkably similar, suggesting a common mediator. Recent evidence suggests that the common mediators may be prokaryotic peptides— released from invading microorganisms in the setting of sepsis, and from native mitochondria in the setting of trauma.[2]

The complications of hemorrhagic and septic shock, organized by specific type of organ dysfunction, are listed in this chapter. A summary of means to treat and avoid each general complication is also provided.

11.2 Individual Organ System Dysfunction

11.2.1 Renal Complications: Acute Kidney Injury and Acute Renal Failure

Acute renal dysfunction can be defined and classified by the RIFLE (Risk, Injury, Failure, Loss, and End-stage

renal disease) criteria. In this system, at-risk patients are determined by a serum creatinine increase of 50% above baseline, or sustained urine output <0.5 mL/kg/h for 6–12 h. By contrast, injury is characterized by a doubling of creatinine, or urine output <0.5 mL/kg/h for 12 h, and failure as a tripling of creatinine, serum creatinine >4 mg/dL, urine output less than 0.3 mL/kg/h for 24 h, or anuria for 12 h. Loss and End-stage renal disease are diagnosed by the absence of renal function ranging from weeks to months. Worsening degrees of dysfunction based on the RIFLE criteria correlate with worse outcomes and mortality. As many as one-third of ICU patients develop acute kidney injury (AKI).[3] The AKI network (AKIN) criteria for AKI is a modification of the RIFLE criteria, in that AKI is defined as a rapid (within 48 h) rise in creatinine ≥0.3 mg/dL, a percentage increase of serum creatinine ≥50%, or a reduction in urine output to <0.5 mL/kg/h for >6 h (similar to "at risk" patients by the original RIFLE criteria).

Under normal physiologic conditions, the kidneys receive about one quarter of cardiac output, a disproportionately large fraction given their relatively small mass. Along with the skin and gastrointestinal tract, the kidneys are particularly sensitive to hypotension, whether hypotension results from hemorrhage or sepsis. Renal dysfunction in these settings has usually been attributed to ischemia—oxygen demand exceeding supply. However, apoptosis occurs in addition to the random necrosis one would expect in a purely ischemic scenario. Oxygen-free radicals and several other mediators in the inflammatory cascade have been isolated (including TNF-α, IL-1β, and thromboxane A2), suggesting reperfusion injury.[4]

Prevention of renal dysfunction, as one would expect, centers on resuscitation with early achievement of hemodynamic goals. Typically, this process entails liberal administration of intravenous fluids. Isotonic crystalloids are a practical and cost-effective choice; colloids offer no apparent benefit over crystalloids, and hydroxyethyl-starch solutions such as hetastarch may worsen renal function.[5] Judicious use of certain vasopressors, including norepinephrine, dobutamine, and vasopressin, following optimization of fluid status, may also protect renal function for persistently hypotensive patients. The theoretical benefits of low-dose, "renal dose" dopamine, however, have not been substantiated, although fenoldopam, a dopamine receptor agonist highly selective for vasodilation of the renal and splanchnic beds, may be of some use in the perioperative period.[6] Of course, shock is rarely the sole threat to the kidneys in any critically ill patient. Nephrotoxic medications, intravenous contrast agents, and rhabdomyolysis frequently may threaten renal function in the setting of shock.

Treatment and reversal of renal dysfunction following shock is a complicated and often unsatisfying endeavor. Loop diuretics are commonly used with the hope of maintaining urine output as well as fluid and electrolyte balance. However, clinical trials using loop diuretics following the onset of renal failure failed to show a change in mortality or recovery of renal function and may even increase the risk of end-stage disease.[7] Early initiation of certain renal replacement therapies has also been investigated, both as a supportive measure and as a means to restore renal function. Given the role of inflammatory mediators in shock and AKI, high-volume continuous veno-venous hemofiltration (CVVH) appears intuitively promising for ridding the body of such mediators and potentially halting or reversing renal injury. While some small studies suggest that CVVH improves in renal function, two large, randomized controlled multicenter trials failed to demonstrate a reduction in either mortality or renal failure in patients with AKI injury on high-volume hemofiltration versus conventional renal replacement therapies.[8,9] Regardless, short- and long-term means of renal replacement are necessary to maintain metabolic homeostasis for 5% of critically ill patients, and for patients experiencing hemodynamic instability due to shock, continuous methods such as hemofiltration appear better tolerated than intermittent hemodialysis. Moreover, early renal replacement therapy appears to result in better outcomes.

11.2.2 Pulmonary Complications: Acute Lung Injury and Acute Respiratory Distress Syndrome

Like the kidney, the lung is a common casualty of hypovolemic and septic shock. Pulmonary complications of shock are typically manifest by a clinical syndrome known as acute respiratory distress syndrome (ARDS). ARDS has the following clinical features: bilateral infiltrates on plain x-ray of the chest, resembling pulmonary edema, the absence of clinical evidence of congestive heart failure, severe hypoxemia resulting in an arterial to inhaled oxygen ratio (PaO_2/FiO_2) of <200, and the presence of a known risk factor. Acute lung injury (ALI) represents a less severe form of this picture, with a PaO_2/FiO_2 ratio of <300. The multiple, widely divergent underlying pathologies known to cause ARDS and ALI converge on a single downstream effector: damaged and leaky pulmonary capillary endothelium. The microscopic consequence is thrombosis and even obliteration of distal pulmonary vasculature, with proteinaceous fluid escaping to flood the alveoli.

ARDS is responsible for an abundance of ICU morbidity, mortality, and resource expenditure, prompting a correspondingly high degree of investigation.[10] Although mortality has diminished, definitive answers on the questions of prevention and treatment remain quite limited. In patients with ALI, the more hemorrhage and blood transfusions, the greater is the risk

progression to ARDS, raising the hope that expedient patient management combined with a restrictive transfusion strategy may confer some protection. A relatively restrictive approach to fluid resuscitation has been shown to improve lung function in patients with ALI, and decrease total ventilator days, but nonetheless failed to demonstrate a change in survival.[11] Despite prior observational studies to the contrary, the recent EDEN trial showed no difference in infectious complications or ventilator days among patients with ALI receiving initial trophic or "trickle" tube feeding (10–20 mL/h) for 6 days versus those rapidly advanced to full caloric needs.[12]

After the onset of ARDS, treatment options are plentiful, but treatment options with known benefits are less so. To date, only volume-restricted, "lung-protective" ventilation is widely accepted to reduce mortality in patients with ARDS, due largely to findings of the ARDSNet study.[13] This study compared ARDS patients ventilated with 12 mL/kg ideal body weight tidal volume and plateau pressures <50 mm Hg, to those receiving 6 mL/kg ideal body weight and plateau pressures <30 mm Hg. Restricting tidal volumes produced a significant relative reduction in mortality of 25%. Permissive hypercapnea associated with this strategy is generally well-tolerated.

Other treatment strategies for ARDS and ALI include the popular "open lung" ventilation techniques, but they lack such a clear-cut survival benefit. Open lung ventilation is defined by a positive end-expiratory pressure (PEEP) set above the initial opening alveolar pressure, as determined by the lower inflection point on the sigmoidal pressure–volume curve (Figure 11.1). Recruitment maneuvers (a few moments of sustained high inspiratory pressure at the initiation of mechanical ventilation) are commonly used to open collapsed alveoli, followed by PEEP to maintain their patency and capacity for gas exchange. PEEP improves oxygenation, but studies seeking to demonstrate a mortality benefit have yielded conflicting data. In patients with ALI, as opposed to ARDS, higher levels of PEEP may actually be harmful. PEEP and recruitment maneuvers can produce deleterious hemodynamic effects that may account for some mixed success in ARDS, especially in the setting of hypovolemic or septic shock. Airway pressure release ventilation (APRV) is a ventilatory mode that supports spontaneous ventilation at consistent moderately elevated airway pressures (around 25 mm Hg), with the hope of re-establishing normal chest wall compliance and avoiding shear forces related to pressure changes. High-frequency oscillatory ventilation (HFOV) uses a piston-driven ventilator to administer relatively tiny tidal volumes well below the dead-space volume. This creates continuous convection and other complex patterns of air flow, while maintaining mean airway pressure. HFOV is currently under investigation in the randomized multicenter OSCILLATE and OSCAR trials.

Prone positioning has become popular as a means to address the ventilation–perfusion mismatch associated with ARDS. Directing blood flow by gravity into the better aerated, upper and anterior regions of the lungs indeed improves oxygenation (Figure 11.2), but two large, multicenter randomized controlled clinical trials showed no change in survival, and even raised some concerns for airway loss and decubitus ulcer formation in prone patients.[14,15] Inhaled vasodilators such as nitric oxide and aerosolized prostacyclin offer the same theoretical advantage as prone positioning, by drawing increased blood flow to functioning alveoli, but neither has conferred improved survival.

Extracorporeal membrane oxygenation (ECMO) bypasses native lung function and avoids the downsides of both "lung-protective" and "open lung" ventilation strategies entirely.[16] The CESAR trial demonstrated a significant drop in mortality of adult patients with ARDS following transfer to a ECMO referral center, but since many of the transferred patients never received the intended ECMO intervention, it is unclear whether the

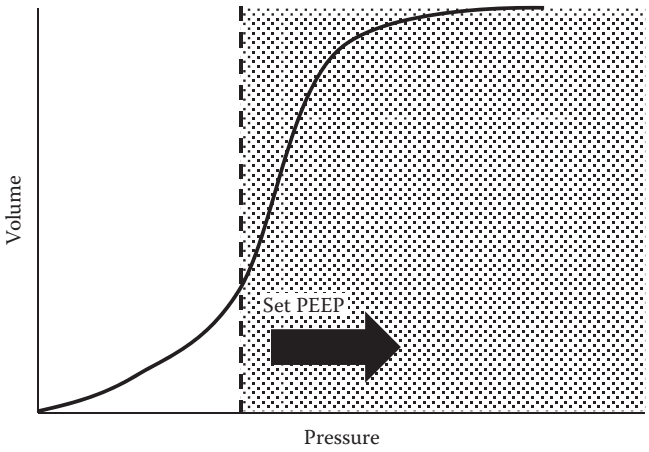


FIGURE 11.1
Open lung ventilation. The alveoli are maintained at or above their opening pressure by setting the PEEP higher than the lower inflection point on the pressure–volume curve.

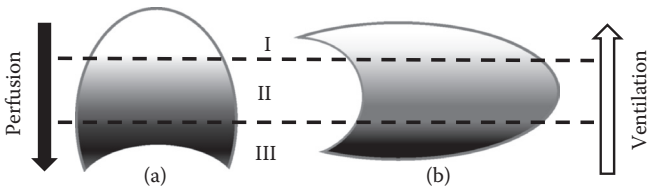


FIGURE 11.2
Zones of the lung according to ventilation and perfusion in the (a) upright and (b) supine patient. Prone positioning temporarily directs blood flow by gravity into the better aerated, more open lung regions, thus helping correct a ventilation–perfusion mismatch.

mortality benefit can be attributed to ECMO or rather the protocolized, system-wide evidence-based management provided by a tertiary center.[17] While we await the results of future studies, current data suggest that, when feasible, earlier implementation of APRV, HFOV, and ECMO may improve outcomes, and such interventions should not be viewed solely as strategies of last resort.

11.2.3 Cardiac Complications: Systolic and Diastolic Dysfunction

The heart is vulnerable to septic and hypovolemic shock, although the definitions of this dysfunction and descriptions of the underlying pathophysiology are considerably more vague. Rubrics to grade cardiac dysfunction include such parameters as systolic blood pressure, heart rate, central venous pressure (CVP), arrhythmias, and cardiopulmonary arrest, and therefore generally incorporate the entire cardiovascular system as a whole rather than isolate the cardiac muscle itself. Physiologically, this is a sound approach, since each component of the hemodynamic circuit is intimately dependent on the others, and cardiac dysfunction in the setting of shock is perhaps inherently multifactorial, resulting as much from variations in preload and afterload as from electrolyte imbalances and derangements in autonomic and endocrine input.

Multiple animal studies on hemorrhagic shock demonstrate alterations specifically in systolic cardiac muscle contractility, and a number of potential inflammatory mediators with known cardiac depressant effects have been isolated.[18] In addition, there appears to be a component of diastolic dysfunction (defined as impaired ventricular relaxation) following hemorrhage. Septic shock is another culprit, resulting in myocardial suppression and impaired cardiac relaxation, a phenomenon well-documented in reproducible animal models and in clinical observation. Most clinicians are familiar with the entity termed "troponin leak" as well as the spikes in B-type natriuretic peptide believed to be a manifestation of this cardiac insult. A growing number of surgical intensivists are now trained in echocardiography, and have found that some degree of diastolic dysfunction may exist in one-third of critically ill trauma and surgery patients undergoing echocardiogram. Diastolic dysfunction has been identified as an independent predictor of mortality and prolonged ventilator dependence.[19]

While shock-induced cardiac dysfunction can be quite profound initially, long-term prognosis for survivors is good, and many patients return to normal levels of cardiac performance. The mainstay of both treatment and prevention to date remains early, goal-directed therapy, including fluid resuscitation and inotropic support titrated to specific clinical end points.[20] Multiple other therapies remain in the experimental stages, including various antioxidants, anti-inflammatory agents, statins, and beta-blockers. Ventricular assist devices have been trialed in animal models following resuscitation from hemorrhagic shock with promising results. However, it remains to be seen which, if any, of these therapies will prove superior to conventional goal-directed resuscitation and supportive management.

11.2.4 Endocrine Complications: Adrenal Failure, Hypothyroidism, and Insulin Resistance

Sheehan syndrome was described in 1937 as a disruption of the hypothalamic–pituitary axis secondary to peripartum hemorrhagic shock. Findings include hypothyroidism, adrenocortical insufficiency, failure of lactation, and cessation of menses, resulting from ischemic necrosis of the pituitary gland. In some cases, computed tomography or magnetic resonance imaging actually demonstrate an empty sella turcica. The lesser-known Simmonds syndrome is pituitary dysfunction in either gender following traumatic hemorrhage. A great deal of interest has centered on adrenocortical insufficiency from either hypovolemic or septic shock. The most obvious clinical manifestation of adrenocortical insufficiency is refractory hypotension, perpetrating a vicious cycle. Adrenocortical insufficiency has been variously defined as a baseline serum cortisol concentration <10–25 μm/dL or an increase of <9 μm/dL within 1 h following administration of 250 μm of cosyntropin. In some cohorts, more than half of the patients with sepsis or hemorrhagic shock have at least occult adrenocortical insufficiency on the basis of laboratory values.[21] Severe hyperacute adrenal insufficiency is present at the time of admission in 16% of trauma patients with evidence of ongoing hemorrhage.[22] Most recently, studies suggest the existence of relative adrenal insufficiency, defined by shock that improves following administration of steroid replacement therapy, regardless of serum laboratory values.

Compared to hemorrhage patients without adrenal dysfunction, hypoadrenal patients may have worse outcomes in terms of mortality and ICU length of stay. In septic patients, poor adrenal function appears to correlate with mortality as well. Treatment of adrenal insufficiency remains a topic of controversy. Earlier controlled clinical trials demonstrated a 10% absolute reduction in mortality associated with steroid replacement therapy in adrenally insufficient septic patients,[23] but the more recent CORTICUS trial found no such difference in survival.[24] Both studies, however, demonstrated a rapid weaning from vasopressor support following administration of intravenous hydrocortisone. Moreover, the study protocols and populations were markedly different, suggesting that patients with the most severe sepsis

were most likely to benefit. The CORTICUS trial also demonstrated that results of the commonly performed cosyntropin stimulation test had little or no bearing on whether a patient would benefit from steroid therapy, prompting guidelines that patients with severe sepsis or septic shock should receive a course of hydrocortisone and possibly fludrocortisone (a mineralocorticoid) whether or not they are found to be adrenally insufficient by serum laboratory measures. In patients with adrenal insufficiency following hemorrhage, hydrocortisone potentiates the sympathetic vasoconstrictive mechanism, but downstream improvements in mortality or other end points are as yet unsubstantiated. Thus, exogenous steroid administration continues to play a relatively minor role in patient management following hemorrhagic shock. In both septic and hemorrhagic adrenal insufficiency, spontaneous recovery of endocrine function following resolution of the initial insult is typical.

Hypothyroidism is another very common complication of hemorrhagic or septic shock, but, again, treatment in the acute setting of critical illness remains controversial. The terms "sick euthyroid syndrome" and "nonthyroidal illness syndrome (NTIS)" have arisen to describe a state of suppressed triiodothyronine (T3), with normal or decreased thyroxine (T4) and thyroid-stimulating hormone (TSH). It would seem logical that low thyroid hormone levels would exert deleterious metabolic and cardiovascular effects, and in some specific scenarios, such as severe traumatic brain injury, T4 supplementation may prove key to maintaining hemodynamic stability. In 10% of patients with shock, hypothyroidism may coincide with hypoadrenalism, and the concern for synergistic effects frequently prompts thyroid hormone supplementation. However, despite many studies on the subject, no clear evidence exists that correcting the apparent thyroid hormone deficiency will alter outcome, and the clinical significance of the syndrome itself remains in question.[25]

Unlike adrenocortical insufficiency and hypothyroidism, the well-documented phenomenon of hyperglycemia accompanying both septic and hemorrhagic shock appears to be a failure of end-organ sensitivity, not hormone production itself. To prevent hyperglycemia, parenteral nutrition should be avoided if at all possible, and enteral nutrition provided on a regular, and ideally continuous, basis. Medications such as steroids known to cause hyperglycemia should be given in the minimum effective dosing regimen, and discontinued promptly when no longer needed. Treatment of insulin resistance is typically accomplished by the administration of exogenous subcutaneous insulin—four to six times per day on a sliding scale dosing regimen, or, when necessary, with a continuous intravenous drip and hourly blood glucose monitoring. Long-acting glargine insulin is often added once or twice daily when predictable insulin requirements are established.

The debate over the optimal degree of glucose control, however, is far from settled. Van den Berghe and colleagues demonstrated significantly decreased rates of organ dysfunction, infectious complications, and overall mortality in a large cohort of surgical ICU patients when goal blood glucose was maintained at 80–110 mg/dL.[26] This finding, however, was not substantiated by the subsequent NICE–SUGAR trial in 2009, demonstrating a slight but significant increase in 90-day mortality when attempts were made to maintain blood glucose between 81 and 108 mg/dL, as opposed to <180 mg/dL, in a combined cohort of critically ill medical and surgical patients.[27] The populations studied were not directly comparable, and the full extent of this controversy is beyond the scope of this chapter. Multiple studies supporting both sides of the glycemic control issue have been published since then, and the fact remains that some effort at hyperglycemic control with insulin supplementation appears beneficial, although the degree of control likely hinges on the particular patient population.[28] In particular, perioperative cardiac surgery patients are one population believed to gain substantial benefit from strict blood glucose regulation.[29]

11.2.5 Hematology: Coagulopathy and Bone Marrow Failure

Inflammation—whether from sepsis or traumatic hemorrhage—and the clotting cascade are extensively intertwined, each triggering the other at multiple levels. Tumor necrosis factor-alpha (TNF-α), interleukin-1, and interleukin-6 are all cytokines known to affect the coagulation cascade. These cytokines stimulate endothelial cells to produce tissue factor, making this a convergence point of the coagulation cascade in both trauma and sepsis. Nonspecific activation of the clotting mechanism can culminate in an exhaustive consumption of the available factors. Thus, the resulting coagulopathy is best characterized as a dysregulation of homeostasis, in which both hypercoagulable and hypocoagulable states coexist.

The coagulopathy of acute trauma occurs within minutes of injury, suggesting aberrant stimulation of the pathways. For hypoperfused, severely injured trauma patients, there is evidence to suggest overactivation of protein C, resulting in a specific decline in Factor V and VII.[30] Hyperfibrinolysis also plays a role, accompanied by a rapid decline in fibrinogen immediately following injury. Thrombocytopenia is present in some patients with severe hemorrhagic shock, but it is unclear how much platelet dysfunction may or may not contribute to trauma-related coagulopathy.[31, 32] In an aging population, iatrogenic platelet dysfunction, resulting from

platelet-inhibiting medications prescribed for preexisting comorbidities such as cardiovascular or cerebrovascular disease, is probably of greater concern. Platelet dysfunction as determined via the epinephrine/collagen platelet function assay is highly specific (90%) for aspirin use. However, most trauma patients actually exhibit supranormal platelet function relative to the normal population, rather than dysfunction.

Maintenance of normothermia and reversal of acidosis are time-honored means to correct and protect against trauma-associated coagulopathy, giving rise in part to the concept of "damage-control laparotomy.[33]" Calcium supplementation should be provided to patients receiving massive transfusions, since this cation is central to the coagulation cascade and chelating agents in packed red blood cell units can deplete serum levels (some authors also cite decreased bone perfusion, resulting in impaired calcium ion mobilization, as a mechanism). Various other methods to treat coagulopathy have been explored, but not yet widely practiced. Results of an international, randomized, controlled, and blinded clinical trial of tranexamic acid (TXA), a plasmin inhibitor related to ε-aminocaproic acid, showed a statistically significant but clinically rather marginal reduction in mortality secondary to hemorrhage, and only when administered quite early, within 1 h of injury (7.7% vs. 5.3%). When administered 3 h or more after injury, TXA actually increased the risk of fatal hemorrhage.[34] Consequently, routine use of TXA has yet to be widely embraced by many trauma centers. Fibrinogen depletion may be best addressed via early cryoprecipitate supplementation, although further study will be needed to fully ascertain this. Recombinant activated factor VIIa enjoyed a period of relative popularity for a time, but failure to demonstrate a survival benefit, coupled with considerable expense, have relegated use mostly to heroic salvage efforts.[35] Various other factor and multifactor concentrates are under investigation, with promising but limited data thus far.

Finally, it should be noted that while high plasma and/or platelet to red cell transfusion ratios have been advocated to treat or possibly prevent the acute coagulopathy of trauma, and are now widely used at many trauma centers, there are currently no large-scale, randomized controlled clinical trials to support this practice. The relatively late availability of thawed fresh frozen plasma (relative to packed red blood cells, which are often administered immediately), implies a survival bias (i.e., patients received plasma because they lived longer; they did not live longer because they received plasma), and preliminary results from the multicenter, prospective observational Activation of Coagulation and Inflammation after Trauma trial (ACIT) attempting to correct for this bias suggest there may be no survival benefit behind increased plasma to blood cell transfusion ratios.

The coagulopathy associated with septic shock is typified by diffuse intravascular coagulation (DIC), a consumptive exhaustion of clotting factors and platelets compounded by microvascular obstructive thrombi, thus worsening end-organ hypoperfusion. Diagnosis of DIC can be made on the basis of the International Society on Thrombosis and Haemostasis (ISTH) scoring system incorporating platelet count, fibrinogen level, prothrombin time, and fibrin split product level. A peripheral blood smear demonstrating megakaryocytes and schistocytes supports the diagnosis. Knowledge of this pathogenesis prompted an interest in recombinant activated protein C (drotrecogin alpha), to inhibit disordered coagulation. While initial experience with this therapy in the PROWESS trial showed potential to improve organ function, the follow-up multicenter randomized controlled PROWESS–SHOCK trial as well as a Cochrane meta-analysis demonstrated no survival benefit. In light of the risk of associated bleeding complications, drotrecogin alpha was withdrawn from the market in 2011.[36] The OPTIMIST trial of tissue factor pathway inhibitor (TFPI, or tifacogin) for septic shock was likewise disappointing, as were monoclonal antibodies to TNF-α. Investigators continue to pursue other avenues, but addressing the underlying etiology of sepsis remains the best therapeutic approach for DIC at this time.

Myelopoietic failure can complicate the picture of both hemorrhagic and septic shock. Inflammatory mediators from the bowel may suppress erythrocyte progenitor cells following hemorrhagic shock, resulting in anemia and low reticulocyte counts. Myeloid progenitor cells may also be affected, resulting in neutropenia. Apoptosis and phagocytosis of precursor cells may contribute to anemia and thrombocytopenia in septic patients. Somewhat paradoxically, however, therapeutic administration of erythropoietin alpha does not significantly affect long-term transfusion requirements, hemoglobin concentrations, overall functionality, or mortality.[37] Numerous studies have demonstrated the detrimental effects of unnecessary red cell transfusion, including the landmark TRICC and ABC trials.[38] Most patients appear to benefit from a restrictive approach to transfusion with a threshold hemoglobin of approximately 8 mg/dL.

11.2.6 Gastrointestinal Complications: Stress Peptic Ulcers, Bowel Ischemia, and Acute Liver Failure

Like the genitourinary tract and skin, the splanchnic circulation experiences decreased blood supply early in the course of hemorrhagic shock. "Stress" peptic ulceration resulting in occasionally brisk upper gastrointestinal bleeding is not uncommon following hemorrhagic

shock,[39] and may perpetuate a vicious cycle of hemorrhage and shock. The large bowel is particularly sensitive to the effects of nonocclusive mesenteric ischemia, a state frequently seen in cardiogenic shock, although it may complicate hemorrhagic shock as well. Postoperative cardiac surgery patients are particularly prone to experience bowel ischemia.[40] In milder cases, end arterioles are principally affected, resulting in isolated mucosal ischemia and sloughing, although in severe instances the insult may be transmural. Rarely, the small bowel is also involved, with sometimes disastrous consequences, including pneumatosis intestinalis, gangrene, and perforation. Mortality rates approach 80%. Ileus and diarrhea, symptoms commonly seen in the intensive care unit, may in fact represent mild gut ischemia. Septic shock can precipitate similar ischemic insults to the gut. Although gut perfusion as a whole may be normal or even increased in the setting of sepsis, shunting on a microvascular level— and mitochondrial decoupling on a cellular level—are no less damaging.

Hepatic dysfunction, or "shock liver" is an especially dreaded consequence of gastrointestinal hypoperfusion. Following an ischemic injury—whether hemorrhagic or septic—hepatic Kupffer cells perpetrate an explosive inflammatory response mediated by TNF-α. This response is principally manifest as a rise in serum levels of hepatic enzymes, although overt hepatic dysfunction and eventual fulminant failure may develop as well, in the form of hyperbilirubinemia, hypoalbuminemia, and coagulopathy.

Prevention and management of gastrointestinal hypoperfusion center on reversal of the underlying cause of shock. In addition, stress ulcer prophylaxis with proton-pump inhibitors, histamine-2 blockers, and sucralfate have remarkably reduced the incidence of upper gastrointestinal bleeding in high-risk populations (e.g., mechanically ventilated patients). In cases where prophylaxis fails, endoscopic techniques and even minimally invasive catheter-based methods are usually sufficient to address the hemorrhage, although surgical control is occasionally required. The issue of whether enteral feeding protects against or worsens gut ischemia is not definitely settled, although the beneficial effects of at least minimal trophic feedings in critically ill patients are widely acknowledged. A low index of suspicion for abdominal pathology should be maintained in all patients affected by shock, particularly those on enteral feeds, and feeds should be given with caution if clinical signs such as abdominal pain, tenderness, or distension develop. Complex nutrients, which are especially taxing to splanchnic metabolism, and high-residue formulas, which can increase intraluminal pressure and decrease mural blood flow, should be utilized with care. Semi-elemental nutritional formulations may be an option for those patients with difficulty tolerating standard feeding regimens. Vasopressor agents should be minimized if at all possible, although currently established therapeutic ranges are unlikely to cause overt bowel ischemia. When peritonitis, radiologic evidence of transmural necrosis, or substantial clinical deterioration occur, surgical exploration and intestinal resection may be necessary. Abdominal colectomy with ileostomy is an extreme but acceptable option where circumstances warrant; diffuse small bowel ischemia is often less amenable to successful operative intervention.

11.3 Multiorgan Dysfunction Syndrome

The development of dysfunction in more than one organ system is an ominous sign, correlating highly with mortality. The Sequential Organ Failure Assessment (SOFA) score assigns a relative severity of 1–4 points (higher being worse) to objective markers of failure in six systems: respiratory (PaO_2/FiO_2 ratio), neurologic (Glasgow Coma Scale, or GCS), cardiovascular (mean arterial blood pressure, MAP, or pressor requirement), hepatic (total serum bilirubin), hematologic (platelet count), and renal (serum creatinine). SOFA scores >11, implying severe organ dysfunction in four or more systems, portend mortality rates in excess of 95%. The Acute Physiology and Chronic Health Evaluation (APACHE) IV predictive equations, based on the APACHE III score, are complex formulas incorporating 27 or more variables to generate probabilities regarding mortality and hospital length of stay. The Marshall score distills multiple parameters into an optimized system where organ failure is defined dichotomously as a PaO_2/FiO_2 ≤150, serum creatinine ≥4 mg/dL, serum total bilirubin ≥7.1 mg/dL, platelet count ≤50,000/μL, and GCS ≤9 for their respective organ systems. Cardiovascular function in the Marshall score is based on an index termed the pressure-adjusted heart rate (PAR): the product of heart rate in beats per minute and CVP in mm Hg, divided by the MAP. Failure is defined as PAR ≥20. Failure of all six systems in the Marshall score conferred mortality of 66%, and failure of three systems was associated with 50% mortality.[41]

MODS is largely responsible for the third, delayed peak in trauma-related mortality, occurring weeks after the initial insult.[42] At present, there is a paucity of methods to reliably prevent MODS once the initial shock event has occurred. In fact, a growing body of literature suggests that genetics may play a pivotal role in predisposing certain patients to MODS following either hemorrhagic or septic shock. However, some evidence in animal models supports use of enterally administered intraluminal pancreatic enzyme

inhibitors such as nafamostat mesilate and TXA shortly after hemorrhage.[43] The theory is that the overwhelming inflammatory response that results in MODS originates in the gut, and such a response may be quenched by administration of enzyme inhibitors before irreversible damage ensues. Clinical utility remains to be established.

11.4 Complications of Fluid Overresuscitation

In 1984, Kron published the first modern physiologic explanation of abdominal compartment syndrome (ACS) in patients following open repair of ruptured abdominal aortic aneurysms—clear evidence of the iatrogenic detriment associated with overly aggressive fluid resuscitation.[44] ACS is defined as supraphysiologic abdominal pressure (i.e., abdominal hypertension, variously defined as >12–25 mmHg), secondary to intraperitoneal free fluid accumulation, bowel wall, and retroperitoneal edema, with hypotension, oliguria, and high peak inspiratory pressures. Treatment is via decompressive laparotomy; prevention consists of leaving the abdominal fasciae unapproximated in high-risk patients following celiotomy. In the decades following Kron's original description, a rising comfort level with damage control laparotomy and management of the resultant "open abdomen" brought many more complications to light—including chronic wounds, massive ventral hernias, and entero-atmospheric fistulae—which could also be indirectly attributed to overresuscitation. Even in a closed abdomen, diffuse anasarca may lead to poor healing and skin breakdown.

Other consequences are less obvious but just as concerning. Excessive fluid likely contributes to atrial fibrillation and pulmonary compromise. The specific choice of intravenous fluid can also lead to specific complications. Saline in large volumes has proinflammatory effects and leads to hyperchloremic metabolic acidosis.[45] Colloids such as albumin offer no known mortality benefit, and hydroxyl-ethyl starch may even lead to renal failure in septic patients.[5, 46] While frequently necessary in acutely hemorrhaging, hypotensive patients, blood transfusion in critically ill patients is associated with worse outcomes even after correcting for disease severity, likely via immunosuppressive effects, among other mechanisms.

Despite a growing appreciation for the burden of complications, the operating room itself traditionally remains a soap box for the principles of aggressive, and often excessive, fluid resuscitation. Concerns regarding third-spacing, evaporation via exposed peritoneal surfaces, pre- and postoperative fasting periods, hypotension secondary to anesthesia, and either actual or threatened substantial blood loss, all understandably prompt proactive correction with volume preloading. However, in a 2003 randomized, prospective multicenter trial, Brandstrup et al. demonstrated that a restricted intraoperative fluid regimen designed to maintain current body weight was associated with a significantly reduced incidence of postoperative cardiopulmonary and tissue-healing complications among 172 otherwise healthy patients undergoing elective colorectal resection (when compared to a fluid strategy which prophylactically replaced predicted third-spacing and other insensible losses).[47] A subsequent study from Lobo et al., comparing 12 mL/kg/h intraoperative fluid maintenance to 4 mL/kg/h, showed a similar benefit for fluid restriction during elective surgery in high-risk patients, as defined by advanced age, cardiovascular comorbidities, and/or patients undergoing prolonged surgical procedures associated with large volume shifts or blood loss.[48] Most recently, a retrospective analysis of hypotensive trauma patients undergoing damage control operations for penetrating torso injuries extended evidence that restricting intraoperative fluids may shorten hospital stay and decrease overall mortality even among severely injured patients in overt shock.[49]

Suggested methods to prevent and/or treat complications associated with volume resuscitation are summarized at the end of this chapter. However, the mainstay of prevention remains adherence to early goal-directed therapy. This philosophy of resuscitation, as championed by Rivers et al. in 2001, is based on the rapid and precise manipulation of oxygen delivery.[20] Physiologically, tissue oxygen delivery is determined principally by two variables: cardiac output and the concentration of saturated hemoglobin (free dissolved oxygen in the blood contributes exponentially less than oxygen bound by hemoglobin). Cardiac output is in turn determined by end-diastolic volume and ejection fraction. In the prospective, randomized study by Rivers and colleagues, continuous or serial measurement of central (vena cava) venous oxygenation saturation (SVO_2), CVP (a surrogate for end-diastolic volume), and hematocrit subsequently directed optimization to predetermined end points. Adult participants with suspected sepsis and SVO_2 <70% were bolused with crystalloid in 500 mL increments to maintain a CVP 8–12 mm Hg, and red cells were transfused to a goal hematocrit of 30%. Vasopressor agents were given for MAP < 65 mm Hg. If SVO_2 <70% persisted despite these interventions, inotropic infusion was added and oxygen consumption minimized using sedation and mechanical ventilation. With these measures, wherever possible, goals for CVP, hematocrit, SVO_2, and MAP were met within 6 h of presentation. During their subsequent hospital stay, patients randomized to a protocol of early goal-directed

therapy were significantly more likely to survive, less likely to require mechanical ventilation and blood transfusions, and had shorter hospital stays, when compared to patients receiving a less-defined treatment strategy. This study should be interpreted with some caution given that trauma patients were excluded and end points were designated somewhat arbitrarily (e.g., a hematocrit of 30% as opposed to a hemoglobin concentration of 7 mg/dL). Nonetheless, the appeal of early goal-directed therapy is clear, and it has been adopted as a standard of care at many institutions.

The continued prevalence of resuscitation-related complications to date, however, suggests that some traditional end points for determining the optimal volume of fluid resuscitation are inadequate. Blood pressure, heart rate, and laboratory values such as lactate and hemoglobin concentration are nonspecific, insensitive, and slow to respond to interventions. Alternative real-time monitoring technologies are gaining attention, including arterial waveform analysis and surgeon-performed bedside echocardiography.[50, 51] Laser Doppler imaging of the skin, bladder mucosal pH monitoring, and hyperspectral imaging are among the many promising noninvasive technologies emerging from the laboratory.[52–54]

11.5 Summary

Shock is defined as end-organ hypoperfusion, resulting from a variety of mechanisms. Hemorrhagic and septic shock frequently result in similar patterns of organ dysfunction, likely through a common mediator. Renal, pulmonary, cardiac, myelopoietic, and gastrointestinal failure are all potential manifestations. Multiorgan system dysfunction, which is responsible for most "late" deaths following trauma, can be graded via various scoring systems, which directly correlate to mortality risk. Certain strategies, such as low tidal volume ventilation in the setting of ARDS and ALI, have proven mortality benefit, but prevention and treatment of shock-induced organ dysfunction generally center on reversal of the underlying etiology, with goal-directed fluid resuscitation as the mainstay of therapy. Overresuscitation, however, is associated with its own deleterious consequences. New efforts are underway to establish gold standard, real-time, minimally or noninvasive means to monitor for the presence of both ongoing hemorrhage and adequate resuscitation.

Complications of Hypovolemic and Septic Shock in the Surgical and Trauma ICU Populations: Estimated Prevalence

Complications	Prevalence	References	Comment
AKI Acute renal failure	~30% ~1%–3%	[3]	Varies depending on the definition used
ALI/ARDS	~5%–10%	[10]	
Cardiac dysfunction	Unknown, ≤30%	[18,19]	Among patients with hypotension or other indications for echocardiography; full extent unknown
Adrenal insufficiency	1%–30%	[21,22]	Prevalence higher in frankly hypotensive patients
Insulin resistance/ hyperglycemia	40%–100%	[26,27]	Varies depending on goal blood glucose
Hypothyroidism/decreased serum thyroid hormone	100%	[25]	Laboratory abnormality; uncertain clinical significance
Coagulopathy	10%–25%	[30, 31]	Acute coagulopathy among trauma patients
Thrombocytopenia	~10%–30%	[32]	
Anemia	~20%–60%	[37, 38]	Defined as Hgb <9 mg/dL, or requiring blood transfusion
Stress peptic ulcer/upper gastrointestinal bleeding	~5%	[39]	With modern gastrointestinal prophylaxis
Bowel ischemia	<0.5%	[40]	Milder forms likely underdiagnosed; associated with cardiac surgery, cardiopulmonary bypass
Acute liver dysfunction/ failure	~5%	[41]	
Multiorgan dysfunction	~2%	[42]	

Complications of Hypovolemic and Septic Shock in the Surgical and Trauma ICU Populations: Prevention and Treatment

Complications	Preventative Measures	Treatment	Comment
AKI Acute renal failure	• Fluid resuscitation • ±Vasopressors • ±Fenoldapam • Discontinue nephrotoxic drugs	• Renal replacement therapy	
ALI/ARDS	• Control hemorrhage • Restrict transfusions • Conservative fluid resuscitation	• Volume-restricted ventilation (6–8 mL/kg ideal body weight), ±permissive hypercapnea • Recruitment maneuvers and PEEP • APRV • HFOV • Inhaled vasodilators (NO and prostacyclin) • ECMO	Only volume-restricted ventilation has been shown to decrease mortality
Cardiac dysfunction	• Unknown	• Targeted fluid resuscitation • ±inotropes	
Adrenal insufficiency	• Unknown	• Empiric trial of glucocorticoids, ±fludrocortisone	Cortisol levels and consyntropin-stimulation testing are no longer recommended prior to empiric steroid trial
Insulin resistance/ hyperglycemia	• Avoid TPN • Administer enteral nutrition regularly and continuously; minimize NPO (*nil per os*, or nothing by mouth) periods • Wean steroids	• Subcutaneous ISS • Intravenous continuous insulin drip • Glargine insulin	Optimal degree of blood glucose control not known; generally agreed to be ≤180 mg/dL
Hypothyroidism/ decreased serum thyroid hormone	• Unknown	• None	In certain patient populations, such as traumatic brain injury with shock, thyroid hormone supplementation may be of some benefit
Coagulopathy	• Avoid acidosis, maintain normothermia; judicious use of damage control laparotomy • Calcium • High plasma and/or platelets to red blood cell transfusion ratio	• Calcium • Plasma, platelets, and cryoprecipitate transfusion • ±Multifactor concentrates, activated factor VII	The optimal plasma to red blood cell transfusion ratio has not been established
Thrombocytopenia	• Unknown (avoid other causes, such as medications: heparin, histamine blockers, ticarcillin-clavulanate)	• Transfuse for active bleeding or anticipated major surgery to goal platelets >100,000/μL • Transfuse to goal platelets >10–20,000/μL in all others • Treat uremic platelet dysfunction with desmopressin, dialysis	
Anemia	• Unknown (prevent, treat or minimize other causes, such as phlebotomy, upper gastrointestinal bleeding, coagulopathy)	• Restrictive transfusion strategy to goal Hgb ≥8 mg/dL in hemodynamically stable patients without ongoing hemorrhage • ±Iron supplementation	Epoietin alpha indicated only for patients with chronic renal failure; ideal threshold hemoglobin concentration for transfusion not yet known
Stress peptic ulcer/upper gastrointestinal bleeding	• Sucralfate, histamine blockers, or proton pump inhibitors for high-risk patients (e.g., mechanically ventilated) • Correct coagulopathy	• Proton pump inhibitors • Upper endoscopy • Angioembolization • Operative ligation	Operative ligation rarely necessary
Bowel ischemia	• Cautious, possibly trophic, enteral feeding in high-risk patients (e.g., overtly hypotensive) • Minimize vasopressors • Elementary, low residual tube feeding formulas	• Operative intervention and resection when necessary	

Complications	Preventative Measures	Treatment	Comment
Acute liver dysfunction/ failure	• Fluid resuscitation (avoid/ treat other causes of hepatotoxicity, including medications, right heart failure, biliary obstruction)	• Supportive measures, including treatment of coagulopathy, encephalopathy, and cerebral edema • May require transplantation	
Multiorgan dysfunction	• Prevention is by individual system; possibly enteric administration of pancreatic enzyme inhibitors	• Supportive measures according to the affected systems	

Note: ISS, insulin sliding scale; TPN, total parenteral nutrition.

Complications of Fluid Overresuscitation in the Surgical and Trauma ICU Populations: Prevention and Treatment

Complications	Prevention[a]	Treatment	Comment
Intra-abdominal hypertension/ACS	• Leave fascia unapproximated following exploration in high-risk patients • Nasogastric decompression • Sedation, neuromuscular paralysis	• Decompressive laparotomy	In cases of known intraperitoneal free fluid (as opposed to bowel wall or retroperitoneal edema), minimally invasive percutaneous catheter evacuation and/or mini-laparotomy may be sufficient
• Giant ventral hernia	• Rapid fascial closure • Interpose nonadherent dressing between visceral block and abdominal wall to halt loss of domain	• Delayed complex abdominal wall reconstruction, which may include use of mesh and/or component separation	Among patients undergoing damage control or decompressive laparotomy
• Entero-atmospheric fistula	• Minimize/protect enterotomies, gastrointestinal anastomoses • Protect exposed bowel from dessication, direct contact with suction sponges	• Washout and control fistula • Optimize conditions for spontaneous closure (e.g., nutrition, minimize flow through fistula, treat downstream obstruction) • May require substantially delayed resection and re-anastomosis	Among patients undergoing damage control or decompressive laparotomy
Skin breakdown	• Absorbent dressings, linen changes for moist skin • Frequent (every 2 h) turning • Low-air loss mattresses, heel floating boots, and other equipment to offset pressure in high-risk patients • Optimize nutrition • Minimize sedation, neuromuscular paralysis • Physical/occupational therapy	• Chronic wound care (e.g., wet-to-dry dressing, debridement, negative pressure therapy) • May require operative interventions such as skin graft, vascularized flap reconstruction, and diverting ostomy	
Atrial fibrillation	• Statins • β-blockade • ±Diltiazem • ±ACEI/ARB	• β-blockade • Diltiazem • Amiodarone • Digoxin • Cardioversion	Incidence particularly high in postoperative cardiac and thoracic patients, where prevention/ treatment may be slightly different; treatment focuses on ventricular rate-control and/or conversion to sinus rhythm; anticoagulation may be given for chronic or recurrent atrial fibrillation

Note: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[a] All methods of prevention are in addition to judicious, goal-directed fluid resuscitation.

References

1. Acosta JA, Yang JC, Winchell RJ et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg*. 1998;186(5):528–533.
2. Zhang Q, Raoof M, Chen Y et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010 4;464(7285):104–107.

   Landmark basic science investigation of common mediators underlying septic and traumatic shock
3. Bagshaw SM, George C, Dinu I et al. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant*. 2008;23(4): 1203–12010.
4. Jacobs R, Honore PM, Joannes-Boyau O et al. Septic acute kidney injury: The culprit is inflammatory apoptosis rather than ischemic necrosis. *Blood Purif*. 2011;32(4):262–265.
5. Perner A, Haase N, Guttormsen AB et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124–134.
6. Landoni G, Biondi-Zoccai GG, Tumlin JA et al. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: A meta-analysis of randomized clinical trials. *Am J Kidney Dis*. 2007;49(1):56–68.
7. Joannidis M, Druml W, Forni LG et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit. Expert opinion of the Working Group for Nephrology, ESICM. *Intensive Care Med*. 2010;36(3):392–411.
8. Network VNARFT, Palevsky PM, Zhang JH et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008 3;359(1):7–20.
9. Investigators RRTS, Bellomo R, Cass A et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361(17):1627–1638.
10. Navarrete-Navarro P, Rodriguez A, Reynolds N et al. Adult respiratory distress syndrome among blunt and penetrating trauma patients: Demographics, mortality, and resource utilization over 8 years. *J Crit Care*. 2001;16(2):47–53.
11. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564–2575.

    Trial establishing the beneficial effect of conservative fluid management in patients with ARDS.
12. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW et al. Initial trophic vs full enteral feeding in patients with acute lung injury: The EDEN randomized trial. *JAMA*. 2012;307(8):795–803.
13. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301– 1308. *Trial establishing decreased mortality in ARDS patients ventilated with limited lung volume and peak inspiratory pressure*.
14. Gattinoni L, Tognoni G, Pesenti A et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med*. 2001; 345(8):568–573.
15. Guerin C, Gaillard S, Lemasson S et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA*. 2004; 292(19):2379–2387.
16. Bartlett RH. Extracorporeal life support in the management of severe respiratory failure. *Clin Chest Med*. 2000;21(3):555–561.

    Review of the principles, design, and uses of ECMO, by one of the original inventors.
17. Peek GJ, Mugford M, Tiruvoipati R et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351–1363.
18. Chatpun S, Cabrales P. Cardiac systolic function recovery after hemorrhage determines survivability during shock. *J Trauma*. 2011;70(4):787–793.
19. Papanikolaou J, Makris D, Saranteas T et al. New insights into weaning from mechanical ventilation: Left ventricular diastolic dysfunction is a key player. *Intensive Care Med*. 2011;37(12):1976–1985.
20. Rivers E, Nguyen B, Havstad S et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368–1377.

    Landmark paper establishing the principles and protocol of early goal-directed therapy.
21. Ho HC, Chapital AD, Yu M. Hypothyroidism and adrenal insufficiency in sepsis and hemorrhagic shock. *Arch Surg*. 2004;139(11):1199–1203.
22. Stein DM, Jessie EM, Crane S, et al. Hyperacute adrenal insufficiency after hemorrhagic shock exists and is associated with poor outcomes. *J Trauma Acute Care Surg*. 2013;74(2):363–370.
23. Annane D, Sebille V, Charpentier C et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862–871.

    Landmark trial supporting the mortality benefit of supplemental steroids for patients in septic shock with adrenal insufficiency.
24. Sprung CL, Annane D, Keh D et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111–124.

    Landmark "CORTICUS" trial showing no mortality benefit to steroid supplementation and disputing laboratory parameters of adrenal insufficiency.
25. Stathatos N, Levetan C, Burman KD et al. The controversy of the treatment of critically ill patients with thyroid hormone. *Best Pract Res Clin Endocrinol Metab*. 2001;15(4):465–478.

26. Van den Berghe G, Wouters P, Weekers F et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359–1367.

    Landmark paper establishing the benefits of strict blood glucose control in critically ill patients.

27. Investigators N-SS, Finfer S, Chittock DR et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297.

    Landmark "NICE-SUGAR" trial supporting more lenient approach to blood glucose control in critically ill patients.

28. Buchleitner AM, Martinez-Alonso M, Hernandez M et al. Perioperative glycaemic control for diabetic patients undergoing surgery. *Cochrane Database Syst Rev*. 2012;9:CD007315.

29. Gandhi GY, Nuttall GA, Abel MD et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Proc*. 2005;80(7):862–866.

30. Cohen MJ, Call M, Nelson M et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann Surg*. 2012;255(2):379–385.

31. Brohi K, Singh J, Heron M et al. Acute traumatic coagulopathy. *J Trauma*. 2003;54(6): 1127–1130.

32. Hui P, Cook DJ, Lim W et al. The frequency and clinical significance of thrombocytopenia complicating critical illness: A systematic review. *Chest*. 2011;139(2): 271–278.

33. Rotondo MF, Schwab CW, McGonigal MD et al. "Damage control": An approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma*. 1993; 35(3):375–382; discussion 82–83.

    Historical paper establishing the principles and potential benefits of damage-control laparotomy.

34. Shakur H, Roberts I, Bautista R et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32.

35. Boffard KD, Riou B, Warren B et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: Two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*. 2005;59(1):8–15; discussion 8.

    Trials establishing lack of mortality benefit for factor VIIa in trauma patients.

36. Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366(22):2055–2064.

    "PROWESS-SHOCK" trial showing no mortality benefit in patients with septic shock treated with activated Protein C.

37. Luchette FA, Pasquale MD, Fabian TC et al. A randomized, double-blind, placebo-controlled study to assess the effect of recombinant human erythropoietin on functional outcomes in anemic, critically ill, trauma subjects: The long term trauma outcomes study. *Am J Surg*. 2012;203(4):508–516.

    Trial establishing absence of benefit for use of recombinant erythropoietin supplementation in critically ill trauma patients.

38. Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999; 340(6):409–417.

    Landmark "TRICC" trial establishing the safety of a lower transfusion threshold for critically ill patients.

39. Zeltsman D, Rowland M, Shanavas Z et al. Is the incidence of hemorrhagic stress ulceration in surgical critically ill patients affected by modern antacid prophylaxis? *Am Surg*. 1996;62(12):1010–1013.

40. Kurt M, Litmathe J, Roehrborn A et al. Abdominal complications following open heart surgery: A report of 12 cases and review of the literature. *Acta Cardiol*. 2006;61(3): 301–306.

41. Marshall JC, Cook DJ, Christou NV et al. Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995; 23(10):1638–1652.

    Useful scoring system for prognosis of multi-organ failure.

42. Durham RM, Moran JJ, Mazuski JE et al. Multiple organ failure in trauma patients. *J Trauma*. 2003; 55(4):608–616.

43. Kim HD, Malinoski DJ, Borazjani B et al. Inhibition of intraluminal pancreatic enzymes with nafamostat mesilate improves clinical outcomes after hemorrhagic shock in swine. *J Trauma*. 2010;68(5):1078–1083.

44. Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal reexploration. *Ann Surg*. 1984;199(1):28–30.

    Historical paper exploring the physiology of abdominal compartment syndrome and decompressive laparotomy.

45. Cotton BA, Guy JS, Morris JA, Jr. et al. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock*. 2006;26(2):115–121.

46. Finfer S, Bellomo R, Boyce N et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–2256.

    "SAFE" trial establishing the equivalency of albumin and saline resuscitation.

47. Brandstrup B, Tonnesen H, Beier-Holgersen R et al. Effects of intravenous fluid restriction on postoperative complications: Comparison of two perioperative fluid regimens: A randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238(5):641–648.

48. Lobo SM, Ronchi LS, Oliveira NE et al. Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases major complications after high-risk surgery. *Crit Care*. 2011; 15(5):R226.

49. Duke MD, Guidry C, Guice J et al. Restrictive fluid resuscitation in combination damage control resuscitation: Time for adaptation. *J Trauma Acute Care Surg*. 2012;73(3):674–678.

50. Hata JS, Stotts C, Shelsky C et al. Reduced mortality with noninvasive hemodynamic monitoring of shock. *J Crit Care*. 2011;26(2):224 e1–e8.

51. Murthi SB, Hess JR, Hess A et al. Focused rapid echocardiographic evaluation versus vascular cather-based assessment of cardiac output and function in critically ill trauma patients. *J Trauma Acute Care Surg*. 2012; 72(5):1158–1164.
52. Kaiser ML, Kong AP, Steward E et al. Laser Doppler imaging for early detection of hemorrhage. *J Trauma*. 2011;71(2):401–406.
53. Clavijo-Alvarez JA, Sims CA, Menconi M et al. Bladder mucosa pH and Pco2 as a minimally invasive monitor of hemorrhagic shock and resuscitation. *J Trauma*. 2004; 57(6):1199–209; discussion 209–210.
54. Cancio LC, Batchinsky AI, Mansfield JR et al. Hyperspectral imaging: A new approach to the diagnosis of hemorrhagic shock. *J Trauma*. 2006;60(5):1087–1095.

12

Complications Associated with the Use of Invasive Devices in the Intensive Care Unit

J. Martin Perez

CONTENTS

The ability of the practitioner to care for the critically ill patient is closely associated with the types and functions of the many invasive and noninvasive devices that can be utilized in the intensive care unit (ICU). Despite the low incidence of complications associated with these invasive and noninvasive devices, if mortality and morbidity rates are to be reduced even further, the clinician must be aware of the many complications that may accompany the use of each type of device. Knowledge of these complications will enable the practitioner to not only implement preventive measures but also rapidly recognize and treat complications that may arise. This chapter will discuss the preventive measures and the treatment of complications associated with the use of central venous lines, arterial lines, intracerebral pressure monitors, gastric tubes, and thoracostomy tubes.

12.1 Central Venous Catheterization

The increasing complexity of the ICU has paralleled the development and increased use of central venous catheterization (CVC). The CVC has become a mainstay in the ICU; several million devices are used annually. Unlike the catheters introduced by Broviac et al. and

Hickman et al., the catheters used in the ICU lack cuffs and do not require tunneling. Thus, they can be easily placed at the bedside with the Seldinger method or other percutaneous techniques. Although central venous lines are technically less challenging to use and care than the Broviac and Hickman catheters, central venous lines are associated with their own set of complications.

12.1.1 Venous Air Embolus

The complication of venous air embolism is rare; in fact, the occasional case report represents the majority of the literature about this entity. However, this complication should be suspected if a patient becomes dyspneic on insertion of a central venous line. Venous air embolism can lead to hypotension, acute pulmonary edema, and cardiac arrest. If the foramen ovale is patent, the risk of an ischemic stroke also exists. During the physical examination of a patient with a venous air embolism, a murmur with a characteristic mill wheel may be heard over the right side of the heart. Because a small pressure gradient of 4 mmHg can cause enough air to enter in 1 s to cause a fatal air embolus, prevention techniques should include attempts to increase intrathoracic pressure. Such an increase can be accomplished by placing the patient in Trendelenburg position or by asking the patient to perform a Valsalva maneuver or to hum during placement of a central venous line. Intrathoracic pressure can also increase during exchange over a guide wire. Once venous air embolism occurs, the patient should be placed in the left lateral decubitus position; a syringe should be used to aspirate fluid, air, or both from the line; and a pericardiocentesis can be performed, if necessary, by inserting a needle into the right ventricle in an attempt to aspirate air.

12.1.2 Pneumothorax

A pneumothorax from central venous lines occurs when the needle injures lung parenchyma and air escapes into the pleural space. This type of complication occurs in approximately 1%–4% of all central venous line attempts. Symptoms such as coughing, wheezing, chest pain, and dyspnea may be evident; however, in approximately 0.5% of cases, the appearance of symptoms may be delayed [1]. Regardless of when the symptoms appear, a pneumothorax may develop into a tension pneumothorax, and patients who are on a ventilator may be at increased risk [1]. In a study of patients with cancer for whom CVC was established through the subclavian approach, older patients with a body mass index of <19 were more likely to experience pneumothorax [2]. Pneumothoraces may occur with the same frequency whether the subclavian approach is used or the internal jugular approach is used. A relatively high rate of pneumothorax development is also associated with a difficulty in obtaining CVC, such as repeated attempts at cannulation [2].

The diagnosis of pneumothorax is facilitated by an expiratory chest radiograph of the upright patient; however, most chest x-rays taken in the ICU are performed with the patient in the supine position. When patients are supine, air usually presents along the lung base and mediastinum, and this makes the diagnosis of a pneumothorax by x-ray relatively more difficult.

The risk of a pneumothorax can be reduced if the patient lies on a rolled towel placed under the thoracic spine and between the scapulae during cannulation of the vessel. If the risk of a pneumothorax is to be eliminated, a cut-down of the cephalic vein can be performed. Rates of pneumothorax are lower if experienced physicians perform the CVC procedure. Management of this complication may include observation if pneumothoraces are <30% and placement of a pigtail catheter or chest tube if the pneumothorax is larger than 30% or expands after initial observation, or if the patient is on a ventilator.

12.1.3 Hemorrhage and Hemothorax

Hemorrhage resulting from central line catheterization can be categorized as either localized or regional. Localized hemorrhage is confined to the site of access, whereas regional hemorrhage occurs in the soft tissue of the neck or extends to the thoracic and mediastinal spaces. Localized hemorrhage due to central line access is uncommon, even if coagulopathy or thrombocytopenia is present.

Carotid artery puncture, a complication that occurs during approximately 2%–10% of attempts at internal jugular line placement [3], usually manifests itself as a hematoma when the needle is removed from the artery. Insertion of a needle into the carotid artery may be indicated by bright red, pulsatile blood that fills the hub of the syringe. Removing the needle and applying pressure usually suffices in arresting the bleeding. Close follow-up of the patient who has experienced carotid artery puncture is prudent because acute airway obstruction has been reported from a large cervical hematoma [4]. Complications have also resulted from cannulation of the carotid artery [5]; these complications include hematoma, arteriovenous fistula, stroke, and death [6]. If cannulation of the carotid artery is suspected but the chest x-ray does not reveal it or is inconclusive, an arterial blood gas can be obtained, or catheter pressures can be transduced to confirm a venous wave form.

Hemorrhage that results in a hemothorax is not commonly reported. A hemothorax can be caused by an injury to the subclavian artery or vein at the time of insertion or by the gradual erosion of the superior vena

cava (SVC). A hemothorax can occur ipsilaterally or contralaterally to the insertion site. Reports of hemothorax caused by the internal jugular approach are rare.

Diagnosis of hemothorax can be based on the results of plain-film radiography. However, a substantial hemothorax can cause tachycardia and hypotension. Hemothorax resulting from erosion of the SVC can be prevented by careful placement of the catheter tip so that it does not press against the SVC when placed from left side [7]. Once the SVC has been injured, conservative measures are recommended for maintaining the volume and treating any coagulopathy. However, surgical intervention is usually required for both adults and children.

Bleeding into the mediastinum can occur when a vein is injured or the catheter penetrates the mediastinum. This complication most commonly appears initially on chest radiographs as a widened mediastinum, but it can also cause chest pain after line insertion. When the mediastinum is widened after the placement of a central line, additional chest radiographs should be obtained with the injection of contrast material through the central catheter. If extravasation of the contrast agent occurs and the catheter is in the mediastinum, it should be withdrawn quickly; however, if the catheter is in the vein, it can be left in place, with careful observation of the patient's condition. Most mediastinal hematomas are self-limiting, and the venous injury will resolve without intervention. This is unlike a hemorrhage into the pleural space, which usually requires further intervention. Mediastinal hematomas occur in <1% of patients who undergo line placement. The unrecognized presence of a catheter in the mediastinum, regardless of the type of fluid being administered, is associated with high morbidity and mortality rates [8].

12.1.4 Cardiac Tamponade

According to the 1989 Food and Drug Administration (FDA) drug bulletin, cardiac tamponade is the most commonly reported lethal complication associated with CVC. Cardiac tamponade occurs when the catheter tip penetrates the pericardium. Cardiac tamponade is signaled by an acute onset of tachycardia, hypotension, jugular venous distention, and *pulsus paradoxus*. However, the symptoms of tamponade may also be delayed.

Cardiac tamponade can be prevented by careful placement of the catheter tip. The FDA has stated that placing the tip into the atrium is associated with a higher risk of tamponade. There have also been reports of cardiac tamponade when the catheter tip is placed in the SVC [9]. Cardiac tamponade is treated by rapidly increasing intravenous volume followed by subxiphoid pericardiocentesis to stabilize the patient's condition. Surgical intervention may be warranted to repair lacerations of the atria or the SVC, as well as the need for a pericardial window as a more definitive measure.

12.1.5 Central Line–Associated Bloodstream Infection

CVC devices are a common source for bacterial nosocomial infections in the ICU setting. In fact, central line-associated bloodstream infection (CLABSI) is the most frequently occurring type of bloodstream infection in the ICU: approximately 250,000 patients develop CLABSI each year [10]. According to one study [11], the incidence of CLABSI can be as high as 2.7 of every 100 patients admitted to a surgical ICU. A case–control analysis found that such infections are associated with a 35% increase in mortality, a 24-day increase in median length of stay, and a $40,000 increase in expense per survivor. The National Nosocomial Infections Surveillance (NNIS) system reported that a median range of bloodstream infections associated with central lines was 2.4–7.8 central-line patient days [12].

The pathogenesis of CLABSI involves colonization of the catheter by microorganisms that inhabit the skin surface at the site of catheter insertion [10]. Other important sources of catheter colonization are contaminated infusates, distant sites of infection, and hub contamination. Microorganisms migrate along the transcutaneous tract and adhere to the catheter's biofilm. The exact sequence of events leading from biofilm colonization to bloodstream infection is poorly defined, as are the factors that determine establishment of infection. According to the NNIS, the most commonly reported organisms involved in CLABSI, in decreasing order of frequency, are coagulase-negative *Staphylococcus* spp. (39.3%), *Staphylococcus aureus* (10.7%), *Enterococcus* spp. (10.3%), *Candida albicans* (4.9%), and other Gram-negative organisms.

CLABSI is defined as an infection in which the same organism with a similar drug susceptibility pattern is isolated from a catheter segment and simultaneously from peripheral blood in a patient with clinical manifestations of sepsis and no other apparent source of bloodstream infection [13]. If signs of local infection, such as erythema, induration, tenderness, or purulent drainage, develop at the site of catheter insertion, the catheter should be removed and the catheter segment submitted for culture. If CLABSI is established, in addition to catheter removal, systemic antibiotics are usually indicated. Currently, a lack of consensus exists regarding antibiotic selection and duration of therapy; however, with the increasing emergence of methicillin-resistant strains, vancomycin is commonly used as first-line therapy. Most clinicians will develop a treatment plan according to the isolate, known susceptibility patterns, and response to therapy; this response is indicated by clinical variables

such as fever and leukocytosis. Persistent fever, leukocytosis, and bacteremia may warrant further investigation of a deep-seated infection such as suppurative thrombophlebitis. In patients who are febrile but have no obvious clinical source of infection and no clinical signs of infection at the site of catheter insertion, the catheter segment may be submitted for quantitative culture. If the culture of the catheter segment demonstrates significant microbial growth, the replacement catheter should be removed and a new catheter should be inserted at a different site.

A decline in national CLABSI rate was found in all ICUs in the United States over an 8-year period. In 2009, an estimated 25,000 fewer CLABSIs occurred in the US ICUs in comparison to 2001, representing a 58% reduction with 6000 fewer deaths and savings to the healthcare system of $414 million. In 2001, the pooled mean ICU CLABSI adjusted for definition change was 3.64 per 1000 central-line days as reported by the NNIS system, 1999–2003. By 2009, the pooled mean ICU CLABSI rate had fallen to 1.65 per 1000 central- line days as reported by the National Healthcare Safety Network, 2009 [14].

The decline has been attributed in large part to large-scale regional and statewide projects such as the Michigan Keystone Project that have demonstrated substantial reductions in CLABSI rates by adhering to recommended best practices for the insertion of central lines. Utilization of a "bundle" of evidence-based practices coupled with programs that improve staff communication and teamwork known as the Comprehensive Unit-Based Safety Program (CUSP) have likely contributed to the decline of CLABSI rates [15].

Multiple methods have been studied for preventing CLABSI. Ruesch et al. [16] have reviewed several prospective studies demonstrating that the subclavian site of insertion is associated with a lower risk of infection than is the jugular or femoral sites. Another study [17] has shown that chlorhexidine gluconate is superior to 10% povidone–iodine for skin preparation in the prevention of CLABSI. A prospective observational study [18] showed that full-barrier precautions, including sterilized gloves, gown, cap, mask, and barrier drape that covers the entire patient, reduce the incidence of CLABSI associated with the insertion of central venous devices. Several studies have demonstrated that the use of transparent occlusive dressings increases the risk of clinically significant catheter colonization. The use of antibiotic ointments at the catheter insertion site appears to increase catheter colonization with fungi. Using chlorhexidine-impregnated sponges as a dressing for central venous, pulmonary artery, and arterial catheters has been shown to significantly decrease catheter colonization and CLABSI [19]. Minocycline- or rifampin-impregnated catheters are associated with lower rates of catheter colonization and CLABSI than are catheters impregnated with chlorhexidine/silver sulfadiazine [20]. Patients should be asked about the potential allergic reactions to the components of the catheter before it is placed. The emergence of resistant organisms in response to the use of antibiotic-impregnated catheter may have an impact on future clinical use.

Preventative measures that have been proven to reduce catheter colonization and CLABSI should be implemented and adhered to as a part of an overall effort to reduce nosocomial infection rates associated with the use of central venous access devices.

12.1.6 Thrombosis

Central venous thrombosis after placement of a central line appears to be related to several factors. Larger catheters, which are more likely to obstruct flow, have been shown to be associated with higher thrombosis rates [21]. Moreover, the location of the catheter tip may be a factor. An analysis of several retrospective studies has shown a correlation between placement of catheter tips high in the SVC and higher rates of thrombosis [22].

Patients with bone marrow transplants, malignancies, sickle cell disease, and renal failure are more likely to experience thrombosis [23]. Other factors that play a role in thrombosis are hypercoagulable states secondary to illness and endothelial injury from catheter insertion.

Venous thrombosis can be diagnosed by duplex ultrasonography. However, duplex ultrasound is unable to adequately visualize the subclavian vein deep to the clavicle. This limitation is partially overcome by the fact that the presence of subclavian thrombosis can be predicted by a lack of flow in the internal jugular or axillary vein. This observation of a lack of flow may be adequate for the diagnosis of thrombosis. However, if a patient exhibits symptoms such as superficial venous engorgement, unilateral arm swelling, pain, and discoloration, contrast venography should be performed even if the findings of venous duplex ultrasonography are negative.

Management of thrombosis depends on the patient's symptoms and on whether the catheter is functioning properly. If a patient has no symptoms, a functional catheter can safely be left in place while anticoagulation therapy is started to prevent clot propagation, or to prevent the formation of a pulmonary embolism from an upper-extremity thrombosis (the risk of such an embolism is <10%) [24]. If the catheter is clotted or if the patient's symptoms worsen, the catheter should be removed.

Prevention of thrombosis should take into account the location of the catheter, with the optimal placement being just proximal to the right atrium. Anticoagulation has also been useful in preventing the formation of thrombosis. Both heparin [25] and low doses of Coumadin [1] (warfarin sodium; 1 mg/day) [26] have been shown to effectively reduce the rate of thrombosis

formation. However, no studies have compared the effectiveness of heparin with that of Coumadin in preventing thrombosis.

The incidence of complications such as fracture of the catheter, loss of the guide wire, and arteriovenous fistula is unknown. However, when fracture or loss of the guide wire has occurred, the catheter can be safely removed via interventional radiologic techniques [27].

12.2 Arterial Lines

The radial, brachial, dorsal pedal, and femoral arteries can be safely cannulated for invasive blood pressure monitoring and frequent blood draws. The complications commonly associated with these catheters are those associated with central venous lines—infection, bleeding, and thrombosis. The most common complication associated with these catheters, however, is not infection, as is the case with central venous lines. In a study of more than 2000 patients [28], the most common complications were vascular insufficiency (4%), hemorrhage (2%), and infection (0.5%).

Arterial thrombosis due to catheterization can occur in as many as 25% of patients with radial arterial lines, but the occurrence of this complication is lower among patients with femoral arterial lines [29]. Fortunately, thrombosis of the radial or femoral artery rarely causes ischemia to the distal extremity. Flushing the catheter with heparin has been shown to decrease the rate of thrombosis in both femoral and radial arterial lines [30].

The incidence of infection is similar with femoral and radial arterial lines. Staphylococcal species continue to be the most common organisms associated with catheter-related infections. Although many ICUs routinely change arterial line tubing and solution in an attempt to decrease infection rates, O'Malley et al. [31] demonstrated in a prospective study that routinely changing the tubing increases the likelihood of introducing contamination into the pressure-monitoring system.

Preventing arterial catheter infections requires methods similar to those used to prevent infection of central venous lines. Sterile techniques should be used during catheter placement, and hygienic manipulation should be employed when the line is accessed.

12.3 Gastrostomy Tubes

Although their use for gastrointestinal decompression has been widely accepted for some time, it was not until the late 1970s that their usefulness in providing enteral access for nutritional support was appreciated. Alexander [32] reported that the outcome of children with burns to 60% of their total body surface area was improved when enteral nutrition rather than parenteral nutrition was used. Several subsequent studies continued to report the benefits of enteral nutrition over parenteral nutrition in reducing the rates of nosocomial infection.

Although gastrointestinal intubation has improved clinical outcome by providing enteral nutrition and gastric decompression, the placement of nasogastric tubes (NGT) can result in aspiration pneumonia, esophageal perforation, sinusitis, malposition, and arterial esophageal fistula.

12.3.1 Aspiration Pneumonia

The incidence of aspiration pneumonia increases among patients with certain risk factors. Mullan and Roubenoff [33] have stated that the incidence of aspiration ranges from 1% to 30%. Risk factors in aspiration pneumonia include delayed gastric emptying, decreased airway or swallow reflexes, mechanical ventilation, large-bore feeding tubes, and neurologic injury. This variation is most likely due to the variety of patient populations included and the different methods used in the diagnosis of aspiration pneumonia. In one study, the incidence of aspiration among patients receiving enteral nutrition was approximately 5%, and mortality from aspiration in this population was <5%. A retrospective analysis using national medical claims has reported the mortality of aspiration pneumonia to be as high as 23.9%. Mortality is correlated with the amount of aspiration, acidity of aspirate, number of lobes involved, and the overall condition of the patient.

A dramatic change in the appearance of the chest on radiograph can suggest the diagnosis of aspiration pneumonia; however, such changes may not be evident until 24 h after aspiration has occurred. The diagnosis of aspiration may be aided by testing the pulmonary aspirate for glucose. Previously, Food Drug and Cosmetic Blue No.1 dye was added to enteral nutrition formulas in order to facilitate the detection of gastric aspirate in tracheal secretions. However, reports [34] of systemic blue dye absorption and associated adverse outcomes are emerging. This has caused many hospitals to withdraw the practice of adding dye to their enteral formulas. Bronchoscopy is a helpful tool that can be used to diagnose aspiration in addition to providing immediate lavage for removing aspirate.

Aspiration can be prevented by correctly placing the NGT and closely monitoring gastric residuals. Other preventive measures include elevating the head of a patient's bed to an angle of 30°–45° so that the patient is not

supine. Using small-bore NGT has also been suggested as a means of decreasing aspiration pneumonia and reflux. Conversely, the incidence of pneumothorax and tracheal intubation with the insertion of a feeding tube is increased with small-bore nasoenteral tubes (<5 mm diameter). Aspiration should be treated by removing the aspirate with nasotracheal suction or bronchoscopy when necessary. Antibiotics, intubation, and ventilator support may be indicated. Other treatments such as corticosteroids therapy have not proven to be beneficial.

12.3.2 Esophageal Perforation

Esophageal perforation is a rare complication of nasogastric intubation; however, its occurrence may be fatal. One study of hospitalized patients with esophageal perforation showed that the most common cause of this complication is iatrogenic [35].

The most common site of iatrogenic perforation is the thoracic esophagus. The mortality rates associated with esophageal perforation range from 16% to 30%, but the mortality rate is lower when the cause of perforation is iatrogenic or when the injury is promptly recognized and treatment is not delayed. The risk of esophageal perforation is higher among patients with carcinoma, stricture, or altered mental status, as well as among those who have undergone tracheal intubation or have undergone multiple attempts at nasogastric intubation [36].

In the critically ill, the diagnosis of esophageal perforation may be difficult and requires a high level of clinical suspicion. The most common clinical features are neck and substernal pain, fever, and subcutaneous or mediastinal emphysema that may cause nuchal crepitus or xiphisternal crepitus (also known as Hamman's sign). Radiography of the chest or abdomen with the patient in the upright position is diagnostic in most cases. However, when the results are negative and the level of clinical suspicion remains high, esophageal study using Gastrografin [1] as a contrast agent should be performed. The prognosis of esophageal perforation is dependent upon early diagnosis and treatment and the site and size of the perforation. Medical management includes the use of broad-spectrum antibiotics and nasogastric decompression. These treatments may be adequate for patients with cervical perforation, who are asymptomatic and whose condition is hemodynamically stable. Surgical management, if necessary, involves drainage alone, drainage and repair, or drainage and diversion.

12.3.3 Sinusitis

The use of a NGT with tracheal intubation has been associated with an increased risk of sinusitis. In these cases, sinusitis occurs because the NGT obstructs the ostial meatal complex and impairs the drainage of mucus. According to Fasqualle et al. [37], nosocomial sinusitis occurs mostly in the ICU, and the most commonly involved organism is *Pseudomonas aeruginosa*, *Streptococcal pneumonia*, and *Hemophilus influenza*.

Pain and pressure over the cheeks are the most common symptoms of sinusitis, but may be difficult to assess among ICU patients. Purulent nasal discharge may not be present, but if it is, the likelihood of sinusitis is increased. Often, patients initially present with fever of unknown etiology. Once the most common causes of fever have been ruled out, further evaluation of the sinuses is warranted if intubation and an NGT are in use. Westergren et al. [38] have advocated the use of ultrasonography as a sensitive test for the presence of fluid and edema in the sinuses of critically ill patients. For improved diagnostic accuracy, computer tomography of the sinuses (coronal view) can be performed. Sinoscopy can aid in the diagnosis by yielding a culture specimen that can be tested for the purpose of directing antibiotic therapy; sinoscopy can also be used to treat sinusitis by creating an ostium to allow drainage of sinus secretions. Treatment consists of antibiotic therapy targeted at specific bacteria, removal of any foreign objects from the nose, using nasal decongestants, and if necessary, sinoscopy drainage.

12.3.4 Malposition

Retrospective case reviews of complications associated with NGT have indicated that approximately 0.5%–1% of NGT are malpositioned [39] The most common location of malpositioning is the tracheal bronchial tree, especially the bronchi of the right lower lobe; misplacement in the pleural space, intracranial space, and internal jugular vein is rarely reported. The most common types of complication of malpositioned NGT are loss of tidal volume, pneumonia, and pneumothorax.

NGT are contraindicated for patients with basal skull injuries, because such injuries increase the likelihood of intracerebral placement of the tube. However, this type of malpositioning has also been observed in patients without basal skull fractures [40]. Diagnosis of malpositioning has been based on several commonly acceptable clinical guidelines. Proper placement of the NGT can be performed by insufflation of air in the tube with auscultation over the stomach or by aspiration of gastric contents. Aspiration prior to insufflation is preferred, in order to prevent a fatal air embolus, in the rare case of NGT malposition in a vascular structure. However, malpositioning of the NGT in the left lung base can also be detected by auscultation over the stomach, and secretions can also be suctioned from the bronchial tree, the esophagus and stomach, or the brain. Bankier et al. [39] have demonstrated that the clinical signs of NGT

malpositioning may not accurately indicate the tube's location. A chest radiograph taken with the patient in the supine position can accurately detect malpositioning. Prevention lies in the use of clinical guidelines described earlier and of chest radiographs when there is any doubt about the position of the NGT.

12.3.5 Arterial Esophageal Fistula

Arterial esophageal fistula is a rare complication of gastric esophageal intubation and can involve the aorta and other great vessels in the chest. Symptoms are similar to those of aortic enteric fistulas. Sentinel hemorrhage, which first alerts the practitioner to the presence of this complication, is followed by a symptom-free period that precedes exsanguinations. Reports [41] suggest that anomalies of the aortic arch predispose patients to this complication.

12.4 Thoracostomy Tubes

Thoracostomy tubes have been used since the time of Hippocrates but were not popularized until the Korean War. Indications for chest tube placement are pneumothorax, tension pneumothorax, penetrating chest injury, hemothorax, empyema, chylothorax, postthoracic surgery, and bronchopleural fistula. Thoracostomy tubes can be placed via sharp cut-down, by the trochar method (the use of a sharp metal rod), or by percutaneous Seldinger techniques. The percutaneous technique using the Seldinger method is employed when smaller pigtail-type chest tubes are used. Complications associated with chest tubes can be separated into three categories.

12.4.1 Empyema

Empyema occurs in 1%–16% of patients; the higher incidence occurs among trauma patients [42]. Chest tubes placed for pleural effusions are associated with higher rates of empyema. This complication is indicated by purulent exudative fluid with a low pH, low glucose concentrations, and a high white blood cell count. Empyema is treated with intravenously administered antibiotics, chest tube drainage, and, possibly, open thoracotomy.

Prevention of empyema begins with the use of appropriate sterile technique. The use of antibiotics remains controversial, with early studies demonstrating no benefit or only minimal benefit in association with their use. However, more recent studies and a meta-analysis by Evan et al. [43] of six prospective, randomized studies found that a beneficial effect was associated with the use of antibiotics effective against *Staphylococcus* spp.

12.4.2 Pneumothorax and Hemothorax

Pneumothorax and hemothorax are the most common indications for chest tube placement; however, these complications may also occur in association with thoracostomy tube placement and use. Thoracostomy tube placement may fail as an effective treatment for these conditions, and pneumothorax and hemothorax may recur after the tube has been removed or may be an iatrogenic sequela of removal. A study of chest radiographs after thoracostomy tube insertion demonstrated that the most common complications were tube malposition and unresolved pneumothorax and hemothorax [44]. Recurrence of a pneumothorax after thoracostomy tube removal is most likely caused by the entry of air through the wound or by reaccumulation from a small air leak. To prevent such pneumothoraces, the thoracostomy tube should be pulled out quickly while the patient is exhaling, so that intrapleural pressure is positive, thus decreasing the risk of air entry. When placing chest tubes, some practitioners place a second stitch through the site of chest tube insertion; this stitch is left untied. When the chest tube is removed, a second person places tension on this stitch to close the incision as the chest tube is being removed.

To decrease the likelihood of a recurrent pneumothorax caused by an undetected small air leak, it is best to convert the tube to water seal before the tube is removed. In a randomized trial, Martino et al. demonstrated that converting thoracostomy tubes to water seal before removing them reduces the number of pneumothoraces that occur after tube removal and also reduces the need for chest tube replacement [45].

Pneumothorax associated with thoracostomy tube placement can be treated in several ways. The pneumothorax can be carefully observed and may resolve even if it is not adequately drained by the tube. Increasing the suction of the thoracostomy tube, by increasing the column of fluid in a wet hemovac system or simply turning the pressure dial on a dry hemovac system, can resolve a persistent pneumothorax. A second thoracostomy tube can also be placed to resolve the pneumothorax or hemothorax. Pleurodesis may be necessary to resolve a persistent leak or effusion, but a thoracotomy is rarely necessary for adequate resolution of a pneumothorax.

12.4.3 Malpositioning

In one radiologic evaluation of thoracostomy tubes placed in the emergency room, tube malpositioning was the reason for as many as 26% of inadequate tube placements and was the most common complication [44]. Malpositioned chest tubes can be located in the subcutaneous tissue of the chest wall or in incorrect locations in the intrathoracic and intra-abdominal regions. A malpositioned thoracostomy tube may cause injury to the

visceral organs and may even result in death. One study [44] suggests that chest tube placement by clinicians other than surgeons is associated with a higher rate of complications. The use of trochars for insertion is also associated with a high rate of complications; thus, this method of tube insertion has largely been replaced by blunt dissection.

12.4.4 Re-expansion Pulmonary Edema

Re-expansion pulmonary edema (RPE) can occur after pulmonary re-expansion by thoracostomy tube for pneumothorax, pleural effusion, or atelectasis. One retrospective review of the placement of thoracostomy tubes for pneumothorax in Japan [46] suggested that RPE occurs in approximately 14% of cases. However, in the United States, RPE is generally considered a rare complication; the mortality rate associated with RPE may be as high as 20% [47]. Although the cause of RPE is unknown, certain risk factors such as young age, a large pneumothorax, and long duration of collapse are associated with RPE [48]. Some patients with RPE may exhibit no symptoms other than radiographic findings; others may experience severe tachypnea, tachycardia, hypoxemia, or chest pain. The two most common symptoms are dyspnea and chest pain, which usually occur within minutes to hours of re-expansion.

Diagnosis of RPE is based on chest radiography, which shows pulmonary edema in a previously collapsed lung. Cases of contralateral RPE have also been reported [47]. Treatment involves supportive care, which may include hemodynamic and ventilatory support; most cases are self-limiting and resolve within a week.

12.5 Intracranial Pressure Monitoring

Intracranial pressure (ICP) monitoring plays a key role in the management of increased ICP. ICP monitoring is frequently used for patients with brain injuries and those undergoing elective neurosurgery. Complications associated with ICP monitoring include infection and hemorrhage, as well as malfunction, obstruction, and malpositioning of the tube. Long-term morbidity and mortality associated with complications of ICP monitoring appear to be rare.

12.5.1 Infection

Infection related to ICP monitoring is characterized by positive results from either a culture of cerebrospinal fluid or a culture of material on the intracranial portion of the catheter, along with clinical signs of infection. No semiquantitative or quantitative methods exist for distinguishing infections of the ICP monitoring device from colonization of the device, and clinical signs of infection are needed to establish the diagnosis of infection. Colonization of ICP monitors has been associated with either implantation for more than 5 days or irrigation of fluid-coupled devices. In one study, the incidence of bacterial colonization increases from 6% to 19% when irrigation was employed [49]. Differences in the rates of colonization of ICP devices appear to be related to the type of device used. Parenchymal devices are associated with the highest average rates of colonization (14%; range, 11.7%–16.6%); the other types of devices associated with colonization are subdural devices (4%; range, 1%–10%), subarachnoid devices (5%; range, 0%–10%), and ventricular devices (5%; range, 0%–9.5%) [48]; for all types of devices, the rates of colonization increased as time of implantation increased. A retrospective cohort study [50] yielded similar results in a pediatric subgroup of patients; the infection rate associated with Camino [1] fiberoptic monitors was 0.3%. There is no evidence-based consensus regarding antibiotic prophylaxis for various classes of devices or for duration of implantation.

12.5.2 Hemorrhage

Hemorrhage associated with ICP monitoring has not been clearly defined in many reports but appears to occur infrequently; the overall incidence of hematoma is 1.4%. In one study, substantial hematomas requiring evacuation occurred in 0.5% of patients who required ICP monitoring [51].

12.5.3 Malfunctioning and Malpositioning of ICP Monitors

Malfunctioning and displacement of ICP monitors are the most frequently reported complications associated with the use of these devices. Malfunction or obstruction has been observed in association with 6.3% of fluid-coupled ventricular devices, 16% of subarachnoid bolts, and 10.5% of subdural catheters [52,53]. In a pediatric population, Camino fiberoptic monitors malfunctioned in 2.6% of cases and were displaced in 1% [50]. The implications of malfunction and displacement include inaccurate ICP readings, potential morbidity associated with reinsertion, and additional cost.

12.6 Conclusion

Invasive devices, such as lines and tubes, have increased the ability of the practitioner to care for critically ill

patients in the ICU. However, although such devices can be invaluable tools in caring for patients, their use is also associated with significant morbidity and mortality. Understanding the potential pitfalls associated with these devices will increase the clinician's ability to diagnose and treat such complications and to implement strategies that may prevent the occurrence of such complications in the future.

Complications with the Use of Invasive Devices in the ICU

CVC	Complications	Prevention
Venous air embolism	Case reports (rare)	Trendelenburg
Pneumothorax	1%–4%	Technique
Hemorrhage (local)	Case reports (rare)	Technique INR platelets—normal
Carotid artery puncture	2%–10% [9]	Ultrasound
Hemorrhage (mediastinal)	<1% [14]	Catheter position, CXR
Cardiac tamponade	Case reports (rare)	Catheter position, CXR
CLABSI	1.65–3.64 per 1.000 line days	Scrub the hub [23] Chlorhexidine patch [23]
Thrombosis	Rate unknown	Heparin
Catheter fracture	Rate unknown	
Arteriovenous fistula	Rare	
Guidewire loss	Rare	Technique
Arterial catheterization		
Vascular insufficiency	4% [35]	Allen test
Hemorrhage	2% [35]	
Infection	0.5% [35]	Technique, site
Arterial thrombosis	25%	
Gastrostomy tubes		
Aspiration	1%–30% [41]	CXR, auscultate, aspirate
Esophageal perforation	Rare	Technique
Sinusitis		Avoid nares
Malposition		CXR, auscultate, aspirate
Arterial esophageal fistula	Rare	
Thoracostomy tubes		
Infections		
Empyema	1%–16% [50]	Technique
Chest tube site infection		Antibiotic, technique
Pneumonia		Antibiotic
Anatomic		
Subcutaneous emphysema		Technique, CXR
Pneumothorax		Technique
Hemothorax/pleural effusion		Technique
Arterovenous fistula		
Malposition (subcutaneous, intrathoracic, intraabdominal)		Technique
Physiologic (re-expansion pulmonary edema, Horners Syndrome, myocardial ischemia)		
ICP		
Infection	1%–16%	Technique
Hemorrhage	1.4%	Technique
Malfunction	6%–16%	

References

1. Plewa MC, Ledrich D, Sferra JJ. Delayed tension pneumothorax complicating central venous catheterization and positive pressure ventilation. *Am J Emerg Med* 1995; 13(5):532–535.
2. Harrington KJ, Pandha HS et al. Risk factors for pneumothorax during percutaneous Hickman line insertion in patients with solid and hematologic tumors. *Clin Oncol* 1995; 7(6):373–376.
3. Seneff MG. Central venous catheterization: A comprehensive review. *Intensive Care Med* 1987; 2:163–175, 218–232.
4. Wiemann J, Frass M, Traindl O. Acute upper airway obstruction caused by cervical hematoma as a complication of internal jugular venous catheterization. *Acta Med Aust* 1990; 17(4):77–79.
5. Silverman JM, Olson KW. Avoiding unintentional arterial cannulation. *Crit Care Med* 1990; 18(4):460.
6. Heffner JE. A 49 year-old man with tachypnea and a rapidly enlarging pleural effusion. *J Crit Illness* 1994; 9:101–109.
7. Harrer J, Brtico M, Zacek P et al. Hemothorax-a complication of subclavian vein cannulation. *Acta Med* 1997; 40(1):21–23.
8. Sheep RE, Guiney WB. Fatal cardiac tamponade occurrence with other complications after left internal jugular vein catheterization. *JAMA* 1982; 248:1632–1635.
9. Karnauchow PN. Cardiac tamponade from central venous catheterization. *J Can Med Assoc* 1986; 135:1145–1147.
10. Maki DG. Infection caused by intravascular devices used for infusion therapy: Pathogenesis, prevention, and management. *Infections Associated with Indwelling Medical Devices*, 2nd edn. Washington, DC: ASM Press, 1994, pp. 155–205.

    An outstanding review of the basic areas of pathogenesis, prevention, and management of catheter-associated bloodstream infection.
11. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infections in critically ill patients: Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994; 271:598–601.

12. National Nosocomial Infections Surveillance (NNIS) System. December 2000. Available at http://www.cdc.gov/ncidod/dhqp/pdf/nnis/DEC2000sar.PDF. Accessed June 16, 2006.

    The National Healthcare Safety Network (NHSN) is a secure, Internet-based surveillance system that integrates and expands legacy patient and health-care personnel safety surveillance systems managed by the Division of Healthcare Quality Promotion (DHQP) at CDC. NHSN also includes a new component for hospitals to monitor adverse reactions and incidents associated with receipt of blood and blood products. Enrollment is open to all types of health-care facilities in the United States, including acute care hospitals, long-term acute care hospitals, psychiatric hospitals, rehabilitation hospitals, outpatient dialysis centers, ambulatory surgery centers, and long-term care facilities.
13. Pearson ML. Hospital Infection Control Advisory Committee. Guidelines for prevention on vascular device-related infections. *Am J Infect Control* 1996; 23: 262–277.
14. Srinivasan A, Wise M, Bell M et al. Vital signs: Central line-associated blood stream infections—United States, 2001, 2008, and 2009. *MMWR Morb Mortal Wkly Rep* 2011; 60(8):243–248.
15. Pronovost P, Weast B, Rosenstein B et al. Improving patient safety in intensive care units in Michigan. *J Crit Care* 2008; 23:207–221
16. Ruesch S, Walder B, Tramer MR. Complications of central venous catheters: Internal jugular versus subclavian access—A systemic review. *Crit Care Med* 2002; 30(2):454–460.
17. Chaiyakunapruk N, Veenstra DL, Lipsky BA et al. Chlorhexadine compared with povidone-iodine solution for vascular catheter site care: A meta-analysis. *Ann Intern Med* 2002; 136(11):792–801.
18. Raad II, Hohn DC, Gilbraith BJ. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994; 15:231–238.

    Randomized controlled trial of maximum barrier precautions versus use of sterile gloves and small drape during insertion of nontunneled central venous catheters for cancer chemotherapy. Maximal barrier precautions markedly reduced the early infection rate.
19. Maki DG, Ringer M, Alvarado CJ. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991; 338:339–343.

    668 catheters were randomized to 10% povidone-iodine, 70% alcohol, or 2% aqueous chlorhexidine disinfection of the site before insertion and for site care every other day thereafter. Chlorhexidine was associated with the lowest incidence of local catheter-related infection (2.3 per 100 catheters vs. 7.1 and 9.3 for alcohol and povidone-iodine, respectively, p = 0.02) and catheter-related bacteraemia (0.5 vs. 2.3 and 2.6). They conclude that use of 2% chlorhexidine, rather than 10% povidone-iodine or 70% alcohol, for cutaneous disinfection before insertion of an intravascular device and for postinsertion site care can substantially reduce the incidence of device-related infection.
20. Veenstra DL, Lipsky BA, Saint S. The cost effectiveness of minocycline/rifampin versus chlorhexidine/silver sulfadiazine central venous catheters. In *10th Annual Meeting for the Society for Hospital Epidemiology of America*, Atlanta, GA, March 5–9, 2000.
21. Puel V, Candry M, LeMetayer P et al. Superior vena cava thrombosis related to catheter malposition in cancer chemotherapy. *Cancer* 1993; 72:2248–2252.
22. Dierks MM, Whitman ED. Catheter tip position in the analysis of central venous access device outcome. *J Can Intra Nurses Assoc* 1997; 13(3):7–10.
23. Whitman ED. Complications with the use of central venous access devices. *Curr Probl Surg* 1996; 33(4):309–378.
24. Becker DM, Philbrick JT, Walker FB. Axillary and subclavian venous thrombosis. *Arch Intern Med* 1991; 151:1934–1943.
25. Randolph AG, Cook DJ, Gonzalez CA et al. Benefit of heparin in central venous and pulmonary artery catheters: A meta-analysis of randomized control trials. *Chest* 1998; 113(1):165–171.
26. Bern MM, Lokich JJ, Wallach SR et al. Very low dose of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. *Ann Intern Med* 1990; 112(6):423–428.
27. Coles CE, Whitear WP, Levay JH. Spontaneous fracture and embolization of central venous catheter: Prevention and early detection. *Clin Oncol* 1998; 10(6):412–414.
28. Frezza EE, Mezghebe H. Indications and complications of arterial catheter use in surgical and medical intensive care units. *Am Surg* 1998; 64(2):127–131.
29. Sfeir R, Khoury S, Khoury G et al. Ischemia of the hand after radial artery monitoring. *Cardiovasc Surg* 1996; 4(4):456–458.
30. Zevola DR, Dioso J, Maggio R. Comparison of heparinized and nonheparinized solutions for maintaining patency of arterial and pulmonary artery catheters. *Am J Crit Care* 1997; 6(1):52–55.
31. O'Malley MK, Rhames FS, Cerra FB et al. Value of routine pressure monitoring system changes after 72 hours of continuous use. *Crit Care Med* 1994; 22(9): 1424–1430.
32. Alexander JW. Nutrition and infection. New perspective for an old problem. *Arch Surg* 1986; 121(8):966–972.
33. Mullan H, Roubenoff RA, Roubenoff R. Risk of pulmonary aspiration among patients receiving enteral nutrition. *J Parenteral Enteral Nutr* 1992; 16(2):160–164.

    More frequent aspiration among ward than intensive care unit patients suggests that aspiration is not an inevitable consequence of severe illness, but can be prevented with adequate nursing care and pulmonary precautions. The fear of aspiration is not a sufficient cause to withhold enteral nutrition support in acutely ill patients.
34. Lucarelli MR, Shirk MB, Julian MW et al. Toxi-city of food drug and cosmetic blue No. 1 dye in critically ill patients. *Chest* 2004; 125(2):793–795.
35. Norman EA, Sosis M. Iatrogenic esophageal perforation due to tracheal or nasogastric intubation. *J Can Anaesth Soc* 1986; 33:222–226.

36. Jackson RH, Payne DK, Bacon BR. Esophageal perforation due to nasogastric intubation. *Am J Gastroenterol* 1990; 37:439–442.
37. Fasqualle D, Alami M, Dumas G et al. Epidemiology of sinusitis seen in hospitalized patients. *Pathologie Biologie* 1998; 46(10):751–759.
38. Westergren U, Berg S, Lundreg J. Ultrasonographic bedside evaluation of maxillary sinus disease in mechanically ventilated patients. *Intensive Care Med* 1997; 23(4):393–398.
39. Bankier AA, Wiesmayr MN, Henk C et al. Radiographic detection of intrabronchial malpositions of nasogastric tubes and subsequent complication in ICU patients. *Intensive Care Med* 1997; 23:406–410.
40. Frei RM, Mullet ST. Inadvertent intracranial insertion of a nasogastric tube in a non trauma patient. *Emerg Med J* 1997; 14(1):45–47.
41. Minyard AN, Smith DM. Arterial-esophageal fistulae in patients requiring nasogastric esophageal intubation. *Am J Forensic Med Pathol* 2000; 21(1):74–78.
42. Etoch SW, Bar-Natam MF, Miller FB et al. Tube thoracostomy. Factors related to complications. *Arch Surg* 1995; 130(5):521–525.
43. Evan JT, Green JD, Carlin PE et al. Meta-analysis of antibiotics in tube thoracostomy. *Am Surg* 1995; 61(3):215–219.
44. Baldt MM, Bankier AA, Germann PS et al. Complications after emergency tube thoracostomy: assessment with CT. *Radiology* 1995; 195(2):539–543.
45. Martino K, Merrit S, Sernas T et al. Prospective of randomized trial of thoracostomy removal algorithms. *J Trauma Injury Infect Crit Care* 1999; 46(3): 369–373.
46. Matsura Y, Nomimura T, Murakami H et al. Clinical analysis of reexpansion pulmonary edema. *Chest* 1991; 100(6):1562–1566.
47. Heller BJ, Grathwohl MK. Contralateral reexpansion pulmonary edema. *Southern Med J* 2000; 17(3):234.
48. Murat A, Arslan A, Balci AE. Re-expansion pulmonary edema. *Acta Radiol* 2004; 45(4):431–433.
49. Aucoin PJ, Kotilainen HR, Gantz NM et al. Intracranial pressure monitors. Epidemiologic study of risk factors and infections. *Am J Med* 1986; 80:369–376.
50. Pople IK, Muhlbauer MS, Sanford RA et al. Results and complications of intracranial pressure monitoring in 303 children. *Pediatr Neurosurg* 1995; 23(2):64–67.
51. Paramore CG, Turner DA. Relative risks of ventriculostomy infection and morbidity. *Acta Neurochir (Wien)* 1994; 127:79–84.
52. Barlow P, Mendelow AD, Lawrence AE et al. Clinical evaluation of two methods of subdural pressure monitoring. *J Neurosurg* 1985; 63:578–582.
53. North B, Reilly P. Comparison among three methods of intracranial pressure recording. *Neurosurgery* 1986; 18:730.

Section III

Abdomen

13

Complications of Abdominal Wall Surgery and Hernia Repair

Ethan A. Taub, Jane Kayle Lee, and James C. Doherty

CONTENTS

Abdominal wall closure, including ventral and inguinal hernia repair, is associated with inherent risks and complications. These complications, although associated with low absolute rates, are encountered quite frequently due to the high frequency with which abdominal wall surgeries are performed, and are among the most commonly encountered in general surgery.

13.1 Complications of Abdominal Wound Closure

The complications related to the closure of abdominal wounds can be classified broadly as infectious (superficial or deep), acute wound failure, and incisional ventral hernia.

13.1.1 Wound Infection

The risk factors for developing an abdominal wound infection are similar to surgical site infections elsewhere in the body and include the degree of bacterial wound contamination, length of operation, and patient factors such as diabetes, nutritional state, immune status, and obesity. Additional factors include inadequate skin preparation, hair removal technique, lack of or inappropriate perioperative antimicrobial prophylaxis, intraoperative patient temperature, tissue trauma, and break in sterile technique.[23]

Wounds are classified based on the potential degree of bacterial contamination with rates ranging from 1.5% for class I (clean) up to 40% for class IV (dirty/contaminated).[1]

13.1.2 Acute Abdominal Wound Failure

Acute wound failure includes two distinct entities: dehiscence and evisceration. Dehiscence is defined as separation of the wound edges. Evisceration occurs when intra-abdominal viscera exit the wound. Dehiscence can occur without evisceration; however, in rare cases, the first sign of dehiscence is acute evisceration.

The average time occurrence for wound failure is on the seventh postoperative day.

Laparotomy wound dehiscence has an incidence of 0.2%–2.3%.[2] The most common cause of acute wound failure is technical. In addition to technical failure, there are a number of patient risk factors. These include age over 65, anemia, wound infection, emergency procedure, pulmonary disease, malnutrition, sepsis, obesity, hemodynamic instability, ascites, immunosuppression, uremia, and malignancy.[2,24] Postoperative risk factors include vomiting, prolonged ileus, urinary retention, and cough. Despite the presence of these multiple risk factors, the most common cause of acute wound failure is technical failure. Sutures placed too close together or too far apart and with inadequate bites are all at risk for tearing through the fascia, resulting in adverse outcomes.[13]

Management of acute wound failure, which may present with obvious dehiscence or with leakage of serous fluid from the closure, consists of immediate exploration with reduction of any eviscerated bowel, irrigation, and primary closure if possible. Controlled dehiscence occurs when only a small portion of the fascia separates. This may be managed nonoperatively with careful observation and local wound care. It is important to note that bowel exposed to the atmosphere is at risk for fistula formation. Nonoperative management will almost always progress to form a clinically evident incisional hernia that may require future repair.

Fascial dehiscence is associated with a mortality ranging from 18% to 36%[2] often due to cardiorespiratory failure and peritonitis. Other complications include recurrent dehiscence, incisional hernia, infection, fistula, and intra-abdominal abscess.

13.1.3 Incisional Hernia

The incidence of incisional hernia following laparotomy ranges from 11% to 23%.[6] In 5.9%, the hernia will be evident within 1 year, 78% within 2 years, and 90% within 3 years.[3] The main risk factor for development of an incisional hernia is infection. Additional risk factors are those similar to the development of acute wound failure—advanced age, obesity, poor nutrition, jaundice, early reoperation, pulmonary disease, abdominal distension, emergency surgery, and midline laparotomy.

Several technical factors are related to an increased risk of developing an incisional hernia. There has not been a difference found comparing interrupted versus continuous running suture.[3,25] There have been studies that associate incisional hernia with factors such as the ratio of suture length to wound length, a measure of suture tension, and size of tissue bites. A ratio <4 has been associated with an increased risk of incisional hernia. Also, stitch length, the ratio of suture length to number of stitches, is a measure of wound tension. A stitch length of 5 or greater has been associated with an increased risk of wound infection.[26,27] Inadequate healing may occur if blood flow to the fascial edges is compromised. This may occur if excessive tension is applied or during times of increased intra-abdominal pressure.

13.1.4 Other Complications

Rare, yet devastating, complications may result from the closure of an abdominal wound. These include enterocutaneous fistulae and inadvertent visceral injury. In addition, local complications such as a hypertropic scar, scar ossification, chronic incisional pain, peri-incisional numbness, and stitch abscesses or fistulae may occur with minimal morbidity and are mentioned here for completeness.

13.2 Complications of Ventral Hernia Repair

The diagnosis of ventral hernia includes a mixed group of abdominal wall defects ranging in size and complexity from a small umbilical hernia to a large planned ventral hernia of the open abdomen. Large ventral hernias are associated with increased trophic changes in the overlying skin, alterations in pulmonary mechanics, and atrophy of the abdominal musculature. This may result in the need for a release of components, prosthetic mesh, or a combination of the two in order to repair the defect. Ventral hernias may be repaired utilizing either open or laparoscopic technique.

13.2.1 Complications of Open Ventral Herniorrhaphy

Recurrence is the most common complication of open ventral hernia repair. The risk factors are identical to those leading to hernia formation following laparotomy. Infection substantially increases the rate of recurrence. Measures should be taken to minimize wound infections by utilizing preoperative antimicrobial coverage and strict adherence to sterile technique. When possible, the patient's immune status should be optimized by correcting nutritional deficiencies, aggressive perioperative glucose control in diabetics, and timing elective surgery as remotely as possible from the administration of immunosuppressive drug therapies such as corticosteroids and chemotherapy agents.

There are basic principles that must be adhered to when performing an open ventral hernia repair similar to that of a successful laparotomy closure. The approximated fascia must be healthy and approximated with minimal tension. Fascial bites should be placed 1 cm from the edge and be placed no further than 1 cm apart. Prior to the use of mesh repair, recurrence rates for primary suture closure of large ventral incisional hernias ranged from 30% to 67%.[28] Several modifications of primary closure have been advocated to decrease recurrence. These include using internal retention sutures or relaxing incisions.[24]

Prosthetic mesh repair of incisional hernias has decreased recurrence rates to the current level of 0%–17%.[28,29] While some studies recommend against suture repair for all incisional hernias,[28] prosthetic mesh should not be used indiscriminately. The ideal prosthetic mesh has eight key characteristics: chemically inert, resistant to mechanical strain, capable of being sterilized, able to limit foreign-body reaction, unresponsive to body and tissue fluids, modifiable to the size of the defect, noncarcinogenic, and unlikely to cause allergic reaction.[30] Prosthetic materials are classified as absorbable or nonabsorbable and can be synthetic, composite, or biologic.

Permanent synthetic mesh products are composed of polypropylene (PP), polyester (polyethylene terephthalate), or expanded polytetrafluoroethylene (ePTFE). PP is available in both lightweight and heavyweight varieties. The heavyweight PP incites a considerable foreign-body and chronic inflammatory response, which can result in contracture, scar formation, sensation of the mesh in the abdominal wall, loss of compliance, and chronic pain. The lightweight mesh is thinner with larger pores and causes less tissue reaction resulting in greater patient comfort and pliability. PP is unsuitable for intra-abdominal placement due to the risk of dense adhesions that form with the viscera, and resultant bowel obstruction, or fistula formation. Untreated PP is vulnerable to bacterial contamination.

The polyester mesh is designed to have a greater pliability and reduced adhesiogenic properties.[31] The main advantage of polyester mesh over PP may be a lower risk of infection.

The third type of synthetic mesh, ePTFE, can be placed safely in contact with the viscera. There is minimal patient discomfort with ePTFE as it is very soft and pliable. Two commonly used ePTFE prosthetics include GORE-TEX® and Teflon®.

A composite mesh is two-sided with a barrier on the visceral side that repels tissue ingrowth and adhesions, while the parietal side is synthetic to promote tissue ingrowth. Examples include a lightweight PP supplemented with oxidized cellulose, and a PP coated with a hyaluronate carboxymethylcellulose.

A biologic mesh is a collagen-based porcine, bovine, or human matrix that may be implanted in the extraperitoneal or intraperitoneal positions.[30] The advantage of the biologic mesh is that it may be implanted in a situation when a synthetic mesh would be contraindicated, such as a high-infection risk. The biologic mesh, unlike the synthetic products mentioned earlier, supports angiogenesis and thus allows the delivery of antibiotics and white blood cells. The biologic mesh is not immune from infection. When infected, the mesh becomes encapsulated, rather than incorporated, or degrades. A 2009 study evaluating adverse effects associated with the biologic mesh identified the following: acute mechanical failure/evisceration (42%), mesh disintegration (13%), postoperative infection (5%), and fistula (3%).[32]

A number of studies have shown that the technique employed for mesh fixation or mesh position (extrafascial, subfascial, or intraperitoneal) does not affect recurrence rates.[33]

As mentioned earlier, there is sufficient evidence supporting the use of a mesh over direct suture repair with regard to a significantly lower recurrence rate.[33] The use of a prosthetic mesh, however, is associated with increased local wound complications and additional unique complications. Infection is the most critical of the complications associated with the prosthetic mesh. Infection in the setting of a synthetic or composite mesh requires its explantation. This difficult procedure often leaves the patient with a colonized abdominal wall defect.[30] Infection rates may be as high as 10% with open mesh repairs.[34]

In addition to infection, a variety of early and late complications associated with the use of the prosthetic mesh were outlined by Leber et al.[35] The early complications included ileus, cellulitis, wound drainage, hematoma/seroma, pneumonia, pulmonary embolus, and deep venous thrombosis (DVT). Late complications included recurrence (median of 1 year), chronic infection/sinus (6% at a median of 6 months), small-bowel obstruction (5.5% at a median of 18 months), and enterocutaneous fistula.

13.2.2 Complications of Laparoscopic Ventral Herniorrhaphy

Similar to open ventral hernia repair with a mesh, the laparoscopic technique involves reduction of the hernia contents, intraperitoneal placement of a prosthetic mesh, and fixation of the mesh to the anterior abdominal wall. To limit the inflammatory reactions between the mesh and the abdominal contents (thus decreasing the incidence of adhesions and fistulae), the least reactive prosthetic material should be used.

Multiple retrospective and prospective studies[8,9,16,36–38] have demonstrated overall complication rates ranging

from 1% to 20% for the laparoscopic approach. Intraoperative complications are subcutaneous emphysema and hypercarbia from abdominal insufflation (0.7%), respiratory failure (0.7%), and unintentional enterotomy (0%–4.8%). Postoperative complications are seroma (1.2%–16%), mesh infection (0%–3.6%), trocar site infection (0%–3.3%), ileus (2%–10%), small-bowel obstruction (0%–4.8%), pulmonary compromise (0%–4.8%), and chronic pain (0%–3.6%).

When comparing laparoscopic to open ventral and incisional hernias, one large meta-analysis[39] concluded that there are lower perioperative complication rates and shorter lengths of hospital stay. An analysis of the National Surgical Quality Improvement Program (NSQIP)[38] compared 30-day morbidity and mortality between laparoscopic and open ventral hernia repairs. The authors concluded that there are equivalent mortality rates between the two procedure types and that there is a "significantly greater [complication] risk" associated with open repairs. Another large meta-analysis performed by the Cochrane Group in 2011[9] concluded that laparoscopic repairs have a lower wound infection rate and quicker recovery versus open, but were associated with a potentially higher risk of bowel injury.

13.3 Complications of Inguinal Hernia Repair

The following discussion outlines the main complications of open and laparoscopic inguinal herniorrhaphy. Specific approaches and techniques are discussed only in reference to their association with specific complications and to the differences in their rates of recurrence.

Inguinal hernia repair is one of the most commonly performed procedures in general surgery, with nearly 800,000 being performed in the United States each year.[40] Because of the complex anatomical relationships within the inguinal region and the large number of important structures susceptible to injury, there are a number of unique challenges during inguinal hernia repair.

13.3.1 Complications of Open Inguinal Herniorrhaphy

Complications of open inguinal herniorrhaphy can be either intraoperative or postoperative. In general, both intraoperative and postoperative complications are technical in nature and can be avoided by precise knowledge of inguinal anatomy, the experience of the surgeon, and keen attention to detail during the performance of the operation.

13.3.1.1 Intraoperative Complications

Intraoperative complications include: injury to vascular structures, spermatic cord transection, injury to the vas deferens, nerve injury, testicular devascularization, and injury to the viscera.[41] These complications often are not recognized at the time of surgery and may present during the postoperative period. Nevertheless, they are discussed here as intraoperative complications, because the initial technical error occurs during the surgical procedure itself.

Hemorrhage can result from injury to any of the multiple vascular structures in the inguinal region: the pubic branch of the obturator artery; cremasteric artery; inferior, deep epigastric vessels; deep circumflex iliac vessels; external iliac vessels; and femoral vessels. Injuries to the epigastric, pubic, and cremasteric vessels can usually be managed safely and effectively with direct ligation of the bleeding vessel. Injuries to the deep circumflex iliac, external iliac, and femoral vessels usually result from errant suture placement, and are best managed by removing the offending suture and applying direct pressure. If direct pressure fails to provide adequate hemostasis, wide exploration of the femoral sheath is necessary for more effective manual compression or for further suture repair when necessary.

When a vascular injury occurs intraoperatively, careful postoperative observation is necessary so that arterial or venous thrombosis or thromboembolic events can be detected. Perioperative venous thrombosis has been associated with thrombophlebitis of the dorsal vein of the penis, a complication with an incidence as high as 0.65%.[41] Delayed complications of vascular injury are arterial or venous stenosis, pseudoaneurysm, and arteriovenous fistula. Failure to detect or adequately address small vascular injuries at the time of surgery often results in the formation of postoperative hematomas in the wound or in the scrotum. These hematomas usually resolve spontaneously and rarely require exploration, but they can cause substantial discomfort for the patient and can become secondarily infected.

Hernia repair may occasionally require intentional sacrifice of the spermatic cord. This maneuver is usually reserved for particularly difficult large or recurrent inguinal hernias in elderly men. After inguinal herniorrhaphy, unintentional cord transection usually causes fever, and testicular swelling and tenderness; it may cause long-term complications of testicular atrophy or hydrocele formation rarely requiring orchiectomy in the future.

The nerves at risk of injury during open inguinal hernia repair are the ilioinguinal nerve, iliohypogastric nerve, and genital and femoral branches of the genitofemoral nerve. The ilioinguinal nerve lies beneath the external oblique aponeurosis along the surface of the

spermatic cord. Injury most commonly occurs when the external oblique is opened for exposure of the inguinal canal. It results in loss of sensation to the base of the penis, upper scrotum, and inner thigh. The iliohypogastric nerve can be injured by relaxing incisions in the rectus sheath or by medial dissection during preperitoneal hernia repair. Such injury usually causes sensory loss to the suprapubic area. The genitofemoral nerve perforates the internal oblique muscle at the origin of the cremaster muscle. Injury to this nerve causes motor weakness of the cremaster muscle and cutaneous sensory loss in the penis and scrotum. The femoral branch of this nerve lies deep to the inguinal canal; injury to this branch causes sensory loss to the lateral thigh. Injury to any of these nerves usually produces only temporary symptoms that characteristically resolve within 6 months. Reports indicate that as many as 18%–20% of patients with hernias experience neurapraxia and hyperesthesia.[41]

When nerve transection is recognized during surgery, the severed nerve end should be ligated so as to reduce the possibility of the formation of a painful neuroma.

Unlike nerve transection, nerve entrapment can result in the development of serious long-term pain syndromes. Chronic (persisting greater than 12 months) pain after herniorrhaphy has been reported to occur in as many as one-third of cases.[42] Genitofemoral neuralgia is a well-described chronic pain syndrome associated with inguinal herniorrhaphy. Symptoms are hyperesthesia in the cutaneous distribution of the genitofemoral nerve and chronic inguinal pain extending to the genitalia and upper thigh. This pain is often exacerbated by walking, hip extension, and pubic tubercle pressure, and can frequently be relieved by hip flexion at rest. Pain and paresthesias associated with nerve entrapment and neuroma formation can initially be managed with local nerve blocks. The iliohypogastric and ilioinguinal nerves can be blocked by using an L1 and an L2 block. Persistent symptoms may require reexploration, with ligation and severance of the involved nerve. The presence of a short-lived response to a local block can help guide therapy toward a specific nerve, but in the absence of such evidence, therapy is best directed empirically at all three nerves. Occasionally, the condition does not respond to appropriate nonsurgical and surgical therapies; in such cases, patients should be referred to a chronic pain specialist.

The blood supply to the testis is primarily derived from the internal spermatic artery, which is a part of the spermatic cord. In the event of any interruption of flow in the internal spermatic artery, collateral circulatory input provided by branches of the vesical, prostatic, and deferential arteries can prevent testicular ischemia. If the collateral circulation is also disrupted, acute testicular necrosis or testicular atrophy may result. Thus, care must be taken to preserve the collateral vessels and the internal spermatic artery during inguinal herniorrhaphy.

Because of its potential impact on fertility, injury to the vas deferens is a serious concern of all surgeons performing inguinal hernia surgery. When it occurs, transection of the vas deferens mandates immediate repair. Approximately 50% of such repairs yield a functional result. Improper handling of the vas deferens can cause injury in the absence of transection. Such injury may involve obstruction of the lumen of the vas, a lesion that can cause painful ejaculatory dysfunction.

Injury to abdominal viscera during inguinal herniorrhaphy usually occurs in association with sliding hernias involving bladder or bowel wall. The wall of the urinary bladder can participate as a sliding component of the medial aspect of a direct inguinal hernia. As such, it can be injured during the placement of medial sutures or with dissection or opening of the hernia sac during the hernia repair. When recognized intraoperatively, injury to the urinary bladder should be repaired immediately, and the repair should be protected with bladder decompression via an external bladder catheter. Bowel injury can occur during high ligation of an indirect hernia sac, when the bowel wall is a component of the sac. The injury can be a simple enterotomy or a mesenteric injury with segmental vascular compromise. In either case, potential sequelae are bowel obstruction, fistula, and abscess formation. Enterotomies are best managed with primary repair, wound irrigation, and hernia repair without prosthetic material if possible. Devascularization of bowel may require resection, with or without laparotomy, and proximal diversion may occasionally be required for colon injuries.

13.3.2 Postoperative Complications

In addition to the postoperative complications of scrotal ecchymosis, testicular atrophy, and neuroma mentioned in Section 13.4.1, a number of other postoperative complications are associated with open inguinal herniorrhaphy. These are urinary retention, osteitis pubis, testicular swelling, hydrocele, infection, missed hernia, and recurrence.

Urinary retention, defined as a need for urinary catheterization, can occur following hernia repair. It appears to be more common when bilateral hernia repair is performed and when the hernia is performed under general or spinal anesthesia.[42] One large review performed by Jensen et al. with over 25,000 patients found the incidence to be 3% of patients undergoing general anesthesia, 2.4% with regional anesthesia, and 0.37% with local anesthesia.[20] There also appears to be

a direct relationship with the administration of increasing doses of postoperative narcotics and postoperative intravenous fluid administration.[43] This complication is exacerbated by the presence of other conditions associated with urinary retention, such as benign prostatic enlargement. Initial management of postoperative urinary retention is intermittent bladder catheterization until the patient is able to void spontaneously. In some cases, long-term bladder catheterization and referral to a urologist may be necessary. To avoid this complication, urology referral and treatment of known or suspected prostatic disease may be advisable prior to elective hernia repair.[44]

The placement of suture material in the periosteum of the pubic bone during inguinal herniorrhaphy has been associated with persistent inflammation of the periosteal layer, a condition known as osteitis pubis. This painful syndrome is usually self-limiting and responds to the administration of nonsteroidal anti-inflammatory agents. Although osteitis pubis was once a well-described complication of inguinal hernia repair, modern techniques of inguinal herniorrhaphy have rendered this complication exceedingly rare.

A swollen testis after inguinal hernia repair may be caused by tight closure of the tissues or mesh around the spermatic cord. Occasionally, such swelling results from lymphatic injury, venous injury, or venous thrombosis induced by dissection of the cord; other causes are hematoma or seroma. Regardless of its cause, postoperative testicular swelling is usually self-limiting. The management involves scrotal support and pain control until swelling resolves. Postoperative swelling associated with severe testicular pain and fever may indicate ischemic orchitis. In the absence of obvious arterial injury, ischemic orchitis may result from venous thrombosis of the cord vessels. In severe cases, the pain may last for as long as 6 weeks, and the condition may progress to testicular atrophy. The incidence of testicular atrophy has been estimated to be 0.036% after primary repairs and 0.46% after repair of recurrent hernias.[41] Limited dissection and trauma to the spermatic cord are paramount to prevention of testicular atrophy.[45]

The development of fluid collections along the course of the spermatic cord is not uncommon after inguinal hernia repair; it occurs with an incidence of 0.7%.[23] These collections are commonly referred to as hydroceles, but they actually result from a number of different causes such as retained distal hernia sac, impaired lymphatic or venous drainage, and inflammatory fluid accumulations in proximity to mesh. Postoperative formation of seromas has been associated with the degree of tissue trauma and the use of prosthetic mesh material; its incidence ranges from 0% to 17.6%.[41] Hydroceles and seromas rarely require operative intervention unless they become infected. Those that persist for more than 6–8 weeks may require aspiration, open drainage, or both.

The incidence of wound infection after open inguinal herniorrhaphy is approximately 1%. Factors that increase infection rates are advanced age (3.2-fold increase), female sex (2.1-fold increase), presence of a drain (9-fold increase), duration of operation (increased infection risk from 2.7% to 9.9% with increased duration from 30 to 90 min), incarceration (7.8% infection rate), and recurrent hernia (10.8% infection rate).[41] The use of prosthetic mesh does not appear to increase these rates, but it has been associated with the phenomenon of delayed infection, months to years after herniorrhaphy. Moreover, the presence of infection or contamination typically precludes the use of synthetic mesh. Wound infections are managed with drainage and local wound care. Antibiotics are rarely indicated. The presence of deep infections after inguinal herniorrhaphy increases the risk of hernia recurrence.

Occasionally, a new hernia will be noted after an apparently successful inguinal hernia repair. Such cases usually involve a small indirect or femoral hernia not appreciated at the time of direct inguinal herniorrhaphy. A second hernia is present in >13% of cases.[41] This complication is entirely preventable and can be avoided by careful palpation for other hernias at the time of repair and by complete opening of the floor of the inguinal canal, a maneuver not performed by a large number of surgeons.

Although fascial weakness may contribute to some hernia recurrences, the cause of recurrence is almost always a technical error. The primary technical factor influencing hernia recurrence is the degree of tension on the repair. Tension causes impaired healing and renders the repair susceptible to disruption and subsequent recurrence. The differences in recurrence rates among the various techniques of open inguinal hernia repair probably reflect differences in the degree of intrinsic tension of the repair. The recurrence and re-recurrence rates associated with the two techniques of open inguinal hernia repair most commonly used today, the tension-free mesh technique (Lichtenstein) and the mesh plug technique, are similarly low (0%–1.6%).[41] The widespread acceptance of these two tension-free approaches to inguinal herniorrhaphy is due primarily to the widespread recognition of the important relationship between tension and recurrence. For completeness and historical perspective, the following is a summary of the recurrence and re-recurrence rates, respectively, for three common tissue repairs of inguinal hernia: Bassini—2.9%–25% and 6.5%–13.4%, Shouldice—0.2%–27% and 2.6%–6.4%, and McVay—1.5%–15.55% and 2.4–5.5%.[41]

A recent review of over 1000 groin hernia repairs from 2001 to 2009 compared various outcomes and

complication rates between elective and acute repairs. This retrospective study found that acute repairs had a statistically significant higher overall complication rate 27% versus 15%. There was also a higher rate of organ resection 11.1% versus 0.2% and a higher rate of reoperation in the acute group. In addition, the study showed a significantly shorter survival rate in patients undergoing acute repairs.[46]

13.3.3 Complications of Laparoscopic Inguinal Herniorrhaphy

Laparoscopic inguinal hernia repair recently entered its second decade of existence, and substantial improvements in techniques and instrumentation continue to advance the field. The three main techniques of laparoscopic inguinal herniorrhaphy are the intraperitoneal onlay method (IPOM), the transabdominal preperitoneal repair (TAPP), and the total extraperitoneal repair (TEP). The evolution of laparoscopic inguinal herniorrhaphy from IPOM to TAPP to TEP has been driven by the desire to maintain low recurrence rates while reducing operative time, cost, complications, and anesthetic risk. The IPOM technique involves placing an intraabdominal sheet of mesh directly over the hernia defect. Although IPOM remains important from a historical perspective, the TAPP and TEP repairs have become the favored approaches of nearly all laparoscopic surgeons. The TAPP repair involves transabdominal laparoscopic dissection of the anterior abdominal wall and secure coverage of the mesh with peritoneum. This approach has the advantage of preperitoneal mesh placement, but it has the disadvantage of requiring entry into the peritoneal cavity and the use of general anesthesia. The TEP repair involves extraperitoneal dissection to separate the peritoneum from the inguinal area, laparoscopic dissection and reduction of the hernia, and placement of mesh between the peritoneum and the transversalis fascia defect.

With increasing experience and use, the complication rate associated with laparoscopic inguinal herniorraphy has declined. There is however only one published randomized controlled trial directly comparing TEP and TAPP.[47] The complications of laparoscopic inguinal herniorraphy can be classified as those related to laparoscopy, complications specific to TAPP or TEP, and complications common to both.

The decision of whether to perform a TEP or TAPP depends largely on surgeon preference and experience. Many studies have shown no difference in the overall complication rates.[18] Many experts agree that TEP may be more advantageous for repair of direct hernias, especially when bilateral. TAPP may be better in strangulated hernias, very large hernias, scrotal hernias, and in those with a previous preperitoneal repair or prior radical prostatectomy.[18]

13.3.4 Complications Related to Laparoscopy

The complications related to laparoscopy itself are those related to the access technique and those related to pneumoperitoneum. Those related to access technique are Veress needle or trocar injuries to abdominal viscera with the TAPP approach. Complications related to CO_2 insufflation are pneumothorax, hypercarbia, and subcutaneous emphysema.

13.3.5 Complications Related to Transabdominal Preperitoneal Repair

Complications unique to the TAPP approach are those related to the administration of general anesthesia and those related to mesh placement and fixation. The TAPP approach requires general anesthesia to allow pneumoperitoneum and adequate operative exposure. Although most patients tolerate general anesthesia without serious adverse sequelae, the use of general anesthesia for high-risk patients, such as those with severe cardiac and pulmonary disease, is associated with considerable risk. The TAPP approach may therefore expose such patients to substantial risk for perioperative cardiac and pulmonary complications. The TAPP approach also requires that the mesh prosthesis be adequately secured and isolated from the abdominal contents by the peritoneum. Failure to achieve adequate fixation or coverage may result in fistula, internal hernia, bowel obstruction, or hernia recurrence.

13.3.6 Complications Related to Total Extraperitoneal Repair

Complications related to the TEP approach are primarily those associated with extraperitoneal dissection and exposure of the inguinal area. Injury to the epigastric vessels can be avoided by midline port placement and preservation of the vessel's location on the abdominal wall. Peritoneal injury can cause loss of exposure due to the leakage of insufflated CO_2 into the peritoneal cavity. Although this loss of exposure may precipitate conversion to TAPP or open repair, restoration of the operative exposure may be possible by venting the pneumoperitoneum with a Veress needle and repairing the peritoneal defect laparoscopically.

13.3.7 Complications Common to Transabdominal Preperitoneal Repair and Total Extraperitoneal Repair

In general, the complications common to TAPP and TEP are also shared with open techniques of inguinal

herniorrhaphy. These are vascular injury, visceral injury, testicular atrophy, nerve injury, hematoma/seroma, recurrence, and complications related to the use of mesh.

Vascular structures at particular risk of injury during laparoscopic hernia repair are the iliac, iliopubic, and accessory obturator vessels. Most studies show a tendency toward more vascular complications (0.42 vs. 0.25) with TEP. TEP also places abdominal wall vessels such as the epigastric vessels at risk due to the need for a wide preperitoneal dissection.[48]

Visceral injury can occur during laparoscopic repair and is often associated with port placement and access to the abdomen. There is no definitive evidence supporting an open entry technique for establishing pneumoperitoneum compared to other techniques. The International Endohernia Society 2011 guidelines recommend open access over Veress needle in the setting of previous open abdominal surgery.[18] The incidence of visceral lesions may be higher during a TAPP with an incidence of 0.6 versus 0.05 with the TEP approach.[18]

Bladder injury can occur with either TAPP or TEP, and occurs with an incidence of 0%–0.2%.[48] Bladder injury during TAPP can be avoided by limiting dissection to the area lateral to the medial umbilical ligament. The management principles for bladder injuries sustained during laparoscopic herniorrhaphy are the same as those for bladder injuries that occur during open inguinal herniorrhaphy. The bladder should be repaired primarily by using laparoscopic techniques, and bladder decompression should be maintained postoperatively via an indwelling bladder catheter.

Although ischemic orchitis and testicular atrophy are relatively common complications of open inguinal herniorrhaphy, these complications are rarely seen after laparoscopic repair. The low incidence of these complications is mainly due to the fact that both TAPP and TEP laparoscopic techniques use preperitoneal approaches and avoid excessive cord dissection, thus limiting the risk of testicular devascularization.

The overall incidence of nerve injuries in association with laparoscopic inguinal hernia repair (TEP and TAPP) has been reported to be 3.9%–11.2%.[11] The specific nerves at risk of injury are the genitofemoral nerve (most commonly), the ilioinguinal nerve, and the lateral femoral cutaneous nerve.[49] In general, nerve injuries can be avoided by minimizing or eliminating the use of fixation devices or avoiding placement of fixation devices within the area lateral to the deep inguinal ring and ventral to the iliopubic tract, the so-called "triangle of pain."[49] As is true of nerve injuries after open hernia repair, those that occur after laparoscopic repair usually resolve spontaneously, but nerve blocks, surgical reexploration, or both may be required.

Recurrence rates in patients undergoing laparoscopic inguinal hernia repair (TEP or TAPP) vary with surgeons' experience. One large randomized controlled trial by Neumayer found the recurrence rate with laparoscopic repair to be significantly greater than open repair (10.1% vs. 4.0%).[10] Experienced laparoscopic surgeons with more than 250 procedures seem to have a recurrence rate that approaches that of open repair.

Wound, hematoma, and seroma are also known complications of laparoscopic inguinal hernia repair—both TEP and TAPP. The wound infection, hematoma, and seroma rates, in a large meta-analysis of randomized controlled trials,[11] are 1.1%, 13.1%, and 12.2%, respectively. Wound infection and hematoma are significantly lower in the laparoscopic group when compared to open techniques. Seroma occurs more frequently in the laparoscopic group and was found to be statistically significant.

As is also true of open hernia repair, with laparoscopic repair, mesh complications such as infection and erosion into adjacent structures (i.e., bowel or urinary bladder) can also occur.

13.4 Conclusion

Complications of abdominal wall surgery and hernia repair are some of the most common complications encountered by general surgeons. Therefore, a thorough knowledge of the causes and implications of these complications and of their management is essential to the successful practice of general surgery.

Major Complications of Abdominal Wound Closure

Complications	Incidence (%)	References	Comments
Wound infection	1.5–40	[1,12]	Variation based on wound class Avoid by adherence to the CDC guidelines for prevention of surgical site infection
Acute wound failure	0.2–2.3	[2]	Most commonly occurs on seventh postoperative day
Incisional hernia	4–20	[3,13,14]	78% evident within 2 years; avoid by utilization of good technique; suture length to wound length ratio = 4–5; avoidance of tissue strangulation

Major Complications of Open and Laparoscopic Ventral Hernia Repair

	Incidence			
Complications	**Open (%)**	**Lap (%)**	**References**	**Comments**
Infection	10.4	2.3	[5]	
Recurrence	0–49	4.3	[5,6]	Variation depends on the type of repair (i.e., mesh vs. suture)
Seroma	12.0	10.6–16.7	[5,9]	Varies based on the mesh position
Mesh infection	3.2	1.5	[5,7]	*S. aureus* = most common organism; must be confirmed with culture-positive mesh or culture-positive fluid surrounding the mesh
Total wound complications	16.8	5.3	[5]	Hematoma, cellulitis, dehiscence, fat necrosis (includes infection)
Enterotomy	1.2	1.55	[5]	
Ileus	4.0	—	[8]	

Major Complications of Open and Laparoscopic Inguinal Hernia Repair

	Incidence			
Complications	**Open (%)**	**TEP/TAPP (%)**	**References**	**Comments**
Wound infection	1.4	1.0	[10]	Risk increases with age, female sex, incarceration, recurrence
Recurrence	2.7	3.2–5.5	[11]	Incidence with laparoscopy varies with experience
Spermatic cord injury	0.8	0.1	[10]	
Major vascular injury	0	0.09	[11]	
Inguinal paresthesias	8.0	3.9	[11]	
Testicular complications	0.8`	0.6	[11]	
Bowel injury	0.06	0.1	[11]	
Bladder injury	0	0.1	[11]	
Chronic pain	12.7	7.6	[11]	
Hematoma	16.0	13.1	[11]	
Wound infection	2.7	1.0	[11]	
Seroma	8.9	12.2	[11]	
Urinary retention	2.7	3.5	[11]	Statistically significantly greater when compared to all open repairs

How to Avoid Complications of Ventral and Inguinal Hernia Repair

Complications	**Methods of Avoidance**	**Comments**	**References**
Mesh infection	Decrease operative time, avoid additional concomitant procedures, and increase tissue coverage	Must be confirmed with positive culture of the mesh or a deep culture from surrounding fluid	[7]
Intraoperative hemorrhage	Utilization of noncutting trocars, direct visualization of trocar placement	Hemorrhage must be controlled to avoid intramuscular or extraperitoneal hematoma	[15]
Enterotomy	Open technique for placement of initial trocar; gentle traction and direct visualization	May be unavoidable; presence of ascites or free air; increasing pain; fever; leukocytosis should warrant further work-up	[15]
Seroma/hematoma	Avoid use of cutting trocars during laparoscopic repair	Observation and conservative management usually will suffice	[15]
Trocar site hernia	Use of dilating trocar over cutting; closure of trocar sites >10 mm		[15]
Chronic pain	May be unavoidable	Can attempt to instill bupivacaine at the site of chronic pain	[15]

Complications	Methods of Avoidance	Comments	References
Recurrence	Appropriate fixation and mesh size (>3 cm overlap)		[16]
Vascular injury	Meticulous dissection and avoidance of the "triangle of doom"	"Triangle of doom" houses the common iliac vessels = vas deferens superomedially and gonadal vessels superolaterally	[17]
Testicular atrophy/orchitis/ vas deferens injury	Avoidance of rough handling or overdissection of the spermatic cord	Avoid excess use of electrocautery on and around spermatic cord	[17]
Nerve injury	Avoid placement of fixation devices within the "triangle of pain" during laparoscopic repair	Anchorage device should be removed and local anesthesia infiltrated in the region	[17]
Visceral injury	Meticulous dissection especially with incarcerated and sliding hernias	Open technique for achieving pneumoperitoneum during laparoscopic repair	[18]
Chronic pain	Avoidance of nerve injury; avoid placing sutures at medial insertion of inguinal ligament; avoid excess tightness of inguinal ligament at pubic tubercle		[19]
Urinary retention	Use of local anesthesia in lieu of general or spinal	Local anesthesia carries nearly 0% incidence of urinary retention	[20]
Seroma	Decrease tissue trauma with careful dissection and handling		[17]
Infection	Appropriate perioperative antibiotics, strict sterile technique; use only as much prosthetic material as needed		[21]
Recurrence	Utilize adequate mesh size; avoid slitting mesh in laparoscopic repair; adequate dissection of preperitoneal space		[22]

References

1. Cruse PJ, Foord R. The epidemiology of wound infection. A 10-year prospective study of 62,939 wounds. *Surg Clin North Am*. 1980 February;60(1):27–40.
2. Riou JP, Cohen JR, Johnson H. Factors influencing wound dehiscence. *AJS*. 1992 March;163(3):324–330.
3. Carlson MA, Ludwig KA, Condon RE. Ventral hernia and other complications of 1,000 midline incisions. *South Med J*. 1995 April;88(4):450–453.
4. Regueira T, Bruhn A, Hasbun P, Aguirre M, Romero C, Llanos O, et al. Intra-abdominal hypertension: Incidence and association with organ dysfunction during early septic shock. *J Crit Care*. 2008 December; 23(4):461–467.
5. Pierce RA, Spitler JA, Frisella MM, Matthews BD, Brunt LM. Pooled data analysis of laparoscopic vs. open ventral hernia repair: 14 years of patient data accrual. *Surg Endosc*. 2007 March;21(3):378–386.
6. Cassar K, Munro A. Surgical treatment of incisional hernia. *Br J Surg*. 2002 May;89(5):534–545.
7. Sanchez VM, Abi-Haidar YE, Itani KMF. Mesh infection in ventral incisional hernia repair: Incidence, contributing factors, and treatment. *Surg Infect (Larchmt)*. 2011 June;12(3):205–210.

   This large review article published in 2011 focuses on the factors which contribute to mesh infection in ventral incisional hernia repairs. It highlights various etiologies of mesh infection and how to treat them.
8. McGreevy JM, Goodney PP, Birkmeyer CM, Finlayson SRG, Laycock WS, Birkmeyer JD. A prospective study comparing the complication rates between laparoscopic and open ventral hernia repairs. *Surg Endosc*. 2003 November;17(11):1778–1780.
9. Sauerland S, Walgenbach M, Habermalz B, Seiler CM, Miserez M. Laparoscopic versus open surgical techniques for ventral or incisional hernia repair. *Cochrane Database Syst Rev*. 2011;(3):CD007781.
10. Neumayer L, Giobbie-Hurder A, Jonasson O, Fitzgibbons R, Dunlop D, Gibbs J, et al. Open mesh versus laparoscopic mesh repair of inguinal hernia. *N Engl J Med*. 2004 April 29;350(18):1819–1827.
11. Schmedt CG, Sauerland S, Bittner R. Comparison of endoscopic procedures vs Lichtenstein and other open mesh techniques for inguinal hernia repair: A meta-analysis of randomized controlled trials. *Surg Endosc*. 2005 February;19(2):188–199.

    This key article compares via meta-analysis only randomized controlled trials of laparoscopic and open inguinal hernia repair.
12. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control*. 1999; 97–132; quiz133–134; discussion 96.
13. Carlson MA. Acute wound failure. *Surg Clin North Am*. 1997 June.;77(3):607–636.

14. Millbourn D, Cengiz Y, Israelsson LA. Risk factors for wound complications in midline abdominal incisions related to the size of stitches. *Hernia*. 2011 June; 15(3):261–266.
15. LeBlanc KA. Laparoscopic incisional and ventral hernia repair: Complications—how to avoid and handle. *Hernia*. 2004 December;8(4):323–331.
16. Heniford BT, Park A, Ramshaw BJ, Voeller G. Laparoscopic ventral and incisional hernia repair in 407 patients. *J Am Coll Surg*. 2000 June;190(6):645–650.
17. Lomanto D, Katara AN. Managing intra-operative complications during totally extraperitoneal repair of inguinal hernia. *J Minim Access Surg*. 2006 September; 2(3):165–170.
18. Bittner R, Schwarz J. Inguinal hernia repair: Current surgical techniques. *Langenbecks Arch Surg*. 2012 February;397(2):271–282.

    In this article Bittner et al. compare and review the wide variety of surgical techniques and technologies of both laparoscopic and open inguinal hernia repair. Published in 2012, it provides a great compilation of the findings comparing the multiple modalities of repair.
19. Ferzli GS, Edwards E, Al-Khoury G, Hardin R. Postherniorrhaphy groin pain and how to avoid it. *Surg Clin North Am*. 2008 February;88(1):203–216.
20. Jensen P, Mikkelsen T, Kehlet H. Postherniorrhaphy urinary retention—Effect of local, regional, and general anesthesia: A review. *Reg Anesth Pain Med*. 2002 November;27(6):612–617.
21. Falagas ME, Kasiakou SK. Mesh-related infections after hernia repair surgery. *Clin Microbiol Infect*. 2005 January; 11(1):3–8.
22. Forbes SS, Eskicioglu C, McLeod RS, Okrainec A. Meta-analysis of randomized controlled trials comparing open and laparoscopic ventral and incisional hernia repair with mesh. *Br J Surg*. 2009 August;96(8):851–858.
23. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med*. 1996 May 9;334(19):1209–1215.
24. Mäkelä JT, Kiviniemi H, Juvonen T, Laitinen S. Factors influencing wound dehiscence after midline laparotomy. *AJS*. 1995 October;170(4):387–390.
25. Hodgson NC, Malthaner RA, Ostbye T. The search for an ideal method of abdominal fascial closure: A meta-analysis. *Ann Surg*. 2000 March;231(3):436–442.
26. Israelsson LA, Jonsson T. Overweight and healing of midline incisions: The importance of suture technique. *Eur J Surg*. 1997 March;163(3):175–180.
27. Israelsson LA, Jonsson T, Knutsson A. Suture technique and wound healing in midline laparotomy incisions. *Eur J Surg*. 1996 August;162(8):605–609.
28. Burger JWA, Luijendijk RW, Hop WCJ, Halm JA, Verdaasdonk EGG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. *Ann Surg*. 2004 October;240(4):578–883; discussion 583–585.
29. Santora TA, Roslyn JJ. Incisional hernia. *Surg Clin North Am*. 1993 June;73(3):557–570.
30. Cevasco M, Itani KMF. Ventral hernia repair with synthetic, composite, and biologic mesh: Characteristics, indications, and infection profile. *Surg Infect (Larchmt)*. 2012 August;13(4):209–215.
31. Sadowski B, Rodriguez J, Symmonds R, Roberts J, Song J, Rajab MH, et al. Comparison of polypropylene versus polyester mesh in the Lichtenstein hernia repair with respect to chronic pain and discomfort. *Hernia*. 2011 December;15(6):643–654.
32. Segan RD. A response to "Major complications associated with xenograft biologic mesh implantation in abdominal wall reconstruction" (Harth KC, Rosen MJ. *Surg Innov*. 2009;16:324–329) and discussion of the MAUDE (manufacturer and user facility device experience) database, FDA regulation of biologic implants, and evidence-based medicine. *Surg Innov*. 2010 September;17(3):273–275; author reply 276.
33. Hartog den D, Dur AHM, Tuinebreijer WE, Kreis RW. Open surgical procedures for incisional hernias. *Cochrane Database Syst Rev*. 2008;(3):CD006438.
34. Cobb WS, Carbonell AM, Kalbaugh CL, Jones Y, Lokey JS. Infection risk of open placement of intraperitoneal composite mesh. *Am Surg*. 2009 September;75(9):762–767; discussion 767–768.
35. Leber GE, Garb JL, Alexander AI, Reed WP. Long-term complications associated with prosthetic repair of incisional hernias. *Arch Surg*. 1998 April;133(4):378–382.
36. Park A, Birch DW, Lovrics P. Laparoscopic and open incisional hernia repair: A comparison study. *Surgery*. 1998 October;124(4):816–821; discussion 821–822.
37. Park A, Gagner M, Pomp A. Laparoscopic repair of large incisional hernias. *Surg Laparosc Endosc*. 1996 April;6(2):123–128.
38. Mason RJ, Moazzez A, Sohn HJ, Berne TV, Katkhouda N. Laparoscopic versus open anterior abdominal wall hernia repair: 30-day morbidity and mortality using the ACS-NSQIP database. *Ann Surg*. 2011 October;254(4):641–652.

    Utilizing the data from the American College of Surgeons NSQIP database, this article compares the laparoscopic and open ventral hernia repair from a 30-day morbidity and mortality prospective.
39. Sajid MS, Bokhari SA, Mallick AS, Cheek E, Baig MK. Laparoscopic versus open repair of incisional/ventral hernia: A meta-analysis. *Am J Surg*. 2009 January;197(1):64–72.
40. Rutkow IM. Demographic and socioeconomic aspects of hernia repair in the United States in 2003. *Surg Clin North Am*. 2003 October;83(5):1045–1051–v–vi.
41. Bendavid R. Complications of groin hernia surgery. *Surg Clin North Am*. 1998 December;78(6):1089–1103.
42. Stephenson BM. Complications of open groin hernia repairs. *Surg Clin North Am*. 2003 October;83(5): 1255–1278.
43. Koch CA, Grinberg GG, Farley DR. Incidence and risk factors for urinary retention after endoscopic hernia repair. *AJS*. 2006 March;191(3):381–385.
44. Cramer SO, Malangoni MA, Schulte WJ, Condon RE. Inguinal hernia repair before and after prostatic resection. *Surgery*. 1983 October;94(4):627–630.

45. Wantz GE. Testicular atrophy and chronic residual neuralgia as risks of inguinal hernioplasty. *Surg Clin North Am*. 1993 June;73(3):571–581.
46. Abi-Haidar Y, Sanchez V, Itani KMF. Risk factors and outcomes of acute versus elective groin hernia surgery. *J Am Coll Sur*g. 2011 September;213(3):363–369.
47. Schrenk P, Woisetschläger R, Rieger R, Wayand W. Prospective randomized trial comparing postoperative pain and return to physical activity after transabdominal preperitoneal, total preperitoneal or Shouldice technique for inguinal hernia repair. *Br J Surg.* 1996 November;83(11):1563–1566.
48. Leibl BJ, Jäger C, Kraft B, Kraft K, Schwarz J, Ulrich M et al. Laparoscopic hernia repair—TAPP or/and TEP? *Langenbecks Arch Surg*. 2005 April;390(2):77–82.
49. Stark E, Oestreich K, Wendl K, Rumstadt B, Hagmüller E. Nerve irritation after laparoscopic hernia repair. *Surg Endosc*. 1999 September;13(9):878–881.

14

Complications of Biliary Tract Surgery and Trauma

Mary Frances Stuever and Akpofure Peter Ekeh

CONTENTS

Gallbladder and biliary tract operations are among the most common abdominal procedures performed in the United States. Approximately 800,000 new cases of cholelithiasis are diagnosed annually, half of which are symptomatic. Gallstones are present in approximately 10% of the adult population of the United States.[1] Minimally invasive approaches for cholecystectomy have become the standard over the last 20 years and have added a new dimension to biliary surgery and its resulting complications. While laparoscopic techniques have produced shorter hospital stays,

less postoperative pain, earlier return to full activity, and overall lower complication rates compared with open cholecystectomies, these gains were accompanied initially by an increased rate of injuries to the biliary ducts. Over time, these rates have ultimately remained stable.[1–3] Timely recognition of injuries, prompt referral, and a multidisciplinary approach involving surgeons, interventional radiologists, and gastroenterologists are imperative for the proper management of these complications.

Patients undergoing biliary procedures are prone to the usual complications that may occur after any major abdominal procedure. Elderly patients are at highest risk for morbidity and mortality, especially when perioperative presentation is taken into consideration.[4,5]

14.1 Introduction

It is estimated that 500,000–700,000 cholecystectomies are performed annually in the United States. Karl Langenbuch performed the first cholecystectomy in 1882,[6,7] and the operation remained the gold standard for the treatment of gallbladder disease for the next 100 years. Alternative treatments such as shock wave lithotripsy and gallstone dissolution emerged over the years but have been demonstrated to be inferior to surgical therapy.[8,9] Initial reports of laparoscopic cholecystectomy (LC) originated from Europe, where Professor Muhe of Boblingen, Germany, reportedly performed the first LC on September 12, 1985. A few years later in the United States, McKernan and Saye performed the first LC in Marietta, Georgia in 1988. Currently, approximately 85%–90% of cholecystectomies in the United States are being performed in this fashion. Symptomatic cholelithiasis is the most common indication for this operation. The overall complication rate associated with LC is 5%,[10] whereas that with open cholecystectomy (OC) is 14%.[10] At the onset of LC, the incidence of bile duct injury was twice higher than that of OC (0.5% and 1%, respectively). This initial higher rate was attributed to the learning curve adopting the new procedure. Over time, the bile duct injury rate has reached a plateau of 0.2% with LC. Currently, no difference has been shown in the rates of bile duct injury, bile leak, or other operative complications between LC and OC.[1]

Operations on the common bile duct (CBD), such as common bile duct explorations (CBDEs) for biliary calculi, are now performed less frequently because of the widespread use of endoscopic retrograde cholangiopancreatography (ERCP). This procedure has been very effective in stone removal, both preoperatively and postoperatively; thus, CBDE can be avoided in many cases.

14.2 Prevention of Potential Pitfalls during Elective Biliary Surgery

LC is now the gold standard for the treatment of cholelithiasis. Injury to the bile duct is the most concerning complication and has profound immediate and long-term consequences for the patient. The rate of bile duct injury in association with LC over time has remained steady with reported ranges of 0.18%–0.6%. Conversion to OC when LC cannot be performed safely or when injury is suspected should always remain an option for surgeons. The conversion rate from LC to OC is reported to be 5%–10%.[11] Common cited reasons for conversion are acute inflammation, severe chronic inflammation, adhesions from previous surgery, aberrant anatomy, equipment problems, stone spillage, bile duct laceration, bowel injury, the need for common duct exploration, and gallbladder carcinoma. Factors predictive of conversion to OC include the male gender, previous abdominal surgery, obesity, gallbladder wall thickening, suspicion of CBD stones, jaundice, acute cholecystitis, leukocytosis, surgeon experience, and obesity.

Several studies have found that certain factors are associated with an increased propensity for injury during LC. These include acute inflammation, chronic scarring or fibrosis of the gallbladder and biliary tree, fat in the porta hepatis, bleeding during the procedure, and aberrant anatomy.

Wound infection (usually at the site of the umbilical trocar), bleeding due to trocar insertion, bowel injury, retained stones, and subcutaneous emphysema are other complications that may occur after LC. Simple attention to detail can help prevent unnecessary complications during LC and OC. Certain safeguards and tips for the performance of LC are highlighted in the following sections.

14.2.1 Trocar Placement during Laparoscopic Cholecystectomy

Serious injuries have occurred with the establishment of access into the abdominal cavity, including bowel perforation, retroperitoneal hematoma, and omental injuries. Vascular injuries, such as lacerations of the aorta, the inferior vena cava, and the iliac vessels, although rare, have been reported. The Hasson and Veress techniques are the two standard access techniques used to establish a pneumoperitoneum. Recent studies show no statistically significant difference in complications between the two techniques. The Hasson technique lessens the risk of vascular injuries; however, it does not decrease the rate of bowel injuries.[12,14,15] Whatever method is used, care must be taken when establishing access, and proceeding to a laparotomy should be

strongly considered if an injury is suspected. A third method of access is the use of visual techniques, that is, a trocar insertion under direct vision with a scope in situ. This method is similarly not totally "injury proof" and should be avoided in areas where there are prior laparotomy scars.

Subcutaneous emphysema, pneumothorax, and gas embolism are rarely reported complications resulting from the creation of a pneumoperitoneum.

14.2.2 Gallbladder Dissection and Retraction

A surgical approach to dissection that involves cephalad and lateral traction of the gallbladder tends to align the cystic duct in parallel with the CBD and offers a better view for anatomical identification. Additionally, blunt dissection of the cystic duct and artery should begin laterally and proceed medially only to an area where a "critical view of safety" is obtained.[13–15] This critical view is the identification of the gallbladder wall on the right, the cystic duct inferiorly, and the cystic artery on the left. The entire fatty dissection of this triangle and the mobilization of the infundibulum, both anteriorly and posteriorly, permit visualization of the liver surface through the Calot triangle. Studies have shown that this systematic approach can identify appropriate landmarks and any anatomical anomalies.

Hunter has proposed some specific technical steps aimed at preventing bile duct injuries during LC. These are (1) the liberal use of the 30° laparoscope, (2) firm cephalad–fundal retraction, (3) lateral infundibular retraction, and (4) dissection of the cystic duct.[16]

A retrospective review of 10,000 cholecystectomies without any CBD injuries performed at a center in China highlighted their keys to excellent patient outcomes—surgeon's expertise in biliary surgery, preoperative imaging, precise operative procedures, and conversion from LC to OC when needed.[17]

Common situations that can lead to complications include severe inflammation, scarring, or bleeding, which in turn lead to the CBD easily being confused with the cystic duct, and chronic inflammation that may result in the fusion of the cystic duct and the common hepatic duct (CHD). This scenario could lead to a CHD injury. Conversion to an open procedure should be performed without hesitation in the face of severe scarring or inability to properly retract or grasp the gallbladder. Another commonly employed technique is to decompress a distended gallbladder with needle aspiration, thus possibly making it easier to handle, particularly in cases of acute inflammation.[14] Top-down approaches, that is, dissecting the gallbladder from the fundus down with retention of a small portion of the infundibulum and leaving the posterior wall of the gallbladder in situ are techniques that have been described in difficult situations. Summarily, if ever in doubt, conversion to OC is the safest option.

14.2.3 Use of Intraoperative Cholangiography

The debate regarding the routine use of intraoperative cholangiography (IOC) predates the laparoscopic era. Some authors currently still advocate cholangiography in all cases for delineating the anatomy and improving the surgeon's laparoscopic skills.[18–21] Other authors have argued for the selective use of this procedure.[21–24] When used, IOC should be performed dynamically under fluoroscopic guidance rather than statically, and proper interpretation of the findings is very important.[25] IOC aids in identification of injuries and possibly minimizing the extent of injury as well as directing the course of management in cases of retained common duct stones. Cholangiography should always be used in cases of uncertain or aberrant anatomy. Furthermore, rates of incidence of major bile duct injuries during LC without IOC in the scientific literature range from 0.25% to 1%, and of minor injuries from 0.28% to 1.7%.[1,26]

Recent studies have shown that the use of routine IOC is not necessary to prevent bile duct injuries and advocated for its selective use. LC can be performed safely without the use of IOC and with acceptable low rates of biliary complications. An accurate preoperative evaluation of clinical risk factors, precise operative procedures, and conversion to an open approach in doubtful cases are important measures that must be taken to prevent CBD injury.[27] Intraoperative laparoscopic ultrasonography is another technique that has emerged as an alternative to IOC. This method requires specific equipment and appropriate training to become facile in its use.

14.2.4 Cholecystectomy for Patients with Cirrhosis

The morbidity and mortality rates associated with cholecystectomy are higher for patients with liver disease than for the general population. Bleeding, both intraoperatively and postoperatively, is a serious concern. Factors contributing to the tendency for bleeding among patients with cirrhosis include portal hypertension with portosystemic shunting, thrombocytopenia, and coagulopathy. Historically, some authors have proposed that leaving the posterior wall of the gallbladder adherent to the liver will aid in preventing intraoperative and postoperative bleeding from the liver bed.[28] Fulguration of the retained mucosa with electrocautery or an argon beam coagulator is advised in these instances.

LC, once considered to be contraindicated in patients with cirrhosis and symptomatic cholelithiasis, is currently accepted as the procedure of choice for patients with early or well-compensated cirrhosis, Child's class A and B.[29] Overall, for patients with cirrhosis,

preoperative optimization of liver function is imperative. Only patients with symptoms clearly indicative of cholecystitis should undergo cholecystectomy. The simplest and most expeditious procedure is recommended. Tube cholecystostomy, in the setting of cholecystitis, should be considered as an option to surgery when the operative risk is very high.

A recent meta-analysis of cirrhotic patients undergoing LC demonstrated that in Child's class A and B patients, LC was associated with fewer postoperative complications, a shorter hospital stay, and quicker resumption of a normal diet when compared with OC.[29]

14.2.5 Preoperative Administration of Antibiotics

Most patients are given a single dose of preoperative antibiotics just before undergoing cholecystectomy. The Surgical Care Improvement Project (SCIP), developed by the Centers for Medicare and Medicaid Services and implemented in 2006, was designed as an evidence-based initiative to be applied broadly across selected surgical services, with a stated goal of reducing morbidity and mortality rates 25% by the year 2010. Preoperative dosing of prophylactic antibiotics, case-specific dosing, and withdrawal of antibiotic therapy within 24 h, have been added to standard practices in the OR. Follow-up studies have shown conflicting data, and the discussion on its utility in routine gallbladder cases is beyond the scope of this chapter.[30] Studies have demonstrated that preoperative antibiotic use is of no value in low-risk elective LC procedures.[31,32] For patients with clinical evidence of complicated biliary disease, such as age >65, jaundice, acute cholecystitis, choledocholithiasis, cholangitis, obesity, or diabetes mellitus, antibiotics have demonstrated value in decreasing the incidence of wound and intra-abdominal infections.[33]

14.2.6 Recent Technical Innovations in Laparoscopic Cholecystectomy

A discussion about biliary surgery and complications will be incomplete without a brief mention of some of the emerging techniques and technologies that have been introduced over the last few years. Single-incision laparoscopic surgery (SILS), robotic-assisted laparoscopic cholecystectomy, and natural orifice transluminal endoscopic surgery (NOTES) fall into this category.

14.2.6.1 Single-Incision Laparoscopic Surgery

Shortly after the introduction of LC, reports of utilizing single incision within the umbilicus for the procedure began to emerge. This technique was introduced with hopes of decreasing the amount of postoperative pain and improved cosmetic appearance by avoiding the additional two or three ports used in traditional LC. Indications have been reported to be similar to LC, and patient selection criteria have varied widely with previous studies limiting the BMI to <38 with no history of previous abdominal surgeries. However, other studies have reported no significant contraindication to SILS and have left the decision to the surgeon and the patient. Retrospective chart reviews have demonstrated the noninferiority of SILS to multiport LC, but no statistically significant advantages or disadvantages have been reported to date.[34–37] Complications reported with the SILS approach are similar to that of the traditional LC, which include injury to the bile duct and bile duct leaks. To date, there have been no statistically significant increases in complications when compared to the multiport laparoscopic approach.

14.2.6.2 Robotic-Assisted Laparoscopic Cholecystectomy

Robotic enhancements to minimally invasive procedures have been introduced over the last decade, with the aim of further reducing postoperative pain and improved cosmetic appearance, particularly by utilizing a single port. A few case reports and retrospective reviews have shown no increase in operative complications in LC.[38] It is uncertain at this point if this technology will have a major role in LC in the future.

14.2.6.3 Natural Orifice Transluminal Endoscopic Surgery

This technique is at this point limited to a few centers in the United States and internationally. This approach is still considered by many as experimental and is being developed as a surgical approach designed to further limit postoperative pain and improved cosmetic appearance.[1,38] The transgastric and transvaginal routes are the common access routes utilized. Most of the literature on NOTES centers on case series and animal studies. It is at this point difficult to accurately assess and compare complications with traditional LC, and more information is expected in the future.

14.3 Diagnosis of Biliary Complications

Postoperative bile leaks after cholecystectomy may occur from any portion of the biliary tract. The ducts of Luschka, which arise from the gallbladder bed, are occasionally a source. Leaks from these accessory ducts are usually self-limited and do not require surgical intervention.[1] Biliary leaks may also arise from the

cystic duct stump, the CBD, hepatic duct lacerations or transections, and small bowel injury.

14.3.1 Presentation

Patients with postoperative biliary leaks exhibit a wide range of clinical symptoms and signs. After biliary leaks, the common symptoms are abdominal pain, distension, nausea, vomiting, fever, and jaundice. Other symptoms include prolonged ileus and failure to thrive. Presentation can occur in the immediate postoperative period or as late as several weeks postoperatively. A postoperative bile leak should be considered in any patient who does not follow the expected postoperative course for routine cholecystectomy.

Physical examination may reveal jaundice, abdominal tenderness, or both. Tenderness may be localized to the right upper quadrant or generalized. Fever and other signs of sepsis may accompany these findings in cases of infected bile.

Laboratory findings may be nonspecific. Leukocytosis and hyperbilirubinemia may be present. There is not usually a consistent pattern of direct or indirect hyperbilirubinemia in cases of free bile leakage into the abdomen. Direct hyperbilirubinemia, however, predominates in cases of retained stones or a clipped common duct. Elevations in the hepatic transaminases alkaline phosphatase, and gamma-glutaryl transpeptidase may also be pertinent findings in cases of biliary obstruction.[1,14,15]

14.3.2 Diagnostic Methods

14.3.2.1 Ultrasonography

Ultrasonography (US) is a fast, inexpensive, and noninvasive method of confirming suspected injuries to the biliary tract. Findings of intrahepatic ductal dilatation indicate obstruction of the distal common duct. US easily detects fluid collections. However, this procedure cannot characterize the fluid as a bile collection, a hematoma, a seroma, or a lymphocele. The effectiveness of US is limited by abundant bowel gas, which may accompany cases of ileus. Obesity can also present technical difficulties. US can be used as a guide for percutaneous drainage of bilomas.

14.3.2.2 Computed Axial Tomography

Computed axial tomography (CT) also easily detects and localizes fluid collections but may be unable to accurately characterize them. CT scanning should not be the first choice for diagnosing bile duct injuries because CT does not demonstrate details of the biliary tree as well as US does. CT can also be used for guided percutaneous aspiration and drainage.

14.3.2.3 Hepatobiliary Scintigraphy

Hepatobiliary scintigraphy is a safe, highly sensitive, and noninvasive detector of biliary leaks. Historically, its accuracy has reported to be between 83% and 87% of cases and is more sensitive and specific than CT or US for ongoing biliary leaks.[39] When imaging is delayed to 90 min, the sensitivity of this diagnostic method is further increased. Imaging is performed with technetium 99m-labeled iminodiacetic acid contrast agents. This procedure can be performed in cases of postop hyperbilirubinemia. The entry of the agent into the duodenum is an indication of the continuity of the biliary tract. Although good at detecting bile leaks, hepatobiliary scintigraphy cannot precisely determine the anatomical location of leaks. Other diagnostic studies are needed to pinpoint the exact location of a leak.

14.3.2.4 Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) can be either a diagnostic or a therapeutic procedure in cases of bile duct injury. Cholangiography can easily pinpoint the exact location of injury to the biliary tree. Therapeutic maneuvers such as sphincterotomy, stone extraction, and biliary stent placement may be performed when appropriate. ERCP can easily detect cystic duct leaks and lacerations to the common duct. In cases of transections of the biliary tree, however, ERCP may not allow visualization of proximal anatomy, and complete delineation of the injury may not be possible. In 5% of cases, ERCP is associated with serious complications such as pancreatitis, hemorrhage, cholangitis, and intestinal perforation.[1]

14.3.2.5 Percutaneous Transhepatic Cholangiography

Percutaneous transhepatic cholangiography (PTC) is an excellent method for illustrating the anatomy of the proximal biliary tree. A complete picture of the injury can often be obtained solely by using this method. Furthermore, temporary therapeutic procedures, such as placing drainage catheters and stents, can be performed using this approach as a bridge before definitive repair. PTC allows adequate decompression of the bile ducts. Catheters placed by PTC can serve as guides during operative dissection for definitive repair procedures.

14.3.2.6 Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) has played an increasingly important role in the diagnosis of gallbladder disease in recent years. Utilization of MRCP has been shown to reduce the indications for and

the frequency of use of ERCP. It has consistently demonstrated high sensitivity, specificity, and accuracy in detecting common duct stones, and it allows visualization of the proximal and distal anatomy of the bile duct. Because MRCP is noninvasive, it has a unique advantage over ERCP and PTC. MRCP has also been used to diagnose postoperative biliary leaks. The limitations of using magnetic resonance technology may however limit its use in certain situations.

14.4 Management of Specific Complications

14.4.1 Leaks from the Stump of the Cystic Duct

Cystic duct leaks generally occur after inadequate ligature of the cystic duct or slippage of clips, although they can also be caused by retained stones. Another cause of such leaks is injury to the cystic duct distal to the clips or ligature applied during cholecystectomy. Accumulation of free bile from this source usually occurs in the subhepatic space. Depending on the severity, the rate of the leak, and the length of time before it is detected, bile may spread freely throughout the peritoneal cavity or may be loculated. The symptoms of cystic duct leaks include abdominal pain, fever, and jaundice.

The definitive diagnosis is typically made by either ERCP or PTC. Treatment involves reducing the pressure on the proximal duct by placing an endoscopic stent in the common duct through the ampulla of Vater. Equalization of pressures in the biliary tree and the duodenum by stent placement is believed to be sufficient to allow the healing of these minor leaks. These stents typically remain in place for 6–8 weeks; surgical intervention is rarely necessary. The type of stent used (long, short, or nasobiliary) does not appear to influence the outcome. Cystic duct leaks can be managed with or without sphincterotomy, but sphincterotomy alone without stent placement can result in prolonged bile leakage and delayed healing. Any residual stone can be extracted when ERCP is performed.

14.4.2 Injuries to the Common Bile Duct

14.4.2.1 Bile Duct Injury Classification

14.4.2.1.1 Bismuth–Corlette Classification

The Bismuth–Corlette classification scheme was introduced before LC. It is difficult to apply in LC as most of the technical factors and lesion mechanisms are different from open surgery. It considers the complete section of the CBD and the length of the proximal bile duct stump. Type I is a low injury with a stump length >2 cm. Type II is a middle-level injury with a stump length <2 cm. Type III is a high-level injury without CHD available but preserved confluence. Type IV involves loss of hepatic confluence with no communication between right and left ducts.

14.4.2.1.2 Stewart–Way Classification

In this classification, there are four groups based on the mechanism and anatomy of injury:

1. Class I refers to the incomplete section of bile duct with no loss of tissue. It has a prevalence rate of 7% (among bile duct injuries).
2. Class II is a lateral injury of the CHD that leads to stenosis or bile leak. It is the consequence of thermal damage and clamping the duct with surgical staples. It has a prevalence of 2% with a concomitant hepatic artery injury in 18% of cases. T-tube related injuries are included within this class.
3. Class III injuries are the most common seen (61% of cases) and represent the complete section of the CHD. It is subdivided into type IIIa, remnant CHD; type IIIb, section at the confluence; type IIIc, loss of confluence; and type IIId, injuries higher than confluence with the section of secondary bile ducts. A concomitant injury of right hepatic artery occurs in 27% of cases.
4. Class IV describes the right (68%) and accessory right (28%) hepatic duct injuries with concomitant injury of the right hepatic artery (60%). Occasionally it includes the CHD injury at the confluence (4%) besides the accessory right hepatic duct lesion. Class IV has a prevalence of 10%.

14.4.2.1.3 Strasberg Classification

This classification divides injury into five groups, A–E.

1. Class A represents a bile leak from the cystic duct or an accessory duct. In both conditions, there is continuity with the CBD.
2. Class B is the section of an accessory duct with no continuity with the CBD.
3. Class C represents a leak from a bile duct with no continuity with the CBD.
4. Class D is a partial section of a bile duct with no complete loss of continuity with the rest of the bile duct system.
5. Class E is a complete section of the bile duct with subtypes according to the length of the stump. It also includes the loss of confluence and injury to accessory ducts.

The Hannover classification is another classification scheme not as common as the one mentioned earlier and not as frequently utilized.

The classic injury associated with LC is caused by misidentification of the common duct as the cystic duct followed by resection of parts of the common bile and hepatic ducts. These injuries are detected during the original procedure in 50% of cases, although they may be detected as late as postoperative day 9. Although the precise location of the leak can be determined by either PTC or ERCP, PTC has the distinct advantage of revealing the intrahepatic system and the bifurcation of the hepatic ducts. When the common duct has been transected, the procedure of choice for repair is hepaticojejunostomy.[39] Primary anastomosis and repair of common duct injuries over a T-tube are associated with a high failure rate and are not recommended for the repair of biliary injuries.

Stewart and Way[40] reported that several factors are associated with the successful repair of common duct injuries after biliary surgery. These factors are preoperative cholangiography, the choice of surgical repair, the details of the surgical repair, and the experience of the surgeon performing the repair. These authors demonstrated that 96% of repair procedures for bile duct injury were unsuccessful without preoperative cholangiography. When complete cholangiography was performed preoperatively, 84% of the initial repair procedures were successful. Primary end-to-end anastomosis led to unsuccessful outcomes in all cases, whereas Roux-en-Y hepaticojejunostomy led to success in 63% of cases. The success rate was 94% if the first repair was performed by a tertiary care biliary surgeon, but only 17% if the initial repair was performed by the primary surgeon.

The timing of the repair appears to be crucial. If the injury is detected during the original cholecystectomy, the repair should be performed at that time, provided that the primary surgeon's expertise and experience are sufficient for tackling the problem. For injuries that are not detected until the postoperative period, operative repair can be delayed for days to weeks to allow abatement of inflammation and infection. If a bile leak persists, repair can be postponed for 4–6 weeks, provided that adequate drainage has been obtained. Percutaneous transhepatic catheters may be adequate for controlling an ongoing leak, but separate percutaneous catheters may be necessary for draining bile collections. Some surgeons routinely perform the hepaticojejunostomy repair over a stent. This externalized stent is used for postoperative studies and also for the measurement of biliary pressures. These stents are maintained postoperatively for variable lengths of time. One advantage of these stents is that they allow access to the anastomosis for radiological intervention in the event of stricture formation. Other surgeons remove the stents shortly after the repair has been performed or do not use them at all.

Anastomosis of the small intestine to the CBD, when it is present (choledochojejunostomy), yields poorer results than anastomosis of the intestine to the CHD (hepaticojejunostomy). Initial repair of proximal injury is even more successful, probably because the bile duct closer to the bifurcation has a better blood supply. Long-term results after serious bile duct injury are good when the injury is appropriately managed. The results of repair after laparoscopic injury compare favorably with the results of repair after open injuries if the surgeon has sufficient experience. Five-year success rates of more than 90% have been reported.

A recent study performed at a tertiary center revealed improving results over time. All patients with clinically significant injuries requiring repair were treated with a hepaticojejunostomy. A decrease in using transanastomotic stents was observed. Operative mortality, postoperative cholangitis, anastomosis strictures, short- and long-term complications, and need for reoperation (surgical or radiological) were significantly less in the more recent period. The authors concluded that transition to a high-volume center has improved long-term results for bile duct injury repair.[39]

14.4.3 Biliary Strictures

Strictures arising from biliary surgery typically manifest themselves months to years after the initial procedure. Most benign biliary strictures occur after cholecystectomy. The patient generally experiences an insidious onset of jaundice that is usually complicated by cholangitis. The definitive diagnosis of biliary stricture is made by cholangiography, which can be achieved under the guidance of ERCP, PTC, or MRCP. Benign biliary strictures should be managed operatively. Surgery is the gold standard against which all other methods are measured. The area of stricture is resected and reconstructed with a Roux-en-Y hepaticojejunostomy.[39,41]

Historically some surgeons have repaired benign biliary strictures by using endoscopic dilatational techniques. The use of dilation and stent placement is not recommended as the first line of definitive management of benign strictures. Expandable metallic stents have been used to treat benign biliary strictures, but they should be considered only when the patient is a poor candidate for surgery, when intrahepatic biliary strictures have occurred or when attempts at surgical repair have failed. Most patients treated with metallic stents will experience recurrent cholangitis or stent obstruction and will require repeated intervention.

14.4.4 Retained Common Duct Stones

Gallstones can be dislodged into the common duct in the course of dissection during cholecystectomy.

Smaller stones will pass through uneventfully into the duodenum. Larger stones, however, can be retained and can cause complications.

Common duct stones will be missed in approximately 1%–2% of cases after cholecystectomy. Most of these stones will be asymptomatic. Retained common duct stones can cause biliary stasis, which enhances bacterial replication and can result in postoperative cholangitis.

Patients with suspected retained stones should be treated with broad-spectrum antibiotics for the prophylaxis or treatment of cholangitis. US may demonstrate dilated proximal bile ducts. ERCP is a definitive diagnostic method in this setting. When ERCP is combined with sphincterotomy and stone extraction, successful CBD clearance can be achieved in 95% of cases.[1] Failure of ERCP to achieve stone clearance is an indication for common duct exploration.

14.4.5 Pancreatitis

Pancreatitis can occur as a complication of many abdominal procedures. Biliary surgery particularly tends to precipitate this complication. Pancreatitis may occur after the passage of common duct stones originating from the gallbladder. Pancreatitis can also result from direct instrumentation with probes, catheters, choledoscopes, and other instruments used for CBDE. The postoperative incidence of pancreatitis for OC and LC was found to be 0.96% and 0.34%, respectively.[42]

The treatment of postoperative pancreatitis involves bowel rest, fluid resuscitation, and nutritional support as indicated. Pancreatitis can be complicated by the development of pancreatic abscesses, pseudocysts, or pancreatic ascites. Antibiotics are used only for severe cases and for cases of documented infectious complications.

14.4.6 Infectious Complications

Surgical site infection rates after LC and OC have been reported to be 1.0% and 4.4%, respectively. Biliary microorganisms, most frequently *Escherichia coli*, are usually responsible for wound infection. Wound infection rates are higher after bouts of acute cholecystitis and cholangitis.[33]

Retained common duct stones may lead to cholangitis. Postoperative bile collections may also become infected.

14.5 Biliary Trauma

14.5.1 Introduction

In general, iatrogenic injuries to the biliary tree occur more frequently than injuries that result from blunt or penetrating trauma. Moreover, only approximately 3%–5% of victims of abdominal trauma sustain injuries to the biliary tract.[43] Most traumatic injuries to the biliary system are the result of penetrating trauma and occur in association with more severe injuries to other organs. Most traumatic injuries to the biliary system involve the gallbladder.

14.5.2 Presentation and Diagnosis

The diagnosis of biliary system injury is most frequently made intraoperatively. Such injuries are usually found in conjunction with other injuries, most often hepatic, major vascular, duodenal, and splenic injuries. Accurate preoperative diagnosis of traumatic biliary injuries is difficult. Bile leakage may occasionally elicit clinical signs of bile peritonitis. The presence of bile-stained fluid in the effluent from diagnostic peritoneal lavage may indicate liver or small bowel injury; this finding is not specific for injury to the bile ducts or gallbladder.

Abdominal CT scanning and US are not often useful in detecting isolated biliary tract injuries. Neither of these imaging methods can distinguish biliary collections from the collections of blood or other fluids. Radionuclide scanning may be useful for confirming the suspicion of a disruption in the biliary tree. ERCP is also a method of diagnosing biliary tract lacerations with subsequent leakage. The usefulness of these two diagnostic studies is limited, however, because they cannot be performed on trauma patients in unstable condition.

Gallbladder injuries range from simple disruptions (laceration) to avulsions, contusions, or hemobilia. Bile duct injuries can be simple lacerations or more complex injuries involving transections of more than 50% of the lumen of the duct.

14.5.3 Management

Treatment of traumatic injury to the biliary system follows the same principles as management of injuries produced by iatrogenic mishaps. In the operating room, all immediately life-threatening injuries, such as liver and vascular lesions, should be addressed first. Abbreviated laparotomies without the definitive repair of biliary injuries may be necessary to achieve correction of acidosis, coagulopathy, and hypothermia. Thorough external drainage of extravasated bile is necessary. Definitive repair of injuries can be undertaken if the patient is stable.

Gallbladder injuries are treated by simple cholecystectomy. Ductal injuries are approached as addressed previously. IOC should be used liberally when the surgeon is uncertain about the presence or extent of injury. Patients may require Roux-en-Y hepaticojejunostomy. As is true for elective procedures, emergent procedures involving primary duct-to-duct anastomosis over a T-tube do not yield very good long-term results.[43]

14.6 Summary

Biliary tract surgery and its associated complications can present difficult challenges in management. Important points for surgeons are attention to detail during common gallbladder procedures, discretion during difficult dissections, prompt conversion of laparoscopic procedures to open procedures when indicated, and early identification and prompt management of complications. Referral to tertiary care centers for definitive repair must also continually be a consideration for the management of complicated bile duct injuries and bile duct strictures.

The minimally invasive era has added a new dimension to the treatment of biliary disease. Recent data are consistent with a plateau in the incidence of bile duct injuries. Thus, efforts to prevent and quickly diagnose bile duct injuries continue to be of vast importance. Continued addition of new techniques and patient management options is found through a multidisciplinary approach.

Complications of Biliary Surgery and Trauma

Complications	Incidence	References
Bile duct injury	0%–3% (LC) 0%–0.2% (OC)	[1,2,17,27,41]
Bile leak	0%–0.1%	[1]
Bleeding	0.1%–0.5%	[1,44]
Peritonitis	0.2%	[1]
Intra-abdominal abscess	0.1%	[1]
Bowel injuries	0.16%	[1,44]
Surgical wound infection	4.4% (OC), 1.1% (LC)	[1,33]
Biliary strictures	Found in setting of bile duct injury	[3,45]
Retained common duct stones	1%–2%	[1]
Pancreatitis	1.0% (OC) 0.34% (LC)	[1,42]
Mortality	0%–0.3%	[1]

Avoiding Biliary Complications

Complications	Methods of Avoidance	Comments	References
Bile duct injury	Systematic approach to identifying major anatomical landmarks Conversion to open when necessary Intraoperative cholangiogram	Obtain the "critical view of safety"	[13–15]
Bile leak	Attention to applying clips to the cystic duct Meticulous dissection of gallbladder off the liver bed		[1,14,15,44]
Bleeding	Attention to trocar placement Meticulous dissection of the gallbladder		[1,14,15,44]
Peritonitis	Avoidance of bile spillage		[1]
Intra-abdominal abscess	Avoid spillage of bile Appropriate use of antibiotics		[1,33]
Bowel injuries	Attention to insertion of trocar Attention to location of instruments		[1,44]
Surgical wound infection	Appropriate use of antibiotics Appropriate glycemic control in diabetic patients		[33]
Biliary strictures	Avoid bile duct injuries		[3,45]
Retained common duct stones	Preoperative imaging, i.e., MRCP or ERCP, when clinically indicated Intraoperative cholangiogram when indicated		[1,13,14]
Pancreatitis	Limit instrumentation of the bile duct		[1,14,15,42]
Mortality	Attention to pre- and postoperative resuscitation Appropriate use of antibiotics		

References

1. Duncan CB, Riall TS. Evidence-based current surgical practice: Calculous gallbladder disease. *J Gastrointest Surg*. 2012;16:2011–2025.
2. Pottakkat B, Vijayahari R, Prakash A, Singh RK, Behari A, Kapoor VK, Saxena R. Incidence, pattern and management of bile duct injuries during cholecystectomy: Experience from a single center. *Dig Surg*. 2010;27:375–379.
3. Sikora SS, Pottakkat B, Srikanth G, Kumar A, Saxena R, Kapoor VK. Postcholecystectomy benign biliary strictures–long-term results. *Dig Surg*. 2006;23:304–312.
4. Siegel JH, Kasmin FE. Biliary tract diseases in the elderly: Management and outcomes. *Gut*. 1997;41:433–435.
5. González JJ, Sanz L, Grana JL, Bermejo G, Navarrete F, Martinez E. Biliary lithiasis in the elderly patient: Morbidity and mortality due to biliary surgery. *Hepatogastroenterology*. 1997;44(18):1565–1568.
6. Langenbuch CJA. Ein Fall von Exstirpation der Gallenblase wegen chronischer Cholelithiasis. *Berliner Klin Wochenschr* 1882;19:725–727.

7. Glenn F, Grafe WR Jr. Historical events in biliary tract surgery. *Arch Surg*. 1966;93:848–852.
8. Magnuson TH, Lillemoe KD, Pitt HA. How many Americans will be eligible for biliary lithotripsy? *Arch Surg*. 1989;124:1195–1200.
9. Sackmann M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gallstone recurrence rate after successful shock-wave therapy. *Gastroenterology*. 1990; 98:392–396.
10. A prospective analysis of 1518 laparoscopic cholecystectomies. The Southern Surgeons Club. *N Engl J Med*. 1991;324:1073–1078.
11. Lengyel BI, Azagury D, Varban O, Panizales MT, Steinberg J, Brooks DC, Ashley SW, Tavakkolizadeh A. Laparoscopic cholecystectomy after a quarter century: Why do we still convert? *Surg Endosc*. 2012;26:508–513.
12. Channa GA, Siddiqui AJ, Zafar SN. Open versus closed method of establishing pneumoperitoneum for laparoscopic cholecystectomy. *J Coll Physicians Surg Pak*. 2009; 19 (9):557–560.
13. Vettoretto N, Saronni C, Harbi A, Balestra L, Taglietti L, Giovanetti M. Critical view of safety during laparoscopic cholecystectomy. *J Soc Laparoendosc Surg*. 2011; 15:322–325.
14. Steele K, Lidor A. Minimally invasive surgery. In Cameron J (ed.), *Laparoscopic Cholecystectomy. Current Surgical Therapy*, 9th edn, Maryland Heights, MO: V. Mosby. 2008, pp. 1271–1275.
15. Chari R, Shah S. Chapter 54. Biliary system. In Townsend C, Beauchamp RD, Evers BM, Mattox KL (eds.), *Sabiston Textbook of Surgery. The Biological Basis of Modern Surgical Practice*, 18th edn. Philadelphia, PA: Saunders Elsevier. 2008, pp. 1563–1564.
16. Hunter JG. Avoidance of bile duct injury during laparoscopic cholecystectomy. *Am J Surg*. 1991;162:71–76.
17. Zhi-Bing Ou, Sheng-Wei Li, Chang-An Liu, Bing Tu, Chuan-Xin Wu, Xiong Ding, Zuo-Jin Liu, Ke Sun, Hu-Yi Feng, Jian-Ping Gong. Prevention of common bile duct injury during laparoscopic cholecystectomy. *Hepatobiliary Pancreat Dis Int* 2009;8:414–417.
18. Asbun HJ, Rossi RL, Lowell JA, Munson JL. Bile duct injury during laparoscopic cholecystectomy: Mechanism of injury, prevention, and management. *World J Surg*. 1993;17:547–552.
19. Rossi RL, Schirmer WJ, Braasch JW, Sanders LB, Munson JL. Laparoscopic bile duct injuries. Risk factors, recognition, and repair. *Arch Surg*. 1992;127:596–602.
20. Moossa AR, Easter DW, Van Sonnenberg E, Casola G, D'Agostino H. Laparoscopic injuries to the bile duct. A cause for concern. *Ann Surg*. 1992;215:203–208.
21. Stuart SA, Simpson TI, Alvord LA, Williams MD. Routine intraoperative laparoscopic cholangiography. *Am J Surg*. 1998;176:632–637.
22. Snow LL, Weinstein LS, Hannon JK, Lane DR. Evaluation of operative cholangiography in 2043 patients undergoing laparoscopic cholecystectomy: A case for the selective operative cholangiogram. *Surg Endosc*. 2001; 15:14–20.
23. Borjeson J, Liu SK, Jones S, Matolo NM. Selective intraoperative cholangiography during laparoscopic cholecystectomy: How selective? *Am Surg*. 2000;66:616–618.
24. Braghetto I, Debandi A, Korn O, Bastias J. Long-term follow-up after laparoscopic cholecystectomy without routine intraoperative cholangiography. *Surg Laparosc Endosc*. 1998;8:349–352.
25. Silverstein JC, Wavak E, Millikan KW. A prospective experience with selective cholangiography. *Am Surg*. 1998;64:654–658.
26. Pesce A, Portale TR, Minutolo V, Scilletta R, Destri GL, Puleo S. Bile duct injury during laparoscopic cholecystectomy without intraoperative cholangiography: A retrospective study on 1,100 selected patients. *Dig Surg*. 2012;29:310–314.
27. Pesce A, Portale TR, Minutolo V, Scilletta R, Destri GL, Puleo S. Bile duct injury during laparoscopic cholecystectomy without intraoperative cholangiography: A retrospective study on 1,100 selected patients. *Dig Surg*. 2012;29:310–314.
28. Bornman PC, Terblanche J. Subtotal cholecystectomy: For the difficult gallbladder in portal hypertension and cholocystitis. *Surgery*. 1985;98:1–6.
29. de Goede B, Klitsie1 BJ, Hagen SM, van Kempen BJH, Spronk S, Metselaar HJ, Lange JF, Kazemier G. Meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic cholecystolithiasis. *Br J Surg Soc*. 2012. Paper accepted July 5, 2012. Published online in Wiley Online Library (www.bjs.co.uk). doi: 10.1002/bjs.8911.
30. Edmiston CE, Jr., Spencer M, Lewis BD, Brown KR, Rossi PJ, Henen CR, Smith HW, Seabrook GR. *Surg Inf*. 2011;12(3):169–177. doi:10.1089/sur.2011.036.
31. Shah JN, Maharjan SB, Paudyal S. Routine use of antibiotic prophylaxis in low-risk laparoscopic cholecystectomy is unnecessary: A randomized clinical trial. *Asian J Surg*. 2012;35:136–139.
32. Choudhary A, Bechtold ML, Puli SR, Othman MO, Roy PK. Role of prophylactic antibiotics in laparoscopic cholecystectomy: A meta-analysis. *J Gastrointest Surg*. 2008;121847–121853.
33. Walker AT, Shapiro AW, Brooks DC, Braver JM, Tumeh SS. Bile duct disruption and biloma after laparoscopic cholecystectomy: Imaging evaluation. *Am J Roentgenol*. 1992;158:785–789.
34. Gangl O, Hofer W, Tomaselli F, Sautner T, Függer R. Single incision laparoscopic cholecystectomy (SILC) versus laparoscopic cholecystectomy (LC)—A matched pair analysis. *Langenbecks Arch Surg*. 2011;396:819–824.
35. Leung D, Yetasook A, Carbray J, Butt Z, Hoeger Y, Denham W, Barrera E, Ujiki MB. Single-incision surgery has higher cost with equivalent pain and quality-of-life scores compared with multiple-incision laparoscopic cholecystectomy: A prospective randomized blinded comparison. *J Am Coll Surg* 2012;215:702–708.
36. Sajid MS, Ladwa N, Kalra L, Hutson KK, Singh KK, Sayegh M. Single-incision laparoscopic cholecystectomy versus conventional laparoscopic cholecystectomy: Meta-analysis and systematic review of randomized controlled trials. *World J Surg*. 2012;36:2644–2653.
37. Hall TC, Dennison AR, Bilku, DK, Metcalfe MS, Garcea G. Single-incision laparoscopic cholecystectomy. *Arch Surg*. 2012;147(7):657–666.

38. Morel P, Pugin F, Bucher P, Buchs NC, Hagen ME. Robotic single-incision laparoscopic cholecystectomy. *J Robotic Surg*. 2012;6:273–274.
39. Mercado MA, Domínguez I. Classification and management of bile duct injuries. *World J Gastrointest Surg*. 2011;3(4):43–48.
40. Stewart L, Way LW. Bile duct injuries during laparoscopic cholecystectomy. Factors that influence the results of treatment. *Arch Surg*. 1995;130:1123–1129.
41. Xu XD, Zhang YC, Gao P, Bahrani-Mougeot F, Zhang LY, He ZY, Zhang Y, Ma JZ. Treatment of major laparoscopic bile duct injury: A long-term follow-up result. Southeastern Surgical Congress. *Am Surg*. 2011; 77:1584–1588.
42. Z'graggen K, Aronsky D, Maurer CA, Klaiber C, Baer HU. Acute postoperative pancreatitis after laparoscopic cholecystectomy. *Arch Surg* 1997;132:1026–1030.
43. Ball CG, Dixon E, Kirkpatrick AW, Sutherland FR, Laupland KB, Feliciano DV. A decade of experience with injuries to the gallbladder. *J Trauma Management Outcomes*. 2010;4:3.
44. Chapron CM, Pierre F, Lacroix S, Querleu D, Lansac J, Dubuisson JB. Major vascular injuries during gynecologic laparoscopy. *J. Am Coll Surg*. 1997;185(5):461–465.
45. Kassab C, Prat F, Liguory C, Meduri B, Ducot B, Fritsch J, Choury AD, Pelletier G. Endoscopic management of post-laparoscopic cholecystectomy biliary strictures. Long-term outcome in a multicenter study. *Gastroenterol Clin Biol*. 2006;30(1):124–129.

15

Complications of Intestinal Surgery

Andrew Michael and John J. Hong

CONTENTS

Intestinal surgery, like all other operations, comes with the risk of perioperative complications. Some of these issues such as mild postoperative fever, ileus, and incisional pain are expected, while deviation from the expected course could represent the need for early physician action to improve outcomes. In small bowel surgery, meticulous surgical methods with complete removal of nonviable tissue, attention to detail in recognizing bowel injuries, and adequate drainage of infected tissues clearly improve outcomes.

The safety of colorectal surgery has improved tremendously over the last 50 years with the availability of new antibiotics, detailed preoperative preparation of the patient, improvements in surgical techniques, and postoperative critical care management. The morbidity associated with elective colorectal

surgery has decreased significantly. Age, obesity, diabetes, and cardiopulmonary disorders increase postoperative morbidity and mortality. Emergency colorectal surgery continues to be associated with a considerable morbidity and mortality due to the nature of the disease combined with limited time for preoperative preparation.

15.1 Complications of Small Bowel Surgery

15.1.1 Postoperative Ileus and Pain

Violation of the peritoneum causes a cascade of physiologic events, some of which result in inhibition of gastrointestinal function. Physical manipulation of the viscera further impairs gut motility through splanchnic sympathetic reflex inhibition as well as through stimulation of local inflammatory mediators.[1] Bowel motility commonly seen at laparotomy may not represent effective, coordinated peristalsis. Depending on the site and degree of visceral manipulation, the underlying disease process, and patient characteristics, paralytic ileus may last from hours to days. Postoperative ileus is further exacerbated by the use of opioids for analgesia.

Traditionally, postoperative ileus has been treated with bowel rest, nasogastric suction, and early mobilization. Despite what we commonly tell our patients, early mobilization does not appear to hasten recovery from ileus; more likely, it is a marker for adequate postoperative pain control, which may decrease other postoperative complications. Nasogastric suction and early enteral feeding have been studied, with small, but statistically significant improvements in resolution of postoperative ileus associated with early resumption of enteral nutrition.[2] The use of regional analgesic agents has also been shown to decrease the duration of postoperative ileus.[3] The use of minimally invasive versus open surgical techniques appears to decrease the duration of postoperative ileus.[4]

To date, none of these studies have involved patients undergoing extensive small intestinal surgery. Patients undergoing extensive small bowel manipulation are at greatest risk for having prolonged postoperative ileus. Prolonged paralytic ileus in these patients may rightfully be considered an expected consequence of disease. Conversely, prolonged ileus in a patient who has undergone an elective colorectal procedure or gynecologic procedure may be considered a surgical complication, and appropriate perioperative care can decrease its duration.

15.1.2 Postoperative Obstruction and Adhesion Formation

Prolonged postoperative ileus may be difficult to distinguish from partial mechanical small bowel obstruction (SBO), and both may be present to a degree in patients who have undergone extensive intestinal surgery. Patients who have undergone gynecologic or colorectal procedures are at higher risk for development of SBO in the postoperative period. Postoperative partial SBO usually resolves with nasogastric suction, parenteral fluid, and nutritional support.

Peritoneal adhesions are the most common cause (>90%) of postoperative mechanical obstructions.[5] Adhesion formation is a generalized response to tissue injury. As such, adhesion formation is essentially universal, and has been considered an unavoidable consequence of laparotomy. However, there is clearly individual variation in the amount, severity, and duration of peritoneal adhesions found on reoperation. Some of the factors that contribute to adhesion formation may be preventable.

Means of prevention of peritoneal adhesions have traditionally been the same as those ascribed to reduce the likelihood of postoperative ileus, measures designed to minimize inflammatory peritoneal reaction to laparotomy: gentle tissue handling, meticulous hemostasis, avoidance of contamination with enteric contents, avoidance of tissue dessication, minimization of exposure to foreign bodies, for example, washing powder from surgical gloves prior to peritoneal exposure, etc. In theory, strict attention to surgical technique should minimize preventable causes of adhesion formation; however, no means of reducing peritoneal adhesions have been reproduced and verified; therefore, adhesion formation is still seen as an unavoidable sequela of abdominal surgery.[6]

15.2 Complications in Specific Intestinal Operations

15.2.1 Lysis of Adhesions

Inadvertent bowel injury is the most common complication of adhesiolysis. The bowel is most commonly injured upon initial entry into the peritoneal cavity, when recognition of bowel densely adherent to a previous laparotomy incision is most difficult. Inadvertent enterotomy with spillage of enteric contents is associated with significantly increased morbidity, increased likelihood for wound and intra-abdominal infection, increased likelihood of further postoperative adhesions, increased duration of postoperative ileus, increased likelihood of ICU admission, and increased hospital stay. Full thickness bowel injuries should be immediately repaired with care taken to minimize contamination. There are no definitive data regarding the necessity to repair deserosalized

bowel, but a missed enterotomy is a potentially catastrophic injury. Both small and large bowel should be meticulously examined following any extensive adhesiolysis to identify potential missed injuries.

15.2.2 Bowel Resection and Repair

Bowel resection is performed to remove nonviable or severely diseased bowel. This seemingly simple objective may require considerable surgical judgment to execute properly. We can divide the surgical decision-making process into three phases: (1) diagnosis, or identification and quantification of the severity of diseased bowel; (2) debridement, or resection, drainage, and lavage; and (3) reconstruction, or anastomosis and/or diversion. Each step is accompanied by potential complications.

15.2.3 Inadequate or Excessive Resection

Inadequate resection represents a failure of diagnosis. In the setting of bowel infarction, residual nonviable bowel will result in unrelenting abdominal sepsis in the postoperative period, further complicating a typically complex clinical picture. Evidence of ongoing inflammatory response following bowel resection may be a marker of inadequate resection. Intraoperatively, segments of questionable bowel may be evaluated using a Wood's lamp and intravenous fluorescein administration. A staged laparotomy, with initial exploration and resection followed by aggressive fluid resuscitation and medical optimization, and then a planned "second look" laparotomy, may also allow for preservation of additional viable intestine. In the setting of inflammatory or neoplastic disease, adequate resection requires removal of all disease, with gross or histologic identification of healthy, nondiseased margins of intestine available for anastomosis.

Crohn's disease may pose a difficult clinical dilemma, with the need for resection potentially outweighed by the need to preserve intestinal length, anticipating future progression of disease. A variety of surgical techniques have been described to preserve intestinal length in patients with Crohn's disease.

Excessive intestinal resection may cause a spectrum of disease, from clinically inconsequential removal of nondiseased bowel to diarrhea to debilitating, even lethal, short bowel syndrome. Loss of the ileocecal valve and the terminal ileum is particularly debilitating. Patients with loss of over 100 cm of terminal ileum may develop macrocytic anemia from inadequate B12 absorption, and diarrhea from impaired enterohepatic recycling of bile salts.

Short bowel syndrome may be unavoidable. It is most commonly the result of emergency resection of a large length of nonviable intestine secondary to mesenteric occlusion or midgut volvulus; it is also seen in patients with Crohn's disease who have had multiple enterectomies, and infants following extensive resections for enterocolitis or intestinal atresia. Loss of 80% of intestinal length results in short bowel syndrome that cannot be improved with intestinal adaptation. Short bowel syndrome is caused by a length of remnant viable bowel that is not compatible with adequate enteral nutrition, resulting in malabsorption of nutrients, vitamins, and water. Current therapy is directed first at managing the early fluid and electrolyte abnormalities and maintaining adequate nutritional support, and then later, attempting to optimize intestinal adaptation through the use of enteral nutrition and gut trophic agents. Surgical techniques range from intestinal lengthening techniques to small bowel transplantation.[7,8]

15.2.4 Debridement

Adequate debridement involves removal of nonviable tissue, drainage of areas of questionable viability, and removal and avoidance of further gross contamination. Areas of perforation should be quickly closed to prevent ongoing contamination. Spillage during bowel resection can be minimized by placing intestinal clamps proximal and distal to the segment prior to resection. The abdomen and surgical wound should be protected during bowel resection and anastomosis by draping with moist laparotomy pads or towels. Peritoneal irrigation should be used to remove gross contamination and particulate matter.

15.2.5 Reconstruction

Complications following primary small bowel anastomosis are usually the consequences of technical error. Obstruction at the anastomotic site may be the result of incorporation of too much tissue in a handsewn anastomosis, transient edema, hematoma, or improper suture placement stenosing a bowel segment. Meticulous attention to technique is necessary to avoid these potential errors. There has been no difference in complication rate between handsewn and stapled anastomoses demonstrated in the literature for elective bowel resection.[9]

Bleeding at the anastomosis site is usually self-limited, and resolves without the need for reoperation. Significant hemorrhage may be associated with a preexistent bleeding diathesis, or iatrogenic over-anticoagulation.

Leak is a common serious surgical complication following intestinal anastomosis. Ischemia at the anastomosis site may be caused by ligation of the blood supply too close to the bowel end, by accidental ligation of mesenteric vessels, or by rotation of the ends of the bowel limbs causing arterial or venous insufficiency.[10]

Anastomotic leak, as mentioned earlier, may also be the result of inadequate resection of diseased bowel. Patients' characteristics also influence risk of leak.[11] Clinical manifestations of anastomotic leak are variable, ranging from florid postoperative sepsis to asymptomatic leakage, apparent only radiographically. Given the variable presentation, and variable severity of anastomotic leak, there is little data regarding ideal management. If the leak is small, it may result in localized phlegmon or abscess formation that may be amenable to diagnosis with computerized tomography (CT) of the abdomen and nonoperative treatment with systemic antibiotics and percutaneous drainage if necessary. Larger leaks may require reoperation.

Nonoperative management of an anastomotic leak may result in fistula formation. Enterocutaneous fistulae may also be caused by incorporating intestine into the suture used to close the abdominal wall, or unrecognized injury. A fistulogram and/or CT scan may determine the site of defect and detect any associated abscess. Most fistulas close without surgical intervention, especially if daily output is <500 mL. The initial management is bowel rest with parenteral nutritional support, management of fluid and electrolyte losses, and skin protection. The benefit of octreotide is controversial.[12] Enteral nutrition may be resumed if it does not cause worsening of the fistula output. Fistulas with a distal obstruction, very short tracts, complete epithelialization of the tract, presence of a foreign body, cancer, or inflammatory bowel disease may not heal without surgical intervention.

15.3 Complications of Intestinal Surgery in Trauma

The principles for intestinal surgery for trauma are the same as for elective surgery, with the additional need for the immediate control of hemorrhage. Upon obtaining adequate hemostasis, rapid identification of injuries is carried out by "running" the small bowel from the ligament of Treitz to the ileocecal valve. Temporary control of contamination may be obtained using bowel clamps placed proximal and distal to the site of injury, or Allis clamps placed on multiple enterotomies, prior to definitive repair or resection. With control of ongoing contamination, gross enteric contents and fecal contamination may be lavaged from the peritoneal cavity, and the bowel may be carefully inspected for areas of injury or questionable viability. In severely injured patients requiring staged or "damage control" laparotomies, definitive intestinal reconstruction may await second or even third look laparotomies. Patients with injuries involving mesenteric vessels may also require re-exploration to evaluate the extent of associated ischemic injury to the bowel.

There are some data that suggest that handsewn anastomoses are superior to stapled anastomoses in trauma patients.[13]

Missed small bowel injury following blunt abdominal trauma is potentially an increasingly frequent complication, especially with the widespread use of CT and ultrasonography for the evaluation of trauma, combined with the increasing frequency of nonoperative management of intra-abdominal injuries. The finding of free intraperitoneal fluid in the hemodynamically normal patient following blunt abdominal trauma may be indicative of a small bowel injury. This may be especially confounding when associated with small liver or spleen lacerations; therefore, close monitoring and serial abdominal exams will help in the prevention of a delay in diagnoses.

15.4 Complications of Appendectomy

Complications of appendicitis may be categorized into preoperative, intraoperative, or postoperative.

15.4.1 Preoperative Complications: Misdiagnosis

Errors in diagnosis result in either a "false-positive" (unnecessary) appendectomy, or a "false-negative," or missed (perforated or gangrenous) case of appendicitis. Traditionally, surgeons have accepted a certain number of "negative" appendectomies as not only inevitable, but even desirable, as an indicator of sufficient clinical suspicion in light of the increased morbidity associated with a false-negative diagnosis of acute appendicitis. The number of acceptable normal appendices removed has traditionally been between 10% and 25%, with higher or lower rates depending upon patient demographics.[14] There are some data that suggest the use of CT or a variety of nuclear medicine studies may improve diagnostic accuracy.[15]

15.4.2 Intraoperative Complications: Complicated Appendicitis

Data suggest that the majority of cases of complicated appendicitis are due not to physicians' delay to surgery, but rather to patients' delayed presentation.[16] Patients with a phlegmon or abscess diagnosed prior to surgery are often initially treated with a trial of nonoperative management with antibiotics, with eventual interval appendectomy. This approach may yield complication

rates less than primary appendectomy in the setting of a necrotic appendiceal stump or cecum, which is associated with an increased risk of fecal fistula formation. The necessity for interval appendectomy is controversial; some authors advocate simple observation without surgery, following nonoperative management of perforated appendicitis.[17,18] However, studies examining cases of acute appendicitis treated with antibiotics alone did identify a high rate of recurrent appendicitis.[19]

Surgeons confronting advanced, complicated appendicitis in the operating room must balance the security of the appendiceal stump and the viability of adjacent inflamed cecum with the morbidity associated with resection of additional large and small bowel to obtain viable margins. Typically this occurs in patients who have presented late in the course of neglected disease, or who have failed nonoperative management. Adequate debridement and drainage notwithstanding, the development of fecal fistula and/or intra-abdominal abscess in these patients with severe advanced disease may be unavoidable, even anticipated, complications. There are some data suggesting that laparoscopic appendectomy may be associated with fewer postoperative complications.[20]

15.4.3 Postoperative Complications: Infection

Wound infection and intra-abdominal infection are the most common morbidities following appendectomy. Gangrenous appendicitis and perforation appear to be important independent risk factors for the development of intra-abdominal abscess following appendectomy.[21] Whether laparoscopic (vs. open) appendectomy increases the risk for intra-abdominal abscess is controversial.[22]

Regardless of the method of appendectomy, wounds at high risk of becoming infected should be left open. Primary closure of dirty wounds has been associated with a significantly increased incidence of wound infection as compared to delayed primary or nonclosure of abdominal wounds.[23]

15.5 Complications of Colorectal Surgery

15.5.1 Infection

Infection is the most common postoperative complication following colorectal surgery. Postoperative infection can range from a minor wound infection to septicemia with shock and organ failure. The determining factors are age, associated disorders such as diabetes, and duration and degree of contamination.[24] The incidence of postoperative sepsis can be minimized with good bowel preparation, proper use of antibiotics, meticulous surgical technique, and good judgment.

Wound infections are more common after emergency colorectal surgery as compared to elective cases, and an infection rate as high as 50% has been reported.[25] Wounds at high risk of becoming infected should be left open, with the possibility of delayed primary closure available as an option on postoperative days 4–6. If a wound that has been closed shows evidence of erythema, tenderness or drainage, the wound should be opened and packed with saline-soaked gauze. In the presence of diffuse erythema around the wound, treatment with a parenteral antibiotic effective against streptococci is justified. Necrotizing soft tissue infections are uncommon but extremely morbid, and must be recognized and treated promptly. Possible symptoms are erythema, edema, severe incisional pain, and crepitus. If a necrotizing soft tissue infection is suspected, the patient requires prompt opening of the incision, surgical debridement, and treatment with broad-spectrum parenteral antibiotics.

Mechanical bowel preparations, which are usually not possible prior to emergency colorectal surgery, decrease the fecal mass and may decrease the incidence of wound infections. Usually, there is no time prior to emergency colorectal cases to administer oral antibiotics. However, the effectiveness of oral antibiotics in reducing the risk of wound infections has been demonstrated in multiple studies.[26] Studies have failed to demonstrate the effectiveness of plastic wound drapes in preventing wound infections.[27]

In patients who demonstrate systemic signs of infection with no evidence of wound infection, an intra-abdominal infection should be suspected. CT scan has the greatest sensitivity in detecting an intra-abdominal abscess, with sensitivity reported in excess of 90% by several authors.[28]

CT or less commonly ultrasound-guided percutaneous drainage is often used to drain postoperative abscesses. Clinical signs of sepsis should improve within 48 h of drainage. If they do not, repeat CT scan with possible manipulation or reinsertion of drains should be performed. If percutaneous drainage fails to fully drain the intra-abdominal abscess, surgical drainage of the abscess may be necessary.[29] The presence of an intra-abdominal abscess also mandates the use of parenteral antibiotics.

15.5.2 Anastomotic Leak

Postoperative intra-abdominal infection may be the result of anastomotic leak. Colonic anastomoses pose a greater risk of leak than small intestinal anastomoses. Anastomoses below the peritoneal reflection are at a significantly higher risk of leakage. Other risk factors

involved in the development of an anastomotic leak include: local tissue ischemia, edema, tension, generalized ischemia (shock), sepsis, malnutrition, steroid therapy, previous irradiation, inflammatory bowel disease, inadequate bowel preparation, and obstruction distal to the anastomosis. When an anastomotic leak is suspected, an abdominal CT using intravenous, p.o., and rectal contrast should be performed.

Management of an anastomotic leak depends on the degree and location of leakage and the patient's clinical condition. The main priority in management is control of ongoing contamination. An asymptomatic leak demonstrated only on routine radiographic surveillance typically requires no surgical intervention. These patients may be managed with broad-spectrum parenteral antibiotics and bowel rest. Patients with clinical evidence of anastomotic leak may present along a spectrum ranging from mild "failure to thrive" to septic shock. Lack of clinical improvement with nonoperative management or peritonitis requires surgery to obtain adequate debridement, drainage, and diversion of the fecal stream.

15.5.3 Colocutaneous Fistula

A colocutaneous fistula is usually the late manifestation of an unrecognized anastomotic leak or injury to the bowel. Colonic fistulae are more likely to be low-output than small bowel fistulae, and are more likely to close without the need for operative intervention. Fistulae are managed as described earlier.

15.5.4 Injuries to Adjacent Organs

Vital structures that can be injured during colorectal surgery include the spleen, ureters, bladder, kidneys, duodenum, gallbladder, pancreas, stomach, ovaries and fallopian tubes, and the iliac and superior mesenteric vessels.

The reported incidence of operative ureteral injury varies from 1.5% to 12%.[30] It is the most common intraoperative urological complication. The ureters are most vulnerable to injury at the pelvic brim and at the site of insertion into the bladder. When injury to the ureters occurs, treatment depends on the severity of the injury and the site of injury along the course of the ureter. The different types of ureteral injury include devascularization, crush injury, transaction, and avulsion. Intraoperatively, the diagnosis of ureteral injury can be made by intravenous injection of methylene blue or intravenous pyelography. Postoperatively, the diagnosis is made by intravenous pyelography. The procedure of choice for lower-third injuries is a ureteroneocystostomy. The preferred technique for mid-ureteral repair is a ureteroureterostomy. Proximal-third injuries are the most challenging and sometimes require replacement with ileum. If ureteral injury is undetected, uncontrolled urinary leakage may lead to the development of sepsis and/or cutaneous urinary fistula as well as metabolic derangements associated with resorption of urine in the peritoneal cavity.

Bladder injuries have an incidence of <5%.[31] Intraoperatively recognized injuries may be closed primarily and drained with a Foley catheter. If injuries are not detected immediately, they might lead to significant morbidity and present as an enterovesical fistula or persistent perineal drainage as well as the same metabolic derangements associated with ureteral injury.

Injury to the spleen is most common with left hemicolectomy and subtotal colectomy.[32] Typically occurring during resection or dissection of the splenic flexure, traction on the peritoneum and omentum leads to avulsion of a portion of the splenic capsule. To prevent this complication, adequate visualization is crucial. The proximal descending colon and the distal transverse colon should be mobilized concomitantly to avoid excessive traction on the omentum and the splenocolic ligament. Injured vessels in the splenocolic ligament and splenic hilum are managed by clamping and ligatures. Direct pressure and Avitene, Surgicell, or fibrin glue can be used on capsular tears. Occasionally, splenorrhaphy or even splenectomy may be necessary.

15.6 Stoma Complications

The overall incidence of stoma construction is decreasing. However, stomas are still required in many operations for inflammatory bowel disease, colorectal tumors, trauma, and diverticulitis. When a stoma is required, every effort should be made to create a stoma that functions well, with minimal interference with the patient's lifestyle. The creation of a stoma should not be regarded as a minor surgical procedure. Complications are relatively frequent, and emergency stoma formation seems to be associated with the highest complication rates.[33] Elderly patients have more complications, and obese patients are at a higher risk for development of early complications.[34] Improper position of the stoma also affects the incidence of complications. Many complications are preventable with careful surgical technique. Ideally, stoma location should be chosen and marked preoperatively. Stoma complications are classified by stoma type and the time of occurrence.

15.6.1 Ileostomy and Colostomy

Ileostomies have been associated with the highest morbidity of any type of stoma, with loop ileostomies

demonstrating the greatest number of complications.[35] Ileostomies can have output >1000 mL in a 24 h period, which may lead to significant dehydration and sodium loss, requiring fluid replacement and correction of electrolytes. Chronic dehydration and acid urine can lead to uric acid renal calculi formation. Ileostomy effluent is also rich in proteolytic enzymes that cause skin irritation.

15.6.2 Skin Problems

Skin problems are the most common early and late complications. They are usually the result of poor adherence of the appliance and exposure of skin to the stoma effluent. Predisposing conditions are an improperly placed stoma, inadequate care of a stoma, and allergy to adhesive materials. This most common complication of ileostomy is the most preventable. Proper stoma placement and maintenance can usually eliminate this complication.

15.6.3 Ischemia and Necrosis

The incidence of stoma necrosis is 2%–17%. Predisposing factors of this complication are devascularization of the bowel, obesity, and a tight opening in the abdominal wall. Other contributing factors are shock and arteriosclerosis. If the necrosis is above the fascia, conservative management is justified. However, this may lead to long-term stenosis of the stoma. Necrosis below the fascia necessitates laparotomy, resection of necrotic colon, and revision of the stoma.

15.6.4 Retraction

Retraction in ileostomies occurs in as many as 15% of patients. Predisposing factors are tension on the stoma, ischemia, obesity, and improper placement of the stoma. Retraction may require surgical intervention as it is often associated with severe skin excoriation. The incidence of retraction in colostomies is 1.5%–10%. The main predisposing factor for retraction is tension. When the stoma separates and releases into the peritoneum, immediate wound exploration with stoma revision is required. If this is unsuccessful, laparotomy and further mobilization of colon are necessary to prevent fecal spillage and development of late stoma stenosis.

15.6.5 Obstruction

Obstruction within 6 months after construction is usually caused by impacted enteric contents. This is usually managed with gentle irrigation of the stoma or a hypaque stoma injection. Obstruction after 6 months is usually secondary to adhesions or stenosis which can be due to recurrent inflammatory bowel disease. In these situations, a hypaque study can bring relief. If this maneuver is unsuccessful, stenoses are best treated with local revision or repositioning of the stoma. For colostomies, obstruction early after surgery is unusual. It is usually secondary to a parastomal hernia or stenosis at the skin level. Fecal impaction can usually be managed with injection of water-soluble contrast into the stoma which acts as a laxative.

15.6.6 Stenosis

Stenosis of ileostomies is usually secondary to inflammatory bowel disease, ischemic necrosis, or exposure of ileal serosa to fecal irritants. This complication usually presents with a partial SBO. Management of this problem consists of decompression with a nasogastric tube and local revision or relocation of the stoma. Usually, the problem can be prevented by adequate preservation of the mesentery, preferably to within 2 cm of bowel end, and preventing serosal exposure by turning back 2 cm of ileum on itself. The incidence of this complication in colostomies is 2%–9%, and is usually due to early ischemia or separation at the skin. For urgent relief, stomal dilatation can be performed.

15.6.7 Prolapse

The incidence of colostomy prolapse is 2%–5%, while remaining much lower after ileostomy placement. Occurring early in the postoperative period, it is usually due to improper construction and is usually associated with a parastomal hernia. It is most commonly seen with a transverse loop colostomy. The treatment of this problem is usually not urgent, requiring excision of the redundant segment and lateral fixation of the colon. This is successful in a third of cases. If the prolapse recurs, relocating the stoma or colectomy might be necessary.

15.6.8 Parastomal Hernia

This is the most common complication after colostomy placement and very rare after ileostomy placement. The incidence of this complication ranges from 1% to 58%. It most commonly occurs within the first 2 years after surgery. The risk factors for development of this complication are obesity, chronic obstructive pulmonary disease, and the existence of other hernias. There is controversy about the effect of stoma site on hernia development. The significance of this complication is pain, inability to maintain an ostomy appliance, intestinal obstruction, and incarceration. Only 10%–20% of these hernias require repair, and of these only 16% require surgery for incarceration and obstruction. It is acceptable to attempt local repair with or without mesh. If this is unsuccessful, then the stoma should be relocated.

15.7 Complications of Specific Procedures

15.7.1 Abdominoperineal Resection

Today with the ability to perform low anastomoses and coloanal procedures, abdominoperineal resection (APR) is typically reserved only for rectal carcinomas involving the pelvic floor or upper anal canal and anal cancers that do not respond to chemoradiation therapy. APRs are associated with morbidity as high as 59%, with the highest morbidity among irradiated patients.[36] The most common complications are urinary retention and impotence. Intraoperatively, the two common major complications are ureteral injury and presacral hemorrhage. The incidence of ureteral injury during this procedure ranges from 0.3% to 6%. The diagnosis, treatment, and prevention of this complication are discussed under general complications of colorectal injury. Bladder injuries have an incidence of 0%–5% during this procedure. Most of these injuries respond to prolonged bladder drainage, and rarely is surgical repair necessary. Urethral injuries occur in 0.7%–6.7% of cases, and direct repair is recommended.

During APRs, there are a number of potential sites for bleeding. These include the pelvic sidewalls, iliac veins, and the middle sacral artery. Presacral hemorrhage can sometimes be unpreventable and difficult to control. Methods of control include packing, suture ligation, cautery, and clips. A bleeding basivertebral vein can be controlled with sterile thumbtacks.

Other possible intraoperative complications include extremity compartment syndromes and peripheral neuropathies from poor positioning and excessive retraction. Prevention of injury consists of careful positioning, with adequate padding and avoidance of long operative time.

Common postoperative complications after this procedure involve perineal wound complications, and bladder and sexual dysfunction resulting from nerve injury. Perineal wound complications consist of hemorrhage, abscess, perineal sinus, and perineal hernia formation. Several methods of perineal wound closure have been described including partial closure, primary closure, and closure with continuous irrigation and omental plugging. The incidence of perineal hemorrhage is higher in open packing with a frequency ranging from 0% to 4%.[37] Perineal abscess is almost always associated with primary closure of the perineal wound. The incidence of abscess development is 11%–16%.[38] The main risk factor is fecal contamination. Rectal injury during dissection is another predictive factor of abscess development. Superficial subcutaneous abscesses are to be managed by opening the wound with local wound care. Deeper perineal or presacral abscesses may require percutaneous drainage. A nonhealing perineal wound is called a perineal sinus after 6 months. It is quite a common problem with an incidence ranging from 14% to 40%, especially in patients with inflammatory bowel disease.[39] Risk factors for the development of a perineal sinus are inflammatory bowel disease, radiation therapy, and fecal contamination. Curettage and primary closure can be performed. However, usually large and persistent perineal sinuses require debridement and a gracilis or gluteus myocutaneous flap. Perineal hernias are uncommon and occur in approximately 1% of patients. Evisceration requires immediate surgery with reduction and packing. Symptoms of perineal hernia include a perineal bulge, pain, and possibly voiding problems. Indications for surgery include discomfort refractory to conservative management, impending skin loss, and bowel obstruction. Various techniques have been proposed including primary repair with or without transperitoneal prosthetic material and tensor fascia lata grafts.

Urinary retention, urinary tract infection, and sexual dysfunction are common complications following APR. They are more common in male patients, especially if the procedure is performed for cancer versus inflammatory bowel disease. Voiding problems after APR are due to malalignment of the bladder, neurologic injury, or aggravation of a preexisting outlet obstruction. Sympathetic denervation can lead to urgency or incontinence, and parasympathetic denervation results in decreased bladder emptying and high postvoid residuals. Goldman et al. have recommended the prophylactic use of alpha-adrenergic blockers prior to surgery to prevent postoperative urinary retention and infection.[40]

Sexual dysfunction is reported in 32%–100% of these patients.[41] Sympathetic injury results in ejaculatory difficulty, and parasympathetic injury leads to erectile difficulty. Incidence of sexual dysfunction rises with age and resections for cancer versus inflammatory bowel disease. These injuries can be temporary or permanent, partial or complete.

15.8 Complications of Restorative Proctocolectomy with Ileal Pouch Anal Anastomosis

Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) has become an established procedure for patients with ulcerative colitis and familial adenomatous polyposis. The overall mortality is approximately 1%; however, it continues to have a significant morbidity rate of up to 62.7%.[42] Despite a high complication rate, functional results are good and patient satisfaction is high. Early complications consist of vascular

compromise, bleeding, sepsis, and SBO. Vascular compromise may lead to the development of an anastomotic leak, sepsis, or stricture formation. Patients undergoing this procedure can be on steroid therapy and immunocompromised, and have inflammatory bowel changes, making the tissues especially fragile and at risk of bleeding. Therefore, extra caution is necessary to prevent hemorrhage. Suture or staple line bleeding rarely requires surgical intervention. Pelvic sepsis has an incidence of 5%–15%.[43] This is usually secondary to a suture line leakage and less commonly due to fecal contamination. The diagnosis is usually made with abdominal CT scan. Some abscesses may be amenable to percutaneous drainage. If conservative management with parenteral antibiotics does not lead to improvement, then laparotomy is indicated. Pelvic sepsis is also possible after ileostomy closure. Therefore, a pouchogram is necessary to detect a leak or fistula prior to stoma closure. If pelvic sepsis does occur after ileostomy closure, then reestablishment of fecal diversion is necessary. The incidence of SBO ranges from 7% to 30% after this procedure.[44] This relatively high incidence is partially due to performing two procedures and a temporary diverting ileostomy. Less than 50% of these patients require laparotomy. Nonoperative management initially is justified.

Fistula and stricture formation and pouchitis are the most common late complications of an IPAA. The incidence of fistula formation ranges from 2% to 16%.[45] Predisposing factors include ischemia with anastomotic breakdown, entrapment of adjacent organs, and postoperative sepsis. In these situations, Crohn's disease needs to be ruled out. The most common type of fistula is the pouch vaginal fistula. The technique of repair depends on the site and complexity of the fistula. Pouch excision is rarely required.

Anastomotic strictures have an incidence of 5%–20%.[46] This is the most common anastomotic complication after IPAA. Patients may develop strictures secondary to disuse during fecal diversion. Whether surgical technique (handsewn versus stapled anastomosis) has a role in stricture formation is debatable. It is often due to tension or ischemia at the anastomosis site. The presence of an abscess is also a contributing factor to stricture development. Treatment consists of anal dilatation and rarely pouch revision or permanent fecal diversion.

The incidence of pouchitis is 10%–30%.[47] It is the most common late complication. Pouchitis presents with cramps, diarrhea, urgency, incontinence, malaise, and fever. Pouchitis is more common in patients with ulcerative colitis than familial adenomatous polyposis. Oxygen-free radicals, stasis, and bacterial overgrowth may play a role in the development of pouchitis.[48] These patients require careful anal examination to rule out a stricture leading to stasis. Usually, there is good response to a 5–7 day course of metronidazole. If this treatment is ineffective, then a trial of treatment with ciprofloxacin should be attempted. In very rare cases of recurrence and persistent pouchitis, diversion and/or pouch excision becomes necessary.

15.9 Complications of Colorectal Trauma

Colorectal trauma is typically categorized as blunt or penetrating. Blunt trauma accounts for only 4% of colorectal trauma, with motor vehicle accidents being the most common cause. Anorectal injuries are rare with blunt trauma, and when present are usually associated with pelvic fractures. The majority of colorectal injuries are due to penetrating trauma, frequently caused by projectiles. Projectiles can cause injury by direct penetration, blast effect, or secondary penetration from fragmented bone. Other common causes of penetrating colorectal trauma are stab wounds and impalements.

Injuries to the rectum should be ruled out during initial trauma assessment since they may not be apparent during exploratory laparotomy. The appearance of gross blood on digital rectal exam may indicate colon or rectal injury.

The treatment of colonic injuries continues to be controversial. In general, primary closure is the procedure of choice if feasible. Relative contraindications to primary repair include: time interval between the injury and repair >8 h, shock, multiple organ system injuries, significant colonic damage or contamination, and multiple colonic injuries. Other options of management are exteriorization, repair with proximal diversion, and resection with or without anastomosis. Currently, exteriorization is seldom used as there is up to a 50% risk of leakage or obstruction with this method. The use of this technique is limited to only certain portions of the colon.

Rectal injuries may be difficult to diagnose. Intraperitoneal rectal injuries must be repaired. Extraperitoneal injuries, if extensive, may require proximal diversion and presacral drainage. The necessity for presacral drainage, especially with low-velocity injuries, is debatable.[49]

For all types of injury, debridement of nonviable tissues and removal of gross contamination are critical. Perioperative use of systemic antibiotics provides an important adjunct to therapy. In the presence of significant contamination, skin should be left open as there is a 40%–50% prevalence of wound infection.[50]

The most common cause of death in these patients is exsanguination followed by sepsis. In general, the postoperative complications from surgery to treat colorectal trauma are similar to those from other types of colorectal surgery: anastomotic leakage, infection, abscess, fistulas,

and stoma complications. Intra-abdominal abscess is the most frequent septic complication with a 5%–15% incidence. To reduce the incidence of complications, a systematic approach is necessary. Priorities for management of colorectal trauma are as follows: cessation of exsanguinating hemorrhage, followed by removal of ongoing contamination, and nonviable tissues, and finally reconstruction.

Complications of Small Bowel Surgery

Complications	Incidence
Prolonged ileus	40%[51]
SBO	12.4%–17%[52]
Anastomotic leak	3.4%[11]
Fistula	1.9%[53]
Intra-abdominal infection	3.3%[54]

Complications of Colorectal Surgery

Complications	Incidence
Anastomotic leak	3.4%–6%
Intra-abdominal infection	3.4%[55]
Organ injury	
• Ureter	1.5%–12%[30]
• Bladder	<5%[31]
• Spleen	<1%[32]
Stoma complication	
• Retraction	15%[56]
• Necrosis	2%–17%
• Parastomal hernia	1%–58%
• Prolapse	2%–5%[33–35]
APR	
• Perineal bleeding	0%–4%[37]
• Pelvic abscess	11%–16%[38]
• Perineal hernia	<1%
• Sexual dysfunction	32%–100%[41]
IPAA	
• Pelvic sepsis	5%–15%[43]
• SBO	7%–30%[44]
• Fistula	2%–16%[45]
• Anastomotic stricture	5%–20%[46]
• Pouchitis	10%–30%[47]

Avoiding Complications of Small Bowel Surgery

Complications	Tips
Prolonged ileus	Gentle handling of bowels, judicious use of opioids
SBO	Gentle tissue handling, meticulous hemostasis, avoidance of contamination
Anastomotic leak	Attention to viability of anastomosed bowel, avoidance of contamination, preservation of blood supply to anastomosed segments
Fistula	Attention to viability of anastomosed bowel, avoidance of contamination, preservation of blood supply to anastomosed segments
Infection	Early diagnosis of appendicitis, meticulous examination of bowel to prevent missed enterotomies, delayed primary or nonclosure of contaminated wounds

Avoiding Complications of Colorectal Surgery

Complications	Tips
Anastomotic leak	Attention to viability of anastomosed colon, avoidance of contamination, preservation of blood supply to anastomosed segments
Fistula	Attention to viability of anastomosed colon, avoidance of contamination, preservation of blood supply to anastomosed segments
Infection	Proper bowel prep, oral antibiotics preoperatively, delayed primary or nonclosure of contaminated wounds
Organ injury • Ureter • Bladder • Spleen	Careful dissection when mobilizing colon, avoidance of excessive traction
Stoma complication • Retraction • Necrosis • Parastomal hernia • Prolapse	Avoidance of excessive traction on stoma, creation of adequate abdominal wall opening, preferentially avoiding transverse colostomy when possible, careful selection of stoma site
APR • Perineal bleeding • Pelvic abscess • Perineal hernia • Urinary retention • Sexual dysfunction	Avoidance of fecal contamination, meticulous dissection
IPAA • Pelvic sepsis • SBO • Fistula • Anastomotic stricture • Pouchitis	Meticulous hemostasis, early imaging of pouch to avoid sepsis, early institution of antibiotics (Flagyl for pouchitis), avoidance of tension or ischemia at anastomosis

References

1. Kehlet H, Holte K. Review of postoperative ileus. *Am J Surg* 2001;182:3S–10S.
2. Cutillo G, Maneschi F, Franchi M et al. Early feeding compared with nasogastric decompression after major oncologic gynecologic surgery: A randomized study. *Obstet Gynecol* 1999;93:41–45.
3. Liu SS, Carpenter RL, Mackey DC et al. Effects of perioperative analgesic technique on rate of recovery after colon surgery. *Anesthesiology* 1995;83:757–765.
4. Schwenk W, Bohm B, Haase O et al. Laparoscopic versus conventional colorectal resection: A prospective, randomized study of postoperative ileus and early postoperative feeding. *Langenbecks Arch Surg* 1998; 383:49–55.
5. Stewart RM, Page CP, Brender J et al. The incidence and risk of early postoperative small bowel obstruction: A cohort study. *Am J Surg* 1987;154:643.

Surgeons should always suspect intra-abdominal adhesions in small bowel obstructions in previously operated patients as they are overwhelmingly responsible for a majority of cases.

6. Risberg B. Adhesions: Preventive strategies. *Eur J Surg* 1997;Suppl 577:32–39.
7. Figueroa-Colon R, Harris PR, Birdsong E et al. Impact of intestinal lengthening on the nutritional outcome for children with short bowel syndrome. *J Pediatr Surg* 1996;31(7):912–916.
8. Kaufman SS. Small bowel transplantation: Selection criteria, operative techniques, advances in specific immunosuppression, prognosis. *Curr Opin Pediatr* 2001;13(5):425–428.
9. MacRae HM, McLeod RS. Handsewn vs. stapled anastomoses in colon and rectal surgery: A meta-analysis. *Dis Colon Rectum* 1998;41:180–189.

   The method of anastomosis after large or small bowel resection is a matter of surgeon comfort and preference. Multiple studies have shown no difference between stapled and handsewn anastomoses in the reconstruction after resection.
10. Jex RK, Van Heerden JA, Wolff BG et al. Gastrointestinal anastomoses. Factors affecting early complications. *Ann Surg* 1987;206:138.
11. Golub R, Golub RW, Cantu R Jr, Stein HD. A multivariate analysis of factors contributing to leakage of intestinal anastomoses. *J Am Coll Surg* 1997;184(4):364–372.
12. Dorta G. Role of octreotide and somatostatin in the treatment of intestinal fistulae. *Digestion* 1999;60 (Suppl 2):53–56.
13. Brundage SI, Jurkovich GJ, Hoyt DB. Stapled versus sutured gastrointestinal anastomoses in the trauma patient: A multicenter trial. *J Trauma* 2001;51(6): 1054–1061.
14. Velanovich V, Satava R. Balancing the normal appendectomy rate with the perforated appendicitis rate: Implications for quality assurance. *Am Surg* 1992; 58:264–269.
15. Balthazar EJ, Rofsky NM, Zucker R. Appendicitis: The impact of computed tomography imaging on negative appendectomy and perforation rates. *Am J Gastroenterol* 1998;93:768–771.
16. Pittman-Waller VA, Myers JG, Stewart RM et al. Appendicitis: Why so complicated? Analysis of 5755 consecutive appendectomies. *Am Surg* 2000;66(6):548–554.
17. Oliak D, Yamini D, Udani VM et al. Nonoperative management of perforated appendicitis without periappendiceal mass. *Am J Surg* 2000;179(3):177–181.
18. Ein SH, Shandling B. Is interval appendectomy necessary after rupture of an appendiceal mass? *J Pediatr Surg* 1996;31(6):849–850.
19. Eriksson S, Granstrom L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995;82(2):166–169.
20. Wullstein C, Barkhausen S, Gross E. Results of laparoscopic vs. conventional appendectomy in complicated appendicitis. *Dis Colon Rectum* 2001;44(11):1700–1705.
21. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy (Cochrane Review). *Cochrane Database Syst Rev* 2001;3:CD001439.
22. Paik PS, Towson JA, Anthone GJ et al. Intra-abdominal abscesses following laparoscopic and open appendectomies. *J Gastrointest Surg* 1997;1(2):188–193.
23. Cohn SM, Giannotti G, Ong AW et al. Prospective randomized trial of two wound management strategies for dirty abdominal wounds. *Ann Surg* 2001; 233(3):409–413.
24. Haley RW, Culver DH, Morgan WM et al. Identifying patients at high risk of surgical wound infection. *Am J Epidemiol* 1985;121:206–215.
25. Cruse PJE, Foord R. The epidemiology of wound infection: A ten year prospective study of 62,939 wounds. *Surg Clin North Am* 1980;60:27–40.

   Clinical practices of wound closure should differ when dealing with elective versus emergency colorectal cases. Skin should be closed via delayed primary closure or left open in cases of significant fecal contamination.
26. Condon RE, Bartlett JG, Greenlee H et al. Efficacy of oral and systemic antibiotic prophylaxis in colorectal operations. *Arch Surg* 1993;118:496–502.
27. Psaila JV, Wheeler MH, Crosby DL. The role of plastic wound drapes in the prevention of wound infection following abdominal surgery. *Br J Surg* 1997;64:729–732.
28. Koehler PR, Moss AA. Diagnosis of intra-abdominal and pelvic abscesses by computerized tomography. *JAMA* 1980;244:49–52.
29. Hemming A, Davis NL, Robins RE. Surgical versus percutaneous drainage of intra-abdominal abscesses. *Am J Surg* 1991;161:593–595.
30. Bright TC III, Peters PC. Ureteral injuries secondary to operative procedures. Report of 24 cases. *Urology* 1977;9:22–26.
31. Lapides J, Tank ES. Urinary complications following abdominal perineal resection. *Cancer* 1971;28:230–235.
32. Langevin JM, Rothenberger DA, Goldberg SM. Accidental splenic injury during surgical treatment of the colon and rectum. *Surg Gynecol Obstet* 1984;159(2):139–144.
33. Stothert JC Jr, Brubacher L, Simonowitz DA. Complications of emergency stoma formation. *Arch Surg* 1982; 117(3):307–309.
34. Leenen LPH, Kuypers JHC. Some factors influencing the outcome of stoma surgery. *Dis Colon Rectum* 1989;32:500–504.
35. Brooke BN. The management of an ileostomy including its complications. *Dis Colon Rectum* 1993;36:512–516.
36. Colcock BP, Jarpa S. Complications of abdominoperineal resection. *Dis Colon Rectum* 1958;1:90.
37. Campos RR, Ayllon JG, Paricio PP, Tebar JC, Mompean JAL, Ruiz RL, Martinez JAT, Martinez JM. Management of the perineal wound following abdominoperineal resection: Prospective study of three methods. *Br J Surg* 1992;79:29–31.
38. Tompkins RG, Warshaw Al. Improved management of the perineal wound after proctectomy. *Ann Surg* 1985;202:760–765.
39. Rosen L, Veidenheimer MC, Coller JA, Corman ML. Mortality, morbidity, and patterns of recurrence after abdominoperineal resection for cancer of the rectum. *Dis Colon Rectum* 1982;25:202–208.
40. Goldman G, Kahn PJ, Kashtan H, Stadler J, Wiznitzer T. Prevention and treatment of urinary retention and infection after surgical treatment of the colon and rectum with alpha adrenergic blockers. *Surg Gynecol Ob*stet 1988;166:447–450.

41. Aboseif SR, Matzel KE, Lue TE. Sexual dysfunction after rectal surgery. *Perspect Colon Rectal Surg* 1990; 3:157–172.
42. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW, Schroeder TK. Ileal pouch-anal anastomoses complications and function in 1005 patients. *Ann Surg* 1995;222(2):120–127.
43. Scott NA, Dozois RR, Beart RW, Pemberton JH, Wolff BG, Ilstrup DM. Postoperative intra-abdominal and pelvic sepsis complicating ileal pouch- anal anastomosis. *Int J Colorect Dis* 1988;3:149–152.
44. Marcello PW, Roberts PL, Schoetz DJ, Coller JA, Murray JJ, Veidenheimer MC. Obstruction after ileal pouch-anal anastomosis: A preventable complication? *Dis Colon Rectum* 1993;36:1105–1111.
45. Keighley MRB, Grobler SP. Fistula complicating restorative proctocolectomy. *Br J Surg* 1993;80:1065–1067.
46. McMullen K, Hicks TC, Ray JE, Gathright JB,Timmcke AE. Complications associated with ileal pouch-anal anastomosis. *World J Surg* 1991;15:763–776.
47. Heuschen UA, Autschbach F, Allemeyer EH, Zollinger AM, Heuschen G, Uehlein T, Herfarth C, Stern J. Long-term follow-up after ileoanal pouch procedure: Algorithm for diagnosis, classification, and management of pouchitis. *Dis Colon Rectum* 2001;44(4):487–499.

    Pouchitis remains the most common complication after IPAA. Proper diagnosis and management include pouchoscopy and flagyl.
48. Levin KE, Pemberton JH, Phillips SF, Zinsmeister AR, Pezim ME. Role of oxygen free radicals in the etiology of pouchitis. *Dis Colon Rectum* 1993;35:452–456.
49. Levine JH, Longo WE, Pruitt C, Mazuski JE, Shapiro MJ, Durham RM. Management of selected rectal injuries by primary repair. *Am J Surg* 1996;172(5):575–579.
50. Orsay Cp, Merlotti G, Abcarian H et al. Colorectal trauma. *Dis Colon Rectum* 1989;32(3):188–190.
51. Delaney CP. Clinical perspective on postoperative ileus and the effect of opiates. *Neurogastroenterol Motility* 2004;16(s2):61–66.
52. Beck DE. Incidence of small-bowel obstruction and adhesiolysis after open colorectal and general surgery. *Dis Colon Rectum*. 1999; 42(2):241–248.
53. Fischer PE. A ten-year review of enterocutaneous fistulas after laparotomy for trauma. *J Trauma* 2009; 67(5):924–928.
54. Paik PS, Towson JA, Anthone GJ et al. Intra-abdominal abscesses following laparoscopic and open appendectomies. *J Gastrointest Surg* 1997;1(2):188–193.
55. Chambers WM. Postoperative leakage and abscess formation after colorectal surgery. *Best Pract Res Clin Gastroenterol* 2004; 18(5):865–880.
56. Cheung MT. Complications of an abdominal stoma: An analysis of 322 stomas. *Aust N Z Surg* 1995; 65(11):808–811.

16

Complications of Gastric Surgery

Kevin M. Schuster and Erik Barquist

CONTENTS

Gastric surgery, once a common procedure in general surgery, is now performed much less frequently. However, skill and knowledge in this field are still required, particularly in light of the increasing numbers of antireflux and bariatric procedures that are being performed today. Although the development of endoscopic, radiographic, and laparoscopic equipment allows less-invasive procedures, morbidity and mortality rates remain high.

16.1 Operative Treatment of Duodenal Ulcer

Operative therapy is reserved for complications of duodenal ulcer disease. Intractability, hemorrhage, perforation, and obstruction are the most common indications. Control of hemorrhage usually requires a duodenotomy and direct suturing of the bleeding site. The gastroduodenal artery should always be ligated. For perforated duodenal ulcers, operation may or may not be required as these may spontaneously seal. The procedure of choice is thorough peritoneal irrigation followed by omental patch closure. Gastric outlet obstruction, usually the result of recurrent ulceration, is the least common complication of duodenal ulcer disease. Endoscopic balloon dilation is a safe treatment but provides only temporary relief. Pyloroplasty is rarely feasible, and antrectomy is frequently performed; if this is impossible, truncal vagotomy and gastrojejunostomy are carried out.

16.2 Operative Treatment of Gastric Ulcer

Indications for elective surgical treatment of gastric ulcer include failure of a newly diagnosed ulcer to heal after 12 weeks of medical therapy, failure of a recurrent ulcer to respond to therapy, or recurrence after two initial courses of successful treatment. When gastric ulcers fail to heal completely, malignancy must be ruled out; inability to do so qualifies as an indication for surgery. The goal of operative treatment should be complete excision of the ulcer for histologic examination. The need for a definitive acid-reducing measure to treat gastric ulcer is not usually required.

Hemorrhage, perforation, and obstruction are the three most common complications of gastric ulcer. For ulcers located in the prepyloric region or in the body of the stomach, the preferred operation is antrectomy with Billroth I anastomosis. A truncal vagotomy may be added for prepyloric ulcers or for gastric ulcers associated with a duodenal ulcer.

If the ulcer is located proximally on the lesser curvature, antrectomy with extension of the lesser curvature to include the ulcer is preferred. If the ulcer is bleeding and lies too close to the esophago–gastric junction to allow resection, it is treated by vessel transfixion and ulcer oversewing. In the presence of life-threatening hemorrhage, suture ligation of the ulcer followed by vagotomy and pyloroplasty is an acceptable alternative. Multiple biopsies of the ulcer should be performed whenever possible; this procedure is associated with high rates of rebleeding. Operative treatment of a perforated gastric ulcer is accomplished by distal gastrectomy that includes the site of perforation. For patients in an unstable condition, excision of the ulcer with primary closure and omental patch overlay is an acceptable alternative.

16.3 Gastric Carcinoma

The mainstay of therapy for gastric cancer is surgery, which provides the only hope of cure. At the time of operation, if no gross metastases are found, a curative resection should be attempted. The goal is to completely remove the primary tumor and the associated lymph nodes. However, the extent of gastric resection required and the role of radical lymphadenectomy in achieving cure have been controversial. Margins of 4–6 cm around the primary tumor are required. For distal lesions, subtotal gastrectomy with a Billroth II anastomosis is the most frequently used procedure.[1] Lesions of the midbody or the fundus require total gastrectomy. Other indications for total gastrectomy include gastric stump cancer after distal resection for benign disease, Linitus plastica, and cancer associated with multiple polyps. Reconstruction is usually through an end-to-side Roux-en-Y esophagojejunostomy. Lesions near the gastroesophageal junction require esophagogastrectomy. Proximally, at least 10 cm of esophagus should be resected, with frozen section to ensure adequate margins. Gastric cancer can now be resected by three distinct methods that include laparotomy, laparoscopy, and endoscopic methods. The latter two methods are primarily reserved for lower stage disease. There is less blood loss and fewer complications associated with a laparoscopic approach and similar long-term survival when compared to open methods.[2,3] The types of complications are however similar.

16.4 Gastrointestinal Motility

Gastric surgery inherently has adverse effects on GI motility. The stomach functions to receive and store food, to mix it with gastric juice and begin the process of digestion, and to propel the prepared chyme into the duodenum at a rate optimal for digestion and absorption by the small intestine. The proximal stomach is capable of sustained alteration in tension via two vagally mediated reflexes: accommodation and receptive relaxation. Receptive relaxation refers to the anticipatory relaxation of the proximal stomach to accept a food bolus from the esophagus. Accommodation describes the stomach's ability to adapt to large changes in volume with only minimal increases in intragastric pressure. If accommodation is impaired, proximal gastric tone increases markedly during distension, and this increase leads to increased intragastric pressure and rapid emptying of liquids. Control of gastric emptying of solids is a function of the distal stomach. Solids are retained in the distal stomach, where they are mixed with gastric juice and broken down to particles before they are allowed to pass into the duodenum.

16.5 Effect of Surgical Procedures on Gastric Motor Physiology

Procedures performed on the stomach include resection, vagotomy, and drainage procedures. Each has specific effects on gastric motility and emptying. These disruptions may cause a variety of symptoms, termed *postgastrectomy syndromes*, which occur after 5%–50% of gastric operations.[4]

16.5.1 Vagotomy and Gastric Resection

Two types of vagotomy are currently performed: truncal vagotomy and highly selective vagotomy (HSV). Both procedures remove vagal innervation to the proximal stomach, and this removal severely impairs accommodation and reflexive relaxation. HSV does not disturb the gastric pacemaker or the distal propagation of these potentials. Truncal vagotomy, however, has profound effects on distal gastric motor physiology. Gastric peristalsis is weakened, trituration is impaired, and emptying of digestible and indigestible solids is slowed. Gastric emptying must be facilitated by a drainage procedure. The effect of gastric resection on proximal gastric motor physiology depends on the extent of resection. Distal resection abolishes antral trituration, removes the barrier to duodenal gastric reflux, and results in rapid emptying of solids. Proximal gastrectomy results in rapid emptying of liquids.

16.6 Acute Complications of Gastric Surgery

16.6.1 Rebleeding

Early recurrence of bleeding is more likely after surgery for peptic ulcer disease than after surgery for neoplasm. Bleeding may be intraluminal or intra-abdominal. Intraluminal bleeding most commonly occurs among patients with multiple comorbid conditions who have undergone a simple oversewing of an ulcer without an associated ulcer operation.[5] Overall, intraluminal bleeding occurs among 5% of all postgastrectomy patients. If endoscopic therapeutic measures cannot control the bleeding, open surgery or angiographic embolization is indicated. Intraoperatively, a proximal gastrotomy is performed above any anastomosis or stoma. Bleeding from a lesser-curvature closure or an anastomotic line may be controlled by suture ligation. Alternatively, re-resection and a second anastomosis may be required. Blood coming from the duodenum (in the case of a Billroth I anastomosis) or the afferent limb (in the case of a Billroth II anastomosis) suggests a recurrent bleeding ulcer. The esophagus and cardia should be examined for any ulcers, tears, or varices, and any bleeding should be controlled by suture ligation. If endoscopy points toward an intra-abdominal source, the next step may be CT scanning or ultrasonography. A patient in unstable condition should undergo immediate exploration.

16.6.2 Gastroparesis

Gastroparesis is most commonly seen after surgery for gastric outlet obstruction. Overall, 4% of patients undergoing a gastric procedure will experience delayed gastric emptying. Appropriate laboratory tests or CT scanning must exclude concurrent illness, infections, metabolic disturbances, or other treatable causes, including leaks or abscesses. Once these conditions have been excluded, prolonged conservative management is advised and should consist of gastric decompression, correction of electrolyte abnormalities, nutritional support, and weaning from potentially exacerbating drugs. If gastroparesis continues for more than 7–14 days after surgery, evaluation with barium, a radioisotope, or endoscopy is indicated. Among patients with gastroparesis, 95% will pass some contrast agent by day 14, whereas 95% of patients who pass no contrast agent will have a mechanical obstruction.[7] Surgical intervention is reserved for patients with early marginal ulcers that are unresponsive to medical therapy, for those with anatomic abnormalities of the gastric outlet, and for those without abnormalities whose stomach fails to empty by 1 month after operation.

16.6.3 Duodenal Stump Blowout

The incidence of duodenal stump leak is approximately 3%, with an associated mortality rate close to 10%.[5] A common cause of a blown duodenal stump is acute afferent limb obstruction, caused by kinking or retroanastomotic hernia. Patients with this condition usually exhibit an acute exacerbation of abdominal pain on the fifth to seventh postoperative day. Occasionally, the leak is confined to the right upper quadrant and appears with signs of localized sepsis. CT scanning or ultrasonography may show an abscess cavity; an upper GI series or a dimethyl iminodiacetic acid (hepatobiliary iminodiacetic acid [HIDA]) scan may show a leak. Patients with this type of leak may respond to percutaneous drainage. The more common presentations are severe abdominal sepsis and an acute abdomen. Patients with peritonitis require exploration, drainage of the right upper quadrant. A lateral duodenal fistula occurs when a duodenal leak occurs in the context of a Billroth I procedure, where the duodenum is still in continuity with the stomach. This has historically been associated with a high mortality. In contrast, the end duodenal fistula or duodenal stump blowout occurs after a Billroth II procedure, and avoids activation of pancreatic juices by gastric contents (with a lower associated mortality). The duodenum may be closed around a duodenostomy tube if the end of the duodenal stump has blown out. If the leak occurs laterally, a simple closure with omental buttress may suffice. In either case, pancreatic secretion should be minimized by nil per os status and initiation of parenteral nutrition. While somewhat controversial, somatostatin analogs may help reduce

pancreatic secretion and may play a role in the management of acute duodenal stump leak.

16.6.4 Anastomotic Leak/Endoscopic Perforation

Excluding esophageal anastomoses after total gastrectomy, the overall incidence of anastomotic leak is <2% after gastric operations. Contained leaks may be controlled by percutaneous drainage, parenteral nutrition, nasogastric decompression, and broad-spectrum antibiotics. Unless there is distal obstruction or carcinoma of the suture line, the fistula tract should close. For patients with peritonitis and shock, or those in whom drainage is inadequate, an operation is needed. Small anastomotic defects may be closed primarily and covered with omentum. Commonly, revision of the anastomosis is required. The incidence of leak in a pyloroplasty after an ulcer operation is 5%.[5] If there is minimal contamination, the anastomotic margins can be trimmed, and a new pyloroplasty can be performed. Large defects may require revision of the anastomosis. A Heineke–Mikulicz pyloroplasty may be converted to a Finney pyloroplasty, or, alternatively, a Billroth II anastomosis may be fashioned. For patients in unstable condition, the area should be widely drained, and a gastrostomy should be placed for gastric decompression. Similar treatment is used for a leaking gastroduodenostomy after a Billroth I anastomosis. Leaks along the reconstructed lesser curvature usually require additional resection and conversion to a Billroth II anastomosis. Perforation related to endoscopic mucosal resection and endoscopic submucosal dissection has the potential to expand the number of perforations associated with early gastric cancer as these procedures become more ubiquitous. Management is similar to other causes of perforation with the need for operation based on the presence of diffuse peritonitis or a progressive inflammatory response.[8] Consideration also needs to be given to the status of the cancer resection when making operative plans.

16.6.5 Dumping Syndrome

The dumping syndrome is one of the most common causes of morbidity after gastric surgery. Symptoms develop after the ingestion of food, and patients are free of symptoms under fasting conditions. GI symptoms include crampy abdominal pain, bloating, nausea, vomiting, and explosive diarrhea. Vasomotor symptoms include diaphoresis, dizziness, palpitations, weakness, and flushing. An estimated 25%–50% of patients experience some symptoms of dumping after gastric surgery; however, only 1%–5% experience severe, disabling symptoms.[9,10] Dumping is classified as early or late on the basis of the timing of onset of symptoms. Early dumping starts 10–30 min after eating. Late dumping starts 2–3 h after eating and usually involves only vasomotor symptoms. Liquid foods and meals rich in carbohydrates are particularly poorly tolerated. Severely affected patients may lose weight because of fear of eating. The diagnosis of dumping is based on a thorough medical history and the provocation of signs and symptoms by an oral glucose challenge. Gastric-emptying studies using radionuclide markers in both liquid and solid phases may be used to document accelerated gastric emptying. Endoscopy and barium radiography are helpful in precisely defining the anatomy and in diagnosing other postgastrectomy syndromes that may be present.

Most patients have mild-to-moderate symptoms that improve with time, and dietary modification is the mainstay of therapy. Patients should eat small, frequent meals that are low in carbohydrate and high in protein. It is often helpful to postpone drinking for at least half an hour after eating. In addition, patients should add fiber and a modest amount of fat to their diets and should substitute complex carbohydrates (e.g., raw vegetables) for simple sugars. If symptoms are severe, patients can be told to lie down for half an hour after eating. Octreotide has been used with some success to treat severe symptoms of early and late dumping.

Multiple surgical procedures have been advocated for the treatment of dumping, including pyloric reconstruction, narrowing of the gastrojejunal stoma, conversion of a Billroth II anastomosis to a Billroth I anastomosis, jejunal interposition, and conversion to a Roux-en-Y anastomosis. Although initial success rates vary, long-term results are generally disappointing. Surgery should be the very last resort for treating patients with severe dumping that is unresponsive to dietary and medical therapies.

For patients who have previously undergone pyloroplasty, pyloric reconstruction is a viable option. The pyloroplasty is opened, the sphincter muscle is reapproximated, and the incision is closed longitudinally. Reported success rates vary widely.[11–13] Conversion of a Billroth II anastomosis to a Billroth I anastomosis reestablishes the gastroduodenal flow of food, is associated with low rates of complication, and improves the symptoms of approximately 75% of patients. Many types of jejunal interpositions have been described. The most successful has been the 10 cm antiperistaltic jejunal segment, which may be interposed between the stomach and the duodenum, in the efferent limb of a gastrojejunostomy, or in a Roux-en-Y limb. Several authors report good results with this procedure, but others report a serious risk of gastric outlet obstruction.[14] For patients with a previous Billroth I or II anastomosis, conversion to a Roux-en-Y gastrojejunostomy has provided the most consistent results.[14–16]

16.6.6 Postvagotomy Diarrhea

Although diarrhea is not uncommon after gastric surgery, its incidence is higher among patients who have undergone vagotomy. Severe symptoms are characterized by frequent, watery stools, often nocturnal, and are usually not associated with ingestion of a meal. Attacks may be episodic, lasting a few days and then not recurring for several months. Symptoms generally improve over the first year, and the problem rarely remains debilitating or constant. The diagnosis of postvagotomy diarrhea is made on clinical grounds, with care taken to distinguish other postgastrectomy syndromes that can occur concomitantly. Other causes of diarrhea should be excluded. Medical treatment is similar to that for dumping; dietary measures are the mainstay of therapy. Antidiarrheal agents such as loperamide, diphenoxylate, and opiates are useful. Cholestyramine improves diarrhea for most patients. For patients unresponsive to these measures, octreotide has been used with mixed success. Surgical options should be reserved for the minority of patients with chronic, debilitating symptoms unresponsive to other therapies. The strategy is a slowing of small bowel transit time. The most frequently used procedure is the construction of a 10–15 cm antiperistaltic jejunal segment, 100 cm distal to a gastroenterostomy or the Treitz ligament. The results achieved by this procedure, however, have been mixed.[17]

16.6.7 Alkaline Reflux Gastritis

Five to fifteen percent of patients undergoing gastric surgery will experience alkaline reflux gastritis.[18] The symptoms include burning epigastric pain, which is unrelieved by antacids and frequently made worse by eating or lying down, nausea, and bilious vomiting. Patients often decrease their food intake, and this action results in weight loss and anemia. The incidence of alkaline reflux gastritis is highest after a Billroth II anastomosis and is much less frequent after a Billroth I anastomosis or after truncal vagotomy and drainage.

The diagnosis of alkaline reflux gastritis is made by exclusion. Recurrent ulcer, gastroparesis, afferent or efferent loop obstruction, and diseases of the gallbladder and pancreas must be ruled out. Endoscopic examination with biopsy of the mucosa is the most useful diagnostic procedure. It can rule out recurrent ulcer and afferent loop syndrome, both of which are included in the differential diagnosis of bilious vomiting. An upper GI barium study is often performed, but it is rarely helpful in making the diagnosis. It is useful in defining postoperative anatomy and in excluding other causes of symptoms, including recurrent ulcer and obstruction.

Documentation and quantification of reflux into the stomach may be assessed by HIDA scan with cholecystokinin administration. Additionally, intragastric infusion of alkaline solution as a provocative test appears to be helpful, both in diagnosis and in determining which patients may benefit from surgery. In one series of 147 patients, a 4-year follow-up showed that a positive response to the test was associated with benefit from surgery and that a negative response to the test was associated with a lack of benefit from surgery; the predictive accuracy was 75%–85%.[19].

Medical management generally has been ineffective. Nonetheless, a trial of medical therapy is warranted, and the occasional patient may be adequately treated. Cholestyramine has been used because of the assumption that bile acids are the cause of gastritis. Antacids containing aluminum hydroxide have also been used, because they bind bile acids and lysolecithin. In contrast, adding the bile acid ursodeoxycholic acid to a patient's diet has shown some success in relieving mild symptoms.

The goal of surgical treatment is to divert duodenal contents away from the gastric remnant. The procedure most often used is the Roux-en-Y gastrojejunostomy, which creates a 45 cm roux limb. Other alternatives are the interposition of an isoperistaltic jejunal segment between the residual stomach and intestine, and the Roux-en-Y Tanner-19 gastrojejunostomy, in which the proximal end of the afferent limb is anastomosed to the roux limb, thereby forming a small, circular route for the passage of chyme. No advantages have been shown with any of these procedures. Each, however, is effective in virtually eliminating reflux into the gastric remnant, and all yield good short-term results. Unfortunately, longer follow-up shows that bilious emesis is the only symptom that is consistently relieved. Epigastric pain can recur in as many as 30% of cases, and nausea and vomiting can recur in as many as 50%.[20] A potential problem is the development of delayed gastric emptying of solids; this problem causes early satiety, epigastric pain, and nonbilious vomiting, a constellation of symptoms that has been termed the *roux stasis syndrome*.

16.6.8 Loop Syndromes

The loop syndromes require the presence of an afferent or efferent limb and can occur only after a Billroth II or a Roux-en-Y anastomosis. Either the afferent or the efferent limb may become obstructed, and both types of obstruction can present with either an acute and complete obstruction or a chronic partial obstruction. Afferent limb obstruction is more common and is usually due to anatomic factors. Known causes are internal herniation of the small intestine, volvulus of the loop, and kinking at the anastomosis. Each is thought to occur more frequently when the anastomosis is antecolic, is positioned along the lesser curvature, or when the afferent limb is too long (>10 to 15 cm). Because surgeons have become more cognizant of underlying causes,

the loop syndromes, once more common, now occur among <1% of patients.[21].

Acute afferent limb obstruction is the most common cause of duodenal stump blowout and constitutes a surgical emergency. It most commonly appears within the first or second postoperative week and results from complete obstruction of the afferent limb. The stump is repaired and reinforced with omentum and the underlying cause corrected. An intraoperative finding may be necrosis of the limb. If only the distal portion is involved, the limb may be resected and a Roux-en-Y anastomosis fashioned. Involvement of the duodenal portion of the limb may necessitate a pancreaticoduodenectomy. Volvulus is prone to recurrence, and any redundancy in the limb should be resected. The retroanastomotic space and all mesenteric defects should be closed so that recurrence of hernias can be avoided.

Chronic afferent limb obstruction results from partial obstruction of the limb. Symptoms include nausea, right upper quadrant pain brought on by meals, and bilious vomiting, possibly projectile, which is not mixed with food and which quickly relieves the pain. Stasis in the loop may result in a "blind loop syndrome," with bacterial overgrowth, bile salt deconjugation, steatorrhea, vitamin B12 deficiency, and diarrhea. Clinical history is extremely helpful in diagnosing afferent loop obstruction; however, alkaline reflux gastritis must be ruled out. The results of routine radiologic studies are usually normal because the limb generally obstructs only as it distends. Endoscopy allows direct visualization of the anastomosis and biopsy of any pathologic lesions. Once the diagnosis has been made, surgery is warranted. A Billroth II anastomosis may be converted to a Billroth I or, alternatively, a Roux-en-Y anastomosis.

Obstruction of the efferent loop is less common and is most frequently caused by a retroanastomotic hernia. Other causes of obstruction are adhesions, fibrotic stenosis, and jejunogastric intussusception. Efferent loop obstruction also exists in acute and chronic forms, but the acute form is more common. Symptoms consist of colicky abdominal pain, nausea, and bilious vomiting (with food). A diagnosis of chronic efferent loop obstruction is confirmed by radiography, which shows delayed emptying across a point of obstruction in the efferent limb. Surgical treatment is mandated. The specific therapy depends on the cause and may include lysis of adhesions, reduction of hernias, closure of anatomic defects, revision of the anastomosis, or conversion to a Billroth I or Roux-en-Y anastomosis.

16.6.9 Chronic Gastric Atony and the Roux Stasis Syndrome

Chronic gastric atony is characterized by nausea, vomiting, epigastric pain, postprandial bloating, and frequent bezoar formation. Patients cannot tolerate solids but can usually tolerate liquids, and they intuitively change their diets. The cause is believed to be a loss of gastric vagal innervation, with incidence higher after less selective vagotomies.[22] The assessment of the patient with chronic gastric atony must exclude mechanical obstruction. Upper GI series are most often read as normal but may show a distended, flaccid gastric remnant. Endoscopic examination confirms the absence of any obstruction. Scintigraphic testing reveals severe, delayed gastric emptying of solids. Medical treatment is based on the use of prokinetic drugs. Intermittent or chronic gastric decompression may be necessary, in conjunction with nutritional support and weaning from exacerbating drugs. Overall 30%–40% of patients experience limited relief of symptoms. Surgical therapy aims at decreasing the reservoir capacity of the stomach; the most common procedure is near-total gastrectomy with a Roux-en-Y gastrojejunostomy.

Distinguishing the elements of the roux stasis syndrome from those of gastric atony is difficult. In fact, the existence of roux stasis syndrome as an entity separate from gastric atony has been questioned. Two reviews have placed the incidence at 27%–33%.[23] Evaluation and medical treatment of the patient with possible roux stasis are the same as those of the patient with gastric atony. The most important issue is ruling out mechanical causes of obstruction. Upper GI series and endoscopy are helpful in this regard, and *scintigraphic* studies can document delayed emptying in the gastric remnant, in the roux limb, or in both. Medical therapy is seldom successful. Surgical therapy usually involves a near-total gastrectomy and adjustment of the limb length to 40 cm; this procedure is successful in 70%–80% of patients.[24]

16.6.10 Small Gastric Remnant Syndrome

The small gastric remnant syndrome is also characterized by early satiety, bloating, epigastric pain soon after eating, and vomiting. It is caused by loss of the reservoir function of the stomach. This syndrome is most prevalent after operations that remove 80% or more of the stomach.[25] Symptoms are usually mild, but can be severe enough to cause weight loss, malnutrition, and anemia. Diagnosis is based primarily on clinical history, but mechanical obstruction must be ruled out. Dietary management consisting of frequent, small meals, and the addition of vitamins, iron, and pancreatic enzymes is successful in most patients.

16.6.11 Recurrent Ulcer

Duodenal, gastric, or jejunal ulcers that occur after corrective surgery for peptic ulcer disease are known as recurrent ulcers, stomal ulcers, or marginal ulcers.

Together with alkaline reflux gastritis, they are the leading cause of unsatisfactory long-term postoperative results. The most common symptom of recurrent ulcer is pain, usually similar to the original ulcer pain, which is reported by 80%–95% of patients.[26,27] It is difficult to distinguish this pain from the pain that accompanies several other postgastrectomy syndromes. The first diagnostic test for evaluating a patient's symptoms is endoscopy. Most ulcers occur within 2 cm of the GI anastomosis and are seen on endoscopy; the accuracy rate of endoscopy in the diagnosis of this condition approaches 90%.[26,27] When a recurrent ulcer has been diagnosed, the underlying cause must be determined. Most recurrent ulcers will respond to standard medical therapy.

The leading cause of recurrent ulcer in nearly 60% of cases is an inadequate or inappropriate operation.[27] Inadequate vagotomy is the most common identified cause and is found in as many as one-third of cases. Inadequate resection of antral tissue, which can extend one or more centimeters into the duodenum, can result in the retained antrum syndrome, a rare but highly ulcerogenic cause of recurrence. The retained antral tissue is constantly exposed to an alkaline pH, because an absence of gastric acid in the duodenal stump results in continuous hypersecretion of gastrin from the mucosa. Fasting gastrin levels will be two to four times normal values in these cases and aid in the diagnosis. Antral G-cell hyperplasia and Zollinger–Ellison syndrome may also cause recurrent ulcer, but the fasting gastrin levels will be much higher than those in retained antrum syndrome. Other rare causes are foreign body (stitch) ulcer and gastric cancer. Contributing factors include ulcerogenic drugs, smoking, delayed gastric emptying, enterogastric reflux, bezoar, and primary hyperparathyroidism.

Three diagnostic tests establish the cause of recurrent ulcer in most cases: endoscopy, determination of the serum calcium concentration, and determination of the serum gastrin concentration. If a gastric ulcer is present, biopsy may be able to exclude gastric cancer. If an afferent limb is present, biopsy of the duodenal stump may exclude retained antral tissue. A serum gastrin concentration >1000 pg/mL is virtually diagnostic of Zollinger–Ellison syndrome, whereas a normal serum concentration excludes the diagnosis, except in rare cases.[28] The fasting serum gastrin concentrations of patients with retained antrum syndrome are typically two to four times above the normal range. Delayed gastric emptying caused by obstruction or gastric atony may result in hypergastrinemia due to retained food; gastrin concentrations should decrease after the evacuation of the stomach, thus excluding this cause. Elevated gastrin concentrations due to H2 or proton pump blockers should decrease within 24 h of discontinuing the drug. The differential diagnosis for a modest elevation of gastrin concentration also includes Zollinger–Ellison syndrome, retained antrum, postvagotomy hypergastrinemia, and antral G-cell hyperplasia.

If one of these diagnoses is made, the therapy specific to the diagnosis is instituted. Retained antrum can be cured by resecting the cuff of antral tissue. Antral G-cell hyperplasia responds to antrectomy. A diagnosis of hyperparathyroidism requires parathyroidectomy; multiple endocrine neoplasia (MEN) syndromes should also be excluded. If Zollinger–Ellison syndrome is diagnosed, the patient must undergo additional tests to define the source.

Medical therapy is indicated for patients with uncomplicated recurrent ulcers who have no evidence of hypersecretory state or gastric outlet obstruction. Studies show that standard doses of H2 blockers will heal approximately 80% of recurrent ulcers. A typical regimen involves treatment with proton pump inhibitors until healing is documented endoscopically. Discontinuation of antiulcer therapy is usually associated with rapid recurrence, and lifetime maintenance is generally required. It is also mandatory that ulcerogenic drugs, cigarette smoking, and perhaps even alcohol use be discontinued. Surgery is indicated if the recurrent ulcer does not heal after 3 months of medical therapy; if the ulcer recurs within 1 year despite maintenance therapy; if the ulcer disease is characterized by cycles of prolonged activity with brief or absent remissions, so that lifestyle is severely affected; or if the patient cannot comply with medical therapy.

It has been recently shown that duodenal ulcers can, in many cases, be treated with simple closure via a laparoscopic approach. If treatment for *Helicobacter pylori* is given postoperatively, the majority of these ulcers do not recur. Due to a lack of data, it is unclear if the same is true of perforated gastric ulcers, but *H. pylori* should certainly be investigated and treated if present in patients with perforated gastric ulcers. Gastric ulcers caused by acute cocaine intoxication appear to have a lower recurrence rate if a formal antiulcer operation is entertained at the time of initial surgery. This may be due to noncompliance with medical therapy in the postoperative period

16.6.12 Gastric Remnant Carcinoma

It has been postulated that gastric surgery for benign disease increases the risk of subsequent gastric cancer. Although the relationship remains tenuous, evidence suggests that the risk of cancer is increased approximately twofold to fourfold after a latency period of 15 years. The most frequent symptoms of this carcinoma are epigastric pain, fullness, vomiting, dysphagia, weight loss, upper GI bleeding, weakness, obstruction, and diarrhea. Given the long latency period of gastric cancer, the diagnosis should be strongly suspected when new GI complaints occur among patients who have experienced years with no symptoms.

16.7 Complications Related to Bariatric Surgery

Due to the nationwide obesity epidemic, bariatric surgical procedures are among the most common abdominal procedures performed with an approximate average of 115,000 cases per year from 2004 to 2007.[31] These procedures are best performed by high volume surgeons, although the qualifying volume is yet to be defined. Unfortunately, these surgeons will rarely be available to care for the complication of bariatric surgery, and all general surgeons need to be aware of these potential complications and their immediate management.

16.8 Gastric Band Complications

Complications of adjustable gastric banding include band slippage or prolapse, pouch dilation, erosion, mechanical complications related to filling of the band, and overfilling of the band. Prolapse or band slippage may occur in up to 36% of patients, depending on the series.[32] Patients may present with dysphagia, nausea, vomiting, reflux, or food intolerance. Diagnosis is confirmed by a contrast esophagram demonstrating either vertical or horizontal positioning of the band with contrast pooling in the prolapsed portion. If there are clinical signs of ischemia of the prolapsed portion, this constitutes a surgical emergency and mandates immediate exploration. In the absence of ischemia, deflation of the band may be an initial first step. Removal of the band with either replacement or conversion to Roux-en-Y gastric bypass is almost universally required.[33] Pouch dilation without prolapse may also occur and has a similar clinical presentation; however, the band appears appropriately positioned by fluoroscopy and there is no pooling of contrast on esophagram, but poor progression of contrast across the band. Fluid removal from the band is usually curative. Mechanical complication related to failure of the band-filling mechanism generally is in the form of a system leak. These are best addressed by an experienced band surgeon as the problem often presents during routine band-filling visits, and is difficult to diagnose.

The most feared complication of adjustable gastric banding band erosion occurs in up to 3% of cases; however, this rate may increase as bands are in place for longer periods of time. The outcome for this complication is usually good as patients do not typically present with catastrophic peritonitis. Patients usually present with vague abdominal pain and weight gain. Port site infections are another common presentation. Any of these complaints mandates endoscopy with retroflexion once the endoscope is distal to the band. Treatment generally will involve band removal by laparoscopy and repair of the gastric wall, although endoscopic removal has been reported.[34] One of the more common complications of gastric band surgery is a failure of the procedure with regard to loss of excess body weight. The treatment for this complication remains unclear, however the most common treatment is conversion to a Roux-en-Y gastric bypass.[33] Gastroesophageal reflux and esophageal failure require deflation of the band; however, this does not always resolve the symptoms.[35]

16.9 Gastric Bypass Complications

With the exception of pulmonary embolism, life-threatening surgical complications after gastric bypass include anastomotic leak, bowel obstruction related to an internal hernia, and gastrointestinal bleeding (GIB). The rates of these complications do not differ between open and laparoscopic approaches.[36] Anastomotic leaks are the second most common cause of death after gastric bypass and the most surgically challenging. Most leaks occur 5–7 days after surgery, and diagnosis requires a high index of suspicion. Patients may present with abdominal pain or signs of sepsis. Diagnosis is generally by CT or esophagram, which may demonstrate fluid collections adjacent to the leak, free intra-abdominal air, or contrast extravasation. The management strategy for this complication depends on the stability of the patient. Stable patients with small leaks may be managed with drainage and nutritional support. Patients who demonstrate early signs of sepsis should be managed by operative exploration, primary repair of the leak if possible, and drainage.

GIB can occur at any of the staple lines, and although rare may be life-threatening.[37] In the immediate postoperative setting, re-exploration is commonly required as the bleeding may be either intraluminal or intra-abdominal, and both of these sources can be identified and controlled operatively. In the subacute setting, endoscopy may be of value especially for intraluminal sources at the gastrojejunostomy. Upon exploration in the acute setting, if an intra-abdominal source of bleeding cannot be identified, all limbs of the bypass including the gastric remnant should be carefully examined for the presence of intraluminal blood.

Bowel obstructions related to internal hernias occur later in the postoperative period and occur in up to 4.5% of patients.[38] The three areas of concern are related to the jejeunojejunostomy, Peterson's space behind the Roux limb, and in the retrocolic method, the transverse mesocolic defect. These may present in a subacute fashion with intermittent vague abdominal pain as the hernia occurs

and spontaneously reduces. These may also present as closed loop obstructions with life-threatening bowel ischemia. Other obstructions can occur due to technical errors or anastomotic edema at the jejeunojejunostomy, incisional hernias, adhesive bands, or anastomotic strictures. Because the anatomy of these patients is often difficult to interpret on cross-sectional imaging, a high index of suspicion should be maintained and laparoscopic or open exploration undertaken, depending on surgeon experience, when these patients present with clinical signs and symptoms of bowel ischemia.

Marginal ulcers typically are another common complication occurring in up to 16% of patients.[39] Patients present with epigastric pain, nausea, vomiting, or dysphagia, and the diagnosis is typically made by endoscopy. Treatment is primarily medical with most responding to proton pump inhibitors, and documentation of healing by endoscopy is recommended. Surgery is indicated only for intractability or gastrogastric fistula usually requiring revision of the anastomosis. Like marginal ulceration, gastrojejunostomy stricture presents with postprandial vomiting and in some cases pain. The diagnosis is by endoscopy, and most cases will respond to balloon dilation; however, several sessions may be required.[40]

16.10 Nutritional Consequences of Gastric Surgery

Commonly encountered nutritional impairments after gastric surgery are maldigestion and malabsorption of polymeric foods, sustained underweight, abnormal satiety, iron deficiency, and osteomalacia. Absorption of salt, water, and monomeric nutrients such as glucose and fatty acids is however not impaired. Steatorrhea may follow any procedure that destroys or bypasses the pylorus or resects all or part of the stomach. Steatorrhea is aggravated in the presence of an afferent loop or a Roux-en-Y anastomosis. All operations for ulcer disease, with the notable exception of HSV, lead to substantial weight loss. The amount of weight loss correlates most closely with reduced intake of food rather than with malabsorption, as measured by steatorrhea. Patients are advised to eat small, frequent meals, which serve to keep pancreatic secretions flowing and to limit the speed of gastric emptying.

Mild-to-moderate anemias are common after gastric surgery. Iron deficiency is the most common cause. Folate and vitamin B12 concentrations may also decrease after gastric operations; such decreases cause a mixed anemia. Pure macrocytic anemias are rare except after total gastrectomy. Because intrinsic factor is produced in great excess, resections less than a total gastrectomy rarely cause decreases in vitamin B12 concentrations that are severe enough to cause clinical symptoms. Folate deficiency occasionally contributes to a mixed anemia. Deficiencies in iron, folate, or vitamin B12 respond well to replacement. Iron should be given in the ferrous form, and tablets should be crushed so that they can be better absorbed.

Gastric resection accelerates the process of osteoporosis, and this acceleration becomes more pronounced with time after surgery.[41,42] This process is faster after total gastrectomy than after subtotal gastrectomy, and it is only minimally affected after vagotomies without resection. Calcium and vitamin D supplements have been prescribed to prevent postoperative bone disease; however, their effectiveness has not been documented.

Complications of Gastric Surgery

Complications	Incidence	References	Comments
Rebleeding	5%	[5]	Generally treated with endoscopic therapy.
Gastroparesis	4%	[6]	Generally treated nonoperatively.
Duodenal stump leak	3%	[5]	Afferent limb obstruction is the likely cause. CT, HIDA, and ultrasound are potential tests.
Anastomotic leak	<2%	[5]	Can most often be managed by percutaneous drainage and parenteral nutrition.
Dumping syndrome	25%–50%, 1%–5% disabling	[9, 10]	Defined as early or late based on symptoms, but initial treatment is dietary modification regardless of timing.
Postvagotomy diarrhea	Common	[17]	Medical management is generally effective, and surgical intervention is rarely required.
Alkaline reflux gastritis	5%–15%	[18]	Diagnosis of exclusion, but HIDA and provocative testing may be helpful. Management is medical.
Afferent loop syndrome	<1%	[21]	Acutely results in stump leak, chronically diagnosis is by history. Corrective surgery is usually required.
Efferent loop syndrome	<1%	[21]	Occurs in acute and chronic forms, both diagnosed by contrast study, and both generally require corrective surgery.

Complications	Incidence	References	Comments
Delayed gastric emptying/ roux stasis syndrome	27%–33%	[23]	Diagnosis is generally by scintigraphy, and prokinetic agents may be helpful, but near-total gastrectomy or reducing the roux limb to about 40 cm is often required.
Small gastric remnant	Uncommon	[25]	Treatment is dietary modification.
recurrent ulcer		[29]	Must rule out syndromic causes, but treatment is generally medical.
Gastric band slippage or pouch dilatation	Up to 36%	[32]	Initially managed by band deflation, but almost always require band removal and/or conversion to Roux-en-Y gastric bypass.
Gastric band erosion	3%	[32]	Requires band removal and gastric repair.
Anastomotic leak after gastric bypass	3%	[36]	Second most common cause of death. May be managed without re-exploration in stable patients with small leaks.
GIB after gastric bypass	2%	[37]	Acutely—usually due to staple line bleeding and managed with reoperation, chronically—diagnosis and initial management is endoscopic.
Internal hernias and obstruction	4.5%	[38]	Acute and subacute forms occur. Treatment is surgical reduction and closure.
Marginal ulcers	16%	[39]	Treatment is primarily medical.

Avoiding Complications of Gastric Surgery

Complications	Method of Avoidance
Rebleeding	Suture control of major bleeding vessels
Gastroparesis	Preoperative evaluation of gastric emptying if possible and adjust resection strategy
Duodenal stump leak	Minimize duodenal devascularization with aggressive dissection, avoid afferent limb kinking
Anastomotic leak	Maintain good surgical technique with well-vascularized anastomosis under no tension
Dumping syndrome	Instruct patients to eat small meals and avoid high carbohydrate diets, and delay drinking after solids for at least 30 min
Postvagotomy diarrhea	Choose the most selective vagotomy possible that addresses the disease process
Alkaline reflux gastritis	If possible choose a procedure other than Billroth II anastomosis
Afferent loop syndrome	Construct the afferent limb <15 cm in length and use a retrocolic reconstruction
Efferent loop syndrome	Close all spaces potentially leading to retro-anastomotic hernia
Delayed gastric emptying roux stasis syndrome	Avoid truncal vagotomy if possible Use a shorter roux limb (40 cm), though this must be balanced against the risk of bile reflux gastritis
Small gastric remnant	If possible maintain at least 20% of the gastric volume
Recurrent ulcer	Perform a definitive ulcer operation and avoid retained antrum
Gastric band slippage or pouch dilatation	Use of the pars-flaccida technique and gastropexy may reduce the risk of this complication
Gastric band erosion	Place the band fully below the GE junction and avoid overtightening of the band
Anastomotic leak after gastric bypass	Use properly sized staples, use biologic buttress material, avoid ischemic tissue or creating tension on the anastomosis, perform an intraoperative leak test
GIB after gastric bypass	Consider oversewing of staple lines if possible
Internal hernias and obstruction after gastric bypass	Use an antecolic technique and consider closing all mesenteric defects if possible
Marginal ulcers	Insist on smoking cessation, minimize pouch size, test for and treat *H. pylori* preoperatively

References

1. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. *Ann Surg* 1993; 218:583–592.
2. Wei HB, Wei B, Qi CL et al. Laparoscopic versus open gastrectomy with D2 lymph node dissection for gastric cancer: A meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2001;21:383–390.
3. Zeng YK, Yang ZL, Peng JS Lin HS, Cai LC. Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer. Evidence from randomized and nonrandomized clinical trials. *Ann Surg* 2012;256:39–52.
4. Johnston D, Blackett RL. A new look at selective vagotomies. *Am J Surg* 1988; 156:416–427.
5. Pappas TN. Historical aspects, anatomy, pathology, physiology, and peptic ulcer disease. In: Sabiston DC Jr, Bralow L, eds. *Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. Philadelphia, PA: Saunders, 1997, pp. 847–868.
6. Bushkin FL, Woodward ER. Delayed gastric emptying. In: Bushkin FL, Woodward ER, eds. *Major Problems in Clinical Surgery. Vol. XX. Postgastrectomy Syndromes*. Philadelphia, PA: Saunders, 1976, pp. 72–79.
7. Hermann G, Johnson V. Management of prolonged gastric retention after vagotomy and drainage. *Surg Gynecol Obstet* 1970;130:1044–1048.
8. Kim SH, Moon JS, Youn YH, Lee KM, Lee SJ. Management of the complications of endoscopic submucosal dissection. *World J Gastroenterol* 2011;17:3575–3579.
9. Lamers CB, Bijlstra AM, Harris AG. Octreotide, a long-acting somatostatin analog, in the management of postoperative dumping syndrome. An update. *Dig Dis Sci* 1993;38:359–364.
10. Sawyers JL. Management of postgastrectomy syndromes. *Am J Surg* 1990;159:8–14.
11. Cheadle WG, Baker PR, Cuschieri A. Pyloric reconstruction for severe vasomotor dumping after vagotomy and pyloroplasty. *Ann Surg* 1985;202:568–572.

    This paper provides description of a procedure to reconstruct gastric anatomy after gastric surgery leading to dumping syndrome.
12. Koruth NM, Krukowski ZH, Matheson NA. Pyloric reconstruction. *Br J Surg* 1985;72:808–810.
13. Kelly KA, Becker JM, van Heerden JA. Reconstructive gastric surgery. *Br J Surg* 1981;68:687–691.
14. Miranda R, Steffes B, O'Leary JP, Woodward ER. Surgical treatment of the postgastrectomy dumping syndrome. *Am J Surg* 1980;139:40–43.
15. Lygidakis NJ. A new method for the surgical treatment of the dumping syndrome. *Ann R Coll Surg Engl* 1981;63:411–414.
16. Vogel SB, Hocking MP, Woodward ER. Clinical and radionuclide evaluation of Roux-Y diversion for postgastrectomy dumping. *Am J Surg* 1988;155:57–62.
17. Cuschieri A. Postvagotomy diarrhoea: Is there a place for surgical management? *Gut* 1990;31:245–246.
18. Stabile BE, Passaro E Jr. Sequelae of surgery for peptic ulcer. In: Berk JE, Kalser MH, Haubrich WS, eds. *Bockus Gastroenterology*. Vol. 7. 4th edn. Philadelphia, PA: Saunders, 1985, pp. 1225–1242.
19. Rutledge PL, Warshaw AL. Diagnosis of symptomatic alkaline reflux gastritis and prediction of response to bile diversion operation by intragastric alkali provocation. *Am J Surg* 1988;155:82–87.
20. Ritchie WP Jr. Alkaline reflux gastritis. Late results on a controlled clinical trial of diagnosis and treatment. *Ann Surg* 1986;203:537–544.
21. Herrington JL Jr, Sawyers JL. Complications following gastric operation. In: Schwartz SI, Ellis H, eds. *Main-got's Abdominal Operations*. Norwalk, CT: Appleton & Lange, 1990, pp. 701–712.
22. Hom S, Sarr MG, Kelly KA, Hench V. Postoperative gastric atony after vagotomy for obstructing peptic ulcer. *Am J Surg* 1989;157:282–286.
23. McAlhany JC Jr, Hanover TM, Taylor SM, Sticca RP, Ashmore JD Jr. Long-term follow-up of patients with Roux-en-Y gastrojejunostomy for gastric disease. *Ann Surg* 1994;219:451–457.
24. Hinder RA, Esser J, DeMeester TR. Management of gastric emptying disorders following the Roux-en-Y procedure. *Surgery* 1988;104:765–772.

    This study demonstrates the improved gastric emptying that can be achieved by near total gastrectomy for patient suffering from poor emptying after gastric surgery.
25. Delcore R, Cheung LY. Surgical options in postgastrectomy syndromes. *Surg Clin North Am* 1991;71:57–75.
26. Zinner MJ, McFadden DW. Surgery for recurrent peptic ulcer disease. In: Fry DE, ed. *Reoperative Surgery of the Abdomen*. New York: Marcel Dekker, 1986, pp. 53–58.
27. Stabile BE, Passaro E Jr. Duodenal ulcer: A disease in evolution. *Curr Probl Surg* 1984;21:1–79.
28. Wolfe MM, Jain DK, Edgerton JR. Zollinger-Ellison syndrome associated with persistently normal fasting serum gastrin concentrations. *Ann Intern Med* 1985;103:215–217.
29. Gugler R, Lindstaedt H, Miederer S et al. Cimetidine for anastomotic ulcers after partial gastrectomy. A randomized controlled trial. *N Engl J Med* 1979;301:1077–1080.
30. Kennedy T, Spencer A. Cimetidine for recurrent ulcer after vagotomy or gastrectomy: A randomised controlled trial. *Br Med J* 1978;1:1242–1243.
31. Zevin B, Aggarwal R, Grantcharov TP. Volume-outcome association in bariatric surgery: A systematic review. *Ann Surg* 2012;256:60–71.
32. Tice JA, Karliner L, Walsh J et al. Gastric banding or bypass? A systematic review comparing the two most popular bariatric procedures. *Am J Med* 2008;121:885–893.
33. Snow MJ, Severson PA. Complications of adjustable gastric banding. *Surg Clin N Am* 2011;91:1249–1264.

    A complete list of complications after adjustable gastric banding is presented in this manuscript, along with the potential medical and surgical therapies.
34. Neto MP, Ramos AC, Campos JM et al. Endoscopic removal of dysfunctioning band or rings after restrictive bariatric procedures. *Gastrointest Endosc* 2010; 71:468–474.

35. Naef M, Mouton WG, Naef U et al. Esophageal dysmotility disorders after laparoscopic gastric banding—An underestimated complication. *Ann Surg* 2010;253: 285–290.
36. Fernandez AZ Jr, DeMaria EJ, Tichansky DS et al. Experience with over 3000 open and laparoscopic bariatric procedures: Multivariate analysis of factors related to leak and resultant mortality. *Surg Endosc* 2004;18:193–197.

    This study is one of the largest single series of gastric bypass, open, and laparoscopic, in the literature.
37. Nguyen NT, Longoria M, Chalifoux S et al. Gastrointestinal hemorrhage after laparoscopic gastric bypass. *Obes Surg* 2004;14:1308–1312.
38. Garza E Jr, Kuhn J, Arnold D et al. Internal hernias after laparoscopic Roux-en-Y gastric bypass. *Am J Surg* 2004;188:796–800.
39. Rasmussen JJ, Fuller W, Ali MR. Marginal ulceration after laparoscopic gastric bypass: An analysis of predisposing factors in 260 patients. *Surg Endosc* 2007; 21:1090–1094.
40. Ryskina KL, Miler KM, Aisenberg J et al. Routine management of stricture after gastric bypass and predictors of subsequent weight loss. *Surg Endosc* 2010;24:554–560.
41. Aukee S, Alhava EM, Karjalainen P. Bone mineral after partial gastrectomy II. *Scand J Gastroenterol* 1975; 10:165–169.
42. Bisballe S, Eriksen EF, Melsen F, Mosekilde L, Sorensen OH, Hessov I. Osteopenia and osteomalacia after gastrectomy: Interrelations between biochemical markers of bone remodeling, vitamin D metabolites, and bone histomorphometry. *Gut* 1991;32:1303–1307.

17

Complications of Hepatic Surgery and Trauma

Adrian W. Ong and Kusum Tom

CONTENTS

17.1 Introduction

The liver is a complex, vascular organ occupying most of the right upper quadrant of the abdomen. Surgery of the liver, whether emergent or elective, can involve significant blood loss, and delayed complications such as hepatic failure can be life threatening. A multimodality approach to the management of hepatic-related complications is essential and calls for close cooperation between the disciplines of surgery, gastroenterology, critical care, and radiology.

17.2 Liver Trauma: Management Strategies

The American Association for the Surgery of Trauma (AAST) Organ Injury Scale (OIS) for liver injuries is a common grading scale used to describe the severity of liver injury. Its grading system is based on findings from operative procedures, radiologic imaging, or autopsy.[1] Patients presenting with refractory shock with a positive focused assessment of sonography in trauma (FAST) will need urgent laparotomy. Patients who can be stabilized after blunt trauma typically undergo computed tomographic (CT) scanning of the abdomen. If a liver injury is found, the majority of patients will be candidates for nonoperative management (NOM).

Criteria for NOM include hemodynamic stability, absence of peritonitis, and the absence of associated intra-abdominal injuries requiring laparotomy. In about 70%–90% of patients with blunt liver injuries, NOM can be attempted. Of these, the success rate is high (85%–92%).[2–4] Higher grade liver injuries (AAST OIS Grades 3–5) are more likely to require urgent operation, but for those selected to undergo NOM, the failure rate is still low (about 6%–8%).[5,6] Other findings on CT besides liver injury grade such as the presence of a vascular blush or contrast extravasation (CE), and hemoperitoneum have been shown to be more important in predicting failure of NOM.[4]

On the other hand, in patients sustaining penetrating abdominal injuries, operative intervention is largely necessary in gunshot wounds, and less so if the mechanism is stabbing. In the occasional patient who is hemodynamically stable, with a suspected tangential trajectory and without peritonitis, gastrointestinal bleeding or hematuria, CT scanning has been utilized in helping to decide if NOM is feasible. In one series, 15% of patients with penetrating liver injuries underwent NOM based on CT findings, with a low failure rate (3%).[7]

When surgery is contemplated, an autologous blood recovery system should be prepared. Once the abdomen

has been entered, blood is quickly evacuated, and the four quadrants of the abdomen are packed. After removal of the perihepatic packing, the liver injury is inspected. The need for further treatment depends on the severity of bleeding. Such treatments may consist of direct pressure, topical hemostatic agents, electrocautery, or argon beam coagulation. Further bleeding may require full mobilization of the liver to the midline. If simple packing has failed to control the hemorrhage, the Pringle maneuver (occlusion of the hepatoduodenal ligament) is used, along with other techniques such as hepatotomy with finger fracture and direct suturing of the liver. The use of omentum to pack the injury is another technique that may control hemorrhage.

When large lacerations involve anatomic segments of the liver, removal of injured liver peripheral to the line of fracture may control bleeding, but this is not commonly done. With good perioperative management and ready availability of hepatobiliary specialists, the liver-related mortality for liver resections is acceptable (9% in one recent series).[8]

When uncontrolled bleeding occurs from hepatic veins or the retrohepatic vena cava, simple packing is usually not sufficient. Finger fracture of the parenchyma with venorrhaphy has been used successfully. Total hepatic vascular isolation techniques may rarely be necessary, and have been used with or without either atriocaval shunting[9,10] or extracorporeal veno-venous bypass. It is unclear whether the outcomes of hepatic venous injuries are better with shunting compared to no shunting, because when these complex techniques are utilized, the patient typically is in extremis.

In cases of severe liver injury where bleeding is controlled, abbreviating the laparotomy is commonly done in a "damage control" strategy. The abdomen is temporarily closed, and the patient is taken to the intensive care unit. During this period, angioembolization (AE) is an essential adjunct if intraoperative hemostasis has not been satisfactory. Once the patient's condition has been optimized, early planned reoperation with removal of packing is performed, usually in 24–48 h.

AE is also used as a primary treatment when NOM is planned. In this situation, CT findings are used to guide therapy and determine the need for angiography.

17.3 Elective Liver Resection: Operative Strategies

The most commonly used incision for elective liver resection is a right subcostal incision with an extension either across the midline to a bilateral subcostal incision, or extension into the midline up to the xiphoid process. Both of these incisions provide excellent exposure to the liver as well as the hilum. A major liver resection is defined as removal of three or more Couinaud segments.

Isolation of both the vascular inflow and outflow of the area in question is vital, and in order to have vascular control, it is necessary to mobilize the liver adequately. Adequate mobilization of the liver entails taking down the falciform, coronary, and the right triangular ligaments. The gastrohepatic ligament should be taken down as well in order to allow one to perform a Pringle maneuver in order to curtail blood loss.[11,12] Care should be taken when opening the gastrohepatic ligament to avoid injury to an accessory left hepatic artery if present. The Pringle maneuver should not exceed 20–30 min at a time if possible to reduce complications associated with splanchnic congestion and ischemia–reperfusion injury.[13] The porta hepatis, once identified, should be dissected to expose and ligate the arterial and portal branches supplying the relevant area of resection. Once the vessels are ligated, the liver parenchyma will demarcate. The venous drainage can be best approached by dissection along the bare area of the liver to the retrohepatic cava for the right hepatic vein, and along the left triangular ligament and the falciform ligament for the left and middle hepatic veins. The hepatic vein can be divided and oversewn with nonabsorbable sutures, or, alternatively can be ligated and divided with an endovascular stapling device. Parenchymal dissection can be accomplished with a number of techniques ranging from simple finger fracture or crushing the tissue with a Kelly clamp, to the more contemporary techniques of stapling, ultrasonic dissection, and devices that use monopolar energy to name a few.[14] Any small biliary radicals and vessels encountered can then be ligated using either clips or sutures.

17.4 Complications

17.4.1 Hemorrhage

For patients initially managed nonoperatively, delayed bleeding mostly occurs in higher grade liver injuries with an incidence of 4%–7%,[5,6,15] and very rarely in lower grade injuries. Where AE is utilized in NOM of these injuries, delayed bleeding can still occur in 5%–12% of patients. [5,6,16] When NOM is contemplated for these injuries, CE on CT can predict transfusion requirements and failure of NOM. As accumulated experience with CT grows, the optimal management strategy for CT-detected CE will necessarily involve some degree of

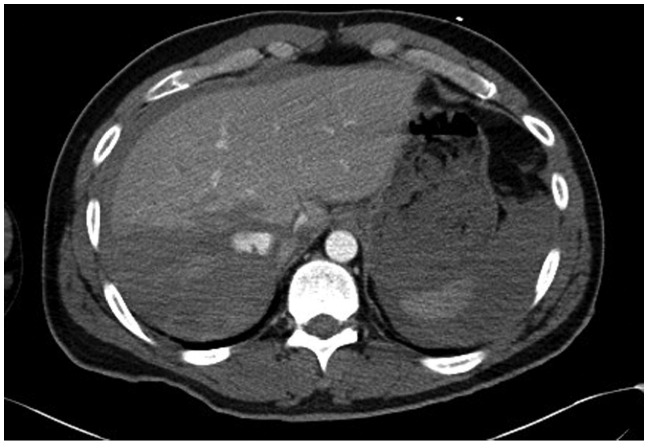


FIGURE 17.1
CT showing CE with hemoperitoneum. This patient became hypotensive after CT, requiring urgent laparotomy and hemostasis. Postoperative angiography showed no bleeding requiring embolization.

individualization, based on the size of contrast pooling, presence or absence of free intraperitoneal extravasation, and the magnitude of hemoperitoneum. A patient with a small degree of CE confined to the hepatic parenchyma without hemoperitoneum may not require further intervention other than close observation, whereas CE with free intraperitoneal leakage and associated large hemoperitoneum will require urgent AE or laparotomy[16,17] (Figure 17.1). Similarly, in children, CE on CT may not automatically mandate further intervention. A series of 75 children with blunt liver injury with a 29% incidence of CE found that 97% could be treated nonoperatively with none undergoing AE, with one liver-related death.[18] On the other hand, there have been sporadic reports of late fatal hemorrhages in the pediatric population.[19]

The more common scenario of delayed bleeding after liver injury is seen when urgent surgical intervention is required initially. This is likely due to the severity of the liver injury. As mentioned previously, if packing is initially successful but hemostasis is deemed suboptimal by the surgeon in the damage control setting, AE should be considered postoperatively to minimize the possibility of delayed bleeding. Also, removal of packing during relaparotomy can, on occasion, precipitate bleeding. Packing should be removed unhurriedly and only when well-soaked. If removal of packing precipitates bleeding, repacking may be necessary in some cases. The incidence of recurrent hemorrhage after packing removal was 21% when packs were removed early (<36 h), and only 4% when packs were removed after 36 h in a retrospective study.[20]

Delayed bleeding after the acute damage control phase is seen uncommonly, but has been reported to be fatal in the pediatric population as mentioned previously. If there is suspicion, and patient condition allows, CT is useful to assess the presence of a hepatic artery pseudoaneurysm which may benefit from AE. If there is a known subcapsular liver hematoma, managed nonoperatively, repeat CT or FAST can confirm rupture by demonstrating new or increased hemoperitoneum. Operative intervention is usually necessary.

Bleeding during major liver resections is largely unavoidable. However, the general magnitude of bleeding during the procedure measured by the amount of blood transfusion has decreased significantly since the 1970s. During that time period there was a significant mortality of 20% associated with a major liver resection, with exsanguination representing one-fifth of the deaths. In the 1990s, with the use of vascular occlusion, advances in surgical technology, and better intraoperative management of the patient, the incidence of major bleeding has decreased.[21] Currently the incidence of bleeding ranges from 1% to 8%.[22] Cirrhotic patients are more likely to have postoperative bleeding compared to patients with normal liver function.

Hemorrhage most frequently occurs during the parenchymal dissection of the liver. There are a few maneuvers that will aid in minimizing the bleeding during this time. Intermittent Pringle maneuver of clamping the porta for 20–30 min, with a 5 min break will help decrease intraoperative bleeding.[23] The central venous pressure should also be kept low (at or <5) during the procedure as well to curtail blood loss.

17.4.2 Bile Leak

A bile leak after liver injury is usually manifested by bile in perihepatic drains placed intraoperatively or percutaneously, by a localized perihepatic fluid collection (biloma), or by generalized ascites (bile peritonitis). These biliary complications are associated with high-grade liver injuries (4%–24%),[5,15] and are mostly due to an intrahepatic source. The more complex the liver injury, the higher the incidence of biliary complications (5% in grade three injuries vs. 52% in grade five injuries, in one study).[5] Patients with bilomas may have no symptoms or may exhibit right upper quadrant fullness or tenderness, fever, or jaundice, weeks after the initial operation or injury. CT or ultrasound-guided drainage is the treatment of choice if the patient exhibits symptoms, fever, or leukocytosis, with initiation of empiric antibiotics.

For patients undergoing operation, the decision as to whether or not the injury should be drained should be made intraoperatively. In a series of 472 patients randomized to no drainage versus sump drainage versus closed drainage, the rates of hepatic abscess were no different between no drainage and closed drainage (6.7% vs. 3.5%), but both were lower than that with sump drainage (13%).[24] In another randomized trial

where patients without evidence of bile leak intraoperatively were randomized to no drainage versus open drainage with Penrose drains, there was no difference in the incidence of intra-abdominal abscess.[25] Therefore, if there is evidence of a bile leak, a closed suction drain should be placed. If there is no bile leak, the decision to drain a liver injury should take into account the severity of the liver injury and the extent of surgical dissection, debridement, and resection undertaken.

Bile peritonitis should be suspected when a patient develops signs of sepsis, and has diffuse abdominal pain or tenderness and jaundice The patient may still be able to have bowel function and tolerate enteral nutrition. CT will show generalized ascites. Laparoscopy with placement of perihepatic drains and expeditious endoscopic retrograde cholangiopancreatography (ERCP) to assess for a bile leak is initially preferred.[26]

The majority of bile leaks mentioned earlier are due to an intrahepatic bile duct injury. Extrahepatic duct injuries are rare and almost always are associated with a penetrating mechanism of injury.[27,28] Primary closure can be done if there is no need for excessive mobilization and the duct injury is minimal. For most injuries, a biliary–enteric anastomosis is recommended to minimize biliary stricture formation.

Bile leaks after elective liver resections have been reported to be anywhere from 0% to 33%.[29,30] The highest rates of bile leak are reported in patients who have a liver resection with concomitant hepaticojejunostomy. The incidence in this cohort of patients is up to 14% in one study, as opposed to 3% in patients who did not have a bilioenteric anastomosis.[29] Leaving a drain in the empty fossa of the resection site is imperative in all major liver resections, so that an early postoperative bile leak can be detected. In minor resections, drainage may not be as critical. The majority of bile leaks originate from the cut surface of the liver, usually from a small biliary radicle, and are typically self-limiting. Bile leaks after liver injury or elective resection may take up to 6 weeks to resolve completely. If the amount of drainage consistently decreases over this period of time, it is likely that the leak will resolve. ERCP with sphincterotomy, and placement of a biliary stent or a nasobiliary drain is increasingly utilized to expedite closure and is almost always successful.[31,32] Ultimately, 90% of bile leaks will resolve without any need for surgical intervention.

17.4.3 Hepatic Necrosis and Hepatic Failure

Hepatic necrosis with associated hepatic failure is an unusual complication after injury, and is only seen with severe injuries with significant hemorrhagic shock. The incidence among high-grade injuries is low (0.4%–3%) in two retrospective studies.[6,15] However, hepatic necrosis appears to be more common among patients who have undergone AE for liver injuries. The incidence can be as high as 20%–42% in this setting.[33,34] Similarly, gallbladder infarction associated with AE of the right hepatic artery has also been observed. Patients with hepatic necrosis after AE had a liver-related mortality rate of 7% which was not significantly different than patients without hepatic necrosis after AE, in one study.[33] While this is an important problem in the current multimodality approach to complex liver injuries, other factors such as the duration of hemorrhagic shock and the degree of selectivity of the embolization should be considered in assessing these complications.

The noncirrhotic liver has a remarkable ability for compensatory growth after major resection. (The likelihood of hepatic failure after a major elective liver resection depends on the function and volume of the remnant liver [>25%–30% is desirable].) The incidence has been quoted from 0% to 13%,[35,36] but is generally low in noncirrhotic patients (2%–7%). In cirrhotic patients, elective liver resection should be avoided as the incidence of liver failure is as high as 20%.[37] The Child–Pugh classification and more recently the Model for End Stage Liver Disease (MELD) score have been used as predictive tools for outcomes after abdominal surgery in cirrhotic patients.[38] Retrospective studies have shown that cirrhotic patients undergoing an elective liver resection with MELD score >11 are at a high risk of developing postoperative liver failure.[39–41] Mortality from liver failure in a cirrhotic patient approaches 100%. Careful preoperative evaluation of liver function should be done in all cases. A variety of tests have been developed to assess liver function especially in cirrhotic patients. The indocyanine green retention rate at 15 min (ICGR-15) is the most commonly used. A value of <14% in cirrhotic patients means they will tolerate a liver resection, whereas a rate >20% means that a liver resection should be avoided.[35] Other risk factors for hepatic failure after liver resection include active viral hepatitis, steatosis, cholestasis, and chemotherapy-associated hepatotoxicity; each of these factors have a negative impact on the regenerative capacity of the liver.[37] Treatment for acute liver failure after resection should focus on the support of the remnant liver. These patients are at significant risk for development of septic complications; therefore, the administration of prophylactic antibiotics and antifungal agents is advantageous.[41] As a final desperate measure, liver transplantation can be utilized as a rescue measure in certain situations. If the resection is done for hepatocellular carcinoma and there is no evidence of extrahepatic disease, a patient can be considered for a liver transplant. Liver transplantation has also been performed in the setting of hepatic failure after trauma and can be life-saving.[42]

17.4.4 Intra-Abdominal Abscess

In patients undergoing operative treatment of liver injuries, the abscess rate is about 5%–10%.[24] The rate of liver-related abscess formation is lower (<2%) when liver injuries are managed nonoperatively.[6] Abscess formation is associated with the severity of the liver injury, the presence of other intra-abdominal injuries requiring therapeutic intervention, and the number of blood transfusions. When complex liver injuries require perihepatic packing for hemorrhage control, the rate of abscess formation may be as high as 30% among patients who survive the perioperative period.[43,44] Perioperative antibiotics administered prophylactically have not been proven to decrease abscess rates after perihepatic packing when the abdomen is left open.

The incidence of intra-abdominal abscess formation after elective liver resections is about 8%–10%.[45,46] Risk factors associated with abscess formation were repeat liver resection (which has increased with advances in surgical techniques and perioperative management), prolonged operative time, and liver resections for cholangiocarcinoma. The treatment of choice is with percutaneous drainage and antibiotic therapy.

17.4.5 Delayed Diagnosis of Intra-Abdominal Injuries

The incidence of hollow viscus injuries requiring intervention is about 0%–1.9%.[3,5,6] During NOM of solid intra-abdominal injuries, a deteriorating clinical course manifested by the development of organ failure should raise concern for missed hollow viscous injuries. The importance of bedside physical examination, while often unreliable in critically ill ICU patients, is often minimized, thus contributing to a delay in diagnosis. Repeat CT is usually performed, but the lack of free intraperitoneal air or pneumatosis does not exclude a bowel injury. Diagnostic peritoneal lavage and diagnostic laparoscopy are also options in helping to make the diagnosis. Laparotomy may ultimately be necessary if the patient is deteriorating and no definite extra-abdominal cause is found.

17.4.6 Biliary Stricture

For bile duct injuries with complete transection, primary repair is not recommended due to the high incidence (>50%) of stricture formation. The incidence is lower (<5%) if a bilioenteric anastomosis is performed in this setting. After primary repair for incomplete transections, the incidence of stricture is also low (5%).[27] When injury occurs to the hepatic ducts at the level of the porta hepatis, hepaticojejunostomy is preferred to primary repair.

After elective liver resection, biliary strictures are usually a late complication and are extremely rare. In the absence of a bilioenteric anastomosis, if a biliary stricture develops, one should suspect either an arterial injury or tumor recurrence. Strictures after hepatectomy have otherwise been uncommonly reported in patients who had had prior hepatectomy, manifesting as persistent bile leaks.[47] Indeed, they are recognized more as a complication associated with radiofrequency ablation and transarterial chemoembolization of liver tumors.[48,49] A stricture which develops at the bilioenteric anastomosis may be treated by a percutaneous transhepatic catheter with sequential dilatation of the stricture. If this is unsuccessful, then surgical resection of the stricture and revision of the bilioenteric anastomosis may be necessary.

17.4.7 Hemobilia

Hemobilia rarely occurs as a consequence of a hepatic artery pseudoaneurysm after liver injuries. In a series of adult patients with liver injuries managed operatively, 6 of 482 (1.2%) were found to have hepatic artery pseudoaneurysm with hemobilia,[50] while in a series of 78 unselected patients with liver injuries, the incidence was 1 in 78 (1.3%).[3] While rare in the setting of liver injury, this complication has been well-recognized in association with percutaneous transhepatic procedures.[51] In a large series, hepatic arterial injuries occurred in 2.3%, with the majority (>85%) presenting as hemobilia.

In elective liver resections, hemobilia is an extremely rare problem and its incidence is not well-documented.

This complication can occur days to months or even years after injury. This problem should be considered in a patient with a high-grade liver injury or who has had a percutaneous liver procedure, presenting with gastrointestinal bleeding. There may or may not be associated shock, signs of sepsis, jaundice, or abdominal pain. Upper endoscopy is usually nondiagnostic, because the bleeding is often intermittent, but this procedure should be performed to rule out other sources of gastrointestinal bleeding. There may be radiologic evidence of a dilated common bile duct due to blood clots in the biliary tract. A CT scan performed with the use of intravenous contrast material may reveal a "blush" in the liver parenchyma. The management of choice is arteriography with selective embolization of the feeding artery.

Besides a hepatic artery to biliary tract communication, bilhemia (mixing of bile and blood) as a result of a biliary–venous fistula can occur rarely. This is suspected when there are very high levels of direct hyperbilirubinemia, and only moderately elevated liver enzymes. It occurs rarely, in 0.2% of patients managed nonoperatively.[6] Treatment is aimed at decreasing intrabiliary tract pressure by ERCP and biliary stenting, and/or external drainage of bilomas if present.[52]

Incidence of Complications of Liver Surgery and Trauma

Complications	Incidence and Setting	References
Hepatic failure	Elective liver resection: 0%–13%	[35–37]
	Noncirrhotic patients: 2%–7%	
	Cirrhotic patients: 20%	
	Trauma: 0.4%–3%	
		[6,15]
Hepatic necrosis	Trauma: After AE—20%–42%	[33,34]
Intra-abdominal abscess	Trauma: 5%–30% (operative management)	[43,44]
	Higher with perihepatic packing	
	0%–2% with NOM	[6]
	Elective surgery: 8%–10%	[45,46]
Bile leak/ biloma/bile peritonitis	Trauma: Higher in higher grade injuries—4%–24%	[6,15]
	Elective liver resection: 0%–33%	[29,30]
Hemobilia	Trauma: Rare in an unselected cohort. Injuries requiring operative management: 1.2%	[50]
	Percutaneous transhepatic procedures: 2%	[51]
	Elective surgery: Rare, not well-documented	
Bilhemia	Trauma: 0.2%	[6]
Biliary stricture	Trauma: Primary repair of complete bile duct transection—>50%	[27]
	Bilio-enteric anastomosis for bile duct injury: 5%	
	Elective surgery: Rare; not well-documented. Usually attributable to prior liver procedures or history of radiofrequency ablation	
Delayed bleeding	Elective surgery: 1%–8%	[22]
	Trauma: NOM—4%–12%	[5,6,15,16,20]
	Recurrent bleeding after abbreviated laparotomy: 4%–21%	
Delayed diagnosis of intra-abdominal injuries	NOM: 0%–1.9%	[3,5,6]

Avoiding Complications in Liver Surgery and Trauma

- Cirrhotic patients should be carefully evaluated when elective liver resection is contemplated.
- Hemodynamic stability is the most important factor in the decision to pursue a NOM strategy for liver injuries.

Avoiding Complications in Liver Surgery and Trauma

- In assessing liver injuries on CT, factors such as the presence or absence of CE, the degree of CE, whether or not it is contained within the parenchyma, and the degree of hemoperitoneum should be taken into consideration together with clinical assessment of the patient to plan further management.
- AE may be used in primary treatment during NOM or as an adjunct to operative hemostasis for liver injuries, with the recognition that hepatic necrosis may occur. Prior to embolization, the surgeon and radiologist should discuss findings on angiography.
- Biliary–enteric anastomosis should be used for complete or near-complete traumatic transection of the bile ducts rather than primary repair.
- Avoiding high central venous pressure may lessen blood loss during major liver resections.
- Preparation for total hepatic vascular isolation with or without bypass is important for major liver resection and trauma.
- Adequate mobilization of the liver to allow maneuverability of the liver and access to the inflow and outflow of the liver is necessary during major liver resections in elective or emergent situations.
- Utilize the Pringle maneuver judiciously (only 20–30 min at a time with a 2–5 min break) in order to avoid cardiac complications with reperfusion of the liver.
- A drain should be left in the empty space after a liver resection to allow early recognition of a bile leak and avoid a potential biloma and its associated complications.

References

1. Moore EE, Cogbill TH, Jurkovich GJ, Shackford SR, Malangoni MA, Champion HR. Organ injury scaling: Spleen and liver (1994 revision). *J Trauma* 1995; 38: 323–324.
2. Giss SR, Dobrilovic N, Brown RL, Garcia VF. Complications of nonoperative management of pediatric blunt hepatic injury: Diagnosis, management, and outcomes. *J Trauma* 2006; 61: 334–339.
3. Velmahos GC, Toutouzas K, Randin R et al. High success with nonoperative management of blunt hepatic trauma. *Arch Surg* 2003; 138: 475–481.
4. Malhotra AK, Fabian TC, Croce MA et al. Blunt hepatic injury: A paradigm shift from operative to nonoperative management in the 1990s. *Ann Surg* 2000; 231(6): 804–813.
5. Van der Wilden GM, Velmahos GC, Emhoff T et al. Successful nonoperative management of the most severe blunt liver injuries. A multicenter study of the research consortium of New England centers for trauma. *Arch Surg* 2012; 147: 423–428.
6. Kozar RA, Moore FA, Cothren CC et al. Risk factors for hepatic morbidity following nonoperative management. Multicenter study. *Arch Surg* 2006; 141: 451–459.

   Detailed description of complications with nonoperative management of liver injuries in a large database
7. Schnüriger B, Talving P, Barbarino R et al. Current practice and the role of the CT in the management of penetrating liver injuries at a Level I trauma center. *J Emerg Trauma Shock* 2011; 4: 53–57.

8. Polanco P, Leon S, Pineda J et al. Hepatic resection in the management of complex liver injury to the liver. *J Trauma* 2008; 65: 1264–1270.
9. Chen RJ, Fang JF, Lin BC et al. Surgical management of juxtahepatic venous injuries in blunt hepatic trauma. *J Trauma* 1995; 38: 886–890.
10. Khaneja SC, Pizzi WF, Barie PS, Ahmed N. Management of penetrating juxtahepatic inferior vena cava injuries under total vascular occlusion. *J Am Coll Surg* 1997; 184: 469–474.
11. Hoekstra LT, van Trigt JD, Reiniers MJ et al. Vascular occlusion or not during liver resection: The continuing story. *Dig Surg* 2012;29:35–42.
    Review of strategies for control of vascular inflow and outflow to minimize complications during liver resection.
12. Agrawal S, Belghiti J. Oncologic resection for malignant tumors of the liver. *Ann Surg* 2011; 253: 656–665.
13. Teoh NC. Hepatic ischemia reperfusion injury: Contemporary perspectives on pathogenic mechanisms and basis for hepatoprotection-the good, bad and deadly. *J Gastroenterol Hepatol* 2011; 26(Suppl 1):180–187
14. Sarpel U, Ayo DM, Newman E. Choice of device for parenchymal transection in laparoscopic hepatectomy. *Surg Technol Int* 2012; XXII Epub.
15. Bala M, Gazalla SA, Faroja M et al. Complications of high grade liver injuries: Management and outcome with focus on bile leaks. *Scand J Trauma Resusc Emerg Med* 2012; 20: 20.
    Contemporary study of complications in high-grade liver injuries.
16. Huang Y-C, Wu S-C, Fu C-Y et al. Tomographic findings are not always predictive of failed nonoperative management in blunt hepatic injury. *Am J Surg* 2012; 203: 448–453. *Characterization of contrast extravasation on CT and relationship to subsequent outcomes*.
17. Fang JF, Chen RJ, Wong YC et al. Classification and treatment of pooling of contrast material on computed tomography scan of blunt hepatic trauma. *J Trauma* 2000; 49: 1083–1088.
18. Eubanks JW, Meier DE, Hicks BA et al. Significance of "blush" on computed tomography scan in children with liver injury. *J Pediatr Surg* 2003; 38: 363–366.
19. Shilansky J, Navarro O, Superina RA et al. Delayed hemorrhage after nonoperative management of blunt hepatic trauma in children: A rare but significant event. *J Pediatr Surg* 1999; 34: 60–64.
20. Caruso DM, Battistella FD, Owings JT et al. Perihepatic packing of major liver injuries: Complications and mortality. *Arch Surg* 1999; 134: 958–962.
21. Belghiti J, Hiramatsu K, Benoist S et al. Seven hundred forty-seven hepatectomies in the 1990's: An update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000; 191(1): 38–46.
22. Rahbari NN, Garden OJ, Padbury R et al. Post-hepatectomy haemorrhage: A definition and grading by the International Study Group of Liver Surgery (ISGLS). *HBP* 2011; 13: 528–535.
23. Fu SY, Lau WY, Li GG et al. A prospective randomized controlled trial to compare Pringle maneuver, hemihepatic vascular inflow occlusion, and main portal vein inflow occlusion in partial hepatectomy. *Am J Surg* 2011; 201(1): 62–69.
24. Fabian TC, Croce MA, Stanford GG et al. Factors affecting morbidity following hepatic trauma. A prospective analysis of 482 injuries. *Ann Surg* 1991; 213: 540–548.
25. Mullins RJ, Stone HH, Dunlop WE, Strom PR. Hepatic trauma: Evaluation of routine drainage. *Southern Med J* 1985; 78: 259–261.
26. Carrillo EH, Reed DN, Gordon L et al. Delayed laparoscopy facilitates the management of biliary peritonitis in patients with complex liver injuries. *Surg Endosc* 2001; 15: 319–322.
27. Ivatury RR, Rohman M, Nallathambi M et al. The morbidity of injuries of the extra-hepatic biliary system. *J Trauma* 1985; 25: 967–973.
28. Bade PG, Thomson SR, Hirshberg A, Robbs JV. Surgical options in traumatic injury of the extrahepatic biliary tract. *Br J Surg* 1989; 76: 256–258.
29. Hoekstra LT, van Gulik TM, Gouma DJ et al. Posthepatectomy bile leakage: How to manage. *Dig Surg* 2012; 29: 48–53.
30. Ishii H, Ochiai T, Murayama Y et al. Risk factors and management of postoperative bile leakage after hepatectomy without bilioenteric anastomosis. *Dig Surg* 2011; 28:198–204.
31. Anand RJ, Ferrada RA, Darwin PE et al. Endoscopic retrograde cholangiopancreatography is an effective treatment for bile leak after severe liver trauma. *J Trauma* 2011; 71: 480–485.
32. Lubezky N, Konikoff FM, Rosin D et al. Endoscopic sphincterotomy and temporary internal stenting for bile leaks following complex hepatic trauma. *Br J Surg* 2006; 93: 78–81.
33. Dabbs DN, Stein DM, Scalea TM. Major hepatic necrosis: a common complication after angioembolization for treatment for high grade liver injuries. *J Trauma* 2009; 66: 621–629.
34. Mohr AM, Lavery RF, Barone A et al. Angiographic embolization for liver injuries: Low mortality, high morbidity. *J Trauma* 2003; 55: 1077–1082.
35. Hammond JS, Guha IN, Beckingham IJ et al. Prediction, prevention and management of postresection failure. *Br J Surg* 2011; 98: 1188–1200.
    Review of risk factors associated with hepatic failure after liver resection
36. Schreckenbach T, Liese J, Bechstein WO et al. Posthepatectomy liver failure. *Dig Surg* 2012; 29: 70–85.
37. Garcea G, Maddern GJ. Liver failure after major hepatic resection. *J Hepatobil Pacreat Surg* 2009; 16: 145–155.
38. Inaba K, Barmparas G, Resnick S et al. The model for end-stage liver disease score-an independent prognostic factor of mortality in injured cirrhotic patients. *Arch Surg* 2011; 146(9): 1074–1078.
39. Cucchetti A, Ercolani G, Cescon M et al. Recovery from liver failure after hepatectomy for hepatocellular carcinoma in cirrhosis: Meaning of the model for end-stage liver disease. *J Am Coll Surg* 2006; 203(5): 670–676.
40. Cucchetti A, Ercolani G, Vivarelli M et al. Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. *Liver Transpl* 2006; 12: 966–971.

The importance of the MELD score in cirrhotic patients undergoing liver resection.
41. Van den Broek MA, Olde Damink SW, Dejong CH et al. Liver failure after partial hepatic resection: Definition, pathophysiology, risk factors and treatment. *Liver Int* 2008; 28(6): 767–780.
42. Tucker ON, Marriott P, Rela M, Heaton N. Emergency liver transplantation following severe liver trauma. *Liver Transpl* 2008; 14: 1204–1210.
43. Krige JE, Bornman PC, Terblanche J. Therapeutic perihepatic packing in complex liver trauma. *Br J Surg* 1992; 79: 43–46.
44. Carmona RH, Peck DZ, Lim RC. The role of packing and planned reoperation in severe hepatic trauma. *J Trauma* 1984; 24: 779–784.
45. Sadamori H, Yagi T, Shinoura S et al. Risk factors for major morbidity after liver resection for hepatocellular carcinoma. *Br J Surg* 2013 Jan;100(1):122–129.
46. Sadamori H, Yagi T, Shinoura S et al. Risk factors for organ/space surgical site infection after hepatectomy in 359 recent cases. *J Hepatobil Pancreat Sci* 2013 Feb;20(2):186–196.
47. Sadamori H, Yagi T, Matsuda H et al. Intractable bile leakage after hepatectomy for hepatocellular carcinoma in 359 recent cases. *Dig Surg* 2012; 29: 149–156.
48. Wong SL, Mangu PB, Choti MA et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol* 2010; 28(3): 493–507.
49. Jansen MC, van Duijnhoven FH, van Hillegersberg R et al. Adverse effects of radiofrequency ablation of liver tumours in the Netherlands. *Br J Surg* 2005; 92: 1248–1254.
50. Croce MA, Fabian TC, Spiers JP, Kudsk KA. Traumatic hepatic artery pseudoaneurysm with hemobilia. *Am J Surg* 1994; 168: 235–238.
51. Fidelman N, Bloom AI, Kerlan RK et al. Hepatic arterial injuries after percutaneous biliary interventions in the era of laparoscopic surgery and transplantation: Experience with 930 patients. *Radiology* 2008; 247: 880–886.
52. Homme M, Kazemier G, van Dijk L et al. Complex liver trauma with bilhemia treated with perihepatic packing and endovascular stent in the vena cava. *J Trauma* 2009; 67: E51–E53.

18

Complications of Pancreatic Surgery and Trauma

Christopher K. Senkowski and Lorena P. Suarez-Kelly

CONTENTS

Pancreatic surgery has undergone a number of changes during the past few decades. The trend is toward an increase in the incidence of pancreatic adenocarcinoma but a decrease in the incidence of periampullary tumors. The mortality and morbidity rates associated with major pancreatic resection have decreased dramatically because diagnostic and treatment methods have been refined. The increased survival rates of patients with multisystem trauma, coupled with advances in imaging techniques, have increased the frequency with which pancreatic injury is diagnosed. For the trauma surgeon, resident, or student who performs pancreatic surgery only occasionally, it is crucial to study the pancreas and its response to surgery so that the potential complications of pancreatic surgery can be recognized and pancreatic injury can be managed. All elective and emergent pancreatic surgery procedures as well as pancreatic trauma are associated with a commonly occurring set of complications.

18.1 Anatomy

The pancreas is situated in a relatively fixed position in the retroperitoneum and is surrounded by crucial structures. It is divided into a head, a neck, a body, and a tail (Figure 18.1). The gland lies across the second lumbar vertebra; thus, it is commonly injured by blunt trauma. Penetrating injury can affect any area of the gland and is associated with a high mortality rate, before the injured patient even reaches the hospital. The intricate involvement of the pancreas with the duodenum, the mesenteric vessels, and the portal venous system make elective surgery on the pancreas technically challenging.

The pancreas has both exocrine and endocrine functions. Production of insulin is an endocrine function, and the potential complications of resection or injury include diabetes mellitus. The exocrine pancreas consists of the acinar cells with their ductal system, which delivers enzymes to the duodenum. The average human produces 750–1500 mL of pancreatic fluid daily. The enzymes secreted in this fluid include proteases, amylase, nucleases, elastases, collagenases, and lecithinases. These proteolytic enzymes are the most potentially damaging, but fortunately they are secreted in their inactive form as zymogens. However, when these enzymes are activated in the interstitium of the gland or in the retroperitoneum, or when they leak from an anastomosis, severe inflammation and necrosis occur. As a result of this mechanism, the exocrine pancreas causes most pancreatic complications. Controlling the exocrine pancreas is crucial to managing complications associated with pancreatic surgery.

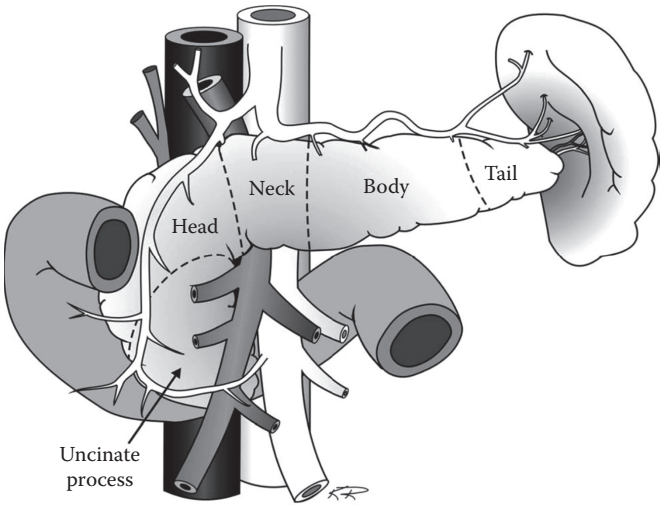


FIGURE 18.1
Anatomy of pancreas.

Knowledge of the anatomy of the pancreatic ducts is important for any pancreatic or trauma surgeon. The main pancreatic duct, the Wirsung duct, traverses the entire gland, lies slightly superior in the gland, and ends by joining the common bile duct and emptying into the duodenum. The accessory duct, the Santorini duct, drains the superior proximal portion of the gland through an accessory opening directly into the duodenum about 2–2.5 cm above the papilla. A substantial number of pancreatic ductal anomalies exist (Figure 18.2). The common bile duct and the pancreatic duct may have separate openings into a combined papilla or they may share a common channel.

The arterial and venous anatomies are relatively constant in the pancreas; however, knowledge of the main vascular branches is important when the gland is to be dissected and particularly when such dissection occurs near the portal triad. The common hepatic artery traverses the superior border of the pancreas toward the portal triad. It divides to form the proper hepatic artery and the gastroduodenal artery. The gastroduodenal artery descends retrograde and within the gland itself. In about 15% of cases, there is an aberrant right hepatic artery directly off the superior mesenteric artery. Whether this artery is replaced or aberrant is difficult to determine at the time of surgery; therefore, the artery must be carefully preserved. The venous drainage system includes the splenic vein and the portal vein. This anatomy is familiar to any surgeon who performs pancreatic surgery.

18.2 General Complications Associated with Pancreatic Surgery

Whenever the pancreas is injured, incised, or inflamed, the pancreatic ducts are disrupted. When pancreatic secretions leak into the retroperitoneal space or into the true peritoneal cavity, complications will include fluid collections, abscess, or fistula. If the enzymes erode into blood vessels, the complication is hemorrhage. The other main difficulty occurs with repeated insult, which results in scar formation within the pancreas; this scarring causes biliary obstruction, obstruction of the pancreatic duct, or both.

18.2.1 Fluid Collections and Pancreatic Pseudocyst

Understanding fluid collections is particularly important because the nomenclature can be confusing. In 2008, a group of pancreatic experts convened the Acute Pancreatitis Working Group and redefined the 1992 Atlanta Classification, given the new advancements in

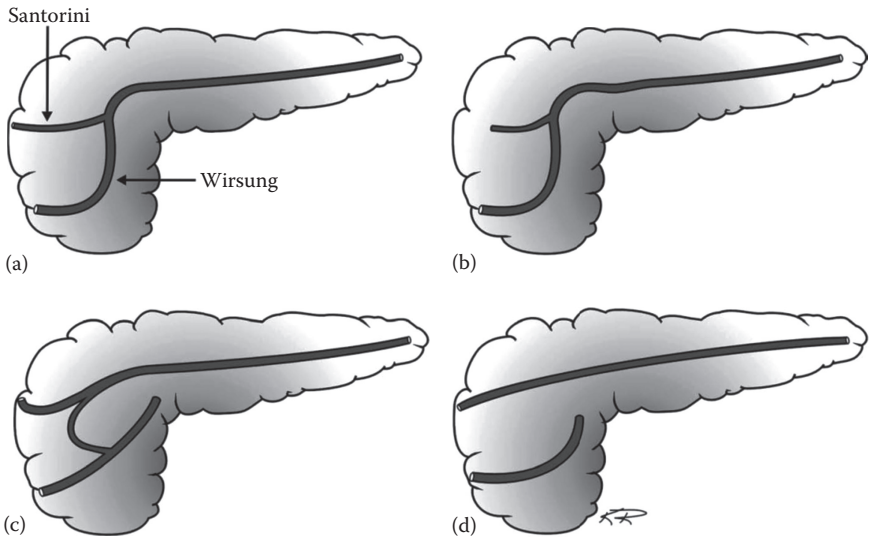


FIGURE 18.2
Pancreatic ductal variants: (a) normal (60%), (b) regression dorsal duct (<10%), (c) functional divisum (<10%), and (d) divisum (15%).

diagnostic and management techniques. Appropriate terms for various peripancreatic fluid collections have been established [5]. These definitions are very important in discussions of treatment. *Acute peripancreatic fluid* collections occur within the first 4 weeks after the onset of interstitial edematous pancreatitis, arising presumably from local edema related to pancreatic inflammation or from a rupture of the main duct or a small peripheral pancreatic ductal side branch. Most of these fluid collections remain sterile and *reabsorb spontaneously*. If the fluid collection is clinically associated with acute pancreatitis, the appropriate initial therapy is observation because many of these fluid collections will resolve. Aspiration or CT-guided drainage is not recommended.

A *pseudocyst* develops from an acute peripancreatic fluid collection that persists for over 4 weeks and is defined as a "well-circumscribed, usually round or oval, homogenous fluid collection surrounded by a well-defined wall with no associated tissue necrosis within the fluid collection" [5] (Figure 18.3). The fluid in these cysts is rich in pancreatic enzymes and is usually sterile. Importantly, the 2008 Working Group redefined an infected pancreatic pseudocyst as containing purulent liquid without an associated solid component (necrosis), differentiating it from infected postnecrotic pancreatic fluid collections (PNPFC) and infected walled-off pancreatic necrosis (WOPN). PNPFC are seen in patients with acute necrotizing pancreatitis and contain both fluid and necrotic contents. An interface between the adjacent viable tissue and the necrosis develops as the PNPFC matures and a thick wall without epithelial lining is seen, giving rise to a WOPN [5]. Both PNPFC and WOPN may be sterile or infected.

It is crucial to remember that any cystic lesion of the pancreas must be suspected to be a cystic neoplasm before it is erroneously labeled a pseudocyst. Endoscopic or surgical therapy should be considered for collections that have a definite wall, have been present for more than 6 weeks, and are larger than 6 cm in diameter. In Bradley's classic study [6], 40% of pseudocysts that had been present for less than 6 weeks resolved with a complication rate of 20%, whereas pseudocysts that had been present for more than 12 weeks did not resolve and were associated with a complication rate of 67%.

18.2.2 Pancreatic Abscess

Pancreatic abscesses occur in 2%–9% of cases of acute pancreatitis [7]. Abscesses are more common among patients with pancreatitis resulting from gallstones or trauma lower in association with alcoholic pancreatitis [8]. It is important to understand that pancreatic abscess and infected pancreatic necrosis are two separate entities. Both conditions will be associated with symptoms such as fever, leukocytosis, and intestinal ileus; however, a pancreatic abscess will be seen on CT scans as a fluid collection with air.

In select cases, when abscesses are localized and accessible, percutaneous drainage can be performed. In such cases, the fluid in the abscess should be cultured, and treatment with appropriate antibiotics should be initiated. If the fluid collection is not amenable to percutaneous drainage, endoscopic transgastric drainage may be performed [9]. However, some cases will require operative exploration and drainage of the abscess via a video-assisted retroperitoneal approach or standard

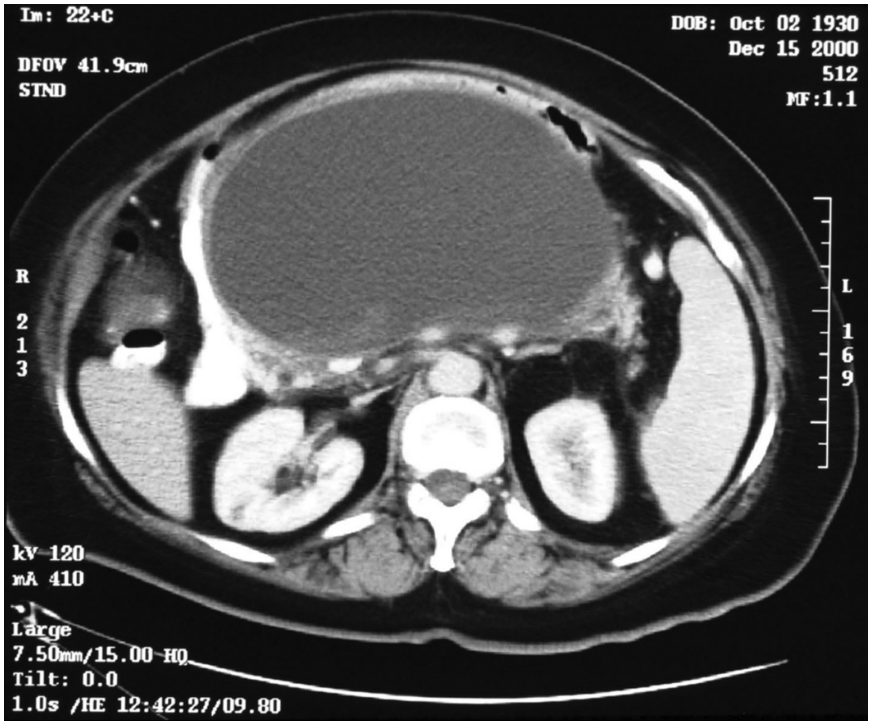


FIGURE 18.3
CT scan of patient with giant pancreatic pseudocyst as a late sequelea of pancreatitis. Stomach is compressed anteriorly.

open approach [10]. The mortality rate associated with this condition is approximately 5%, a rate lower than that associated with pancreatic necrosis [11].

18.2.3 Pancreatic Necrosis

Unlike pancreatic abscesses, which are localized, pancreatic necrosis is associated with inflammation that spreads throughout the retroperitoneum with massive release of cytokines. Pancreatic necrosis runs a more indolent course than pancreatic abscess. The agents typically responsible for the condition include, in the order of frequency, *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Enterobacter* species [11].

Necrosectomy is reserved for cases of infected pancreatic necrosis or significant sterile necrosis that is unresponsive to aggressive care and organ support in the intensive care unit (ICU), but the effectiveness of necrosectomy in sterile necrosis is still intensely debated [12]. After the onset of symptoms, pancreatic necrosectomy is usually performed within 2–4 weeks of a severe episode. Earlier intervention is less beneficial because the pancreatic tissue is still formed and is impossible to debride. After a short period of time, ongoing injury, infection, and necrosis will soften and liquefy the gland.

The approach to pancreatic necrosectomy has evolved recently. Santvoort et al. study advocates for a minimally invasive approach that may be beneficial when compared to standard open approach in terms of preventing surgery and both short-term and long-term complications. The minimally invasive "step-up approach" has been described with the first step being percutaneous or endoscopic transgastric drainage followed by the second step of operative drainage via video-assisted retroperitoneal debridement with postoperative lavage [10]. Using electrocautery, a fenestration is cut around the catheter to permit the insertion of a laparoscope into the cavity. Necrosectomy is then performed with laparoscopic grasping forceps. After necrosectomy, 1–3 large-bore drains were inserted into the cavity and left in place until full resolution of the pancreatic necrosis and then removed [13].

Open necrosectomy may be performed via bilateral subcostal incision or midline incision, drainage through the gastrocolic omentum or through the transverse mesocolon, open packing or continuous lavage, and closed treatment [14]. The main principles of the procedure are adequate first-time debridement and drainage of the lesser sac.

Crucial to any pancreatic debridement is placement of a postpyloric or jejunal feeding tube [12]. Enteral nutrition is the preferred method of feeding. Prospective randomized trials indicate that this type of feeding decreases the incidence of septic complications [15]. Cholecystectomy with T-tube drainage is often difficult

and is performed only if gallstones caused the pancreatitis. If the inflammation is too severe for the safe performance of cholecystectomy, then a cholecystostomy provides drainage and later access for interventional techniques. Gastrostomy, rather than a nasogastric tube, can be used selectively for decompression.

Necrotizing pancreatitis is associated with an 8%–39% rate of death [10]. The mortality rate associated with infected pancreatic necrosis is 100% when the condition is not treated with surgery and approximately 11%–39% when it is treated with surgery [10]. The morbidity rate of operative management is 34%–95%; 30% of patients require an additional surgical procedure, and 20% experience major organ failure [14]. These complex cases test the surgeon's skills to the fullest.

18.2.4 Hemorrhage

The pancreas is intimately associated with the abdominal vascular structures. Penetrating injury to the pancreas alone carries an estimated mortality rate of 5% [16]; however, isolated injury is an exception, and the mortality rate increases to 34% when the injury is associated with vascular injury [17]. Blunt pancreatic injury requires a substantial kinetic force. At times, this force can result in an isolated injury, but it is more often associated with multiple injuries with subsequent risk of hemorrhage.

After major elective procedures for resection, 2%–4% of patients experience hemorrhage. In this situation, either a technical error in hemostasis or an erosion of a vessel resulting from leakage of pancreatic enzymes has occurred [18]. Both situations require prompt operative intervention; when vessel erosion is involved, it is crucial to rule out anastomotic leak as the cause of the hemorrhage.

Hemorrhage resulting from pancreatitis is rare but lethal. With this condition, hemorrhage occurs as the result of erosion of a major vessel or rupture of a pseudoaneurysm, although it is most common after the formation of a pseudocyst. The incidence of hemorrhage associated with pseudocyst is 1%–2.5%, and approximately 10% of patients who experience such hemorrhage will have chronic pancreatitis with angiographic evidence of pseudoaneurysms [18]. The splenic artery or its branches are the most common sites of bleeding [19]. Angiographic embolization is the key tool in the management of this problem; it identifies the source of bleeding in 90% of cases. Resection is exceptionally difficult in the acute situation.

When hemorrhage occurs among patients with chronic pancreatitis, the presentation is usually less dramatic, but is nonetheless extremely serious. If pseudoaneurysm erodes into the pancreatic ductal system, the result is a condition known as "hemosuccus pancreaticus," which causes blood to drain from the ampulla, as shown by endoscopic retrograde cholangiopancreatography (ERCP). In such cases, initial diagnosis and treatment require angiography and embolization.

18.2.5 Biliary or Pancreatic Duct Obstruction/Stricture

Jaundice is a common complication of pancreatic surgery, trauma, or acute pancreatitis. Among patients with chronic pancreatitis, biliary obstruction resulting from intrapancreatic scar tissue causes jaundice and often requires surgical correction by either a local resection of the pancreatic head or a biliary bypass procedure. Occasionally, a patient may have both a pseudocyst and jaundice. Treatment of the pseudocyst relieves extrinsic biliary obstruction, but when chronic scarring causes the biliary obstruction, a drainage procedure is indicated [20].

Persistent jaundice in a patient with acute pancreatitis suggests the need for evaluating the ductal system with ERCP or magnetic resonance cholangiopancreatography (MRCP) so that choledocholithiasis or other causes of mechanical obstruction, such as tumor or stricture, can be ruled out. The technological advances made possible by ERCP and MRCP have largely replaced transhepatic cholangiography [21,22].

After pancreatic resection of the head of the pancreas, jaundice is uncommon and suggests a technical problem with the biliary–enteric anastomosis.

18.2.6 Fistula

Pancreatic fistulas can be internal or external and are the result of unrecognized ductal injury, leakage, or rupture of a pseudocyst. Internal fistulas within the peritoneal cavity are classified as pancreatic ascites. This condition is uncommon but produces peritoneal fluid that is rich in amylase. Fistulas can also communicate to the pleural cavity. Most fistulas are external and track along previous drain sites. The fluid they produce is grey, thin, foul smelling, and rich in amylase. It is relatively innocuous to the skin because the zymogens have not yet been activated. Pancreatic fistulas that coexist with biliary or gastric secretions are more caustic because the zymogens have been activated.

Initial treatment involves controlling external drainage and treating the associated sepsis. ERCP documents the integrity of the ductal system. Generally, when a fistula is persistent, a ductal leak has occurred. Performing a sphincterotomy, placing a pancreatic stent, or both will decrease the time required for healing [23]. If the leak is distal or persistent, a distal resection is required.

After distal resection of the pancreas, the rate of ductal leakage is approximately 20% [24]. As many as 90%

cases of ductal leakage will heal with closed suction drainage [25]. When the output is high or persistent, ERCP provides additional information. Reasons for failure to close include proximal stricture, stone, or plug; epithelialization of the tract; or superinfection of the pancreatic fluid. Leakage of a pancreatic anastomosis occurs in approximately 10% of cases and is controlled with prolonged drainage. With current techniques of percutaneous drainage, parenteral nutrition, sphincterotomy, and pancreatic stent, many of these fistulas heal without the need for operative management.

Administering octreotide can decrease the volume or output of the fistula, but such treatment does not shorten the time required for closing off the fistula [26].

18.2.7 Exocrine Insufficiency

Loss of exocrine function is a common problem among patients with chronic pancreatitis. Forty percent of these patients have some exocrine insufficiency [27]. Consequently, surgical procedures for chronic pancreatitis, especially resection, invariably result in some level of exocrine insufficiency. Patients who undergo these procedures are usually discharged from the hospital with pancreatic enzyme supplementation. Pancreaticoduodenectomy is associated with a 20%–30% risk of symptomatic exocrine insufficiency [28]. This risk is obviously higher after subtotal pancreatectomy and is 100% after total pancreatectomy. Symptoms of exocrine insufficiency are gas bloating, postprandial cramping, and foul, loose stools (steatorrhea). Acute pancreatitis, pancreatic trauma, and distal resection usually do not result in exocrine insufficiency. Fortunately, when this diagnosis is confirmed, the treatment is straightforward. Commercially available enzyme supplements, given orally and titrated to effect, are suggested.

18.2.8 Diabetes Mellitus

Approximately 80%–90% of a normal pancreas can be resected without causing endocrine insufficiency [29]. Diabetes mellitus develops spontaneously among 30% of patients with chronic pancreatitis [30]. In these cases, the pancreas is atrophic and fibrotic; resection of 50% of the organ can result in diabetes. Acute pancreatitis and traumatic pancreatic injury rarely result in endocrine insufficiency.

18.2.9 Debilitating Pain

Many patients experience debilitating pain from chronic pancreatitis. This complication is often treated with longitudinal pancreaticojejunostomy (LPJ). In such cases, the pancreas, after years of chronic inflammation, is fibrotic and scarred. As a result, incision, biopsy, and anastomosis are easier to perform, and the firm gland will hold a suture. During LPJ, the pancreatic duct is opened throughout its entire length. It is crucial to remove all stones and debris within the duct before anastomosis of the jejunum is performed. LPJ is a relatively safe procedure. Leaks are uncommon but can be controlled with closed suction drainage.

Nevertheless, LPJ often fails to achieve 100% pain relief (Table 18.1) [31–34]. Some surgeons believe that the

TABLE 18.1

Results of Classic and Extended Resection for Chronic Pancreatitis

Results	Pylorus-Preserving Pancreatoduodenectomy (Stapleton and Williamson [31]) ($n = 45$)	Partial Pancreatoduodenectomy (Saeger et al. [32]) ($n = 111$)	Longitudinal Pancreaticojejunostomy Combined with Local Pancreatic Head Excision (Frey and Amikura [33]) ($n = 50$)	Duodenum-Preserving Resection of the Head of the Pancreas (Buchler et al. [34]) ($n = 298$)
Pain relief or substantial alleviation (%)	80	79	75	88
Hospital morbidity rate (%)	47	10	22	29
Hospital mortality rate (%)	0	1	0	1
Late mortality rate (%)	7	10	4	9
Endocrine insufficiency rate (%)	37	39	11	2
Exocrine insufficiency rate (%)	80	40	11	—
Increase of body weight (%) >5 kg	100	77	64	81
Occupational rehabilitation rate (%)	—	66	32	63
Follow-up period (years)	2–12	0.5–16.0	2–9	1–22

Source: Jones, R.C., *Am. J. Surg.*, 150(6), 698, 1985; Moore, E.E. et al., *J. Trauma*, 30(11), 1427, 1990; Patton, J.H., Jr. et al., *J. Trauma*, 43(2), 234, 1997; Peitzman, A.B. et al., *J. Trauma*, 26(7), 585, 1986.

clearance of the proximal duct in the head of the gland is important for pain control. Thus, they advocate resection in combination with LPJ [35]. Others believe that the pancreatic head is the pacemaker for the pain associated with this disease.

18.3 Complications of Surgery for Pancreatic Pseudocyst

Once surgical intervention is required for a patient with a persistent pseudocyst, the first decision to be made is whether an endoscopic or an open procedure will be performed. Advancements in endoscopic techniques have lead to successful use of transpapillary stenting and transmural drain placement for the treatment of duct disruptions. With transpapillary stenting, healing is accomplished by covering the damaged duct by bridging the disruption or by traversing the pancreatic sphincter, which converts a high-pressure system to a low-pressure pancreatic duct system from a, allowing preferential flow through the stent/drain. Transmural drainage has further developed to allow internal drainage of most retrogastric and retroduodenal pseudocysts and has evolved to include endoscopic ultrasound as a standard procedure to localize the cyst, identify potential intervening blood vessels, and locate the optimal site for puncture and stent/drain placement. With direct visualization, cautery is used to enter the cyst. One or more stents are placed to create either a cystgastrostomy or a cystduodenostomy [36,37]. Complications occur in 18%–19% patients and include bleeding, leakage, particularly when the pseudocyst is not adherent to the viscera, infection of the collection, stent migration into the pseudocyst, and pneumoperitoneum [37]. Therefore, careful patient selection is crucial.

18.3.1 Cystjejunostomy and Cystgastrostomy

Cystgastrostomy is a useful procedure when retrogastric pseudocysts are adherent to the stomach wall, which they are in most cases. However, approximately 11% of these pseudocysts are not adherent to the stomach wall [6], and in such cases, the better option is to perform a Roux-en-Y cystjejunostomy.

Occasionally, the diagnosis of pseudocyst is erroneous (Figure 18.4). For this reason, a biopsy of the cyst wall should be performed. A true pseudocyst consists of a fibrous wall but no epithelium. If the sample contains epithelium, the lesion is instead a cystic neoplasm, and it must be resected. If examination of the internal aspect of the pseudocyst reveals frond-like papillary projections, a cystic neoplasm must be suspected.

Leakage from the anastomosis may occur but can be prevented by good technique and closed suction drainage. Recurrence rates are less or equal to 5%.

18.3.2 Cystduodenostomy

Cystduodenostomy is infrequently performed to treat pseudocysts; it is indicated only for cysts that are clearly located in the head of the pancreas, where drainage through the posterior duodenal wall provides the

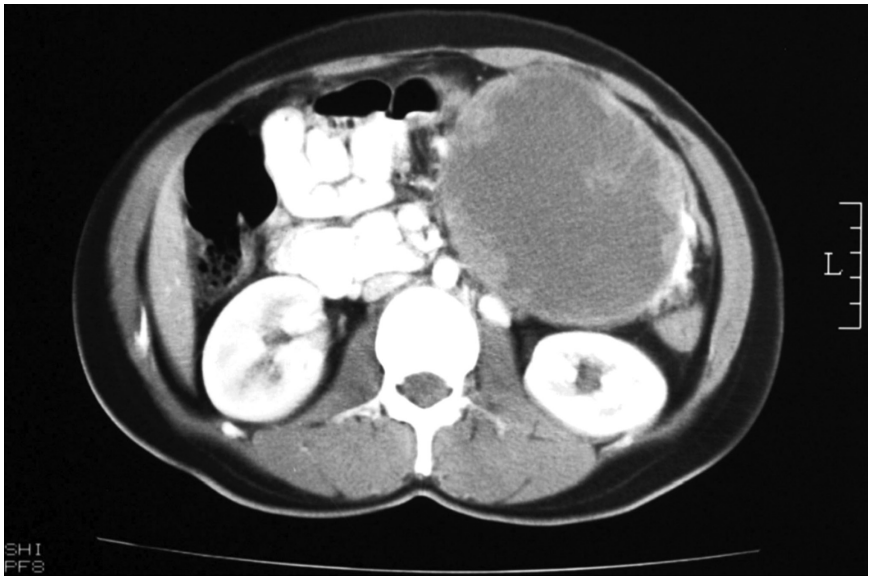


FIGURE 18.4
Papillary cystic tumor in a young female with no previous history of pancreatitis. Notice heterogeneous frond-like projections into the cyst.

best access. This procedure can be performed endoscopically, although cysts larger than 10 cm in diameter should be drained with a cystjejunostomy. When a patient with jaundice experiences a pseudocyst in the head of the pancreas, relieving the pseudocyst may or may not relieve the jaundice, and a biliary bypass procedure may be required. Liberal intraoperative use of cholangiography ensures relief of the obstruction.

Complications of cystduodenostomy include injury to the bile duct, gastrointestinal bleeding, and duodenal leakage. The use of closed suction drainage is prudent in most cases, especially when the duodenal closure is difficult. Injuries to the bile duct can be prevented by carefully identifying the ampulla and placing a stent into that structure.

18.3.3 Resection

Resection is the procedure of choice when distal pancreatic pseudocysts are small and are the result of focal pancreatitis in the tail of the gland. Such resections are difficult because of inflammation and desmoplastic reaction. Preserving the spleen is normally very difficult; the surgeon contemplating distal resection of pseudocysts should plan to perform a splenectomy in conjunction with distal pancreatectomy. The most common intraoperative complication is bleeding from the multiple aneurysmal, dilated arteries, and veins. Careful hemostasis and ligation of the pancreatic duct at the margin of resection are crucial. Another serious complication of resection is postoperative leakage of the pancreatic duct. When distal resection is contemplated, preoperative ERCP is prudent because there may be strictures in the proximal duct.

The rate of leakage in association with distal resection is higher if the proximal duct is obstructed. In such cases, a stent should be placed preoperatively. Should a postoperative pancreatic fistula develop, it will close spontaneously with closed suction drainage. If the fistula persists, ERCP may be helpful in defining proximal obstruction.

18.4 Complications of Surgery for Pancreatic Trauma

Penetrating trauma from either a bullet or a blade can injure the pancreas. The mortality rate directly attributable to pancreatic injury is approximately 5%, but can be as high as 40%–50% with concomitant vascular injuries. Blunt pancreatic trauma usually results from the application of blunt force to the midabdomen. Approximately 70%–90% of patients with pancreatic trauma will have other injuries in the abdomen [38]. Mortality rates associated with blunt trauma range from 10%–30%, depending on associated injuries [39,40] (Table 18.2). Because many of these injuries are found intraoperatively rather than by a preoperative workup, the surgeon must be very familiar with the pancreatic anatomy so that any injury can be exposed and treated. Two important intraoperative questions must be answered: whether pancreatic injury is combined with duodenal injury and whether the pancreatic duct is disrupted. These factors are the key determinants of outcome for patients with pancreatic trauma.

In general, patients with pancreatic trauma have a 30%–40% likelihood of experiencing hemodynamic instability; patients often require operative intervention without a preoperative workup. In cases of penetrating trauma, simply following the trajectory of the missile leads to the diagnosis of a pancreatic injury. In the case of blunt trauma, examination of the pancreas includes complete opening of the lesser sac. If a contusion, hematoma, or swelling is seen, the pancreatic capsule must be opened because complete transection of the pancreatic tissue can occur even if the capsule is intact. Some surgeons hesitate to explore pancreatic hematomas that are not expanding or are not actively hemorrhaging; however, a thorough examination markedly decreases the morbidity rates associated with a missed pancreatic injury.

Intraoperative assessment of the integrity of the pancreatic duct is crucial when an injury to the gland is found. The surgeon must be confident in

TABLE 18.2

Pancreatic Organ Injury Scale

Grade	Type	Injury Description	ICD-9	AIS-90
I	Hematoma	Minor contusion without ductal injury	863.81–863.84	2
	Laceration	Superficial laceration without ductal injury		2
II	Hematoma	Major contusion without ductal injury or tissue loss	863.81–863.84	2
	Laceration	Major laceration without ductal injury or tissue loss		3
III	Laceration	Distal transection or parenchymal injury with ductal injury	863.81–863.84	3
IV	Laceration	Proximal transection or parenchymal injury involving ampulla	863.91	4
V	Laceration	Massive disruption of the pancreatic head	863.91	5

Source: Sohn, T.A. et al., *J. Gastrointest. Surg.*, 4(6), 567, 2000.
Note: ICD-9, International Classification of Disease 9th Revision; AIS-90, Abbreviated Injury Scale.

performing various maneuvers that help determine whether a ductal injury is present. A ductal injury is easier to see when direct inspection of the wound is accompanied by systemic injection of cholecystokinin or secretin to stimulate pancreatic enzyme secretion. Another radiologic technique that can aid in visualizing the pancreatic duct is transcholecystic cholangiography, with concomitant intravenous administration of morphine to cause ampullary contraction. Most surgeons are comfortable with this simple technique, which is a good first choice. Less commonly used is duodenotomy with injection through the ampulla. A more reasonable option is to transect the very distal tip of the pancreas and cannulate the duct distally. The trauma surgeon dealing with pancreatic trauma should be capable of performing all of these techniques.

18.4.1 Injuries to the Left Side of the Pancreas

Pancreatic injuries to the left side of the portal vein, including those to the neck, body, and tail, are more straightforward in their management than are proximal injuries. Usually the duodenum is not injured. In cases of penetrating trauma, gastric and colonic injuries are common. The main intraoperative decision is determining whether the duct is intact. If there is no ductal damage, simple drainage is appropriate. However, if there is any question of a ductal injury with penetrating trauma, a distal resection is necessary. Resections to the left of the portal vein include approximately 60% of the pancreas, and most patients who undergo such procedures will not experience postoperative endocrine or exocrine deficiencies. In a number of series, resection for ductal injury rather than drainage decreased the mortality and morbidity rates [3].

Complications associated with this procedure include pseudocyst formation, pancreatic leak from the resection line, and the rare hemorrhage or abscess. Closed suction drainage controls pancreatic leaks, 90% of which will heal.

18.4.2 Injuries to the Right Side of the Pancreas

Injuries to the head or the right side of the gland range from simple contusions to severe combined duodenal and pancreatic injuries requiring pancreaticoduodenectomy. In truth, a Whipple procedure is rare in trauma surgery because simpler techniques are usually adequate. More commonly, when both the duodenum and the pancreas are injured by penetrating trauma, the duodenal injuries can be managed with standard techniques of either primary pair or diversion, and the pancreatic injury can normally be drained. If the ampulla is available, that is, if the duodenum is already lacerated by the injury, injection for pancreatic duct visualization is an important adjunct. Recent reports advocate drainage of any proximal pancreatic injury, with or without ductal injury, because the magnitude of the resection is so large that delayed or staged operations can be performed should a leak persist [41]. Closed suction drainage, anterior and posterior to the gland, is performed after "kocherization" of the duodenum.

18.4.3 Delayed Presentation of Pancreatic Injuries

Patients who do not undergo emergent surgery may exhibit delayed presentation of pancreatic injury, particularly in cases of blunt trauma. Patients with blunt abdominal trauma, if their condition is stable, are evaluated with ultrasound for the presence of free fluid. If the results of the ultrasound are positive or if the patient experiences persistent tenderness, a CT scan is performed with the sensitivity of detecting pancreatic injury of 80% [42].

Measurements of serum amylase activity are not very effective in diagnosing pancreatic trauma, except in one situation. If the serum amylase activity is normal when measured more than 3 h after injury, the negative predictive value of this result is approximately 95% [43]. An elevation in amylase activity is not a reliable indicator of injury. The findings of CT scans can indicate contusion, fluid, hematoma, or obvious fracture (Figure 18.5). If the patient's condition seems to be improving, the injury is probably a contusion that can be treated by observation. A few such patients may later experience pseudocysts, but these problems can be managed later. If the patient's condition is not improving, the integrity of the duct must be evaluated. In this situation, posttraumatic ERCP is indicated for diagnostic purposes. If the duct is intact, no therapy is needed. If the duct is injured, particularly distally, surgical intervention is advised and should include distal resection. Pancreatic stenting is not advised for the acute trauma patient, although some case reports have suggested limited success [44].

18.4.4 Surgical Complications

The complications associated with all of these procedures are similar to those associated with elective resection. (See above) The most severe complication is operating on a patient with trauma to the pancreas but failing to recognize the injury. Wide drainage should be instituted for all patients with pancreatic injuries, and appropriate resection should be performed for those with ductal injury. Postoperative problems include bleeding with hematoma formation, pseudocyst, and the rare abscess.

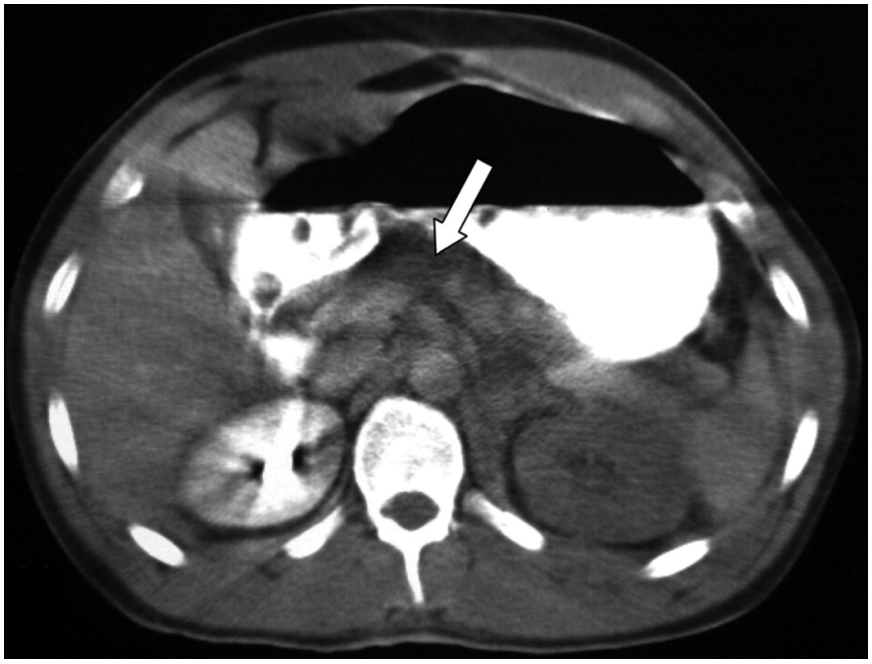


FIGURE 18.5
Pancreatic neck transection after blunt trauma (arrow). Also, the left kidney devascularized, with no contrast.

18.5 Complications of Surgery for Cancer

18.5.1 Pancreatic Biopsy

Currently, pancreatic tissue obtained by biopsy can be examined with either radiologic or surgical techniques. Radiologic procedures include fine-needle aspiration (FNA). Complications associated with this technique are uncommon. Biopsy material can also be obtained by endoscopic ultrasonography. Intraoperative techniques used to obtain pancreatic tissue include laparoscopic or open surgical biopsy, either directly into the pancreas by FNA or a core needle, or via a transduodenal route with a true-cut needle. The duodenum is kocherized to lift the head of the pancreas, and the 16 g true-cut needle is passed through the second portion of the duodenum into the pancreas. This technique allows any leakage from the pancreatic biopsy site to go into the duodenum; a single suture is placed at the site of duodenal penetration. When the lesion is in the body or tail of the pancreas, a direct biopsy should be performed. Wedge biopsies should be avoided unless the lesion can be completely enucleated. Careful attention to the anatomy of the duct is necessary if serious ductal injury is to be avoided.

Complications after a biopsy are rare. The most feared complication of pancreatic biopsy is pancreatitis [45], which occurs in 1% of cases and can, at times, be severe. As in the treatment of acute pancreatitis, supportive care should be sufficient.

18.5.2 Distal Resection

Distal resections for pancreatic cancer are generally uncommon because tumors in the body and the tail of pancreas are usually found too late to allow curative resection. However, in these rare cases, distal resection with a good margin is the appropriate operation when possible. Tumors other than adenocarcinomas, such as slowly growing cystic neoplasms or neuroendocrine tumors are good candidates for this procedure. Within the last 10–15 years, there have been developments in laparoscopic surgery with increased expertise and manufacturing new surgical devices that have allowed the progression of laparoscopic pancreatic surgery. A number of series have demonstrated good technical success of minimally invasive distal pancreatectomy (Table 18.3) [46]. Distal pancreatectomy for benign or low-grade malignant tumors represent the majority of pancreatic resections performed laparoscopically [46]. Laparoscopic distal pancreatectomy is characterized by improved postoperative short-term outcomes compared to open surgery. Resection is typically performed using 3–5 (5-mm) ports and a supraumbilical 5- to 12-mm port.

When performing open distal pancreatectomy, careful ligation of the main pancreatic duct is important for preventing leaks from the pancreatic duct. Several techniques are available for closing the pancreatic stump, including horizontal mattress sutures and staplers. Whichever method is chosen, independent ligation of the main pancreatic duct is crucial. Operations that attempt

TABLE 18.3

Series Demonstrating Good Technical Success of Minimally Invasive Distal Pancreatectomy

Author/Year	*n*	DP-AS	DP-WOS	OR Time (min)	EBL (mL)	Conversion (%)	Mortality (%)	Morbidity (%)	Pancreatic Fistula (%)	LOS (Days)
Mabrut (2005)	98	24	58	95 (90–200)^{DPAS} 200 (65–400)^{DPWOS}	NR	10	0	53	16	7
Fernandez Cruz (2007)	82	30	52	NR	NR	7	0	20	9	7
Kim (2008)	93	56	38	195 (82–453)	NR	0	0	24.7	8.6	10 (5–36)
Kooby (2008)	159	109	50	233 ± 39	371 ± 526	13	0	40	26	5.9 ± 3.7
Weber (2009)	219	NR	NR	245 ± 108	NR	10	0	39	23	5.6 ± 3.3
Rosok (2010)	117	80	37	185.5 (100–690)^{DPAS} 210 (88–237)^{DPWOS}	200^{DPAS} 100^{DPWOS}	7.5^{DPAS} 0^{DPWOS}	NR	NR	11^{DPAS} 8^{DPWOS}	5 (1–35)

Source: Addeo, P. and Giulianotti, P.C., *Miverva Chir*., 65(6), 655, 2010.
Note: DPAS, distal pancreatectomy and splenectomy; DPWOS, distal pancreatectomy without splenectomy.

splenic preservation are more time-consuming and more meticulous than distal resection because of the need for dissection of the small venous tributaries that come off the splenic vein. Oncologically, for adenocarcinoma, the procedures of choice are distal pancreatectomy and splenectomy. Complications include pancreatic leakage (which can be controlled with closed suction drainage), bleeding, abscess, or pseudocyst formation.

18.5.3 Proximal Resection

A number of techniques may be used for resecting cancers of the pancreatic head, including the standard Whipple procedure. The proximal resection has changed rapidly during the past 15–20 years; most of the improvement has occurred in perioperative, operative, and postoperative management. The mortality rate associated with this procedure, which was once 20%–30%, is now routinely 2%–5% for experienced surgeons [47]. The morbidity rate, however, is still approximately 30%.

18.5.4 Preoperative Considerations

Patients who are to undergo a large procedure such as cancer resection must be in good physiologic condition at the time of surgery. The patient's nutritional status is also important. The evidence indicates that preoperative treatment with octreotide does not decrease the incidence of postoperative pancreatic fistula. Preoperative biliary decompression neither decreases nor increases the rate of serious postoperative complications [48].

18.5.5 Intraoperative Therapy and Pitfalls

The details of pancreaticoduodenectomy will not be discussed here, but several pitfalls associated with this surgical procedure will be highlighted.

18.5.6 Inadvertent Ligation of Hepatic Blood Vessels

Hepatoduodenal dissection involves dissection of the hepatic artery from the common bile duct so that the posterior portal vein can be exposed. Such an exposure is achieved by dividing and ligating the gastroduodenal artery. Inadvertent ligation of the proper or common hepatic artery is lethal. Avoiding this complication requires dissecting the gastroduodenal artery to its origin. If the hepatic artery is transected, reanastomosis with good vascular technique is mandatory. In approximately 10%–15% of patients, a right hepatic artery may originate from the SMA; this artery is seen in the posterior aspect of the portal triad, tracking posterior to the portal vein. This artery must be preserved.

18.5.7 Injury to the Superior Mesenteric Vein

The superior mesenteric vein (SMV) is usually dissected from below the pancreatic neck. Injury to this vein during dissection can be difficult. Should such an injury occur, bimanual pressure should be applied while the pancreatic neck is divided so that the bleeding from the SMV below can be controlled.

18.5.8 Leaks from the Pancreatic Anastomosis

The most difficult and problematic anastomosis associated with pancreaticoduodenectomy is reconstructing the cut ends of the pancreas and the jejunum. Current standard is the "duct to mucosa" technique. With good technique and fibrotic gland in experienced hands, the leak rate is less than 10%. If the duct is small or gland is soft, then a good option is to perform a pancreaticogastrostomy by invaginating the pancreatic stump into the back of the stomach.

18.5.9 Postoperative Complications

A number of large series demonstrate substantial improvement in the mortality and morbidity rates associated with pancreatic resection. Two large series report a mortality rate of 2% and a morbidity rate of 30% (Table 18.4) [47,49–51].

The most feared complication of this procedure is pancreatic fistula resulting from leakage at the anastomosis. This complication occurs in approximately 5%–15% of cases, but can often be controlled with closed suction drainage. The problem is more difficult to treat if both enteric fluid and pancreatic fluid are draining; in such cases, a larger disruption of the pancreaticojejunostomy should be suspected, and a repeated operation is indicated. Additionally, if the fluid from a pancreatic fistula becomes bloody after initially being clear, a second operation should be strongly considered because this finding suggests inflammation and erosion of surrounding vessels. In two large series, the rate of reoperation was approximately 4%; the second procedure was performed largely because of bleeding.

Delayed gastric emptying (DGE) is a nuisance problem that occurs in approximately 15%–30% of cases [49] and is the most commonly observed complication. Routinely administering erythromycin postoperatively reduces the incidence of DGE from 30%–19% [52]. Even if gastric atony persists for more than 3 weeks, reoperation is not recommended until a full 6 weeks have passed without improvement. Postoperative upper endoscopy shows a patent anastomosis. The problem is related to functional gastroparesis caused by disruption of the gastric pacemaker. When a patient requires delayed reoperation because of persistently poor gastric emptying, the gastrojejunostomy should be revised with a larger resection of the stomach and a Roux-en-Y reconstruction.

Another complication of pancreatic resection is bile leakage, which usually resolves within 48 h postoperatively and is purely a technical problem. Cholangitis occurs in a small percentage of cases; wound infection and abdominal abscess occur in 3%–5% of cases. The average length of stay for a large series of patients undergoing pancreatic resection was 10–15 days.

TABLE 18.4

Complications of Pancreaticoduodenectomy

	Cameron et al. [50] ($n = 564$)	Warshaw et al. [51] ($n = 489$)
Perioperative mortality	2.3%	1%
Overall complications	31%	37%
Specific complications		
Reoperation	3%	2%
Delayed gastric emptying	14%	12%
Cholangitis	3%	0.6%
Bile leak	2%	0.8%
Wound infection	7%	5.1%
Pancreatic fistula	5%	11%
Intra-abdominal abscess	3%	1.6%
Pneumonia	1%	1.0%
Pancreatitis	1%	—
Postoperative length of stay		
Mean ± SE	14.0 ± 0.4 days	9.5 ± 0.4 days
Median	11 days	8 days

Source: Balcom, J.H. IV et al., *Arch Surg*., 136(4), 391, 2001; Sohn, T.A. et al., *J Gastrointest Surg*., 4(6), 567, 2000.

18.5.10 Total Pancreatectomy

Total pancreatectomy is not commonly performed for adenocarcinoma, but patients with positive intraoperative pancreatic margins after a Whipple procedure may be candidates for such an operation. The most common indication for total pancreatectomy is probably intraductal papillary mucinous tumors or chronic pain in combination with auto islet cell transplantation.

Total pancreatectomy proceeds as with the Whipple procedure, but also includes resection of the spleen and the distal tail of the pancreas. Reconstruction includes a biliary jejunal anastomosis and a gastrojejunostomy or a duodenojejunostomy. The biggest difference between a total pancreatectomy and a Whipple procedure is that total pancreatectomy avoids the need for a pancreatic anastomosis and thus also avoids many of the postoperative complications associated with the Whipple procedure. However, the patient will now require insulin and pancreatic enzyme substitution unless autotransplanted. DGE complicates this procedure, as do biliary leaks, cholangitis, bleeding, sepsis, and wound infection. Pancreatic fistula is not an issue with pancreatectomy.

The most serious postoperative complications are exocrine and endocrine insufficiency. Exocrine insufficiency is readily controlled with pancreatic enzyme supplementation, but control of the endocrine problem is somewhat more difficult. With good compliance and some of the newer insulin pump technologies, most issues related to diabetes are controllable after total pancreatectomy.

Complications

Trauma	Pancreatitis	General Surgery	Trauma
Pancreatitis	—	1% after pancreatic biopsy	4.3%–23.1% [1]
Pancreatic fistula		30% after necrosectomy [2]	10%–20% with isolated pancreatic trauma 35% with associated duodenal trauma [3]

Trauma	Pancreatitis	General Surgery	Trauma
Pancreatic abscess	2%–3%	10% [4]	34% [1]
Pancreatic necrosis	10%	2%–5%	Rare
Pancreatic pseudocyst	10%–20%	5% after Lap Chole for gallstone pancreatitis	1.9%–22% [1]
Hemorrhage	1%–2.5%	2%–4%	2.8%–8.5% [1]
Exocrine insufficiency	—	10%–20% with pancreaticoduodenectomy	
Diabetes mellitus	If patient is already diabetic, it will worsen; if not, then usually a rare sequelae		

Avoiding Complications

Pancreatic fistula	Independent ligation of the main pancreatic duct when closing the pancreatic stump, although stapling techniques are improving as regards distal resections. Drain when in doubt.
Anastomotic leak	Trauma—use drain. Distal resection 20% leak—use drain. Proximal resection depends on quality of anastomosis. Drain when in doubt. Duct-to-mucosa anastomosis for proximal resections. Pancreaticogastric anastomosis if pancreas is soft.
Pancreatic abscess	Better prognosis than necrosis. Percutaneous drain acceptable. Antibiotics required.
Pancreatic necrosis	Aggressive supportive care for patients with pancreatitis. Recognize 10% can fall into the risk group for severe acute pancreatitis.

References

1. Recinos G, DuBose JJ, Teixeira PG et al. Local complications following pancreatic trauma. *Injury* 2009; 40:516–520.
2. Sarr MG, Nagorney DM, Mucha P Jr, Farnell MB, Johnson CD. Acute necrotizing pancreatitis: Management by planned, staged pancreatic necrosectomy/debridement and delayed primary wound closure over drains. *Br J Surg* 1991; 78(5):576–581.
3. Jurkovich GJ, Carrico CJ. Pancreatic trauma. *Surg Clin North Am* 1990; 70(3):575–593.

   Excellent review of traumatic pancreatic injury with classic articles referenced along with scoring systems
4. Warshaw AL. Pancreatic necrosis: To debride or not to debride-that is the question. *Ann Surg* 2000; 232(5): 627–629.
5. Acute Pancreatitis Classification Working Group. Revision of the Atlanta classification of acute pancreatitis. 2008. http://www.pancreasclub.com/resources/AtlantaClassification.pdf (accessed February 2, 2013).

   Updated revisions to the original Atlanta Symposium from 1990. This manuscript represents current nomenclature for all aspects of pancreatitis and serves as a consensus statement
6. Bradley EL, Clements JL Jr, Gonzales AC. The natural history of pancreatic pseudocysts: A unified concept of management. *Am J Surg* 1979; 137(1):135–141.
7. Bassi C, Vesentini S, Nifosi F et al. Pancreatic abscess and other pus-harboring collections related to pancreatitis: A review of 108 cases. *World J Surg* 1990; 14(4):505–512.
8. Howard TJ, Wiebke EA, Mogavero G et al. Classification and treatment of local septic complications in acute pancreatitis. *Am J Surg* 1995; 170(1):44–50.
9. Bakker OJ, van Santvoort HC, van Brunschot S et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: A randomized trial. *JAMA* March 14, 2012; 307(10):1053–1061.
10. van Santvoort HC, Besselink MG, Bakker OJ et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010; 362:1491–1502.

    The paper validates a less aggressive but still surgical technique for debriding pancreatic necrosis.
11. Uhl W, Isenmann R, Buchler MW. Infections complicating pancreatitis: Diagnosing, treating, preventing. *New Horiz* 1998; 6(2 suppl):S72–S79.
12. Bradley EL III, Allen K. A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. *Am J Surg* 1991; 161(1):19–25.
13. Bausch D, Wellner U, Kahl S et al. Minimally invasive operations for acute necrotizing pancreatitis: Comparison of minimally invasive retroperitoneal necrosectomy with endoscopic transgastric necrosectomy. *Surgery* 2012; 152(3):S128–S134.
14. Beger HG, Isenmann R. Surgical management of necrotizing pancreatitis. *Surg Clin North Am* 1999; 79(4):783–800.
15. Kalfarentzos F, Kehagias N, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: Results of a randomized prospective trial. *Br J Surg* 1997; 84(12): 1665–1669.
16. Wilson RH, Moorehead RJ. Current management of trauma to the pancreas. *Br J Surg* 1991; 78(10): 1196–1202.
17. Jordan GL Jr. Pancreatic resection for pancreatic cancer. *Surg Clin North Am* 1989; 69(3):569–597.
18. Waltman AC, Luers PR, Athanasoulis CA, Warshaw AL. Massive arterial hemorrhage in patients with pancreatitis. Complementary roles of surgery and transcatheter occlusive techniques. *Arch Surg* 1986; 121(4): 439–443.
19. Boudghene F, L'Hermine C, Bigot JM. Arterial complications of pancreatitis: Diagnostic and therapeutic aspects in 104 cases. *J Vasc Interv Radiol* 1993; 4(4):551–558.
20. Warshaw AL, Rattner DW. Fact and fallacies of common bile duct obstruction by pancreatic pseudocysts. *Ann Surg* 1980; 192(1):33–37.
21. Cotton PB. ERCP. *Gut* 1977; 18(4):316–341.
22. Reinhold C, Bret PM. MR cholangiopancreatography. *Abdom Imaging* 1996; 21(2):105–116.
23. Kozarek RA. Endoscopic therapy of complete and partial pancreatic duct disruptions. *Gastrointest Endosc Clin N Am* 1998; 8(1):39–53.

24. Martin FM, Rossi RL, Munson JL, ReMine SG, Braasch JW. Management of pancreatic fistulas. *Arch Surg* 1989; 124(5):571–573.
25. Pederzoli P, Bassi C, Vesentini S, eds. *Pancreatic Fistulas*. New York: Springer, 1992.
26. Li-Ling J, Irving M. Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistula: A systematic review of randomized controlled trials. *Br J Surg* 2001; 88(2):190–199.
27. Lankisch PG, Lohr-Happe A, Otto J, Creutzfeldt W. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. *Digestion* 1993; 54(3):148–155.
28. Doty JE, Fink AS, Meyer JH. Alterations in digestive function caused by pancreatic disease. *Surg Clin North Am* 1989; 69(3):447–465.
29. Cogbill TH, Moore EE, Morris JA Jr et al. Distal pancreatectomy for trauma: A multicenter experience. *J Trauma* 1991; 31(12):1600–1606.
30. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994; 107(5):1481–1487.
31. Stapleton GN, Williamson RC. Proximal pancreatoduodenectomy for chronic pancreatitis. *Br J Surg* 1996; 83(10):1433–1440.
32. Saeger HD, Schwall G, Trede M. Standard Whipple in pancreatitis. In: Beger HG, Buchler M, Malfertheiner P, eds. *Standards in Pancreatic Surgery*. New York: Springer, 1993, pp. 385–391.
33. Frey CF, Amikura K. Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. *Ann Surg* 1994; 220(4):492–507.
34. Buchler MW, Friess H, Bittner R et al. Duodenum-preserving pancreatic head resection: Long-term results. *J Gastrointest Surg* 1997; 1(1):13–19.
35. Frey CF, Smith GJ. Description and rationale of a new operation for chronic pancreatitis. *Pancreas* 1987; 2(6):701–707.
36. Bhasin DK, Rana SS, Rao C, Gupta R, Verma GR, Kang M, Nagi B, Singh K. Endoscopic management of pancreatic injury due to abdominal trauma. *JOP* March 10, 2012; 13(2):187–192.
37. Kahaleh V, Shami1 M, Conaway R et al. Endoscopic ultrasound drainage of pancreatic pseudocyst: A prospective comparison with conventional endoscopic drainage. *Endoscopy* 2006; 38(4): 355–359.
38. Stone HH, Fabian TC, Satiani B, Turkleson ML. Experiences in the management of pancreatic trauma. *J Trauma* 1981; 21(4):257–262.
39. Jones RC. Management of pancreatic trauma. *Am J Surg* 1985; 150(6):698–704.
40. Moore EE, Cogbill TH, Malangoni MA et al. Organ injury scaling, II: Pancreas, duodenum, small bowel, colon, and rectum. *J Trauma* 1990; 30(11): 1427–1429.
41. Patton JH Jr, Lyden SP, Croce MA, Pritchard FE, Minard G, Kudsk KA, Fabian TC. Pancreatic trauma: A simplified management guideline. *J Trauma* 1997; 43(2):234–241.
42. Peitzman AB, Makaraoun MS, Slasky BS, Ritter P. Prosepective study of computed tomography in initial management of blunt abdominal trauma. *J Trauma* 1986; 26(7):585–592.
43. Bouwman DL, Weaver DW, Walt AJ. Serum amylase and its isoenzymes: A clarification of their implications in trauma. *J Trauma* 1984; 24(7):573–578.
44. Kim HS, Lee DK, Kim IW et al. The role of endoscopic retrograde pancreatography in the treatment of traumatic pancreatic duct injury. *Gastrointest Endosc* 2001; 54(1):49–55.
45. Buice WS, Walker LG Jr. The role of intra-operative biopsy in the treatment of resectable neoplasms of the pancreas and periampullary region. *Am Surg* 1989; 55(5):307–310.
46. Addeo P, Giulianotti PC. Update on laparoscopic pancreatectomy in 2010. *Miverva Chir*. December 2010; 65(6):655–666.
47. Balcom JH IV, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections: Changing indications, older patients, and decreasing length of hospitalization. *Arch Surg* 2001; 136(4):391–398.
    Great review of large series of pancreatic resections and the outcomes, morbidities etc.
48. Pisters PW, Hudec WA, Hess KR et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001; 234(1):47–55.
49. Sohn TA, Yeo CJ, Cameron JL et al. Resected adenocarcinoma of the pancreas-616 patients: Results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000; 4(6):567–579.
50. Balcom JH IV, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections: Changing indications, older patients, and decreasing length of hospitalization. *Arch Surg*. 2001;136(4):391–398.
51. Sohn TA, Yeo CJ, Cameron JL et al. Resected adenocarcinoma of the pancreas-616 patients: Results, outcomes, and prognostic indicators. *J Gastrointest Surg*. 2000;4(6):567–579.
52. Yeo CJ, Barry MK, Sauter PK et al. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. *Ann Surg* 1993; 218(3):229–238.

19

Complications of Splenic Surgery and Splenic Injury

David J. Ebler and Louis R. Pizano

CONTENTS

19.1 Categories of Splenic Surgery

As surgical procedures, involving the spleen have become more commonplace, two basic categories of splenic disease have emerged. These are splenic diseases that lead to elective surgery and splenic injuries. Splenic diseases, which require elective procedures, include hematologic disorders and malignancies. Injuries to the spleen that can lead to emergent surgery can be blunt, penetrating, or iatrogenic.

19.2 Complications of Elective Surgery

An accurate determination of the morbidity and mortality rates associated with elective splenic surgery is difficult because of several factors. With laparoscopic splenic surgery becoming more prevalent, there is a paucity of larger series involving open splenectomies over the past several decades. Advances in diagnosis, surgical technique, and perioperative care are likely to have decreased the complication rates reported in some of the earlier studies [1]. Currently, with greater reliance on radiological staging and advances in chemotherapy, staging laparotomy has almost been completely eliminated as an indication for splenectomy [1]. Therefore, older series, which included splenectomies done on young, immunologically healthy patients with Hodgkin's disease, may have reported a complication rate that is lower than those seen in current practice. This may be because this patient population should be expected to have a lower rate of complications [1].

The fact that there remain a large number of hematologic indications for splenectomy further compounds the difficulty of assessing the morbidity rates of elective splenic surgery. Within the larger series, investigating both open and laparoscopic elective splenectomies, there are multiple disorders included as indications for elective splenectomy [1,2]. There are no series, with a single indication, that are large enough to elucidate specific complications that are associated with a specific indication. When the indications for elective splenectomy are grouped into larger categories, splenectomies for hematologic malignancies are typically associated with overall higher rates of complications and have been reported as high as 52% [3]. Myeloproliferative disorders are among the malignancies with the highest

complication rates. The rate of complications after elective splenectomy for these disorders has been reported to be as high as 58% over the past two decades [1,4]. This is not surprising since these patients have a prolonged course of disease, increased susceptibility to infection, thrombosis, and hemorrhage, as well as severe enlargement of their spleens. The complication rate after splenectomy for lymphoproliferative disorders has been reported around 25% [4]. Elective splenectomy for benign diseases, such as idiopathic thrombocytopenic purpura (ITP), is associated with a complication rate of around 15% [2,4].

19.2.1 Laparoscopic Splenectomy

Laparoscopic splenectomy was first reported by Delaitre and Maignien [5]. Since this initial report, there have been many advances in laparoscopic techniques and equipment. Laparoscopic surgery can be performed safely and effectively, with low rates of mortality and morbidity. It has now become the "gold standard" for elective splenectomy in most circumstances at many centers [6,7]. The increased prevalence of the laparoscopic approach has changed both the complication rates and the specific morbidity rates associated with elective splenectomy. Some complications, such as physiologic effects of insufflation and trocar injuries, arise from laparoscopy in general rather than from its application specifically to laparoscopic splenectomy. It is the goal of this chapter to address only complications related to laparoscopic splenectomy and not laparoscopy in general.

When laparoscopic and open splenectomy are directly compared for hematologic disorders, it is almost invariably shown that the laparoscopic approach is associated with longer operative times [8–10]. Laparoscopic splenectomy, however, has been consistently associated with shorter hospital stays and a more rapid return to a diet [8–10]. Some reports have suggested a lower operative blood loss with laparoscopic splenectomy, but this trend is equivocal, even in the setting of splenomegaly [7,8,10,11].

Even though laparoscopic splenectomy showed distinct advantages regarding hospital length of stay and return to a diet, it is not clear whether it is associated with an overall lower rate of complications than open splenectomy [9,11]. However, two recent meta-analyses have shown laparoscopic splenectomy to be adventitious over open splenectomy with regard to overall complication rate (15% vs. 26.6%, respectively). The largest component of this reduction was due to a lower rate of pulmonary complications followed by lower rates of incisional infections [8,10]. Again, it is difficult to determine how many deaths were directly related to the splenectomy or from the underlying disease process.

19.3 Complications of Splenic Injury

The treatment of splenic injuries has changed greatly over the past several decades. Despite this, the mortality associated with splenic rupture, especially when caused by blunt trauma, ranges from 3% to 37% even in the modern era of advanced imaging methods and the availability of multiple therapeutic interventions [12]. These rates of mortality are likely skewed due to concomitant injuries, and it is often difficult to determine if a patient's death was directly attributable to a splenic injury alone. Therefore, mortality may be related more closely to the severity of injury than to the approach of treatment.

The various treatment options are associated with their own unique complications. When deciding on a course of care, the surgeon must understand the individual risks associated with each of the three types of general treatment options.

19.3.1 Splenectomy

For the majority of the twentieth century, splenectomy was the treatment of choice for all splenic injuries. In recent decades, the prevalence of splenectomy after splenic injury has decreased. Therefore, the majority of contemporary data regarding the complications associated with this approach were gathered in the 1970s.

Infectious complications are common after splenectomy for trauma. Patients who undergo a splenectomy in the setting of traumatic injury experience a postoperative intra-abdominal abscess rate between 6% and 13% [13–15]. The overall infection rate among such patients ranges from 30% to 45% as compared to 9% to 30% rate of infection for those who do not undergo splenectomy [13–15]. Even when controlled for severity of injury, patients undergoing splenectomy experience higher rates of infectious complications (30%–45%) than those who have splenic injury and do not undergo splenectomy (9%–30%) [13–15].

19.3.2 Splenorrhaphy

Splenorrhaphy provides many benefits over splenectomy. It prevents the increased risk of overwhelming postsplenectomy infection (OPSI) that is seen after splenectomy. Furthermore, splenic repair has generally been found to be associated with lower rates of morbidity than those seen with splenectomy with trauma. In fact, the overall complication rates seen with splenectomy range from 5% to 12%, which is similar to those associated with laparotomy for trauma in general [16–18]. Most complications reported with splenorrhaphy, such as pneumonia, atelectasis, ileus, and organ space surgical

site infections, could be attributed to laparotomy rather than the splenic repair itself.

One potential complication, which can be anticipated after splenorrhaphy, is a failure of the repair, leading to renewed bleeding. In most reports, however, the failure of the repair is noted at the time of the initial surgery. When this occurs, the procedure can be converted to a splenectomy. Rates of renewed bleeding range from 0% to 3% [17,18].

19.3.3 Nonoperative Management

Even though it has been shown that splenorrhaphy can be safely accomplished in selected patients, over the past several decades, selective nonoperative management (SNOM) has almost completely replaced emergent splenectomy and splenorrhaphy in hemodynamically stable patients [19,20]. The use of SNOM has become popular because it can avoid all the complications associated with laparotomy as well as those associated with splenectomy. Additional benefits include fewer blood transfusions, shorter hospital stays, and lower surgical costs [21].

Recommendations concerning the value of serial postadmission diagnostic imaging, selective angiography, and imaging studies in the setting of long-term follow-up remain unclear [22]. The majority of patients who fail SNOM do so within the first 72 h following admission [20]. However, delayed splenic rupture has been reported in patients up to several months after initial injury [23]. These occurrences are particularly worrisome because most patients with isolated splenic trauma will have been discharged from the hospital by this time. Zarzaur et al. published an analysis of readmissions after SNOM of splenic injury. They showed a 1.4% rate of readmission for splenectomy within 180 days post discharge [24]. This suggests a need for improved outpatient management and follow-up.

Despite the proven benefits and safety of SNOM, failure of SNOM is not without its consequences and can be a life-threatening event with increased expenditure of resources and length of stay. Spontaneous hemorrhage, missed intra-abdominal injury, delayed splenic rupture, and development of a splenic artery pseudoaneurysm have been cited as causes of SNOM failure. It has also been postulated that failure is related to delayed hemorrhage from splenic artery injuries that subsequently bleed after initial imaging, due to lysis of clot at the site of injuries.

19.4 Infection and Mortality

King and Shumacker first described fulminant postsplenectomy sepsis in 1952 [25]. Since then, the term overwhelming postsplenectomy infection, or OPSI, [26] has been used to describe fulminant sepsis, meningitis, or pneumonia mainly caused by *Streptococcus pneumonia, Neisseria meningitidis,* and *Haemophilus influenzae* type b. These bacteria are encapsulated and are therefore poorly opsonized [27]. This type of infection is known for its rapid onset of symptoms and can produce hypotension and shock within a matter of hours after onset. The risk of mortality from OPSI has been reported as high as 40%–50% in those who develop invasive infections after splenectomy. The risk of sepsis and mortality are strongly associated with the indication for which the splenectomy was done. Thalassemia major has been associated with the highest risk of serious infection after splenectomy at 8.2%, whereas splenectomy for trauma and idiopathic thrombocytopenic purpura have lower rates of infection (2.2% and 2.1%, respectively) [28].

Schwartz et al. conducted a retrospective review of 193 patients who underwent splenectomy over a 25-year period. Forty-eight (24%) of the splenectomies were done for trauma, 36 (19%) were incidental to abdominal surgery being done for malignancy, 53 (27%) were incidental to other abdominal procedures, 46 (24%) were for hematologic diseases including lymphoma, and 10 (5%) were for primary splenic disorders. Despite a large number of patients having severe comorbidities, they only documented two cases of fulminant sepsis after a total of 1090 person-years of follow-up. This resulted in a cumulative incidence of fulminant sepsis of 0.18 per 100 person-years or one case for every 545 patient-years of observation. Only one patient died as a result of fulminant sepsis. The overall incidence of any type of serious infection following splenectomy was 7.16 per 100 person-years. The patients who had a splenectomy with abdominal surgery for malignancy were five times more likely to have a serious infection than those who have a splenectomy for trauma. The mortality rate with this one death was only 0.9 per 1000 patient-years of follow-up. Interestingly, even in the absence of sepsis, they observed an impaired survival rate of 80% in those that underwent a splenectomy compared with an expected 98% of people in a comparable cohort from the general population. This could be due to the underlying diseases of the patients since survival varied least among trauma patients and was great among patients who underwent splenectomy at the time of operation for an abdominal malignancy [29].

Bisharat et al., looking at the English language literature over a 30-year period from 1966 to 1996, conducted a retrospective review of 28 studies including 6942 splenectomized patients. Two hundred and nine (3%) of those patients developed an invasive infection and 106 died, resulting in a mortality rate of 1.5%. The mean time interval between splenectomy and infection was 22.6 months. ITP and trauma patients had the lowest

risk of infection (2.1% and 2.3%). These patients also had the lowest risk of mortality, which was just over 1% for both groups. The patients with the highest risk of infection (12% and 9%) as well as the highest all-cause mortality were those with thalassemia major and sickle cell disease, respectively [28]. However, it should be noted that sickle cell disease results in complex multiorgan manifestations that have a major impact on mortality [30]. Patients with sickle cell disease are functionally asplenic, secondary to autoinfarction, and are particularly prone to develop infections. Because of this, it is not clear if splenectomy increases the risk of infection and death [31].

A population-based study conducted in Denmark looked at the risk of bacteremia after splenectomy. The study examined 538 patients who underwent splenectomy for various reasons. This study estimated the crude risk of bacteremia following splenectomy to be 2.3 per 100 person-years at risk. The predominant cause of bacteremia was enteric rods. Encapsulated bacteria were not found to have caused any cases of bacteremia in patients greater than 30 days postsplenectomy. Even though only 60% of the patients had received the pneumococcal vaccination, only one case of early bacteremia, due to an encapsulated species (in this case *S. pneumonia*), was reported [32].

An analysis of the Danish National Patient Registry examined the risk of infection in 3812 patients who underwent splenectomy between 1996 and 2005. The infection risk of these postsplenectomy patients was compared to three cohorts. The comparison cohorts were matched for age and sex and included randomly chosen members of the general population, postappendectomy patients, and nonsplenectomy patients with the same underlying medical condition. Of the 3812 postsplenectomy patients, 955 (25.1%) had at least one hospital contact for infection during a median follow-up of 2.2 years versus 10.8% and 5.1 years in the general population comparison cohort. All subgroups of postsplenectomy patients were at higher risk of infection than both postappendectomy patients and the general population. The greatest risk of infection was seen within the first 90 days after splenectomy. During this time period, the prevalence of infection among the postsplenectomy patients was 10.2% compared to 0.6% among the general population cohort (adjusted relative risk [RR] = 18.1). The adjusted RR progressively declined to 4.6 at 3–12 months and 2.5 after the 1st year [33]. The subgroups that were at greatest risk compared to the general population were those that underwent splenectomy for splenomegaly or splenic disease (RR = 118), nonspecific thrombocytopenia (RR = 46.6), and hereditary hemolytic anemias (RR = 32). Patients who underwent splenectomy for ITP (RR = 14.8) and trauma (RR = 21.2) had the lowest risk of infection when compared to the general population. In general, the odds of a 90-day infection were two- to three-fold higher when comparing postsplenectomy patients with matched nontraumatic nonsplenectomy patients in the matched-indication cohorts. Patients who underwent a splenectomy for trauma had a similar risk to their matched-indication cohorts. This study helps clearly separate the negative effects of the underlying comorbidities from effects of splenectomy itself on the risk of infection and demonstrated that the magnitude of the infection risk in patients undergoing splenectomy mainly depends on the underlying disease and the time interval after splenectomy [33].

Certain disease processes carry an inherent baseline risk of infection even before splenectomy. The increased risk of infection and death, in patients with sickle cell disease, is more likely attributable to the disease itself rather than splenectomy [31]. These patients are usually in a hyposplenic or asplenic state prior to surgery with dysfunctional phagocytic activity and defective activation of the alternate complement pathway [28]. Patients with thalassemia major have a defective activation of their alternate complement pathway and low immunoglobulin levels. Splenectomy increases the risk of infection in these patients [28].

With regard to mortality, a population study, including 3812 cases, conducted by Yong et al., revealed that when compared to the general population, patients who underwent splenectomy had an overall adjusted RR of death = 33.6 during the first 90 days after splenectomy. The patients at highest risk within 90 days of splenectomy, when compared to the general population, were trauma patients (RR = 84.5), and the patients at lowest risk were those with hematopoietic cancers (RR = 15.5). The risk declined markedly after the first 90 days after splenectomy, and at 1 year postsplenectomy RR was 2.3 when compared to the general population if all indications were included. After 1 year, the risk of death compared to the general population was highest among patients with hereditary hemolytic anemias (RR = 4.2) and lowest among ITP patients (RR = 1.4) [12]. Regrettably, causes of death were not reported and the high mortality risk could be inflated by associated comorbidities.

19.4.1 Prevention of OPSI

There is a lifetime risk for OPSI after splenectomy. It should be considered a medical emergency, since the clinical course progresses in hours rather than days. Prompt diagnosis and treatment can reduce mortality [34]. Once a patient who is at risk presents with symptoms of OPSI, particularly fever, treatment with empiric antibiotics is imperative. The empiric treatment should involve intravenous infusion of a third-generation cephalosporin with gentamicin or ciprofloxacin.

Education plays an important role in the management and reduction of infections and complications in the postsplenectomy patient. It has been estimated that up to 84% of patients are not fully aware of any healthcare precautions relating to their asplenic state [35]. It has been shown that a patient's understanding of the health consequences relating to splenectomy reduces the prevalence of infectious complications. El-Alfy et al. reported that the prevalence of OPSI was 1.4% among patients with the greatest knowledge of the health risks related to splenectomy compared to 16.5% amongst those with the poorest knowledge [36]. Patients and their families should be instructed to seek medical attention in the setting of any acute febrile illness. Patients should understand the need to inform any new healthcare providers of their asplenic state. Patients also need to be educated regarding an increased risk for travel-related infections, specifically babesiosis and malaria. They should also be informed about the need for prompt treatment after even minor animal bites [34].

The use of prophylactic antibiotics for the prevention of OPSI is not evidence-based. There is no consensus on how long these drugs should be taken and which subgroups would receive any benefit with treatment. The recommendations vary widely, from only-as-needed to life-long prophylaxis. In addition, the actual effectiveness of antibiotics is unknown. Furthermore, risk factors, such as poor compliance, could lead to the development of resistant strains of bacteria [37]. Most authorities recommend prophylaxis in asplenic or hyposplenic children for at least 2 years after splenectomy. There remains no agreement between the Canadian, British, and American guidelines on when to discontinue prophylaxis in adults. Despite a paucity of prospective data concerning prophylaxis in adults, current guidelines recommend treatment with amoxicillin or penicillin [27,34].

A 23-valent pneumococcal polysaccharide vaccine (PPV-23), 7-valent diphtheria cross reactive material 197 protein-conjugated pneumococcal vaccine, the *H. influenzae* type b conjugated vaccine, and the meningococcal vaccine should be given to patients at risk for OPSI. Optimally, the pneumococcal vaccination should be given 2 weeks prior to elective splenectomy. However, if this time frame is not practical, such as is in the event of emergent splenectomies, the vaccine should be given 2 weeks after surgery [38]. The protection the PPV-23 vaccine provides against encapsulated antigens is temporary. Revaccination is recommended every 5–6 years. Patients in certain subgroups (sickle cell anemia, myeloproliferative diseases, and lymphoproliferative diseases) can be expected to have an accelerated decline in antibody titers and revaccination should be performed more frequently [27,34]. The requirement for reimmunization with the *H. influenzae* type b vaccine remains undefined. However, a single vaccination seems to be sufficient in adults [39]. The conventional meningococcal immunization is a tetravalent vaccine, which protects against strains A, C, Y, and W135. A single dose produces an effective antibody response in 80% of patients. This increases to 93% with revaccination, which has lead to the proposal of revaccination if protective levels of titers are not achieved [40].

Another potential method for decreasing the risk of OPSI in patients undergoing splenectomy for trauma or iatrogenic injury is autotransplantation of splenic tissue at the time of operation. There have been multiple techniques described for the autotransplantation of splenic tissue and most of them involve the implantation of 5–10 small pieces of spleen within the omentum. It has been shown that autotransplantation can safely be done during a splenectomy for trauma [41]. Both immunologic activity against encapsulated bacteria and reticuloendothelial function are better preserved by autotransplantation than by total splenectomy, even when only a small quantity of splenic tissue is implanted [42]. No studies, however, have demonstrated that autotransplantation at the time of splenectomy decreases the rate of postoperative infection or the rate of OPSI.

19.4.2 Asplenic and Hyposplenic States

Certain disease processes carry an inherent baseline risk of infection even before splenectomy. Sickle cell disease results in complex multiorgan manifestations that have a major impact on mortality [30]. Patients with sickle cell disease are functionally asplenic, secondary to autoinfarction, and are particularly prone to develop infections. Because of this, it is not clear if splenectomy increases the risk of infection and death [31]. The increased risk of infection and death, in patients with sickle cell disease, is more likely attributable to the disease itself rather than the splenectomy since these patients are usually in a hyposplenic or asplenic state prior to surgery with dysfunctional phagocytic activity and defective activation of the alternate complement pathway [28,31]. Patients with thalassemia major have a defective activation of their alternate complement pathway and immunoglobulin levels. Splenectomy increases this risk [28].

19.4.3 Vascular Events

The risk of venous thromboembolism, outside the splenic and portal venous system, in the immediate postoperative period following splenectomy is low, unless preexisting risk factors are present. The overall rate of venous thromboembolism, as reported by Thomsen et al., is 1.86% within 90 days of splenectomy. They also reported the incidence of deep vein thrombosis and pulmonary embolism to be 0.63% and 0.73%, respectively, within the same time period. However, the overall adjusted odds ratio, in the immediate postoperative period, for

splenectomy patients was 32.6 when they are compared to the general population and 3.2 when they are compared to postappendectomy patients [43].

Acute portal vein thrombosis (PVT) has been reported after splenectomy for a wide variety of indications. Prospective studies revealed the incidence of PVT after splenectomy to be from 0.9% to 37%, all occurring within 2 months and the majority within 2 weeks of surgery [44,45]. This is probably the result of general factors contributing to PVT, which include surgery itself and the need to induce pneumoperitoneum in laparoscopic splenectomy, as well as local factors such as propagation of thrombus from the splenic vein stump into the portal vein [44,45]. There also appears to be a higher rate of PVT with laparoscopic splenectomy when compared to open splenectomy [44].

A platelet count of more the $650 \times 10^3/\mu L$ has been shown to be directly associated with the development of portal system thrombosis [46]. Therefore, it is probably advisable to start antiplatelet therapy, such as aspirin, when severe thrombocytosis is encountered postsplenectomy. The risk of bleeding while using antiplatelet therapy in the immediate postoperative period should also be taken into consideration.

19.4.4 Pancreatic Complications

Pancreatic injury is a potentially lethal complication known to occur in both open and laparoscopic splenectomy [47]. This type of injury can be attributed to the close anatomic proximity of the tail of the pancreas to the splenic hilum. Pancreatic complications ranging from 0% to 15% have been reported for both open and laparoscopic splenectomies [1,6,11,47]. A retrospective review by Chand et al. looked at 94 patients undergoing elective laparoscopic splenectomy. They reported a pancreatic injury rate of 15%, which was the most common morbidity associated with laparoscopic splenectomy. They also noted that in the era of laparoscopic surgery and rapid discharge, half of the patients with major injury required readmission to evaluate persistent abdominal pain. Because of this trend, they suggested routine postoperative monitoring of serum amylase levels. This might alert the surgeon to a potential problem as a result of unrecognized pancreatic manipulation during the surgery. Once a potential problem is identified, the surgeon can alter the postoperative routine as appropriate [47].

In an effort to provide a rational basis for a suggested strategy to minimize the likelihood of injury to the pancreas during splenectomy, computed tomography scan mapping of the tail of the pancreas in relation to the splenic hilum has been investigated. It was found that the average distance from the tail of the pancreas to the splenic hilum was 3.42 cm. In addition, the tail of the pancreas was found to be located more than 1 cm away from the hilum of the spleen in all cases regardless of the patient's age, gender, size of the spleen, BMI, or whether the tail was superior, inferior or at the level of the splenic vessels [48]. From this, it can be safely suggested that staying within 1 cm from the hilum of the spleen, while gaining splenic vascular control, should minimize the risk of pancreatic injury. However, no studies have been done to test this recommendation.

19.4.5 Gastric Perforation

Gastric perforation is rare but a potentially devastating complication of splenectomy, which may result in death or prolonged disability. It is estimated to occur in fewer than 1% of open splenectomies, but is associated with a mortality rate as high as 25%, even with appropriate treatment [49]. The perforation is usually situated high on the greater curvature of the stomach where the short gastric vessels in the gastrosplenic omentum have been transected. The perforation of the stomach can be a consequence of disrupting the vascular supply to the greater curvature rather than a result of direct injury [50]. It can also result from unrecognized thermal injury during dissection and control of the short gastric vessels.

Patients with this complication will often develop pain in the left upper quadrant and left shoulder, fever, tachycardia, and abdominal tenderness. Although drain placement is not recommended for an uncomplicated splenectomy, if a surgical drain was placed in the left upper quadrant, increased drainage is commonly noted. Chest radiographs will frequently reveal a left-sided pleural effusion. The diagnosis can be made radiologically after ingestion of a water-soluble iodinated radiopaque contrast medium. Treatment includes gastric decompression with nasogastric suction and wide drainage of the left subphrenic space. Operative closure will be required in some cases.

Incidence of Complications after Splenic Surgery

Complications	Rates	References
Infectious		
Intra-abdominal abscess	4.5%–39%	[13,15,29,32,33]
Wound infection	4%–9%	
Pneumonia	1.1%–30%	
Septicemia	3.3%–19%	
OPSI	0.18 per 100 person-years observed post splenectomy	
Early thrombotic events		
Portal	0.9%–37%	[43–45]
Nonportal	1.86%	[43]
Gastric injury	<1%	[49,50]
Pancreatic injury	0%–15%	[1,6,11,47]

Avoiding Complications after Splenic Surgery

Complications	Suggestions	Comments
Postsplenectomy sepsis	• Vaccination • Prophylactic antibiotics • Education • Autotransplantation of splenic tissue	
Thrombotic events Portal Nonportal	• Antiplatelet therapy • Use of low molecular weight heparins	For platelet count >650 × $10^3/\mu L$ [46]
Pancreatic injury	• Preoperative computer tomography mapping of splenic hilum • Staying within 0.5 cm of splenic hilum • Minimizing pancreatic manipulation	
Gastric injury	• Avoid disruption of vascular supply to greater curvature • Judicious use of thermal dissection while controlling the short gastric vessels	

References

1. Arnoletti JP, Karam J, Brodsky J. Early postoperative complications of splenectomy for hematologic disease. *American Journal of Clinical Oncology*. 1999;22(2):114–118. Epub 1999/04/13.
2. Rosen M, Brody F, Walsh RM, Tarnoff M, Malm J, Ponsky J. Outcome of laparoscopic splenectomy based on hematologic indication. *Surgical Endoscopy*. 2002;16(2):272–279. Epub 2002/04/23.
3. Horowitz J, Smith JL, Weber TK, Rodriguez-Bigas MA, Petrelli NJ. Postoperative complications after splenectomy for hematologic malignancies. *Annals of Surgery*. 1996;223(3):290–296. Epub 1996/03/01.
4. MacRae HM, Yakimets WW, Reynolds T. Perioperative complications of splenectomy for hematologic disease. *Canadian Journal of Surgery*. 1992;35(4):432–436. Epub 1992/08/01.
5. Delaitre B, Maignien B. Splenectomy by the laparoscopic approach. Report of a case. *Presse Medicale*. 1991;20(44):2263. Epub 1991/12/21.
   Splenectomie par voie coelioscopique. 1 observation (letter).
6. Donini A, Baccarani U, Terrosu G, Corno V, Ermacora A, Pasqualucci A et al. Laparoscopic vs open splenectomy in the management of hematologic diseases. *Surgical Endoscopy*. 1999;13(12):1220–1225. Epub 1999/12/14.
7. Kucuk C, Sozuer E, Ok E, Altuntas F, Yilmaz Z. Laparoscopic versus open splenectomy in the management of benign and malign hematologic diseases: A ten-year single-center experience. *Journal of Laparoendoscopic and Advanced Surgical Techniques Part A*. 2005;15(2):135–139. Epub 2005/05/19.
8. Bai YN, Jiang H, Prasoon P. A meta-analysis of perioperative outcomes of laparoscopic splenectomy for hematological disorders. *World Journal of Surgery*. 2012;36(10):2349–2358. Epub 2012/07/05.
9. Franciosi C, Caprotti R, Romano F, Porta G, Real G, Colombo G et al. Laparoscopic versus open splenectomy: A comparative study. *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques*. 2000;10(5):291–295. Epub 2000/11/18.
10. Winslow ER, Brunt LM. Perioperative outcomes of laparoscopic versus open splenectomy: A meta-analysis with an emphasis on complications. *Surgery*. 2003;134(4):647–653; discussion 54–55. Epub 2003/11/08.
11. Park AE, Birgisson G, Mastrangelo MJ, Marcaccio MJ, Witzke DB. Laparoscopic splenectomy: Outcomes and lessons learned from over 200 cases. *Surgery*. 2000;128(4):660–667. Epub 2000/10/03.
12. Yong M, Thomsen RW, Schoonen WM, Farkas DK, Riis A, Fryzek JP et al. Mortality risk in splenectomised patients: A Danish population-based cohort study. *European Journal of Internal Medicine*. 2010;21(1):12–16. Epub 2010/02/04. Study showing the risk of mortality related to indication for splenectomy.
13. Demetriades D, Scalea TM, Degiannis E, Barmparas G, Konstantinidis A, Massahis J et al. Blunt splenic trauma: splenectomy increases early infectious complications: A prospective multicenter study. *The Journal of Trauma and Acute Care Surgery*. 2012;72(1):229–234. Epub 2012/02/09.
   Prospective study defining the infectious risk associated with splenecotomy in the setting of trauma.
14. Hebeler RF, Ward RE, Miller PW, Ben-Menachem Y. The management of splenic injury. *The Journal of Trauma*. 1982;22(6):492–495. Epub 1982/06/01.
15. Wiseman J, Brown CV, Weng J, Salim A, Rhee P, Demetriades D. Splenectomy for trauma increases the rate of early postoperative infections. *The American Surgeon*. 2006;72(10):947–950. Epub 2006/10/25.
16. Beal SL, Spisso JM. The risk of splenorrhaphy. *Archives of Surgery*. 1988;123(9):1158–1163. Epub 1988/09/01.
17. Flancbaum L, Dauterive A, Cox EF. Splenic conservation after multiple trauma in adults. *Surgery, Gynecology and Obstetrics*. 1986;162(5):469–473. Epub 1986/05/01.
18. Pickhardt B, Moore EE, Moore FA, McCroskey BL, Moore GE. Operative splenic salvage in adults: A decade perspective. *The Journal of Trauma*. 1989;29(10):1386–1391. Epub 1989/10/01.
19. Pachter HL, Guth AA, Hofstetter SR, Spencer FC. Changing patterns in the management of splenic trauma: The impact of nonoperative management. *Annals of Surgery*. 1998;227(5):708–717; discussion 17–19. Epub 1998/05/30.
20. Peitzman AB, Heil B, Rivera L, Federle MB, Harbrecht BG, Clancy KD et al. Blunt splenic injury in adults: Multi-institutional Study of the Eastern Association for the Surgery of Trauma. *The Journal of Trauma*. 2000;49(2):177–187; discussion 87–89. Epub 2000/08/30. Multicenter trial examining blunt splenic trauma in adults.
21. Smith JS, Jr., Cooney RN, Mucha P, Jr. Nonoperative management of the ruptured spleen: A revalidation of criteria. *Surgery*. 1996;120(4):745–750; discussion 50–51. Epub 1996/10/01.

22. Weinberg JA, Magnotti LJ, Croce MA, Edwards NM, Fabian TC. The utility of serial computed tomography imaging of blunt splenic injury: Still worth a second look? *The Journal of Trauma*. 2007;62(5):1143–1147; discussion 7–8. Epub 2007/05/15.
23. Smith J, Armen S, Cook CH, Martin LC. Blunt splenic injuries: Have we watched long enough? *The Journal of Trauma*. 2008;64(3):656–663; discussion 63–65. Epub 2008/03/12.
24. Zarzaur BL, Vashi S, Magnotti LJ, Croce MA, Fabian TC. The real risk of splenectomy after discharge home following nonoperative management of blunt splenic injury. *The Journal of Trauma*. 2009;66(6):1531–1536; discussion 6–8. Epub 2009/06/11.
25. King H, Shumacker HB, Jr. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. *Annals of Surgery*. 1952;136(2):239–242. Epub 1952/08/01. First report of OPSI.
26. Buntain WL, Gould HR, Maull KI. Predictability of splenic salvage by computed tomography. *The Journal of Trauma*. 1988;28(1):24–34. Epub 1988/01/01.
27. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet*. 2011;378(9785):86–97. Epub 2011/04/09.
28. Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. *The Journal of Infection*. 2001;43(3):182–186. Epub 2002/01/19.
29. Schwartz PE, Sterioff S, Mucha P, Melton LJ, 3rd, Offord KP. Postsplenectomy sepsis and mortality in adults. *The Journal of the American Medical Association*. 1982;248(18):2279–2283. Epub 1982/11/12.
30. Hebbel RP. Reconstructing sickle cell disease: a data-based analysis of the "hyperhemolysis paradigm" for pulmonary hypertension from the perspective of evidence-based medicine. *American Journal of Hematology*. 2011;86(2):123–154. Epub 2011/01/26.
31. Wright JG, Hambleton IR, Thomas PW, Duncan ND, Venugopal S, Serjeant GR. Postsplenectomy course in homozygous sickle cell disease. *The Journal of Pediatrics*. 1999;134(3):304–309. Epub 1999/03/04.
32. Ejstrud P, Kristensen B, Hansen JB, Madsen KM, Schonheyder HC, Sorensen HT. Risk and patterns of bacteraemia after splenectomy: A population-based study. *Scandinavian Journal of Infectious Diseases*. 2000;32(5): 521–525. Epub 2000/10/31.
33. Thomsen RW, Schoonen WM, Farkas DK, Riis A, Jacobsen J, Fryzek JP et al. Risk for hospital contact with infection in patients with splenectomy: A population-based cohort study. *Annals of Internal Medicine*. 2009;151(8):546–555. Epub 2009/10/21.
    Defines risk of infection by indication for splenectomy.
34. Brigden ML, Pattullo AL. Prevention and management of overwhelming postsplenectomy infection—An update. *Critical Care Medicine*. 1999;27(4):836–842. Epub 1999/05/13.
35. White KS, Covington D, Churchill P, Maxwell JG, Norman KS, Clancy TV. Patient awareness of health precautions after splenectomy. *American Journal of Infection Control*. 1991;19(1):36–41. Epub 1991/02/01.
36. El-Alfy MS, El-Sayed MH. Overwhelming postsplenectomy infection: Is quality of patient knowledge enough for prevention? *The Hematology Journal: The Official Journal of the European Haematology Association*. 2004;5(1):77–80. Epub 2004/01/28.
37. Kaplinsky C, Spirer Z. Post-splenectomy antibiotic prophylaxis—Unfinished story: To treat or not to treat? *Pediatric Blood and Cancer*. 2006;47(5 Suppl):740–741. Epub 2006/08/26.
38. Shatz DV, Romero-Steiner S, Elie CM, Holder PF, Carlone GM. Antibody responses in postsplenectomy trauma patients receiving the 23-valent pneumococcal polysaccharide vaccine at 14 versus 28 days postoperatively. *The Journal of Trauma*. 2002;53(6):1037–1042. Epub 2002/12/13.
39. Cimaz R, Mensi C, D'Angelo E, Fantola E, Milone V, Biasio LR et al. Safety and immunogenicity of a conjugate vaccine against *Haemophilus influenzae* type b in splenectomized and nonsplenectomized patients with Cooley anemia. *The Journal of Infectious Diseases*. 2001;183(12):1819–1821. Epub 2001/05/24.
40. Borrow R, Andrews N, Goldblatt D, Miller E. Serological basis for use of meningococcal serogroup C conjugate vaccines in the United Kingdom: reevaluation of correlates of protection. *Infection and Immunity*. 2001; 69(3):1568–1573. Epub 2001/02/17.
41. Moore FA, Moore EE, Moore GE, Millikan JS. Risk of splenic salvage after trauma. Analysis of 200 adults. *American Journal of Surgery*. 1984;148(6):800–805. Epub 1984/12/01.
42. Zoli G, Corazza GR, D'Amato G, Bartoli R, Baldoni F, Gasbarrini G. Splenic autotransplantation after splenectomy: Tuftsin activity correlates with residual splenic function. *The British Journal of Surgery*. 1994;81(5): 716–718. Epub 1994/05/01.
43. Thomsen RW, Schoonen WM, Farkas DK, Riis A, Fryzek JP, Sorensen HT. Risk of venous thromboembolism in splenectomized patients compared with the general population and appendectomized patients: A 10-year nationwide cohort study. Defines risk of thrombembolism by location and time period after splenectomy. *Journal of Thrombosis and Haemostasis*. 2010;8(6):1413–1416. Epub 2010/03/12.
44. Ikeda M, Sekimoto M, Takiguchi S, Kubota M, Ikenaga M, Yamamoto H et al. High incidence of thrombosis of the portal venous system after laparoscopic splenectomy: A prospective study with contrast-enhanced CT scan. *Annals of Surgery*. 2005;241(2):208–216. Epub 2005/01/15.
45. Romano F, Caprotti R, Scaini A, Conti M, Scotti M, Colombo G et al. Elective laparoscopic splenectomy and thrombosis of the spleno-portal axis: A prospective study with ecocolordoppler ultrasound. *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques*. 2006;16(1):4–7. Epub 2006/03/23.
46. Stamou KM, Toutouzas KG, Kekis PB, Nakos S, Gafou A, Manouras A et al. Prospective study of the incidence and risk factors of postsplenectomy thrombosis of the portal, mesenteric, and splenic veins. *Archives of Surgery*. 2006;141(7):663–669. Epub 2006/07/19.

47. Chand B, Walsh RM, Ponsky J, Brody F. Pancreatic complications following laparoscopic splenectomy. *Surgical Endoscopy*. 2001;15(11):1273–1276. Epub 2001/12/01.
48. Saber AA, Helbling B, Khaghany K, Nirmit G, Pimental R, McLeod MK. Safety zone for splenic hilar control during splenectomy: A computed tomography scan mapping of the tail of the pancreas in relation to the splenic hilum. *The American Surgeon*. 2007;73(9):890–894. Epub 2007/10/18.
49. McClenathan JH. Gastric perforation as a complication of splenectomy: Report of five cases and review of the literature. *Canadian Journal of Surgery*. 1991;34(2):175–178. Epub 1991/04/01.
50. Harrison BJ, Glanges E, Sparkman RS. Gastric fistula following splenectomy: Its cause and prevention. *Annals of Surgery*. 1977;185(2):210–213. Epub 1977/02/01.

20

Complications of Laparoscopy in General Surgery

James G. Bittner IV and J. Esteban Varela

CONTENTS

20.1 Physiologic Changes

Pneumoperitoneum results in transient physiologic alterations of the heart, lung, kidney, and liver. Among these, hemodynamic and respiratory changes are the most clinically relevant and well studied. In otherwise healthy patients, these changes rarely result in complications. However, in patients with preexisting cardiac, pulmonary, renal, or hepatic dysfunction, pneumoperitoneum may lead to serious morbidity or mortality. Surgeons who perform laparoscopy must be aware of these potential events and take appropriate action when necessary.

20.1.1 Pulmonary Effects

Pneumoperitoneum alters ventilation parameters and gas exchange. One of the most common alterations is an increase in airway pressures. This increase results from a decrease in diaphragmatic excursion and lung and chest wall compliance [1]. Clinically, peak-and end-inspiratory pressures increase by as much as 30%–40% above baseline with insufflation pressures of 10–15 mmHg [1–3]. Measured respiratory compliance decreases by approximately 35% as a result of pneumoperitoneum. Airway pressures rapidly return to normal levels after the release of the pneumoperitoneum. Therefore, the surgeon should immediately discontinue the inflow of insufflation and evacuate the existing pneumoperitoneum whenever any untoward ventilatory or hemodynamic changes occur.

Carbon dioxide is used to establish and maintain pneumoperitoneum. Hypercarbia and subsequent respiratory acidosis can result from abdominal insufflation and transperitoneal absorption of carbon dioxide. This increase in carbon dioxide absorption results

in an increase in arterial carbon dioxide levels. Arterial partial pressure of carbon dioxide (pCO_2) commonly increases by approximately 8–12 mmHg above baseline, and pH dips to approximately 7.35–7.38 during routine laparoscopic cases [2]. However, repetitive arterial pCO_2 monitoring is not necessary or practical in most routine laparoscopic cases. Therefore, surgeons commonly use end-tidal CO_2 measurements to assess the adequacy of ventilation [3]. End-tidal CO_2 levels normally increase by about 10% at normal insufflation pressures [2]. Fortunately, such alterations are generally well tolerated by otherwise healthy patients [2,3]. If need be, the anesthesiologist can lower CO_2 levels by increasing the ventilation rate. Remember that changes in end-tidal CO_2 levels generally underestimate the actual increase in arterial pCO_2. For all patients, abnormal CO_2 and pH values generally return to baseline within several minutes after the release of pneumoperitoneum [2,3].

20.1.2 Hemodynamic Effects

Previous studies demonstrated that hemodynamic changes occur during abdominal insufflation. The increase in intra-abdominal pressure during pneumoperitoneum decreases venous return via the inferior vena cava [4]. This yields a decrease in cardiac preload and left ventricular (LV) function. The most striking and observable hemodynamic change is a decrease of 10%–30% in cardiac output [2,5–7]. Altered hemodynamic indices often contribute to other physiologic changes such as an elevated mean arterial pressure (7–15 mmHg) and decreased renal blood flow and glomerular filtration rate [1,2,4].

Cardiac arrhythmias may occur in as many as 47% of patients who undergo laparoscopy [8]. Tachycardia is the most common arrhythmia and results from a decrease in cardiac output. On rare occasions, otherwise healthy patients may experience dangerous bradyarrhythmias. The most likely cause of bradyarrhythmias is hypercapnia that develops as a result of increased cardiac afterload. Unlike tachycardia, bradyarrhythmias are not as well tolerated and should be treated aggressively with evacuation of pneumoperitoneum and appropriate pharmacologic measures to restore normal rhythm [8–10].

The cardiovascular effects of pneumoperitoneum, like the pulmonary changes, are of minimal clinical importance for most patients undergoing elective laparoscopic operations. This statement assumes, however, that insufflation pressure is maintained within the normal range of 10–15 mmHg. Surgeons should be careful to ensure that these levels are not exceeded throughout the operative procedure and be aware that patients with compromised cardiac or respiratory function may not tolerate pneumoperitoneum. In such circumstances, the surgeon must consider the use of more invasive intraoperative monitoring, or even a different surgical approach, especially in patients whose respiratory or cardiac function may be compromised.

20.2 Complications Related to Laparoscopic Access

Laparoscopy is associated with a morbidity rate between 2% and 10%, depending on the type of operation and the experience of the surgeon. When complications arise they are often related to accessing the abdomen. In fact, access-related complications make up a significant portion of the morbidity related to minimally invasive surgery. The overall incidence of access-related injury ranges from 0.2% to 5% [11–14].

20.2.1 Injuries Caused by Needle or Trocar

Vascular injury to the abdominal wall and the retroperitoneal vessels is the most common complication, accounting for approximately 65% of access-related injuries [14]. Fortunately, the majority of vascular injuries involve the epigastric vessels. The overall incidence of abdominal wall bleeding ranges from 0.5% to 2% [15]. Temporary control of abdominal wall bleeding can often be attained by simple but effective method including direct pressure against the bleeding site, percutaneous suture ligation, or open suture ligation. Injury to small vessels of the omentum may be controlled with clips or an endoloop.

Major retroperitoneal vascular injury occurs in 0.1% to 0.25% of all laparoscopic operations, but injury to these vessels accounts for 35% of all deaths [12,14,16]. In order of decreasing frequency, the major vessels commonly injured are the iliac artery and vein (24%–27%), the aorta, the inferior vena cava, or both (10%–15%), and the major visceral or mesenteric vessels (5%–10%) [12,14]. Earlier studies found that combined aortocaval injuries were associated with mortality rates of 80%–100%. In the face of a major vascular injury, control the hemorrhage by any means necessary. In general, perform a midline laparotomy to allow definitive proximal and distal control and repair of the injury. Depending on surgeon judgment and experience, a board-certified vascular surgeon should be consulted for repair and/or reconstruction.

Visceral injuries reportedly occur during 0.1%–0.2% of all laparoscopic procedures [13,15,16]. Most large series indicate that small-bowel perforations account

for nearly 90% of visceral injuries, followed, in decreasing frequency, by perforations of the liver, colon, and stomach [15]. The overall mortality rate associated with intestinal injury during laparoscopy is approximately 3%–5% [14,16]. As many as 69% of all access-related visceral injuries go unrecognized during the procedure [16]. Failure to recognize such injuries is associated with a 10-fold increase in mortality rates (20%–25%) [12,14]. A recent review of 182 access-related visceral injuries demonstrated that the mortality rate was zero if all injuries were identified intraoperatively. However, 21% of unrecognized bowel injuries resulted in death [14]. This finding reiterates the importance of performing a thorough diagnostic survey of the abdomen at the completion of each procedure, especially if there is any suspicion of visceral injury.

Gas embolism, which occurs in approximately one of every 100,000 laparoscopic cases, is nearly always associated with insertion of a Veress needle into a major vascular structure and subsequent insufflation. The associated mortality rate is more than 30% [17]. Gas embolism is managed by deflating the pneumoperitoneum, placing the patient into a Trendelenburg and left lateral decubitus position, administering 100% oxygen, and instituting general supportive measures. Some surgeons advocate central venous catheter placement to attempt aspiration of intravascular gas. Unfortunately, there is little time for deploying these management techniques and only limited success.

An additional access-related complication is extraperitoneal dissection of carbon dioxide. This is generally a minor issue with little attendant morbidity. However, it can be alarming to the surgeon, the anesthesiologist, or the patient. The anesthesiologist may be concerned because of subcutaneous emphysema tracks around the neck and chest, suggestive of a serious airway disruption. Subcutaneous emphysema can occur anywhere, from the lower extremities, as seen after hernia repair, to the head, neck, and chest, as can occur after mediastinal dissection during transhiatal operations. Patients should be made aware that the subcutaneous emphysema is generally harmless and usually resolves within 48–72 h. Like many access-related complications, extraperitoneal insufflation can be avoided by the use of proper access techniques.

Surgeons must have a good working knowledge of such injuries and understand the best methods for prevention. For Veress needle access, the surgeon should stabilize the needle once inserted to avoid inadvertent injury to the underlying viscera, perform a saline drop test, and ensure low intra-abdominal pressure. For open access, the surgeon should visualize and identify all layers of the abdominal wall to ensure a safe entrance into the peritoneal cavity.

20.2.2 Choice of Access Technique

The data remain equivocal as to the relative safety of open and closed access techniques. On one hand, several large series that include as many as 20,000 patients demonstrate equivalent complication rates for the two access approaches [15]. Other reports substantiate a decrease in morbidity with the open technique [14,17]. A meta-analysis including nearly 500,000 patients found that the rate of visceral injury during closed access (0.08%) was greater than with open access (0.05%) [17]. Major retroperitoneal vascular injury was nearly nonexistent during open access but occurred at a rate of 0.08% with closed access [17]. Another advantage of the open technique is the increased likelihood of intraoperative recognition of an injury [14,17]. Both open and closed techniques are well established and generally safe.

20.2.3 Trocar-Site Hernias

Trocar-site hernias represent potential morbidity following any laparoscopic procedure, especially after weight loss operations. The largest studies of trocar-site hernias cite an incidence of approximately 0.2%–0.6% [18,19]. A recent review of 2644 patients who underwent laparoscopic weight loss operations confirmed a relatively low rate of trocar-site hernia (0.57%), with a mean follow-up of 67.4 months [19]. Because these patients are often seen by other than the initial operating surgeon, the true incidence of trocar-site hernias is likely much higher. Leibl et al. [18] demonstrated that the incidence of trocar-site incisional hernia is approximately nine times higher when cutting trocars are used (1.8%) compared to blunt or optical-type trocars (0.2%). Trocar-site hernias have been reported at both 5 and 10 mm trocar sites and can result in incarcerated or strangulated viscera. However, more than 95% of all reported trocar-site hernias occur at incision sites involving trocars 10 mm or more in diameter. It is also recognized that trocar-site hernias tend to occur more commonly among obese patients for whom closure of the fascial defect poses the greatest challenge. Because these hernias are small, detecting them by physical examination is often difficult, especially among obese patients. Therefore, the sudden occurrence or persistent presence of trocar-site pain should prompt radiological and possibly operative evaluation.

When complications occur, the surgeon must follow time-honored principles to minimize morbidity. For major vascular and visceral injuries, a high index of suspicion must be maintained. When these injuries are recognized, immediate repair must be undertaken whether or not the repair is performed in a laparoscopic or open fashion. If the surgeon lacks extensive experience with laparoscopy or the injury is severe, an open approach is warranted.

20.3 Altered Visualization, Unique Instrumentation, and the Role of the Learning Curve

Several authors cite the two-dimensional nature and image reversal of laparoscopy as influential reasons for complications [20–22]. However, there exists no data to confirm the notion that visual alterations and intraoperative complications are linked. Interestingly, three-dimensional optics may offer little benefit for experienced surgeons [22].

Studies related to the learning curve of laparoscopy demonstrate that operative times and conversion rates are increased during the first 20–250 cases depending on the procedure. This observation holds true across many procedures, including antireflux operations [23], inguinal hernia repair [24], and colectomy [25]. To minimize the potential for complications during the learning curve, surgeons should participate in educational programs that offer didactic instruction, skills training, and laboratory practice. While fellowship training in minimally invasive surgery and/or bariatric surgery may be ideal, other strategies to help overcome the learning curve include hands-on short courses and individual proctorships with experienced surgeons.

20.4 Common Laparoscopic Operations

20.4.1 Laparoscopic Cholecystectomy

Several large series involving 12,000–115,000 patients demonstrate that the overall complication rate associated with laparoscopic cholecystectomy is lower than that associated with the open procedure, with the very important exception of bile duct injury. The overall morbidity rates associated with laparoscopic cholecystectomy range from 2.0% to 4.8%, whereas those associated with open cholecystectomy range from 8% to 18.7% [26].

20.4.2 Bile Duct Injury

The incidence of serious bile duct injuries during laparoscopic cholecystectomy is 0%–2% [16,25,26]. A meta-analysis of more than 40 published series found that the mean incidence of major bile duct injury was 0.5%, significantly higher than the rate for open cholecystectomy (0.1%–0.25%) [27]. However, the validity of these results should be questioned. First, the higher rates of injury found by early studies of laparoscopic cholecystectomy may be a reflection of the learning curve for this procedure. Second, many of the large series of open cholecystectomy are retrospective reviews. These reports were published when large databases, patient registries, and sophisticated data collection systems were not as readily available. Thus, the true rate of bile duct injury during open cholecystectomy may have been underestimated.

Careful identification of the important anatomic landmarks is the key to avoiding bile duct injury, regardless of the operative approach. A clear delineation of the individual steps for dissection is beyond the scope of this chapter; however, a necessary step is to establish the Critical View of Safety before clipping or cutting any structures [28]. Aside from specific dissection techniques, the authors and others advocate the use of routine intraoperative cholangiography [29]. The liberal use of cholangiography will identify most bile duct injuries intraoperatively, when they can be repaired with better long-term results than injuries discovered postoperatively [27]. Bile duct reconstruction and the management of severe bile leaks are discussed elsewhere.

20.4.3 Miscellaneous Complications

Spilling bile or stones during laparoscopic cholecystectomy may concern some surgeons. In most cases, spilling biliary contents does not increase morbidity. Memon et al. [30] reported that dropped stones, bile spillage, or both occur during 40% of laparoscopic cholecystectomy operations but cause long-term complications in only 5% of cases. All complications in this series were managed successfully with antibiotics alone or percutaneous drainage (0.6%). Thus, a lengthy and unrewarding search for lost stones should be avoided because it may increase the risk of visceral and vascular injuries.

Vascular injuries unique to laparoscopic cholecystectomy can be related to the anomalous nature of the blood supply to the liver and gallbladder. An aberrant right hepatic artery arising from the superior mesenteric artery and passing through or near Calot's triangle is one recognized variation. Multiple cystic arteries or accessory hepatic arteries passing near the operative field are also prone to injury during laparoscopic cholecystectomy. Bleeding from the liver parenchyma can be troublesome. Finally, the proximity of the duodenum and the hepatic flexure of the colon raise the potential for visceral injury.

20.4.4 Laparoscopic Fundoplication

Laparoscopic fundoplication for gastroesophageal reflux conveys significant benefits as evidenced by few complications and remarkably low 30-day morbidity (3.8%) and mortality (0.19%) [31]. A recent meta-analysis including 12 trials and over 1000 patients confirmed that laparoscopic fundoplication reduced the odds of

complications by 65% compared to open fundoplication. The laparoscopic approach resulted in a shorter hospital length of stay and an earlier return to normal activity [32]. The higher morbidity associated with open fundoplication may stem from impaired visualization above the hiatus, greater postoperative pain, and longer hospital length of stay.

The most common complication after fundoplication is wrap failure, which occurs more often after open (15%–20%) than laparoscopic fundoplication (5%–10%) [33]. Most laparoscopic failures (84%) are caused by transdiaphragmatic herniation of the wrap, whereas open failures are evenly distributed between transdiaphragmatic migration, slipped or misplaced fundoplication, and twisted wraps. Overly tight wraps and subsequent dysphagia occur more commonly after open fundoplication (10% vs. 4%) [33].

Complications other than wrap failure are uncommonly associated with laparoscopic fundoplication. Most conversions to an open approach result from technical difficulties, including adhesions and problems associated with obesity, or surgeon inexperience rather than from intraoperative complications [34]. Serious complications, including gastric, bowel, or esophageal perforation occurred infrequently. Two steps of laparoscopic fundoplication may pose a greater risk of injury to the esophagus: passage of the bougie dilator and creation of a retroesophageal window. With surgeon experience, the risk of esophageal injury from these two steps can be mitigated.

20.4.5 Laparoscopic Inguinal Hernia Repair

With the increasing adoption of laparoscopic totally extraperitoneal (TEP) and transabdominal preperitoneal (TAPP) herniorrhaphy, it is important to be aware of the potential complications. Studies comparing the two approaches found that certain complications (trocar-site hernia, small-bowel obstruction, and bowel injury from dissection or trocar placement) occurred less frequently during laparoscopic TEP compared to TAPP herniorrhaphy.

Several studies, including a large meta-analysis involving more than 2400 patients, demonstrate that both types of laparoscopic repair are associated with less postoperative pain and more rapid recovery rates compared to open repair [35,36]. A randomized controlled trial reported a significantly lower rate of recurrence at 5 years after laparoscopic TAPP (3%) than Shouldice repair (8%) [36]. Equivalent rates of recurrence (2%–3%) and long-term postoperative pain (2%–3%) are reported for laparoscopic and tension-free repairs [35]. For primary unilateral inguinal hernia, TEP is associated with an increased risk of recurrence relative to open mesh repair but TAPP is not. TAPP is associated with increased risk of perioperative complications relative to open mesh repair. Laparoscopic inguinal hernia repair has a reduced risk of chronic pain and numbness relative to open mesh repair [37]. In general, complications of laparoscopic hernia repair include hematomas, seromas, and hydroceles (8%–10%), urinary retention (1%–2%), cutaneous nerve injuries (2%), and persistent pain (2%–3%) [36,37].

Although serious complications are very uncommon during laparoscopic herniorrhaphy, surgeons who choose a laparoscopic approach must keep in mind the special risk to the iliac vessels associated with this operation. Be wary of the "triangle of doom" that is bounded by the iliac vessels laterally and the ductus deferens medially. Reports of injuries to these structures during laparoscopic herniorrhaphy are rare; however, serious complications are most likely to occur in this anatomic area. According to a recent comparative effectiveness review conducted by the Agency for Healthcare Research and Quality, many studies report the fact that surgeon experience lowers the risk of complications and recurrence but the data are reported unevenly and as yet do not clearly define the precise length of the learning curve for laparoscopic TEP and TAPP herniorrhaphy [38].

20.4.6 Laparoscopic Appendectomy

At least 67 studies of appendectomy were recently evaluated in a large meta-analysis. Of those, 56 studies compared laparoscopic to open appendectomy in adults. Wound infections were less likely after laparoscopic than open appendectomy (OR 0.43; CI 0.34–0.54), but the incidence of intra-abdominal abscesses was increased (OR 1.87; CI 1.19–2.93). Hospital stay was shortened by 1.1 days and return to normal activity, work, and sport occurred earlier after laparoscopic appendectomy. In those clinical settings where surgical expertise and equipment are available, laparoscopic appendectomy offers advantages over the open approach. Some of the clinical effects of laparoscopic appendectomy, however, are small and of limited clinical relevance [39]. When performing appendectomy, it is important to follow established general surgical principles for the treatment of appendicitis, particularly perforated or suppurative appendicitis, where aspiration of the cul-de-sac may help prevent intra-abdominal abscess.

20.4.7 Laparoscopic Primary Ventral and Incisional Hernia Repair

Recent prospective and retrospective comparisons of open and laparoscopic techniques for primary ventral and incisional hernia repair demonstrate that the laparoscopic approach offers several advantages. A randomized controlled trial of 146 patients who

underwent laparoscopic ($n=73$) and open ($n=73$) ventral incisional hernia repair between 2004 and 2007 at Veterans Affairs Medical Centers was conducted. The laparoscopic repair required the use of polytetrafluoroethylene (PTFE) mesh secured using transfascial sutures and titanium tacks with a mesh to fascia overlap of at least 3 cm. The open repair was performed using the Chevrel technique with onlay, uncoated polypropylene mesh. In the laparoscopic group, patients experienced fewer overall complications, significantly fewer surgical site infections through 8 weeks (5.6% vs. 23.3%), less postoperative pain at 52 weeks, and earlier return to work by 5 days. There was no significant difference in hernia recurrence rate at 2 years in the laparoscopic and open groups (12.5% vs. 8.2%) [40]. Outside the Veterans Affairs population, laparoscopic ventral hernia repair is associated with significantly lower rates of wound infection (3.8% vs. 16.8%) compared to open repair [41]. In a recent review of the National Inpatient Sample, 18,223 cases of laparoscopic (27.6%) and open ventral hernia repair were compared using multivariate regression while controlling for confounding variables. The study found that laparoscopic ventral hernia repair resulted in significantly lower complication rates (approximately 8% vs. 4%), shorter hospital length of stay (almost 2 days), less hospital charges, and lower 30-day mortality (0.88% vs. 0.36%) compared to open ventral hernia repair [42].

A recent prospective trial of 310 patients who underwent laparoscopic ventral incisional hernia repair was conducted to identify risk factors for hernia recurrence. The overall recurrence was low (6%) after an average follow-up of 60 months. Multivariate regression analysis of variables for hernia recurrence including defect size revealed that obesity and defect size (>10 cm) were independent prognostic factors. Hence, in patients for whom long-term prevention of hernia recurrence is the primary goal, perhaps larger defects may be more amenable to an open approach [43].

These data may continue to change as surgeons adopt different strategies to lower recurrence rates following laparoscopic ventral incisional hernia repair. Such strategies include primary suture closure plus intraperitoneal placement of barrier-coated synthetic mesh with or without endoscopic component separation. For open ventral incisional hernia repair, techniques designed to lower complication and recurrence rates and reestablish abdominal wall function include primary suture repair plus anterior and/or posterior component separation along with retromuscular and preperitoneal placement of non-barrier-coated synthetic mesh. Of course, the mesh materials themselves continue to change and improve alongside the development of various herniorraphy techniques. However, it is clear that experienced surgeons can perform laparoscopic ventral incisional hernia repair safely and with relatively low morbidity.

20.4.8 Laparoscopic Roux-en-Y Gastric Bypass

Adverse events are a well-known entity of weight loss procedures, particularly intraoperative complications and those that occur following gastric bypass. Laparoscopic gastric bypass results in less intraoperative bleeding and postoperative pain compared to the open procedure [44]. Additionally, a recent meta-analysis compared the effects of laparoscopic and open gastric bypass for morbid obesity. In total, six randomized controlled trials involving a total of 422 (214 laparoscopic, 208 open) patients were analyzed. Laparoscopic gastric bypass significantly shortened hospital length of stay (1 day) with no statistical difference in complication rates [45]. A recently published cohort study analyzed 5882 patients who underwent an operation for morbid obesity. There were 1608 laparoscopic adjustable gastric banding, 3770 laparoscopic gastric bypass, and 504 open gastric bypass operations. Overall, 5% of patients suffered an intraoperative complication, which were most frequent during open gastric bypass (7.3%), followed by laparoscopic gastric bypass (5.5%) and laparoscopic adjustable gastric banding (3%). Independent of procedure type, patients who suffered an intraoperative complication were at significantly greater risk of morbidity [46].

Intraoperative and short-term postoperative complications after gastric bypass include but are not limited to gastrointestinal hemorrhage usually from the gastrojejunostomy staple line, stricture of the anastomosis, obstruction, leaks, and venous thromboembolism. Recent research on gastric bypass suggests that the risk of hemorrhage from the gastrojejunostomy staple line may be lowered by using a 25 mm circular stapler with 3.5 mm staples compared to 4.8 mm staples [47]. On the other hand, a large review of nine trials including 9374 patients who underwent laparoscopic gastric bypass showed a significantly increased risk of gastrojejunostomy stricture associated with circular-stapled compared to linear-stapled anastomosis [48]. Leaks are most common at the gastrojejunostomy and may be detected early or late in the postoperative course. Early leaks are often detected by clinical suspicion, radiological evaluation, or both, and treated by reoperation. Late leaks are most commonly diagnosed by radiological studies 7–14 days postoperatively. Some leaks may be treated nonoperatively or with flexible endoscopy; however, the surgeon must be aware that physical examination findings and radiological studies may underestimate the severity of the problem. Therefore, a high clinical suspicion and urgent abdominal exploration are often critical to the management of late gastrointestinal leaks. When patients present to the emergency department with an acute abdomen and/or signs and symptoms suggestive of anastomotic leak or internal hernia after gastric bypass, the patient should be evaluated expeditiously

by a general surgeon. A lengthy delay to another facility for evaluation and management by a bariatric surgeon can compromise the patient's outcome. Emergent operation can be lifesaving. Therefore, general surgeons must be familiar with the management of acute, life-threatening complications after gastric bypass.

It is important to recognize risk factors for venous thromboembolism in bariatric patients (male, high preoperative body mass index, history of venous thromboembolism or inferior vena cava filter) and to mitigate the risk of venous thromboembolism by selecting a laparoscopic approach and mandating adherence to clinical pathways.

20.4.9 Laparoscopic Splenectomy

The laparoscopic approach is widely used for splenectomy and considered to be the gold standard for elective splenectomy. Patients who underwent elective laparoscopic splenectomy experienced shorter hospital stays (3.6 vs. 7.2 days) despite longer operative times (180 vs. 114 min) than those who had open splenectomy [49]. Complication rates are also lower for patients who underwent laparoscopic splenectomy (15.5% vs. 26.6%) when matched for demographic characteristics and underlying disease [49]. Splenosis associated with missed accessory splenic material can result in failure to accomplish the goal of the operation: the eradication of splenic function. However, with a meticulous technique and an exhaustive search for accessory or dropped splenic material, the incidence of this complication (11%) is equivalent for laparoscopic and open splenectomy [49]. In patients with massive splenomegaly or complicated anatomy, the surgeon should consider hand-assisted laparoscopic splenectomy, which conveys the benefits of laparoscopy without sacrificing safety or efficacy.

20.4.10 Laparoscopic Adrenalectomy

The timely, accurate, and cost-effective evaluation and management of adrenal lesions can be challenging. Evaluation begins with biochemical screening and additional imaging but rarely includes biopsy. Management strategies vary by patient factors and tumor characteristics. Adrenalectomy is indicated for lesions that are hormonally active, larger than 4–5 cm, symptom-related, and have an imaging appearance that is atypical of a benign lesion.

During the last decade, laparoscopic adrenalectomy has replaced open adrenalectomy as the preferred method for removal of most adrenal tumors. This paradigm shift has occurred as a result of multiple factors including greater surgeon experience with advanced laparoscopy, improved technology, and better short-term patient outcomes. Case series, cohort studies, and database reviews have demonstrated less pain, shorter hospital stay, and fewer postoperative complications following laparoscopic adrenalectomy [50]. A growing body of literature suggests that experienced surgeons are performing laparoscopic adrenalectomy for a wider range of indications than ever before [50]. However, few studies clearly characterize the preoperative risk factors that may influence the choice of operative approach and, thereby, affect outcomes after adrenalectomy.

A recently presented retrospective cohort study of 402 patients aimed to determine the variables important in selecting patients for open adrenalectomy and predict the risks of conversion from the laparoscopic to open approach. Additionally, the study sought to compare 30-day outcomes of open and laparoscopic adrenalectomy. Preoperative factors that predicted selection for open adrenalectomy were increasing patient age, higher ASA score, large tumor size, the presence of a nonfunctioning lesion, the diagnosis of adrenocortical carcinoma, and the need for concomitant procedures. Conversion to open or hand-assisted approaches occurred in 6.2% of patients selected for laparoscopic adrenalectomy. Preoperative risks for conversion included large tumor size (>8 cm) and need for concomitant procedures. Multivariate analysis revealed that the preoperative diagnosis of large indeterminate adrenal mass or adrenocortical carcinoma, a radiological tumor size greater than 6 cm, and initial selection for open adrenalectomy (OR 8.1) increased 30-day morbidity. Likewise, a need for conversion from a laparoscopic to open approach (OR 3.5), a requirement for concomitant procedures (OR 3.8), operative time greater than 180 min, and an estimated blood loss of more than 200 mL predicted 30-day morbidity. Therefore, the nature of the underlying adrenal pathology and need for concurrent procedures both significantly impact the selection of patients for open adrenalectomy, the likelihood of conversion from a laparoscopic to open approach, and 30-day morbidity. The authors felt these metrics should be considered when choosing an operative approach and considering risks for adrenalectomy [51].

20.5 Conclusions

Minimally invasive surgery is a rapidly growing and maturing discipline that requires significant training and experience on the part of the surgeon as well as the healthcare team. When surgeon experience and facility resources allow, laparoscopy may offer the advantages of less pain, fewer wound-related complications, shorter hospital length of stay, and other benefits. Surgeons who gain sufficient experience with basic and advanced laparoscopy during their residency

and fellowship training, hands-on courses, or proctorships fully appreciate the causes and incidences of potential complications associated with laparoscopy. As with any procedure, prevention and management of complications is paramount; moreover, the method of management should adhere to time-honored surgical principles. These complications are best avoided by perfecting and using proper laparoscopic technique and by understanding the unique pitfalls of each laparoscopic operation.

Incidence of General Complications of Laparoscopy

Complications	Incidence	Comments	References
Pneumoperitoneum			
Increased airway pressures	Almost all cases	Airway pressures rise by 30%–40% but return to baseline after release of pneumoperitoneum	[2,3]
Hypercarbia	Almost all cases	End-tidal CO_2 rises by 10% but returns to baseline after release of pneumoperitoneum	[4]
Decreased cardiac output	Almost all cases	Output decreases by 10%–30% at 12–15 mmHg but returns to baseline after release of pneumoperitoneum	[5–7]
Arrhythmias	Up to 47%	Tachycardia is more common than bradycardia	[8]
Access			
Vascular injury	Minor 0.5%–2% Major 0.1%–0.25%	Major vascular injury accounts for 35% of all deaths	[11–14]
Visceral injury	0.1%–0.2%	Missed injury increases mortality 10-fold	[12–16]
Gas embolism	0.001%	Mortality rate approaches 30%	[17]
Subcutaneous emphysema	Unknown	Concern prompts chest radiography	[17,18]
Trocar-site hernia	0.2%–1.8%	Cutting trocars and defects >10 mm increase hernia rate	[18,19]

How to Avoid General Complications of Laparoscopy

Complications	Methods of Avoidance	Comments	References
Pneumoperitoneum			
Increased airway pressures	Preoperative pulmonary assessment; adjust tidal volumes	Evacuate pneumoperitoneum	[2,3]
Hypercarbia	Monitor end-tidal CO_2	Increase ventilation rate	[4]
Decreased cardiac output	Preoperative cardiac assessment; intraoperative resuscitation	Evacuate pneumoperitoneum; consider invasive cardiac monitoring, pharmacologic measures, and/or conversion	[5–7]
Arrhythmias	Pharmacologic measures; intraoperative resuscitation		[8]
Access			
Vascular injury	Stabilize the Veress needle, perform saline drop test, and ensure low intra-abdominal pressure; consider open access	Gain control, apply direct pressure, suture ligate, and/or consider conversion	[11–14]
Visceral injury		Survey the viscera upon completion	[12–16]
Gas embolism		Evacuate pneumoperitoneum, place in Trendelenburg and left lateral decubitus position, administer 100% oxygen	[17]
Subcutaneous emphysema	Avoid extraperitoneal insertion of Veress needle and trocars	Monitor spontaneous resolution	[17,18]
Trocar-site hernia	Use noncutting trocars; close fascial defects >10 mm	Investigate trocar-site pain thoroughly	[18,19]

How to Avoid and Manage Key Complications of Laparoscopic Procedures

Complications	Methods of Avoidance	Comments	References
Cholecystectomy			
Bile duct injury	Establish critical view of safety; perform cholangiography; consider fundus-first technique and/or subtotal cholecystectomy	Transect difficult cystic ducts using clip, suture, vessel sealing device, or stapler methods	[27–29]
Vascular injury	Establish critical view of safety		[28]
Bile and stone spillage	Dissect carefully; avoid excessive electrosurgery	Aspirate bile and extract stones when feasible	[30]
Fundoplication			
Bleeding	Avoid blind use of electrosurgery; protect spleen	Control short gastric vessels with sealing device or clips; control splenic injury with pressure, hemostatic agents, and/or electrosurgery	[31]
Wrap failure	Use permanent suture; close hiatal defect; incorporate esophagus into wrap stitches; ensure adequate intra-abdominal esophageal length	Dilate for dysphagia initially; reoperate for symptoms	[31–33]
Overly tight wrap	Calibrate with 54–60 F bougie		[33]
Esophageal injury	Pass blunt bougie slowly; avoid anterior retraction of esophagus	Repair perforation and cover with wrap intraoperatively; repair, divert, and/or stent postoperatively	[34]
Inguinal herniorrhaphy			
Bleeding	Identify triangle of doom; avoid retraction of epigastric vessels	Control minor vessel bleeding; convert for major vessel hemorrhage	[35,36]
Wound infection	Use perioperative antibiotics	Treat with antibiotics	[35–37]
Seroma/hematoma	Completely reduce the hernia sac	Counsel patients regarding the likelihood of seroma	[35–37]
Urinary retention	Minimize perioperative fluids; insert catheter	Catheterize and administer medications as indicated	[35–37]
Recurrence	Impact modifiable risk factors; reduce entire hernia sac; select a lightweight mesh that covers myopectineal orifice	Train to proficiency so as to lower rate of recurrence	[35–38]
Chronic pain	Secure lightweight mesh above the inguinal ligament using absorbable fixation; avoid Triangle of Pain	Maximize medical management; consider reoperation (triple neurectomy) for pain >1 year	[35–38]
Ventral herniorrhaphy			
Visceral injury	Stabilize the Veress needle, perform saline drop test, and ensure low intra-abdominal pressure; consider open access	Survey the viscera upon completion	[12–16] [40–43]
Postoperative pain	Augment narcotics with nonsteroidal anti-inflammatory drugs; inject local anesthetic	Consider preoperative epidural in select cases	[40–43]
Paralytic ileus	Minimize narcotics		[40–43]
Wound infection	Use perioperative antibiotics	Treat with antibiotics	[40–43]
Seroma/hematoma	Use semi-permeable mesh; excise hernia sac	Counsel patients regarding the likelihood of seroma	[35–37] [40–43]
Recurrence	Impact modifiable risk factors; remove foreign body; implant barrier-coated synthetic mesh with 4–5 cm overlap; secure mesh with transfascial sutures	Counsel patients regarding smoking cessation and weight loss; select the right mesh for the right patient; maximize tissue ingrowth by good technique	[40–43]
Gastric bypass			
Anastomotic bleeding	Use lower staple height (3.5 mm); inspect lumen for staple line bleeding	Manage medically in most cases	[46,47]
Anastomotic stricture	Use linear or wider (25 mm) circular stapler; minimize ischemia	Dilate and/or reoperate for symptoms	[48]
Anastomotic leak	Use meticulous technique, minimize ischemia; avoid electrosurgery around staples	Reoperate for early leaks; consider nonoperative vs. operative management for late leaks	[44–48]

Complications	Methods of Avoidance	Comments	References
Internal hernia	Close small mesenteric defects	Maintain high clinical suspicion; operate early	[44–48]
Venous thromboembolism	Recognize risk factors; shorten operative time; adhere to clinical pathways	Use appropriate weight-based prophylaxis; consider empiric vena cava filter placement	[44–48]

Disclosures: None.

References

1. Rauh R, Hemmerling TM, Rist M, Jacobi KE. Influence of pneumoperitoneum and patient positioning on respiratory system compliance. *J Clin Anesth* 2001; 13(5):361–365.
2. Galizia G, Prizio G, Lieto E et al. Hemodynamic and pulmonary changes during open, carbon dioxide pneumoperitoneum and abdominal wall-lifting cholecystectomy. A prospective, randomized study. *Surg Endosc* 2001; 15(5):477–483.
3. D'Ugo D, Persiani R, Pennestri F et al. Transesophageal echocardiographic assessment of hemodynamic function during laparoscopic cholecystectomy in healthy patients. *Surg Endosc* 2000; 14(2):120–122.
4. Ortega AE, Richman MF, Hernandez M et al. Inferior vena caval blood flow and cardiac hemodynamics during carbon dioxide pneumoperitoneum. *Surg Endosc* 1996; 10(9):920–924.
5. Nguyen NT, Ho HS, Fleming NW et al. Cardiac function during laparoscopic vs open gastric bypass. *Surg Endosc* 2002; 16(1):78–83.
6. Zuckerman RS, Heneghan S. The duration of hemodynamic depression during laparoscopic cholecystectomy. *Surg Endosc* 2002; 16(8):1233–1236.
7. Zuckerman R, Gold M, Jenkins P, Rauscher LA, Jones M, Heneghan S. The effects of pneumoperitoneum and patient position on hemodynamics during laparoscopic cholecystectomy. *Surg Endosc* 2001; 15(6):562–565.
8. Myles PS. Bradyarrhythmias and laparoscopy: A prospective study of heart rate changes with laparoscopy. *Aust NZ J Obstet Gynaecol* 1991; 31(2):171–173.
9. Reed DN Jr., Nourse P. Untoward cardiac changes during CO_2 insufflation in laparoscopic cholecystectomies in low-risk patients. *J Laparoendosc Adv Surg Tech A* 1998; 8(2):109–114.
10. Reed DN Jr., Duff JL. Persistent occurrence of bradycardia during laparoscopic cholecystectomies in low-risk patients. *Dig Surg* 2000; 17(5):513–517.
11. Champault G, Cazacu F, Taffinder N. Serious trocar accidents in laparoscopic surgery: A French survey of 103,852 operations. *Surg Laparosc Endosc* 1996; 6(5):367–370.
12. Chandler JG, Corson SL, Way LW. Three spectra of laparoscopic entry access injuries. *J Am Coll Surg* 2001; 192(4):478–491.
13. Schafer M, Lauper M, Krahenbuhl L. Trocar and Veress needle injuries during laparoscopy. *Surg Endosc* 2001; 15(3):275–279.
14. Bhoyrul S, Vierra MA, Nezhat CR, Krummel TM, Way LW. Trocar injuries in laparoscopic surgery. *J Am Coll Surg* 2001; 192(6):677–683.
15. Mayol J, Garcia-Aguilar J, Ortiz-Oshiro E, De-Diego Carmona JA, Fernancez-Represa JA. Risks of the minimal access approach for laparoscopic surgery: Multivariate analysis of morbidity related to umbilical trocar insertion. *World J Surg* 1997; 21(5):529–533.
16. Deziel DJ, Millikan KW, Economou SG, Doolas A, Ko STG, Airan MC. Complications of laparoscopic cholecystectomy: A national survey of 4,292 hospitals and an analysis of 77,604 cases. *Am J Surg* 1993; 165(1):9–14.
17. Bonjer HJ, Hazebroek EJ, Kazemier G, Guffrida MC, Meijer WS, Lange JF. Open versus closed establishment of pneumoperitoneum in laparoscopic surgery. *Br J Surg* 1997; 84(5):599–602.
18. Leibl BJ, Schmedt CG, Schwarz J, Kraft K, Bittner R. Laparoscopic surgery complications associated with trocar tip design: Review of literature and own results. *J Laparoendosc Adv Surg Tech A* 1999; 9(2):135–140.
19. Swank HA, Mulder IM, la Chapelle CF, Reitsma JB, Lange JF, Bemelman WA. Systematic review of trocar-site hernia. *Br J Surg* 2012; 99(3):315–323.
20. Hanna GB, Shimi SM, Cuschieri A. Randomised study of influence of two-dimensional versus three-dimensional imaging on performance of laparoscopic cholecystectomy. *Lancet* 1998; 351(9098):248–251.
21. Hofmeister J, Frank TG, Cuschieri A, Wade NJ. Perceptual aspects of two-dimensional and stereoscopic display techniques in endoscopic surgery: Review and current problems. *Semin Laparosc Surg* 2001; 8(1):12–24.
22. Bittner JG IVth, Hathaway CA, Brown JA. Three-dimensional visualization and articulating instrumentation: Impact of simulated laparoscopic tasks. *J Minim Access Surg* 2008; 4(2):31–38.
23. Okrainec A, Ferri LE, Feldman LS, Fried GM. Defining the learning curve in laparoscopic paraesophageal hernia repair: A CUSUM analysis. *Surg Endosc* 2011; 25(4):1083–1087.
24. Schouten N, Simmermacher RK, van Dalen T et al. Is there an end of the "learning curve" of endoscopic totally extraperitoneal (TEP) hernia repair? *Surg Endosc* 2012; Epub ahead of print.
25. Pendlimari R, Holubar SD, Dozois EJ, Larson DW, Pemberton JH, Cima RR. Technical proficiency in hand-assisted laparoscopic colon and rectal surgery: Determining how many cases are required to achieve mastery. *Arch Surg* 2012; 147(4):317–322.

26. Kaafarani HM, Smith TS, Neumayer L, Berger DH, Depalma RG, Itani KM. Trends, outcomes, and predictors of open and conversion to open cholecystectomy in Veterans Affairs Administration hospitals. *Am J Surg* 2010;200(1):32–40.
27. MacFadyen BV, Vecchio R, Ricardo AE, Mathis CR. Bile duct injury after laparoscopic cholecystectomy: The United States experience. *Surg Endosc* 1998; 12(4):315–321.
28. Strasberg SM, Brunt LM. Rationale and use of the critical view of safety in laparoscopic cholecystectomy. *J Am Coll Surg* 2010; 211(1):132–138.

    The primary purpose of this article is to present the rationale for the critical view of safety so that surgeons can better understand and apply it. Also, this article reviews the current use of this technique and suggests approaches that might reduce the incidence of biliary injury.
29. Soper NJ, Brunt LM. The case for routine operative cholangiography during laparoscopic cholecystectomy. *Surg Clin North Am* 1994; 74(4):953–959.
30. Memon MA, Deeik RK, Maffi TR, Fitzgibbons RJ Jr. The outcome of unretrieved gallstones in the peritoneal cavity during laparoscopic cholecystectomy: A prospective analysis. *Surg Endosc* 1999; 13(9): 848–857.
31. Niebisch S, Fleming FJ, Galey KM et al. Perioperative risk of laparoscopic fundoplication: Safer than previously reported—Analysis of the American College of Surgeons National Surgical Quality Improvement Program from 2005 to 2009. *J Am Coll Surg* 2012; 215(1):61–68.
32. Peters MJ, Mukhtar A, Yunus RM et al. Meta-analysis of randomized clinical trials comparing open and laparoscopic anti-reflux surgery. *Am J Gastroenterol* 2009; 104(6):1548–1561.

    This meta-analysis of 12 randomized trials totaling 1,036 patients with gastroesophageal reflux assessed the impact of laparoscopic anti-reflux procedures on six variables (operating time, hospital stay, return to normal activity, perioperative complications, treatment failure, and requirement for further surgery). The laparoscopic approach enables a faster convalescence and return to activity, a reduced risk of complications, and a similar treatment outcome compared to an open approach.
33. Hunter JG, Smith CD, Branum GD et al. Laparoscopic fundoplication failures: Patterns of failure and response to fundoplication revision. *Ann Surg* 1999; 230(4):595–606.
34. Zaninotto G, Molena D, Ancona E. A prospective multicenter study on laparoscopic treatment of gastroesophageal reflux disease in Italy: Type of surgery, conversions, complications, and early results. *Surg Endosc* 2000; 14(3):282–288.
35. Chung RS, Rowland DY. Meta-analyses of randomized controlled trials of laparoscopic vs conventional inguinal hernia repairs. *Surg Endosc* 1999; 13(7):689–694.
36. Tschudi JF, Wagner M, Klaiber C et al. Randomized controlled trial of laparoscopic transabdominal preperitoneal hernioplasty vs Shouldice repair. *Surg Endosc* 2001; 15(11):1263–1266.
37. O'Reilly EA, Bruke JP, O'Connell PR. A meta-analysis of surgical morbidity and recurrence after laparoscopic and open repair of primary unilateral inguinal hernia. *Ann Surg* 2012; 255(5):846–853.

    This meta-analysis of 27 randomized trails totaling 7,161 patients with primary unilateral inguinal hernias assessed the impact of laparoscopic inguinal herniorrhaphy on multiple variables including hernia recurrence and complications. The laparoscopic totally extraperitoneal (TEP) approach for primary unilateral inguinal hernia is associated with an increased risk of recurrence relative to open repair but the laparoscopic trans-abdominal preperitoneal (TAPP) approach is not. However, TAPP is associated with an increased risk of complications relative to open repair. A laparoscopic approach reduces the risk of chronic pain and numbness.
38. Treadwell J, Tipton K, Oyesanmi O, Sun F, Schoelles K. Surgical options for inguinal hernia: Comparative effectiveness review. In: *Comparative Effectiveness Reviews, No 70*. Rockville, MD: Agency for Healthcare Research and Quality; 2012. http://www.ncbi.nlm.nih.gov/books/NBK100633/. Accessed November 19, 2012.
39. Sauerland F, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2010; 6(10):CD00154639.
40. Itani KM, Hur K, Kim LT et al. Comparison of laparoscopic and open repair with mesh for the treatment of ventral incisional hernia: A randomized trial. *Arch Surg* 2010; 145(4):322–328.
41. Pierce RA, Spitler JA, Frisella MM, Matthews BD, Brunt LM. Pooled data analysis of laparoscopic vs. open ventral hernia repair: 14 years of patient data accrual. *Surg Endosc* 2007; 21(3):378–386.

    The purpose of this study was to analyze published perioperative results and outcomes of laparoscopic and open ventral hernia repair focusing on complications and hernia recurrences. Data were derived from 31 reports of laparoscopic alone and 14 that compared laparoscopic to open repair. Forty-five published series representing 5,340 patients were included. In the pooled analysis, laparoscopic ventral hernia repair was associated with significantly fewer wound complications, total complications, hernia recurrences, and a shorter length of stay.
42. Colavita PD, Tsirline VB, Walters AL, Lincourt AE, Belyansky I, Heniford BT. Laparoscopic versus open hernia repair: Outcomes and sociodemographic utilization results from the nationwide inpatient sample. *Surg Endosc* 2012; Epub ahead of print.
43. Moreno-Egea A, Carrillo-Alcaraz A, Aguayo-Albasini JL. Is the outcome of laparoscopic incisional hernia repair affected by defect size? A prospective study. *Am J Surg* 2012; 203(1):87–94.
44. Nguyen NT, Goldman C, Rosenquist CJ et al. Laparoscopic versus open gastric bypass: A randomized study of outcomes, quality of life, and costs. *Ann Surg* 2001; 234(3):279–291.
45. Tian HL, Tian JH, Yang KH, Yi K, Li L. The effects of laparoscopic vs. open gastric bypass for morbid obesity: A systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 2011; 12(4):254–260.

This meta-analysis of 6 randomized trials totaling 422 patients with morbid obesity assessed the impact of operative approach on multiple outcome variables. The effects of laparoscopic and open gastric bypass for morbid obesity were basically the same except that the laparoscopic approach had a shorter hospital stay while the open approach had a lower reoperation rate and shorter operative time.

46. Greenstein AJ, Wahed AS, Adenjii A et al. Prevalence of adverse intraoperative events during obesity surgery and their sequelae. *J Am Coll Surg* 2012; 215(2):271–277.
47. Nguyen NT, Dakin G, Needleman B et al. Effect of staple height on gastrojejunostomy during laparoscopic gastric bypass: A multicenter prospective randomized trial. *Surg Obes Relat Dis* 2010; 6(5):477–482.
48. Penna M, Markar SR, Venkat-Raman V, Karthikesalingam A, Hashemi M. Linear-stapled versus circular-stapled laparoscopic gastrojejunal anastomosis in morbid obesity: Meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2012; 22(2):95–101.
49. Winslow ER, Brunt LM. Perioperative outcomes of laparoscopic versus open splenectomy: A meta-analysis with an emphasis on complications. *Surgery* 2003; 134(4):647–653.

    This meta-analysis of 51 published reports totaling 2,940 patients who underwent splenectomy assessed the impact of operative approach on multiple outcome variables. Although operative times are longer for laparoscopic splenectomy compared to open splenectomy, the laparoscopic approach is associated with a significant reduction in splenectomy-related morbidity, primarily as a function of fewer pulmonary, wound, and infectious complications.
50. Brunt LM. The positive impact of laparoscopic adrenalectomy on complications of adrenal surgery. *Surg Endosc* 2002; 16:252–257.
51. Bittner JG et al. Presented at *SAGES Annual Meeting*, San Diego, CA, March 2012.

Section IV

Endocrine

21

Complications of Breast Surgery

Sayl Bunyan Al-Saedi and Ismail Jatoi

CONTENTS

This chapter will focus on various complications associated with diagnostic and therapeutic breast interventions.

21.1 Complications Associated with Diagnostic Interventions

Obtaining tissue biopsy is the key to proceeding with any abnormal clinical or radiological findings when it comes to breast lesions. Various methods exist, depending whether the lesion is palpable or not.

For nonpalpable lesions: Options include ultrasound (US)-guided fine-needle aspiration cytology (FNAC), core needle biopsy (CNB) with US or stereotactic guidance, vacuum-assisted stereotactic (mammotome) CNB, and excisional biopsy with US-guided or mammographically assisted needle localization.

For palpable lesions: Options include FNAC, CNB, incisional biopsy, and excisional biopsy.

Regardless of the modality used to obtain tissue diagnosis, the complications associated with the aforementioned procedures are generally rare and associated with low morbidity. These include the following:

1. *Hematoma/seroma*: Incidence ranges from 1%–3% [1], usually evident within the first 24–48 h after the procedure. Most can be treated with reassurance and expectant management. Some will drain spontaneously; others with be reabsorbed. Surgical drainage is generally reserved for hematomas that are large and expanding or occurring immediately after surgery.

   Seromas can sometimes develop, and usually are managed expectantly. Fluid collections may also become infected; in these cases, the purulent fluid needs surgical drainage.
2. *Wound infections*: Wound infections are relatively rare, with an overall incidence of 1%–2%. Treatment is with oral or intravenous antibiotics.
3. *Sample error (false negative rates)*: The incidence of sampling error is low (0.5%–2%). The significant improvement in imaging modalities has minimized these types of errors, although they are still considered operator dependent. An important aspect to invasive diagnostic modalities is to image the excised tissue to confirm accurate procurement of the pathology. Surgeons typically send the needle localizing (NLOC) partial

mastectomy samples to radiology immediately, to confirm complete removal of the mammographic abnormality.

21.2 Complications of Breast Conservation Therapy for Breast Cancer

This section includes complications associated with surgery as well as subsequent radiation therapy.

21.2.1 Wound Complications

Lymphedema and cellulitis of the breast after breast conservation therapy [2–4] should not be confused with the prototypical postsurgical wound infection (characterized by substantial wound site warmth, tenderness, redness, and seropurulent drainage that occurs within the first postoperative week). The lymphatic channels of the breast are compromised by axillary dissection and breast irradiation [5–7]. The resulting lymphedema is often early and temporary because collateral lymphatic drainage develops through the dermal and subcutaneous lymph vessels of the breast, chest, and shoulder and through higher-level axillary nodes, interpectoral nodes, and internal mammary nodes.

Cellulitis or lymphangitis is not always bacterial in origin. It may also be caused by an inflammatory reaction to stagnant lymphatic drainage and protein exudates. In such cases, the problem responds to expectant management or anti-inflammatory agents.

Clinically significant lymphedema in the upper extremity occurs in 5%–8% of patients after axillary dissection, whereas debilitating lymphedema rarely occurs [3,4].

Staren et al. [4] reported 5% incidence of chronic cellulitis or lymphangitis among 184 breast cancer patients treated with conservation therapy (lumpectomy, axillary dissection, and irradiation). Age, volume of breast tissue excised, number of lymph nodes excised, tumor location, stage of disease, and adjunctive therapy were significant risk factors for such complications. The cellulitis may take several weeks to clear, and/or it may recur or persist. It must always be remembered that cellulitis or lymphangitis can represent an aggressive, inflammatory recurrence of breast cancer; so if the cellulitis persists for more than 4 months, biopsy is indicated.

21.2.2 Cosmesis

Multiple studies looked at the cosmetic outcomes from breast conservation therapies and classified them using a four-point system (excellent, good, fair, and poor), with the last two being considered a failure in achieving the targeted cosmetic outcome. If breast conservation is to be an acceptable alternative to mastectomy, it must routinely achieve a very high cosmetic or aesthetic standard.

Surgical factors that contribute to a poor or only fair cosmetic outcome are excessive resection, the use of drains to evacuate fluid from the lumpectomy defect, multiple reexcisions, and excessive undermining of surrounding skin [8]. The placement and orientation of the incision are important for cosmesis and optimal local control: transverse or curvilinear incisions are optimal for lumpectomy in the upper hemisphere of the breast; inferior radial incisions also are acceptable.

Radiotherapy is an important factor for cosmetic outcome. Whole-breast doses in excess of 20 Gy, the use of tumor bed boosts, the use of multiple radiation fields, and irradiation of the regional lymph vessels are significant risk factors for an adverse cosmetic outcome. The adverse effects of radiotherapy on cosmesis are time dependent, evolving over a period of years [9–11].

21.2.3 Ipsilateral Recurrence of a Breast Tumor

Of the many factors that influence the incidence of ipsilateral recurrence of a breast tumor, only margin status, tumor size, and multicentricity relate directly to the surgical procedure. Excision of all gross disease is essential for control of tumor in the breast. Recurrence is four to five times more likely when gross tumor involves one or more surgical margins, even when the breast is adequately irradiated [12]. Tumor resection with histologically demonstrated tumor-free margins provides optimal disease control [13]. Most surgeons and oncologists consider such clear margins the standard of care for breast-conserving surgery in the management of early breast cancer.

There is little agreement among surgeons and pathologists, however, about the optimal method of assessing surgical margins during breast-conserving procedures. The method used in the trials supported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) provides a useful reference point because it has been validated in multiple clinical studies. Using intraoperative frozen sections or touch preparations to verify that the margins are clear minimizes the need for repeat lumpectomy or completion mastectomy [14,15].

Tumor size and the presence of multicentricity are important factors in determining whether breast-conserving procedures are appropriate. Recurrence is more likely with increased tumor size and with multifocality or multicentricity [15]. Tumors larger than 4 cm in diameter are generally not amenable to breast conservation unless the breast is large. One of the most subtle surgical judgments related to management recommendations is the size of the tumor relative to the

size of the breast. Histologically demonstrated clearance of tumor must be achieved, and a cosmetically acceptable result should be realized. If the results of the tumor resection are suboptimal, mastectomy with reconstruction is preferable for both tumor control and aesthetics. Excellent results can be achieved with current methods of breast reconstruction (see later text).

21.2.4 Late Carcinogenesis

Earlier studies showed that patients who undergo breast or chest wall radiotherapy (XRT) for cancer of the breast have a slightly elevated risk of second neoplasms; this increased risk becomes evident many years after treatment. Therefore, it has been assumed that patients most at risk of late carcinogenesis are those treated for breast cancer at a young age and those with a good prognosis (those who are likely to be long-term survivors). However because the patients included in the studies that led to these assumptions were treated with radiotherapy techniques that are now outdated, the risk of second neoplasms may have been overstated. The many recent technological improvements in the types of ionizing radiation used and in the methods of delivering such radiation may reduce the risk of late carcinogenesis for patients with breast cancer, who are currently undergoing breast conservation treatment with XRT.

Bone marrow cancer: The NSABP trials [16] and a large case–control study of 82,700 patients treated between 1973 and 1985 reported a late increase in the incidence of leukemia among patients with breast cancer who were treated with XRT [17]. The estimated radiation dose to the bone marrow in the 1985 study was 7.5 Gy.

Fisher et al. described 5 of 646 women receiving postoperative regional radiation developed leukemia, an overall risk of 1.39% ± 0.49% at 10 years. Twenty-seven cases of leukemia (0.5%) and seven cases of myeloproliferative syndrome (0.1%) were recorded in 5299 patients who received L-phenylalanine mustard (L-PAM)-containing regimens. The maximum cumulative risk of leukemia in chemotherapy recipients (leukemia of any type and myeloproliferative syndrome) was 1.68% ± 0.33% at 10 years following operation [16].

Contralateral breast cancer: Current methods of irradiating the breast after lumpectomy unavoidably expose the opposite breast to a low dose of ionizing radiation, approximately 0.5 Gy [18,19]. Three large population-based studies demonstrated that adjuvant XRT to the breast or chest wall modestly increases the relative risk of contralateral breast cancer (RR 1.33) [19,20,24]. This finding suggests that the magnitude of the carcinogenic effect is very low. A case–control study reported a small but significant increase in the risk of contralateral breast cancer only for patients 45 years of age or younger at the time of XRT (fewer than 3% of all second breast cancers in this study could be attributed to previous radiation treatment) [20].

Lung cancer: A study obtained from 1983 through 1986 showed that patients with breast cancer treated with XRT to the conserved breast or the chest wall were at increased risk of squamous cell carcinoma, small cell carcinoma, and adenocarcinoma of the ipsilateral lung [21]. The latency period was 10 years. Radiation dosimetry suggests that whole-breast megavoltage teletherapy at a dose of 6 MeV exposes the ipsilateral breast to 21% of the entire dose and the lungs to 1.2% of the entire dose. According to Inskip et al. approximately nine cases of radiotherapy-induced lung cancer per year would be expected to occur among 10,000 women who received an average lung dose of 10 Gy and survived for at least 10 years. For these 10-year survivors of breast cancer, the overall relative risk (RR) of lung cancer associated with initial radiotherapy for breast cancer was 1.8 (95% confidence interval [CI] = 0.8–3.8), and the RR increased with time following treatment. The RR for periods of 15 years or more after radiotherapy was 2.8 (95% CI = 1.0–8.2). Mean dose was 15.2 Gy to the ipsilateral lung, 4.6 Gy to the contralateral lung, and 9.8 Gy for both lungs combined. The excess RR was 0.08 per Gy [22].

Another case–control study in Connecticut looked at women with primary breast cancers treated with XRT who developed secondary malignancy between 1986 and 1989. No radiation effects were observed within 10 years of initial primary breast cancer. Among both smokers and nonsmokers diagnosed with second primary cancers more than 10 years after an initial primary breast cancer, radiation therapy was associated with a threefold increased risk of lung cancer. A multiplicative effect was observed, with women exposed to both cigarette smoking and breast cancer radiation therapy having a RR of 32.7 (95% confidence interval [CI], 6.9–154). The radiation carcinogenic effect was observed only for the ipsilateral lung and not for the contralateral lung both in smokers and nonsmokers [23].

Esophageal cancer: A retrospective, population-based cohort study of more than 220,000 patients with breast cancer demonstrated that, after 10 years of follow-up, the RR of squamous cell carcinoma of the esophagus for women undergoing XRT was 5.42 (95% CI, 2.33–10.68), whereas that for esophageal adenocarcinoma was 4.22 (95% CI, 0.47–15.25).

Soft-tissue sarcomas: (Angiosarcoma, lymphangiosarcoma, and Stewart–Treves syndrome) may arise in irradiated tissues many years after XRT for breast cancer. Although the incidence of these sarcomas is low and the latency period is long, these are virulent neoplasms. Lymphangiosarcoma accounts for the most common histological subtype (46%). Younger patients may be at higher risk than are older patients for the development of nonlymphangiosarcoma posttreatment sarcoma [25].

21.2.5 Cardiac Morbidity and Mortality

Excessive rates of late cardiac morbidity and mortality among breast cancer patients treated with XRT have been documented in several long-term studies [26], mostly related to acceleration of the atherosclerotic process. However, newer techniques in radiotherapy have been implemented to reduce the risk of postradiation cardiac morbidity.

Trastuzemab, which has shown to improve survival in HER2 positive early breast cancer, has adverse effects on the heart (namely, trastuzemab-induced cardiotoxicity [TIC] and heart failure). One study showed that among 179 patients, 78 cases of TIC (44%, 95% CI 37%–51%) and 4 cases of heart failure (2%, 95% CI 0%–4%) were reported. Fourteen patients stopped trastuzemab as a result of TIC [27].

TIC is a frequent, but generally mild, adverse event in clinical practice. Further studies are warranted to better define the risk of and protective factors for TIC.

21.2.6 Compromised Surveillance of the Treated Breast

The combined effects of surgery and irradiation can make posttreatment surveillance of the conserved breast a challenge. Early effects such as dermal and parenchymal edema and late effects such as fibrosis and fat necrosis in the treated breast can confound clinical and mammographic surveillance for recurrent disease or new primary tumors [28].Consequently, in such cases the surgeon must more frequently resort to CNB or open biopsy.

21.2.7 Complications of Breast Biopsy after Breast Conservative Therapy

Biopsy of the treated breast is associated with an increased risk of wound complications and is detrimental to cosmesis. The exaggerated postoperative fibrotic response hinders subsequent surveillance of the breast. Pezner et al. reported that wound infections occurred after 8 of 27 open biopsies performed on patients who had undergone breast-conserving therapy [29]. Three infections resolved within 4 weeks; four required 3–7 months for complete resolution; and one failed to resolve. On rare occasions, intractable wound complications, biopsy-induced cosmetic deterioration, or the inability to evaluate the breast for disease can necessitate total mastectomy in the absence of recurrent cancer. Reported complication rates associated with salvage surgery for recurrence after breast conservation range from 7% to 26% [30,31].

21.3 Complications Associated with Axillary Lymph Node Dissection and Sentinel Lymph Node Biopsy

Sentinel node biopsy (SNB) technology has dramatically improved the quality of life for women with breast cancer. One method of SNB entails injecting a blue dye (iosulfan blue) around the areola or around the tumor. The dye will terminate in the lymphatics around the subclavian vein after passing an isolated node (the sentinel node), which drains the lymph first. Another way of performing SLNB is by injecting a radiocolloid and using a gamma probe to detect the strongest signal from the axilla. Some surgeons use both techniques simultaneously to enhance the ability to accurately identify the sentinel node.

Multiple studies were done comparing complications associated with ALND vs. SNLB, followed by ALND dissection; only if the SLN was positive, there was a significant reduction in all complications in the SLN group of patients [32,33].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial randomized 5611 women with clinically node-negative breast cancer either to SNB plus ALND or to SNB alone, with ALND performed only if there was evidence of metastasis to the sentinel nodes. With a median time of follow-up of 95.6 months, the overall survival, disease-free survival, and regional control were equivalent between the two groups. Thus, when the sentinel node reveals no evidence of metastatic disease, SNB alone with no further ALND appears to be a safe and effective therapy. In this trial, a total of 1975 ALND and 2008 sentinel node-negative breast cancer patients had shoulder range of motion and arm volumes assessed along with self-reports of arm tingling and numbness. Significant shoulder abduction deficits were seen in the ALND group compared with the SNB group at 6 months. Arm volume differences and numbness and tingling at 36 months also were significantly worse for the ALND groups [32,33].

In the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, Mansel et al. randomized 1031 patients with primary breast cancer to SNB vs. standard ALND. The SNB group had a lower incidence of lymphedema, shorter drain usage and hospital stay, and reduced time to resumption of everyday activities compared with the ALND group. The RRs of lymphedema and sensory loss for the SNB group compared with the ALND group at 12 months were 0.37 (95% confidence interval (CI), 0.23–0.6), and 0.37 (95% CI, 0.27–0.5), respectively, and patient-recorded quality of life and arm functioning scores were significantly better in the SNB group [32,33].

In a trial conducted in Milan, Veronesi et al. randomized 516 patients with tumor size 2 cm or less in diameter to ALND vs. SNB followed by ALND only for patients with metastasis to the sentinel nodes. After 2 years of follow-up, patients who underwent SNB alone had significantly less pain (8% vs. 39%), less numbness (1% vs. 68%), and better arm mobility (0% vs. 21%) compared with patients who had a routine ALND, indicating a significant quality of life (QoL) improvement with SNB alone [32,33].

The Gruppo Interdisciplinare Veneto di Oncologia Mammaria (GIVOM) trial randomized 697 patients to SNB vs. ALND and reported significantly less lymphedema, movement restrictions, and numbness in patients who underwent SNB at 24 months of follow-up. In addition, the investigators found that overall QoL was better in the SNB group.

Purushotham et al. randomly assigned 298 patients with tumors less than 3 cm to ALND (control group) vs. SNB followed by ALND only if sentinel nodes were positive (study group). They reported significant reductions in sensory deficits in the study group compared with the control group, including numbness (48% vs. 65%), loss of sensitivity to light touch (57% vs. 78%), and pinprick (55% vs. 76%; P0.001). However, with prolonged follow-up, the benefit of SNB appeared to diminish [32,33].

Greater body weight, higher body mass index (BMI), and infection or injury in the ipsilateral arm since surgery were found to be significant risk factors associated with lymphedema. Kell et al. published the results of a meta-analysis of seven randomized, controlled trials with a total of 9608 patients, which examined the effect of SNB on morbidity. The trials included were NSABP-B32, SNAC, GIVOM, ACOSOG Z0011, ALMANC, Milan, and Purushotham's trial. This meta-analysis demonstrated a significant reduction in the risk of postoperative seroma (OR= 0.4, P = 0.0071), wound infection (OR = 0.58, P = 0.0011), lymphedema (OR = 0.3, P = 0.0028), and extremity numbness (OR = 0.25, P = 0.0018) in the SNB group compared with the ALND group.

21.4 Complications Associated with Breast Reconstruction

Breast reconstruction is well accepted as an important part of overall therapy for breast cancer. Numerous techniques are available for reconstruction. The surgical oncologist, medical oncologist, and plastic/reconstructive surgeon must therefore work together to provide a safe and effective treatment plan that eliminates the cancer and restores the patient's appearance. One of the first decisions is whether breast reconstruction should be performed immediately after mastectomy or be delayed. Both methods are effective, but most reconstructive surgeons believe that immediate reconstruction, especially with the skin-sparing mastectomy technique, provides psychological benefits and better overall results, by reducing the scar burden, and eliminating the effect of color difference with no effect on local recurrence [34,35].

The overall benefit should, however, be placed into the context of new information about adjuvant therapy such as postoperative chemotherapy and irradiation and the effects of immediate reconstruction on the treatment plan. Consequently, the risks and benefits of each type of reconstruction must be carefully discussed with the patient to allow for a completely informed decision about reconstruction. Whether immediate or delayed reconstruction is chosen, it should be initiated only after the patient has recovered from any adjuvant therapy that may have been administered. An adequate recovery period should be allowed after reconstructive surgery so that healing can occur before other potentially complicating therapy such as chemotherapy or irradiation is administered.

Breast reconstruction can be viewed as providing a replacement for the skin and tissue volume that were removed during the mastectomy. Two approaches are used to achieve this result. One approach, tissue expansion and implant placement, expands the adjacent skin and muscle to cover a silicone prosthesis filled with saline solution or silicone gel, which is used to replace lost breast volume. The second technique replaces the lost skin and volume with an autologous tissue flap composed of skin, subcutaneous fat, and, at times, fascia and muscle. Some hybrid techniques use the implant to provide missing volume and a flap of tissue to replace the skin deficit. Because a diagnosis of breast cancer is stressful and the treatment decisions are complicated, it is most important that patients have a clear understanding of the options for reconstruction and the necessary risks of reconstruction. Once this understanding has been obtained, most complications associated with breast reconstruction can be treated effectively.

21.4.1 Implant Reconstruction

Implant reconstruction in the form of tissue expansion followed by placement of a permanent implant is an accepted practice. Because the operative time and hospitalization period associated with this procedure are short, implant reconstruction is popular among surgeons and patients. This technique involves placing an underfilled tissue expander into a surgically created pocket behind the lower portion of the pectoralis muscle

at the base of the inframammary fold. This procedure can be performed as an immediate reconstruction after a mastectomy or as a delayed reconstructive procedure. In either case, after the wound has adequately healed, an injection port connected to the implant is accessed with a needle, and normal saline solution is injected at intervals to expand the skin and muscle and thus to create a pocket large enough for the subsequent, permanent implant. Once the tissue has been expanded, a second surgical procedure is performed to exchange the expander for a permanently placed implant that gives the patient a new breast with volume and adequate soft-tissue coverage. This operation can be followed by nipple reconstruction and, if needed, a symmetry procedure for the opposite breast.

Implant reconstruction is best suited for patients who do not smoke and who have smaller, less ptotic breasts because creating ptosis with implants is difficult (meaning that the angle between the inferior breast margin and the chest wall is greater than 90°). A study from Finland has shown that it will take 3 months after placing the tissue expander to create the inframammary fold, before a permanent implant placement [36].

Although implant reconstruction requires relatively short procedures that are not systemically stressful, the multiple stages and demanding office visits for expansion are undesirable. Most important, the number of potential complications and the frequency with which they occur make tissue expansion and implant reconstruction less attractive than other procedures.

The Saline Prospective Study [37], conducted over a 3-year period and published by implant manufacturer Mentor Corporation, determined the cumulative individual risk rates for the following complications: capsule contracture, 30%; infection, 9%; rupture or deflation, 9%; asymmetry, 28%; wrinkling of the implant, 20%; extrusion, 2%; seroma, 6%; hematoma, 1%; and breast pain or inflammation, 17%. The reported reoperation rate for patients who underwent this type of reconstruction was 40%.

The incidence of capsule contracture associated with tissue expansion and implant reconstruction has been reported to be as high as 50%, particularly with silicone implants [38]. Capsule contracture can be very difficult to correct. In such cases, the implants will become firm or even hard and can even be displaced. Capsule contracture can have many causes, but contributing factors may be low-grade infections, undrained hematomas, silicone gel leakage, and foreign-body reactions [39]. The rates of contracture appear to be lower when implants are placed below the pectoralis muscle. Saline-filled implants, antibiotic irrigation (as described by Burkhardt et al. using 5% povidone iodine), and intraluminal administration of steroids may decrease the rate of these complications [39]. Treatment includes removal of the implant and, if possible, total capsulectomy with removal of any leaking silicone gel. A new implant is placed under the pectoralis muscle.

Radiation therapy before or after reconstruction further complicates implant reconstruction. Radiation therapy after such reconstruction is associated with high infection rates, which may subject the patient to further procedures or even removal of the implant.

Infections can be managed with intravenous antibiotics. Failure of medical management will require removal of the implant.

Rupture of a saline implant is easily detected because of the loss of breast volume, but rupture of a silicone gel implant can be more difficult to diagnose because the gel frequently remains in the capsule. Breast US can be helpful, but magnetic resonance imaging performed with a machine equipped with a breast coil is associated with higher sensitivity and specificity [40]. Treatment includes removing the implant and any remaining gel and, if possible, a total capsulectomy to remove the excess silicone gel.

Postoperative hematomas usually occur early but may occur as late as 7–14 days after surgery [41]. The cause is either bleeding from a previously controlled vessel or diffuse oozing. Careful intraoperative hemostasis is the key to prevention. Seromas result from pocket dissection and are generally detectable as a soft, nontender swelling that results in asymmetry. Many seromas will resolve spontaneously within a week or two. Placing a drain can help, but prolonged use of drains can lead to infection.

One important point that cannot be overlooked is the relationship between breast implants, particularly those used in augmentation mammoplasty, and breast cancer.

Breast implants obscure some portion of the breast during mammography. One report demonstrated that as much as 44% of the breast can be obstructed by subglandular silicone gel breast implants and as much as 25% can be obstructed by submuscular implants [42]. Capsule contracture also limits the amount of breast tissue that can be seen on postoperative mammograms [43]. Long-term studies have shown that delayed detection of breast cancer does not appear to be a serious problem for patients with breast implants, nor is their prognosis poorer than that of patients without implants [44]. Diagnostic procedures such as needle biopsies and lymphatic mapping may not be recommended for patients with breast implants; open procedures should be used instead. For patients with breast cancer, implants may make lumpectomy impossible and may necessitate mastectomy.

21.4.2 Autologous Reconstruction

The unique aspect of autologous reconstruction is that the entire reconstruction is achieved with the patient's

own tissue in a more aesthetically pleasing breast than does implant reconstruction. In addition, autologous reconstruction may provide a psychological benefit to the patient [45].

Several donor sites can be used for autologous reconstruction. Each site is associated with particular types of morbidity and with potential benefits to the patient, but not all options will be possible for all patients. The surgeon and the patient should carefully consider the options and develop a plan that is acceptable to both.

The technique most commonly used for autologous breast reconstruction is the transverse rectus abdominis myocutaneous (TRAM) flap. This ideal flap uses the skin, fat, and muscle of the lower abdomen to replace the breast defect. The TRAM flap can be transferred as a pedicled flap based on the deep superior epigastric artery and the rectus abdominis muscle. Others have used the same abdominal tissue with a segment of the rectus muscle and transferred it as a microvascular free flap based on the deep inferior epigastric artery. Both the free flap and the pedicled flap provide a large amount of viable tissue and allow the reconstruction to be tailored to the desired shape and size. Because it is a complicated procedure, TRAM flap reconstruction requires a lengthy operation and an extended hospitalization. A relatively long recuperation period with limited activity is required for limiting some of the morbidity associated with the procedure, such as incisional hernias or lower abdominal bulges. However, the aesthetic result is better than that achieved with other reconstructive procedures. An outcome study at the University of Michigan found that breast reconstruction with the TRAM flap was generally and aesthetically more satisfying than reconstruction with tissue expansion and implants [46].

Several potential complications are associated with the use of the TRAM flap, including partial or total flap loss, improper wound healing at the donor or recipient site, palpable fat necrosis of the flap, and abdominal bulging, hernia, or weakness. Deep venous thrombosis and pulmonary embolus are extreme complications. Patient choice is crucial if these complications are to be kept at an acceptable level. Hartrampf [47] identified the risk factors associated with poor outcome in TRAM flap reconstruction, to help identify the patients who are candidates for this procedure. The most important risk factors were obesity, smoking, autoimmune diseases such as scleroderma, diabetes (especially insulin-dependent diabetes), psychosocial problems, abdominal scars that could affect the perfusion of the abdominal flap, and, of course, a serious systemic disease such as chronic lung or heart disease.

Probably the most serious complication of TRAM flap reconstruction is flap necrosis. The incidence of necrosis ranges from 2% to 6% [48]. Some studies have shown that some degree of necrosis will be detected clinically or radiologically in up to 19% of patients undergoing TRAM reconstruction. Occasionally, contour deformity may require repeated excision of excess tissue. Several procedures have been devised to improve the vascular perfusion to the flap tissue.

A delayed TRAM flap procedure performed approximately 2 weeks before transfer may improve the vascular perfusion of pedicled TRAM flaps and may reduce the incidence of partial or full necrosis of the flap [49]. Some surgeons choose to use the free-vascularized TRAM flap for breast reconstruction because of its more direct blood supply, and because clinical evidence shows that the free flap is less subject to fat necrosis than the pedicled TRAM flap [50]. Small areas of flap necrosis can be managed by simple observation and local care, and revisions can be performed at a later stage of reconstruction. Large necrotic areas on mastectomy skin flaps or on the TRAM flap should be excised and closed in the earlier stages of reconstruction so that the optimal final result can be achieved.

Abdominal bulging and hernia formation are common problems associated with the use of either free or pedicled TRAM flaps for breast reconstruction, with an incidence of 3.8% and 2.6%, respectively. Reinforcing the rectus fascia closure with mesh is most helpful in reducing the incidence of this problem [51].

More recently, a modification of the TRAM flap, the deep inferior epigastric artery perforator (DIEP) flap, has been shown to be an improvement over the free or pedicled TRAM flap. The DIEP flap uses the same abdominal tissue for reconstruction as the TRAM flap; however, the rectus muscle and the abdominal fascia are completely spared. Although this flap requires a complicated dissection of the perforatoring vessels passing from the deep inferior epigastric artery and vein through the rectus abdominis muscle to the abdominal fat and also requires a microvascular anastomosis, the reported results have been excellent. Most postoperative abdominal bulges and hernias are eliminated. Muscle strength and function are outstanding. Postoperative pain is reduced and hospitalization may be shorter [52–55]. Although the vascular supply to this flap is more compromised than that of the free TRAM flap, careful patient choice will keep flap necrosis rates similar to those associated with the free TRAM flap [55].

Some patients, particularly those who are very thin or who have abdominal scars, will not be the candidates for breast reconstruction with abdominal flaps. Alternative autologous flaps, such as the latissimus dorsi flap, the gluteus myocutaneous flap, and the thigh and hip flaps can be used.

Hybrid flaps such as the TRAM flap or the latissimus dorsi myocutaneous flap with permanent implants are alternatives for reconstruction. Covering a permanent

implant with autologous tissue allows the skin defect to be replaced by the flap and the volume to be replaced by an implant. The results obtained by using hybrid flaps can be excellent; however, these procedures are associated with some of the same long-term problems as are implants, such as infection, rupture, and capsule contracture. The latissimus dorsi myocutaneous flap with implant is the most popular of these hybrid flaps. The most common complication associated with this flap is seroma formation at the donor site. This complication can be easily managed by repeated aspiration. The postoperative function of the shoulder muscle is good, with only minimal limitations [56–58].

The gluteus myocutaneous flap and its modification and the superior gluteal artery perforator (S-GAP) flap (a perforator flap based on the superior gluteal artery) are alternatives for autologous reconstruction. These flaps can provide a good volume of adipose tissue, even in thin patients, and can also provide sensory innervation. Donor-site morbidity is minimal and the scar can be well hidden. One criticism of breast reconstruction with the gluteus myocutaneous free flap is that the dissection is difficult and the vascular pedicle is very short. When the perforator to the superior gluteal artery (the S-GAP flap) is used, the pedicle is much longer and the microvascular anastomosis can be performed to the internal mammary artery or the thoracodorsal artery [59]. The main complications associated with the S-GAP flap, such as flap loss and necrosis, appear to be similar to those associated with other microvascular breast reconstruction techniques.

21.5 Conclusion

Breast interventions, both diagnostic and therapeutic, may result in complications that may in turn contribute significantly to the patient's morbidity. Knowing these complications, how to deal with them, and most importantly, how to avoid them is crucial. Proper patient selection significantly affects the outcome in breast interventions, especially when it comes to history of smoking, obesity, multiple comorbidities, and radiation exposure. The role of breast conservative surgery, sentinel lymph node biopsy, and the plastic/reconstructive surgery plays an important role in improving the psychological and aesthetic outcome. However, these procedures are not risk free.

Incidence of Complications of Breast Surgery

Breast Intervention	Complications	Percentage (%)	References
Diagnostic interventions	Hematoma/seroma	1–3	Say et al. [1]
	Wound infections	1–2	Say et al. [1]
	Sampling error	0.5–2	Say et al. [1]
Breast conservation therapy	Cellulitis/lymphangitis	5	Staren et al. [4]
	Poor cosmesis	12–22	Olivotto et al. [9]
	Ipsilateral recurrence	9	Fisher et al. [15]
Late carcinogenesis	Bone marrow	0.1–0.5	Fisher et al. [16]
	Contralateral breast CA	<3	Boice et al. [20]
	Lung cancer	0.0009	Inskip et al. [22]
Cardiac toxicity	Trastuzemab-induced cardiotoxicity	44	Farolfi et al. [27]
	Trastuzemab-induced heart failure	2	Farolfi et al. [27]
Sentinel node biopsy vs. axillary dissection SNB/ALND	Pain	8/39	Kumar et al. [33]
	Numbness	1/68	Kumar et al. [33]
	Arm mobility restriction	0/21	Kumar et al. [33]
	Lymphedema	0/68	Kumar et al. [33]
Breast reconstruction Implant reconstruction	Capsule contracture	30	SPS [37]
	Infection	9	SPS [37]
	Rupture	9	SPS [37]
	Asymmetry	28	SPS [37]
	Wrinkling of implant	20	SPS [37]
	Extrusion	2	SPS [37]
	Seroma	6	SPS [37]
	Hematoma	1	SPS [37]
	Breast pain	17	SPS [37]
Autologous reconstruction	Flap necrosis	2–6	Kroll et al. [48]
	Abdominal bulge	3.8	Kroll et al. [50]
	Hernia	2.6	Kroll et al. [50]

Avoiding Complications of Breast Surgery

Breast Intervention	Complications	Methods of Prevention
Diagnostic interventions	Hematoma/seroma	Hemostasis/use of drains
	Wound infections	Preop antibiotics, sterile techniques
	Sampling error	Imaging of excised tissue
Breast conservation therapy	Cellulitis/lymphangitis	Avoid excessive tissue excision
	Poor cosmesis	Lumpectomy of <70 cm^3 if possible free margins,
	Ipsilateral recurrence	intraop frozen section
Late carcinogenesis	All types	Limitation of radiation dose
Cardiac toxicity	Trastuzemab-induced cardiotoxicity	Frequent cardiac function assessment
	Trastuzemab-induced heart failure	
	Pain	
Axillary lymph node dissection	Numbness	Routine use of sentinel node biopsy
	Arm mobility restriction	
	Lymphedema	
Breast reconstruction	Capsule contracture	Place the implant below pectoralis
Implant reconstruction		Use of saline-filled implants
		Antibiotics irrigation
		Steroids
	Infection	Antibiotics, surgery after completion of radiation
	Seroma	Drain placement
	Hematoma	Absolute hemostasis
	Flap necrosis	Use of delayed flap/free flap procedures
Autologous reconstruction	Abdominal bulge	Approximation of fascia
	Hernia	Use of mesh

References

1. Say CC, Donegan W. A biostatistical evaluation of the complications from mastectomy. *Surg Gynecol Obstet*. 1974; 138:370–376.
2. Aitken DR, Minton JP. Complications associated with mastectomy. *Surg Clin North Am*. 1983; 63:1331–1352.
3. Simon MS, Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. *Am J Med*. 1992; 93:543–548.
4. Staren ED, Klepac S, Smith AP et al. The dilemma of delayed cellulitis after breast conservation therapy. *Arch Surg*. 1996; 131:651–654.
5. Gallagher PG, Algird JR. Post radical mastectomy edema of the arm: The role of phlebitis. *Angiology.* 1966; 17:377–388.
6. Veronesi U, Saccozzi R, Del Vecchio M et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med*. 1981; 305:6–11.
7. Babb RR, Spittell JA Jr, Martin WJ, Schirger A. Prophylaxis of recurrent lymphangitis complicating lymph-edema. *JAMA.* 1966; 195:871–873.
8. Winchester PD, Cox JD. Standards for breast-conservation treatment. *CA Cancer J Clin*. 1992; 42:134–162.
9. Olivotto IA, Rose MA, Osteen RT et al. Late cosmetic outcome after conservative surgery and radiotherapy: Analysis of causes of cosmetic failure. *Int J Radiat Oncol Biol Phys*. 1989; 17:747–753.
10. Van Limbergen E, Rijnders A, van der Schueren E, Lerut T, Christiaens R. Cosmetic evaluation of breast conserving treatment for mammary cancer. 2. A quantitative analysis of the influence of radiation dose, fractionation schedules, and surgical treatment techniques on cosmetic results. *Radiother Oncol*. 1989; 16:253–267.
11. Wazer DE, DiPetrillo T, Schmidt-Ullrich R et al. Factors influencing cosmetic outcome and complication risk after conservative surgery and radiotherapy for early-stage breast carcinoma. *J Clin Oncol*. 1992; 10:356–363.
12. Recht A, Silver B, Schnitt S, Connolly J, Hellman S, Harris JR. Breast relapse following primary radiation therapy for early breast cancer. I. Classification, frequency and salvage. *Int J Radiat Oncol Biol Phys*. 1985; 11:1271–1276.
13. Veronesi U, Volterrani F, Luini A et al. Quadrantectomy versus lumpectomy for small size breast cancer. *Eur J Cancer.* 1990; 26:671–673.
14. Fisher B, Wolmark N, Fisher ER, Deutsch M. Lumpectomy and axillary dissection for breast cancer: Surgical, pathological, and radiation considerations. *World J Surg*. 1985; 9:692–698.
15. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: Pathological findings from NSABP protocol B-06. *Semin Surg Oncol*. 1992; 8:161–166.
This paper reflects the importance of tumor free tissue excision, and the use of intra op frozen section.
16. Fisher B, Rockette H, Fisher ER, Wickerham DL, Redmond C, Brown A. Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiation: The NSABP experience. *J Clin Oncol.* 1985; 3:1640–1658.

17. Curtis RE, Boice JD Jr, Stovall M et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med*. 1992; 326:1745–1751.
18. Fraass BA, Roberson PL, Lichter AS. Dose to the contralateral breast due to primary breast irradiation. *Int J Radiat Oncol Biol Phys*. 1985; 11:485–497.
19. Hankey BF, Curtis RE, Naughton MD, Boice JD Jr, Flannery JT. A retrospective cohort analysis of second breast cancer risk for primary breast cancer patients with an assessment of the effect of radiation therapy. *J Natl Cancer Inst*. 1983; 70:797–804.
20. Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med*. 1992; 326:781–785.
21. Neugut AI, Robinson E, Lee WC, Murray T, Karwoski K, Kutcher GJ. Lung cancer after radiation therapy for breast cancer. *Cancer*. 1993; 71:3054–3057.
22. Inskip PD, Stovall M, Flannery JT. Lung cancer risk and radiation dose among women treated for breast cancer. *J Natl Cancer Inst*. 1994; 86:983–988.
23. Neugut AI, Murray T, Santos J, Amols H, Hayes MK, Flannery JT, Robinson E. *Increased Risk of Lung Cancer after Breast Cancer Radiation Therapy in Cigarette Smokers*. Department of Medicine, Columbia University, New York. p. 10032.
24. Harvey EB, Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935–82. *J Natl Cancer Inst Monogr*. 1985; 68:99–112.
25. Brady MS, Garfein CF, Petrek JA, Brennan MF. Post-treatment sarcoma in breast cancer patients. *Ann Surg Oncol*. 1994; 1:66–72.
26. Ebbs SR, Yarnold JR. Patient and anatomical selectivity in postoperative radiotherapy for early breast cancer: A British perspective. *Semin Surg Oncol*. 1992; 8:167–171.
27. Farolfi A, Melegari E, Aquilina M et al. *Trastuzumab-Induced Cardiotoxicity in Early Breast Cancer Patients: A Retrospective Study of Possible Risk and Protective Factors*. Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST-IRCCS), Meldola, Italy.
Importance of frequent cardiac assessment after initiation of trastuzemab therapy.
28. Dershaw DD, McCormick B, Cox L, Osborne MP. Differentiation of benign and malignant local tumor recurrence after lumpectomy. *Am J Roentgenol*. 1990; 155:35–38.
29. Pezner RD, Lorant JA, Terz J, Ben-Ezra J, Odom-Maryon T, Luk KH. Wound-healing complications following biopsy of the irradiated breast. *Arch Surg*. 1992; 127:321–324.
30. Osborne MP, Borgen PI, Wong GY, Rosen PP, McCormick B. Salvage mastectomy for local and regional recurrence after breast-conserving operation and radiation therapy. *Surg Gynecol Obstet*. 1992; 174:189–194.
31. Stotter A, Kroll S, McNeese M, Holmes F, Oswald MJ, Romsdahl M. Salvage treatment for locoregional recurrence following breast conservation therapy for early breast cancer. *Eur J Surg Oncol*. 1991; 17:231–236.
32. Jatoi I. Axillary vs sentinel lymph node dissection for invasive breast cancer. *JAMA*. 2011; 305(22):2288 author reply 2290–2281.
33. Kumar A, Puri R, Gadgil PV, Jatoi I. Sentinel lymph node biopsy in primary breast cancer: Window to management of the Axilla. *World J Surg*. 2012; 36:1453–1459. DOI 10.1007/s00268-012-1635-8.
This paper provides a summary of all major studies comparing complications associated with axillary dissection and the role of sentinel node biopsy.
34. Hidalgo DA, Borgen PJ, Petrek JA, Heerdt AH, Cody HS, Disa JJ. Immediate reconstruction after complete skin-sparing mastectomy with autologous tissue. *J Am Coll Surg*. 1998; 187(1):17–21.
35. Wellisch DK, Schain WS, Noone RB, Little JW III. Psychosocial correlates of immediate versus delayed reconstruction of the breast. *Plast Reconstr Surg*. 1985; 76(5):713–718.
36. Fan J, Raposio E, Wang J, Nordstrom RE. Development of the inframammary fold and ptosis in breast reconstruction with textured tissue expanders. *Aesthetic Plast Surg*. 2002; 26(3):219–222.
37. Mentor Corporation. *Saline Prospective Study (SPS). Saline Filled Breast Implant Surgery: Making an Informed Decision*, Mentor Corporation, Santa Barbara, CA, 2000, p. 13.
This study described various complications with implant reconstruction and their percentages.
38. Gylbert L, Asplund O, Jurell G. Capsular contracture after breast reconstruction with silicone-gel and saline-filled implants: A 6-year follow-up. *Plast Reconstr Surg*. 1990; 85:373–377.
39. Burkhardt BR, Dempsey PD, Schnur PL, Tofield JJ. Capsular contracture: A prospective study of the effects of local antibacterial agents. *Plast Reconstr Surg*. 1986; 77:919–932.
40. Cronin TD, Greenberg RL. Our experiences with the silastic gel breast prosthesis. *Plast Reconstr Surg*. 1970; 46:1–7.
41. Courtiss EH, Goldwyn RM, Anastasi GW. The fate of breast implants with infections around them. *Plast Reconstr Surg*. 1979; 63:812–816.
42. Silverstein MJ, Handel N, Gamagami P. The effect of silicone-gel-filled implants on mammography. *Cancer*. 1991; 68(suppl 5):1159–1163.
43. Deapen D, Hamilton A, Beernstein L, Brody GS. Breast cancer stage at diagnosis and survival among patients with prior breast implants. *Plast Reconstr Surg*. 2000; 105:535–540.
44. Birdsell DC, Jenkins H, Berkel H. Breast cancer diagnosis and survival in women with and without breast implants. *Plast Reconstr Surg*. 1993; 92:795–800.
45. Kroll SS. Why autologous tissue? *Clin Plast Surg*. 1998; 25(2):135–143.
46. Alderman AK, Wilkins EG, Lowery JC, Kim M, Davis JA. Determinants of patient satisfaction in post-mastectomy breast reconstruction. *Plast Reconstr Surg*. 2000; 106(4):769–776.
47. Hartrampf CR Jr. The transverse abdominal island flap for breast reconstruction. A 7-year experience. *Clin Plast Surg*. 1988; 15:703–716.
48. Kroll SS, Gherardini G, Martin JE et al. Fat necrosis in free and pedicled TRAM flaps. *Plast Reconstr Surg*. 1998; 102(5):1502–1507.

49. Kroll SS. The early management of flap necrosis in breast reconstruction. *Plast Reconstr Surg*. 1991; 87(5):893–901.
50. Kroll SS, Schusterman MA, Reece GP, Miller MJ, Robb G, Evans G. Abdominal wall strength, bulging, and hernia after TRAM flap breast reconstruction. *Plast Reconstr Surg*. 1995; 96(3):616–619.
51. Blondeel PN. One hundred free DIEP flap breast reconstructions: A personal experience. *Br J Plast Surg*. 1999; 52(2):104–111.
52. Nahabedian MY, Momen B, Galdino G, Manson PN. Breast reconstruction with the free TRAM or DIEP flap: Patient selection, choice of flap, and outcome. *Plast Reconstr Surg*. 2002; 110(2):466–477.
53. de la Torre JI, Fix RJ, Gardner PM, Vasconez LO. Reconstruction with the latissimus dorsi flap after skin-sparing mastectomy. *Ann Plast Surg*. 2001; 46:229–233.
54. Menke H, Erkens M, Olbrisch RR. Evolving concepts in breast reconstruction with latissimus dorsi flaps: Results and follow-up of 121 consecutive patients. *Ann Plast Surg*. 2001; 47:107–114.
55. Clough KB, Louis-Sylvestre C, Fitoussi A, Couturaud B, Nos C. Donor site sequelae after autologous breast reconstruction with an extended latissimus dorsi flap. *Plast Reconstr Surg*. 2002; 109:1904–1911.
56. Dowden RV. Selection criteria for successful immediate breast reconstruction. *Plast Reconstr Surg*. 1991; 88(4):628–634.
57. Padubidri AN, Yetman R, Browne E et al. Complications of postmastectomy breast reconstructions in smokers, ex-smokers, and nonsmokers. *Plast Reconstr Surg*. 2001; 107(2):342–351.
58. Chang DW, Reece GP, Wang B et al. Effect of smoking on complications in patients undergoing free TRAM flap breast reconstruction. *Plast Reconstr Surg*. 2000; 105(7):2374–2380.
59. Paige KT, Bostwick J 3rd, Bried JT, Jones G. A comparison of morbidity from bilateral, unipedicled and uni-lateral, unipedicled TRAM flap breast reconstructions. *Plast Reconstr Surg*. 1998; 101(7):1819–1827.

22

Complications of Thyroidectomy and Parathyroidectomy

Denise M. Carneiro-Pla and George L. Irvin III

CONTENTS

22.1 Introduction

Complications associated with surgical procedures involving the thyroid and parathyroid glands are fortunately uncommon when these procedures are performed by experienced surgeons. Conversely, even in experienced hands, these complications still occur, leading to substantial morbidity to these patients. This chapter will discuss the specific problems that may occur during operations on these important endocrine glands and will describe some methods that can reduce the risk of postoperative hematoma, recurrent and superior laryngeal nerve palsy, hypocalcemia, seroma, wound infection, and parathyroidectomy operative failure.

22.2 Postoperative Cervical Hematoma

Bleeding within the closed deep cervical fascia can be life threatening after thyroid resection. This complication is unusual after parathyroidectomy, unless extensive exploration has been done. On the other hand, the thyroid gland is very vascular, and if any cut surface of this gland remains, as is common after lobectomy or partial thyroidectomy, significant bleeding may occur in as high as 1.6% of the patients.[1–3]

Hematoma formation resulting from either venous bleeding or an acute hemorrhage of a major artery can cause airway obstruction, which must be recognized early and treated with the utmost urgency. Should obstructive respiratory distress with cyanosis, agitation, stridor, or an expanding neck mass occur, the wound and the deep cervical fascia must be opened immediately at the bedside to relieve pressure on the trachea. This procedure, rather than an attempt to reinsert a tube into the trachea of a patient who is awake and hypoxic, is the best way to obtain airway patency. Once the airway is clear, the patient should be sedated and returned to the operating room for safe evacuation of the remaining hematoma, hemostasis, and wound closure. Although this type of hemorrhage and airway obstruction is unusual, it is life threatening and calls for emergent therapeutic intervention. In contrast, cervical hematoma without airway compromise can be managed in a less urgent manner with reexploration in the operating room. This procedure requires careful monitoring of the airway while the patient is being transported to the operating room, and the surgeon should be prepared to open the wound immediately if progressive respiratory distress occurs.[4]

Several factors may help prevent postoperative cervical hematoma. Because many surgical patients may be receiving anticoagulation therapy, a good history should be collected, and these drugs should be withheld for an appropriate interval perioperatively, depending on the particular anticoagulant used. Meticulous attention to

hemostasis is useful and should include double ligation of a divided superior thyroid artery either with clips, ties, or additional energy devices. Some surgeons recommend suture ligation of the cut edge of any incised thyroid tissue with careful cauterization of its surface. Currently, many surgeons use energy devices for ligation of vessels and division of isthmus, reporting no increase in postoperative bleeding.[5] A tubular, closed suction drain can be used for patients who have undergone extensive dissection or who are experiencing continued loss of venous blood, but this drain may not prevent the formation of a hematoma, which may lead to a compromised airway.[4,6] A small incisional dressing, instead of a bulky one, will allow good monitoring of the neck and because most hematomas occur in the immediate postoperative period (4–6 h) or within 24 h after surgery, an overnight hospital stay for observation seems prudent. Routinely elevating the head to an angle of 30° decreases venous pressure in the neck area and it might decrease bleeding, although there is no data that supports this recommendation. Good anesthesia with spontaneous respirations and deep extubation at the end of the procedure will prevent coughing or retching on the endotracheal tube and possibly decrease the incidence of hematoma.

22.3 Recurrent Laryngeal Nerve Injury

Injury to the recurrent laryngeal nerves during surgical procedures involving the thyroid gland or the parathyroid gland is a very serious complication with a reported incidence of 0.3%–8%.[7,8] On the other hand, voice change following thyroidectomy is a frequent complication occurring in 14%–17% of patients due to injury of superior laryngeal nerve, with some of these changes not showing any neural injury origin.[9,10] Stretching, clamping, pinching, or cutting the nerve, or using electrocautery near the nerve can cause palsy that may result in voice change, aspiration, and partial airway obstruction due to paralysis of a vocal cord. If both recurrent nerves are damaged, the paralyzed vocal cords may remain permanently in adduction, causing complete airway obstruction and necessitating reintubation and tracheostomy.

The best way to prevent this serious complication is to develop a good understanding of the normal anatomic position of these nerves, including variations that are either natural or caused by a slowly growing goiter. In approximately 20% of cases, the external branch of the superior laryngeal nerve extends inferiorly with the superior thyroid artery to a position at which damage is likely to occur when the blood supply to the superior pole of the thyroid is ligated. During resection of a large goiter, meticulous dissection as close as possible to the capsule of the thyroid, followed by clamping and ligation of individual vessels, will help prevent injury to this nerve, which is often not visualized. The right recurrent laryngeal nerve arises from the vagus in the inferior portion of the neck, passes around the innominate artery, and ascends obliquely in the tracheoesophageal groove until it penetrates the larynx at the level of the inferior horn of the thyroid cartilage lateral to Berry's ligament. In 1% of patients, this nerve is nonrecurrent, traversing directly from the vagus.[11] The left recurrent laryngeal nerve arises from the vagus, passes behind the aorta at the level of the ligamentum arteriosum, and then ascends, assuming the same trajectory as the right nerve.

The first step in preventing nerve injury is proper identification of the nerve, using blunt dissection without cautery for hemostasis. The gland is lifted from its bed, while all branches of the nerve along its course to the entrance into the larynx are preserved. The recurrent nerve can be identified in several ways depending on the pathological anatomy. One way is to find the inferior thyroid artery and to follow its medial course to the thyroid gland. The disadvantage of finding the nerve in relation to the inferior thyroid artery is that the anatomy can vary; the nerve can be located medial to, lateral to, or between the branches of this vessel, and it often branches before it reaches this area. Another way of identifying the recurrent nerve is to mobilize the inferior pole of the thyroid to find the nerve in the tracheoesophageal groove. This dissection is also useful, but it is somewhat limited in the presence of a large goiter with substernal extension.

When the nerve has been found, dissection of the gland is continued, but always with good visualization of the nerve in an attempt to avoid trauma to this delicate structure. It is imperative that patients be informed preoperatively about the risk of damage to the laryngeal nerves and about the consequences of such injuries. The informed consent process should include a discussion of the risk of this specific complication and such a discussion should be carefully documented in the patient's chart since despite surgeon's experience, recurrent laryngeal nerve injury will still occur in less than 1% of the patients undergoing thyroidectomy, usually due to neuropraxis.

Some surgeons have advocated nerve stimulation as helpful, but this technique has yet to gain wide acceptance especially among general surgeons. The surgical technique can be maintained, as described earlier, despite nerve monitoring, since the most commonly used nerve monitor system (NIM) required nerve

visualization.[12] There are other nerve monitors with one particular value since it is also a dissector. This monitor allows continued nerve monitoring during dissection, thereby locating the nerve without visualization. Although the majority of studies evaluating nerve monitoring during thyroidectomy show no decrease in the incidence of permanent nerve injury and vocal cord paralysis, the incidence of temporary recurrent laryngeal nerve injury decreases when intraoperative nerve monitoring is used.[13] The use of intraoperative nerve monitoring can also prevent the devastating complication of bilateral nerve injury causing airway obstruction, since the surgeon can assure the proper function of the initially explored nerve before excision of the opposite thyroid lobe.

22.4 Hypocalcemia

Postoperative hypocalcemia can be a serious complication after total thyroidectomy or extensive parathyroidectomy. Although this complication cannot always be predicted, it must be anticipated and treated as soon as symptoms appear, usually 6–16 h after surgery. Symptoms will include numbness or tingling in the fingers or toes, or paresthesia around the lips. Chvostek's and Trousseau's signs may be useful in making the diagnosis, but symptoms are more important since they develop earlier than these signs. Treatment should be started as early as possible. A precipitous fall in serum calcium concentrations 12–16 h after surgery, or a total serum calcium concentration of less than 8 mg/dL on the morning after surgery, is an indication that calcium supplementation should be instituted. Permanent hypocalcemia occurs in 3.4%–8.6% of patients after total thyroidectomy.[14,15] This complication has been reported to occur in 1%–30% of patients after parathyroidectomy, depending on the extent of the resection.[16–18] Orally administered calcium preparations of 1 g given two or three times per day may be sufficient to prevent symptoms in patients undergoing parathyroid or thyroid resections, until the portion of the gland that remains responds to hypocalcemia and regains function. More severe hypocalcemia resulting in frank tetany may occur either temporarily or permanently. In these cases, vitamin D supplementation or intravenously administrated calcium gluconate may be needed. Some surgeons would suggest prophylactic calcium supplementation for all patients undergoing total thyroidectomy, demonstrating great results. Others use PTH levels postoperatively to decide whether patients should undergo calcium supplementation postoperatively.

The best course of action is prevention of postoperative hypocalcemia. Parathyroid glands of normal size should always be preserved. Performing a biopsy of these glands increases the incidence of postoperative hypocalcemia; therefore, biopsy should be performed only when absolutely necessary; for example, to differentiate a normal parathyroid from a metastatic lymph node in a patient with thyroid cancer.[18]

During parathyroidectomy, the surgeon should never excise any gland of normal size in an attempt to return the patient to normocalcemia. During unilateral thyroidectomy, normal parathyroid glands should not be resected on the basis of an assumption that contralateral thyroid lobectomy will not be necessary in the future. Devascularized normal parathyroid gland should be implanted on the sternocleidomastoid muscle even during thyroid lobectomies.

Preservation of normal parathyroid gland function is helped by a sound knowledge of topographic anatomy. The superior gland is usually found lateral to the recurrent nerve at the level of the suspensory ligament of the thyroid, and the inferior gland is anterior to the recurrent laryngeal nerve and caudal to the location at which this structure crosses the inferior thyroid artery. The position of the inferior glands can vary. Injury to the parathyroid glands can best be avoided by blunt dissection with good visualization and meticulous hemostasis without cautery. During thyroidectomy, most surgeons try to ligate the branches of the inferior thyroid artery directly on the side of the thyroid lobe because the nutrient branch to the parathyroid can often be seen and preserved. If a parathyroid gland is devascularized or blood supply appears compromised, excision and autotransplantation of small pieces of the gland into the sternocleidomastoid muscle is recommended.[19]

22.5 Seroma and Wound Infection

Seroma is a common complication after resection of the thyroid or parathyroid gland but rarely requires surgical intervention. Fluid usually collects between the skin flaps and the deep cervical fascia. When the collection is large and cosmetically unsightly, aspiration is indicated. Small collections resolve spontaneously within a few weeks and should not be aspirated so that the risk of bacterial contamination can be avoided. If seroma is large, it can be aspirated with a 24-gauge needle and preferably under ultrasound guidance. Usually it does not recur, but it might require reaspiration. This complication can occur in as many as 5% of the patients.[20]

Wound infection is unusual in association with these cervical procedures because of the excellent blood supply in this area; however, it can occur in about 0.5%–2% of the cases.[20,21] Prophylactic antibiotics are not indicated for these clean, uncontaminated endocrine procedures unless the patient is immunosuppressed or diabetic. Patients with skin infection and acne are more prone to have wound infection and further antibiotic treatment might help.

22.6 Parathyroidectomy Operative Failure

Parathyroidectomy is performed to eliminate the excess secretion of parathyroid hormone. Every disease involving the parathyroid glands requires a different type of resection with extirpation of one or more parathyroid glands in an attempt to correct this imbalance. The extent of the resection will determine not only the operative success, but also the incidence of complications. The ideal way to treat sporadic primary hyperparathyroidism is to excise only abnormal parathyroid glands and to preserve normally functioning ones.

In most large centers, the operative failure rate is reported to range from 1% to 10% for patients with sporadic primary hyperparathyroidism (SPHPT).[22–24] In institutions where parathyroid disease is treated less frequently, the failure rate is reported to be as high as 30%.[25] Operative failure is defined as persistent hypercalcemia with high levels of intact parathyroid hormone (PTH) within 6 months after parathyroidectomy. Persistent hypoparathyroidism is caused by overzealous parathyroid resection, which is also an undesirable operative outcome. An insufficient excision can be due to unrecognized multiglandular disease (MGD) or the inability to find and resect a single abnormal gland. On the other hand, postoperative hypoparathyroidism is due to not having enough normal parathyroid tissue left in situ to support eucalcemia. The reported incidence of hypoparathyroidism, after 3.5 glands have been resected to treat parathyroid hyperplasia, ranges from 12% to 24%.[16,17] Furthermore, total parathyroidectomy with autotransplantation results in low normal serum calcium levels in 4%–30% of cases, depending on the cause of the parathyroid disease.[17,26] Because of these complications, resection of 3.5 glands for the treatment of primary hyperparathyroidism should be reserved for patients with four markedly enlarged glands and should not be used to treat patients with "slightly large" parathyroid glands, or those with hyperplasia diagnosed by frozen-section histopathologic analysis alone. The limitations of histopathologic analysis in determining single gland or MGD are well known; thus, the results of such analyses should not be used to determine the extent of parathyroid resection.[23,27–29] For patients with single or double adenoma, biopsy of normal glands substantially increases the incidence of postoperative hypocalcemia.[18] Because of this risk and the limited benefit of frozen-section histopathologic analysis, many surgeons perform bilateral neck exploration to allow visualization of all four glands and perform parathyroidectomy on the basis of gland size alone. However, judging gland abnormality exclusively on the basis of gross appearance may lead to unnecessary parathyroid resection because the size of the gland is not always correlated with its function.[30–32]

Two surgical adjuncts are available to help prevent these complications: (a) the quick intraoperative parathyroid hormone assay and (b) the use of preoperative localization studies. The intraoperative measurement of parathyroid hormone levels predicts the postoperative outcome and assures the surgeon that all hypersecreting tissue has been excised. At the same time, its results show that the remaining glands are not hypersecreting and therefore neither visualization nor biopsy is necessary.[33–36] Furthermore, the intraoperative PTH dynamics will indicate the presence of additional hypersecreting parathyroid glands after excision of a suspected adenoma or will guide the surgeon to perform further exploration. This approach has shown improvement on the operative success of primary hyperparathyroidism.[37,38]

Currently, the most sensitive preoperative localization study is the Tc-99m-sestamibi nuclear scan with tomographic imaging. This study is used to locate hyperfunctioning parathyroid glands, including those in an ectopic position, such as in the mediastinum. The benefit of using preoperative localization studies and intraoperative PTH monitoring (IPM) is that patients with SPHPT can be safely treated with unilateral neck exploration, which leaves the normally secreting parathyroid glands in situ and undisturbed. This approach, which is associated with an intraoperative localization success rate of 98%, should also decrease the risk of hypocalcemia.

Finally, a sure diagnosis and clear surgical indications are of utmost importance in obtaining a successful outcome after parathyroidectomy. Primary hyperparathyroidism is diagnosed when patients exhibit persistent hypercalcemia, elevated intact parathyroid hormone levels, normal renal function, and normal or elevated 24 h urinary calcium levels. The guidelines for operative management of primary hyperparathyroidism have changed as the surgical approaches to this disease have evolved. With a sure diagnosis and strict surgical indications for parathyroidectomy, the operative results will be satisfactory, with a low incidence of complications.[39]

Complications of Thyroid and Parathyroid Procedures

Complications	Incidence (%)	References	Comments
Hematoma	0.1–1.6	[1–3]	When associated with significant respiratory distress, opening of the wound and deep cervical fascia is the first approach instead of intubation.
Recurrent laryngeal nerve injury		[7,8]	The incidence varies based on surgeons' experience and if vocal cord function is verified postoperatively. Temporary vocal cord palsy can occur following thyroidectomy in as high as 8% but permanent palsy is usually <1%.
Permanent	0.3–3		
Temporary	1.4–8		
Superior laryngeal nerve injury	14–17	[9,10]	Many of the postoperative voice changes are not associated with neural injury.
Hypocalcemia	1–8.6	[14,15,19]	Most large centers report permanent hypocalcemia incidence of 1%–2% for total thyroidectomy.
Seroma	5	[20]	The more extensive the procedure, the higher is the incidence of seroma formation.
Wound infection	<1–2	[20]	Incidence increases in patients with acne, infected skin lesions, or immunosuppression.
Parathyroidectomy operative failure	1–30	[22–25]	This wide range is due to surgeons' experience, use of intraoperative PTH monitoring, and preoperative localization studies.

How to Avoid Complications of Thyroid and Parathyroid Procedures

Complications	Methods of Avoidance	References
Hematoma	Careful hemostasis and stop anticoagulation perioperatively	[1–3]
Recurrent laryngeal nerve injury	Dissection of the nerve on its trajectory or use of nerve monitoring. Prevent use of cautery or energy devices close to the nerves	[7,12,13]
Superior laryngeal nerve injury	Ligation of superior pole vessels at the thyroid capsule and avoid mass ligation of these vessels	[9]
Hypocalcemia	Dissection close to thyroid capsule and understanding of parathyroid anatomy. Devascularized normal glands should be autotransplanted. Routine parathyroid gland biopsy should be avoided during parathyroidectomy	[19]
Seroma	Decrease use of energy devices and the extent of the dissection	[20]
Wound infection	Treat patients with skin infections, and preoperative antibiotics on immunosuppressed patients	
Parathyroidectomy operative failure	Knowledge of anatomy, use of preoperative localization studies, and intraoperative PTH monitoring	[37,38]

References

1. Rosenbaum MA, Haridas M, McHenry CR. Life-threatening neck hematoma complicating thyroid and parathyroid surgery. *Am J Surg*. 2008;195: 339–343; discussion 343.
   Good review of hematomas following neck procedures.
2. Bergamaschi R, Becouarn G, Ronceray J, Arnaud JP. Morbidity of thyroid surgery. *Am J Surg*. 1998;176: 71–75.
3. Palestini N, Tulletti V, Cestino L et al. Post-thyroidectomy cervical hematoma. *Minerva Chir*. 2005;60: 37–46.
4. Shaha AR, Jaffe BM. Practical management of post-thyroidectomy hematoma. *J Surg Oncol*. 1994;57: 235–238.
   Well written review about management of neck hematomas.
5. Baldwin K, Haniff M, Somasundar P. Initial experience using a bipolar radiofrequency ablation device for hemostasis during thyroidectomy. *Head Neck*. 2013;35: 118–122.
6. Samraj K, Gurusamy KS. Wound drains following thyroid surgery. *Cochrane Database Syst Rev*. 2007;4: CD006099, doi: 10.1002/14651858.CD006099.pub2.
7. Lo CY, Kwok KF, Yuen PW. A prospective evaluation of recurrent laryngeal nerve paralysis during thyroidectomy. *Arch Surg*. 2000;135: 204–207.
8. Hayward NJ, Grodski S, Yeung M et al. Recurrent laryngeal nerve injury in thyroid surgery: A review. *ANZ J Surg*. 2012;83: 15–21.
9. Kark AE, Kissin MW, Auerbach R, Meikle M. Voice changes after thyroidectomy: Role of the external laryngeal nerve. *Br Med J (Clin Res Ed)*. 1984;289: 1412–1415.

10. Stojadinovic A, Shaha AR, Orlikoff RF et al. Prospective functional voice assessment in patients undergoing thyroid surgery. *Ann Surg*. 2002;236: 823–832.

Study showing the reasons for postoperative voice changes.

11. de Roy van Zuidewijn DB, Songun I, Kievit J, van de Velde CJ. Complications of thyroid surgery. *Ann Surg Oncol*. 1995;2: 56–60.
12. Dralle H, Sekulla C, Haerting J et al. Risk factors of paralysis and functional outcome after recurrent laryngeal nerve monitoring in thyroid surgery. *Surgery.* 2004;136: 1310–1322.

Important study demonstrating the results of thyroidectomy guided by nerve monitoring.

13. Barczynski M, Konturek A, Cichon S. Randomized clinical trial of visualization versus neuromonitoring of recurrent laryngeal nerves during thyroidectomy. *Br J Surg*. 2009;96: 240–246.

Important study showing the decrease in temporary vocal cord palsy due to nerve monitoring use.

14. Pederson WC, Johnson CL, Gaskill HV et al. Operative management of thyroid disease. Technical considerations in a residency training program. *Am J Surg*. 1984;148: 350–352.
15. Glinoer D, Andry G, Chantrain G, Samil N. Clinical aspects of early and late hypocalcaemia after thyroid surgery. *Eur J Surg Oncol*. 2000;26: 571–577.
16. Burgess JR, David R, Parameswaran V et al. The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg*. 1998;133: 126–129.
17. Hellman P, Skogseid B, Juhlin C et al. Findings and long-term results of parathyroid surgery in multiple endocrine neoplasia type 1. *World J Surg*. 1992;16: 718–722; discussion 722–713.
18. Tibblin S, Bizard JP, Bondeson AG et al. Primary hyperparathyroidism due to solitary adenoma. A comparative multicentre study of early and long-term results of different surgical regimens. *Eur J Surg*. 1991;157: 511–515.
19. Lo CY, Lam KY. Postoperative hypocalcemia in patients who did or did not undergo parathyroid autotransplantation during thyroidectomy: A comparative study. *Surgery.* 1998;124: 1081–1086; discussion 1086–1087.
20. Lee YS, Nam KH, Chung WY et al. Postoperative complications of thyroid cancer in a single center experience. *J Korean Med Sci*. 2010;25: 541–545.
21. Eltahawy AT, Mokhtar AA, Khalaf RM, Bahnassy AA. Postoperative wound infection at a university hospital in Jeddah, Saudi Arabia. *J Hosp Infect*. 1992;21: 79–83.
22. Low RA, Katz AD. Parathyroidectomy via bilateral cervical exploration: A retrospective review of 866 cases. *Head Neck.* 1998;20: 583–587.

Study showing the results of bilateral neck exploration performed by experienced surgeons.

23. Kaplan EL, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s. Choice of surgical procedures for this disease. *Ann Surg*. 1992;215: 300–317.
24. van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: An institutional perspective. *World J Surg*. 1991;15: 688–692.
25. Malmaeus J, Granberg PO, Halvorsen J et al. Parathyroid surgery in Scandinavia. *Acta Chir Scand*. 1988;154: 409–413.
26. Monchik JM, Bendinelli C, Passero MA, Jr., Roggin KK. Subcutaneous forearm transplantation of autologous parathyroid tissue in patients with renal hyperparathyroidism. *Surgery.* 1999;126: 1152–1158; discussion 1158–1159.
27. Tezelman S, Shen W, Shaver JK et al. Double parathyroid adenomas. Clinical and biochemical characteristics before and after parathyroidectomy. *Ann Surg*. 1993;218: 300–307; discussion 307–309.
28. Ghandur-Mnaymneh L, Kimura N. The parathyroid adenoma. A histopathologic definition with a study of 172 cases of primary hyperparathyroidism. *Am J Pathol*. 1984;115: 70–83.
29. Carneiro-Pla DM, Romaguera R, Nadji M et al. Does histopathology predict parathyroid hypersecretion and influence correctly the extent of parathyroidectomy in patients with sporadic primary hyperparathyroidism? *Surgery*. 2007;142: 930–935; discussion 930–935.

Study shows the inability of pathology to determining the glandular involvement in primary hyperparathyroidism.

30. Berger AC, Libutti SK, Bartlett DL et al. Heterogeneous gland size in sporadic multiple gland parathyroid hyperplasia. *J Am Coll Surg*. 1999;188: 382–389.
31. Liechty RD, Teter A, Suba EJ. The tiny parathyroid adenoma. *Surgery.* 1986;100: 1048–1052.
32. Carneiro DM, Irvin GL, 3rd. Late parathyroid function after successful parathyroidectomy guided by intraoperative hormone assay (QPTH) compared with the standard bilateral neck exploration. *Surgery.* 2000;128: 925–929; discussion 935–926.
33. Sokoll LJ, Drew H, Udelsman R. Intraoperative parathyroid hormone analysis: A study of 200 consecutive cases. *Clin Chem*. 2000;46: 1662–1668.
34. Garner SC, Leight GS, Jr. Initial experience with intraoperative PTH determinations in the surgical management of 130 consecutive cases of primary hyperparathyroidism. *Surgery.* 1999;126: 1132–1137; discussion 1137–1138.
35. Carneiro DM, Solorzano CC, Nader MC et al. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: Which criterion is the most accurate? *Surgery.* 2003;134: 973–979; discussion 979–981.
36. Molinari AS, Irvin GL, 3rd, Deriso GT, Bott L. Incidence of multiglandular disease in primary hyperparathyroidism determined by parathyroid hormone secretion. *Surgery.* 1996;120: 934–936; discussion 936–937.
37. Irvin GL, 3rd, Carneiro DM, Solorzano CC. Progress in the operative management of sporadic primary hyperparathyroidism over 34 years. *Ann Surg*. 2004;239: 704–708; discussion 708–711.
38. Irvin GL, 3rd, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: Surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. *World J Surg*. 2004;28: 1287–1292.

Study shows that intraoperative PTH monitoring decreases operative failures in primary hyperparathyroidism.

39. Irvin GL, 3rd, Carneiro DM. Management changes in primary hyperparathyroidism. *JAMA.* 2000;284: 934–936.

23

Complications of Adrenal Gland Surgery

Jane Kayle Lee, Andrew A. Gonzalez, and James C. Doherty

CONTENTS

The adrenal gland is responsible for a diverse set of endocrine and exocrine functions. Its unique anatomic and physiologic features create interesting issues and challenging decision making at the preoperative, intraoperative, and postoperative stages of care. This chapter will present common complications and preventive methods.

23.1 Indications for Adrenalectomy

When the potential risks of adrenalectomy are assessed, the first consideration is the specific disease process requiring surgical intervention. Among the common adrenal diseases amenable to surgical therapy are a variety of functional and neoplastic disorders. These include aldosterone-producing adrenocortical adenoma, cortisol-producing adrenocortical adenoma, pheochromocytoma, nonfunctional adrenocortical adenoma, adrenocortical adenocarcinoma, and adrenal metastases.

23.1.1 Aldosteronoma

Aldosteronomas are aldosterone-secreting adenomas usually associated with primary hyperaldosteronism. In fact, 62% of patients with this syndrome have a unilateral functional adenoma that is amenable to surgical therapy.[1] The clinical features of primary hyperaldosteronism are nonspecific and include hypertension, hypokalemia, polyuria, weakness, and muscle cramping. Some patients exhibit minimal symptoms or have no symptoms at all. Almost all patients exhibit suppressed plasma renin activity.

23.1.2 Cortisol-Producing Adenomas

Cortisol-producing adenomas are often associated with Cushing's syndrome, a clinical syndrome that includes hypertension, truncal obesity, muscle wasting, diabetes mellitus, and, occasionally, psychological disturbance. Patients with subclinical hypercortisolism may also have cortisol-producing adenomas. The first step in working up a patient with signs and symptoms of hypercortisolism is to determine if the cause is Cushing's syndrome (primary adrenal hypercortisolism) or Cushing's disease (secondary to a pituitary tumor producing adrenocorticotrophic hormone). Initial screening is accomplished with urinary free cortisol, late-night salivary cortisol, or low-dose dexamethasone suppression testing. If results show an ACTH level below 5 pg/mL on two occasions, this indicates primary adrenal Cushing's syndrome and adrenal imaging is recommended.

Although Cushing's disease is usually managed with transsphenoidal hypophysectomy, total bilateral adrenalectomy may be indicated under some circumstances. Among these are persistent or severe disease after hypophysectomy or contraindications to hypophysectomy, such as the desire to preserve fertility. When performed for this indication, total bilateral adrenalectomy has a cure rate approaching 100%.[2]

23.1.3 Pheochromocytoma

Pheochromocytoma is a tumor of the adrenal medulla or of other sympathetic ganglion cells of the peripheral nervous system. Approximately 10% of these tumors are malignant, 10% are bilateral, 10% are familial, and 10% are extra-adrenal. The symptoms caused by these tumors fall into three general groups. One-third of patients experience an episode of palpitations, diaphoresis, headache, and a "feeling of impending doom." An additional one-third of patients exhibit normotension with transient symptomatic episodes in conjunction with episodic hypertension. The remaining one-third of these patients exhibit asymptomatic chronic hypertension, which is often misdiagnosed as essential hypertension. Diagnostic testing includes determination of plasma and urinary catecholamine levels, as well as urinary levels of catecholamine degradation products (metanephrines and vanillylmandelic acid). The location of the tumors is determined by abdominal computed tomography (CT) or magnetic resonance imaging (MRI) or by 131-iodine metaiodobenzylguanidine (^{131}I-MIBG) scanning when necessary.

23.1.4 Nonfunctional Adrenocortical Adenomas

Nonfunctional adrenocortical adenomas or "benign incidentalomas" are the most common adrenal lesion in clinical practice (0.6%–4% of all thoracic and abdominal CT scans). The first step in evaluation is screening for functional tumors. If this is negative, the lesion is most likely a nonfunctional adenoma (60%) but may also be a myelolipoma (10%), adrenal cyst (5%), or a ganglioneuroma (5%). However, since up to 20% of incidentalomas identified by CT turn out to be malignant, surgeons may consider resection based upon size criteria. Although specific criteria vary, most surgeons will resect a nonfunctional adrenal mass more than 5 cm in diameter if the appearance is atypical for an adenoma. Smaller nonfunctional lesions without an atypical appearance should be followed up with serial imaging studies to re-evaluate the risk of malignancy.

23.1.5 Adrenocortical Adenocarcinoma

Adrenocortical adenocarcinoma is a rare tumor often first detected as a large, advanced-stage lesion. Imaging methods such as CT and MRI scans can be very useful in determining the extent of disease preoperatively. Half of these tumors are functional, with clinical evidence of cortisol or androgen excess. Complete surgical resection of adrenocortical adenocarcinoma is the only potentially curative therapy and can substantially palliate the signs and symptoms associated with functional tumors. Initial complete resection is possible in approximately 75% of cases, but recurrent disease develops after 85% of these procedures, with a mean disease-free interval of 2.5 years.[3] Reoperation provides a substantially better survival rate than drug therapy.

23.1.6 Adrenal Metastases

Lung, breast, and renal cell carcinomas often metastasize to the adrenal glands. Like nonfunctional adrenocortical adenomas, these tumors sometimes are resected as large incidentalomas that have been diagnosed radiographically. On the other hand, the adrenal mass known to be a metastatic lesion may also be resected for cure under certain circumstances, namely, favorable histologic type and the absence of extra-adrenal malignant disease. In clinical practice, these circumstances rarely occur and are an extremely rare indication for adrenalectomy.

23.2 Patient Factors Associated with Increased Morbidity and Mortality

There are several patient factors that are associated with increased morbidity and mortality. In addressing these risks, it is important not only to medically optimize patient comorbidities, but also to obtain appropriate

informed consent, specifically noting the significantly increased risk of death and complications.

Advanced age and number of comorbidities are independent predictors of significantly higher mortality, even after adjusting for race, gender, surgical technique, and hospital teaching status. Risk-adjusted mortality is more than four times higher in patients over the age of 65 as compared to patients younger than 45. Patients with at least two comorbidities have similarly increased odds of death.[4,5]

23.3 Surgeon and Hospital Volume–Outcome Relationship for Adrenalectomy

Hospitals averaging <3 adrenalectomies/year fall into the lowest tercile of procedural volume. Those performing 3–6 adrenalectomies/year are in the middle tercile, and those performing >6 adrenalectomies/year are in the highest tercile. Due to the infrequency of adrenal surgery, there are no reported volume-threshold criteria to accredit an institution as a "center of excellence" as is practiced in cardiac or bariatric surgery. Although most adrenal operations are performed at nonteaching (69%) or low to medium volume hospitals (65%), there is not an association between hospital volume and in-hospital mortality.[4]

23.4 Endocrine and Metabolic Complications of Adrenalectomy

In discussing endocrine and metabolic complications of adrenalectomy, it is important to recognize that most are directly related to the underlying disease process.

23.4.1 Complications of Adrenalectomy for Hypercortisolism

Patients with hypercortisolism may experience poorly controlled diabetes mellitus before surgery. Glucose levels must be carefully monitored and aggressively treated during the perioperative period so that patients can avoid the complications of hypoglycemia, diabetic ketoacidosis, and poor wound healing. As is true for any elective surgical procedure, adrenalectomy should be delayed until altered potassium metabolism and hypertension have been corrected so that the complications of anesthesia can be minimized. In severe cases, therapy with the adrenolytic agent mitotane or with steroidogenesis inhibitors such as metyrapone, aminoglutethimide, or ketoconazole may be necessary to control the metabolic derangements of hypercortisolism preoperatively.[6] Of note, ketoconazole should not be used in pregnant patients owing to its teratogenic effects.[7]

The obesity associated with Cushing's syndrome and Cushing's disease exposes the patient to substantial risk of a variety of complications, including poor wound healing, wound infection, and respiratory complications. Central obesity may complicate mechanical ventilation, and all patients should be aggressively treated postoperatively so that hypoxemia, hypoventilation, and atelectasis can be limited or reversed. This treatment usually involves early ambulation and incentive spirometry, measures designed to recover functional residual capacity and reverse alveolar collapse. Patients with hypercortisolism often have thin, easily bruised skin and are susceptible to skin breakdown. Care must be taken to pad all pressure points during the surgical procedure and to aggressively monitor skin integrity postoperatively. Thin skin and vascular fragility may also complicate the establishment of durable intravenous access. In the operating room, patients should be positioned with great care so that pathologic fractures can be prevented because osteopenia is common.[8] Fasciculations related to depolarizing paralytic agents should be minimized for the same reason.

Patients undergoing adrenalectomy for hypercortisolism are at high risk of postoperative adrenal insufficiency. Although the cause of adrenal insufficiency after bilateral adrenalectomy is obvious, the cause is more complicated after unilateral adrenalectomy. A chronic state of cortisol excess induces functional suppression and atrophy of the contralateral gland and chronic suppression of the entire pituitary–adrenal axis. The abrupt withdrawal of cortisol that accompanies adrenalectomy among these patients can cause acute adrenal insufficiency. To prevent this potentially life-threatening complication, all patients undergoing unilateral adrenalectomy for hypercortisolism, or bilateral adrenalectomy, should be given supplemental steroids perioperatively. Given its potential for adrenal suppression, etomidate is not advised for induction of anesthesia in patients with Cushing's syndrome.[9]

No clear recommendations for perioperative glucocorticoid dosing exist for adrenalectomy per se, but in general, one should assume complete adrenal insufficiency postoperatively and a low to moderate degree of surgical stress. When the most recent recommendations for perioperative corticosteroid management are followed, the glucocorticoid target would probably be 50–60 mg of hydrocortisone per day on the day of surgery and for the first 24 h of the postoperative period.[10] This dose can be rapidly tapered to a maintenance dosage of approximately 25 mg of hydrocortisone equivalent (usually oral prednisone) daily, given in two divided doses. The daily dose may be decreased to 20 or even 15 mg as tolerated, with adjustment based on the presence

of any symptoms of adrenal insufficiency. Function of the pituitary–adrenal axis can be monitored postoperatively by using periodic ACTH stimulation tests or late night salivary cortisol levels. The usual timeframe for normalization of adrenal function is 12–24 months. Adrenal autotransplantation has been attempted for the purpose of avoiding the necessity for long-term adrenal replacement therapy after bilateral adrenalectomy, but only 21% of the patients who underwent this procedure were successfully weaned from steroid therapy. Thus, this procedure is generally not recommended.[11]

All patients subjected to adrenal replacement therapy should be carefully monitored for clinical signs and symptoms of steroid imbalance. One such sign is the previously mentioned syndrome of adrenal insufficiency, also known as Addison's disease. Chronic adrenal insufficiency after adrenalectomy is characterized by hypotension, hyponatremia, hypoglycemia, fever, and a variety of constitutional symptoms, including weakness, fatigue, weight loss, and anorexia. This weakness may contribute to difficulty in weaning patients with respiratory insufficiency from mechanical ventilation. When the condition of patients with chronic adrenal insufficiency has stabilized, steroid replacement therapy can be started at physiologic doses. For severe acute adrenal insufficiency (Addisonian crisis), hydrocortisone should be given as an initial intravenously administered bolus of 100 mg followed by intravenous administration of 100–200 mg over the next 24 h. At this dosage, there is sufficient mineralocorticoid activity to make additional supplementation with fludrocortisone unnecessary. Important adjunctive therapy includes aggressive volume expansion with isotonic fluids and treatment of hypoglycemia. Once the patient's condition has stabilized, hydrocortisone dosages can be tapered and maintenance therapy can be instituted.

If a patient receiving chronic steroid replacement therapy requires surgical intervention, careful perioperative glucocorticoid management is essential to the prevention of postoperative adrenal insufficiency. Although "stress dose" perioperative steroid dosing has enjoyed widespread use since the 1950s, this approach has been challenged during the last decade as anecdotal and without scientific justification. Currently, it is recommended that adjustment in perioperative steroid dosing should be based on consideration of the maintenance steroid dose, the duration of steroid therapy, and the extent of the anticipated surgery.[9] High doses of corticosteroid, as were commonly given in the past, are rarely necessary. Further, administration of high-dose corticosteroids can lead to postoperative complications such as wound infections.

Recurrent hypercortisolism after adrenalectomy usually indicates residual abnormally functioning adrenal tissue. For nonmalignant adenomas, this condition indicates incomplete resection or failure to diagnose bilateral disease. In the case of adrenalectomy for adrenocortical adenocarcinoma, postoperative hypercortisolism mandates a workup for recurrent tumor or metastatic disease.

A unique complication of bilateral adrenalectomy performed for Cushing's disease is the development of Nelson's syndrome—hyperpigmentation, headache, and visual changes. The culprit is a locally aggressive ACTH-secreting pituitary tumor. In one study, this complication occurred in 9% of cases at a median of 9.5 years after the original operation.[7] Treatment options include hypophysectomy and radiotherapy.[12]

23.4.2 Complications of Adrenalectomy for Hyperaldosteronism

Like patients with hypercortisolism, patients with hyperaldosteronism are often first seen with poorly controlled hypertension and metabolic derangements. If inadequately addressed preoperatively, these abnormalities can substantially increase the patient's anesthetic risk. The hypertension associated with primary hyperaldosteronism is salt- and water-dependent, and responds well to salt and water restriction. For this reason, several authors recommend 2–4 weeks of pharmacologic therapy before adrenalectomy for hyperaldosteronism. Combination diuretic therapy with either hydrochlorothiazide or furosemide and either spironolactone or amiloride has been suggested as an appropriate medical approach to primary hyperaldosteronism.[13] The aldosterone resolution score is one method for determining the probability of complete resolution of hypertension after adrenalectomy for aldoseronoma. This score incorporates four elements: three or more antihypertensive medications, body mass index (BMI) >26 kg/m^2, duration of hypertension >7 years, and male gender. Two points are given for the medication criteria, and one point for all others. A total score of 0–1 is predictive of complete resolution of hypertension without the need for lifelong antihypertensive medications (negative predictive value of 72.4%). Conversely, a score of 4–5 is predictive of the need for ongoing pharmacotherapy for blood pressure management (positive predictive value of 75%).[14]

Although the hypokalemia associated with hyperaldosteronism is almost always cured by adrenalectomy, the hypertension associated with primary hyperaldosteronism often does not respond to surgical therapy. In fact, only 60%–80% of patients with unilateral benign disease are cured by unilateral adrenalectomy.[15,16] The cure rate appears to be higher among patients less than 44 years of age, those whose hypertension responds to spironolactone administration preoperatively, those with hypertension of less than 5 years' duration before

resection, and those whose resected adrenal gland does not demonstrate multinodular disease.[17]

While uncommon in clinical practice, mineralocorticoid deficiency can occasionally occur after adrenalectomy for hyperaldosteronism. This condition is characterized by salt wasting, hyponatremia, and hyperkalemia. Symptoms are usually easily controlled with saline administration and mineralocorticoid replacement with fludrocortisone, and such therapy rarely is required for more than 3 months postoperatively.

23.4.3 Complications of Adrenalectomy for Pheochromocytoma

The functional nature of pheochromocytoma presents a unique challenge to the surgical team in all phases of perioperative care. Hypertensive crisis, atrial and ventricular arrhythmia, myocardial infarction, cerebrovascular accident, acute congestive heart failure, and pulmonary edema are some of the serious and potentially life-threatening cardiovascular complications associated with resection of these catecholamine-producing tumors. To minimize the risk of these complications, all patients are treated with a combination of antiadrenergic and vasodilatory agents during the perioperative period. Treatment begins with alpha-adrenergic blockade with 30–60 mg of phenoxybenzamine daily for at least 1 week preoperatively. The alpha-blockade is initiated at a low dosage and is increased as needed to control blood pressure.[18] Symptoms such as dizziness and abdominal cramps often accompany the establishment of adequate alpha-blockade. Other antihypertensive agents, including calcium channel blockers and angiotensin-converting enzyme inhibitors, may be added. Metyrosine, a tyrosine hydroxylase inhibitor, is useful for refractory hypertension in pheochromocytoma but is contraindicated in essential hypertension.

Beta-adrenergic blockade with drugs such as propranolol or atenolol is often necessary for treating tachycardia, but beta-blockers should only be given after the initiation of alpha-blockade. In the absence of adequate alpha-blockade, beta-blockers can induce unopposed vasoconstriction, which can precipitate an acute hypertensive crisis. Another potential drawback of preoperative beta-blockade is that it may cause the body to lose the ability to compensate for episodes of hypotension by developing tachycardia; this loss may complicate blood pressure management. In addition to pharmacologic therapy, all patients are treated with aggressive volume loading before surgery so that intravascular volume status can be optimized.

Even with effective preoperative pharmacotherapy, substantial hemodynamic changes can occur intraoperatively. In order to reduce the risk of adverse cardiovascular events related to systemic catecholamine release, tumor manipulation should be minimized, and the tumor's venous drainage should be controlled and ligated expeditiously. To facilitate detection of changes in hemodynamic parameters, all patients should undergo invasive arterial blood pressure monitoring, and central venous access should be strongly considered. Acute hypertension during adrenalectomy for pheochromocytoma is best managed with intravenous infusion of nicardipine or sodium nitroprusside. Tachycardia can be effectively managed with intravenously administered beta-blocking agents such as labetalol or esmolol. Again, goal-directed volume resuscitation should be standard for all patients.

Postoperatively, patients should be sent to a unit capable of frequent hemodynamic monitoring and effective management of any hemodynamic instability. Loss of adrenergic stimulation can cause hypotension lasting several days and can be further exacerbated by preoperative beta-blockade. This is effectively treated with volume expansion. In extreme cases, an alpha-adrenergic agonist may be necessary so that normal blood pressure can be maintained. Beta-antagonists are to be tapered off over the first postoperative week to avoid reflex tachycardia.

Several isolated case reports detail acute and protracted hypoglycemia as an uncommon postoperative complication of adrenalectomy (approximately 13% of cases).[19] Although this complication is rare, the authors advise considering intraoperative and postoperative spot glucose monitoring if there is patient distress. The etiology of prolonged hypoglycemia is believed to be related to catchecolamine-mediated modulation of insulin and explains the postoperative improved insulin sensitivity in pheochromocytoma patients.[20]

All patients who undergo resection of pheochromocytoma should be carefully monitored for hypertension. Persistent or recurrent hypertension after adrenalectomy raises suspicion of recurrent or residual functional disease. Recurrence rates of malignant disease after adrenalectomy for pheochromocytoma (malignant and benign) have been reported to be as high as 23%.[21] Clinical investigation, including biochemical studies and ^{131}I-MIBG scanning, should be performed so that the diagnosis can be confirmed and the disease localized.

Pheochromocytoma is rare among pregnant women, but many of its symptoms (e.g., hypertension, diaphoresis, and nausea) are also seen in association with preeclampsia. Misdiagnosis of the condition can have fatal consequences. The risk of hypertensive crisis makes labor and delivery extremely dangerous for pregnant patients with pheochromocytoma. Maternal mortality rates as high as 40%–58% and fetal mortality rates of 10%–56% have been reported.[22] During the first trimester, women who do not desire to terminate the pregnancy can be treated medically, and resection can

be delayed until the second trimester. During the third trimester, medical management should be used, and elective Cesarean section should be performed at term. Adrenalectomy can be performed immediately after Cesarean section or at a later date.

23.5 Technical Complications of Adrenalectomy

Unlike the endocrine complications of adrenalectomy, the technical complications are less dependent on the underlying disease than they are on anatomical factors such as size and location of the lesion. The exception to this rule is adrenocortical carcinoma because the malignant nature of the disease can substantially affect both the extent of resection and the operative approach, factors known to contribute to perioperative complications. Preoperative imaging studies (CT and MRI scans) are extremely important sources of anatomical information about patients undergoing elective adrenalectomy. These studies provide crucial information about tumor size, location, and extent of local invasion; this information strongly influences the choice of operative approach. Ideally, the chosen approach to adrenalectomy should be the one that allows the most effective treatment of the adrenal pathologic state (neoplasm or endocrinopathy) but subjects the patient to the fewest potential complications.

Laparoscopic adrenalectomy was first described in 1992 by Gagner et al.[23] Since then, it has become the standard option for most benign disease.[24] Relative to open surgery, laparoscopy decreases the length of stay and pain. The conversion to open rate is 3.5% with no preoperative patient factors predictive for conversion.[25] For instance, there was no increased risk of conversion by patient gender, BMI, ASA grade, or tumor size. A variety of operative approaches are available to the surgeon. Those approaches and the relative advantages and disadvantages of each are listed later.

23.5.1 Transabdominal or Anterior Approach

The earliest approach developed for adrenalectomy, the transabdominal or anterior approach, allows the surgeon to perform a thorough exploration of the entire peritoneal cavity via either a midline or a subcostal incision. Because of the optimal exposure that it affords, this approach is preferred when bilateral or extra-adrenal disease is suspected. Furthermore, in cases of bulky or invasive adrenocortical carcinomas, this method provides excellent exposure of the surrounding organs, thus allowing the surgeon to perform en bloc resection if necessary.

Because of the different anatomic relationships of the right and left adrenal glands, the technique of adrenalectomy and the structures that can be injured differ, depending on which gland is being addressed surgically.[26] The right gland sits atop the right kidney posterior to the inferior vena cava (IVC), with its anterior aspect in close proximity to the lateral border of the IVC. The right gland lies anterior to the diaphragm and posterior and inferior to the right lobe of the liver. The right adrenal vein is short and empties directly into the posterior aspect of the IVC. The vein must be dissected with great care so that caval injury and associated massive blood loss can be avoided. The potential for injury to the IVC can be reduced by dissecting the IVC away from the adrenal gland rather than by inferolateral retraction of the adrenal to expose the IVC. Exposure of the right adrenal gland requires mobilization of the hepatic flexure of the colon, retraction of the right lobe of the liver, and mobilization of the duodenum via a Kocher maneuver. When wider exposure of the right adrenal gland is necessary, complete mobilization of the right hepatic lobe may be necessary. This technique requires division of the falciform and right triangular ligaments and dissection of the bare area of the liver from the diaphragm, thus allowing medial retraction of the entire right lobe.[27] This technique may obviate the need for the more morbid thoracoabdominal approach traditionally necessary for large en bloc resections.

The left adrenal gland sits atop the left kidney posterior to the stomach and pancreas and lateral to the aorta and the left crus of the diaphragm. The left adrenal vein is long and drains into the inferior phrenic vein, which courses downward and empties into the left renal vein. Care must be taken to avoid injury to the renal vessels when vascular control of the left adrenal vein is obtained. Exposure of the left adrenal gland requires entry into the lesser sac by division of the gastrocolic omentum, mobilization and cephalad retraction of the pancreatic body, and, occasionally, mobilization and medial rotation of the spleen and distal pancreas.

The literature reports injuries to each of the structures mobilized during exposure of the right and left adrenal glands. In addition to the IVC, other structures that may be injured are the liver, pancreas, spleen, duodenum, renal vessels, ureter, and diaphragm. The anterior approach also carries the added operative morbidity associated with violation of the peritoneal cavity and extensive manipulation of the bowel. These complications include ileus, small bowel obstruction, wound infection, and incisional hernia. As is true of any surgical procedure involving the upper abdomen and specifically the subphrenic area, the transabdominal approach is also associated with respiratory complications including pneumonia and atelectasis.

23.5.2 Thoracoabdominal Approach

The thoracoabdominal approach provides the best exposure of the adrenal gland. Because it requires entry into both the peritoneal cavity and the pleural cavity, this approach generally is reserved for technically challenging recurrent tumors, very large tumors (10–15 cm), and bulky tumors requiring en bloc resection of the adrenal glands and adjacent organs. The obvious disadvantage of this approach is the extensive operative dissection and exposure involved. The patient is exposed not only to the morbidity associated with the transabdominal approach, but also to that associated with thoracic exploration. Moreover, the positioning required for this approach greatly limits access to the contralateral adrenal gland and may preclude exploration for bilateral disease.

23.5.3 Posterior Approach

The posterior approach, developed as an alternative to the anterior approach, avoids the morbidity associated with entering the peritoneal cavity. It has been associated with better pain control, fewer wound complications, shorter recovery time, and a reduction in respiratory complications.[28] Furthermore, when the posterior approach is used rather than the anterior approach, intraoperative factors such as operative time, intraoperative blood loss, and pancreatic and splenic injury rates are reduced. The disadvantages of the posterior approach are that it does not allow exploration of the abdomen for bilateral or extra-adrenal disease and that it may be inadequate for removal of large tumors. Inadvertent peritoneotomy or pleurotomy can occur when this approach is used, but these injuries are easily repaired primarily at the time of operation. Airtight closure of a pleurotomy can be accomplished with aspiration of air from the pleural cavity under conditions of positive-pressure lung expansion. Tube thoracostomy is rarely necessary. Control of the adrenal vein can be difficult when the posterior approach is used, especially when the procedure is performed on the right adrenal gland. If substantial hemorrhage occurs, packing and emergent repositioning for laparotomy may be necessary. In general, the posterior approach is best for small, unilateral benign tumors. However, in the twenty-first century, most centers usually resect these tumors with a laparoscopic approach.

23.5.4 Lateral Approach

Like the posterior approach, the lateral approach has the advantage of avoiding entry into the peritoneal cavity. However, the exposure it provides is superior to that provided by the posterior approach, especially for obese patients. The lateral approach also allows easier vascular control and removal of larger tumors. Like the posterior approach, the lateral approach does not provide adequate exposure for the assessment of bilateral and extra-adrenal tissue. Postoperative pain can be a significant issue, and recovery time is longer than that associated with the posterior approach. Frequently, resection of the 12th rib is necessary, and postoperative pain can be avoided by sparing the 12 intercostal nerve.

23.5.5 Laparoscopic and Robotic Adrenalectomy

In the United States, the use of laparoscopic adrenalectomy has increased twofold between 1998 and 2006. One reason is the lower associated complication rate of 4.5% vs. 7.8% seen with open surgery. There is a similar decrease in length of stay (3.2 days vs. 5.3 days). Since the early 2000s, robotic-assisted laparoscopic adrenalectomy has also been used as a viable alternative technique. The advantages over open surgery include reducing length of stay and postoperative pain. The advantages over traditional laparoscopy include increased dexterity owing to additional degrees of freedom, motion scaling, dampening to overcome an unsteady camera, and three-dimensional vision resulting from high-definition stereoscopic cameras.[29]

23.5.6 Transperitoneal Laparoscopic Adrenalectomy

Like the open lateral approach, the transperitoneal laparoscopic approach is performed with the patient in the lateral decubitus position. However, unlike the open lateral approach, this approach involves entry into the peritoneal cavity for exposure of the left or right adrenal gland. This same positioning may be used when performing robotic-assisted adrenalectomy.[30] For robotic adrenalectomy, an alternative positioning involves placing the patient in the supine position on tilting table and rotating the patient 20° to the contralateral side.[28]

When the procedure is performed on the right adrenal gland, the triangular ligament is dissected, thus mobilizing the right liver for medial retraction and exposure of the adrenal gland. When the procedure is performed on the left adrenal gland, the splenorenal attachment is dissected laterally and the spleen and pancreas are retracted medially to expose the adrenal gland. Since left-sided surgeries are an independent predictor of complications, special caution should be exercised during the dissection.[24] Vascular control is obtained with laparoscopic clips, and an endoscopic specimen bag is employed so that the gland can be removed without tumor spillage. The organs that can be injured with this approach are essentially the same as in the open anterior approach.

Complications are relatively minor, with complication rates ranging from 2% to 12%. Conversion from laparoscopic surgery to open laparotomy has been reported to

occur in 0%–14% of cases; hemorrhage is the most common indication.[31–35] Operative mortality rates are less than 1%. In several cases, tumor recurrence has occurred after this technique was used for resection of malignant adrenal tumors. As a result, the transperitoneal laparoscopic approach is contraindicated when malignant disease is known to be present or is suspected.

One complication specific to the laparoscopic approach is the occasional difficulty experienced in finding small lesions on the left side. Small adrenal tumors may be indistinguishable from surrounding structures such as pancreas, Gerota's fascia, and retroperitoneal fat. When the laparoscopic approach is used, the ability to perform manual palpation is lost, and small adrenal tumors can be difficult to identify with laparoscopic visualization alone. In such circumstances, laparoscopic ultrasound can be a valuable tool for intraoperative localization.

23.5.7 Posterior Laparoscopic Adrenalectomy

Like the open posterior approach, the posterior laparoscopic approach is performed with the patient in the prone position, and the dissection is carried out entirely in the retroperitoneum. So that exposure can be facilitated, the retroperitoneal space is expanded with a balloon dissector and laparoscopic ultrasonography is used to assist in localization. The overall complication rate for this approach is 10%–11%.[36,37] Intraoperative complication rates are negligible. One unique postoperative complication that has been reported is self-limiting unilateral nerve root pain related to trocar placement.[35] Additionally, there is the potential for pneumothorax, which has been reported in 3% of cases.[38] The incidence of peritoneal tears, as high as 33% in one study, appears to correlate with the experience level of the surgeon.[36] These injuries are easily repaired via the laparoscope and rarely require conversion to open surgery. Conversion to open laparotomy is a relatively uncommon event (4.5%–6.6%).[36] This technique is not recommended for patients with tumors >7 cm. Recently, some centers have begun to use the posterior retroperitoneal approach for robotic adrenalectomy.[39]

23.6 Conclusion

Adrenalectomy offers the surgeon a unique combination of technical and physiologic challenges. Knowledge and consideration of these issues are essential to the avoidance of complications during the preoperative, intraoperative, and postoperative treatment of patients who undergo this procedure. When the surgeon is experienced and knowledgeable, adrenalectomy can be safe and effective for most patients.

Complications of Adrenal Surgery

	Incidence		
Complications	**Open Surgery (%)**	**Laparoscopic (%)**	**References**
Major	7.8	4.5–13	[4,41]
Pulmonary failure	3.9	1.9–3	[4,41]
DVT/PE	0.8	0.3–1.5	[4,40,41]
Hemorrhage	0.7	0.3–1.9	[4,41]
Other	2.4	1.8	[4,41]

Prevention of Complications in Adrenal Surgery

Complications	**Method of Prevention**	**References**
Inability to find tumor during laparoscopy	Laparoscopic ultrasound	[23]
Pulmonary complications (pneumonia, atelectasis)	Use laparoscopic approach; early ambulation; incentive spirometry	[4]
IVC injury	Dissect the IVC away from the adrenal gland rather than by inferolateral retraction of the adrenal to expose the IVC	—
Pneumothorax with posterior laparoscopic approach	Ensure that trocar is not placed too far cephalad. Early recognition is the cornerstone of therapy. Some centers routinely procure a portable CXR upon arrival to the recovery room	[37,28]
Hemorrhage	Ensure surgical hemostasis	[41]
Intraoperative hemodynamic lability	Invasive arterial monitoring, central venous catheterization	[42]
Intraoperative acute hypertension	Sodium nitroprusside, esmolol, labetolol, nitroglycerin	[40]
Intraoperative tachycardia	IV beta-blocking agents, calcium channel blocker, metyrosine	[40]
Perioperative hypertension during operation for pheochromocytoma	Pretreatment with spironolactone or amiloride and either hydrochlorothiazide or furosemide for 2–4 weeks prior to surgery	[12]
Postoperative adrenal insufficiency (Addison's disease)	Preoperative steroids; avoid etomidate during induction of anesthesia	[8]
Preoperative hypercortisolism	Pretreat with mitotane, metyrapone, aminoglutethimidine, or ketoconazole (not for pregnancy secondary to teratogenesis)	[6,7]
Pathologic fractures	Careful positioning and padding in the operating room	[8]

Complications	Method of Prevention	References
Pulmonary complications	In obese patients being treated for Cushing's disease, be especially vigilant about early postoperative ambulation and incentive spirometry usage	[5]
Cardiovascular complications after resection for pheochromocytoma	Pretreat with phenoxybenzamine for at least 1 week prior to surgery, low threshold for intraoperative beta-blockade, goal-directed fluid resuscitation	[18]

References

1. Doppman JL, Gill JR Jr, Miller DL et al. Distinction between hyperaldosteronism due to bilateral hyperplasia and unilateral aldosteronoma: Reliability of CT. *Radiology.* 1992; 184:677–682.
2. Welbourn RB. Survival and causes of death after adrenalectomy for Cushing's disease. *Surgery.* 1985; 97(1):16–20.
3. Pommier RF, Brennan MF. An eleven-year experience with adrenocortical carcinoma. *Surgery.* 1992; 112(6):963–971.
4. Murphy MM, Witkowski ER, Ng SC et al. Trends in adrenalectomy: A recent national review. *Surg Endosc*. 2010; 24:2518–2526.

   Uses National Inpatient Sample dataset to detail secular trends in utilization of laparoscopy, rates complication, and operative volume for the United States.
5. Kazaure HS, Roman SA, Sosa JA. Obesity is a predictor of morbidity in 1,629 Patients who underwent adrenalectomy. *World J Surg*. 2011; 35:1287–1295.
6. Sonino N, Boscaro M. Medical therapy for Cushing's disease. *Endocrinol Metab Clin North Am*. 1999; 28(1):211–222.
7. Heyn J, Geiger C, Hinske CL et al. Medical suppression of hypercortisolemia in Cushing's syndrome with particular consideration of etomidate. *Pituitary.* 2012; 15:117–125.
8. Valassi E, Santos A, Yaneva M et al. The European registry on cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *Eur J Endocrinol*. 2011; 165(3):383–392.
9. Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: A meta-analysis. *Crit Care Med*. September 11, 2012; 40:2945–2953.
10. Salem M, Tanish RE Jr, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. *Ann Surg*. 1994; 219(4):416–425.
11. Demeter JG, De Jong SA, Brooks MH, Lawrence AM, Paloyan E. Long-term results of adrenal autotransplantation in Cushing's disease. *Surgery.* 1990; 108:1117–1123.
12. Newell-Prince J, Bertagna X, Grossman AB et al. Cushing's syndrome. *Lancet.* 2006; 367:1605–1617.
13. Bravo EL. Primary aldosteronism. Issues in diagnosis and management. *Endocrinol Metab Clin North Am*. 1994; 23(2):271–283.
14. Zarnegar R, Young WF, Lee J et al. The aldosteronoma resolution score: Predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. *Ann Surg*. 2008; 247:511–518.
15. Lim RC, Nakayama DK, Biglieri EG, Schambelan M, Hunt TK. Primary aldosteronism: Changing concepts in diagnosis and management. *Am J Surg*. 1986; 152:116–121.
16. Favia G, Lumachi F, Scarpa V, D'Amico DF. Adrenalectomy in primary aldosteronism: A long-term follow-up study in 52 patients. *World J Surg*. 1992; 16(4):680–684.
17. Celen O, O'Brien MJ, Melby JC, Beazley RM. Factors influencing outcome of surgery for primary aldosteronism. *Arch Surg*. 1996; 131:646–650.
18. Parnaby CN, Serpell Mg, Cornnell JM et al. Perioperative haemodynamic changes in patients undergoing laparoscopic adrenalectomy for phaeochromocytomas and other adrenal tumours. *The Surgeon.* 2010; 8:9–14.
19. Akiba M, Kodama T, Ito Y, Obara T, Fujimoto Y. Hypoglycemia induced by excessive rebound secretion of insulin after removal of pheochromocytoma. *World J Surg*. 1990; 14(3):317–324.
20. Wiesner TD, Blüher M, Windgassen M et al. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. *J Clin Endocrinol Metab*. 2003; 88(8):3632–3636.
21. Scott HW Jr, Halter SA. Oncologic aspects of pheochromocytoma: The importance of follow-up. *Surgery.* 1984; 96(1):1061–1066.
22. Ellison GT, Mansberger JA, Mansberger AR Jr. Malignant recurrent pheochromocytoma during pregnancy: Case report and review of the literature. *Surgery.* 1988; 103(4):484–489.
23. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med*. 1992; 327:1033.
24. Nguyen PH, Keller JE, Novitsky YW et al. Laparoscopic Approach to adrenalectomy: Review of perioperative outcomes in a single center. *Am Surg*. May 2011; 77(5):592–596.
25. Gaujoux S, Bonnet S, Leconte M. Risk factors for conversion and complications after unilateral laparoscopic adrenalectomy. *Br J Surg*. 2011; 98:1392–1399.

   Provides evidence that left-sided surgery is a predictor of overall complications and conversion to open is a predictor to post-operative medical complications.
26. Avisse C, Marcus C, Patey M, Ladam-Marcus V, Delattre JF, Flament JB. Surgical anatomy and embryology of the adrenal glands. *Surg Clin North Am*. 2000; 80(1):403–415.

27. Prinz RA. Mobilization of the right lobe of the liver for right adrenalectomy. *Am J Surg*. 1990; 159:336–338.
28. Russell CF, Hamberger B, van Heerden JA, Edis AJ, Ilstrup DM. Adrenalectomy: Anterior or posterior approach. *Am J Surg*. 1982; 144:322–324.
29. Giulianotti PC, Buchs NC, Addeo P et al. Robot-assisted adrenalectomy: A technical option for the surgeon? *Int J Med Robot Comput Assist Surg*. 2011; 7:27–32.

    Reviews of technical consideration when contemplating robotic-assisted adrenalectomy for right-sided, left-sided, and bilateral disease.
30. Brunaud L, Bresler L, Ayav A et al. Robotic-assisted adrenalectomy: What advantages compared to lateral transperitoneal laparoscopic adrenalectomy? *Am J Surg*. 2008; 195:433–438.
31. Gagner M, Pomp A, Heniford BT, Pharand D, Lacroix A. Laparoscopic adrenalectomy: Lessons learned from 100 consecutive procedures. *Ann Surg*. 1997; 226:238–247.
32. Rutherford JC, Stowasser M, Tunny TJ, Klemm SA, Gordon RD. Laparoscopic adrenalectomy. *World J Surg*. 1996; 20:758–761.
33. Thompson GB, Grant CS, van Heerden JA et al. Laparoscopic versus open posterior adrenalectomy: A case-control study of 100 patients. *Surgery.* 1997; 122:1132–1136.
34. Walz MK, Peitgen K, Hoermann R, Giebler RM, Mann K, Eigler FW. Posterior retroperitoneoscopy as a new minimally invasive approach for adrenalectomy: Results of 30 adrenalectomies in 27 patients. *World J Surg*. 1996; 20:769–774.
35. Brunt LM, Doherty GM, Norton JA, Soper NJ, Quasebarth MA, Moley FJ. Laparoscopic adrenalectomy compared to open adrenalectomy for benign adrenal neoplasms. *J Am Coll Surg*. 1996; 183:1–10.
36. Siperstein AE, Berber E, Engle KL, Duh QY, Clark OH. Laparoscopic posterior adrenalectomy: Technical considerations. *Arch Surg*. 2000; 135:967–971.
37. Bonjer HJ, Sorm V, Berends FJ et al. Endoscopic retroperitoneal adrenalectomy: Lessons learned from 111 consecutive cases. *Ann Surg*. 2000; 232(6):796–803.
38. Dickerson PV, Jimenez C, Chisholm GB et al. Posterior retroperitoneoscopic adrenalectomy: A contemporary American Experience. *J Am Coll Surg*. 2011; 212:659–667.

    This article contains detailed information regarding the advantages, disadvantages, and technical details of posterior retroperitoneal adrenalectomy.
39. Berber E, Mitchell J, Milas M et al. Robotic posterior retroperitoneal adrenalectomy: Operative technique. *Arch Surg*. 2010; 145(8):781–784.
40. Gupta PK, Natarajan B, Pallati PK et al. Outcomes after laparoscopic adrenalectomy. *Surg Endosc*. March 2011; 25(3):784–794. [Epub August 18 2010].
41. Brunt LM. The positive impact of laparoscopic adrenalectomy on complications of adrenal surgery. *Surg Endosc*. 2002; 16:252–257.
42. Weingarten TN, Cata JP, O'Hara JF et al. Comparison of two preoperative medical management strategies for laparoscopic resection of pheochromocytoma. *Urology.* 2010; 76:508.e6–508.e11.

24

*Complications in Pancreatic and Gastrointestinal Neuroendocrine Tumors**

Regan J. Berg and Kenji Inaba

CONTENTS

* The authors have no conflict of interest to report and have received no financial or material support related to this manuscript.

24.1 Complications of Pancreatic Neuroendocrine Tumors

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a group of biologically complex, heterogenous lesions originating from the diffuse neuroendocrine cells of the embryologic gastrointestinal (GI) tract. Although rare, the US Surveillance Epidemiology and End Results (SEER) database reports a near fivefold increase in incidence from 1974–2005, likely partly reflecting increasing clinician awareness and radiologic diagnosis.[1] Despite some commonalities, these lesions differ greatly across specific tumor type and location within the GI tract, and surprisingly little is known about their cellular biology and physiologic regulation.[2] Notable for a relatively indolent course compared to GI adenocarcinoma, these tumors are characterized by the secretion of peptides and neuroamines that, in a subset of lesions, produce specific clinical syndromes. Gastrointestinal neuroendocrine tumors (G-NETs) account for two-thirds of all GEP-NETs, pancreatic tumors (P-NETs) the remaining third.[3]

Tumor description, terminology, and understanding have changed substantially over the past few decades secondary to increasing radiologic detection of nonfunctioning tumors; the impact of immunohistochemistry on diagnosis; and the evolution of multiple pathologic and prognostic classification systems. These combined changes have made understanding these rare but complex clinical entities challenging. Additionally, the rarity and heterogeneity of these tumors have resulted in a paucity of good-quality evidence to direct management. The current chapter reviews the management of GEP-NETs, examining the potential for complications during the phases of (1) diagnosis and preoperative management, (2) operative management, and (3) postoperative management, including the treatment of recurrent disease.

24.1.1 Introduction

Pancreatic neuroendocrine tumors (P-NETs) are a collection of heterogeneous and biologically complex tumors notable for variable risk of malignancy, a generally more indolent behavior compared to pancreatic adenocarcinomas, and for specific clinical syndromes, in a subset of these lesions, due to secretion of vasoactive peptides. These rare tumors account for 1%–4% of all pancreatic malignancies with reported incidence of 1/100,000 per year.[4] P-NETs are characterized as functional or nonfunctional, dependent on whether they secrete biologically active peptides associated with an identifiable clinical syndrome. P-NETs, both functional and nonfunctional, may also be associated with genetic syndromes, most commonly, Multiple Endocrine Neoplasia Syndrome, Type 1 (MEN-1), but also von Hippel Landau, neurofibromatosis type I (von Recklinghausen Disease), and tuberous sclerosis complex.[5]

Nonfunctional tumors account for 60%–85% of all P-NETs, a rising incidence likely secondary to the increasing utilization of CT and MRI imaging.[6] Among functional tumors, five major distinct clinical syndromes occur: insulinoma, gastrinoma, somatostatinoma, VIP-oma, and glucagoma. Given the rarity of these tumors, few reports capably describe incidence and complications, or how complications vary across tumor type. Complications relating to P-NET management can occur with: (1) diagnosis and preoperative management, including treatment of associated endocrinopathy and tumor localization; (2) operative management, including treatment of locally advanced and hepatic metastatic disease, or; (3) postoperative management, including management of surgical complications and recurrent disease.

24.1.2 Complications of Diagnosis and Preoperative Management

Uncomplicated preoperative management of P-NETs requires (1) timely diagnosis, (2) accurate preoperative tumor localization, and (3) management of associated clinical syndromes. The relative rarity of these tumors in combination with their intermittent and nonspecific symptomatology can complicate and delay diagnosis. Up to 75% of patients have lymphatic or distant metastatic disease at presentation.[7] High incidence of metastatic disease at initial diagnosis is noted even with functional tumors. Of the functional P-NETs, VIP-omas, somatostatinomas, and glucagonomas are particularly associated with large size and high incidence of metastatic spread, partly due to difficulty in diagnosing their clinical syndromes. Given the differences in behavior and management across the two major tumor types, nonfunctional and functional P-NETs are examined separately.

24.1.2.1 Nonfunctional P-NETs

24.1.2.1.1 Diagnosis

Nonfunctional P-NETs do not produce distinct clinical syndromes, although they may still secrete biochemically detectable peptides, including chromogranin A, pancreastatin, human chorionic gonadotropin, neuron-specific enolase, neurotensin, or pancreatic polypeptide.[5] Diagnosis may be incidental or secondary to the investigation of nonspecific symptoms such as nausea, vomiting, weight loss, or anorexia. Vague abdominal pain or discomfort is the most commonly reported

symptom.[8] Reported diagnostic delay in patients with nonfunctioning P-NETs ranges up to 7 years.[9] Locally advanced disease may cause obstructive jaundice, duodenal obstruction or bleeding, portal vein thrombosis, and portal hypertension.[3] Symptoms due to metastatic (primarily hepatic) disease may be the first suggestion of pathology.[10] Serum chromogranin A, the most sensitive biomarker for both functional and nonfunctional P-NETs, can aid diagnosis but is dependent on tumor burden, with reported sensitivity of 60%–100% in metastatic disease but ≤50% in less advanced tumors.[6] Pancreatic polypeptide has also been used as a serum marker. Combined use with chromogranin A was associated with a diagnostic sensitivity of 94%.[11]

24.1.2.1.2 Localization

Contrast enhanced, multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI) is the modality most commonly associated with diagnosis of these incidentally or late-presenting tumors. The majority (60%) are located in the pancreatic head but may occur throughout the pancreas.[3,9] P-NETs are hypervascular, enhancing during the arterial phase of contrast-enhanced CT. Thin sections through the pancreas improve sensitivity for lesions ≤1 cm. On MRI, P-NETs demonstrate low signal density on T1-weighted and high signal density on T2-weighted images. Endoscopic ultrasound with fine-needle aspiration (EUS+FNA) is useful for the diagnosis of cystic or solid lesions of the pancreas. Diagnosis of P-NET requires demonstration of chromogranin A and synaptophysin on immunohistochemical staining.[12]

Somatostatin receptor scanning (SRS) is considered the most sensitive modality for the localization of NETs and screening for extrahepatic disease, as over 80% of P-NETs have high densities of somatostatin receptors. Reported sensitivity and specificity for this modality are 90% and 80%, respectively.

24.1.2.2 Functional P-NETs

Despite the presence of characteristic clinical syndromes, diagnosis of functional P-NETs can still be challenging due to intermittent symptomatology. Identification of a characteristic symptom pattern, biochemical and/or radiologic diagnosis, and preoperative management of the clinical syndrome are essential for uncomplicated operative management.

24.1.2.2.1 Insulinoma

Insulinomas are the most commonly encountered functional P-NETs, accounting for 30%–45%. Oversecretion of insulin produces both neuroglycopenic (confusion, obtundation, seizure, and coma) and autonomic (diaphoresis, palpitations, and tachycardia) symptoms. Whipple's triad is the classic presentation of symptomatic hypoglycemia, fasting blood sugar <40 mg/dL, and relief of hypoglycemic symptoms with glucose administration.

Biochemical diagnosis requires low fasting blood glucose (<55 mg/dL) and subsequent inappropriate elevation of serum insulin (>3 U/mL), C-peptide (>0.6 ng/mL), and proinsulin (>5 pmol/L). Elevation of proinsulin and C-peptide confirms the diagnosis and excludes exogenous insulin administration. Up to 5%–10% of insulinomas occur in association with the MEN-1 syndrome.

24.1.2.2.1.1 Localization of the Tumor The majority (90%–95%) are benign, small (<2 cm) solitary lesions. Most are localized to the pancreas and up to 10% occur as multiple lesions with equal distribution throughout the pancreas. Extra-pancreatic lesions occur in 3%, most commonly in the duodenum.[5] Due to their small size, preoperative localization of insulinomas can be difficult. Multiphase CT remains a common initial diagnostic study, with insulinomas demonstrating the arterial enhancement, but lacks sensitivity for small lesions. MRI may slightly increase sensitivity; however, even with gadolinium contrast, the sensitivity for tumors ≤2 cm is less than 50%. EUS appears the most accurate modality for localization, with reported sensitivities of 80%–90%. Insulinomas are not well localized with SRS due to variable expression of somatostatin receptors. A significant number of tumors (20%–60%) remain unlocalized before surgery, and some authors maintain extensive attempts at preoperative localization are unnecessary.[7] Surgical exploration by an experienced pancreatic surgeon with full pancreatic mobilization, bimanual palpation, and intraoperative ultrasound are associated with successful localization in 95%.

24.1.2.2.1.2 Management of Medical Symptoms Surgery provides the only definitive management for insulinomas. Preoperative symptom management is facilitated by dietary counseling (consumption of more frequent, smaller meals) and potential medical treatment with verapamil or diazoxide, which transiently reduce insulin secretion.

24.1.2.2.2 Gastrinoma

The second most common functional, and the most common malignant P-NET, gastrinomas present with recurrent peptic ulcer disease (Zollinger–Ellison Syndrome) and secretory diarrhea secondary to elevated and unregulated serum gastrin levels. Tumors typically occur in the "gastrinoma triangle"—a region roughly defined by the confluence of the cystic and common bile ducts superiors, the second and third portion of the duodenum inferiorly, and the neck and body of the pancreas

medially. Duodenal lesions account for 50%–88% of sporadic gastrinomas and 70%–100% of lesions seen in MEN 1.[13] MEN 1 is diagnosed in up to 30% of patients with ZES. Pancreatic gastrinomas are typically seen as solitary ≥2 cm lesions in sporadic ZES. Gastrinomas are malignant in 50%–85% of cases, up to 25% having liver metastases at diagnosis.[13]

Biochemical diagnosis requires the presence of elevated (>1000 pg/mL) fasting serum gastrin levels (measured at least 72 h off PPI therapy) in the absence of alternative etiologies for hypergastrinemia, such as pernicious anemia, atrophic gastritis, renal failure, or retained antrum and short gut syndromes. When indeterminate results are obtained, a secretin stimulation test with measurement of subsequent fasting gastrin levels should be performed. Postsecretin increase in serum gastrin of >200 pg/mL above baseline is 83% sensitive and 100% specific for gastrinoma.[14] Given the association of these tumors with MEN 1, patients should undergo serum parathyroid hormone, fasting ionized calcium, and prolactin testing.

In patients diagnosed with gastrinoma, tumor localization is best accomplished with endoscopy and examination of the duodenum and multiphase MDCT, followed by SRS to further evaluate both primary and metastatic disease. SRS appears to be the best study for staging and detection of metastases. Endoscopic ultrasound may play a role in the detection of smaller pancreatic lesions but its utility in detection of duodenal gastrinomas is questionable.[13] Proton pump inhibitor therapy should be initiated prior to surgery in patients with gastrinoma.

24.1.2.2.3 Glucagonoma

These rare tumors are the third most common functional P-NETs and are associated with a pattern of symptoms that includes a characteristic migratory, pruritic rash (necrolytic migratory erythema). These patients also experience type II diabetes, increased risk of deep venous thromboembolic events, and depression, a symptom constellation referred to as the "4 Ds." Dermatitis is the most common presenting symptom and can precede other symptoms by years, increasing the risk of delayed or missed diagnosis.

Elevated plasma glucagon levels (>500 pg/mL) and low levels of serum amino acids provide biochemical diagnosis. Skin biopsy is also diagnostic. Conventional CT imaging is usually sufficient for localization due to the tendency of late presentation and large (≥5 cm) tumor size of these lesions. The majority of tumors are found in the pancreatic body and tail.[5]

Glucagonomas require aggressive nutritional optimization and control of hyperglycemia prior to surgery. Amino acid supplementation and somatostatin analogue therapy to control glucagon levels are indicated preoperatively.

24.1.2.2.4 VIP-oma

Tumors secreting vasoactive intestinal peptide (VIP) cause a symptom constellation known as the Verner–Morrison syndrome; the WDHA (watery diarrhea, hypokalemia, and achlorhydria) syndrome; or pancreatic cholera. These patients experience intermittent, large-volume (≥3–5 L/daily) secretory diarrhea, hypocalcemia from fecal potassium loss, and achlorhydria. Elevated serum VIP levels (>200 pg/dL) establish the biochemical diagnosis. Localization can be accomplished through CT, EUS, or SRS. Up to 78% have hepatic metastases at presentation.[15]

Surgery provides the only cure. Preoperative fluid and electrolyte therapy is required. Somatostatin analogue therapy is very effective in controlling the diarrhea and optimizing the patient for surgery.

24.1.2.2.5 Somatostatinoma

Somatostatinomas are the least common functional P-NET. The stomatostatinoma syndrome (cholelithiasis, Type II diabetes, steatorrhea, and hypochloridia) results from the inhibitory effects of somatostatin on gastrointestinal endo- and exocrine glands. The diagnostic difficulty of this entity is such that tumors may be undetected until symptoms of advanced local or metastatic disease occur. Elevated serum somatostatin levels confirm diagnosis. Most tumors are localized to the head of the pancreas, most are malignant, and metastatic disease at presentation is common. Due to this tendency to late presentation, tumors are large and can be localized with CT imaging.

24.1.3 Complications of Surgical Management

Surgery is the only cure for both functional and nonfunctional P-NETs. Appropriate surgical strategy depends on the nature and extent of the tumor. Both enucleation and organ-sparing resections may be alternatives to distal pancreatectomy and pancreaticoduodenectomy in selected patients.

24.1.3.1 Nonfunctional P-NETs

Increasing tumor size is associated with greater risk of malignancy, with lesions ≥2 cm mandating aggressive surgical resection (removal of the primary and en bloc resection of any involved adjacent organs with the goal of an R0 resection).[4,10] For tumors ≤2 cm, surgical management is controversial. These represent benign to intermediate risk tumors and, given the indolent natural history noted in many series, the benefits of resection require balance against operative risk.[12] Some authors advocate surgical treatment for all symptomatic lesions regardless of size and asymptomatic tumors ≥1 cm.[10] For these smaller tumors (≤2 cm), without

evidence of malignancy, enucleation or organ-sparing surgery is appropriate. Distal pancreatectomy, with or without splenectomy, or central pancreatectomy with roux-en-y jejunal reconstruction is advocated for tumors of the body and tail unsuitable for enucleation. Nonfunctioning, asymptomatic tumors ≤1 cm are generally felt safe for observation, although this size cut-off is arbitrary and clear data on the nature and frequency of follow-up is lacking. A recent report of incidentally discovered nonfunctional P-NETs undergoing resection found that 7.7% of patients with initial tumors ≤2 cm developed late metastases or recurrence, providing argument for mandatory resection regardless of size.[8]

A significant number of patients present with locally advanced disease. Large tumors with portal or superior mesenteric vein involvement may be treated with resection and vascular reconstruction. Surgical debulking of locally unresectable, nonfunctioning primary tumors is generally not supported by the literature, as median survival in unresected patients has been reported to be 5 years.[12,16] In these patients, debulking results in high recurrence rates, exposure to the considerable morbidity of palliative pancreatic resections, and no demonstrated survival benefit.[12] For locally unresectable tumors of the pancreatic head causing biliary or gastric outlet obstruction, some authors advocate surgical bypass over nonsurgical palliation as the primary treatment modality, given these patients' long median survival.

Resection of the primary tumor in patients with diffuse metastatic disease does not improve survival.[12] Consensus opinion supports a very limited role for palliative surgery in selected patients with severe tumor-related symptoms and minimal volume of hepatic metastatic disease. Palliative pancreaticoduodenectomy may have a rare role for low-risk patients with a symptomatic nonfunctioning tumor in the pancreatic head, causing severe symptoms from duodenal bleeding or biliary or gastric obstruction, but the decision to pursue this route clearly must be individualized.

With isolated hepatic metastatic disease, liver resection is associated with 5-year survival rates of 47%–76%, compared to 30%–40% in untreated patients. Recurrence rates are as high as 76%, the majority occurring within 2 years.[17,18] Surgery for isolated hepatic metastatic disease is only advocated if ≥90% of the tumor burden can be resected. Enucleation and both anatomic or nonanatomic resections are all options. Recent retrospective review of 72 patients with hepatic metastatic disease from nonfunctional P-NETs found 1- and 5-year, disease-free survival rates among those undergoing palliative resection (≥90% tumor debulking) to be comparable to those receiving curative surgery (59% and 3.5% vs. 54% and 10%, respectively).[19] Adjunctive medical treatment of metastatic disease with somatostatin analogues or hepatic artery chemoembolization increases the risk of cholelithiasis and gallbladder necrosis, respectively, mandating cholecystectomy during any resection of hepatic disease.

24.1.3.2 Functional P-NETs

24.1.3.2.1 Insulinoma

Regardless of preoperative localization attempts, intraoperative ultrasound and bimanual palpation identifies nearly all insulinomas. Intraoperative ultrasound allows detection of tumors ≥3 mm and guides dissection and surgical strategy through delineation of ductal anatomy. The small size of these tumors (over 90% are ≤2 cm) makes enucleation the preferred approach.[4] Spleen preserving, distal pancreatic resection is appropriate for lesions adjacent to the pancreatic duct. Although ≥90% insulinomas are benign, large tumor size or local infiltration increases the likelihood of malignancy, mandating aggressive resection with pancreaticoduodenectomy for pancreatic head lesions or distal pancreatectomy and splenectomy for body and tail tumors.

Laparoscopic enucleation or distal pancreatic resection is an option in experienced centers. When intraoperative localization is unsuccessful, blind resection should be avoided as these lesions have equal distribution throughout the pancreas.[3,20]

24.1.3.2.2 Gastrinoma

Diagnosis of gastrinoma demands surgical management, with routine exploration and intended curative resection for all surgical candidates. Resection is curative in 26%–100% and decreases incidence of hepatic metastatic disease.[4,21,22] The majority of gastrinomas occur in the submucosal layer of the proximal duodenum, so palpation from the pylorus to the level of the superior mesenteric vein, followed by lateral duodenotomy over the second portion, is required. Enucleation of tumors ≤5 mm is possible; larger lesions require full-thickness excision.[4] For pancreatic head lesions, small tumors may be enucleated but large pancreatic head or duodenal lesions may require pancreaticoduodenectomy.

Laparoscopic resection for gastrinomas is not advised as these tumors may not be localized prior to laparotomy, require careful duodenal inspection, and have frequent lymph node metastases.[22] Surgical exploration is an efficacious approach, even in those patients with sporadic ZES and negative imaging studies. Experienced surgeons can localize nearly all tumors and provide cure in almost half of this group, 7% of whom may have hepatic metastases at laparotomy.[23]

24.1.3.2.3 Glucagonoma

Glucagonomas are most commonly found in the tail of the pancreas and are typically large (≥5 cm), with high incidence of locally advanced and metastatic disease.

These patients require distal pancreatectomy, regional lymphadenectomy, and resection of any hepatic metastases. Complete resection is typically possible in a third of patients. The tendency to develop deep venous thrombosis mandates use of perioperative thromboprophylaxis. Repeated resection of recurrent lymphatic or hepatic disease is advocated due to the indolent progress of these tumors. The survival benefit of this approach has not been specifically examined.

24.1.3.2.4 VIP-oma

The distal location of the majority of these tumors and high incidence of metastatic disease mandates aggressive resection. Expert opinion advocates subtotal pancreatic resection and removal of hepatic metastates. Debulking procedures for advanced disease are thought to decrease tumor burden with subsequent partial alleviation of symptoms. Cholecystectomy prevents cholelithiasis associated with subsequent somatostatin analogue therapy.

24.1.3.2.5 Somatostatinoma

Most somatostatinomas are found in the head of the pancreas and ≤75% have metastases at diagnosis. Surgery typically requires pancreaticoduodenectomy. Debulking of the primary and metastatic disease for symptomatic palliation is considered appropriate. Cholecystectomy is also mandated due to the association of elevated somatostatin levels with cholelithiasis.[5]

24.1.4 Resection of Hepatic Metastatic Disease

Aggressive treatment of hepatic metastatic disease is generally advocated for functional P-NETs and indicated with metastases confined to a solitary lobe or when ≥90% of tumor burden can be removed. Options for hepatic disease not amenable to resection, or for adjunctive treatment, include transarterial chemoembolization (TACE), radiofrequency ablation (RFA), or cryotherapy.[13,20,24] In a small review of liver-only neuroendocrine metastases, surgical therapy with resection, ablation, or a combination was associated with 83% survival at 3 years compared to only 31% in those treated medically.[25] The 5-year survival for patients with P-NET hepatic metastases treated by either a combination of resection and ablation or TACE alone differed significantly from those patients treated medically (72% and 50% vs. 25%).[26] Major hepatic resection of neuroendocrine disease was associated with a 14% perioperative complication and 1% mortality rate, but 5- and 10-year survival rates of 61% and 35%, respectively, although tumor recurrence at 5 years was 84%.[27] The role of extended surgery in patients with both locally advanced and hepatic P-NET disease is broadening as accumulating literature appears to support increased disease-free survival and acceptable morbidity and mortality with this approach.[28]

24.1.5 Postoperative Complications and the Management of Recurrent Disease

24.1.5.1 Postoperative Complications

The precise incidence and range of postoperative complications seen in patients with P-NETs is difficult to determine due to the rarity of these tumors, the range of operative procedures employed in their management, and the biological diversity of the lesions. Outcome data derives from single-center series with significant variability. Many of the postoperative complications seen in patients with P-NETs parallel those seen in patients undergoing pancreatic or hepatic resection for other indications.

Review of the largest reported series of surgery for P-NETs (ranging in size from 70 to 168 patients) establishes the following rates of postoperative complications: medical complications, 17%–44%; wound infection; 1%–7%; intra-abdominal abscess; 1%–4%; delayed gastric emptying, 3%–19%; biliary fistula, 5%, postoperative hemorrhage; 4%; and pancreatic fistula, 9%–19%. Reported perioperative mortality ranges from 0% to 3%.[8,29–31]

These studies all report patients with a heterogeneous mix of tumors undergoing varying surgical approaches. Incidence of any surgical complication ranges from 23% to 29%, but risk varies with the type and extent of surgical procedure, as well as tumor and patient factors. The largest review of exclusively nonfunctioning P-NETs, all detected incidentally, reported a 44% incidence of any 30-day postoperative complication, pancreatic fistula (PF) occurring in 15%, intra-abdominal abscess in 4%, wound infection in 3%, and intestinal fistulae in 1%.[8] A retrospective review of 70 patients with P-NET found unsurprisingly that pancreaticoduodenectomy had the highest complication incidence (48%), distal pancreatectomy lesser incidence (13%), with no complications in a small subgroup (n = 11) undergoing enucleation.[30]

24.1.5.1.1 Pancreatic Fistula

Postoperative PF is one of the most common complications of pancreatic surgery, with incidence ≤30% after pancreaticoduodenectomy. Unlike pancreatic adenocarcinoma or chronic pancreatitis, P-NETs are not associated with significant glandular desmoplastic or fibrotic change. Surgery for these tumors may be associated with higher PF rates. A review of 639 patients undergoing pancreatic surgery noted 36% of those with P-NET developed a PF compared with 15% for those with adenocarcinoma or chronic pancreatitis.[32] PF rates after enucleation were 40%. A multicenter retrospective review

of 122 patients with P-NET also found enucleation to be associated with significantly higher PF rates compared to resection (38% vs. 15%).[33] When only clinically significant PF (defined as major fistula prolonging hospital stay or requiring surgical repair) were examined in another series of 122 patients, overall incidence was 24% with no difference noted between enucleation and resection.[34] Another small series of 46 patients undergoing surgery for P-NETs ≤4 cm noted nonsignificant, increased incidence of PF (33% vs. 13%) and all postoperative complications (47% vs. 19%) for enucleation compared to resection.[35] A more recent matched-cohort study noted no difference in PF incidence, although enucleation was associated with significantly less "serious" postoperative morbidity.[36] No patients experienced PF in another small series of enucleation for P-NET.[30] All these studies have suffered from small sample size and methodological limitations. The limited data available, however, suggest that P-NETs, lacking the firm fibrotic change seen in other pathologies, are more prone to postoperative PF, but the relative risks of different resective procedure requires larger study. Use of somatostatin analogues (octreotide) for prevention and management of PF remains controversial among pancreatic surgeons. The most recent Cochrane Collaboration meta-analysis determined an overall reduced PF incidence, without subsequent effect on mortality, leading the authors to advocate for octreotide.[37] However, high-quality data are lacking. Bowel rest, nutritional support, drainage of intra-abdominal collections, and correction of fluid and electrolyte disturbances remain the mainstay of PF treatment.

24.1.5.1.2 Laparoscopic Surgery

The use of minimally invasive techniques for hepatobiliary and pancreatic disease is increasing. A 15-year review of patients undergoing resection for P-NET found minimally invasive and parenchymal-sparing surgeries doubled over the study period, with subsequent shortening of hospital stays without negative impact on morbidity or survival.[38] Studies of outcomes of minimally invasive surgery for P-NET are confined to small case series. Conversion rates range from 0% to 40%. Laparoscopic surgery for patients with small, benign tumors requiring enucleation or distal pancreatectomy appears reasonable, but definitive data to guide patient selection and expected outcomes are lacking.

24.1.5.2 Long-Term Outcomes

P-NETs are characterized by an indolent course and less aggressive biology compared to pancreatic adenocarcinoma. Prediction of tumor behavior and risk of recurrent disease has been assisted by the evolution of three classification systems. The World Health Organization (WHO) classification subdivides neuroendocrine tumors into three categories based on the presence of local infiltration or metastatic spread, tumor histology, size, presence of perineural or angioinvasion, and Ki-67 proliferative index. Benign lesions are well differentiated, confined to the pancreas, and ≤2 cm in size, with ≤2 mitosis/10 hpf, ≤2% Ki-67 expression, and no angio or perineural invasion. Intermediate-risk tumors are those that remain confined to the pancreas but are ≥2 cm, ≥2% Ki-67, have 2–10 mitoses/10 hpf and demonstrate angio or perineural invasion. Malignant tumors are distinguished by frank local invasion or metastatic spread. Reported 5-year survival rates for well-differentiated benign tumors, intermediate tumors, and malignant tumors range from 91% to 100%, 56% to 57%, and 0% to 8%, respectively.[8,39] The WHO system has since been supplemented by the addition of TNM-based staging by both the American Joint Committee on Cancer (AJCC) and the European Neuroendocrine Tumor Society (ENETS). The addition of TNM staging to the prognostication of P-NETs has been validated across multiple clinical studies.

24.2 Complications of Gastrointestinal Neuroendocrine Tumors (Carcinoid)

24.2.1 Introduction

The term "karzinoid" (carcinoma-like) was coined by Oberndorfer in 1907 to describe small bowel neoplasms initially presumed benign. These tumors' potential malignant nature was later appreciated, but the term "carcinoid" persists, both to describe neuroendocrine tumors of the gastrointestinal or bronchopulmonary systems and the seratonergic syndrome associated with these lesions. Most frequently "carcinoid" is used to describe a neuroendocrine tumor of the GI tract and, although this usage remains common, it is also anachronistic. These lesions are best characterized by their primary location or embryologic origin, histologic features, and any associated biochemical activity. However, given the complexity of the WHO classification system and the diversity of these tumors throughout the GI tract, "carcinoid" as a general descriptor is likely to persist. For the purposes of this text, G-NET will be used. Tumors of the GI tract account for two-thirds of all GEP-NETs. Like P-NETs, these lesions present a spectrum of clinical activity and tumor biology.

24.2.2 Complications of Diagnosis and Operative Management

The majority of G-NETs present asymptomatically, found during radiologic, endoscopic, or surgical

intervention for other symptoms.[40] The spectrum of presentation varies by tumor location within the GI tract and any associated biochemical activity.

24.2.2.1 Biochemical and Radiologic Diagnosis

G-NETs produce serotonin, metabolized in the liver and lungs to 5-hydroxyindoleacetic acid (5-HIAA). Detection of G-NETs is facilitated by measure of 24 h urine 5-HIAA levels. The reported sensitivity is 73%–75%, with specificities from 88% to 100%.[41] Most patients with G-NET have 5-HIAA excretion ≥100 mg/day. Foregut and hindgut tumors are associated with minimal secretion of seratonin, making 5-HIAA an inappropriate biomarker for diagnosis. Chromogranin A can also diagnose both functioning and nonfunctioning tumors, elevated in up to 80% of those with G-NET. Chromogranin A is also useful for assessing overall tumor burden, response to treatment, and disease prognostication.

Radiologic evaluation with MDCT or MRI is usually the first imaging modality utilized in these patients. SRS is the major technology used to detect metastatic disease. Endoscopy is often the initial means of identifying gastric, duodenal, rectal, and colonic lesions and can be combined with endoscopic ultrasound to determine the extent of tumor invasion.

24.2.3 Surgical Management of G-NETs

Management of G-NETs depends on tumor location, size, and the presence of biochemically active secretory products.

24.2.3.1 Gastric G-NETs

Four major types of gastric G-NETS have been characterized. Types I and II have excellent prognosis but Type III is an aggressive form and Type IV lesions are rarely amenable to intervention. Type I tumors account for ≥75% of all gastric NETs and are associated with a history of hypergastrinemia such as autoimmune chronic gastritis. These lesions are generally small (≤1 cm) with an indolent course. Endoscopic mucosal resection is appropriate for lesions ≤1 cm. Local excision is required for larger lesions.

Type II gastric G-NETs occur in the setting of MEN-1 and ZES. They have greater risk of nodal metastases than Type I lesions and are frequently larger with angioinvasion and local infiltration. Treatment consists of removing the impetus for the hypergastrinemia (e.g., treatment of duodenal lesions associated with ZES) and surgical resection.

Type III lesions are sporadic and unrelated to chronic atrophic gastritis or MEN 1. The lesions are larger (3–5 cm) and highly aggressive with 5-year survival rates ≤75%. Rarely, Type III lesions produce an "atypical" carcinoid syndrome, consisting of the classic symptoms without diarrhea. Treatment is similar to that for gastric adenocarcinoma. Type IV gastric lesions are poorly differentiated NETs, highly malignant with significant incidence of metastatic disease on presentation. Prognosis is poor as these tumors are usually not amenable to surgical intervention.

24.2.3.2 Small Bowel G-NETs

The small bowel, particularly the terminal ileum, is the most common location for G-NETs. Tumors may present late after a prolonged history of nonspecific abdominal pain or intermittent obstructive symptoms. These tumors are more likely to metastasize than any other G-NET and are responsible for 75%–80% of carcinoid syndromes. All tumors, regardless of size, are considered malignant, mandating resection. Significant desmoplastic reactions cause mesenteric foreshortening and kinking, causing bowel obstruction. Venous stasis, secondary to mesenteric vessel encasement, can also cause segmental bowel ischemia. Management requires en bloc resection with appropriate lymphadenectomy. Full intraoperative evaluation is required to rule out additional lesions or metastatic disease.

24.2.3.3 Appendiceal G-NETs

Most appendiceal G-NETs are diagnosed following appendectomy for acute appendicitis. These tumors rarely cause carcinoid syndrome. Most tumors occur at the appendiceal tip and are typically ≤2 cm. Appendectomy alone is sufficient treatment for tumors ≤1 cm. Traditional indications for right hemicolectomy are tumors ≥2 cm, mesoappendiceal invasion, tumors at the base with positive resection margins, and high-grade malignant or goblet-cell histology.[42] The treatment of lesions 1–2 cm remains controversial. Some authors question the 2 cm size criteria for hemicolectomy, citing a low rate of lymphatic invasion, but this study's population is too small to justify any conclusions.[43]

24.2.3.4 Large Bowel G-NETs

Clinical presentation of large bowel G-NETs may not occur until a late stage due to the large colonic diameter and relative immunity to local mass effect. These lesions are often discovered at endoscopy. Tumors ≤1 cm are rarely associated with lymphatic involvement and, like other areas of the GI tract, may be treated with endoscopic resection. A recent review of over 90,000 colonic tumors identified 345 G-NETs, finding that lesions <11 mm without lymphovascular invasion could be treated by local resection alone.[44] All other lesions require resection with lymphadenectomy.

24.2.3.5 Rectal G-NETs

Treatment of rectal G-NETs depends on the lesion size and extent of invasion. Carcinoid syndrome rarely occurs in rectal tumors and SRS is rarely positive due to low incidence of somatostatin receptors.[45] Incidence of nodal metastases depends on tumor size with lesions ≤1 cm having little risk of metastatic spread. Small lesions ≤1 cm without muscular or lymphatic invasion can be treated with endoscopic resection. Transanal lesions of 1–2 cm may be amenable to transanal excision but require endoanal ultrasound or MRI for accurate staging. Low anterior or abdominal perineal resection may be required for tumors ≥2 cm with histologic or lymphatic invasion or atypical features.

24.2.4 Systematic Complications of Carcinoid Tumors

24.2.4.1 Carcinoid Syndrome

G-NETs are primarily associated with a constellation of cutaneous and systematic symptoms, the "carcinoid syndrome." Tumors of the midgut, arising from the enterochromaffin cells of the GI tract, secrete a variety of biologic amines including seratonin. The carcinoid syndrome, occurring in ≤10% of patients, is presumed largely secondary to seratonin but other contributors, such as 5-HTP, histamine, dopamine, prostaglandins, neuropeptide K, and kallikrein, are potentially implicated.

Carcinoid syndrome occurs primarily with small bowel tumors, when venous drainage of tumor-secreted vasoactive substances bypasses the liver in those with hepatic or retroperitoneal metastatic disease. Despite access to systemic circulation, rectal carcinoids almost never produce carcinoid syndrome.[41] Flushing is the most common symptom (63%–95%) but abdominal pain, telangiectasia, bronchoconstriction, pellagra, and diarrhea also occur. Pellagra refers to the combination of diarrhea, dementia, and dermatitis due to niacin deficiency. G-NETs can consume large amounts of body niacin in the production of serotonin. Diarrhea occurs in approximately 80% of patients. In addition to the systemic symptoms secondary to hepatic metastatic disease, pain related to tumor bulk and liver capsule involvement can occur.

24.2.4.2 Carcinoid Heart Disease

Carcinoid heart disease occurs in up to 40%–50% of patients with carcinoid syndrome, characterized by the presence of fibrotic plaques on the right side of the heart, typically involving the pulmonary and tricuspid valves and endocardium.[46,47] The tricuspid valve is most commonly involved. Left-sided heart disease is rare without a patent foramen ovale, likely due to biologic clearance or inactivation of disease mediators before they reach the left side of the heart. The pulmonary endothelium can metabolize serotonin to 5-HIAA, contributing to the lack of left-sided findings in these patients. Seratonin is again thought to be the primary causative agent in carcinoid-related heart disease, and patients with heart disease have consistently higher urinary 5-HIAA concentrations than those without, suggesting the heart disease reflects failure to effectively diagnose and manage carcinoid syndrome.[47] Unsuspected right heart disease complicates intraoperative fluid management and confounds central venous pressure monitoring, leading to significant patient harm.

The presence of cardiac disease increases the risk of abdominal operation in patients with carcinoid. Patients with carcinoid syndrome require careful cardiac evaluation with both 2D and Doppler echocardiography. Screening is recommended for all patients with midgut G-NETs, regardless of hepatic metastatic disease, and all patients with carcinoid syndrome.[41] Cardiologic consultation for all, and cardiothoracic surgical for those with significant lesions, is required for preoperative optimization. For those with advanced disease, treatment options include balloon vavuloplasty or valve replacement.[2,46] Significant valvular disease warrants infective endocarditis prophylaxis.

24.2.4.3 Carcinoid Crises

Carcinoid crises present a spectrum of findings ranging from exacerbation of typical carcinoid syndrome symptoms to fulminant bronchospasm and hemodynamic derangement with profound hypotension or, more rarely, hypertensive urgencies or emergencies. Symptoms occur in response to stressor such as induction of anesthesia, surgery, or chemotherapy but can occur spontaneously. Carcinoid crises are a major potential complication of operative management, though secondary to catecholamine release in response to pain or physiologic stress. Tumor manipulation may also precipitate a crisis. Spinal anesthesia is also associated with increased risk, related to the catecholamine response stimulated by hypotension, making dural anesthesia preferable for pain management.[46]

Octreotide prophylaxis should be used to prevent carcinoid crises in patients undergoing surgery. Intraoperatively, adrenergic drugs should be avoided for hypotension, as these can react with tumor adrenoreceptors, causing increased release of serotonin. An acute crisis requires cessation of tumor manipulation, support of blood pressure with fluids, and further intravenous octreotide administration. Bronchospasm is treated with octreotide and steroids.

24.2.4.4 Intestinal and Mesenteric Fibrosis

Small bowel G-NETs cause significant desmoplastic reaction, producing mesenteric fibrosis and ischemia. These processes complicate intraoperative management but also suggest diagnosis when found at laparotomy. Extreme desmoplastic reactions can complicate resection and anastomosis, requiring careful surgical judgment. Mesenteric vascular entrapment can often be freed with careful dissection. Surgical debulking of mesenteric disease can palliate symptoms of bowel obstruction and ischemia.[48]

24.3 Medical Therapy for Recurrent or Unresectable Disease

Patients with recurrent or unresectable neuroendocrine tumors may be treated with somatostatin analogs; interferon alpha; or systemic single-agent or combination chemotherapy with streptozocin (currently the only FDA-approved agent for P-NET), fluorouracil, doxirubicin, chlorozotocin, and dacarbazine. The tyrosine kinase inhibitor Sunitinib maleate and the mTOR inhibitor Everolimus have been shown to have some benefit, although with these agents response is typically less than 1 year. As in any complex oncologic disease process, these patients are best managed through multidisciplinary treatment teams and in high-volume centers. Repeated surgical intervention for locoregional recurrence may increase survival in that population undergoing initial cytoreductive surgery.[49]

24.4 Management of Recurrent or Metastatic Disease

Patients with isolated hepatic metastatic disease should be considered for multimodal treatment, including surgical debulking, radiofrequency ablation, and hepatic artery embolization. The goal of treatment is removal of ≥90% of gross disease. Recurrence is the norm and re-resection may be required for disease control. Cholecystectomy is indicated for patients who will receive subsequent somatostatin therapy. For more diffuse metastatic disease, the primary medical option is somatostatin analogue therapy. Response rates to single-agent chemotherapy have not significantly progressed beyond 20%. Streptozocin remains the primary agent, alone or in combination with doxorubicin, dacarbazine, Paclitaxel, or 5-fluorouracil. Newer therapies with tyrosine kinase inhibitors, mTOR inhibitors, and anti-angiogenic therapies with monoclonal antibodies targeting vascular endothelial growth factor (VEGF) continue to be studied. In patients with locally advanced or metastatic disease, aggressive surgery (removal of the primary and/or extensive debulking and cholecystectomy), along with multimodal medical treatment may palliate symptoms and impact survival.[50] As in P-NETs, improved survival in patients with liver-only metastatic disease treated with resection and ablation is also noted.[18,25]

References

1. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008, June 6;26(18):3063–3072.

   *The largest epidemiological review of these tumors, reporting an increased incidence as well as increased survival over time***.**
2. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. January 2008; 9(1):61–72.
3. Akerström G and Hellman P. Surgical aspects of neuroendocrine tumours. *Eur J Cancer* September 2009; 45(Suppl):1237–1250.
4. Fendrich V and Bartsch DK. Surgical treatment of gastrointestinal neuroendocrine tumors. *Langenbecks Arch Surg*. March 2011;396(3):299–311.
5. Ellison TA and Edil BH. The current management of pancreatic neuroendocrine tumors. *Adv Surg*. September 2012;46(1):283–296.
6. Minter RM and Simeone DM. Contemporary management of nonfunctioning pancreatic neuroendocrine tumors. *J Gastrointest Surg*. February 2012;16(2):435–446.
7. Abood GJ, Go A, Malhotra D, and Shoup M. The surgical and systemic management of neuroendocrine tumors of the pancreas. *Surg Clin North Am*. February 2009;89(1):249–266, x.
8. Haynes AB, Deshpande V, Ingkakul T, Vagefi PA, Szymonifka J, Thayer SP et al. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: Short-term and long-term patient outcomes. *Arch Surg*. May 2011;146(5):534–538.
9. Bartsch DK, Schilling T, Ramaswamy A, Gerdes B, Celik I, Wagner H-J et al. Management of nonfunctioning islet cell carcinomas. *World J Surg*. November 11 2000;24(11):1418–1424.
10. Dralle H, Krohn SL, Karges W, Boehm BO, Brauckhoff M, and Gimm O. Surgery of resectable nonfunctioning neuroendocrine pancreatic tumors. *World J Surg*. December 2004;28(12):1248–1260.

11. Panzuto F, Severi C, Cannizzaro R, Falconi M, Angeletti S, Pasquali A et al. Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors. *J Endocrinol Invest*. January 2004;27(1):6–11.
12. Falconi M, Plockinger U, Kwekkeboom DJ, Manfredi R, Korner M, Kvols L et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. *Neuroendocrinology* 2006;84(3):196–211.

    The European Neuroendocrine Tumor Society (ENETs) Consensus Guidelines for the Standard of Care in Neuroendocrine Tumors represent the most recent and exhaustive set of recommendations for all aspects of patient care. These excellent reviews are cited throughout this chapter.
13. Jensen RT, Niederle B, Mitry E, Ramage JK, Steinmuller T, Lewington V et al. Gastrinoma (duodenal and pancreatic). *Neuroendocrinology* 2006;84(3):173–182.
14. Berna MJ, Hoffmann KM, Serrano J, Gibril F, and Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. *Medicine (Baltimore)* November 2006;85(6):295–330.
15. Smith SL, Branton SA, Avino AJ, Martin JK, Klingler PJ, Thompson GB et al. Vasoactive intestinal polypeptide secreting islet cell tumors: A 15-year experience and review of the literature. *Surgery* December 1998;124(6):1050–1055.
16. Solorzano CC, Lee JE, Pisters PW, Vauthey JN, Ayers GD, Jean ME et al. Nonfunctioning islet cell carcinoma of the pancreas: Survival results in a contemporary series of 163 patients. *Surgery* December 2001;130(6):1078–1085.
17. Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS et al. NANETS treatment guidelines: Well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* August 2010;39(6):735–752.
18. Chamberlain RS, Canes D, Brown KT, Saltz L, Jarnagin W, Fong Y, and Blumgart LH. Hepatic neuroendocrine metastases: Does intervention alter outcomes? *J Am Coll Surg*. April 2000;190(4):432–445.
19. Cusati D, Zhang L, Harmsen WS, Hu A, Farnell MB, Nagorney DM et al. Metastatic nonfunctioning pancreatic neuroendocrine carcinoma to liver: Surgical treatment and outcomes. *J Am Coll Surg*. July 2012;215(1):117–124; discussion 124–125.

    Although still a relatively small study (n = 77), this recent paper continues the thread of evidence supporting palliative dubulking of hepatic metastases when ≥90% of tumor burden can be removed.
20. de Herder WW, Niederle B, Scoazec J-Y, Pauwels S, Kloppel G, Falconi M et al. Well-differentiated pancreatic tumor/carcinoma: Insulinoma. *Neuroendocrinology* 2006;84(3):183–188.
21. Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ, and Jensen RT. Surgery increases survival in patients with gastrinoma. *Ann Surg*. September 2006;244(3):410–419.
22. Norton JA and Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. *Ann Surg*. November 2004;240(5):757–773.
23. Norton JA, Fraker DL, Alexander HR, and Jensen RT. Value of surgery in patients with negative imaging and sporadic Zollinger-Ellison syndrome. *Ann Surg*. September 2012;256(3):509–517.

    A key recent paper indicating that even with the use of somatostatin receptor scanning gastrinomas may remain unlocalized. In this setting operative exploration can localize nearly all (98%) of tumors and provide cure in nearly half (46%), similar to the rates seen in those with positive pre-operative localization.
24. O'Toole D, Salazar R, Falconi M, Kaltsas G, Couvelard A, de Herder WW et al. Rare functioning pancreatic endocrine tumors. *Neuroendocrinology* 2006;84(3):189–195.
25. Musunuru S, Chen H, Rajpal S, Stephani N, McDermott JC, Holen K et al. Metastatic neuroendocrine hepatic tumors: Resection improves survival. *Arch Surg*. October 2006;141(10):1000–1004; discussion 1005.
26. Touzios JG, Kiely JM, Pitt SC, Rilling WS, Quebbeman EJ, Wilson SD, and Pitt HA. Neuroendocrine hepatic metastases. *Ann Surg*. May 2005;241(5):776–785.

    A key 14-year review of 153 patients with neuroendocrine pancreatic or gastrointestinal tumors indicating a survival benefit from aggressive, multi-modal management of hepatic metastatic disease.
27. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, and Que FG. Surgical treatment of neuroendocrine metastases to the liver: A plea for resection to increase survival. *J Am Coll Surg*. July 2003; 197(1):29–37.
28. Kleine M, Schrem H, Vondran FWR, Krech T, Klempnauer J, and Bektas H. Extended surgery for advanced pancreatic endocrine tumours. *Br J Surg*. January 2012;99(1):88–94.
29. Vagefi PA, Razo O, Deshpande V, McGrath DJ, Lauwers GY, Thayer SP et al. Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: The Massachusetts General Hospital experience from 1977 to 2005. *Arch Surg*. April 2007;142(4):347–354.
30. Kazanjian KK, Reber HA, and Hines OJ. Resection of pancreatic neuroendocrine tumors: Results of 70 cases. *Arch Surg*. August 2006;141(8):765–769; discussion 769–770.
31. Fischer L, Kleeff J, Esposito I, Hinz U, Zimmermann A, Friess H, and Büchler MW. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg*. May 2008;95(5):627–35.
32. Fendrich V, Merz MK, Waldmann J, Langer P, Heverhagen AE, Dietzel K, and Bartsch DK. Neuroendocrine pancreatic tumors are risk factors for pancreatic fistula after pancreatic surgery. *Dig Surg*. 2011;28(4):263–269.
33. Pitt SC, Pitt HA, Baker MS, Christians K, Touzios JG, Kiely JM et al. Small pancreatic and periampullary neuroendocrine tumors: Resect or enucleate? *J Gastrointest Surg*. September 2009;13(9):1692–1698.
34. Inchauste SM, Lanier BJ, Libutti SK, Phan GQ, Nilubol N, Steinberg SM et al. Rate of clinically significant postoperative pancreatic fistula in pancreatic neuroendocrine tumors. *World J Surg*. July 2012;36(7):1517–1526.
35. Casadei R, Ricci C, Rega D, D'Ambra M, Pezzilli R, Tomassetti P et al. Pancreatic endocrine tumors less than 4 cm in diameter: Resect or enucleate? A single-center experience. *Pancreas* August 2010;39(6):825–828.

36. Cauley CE, Pitt HA, Ziegler KM, Nakeeb A, Schmidt CM, Zyromski NJ et al. Pancreatic enucleation: Improved outcomes compared to resection. *J Gastrointest Surg*. July 2012;16(7):1347–1353.
37. Gurusamy KS, Koti R, Fusai G, and Davidson BR. Somatostatin analogues for pancreatic surgery. *Cochrane Database Syst Rev*. 2012;6:CD008370.

    *The most recent review by the Cochrane Collaboration suggesting potential benefit for use of octreotide in the prevention and management of pancreatic fistulae***.**
38. DiNorcia J, Lee MK, Reavey PL, Genkinger JM, Lee JA, Schrope BA et al. One hundred thirty resections for pancreatic neuroendocrine tumor: Evaluating the impact of minimally invasive and parenchyma-sparing techniques. *J Gastrointest Surg*. October 2010;14(10):1536–1546.
39. Ito H, Abramson M, Ito K, Swanson E, Cho N, Ruan DT et al. Surgery and staging of pancreatic neuroendocrine tumors: A 14-year experience. *J Gastrointest Surg*. May 2010;14(5):891–898.
40. Stinner B, Kisker O, Zielke A, and Rothmund M. Surgical management for carcinoid tumors of small bowel, appendix, colon, and rectum. *World J Surg*. February 1996;20(2):183–188.
41. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* January 2012;61(1):6–32.
42. Goede AC, Caplin ME, and Winslet MC. Carcinoid tumour of the appendix. *Br J Surg*. November 2003;90(11):1317–1322.
43. Bamboat ZM and Berger DL. Is right hemicolectomy for 2.0-cm appendiceal carcinoids justified? *Arch Surg*. April 2006;141(4):349–352; discussion 352.
44. Konishi T, Watanabe T, Kishimoto J, Kotake K, Muto T, Nagawa H, and Japanese Society for Cancer of the Colon and Rectum. Prognosis and risk factors of metastasis in colorectal carcinoids: Results of a nationwide registry over 15 years. *Gut* June 2007;56(6):863–868.
45. Akerström G and Hellman P. Surgery on neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab*. March 2007;21(1):87–109.
46. Akerström G, Falconi M, Kianmanesh R, Ruszniewski P, Plöckinger U, and European Neuroendocrine Tumor Society. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and perioperative therapy in patients with neuroendocrine tumors. *Neuroendocrinology* 2009;90(2):203–208.
47. van der Horst-Schrivers ANA, Wymenga ANM, Links TP, Willemse PHB, Kema IP, and de Vries EGE. Complications of midgut carcinoid tumors and carcinoid syndrome. *Neuroendocrinology* 2004;80(Suppl):128–132.
48. Ohrvall U, Eriksson B, Juhlin C, Karacagil S, Rastad J, Hellman P, and Akerström G. Method for dissection of mesenteric metastases in mid-gut carcinoid tumors. *World J Surg*. November 2000;24(11):1402–1408.
49. Schurr PG, Strate T, Rese K, Kaifi JT, Reichelt U, Petri S et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: An institutional experience. *Ann Surg*. February 2007;245(2):273–281.
50. Boudreaux JP, Putty B, Frey DJ, Woltering E, Anthony L, Daly I et al. Surgical treatment of advanced-stage carcinoid tumors. *Ann Surg*. June 2005;241(6):839–846.

    A small series of advanced midgut gastrointestinal tumors supporting a role for aggressive resection of locally advanced disease in symptom palliation.

Section V

Cardiothoracic

25

Complications of Cardiopulmonary Resuscitation

Abhijit S. Pathak, Amy J. Goldberg, and Lars O. Sjoholm

CONTENTS

The surgeon is most likely to encounter a patient who has sustained a cardiac arrest in a hospital environment, where adequate monitoring will be in place and support personnel competent to initiate cardiopulmonary resuscitation (CPR) and advanced cardiovascular life support.

Patients are usually in one of three locations: the emergency department, the operating room, or the intensive care unit (ICU). The surgeon's initial response to cardiac arrest depends on the presumed cause of the arrest, on whether the arrest was witnessed, and on the patient's clinical status (e.g., whether the arrest occurred intraoperatively while the patient's abdomen or chest was open).

The 2010 American Heart Association (AHA) Guidelines for CPR and Emergency Cardiovascular Care (ECC) have emphasized the immediate performance of chest compressions. The surgeon must determine whether the patient would benefit from open cardiac massage, rather than closed chest compressions. Complications of CPR will be determined by the length of time to return of spontaneous circulation and the mode of delivery chosen for the cardiac compressions.

Only rarely will surgeons be involved in treating a patient who suffers sudden cardiac death. With a few exceptions, such as trauma, sudden massive pulmonary thromboembolism, or massive myocardial infarction, most episodes of cardiac arrest with which surgeons are involved are associated with serious multiorgan dysfunction.

25.1 Causes and Factors Underlying Cardiac Arrest

If cardiac arrest is to be successfully managed, certain underlying factors must be recognized and corrected. In general, cardiac compromise or arrest can be broadly categorized as due to nontraumatic or traumatic causes. Nontraumatic arrest can be further categorized as resulting from respiratory factors, cardiac factors, neurologic factors, or metabolic or electrolyte disturbances. Table 25.1 outlines the causes of nontraumatic arrest, and Table 25.2 outlines the causes of traumatic arrest.

TABLE 25.1

Factors Causing or Contributing to Nontraumatic Cardiac Arrest

Respiratory factors	*Neurologic factors*
Airway obstruction	Central depression
CNS injury	Stroke
Foreign body	Anesthesia
Infection	Drugs or toxins
Trauma	
Tumor	*Metabolic or electrolyte factors*
Insufficient ventilation	Acidosis
CNS injury	Alkalosis
Neuromuscular disease	Hypokalemia or hyperkalemia
Drugs	Hypomagnesemia or hypermagnesemia
Hypoxemia or pulmonary dysfunction	Hypocalcemia
COPD	Hypothermia
Asthma	
Pulmonary edema	
Venous thromboembolism	*Drugs or toxins*
Pneumonia	Beta-blockers
	Calcium channel blockers
Cardiovascular factors	Digoxin
Cardiac factors	Antiarrhythmics
Acute coronary occlusion	Tricyclic antidepressants
Coronary artery disease	Carbon monoxide
Drugs	Cyanide
Reduced cardiac output	Cocaine
Cardiomyopathy	
Valvular or structural abnormalities	
Tension pneumothorax	
Pericardial tamponade	
Pulmonary embolism	
Circulatory factors	
Hypovolemia or hemorrhage	
Distributive shock	
Sepsis	
Neurogenic shock	

Note: CNS, central nervous system; COPD, chronic obstructive pulmonary disease.

25.2 Pathophysiology of Cardiac Arrest

Understanding the pathophysiology of the precipitating event will help guide and direct the management of cardiac arrest during the resuscitation phase and the post-resuscitation period.

Cardiac arrest results in cessation of blood flow; however, the vulnerability of organs to ischemic injury differs. The central nervous system, particularly the brain, is the most susceptible to such injury; the most vulnerable areas of the brain are the cerebral cortex, the hippocampus, and the cerebellum. Irreversible brain damage can be expected after 5 min of normothermic cardiac arrest. If the blood flow to the brain is not restored within 10 min, restoration of neurologic function rarely occurs. The heart is the second most vulnerable organ to ischemia; the endocardium is more sensitive than the epicardium. The kidneys, gastrointestinal tract, and musculoskeletal system are much more tolerant to the disruption of blood flow and can tolerate longer periods of normothermic ischemia (up to 1 h) without permanent damage, if adequate reperfusion is reestablished.

Cessation of cardiac function results from one of three causes: ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), ventricular asystole, or pulseless electrical activity (PEA) [1].

TABLE 25.2

Factors Causing or Contributing to Traumatic Cardiac Arrest

Exsanguination
Hypovolemia
Cardiac injury
Pericardial tamponade
Tension pneumothorax
Air embolism
Airway obstruction
Extrinsic compression
CNS depression
Direct injury
Intraluminal or oropharyngeal bleeding
Hemic drowning
Drowning or near-drowning
Severe brain injury
Spinal cord injury
Electrocution
Hypothermia

Note: CNS, central nervous system.

25.2.1 Ventricular Fibrillation or Pulseless Ventricular Tachycardia

VF or pulseless VT usually results from a primary cardiac event such as acute myocardial infarction or ischemia. The presence of antecedent multifocal premature ventricular contractions may serve as a warning sign for these serious conditions. Certain electrolyte disturbances, such as hypokalemia, hypomagnesemia, or hypocalcemia, may complicate or contribute to this scenario (Table 25.1). In cases of traumatic cardiac arrest, ventricular irritability may suggest air embolism or cardiac compression caused by a tension pneumothorax or pericardial tamponade. Electrocution with alternating current in the range of 100 mA–1 A can also cause VF (Table 25.2).

25.2.2 Ventricular Asystole

Asystole usually results from cardiac arrest while the heart is in diastole. Asystole may be the final outcome of a process beginning with bradycardia in patients with hypoxemia caused by respiratory failure, by a vasovagal event, or by a metabolic disturbance such as hyperkalemia. Furthermore, asystole may be the result of exsanguination: in this event, the progression from tachycardia to bradycardia and PEA finally degenerates to asystole. Electrocution with alternating current of more than 10 A can also result in ventricular asystole.

25.2.3 Pulseless Electrical Activity

PEA occurs when a heart rhythm is present on the monitor but cardiac output is absent. Common causes of PEA include severe hypoxia, hypovolemia, hypothermia, acidosis, tension pneumothorax, and pericardial tamponade. Immediate recognition and treatment of these readily reversible causes of PEA can lead to return of normal sinus rhythm.

25.3 Physiology of Standard Closed-Chest Cardiopulmonary Resuscitation

25.3.1 Cardiac Pump Model

Kouwenhoven et al. [2] first suggested that CPR works as a cardiac pump by squeezing the heart between the sternum and the spine. Each chest compression results in systole, with the left ventricle compressed and blood propelled forward. Because the cardiac valves operate in only one direction, prograde flow into the arterial circulation is guaranteed. The relaxation phase of CPR, which allows the sternum to return to its normal position, corresponds to diastole, during which intracardiac pressures fall, the atrioventricular valves open, and venous return occurs.

25.3.2 Thoracic Pump Model

Most physiologists favor the thoracic pump model of CPR [3]. In this model, forward flow is generated by an arteriovenous pressure gradient that is established by chest compression. External compression of the chest generates an increase in thoracic pressure that is transmitted throughout the thorax, including the heart, the aorta, and the great veins. According to this model, the mitral and tricuspid valves are incompetent and no significant atrioventricular or ventriculoaortic pressure gradients are present.

25.3.3 Perfusion during Cardiopulmonary Resuscitation

Closed-chest CPR results in only limited perfusion of vital organs. Cardiac output is believed to be no more than 25%–30% of normal, and cerebral blood flow is believed to be only about 10%–15% of normal [3,4]. Furthermore, coronary blood flow during standard CPR may be as low as 5% of normal [4,5]. If the surgeon performs open cardiac massage, through a left anterolateral thoracotomy, cardiac output can be twice that *achieved by* closed-chest compressions [5,6].

25.4 Management of Cardiac Arrest

The AHA has established guidelines for CPR and ECC [7]. These standards and guidelines are readily available and will not be discussed in detail here. However, a significant change to the 2010 AHA guidelines was the performance of chest compressions prior to airway and breathing in out-of-hospital adult resuscitations. Although ventilations are an important part of resuscitation, evidence supports that chest compressions are the critical component in an adult resuscitation.

If an automated external defibrillator (AED) is available in the field and reveals VF or if a patient who is being monitored experiences VF, immediate defibrillation takes precedence over airway management, pharmacotherapy, and CPR because hypoxemia and prolonged fibrillation have not yet developed, and the chances of restoring normal circulation are maximized.

As stated earlier, closed-chest compressions provide only a fraction of the normal cardiac output, even under optimal conditions. If standard closed-chest CPR fails to provide effective circulation, the surgeon may consider using open-chest cardiac massage. Under certain circumstances, resuscitative left thoracotomy and open-chest cardiac massage may be the only means of effective resuscitation after nontraumatic cardiac arrest. Because most physiologists subscribe to the thoracic pump model of CPR, effective circulation may not be provided when the transmission of pressure throughout the thorax is impossible, such as when the abdomen or chest is open. Especially for trauma victims, the situation may be compounded by hypovolemia, cardiac tamponade, or an unstable chest wall, which renders conventional CPR ineffective [5]. These conditions are most commonly encountered in the trauma bay, operating room, during laparotomy or thoracotomy, and in the ICU, where patients may have an open abdomen after a damage control laparotomy. In such circumstances, open cardiac massage

via resuscitative thoracotomy may be the only hope for survival.

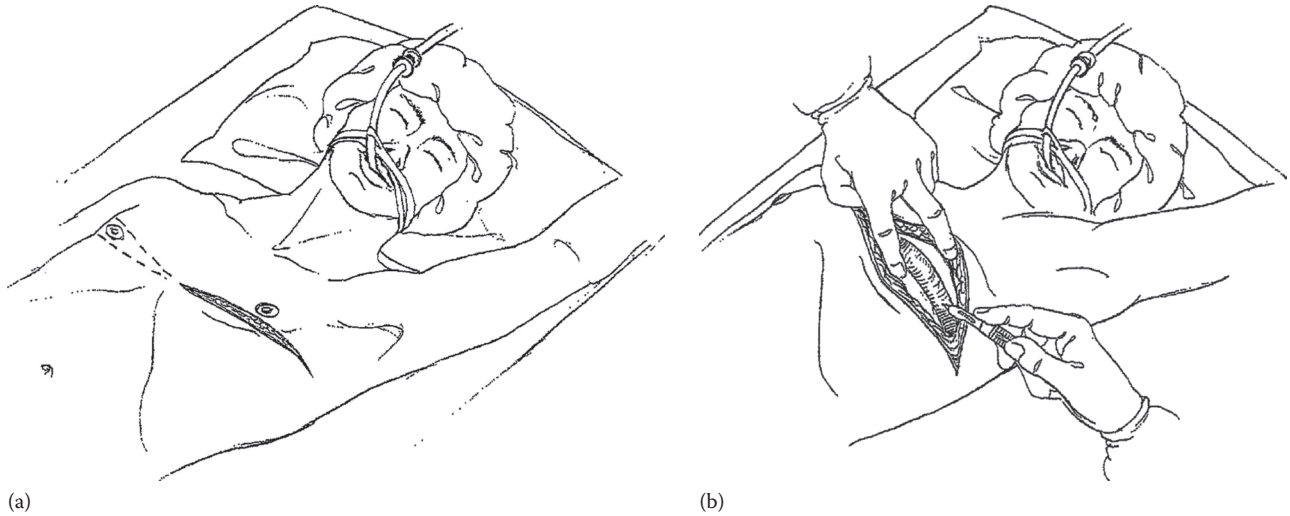
Direct cardiac massage through a minimally invasive approach rather than an open thoracotomy has been reported [8,9]. This procedure, called minimally invasive direct cardiac massage (MID-CM), involves inserting a heart-contacting padded baseplate, connected to a handle, through a 2–3 cm incision in the left parasternal area. The handle remains outside the chest, and the baseplate is positioned directly on the ventricles with the pericardium intact. Manual decompression of the device compresses the heart and causes an artificial systole. In a swine model of cardiac arrest [8], this technique provided coronary and cerebral perfusion similar to that achieved using standard open-chest cardiac massage. A European pilot study [9] using this technique in the prehospital setting demonstrated promising results. Dissection and insertion was rapid, less than 1 min. Compared with standard CPR, MID-CM showed an improvement of hemodynamic parameters. A strong carotid pulse was obtained in all 25 patients. This technique has not gained acceptance due to the need for adequate training and potential complications.

The management scheme described earlier is appropriate in cases of nontraumatic cardiac arrest. In cases of trauma, resuscitative thoracotomy is vital for patients who are in extremis or whose condition deteriorates so that cardiac arrest appears imminent. For trauma victims, thoracotomy may be necessary to relieve pericardial tamponade, control thoracic bleeding, control air embolism, allow open cardiac massage, provide temporary aortic occlusion so as to maximize cerebral and coronary perfusion, and limit infradiaphragmatic bleeding [10,11].

25.5 Technique of Resuscitative Thoracotomy and Open Cardiac Massage

The technique of resuscitative thoracotomy and open cardiac massage has been reviewed by Cothren and Moore [10] and Seamon et al. [11]. In most instances, the patient is placed supine with the left arm raised above the head. For men, a standard left anterolateral thoracotomy incision is begun just lateral to the left border of the sternum and carried in a straight line laterally to a point just below the nipple (Figure 25.1). For women, the incision is placed in the inframammary crease, and the breast is held under cephalad traction. The chest is entered through the fifth intercostal space. During most emergency thoracotomy procedures, the pericardium is opened with an incision that begins anterior to the left phrenic nerve and proceeds longitudinally so as to avoid transecting the nerve. The pericardium must be opened widely so that the heart can be delivered through the incision (Figure 25.2). An inadequate pericardiotomy may impede effective cardiac output during open massage or result in cardiac arrest because inflow is occluded.

Manual cardiac massage should be performed with both hands. In this technique, the hands should be slightly cupped and placed on the anterior and posterior surfaces of the heart. The ventricles are cyclically



(a) (b)

FIGURE 25.1
(a) The standard skin and soft-tissue incision for a left anterolateral resuscitative thoracotomy extends in a straight line from the left border of the sternum to the posterior axillary line. The incision may be extended into the right chest at the same level or one intercostal space higher. (b) Once the plane of the ribs and intercostal muscles has been reached, the intercostal muscle is thinned with a knife, but the pleura is entered with a finger or blunt-tipped scissors to avoid iatrogenic laceration of the heart or the lungs. The intercostal space is then opened widely with heavy scissors.

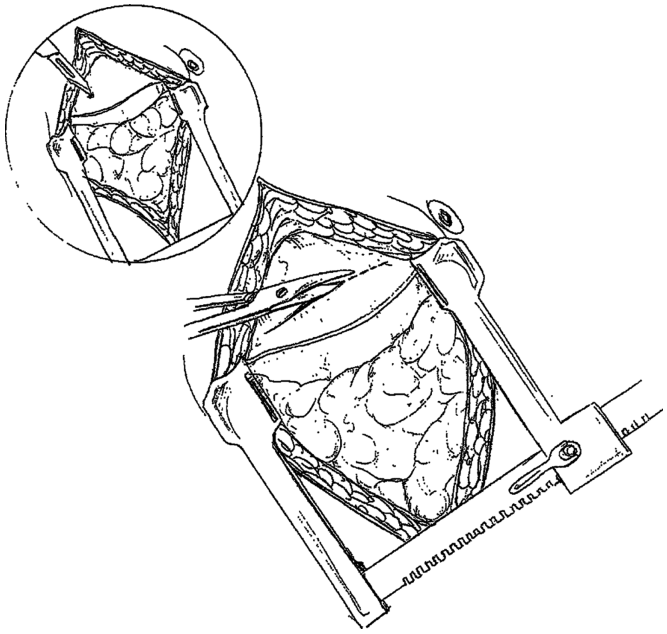


FIGURE 25.2
In cases of cardiac tamponade, the pericardium is initially nicked with a scalpel anterior to the left phrenic nerve, as shown in the inset. The pericardiotomy is then extended vertically with scissors with care to avoid injury to the heart and phrenic nerve.

FIGURE 25.3
Bimanual cardiac massage is performed via a left anterolateral thoracotomy. The fingertips must be kept flat on the cardiac surface to avoid iatrogenic cardiac penetration. Excessive traction on the heart should be avoided because it can result in obstruction of venous inflow.

compressed as shown in Figure 25.3. The fingertips should be flat against the epicardial surface. Most studies have indicated that the optimal rate of manual cardiac massage is approximately 100 bpm.

Aortic cross-clamping is generally performed at the outset of cardiac massage; its purpose is to help maximize

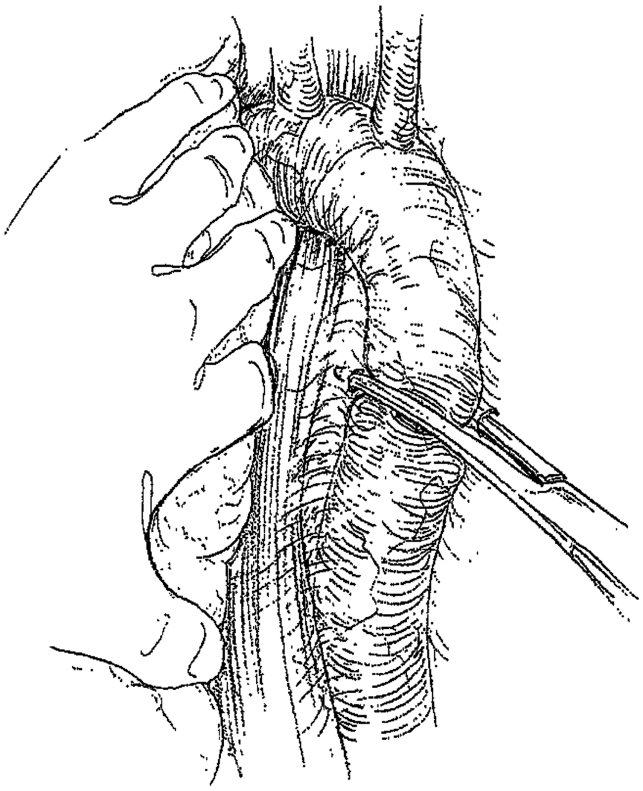


FIGURE 25.4
Aortic cross-clamping is carried out after the anterior retraction of the left lung and the penetration of the mediastinal pleura so that the jaws of the vascular clamp securely grip the aortic adventitia.

cerebral and coronary flow. The first step in clamping the aorta is to locate the descending vessel by anteriorly retracting the left lung with the left hand, a maneuver that is facilitated if the lung is deflated. Direct visualization of the aorta is ideal but can be very difficult to achieve; blind dissection may be necessary. The surgeon should run the fingers over the anterior spine until the space between the spine and aorta can be palpated; this space should be entered by blunt dissection with the surgeon's fingers. The mediastinal pleura is opened just anterior and posterior to the aorta at the site of intended occlusion. The jaws of the clamp are then passed through the created apertures to securely grasp the aorta, as shown in Figure 25.4.

25.6 Complications of Cardiopulmonary Resuscitation

25.6.1 Standard Closed-Chest Cardiopulmonary Resuscitation

Most complications after closed-chest CPR are related to thoracic wall damage and include rib or sternal fractures

and costochondral separation. These injuries can lead to more severe problems such as pneumothorax, hemothorax, cardiac injury, and even aortic injury.

The thorax is not the only cavity at risk of damage from CPR. Compression of the liver against the xiphoid process can damage that organ [12]. In addition, gastric injury, splenic injury [13], or fat embolism may occur. It is important to remember that an endotracheal tube may become dislodged or malpositioned by closed-chest compression. Thus, chest radiographs should be obtained as soon as possible after successful resuscitation. The true incidence of complications after CPR may not be accurately estimated or known because the primary event that caused the cardiac arrest usually causes death.

Despite these potential complications, fibrinolytic use may benefit patients who have suffered a cardiac arrest secondary to a massive pulmonary embolism or acute myocardial infarction [14,15]. In the absence of bleeding, CPR itself is not a contraindication to the use of lytic therapy and does not appear to cause an unacceptable risk [16,17].

25.6.2 Open-Chest Cardiac Massage and Thoracotomy

When an emergency thoracotomy is performed, technical complications can occur. Iatrogenic injuries to the lung, pericardium, heart, phrenic nerves, aorta, esophagus, and chest wall have been described [10,18].

The standard approach for left anterolateral thoracotomy, as noted earlier, is through the fifth intercostal space below the nipple of male patients and in the inframammary crease of female patients. Exposure can be limited if the skin incision is improperly placed or if the correct intercostal space is not entered. Bleeding from the chest wall, especially from the internal mammary vessels, can be troublesome, and these vessels should be ligated during the procedure. During attempts at occluding the descending thoracic aortic, damage to the aorta, the esophagus, or the intercostal branches of the aorta may occur [10,18].

Cardiac injuries can occur during open cardiac massage. Perforation of the right ventricle is a serious complication and is usually caused by incorrectly applied cardiac compression. This lethal complication can be avoided if compression is performed with both hands and with the digits flat rather than curled. The right ventricle is particularly susceptible to injury because it is thinner than the left ventricle and is often distended as a result of fluid resuscitation [1]. If perforation occurs, it should be repaired with sutures buttressed with pledgets. As a temporary measure, skin staples can be applied to the perforation until a definitive repair can be performed. Under these circumstances, the right ventricle is usually very friable and repair can be difficult.

Injury to surrounding structures and bleeding are the two most serious concerns after emergency thoracotomy. After successful resuscitation, the patient should be taken to the operating room for hemostasis, wound irrigation, and closure. Surprisingly, little is reported about the infection rate post emergency thoracotomy. Unpublished review of the authors' own emergency thoracotomy series has revealed wound infection, mediastinitis, and/or empyema rates of less than 1%.

The most serious complication of either closed-chest or open-chest CPR, of course, is failure to resuscitate. The rates of successful resuscitation vary depending on the cause of cardiac arrest but are, in general, poor. Survival from in-hospital cardiac arrest to discharge has been reported to be approximately 17%. During the past decade, there seems to have been a trend in improved survival rate followed by a decreased rate of neurologic disability in these patients. The reason for this is not completely understood but could possibly be contributed to the introduction of rapid response teams. Future investigations are needed to further study the problem [19]. Investigations continue in an attempt to improve the outcome of CPR.

25.7 Management after Successful Cardiopulmonary Resuscitation

Once spontaneous circulation has resumed, the underlying cause of arrest should be identified and treated and the adequacy of tissue perfusion should be assured and maintained. Cardiovascular and hemodynamic dysfunction are common after cardiac arrest; such dysfunction include hypovolemic shock, cardiogenic shock, and the systemic inflammatory response syndrome [7]. Invariably, some form of cardiovascular dysfunction is present, and normal cardiac function may not return for 12–24 h [7]. The primary goal of management after CPR is reestablishing global and regional perfusion of tissues. Traditional end points, such as restoration of blood pressure, may not adequately reflect peripheral organ perfusion. Regional tissue malperfusion may exist, particularly in the splanchnic bed, and this condition is believed to contribute to the multiple-organ dysfunction syndrome (MODS). Other measurements of end points of resuscitation such as lactate level, base deficit, and central venous saturation should be followed closely. Early goal-directed therapy protocols should be initiated immediately.

Bedside echocardiography can be utilized to assist in the evaluation and resuscitation of the cardiac arrest and post-resuscitation patient. The use of transthoracic echocardiography in the ICU has gained wider acceptance. The Focused Assessed Transthoracic Echocardiography (FATE) protocol is one example. The FATE examination screens for volume status and contractility of the heart as well as any significant cardiac pathology [20].

Neurologic impairment is common among survivors of cardiac arrest; approximately 80% of patients remain comatose for various time periods [21]. As many as 40% of survivors enter a persistent vegetative state and 79% die within 1 year [22]. A recent retrospective review of patients sustaining in-hospital cardiac arrest revealed improvements in both survival and neurologic outcomes. As mentioned earlier, this may be, in part, by the introduction of rapid response teams [19]. However, the overall poor outcome after cardiac arrest has prompted many physicians to attempt to develop a means of predicting outcome during the early post-resuscitative phase. When coma lasts for more than 6 h after CPR, the prognosis for full neurologic recovery is poor. The prognosis worsens when the coma persists for more than 3 days; in such cases, patients rarely survive without severe neurologic disability [22].

As mentioned before, awakening after resuscitation for cardiac arrest generally occurs within 3 days and some degree of neurologic impairment will be present if the patient fails to do so. Furthermore, clinical findings that accurately predict poor outcome include myoclonus within the first 24 h, absence of pupillary response and corneal reflexes within 1–3 days, and absent or extensor motor response after 3 days [23]. It should be noted that most clinicians will have performed some type of imaging study such as a brain CT or MRI as well as a neurologic consultation in those patients that have not awoken within the first 24 h. Although no definitive time period within which further testing should be performed has been established, if a patient fails to awaken after cardiac arrest, further studies may be helpful in determining neurologic outcome. These tests include EEG, evoked/event-related potential (EP) studies (usually somatosensory-evoked potentials or SSEP), and serum neuron-specific enolase (NSE). In particular, EEG findings revealing suppression to ≤20 μV, burst suppression pattern with generalized epileptiform activity, or generalized periodic complexes on a flat background are strongly associated with a poor outcome [23]. Furthermore, bilateral absence of the N20 component of the SSEP with median nerve stimulation performed 1–3 days or later after cardiac arrest accurately predicts a poor outcome [23]. Finally, serum NSE, a marker of brain damage, can be used to predict neurologic outcome as well. Serum NSE levels >33 μg/L at days 1–3 post-resuscitation accurately predict poor outcome [23].

These dismal neurologic outcomes prompted investigators to evaluate therapies that might improve brain function post-resuscitation. Therapeutic hypothermia (the lowering of body temperature to 32°C–34°C for 12–24 h) has been shown to improve neurologic outcome and survival after successful resuscitation of out-of-hospital VF arrest [24]. Currently, the 2010 AHA Guidelines recommend therapeutic hypothermia for comatose adult patients who have suffered out-of-hospital VF cardiac arrest and it may be considered for comatose patients after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of PEA or asystole [7].

25.8 Conclusion

The 2010 AHA Guidelines for CPR and ECC included significant updates from prior years. Ongoing research to evaluate the effects of some of these advances, hypothermia to improve neurologic outcome and the use of lytic therapy during and after CPR, will determine whether patient outcomes post-resuscitation will be markedly improved.

The surgeon will continue to utilize emergency thoracotomy and open cardiac massage for the appropriate surgical patient. Further investigation of MID-CM will determine whether these devices will replace open resuscitative thoracotomy and its associated complications.

Complications of CPR

Rib fractures	32%
Sternal fractures	21%
Anterior mediastinal hemorrhage	18%
Hemopericardium	8%
Cardiac or great vessel rupture	4%
Pneumothorax	3%
Hemothorax	1%
Liver injury	2%
Splenic injury	<1%
Gastric rupture	<1%
Tracheal injury	<1%

Source: Corbett, S.W. and O'Callaghan, T., *Ann. Emerg. Med.*, 29, 317, 1997; Krischer, J.P. et al., *Chest*, 92, 287, 1987.

Avoiding Complications from CPR

During performance of closed-chest compressions, fractures of the ribs and sternum may occur, leading to mediastinal hemorrhage and/or injury to the heart, great vessels, or lungs
Perform proper technique with appropriate hand positioning and depth of compressions
During management of the airway, gastric distension may result in emesis and aspiration and/or decreased ventilation by reducing lung volume from increased intraabdominal pressure
Proper head positioning and depth of rescue breathing
Minimize bag valve mask ventilation
Proper endotracheal intubation
Failure of CPR
Initiate CPR in a timely manner
Ensure proper technique
Adhere to ACLS protocol

References

1. Pathak AS, Goldberg AJ, and Buckman RF. Complications after cardiopulmonary resuscitation and cardiac arrest. In: Cohn SM, ed. *Complications in Surgery and Trauma*. 2nd ed. New York: Informa Healthcare, 2007: pp. 299–304.
2. Kouwenhoven WB, Jude JR, and Knickerbocker CG. Closed-chest cardiac massage. *JAMA.* 1960; 173: 1064–1067.
3. Niemann JT. Cardiopulmonary resuscitation. *N Engl J Med*. 1992; 327(15):1075–1080.
4. Mattox KL and Feliciano DV. Role of external cardiac compression in truncal trauma. *J Trauma.* 1982; 22(11):934–936.
5. Luna GK, Pavlin EG, Kirkman T et al. Hemodynamic effects of external cardiac massage in trauma shock. *J Trauma.* 1989; 29(10):1430–1433.

   Internal cardiac massage is at least twice as effective in maintaining cardiac output compared to external compression and has demonstrated to be far superior to external cardiac massage in providing cerebral and coronary perfusion.
6. Boczar ME, Howard MA, Rivers EP et al. A technique revisited: Hemodynamic comparison of closed- and open-chest cardiac massage during human cardiopulmonary resuscitation. *Crit Care Med*. 1995; 23(3): 498–503.
7. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 1, 4, 8, 9. *Circulation.* 2010; 122:S640–S656, S676–S684, S729–S767, S768–S786.
8. Buckman RF Jr, Badellino MM, Mauro LH et al. Direct cardiac massage without major thoracotomy: Feasibility and systemic blood flow. *Resuscitation.* 1995; 29(3):237–248.
9. Rozenberg A, Incagnoli P, Delpech P et al. Prehospital use of minimally invasive direct cardiac massage (MIDCM): A pilot study. *Resuscitation.* 2001; 50(3):257–262.
10. Cothren CC and Moore EE. Emergency department thoracotomy for the critically injured patient: Objectives, indications and outcomes. *World J Emerg Surg*. 2006; 1:4–16.

    In patients with cardiopulmonary arrest, external chest compression provides approximately 20%–25% of baseline cardiac output, with 10%–20% of normal cerebral perfusion. In models of hemorrhagic shock or pericardial tamponade, external chest compression fails to provide adequate systemic perfusion.
11. Seamon MJ, Chovanes J, Fox N et al. The use of emergency department thoracotomy for traumatic cardiopulmonary arrest. *Injury.* 2012; 43:1355–1361.
12. Adler SN, Klein RA, Pellecchia C, and Lyon DT. Massive hepatic hemorrhage associated with cardiopulmonary resuscitation. *Arch Intern Med*. 1983; 143:813–814.
13. Fitchet A, Neal R, and Bannister P. Lesson of the week: Splenic trauma complicating cardiopulmonary resuscitation. *BMJ.* 2001; 322:480–481.
14. Fatovich DM, Dobb GJ, and Clugston RA. A pilot randomized trial of thrombolysis in cardiac arrest (The TICA trial). *Resuscitation.* 2004; 61:309–313.
15. Perrott J, Henneberry RJ, and Zed PJ. Thrombolytics for cardiac arrest: Case report and systematic review of controlled trials. *Ann Pharmacother*. 2010; 44:2007–2013.
16. Bottiger BW, Bode C, Kern S et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: A prospective clinical trial. *Lancet.* 2001; 357:1583–1585.
17. Janata K, Holzer M, Kurkciyan I et al. Major bleeding complications in cardiopulmonary resuscitation: The place of thrombolytic therapy in cardiac arrest due to massive pulmonary embolism. *Resuscitation.* 2003; 57:49–55.
18. Ivatury R. Cardiac injuries and resuscitative thoracotomy. In: Maull KI, Rodriguez A, and Wiles CE, eds. *Complications in Trauma and Critical Care*. Philadelphia, PA: W.B. Saunders, 1996: pp. 279–288.
19. Saket G, Brahmajee KN, Spertus JA et al. Trends in survival after in-hospital cardiac arrest. *N Engl J Med*. 2012; 367:1912–1920.
20. Jensen MB, Sloth E, Larsen KM, and Schmidt MB. Transthoracic echocardiography for cardiopulmonary monitoring in the intensive care unit. *Eur J Anaesthesiol*. 2004; 21:700–707.
21. Madl C, Kramer L, Domanovits H et al. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. *Crit Care Med*. 2000; 28(3):721–726.
22. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrell K, Safar P, and BRCT I Study Group. Assessment of neurological prognosis in comatose survivors of cardiac arrest. *Lancet.* 1994; 343:1055–1059.
23. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, and Wiebe S. Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review). *Neurology.* 2006; 67:203–210.

    American Academy of Neurology (AAN) evidence-based guideline reviewing evidence on the prognostic value of the clinical examination and ancillary investigations (electrophysiologic, biochemical, and radiologic) for poor outcome in comatose survivors after cardiopulmonary resuscitation. Clinical findings that accurately predict poor outcome include myoclonus within the first 24 h, absence of papillary response and corneal reflexes within 1–3 days, and absent or extensor motor response after 3 days. If a patient fails to awaken after cardiac arrest further studies may be helpful in determining neurologic outcome. These tests include EEG, evoked/event-related potential (EP) studies (usually somatosensory evoked potentials or SSEP), and serum neuron-specific enolase. These guidelines can be accessed at www.aan.com.
24. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002; 346(8):549–556.

Randomized controlled trial to therapeutic hypothermia or to standard treatment with normothermia, with blinded assessment of the outcome, of patients who had been resuscitated after cardiac arrest due to ventricular fibrillation. Therapeutic mild hypothermia increased the rate of favorable neurologic outcome and reduced mortality.

25. Corbett SW and O'Callaghan T. Detection of traumatic complications of cardiopulmonary resuscitation by ultrasound. *Ann Emerg Med*. 1997; 29:317–322.
26. Krischer JP, Fine EG, Davis JH, and Nagel EL. Complications of cardiac resuscitation. *Chest.* 1987; 92:287.

26

Complications of Pulmonary and Chest Wall Resection

Daniel T. DeArmond, Hao Pan, and Scott B. Johnson

CONTENTS

Lung resection is commonly performed for a number of diagnoses including primary or metastatic lung malignancy or inflammatory lung disease. Chest wall resection is performed for primary chest wall tumors, primary lung malignancies with chest wall invasion, or chest wall infections. A clear understanding of common complications as well as the relevant anatomic relationships and physiology helps to prevent the occurrence of morbidity and mortality with these operations.

26.1 Pain

Any discussion of the complications of lung and chest wall resection has to begin with postoperative pain. Because the incisions for lung and chest wall resection necessarily involve the structures involved with respiratory mechanics, respiration is always adversely affected by lung and chest wall resection, resulting in conditions that increase the risk of the development of a wide variety of complications. Deep breathing elicits incisional pain, and patients may compensate by lowering tidal volumes, which in turn leads to atelectasis and increased work of breathing associated with tachypnea. Atelectasis may lead to subtotal expansion of the lung within the thorax, which may result in a failure to achieve apposition of the visceral and parietal pleurae. As visceral-to-parietal pleural apposition is thought to be central to the resolution of air leaks after lung surgery, the atelectasis resulting in subtotal lung expansion brought on by pain may lead to prolonged air leaks in patients recovering from lung resection. By a similar mechanism, pleural fluid may accumulate in a pleural space in which the lung is not fully expanded, leading to pleural effusions requiring additional procedures to evacuate or to empyema should infection be introduced into that effusion. Coughing after lung or chest wall surgery is important in terms of clearing the airways of secretions that result from intubation with airway trauma or secretions from regions of lung that have undergone resection. Failure to cough and clear secretions may result in retention of bronchial secretions, leading to pneumonia or mucus plugging of the bronchus. Often patients will state that the only pain they experience in the postoperative period is associated with coughing, which may lead them to avoid coughing [13]. Efforts at controlling postoperative pain must address the pain associated with cough so that patients will not avoid the maneuvers required to clear bronchial secretions.

Controlling post-thoracotomy pain and reducing the amount of systemic opioids used have been well studied via continuous intercostal blockade, paravertebral blockade, and epidural opioids, and/or anesthetics. For thoracotomies, thoracic epidural catheters have become commonplace as are the use of patient-controlled analgesia pumps (PCA) and intravenous ketorolac [14]. One-time intraoperative intercostal blockade may

reduce immediate postoperative pain; however, the effectiveness of continuous intercostal analgesia pumps, even with proper technique, appears inferior to epidural and other regional techniques [15]. Aggressive perioperative and postoperative pain management is imperative in reducing morbidity in post-thoracotomy patients and appears to be best accomplished with use of an epidural anesthetic and covering breakthrough pain with patient-controlled anesthesia [16].

For thoracoscopic operations, pain is significantly reduced as compared to thoracotomy due to the fact that major muscles of the chest wall are spared and no rib spreading is employed [17]. Thoracoscopy has also been associated with a significant reduction in analgesic requirements during the postoperative period [18]. As a result, the use of epidural catheters for thoracoscopic lung resection may not be as important for pain control and may in fact slow down key postoperative clinical endpoints such as bladder catheter removal, return of bowel function, and discharge. For thoracoscopy, oral narcotic analgesics in association with intravenous ketorolac where appropriate may suffice for pain control; PCA may be introduced, if pain scores are higher [14].

26.2 Bleeding

Bleeding that occurs with lung or chest wall resection originates from three broad categories of sources: pulmonary hilar vasculature (pulmonary artery or vein); arterial sources from the chest wall or mediastinum (intercostal, bronchial, or lymphatic associated arteries); and pulmonary parenchyma.

Bleeding that originates from the pulmonary artery or vein can be massive and immediately life threatening. Even when bleeding from these vessels is relatively low volume, it may still be enough to obscure dissection planes within the operative field and prevent forward progress of an operation. When performing major lung resection, most practitioners individually ligate and divide the artery and vein to the portion of lung to be resected; great care must be exercised in dissecting these structures because even small tears to major pulmonary arteries or veins may result in major hemorrhage. Furthermore, because the pulmonary artery and vein may be relatively thin-walled vessels, attempts at repair may extend the injury if the tissues of the vessel are too thin to hold suture. Because the intravascular pressure in the pulmonary artery and vein is relatively low compared to systemic arterial pressure, simple tamponade of a bleeding site on one of these vessels, with, for example, a sponge on a ringed grasper, may suffice and should often be the first maneuver undertaken to try to achieve hemostasis [19]. Often this maneuver alone will allow the bleeding to be at least temporarily controlled so that lung resection can proceed; when the resection is completed, the surgeon can then go back and look for sites of pulmonary venous or arterial injury that may require additional suture repair. Suture repair of the pulmonary artery or vein can usually be performed with 4–0 or 5–0 monofilament polypropylene suture ligatures for focal sites of bleeding or injury. If bleeding is massive and prolonged hemostasis cannot be achieved with sponge stick tamponade or suture repair, clamping of the proximal pulmonary artery and pulmonary veins can be performed to temporarily interrupt all blood flow to the lung so that the hilar vessels can be examined for sites of injury and repair can be performed. In these situations, bleeding is controlled with compression of the right or left pulmonary artery with a sponge stick until a vascular clamp can be placed around the entire hilum or the proximal pulmonary artery can be dissected free and individually clamped. When clamping of the left pulmonary artery is required, the clamp is usually placed in the region of the aortopulmonary window and care to avoid injury to the recurrent laryngeal nerve must be exercised. The proximal extent of the right pulmonary artery may be accessed by entering the pericardium medially to the superior vena cava and performing circumferential dissection of the right pulmonary artery just medially to where it passes posterior to the superior vena cava. Vascular control of the pulmonary vessels can be achieved with clamps or vessel loops. Injury to and bleeding from the pulmonary artery is particularly an issue when performing upper lobe resection because the arterial branches to the upper lobes emanate from the proximal pulmonary artery and irreparable injury to the artery in this location may mandate pneumonectomy to achieve hemostasis. The risk of bleeding from the pulmonary vessels is generally confined to the intraoperative period and is not a common cause of bleeding in the postoperative period.

Bleeding in the postoperative period that requires reoperation usually originates from systemic arteries in the chest wall or mediastinum such as intercostal, bronchial, or lymphatic-associated mediastinal arteries. These arteries are relatively small and may not accumulate significant hemothorax until several hours into the postoperative period. Meticulous attention to achieving hemostasis in these vessels should be exercised prior to closure of thoracotomy or thoracoscopy incisions as bleeding is the most common indication for rethoracotomy [20]. Consideration must be given to the relatively hypotensive and hypothermic anesthetized patient. Arteries may undergo temporary vasospasm in the operating room and

manifest little to no bleeding only to undergo vasodilation in the normothermic and normo- or hypertensive patient, leading to occult hemorrhage in the postoperative patient. In particular, areas of dense pleural adhesions or where a tumor may be in contact or even frankly invading the chest wall are likely culprits of intercostal arterial bleeding. Systemic collaterals from intercostal arteries may develop in dense pleural adhesions, leading to hemorrhage when these adhesions are divided. In the current era, the bronchus is divided during lobectomy or pneumonectomy using surgical staplers in which case bronchial arteries are effectively ligated; however, careful examination of the bronchus to assure hemostasis is important to avoid bleeding that necessitates returning to the operating room in the postoperative period. Similarly, during the lymphadenectomy portion of the operation that accompanies major lung resection for lung cancer, mediastinal arteries associated with lymph node basins may be disrupted, leading to high sanguinous chest tube output or slow but steady accumulation of hemothorax. A high index of suspicion must be maintained for systemic arterial bleeding because it may be delayed in its presentation; any excessive bleeding from the chest tubes placed during surgery for lung or chest wall resection should be followed by plain films of the chest to rule out hemothorax, the presence of which mandates a return to the operating room for hemothorax evacuation and control of bleeding sources. Frankly sanguinous output from chest tubes in excess of 100 cc/h in the first few hours after surgery should prompt serious consideration of immediate reoperation. Operative reexploration can occur either via thoracoscopy or thoracotomy regardless of the operative approach of the primary surgery and depends upon the stability of the patient; hypotensive or hypoxic patients are less likely to be amenable to a thoracoscopic approach given the requirement for more meticulous lung isolation.

Bleeding from the lung parenchyma after wedge resection or enucleation of lung nodules is usually self-limited due to the low pressure of the pulmonary arterial system and small caliber of the vessels in the periphery of the lung. Exceptions include patients with pulmonary hypertension due to progressive cardiopulmonary disease or coagulopathic patients. In general, small bleeders from the lung parenchyma may undergo coagulation with electrocautery or clip ligation. For more extensive bleeding from lung parenchyma, consideration should be given to topical hemostatic agents, bovine pericardium-reinforced staple lines, or pledgeted suture ligation of bleeding sites. Only in extreme cases would anatomic pulmonary resection be required to control lung parenchymal bleeding.

26.3 Infection

Two infectious complications are particularly associated with lung or chest wall resection: pneumonia and empyema.

Infectious bacteria that are the source of pneumonia in patients who have recently undergone lung or chest wall resection are most likely to be nosocomial organisms introduced into the airway during endotracheal intubation for the delivery of general anesthesia/lung isolation or organisms associated with aspiration. Meticulous attention to maintaining antiseptic airway conditions must be adhered to at all phases of the care of patients undergoing lung resection; if bronchoscopy is to be performed at the start of an operation to assess the extent of resectability of a lung mass or for primary diagnosis of endobronchial pathology, endoscopists should adhere to accepted hand hygiene practices, wear gloves when handling the bronchoscope, and prevent the bronchoscope from coming into contact with potentially contaminated surfaces such as the patient's hair or skin.

In the postoperative period, particularly after major lung resection, endobronchial secretions may be increased due to inspissated secretions due the presence of an endotracheal tube during surgery, bloody secretions from airway injury from the endotracheal tube or from bronchial or parenchymal surgical staple lines, or bronchorrhea associated with recent smoking cessation. Patients should be encouraged to participate in incentive spirometry and coughing to encourage the clearing of these secretions, which otherwise may, if not cleared, come to harbor infection. In particular, patients with advanced emphysema as evidenced by a decreased forced expiratory volume in 1 s may be at higher risk for pneumonia due to their diminished ability to generate a forceful cough to clear secretions. If patients have demonstrated responsiveness to bronchodilators on their preoperative pulmonary function tests, bronchodilators may be used in the postoperative period to improve lower airway patency and forced expiratory capacity. Chest percussive physiotherapy can be used to aid in the clearing of secretions but its use may be limited by thoracic incisional pain. When performed by specialized therapists, chest physiotherapy may reduce the rates of pulmonary morbidity from 15.5% to 4.7% [21]. Positive expiratory pressure therapy devices may also be considered.

A common presentation of pneumonia in the postoperative period is increasing oxygen requirements or decreased mental status in a patient on the first to third postoperative day after major lung resection; fever may or may not be present. These clinical findings should prompt immediate physical exam assessment of the

patient along with plain radiographs of the chest and serologic tests, including complete blood cell count and arterial blood gas as well as consideration of transfer of the patient to an intensive care unit. Broad-spectrum antibiotics are initiated if the patient's white blood cell count is elevated, even in the absence of clear sputum culture evidence of pneumonia, as the early institution of antibiotics in these patients may be life-saving. Arterial blood gas will commonly show elevated arterial carbon dioxide partial pressure. If indicated, a computed tomography scan of the chest is obtained, if possible with intravenous contrast to rule out the presence of pulmonary embolism; this study may also confirm the presence of pneumonia. Noninvasive bilevel positive airway pressure delivered by occlusive mask may be instituted to assist in ventilation in patients with respiratory acidosis; invasive mechanical ventilation is reserved for patients unable to maintain adequate oxygenation or ventilation by noninvasive means, in patients who require bronchoscopy, or for airway protection in obtunded patients. If pneumonia after lung or chest wall resection is recognized early with early initiation of broad-spectrum antibiotics, patients with this condition may demonstrate significant clinical improvement within 24–48 h; however, vigilance should be maintained for the possibility of a longer and more complicated postoperative course.

In the past, patients undergoing major lung resection were maintained with endotracheal intubation on mechanical ventilation for several days in the postoperative period to facilitate frequent bronchoscopy with aspiration of endobronchial secretions. This practice has been largely abandoned due to the increased risk of nosocomial pneumonia with prolonged endotracheal intubation and due to the observation that with appropriate encouragement patients are better at clearing their own secretions. Furthermore, length of stay is shortened and overall recovery is accelerated by early extubation of these patients in the operating room at the termination of the operation.

Empyema can occur after any surgery that involves exposure of the pleural space; however, it occurs relatively uncommonly in cases of lung or chest wall resection where the lung is fully expanded within the thorax because the rich blood supply of the lung provides a robust immune presence within the pleura. Empyema tends to occur after lung or chest wall resection in cases where the lung is not fully expanded in the hemithorax due either to a large lung parenchymal or bronchial air leak or due to the development of pneumonia [22]. With respect to air leak from the lung parenchyma after lung resection, considerable data has shown that thoracostomy tubes placed at the time of surgery that are maintained to suction tend to promote the persistence of air leaks while changing from suction to "water seal" promotes closure of air leaks. However, removing thoracostomy tubes from suction necessitates that the patient take an active role in the evacuation of air from the pleural space through active lung expansion as encouraged by compliance with incentive spirometry, getting out of bed to chair to sit upright, ambulating in the halls, etc. With tubes off suction, if the air leak from the lung parenchyma is greater in magnitude than the patient can expel actively, air will accumulate in the pleural space, leading to lung collapse, which may be relatively irreversible due to adhesion-forming fibrinous material in the pleural space; this may trap the lung in a collapsed configuration. Factors that hinder patients from actively evacuating air from the pleural space include poor lung function and poor pain control. The development of empyema and lung collapse may be associated with a number of signs and symptoms but the most obvious are fever, increasing supplemental oxygen requirements, and decreased breath sounds in the involved hemithorax. In the case of empyema associated with prolonged thoracostomy tube therapy and lung collapse, the introduction of pathogenic bacteria into the pleural space may occur via the thoracostomy tube. In the case of pneumonia-associated empyema after lung or chest wall resection, pathogenic bacteria enter the pleural space via the lung. The risk factors for the development of pneumonia have been previously described above. Usually, a return trip to the operating room for decortication is required to treat postoperative empyema; this can be performed either via thoracoscopy [23] or thoracotomy, regardless of the surgical approach of the primary operation.

26.4 Prolonged Air Leak

The definition of prolonged air leak after lung resection is leakage of air from a chest tube for greater than 5 days after surgery. Leakage of air from a lung that has undergone major pulmonary resection may arise from two sources: the bronchus, in which case the air leak is referred to as bronchopleural fistula; or the peripheral alveolar spaces of the lung parenchyma, in which case the air leak is referred to as alveolar pleural fistula.

The risk of bronchopleural fistula with peripheral lung wedge resection is essentially nil. With the advent of surgical staplers, the risk of bronchopleural fistula complicating the typical lobectomy or segmentectomy for lung cancer should be less than 1%; this number is higher if the lobectomy is being performed for inflammatory or infectious disease of the lung in an infected pleural space or if the patient has undergone previous radiation to the hilum. Bronchopleural fistula occurs

more commonly with pneumonectomy in which setting the incidence may be as high as 2% [24]. A hallmark of bronchial stump management during pneumonectomy to prevent the development of bronchopleural fistula is division of the mainstem bronchus flush with the carina as undue length of the bronchial stump leads to stump ischemia and pooled secretions predisposing to fistulization. If pneumonectomy is being carried out in an infected field with a high suspicion of risk of bronchopleural fistula formation, the bronchial stump can be bolstered by the use of muscle flaps (intercostal, latissimus, etc.) or an omental flap to promote its integrity [7,22,24]. Bronchopleural fistula after pneumonectomy presents with very distinctive signs and symptoms: increasing air in the pleural space noted on chest radiographs; and productive cough made worse by lying on the side opposite the pneumonectomy. The patient may also present with fever due to a contaminated pleural space on the side of the pneumonectomy or the development of pneumonia resulting from contaminated pleural fluid passing into the remaining lung through the fistula. When bronchopleural fistula arises after pneumonectomy, the first steps in treatment are to relieve infection under pressure in the evacuated pleural space and prevent ongoing sepsis of the remaining lung [7]. Broad-spectrum antibiotics are initiated and while initial treatment of the pleural space with thoracostomy tube placement may be attempted, ultimately the performance of an Eloesser flap will be necessary with daily dressing changes directly to the pleural space. Packing the pleural space with daily dressing changes rids the pleural space of infection and also helps to minimize the air leak that results from bronchopleural fistula. Computed tomography scanning of the chest as well as bronchoscopy is performed to characterize the fistula and formulate a plan for surgical repair. Repair of a bronchopleural fistula generally consists of reclosure of the bronchial defect flush with the carina; this may be performed via sternotomy as the bronchus may be difficult to access through the pleural space due to extensive inflammation and scarring. Bronchial reclosure can also be reinforced as noted previously with muscle or omental flaps. Once bronchial closure is felt to have been successful over a period of several weeks and as long as the pleural space remains relatively aseptic with daily dressing changes, the Eloesser flap may be closed after filling the pleural space with antibiotic-containing irrigation fluid (modified Claggett procedure).

Alveolar pleural fistula may occur after a wide variety of lung resection operations, including lung volume reduction for emphysema, resection of emphysematous blebs, segmentectomy or lobectomy for lung cancer or benign disease, or even simple wedge resection or decortication in patients with advanced pulmonary emphysema or immunosuppression. All post lung resection patients have thoracostomy tubes in place after surgery and alveolar pleural fistula manifests as an air leak, which may be further described as continuous, inspiratory, expiratory, or forced expiratory. Air leaks may also manifest as subcutaneous emphysema, which results from the dissection of inspired air into the subcutaneous tissues of the trunk, head, and extremities through surgical breeches in the parietal pleura. Subcutaneous emphysema is not a life-threatening condition even when massive; however; it can be very disquieting to patients, causing anxiety and severe discomfort.

Studies have demonstrated that alveolar pleural fistula closure is promoted in the postoperative period by removing thoracostomy tubes from suction and placing them to "water seal" only [25]. If alveolar pleural fistula persists despite this maneuver, chest tubes can be placed to a Heimlich valve and if appropriate, the patient can be discharged. Alternatively, chemical pleurodesis can be performed at the bedside. For patients who are unable to be compliant with home chest tube management or for whom extensive subcutaneous emphysema is causing discomfort and/or morbidity, a return to the operating room may be indicated either via thoracotomy or thoracoscopy for lysis of adhesions, assurance of complete lung expansion, and creation of a parietal pleural tent to promote air leak closure; aerostatic tissue sealants may also be employed to this end.

26.5 Damage to Adjacent Structures

Several intrathoracic nervous structures bear mentioning as being at risk to injury during lung or chest wall resection: the phrenic nerve, left recurrent laryngeal nerve, and intercostal nerves.

The phrenic nerve is at greatest risk of injury during dissection of hilar structures during major lung resection. On the right, the phrenic nerve runs very close to hilar structures. To avoid injury to the phrenic nerve on the right side, blunt dissection is performed to exclude the nerve from the operative site prior to more involved dissection of hilar structures; dissection of hilar structures often involves sharp dissection with cautery and efforts to distance this dissection from the phrenic nerve may decrease the chance of injury. On the left, the phrenic nerve tends to be more anterior with respect to the hilar structures, so sharp dissection in the left hilum is met with less risk of injury. However, on the left side, dissection of aortopulmonary lymph nodes in conjunction with lobectomy for lung cancer may bring the phrenic nerve into greater risk of injury as the phrenic nerve runs very close to this lymph node station. The phrenic nerve may also

be at risk of injury during lysis of pleural adhesions, which may be present in smokers or other patients with chronic lung disease undergoing lung resection. Great care must be exercised dividing adhesions in the region of the upper mediastinum in proximity to the superior vena cava on the right and superior mediastinum on the left and in the medial lower mediastinum in proximity to the diaphragm bilaterally as visualization of the nerve may be significantly impaired by pleural symphysis. Injury to the phrenic nerve results in ipsilateral diaphragmatic paralysis, which produces two physiologic effects: first, the normal contraction of the diaphragm that promotes lung expansion during inspiration is lost; second, paradoxical elevation of the paralyzed diaphragm during inspiration caused by a pressure wave from the contraction of the contralateral diaphragm transmitted through intra-abdominal contents causes restriction of the lung on the side of the injury at the moment of inspiration, leading to significant dyspnea. Diaphragmatic paralysis manifests as dyspnea, which generally prompts plain film imaging of the chest, demonstrating diaphragmatic elevation. Paradoxical diaphragmatic elevation on rapid inspiration as visualized on chest fluoroscopy ("sniff" test) is confirmatory [26]. Diaphragmatic plication performed via thoracoscopy or thoracotomy generally provides significant symptomatic relief of dyspnea [26,27].

The right recurrent laryngeal nerve is beyond risk of damage by chest surgeons but the left recurrent nerve is directly in harm's way. As a branch of the left vagus nerve, the left recurrent nerve travels on the lateral aspect of the mediastinum, then separates from the vagus and curls under the aortic arch at roughly the level of the aortopulmonary window, at which point it travels along the trachea to innervate the intrinsic muscles of the larynx responsible for movement of the left vocal cord. The recurrent nerve is most directly at risk during dissection of aortopulmonary lymph nodes during the lymphadenectomy portion of lung resection for lung cancer. Injury to the left recurrent nerve results in left vocal cord paralysis. Hoarseness is usually the most immediate and obvious manifestation of left vocal cord paralysis but other sequelae may carry more clinical importance. First, apposition of the vocal cords is an important protective mechanism against aspiration; the inability of the vocal cords to close predisposes patients to aspiration pneumonia, which can be fatal in the postoperative period from major lung resection. Second, apposition of the vocal cords is an important mechanism for generating the high intrathoracic pressures associated with forceful cough; patients without functional vocal cords may experience impaired cough leading to a compromised ability to clear endobronchial secretions and a subsequently higher risk of developing pneumonia. Vocal cord paralysis may be treated with a high degree of success by vocal cord medialization via paraglottic injection.

26.6 Chylothorax

Chylothorax is a relatively uncommon complication of lung resection as the thoracic duct is protected from injury in the absence of retroesophageal dissection. When chylothorax does occur in the setting of lung resection, it is most often associated with the lymph node dissection for staging that accompanies lobectomy for lung cancer. The removal of lymph nodes from the subcarinal or paratracheal stations may result in the disruption of large lymphatics that may result in high-volume chylous leakage into the pleural space. Pursuit of the diagnosis of chylothorax classically is initiated by the presence of milky white drainage from a pleural catheter; however, in the first few days after lung resection complicated by chylothorax, the chest tube effluent may be serous. In the first few days after surgery, patients' oral intake may be limited due to poor appetite, in which case lipid transit through the intestinal lymphatics may be low, leading to a low lipid-containing chyle that appears serous. Early indication, then, of the presence of chylothorax may be a high-volume serous chest tube output. After the patient resumes more regular dietary patterns the milky, lipid-laden chylous effusion presents. Daily chest tube outputs greater than 1 L are commonplace. Lipid analysis of the pleural effusion can often make the diagnosis of chylothorax with a triglyceride level greater than 110 mg/dL or presence of chylomicrons confirmatory [28,29]. Prolonged chylothorax can result in severe malnutrition due to the loss of ingested lipids as well as immunosuppression due to the loss of lymphocytes and prompt intervention is indicated. In general, for postsurgical chylothorax, the treatment approach is surgical. Exploration of the affected hemithorax is undertaken either via thoracotomy or thoracoscopy in an attempt to identify the source of chylous leak; ligation of the leak source is performed with surgical clips or suture ligatures [30]. Heavy cream or olive oil may be administered to the patient either orally or by oroenteral feeding tube in an effort to increase chylous flow and thereby render the chylous fluid more milky in an attempt to improve the chances of identifying the source of leak. If the patient is not clinically able to undergo re-exploration surgery for lymphatic ligation, an attempt at conservative management with nothing by mouth, no enteral feeding, and total parenteral nutrition may be attempted. This may be supplemented by pleurodesis with talc or other sclerosant agents through the chest tube.

26.7 Cardiac Complications

The two most common cardiac complications after lung or chest wall resection are atrial fibrillation (AF) and myocardial infarction. After pneumonectomy, special consideration must be given to the possibility of cardiac herniation.

Supraventricular arrhythmias, in particular AF, are the most common arrhythmias after major lung resection [31]. The risk of atrial arrhythmia after major lung resection is approximately 20% [1,11]. The risk of atrial arrhythmia may be lower when a thoracoscopic approach is employed compared to thoracotomy; however, this may in part be due to underreporting as patients are often discharged after thoracoscopic procedures within the 3–4 day initial postoperative window when the development of AF is most common and atrial arrhythmias in this population may be clinically silent. The etiology of AF after major lung resection is not entirely clear and is likely multifactorial. In the absence of an antecedent history of atrial arrhythmias, AF in this patient population is generally short lived and usually can be resolved prior to discharge. In a meta-analysis of 11 randomized controlled studies of AF prophylaxis, Sedrakyan and colleagues showed that calcium-channel blockers and beta-blockers are effective in reducing postoperative atrial tachyarrhythmia [32]. Treatment is aimed at hemodynamic support when necessary, rate control, and cardioversion. Regarding treatment of postoperative AF, the Class I recommendation for patients with hemodynamically unstable postoperative AF is electrical cardioversion. Patients who are hemodynamically stable but with symptomatically intolerable AF should be chemically cardioverted, with electrical cardioversion if chemical cardioversion fails [33]. Patients who are hemodynamically stable and have symptomatically acceptable postoperative AF should receive a trial of rate control lasting approximately 24 h [33]. While long-term amiodarone therapy may result in pulmonary toxicity, this does not represent a contraindication to its short-term use after major lung resection, including discharge home on oral amiodarone, if necessary [34].

While smoking is a common risk factor to the development of lung cancer and coronary artery disease, the risk of myocardial infarction after major lung resection is not greater than for abdominal or vascular surgery. Some controversy exists about the value of an extensive work up for coronary artery disease prior to lung resection; cardiology studies including coronary angiography and possible intervention on critical coronary lesions may not prevent postoperative myocardial infarction but may often delay curative resection for a known lung cancer. The single most useful cardiac study in patients being selected for lung or chest wall resection is echocardiography as it assesses global cardiac function, can identify local wall motion abnormalities indicative of prior myocardial infarction, and may be useful in identifying the presence of pulmonary hypertension.

Cardiac herniation is an uncommon complication of pneumonectomy, but certain steps must be followed at the time of surgery to prevent its occurrence. The balanced inflation of two lungs within the thoracic cavity serves to maintain a midline position of the heart. When a lung is surgically removed, that balance is upset and there is a tendency for the heart to be displaced into the evacuated hemithorax. This displacement necessarily occurs over the course of months to years after pneumonectomy in a process of slow anatomic accommodation, but as it occurs gradually, no physiologic derangement ensues. However, if cardiac herniation occurs acutely, it results in kinking of the great vessels and impaired venous return to the heart, which presents as tension pneumothorax physiology and can be rapidly fatal. The situation may be exacerbated by the need to enter the pericardium to perform the pneumonectomy as may be required if the tissue planes of the intrapleural extent of the hilar structures are obscured by tumor, scarring, or inflammatory changes; the pericardial defect that results may serve as a portal through which the heart may rapidly herniate into the evacuated hemithorax. For this reason, pericardial defects created during pneumonectomy must be closed either primarily if possible or with the use of prosthetic mesh for larger defects [35,36]. The mesh must be porous or fenestrated to allow for the passage of pericardial fluid and/or blood into the evacuated hemithorax to avoid the risk of pericardial tamponade. Chest tubes may be used in the immediate postoperative period after pneumonectomy to drain the evacuated hemithorax, but great care must be taken to assure these cannot be placed to suction as this will exacerbate mediastinal and cardiac shift even in the absence of a pericardial defect. Nursing care must be carefully counseled about this risk, and some surgeons will also modify the chest tube effluent collection apparatus to assure that it cannot be placed to suction. The advantage to the use of chest tube drainage is that hemorrhage that occurs on the side of the pneumonectomy can be quickly recognized by high-volume sanguinous chest tube output. Alternatively, a chest-tube-free approach to the postpneumonectomy patient can be adopted. If this approach is adopted, after closure of the chest incision, air is insufflated into the evacuated hemithorax to encourage the heart and mediastinal structures to be maintained in a midline position; this is aided by chest radiography to verify the position of the heart with additional air insufflation added as necessary. The advantage to this approach is that there is no chance of inducing tension physiology by a chest tube

being inadvertently placed to suction. The downside is that hemorrhage is more difficult to identify in the early postoperative period; serial chest radiographs and serum hematocrit determination must be obtained to identify hemorrhage if this strategy is adopted.

26.8 Lobar Torsion

After lobectomy, the hemithorax on the side of resection contains free space that was previously occupied by the resected lobe. As a result, the remaining lobe or lobes have more freedom of motion and may rotate on their bronchovascular pedicles, resulting in a phenomenon known as lobar torsion. The incidence of lobar torsion has been reported to be 0.2% in the population of all patients undergoing intrathoracic surgery and carries with it a mortality rate of 22% [30,31]. Torsion of the lobe with respect to its bronchovascular pedicle results primarily in impaired clearance of bronchial secretions and pulmonary venous return, leading to marked pulmonary congestion and pneumonia. The most common lobe to experience torsion is the middle lobe after right upper lobe resection. The minor fissure on the right side is generally incomplete, that is, the middle lobe is generally fused to the upper lobe at the minor fissure, while the oblique fissure, which represents the interface between the middle and lower lobes, is generally complete, that is, the middle lobe is generally anatomically completely separated from the lower lobe. Therefore, when the right upper lobe is resected, the middle lobe finds itself relatively untethered in a partially evacuated right hemithorax; these factors underlie the proclivity of the middle lobe to undergo torsion after upper lobe resection. To prevent middle lobe torsion after right upper lobe resection, a pexy of the middle lobe to the lower lobe is performed with a surgical stapler, or alternatively with suture material. This effectively bonds the middle lobe to the lower lobe at their major fissure contact point to reduce the degrees of freedom of movement afforded the middle lobe.

Clinical signs and symptoms of pulmonary torsion are not subtle and include fever and productive cough or hemoptysis. Plain films of the chest demonstrate lobar consolidation, which in the current era should mandate prompt contrast-enhanced CT of the chest, which confirms the diagnosis based on impaired contrast uptake and atelectasis in the involved lobe. The radiographic hallmark of lobar torsion is lobar engorgement/enlargement due to impaired pulmonary venous return.

Lobar torsion represents a surgical emergency and immediate re-exploration via thoracotomy or thoracoscopy is mandated for lobectomy of the compromised lobe [37]. While lobar salvage by detorsion of the lobe has been advocated, the risk of ischemia–reperfusion injury to the involved lobe after detorsion generally prohibits this approach.

26.9 Chest Wall Defects

The most common indications for chest wall resection include lung or breast cancer with chest wall invasion, chest wall sarcomas, severe pectus deformities, radiation necrosis of the chest wall, or infection. Chest wall defects involving the loss of two or more ribs or that are 5 cm or greater in diameter require structural reconstruction; failure to reconstruct results in exposed vital structures and lung herniation with compromised respiratory mechanics [38]. Defects located deep in the scapula may not require reconstruction as lung herniation is prevented by scapular coverage. However, in cases involving a chest wall defect in proximity to the tip of the scapula, reconstruction may be required to avoid scapular tip entrapment [38]. A wide variety of synthetic mesh materials may be employed for chest wall reconstruction including polytetrafluoroethylene mesh (Gore Tex), prolene mesh, Vicryl mesh, Marlex mesh, or methyl methacrylate (usually sandwiched between two layers of mesh). Biomaterials including bovine pericardium and polylactic acid bars have been employed for chest wall reconstruction and may be preferable in infected defects due to the fact that they are remodeled or absorbed over time making them less likely to harbor infection [39]. Additionally, a wide variety of muscle or myocutaneous flaps have been described for the coverage of chest wall defects including latissimus dorsi, pectoralis major, and rectus abdominus.

26.10 Conclusion

Lung and chest wall resections can be performed safely for a number of diagnoses. A clear understanding of the potential complications along with the means to avoid or mitigate them may minimize morbidity and mortality with these operations.

Incidence of Complications Following Pulmonary and Chest Wall Resection

Complications	Incidence (%)
Bleeding requiring transfusion	9.5 [1]
Pneumonia	4.2–25 [1–6]
Empyema	0.4–5.0 [1,2,7]

Complications	Incidence (%)
Prolonged air leak	4.0–5.6 [5,8]
Chylothorax	1.0–3.8 [9,10]
Myocardial infarction	0.4–1.0 [1,5,11]
Atrial arrhythmia	12.6–19.9 [1,11]
Lobar torsion	0.1 [12]

Prevention and Treatment of Common Complications Following Pulmonary and Chest Wall Resection

Complications	Prevention
Bleeding requiring transfusion	Meticulous attention to hemostasis Sponge stick tamponade of pulmonary artery bleeding
Pneumonia	Encourage pulmonary toilet Early extubation Early ambulation
Alveolar pleural fistula	Pleural tent Aerostatic tissue sealants Chest tubes to water seal
Bronchopleural fistula	Reoperation for repair Muscle flap or omental reinforcement of the bronchial stump
Lobar torsion	Stapled/sutured lobar pexy

References

1. Onaitis M, D'Amico T, Zhao Y, O'Brien S, Harpole D. Risk factors for atrial fibrillation after lung cancer surgery: Analysis of The Society of Thoracic Surgeons General Thoracic Surgery Database. *Ann Thorac Surg*. August 1 2010;90(2):368.

   A thorough breakdown covering major postoperative complications following thoracotomy from the major national thoracic surgery database.
2. Tarkka M, Pokela R, Lepojarvi M, Nissinen J, Karkola P. Infection prophylaxis in pulmonary surgery: A randomized prospective study. *Ann Thorac Surg*. November 1987 1;44(5):508.
3. Kachare S, Dexter EU, Nwogu C, Demmy TL, Yendamuri S. Perioperative outcomes of thoracoscopic anatomic resections in patients with limited pulmonary reserve. *J Thorac Cardiovasc Surg*. February 2011;141(2):459–462.
4. Radu DM, Jaureguy F, Seguin A, Foulon C, Destable MD, Azorin J et al. Postoperative pneumonia after major pulmonary resections: An unsolved problem in thoracic surgery. *Ann Thorac Surg*. November 2007;84(5):1669–1673.
5. Onaitis MW, Petersen RP, Balderson SS, Toloza E, Burfeind WR, Harpole DH et al. Thoracoscopic lobectomy is a safe and versatile procedure. *Ann Surg*. September 2006;244(3):420–425.
6. Schussler O, Alifano M, Dermine H, Strano S, Casetta A, Sepulveda S et al. Postoperative pneumonia after major lung resection. *Am J Respir Crit Care Med*. May 2006;173(10):1161–1169.
7. Wain JC. Management of late postpneumonectomy empyema and bronchopleural fistula. *Chest Surg Clin North Am*. August 1996;6(3):529–541.
8. Liberman M, Muzikansky A, Wright CD, Wain JC, Donahue DM, Allan JS et al. Incidence and risk factors of persistent air leak after major pulmonary resection and use of chemical pleurodesis. *Ann Thorac Surg*. March 2010;89(3):891–898.
9. Pool KL, Munden RF, Vaporciyan A, O'Sullivan PJ. Radiographic imaging features of thoracic complications after pneumonectomy in oncologic patients. *Eur J Radiol*. January 2012;81(1):165–172.
10. Shah RD, Luketich JD, Schuchert MJ, Christie NA, Pennathur A, Landreneau RJ et al. Postesophagectomy chylothorax: Incidence, risk factors, and outcomes. *Ann Thorac Surg*. March 2012;93(3):897–903; discussion 903–904.
11. Powell E, Pearce A, Cook D, Davies P, Bishay E, Bowler G et al. UK pneumonectomy outcome study (UKPOS): A prospective observational study of pneumonectomy outcome. *J Cardiothorac Surg*. July 2009;4(1):41.
12. Cable DG, Deschamps C, Allen MS, Miller DL, Nichols FC, Trastek VF et al. Lobar torsion after pulmonary resection: Presentation and outcome. *J Thorac Cardiovasc Surg*. December 2001;122(6):1091–1093.
13. Förster R, Storck M, Schäfer J, Hönig E, Lang G, Liewald F. Thoracoscopy versus thoracotomy: A prospective comparison of trauma and quality of life. *Langenbeck's Arch Surg*. April 2002;387(1):32–36.
14. Carretta A, Zannini P, Chiesa G, Altese R, Melloni G, Grossi A. Efficacy of ketorolac tromethamine and extrapleural intercostal nerve block on post-thoracotomy pain. A prospective, randomized study. *Int Surg*. September 1996;81(3):224–228.
15. Savage C, McQuitty C, Wang D, Zwischenberger JB. Postthoracotomy pain management. *Chest Surg Clin North Am*. May 2002;12(2):251–263.
16. Koehler RP, Keenan RJ. Management of postthoracotomy pain: Acute and chronic. *Thorac Surg Clin*. August 2006;16(3):287–297.
17. Hazelrigg S, Landreneau R, Boley T, Priesmeyer M, Schmaltz R, Nawarawong W et al. The effect of muscle-sparing versus standard posterolateral thoracotomy on pulmonary function, muscle strength, and postoperative pain. *J Thorac Cardiovasc Surg*. July 1991;101(3):394–400.
18. Gebhard FT, Becker HP, Gerngross H, Brückner UB. Reduced inflammatory response in minimal invasive surgery of pneumothorax. *Arch Surg*. October 1996;131(10):1079–1082.
19. Dunning J, Walker WS. Pulmonary artery bleeding caused during VATS lobectomy–Dunning. *Ann Cardiothorac Surg* [Internet]. [cited December 3, 2012]. Available from: http://www.annalscts.com/article/view/486/562.

    Important article that covers specific maneuvers to control bleeding from the pulmonary artery during thoracic surgery.
20. Sirbu H, Busch T, Aleksic I, Lotfi S, Ruschewski W, Dalichau H. Chest re-exploration for complications after lung surgery. *Thorac Cardiovasc Surg*. April 1999;47(2):73.

21. Novoa N, Ballesteros E, Jiménez MF, Aranda JL, Varela G. Chest physiotherapy revisited: Evaluation of its influence on the pulmonary morbidity after pulmonary resection. *Eur J Cardiothorac Surg*. July 2011;40(1):130–134.
22. Deschamps C, Bernard A, Nichols III FC, Allen MS, Miller DL, Trastek VF et al. Empyema and bronchopleural fistula after pneumonectomy: Factors affecting incidence. *Ann Thorac Surg*. July 2001;72(1):243–248.

    Key article covering major pulmonary complications following pneumonectomy.
23. Gossot D, Stern J-B, Galetta D, Debrosse D, Girard P, Caliandro R et al. Thoracoscopic management of postpneumonectomy empyema. *Ann Thorac Surg*. July 2004;78(1):273–276.
24. Asamura H, Naruke T, Tsuchiya R, Goya T, Kondo H, Suemasu K. Bronchopleural fistulas associated with lung cancer operations. Univariate and multivariate analysis of risk factors, management, and outcome. *J Thorac Cardiovasc Surg*. November 1992;104(5):1456–1464.
25. Cerfolio RJ. Recent advances in the treatment of air leaks. *Curr Opin Pulm Med*. July 2005;11(4):319–323.
26. Graham DR, Kaplan D, Evans CC, Hind CR, Donnelly RJ. Diaphragmatic plication for unilateral diaphragmatic paralysis: A 10-year experience. *Ann Thorac Surg*. February 1990;49(2):248–251; discussion 252.
27. Celik S, Celik M, Aydemir B, Tunckaya C, Okay T, Dogusoy I. Long-term results of diaphragmatic plication in adults with unilateral diaphragm paralysis. *J Cardiothorac Surg*. November 2010;5:111.
28. Staats BA, Ellefson RD, Budahn LL, Dines DE, Prakash UB, Offord K. The lipoprotein profile of chylous and nonchylous pleural effusions. *Mayo Clin Proc*. November 1980;55(11):700–704.
29. Agrawal V, Doelken P, Sahn SA. Pleural fluid analysis in Chylous Pleural Effusion*. *Chest*. June 2008;133(6):1436–1441.
30. Fahimi H, Casselman FP, Mariani MA, Van Boven WJ, Knaepen PJ, Van Swieten HA. Current management of postoperative chylothorax. *Ann Thorac Surg*. February 2001;71(2):448–450; discussion 450–451.
31. Von Knorring J, Lepantalo M, Lindgren L, Lindfors O. Cardiac arrhythmias and myocardial ischemia after thoracotomy for lung cancer. *Ann Thorac Surg*. April 1 1992;53(4):642.
32. Sedrakyan A, Treasure T, Browne J, Krumholz H, Sharpin C, Van der Meulen J. Pharmacologic prophylaxis for postoperative atrial tachyarrhythmia in general thoracic surgery: Evidence from randomized clinical trials. *J Thorac Cardiovasc Surg*. May 2005;129(5):997–1005.
33. Fernando HC, Jaklitsch MT, Walsh GL, Tisdale JE, Bridges CD, Mitchell JD et al. The Society of Thoracic Surgeons practice guideline on the prophylaxis and management of atrial fibrillation associated with general thoracic surgery: Executive summary. *Ann Thorac Surg*. September 2011;92(3):1144–1152.

    Current Society of Thoracic Surgeons Guidelines regarding postoperative atrial fibrillation management.
34. Riber LP, Christensen TD, Jensen HK, Hoejsgaard A, Pilegaard HK. Amiodarone significantly decreases atrial fibrillation in patients undergoing surgery for lung cancer. *Ann Thorac Surg*. August 2012;94(2):339–346.
35. Baisi A, Cioffi U, Nosotti M, De Simone M, Rosso L, Santambrogio L. Intrapericardial left pneumonectomy after induction chemotherapy: The risk of cardiac herniation. *J Thorac Cardiovasc Surg*. June 2002; 123(6):1206–1207.
36. Buniva P, Aluffi A, Rescigno G, Rademacher J, Nazari S. Cardiac herniation and torsion after partial pericardiectomy during right pneumonectomy. *Tex Heart Inst J*. 2001;28(1):73.
37. Kanemitsu S, Tanaka K, Suzuki H, Tokui T, Kinoshita T. Pulmonary torsion following right upper lobectomy. *Ann Thorac Cardiovasc Surg*. December 2006;12(6): 417–419.
38. Skoracki RJ, Chang DW. Reconstruction of the chest wall and thorax. *J Surg Onc*. 2006;94:455–465.
39. Miller DL, Force SD, Pickens A, Fernandez FG, Luu T, Mansour KA. Chest wall reconstruction using biomaterials. *Ann Thorac Surg*. March 2013;95(3):1050–1056.

27

Complications of Esophageal Surgery and Trauma

Peter P. Lopez, Joseph R. Buck, and Lawrence N. Diebel

CONTENTS

Optimal management of conditions affecting the esophagus challenges even the most experienced surgeon. The esophagus is subject to the same complications that affect other portions of the gastrointestinal (GI) tract (obstruction, anastomotic leak, perforation, and stricture). Several unique features of the esophagus contribute to the higher morbidity and mortality rates associated with esophageal trauma and surgery. These complications are not only more devastating but also are more difficult to diagnose early and treat. Meticulous technique and careful attention to detail must be applied during esophageal surgery, in order to avoid the devastating physiologic consequences from postoperative complications. This chapter will review the anatomy and physiology of the esophagus and describe some of the more common complications after esophageal surgery and trauma.

27.1 Anatomy and Physiology of the Esophagus

The esophagus is a muscular tube 25 cm in length that extends from the cricoid cartilage to the stomach. The esophagus extends approximately 40 cm from the incisors to the gastric cardia. The esophagus makes three minor deviations from the midline as it descends from the neck, through the posterior mediastinum, and into the abdomen. In the neck, it courses to the left of the midline; at the level of the seventh thoracic vertebra, it deviates to the right; and finally, just above the diaphragm, it again deviates to the left.

The esophagus also narrows in three areas, and injuries caused by foreign bodies, caustic burns, strictures, iatrogenic perforations, and cancer usually occur at one of these three sites. The first of these is the cricopharyngeal sphincter; it is also the narrowest portion of the GI tract, which is found at the origin of the esophagus (15 cm from the incisors) and at the level of the sixth cervical vertebra, just above the thoracic inlet. A second narrowing is located 20 cm from the incisors at the point at which the left main stem bronchus and the aortic arch cross, at the level of the angle of Louis anteriorly and the fourth thoracic vertebra posteriorly. The resting tone of the lower esophageal sphincter creates the third narrowing of the esophagus located at the gastroesophageal junction, 40 cm from the incisors.

The esophagus differs from the rest of the GI tract in that it has no mesentery or serosa. The esophageal wall is composed of three layers: the outer external longitudinal muscle layer, the inner circular muscle layer, and the submucosal/mucosa. In the upper-third of the esophagus, the muscle fibers are primarily striated (voluntary), whereas in the distal-third of the esophagus, the muscle fibers are primarily smooth (involuntary). In the middle-third of the esophagus, smooth and striated muscle fibers are intermingled. Because most esophageal motility disorders are due to an abnormality in smooth muscle fibers, esophageal myotomy needs to span only these muscle fibers. The submucosa contains coarse elastic fibers, an arteriolar plexus, fibrous tissue, and nerve cell bodies of Meissner's plexus. Together with the mucosa, this thick submucosal layer is the strongest portion of the esophageal wall. These layers must be considered as one layer, and both must be sewn together if a watertight anastomosis is to be created. The mucosa makes up the inner layer of the esophageal wall. It is lined with a thick layer of nonkeratinizing, stratified squamous epithelium that is continuous with the mucosa of the oropharynx.

The arterial blood supply of the esophagus is derived from the inferior thyroid artery (neck), the segmental esophageal arteries branching off the aorta (thorax), and the left gastric and splenic artery (abdomen). These arteries branch into small vessels some distance from the esophagus before penetrating the esophageal muscle layers. This branching allows blunt mobilization of the esophagus during a transhiatal esophagectomy because these small vessels contract to assist in hemostasis. Upon entering the esophagus, these arteries branch at right angles, thereby establishing a longitudinal anastomosing network of vessels. This early branching and collaterization between the cervical, thoracic, and gastric segments desegmentalizes the esophageal blood supply. Thus, the entire esophagus can be mobilized with a blood supply based on the inferior thyroidal artery. Poor technique rather than poor blood supply is the usual reason for anastomotic failure [1]. However, the surgeon must exercise caution if the inferior thyroid arteries have been compromised by prior partial or complete thyroidectomy or by any other previous surgical procedure or radiotherapy.

The venous drainage of the esophagus parallels its arterial supply. The venous system also has an extensive intramural venous plexus in the submucosa. Because of its location, the azygos vein may be easily damaged during blunt dissection; if tumor adheres to the vein, blunt dissection can cause massive bleeding. Additionally, esophageal resection through a right thoracotomy may lead to severe hemorrhage if the hemiazygos vein is not ligated [2].

The lymphatic system is made up of capillaries that drain into long and widely anastomosing collecting channels in the submucosa and then out to regional nodes. These nodes may precipitate the intramural spread of cancer, predominately in the submucosa. Because esophageal cancer has been found to spread for approximately 6–10 cm both proximally and distally, some surgeons believe that anything less than a subtotal esophagectomy is unwise [3]. Lymphatic drainage from the upper esophagus flows primarily into the cervical and peritracheal lymph nodes, whereas lymphatic drainage from the lower esophagus flows into the retrocardiac and celiac nodes.

27.2 Esophageal Perforation

27.2.1 Causes of Perforation

Most perforations of the esophagus are iatrogenic, occurring during diagnostic and therapeutic endoscopic procedures. Successful management depends on four main factors: (1) age and overall condition of the patient, (2) cause and location of the perforation, (3) time

interval between diagnosis and treatment, and (4) presence of any underlying esophageal disease.

Iatrogenic perforations most commonly occur during rigid (0.03%) or flexible esophagoscopy (0.11%), transesophageal echocardiography (0.01%), pneumatic dilatation (4%), esophageal stenting (5%–15%), bougienage (0.09%), endoscopic dynamic phototherapy (4.6%), or sclerotherapy (1%) [4]. Perforation commonly occurs at anatomically narrowed areas of the esophagus; the most common site being at the cricopharyngeal sphincter [5]. Spontaneous rupture of the esophagus occurs with a sudden increase in intra-abdominal pressure, usually related to vomiting, weight lifting, excessive coughing, or childbirth. This increase in pressure is transmitted to the lower thoracic esophagus and usually causes a perforation laterally into the left pleural cavity.

27.2.2 Symptoms of Perforation

The symptoms of esophageal perforation depend on the size and site of the perforation and on the elapsed time since perforation. Patients with cervical perforation usually experience cervical pain and dysphagia. Emphysematous crepitus is commonly detected in the neck after cervical perforations; it is palpable in 60% of cases and detected radiographically in more than 95% [6]. Thoracic perforations cause pain substernally or in the epigastric area. Mediastinal emphysema and pleural effusions are present in approximately 50% of cases. Pleural effusions commonly occur on the right side after upper perforation and on the left side after middle to distal perforation. Patients with abdominal perforation experience epigastric pain that is often referred to the back or left shoulder, or experience peritonitis.

27.2.3 Management of Esophageal Perforation

After esophageal perforation, the dissection of oral secretions (bacteria and salivary enzymes) and gastric contents into the fascial planes of the neck and mediastinum initiates a chemical and bacterial inflammatory response. Fever, sepsis, and shock develop with the increasing contamination of the mediastinal, pleural, and abdominal cavities. If this contamination is left untreated, sepsis, cardiopulmonary collapse, and multisystem organ failure occur. The outcome of treatment of esophageal perforation has traditionally been poor, often because of a delay in diagnosis brought about by the clinician's failure to consider the diagnosis. Fifty percent of patients will give a history of recent vomiting, esophageal instrumentation, or surgery; the presentation will be atypical in the remaining 50% of patients [7]. All patients complaining of pain after upper endoscopy, esophageal manipulation, or esophageal surgery should undergo testing to rule out an esophageal perforation. The diagnosis is confirmed with a Gastrografin (Bracco Diagnostics, Ontario, Canada) or barium swallow. If Gastrografin esophagography shows no leak, a thin-barium swallow study should be performed. Esophagoscopy can be helpful in cases of penetrating trauma and foreign body perforation. Computed tomography (CT) also can aid in making the diagnosis. Common CT findings are pneumomediastinum, a periesophageal abscess, mediastinal air fluid levels, and pleural effusions (Table 27.1).

TABLE 27.1

Surgical Options for the Management of Esophageal Perforations

Primary closure
Primary closure with viable flap buttressing of the suture line
Exclusion and diversion
T-tube drainage
Esophageal resection with primary or delayed reconstruction
Intraluminal stent
Wide drainage only

The optimal management of esophageal perforations remains controversial. Delay in the diagnosis and definitive treatment of esophageal perforation leads to increased complications and poor outcomes [8]. The treatment of esophageal perforation should be individualized and is based on four basic principles: (1) eliminating the source of contamination and preventing continued soilage; (2) performing adequate cervical, mediastinal, and pleural debridement and drainage; (3) providing aggressive resuscitation with fluids, antibiotics, and nutritional support; and (4) correcting any distal obstructing process, functional or organic. The following factors should be considered when therapy is selected for the individual patient: the clinical toxic effects experienced by the patient, the elapsed time since perforation, the extent of containment of the leak, and any preexisting pathology of the esophagus.

Nonoperative therapy of esophageal perforations has been described [9]. Sawyer et al. [10] recommend nonoperative treatment according to the following strict clinical criteria: (1) a recent perforation (within 24 h), (2) no food intake after the perforation occurred, (3) no high-grade obstruction distal to the perforation, (4) minor clinical symptoms without sepsis or hemodynamic compromise, (5) containment of the perforation within the mediastinum, and (6) results of a contrast study showing good and prompt drainage from a small perforation into the esophageal lumen.

Most surgeons today recommend immediate surgical treatment of esophageal perforation [4,5,11]. Multiple surgical options are available to treat esophageal

perforations. Timely primary repair of the esophagus with suture line reinforcement using muscle flaps and wide drainage has the lowest morbidity and mortality of any surgical treatment modality for esophageal perforation.

Self-expandable metal endoscopic stents or the newer, removable silicone-coated polyester stents may be used in selective cases of esophageal perforation, fistula and anastomotic disruption. Metallic stents have been used in patients with esophageal cancer who have developed an esophageal fistula to the mediastinum, trachea, or lung [12]. Stents can also be used in patients with spontaneous esophageal perforation who are not medical candidates for a thoracotomy [23]. Immediate and complete closure of the esophageal perforation has been reported to be 89% with a 21% stent migration rate [4]. Temporary stent therapy using removable stents seems to be an effective way of sealing off esophageal perforations and may be an effective alternative to open surgery for carefully selected patients with limited contamination [14].

Most cases of acute esophageal perforation continue to be treated surgically. Primary closure with buttressing of the suture line is performed along with wide adequate drainage [15,16]. Gauge et al. reported that the mortality and fistula rate for reinforced repairs of the esophagus as 6% and 13%, compared to a 25% and 39% mortality and fistula rate, respectively, for repairs that were not reinforced [17]. Determination of the success of primary closure depends not only on the time from perforation but also on the degree of soilage and contamination of the surrounding tissues.

27.2.4 Surgical Management of Cervical Esophageal Perforation

Cervical esophageal perforation is treated with prompt surgical drainage. The left-side approach is generally preferred because the esophagus is on the left side of the midline in the neck. The carotid sheath and the internal jugular vein are retracted laterally, and the middle thyroid vein is divided if necessary. The trachea and esophagus are gently retracted medially; blunt dissection into the retroesophageal space allows adequate drainage of the prevertebral fascia directly posterior to the esophagus. The surgeon must carefully look for and prevent damage to the recurrent laryngeal nerve during dissection. Blunt finger dissection is carried down into the posterior mediastinum.

Once the perforation is found, it can be repaired with a single or double layer of absorbable suture. In all esophageal perforations, the mucosal tear is often longer than the muscle tear; this is important to remember to insure complete and successful closure. If the cervical perforation cannot be visualized, the area should be copiously irrigated and a soft drain should be left in place. For all penetrating trauma, large perforations, and, if there is severe inflammation involving the trachea or the blood vessels, a viable muscle flap (usually a pedicled flap of sternocleidomastoid or omohyoid muscle) should be used to close and buttress the esophageal repair. Viable muscle flaps should also be interposed between simultaneous tracheal and esophageal repairs [4,5]. The patient should have all oral feedings withheld, nasogastric suction applied, and antibiotics given until cervical drainage ceases. Esophagography should be performed 5–7 days after the repair. At that time, if there is no leak, the patient's diet can be advanced. Once the patient can tolerate a regular diet, the soft cervical drain is removed.

27.2.5 Surgical Management of Thoracic Esophageal Perforation

For thoracic esophageal perforations, aggressive surgical treatment should not be delayed. Intravenous hydration and treatment with antibiotics should be initiated preoperatively. Perforations to the upper- or middle-third of the esophagus are approached through a right posterior lateral thoracotomy between the fourth and fifth intercostal spaces. Lower esophageal perforations are best approached through a left posterior lateral thoracotomy between the sixth and seventh intercostal spaces. Preexisting esophageal disease often must be dealt with at the time of exploration for esophageal perforation. Perforations occurring during pneumatic or hydrostatic dilation for achalasia are managed by primary repair of the perforation and concomitant esophagomyotomy directly opposite the repair [18]. Perforations that occur during dilation for benign strictures should be repaired after such dilation has been completed. If the strictures cannot be dilated, an esophagectomy should be performed because healing is unlikely proximal to a stricture or obstruction. Patients with carcinoma who suffer perforation during endoscopy should undergo esophagectomy [19]. Reconstruction may be immediate or delayed, depending on the patient's clinical condition. When the patient is a poor candidate for surgery, wide local drainage is performed and a feeding jejunostomy is created. A patient with a malignant esophago-respiratory fistula or a perforated esophageal carcinoma with a mediastinal abscess should be considered a candidate for palliative endoscopic stent, because 80% of these patients die within 3 months and only 11% survive for 6 months [20].

A posterolateral thoracotomy is performed through the subperiosteally resected fifth rib on the right and the seventh rib on the left. This approach allows construction of a well-vascularized intercostal musculopleural flap that can buttress the repair. The chest should be copiously irrigated and debrided of all necrotic tissue, and the esophagus should be gently

elevated from its bed so that the opposite mediastinal pleura can be irrigated. If a right or left pleural effusion is found, it must be drained. Next, the esophageal perforation should be visualized and the outer muscular coat of the esophagus incised so that the entire length of the mucosal defect can be seen before it is closed in one or two layers. Failure to transfix the mucosa with each suture results in an inadequate repair that has increased risk of an anastomotic leak [2]. If the muscular layer cannot be closed primarily, various muscle flaps may be used for closing the defect [21]. Muscle flaps should be used to buttress all primary esophageal repairs so that the risk of sutureline disruption or an esophagopleural fistula can be minimized or prevented. Flaps that have been used for closing and buttressing esophageal repairs have consisted of pleura, pedicled intercostal muscle, diaphragm, pericardium, omentum, and gastric fundus. However, with minimal inflammatory reaction, the parietal pleura remains thin and does not produce a good buttress. Wright et al. [15] used an intercostal muscle buttress over the primary repair and achieved primary healing in 89% of 28 patients with thoracic esophageal perforations.

Postoperatively, if one suspects a leak, an esophagram should be performed. If the leak is well drained, the patient exhibits no signs of toxicity, nutritional support is good, and no distal obstruction is present, then the leak should heal with no oral intake and drainage. If the patient shows signs of sepsis or the leak is not well drained, another exploratory procedure should be performed. The area of the leak should then be widely drained; if this is not possible, the patient should undergo esophagectomy with the creation of a cervical esophagostomy and feeding jejunostomy.

Esophageal exclusion has been promoted as a good alternative to primary repair and esophagectomy. Urschel et al. [22] modified the technique of total esophageal exclusion in continuity; initially, umbilical tape was tied over a polytetrafluoroethylene band at the esophagogastric junction while a tube gastrostomy and a lateral cervical esophagostomy were performed. Ladin et al. [23] reported the primary repair of a postemetic perforation of the thoracic esophagus by stapling the esophagus above and below the repair and performing a gastrostomy and a cervical esophagostomy. Six weeks later, the patient's esophageal lumen was patent without strictures after an esophagram.

Others have reported success with the creation of a T-tube fistula and drainage of the perforation. Abbott et al. [24] constructed a large-bore silastic T-tube, which was placed through a distal esophageal perforation. A nasogastric tube was then inserted through the nose, down the esophagus through the T-tube, and into the stomach. The chest cavity was drained with chest tubes. Eventual healing of the perforation requires that perforation be patched by the lung and pleura. Bufkin et al. [25] modified this technique slightly by advocating that the T-tube should be brought out through a lateral incision and sutured to the diaphragm in a position that would avoid aortic erosion.

27.2.6 Surgical Management of Abdominal Esophageal Perforation

The prognosis for patients with abdominal perforation is excellent if the perforation is recognized early. Surgical treatment is achieved with primary closure of the perforation and buttressing of the repair with either a partial gastric fundus wrap or an omental wrap. A gastrostomy and a feeding jejunostomy are usually indicated.

27.2.7 Outcome of Surgery for Esophageal Perforation

The overall mortality rate associated with esophageal perforation is 22%, with the break down as follows: cervical perforation is 6%, thoracic perforation is 34%, and abdominal perforation is 29% [8]. Morbidity and mortality is mainly related to anastomotic failure with continued contamination [4]. All published series demonstrate that early diagnosis and treatment lead to better outcomes; morbidity and mortality rates increase when diagnosis and treatment occur more than 24 h after injury. Gouge et al. [17] reviewed the results of a series of 10 primary suture repairs of thoracic perforations; the overall leak rate was 39%, and the overall mortality rate was 25%. In their series review, the overall mortality rate associated with the T-tube technique for draining perforations is 36%, that associated with exclusion and diversion is 35%, and that associated with resection is 26%. The mortality rates associated with T-tube drainage and exclusion may reflect the severity of these patients' illness.

27.3 Esophageal Trauma

Traumatic injuries to esophagus are rare, with busy trauma centers seeing an average of five such cases per year. Most traumatic injuries to the esophagus are caused by penetrating wounds. Asensio et al. reported that 88% of patients with penetrating esophageal injuries had other associated injuries, which can include tracheal, vascular, pulmonary, diaphragmatic, and spinal cord injuries [50]. Often, it is these other injuries that contribute to the high morbidity and mortality seen after penetrating esophageal injuries.

27.3.1 Blunt Trauma

Blunt esophageal trauma is extremely uncommon. Blunt injuries to the esophagus occur almost exclusively in the neck and abdomen. It may result from a direct blow to the organ when the neck is hyperextended; such a blow crushes the esophagus against bony fragments of the cervical spine. Blunt trauma may also result from an increased intraluminal pressure against a closed glottis, which causes a burst-type injury, usually at the gastroesophageal (GE) junction. Motor vehicle collisions are the most common cause of this type of esophageal injury.

27.3.2 Penetrating Trauma

The incidence of esophageal injuries from penetrating wounds to the neck is 5%–7% [27,28]. Esophageal injuries have been found during 10%–12% of neck explorations performed because of penetration of the platysma [29,30]. Cornwell et al. [31] found only 14 intrathoracic esophageal injuries among 1961 patients (0.7%) with penetrating chest trauma. The rarity of these injuries should not lead to diagnostic complacency in the trauma bay or in the operating suite. Patients with platysmal penetration, posterior chest wounds, transmediastinal penetrating injuries, tracheobronchial injuries, or any wounds whose trajectory may injure the esophagus should undergo testing to rule out esophageal trauma.

27.3.3 Preoperative Assessment of Esophageal Injuries

Clinical signs and symptoms are present among as many as 80% of patients with traumatic esophageal injuries. These signs and symptoms include odynophagia, dysphagia, hematemesis, shortness of breath, cervical crepitus, cough, stridor, complaints of neck and chest pain, hoarseness, and bleeding from the oropharynx. Fever, chills, subcutaneous emphysema, abdominal tenderness, and mediastinal crunching upon auscultation of the chest (Hamman's sign) may be present. Clinical findings of pneumothorax, pneumomediastinum, left-sided pleural effusion, a nasogastric tube passing into the pleural space, food particles draining from a chest tube, or bubbles in the chest tube through both inspiration and expiration may suggest esophageal injury.

The presence of these signs and symptoms will depend on the location of the injury, the size of the perforation, the degree of contamination, the length of time since injury, and other associated injuries such as tracheal and vascular injuries. Overall, these signs and symptoms are unreliable in predicting esophageal injuries; therefore, the clinician must maintain a high index of suspicion.

The results of plain radiography of the neck and chest may be abnormal in as many as 75% of patients with traumatic esophageal injuries. More definitive studies are needed if radiographs show hydrothorax, pneumomediastinum, or pneumothorax; air dissecting into the retropharyngeal spaces; or subcutaneous cervical air. If an esophageal injury is suspected or found, the patient should undergo urgent contrast esophagography. Contrast esophagography has been shown to be 89% sensitive and 100% specific for cervical esophageal injuries [31]. In their review of esophageal injuries, White and Morris [27] found that contrast esophagography was 100% sensitive and 95% specific. Contrast radiography is usually first performed with Gastrografin®, a water-soluble agent that, unlike barium, does not cause severe mediastinitis but may cause a severe chemical pneumonitis if aspirated. Gastrografin is less radiodense than barium and less likely to demonstrate small leaks or perforations. A barium contrast study is usually performed if the results of the Gastrografin study are negative.

Because the results of esophagography may be normal for 15% of patients with esophageal injuries, a high suspicion of injury should prompt the performance of endoscopic esophagoscopy [32]. Esophagoscopy, with either a rigid or a flexible scope, has been helpful in identifying esophageal injuries. Rigid esophagoscopy is more sensitive (89%) for cervical esophageal injuries than flexible esophagoscopy (37%) [31]. Flexible endoscopy is 100% sensitive and specific for thoracic esophageal injuries [27]. When contrast radiography and esophagoscopy are combined, their sensitivity and specificity approaches 100%.

27.3.4 Management of Esophageal Injuries

27.3.4.1 Injuries to the Cervical Esophagus

The cervical esophagus is more commonly injured than the thoracic or abdominal esophagus. Once a cervical esophageal injury has been diagnosed, the patient is given nothing by mouth, nasogastric suction is begun, and the administration of antibiotics active against oral flora is initiated. Prompt surgical drainage and repair of the esophagus are performed through a collar incision or an incision along the anterior border of the sternocleidomastoid muscle.

Most esophageal injuries are repaired primarily with a single-layer, full-thickness closure with interrupted nonabsorbable 3–0 suture or in two layers with an inner absorbable layer and an outer nonabsorbable layer. Failure of the suture to transfix the mucosa is due to the fatty submucosa, which allows the mucosa to retract under the overlying muscular layers. The mucosa must be identified and deliberately transfixed; each

suture must be placed so as to achieve apposition and in order to avoid anastomotic leaks [33]. This principle applies to all repairs performed on all segments of the esophagus.

More complex injuries to the esophagus may require debridement of the devascularized segments or resection. Vascularized tissue flaps should be used when defects are large or when the tissues are too friable for primary closure. Flaps are also used when the esophagus is perforated in two places (as is the case with gunshot wounds) or when primary closure of both injuries would result in substantial narrowing of the lumen [21,34]. If the trachea or the carotid artery is also injured, buttressing the repair with muscle flaps from the sternohyoid, omohyoid, sternothyroid, or sternocleidomastoid muscles is particularly important so that late fistulae can be avoided.

All repairs in the neck should be drained. The drain is placed approximately 2 cm from the esophageal repair and is brought out through a separate wound. Oral intake is started if esophagography shows no leak on the fifth to seventh postoperative day. The drain is removed after 2 days of oral intake if no drainage occurs. Most esophageal fistulas that develop after neck trauma drain directly from the esophagus to the skin. Because as many as 50% of all leaks are symptomatic, a contrast swallow should be used to confirm the presence of suspected leaks and fistulas. If no distal obstruction is present, most of these fistulas will resolve spontaneously after 2–3 weeks of adequate drainage, limited oral intake, and antibiotic administration.

27.3.4.2 Injuries to the Thoracic Esophagus

Thoracic esophageal injuries are less common than cervical esophageal injuries; however, they are more often fatal. These injuries are frequently associated with injuries to the great vessels, trachea, lungs, and diaphragm. During emergent exploration for these other injuries, the surgeon must be careful to rule out an esophageal injury. Intraoperative esophagoscopy should be performed when a complete evaluation of the esophagus is impossible. Emergent intraoperative esophagoscopy has been shown to be 100% sensitive and 80% specific for penetrating thoracic esophageal injuries [35]. Patients who are in stable condition but for whom examination is necessary for ruling out esophageal or other injuries should first undergo contrast-enhanced spiral CT of the chest. This test can rule out associated injuries to lung, great vessels, trachea, and spine and may show the location of esophageal injuries.

Surgical treatment involves local debridement, wide drainage, primary repair of the defect, and buttressing of the repair with a viable muscle flap. Wounds to the upper- and middle-third of the thoracic esophagus are repaired through a right posterolateral thoracotomy at the fifth intercostal space. After the injury has been identified, the esophageal wall should be circumferentially inspected so that the presence of an exit wound can be excluded. Primary repair with either a one-layer or a two-layer technique is performed. After the esophageal wound has been closed, a parietal pleural flap, an intercostal muscle flap, or a pericardial flap should be created to buttress certain repairs, particularly those between the trachea and the esophagus [5]. Other tissue flaps such as pericardial, intercostal muscle, diaphragm, latissmus dorsi, and rhomboid muscle flaps have been used to buttress these repairs and to close large esophageal defects that cannot be closed primarily [21]. The use of these viable flaps to buttress the repair has been associated with improved anastomotic outcomes [36].

The fistulas and leaks that develop after the repair of traumatic esophageal injuries more often than not respond to local drainage and creation of a controlled fistula; usually, diversion or resection is unnecessary. If diagnosis has been delayed or if the injury is so severe that primary repair is not feasible because of the degree of contamination and inflammatory reaction, viable alternatives to primary repair are esophageal diversion, exclusion, or resection. Another alternative is dissecting the superior part of the esophagus up to the chest inlet and exteriorizing the esophagus through a new wound, thereby creating an esophagostomy. The distal end is stapled and dissected to the diaphragm and is removed through a separate incision; a gastrostomy is then performed [37]. At a later date, reconstruction of the continuity of the GI tract is performed with gastric pull-up or colonic interposition.

Wounds to the lower-third of the thoracic esophagus are repaired through a left posterolateral thoracotomy through the sixth intercostal space. Repair is performed as above except that diaphragm, intercostal muscle, or gastric fundus can be used to buttress the repair. After repair but before closure, the mediastinal pleura must be widely opened, thoroughly irrigated and débrided, and finally drained.

27.3.4.3 Injuries to the Abdominal Esophagus

Injuries to the abdominal segment of the esophagus are repaired through a laparotomy; the suture line is covered with either omentum or the gastric fundus as in a Thal 180°- or a Toupe 270°-fundoplication. The true Nissen 360°-wrap should probably be avoided because it may cause a functional distal esophageal obstruction. Creating a feeding jejunostomy is sometimes helpful. The rate of esophageal leak or fistula formation has been reported to be as high as 38% [21].

27.3.4.4 Complications of Surgical Repair of Esophageal Injuries

Esophageal anastomotic leaks are the most common complication after esophageal repair; their incidence is approximately 15%–25% [38]. They are frequently the result of technical misadventures such as inadequate debridement of devitalized tissue, devascularization of tissue, closure under tension, inadequate drainage, failure to buttress the repair, and the presence or development of infection. Other complications that may occur after repair of esophageal injuries include esophageal stricture, wound infection, mediastinitis, empyema, sepsis, and pneumonia. The incidence of complications after repair increases as the time between injury and repair increases. Shock, spinal cord injuries, the need for emergent tracheostomy, and the presence of other associated injuries also increase the rate of complications.

27.3.4.5 Outcome of Surgical Management of Esophageal Injuries

The most important factor contributing to high morbidity and mortality rates is a delay in initiating definitive surgical repair [36]. The mortality rate associated with esophageal injuries ranges from 5% to 25% for patients treated definitively within 12 h after injury, from 10% to 44% for those treated 12–24 h after injury, and from 25% to 66% or more for those treated more than 24 h after injury [39]. The mortality rates associated with injuries to the thoracic esophagus are particularly high because of the severe suppurative mediastinitis that develops within 6–12 h.

27.4 Complications of Esophageal Resection

Surgery on the esophagus is fraught with complications. Rates as high as 25%–80% have been reported. Proper patient selection, precise conduct of the indicated procedure, excellent intraoperative anesthesia management, and meticulous postoperative care will lead to optimal outcomes. Early recognition of the more common complications and how to prevent them will continue to lower the overall complications after esophageal surgery.

27.4.1 Pulmonary Complications

Pulmonary complications are the most common cause of morbidity and mortality after esophageal resection. The most common respiratory complications continue to be pneumonia, ventilator dependence, and acute respiratory distress syndrome (ARDS). Patients who developed a postoperative pneumonia had an almost sevenfold increase in mortality (20.0% vs. 3.1%) [40]. Risk factors that increase the incidence of respiratory complications include advanced age, smoking, chronic obstructive pulmonary disease (COPD), malnutrition, neoadjuvant chemotherapy, recurrent laryngeal nerve injury, loss of more than 1 L of blood during the procedure, and immobility due to pain or malnutrition. Preoperative intervention aimed at optimizing pulmonary hygiene and function can prevent and decrease the incidence of pulmonary complications.

The incidence of pneumonia can be reduced by early ambulation combined with good pain control and aggressive pulmonary toilet. If pneumonia develops, the administration of appropriate antibiotics should be initiated. Early bronchoscopy can improve pulmonary toilet, provide a good specimen for culture, and exclude tracheobronchial injury. If the patient still requires ventilatory support 1 week after surgery, early tracheostomy should be considered.

A rare but disastrous complication is tracheobronchial fistula. Injury to the trachea or the main stem bronchus can occur during the mobilization of the upper half of the esophagus during both transhiatal and transthoracic esophagectomy. Blunt dissection close to the esophagus and away from the trachea and bronchus avoids this potentially lethal technical error. Intraoperative injury is suggested by a loss in returned tidal volume, inability to ventilate the patient, persistent air bubbles in the mediastinum, and the odor of anesthetic gas. Initial intraoperative management of this complication includes advancing the endotracheal tube past the injury. Once the airway has been secured and the patient's condition is otherwise stable, the planned esophagectomy may proceed; the airway should be repaired via an incision in the right chest, and a buttressed flap should be placed between the repair and the esophageal conduit.

27.4.2 Cardiac Complications

Cardiac complications are infrequent, but may cause serious morbidity or death. Perioperative hypotension is most commonly caused by intravascular volume depletion or excessive vasodilation. Intraoperative hypotension can be caused by blunt dissection around the esophageal hiatus and the posterior mediastinum because such dissection can decrease venous return. Hypotension may also result from myocardial ischemia and is a predictor of postoperative cardiac morbidity. A variety of factors such as anemia, hypotension, tachycardia, hypoxia, and fixed coronary lesions predispose patients to myocardial ischemia.

The incidence and severity of perioperative myocardial ischemia appears to be greatest during the first 48 h after surgery [41]. Symptoms of perioperative MI

or ischemia include arrhythmias, hypotension, CHF, impaired mental status, and an increase in the blood sugar level of patients with diabetes. The use of beta-blockers seem to decrease the incidence of perioperative myocardial events associated with noncardiac surgery.

Arrhythmias are common during the perioperative period, but most are clinically benign. The reported incidence of atrial dysrhythmia after esophagectomy ranges from 13% to 60% [42]. Important risk factors for dysrhythmia include advanced age, pulmonary complications, extent of the surgery, and development of an anastomotic leak. Mortality of those patients who develop atrial fibrillation (AF) postoperative is four times higher than those who don't develop AF (23% vs. 6%) [43]. The administration of beta-blockers has been shown to reduce the incidence of postoperative atrial arrhythmia [44].

27.4.3 Bleeding

Bleeding, both intraoperatively and postoperatively, is not only troublesome but also potentially lethal. The occurrence of hypotension and tachycardia on the first postoperative day is usually related to bleeding due to inadequate hemostasis during surgery. This type of bleeding arises from short gastric arteries that have not been thoroughly ligated. If not recognized intraoperatively, injury to the spleen during gastric mobilization can also lead to postoperative bleeding. The azygous vein is usually ligated during thoracotomy but can be injured by blunt dissection during a transhiatal esophagectomy. Bleeding may also result from injury to the internal mammary artery, to the intercostal arteries, and to the aortic arch. When surgeons are careful to keep dissection planes close to the esophageal wall, bleeding from vessels supplying the esophagus is usually self-limited. When bleeding is severe, the mediastinum should be packed first so that the hemorrhage can be arrested and the patient's condition can be stabilized. If possible, the bleeding vessel(s) should be ligated under direct vision.

27.4.4 Thoracic Duct Injury

Injury to the thoracic duct may occur anywhere along the esophagus during dissection and mobilization. The reported incidence of injury to the thoracic duct is 2% for a transhiatal esophagectomy and 3% for a transthoracic esophagectomy [45]. Chylothorax is suspected if a large volume of serous drainage from the chest tube persists beyond the fifth postoperative day. A persistent chyle leak can lead to malnutrition and immunosuppression. The diagnosis may be confirmed by feeding the patient cream, which will turn the chest tube drainage cloudy white. Once the diagnosis has been made, the initial treatment approach is nonoperative. The patient should take nothing by mouth, and total parenteral nutrition, or low-fat diet, along with collection and drainage of the leak. Nonoperative treatment, however, is not always successful. If chest tube output is more than 1 L/day for more than 5 days, or if the leak persists for more than 2 weeks, or if nutritional or metabolic complications occur, exploration may become necessary. Dugue reported that if the chyle leak remained greater than 10 mL/kg on postoperative day 5, the leak was going to fail nonoperative management [46]. At reoperation, through a right thoracotomy, encircle and ligate all the tissue between the aorta, spine, and azygos vein just above the diaphragm, in order to ensure ligation of the thoracic duct.

27.4.5 Nerve Injury

The incidence of recurrent laryngeal nerve (RLN) injury after esophageal resection ranges from 2% to 20% [47]. RLN injury is more common after a transhiatal esophagectomy (11%) than a transthoracic esophagectomy (4.8%) [47]. Injury to the RLN typically causes hoarseness and difficulty in swallowing, which predisposes the patient to aspiration. Fortunately, the injury is usually transient and is most likely related to pressure on or stretching of the nerve that is caused by the placement of retractors in the tracheoesophageal groove. Once nerve injury is suspected, laryngoscopy and a swallow evaluation should be performed. Raymond recommends an aggressive approach to vocal cord paralysis with vocal cord injection for temporal medialization to enhance postoperative pulmonary toilet and prevent aspiration [44].

During esophagectomy, the vagus nerves are transected. This results in two problems. The first problem is pylorospasm and gastric dysmotility, which impair gastric emptying. To avoid this problem, most surgeons today perform a pyloromyotomy or a pyloroplasty during esophageal resection. The second problem is the dumping syndrome. The symptoms of the dumping syndrome are postprandial diarrhea, cramping, nausea, diaphoresis, abdominal pain, and palpitations. These symptoms are usually self-limited and are treated by ensuring that the patient eats frequent small meals and avoiding foods with a high carbohydrate content. Occasionally, antidiarrheal agents may be necessary.

27.4.6 Anastomotic Leak

Anastomotic leaks are the most feared complication of esophageal surgery, leading to an increase in morbidity and mortality. The reported incidence of leaks after esophageal resection ranges from 2% to 30% [48]. The anastomosis must be created without any tension, and the remnant of the esophagus and the conduit must have a good blood supply. Again, it is crucial to ensure

that each stitch transfixes the mucosal edge, which may retract as far as 1 cm from the cut edge of the esophagus [33]. Randomized studies showed that the type of anastomosis created (stapled or hand sewn, one or two layers, running or interrupted) had no affect on the incidence of developing a leak. However, both trials found that the incidence of anastomotic stricture was higher when a stapled anastomosis was created [49,50].

Leaks that occur early, within the first 48 h, are usually due to necrosis of the conduit. Although rare, this complication can be fatal. Immediate surgical intervention is required so that the conduit can be resected, the mediastinum can be debrided, a cervical esophagostomy can be created, and a feeding jejunostomy can be placed. Careful preparation of an esophageal conduit that ensures proper length and good blood supply will allow the creation of an anastomosis without tension. Preserving the right gastroepiploic artery and, if possible, the right gastric artery during mobilization of the stomach is essential to avoid stomach necrosis. Colon conduits require adequate collateralization through the marginal artery.

Although the incidence of cervical leaks is higher than that of thoracic leaks, cervical leaks rarely cause death. In contrast, thoracic leaks often lead to severe mediastinitis and are associated with a mortality rate as high as 50% [51]. Cervical leaks commonly occur during the fifth to tenth postoperative days. A barium swallow should be performed to confirm the leak, and a CT scan of the neck and chest should be performed to delineate the degree of contamination. The wound should then be opened and widely drained. Locating and closing the leak should never be attempted. Almost all cervical leaks heal with conservative management; however, anastomotic strictures develop in as many as one-third of cases [51].

Thoracic leaks most commonly occur during the first postoperative week. Signs and symptoms include fever, tachycardia, leukocytosis, increasing pleural effusions, and bile-stained or turbid fluid in the chest tube drainage. When the first signs of sepsis appear, tests should be performed to rule out a leak. The location and magnitude of a leak are confirmed with water-soluble contrast esophagography. For small, contained leaks with no signs of sepsis, appropriate treatment may be chest tube drainage, CT-guided drainage, or both. Exploration is necessary for large leaks accompanied by sepsis. Direct repair is seldom possible; therefore, the anastomosis must be taken down, the necrotic conduit tissue resected and returned to the abdomen, then mediastinum must be widely drained and debrided, and a diverting esophagostomy must be created. Reconstruction may be performed several months later after the patient makes a full recovery. In all cases, the administration of broad-spectrum antibiotics must be initiated. The patient's nutritional status must be maintained. Asymptomatic leaks that are detected by routine postoperative contrast studies should be treated conservatively by withholding oral feeding until a repeated contrast study shows resolution of the leak.

27.4.7 Stricture

Stricture may occur at the anastomotic site regardless of the type of conduit, the type of anastomosis, or the type of surgical approach. The reported rate of anastomotic stricture ranges from 2% to 40% [51]. The incidence of anastomotic stricture is increased if the esophageal pathology is due to the ingestion of lye, the occurrence of a postoperative leak, the creation of a stapled anastomosis, or the creation of an anastomosis in an irradiated field [51]. Law et al. found that the rate of stricture was 40% after a stapled anastomosis but only 9% after a hand-sewn anastomosis [50]. Fortunately, most strictures do not require surgical intervention and may be dilated over a soft, tapered Maloney dilator. Initial dilation should be performed under endoscopic and fluoroscopic guidance so that injury can be prevented and the degree, length, and nature of the stricture can be determined. Biopsy of all strictures should be performed so that a recurrence of cancer can be ruled out. Significant symptomatic relief is obtained when the stricture is dilated to 40–54 F. Multiple dilations should be performed during the next several weeks so that stricture recurrence can be prevented. The interval between treatments should be gradually extended until a period of 6 months passes with no recurrence of dysphagia. A few strictures will be chronic and resistant; in these cases, surgical intervention may be required.

27.5 Conclusion

Although esophageal surgery is fraught with difficulty, a thorough knowledge of the anatomy and an understanding of esophageal function allow procedures to be performed with an acceptably low morbidity and mortality rate along with a good outcome.

Complications after Esophageal Surgery

Anastomotic leak	5%–26%
Anastomotic stricture	10%–31%
Pulmonary complications	49.5%
Pneumonia	21.4%
Reintubation	16.2%
Ventilator need >48 h	21.8%
Cardiovascular complications	
Atrial fibrillation	11.5%–22%
Myocardial infarction	1.1%–3.8%

Venous thromboembolism (VTE)	2.4%
Pulmonary embolism	0.7%
Deep venous thrombosis	0.9%
Recurrent laryngeal nerve injury	
Cervical	2%–13%
Thoracic	2.1%–8.0%
Chylothorax	0%–8%
Conduit necrosis	1%–2%
Mortality	0%–22%

Source: Raymond, D., *Surg. Clin. North Am.*, 1299, 2012.

Avoiding Complications of Esophageal Surgery

Prevention of anastomotic leaks, stricture, and avoidance of conduit necrosis

Ensure good supply, good visualization of mucosal defect prior to repair of perforation, primary anastomosis created without tension, when available buttress anastomosis, when available use pedicle flap

Prevention of recurrent laryngeal nerve injury

Identify recurrent nerve during dissection, avoid injury from placement of retraction devices

Prevention of chylothorax

Remember the anatomy of the thoracic duct

Prevention of pulmonary complications

Cessation of smoking, aggressive pulmonary toilet, pulmonary rehabilitation, efforts to protect airway—aspiration precautions, postoperative assessment swallowing function, avoidance of recurrent laryngeal nerve injury, and consideration of transhiatal approach

Prevention of cardiac complications

Avoid hypoxia, hypotension, and start and continue beta-blockers

Prevention of venous thromboembolism

Early ambulation, VTE chemical prophylaxis, and sequential compression devices

References

1. Orringer MB. Complications of esophageal surgery and trauma. In: Greenfield LJ, ed. *Complications in Surgery and Trauma*. 2nd edn. Philadelphia, PA: Lippincott, 1989: pp. 302–325.
2. Liebermann-Meffert DM, Duranceau A, Stein HJ. Anatomy and embrology: Anatomy of the esophagus. In: Zuidema GD, Yeo CJ, Orringer MB, Heitmiller R, eds. *Shackelford's Surgery of the Alimentary Tract*. Vol. 1. 5th edn. Philadelphia, PA: Saunders, 2002: pp. 3–22.
3. Symbas PN, Symbas NP. Esophagus and diaphragm. In: Wood WC, Skandalakis JE, eds. *Anatomic Basis of Tumor Surgery*. St. Louis, MO: Quality Medical Publishing, 1999: pp. 272–303.
4. Ozawa S, Kitajima M. Esophageal perforation. In: *Fischer's Mastery of Surgery*. 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2012: pp. 919–925.
   LWW.com (good overview).
5. Fell SC. Esophageal perforation. In: Patterson GA, Copper JD et al. eds. *Pearson's Thoracic & Esophageal Surgery*. 3rd edn. New York: Churchhill Livingstone, 2008: pp. 792–808.
   Very good overview of esophageal perforation.
6. Miller DL. Esophageal perforation. In: Bland KI, ed. *The Practice of General Surgery*. Philadelphia, PA: Elsevier, 2001: pp. 326–331.
7. Blom D, Peters JH. Esophageal perforation. In: Cameron JL, ed. *Current Surgical Therapy*. 7th edn. St. Louis, MO: Mosby, 2001: pp. 7–12.
8. Jones WG II, Ginsberg RJ. Esophageal perforation: A continuing challenge. *Ann Thorac Surg*. 1992; 53:534–543.
9. Cameron JL, Kieffer RF, Hendrix TR, Mehigan DG, Baker RR. Selective nonoperative management of contained intrathoracic esophageal disruptions. *Ann Thorac Surg*. 1979; 27:404–408.
10. Sawyer R, Phillips C, Vakil N. Short- and long-term outcome of esophageal perforation. *Gastrointest Endosc*. 1995; 41:130–134.
11. Michel L, Grillo HC, Malt RA. Operative and non-operative management of esophageal perforation. *Ann Surg*. 1981; 194:57–63.
12. Yakoub D, Fahmy R et al. Evidence-based choice of esophageal stent for the palliative management of malignant dysphagia. *World J Surg*. 2008; 32(9):1996–2009.
13. Freeman RK, Van Woerkom JM et al. Esophageal stent placement for the treatment of spontaneous esophageal perforation. *Ann Thorac Surg*. 2009; 88(1):194–198.
14. Fischer A, Thomusch O et al. Nonoperative treatment of 15 benign esophageal perforations with self-expandable metal stents. *Ann Thorac Surg*. 2006; 81:467–473.
15. Wright CD, Mathisen DJ, Wain JC, Moncure AC, Hilgenberg AD, Grillo HC. Reinforced primary repair of thoracic esophageal perforation. *Ann Thorac Surg*. 1995; 60:245–249.
   Good study on the use of pedicle flaps to reinforce esophageal repairs.
16. Whyte RI, Iannettoni MD, Orringer MB. Intrathoracic esophageal perforation. The merit of primary repair. *J Thorac Cardiovasc Surg*. 1995; 109:140–146.
17. Gouge Th, Depan HJ, Spencer FC: Experience with the Grillo pleural wrap procedure in 18 patients with perforation of the thoracic esophagus. *Ann Surg*. 1989; 209(5):612–619.
18. McKinnon WM, Ochsner JL. Immediate closure and Heller procedure after Mosher bag rupture of the esophagus. *Am J Surg*. 1974; 127:115–118.
19. Blalock J. Primary esophagectomy for instrumental perforation of the esophagus. *Am J Surg*. 1957; 94:393–397.
20. Hill DC, Murray GF. Malignant tracheoesophageal fistula. In: Grillo HC, Austen WG, Wilkins EW, Mathiesen DJ, Flahakes G, eds. *Current Therapy in Cardiothoracic Surgery*. St. Louis, MO: Mosby, 1989: pp. 56–57.

21. Richardson JD, Tobin GR. Closure of esophageal defects with muscle flaps. *Arch Surg*. 1994; 129:541–548.
    Good discussion of muscle flap options for closing esophageal defects.
22. Urschel HC Jr., Razzuk MA, Wood RE, Galbraith N, Pockey M, Paulson DL. Improved management of esophageal perforation: Exclusion and diversion in continuity. *Ann Surg.* 1974; 179:587–591.
23. Ladin DA, Dunnington GL, Rappaport WD. Stapled esophageal exclusion in acute esophageal rupture: A new technique. *Contemp Surg*. 1989; 35:45–51.
24. Abbott OH, Mansour KA, Logan WD Jr., Hatcher CR Jr., Symbas PN. Atraumatic so-called "spontaneous" rupture of the esophagus. A review of 47 personal cases with comments on a new method of surgical therapy. *J Thorac Cardiovasc Surg*. 1970; 59:67–83.
25. Bufkin BL, Miller JI Jr., Mansour KA. Esophageal perforation: Emphasis on management. *Ann Thorac Surg*. 1996; 61:1447–1452.
26. Asensio JA, Chahwan S et al. Penetrating esophageal injuries: Multicenter study of the American Association for the Surgery of Trauma. *J Trauma.* 2001; 50(2):289–296.
27. Demetriades D, Theodorou D et al. Transcervical gunshot injuries: Mandatory operation is not necessary. *J Trauma.* 1996; 40:758–760.
28. White RK, Morris DM. Diagnosis and management of esophageal perforations. *Am Surg*. 1992; 58:112–119.
29. Sheely CH II, Mattox KL, Beall AC Jr., DeBakey ME. Penetrating wounds of the cervical esophagus. *Am J Surg*. 1975; 130:707–711.
30. Meyer JP, Barrett JA, Schuler JJ, Flanigan DP. Mandatory vs selective exploration for penetrating neck trauma. A prospective assessment. *Arch Surg*. 1987; 122:592–597.
31. Cornwell EE III, Kennedy F et al. Transmediastinal gunshot wounds. A reconsideration of the role of aortography. *Arch Surg*. 1996; 131:949–953.
32. Weigelt JA, Thal ER, Snyder WH III, Fry RE, Meier DE, Kilman WJ. Diagnosis of penetrating cervical esophageal injuries. *Am J Surg*. 1987; 154:619–622.
33. Cooke DT, Lau CL. Primary repair of esophageal perforation. *Oper Tech Thorac Cardiovasc Surg*. 2008; 13(2):126–137.
    Nice description of technique.
34. Karmey-Jones RC, Wagner JW, Lewis JW Jr. Esophageal injury. In: Trunkey DD, Lewis FR, eds. *Current Therapy of Trauma.* Philadelphia, PA: Elsevier, 1998: pp. 209–216.
35. Horowitz B, Krevsky B, Buckman RF Jr., Fisher RS, Dabezies MA. Endoscopic evaluation of penetrating esophageal injuries. *Am J Gastroenterol*. 1993; 88:1249–1253.
36. Richardson JD, Martin LF, Borzotta AP, Polk HC Jr. Unifying concepts in treatment of esophageal leaks. *Am J Surg*. 1985; 149:157–162.
37. Symbas PN. Esophageal injuries. In: Symbas PN, ed. *Cardiothoracic Trauma*. Philadelphia, PA: Saunders, 1989: pp. 285–302.
38. Iannettoni MD, Vleissis AA, Whyte RI, Orringer MB. Functional outcome after surgical treatment of esophageal perforation. *Ann Thorac Surg*. 1997; 64:1606–1610.
39. Wilson RF, Steiger Z. Esophageal injuries. In: Wilson RF, Walt AJ, eds. *Management of Trauma: Pitfalls and Practice*. Philadelphia, PA: Lippincott, 1996: pp. 388–405.
40. Atkins BZ, Shah AS et al. Reducing hospital morbidity and mortality following esophagectomy. *Ann Thorac Surg*. 2004; 78(4):1170–1176.
41. Mangano DT, Hollenberg M et al. Peri-operative myocardial ischemia in patients undergoing noncardiac surgery—I: Incidence and severity during the 4 day perioperative period. The Study of Peri-operative Ischemia (SPI) Research Group. *J Am Coll Cardiol*. 1991; 17:843–850.
42. Ritchie AJ, Whiteside M, Tolan M, McGuigan JA. Cardiac dysrhythmia in total thoracic oesophagectomy. A prospective study. *Eur J Cardiothorac Surg*. 1993; 7:420–422.
43. Murthy SC, Law S et al. Atrial fibrillation after esophagectomy is a marker for postoperative morbidity and mortality. *J Thorac Cardiovasc Surg*. 2003; 126:1162.
44. Raymond D. Complications of esophagectomy. *Surg Clin North Am*. October 2012; (92):1299–1313.
    Good review of complications following esophageal surgery.
45. Cerfolio RJ, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Postoperative chylothorax. *J Thorac Cardiovasc Surg*. 1996; 112:1361–1366.
46. Dugue l, Sauvanet A et al. Output of chyle as an indicator of treatment for chylothorax complicating oesophagectomy. *Br J Surg*. 1998; 85(8):1147–1149.
47. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: Clinical experience and refinements. *Ann Surg*. 1999; 230:392–403.
48. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: A review. *Am J Surg*. 1995; 169:634–640.
49. Beitler AL, Urschel JD. Comparison of stapled and handsewn esophagogastric anastomoses. *Am J Surg*. 1998; 175:337–340.
50. Law S, Fok M, Chu KM, Wong J. Comparison of handsewn and stapled esophagogastric anastomosis after esophageal resection for cancer: A prospective randomized controlled trial. *Ann Surg*. 1997; 226:169–173.
51. Wong J, Law SYK. Esophagogastrectomy for carcinoma of the esophagus and gastric cardia, and the esophageal anastomosis. In: Baker CC, Fischer JE, eds. *Mastery of Surgery*. 4th edn. Philadelphia, PA: Lippincott, 2001: pp. 813–827.

28

Complications of Cardiac Surgery and Trauma

Navrose S. Grewal

CONTENTS

28.1 Introduction

Acute complications in cardiac surgery have a serious impact on outcomes. While modern techniques for cardiopulmonary bypass and myocardial protection provide the means to conduct increasingly complex and longer operations, the population of patients presenting for surgery is both older and with greater comorbidities. As a result, the incidence of major complications in cardiac surgery has not changed much in the last decade. At a technical level, cardiac operations involve a level of precision for which even the slightest deviation has the potential for catastrophic consequences. In this chapter, the most common complications encountered in cardiac surgery and cardiac trauma will be reviewed.

28.2 Technical Complications Related to Cardiopulmonary Bypass

28.2.1 Iatrogenic Aortic Dissection

Iatrogenic dissection of the ascending aorta and arch is a rare complication with an incidence of less than 0.1% for cases in which cardiopulmonary bypass is used [1]. The primary risk factor for aortic dissection from cannulation or cross-clamping of the ascending aorta is calcification. The overall mortality rate associated with this complication is greater than 35% [2]. Management requires prompt recognition and action. If dissection occurs at the site of cannulation, the cannula must be immediately removed and replaced at another site (e.g., the femoral artery). The ascending aorta must then be repaired utilizing deep hypothermic cardiopulmonary bypass or even circulatory arrest. Pledgeted sutures may be used to repair small, local dissections at the cannulation site, but a more complex repair with replacement of the ascending aorta and/or arch with a tube graft may be necessary for extensive injury.

There are several strategies to minimize the risk of an aortic dissection. Transesophageal echocardiography and epiaortic ultrasound should be used routinely to identify areas with prominent calcification and thus avoided [3]. Lowering the systolic blood pressure to less than 100 mm Hg prior to aortic cannulation and decreasing pump flow prior to cross-clamping of the aorta also reduce risk. If the aorta cannot be cannulated or cross-clamped safely due to the presence of extensive calcification, the operative plan must be altered or abandoned. In these situations, coronary artery bypass procedures may be completed using off-pump techniques or hypothermic fibrillatory arrest.

28.2.2 Coronary Sinus Rupture

Rupture of the coronary sinus with placement of a retrograde cannula into the coronary sinus for delivery of cardioplegia occurs in less than 0.1% of cases [4]. This complication manifests as heavy venous bleeding from behind the heart. Management again requires prompt recognition and repair. Primary repair is often possible if there is a distinctly visible site of perforation. Often the tip of the retrograde cannula can be seen puncturing out from the coronary sinus. In this case, the puncture site may be repaired primarily with the use of pledgeted sutures. For more difficult ruptures, the preferred method for repair is an epicardial patch to contain the site around the rupture [5]. Autologous pericardium is most often used for the patch. After repair, the remainder of the cardiac operation should be completed with use of antegrade cardioplegia only. In extreme situations in which the site of rupture cannot be visualized due to massive bleeding or the development of a hematoma, the coronary sinus may be ligated with pledgeted sutures both proximally and distally. Even with ligation of the coronary sinus, adequate venous return from the coronary circulation is maintained from thebesian veins to the right atrium.

The risk of coronary sinus rupture may be minimized by gentle insertion of the retrograde cannula, echo guidance during placement, and verifying both visually and manually that the catheter has not been placed into a smaller tributary coronary vein or placed so far into the coronary sinus that the tip of the catheter reaches the left atrial appendage [4]. In addition, during delivery of retrograde cardioplegia, the coronary sinus pressure should be followed carefully and not exceed 30–40 mmHg. Higher coronary sinus pressures during retrograde delivery are associated with coronary sinus rupture, and an initially high coronary sinus pressure followed by an acute drop in pressure often suggests that a rupture has occurred.

28.2.3 Systemic Air Embolism

Systemic air embolism resulting in massive stroke is a rare but catastrophic complication associated with an immediate mortality rate of 22% [6]. There are many potential sources for an air embolism (Table 28.1).

TABLE 28.1

Sources of Systemic Air Embolism

Bypass machine
Drop in reservoir level
Pressurization of cardiotomy lines
Reservoir reversal of pump-head rotation
Disconnection of oxygenator
Inadequate de-airing of lines
Venting
Excessive suction on atrial vent lines
Air entering aorta retrograde via non-occluded coronary arteries when excessive aortic venting is applied
Heart
Retained air in atrial appendage
Retained air in trabeculae
Retained air in pulmonary veins
Unexpected resumption of cardiac activity when the heart is open
Unexpected patent foramen ovale when the patient is on cardiopulmonary bypass and the heart is not arrested
Other
Continued use of intra-aortic balloon pump, which can suck in air when the aorta is opened
Air introduced from venous lines in the setting of patent foramen ovale
Entry via partial occlusion clamp when proximal anastomoses are performed

If an embolus of air is seen passing into the patient via the aortic cannula, a rapid sequence of events must be initiated for management. The bypass circuit must be immediately stopped and reversed to pull air out of the aorta. The patient should be placed in a steep Trendelenberg position and additional air aspirated from the aorta using a needle. Retrograde cerebral perfusion via an SVC cannula can prevent injury in 61% of cases [7]. Maintaining hypothermia at 20°C–22°C will reduce cerebral metabolic requirements and encourage gas solubility [8]. Administering high-dose steroids, mannitol, glycerol, or some combination thereof has been shown to reduce the likelihood of injury [8]. Increasing cerebral perfusion by augmenting pump flow (6.0–6.6 L/min) and blood pressure (with vasopressor drugs) may help purge the cerebral vasculature [8]. Thiopental (40 mg/kg) has been used to quiet brain activity until bypass is complete [9]. Although the use of thiopental is attractive, it is associated with substantial negative effects, including myocardial depression and a delay in early return of consciousness. If available, hyperbaric oxygen therapy may be a useful adjunct [10].

TABLE 28.2

Causes and Risk Factors for Postoperative Bleeding

Preoperative factors
Reoperation
Preoperative anticoagulation
Antiplatelet agents
Thrombolytic agents
Cyanotic heart disease
Liver dysfunction
Coagulation disorders
Von Willebrand's disease
Uremia
Intraoperative factors
Inadequate surgical hemostasis (most common cause)
Long pump run
Core cooling to <32°C
Coagulation impact of bypass
Platelet dysfunction or depletion
Residual heparin effect
Fibrinolysis
Excessive use of cell-saver blood

28.3 Postoperative Complications

28.3.1 Bleeding and Tamponade

Postoperative bleeding requiring re-exploration occurs in 3% of cardiac surgery patients [11]. Causes and risk factors for bleeding are shown in Table 28.2 [11,12]. Bleeding generally presents as rapid and excessive drainage from the mediastinal tubes. Initial interventions include avoiding hypertension (to minimize the risk of bleeding from suture lines or cannulation sites), giving additional protamine (25–50 mg) to neutralize the effects of any remaining heparin, administering intravenous DDAVP (at a dose of 0.3 mcg/kg) to potentially correct some platelet dysfunction (which is the most common cause of coagulopathic bleeding after cardiopulmonary bypass), and transfusing products to correct coagulopathy (platelets, FFP, cryoprecipitate). The use of Factor VII for hemostasis is controversial as there is the potential to thrombose fresh bypass grafts. Some surgeons recommend the use of high levels of positive end-expiratory pressure (PEEP) (up to 20 cm H_2O) to "tamponade" bleeding.

Cardiac tamponade in the postoperative setting may manifest itself in the classic manner, with elevated right heart pressures, jugular venous distention, and shock. This complication should be suspected if chest x-ray shows a widened cardiac silhouette, if there is decreased cardiac output with no apparent cause, or by equalization of right-sided filling pressures [13]. Postoperative echocardiography may also be used to identify early tamponade (presence of a moderate to large pericardial effusion with compression of the right atrium and ventricle) [13]. The unstable patient in extremis from suspected tamponade should undergo immediate reopening of the chest at the bedside.

28.3.2 Atrial Fibrillation

Postoperative atrial fibrillation may be the most common complication after cardiac surgery, with an overall incidence greater than 25% [14]. The incidence is lower for isolated coronary bypass operations and higher for valve surgery and combined coronary/valve procedures. Hypokalemia and hypomagnesemia are particularly common after cardiac operations, and both are risk factors for arrhythmia [15]. Therefore, repletion of these electrolytes is important in maintaining a normal sinus rhythm after surgery. In addition, particularly when bicaval cannulation is used, surgeons must take care not to manipulate the junction of the superior vena cava with the atrium, as this is where the sinoatrial node is located.

Hemodynamically unstable patients should be treated with immediate cardioversion. For hemodynamically stable patients, standard pharmacological approaches for rate control and conversion are used first, followed by elective cardioversion if needed. Persistent atrial fibrillation may necessitate anticoagulation with heparin and warfarin.

28.3.3 Heart Block

Bradycardia and heart block are usually transient and can be managed by pacing with temporary leads placed at the time of surgery. The rate can be varied, but the target is generally 80–90 bpm. The atrioventricular (AV) delay should also be individualized, but in general, a delay of 150 ms provides the most effective output. A shorter delay may more effectively suppress ventricular arrhythmias. Metabolic or pharmacological causes of heart block should be explored, including hypothermia, elevated calcium or potassium concentrations, or the administration of beta-blockers. In most cases, heart block is of short duration, but in a few cases, it may persist for more than a week and a permanent pacemaker may be required. The incidence of heart block requiring permanent pacemaker placement is about 1.5% [16]. The relationship between valve structures and the conduction system is discussed later.

28.3.4 Stroke

The incidence of stroke after cardiac surgery is about 5% for isolated coronary bypass surgery and 7%–8% for combined coronary/valve procedures [17]. Procedures for the ascending aorta and arch have the highest incidence. The majority of strokes are identified within 48 h of surgery, and the associated mortality rate is as high as 40% [17]. Risk factors include preexisting carotid disease and atheromatous disease or calcification of the aorta. Screening for carotid artery stenosis with ultrasound should be routine for older patients with heart disease.

Most perioperative strokes are embolic in etiology, and the primary source of emboli is the aorta itself. Each manipulation of the aorta (cannulation and clamping) is associated with the release of echogenically detectable material into the cerebral circulation [18,19]. This knowledge has led to attempts to avoid manipulation of the aorta in patients at risk of emboli, or at least to identify disease-free areas of the aorta. However, palpation is unreliable in detecting lesions, especially if soft atheroma is present. The best study for defining atheromatous disease of the ascending aorta is epiaortic ultrasound [3]. Attempts to reduce aortic manipulation appear to be associated with improved outcomes (e.g., off-pump bypass, bypass during fibrillatory arrest, circulatory arrest, and use of endoaortic balloon occlusion) [20]. Femoral cannulation should be avoided in patients with evidence of descending aortic disease as this may also send emboli into the cerebral circulation. In this regard, subclavian or innominate artery cannulation has the advantage of moving any potential debris into the distal aorta rather than to a location that could affect the brain [20].

28.3.5 Peripheral Nerve Injuries

Brachial plexus injury occurs after sternotomy in 6%–15% of cases [21]. The precipitating event is compression of the lowest roots of the brachial plexus by the first rib during excessive retraction. The most common symptoms of this injury are paresthesias of the ring and small fingers, with weakness in nearly one-third and pain in 26% of cases [22]. Brachial plexus injuries can be prevented by carefully expanding the sternal retractor and by avoiding excessive spreading at the superior aspect of the incision [23]. More than 90% of complaints will resolve within 3 months, and therapy is generally supportive [22].

Phrenic nerve injury can occur during mobilization of the internal mammary artery, but more commonly results from "cold" injury. One study noted diaphragmatic elevation in 73% of patients when phrenic nerve protection (with a pad or sponge) was not used, but in only 17% of patients when it was used [24]. The predominant impact is on postoperative respiratory function. In general, therapy is supportive, but recovery usually takes several months.

Recurrent nerve injury most commonly occurs after operations on the descending aorta. It affects as many as 10% of patients who require clamping of the aorta proximal to the left subclavian artery [25]. The best method of preventing recurrent nerve injury is avoiding excessive traction on the vagus nerve proximal to the origin of the recurrent nerve. Approximately half of traction injuries will resolve within 6 months, but if hoarseness or ineffective cough presents a problem, medialization of the vocal cord may be required.

28.4 End-Organ Complications of Cardiopulmonary Bypass

28.4.1 Respiratory Complications

Cardiopulmonary bypass is associated with a number of deleterious effects on all organ systems, leading to increased morbidity and mortality rates and longer hospital stays. These effects are mediated by a combination of inflammatory changes, lack of pulsatile flow, and microemboli [26]. The incidence of lung injury with cardiac surgery is 12%, and the incidence of acute respiratory distress syndrome is 1.3% [27]. Acute lung injury after cardiopulmonary bypass is noted by an increased alveolar–arterial oxygenation gradient, intrapulmonary shunting, pulmonary edema, decreased pulmonary compliance, and increased pulmonary vascular resistance. Clinically, lung injury manifests itself as prolonged intubation after surgery. The perioperative use

of steroids does not reduce the incidence of lung injury, but leukocyte depletion through the arterial line filter of the pump and heparin-coated bypass circuits have been shown to limit pulmonary dysfunction [26].

Ventilator-associated pneumonia occurs in about 5% of patients after cardiac surgery and carries a mortality rate of 45% [28]. Risk factors for pneumonia include smoking within 6 weeks of surgery, diminished pulmonary function, and gastroesophageal reflux. Postoperative risk factors include ventilation for more than 48 h, phrenic nerve injury, and severe pain that limits deep inspiration and coughing. The most common infectious agents are gram-negative rods and gram-positive cocci. Initial therapy consists of antibiotics, physiotherapy, and frequent nasotracheal suctioning. If the infection does not respond to antibiotic therapy, bronchoscopy with endobronchial sputum samples should be considered to determine whether antibiotic resistance has occurred [29].

28.4.2 Renal Failure

Renal failure occurs in 1%–2% of patients who undergo cardiopulmonary bypass [30]. Risk factors include age greater than 70, decreased preoperative renal function, diabetes, congestive heart failure, and prolonged pump run [30]. Patients who are at a high risk of renal failure may benefit from the maintenance of perfusion pressures greater than 80 mm Hg and from continuation of "renal" doses of dopamine postoperatively. Evidence of poor renal function should prompt evaluation of cardiac output. Ideally, the administration of vasopressors should be discontinued or minimized. Once renal insufficiency occurs, therapy should be directed at converting the kidneys from oliguric to nonoliguric failure. Furosemide as an intravenous bolus and drip may improve renal function in patients with acute tubular necrosis.

28.5 Infectious Complications

28.5.1 Sternal Wound Infections and Mediastinitis

Superficial sternal wound infections usually present with serosanguineous drainage, with or without associated cellulitis. In general, initial management of sternal wound infections includes sterilizing the wound topically (with betadine or chloraprep) and obtaining cultures of any drainage. Unlike wound infections of incisions elsewhere on the body, the sternotomy incision is not managed by opening the wound at the bedside. Broad-spectrum antibiotics against gram-positive and gram-negative organisms are given until culture results determine a more specific antibiotic selection. If there is any sternal instability or suspicion for deep sternal wound infection, the wound must be reexplored in the operating room. If infection is limited to subcutaneous tissues above the level of the sternum and pectoralis major fascia, the wound may be treated initially with negative pressure (i.e., wound vacuum) and then delayed closure.

Deep sternal wound infection and mediastinitis affect 1% of patients after cardiopulmonary bypass and sternotomy [31,32]. Mortality rates range from 20% to 40%; and in many cases, death is due to persistent sepsis or catastrophic hemorrhage from exposed grafts or the right ventricle [32]. A number of risk factors have been determined (Table 28.3), but a crucial factor is the technique used for sternotomy—whether the division leaves one side too thin or the sternal closure leaves some mobility. Administration of antibiotics prophylactically is routine and often continued for 24–48 h postoperatively, but there is no clear evidence that this reliably prevents mediastinitis. Most cases develop within 2 weeks of the initial surgery. Signs and symptoms can vary from mild malaise and low-grade fever to frank sepsis with obvious purulent drainage from the sternal incision. A new sternal "click" is a serious finding that implies sternal instability. Computed tomography (CT) scans of the chest may show fluid collections and minor sternal separation, but these are often normal early findings after bypass. CT-guided needle aspiration may be useful if it excludes the diagnosis of deep infection, thereby allowing treatment of a minor superficial collection.

TABLE 28.3

Risk Factors for Development of Postoperative Mediastinitis

Preoperative risk factors
Preexisting infection (particularly dental)
Poorly controlled diabetes
Immunocompromise
Preoperative ventilation
Malnutrition
Intraoperative risk factors
Contamination
Prolonged pump run
Transfusion of more than four units of blood
Use of both internal mammary arteries (especially if patient has diabetes)
Thin sternal plates
Postoperative risk factors
Prolonged ventilator dependence
Malnutrition

If wound drainage is accompanied by sternal instability, or if a diagnosis of mediastinitis is suspected on the basis of clinical findings, the wound should be surgically explored. All necrotic tissue, including bone, must be debrided. If the patient's clinical condition is stable, if fungal or staphylococcal infection has been ruled out, and if the bone and surrounding tissues are pliant and have a relatively normal appearance, a reasonable option is to attempt closure over an irrigation system. A number of irrigation solutions have been used, including saline, iodine, and antibiotic solutions (e.g., first-generation cephalosporins, at a total dose of 1–2 g/L given at a rate of 50 cc/h) [33]. The irrigation can be modified on the basis of subsequent cultures, but this procedure is carried out until all signs of infection are gone and the effluent is clear.

Patients who are immunocompromised, who have grossly purulent infections, who have necrotic bone, or who have staphylococcal or fungal infections should undergo closure with vascularized tissue, usually pectoralis or rectus muscle flaps [34]. This treatment may also be necessary for all patients with mammary artery grafts and those for whom more conservative measures have failed. If sepsis is present, temporization with an open dressing or wound vacuum for frequent surgical reexploration may be an option.

28.5.2 Saphenous Vein Harvest Site Infections

Wound infections involving saphenous vein harvest sites occur in 1%–3% of patients [35]. Risk factors for vein harvest site infections include diabetes, obesity, preoperative anemia, peripheral vascular disease, and low cardiac output. Endoscopic vein harvesting techniques are associated with lower wound complication rates, but long-term vein patency rates have been found to be lower [35,36]. Superficial cellulitis involving leg incisions can be treated with compresses, elevation, and antibiotics, but if deeper infection is suspected, the wound must be opened to allow for effective drainage and clearance of infection. Gram-positive organisms are the most common cause of infection.

28.6 Technical Complications of Valve Surgery

28.6.1 Aortic Valve

A normal aortic valve has three leaflets (left, right, and noncoronary), and the anatomy of the valve in relation to subvalvular structures presents several technical complications to avoid [37]. The fibrous subaortic curtain, which represents a continuity between the aortic valve and the anterior mitral valve leaflet, is located beneath the commissure between the left and noncoronary leaflets. The left bundle of His (part of the conduction system) is located beneath the commissure between the right and noncoronary leaflets. The interventricular septum is found below the annulus of the right coronary leaflet. Portions of the right atrium and the left atrium are also in contact with the annulus along the noncoronary leaflet.

Calcification of the valve and annulus is common, and careful debridement is often required for aortic valve replacement. Extensive calcification can extend onto the anterior mitral leaflet and excessive debridement can cause detachment of the anterior mitral leaflet from the subaortic curtain [38]. If detachment occurs, the anterior mitral valve leaflet must be resuspended by placing pledgeted sutures through the anterior mitral leaflet, then through the aortic annulus, and finally through the cuff of the aortic valve prosthesis. Annular perforation into adjacent structures, if recognized, is treated similarly.

Paravalvular leaks after valve replacement are rare. If recognized postoperatively and the leak is large or associated with symptoms or evidence of ventricular strain, early reoperation should be performed [39]. In many instances, only simple sutures will be required, without the need for valve removal and re-replacement.

When procedures are performed for endocarditis, debriding all necrotic tissue is crucial, even if aorto-ventricular discontinuity results. In many (if not most) circumstances, aorto-ventricular discontinuity is anticipated and a homograft is used to reconstruct the aortic root. The coronary "buttons" resuspended from the new root should be placed to prevent kinking of the coronary artery. Acute coronary occlusion may manifest as poor ventricular function when attempts are made to wean the patient from bypass; however, in the postoperative period, this complication often causes acute ischemia involving the specific coronary distribution. Acute coronary occlusion requires immediate reevaluation by echocardiography, with a low threshold for re-exploration.

The AV conduction system can be damaged by the placement of sutures deep into the septum beneath the commissure of the noncoronary and right coronary cusps or by extensive decalcification in the same area. However, in many instances, such damage is due to edema or mechanical injury and will resolve without surgical treatment. Temporary pacing is usually tried for as long as 7–10 days before a permanent pacemaker is recommended [16].

28.6.2 Mitral Valve

Structures at risk for injury during mitral valve repair or replacement include the circumflex artery, the coronary

sinus, the AV node, and the left and noncoronary leaflets of the aortic valve [37]. The circumflex artery runs parallel and deep along the left half of the annulus of the posterior mitral valve leaflet. The coronary sinus runs parallel and deep along the right half of the annulus of the posterior mitral valve leaflet. The AV node is located in the area between the right trigone and the midpoint of the annulus of the anterior mitral valve leaflet. The left and noncoronary leaflets of the aortic valve are at risk for injury along the annulus of the anterior mitral valve as both of these leaflets are adjacent to the subaortic curtain of aortic valve to mitral valve continuity. Given all of these close anatomic relationships, excessively deep sutures in the mitral annulus can cause serious injury, usually manifesting as low cardiac output, ischemic changes, or both as the patient is weaned from bypass or during the early postoperative period. Injury to the circumflex artery will usually require coronary bypass. Injury to the conduction bundle may respond to removal of the offending sutures but may also ultimately require pacemaker placement. New aortic regurgitation after mitral valve surgery is indicative of injury to the aortic valve and will require opening the aorta to inspect the aortic valve before determining repair. Repair may entail revising the mitral annular sutures affecting the aortic valve or proceeding with aortic valve replacement if injury is severe.

Left ventricular rupture is a rare complication of mitral valve replacement. When occurring along the posterior AV groove, it results in catastrophic AV separation. Risk factors include annular resection, forceful traction on the mitral valve apparatus, extensive decalcification, placement of an oversized valve, or elevation of the apex of the heart after valve replacement [40]. LV rupture is noted acutely after coming off bypass as a posterior jet of blood or a rapid welling of blood from behind the heart. Repair must be performed with the patient back on cardiopulmonary bypass because any attempt to elevate the full, beating heart will result in extension of the injury. Repair requires removal of the valve, placement of a pericardial patch to reestablish the LV endocardium, and re-replacement of the valve [40]. Even with early recognition and repair, the mortality rate is 50% [40].

28.6.3 Tricuspid Valve

The most relevant complication associated with tricuspid valve surgery is heart block. While the overall incidence of heart block requiring a permanent pacemaker in cardiac surgery is 1.5% [16], heart block after tricuspid valve replacement occurs in more than 20% [41]. The AV node lies within the triangle of Koch, which is bounded by the coronary sinus, the tendon of Todaro, and the septal leaflet of the tricuspid valve. Sutures should not be placed in this area. Acute heart block that is recognized at the time of operation should be managed by replacing any potentially offending sutures. Although persistent heart block after tricuspid valve annuloplasty can be managed with a percutaneous pacemaker, standard percutaneous endovenous leads from the subclavian vein into the right ventricle cannot be placed after valve replacement. Patients with heart block after valve replacement will require placement of epicardial leads on the surface of the ventricle.

28.7 Complications in Cardiac Trauma

28.7.1 Acute Aortic Transection

Most patients (80%–90%) with acute aortic transection will not reach the hospital alive. Of the patients who initially survive in the field, the in-hospital mortality remains greater than 30% [42]. Acute aortic transection happens when rapid deceleration and sheer forces cause trauma at fixed points of the aorta. This mechanism occurs in motor vehicle collisions and most often involves the aortic isthmus just past the takeoff of the left subclavian artery. Patients who make it to the hospital will have a contained rupture of the aorta. The acute management of these patients begins with the use of an esmolol drip for "anti-impulse" therapy and blood pressure control, but critical extrathoracic hemorrhage from pelvic or intra-abdominal sources must be treated first. Also, intracranial trauma must be taken into consideration as proceeding with emergent repair of an aortic transection (which requires systemic heparinization) in the context of intracranial bleeding will be futile.

The new paradigm in the management of patients with multisystem trauma is an endovascular stent graft placed across the zone of aortic transaction [43]. Most commercially available devices require a 1-cm "landing zone." Given the high morbidity and mortality of open repair in the patient with multiple other injuries, it has become acceptable to proceed with stent placement and sacrifice the left subclavian artery. Although flow to the left upper extremity will be diminished, it should be possible to maintain limb viability until a left carotid to left subclavian bypass can be performed when the patient is more stable.

The incidence of paralysis after operative repair for aortic transection is as high as 20% [43]. A number of factors have been studied, most notably cross-clamp times and the use of bypass as opposed to the clamp-and-sew technique. Zeiger et al. noted that the incidence of paralysis increased if cross-clamp times exceeded 35 min [44]. In reviewing multiple series, these authors also found that

the incidence of paraplegia was 2.9% when bypass was used, 7.9% when shunts were used, and 20.4% when the clamp-and-sew technique was used [44]. In general, most authors recommend limiting clamp times to less than 30 min and favor the use of centrifugal left heart bypass.

28.7.2 Penetrating Cardiac Injuries

In most cases, penetrating cardiac injuries require a technically simple repair, whereas blunt injuries are usually managed by supportive measures alone. Complex injuries, usually defined as those involving the coronary arteries, the valves, or the ventricular septum, have been reported in as many as 10%–20% of clinical reviews [45]. Most cardiac injuries are not detected acutely, especially those caused by blunt injury. The management of these injuries depends upon the overall condition of the patient and on the ability of the heart to provide adequate output.

A serious problem that must be avoided is failure to recognize the injury. Patients who arrive at the emergency department in shock may transiently respond to volume expansion, and this response may cause the mistaken belief that severe injury is unlikely. If hypotension persists or recurs, central venous pressure increases, or a widened mediastinum is detected in association with penetrating injury, surgical exploration with a pericardial window or sternotomy is urgently required [46]. After either blunt or penetrating injury, patients who are in stable condition with only subtle signs of injury but who require repeated volume boluses should at least undergo urgent transthoracic echocardiography [47]. Small fluid collections require further investigation with a pericardial window. If a large hemothorax is present in continuity with the pericardium, echocardiography may not be able to reliably distinguish intrapericardial from extrapericardial clot [47]. Once again, further investigation with a pericardial window may be needed. CT scans of the chest, often performed to determine whether the mediastinum is widened, may show blood totally encircling the heart, which should suggest the diagnosis of cardiac trauma.

Patients who arrive at the emergency department with clinical signs of tamponade, but who have not yet undergone intubation, are at risk of acute arrest at the time of intubation. This acute decompensation is the result of a loss of preload from venodilation with anesthesia, high intrathoracic pressures from overzealous ventilation, or systemic vasodilatation from hyperventilation and anesthetic agents. Draining the pericardium, preferably with ultrasound guidance, just before attempting intubation substantially reduces the risk of acute arrest.

If cardiac injury is suspected, sternotomy best exposes the heart and the proximal great vessels. However, a resuscitative left thoracotomy is often performed in the emergency department for the patient in extremis. If injury to the great vessel or the ascending aorta is known or suspected, dissection should be started within the pericardium. This method will allow for proximal control before the site of injury is entered. If there is a large injury to the ascending aorta and cardiac arrest and cardiopulmonary bypass are not immediately possible, controlling hemorrhage by performing caval occlusion will allow the heart to beat while it is empty. In this way, visualization of the injury site will be improved so that at least initial sutures can be placed.

Mural lacerations can be controlled by finger pressure, followed by the placement of sutures. The atria can be clamped and can usually be easily repaired with direct sutures. Ventricle lacerations are usually controlled with pledgeted horizontal mattress sutures. Injuries to the right atrium adjacent to the ventricle should be approached with caution because the proximal right coronary artery lies in the groove between these chambers and can be inadvertently occluded.

Penetrating coronary artery injuries are usually treated by simple ligation [45,46]. More complex treatment is needed, however, for patients with injuries to the proximal left anterior descending coronary artery and for patients with any injury to a proximal coronary artery that is clearly associated with substantial myocardial ischemia. Off-pump bypass or primary repair may rarely be used, although cardiopulmonary bypass provides the opportunity to rewarm the patient and to correct metabolic derangements [45,46]. Blunt traumas can rarely lead to coronary thrombosis, which is usually detected by ECG changes that prompt angiography. In general, expectant management is employed. Myocardial infarction is a late complication of penetrating cardiac trauma, and there also appears to be an increased association between these injuries and the formation of ventricular aneurysms.

Late complications include a variety of cardiovascular fistulae. Most cardiovascular arteriovenous fistulae occur after stab wounds. Virtually all of these fistulae can be detected by the presence of a "machinery" murmur within 1 week of injury. Innominate arteriovenous fistulae are the most common and require repair or grafting of the artery. Coronary artery fistulae, usually to the right ventricle, present with ischemia, cardiomyopathy, subacute bacterial endocarditis, pulmonary hypertension, or some combination thereof [48]. Treatment involves either ligation of the fistula alone or, more commonly, ligation of the coronary artery and coronary bypass [48]. Aorto-cardiac fistulae most commonly involve the aorta just above the right coronary cusp and connect to the right ventricle. Congestive heart failure is often the presenting picture. Aorto-cardiac fistulae and aorto-pulmonary artery fistulae that can occur just above the aortic valve are closed by patching while the patient is on cardiopulmonary bypass.

28.7.3 Blunt Cardiac Injuries

Blunt cardiac injuries include contusions and valve rupture. Cardiac contusion has been linked to a variety of complications, including cardiogenic shock, life-threatening dysrhythmia, and late myocardial wall rupture. Contusion differs from myocardial infarction in that infarction causes cell necrosis, whereas contusion involves various degrees of hemorrhage but does not invariably lead to cell death. Valve rupture (aortic, mitral, or tricuspid) may be suggested by the presence of a new murmur and heart failure.

ECG and serial cardiac enzymes vary in sensitivity and specificity for both diagnosis and risk stratification. When patients with cardiac trauma are admitted to the hospital, neither normal nor abnormal findings on ECG reliably predict or preclude the presence of cardiac injury. Cardiac enzymes alone do not predict the likelihood of complications and do not appear to be clinically useful [49]. Transthoracic echocardiography (TTE) is a rapid and noninvasive method of identifying wall motion abnormalities, effusions, or valvular damage. Transesophageal echocardiography (TEE) is more labor intensive than TTE, but its results are more accurate.

All patients with blunt or penetrating cardiac trauma should undergo early elective TEE or TTE because many of them will have unrecognized intracardiac injuries. Delayed complications after blunt trauma, such as valvular dehiscence, myocardial dissection, coronary thrombosis, ventricular aneurysm, septal defect, and intraventricular thrombosis, usually occur within the first few weeks after injury. Follow-up echocardiography should therefore be performed after any documented blunt or penetrating injury.

28.7.4 Acute Pericarditis

Inflammatory reactions after cardiac surgery have been reported to occur in about 20% of adult patients [50]. The incidence is higher with penetrating cardiac trauma. The cause of post-op pericarditis is believed to be a post-injury autoimmune reaction that directs antibodies against the myocardium or the pericardium [50]. In addition, the introduction of blood into the pericardium may cause an inflammatory response. The predominant clinical features are recurrent low-grade (38°C–40°C) fever and pleuropericardial. The pain is aggravated by inspiration, recumbency, and twisting the torso. These symptoms usually occur days to weeks after the injury. Exudative nonhemorrhagic pericardial effusions leading to tamponade are rare. A pericardial friction rub may be heard until the effusion reaches a volume large enough to cause muffled heart sounds. Echocardiography is the most specific diagnostic method. It will not only document the effusion but may also demonstrate pericardial thickening, a sign consistent with inflammation. Progressive tamponade is demonstrated initially by collapse of the right atrium and subsequently by collapse of the right ventricle during diastole. Both findings are concerning for impending tamponade, and emergent drainage by pericardiocentesis or pericardial window is indicated. In most instances, pericarditis is a self-limiting condition. Initial treatment, in the absence of tamponade, includes the administration of anti-inflammatory agents. Acetylsalicylic acid is often effective, but if relapses occur, steroids may be required.

28.7.5 Suppurative Pericarditis

Suppurative pericarditis usually occurs after penetrating injury. The diagnosis should be suggested by a history of penetrating injury coupled with a progressively septic course. Echocardiography, chest radiography, or CT may demonstrate air fluid levels, loculations, or both around the heart. If the diagnosis is uncertain, pericardiocentesis may confirm it. Operative intervention involves wide debridement and drainage, ideally through a left anterolateral thoracotomy. Dividing the sternum should be avoided so as to reduce the risk of sternal osteomyelitis.

28.7.6 Constrictive Pericarditis

Constrictive pericarditis is quite uncommon after trauma; its occurrence is generally related to the effect of blood in the pericardial cavity. This complication may occur weeks after the event, but its occurrence is more common years later. Constrictive pericarditis is uncommon after elective cardiac procedures, possibly because the pericardium is left widely open after elective cases. When this complication does occur, especially years after the inciting event, extensive calcification is the rule. The diagnosis of constrictive pericarditis is based on clinical features of elevated systemic venous pressures (including jugular vein distension, pedal edema, and hepatic engorgement) and is confirmed by echocardiography or by measuring chamber pressures at the time of catheterization. Treatment requires pericardial resection, removing or "cobble-stoning" the pericardium from both phrenic nerves laterally, opening the roots of the pulmonary artery and aorta, and ensuring that both cavae are decompressed. Decompressing these vessels may be limited, in cases of severe calcification, to cracking open the anterior surfaces. The left heart should be decompressed first. This maneuver will prevent acute pulmonary edema that might occur if the right heart was decompressed before the left ventricle was sufficiently freed, to allow it to accept the sudden increase in volume from the pulmonary circuit. If pericardial resection is performed after coronary artery bypass, the

status and location of the grafts must be documented, and preparations must be made for possible regrafting in the event that a patent graft is injured. Relative dilation and congestive heart failure may occur postoperatively. These problems can be managed by administering diuretic drugs and digitalis, but the problems may also reflect a degree of underlying cardiomyopathy.

Complications of Cardiac Surgery and Trauma

Complications	Incidence (%)	References
Iatrogenic aortic dissection	<0.1	[1,2]
Coronary sinus rupture	<0.1	[4,5]
Systemic air embolism	<0.1	[6–8]
Re-exploration for bleeding	3	[11]
Tamponade	2	[13]
Atrial fibrillation	26.7	[14]
Heart block requiring permanent pacemaker placement	1.5	[16]
Stroke	5–9	[17]
Brachial plexus injury	6–15	[21–23]
Phrenic nerve injury	17% with an insulating pad, 73% without	[24]
Recurrent laryngeal nerve injury	10	[25]
Ventilator-associated pneumonia	5	[28]
Renal failure	1–2	[30]
Deep sternal wound infection and mediastinitis	1–2	[31,32]
Saphenous vein harvest site infection	1% for endoscopic harvest, 3% for open	[35,36]
Technical complications of aortic or mitral valve surgery	<1	[37–40]
Paralysis associated with repair of aortic transection	20	[43,44]
Acute pericarditis	20	[50]

How to Avoid Complications of Cardiac Surgery and Trauma

Complications	Method of Avoidance	References
Iatrogenic aortic dissection	Evaluation of the ascending aorta for calcifications and atheromatous disease	[3]
Coronary sinus rupture	Guided retrograde cannula insertion, confirmation of retrograde cannula position, coronary sinus pressure monitoring	[4,5]
Systemic air embolism	Systematic check of the cardiopulmonary bypass circuit to exclude potential sources of air, initial de-airing of the heart before cross-clamp removal, additional de-airing of the heart through the antegrade cannula before weaning off bypass	[6–8]
Re-exploration for bleeding	Pre-op risk stratification, correction of coagulopathy	[11–13]
Tamponade	Correction of coagulopathy, frequent stripping of mediastinal tubes, echocardiography to assess for pericardial effusion, early re-exploration for bleeding	[11–13]
Atrial fibrillation	Correction of hypokalemia and hypomagnesemia, post-op use of beta-blocker	[14,15]
Heart block requiring permanent pacemaker placement	Correction of metabolic and pharmacologic disturbances, careful placement of sutures in valve surgery with attention to location of conduction system pathways	[14–16]
Stroke	Carotid screening, evaluation of the ascending aorta for calcifications and atheromatous disease, techniques that avoid manipulation of aorta	[3,20]
Brachial plexus injury	Gradual opening of the chest with sternal retractor, avoiding excessive retraction and rib fractures	[21–23]
Phrenic nerve injury	Use of an insulating pad	[24]
Recurrent laryngeal nerve injury	Avoiding excessive traction on the vagus nerve proximal to the takeoff of the recurrent nerve	[25]
Ventilator-associated pneumonia	Smoking cessation, extubation within 48 h, pain control, incentive spirometry, breathing treatments, chest physiotherapy, early ambulation	[28]
Renal failure	Maintain higher perfusion pressures during cardiopulmonary bypass for high-risk patients, convert from oliguric to nonoliguric with IV diuretics	[30]
Deep sternal wound infection and mediastinitis	Dividing the sternum precisely at the midline, avoiding bilateral internal mammary artery use, diabetic control, optimizing nutrition, minimizing blood transfusion, irrigation systems, muscle flaps	[31–34]
Saphenous vein harvest site infection	Harvesting by endoscopic technique	[35,36]
Technical complications of aortic or mitral valve surgery	Avoiding excessive annular debridement, attention to depth of placement of annular sutures, minimizing traction or lifting of the heart	[37–40]
Paralysis associated with repair of aortic transection	Limiting clamp-and-sew time to less than 30 min, use of a shunt, left heart bypass	[43,44]
Acute pericarditis	Anti-inflammatory medications	[50]

References

1. Leontyev S, Borger MA, Legare JF et al. Iatrogenic type A aortic dissection during cardiac procedures: Early and late outcome in 48 patients. *Eur J Cardiothorac Surg*. 2012; 41(3):641–646.

   In this retrospective review of over 55,000 cases of open heart surgery over 15 years at a single center, the incidence of iatrogenic aortic dissection in open heart surgery was found to be 0.06%. The associated mortality was 35.5% for dissections identified intraoperatively and 60.0% for dissections identified postoperatively.
2. Jonker FH, Schlosser FJ, Indes JE et al. Management of type A aortic dissections: A meta-analysis of the literature. *Ann Thorac Surg*. 2010; 89(6):2061–2066.
3. Whitley WS, Glas KE. An argument for routine ultrasound screening of the thoracic aorta in the cardiac surgery population. *Semin Cardiothorac Vasc Anesth*. 2008; 12(4): 290–297.
4. Kaul TK, Fields BL, Jones CR. Iaterogenic injuries during retrograde delivery of cardioplegia. *Cardiovasc Surg*. 2000; 8(5):400–403.
5. Fleisher AG, Sarabu MR, Reed GE. Repair of coronary sinus rupture secondary to retrograde cardioplegia. *Ann Thorac Surg*. 1994; 57(2):476–478.
6. Mills NL, Ochsner JL. Massive air embolism during cardiopulmonary bypass: Causes, prevention, and management. *J Thorac Cardiovasc Surg*. 1980; 80(5): 708–717.

   In this original review of 13 cases of massive air embolism, Mills and Ochsner bring attention to the principal causes for this catastrophic complication (Table 28.1). The authors also present the steps to be taken for immediate management.
7. Kurusz M, Butler B, Katz J et al. Air embolism during cardiopulmonary bypass. *Perfusion.* 1995; 10(6):361–391.
8. Mills N, Morris J. Air embolism associated with cardiopulmonary bypass. In Waldhausen J, Orringer M, eds. *Complications in Cardiothoracic Surgery*. St. Louis, MO: Mosby Year Book, 1991: pp. 60–67.
9. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. *Anesthesiology.* 1986; 64(2): 165–170.
10. Armon C, Deschamps C, Adkinson C et al. Hyperbaric treatment of cerebral air embolism sustained during an open-heart surgical procedure. *Mayo Clin Proc*. 1991; 66(6):565–571.
11. Karthik S, Grayson AD, McCarron EE et al. Reexploration for bleeding after coronary artery bypass surgery: Risk factors, outcomes, and the effect of time delay. *Ann Thor Surg*. 2004; 78(2):527–534.
12. Ferraris VA, Ferraris SP, Saha SP et al. Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practive guideline. *Ann Thor Surg*. 2007; 83 (5 Suppl):S27–S86.
13. Russo AM, O'Conner WH, Waxman HL. Atypical presentations and echocardiographic findings in patients with cardiac tamponade occurring early and late after cardiac surgery. *Chest*. 1993; 104(1):71–78.
14. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Ann Intern Med*. 2001; 135(12):1061–1073.
15. Karmy-Jones R, Hamilton A, Dzavik V et al. Magnesium sulfate prophylaxis after cardiac operations. *Ann Thorac Surg*. 1995; 59(2):502–507.
16. Merin O, Ilan M, Oren A et al. Permanent pacemaker implantation following cardiac surgery: Indications and long-term follow-up. *Pacing Clin Electrophysiol*. 2009; 32(1):7–12.
17. McKhann GM, Grega MA, Borowicz LM Jr et al. Stroke and encephalopathy after cardiac surgery: An update. *Stroke.* 2006; 37(2):562–571.
18. Barbut D, Hinton RB, Szatrowski TP et al. Cerebral emboli detected during bypass surgery are associated with clamp removal. *Stroke.* 1994; 25(12):2398–2402.
19. Barbut D, Lo YW, Hartman GS et al. Aortic atheroma is related to outcome but not numbers of emboli during coronary bypass. *Ann Thorac Surg*. 1997; 64(2):454–459.
20. Gold J, Barbut D. Prevention of neurological injury during open heart surgery. In: Franco KL, Verrier ED, eds. *Advanced Therapy in Cardiac Surgery*. Hamilton, Ontario, Canada: B.C. Decker, 1999: pp. 51–61.
21. Vander Salm TJ, Cutler BS, Okike ON. Brachial plexus injury following median sternotomy. Part II. *J Thorac Cardiovasc Surg*. 1982; 83(6):914–917.
22. Morin JE, Long R, Elleker MG et al. Upper extremity neuropathies following median sternotomy. *Ann Thorac Surg*. 1982; 34(2):181–185.
23. Baisden CE, Greenwald LV, Symbas PN. Occult rib fractures and brachial plexus injury following median sternotomy for open-heart operations. *Ann Thorac Surg*. 1984; 38(3):192–194.
24. Esposito RA, Spencer FC. The effect of pericardial insulation on hypothermic phrenic nerve injury during open-heart surgery. *Ann Thorac Surg*. 1987; 43(3):303–308.
25. Carter Y, Meissner M, Bulger E et al. Anatomical considerations in the surgical management of blunt thoracic aortic injury. *J Vasc Surg*. 2001; 34:628–633.
26. Rubens, FD. Cardiopulmonary bypass: Technique and pathophysiology. In Sellke FW, del Nido PJ, Swanson SJ, eds. *Sabiston & Spencer Surgery of the Chest*. Philadelphia, PA: Saunders Elsevier, 2010: pp. 957–975.
27. Rady MY, Ryan T, Starr NJ. Early onset of acute pulmonary dysfunction after cardiovascular surgery: Risk factors and clinical outcome. *Crit Care Med*. 1997; 25(11):1831–1839.
28. Hortal J, Giannella M, Perez MJ et al. Incidence and risk factors for ventilator-associated pneumonia after major heart surgery. *Intensive Care Med*. 2009; 35(9):1518–1525.
29. Croce MA, Fabian TC, Schurr MJ et al. Using bronchoalveolar lavage to distinguish nosocomial pneumonia from systemic inflammatory response syndrome: A prospective analysis. *J Trauma.* 1995; 39(6):1134–1139.

30. Mangano CM, Diamondstone LS, Ramsay JG et al. Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med*. 1998; 128(3):194–203.
31. Borger MA, Rao V, Weisel RD et al. Deep sternal wound infection: Risk factors and outcomes. *Ann Thorac Surg*. 1998; 65:1050–1056.

    The incidence of deep sternal wound infection in this retrospective review of over 12,000 consecutive cardiac cases was 0.75%. In coronary bypass cases, the independent predictors for the development of deep sternal wound infection were use of both internal mammary arteries, diabetes, and male sex. In subgroup analysis, diabetic patients who had bilateral internal mammary artery grafts had the highest incidence of infection (14.3%). Based on this finding, the use of both mammary arteries in diabetic patients is not recommended.
32. Marggraf G, Splittgerber FH, Knox M et al. Mediastinitis after cardiac surgery—Epidemiology and current treatment. *Eur J Surg Suppl*. 1999; 584:12–16.
33. Berg HF, Brands WG, van Geldorp TR et al. Comparison between closed drainage techniques for the treatment of postoperative mediastinitis. *Ann Thorac Surg*. 2000; 70(3):924–929.
34. Rand RP, Cochran RP, Aziz S et al. Prospective trial of catheter irrigation and muscle flaps for sternal wound infection. *Ann Thorac Surg*. 1998; 65(4):1046–1049.
35. Lai T, Babb Y, Ning Q et al. The transition from open to endoscopic saphenous vein harvesting and its clinical impact: The Texas Heart Institute Experience. *Tex Heart Inst J*. 2006; 33(3):316–320.
36. Lopez RD, Hafley GE, Allen KB et al. Endoscopic vs open vein-graft harvesting in coronary artery bypass surgery. *N Engl J Med*. 2009; 361(3):235–244.

    In this non-randomized comparison study, a statistically significant difference in vein graft patency rates was identified at 12–18 months after surgery. The rate of vein graft failure which was defined as a stenosis of at least 75% of the vein graft diameter by angiography was 46.7% for endoscopic and 38.0% for open harvest ($P < 0.001$). Despite lower post-operative wound complication rates with the endoscopic technique, this study found worse long term outcome measures of myocardial infarction, repeat revascularization, and death when endoscopic vein graft harvesting was used.
37. Khonsari S, Sintek CF. *Cardiac Surgery: Safeguards and Pitfalls in Operative Technique*. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.
38. Islamoglu F, Apaydin AZ, Degirmenciler K et al. Detachment of the mitral valve anterior leaflet as a complication of aortic valve replacement. *Tex Heart Inst J*. 2006; 33(1):54–56.
39. Orszulak TA, Schaff HV, Danielson GK et al. Results of reoperation for periprosthetic leakage. *Ann Thorac Surg*. 1983; 35(6):584–589.
40. Sersar SI, Jamjoom AA. Left ventricular rupture post mitral valve replacement. *Clin Med Cardiol*. 2009; 3: 101–113.
41. Cooper JP, Jayawickreme SR, Swanton RH. Permanent pacing in patients with tricuspid valve replacement. *Br Heart J*. 1995; 73:169–172.
42. von Oppell UO, Dunne TT, De Groot MK et al. Traumatic aortic rupture: Twenty-year metaanalysis of mortality and risk of paraplegia. *Ann Thorac Surg*. 1994; 58(2):585–593.
43. Fujikawa T, Yukioka T, Ishimaru S et al. Endovascular stent grafting for the treatment of blunt thoracic aortic injury. *J Trauma.* 2001; 50(2):223–229.
44. Zeiger MA, Clark DE, Morton JR. Reappraisal of surgical treatment of traumatic transection of the thoracic aorta. *J Cardiovasc Surg (Torino)*. 1990; 31(5):607–610.

    In this retrospective review, the authors found the incidence of paraplegia with the clamp-and-sew technique to be directly related to the aortic occlusion time. A significant increase in paraplegia was noted for clamp times exceeding 35 min. In reviewing multiple series, the authors also found that the incidence of paraplegia was 2.9% when bypass was used, 7.9% when shunts were used, and 20.4% when the clamp-and-sew technique was used.
45. Wall MJ Jr, Mattox KL, Chen CD et al. Acute management of complex cardiac injuries. *J Trauma.* 1997; 42(5):905–912.
46. Knott-Craig CJ, Dalton RP, Rossouw GJ et al. Penetrating cardiac trauma: Management strategy based on 129 surgical emergencies over 2 years. *Ann Thorac Surg*. 1992; 53(6):1006–1009.
47. Bolton JW, Bynoe RP, Lazar HL et al. Two-dimensional echocardiography in the evaluation of penetrating intrapericardial injuries. *Ann Thorac Surg*. 1993; 56(3):506–509.
48. Lowe JE, Adams DH, Cummings RG *et al*. The natural history and recommended management of patients with traumatic coronary artery fistulas. *Ann Thorac Surg*. 1983; 36(3):295–305.
49. Biffl WL, Moore FA, Moore EE et al. Cardiac enzymes are irrelevant in the patient with suspected myocardial contusion. *Am J Surg*. 1994; 168(6):523–527.
50. Engle MA, Gay WA Jr, McCabe J et al. Postpericardiotomy syndrome in adults: Incidence, autoimmunity and virology. *Circulation.* 1981; 64(2 Pt 2): II58–II60.

Section VI

Vascular

29

Venous Thromboembolism and Therapy

Robert M. Van Haren, Bassan J. Allan, and Enrique Ginzburg

CONTENTS

29.1 Introduction

Venous thromboembolism (VTE) is a common and potentially lethal complication of trauma and surgery. VTE includes two main clinical conditions: deep venous thrombosis (DVT) and pulmonary embolism (PE). PE is commonly the result of DVT, and it is customary to consider both of these conditions as components of VTE syndrome. There are many similarities in pathophysiology, prophylaxis, and treatment. This chapter will summarize current knowledge about the incidence, diagnosis, prophylaxis, and treatment of these complications.

29.2 Deep Venous Thrombosis

29.2.1 Overview

DVT is a serious complication of surgery and trauma, with an annual incidence of 350,000 cases per year and 100,000 deaths due to VTE each year.[1,2] DVT usually involves the veins of the lower extremity such as iliac, deep femoral, popliteal, and calf veins. Thrombus formation is the result of vessel wall injury that results in activation of the coagulation cascade (direct and indirect pathways) and accumulation of platelets and fibrin. The pathogenesis of VTE is thought to involve the components of Virchow's triad: endothelial injury, venous stasis, and hypercoaguability.[3] Over time, this theory has evolved to include more specific risk factors such as age, obesity, history of malignancy, spinal cord injury, and lower extremity fracture. Several risk assessment profiles are available to identify patients at increased risk for DVT.[4,5]

29.2.2 Diagnosis

The risk of bleeding from DVT prophylaxis is extremely low; however, the reality of its existence and increased morbidity in orthopedic patients undergoing joint replacement has made DVT prophylaxis in these patients a challenge nationwide with the use of low-molecular-weight heparins (LMWH) due primarily from fear of bleeding.

Physical examination is unreliable for the diagnosis of DVT, and furthermore, many DVT are asymptomatic.[6] Diagnosis can be made with several serological and imaging methods. The American College of Chest Physicians (ACCP) recommends clinically assessing the pretest probability of DVT, rather than performing the same diagnostic tests in all patients.[7]

D-Dimer is a degradation product from the breakdown of cross-linked fibrin. D-Dimer is a useful screening test and if negative can rule out the diagnosis of DVT.[8] Increased levels of D-Dimer can also be caused by infection, inflammatory disease, pregnancy, malignancy, trauma, burns, and surgery, which limit its clinical utility in surgical and trauma patients.[9]

Duplex ultrasonography (US) is the most widely used method for diagnosing DVT and has a sensitivity and specificity of 98% and 98%, respectively.[10] Advantages of US include being rapid, cost-effective, and noninvasive. Diagnosis is made with a combination of techniques including B-mode US, color flow Doppler, and assessing the compressibility of vessels. The US probe is used to compress the lumen of a vein, and the presence of a thrombus prevents compression and is diagnostic for a DVT. However, the compression technique is not sensitive in diagnosing DVT below the knee.[11] The sensitivity of US is also lower in patients with asymptomatic DVT, largely due to a higher distribution of DVT in the calf veins in these asymptomatic patients.[12] US is also sensitive for the diagnosis of upper-extremity DVT, which is usually associated with central venous catheters.[13] US screening has been effective in high-risk trauma patients[14]; however, controversy remains and routine US screening is not recommended by the ACCP.[15]

Contrast venography has traditionally been considered the gold standard for the diagnosis of DVT.[16] The appearance of a constant intraluminal-filling defect on two or more venographic views is diagnostic.[17] However, it is no longer routinely used due to its invasiveness, high costs, and high complication rate such as contrast-induced nephropathy.[18] Combined CT venography and CT pulmonary angiography (CTVPA) has several advantages such as improved imaging of technically inaccessible areas (above the inguinal ligament and below the knee) and less inter-operator variability. However, it is usually limited to an adjunct in the diagnosis of PE.[19] Contrast venography, CT venography, or magnetic resonance imaging (MRI) are not recommended for the diagnosis of lower-extremity DVT.[7]

29.2.3 Prophylaxis

Appropriate VTE thromboprophylaxis is critical to prevent DVT and PE complications. There are several pharmacologic and mechanical prophylaxis agents, which can be utilized to decrease VTE rates while minimizing adverse events such as bleeding.

Heparin was discovered over 90 years ago and has long been the workhorse of VTE prophylaxis. Heparin binds to antithrombin III, which inhibits a cascade of procoagulation factors, especially IIa and Xa. VTE prophylaxis with unfractionated heparin reduces the odds of a fatal and nonfatal PE by 47% and 41%, respectively. The main adverse effects of heparin are bleeding and, rarely, heparin-induced thrombocytopenia (HIT).[15]

LMWH is a fractionated heparin with fewer pentasaccharide chains. LMWH has less effect on factor IIa, although its inhibitory effect on factor Xa is still substantial. At this time, there are various LMWH, but the two most common products available in the United States are enoxaparin and dalteparin. LMWH is more expensive than heparin, although its advantages include decreased risk of HIT and once-daily dosing in low to moderate risk populations. Several studies have reported a 30% reduced risk of VTE with LMWH compared to heparin, although this difference was not present when analysis was restricted to blinded, placebo-controlled trials. Therefore, the ACCP recommends major trauma patients receive either heparin or LMWH. For general and abdominal–pelvic surgery patients at moderate or high risk for VTE, the ACCP recommends heparin or LMWH for trauma patients although the level of evidence for recommendations by the ACCP has dropped from grade 1A to 2C in 2012.[15]

Direct thrombin inhibitors such as argatroban are the newest agents for prophylaxis. In contrast to other agents, they do not require a plasma cofactor; rather they bind to thrombin and block its enzymatic activity. Their main role is for prophylaxis in patients with HIT, and their use is limited because no specific antidote is available for reversal.[20]

The fear of postoperative bleeding prompted the implementation of lower-extremity compression devices ranging from simple elastic compression stockings to more sophisticated intermittent pneumatic compression (IPC) devices. All of these mechanical prophylaxis devices are used in an attempt to minimize the effect of immobilization and circulatory stasis. Ginzburg et al. found no significant differences in DVT rates between trauma patients receiving compression devices and LMWH.[21] However, mechanical prophylaxis is only recommended for patients who are at low risk for VTE, or for those in which pharmacologic prophylaxis is contraindicated due to high risk for major bleeding. IPCs are the preferred mechanical prophylaxis devices.[15]

Inferior vena cava (IVC) filters are discussed in the next section but are not recommended for primary VTE prevention.[15]

There are several ongoing areas of research in VTE prophylaxis, and recommendations are often changing. Lin et al. demonstrated decreased VTE rates when LMWH is titrated based upon antifactor Xa levels.[22] Clinical trials are underway to examine the utility of using thromboelastography (TEG) to guide prophylaxis regimens. Improved prophylaxis regimens may decrease VTE rates in high-risk patients; however, more studies are needed. Another challenging aspect of VTE prophylaxis is when to start pharmacologic prophylaxis

after traumatic brain injury (TBI). A recent randomized clinical trial compared early versus late enoxaparin prophylaxis after TBI and found that starting prophylaxis 24 h after stable injury was safe.[23] More evidence is needed to determine if these and other exciting strategies can successfully decrease VTE rates, while minimizing complications.

29.2.4 Treatment

The mainstay of acute DVT treatment is therapeutic parenteral anticoagulation. LMWH is recommended over intravenous (IV) heparin or subcutaneous heparin. LMWH is associated with decreased mortality, lower recurrence of VTE, and decreased incidence of major bleeding when compared to IV heparin. LMWH also has the advantage of easier administration. The dosages of subcutaneously administered LMWH differ according to the preparations of the individual drugs. However, the dose should be adjusted for patients with severe renal insufficiency (creatinine clearance < 30 mL/min) to avoid bleeding complications. LMWH can also be given once-daily rather than twice-daily. Intravenous unfractionated heparin can be administered with a weight-based or fixed-dose strategy. For the weight-based regimen, an initial bolus of 80 units/kg is followed by a maintenance infusion of 18 units/kg/h until the patient's partial thromboplastin time (PTT) is 46–70 s. A fixed-dose treatment strategy utilizes a bolus of 5000 units followed by a maintenance infusion of 1000 units/h. Both strategies have similar outcomes and are both recommended.[24]

The transition to oral warfarin is often deferred in the acutely or critically injured patient. The short half-life and faster reversal of IV heparin is advantageous in this patient population. Additionally, these patients are often unable to take oral medications. Long-term anticoagulation with oral warfarin [adjusted to achieve an international normalized ratio (INR) of 2–3] can safely be started on the first or second day after heparin/LMWH therapy is initiated. Anticoagulation therapy should be administered for 3 months for the treatment of an acute DVT.[25]

An IVC filter can be placed for patients with a DVT and a contraindication to anticoagulation. These patients should be switched to conventional anticoagulation as soon as their bleeding risk resolves. More aggressive treatment with thrombectomy or thrombolytic therapy is usually reserved for cases with complicated, massive unresolved ileofemoral thrombosis resulting in phlegmasia cerulea dolens or alba dolens.

29.2.5 Complications

DVT is a unique topic because, in and of itself, it is a complication occurring after surgery and trauma. Additionally, complications occur as a result of a DVT. The most concerning complication of DVT is a PE, which will be discussed in detail in the next section.

Post-thrombotic syndrome is a complication seen in as many as 30% of patients with DVT.[26] Symptoms include pain, leg edema, skin discoloration, and ulceration. The syndrome occurs when thrombosis damages or destroys the venous valves, leading to valvular incompetence, outflow obstruction, and ultimately venous hypertension. The risk of post-thrombotic syndrome is highest among patients with recurrent ipsilateral DVT.[27] Conservative treatment with graduated compression stockings, weight reduction, and continuous nursing care has been shown to reduce the symptoms of 30% of patients, but for approximately two-thirds of patients, the symptoms did not improve or even worsened.[28]

Another rare but feared complication of severe venous outflow obstruction is phlegmasia cerulea dolens. This devastating condition results from increased interstitial pressure that compromises tissue perfusion and leads to progressive ischemia. The mortality rate associated with this condition is estimated to be 30%–40%, with tissue loss appearing in 50% of patients. Aggressive treatment with thrombolysis, fasciotomy, and thrombectomy is necessary once anticoagulation therapy fails.[29]

The recurrence of DVT despite adequate treatment depends on the risk factors of each patient. In a study of recurrent DVT, the risk of recurrence approached 30% after 8 years and was highest among patients with malignancy and lowest among those who had suffered trauma.[30]

29.3 Pulmonary Embolism

29.3.1 Overview

PE is often the sequela and the most frequent cause of death from a DVT. One of the most devastating experiences for any surgeon is to perform a successful operation or to repair a complex injury, only to have the patient succumb to a massive unexpected PE. Acute PE is an unfortunately common and very often fatal postoperative complication.

PE has an estimated average annual incidence of 23 cases per 100,000 persons.[31] In recent years, there has been a rise in the incidence of PE by 60% in surgical admissions from 16.0 to 25.6 per 100,000 US adults. However, these changes correlate with the introduction of computed tomographic pulmonary angiography in 1998. The increased incidence is likely related to increased detection of subclinical PEs rather

than an increase in the true incidence of symptomatic disease.[32] Concomitantly, a decrease in age-adjusted PE mortality by 3% has been noted, which in part may be due to better detection and/or better prophylaxis and treatment strategies.

PE most commonly results from thrombi in the lower extremity veins proximal to and including the popliteal veins. However, half of patients with PE have no detectable DVT. The risk factors for PE are similar to those for DVT because the two conditions occur at different stages of the same disease process.

Autopsy studies performed before prophylactic measures came into use detected PE in 4%–16% of patients who had died of traumatic injury, and PE was considered to be the direct cause of death in approximately half of these patients.[33] Currently, PE occurs in approximately 2% of patients undergoing general surgery without prophylaxis. The use of prophylaxis reduces this overall incidence by more than 50%; with prophylaxis, PE occurs in less than 1% of patients undergoing general surgery and in only 0.3%–2% of patients who have suffered trauma.[34] In fact, clinically apparent PE properly diagnosed and treated becomes an uncommon cause of death.[35] The risk of PE for patients undergoing general surgery is related to each patient's risk factors and to the nature of the procedure. The risk of PE for patients who have sustained trauma is most closely related to the severity of the injury and to the presence of specific injuries involving fractures of the spine, skull, pelvis, and long bones.[36]

For trauma patients, 6% of PEs will occur within the first day after injury and 25% will occur during the first week after injury,[37] probably because prophylaxis cannot be administered to these patients early in their treatment course. Thus, PE is the third most common cause of death among trauma patients.

One percent of patients who develop DVT die from a PE, resulting in approximately 200,000 deaths annually. PE, if left untreated, has a mortality rate between 30% and 40%. However, PE effectively treated with anticoagulation has a 70%–90% reduction in mortality.[38] Of those patients who survive the initial event, 1.5% will die of recurrent PE within a year and an estimated 3% will develop chronic thromboembolic pulmonary hypertension.[24]

29.3.2 Diagnosis

Physical examination has a low sensitivity for diagnosing PE, which is underscored by the fact that it is a common cause of unsuspected death and is often detected only during autopsy. PE should be suspected whenever sudden, unexplained dyspnea at rest or with exertion occurs. All the other "classic signs," such as pleuritic pain and hemoptysis, are nonspecific for diagnosis. Other signs and symptoms of PE include low-grade fever, pleural rub, orthopnea (>2 pillow), cough, and an accentuated second heart sound.

Another important component of the physical examination is a thorough cardiovascular exam. Whether hemodynamic cardiac signs will be evident depends on the extent of the embolus and the degree of acute right heart dysfunction that ensues. The hemodynamic-cardiac signs can be mild such as tachycardia and lightheadedness, but massive obstruction can cause hypotension, cyanosis, neck vein distension, and sudden cardiac arrest.

The importance of electrocardiography (ECG) in diagnosing PE has declined with the development of high-resolution imaging techniques. ECG nevertheless remains an important initial tool for the rapid assessment of underlying cardiac etiology for patients with hemodynamic instability. ECG changes indicative of PE include axis deviation and nonspecific ST-wave and T-wave segment abnormalities in the lateral leads. The diagnostic pattern of the S1Q3T3 sign, right bundle branch block, P pulmonale, and right axis deviation is present in only one-third of patients with massive PE who exhibit clinical signs of acute cor pulmonale. Other nonspecific ECG changes will occur in approximately 87% of patients with proven PE and no underlying cardiac disease; however, the other great value of ECG is its ability to rule out other sources of chest pain such as myocardial infarction.[39]

Arterial blood gas analysis is one of the first tests ordered by most physicians due to the associated dyspnea at presentation in patients with suspected PE. Hypoxemia is common but is not always present, especially in young patients with no underlying pulmonary pathology. Ten percent of patients with acute PE will have no demonstrable hypoxemia.[40] In general, hypoxemia or an elevated alveolar–arterial (a–A) gradient can indicate the possibility of PE, but normal values cannot rule out the diagnosis.[41] Hypocapnea secondary to tachypnea is common as well as hypercapnea, but these are not necessarily diagnostic.

The results of plain chest radiography (CXR) are abnormal but nonspecific for most patients with PE, except for the rare occasion where PE causes lung infarction with its suggestive wedge-shaped consolidation. Other radiographic signs specific for PE include the Westermark sign (decreased vascular marking). CXR is a valuable diagnostic tool because it can detect other pathological conditions that may explain the clinical picture, such as pneumothorax, lobar atelectasis, or pneumonia.

The advantages and disadvantages of D-dimer assays are the same for patients with suspected PE and for patients with suspected DVT. The D-dimer test is most useful in hemodynamically stable patients with

otherwise a low or intermediate clinical risk for a PE, because a negative test can prevent further workup.

For many years, the ventilation/perfusion (V/Q) scan has been the cornerstone of the diagnostic work-up for suspected PE. The study uses two scans: one after intravenous injection of a radioisotope to evaluate lung perfusion and the other after inhalation of the radioisotope for evaluation of ventilation. The results of the scan are read as normal or as demonstrating low, intermediate, or high probability of PE depending on the level of V/Q mismatch. The main disadvantage is coexisting lung disease affects the interpretation of the ventilation scan and, to some extent, the perfusion scan. Thus, the diagnostic interpretation of V/Q scans is difficult and many times its results are interpreted as inconclusive, which severely limits its clinical utility.

Pulmonary angiography is the gold standard for the diagnosis of PE but is only performed if other less-invasive tests fail to confirm or rule out diagnosis of PE. The procedure begins with catheterization of a central vein; the catheter is advanced through the right heart to the pulmonary artery. The lobar or segmental arteries should be injected selectively. The presence of an intraluminal filling defect on two angiographic views is considered diagnostic for PE. Secondary diagnostic criteria are reduced flow, tortuous peripheral vessels, and delayed venous phase.[42]

Because pulmonary angiography is the most invasive method of diagnosing PE, it is associated with the highest rate of complications. The risk of mortality and serious complications after pulmonary angiography is estimated at less than 2% and 5%, respectively.[43] Most complications are related to the contrast agent and the catheterization procedures used, but some critically ill patients with pulmonary hypertension and cor pulmonale may experience severe hemodynamic compromise and even cardiac arrest.[44]

Technological advances in CT scanning during recent years have increased the use of this diagnostic method. During the past decade, the use of helical and multidetector computed tomography pulmonary angiography (CT-PA) as part of the diagnostic work-up for PE has gained increasing popularity, and in most centers, CT-PA has been adopted as the main diagnostic method for patients with suspected PE. CT-PA is appealing because it is less invasive than pulmonary angiography and because it can also demonstrate other pathological conditions of the thorax. The main disadvantage of CT-PA is that it only poorly shows peripheral areas and horizontally oriented vessels; however, with the advent of high-resolution multidetector CT scanners, this may be less of an issue. CT-PA undoubtedly misses some peripheral PEs, but the clinical relevance of peripheral PEs is uncertain. In the largest study to date (PIOPED II), the sensitivity and specificity of CT-PA in detecting PEs was estimated at 83% and 96%, respectively.[40] Moreover, combination of CT-PA with venous-phase imaging increased the diagnostic sensitivity of this modality to 90%.[45]

The newest method for diagnosing PE is magnetic resonance angiography (MRA). In two prospective studies of patients with suspected PE, MRA showed a sensitivity ranging between 78% and 83% and a specificity ranging between 98% and 100%.[46,47] MRA imaging has not been evaluated in large, controlled studies, and there is not enough information to support the routine use of this costly method. However, MRA may prove useful in patients with iodine contrast allergies or in instances where radiation exposure should be avoided (i.e., pregnancy).

Although transthoracic or transesophageal echocardiography has occasionally demonstrated an embolus in the main pulmonary artery, the most common use of these studies is to evaluate right heart dysfunction. Right heart failure is the most common cause of death for patients who suffer a massive PE. Although global or regional right ventricle dyskinesia is evident in more than 80% of patients with PE, it is nonspecific for diagnosis and can be associated with other clinically similar conditions such as chronic obstructive pulmonary disease. The role of echocardiography in diagnosing PE remains minimal.

Currently, researchers are investigating new detection techniques to more safely diagnose acute pulmonary emboli using single-photon emission CT after administration of monoclonal antibodies that bind to D-dimer regions of fibrin.[48]

The findings are promising thus far, but further investigation is necessary.

29.3.3 Prophylaxis

Prophylaxis is the first line of defense against VTE. Evidence-based clinical practice guidelines stratify surgical patients by risk and offer alternatives for treatment and prevention of DVT and PEs[15] (refer to Section 29.4 for details).

29.3.4 Treatment

Therapeutic anticoagulation is the main treatment modality for PE. This therapy reduces the risk of proximal thrombus propagation in the deep vein system and in the pulmonary arteries and reduces the risk of recurrent PE. Guidelines for the treatment of VTE[24] apply to patients with DVT and PE (refer to Section 29.5 for details regarding suggested treatment guidelines, duration of therapy, and therapeutic alternatives). However, some exceptions exist. Specifically, for patients diagnosed with PE who present with concomitant hypotension, recent

guidelines suggest treatment with short (2 h) infusion thrombolytic therapy if patients are at low risk for bleeding. Thrombolysis is associated with a reduction in mortality and recurrent PE and is associated with an increase in major bleeding in hemodynamically unstable patients otherwise refractory to anticoagulant therapy. Patients with PE and hypotension who have contraindications to thrombolysis, failed thrombolysis, or are likely to die due to shock should undergo catheter-assisted embolectomy, and if catheter-assisted embolectomy fails or is not available, surgical pulmonary embolectomy should be performed[24]. The most serious risk is bleeding, but this should be weighed against the high mortality rates experienced by patients with massive pulmonary emboli who are in an unstable condition.

There is no universal agreement about the indications for IVC filter insertion. Most physicians agree that an IVC filter should be placed in patients who have survived a massive PE but whose cardiopulmonary reserve is so limited that another embolic event would be devastating. The same holds true for patients who have undergone pulmonary embolectomy. Furthermore, guidelines support the use of IVC filter in patients with a documented PE and absolute contraindication to anticoagulation.[24] The primary controversy is related to the use of an IVC filter as a prophylactic measure for high-risk patients who have not experienced a documented thromboembolic event. Currently, no studies support the routine use of IVC filters for these patients as prophylaxis against PE.

IVC filters are inserted percutaneously via a femoral or jugular approach and are commonly positioned below the renal veins. The complications associated with the use of IVC filters can be early or late. The most common early complication is thrombosis of the superficial femoral vein; this complication is related to the size of the introducer. The recent development of introducers with smaller diameters may reduce the incidence of this complication. Other early complications include malpositioning, dislodgement, or tilting of the filters. IVC thrombosis occurs in 2%–20% of cases, but recanalization will occur within 4 years in almost all cases. The most common late complication is DVT. About half of patients with permanent IVC filters will experience DVT, and most of them will exhibit clinical symptoms of venous insufficiency.[49] Recurrent PE after insertion of an IVC filter has been reported to occur in 3% of patients, mainly those with chronic hypercoagulable conditions such as cancer.[50]

The use of retrievable filters has become commonplace, but controversy as to when to remove, as well as the low (50%) rate of removal due to patient loss to follow-up, has kept this modality from becoming the gold standard.

Catheter-directed embolectomy involves reduction of thrombus burden via a catheter by a variety of techniques, including rheolytic embolectomy, rotational embolectomy, suction embolectomy, thrombus fragmentation, and ultrasound plus thrombolytic agents. Currently, there are no large studies or randomized controlled trials to evaluate outcomes using this interventional technique, and the published literature has been mostly limited to small case series. The use of these techniques is limited to patients with PE, hemodynamic instability, and who have contraindications to or have failed thrombolytic therapy.[24]

Another treatment option for patients with massive PE whose condition is rapidly deteriorating is surgical pulmonary embolectomy. This procedure is a valid option, especially when thrombolysis has failed or is contraindicated, and catheter-directed embolectomy has failed or is not available. The mortality rate associated with this procedure has been reported to be as high as 75%. No randomized trial has evaluated the efficacy of surgical pulmonary embolectomy in patients with PE. Most authorities recommend the placement of an IVC filter after embolectomy.

Incidence of VTE-Related Complications

Complications	Incidence	References
Deep vein thrombosis	0.48 per 1000	Silverstein et al.[2]
Pulmonary embolus	0.69 per 1000	Silverstein et al.[2]
Post-thrombotic syndrome	30%	Kahn et al.[26]
VTE recurrence	30%	Prandoni et al.[30]

How to Avoid VTE-Related Complications

Complications	Method of Avoidance	References
Deep vein thrombosis	VTE prophylaxis	Gould et al.[15]
Pulmonary embolus	VTE prophylaxis	Gould et al.[15]

References

1. Office of the Surgeon General (US); National Heart, Lung, and Blood Institute (US). The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. Rockville (MD): Office of the Surgeon General (US); 2008. Available from: http://www.ncbi.nlm.nih.gov/books/NBK44178/
2. Silverstein MD, Heit JA, Mohr DN et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. *Arch Intern Med*. 1998;158(6):585–593.
3. Lippi G, Franchini M. Pathogenesis of venous thromboembolism: When the cup runneth over. *Semin Thromb Hemost*. 2008;34(8):747–761.

4. Greenfield LJ, Proctor MC, Rodriguez JL et al. Posttrauma thromboembolism prophylaxis. *J Trauma* 1997;42(1):100–103.
5. Caprini JA. Risk assessment as a guide for the prevention of the many faces of venous thromboembolism. *Am J Surg*. 2010;199(1 Suppl):S3–S10.

   This article discusses the value and need for risk assessment to identify and prevent thromboembolic disease.
6. McLachlin J, Richards T, Paterson JC. An evaluation of clinical signs in the diagnosis of venous thrombosis. *Arch Surg*. 1962;85:738–744.
7. Bates SM, Jaeschke R, Stevens SM et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Diagnosis of DVT, 9th edn. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. *Chest* 2012;141:e351S–e418S.
8. Adam SS, Key NS, Greenberg CS. D-dimer antigen: Current concepts and future prospects. *Blood* 2009; 113:2878–2887.
9. Tan M, van Rooden CJ, Westerbeek RE et al. Diagnostic management of clinically suspected acute deep vein thrombosis. *Br J Haematol*. 2009;146(4):347–360.
10. Kearon C, Julian JA, Newman TE et al. Noninvasive diagnosis of deep venous thrombosis: McMaster diagnostic imaging practice guidelines initiative. *Ann Intern Med*. 1998;175:639–644.
11. Wicky J, Bongard O, Peter R et al. Screening for proximal deep venous thrombosis using B-mode venous ultrasonography following major hip surgery: Implications for clinical management. *Vasa* 1994;23:330–336.
12. Kearon C. Noninvasive diagnosis of deep vein thrombosis in postoperative patients. *Semin Thromb Hemost*. 2001;27(1):3–8.
13. Prandoni P, Polistena P, Bernardi E et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. *Arch Intern Med*. 1997;157(1):57–62.
14. Thorson CM, Ryan ML, Van Haren RM et al. Venous thromboembolism after trauma: A never event? *Crit Care Med*. 2012;40(11):2967–2973.
15. Gould MK, Garcia DA, Wren SM et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Prevention of VTE in nonorthopedic surgical patients, 9th edn. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. *Chest* 2012;141:e227S–e277S.

   This is essential as a well researched guide for thromboprophylaxis and is updated every four years.
16. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg*. February 1972; 104(2):134–144.
17. Tapson VF, Carroll BA, Davidson BL et al. The diagnostic approach to acute venous thromboembolism. Clinical practice guideline. American Thoracic Society. *Am J Respir Crit Care Med*. 1999;160(3):8.
18. Tan M, van Rooden CJ, Westerbeek RE et al. Diagnostic management of clinically suspected acute deep vein thrombosis. *Br J Haematol*. 2009;146(4):347–360.
19. Katz DS, Loud PA, Bruce D et al. Combined CT venography and pulmonary angiography: A comprehensive review. *Radiographics* 2002;22:S3–S24.
20. Garcia DA, Baglin TP, Weitz JI et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Parenteral Anticoagulants, 9th edn. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. *Chest* 2012;141:e24S–e43S.
21. Ginzburg E, Cohn SM, Lopez J et al. Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *Br J Surg*. 2003;90:1338–1344.
22. Lin H, Faraklas I, Saffle J et al. Enoxaparin dose adjustment is associated with low incidence of venous thromboembolic events in acute burn patients. *J Trauma* 2011;71(6):1557–1561.
23. Phelan HA, Wolf SE, Norwood SH et al. A randomized, double-blinded, placebo-controlled pilot trial of anticoagulation in low-risk traumatic brain injury: The delayed versus early enoxaparin prophylaxis I (DEEP I) study. *J Trauma* 2012;73:1434–1441.

   This article discusses the need for thromboprophylaxis in brain injured patients as well as providing guidance on timing of chemoprophylaxis.
24. Kearon C, Akl EA, Comerota AJ et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease, 9th edn. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. *Chest* 2012;141:e419S–e494S.
25. Holbrook A, Schulman S, Witt DM et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Evidence-based management of anticoagulant therapy, 9th edn. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. *Chest* 2012;141:e152S–e184S.
26. Kahn SR, Kearon C, Julian JA et al. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. *J Thromb Haemost*. 2005;3(4):718–723.
27. Bernardi E, Prandoni P. The post-thrombotic syndrome. *Curr Opin Pulm Med*. 2000;6(4):335–342.
28. Milne AA, Ruckley CV. The clinical course of patients following extensive deep venous thrombosis. *Eur J Vasc Surg*. 1994;8(1):56–59.
29. Patel NH, Plorde JJ, Meissner M. Catheter-directed thrombolysis in the treatment of phlegmasiaceruleadolens. *Ann Vasc Surg*. 1998;12:471–475.
30. Prandoni P, Villalta S, Bagatella P et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997;82(4):423–428.
31. Anderson Jr FA, Wheeler HB, Goldberg RJ et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med*. 1991;151:933–938.
32. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: Evidence of overdiagnosis. *Arch Intern Med*. 2011;171:831–837.
33. Sevitt S, Gallagher N. Venous thrombosis and pulmonary embolism: A clinico-pathological study in injured and burned patients. *Br J Surg*. 1961;48:475–489.

34. Geerts WH, Heit JA, Clagett GP et al. Prevention of venous thromboembolism. *Chest* 2001;119:132S–175S.
35. Carson JL, Kelley MA, Duff A et al. The clinical course of pulmonary embolism. *N Engl J Med*. 1992;326: 1240–1245.
36. Winchell RJ, Hoyt DB, Walsh JC et al. Risk factors associated with pulmonary embolism despite routine prophylaxis: Implications for improved protection. *J Trauma* 1994;37:600–606.
37. Owings JT, Kraut E, Battistella F et al. Timing of the occurrence of pulmonary embolism in trauma patients. *Arch Surg*. 1997;132:862–867.
38. O'Malley KF, Ross SE. Pulmonary embolism in major trauma patients. *J Trauma* 1990;30:748–750.
39. The urokinase pulmonary embolism trial: A national cooperative study. *Circulation* 1973;47:II1–II108.
40. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 1990;263:2753–2759.
41. Stein PD, Terrin ML, Hales CA et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Chest* 1991;100:598–603.
42. Newman GE. Pulmonary angiography in pulmonary embolic disease. *J Thorac Imaging* 1989;4:28–39.
43. Stein PD, Athanasoulis C, Alavi A et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 1992;85:462–468.
44. Hofmann LV, Lee DS, Gupta A et al. Safety and hemodynamic effects of pulmonary angiography in patients with pulmonary hypertension: 10-year single-center experience. *Am J Roentgenol*. 2004;183:779–786.
45. Stein PD, Fowler SE, Goodman LR et al. and PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. 2006;354:2317–2327.

    This is an important study substantiating the use of CT angiography for pulmonary embolus detection but brings to light the provocative nature of occult asymptomatic pulmonary emboli.
46. Oudkerk M, van Beek EJ, Wielopolski P et al. Comparison of contrast-enhanced magnetic resonance angiography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: A prospective study. *Lancet* 2002;359:1643–1647.
47. Pleszewski B, Chartrand-Lefebvre C, Qanadli SD et al. Gadolinium-enhanced pulmonary magnetic resonance angiography in the diagnosis of acute pulmonary embolism: A prospective study on 48 patients. *Clin Imaging* 2006;30:166–172.
48. Hassoun PM, Adnot S. Update in pulmonary vascular diseases 2011. *Am J Respir Crit Care Med*. 2012;185:1177–1182.
49. Patton JH Jr, Fabian TC, Croce MA et al. Prophylactic Greenfield filters: Acute complications and long term follow-up. *J Trauma* 1996;41:231–236.
50. David W, Gross WS, Colaiuta E et al. Pulmonary embolus after vena cava filter placement. *Am Surg*. 1999;65:341–346.

30

Complications of Endovascular Procedures

Boulos Toursarkissian

CONTENTS

30.1 Introduction

Endovascular procedures have replaced a good number of open vascular procedures but are associated with unique sets of complications. Complications of peripheral endovascular interventions can be divided into access site complications, systemic complications, and procedure-related specific complications. Access site complications consist of pseudoaneurysm and hematoma formation, external or retroperitoneal bleeding, vessel infections, vessel thrombosis, and obstruction from the sheath. Systemic complications include allergic reactions and renal dysfunction. Procedure-related complications are those brought on by the actual therapeutic procedure attempt and include vessel perforation or rupture, vessel thrombosis, spasm, distal embolization, dissection, recoil, vessel infection, inadequate stent deployments, and persistent aneurysm perfusion after stent grafting. Complications associated with carotid stenting and endovenous procedures will also be discussed.

30.2 Access Site Complications

These are the most common complications of peripheral interventions. They occur in nearly 2%–6% of cases, depending upon the definition used [1,2]. Among access site complications, bleeding and hematoma formation are the most common [3].

Risks factors for hematoma formation include use of anticoagulants, calcified access vessel, sheath exchanges, larger sheath sizes, obesity, advanced age, access in the superficial or profunda femoral, and female gender. Management should consist of manual compression when the hematoma is identified in the acute setting. Compression adjuncts include the use of a FemStop device (St. Jude Medical, Minnesota) or C clamp. An ultrasound may be needed to rule out associated pseudoaneurysm, or a contrast-enhanced CT scan may be needed if there is suspicion of active ongoing bleeding. Transfusion or fluid resuscitation may be required. Only a minority of patients will require surgical evacuation. Indications would include ongoing bleeding with

hemodynamic compromise, adjacent nerve compression, and possibly impending skin necrosis. Wound complications are common postoperatively.

Pseudoaneurysm formation is likely the second most common access site complication. The risk factors are the same as for bleeding problems. Faulty compression technique and incorrect puncture sites are also risk factors. Most are identified a day or two following catheterization as a pulsatile lump with a bruit. Management options include observation for small lesions given a high likelihood of spontaneous resolution in the absence of anticoagulants. Active treatment options include ultrasound-guided compression of the neck of the pseudoaneurysm to induce thrombosis, ultrasound-guided thrombin injection into the pseudoaneurysm to also induce thrombosis, and finally surgical repair. Surgical repair is usually reserved for cases having failed other management options. Other indications for surgical repair include suspicion of infection, continued expansion, and adjacent nerve compression.

Retroperitoneal hematoma formation is probably the most dangerous of the access site complications and is specifically related to femoral access. The most important risk factors is a proximal puncture site. Signs may be subtle and include flank pain without any groin manifestations. Hemodynamic instability is frequent. A contrast-enhanced CT scan is the best diagnostic method. Management includes resuscitation as needed, serial hematocrit monitoring, and reversal of anticoagulation. If these measures do not succeed, open operative repair may be needed. An alternative approach is stent graft coverage of the leak point from a contralateral approach, if the access site is proximal enough.

Arteriovenous fistula formation is a relatively uncommon access site complication [4]. A bruit is the most common finding. Rarely do they cause high output heart failure because of low flows. They have a high incidence of spontaneous resolution. Covered stents have limited applicability because of their risk of fracture and thrombosis, especially in the groin. Surgical repair is an option for persistent problematic fistulas; scarring is often present in the groin.

Access vessel thrombosis may happen when dealing with small or diseased vessels, large sheath sizes, vigorous compression, prior vessel reconstruction or prosthetic graft, or in cases of closure device malfunction. It can also happen when no anticoagulation is used, and clot develops around the sheath. The incidence is about 0.5%. Symptoms of limb ischemia are often evident following sheath removal. Open surgical intervention is preferred with thrombectomy and arterial reconstruction. In other cases, the patient may present later with new onset claudication or rest pain.

Pain in the groin can develop after arterial access in the absence of vascular complications. It is believed to occur due to trauma to the nerve bundle, possibly with scar formation. It has a low incidence of 0.2%. An ultrasound evaluation is indicated and is often normal. Treatment with gabapentin or one of its derivatives can be useful in such cases. Injection therapy is reserved for refractory cases. Nerve dysfunction is more common when brachial or axillary access is used. It can be due to nerve compression in the bundle from a hematoma. In those cases, open surgical nerve decompression is needed to prevent long-term sequelae.

Access vessel infection can rarely happen. It is uncommon in the absence of a hematoma or pseudoaneurysm formation or closure device use. An ultrasound should be done for evaluation. Antibiotics administration and drainage of any abscess is warranted.

Technical tips for avoiding access site complications. It is important to try to access the vessel over a bony area to facilitate subsequent compression. Too high of a stick in the groin predisposes to retroperitoneal hemorrhage and too low predisposes to pseudoaneurysm hematoma or thrombosis. Visualization of landmarks under fluoroscopy is therefore important. It is better to avoid punctures to the posterior wall or access through the lateral walls of the vessel since compression becomes problematic. Compression should be sufficient to control bleeding while maintaining forward flow in the vessels.

Vascular closure devices are widely used for hemostasis. Opinions differ as to whether they decrease the incidence of local access site complications, and most feel that they probably do not. They do, however, allow earlier ambulation and potential earlier discharge of the patient. They also allow earlier removal of the sheath before full reversal of any anticoagulation [5,6]. They can still cause any of the complications listed earlier. Predisposing factors for complications from closure devices include diseased access vessels, especially if small, and calcification. Bleeding and pseudoaneurysm formation are still the most common, from closure device malfunction. Vessel thrombosis is likely the second in frequency, with some devices that use intra-arterial components being more predisposed to that. Vessel thrombosis or narrowing leading to limb ischemia is seen more frequently with closure devices than with manual compression, with an incidence nearing 0.5% [5,7]. Furthermore, they can be associated with superficial or deep infection, at a rate higher than seen with manual compression. A high index of suspicion for those must be kept. In addition to antibiotics, open surgical management may be required, including possibly autogenous vessel reconstruction.

Brachial artery access is associated with slightly higher risk of complications than femoral access, up to 6.5% [8]. Thrombosis may happen in up to 2% of cases due to the smaller size and vasoreactivity of the artery. This usually requires open surgical thrombectomy.

Prevention includes use of anticoagulants and injection of vasodilators locally through the sheath. Even small hematomas in the brachial position may cause median nerve compression, with resultant numbness and tingling in the hand. They should be treated by prompt surgical decompression.

30.3 Systemic Complications

30.3.1 Renal Failure

The most feared complication is the development of renal failure due to contrast-induced nephropathy. It typically happens within 48–72 h after contrast exposure and is not attributable to other causes. The most common definition in the literature is a 25% increase in baseline serum creatinine at 48 h [9]. The risk factors for this complication include the use of ionic or high osmolarity agents, preexisting renal insufficiency (GFR <60 mL/min), diabetes, heart failure, dehydration, advanced age, concurrent use of nephrotoxic agents, hypotension, intra-arterial versus intravenous contrast use, and increasing volumes of contrast agent used [10]. In patients with normal renal function, the incidence is <1%–2%, whereas diabetic patients with preexisting insufficiency may have an incidence as high as 10%. Hydration is the most important measure for prevention [11]. Some studies support the use of a bicarbonate solution whereas others have found a saline solution just as efficacious [12]. Limiting the amount of contrast is also important. The use of acetylcysteine mucomyst showed initial promise but larger randomized studies have failed to consistently show a benefit, and even meta-analyses published have given different recommendations [9,13].

30.3.2 Allergic Reactions

Allergy to contrast agents is not infrequent (<5%) and is treated by premedication with steroids and H1 and H2 blockers. It can range from a mild rash and wheezing to anaphylaxis. Nonionic contrast has a lower incidence and should be used when an allergy history is present.

Vasovagal reactions are more common than allergic reactions and are due often to reaction to pain or skin puncture. Bradycardia and hypotension can be seen and are treated symptomatically with fluids and possibly atropine.

Heparin allergy can be seen in up to 5% of patients undergoing peripheral interventions [14]. Unsuspected thrombotic complications during the procedure should raise possible awareness. Other symptoms can include fever, chills, hypertension tachycardia, and dyspnea within 30 min of heparin bolus. In those cases, in addition to supportive measures, switching to alternative direct thrombin antagonists such as argatroban or bivalirudin should be considered.

30.4 Procedure-Specific Complications

30.4.1 Wire-Induced Complications

These include creation of a dissection and perforation, as well as spasm.

Dissection is more likely to occur with hydrophilic wires. A retrograde dissection may not require treatment as it is tacked down by the flow. An antegrade dissection may require stenting for control. Prevention of dissection requires constant visualization of the wire as it is advanced. Any coiling or resistance should prompt wire redirection.

It is important to make sure the tip of the wire is in the true lumen before proceeding with any intervention. If not sure, a thin diagnostic catheter should be advanced over the wire, the wire withdrawn, and a gentle hand injection of contrast done through the catheter to verify intraluminal positioning.

Perforation is more likely to occur with stiffer wires, especially across tortuous anatomy. It can also happen with other wires when used to attempt crossing a chronic total occlusion (CTO). In cases of perforation, it is important to try to maintain or achieve wire access across the area of perforation. Prolonged balloon inflation may control the situation. In some cases, a covered stent may be required. Occasionally, an open surgical conversion may be needed. In perforation during attempted CTO crossing, the wire may sometimes be redirected in the true lumen or subintimal space and the situation may be controlled and treated with angioplasty or stenting. When this is not successful, it is sometimes necessary to use coil embolization of the bleeding segment to control hemorrhage. Perforation can also happen during renal or visceral angioplasty if the end of the wire is allowed to advance too much, leading to end organ perforation. In some of those cases, conservative management may succeed, although it is sometimes necessary to perform coil or particulate selective embolization for control of the bleeding.

Spasm can occur with any kind of vessel but is more likely in noncalcified, smaller diameter vessels, especially with any motion of the wire within the vessel. The use of embolic protection filters at the end of wires is also a predisposing factor to spasm. It is important to visualize the vessel in many panes to make sure one is not

dealing with an unsuspected dissection, distal embolization, or thrombus formation. Spasm can be treated by intra-arterial injection of nitroglycerin or papaverin and sometimes by judicious wire withdrawal. Angioplasty of the spasming vessel may not always succeed but may cause additional spasm.

In cases of preexisting stents that need to be crossed, it is important to make sure the wire is staying in the lumen and is not going around struts of the stents. Visualization under magnified views is important, as well as the absence of any resistance while trying to advance devices or catheters over the wire.

30.4.2 Angioplasty-Induced Complications

These include dissection, perforation, thrombosis, AV fistula creation, and distal embolization.

Dissection is particularly common with angioplasty. They may be more common if the balloon is slightly oversized or the lesion more heavily calcified. Opinions differ as to whether cutting or scoring balloons have a lower likelihood of causing dissections. These balloons have blades or wires mounted on them to create more controlled cuts. Not all dissections require treatment. If minimal or not flow limiting, they can be observed. If not, the first measure consists of a prolonged inflation of the balloon. If not successful, a directional atherectomy may be attempted to excise the dissection flap. This carries a slight risk of perforation. Stenting is most commonly applied to treat flow-limiting dissections.

Perforation is more likely with eccentric, calcified plaques. It may occur in as many as 1% of iliac angioplasties and 4% of peripheral angioplasty procedures [15,16]. It is paramount to maintain wire access across the perforation. Immediate control should consist of inflation of a compliant balloon across the perforation to control hemorrhage and allow any needed resuscitation. Angioplasty may control the problem, but more frequently a covered stent will be required. If those are not available, an open surgical approach may be needed; in that case, balloon control should be maintained while arrangements for surgery are made. Occlusion devices may sometimes be used for control of bleeding, provided revascularization is then achieved by a different means, often surgical.

Thrombosis of an angioplasty site is often due to an unrecognized dissection with thrombus formation. It is sometimes due to inadequate runoff in the bed distal to the angioplasty site. Systemic causes must be kept in mind such as inadequate anticoagulation or heparin allergy. Aspiration with a catheter or a rheolytic device must be carried out, followed by treatment of the underlying cause.

AV fistula creation is a variant of a perforation, although less severe. It is often seen during attempts to cross CTO. It rarely has any hemodynamic consequences; if significant, prolonged angioplasty or a covered stent can be considered.

Embolization may occur during wire crossing of a lesion or as a result of plaque debris being dislodged during ballooning or stenting. Any thrombus that forms at a treated lesion may also embolize distally. Emboli may be large, causing obvious distal runoff occlusion or more often may be microscopic and more difficult to appreciate [17]. They are more likely to occur with total occlusions. Prevention with use of distal embolic protection devices or filters should be considered in those cases, as well as in cases of compromised distal runoff such as single vessel runoff. When embolization does occur, thromboaspiration may be attempted with catheters with or without thrombolytics use [18].

Restenosis is a significant late complication of angioplasty, occurring in 15%–50% of cases depending on locations. The risk factors include longer lesions, more distal disease, poor runoff, continued smoking, diabetes, and occlusion as opposed to stenoses. Angioplasty with drug-eluting balloons such as paclitaxel holds promise in reducing rates of restenosis.

30.4.3 Stent-Related Complications

These include many of the same ones seen with angioplasty such as perforation, thrombosis and distal embolization, as well as restenosis. Specific stent-related complications include stent migration, nonexpansion, covering of side branches, and stent infection.

Migration refers to the stent ending at a different area of the vessel. This can happen because of inaccurate sizing leading to a stent not opposed to the wall, and subsequent distal migration of the stent. It can also refer to a shearing off of a balloon-expandable stent from the balloon during attempted delivery. This may occur because of vessel tortuosity or lack of sufficient predilatation of the lesion being treated. Preventive measures include adequate predilatation and possibly crossing the lesion with a sheath or guiding catheter, advancing the stent and then withdrawing the sheath before stent deployment. If a stent is sheared off, it may have to be deployed where it ends; a thin, small-diameter balloon is advanced over the wire through the stent, inflated, and followed by progressively larger balloons until the stent is adequately expanded. Alternatively, the stent may be retrieved into the sheath using a snare.

Nonexpansion refers to a failure of the stent to reach its full diameter or the diameter of the vessel around a residual lesion. It is usually due to a focally heavily calcified lesion. Sometimes, a short, high-pressure balloon may succeed. The major risk is rupture of the vessel and covered stents should be available for bail out if such a maneuver is attempted. Prevention might

involve debulking the lesion with atherectomy prior to stent deployment, although this is not always possible if a recanalization is subintimal.

Unintentional coverage of side branches is more likely with self-expanding stents than balloon-expandable ones. It may not result in any impaired flow to the side branch, in which case no specific treatment may be required. If flow is compromised, an attempt should be made to direct a wire into the lumen of the side branch through the struts of the stent. This is followed by balloon dilation of this passage, which essentially enlarges a cell of the offending stent. If the offending stent is a balloon-expandable one, this may be sufficient. If it is a self-expanding stent, the dilated cell will recoil once the balloon is deflated and it will be necessary to hold the passage open with a balloon-expandable stent of the proper size deployed through the struts of the first stent.

Infections of bare metal stents are rare. They can happen because of contamination at the time of insertion or because of late bacteremia. They can manifest as an infected pseudoaneurysm, persistent bacteremia, distal septic embolization, or vessel rupture. Open surgical treatment is often needed with vessel and stent excision and extra-anatomic revascularization [19].

Complications are more likely when stents are used for total occlusions. In a recent review of iliac occlusions treated with stenting, rupture occurred in 3%, embolization in 3%, and hypogastric artery occlusion in 7% [20].

30.4.4 Atherectomy-Related Complications

These are the same as angioplasty and stenting complications, although perforation and distal embolization are the two most frequently encountered, with an incidence of 3%–4% for each. Heavily calcified lesions are prone to embolization, regardless of the type of device used. Device oversizing or aggressive cutting at branch points especially may lead to perforation. The majority of perforations respond to prolonged low-pressure balloon inflations. Rotational atherectomy can sometimes lead to a transient distal no-flow phenomenon. It can be due to spasm with a heavy microembolic load. Vigorous use of vasodilators with or without lytic injection or thromboaspiration often leads to a resolution of the problem.

30.4.5 Peripheral Stent Graft–Related Complications

Stent grafts are used to treat complications of other endovascular procedures or sometimes for recanalizing CTO or covering embolizing lesions. It is very important to size those self-expanding stent grafts very carefully. Any oversizing has potential to lead to infolding of the fabric with resultant thrombosis. For the same reason, the stent graft should then be molded to its nominal size with an appropriate diameter balloon.

Thrombosis of peripheral stent grafts usually has worse implications than uncovered stents in terms of limb ischemia, likely because of the loss of collaterals that have been covered by the stent graft.

30.4.6 Thrombolysis-Related Complications

Bleeding complications can be amplified with thrombolysis, either locally at access sites or systemically if a lytic state is achieved [21] In addition to the sheath access site, possible bleeding sites include the retroperitoneum, although the most feared site is intracranial because of the associated morbidity. Risk factors for such bleeds include prolonged infusions (>24 h), advanced age, and systemic anticoagulation. Risk of intracranial bleed is <1%. Serum fibrinogen levels are not always predictive, although a decline to under 100 mg/dL should prompt caution. Serial hematocrits should be followed and any decline investigated.

Distal embolization due to fragmentation of the clot being treated can take place. Usually it is addressed by advancing the infusion catheter and doing directed lysis delivery in the vascular bed affected.

There is also a risk of a clot developing in or around the indwelling sheath during prolonged infusion. For that reason, as well as because of the risk of distal embolization listed earlier, a low-dose heparin infusion is usually given through the sheath.

30.4.7 Complications of Endovascular AAA Repair

A majority of AAAs are being managed by endovascular stent grafting today. These procedures have a unique set of potential complications. These include iliac artery injuries as well as problems related to fixation or migration of the stents grafts and inadequate AAA exclusion. Up to 20% of patients will require reintervention on long-term follow-up, the majority for endoleaks [22].

Iliac artery injuries happen because of the large size of the delivery systems used. They are more common with the larger thoracic stent grafts. Other risk factors include female sex (smaller vessels), calcification, and tortuosity. Depending on the definition, it may happen up to 15% of the time [23]. In cases of difficult access, it may be preferable to get iliac access via a retroperitoneal exposure. Completion imaging after delivery sheath removal is paramount to identify these problems, and wire access should be maintained to allow endovascular control. Simple dissections can be stented. Ruptures will cause profound hemodynamic instability after sheath removal. Immediate control of the bleeding can be achieved with a large compliant balloon. Stent grafts

should be available to try to control the rupture. If this is not successful, open repair may be warranted.

A type 1 endoleak represents an attachment site failure, proximally or distally [24,25]. Perfusion is maintained to the AAA sac around the stent graft. A type 1 endoleak needs treatment in order to prevent aneurysm sac rupture. Type 1 endoleaks will happen 5%–10% of the time on follow-up, depending on the population study and how well the device IFU are followed. Shorter necks, increasing angulation, increased calcification or thrombus in the neck are risk factors for type 1 endoleaks. Endovascular options (cuff, angioplasty, bare stent, or endoluminal stapler) or open surgical conversion should be entertained for treatment.

A type 2 endoleak indicates flow around the stent graft in the aneurysm sac, usually from the lumbar or inferior mesenteric arteries. Type 2 endoleaks happen in 15%–20% of cases early after stent-grafting. Increasing number of patent lumbars or a patent IMA are risk factors. A majority of these will resolve with observation, and a period of observation can be recommended in the absence of aneurysm enlargement. Type 2 endoleaks can be associated with AAA sac enlargement in up to a quarter of cases, and up to 20% of ruptures after EVAR are due to type 2 endoleaks. In general, in the case of AAA enlargement (more than 5 mm in 6 months or more than 10 mm from pre-EVAR size), intervention should be considered. The endoleak can often be addressed by endovascular means (coil embolization of feeding vessels, obliteration of the cavity with bioglue); other options include surgical control of the feeding vessels, or plain stent graft explantation and open conversion.

Type 3 endoleaks represent fabric defects or leaks where stent graft modular components overlap. They can be seen early or late but are relatively uncommon. Stiffer devices likely have a higher risk of component separation with time. They should be treated whenever seen because of the risk of AAA rupture without treatment. Most can be addressed by endovascular means by relining with a new stent graft component.

Graft infection may happen after endovascular aneurysm repair, although the incidence of <1% is lower than that seen with open repair [26]. Prophylactic antibiotics should be given for prevention at the time of stent graft implantation. In the face in an infection, explantation will often be required with some sort of in situ or extra-anatomic reconstruction. Mortality remains high.

Other complications of stent grafting include limb thrombosis. It may occur acutely due to unrecognized iliac or femoral dissection or may be due to kinking or twisting of the limb. Completion angiography should help identify and control these. Late thrombosis may be due to kinking as the AAA shrinks. It may be corrected by lysis with adjunctive angioplasty or stenting; in some cases, a femoro-femoral bypass may be needed.

30.4.8 Complications of Carotid Stenting

Carotid artery stenting (CAS) can be used as an alternative to carotid endarterectomy (CEA) in selected patients. While the complications are for the most the same as with stenting in other locations, their implications and methods of management differ enough to warrant specific mention.

Stroke is the most feared complication. It happened in 4% of cases in the landmark CREST trial [27]. Neurologic events are more common in patients over the age of 80 as well as in symptomatic patients. Major strokes are less common than TIAs. Most neurologic events are believed due to embolization of particulate debris. Embolic protection filters certainly reduce the impact of such events but cannot stop them fully. Emboli may develop during angioplasty and stenting, but may also develop after filter removal as a result of "cheese-grating" of debris through the stent struts. Emboli may also occur during sheath placement, during initial attempt to cross the lesion with the wire, or during filter placement. Ideally, intracranial views have been obtained before any therapeutic maneuvers have been attempted. Microemboli are very frequent (up to 50% by transcranial dopplers) and most are asymptomatic or silent. If an event is detected during the procedure, it is important to visualize the intracranial circulation again in those cases to try to identify larger emboli that may then be retrieved with one of the available devices such as Merci or Penumbra. It is often necessary in those cases to convert to general anesthesia as patients experiencing a neurologic event will often get agitated and move; visualization is paramount to the delicate intracranial work required for embolic retrieval. Thrombolytic agents may be selectively used. The operator should also ensure that the patient is adequately anticoagulated with either heparin or one of the alternative agents. It is also important to monitor the blood pressure closely to make sure that hypotension is not an underlying cause of mental status alterations. If no macro-emboli are seen, anticoagulation alone may be used. If an event is detected after CAS procedure has been completed, it is important to start with a CT scan to rule out an intracranial hemorrhage. If negative, anticoagulation should be initiated and consideration given to return to the interventional suite for stent and intracranial imaging. If the deficit is very minor or transient, alternative imaging modalities such as CTA may be considered to evaluate the stent patency and look for any technical defects there that might require correction.

Acute stent thrombosis is uncommon, <1%. It can be associated with stroke, TIA, or be asymptomatic. It may be due to inadequate anticoagulation or technical issues with inadequate stent expansion or small carotid diameters. If identified early and symptomatic,

it can be treated with thromboaspiration and directed lytic therapy. An embolic protection device beyond the clotted segment is beneficial in preventing intracranial embolization. In some cases, conversion to open CEA may be needed. Based on empiric data, most patients undergoing CAS are on dual antiplatelets therapy with clopidogrel and aspirin. Addition of IIb/IIIa antagonists may be considered in thrombotic cases, although there are no large studies to support this approach.

Bradycardia is frequently seen during angioplasty or stent deployment and is due to baroreceptors stimulation. It can be sustained and lead to hypotension. Prophylaxis can be given in the form of glycopyrrolate or treatment in the form of atropine. One must be mindful of possible cardiac side effects. Hypotension can be managed with pressors or fluids.

Hypotension is seen in up to 10% of cases, during or after the procedure. Larger stents and one deployed more distally may have a higher risk. It may be prolonged for a couple of days and is managed in the manner described earlier.

Spasm may be noted in the internal carotid artery in 5%–10% of cases. It is usually at the site of filter deployment and can be managed by judicious intra-arterial injections of nitroglycerin.

Reperfusion symptoms may be seen in up to 2% of patients undergoing carotid revascularization. It is not immediate in onset but rather can be delayed. Risk factors are high-grade stenosis and hypertension. Ipsilateral headaches are the initial symptoms. They may be followed by seizures. Extreme cases will show CT evidence of cerebral edema or bleed. Control of hypertension is necessary. In some cases, prophylactic anti-seizure medicines may be beneficial.

Restenosis is seen in up to 10% of cases at 5 years. It is usually due to intimal hyperplasia. It can be treated by redilation. Treatment of comorbidities and use of statins may be of benefit in reducing this risk.

30.4.9 Complications of Venous Interventions

Venous interventions can be associated with inadvertent arterial punctures. It is important to manage those in the same way as any arterial access, with compression and reversal of anticoagulation. In some cases of a large sheath being introduced, a closure device can be considered in selected cases. In some situations, an open surgical cut down may be the best option. For areas difficult to access and/or to compress such as the subclavian artery, one can consider a covered stent graft from a different access site.

Vena cava filters can have a number of complications [28]. The most common can be thrombosis of the venous access site and thrombosis of the vena cava at the site of filter deployment. Access site thrombosis is usually managed as a DVT with anticoagulation if possible. Cava thrombosis management is individualized. Observation may be done if the patient is minimally symptomatic. Thrombolysis is rarely used since most of these cases are discovered in the chronic phase; if in the acute phase, most patients have a relative contraindication to lysis. In chronic cases with severe symptoms, there have been reports of endovascular recanalization followed by stenting of the filter against the caval wall; long-term results are not available. Alternatively open surgical caval reconstruction can be entertained. Either approach must be weighed against the risk of recurrent venous thromboembolism. Penetration of the caval wall by filter struts is not uncommonly seen. In the absence of penetration into adjacent organs, this can often be observed, and is not necessarily a contraindication to endovenous removal of retrievable filters. Frank perforation into the duodenum, aorta or vertebral bodies has been reported. Presenting symptoms can include GI bleed or persistent pain. Most of those cases are managed by open surgery with caval and associated organ reconstruction and repair [29]. Migration of a filter can occur acutely or chronically. Acutely, it is often due to technical mishap or to an oversized 30 mm diameter or more vena cava. *All filters except one are indicated only for cavas with diameters <26 mm. Only the Birdnest filter should be used for larger cavas. One has to be careful when sizing patients about the state of hydration as this can affect cava size, especially in trauma patients*. Migration of a filter in the heart can lead to arrhythmias and necessitates removal. Removal can be done with endovenous snares but may rarely require open surgery. *Tilting of a vena cava filter on the other hand is not uncommon. It does not usually affect the efficacy of the filer in preventing pulmonary emboli. One has to be sure however that the legs of the filter do not extend into large branches such as the renal veins. If that is the case, it might be best to retrieve the filter if possible and redeploy it*.

Venous stenting of the iliac veins is being increasingly performed for chronic stenoses and associated DVTs or leg swelling. Stent thrombosis is likely the most frequent complication of those cases and can be seen in nearly 15% of cases [30]. Some routinely use anticoagulants after these procedures for prevention, while others prefer clopidogrel treatment; there are no prospective trial comparisons of the two modalities, although it appears intuitive to recommend anticoagulants in patients with prior thrombotic episodes.

Stent migration can be a particular problem during stenting of inominate or superior vena cava lesions. This is due to the changes in sizes over short distances. Careful sizing and deployment are important maneuvers to minimize this complication.

Thrombolysis for DVT is commonly performed, either as pure pharmacologic or pharmacomechanical (PMT) using either the Angiojet or Trellis device [31].

Complications of such procedures include bleeding, hemolysis, hyperkalemia, pulmonary embolization, and recurrent thrombosis. PMT has a very low risk of bleeding problems (<1%) compared with pure pharmacologic methods. The risk of significant pulmonary embolism also appears low at <1%. Hemolysis is particularly common and manifested as dark colored urine, which should not be confused with hematuria. Prophylactic hydration measures should be carried out.

Endovenous treatment of refluxing superficial veins is a widely performed procedures for the management of venous insufficiency procedures. Treatment can be by radiofrequency or laser energy [32]. Both procedures are associated with a number of potential complications. DVT happens <1% of the time, saphenous nerve or other paresthesias <10%, and hematoma rarely. Radiofrequency may have less bruising and pain, although the rate of recanalization may be slightly higher. Prevention of complications is based on liberal use of tumescent anesthesia and adequate ultrasound visualization of the saphenofemoral junction to prevent protrusion of the catheters used into the femoral vein. Duplex ultrasound surveillance is then performed within days of the procedure to monitor for complications.

Sclerotherapy is often provided as an adjunct to varicose vein treatment. Extravasation of the sclerosing agent may lead to skin ulceration. The incidence is <1%. Allergic reactions and DVTs are rare.

Selected Complications and Their Incidence

Complications	Incidence (%)	References
Access site pseudoaneurysm	0.5–5	[1,2]
Access site AV fistula	1	[1,2,4]
Retroperitoneal hematoma	0.5	[3]
Femoral neuralgia	0.2	[1,2]
Vessel thrombosis from closure device	0.5	[1,2]
Renal failure	2	[9,10]
Heparin-induced thrombocytopenia	5	[14]
Wire complications	<5	Estimate
Perforation from angioplasty	1–4	[15,16]
Embolization during stenting	3	[17,18,20]
Intracranial bleed during thrombolysis	1	[21]
Type 1 endoleak from AAA stent graft	5	[24,25]
Type 2 endoleak from AAA stent graft	15–20	[22]
Stroke/TIA from carotid stenting	4	[27]
IVC filter access site thrombosis	1–2	[28]
Vena cava filter site thrombosis	2–5	[28]
Vena cava perforation from filter	1	[29]
DVT from EVLT or RFA	<1	[32]

Methods for Preventing and Identifying Selected Complications

Complications	Prevention Means
Access site issues (hematoma, PSA, RPH)	Visualize the common femoral artery fluoroscopically or by ultrasound; access over the femoral head, not low or high; avoid side punctures; apply adequate manual compression; judicious use of closure devices after femoral angiography.
Renal failure	Judicious hydration; control volume of contrast; use nonionic agents if possible.
Wire complications	Constant visualization of the wire as it is moved; avoid unnecessary wire motion during exchanges; soft-tipped wires for work wire; consider intra-arterial vasodilators for spasm prevention.
Angioplasty complications	Avoid oversizing to prevent rupture; look for dissection post angioplasty; avoid PTA in "nonstent" areas and consider alternative measures such as atherectomy; consider embolic protection devices for lesions at risk for embolization.
Stent complications	Judicious sizing to avoid migration; predilate lesion or precross with sheath to avoid stent slippage off balloon during advancement; sterile technique and prophylactic antibiotics to prevent infection; beware of heavily calcified lesions to avoid stent nonexpansion and consider present "debulking."
Atherectomy complications	Consider distal embolic protection device use for embolic protection; have stent grafts available for possible perforation treatment.
Thrombolysis complications	Avoid prolonged infusions to decrease the risk of bleeding; consider low-dose anticoagulants to avoid sheath thrombosis; serial blood and physical monitoring.
AAA stent graft complications	Careful patient selection to minimize chances of endoleaks; careful access evaluation to avoid iliac injuries and identify early; consider retroperitoneal conduits.
Stroke from CAS	Careful patient selection and technique, use of embolic protection devices.
Venous complications	Evaluate cave size to decrease likelihood of filter migration. Use tumescent anesthesia liberally to avoid skin burns or pains; visualize deep vein junction to avoid DVT risk.

References

1. Marso SP, Amin AP, House JA et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA*. 2010; 303: 2156–2164.
2. Tonnessen BH. Iatrogenic injury from vascular access and endovascular procedures. *Perspect. Vasc. Surg. Endovasc. Ther*. 2011; 23(2): 128–135.

3. Doyle BJ, Ting HH, Bell MR et al. Major femorla bleeding complications after percutaneous coronary intervention: Incidence, predictors and impact on long term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. *JACC: Cardiovasc. Interv*. 2008; 1: 202–209.
4. Perings SF, Kelm M, Jax T, Strauer BE. A prospective study on incidence and risk factors of arteriovenous fistulae following transfemoral cardiac catheterization. *Int. J. Cardiol*. 2003; 88: 223–228.
5. Biancari F, D'Andrea V, Di Marco C et al. Meta-analysis of randomized trials on the efficacy of vascular closure devices after diagnostic angiography and angioplasty. *Am. Heart. J*. 2010; 159: 518–531.
6. Schwartz BG, Burstein S, Economides C et al. Review of vascular closure devices. *Cath Lab Digest* 2011; 19(7): 1–20
7. Klocker J, Gratl A, Chemelli A et al. Influence of use of a vascular closure device on incidence and surgical management of access site complications after percutaneous interventions. *Eur. J. Vasc. Endovasc. Surg*. 2011; 42: 230–235.

   A large single center review giving an appreciation of the true incidence of these complications.
8. Alvarez-Tostado JA, Moise MA, Bena JF et al. The brachial artery: A critical access for endovascular procedures. *J. Vasc. Surg*. 2009; 49: 378–385.
9. Stacul F, Van der Molen AJ, Reimer P et al. Contrast induced nephopathy: Updated ESUR contrast media safety committee guidelines. *Eur. Radiol*. 2011; 21: 2527–2541.
10. Mehran R, Aymond ED, Nikolsky E et al. A simple risk score for prediction of contrast induced nephropathy after percutaneous coronary intervention: Development and initial validation. *J. Am. Coll. Cardiol*. 2004; 44: 1393–1399.
11. McCullough A, Adam A, Becker CR et al. Contrast induced nephropathy: Clinical insights and practical guidance. A report from the CIN concensus working panel. *Am. J. Coll. Cardiol*. 2006; 98(S): 1K–77K.

    A useful review of current guidelines.
12. Trivedi H, Natella R, Szabo A. Hydration with sodium bicarbonate for the prevention of contrast induced nephropathy: A meta-analysis of randomized controlled trials. *Clin. Nephrol*. 2010; 74: 288–296.
13. Zaraca I, Wiedermann CJ, Ebner H. Contrast media induced nephropathy in patients undergoing angiography prior to or during vascular surgery: A systematic review. *Minerva Chir*. 2011; 66: 553–560.
14. Linkins LA, Dans, AL, Moores LK et al. Treatment and prevention of heparin induced thrombocytopenia. *Chest* 2012; 141(2S): e495S–e530S.

    Current guidelines from the American College of Chest Physicians.
15. Allaire E, Melliere D, Poussier B et al. Iliac artery rupture during balloon dilatation: What treatment? *Ann. Vasc. Surg*. 2003; 17: 306–314.
16. Hayes PD, Chokkalingam A, Jones R et al. Arterial perforation during infrainguinal lower limb angioplasty does not worsen outcome: Results from 1409 patients. *J. Endovasc. Ther*. 2002; 9:422–427.
17. Lam RC, Shah S, Faries PL et al. Incidence and clinical significance of distal embolization during percutaneous interventions involving the superficial femoral artery. *J. Vasc. Surg*. 2007; 46: 1155–1159.
18. Roffi M, Mukherjee D. Current role of emboli protection devices in percutaneous coronary and vascular interventions. *Am. Heart. J*. 2009; 157(2): 263–270.
19. Hogg ME, Peterson BG, Pearce WH et al. Bare metal stent infections: Case report and review of the literature. *J. Vasc. Surg*. 2007; 46: 813–820.
20. Ozkan U, Oguzkurt L, Tercan F. Technique, complication and long term outcome for endovascular treatment of iliac artery occlusion. *Cardiovasc. Intervent. Radiol*. 2010; 33: 18–24.
21. The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischaemia of the lower extremity. The STILE trial. *Ann. Surg*. 1994; 220: 251–268.
22. Conrad MF, Adams AB, Guest JM et al. Secondary intervention after endovascular abdominal aortic aneuryms repair. *Ann. Surg*. 2009; 250: 383–389.
23. Makaroun MS, Dillavou ED, Kee ST et al. Endovascular treatment of thoracic aortic aneurysms: Results of the phase II multicenter trial of the GORE TAG thoracic endoprosthesis. *J. Vasc. Surg*. 2005; 41: 1–9.
24. Van Marrewijk C, Buth J, Harris PL et al. Significance of endoleaks after end vascular repair of abdominal aortic aneurysms: The EUROSTAR experience. *J. Vasc. Surg*. 2002; 35: 461–473.
25. Rayt HS, Sandford RM, Salem M et al. Conservative management of type 2 endoleaks is not associated with increased risk of aneurysm rupture. *Eur. J. Vasc. Endovasc. Surg*. 2009; 38: 718–723.
26. Sharif MA, Lee B, Lau LL et al. Prosthetic stent graft infection after endovascular abdominal aortic aneurysm repair. *J. Vasc. Surg*. 2007; 46: 442–448.
27. Brott TG, Hobson RW, Howard G et al. Stenting versus endarterectomy for treatment of carotid artery stenosis. *NEJM* 2010; 363: 11–23.
28. Greenfield LJ, Proctor MC. Filter complications and their management. *Sem. Vasc. Surg*. 2000; 13(3): 213–216
29. Malgor RD, Labropoulos N. A systematic review of symptomatic duodenal perforation by inferior vena cava filters. *J. Vasc. Surg*. 2012; 55: 856–861.
30. Raju S, Darcey R, Neglen P. Unexpected major role for venous stenting in deep reflux disease. *J. Vasc. Surg*. 2010; 51: 401–409.
31. Dasari TW, Pappy R, Hennebry TA. Pharmacomechanical thrombolysis of acute and chronic symptomatic deep vein thrombosis: A systematic review of literature. *Angiology* 2012. 63(2): 138–145.

    Discussed various treatment options for DVT.
32. Murad MH, Coto-Yglesias F, Zumaeta-Garcia M et al. A systematic review and meta-analysis of the treatments of varicose veins. *J. Vasc. Surg*. 2011; 53: 49S–65S.

31

Complications of Open Arterial Vascular Surgery

Boulos Toursarkissian

CONTENTS

31.1 Introduction

It is unquestionably true that the practice of vascular surgery has become increasingly safer over the last two decades. Nevertheless, vascular procedures remain fraught with complications due to the ever-advancing age of the patient population, the diffuse nature of atherosclerosis, and the increasing comorbidities.

Systemic complications such as cardiac events, respiratory failure, and renal dysfunction are frequent after vascular surgery, especially in smokers. Such complications will not be addressed in this chapter and are reviewed in detail elsewhere in the book.

Some complications are common to many vascular procedures. These include early graft thrombosis and postoperative bleeding. Underlying reasons are similar. Therefore, these subjects will be covered in an early section of this chapter.

Procedure-specific complications will be addressed for peripheral arterial surgery, carotid procedures, aortic surgery, hemodialysis access procedures, and embolectomy procedures.

31.2 General Complications

31.2.1 Early Graft Thrombosis

When faced with such an event, a number of possibilities must be reviewed. Is the inflow into the graft adequate? What is the nature of the outflow and should it be improved? The quality of the conduit must be considered as well as its tunneling. Were any kinks or compression present? Did hypotension develop that may have led to low flow and thrombosis? Were there technical issues with the anastomoses such as flaps or stenosis? Did any plaques fracture from clamping? Was the posterior wall of the vessel injured while opening the vessel, causing a local dissection? Did any hematomas compress the graft? Was the wound closure tight enough to compress the graft? Does the patient have an unsuspected hypercoagulable condition such as heparin-induced thrombocytopenia? The nature of the clot retrieved at reoperation, or serum laboratory tests such as platelet count, may be indicative of the etiology of early graft thrombosis. In most cases, immediate anticoagulation followed by reoperation with thrombectomy is carried out. Ideally, a completion imaging study is then done if the reason for failure was not readily obvious. If the reason still cannot be identified, strong consideration should be given to continuing anticoagulation if it can be safely done, while proceeding with a hypercoagulable work up.

31.2.2 Postoperative Bleeding

Bleeding can be due to surgical or medical problems. Except for cavitary procedures, bleeding will be obvious after vascular surgery. For intracavitary procedures, early signs might be declining urine output or increasing heart rate, before hypotension. Hematomas can lead to graft compression or wound morbidity. In the neck, airway compromise can occur.

The first management step is to stop any anticoagulation and to reverse any existing coagulopathy. If medical bleeding is not suspected, a return to the operating room will be necessary.

Prevention is by avoiding unnecessary dissection, use of electrocautery whenever possible, staying as close as possible to the arterial plane, adequate tension-free anastomoses, and avoiding large doses of anticoagulants.

Many patients undergoing vascular surgery today are on dual antiplatelet agents including thienopyridines such as clopidogrel. Withholding these agents preoperatively is ideal to minimize the risk of bleeding, but not always possible. Platelets transfusions may need to be given in those cases. Many of the newer anticoagulants such as rivaroxaban and dabigatran have no known reversal agents; if the vascular procedure can be reasonably delayed until the agents have worn off, then this approach should be pursued.

31.3 Peripheral Arterial Procedures

31.3.1 Early Graft Thrombosis

This affects nearly 5% of all bypasses and is more common for infrageniculate bypasses and those done for critical limb ischemia [1].

The location of the clot may offer some hints as to the cause. It may be best therefore to start by exploring the distal anastomotic site. Clot removal may be done by milking the graft or careful use of thromboembolectomy catheters, taking care not to disrupt anastomotic sites or further damage the graft. Catheters may be passable in only one direction when the valves have not been lysed in reversed vein grafts.

When a saphenous vein conduit has been used, and the bypass clots acutely in the perioperative period, one has to consider possible defects within the graft as a potential cause. The possible defects will vary depending on what technique was used. A reversed vein graft may have a sclerotic or relatively narrower segment that may have not been noticed at initial surgery. For in situ bypasses, the possibilities of a retained valve or perivalvular damage from the valvulotome must be considered. Detection of such abnormalities may require visualization of the entire graft after thrombectomy. Angiography may not be the best technique for the detection of certain abnormalities. Intraoperative duplex may be advantageous as would angioscopy, although few are adept with this technique. If a clear cause in the graft itself for failure has not been identified and other causes for graft thrombosis (see earlier section) have been ruled out, it may be necessary to replace the conduit entirely. If a defective segment is identified, it will be necessary to replace that one segment.

Potential areas where a lower extremity graft may get compressed or kinked include the popliteal space, the interosseous membrane, and the distal pretibial area approaching the dorsalis pedis. In the popliteal space, one needs to make sure the graft is passing between the two heads of the gastrocnemius muscle and not through the medial head. It is usually preferable to pass the bypass though any tunnels after having performed the proximal anastomosis and with the graft fully distended, to allow it to straighten out.

If no good reason for graft failure can be identified, the medium-term prognosis is not good, despite thrombectomy and anticoagulation.

31.3.2 Wound and Graft Infection

Prosthetic graft infections occur 3% of the time and are more frequent than vein graft infections [2]. Groin incisions, reoperative procedures, and presence of foot infections are risk factors.

Mortality is up to 10% and amputation rates are up to 50%. Graft infection can manifest as graft thrombosis or hemorrhage from anastomotic disruption. *Staphylococcus aureus* is the most frequent organism.

Fortunately, true graft infections are less common than superficial infections. Avoidance of infections is achieved by careful placement of skin incisions, avoiding large flaps or long continuous cuts, avoiding areas with active infections, and draining any large postoperative hematomas. Treatment of any superficial infections should be aggressive to prevent deep extensions into the planes of the graft.

Localized infections can sometimes be treated with wound debridement; use of vacuum-assisted closure (VAC) devices may be beneficial in those cases, although it is not recommended that such dressings be applied directly onto a patient graft for fear of hemorrhage [3]. Soft tissue interposition is recommended. Extensive graft infection will require total graft removal and repair of anastomotic sites with autogenous tissues. Extra-anatomic bypass may be needed. Occasionally, it is possible to save an exposed prosthetic graft, provided that there is minimal surrounding infection and that most of the graft is incorporated into surrounding tissues [4]. In those cases, coverage of the exposed graft section with a muscle flap is recommended. Infections with particularly aggressive organisms such as *Pseudomonas* may not be amenable to such treatment; such infections can also result in necrosis of vein graft walls.

31.3.3 Lymphatic Complications and Limb Swelling

Lymphatic complications are not uncommon after peripheral vascular procedures. They can involve the groin, thigh, or popliteal fossa and can take the form of lymph leaks, lymphocele, or limb swelling. Small lymph leaks can be treated with appropriate dry sterile dressings or a modified VAC device until they close [5]. Antibiotics should be given for any signs of infection. Small lymphoceles may be treated by a number of attempts at percutaneous aspiration under sterile technique. Persistent lymph leaks that do not close during the first few weeks after surgery and large lymphoceles are probably best treated by reexploration and ligation or cavity obliteration; sclerosing agents can be used at that time to decrease recurrence.

Limb edema after arterial reconstruction is very common, with all patients experiencing this to some degree [6]. Patients with lymphatic complications as described earlier will have more swelling. Patients with redo operations are more predisposed. Edema usually resolves within a few months but can be permanent. Most leg edema can be treated by encouraging leg elevation and

reassuring the patient that the condition is usually temporary. Compression stockings can be used but should be avoided when a bypass is tunneled subcutaneously.

31.3.4 Later Graft Failure

Late graft failure may be due to intimal hyperplasia or due to progression of atherosclerotic disease in the inflow or outflow. The first occurs within the first 2 years (but after the early perioperative period), while the latter happens on a longer time frame. Intimal hyperplasia may affect the anastomotic sites or the vein conduit itself.

Vein graft problems occur in 15%–20% of cases. There are currently no proven methods to control this problem. Cilostazol has been suggested, but large studies are lacking. The only management approach is serial duplex ultrasonography to identify areas of evolving stenoses and address them before they cause thrombosis. Treatment of stenoses can be in the form of percutaneous angioplasty, open patch angioplasty, or segmental replacement [7].

Not all patients whose grafts thrombosed completely will be symptomatic. For a thrombosed bypass, the options are thrombolytic therapy, open thrombectomy and revision, and a redo bypass. Thrombolytic therapy should be considered for grafts that have failed within 15 days of presentation. It is more likely to be successful in grafts that have been patent for longer periods and in nondiabetic patients [8]. After lysis, further endovascular or open treatment will be required in a majority of cases. Reoperation, in the form of a redo bypass, which has poorer results than initial bypasses, should be reserved for those who are significantly symptomatic.

31.4 Carotid Endarterectomy

31.4.1 Stroke

Stroke is the biggest concern associated with carotid endarterectomy (CEA), although not the most frequent complication. Stroke is also a risk of preoperative conventional arteriography, with rates averaging around 1% [9]. The cause relates to catheter manipulation in the aortic arch, causing particulate embolization. CT angiography or magnetic resonance angiography will avoid those complications.

Intraoperative stroke during CEA has a number of potential causes, including embolization during dissection, clamping ischemia, or the development of an intimal flap. The latter is probably the most frequent and can also be a cause of postoperative thrombosis. Narrowing of the vessel if no patch angioplasty is used can also be a cause of thrombosis. Postoperative stroke rates vary with the indication for surgery. Most studies report an incidence of 1%–2% for asymptomatic stenoses [9] and up to 5% for persons with recent symptoms [10]. Prevention of stroke relies on careful dissection, avoiding manipulation of the site of the plaque until after clamping, careful visualization of the endpoint with tacking sutures as needed, routine use of patch angioplasty to avoid narrowing, and some measure to evaluate cerebral perfusion during clamping [11]. The latter involves mainly two choices, each with its strong proponents. Options include routine shunting in all and selective shunting based on some measurement of cerebral perfusion. Measurement can be made by observation of the patient, with the procedure being done under local or regional anesthesia, electroencephalography monitoring under general anesthesia, transcranial Doppler flow measurements, or carotid stump back pressure measurement after clamping.

Postoperative stroke is defined as occurring in the first day after an initial period of normalcy. It can be due to embolization from the operative site or due to thrombosis of that site. Prior algorithms called for an immediate return to the operating room for evaluation with intraoperative angiography if the vessel is noted to be patent. With the widespread availability of CT angiography, an expeditious evaluation by that modality can be recommended. If a thrombosis is noted, or if a defect is seen, the patient can be returned to the operating room for correction. A shunt should be placed during correction. About a quarter of the time, no defect is seen, and consideration then should be given to anticoagulation. If an intracranial embolus is noted, intraoperative lytic treatment or other neuro "rescue" measures such as catheter-guided embolectomy or thrombolysis can be considered. Expeditious treatment in all cases is needed to prevent irreversible deficits.

31.4.2 Reperfusion Syndrome

Reperfusion syndrome refers to a cluster of symptoms that develop one or more days after CEA due to the increased perfusion pressure [12]. The incidence is around 0.5%. Severe ipsilateral headache is often a presenting symptom, possibly associated with hypertension. It can lead to intracerebral hemorrhage or seizure activity or both and carries a nearly 50% mortality. Risk factors are a severe degree of preoperative stenosis, hypertension, and possibly the use of anticoagulants. Patients should be evaluated with a CT scan, preferably to include the CEA site as well. Blood pressure should be aggressively controlled, anticoagulants stopped, and consideration should be given to prophylactic use of steroids or anticonvulsive medications. Intracranial hematomas may need to be evacuated.

31.4.3 Neck Hematoma

Hematomas develop in up to 5% of cases [13]. Risk factors include hypertension postoperatively, severe straining, and use of anticoagulants. Careful control of these factors may help minimize the risk of hematomas. Large hematomas can affect the airway and increase the risk of infection and should therefore be evacuated in the operating room. The use of drains can decrease the incidence of smaller hematomas, but such drains should be removed on postoperative day one to minimize chances of infection.

31.4.4 Cranial Nerve Injury

The incidence of nerve injury depends on the diligence with which one looks for it, as well as on the timing of investigation, because most will resolve with time [14]. The incidence of permanent injury is estimated to be 0.5%, while early transient malfunctions of any degree could be seen in up to 15%–20% of cases. Risk factors include reoperative neck surgery (prior CEA or other neck procedures), high carotid bifurcations or lesions, and anatomic variants. Most studies report the hypoglossal nerve as the most frequently affected with ipsilateral tongue deviation. The marginal mandibular branch of the facial nerve can be affected by upward retraction on the mandible and will manifest as drooping of the side of the mouth on the ipsilateral side. The vagus can be affected by injudicious clamping of the common carotid and will manifest by dysfunction of its recurrent laryngeal branch with hoarseness; bilateral injury will cause airway obstruction. Injury to the glossopharyngeal and spinal accessory nerves is very rare and is seen with high lesions. They are manifested, respectively, by dysphasia/aspiration or shoulder droop, pain, and scapular winging. Greater auricular nerve damage is not uncommon; it is a sensory nerve and supplies the ear and mandible.

31.4.5 Postoperative Hemodynamic Instability

Hypotension is believed due to baroreceptor dysfunction while hypertension is associated with preoperative hypertension [15]. In both cases, cardiac causes must be excluded. Control is paramount to avoid bleeding, clotting, or stroke complications. These changes are frequent enough to warrant close observation of all patients after CEA. Most of these changes will resolve within 48 h.

31.4.6 Pseudoaneurysm Formation, Patch Disruption, and Infection

Pseudoaneurysm formation is a rare late occurrence after CEA (0.05%) [16]. Infection must be ruled out if a prosthetic patch was used. Infection of a patch is rare after CEA occurring less than 0.5% of the time. Patch must be removed and replaced with autogenous vein in those cases. Uninfected pseudaneurysms should be repaired with either surgery or sometimes placement of a covered stent. Acute patch disruption can develop because of technical issues but is more common with saphenous vein harvested from the ankle.

31.4.7 Recurrent Stenosis

If noted within the first year, recurrent carotid stenosis occurs usually due to intimal hyperplasia [17]. The incidence is at least 10% over the first 2 years and is more commonly seen in women, continued smokers, diabetics, and hyperlipidemic patients. Use of statins may be of benefit. Patching helps reduce the incidence of recurrent stenosis. Recurrent symptoms will require reintervention, although most patients will be asymptomatic. There is some evidence that at least some of these stenoses will regress over the first year, so a period of close observation is often recommended. Preocclusive and progressive lesions will need treatment with repeat surgery or carotid stenting. Redo CEA has a higher risk of complications, especially cranial nerve injuries.

Late restenosis is usually due to recurrent atherosclerosis. Reoperation or stenting is used for symptomatic or high-grade disease.

31.5 Aortic Surgery

Aortic surgery may be performed for aneurysmal disease, occlusive disease, or problems with aortic branches such as renal or mesenteric vessels. Mortality from elective open aortic surgery is nearly 5%. Main reasons for mortality are related to the complications listed later.

31.5.1 Bleeding

Dissection should be kept to the minimum needed and as close to the aorta as possible. Review of any preoperative scans should include careful evaluation for venous anomalies such as a retroaortic left renal vein, a circumaortic venous collar, or a left-sided vena cava. Together, such anomalies occur in up to 5% of cases and can lead to severe hemorrhage if not recognized. Recognition of the orientation of wall calcification is also important to allow clamp application in such ways as to avoid cracking of the plaque and resultant bleeding. Transection of the aortic posterior wall for anastomosis is not always necessary. Avoiding the inclusion of heavy calcium plaques in anastomotic sites is preferred. Reversal of heparin with protamine at the end of the case may be

of benefit as well. Surgical bleeding may involve anastomotic suture lines, back-bleeding lumbar vessels, or inadvertent splenic injury from retractor placement.

31.5.2 Graft Limb Thrombosis

Acute graft failures are often due to an intimal flap. A useful rule of thumb to assess the outflow from an aortofemoral graft limb is that a profunda femoris artery that can accommodate a 4 mm probe or allow the passage of a non-inflated catheter for more than 15 cm will be enough to sustain graft limb patency.

Later graft failure can be due to intimal hyperplasia at the distal anastomotic site (usually within the first 2 years), or due to progression of atherosclerosis (later time frame). If caught early, treatment is by open thrombectomy, and revision of distal anastomosis. If not feasible, crossover femorofemoral grafting or axillofemoral grafting may be required [18].

31.5.3 Distal Embolization

Embolization may happen from clamping areas of diseased vessel or from fragmentation of plaque during dissection. Embolization may occur to the renal vessels, the pelvis, or the legs. Emboli can be large particles causing end organ ischemia or microembolic [19]. The incidence is 1%–2%. Large particles, when evident, will require removal by catheter embolectomy. Microembolization to the feet will manifest as the "trash foot" syndrome with bluish discoloration, serpiginous color changes to the soles, pain, and possibly digital gangrene. Doppler signals will be preserved. Renal artery embolization will manifest as renal nonoliguric dysfunction. Prevention is by careful selection of clamping sites, ideally clamping the iliacs before the aorta, and possibly clamping the renals if needed before the aorta, in cases where the preoperative CT scan reveals a "shaggy" aorta. Adequate graft flushing should be done before restoring flow distally. When microembolization occurs, consideration can be given to anticoagulation to prevent additional thrombosis.

31.5.4 Ischemic Colitis

Ischemic colitis is more frequent after aortic aneurysm surgery than reconstruction for occlusive disease [20]. It is most frequent after surgery for ruptured aneurysm. The exact incidence depends on how aggressively the diagnosis is pursued. Colonic ischemia is seen in 4%–7% of elective surgeries and up to half of the patients after open ruptured aneurysm repair. Clinically, it is seen in 1%–2% of elective cases and 35% of ruptures [21]. Contributing factors are hypotension, collateral disruptions, or anatomical issues related to the inferior mesenteric artery. Signs and symptoms include unexplained acidosis, thrombocytopenia, continuing fluid requirements, early postoperative bowel movements (especially if bloody), leucocytosis, and abdominal distention. Flexible sigmoidoscopy is the test of choice and will guide therapy depending on the extent of necrosis. Superficial mucosal sloughing may be treated with antibiotics, intravenous fluids, bowel rest, and careful monitoring. Cases of suspected transmural necrosis require colon resection with stoma formation. Prevention involves preservation of flow to the inferior mesenteric artery (IMA) if needed and to preserve as many of the hypogastric arteries as possible. An IMA, which is occluded or is vigorously backbleeding, can in general be safely ligated. One that is patent but has minimal backbleeding should be reimplanted into the aortic graft if possible.

31.5.5 Renal Failure

Acute kidney injury is most often due to bleeding and insufficient fluid resuscitation, causing acute tubular necrosis. It is therefore more common after ruptured aneurysm repair and is seen in up to 70% of those cases. Some element of postoperative renal dysfunction is seen in 3%–5% of elective open AAA repairs. It can also be due to atheroembolization, even from a juxtarenal clamp. Suprarenal clamping can cause direct renal ischemia as well. Other risk factors include preexisting renal dysfunction [22], as well as contrast-induced nephropathy in patients who have received intravenous contrast agents. Infrarenal clamping causes a nearly 40% reflex decrease in renal cortical blood flow. Preventive measures include controlling all the variables mentioned and minimizing renal ischemic time. Renal perfusion with cold saline solution may also be of benefit because of a decrease in metabolic demands.

31.5.6 Sexual Dysfunction

The most common type of sexual dysfunction seen after aortic surgery is retrograde ejaculation in males. It is usually due to damage to the sympathetic plexus, which lies next to the IMA, the aortic bifurcation, and the origin of the left common iliac artery. Prevention lies in minimizing dissection if possible. In patients who are potent, the incidence may be as high as 30% [23].

Impotence is common in patients undergoing aortic surgery. Nearly half of men undergoing aortic surgery are impotent preoperatively. At least half of those who are not will have dysfunction postoperatively. Prevention should focus on maintaining perfusion to the hypogastric arteries; this may require, in some cases, the use of end-to-side proximal graft anastomosis (when the external iliac arteries are heavily diseased).

31.5.7 Spinal Cord Injury

Spinal cord ischemia occurs in less than 1% of infrarenal aortic reconstructions [24], but in upward of 10%–15% for thoracoabdominal aneurysm repairs. It is more common with supraceliac clamping and in cases of aneurysm rupture. Preventive measures include minimizing supraceliac clamp time and preserving flow to the hypogastric arteries that provide collateral flow to the spinal cord. In cases of thoracoabdominal aneurysm repair, preventive measures include cerebrospinal fluid drainage, use of left heart bypass, and reimplantation of dominant intercostal vessels. Symptoms can range from a posterior sensory syndrome to complete transverse myelopathy and paraplegia.

31.5.8 Graft Infection

The incidence of aortic graft infection is less than 5% [25]. It is higher in emergency cases or those where the graft extends to the groins [26]. Symptoms can range from sepsis to anastomotic pseudoaneurysms to nonspecific complaints such as malaise and weight loss. For late presentation, a CT scan is helpful in the diagnosis, whereas in early infections, CT scan is not as helpful. The most common organism is Staphylococcus spp. Staphylococcus epidermidis causes more indolent late appearing infections. Staphylococcus aureus can cause acute or more chronic infections. Preventive measures include careful sterile technique, prophylactic antibiotics, and extensions to the groins only when necessary. A variety of treatment options have been devised for aortic graft infection [27], ranging from total graft excision with axillobifemoral bypass, replacement of the graft with homograft or superficial femoral vein grafts, to a combination of serial debridements, antibiotic beads placements, and eventual muscle flaps for infections localized to the groins. Mortality and morbidity in terms of limb loss remain very high. Choice of treatment depends on time of presentation, systemic manifestations, degree of ischemia, and the microbiology of the infection.

31.5.9 Aortoenteric Fistula

Aortoenteric fistula (AEF) is a late appearing complication seen in less than 0.5% of cases [28]. Aortoduodenal fistulas are more common than aortosigmoid fistulas. Mortality remains high. Any patient with a prior aortic graft and any form of upper GI bleeding should be evaluated for this complication. In addition to a CT scan, workup usually entails an upper endoscopy to reach the fourth portion of the duodenum. The patient may or may not exhibit signs or symptoms of graft infection. The communication does not necessarily involve the suture line, in which case, the patient likely will have chronic low-grade blood loss from mucosal erosions. If the suture line is involved, the bleeding will be more brisk, although it is not infrequent for the patient to present with a first herald bleeding episode. AEF is best treated [29], with extra-anatomic bypass followed by total graft excision and aortic closure. If the patient is unstable at presentation, temporization can be obtained by placing a covered stent across the bleeding suture line to allow semi-elective treatment. There are case reports of long-term treatment with covered stent and antibiotics. Prevention requires careful interposition of tissues between the graft and bowel. Omentum may be used when there is not enough tissue in the retroperitoneum. Any native aortic wall should also be used to wrap the graft.

31.5.10 Anastomotic Pseudoaneurysm

Pseudoaneurysms occur in about 3% of aortic cases [30]. They are more common at the femoral level where they continue to increase with time after graft placement and may be present in up to 20% of cases after 15 years. They are usually caused by the degeneration of the native vessel at the proximal or distal anastomosis. Preventive measures consist of trying to use as healthy an arterial segment as possible for the anastomoses. Some pseudoaneurysms may be a sign of latent graft infection. Pseudoaneurysms can enlarge, thrombose, or rupture. Groin pseudoaneurysms are more likely to thrombose than rupture. Small pseudoaneurysms under 2 cm can be observed, while larger ones should be considered for treatment. In the groin, this usually involves an open revision. In the abdomen, consideration should be given for stent graft placement across the anastomosis to try to avoid the morbidity of open reoperation [31].

31.5.11 Incisional Hernia

Incidence of incisional hernia is about 5% but may be higher in patients with aneurysms [32]. Underlying connective tissue problems are believed to play a role. The incidence of herniation is higher with the retroperitoneal approach to the aorta, where it is nearly 7%. What is however more common after a retroperitoneal approach is the development of a bulge (pseudohernia) in the flank in up to 30% of cases. It is believed to occur due to denervation of the muscles from intercostal nerve injury. Risk of postoperative bulge is reduced if one does not have to extend into the intercostal spaces [33].

31.5.12 Other Complications (Ureteral Injury, Lymph Leaks)

Ureteral injuries are seen in less than 0.5% of cases, especially in cases of large iliac aneurysms or reoperations

or inflammatory aneurysms [34]. The ureter can also be injured during tunneling of the limbs of an aorto-bifemoral graft due to devascularization. It is recommended that the graft be placed behind the ureter to avoid compressing the latter between the graft and the spine. Depending on the type of injury, management may consist of ureteral stenting or open reconstruction.

Chyloperitoneum can occur in less than 0.1% of cases of abdominal aortic reconstructions [35]. It is due to injury to the cysterna chyli at the level of the renal arteries. Preventive measures consist of ligating any lymphatics seen during dissection of the proximal aorta. Presentation is with abdominal distention and ascites within a month of surgery. Treatment consists of repeated paracenteses and a low-fat diet with medium-chain triglyceride supplementation. Total parenteral nutrition may be needed in refractory cases.

Lymph leak can also occur from groin incisions [36]. Ligating any lymphatics seen during exposure is a good method to try to minimize this complication. Reoperations increase the risk. An initial period of nonoperative management is usually indicated with bed rest and use of a VAC. Failure to resolve may require wound exploration.

Lymphoceles can sometimes develop instead of lymph leak. Meticulous wound closure with avoidance of dead space helps minimize this complication. The patient will present with a non-pulsatile lump. Diagnosis is confirmed by ultrasound and aspiration. Repeated aspiration under sterile technique with pressure dressings may resolve small lymphoceles, although large ones will likely require operative ablation [37].

31.5.13 Graft Failure

Most aortic prosthetic grafts will dilate with time up to 20% over the first decade. True structural failure is very rare, although some grafts can become very friable when handled at reoperation. Aneurysmal degeneration is a more frequent problem with arterial homografts and can lead to thrombosis or rupture. Replacement or relining with stent grafts should be considered.

Vein grafts used to revascularize renal arteries also have a tendency to enlarge over time. Aneurysmal changes in those veins can be seen in up to 30% of pediatric cases. The problem is less frequent when an artery such as the hypogastric artery is used for those cases.

31.6 Vascular Access Surgery

Most procedures performed for vascular access have high complication rates. Catheters likely have the highest, followed by arteriovenous grafts (AVG) and finally arteriovenous fistulas (AVF), which carry the lowest and are therefore preferred whenever possible. The DOQI (Dialysis Outcomes Quality Initiatives) guidelines call for initial creation of AVFs in at least two-thirds of patients needing access placement [38,39].

31.6.1 Failure of Maturation

This is likely the most frequent complication seen in AVF placement. It is estimated to occur in 15%–25% of cases. With the Fistula First initiative and increased attempts to place native AVF as opposed to AVG, non-maturation rates have been significant as veins of questionable suitability may be used.

Preoperative vein mapping by duplex ultrasound should help decrease the rate of non-maturation by allowing the selection of appropriate veins [40,41]. Veins less than 2.5 mm in diameter (with tourniquet) will have higher failure rates, as will donor arteries that are heavily calcified. Diabetics and older patients have a higher initial failure rate and more distal AVFs have higher failure rates than more proximal ones.

AVF should be evaluated at 1 month after placement with ultrasound and physical exam. If the fistula is not satisfactory in terms of maturation, a fistulagram should be performed with the intent to identify and angioplasty any stenoses. Juxta-arterial stenosis in the veins is most frequent. If the vein is diffusely small but the artery good, balloon-assisted maturation may be attempted (sequential dilation over the course of several weeks). Selected lesions can also be surgically revised. A good number of fistulas can be rendered mature with these adjunctive techniques [42,43].

Given the incidence of these problems, it is obvious that the preferred policy is early referral of patients to surgeons for AVF placement and patient education to preserve an extremity from venipunctures for AVF placement.

31.6.2 Stenosis

Even mature AVFs can develop stenoses. This may be detected by physical exam as a pulsatile AVF or by poor clearances, high recirculation rates, or high pressures during use. Routine monitoring for these issues and timely intervention (by angioplasty or surgical revision) will improve patency rates.

31.6.3 Graft Thrombosis

Thrombosis is the most common complication of AVG placement, occurring in up to 50% within 2 years of placement [44]. There are multiple reasons such as low blood pressure, arterial disease, excess compression, but the most common is the development of intimal

hyperplasia at the venous end. Early graft thrombosis is usually due to inadequate arterial flow (small vessel) or more frequently, due to inadequate venous outflow or unsuspected venous stenosis. Use of larger veins (such as the axillary) and preoperative vein study by ultrasound should help minimize the incidence of early thrombosis. Later failure seems more difficult to control but a routine program of pressure and flow monitoring during hemodialysis should help identify grafts developing outflow stenoses before thrombosis; angioplasty in those cases should prevent thrombosis. Management of early postoperative graft thrombosis is by surgical declotting with completion venography to identify and treat stenoses. Later thromboses can be managed by percutaneous or open thrombectomy, focusing on the intimal hyperplasia likely present at the venous end with patching or angioplasty/stenting. Open revision may be minimally better than percutaneous intervention, but both have patencies usually less than 1 year.

AVF thrombosis occurring early is usually due to a poor-quality vein. Unless the surgeon suspects a technical issue with kinking or the anastomosis, the problem is best addressed by creating a new access after evaluation of the arterial and venous segments. Precise incidence is difficult to measure but is likely related to the willingness of the surgeon to use borderline veins in persistent efforts at AVF creation. Late thrombosis is related to underlying stenosis. Autogenous veins do not do as well with thrombectomy (open or percutaneous) as AVGs do, likely because of endothelial damage. Thrombectomy should be attempted but the mid-term patency rates are less than 20%.

31.6.4 Seroma

Seroma formation is generally limited to AVG cases, rather than AVF, with a very low incidence (<0.5%) [45]. It is usually sterile fluid at the arterial end. Aspiration may resolve the problem, though infection is a risk. In some cases, graft replacement is needed.

31.6.5 Infection

Infection is a more common problem with AVG than AVF, especially with those placed in the groin where the incidence is much higher than 5%. It can happen with AVF, especially at sites of aneurysm that erode to the skin. The signs include redness, tenderness, cellulitis, and possible purulent discharge. Management depends on timing of presentation and absence or presence of signs of systemic sepsis. Early infection will usually require removal of the entire graft. Late infection may sometimes be treated by wide bypass around the infected area and by removal of the infected segment, provided no signs of systemic sepsis are present.

31.6.6 Pseudoaneurysm

Pseudoaneurysms more commonly occur in AVG (2%–10%) but are less common in AVF. They are not necessarily associated with infection. Enlarging ones or those associated with severe thinning of the overlying skin (especially those adherent to the skin) should be considered for open surgical repair or stent graft placement to exclude the pseudoaneurysm segment.

31.6.7 Aneurysms

Those are more common with native AVFs than AVGs. Indications for treatment are the same as for pseudoaneurysms. Open repair is preferred to avoid placement of prosthetic materials. It is important to first perform a fistulagram to identify any associated stenoses that may be the underlying cause of aneurysm formation.

31.6.8 Steal Syndromes

Steal represents an under perfusion of the hand or extremity distal to the AVF, due to preferential flow of the blood into the AVF or AVG [46]. It is manifested as coldness, numbness, pain, decreased strength, and muscle weakness. It can develop acutely immediately after AVF or AVG placement or more insidiously over time. The symptoms may be present at rest in severe cases, or only during dialysis in milder cases. The incidence of clinically significant steal ranges from 1% for distal forearm AVFs to almost 10% for brachial-based AVGs. The risk factors include peripheral arterial disease, diabetes, large conduit AVF or AVG, and use of the brachial artery as arterial donor. Testing for steal is based on flat or diminished finger photoplethysmography (PPG), which improves with AVF or AVG compression. It is important to note that many more patients will have abnormal such tests without any symptoms of steal. Angiography of the extremity is recommended for patients with steal [47]. Any lesions proximal to the access should be treated by endovascular or open means. If the disease is only distal, attempts can be made to address that by endovascular means. If not successful or satisfactory, options included banding the access, moving the inflow more proximally to the axilla or distally to the wrist, distal revascularization and interval ligation (DRIL procedure), and lastly, ligation of the access.

31.6.9 Limb Swelling and Central Vein Problems

The causes of venous hypertension include central vein stenosis and incompetent peripheral veins. The result is edema, venous congestion, and discoloration. If

significant, it may lead to inefficient dialysis. If the problem is incompetent peripheral veins causing retrograde flow down the forearm, these veins should be ligated or coiled by endovascular means. Central venous stenosis is more difficult to manage and is the more frequent problem unfortunately. Between 5% and 20% or dialysis patients will develop a central vein stenosis at some point in time [48]. Prior catheters are a frequent culprit as is the increased flow from the AVF or AVG. Stenoses are treated with angioplasty percutaneously [50]. This modality is limited by a high recurrence rate. Stents may help but are also limited by restenosis. Covered stents may be superior to bare metal stents in those cases. Surgical bypasses may be performed but at the cost of sternotomy and morbidity. In some cases, ligation of the access after creation of an access elsewhere may be needed.

31.6.10 Neuropathy

Ischemic monomelic neuropathy is seen in less than 0.5% of access placements [49]. It is usually associated with brachial-based accesses, seen in diabetic patients, and develops very quickly after access placement. It is differentiated from classic steal by the presence of what appears to be adequate hand perfusion and color. It is manifested by pain and severe weakness of the muscles of the hand and forearm. It is thought to be related to relative ischemia of nerves and is treated by either banding or ligation of the access. It should be differentiated from carpal tunnel syndrome, which has increased prevalence in dialysis patients but is more insidious in onset and has symptoms limited to the median nerve distribution.

31.7 Acute Limb Ischemia and Embolectomy

The mainstay of open treatment of acute limb ischemia is thromboembolectomy using balloon Fogarty catheters.

31.7.1 Intimal Injuries and Dissections

Balloon embolectomy catheters have a risk of causing intimal injury, dissection, or perforation. Dilation may lead to intimal hyperplasia and vessel narrowing. The exact incidence of these complications is not known. Prevention consists of using the gentlest possible technique and smallest possible balloon. Incomplete clot removal is not uncommon either, if routine angiography is not used at completion.

31.7.2 Recurrent Ischemia

Recurrent ischemia may develop from recurrent embolization [50]. Inadequate full systemic anticoagulation can be a predisposing factor. Recurrent embolism can occur despite anticoagulation in up to 10% of cases. Incomplete clot removal at initial surgery may also lead to thrombus propagation and recurrent ischemia. Vessel injury from the catheter work may also lead to thrombosis. Prevention should focus on adequate anticoagulation after clot removal.

31.7.3 Reperfusion Injury and Compartment Syndrome

Reperfusion will lead to edema in the muscle compartments [51,52]. If untreated, this may lead to a compartment syndrome with resultant nerve dysfunction and muscle necrosis. Long term, this is referred to as Volkmann's ischemic contracture. Muscle necrosis leads to release of potassium, myoglobin, and tumor necrosis factor (TNF) in the circulation. Alternatively, revascularization after prolonged ischemia leads to reperfusion of ischemic muscle with the same factors released in the circulation. Myoglobin can precipitate in the renal tubules, causing acute renal failure. Hyperkalemia can lead to arrhythmias. TNF release can lead to lung injury.

Prevention consists of performing fasciotomy, either prophylactically after prolonged ischemia or if any signs of compartment syndrome develop after reperfusion. The patient should be adequately hydrated to induce a diuresis and alkalinized to reduce the effects of hyperkalemia and decrease the likelihood of myoglobin precipitating in the renal tubules.

31.7.4 Complications of Fasciotomy

Fasciotomy-related complications are frequent, especially bleeding, given the fact that most of these patients are anticoagulated [53]. If any muscle necrosis is present when fasciotomy is done, there will be a risk of significant infection with resultant limb loss. Incomplete fasciotomy, especially of the deep compartments, may lead to unrecognized muscle necrosis. Poor surgical technique on the lateral upper aspect of the calf may lead to peroneal nerve injury.

Incidence of Selected Complications

Complication	Incidence	References
Peripheral procedures		
Early graft thrombosis	5%	[1]
Prosthetic graft infection	3%	[2]

Complication	Incidence	References
Vein graft stenosis	15%–20% over 2 years	[7]
Carotid endarterectomy		
Stroke	1% for asymptomatic and 5% for symptomatic	[9,10]
Reperfusion	0.5%	[12]
Neck hematoma	5%	[13]
Permanent cranial nerve injury	0.5%	[14]
Pseudoaneuryms	0.5%	[16]
Recurrent stenosis	10% at 5 years	[17]
Aortic surgery		
Ischemic colitis	1% for elective cases; up to 35% for ruptured AAAs	[20,21]
Renal failure	3%–5% for elective cases	[22]
Sexual dysfunction	30%	[22]
Spinal cord injury	<1% in infrarenal cases	[24]
Graft infection	1%–5%	[25,26]
Aortoenteric fistula	<0.5%	[28]
Pseudoaneurysm	3%	[30]
Hernia	5% for transabdominal	[32]
Access procedures		
Failure of AVF maturation	15%–25%	[42,43]
Graft thrombosis	Up to 50% at 2 years	[44]
Steal	1%–10% depending on definition	[46,47]
Central vein stenosis	5%–20%	[48]
Procedures for acute ischemia		
Recurrent embolism	10%	[50]
Reperfusion injury/ compartment syndrome	20%	[51,52]

Selected Complications and Methods of Prevention

Complication	Means of Prevention
Bypass vein graft failure	Duplex surveillance to detect and repair stenoses
Stroke form CEA	Develop a routine way to assess cerebral perfusion during CEA
Recurrent carotid stenosis	Patch use, statins?
Sexual dysfunction after aortic surgery	Nerve preservation at aortic bifurcation and left iliac artery
Aortoenteric fistula	Coverage of graft; omental interposition
Ischemic colitis after aortic surgery	Preserve flow to at least one hypogastric artery; reimplant inferior mesenteric artery when patent but with minimal backbleeding
AVF non-maturation	Careful preoperative vein mapping; surveillance for stenosis and appropriate angioplasty
AV graft thrombosis	Routine monitoring for signs of stenosis during hemodialysis
Central vein stenosis	Avoid the subclavian vein for catheters; early referral for AVF placement to avoid catheters completely
Recurrent embolization	Routine systemic anticoagulation
Compartment syndrome	Selective fasciotomies versus very close monitoring

References

1. Singh N, Sidawy AN, Dezee KJ et al. Factors associated with early failure of infrainguinal lower extremity arterial bypass. *J Vasc Surg*. 2008; 47:556–561.
2. Vogel TR, Dombrovskiy VY, Carson JL et al. Infectious complications after elective vascular surgical procedures. *J Vasc Surg*. 2010; 51(1):122–129, 129–130.
3. Moneta GL. Long-term results of vascular graft and artery preserving treatment with negative pressure wound therapy in Szilagyi Grade III infections justify a paradigm shift. *J Vasc Surg*. 2012; 55(2):615–615.
4. Bandyk DF, Novotney ML, Back MR et al. Expanded application of in situ replacement for prosthetic graft infection. *J Vasc Surg*. 2001; 34:411.
5. Murphy JL, Cole WC, White PM et al. Lymphatic fistula after vascular reconstruction: A case control study. *Can J Surg*. 1991; 34:76.
6. AbuRahma AF, Woodruff BA, Lucente FC. Edema after femoropopliteal bypass surgery: Lymphatic and venous theories of causation. *J Vasc Surg*. 1990; 11:461.
7. Sanchez LA, Suggs WD, Marin ML et al. Is percutaneous balloon angioplasty appropriate in the treatment of graft and anastomotic lesions responsible for failing vein bypasses? *Am J Surg*. 1994; 168:97–101.
8. Nackman GB, Walsh DB, Fillinger MF et al. Thrombolysis of occluded infrainguinal vein grafts: Predictors of outcome. *J Vasc Surg*. 1997; 25:1023–1031.
9. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995; 273:1421–1428.
10. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991; 325:445–453.

    The NASCET trial still remains a useful reference to read for all involved in the care of patients with carotid stenosis.
11. Hamdan AD, Pomposelli FB Jr, Gibbons GW, Campbell DR, LoGerfo FW. Perioperative strokes after 1001 consecutive carotid endarterectomy procedures without an electroencephalogram: Incidence, mechanism, and recovery. *Arch Surg*. 1999; 134(4):412–415.
12. Karapanayiotides T, Meuli R, Devuyst G et al. Postcarotid endarterectomy hyperperfusion or reperfusion syndrome. *Stroke*. 2005; 36:21–26.

13. Gelabert HA, Moore WS. Carotid endarterectomy: Current status. *Curr Probl Surg*. 1991; 28:181–262.
14. Schauber MD, Fontenelle LJ, Solomon JW, Hanson TL. Cranial/cervical nerve dysfunction after carotid endarterectomy. *J Vasc Surg*. 1997; 25:481–487.
15. Bove EL, Fry WJ, Gross WS, Stanley JC. Hypotension and hypertension as consequences of baroreceptor dysfunction following carotid endarterectomy. *Surgery.* 1979; 85:633–637.
16. Rosenthal D, Archie Jr JP, Garcia-Rinaldi R et al. Carotid patch angioplasty: Immediate and long-term results. *J Vasc Surg*. 1990; 12:326–333.
17. Sadideen H, Taylor PR, Padayachee TS. Restenosis after carotid endarterectomy. *Int J Clin Pract*. 2006; 60:1625–1630.
18. Nevelsteen A, Suy R. Graft occlusion following aortofemoral Dacron bypass. *Ann Vasc Surg*. 1991; 5:32.
19. Hallett Jr JW, Marshall DM, Petterson TM et al. Graft-related complications after abdominal aortic aneurysm repair: Reassurance from a 36-year population-based experience. *J Vasc Surg*. 1997; 25:277–284.
20. Steele SR. Ischemic colitis complicating major vascular surgery. *Surg Clin North Am*. 2007; 87:1099.
21. Brewster DC, Franklin DP, Cambria RP et al. Intestinal ischemia complicating abdominal aortic surgery. *Surgery.* 1991; 109(4):447–454.
22. Powell RJ, Roddy SP, Meier GH et al. Effect of renal insufficiency on outcome following infrarenal aortic surgery. *Am J Surg*. 1997; 174:126.
23. Flanigan DP, Schuler JJ, Keifer T et al. Elimination of iatrogenic impotence and improvement of sexual dysfunction after aortoiliac revascularization. *Arch Surg*. 1982; 117:544
24. Picone AL, Green RM, Ricotta JR. Spinal cord ischemia following operations on the abdominal aorta. *J Vasc Surg*. 1986; 3:94.
25. Hallett JW, Marshall DM, Petterson TM et al. Graft-related complications after abdominal aortic aneurysm repair: Population-based experience. *J Vasc Surg*. 1977; 25:277.
26. O'Connor S, Andrew P, Batt M, Becquemin JP. A systematic review and meta-analysis of treatments for aortic graft infection. *J Vasc Surg*. 2006; 44:38–45.
27. Back, MR. Graft Infection. In: Cronenwett JL, Johnston KW Ed. *Rutherford's Vascular Surgery*. Philadelphia, PA, Saunders Elsevier; 2010: pp. 643–661.

    A comprehensive review of aortic graft infections and their management.
28. van Baalen JM, Kluit AB, Maas J et al. Diagnosis and therapy of aortic prosthetic fistulas: Trends over a 30-year experience. *Br J Surg*. 1996; 83:1729.
29. Reilly LM: Aortic graft infection: Evolution in management. *Cardiovasc Surg*. 2002; 10:372.
30. Szilagyi DE, Smithg FR, Elliott JP et al. A thirty year survey of the reconstructive surgical treatment of aorto-iliac occlusive disease. *J Vasc Surg*. 1986; 3:421–436.
31. Sachdev U, Baril DT, Morrissey NJ et al. Endovascular repair of para-anastomotic aortic aneurysms. *J Vasc Surg*. 2007; 46:636.
32. Liapis CD, Dimitroulis DA, Kakisis JD et al. Incidence of incisional hernias in patients operated on for aneurysm or occlusive disease. *Am Surg*. 2004; 70:550–552.
33. Matsen SL, Krosnick TA, Roseborough GS et al. Preoperative and intraoperative determinants of incisional bulge following retroperitoneal aortic repair. *Ann Vasc Surg*. 2006; 20:183–187.
34. Speziale F, Sbarigia E, Grossi R et al. Inflammatory aneurysms of the abdominal aorta involving the ureters: Is combined treatment really necessary? *J Urol*. 2001; 165:27–31.
35. Savrin RA, High JR. Chylous ascites after abdominal aortic surgery. *Surgery.* 1985; 98:866.
36. Kalman PG, Walker PM, Johnston KW. Consequences of groin lymphatic fistulae after vascular reconstruction. *Vasc Surg*. 1991; 25:210.
37. Gloviczki P, Bergman RT. Lymphatic problems and revascularization edema. In: Bernhard VM, Towne JB, eds. *Complications in Vascular Surgery*, 2nd edn. St. Louis, MO: Quality Medical Publishing; 1991: p. 366.
38. http://www.fistulafirst.org (accessed August 24, 2013).
39. Sidawy AN, Spergel LM, Besarab A et al. The Society for Vascular Surgery: Clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access. *J Vasc Surg.* 2008; 48 (5 Suppl):2S–25S.
40. Silva MB, Hobson RW, Pappas PJ et al. A strategy for increasing use of autogenous hemodialysis access procedures: Impact of preoperative noninvasive evaluation. *J Vasc Surg*. 1998; 27:302–308.
41. Huber T, Ozaki C, Flynn TC et al. Prospective validation of an algorithm to maximize native arteriovenous fistulae for chronic hemodialysis access. *J Vasc Surg*. 2002; 36:452–459.
42. McLafferty RB, Pryor RW, Johnson CM et al. Outcome of a comprehensive follow-up program to enhance maturation of autogenous arteriovenous hemodialysis access. *J Vasc Surg*. 2007; 45:981–985.
43. Berman SS, Gentile AT. Impact of secondary procedures in autogenous arteriovenous fistula maturation and maintenance. *J Vasc Surg*. 2001; 34:866–871.
44. Gibson KD, Gillen DL, Capt MT et al. Vascular access survival and incidence of revisions: A comparison of prosthetic grafts, simple autogenous fistulas, and venous transposition fistulas from the United States Renal Data System dialysis morbidity and mortality study. *J Vasc Surg*. 2001; 34:694–700.
45. Schanzer H. Overview of complications and management after vascular access creation. In: Gray RJ, ed. *Dialysis Access*, Philadelphia, PA: Lippincott Williams & Wilkins; 2002: pp. 93–97.
46. Tordoir JH, Dammers R, van der Sande FM. Upper extremity ischemia and hemodialysis vascular access. *Eur J Vasc Endovasc Surg*. 2004; 27:1–5.
47. Dosluoglu HH, Harris LM. Hemodialysis access: Non thrombotic complication. In: Cronenwett JL, Johnston KW, ed. *Rutherford's Vascular Surgery*. Philadelphia, PA: Saunders Elsevier; 2010: pp. 1137–1154.

    A comprehensive review of complications associated with dialysis access procedures.

48. Hernandez D, Diaz F, Rufino M et al. Subclavian vascular access stenosis in dialysis patients: Natural history and risk factors. *J Am Soc Nephrol*. 1998; 9:1507–1510.
49. Kaku DA, Malamut RI, Frey DJ et al. Conduction block as an early sign of reversible injury in ischemic monomelic neuropathy. *Neurology.* 1993; 43:1126–1130.
50. Darling RC, Austen WG, Linton RR. Arterial embolism. *Surg Gynecol Obst*. 1987; 124:106–114.
51. Papalambros EL, Panayiotopoulos YP, Bastounis E et al. Prophylactic fasciotomy of the legs following acute arterial occlusion procedures. *Int Angiol*. 1989; 8:120–124.
52. Bates GJ, Askew AR. Arterial embolectomy: A review of 100 cases. *Aust N Z J Surg*. 1984; 54:137–140.
53. Velmahos GC, Theodorou D, Demetriades D et al. Complications and nonclosure rates of fasciotomy for trauma and related risk factors. *World J Surg*. 1997; 21:247–253.

Section VII

Orthopaedic

32

Complications of Dislocations

Joshua R. Blomberg and Gregory A. Zych

CONTENTS

A dislocation is a complete disruption of a joint so that the articular surfaces are no longer in contact. Most often, the cause of the dislocation is a traumatic event, and the result is a loss of structural stability of the joint. Traumatic dislocation usually causes pain, deformity of the involved extremity, and marked limitation of joint motion. Appropriate treatment of a dislocation involves careful neurovascular evaluation, radiographic studies, and prompt reduction of the involved joint. Complications and long-term sequela of traumatic dislocation include neurovascular injuries, avascular necrosis, heterotopic bone formation, posttraumatic arthritis, musculotendinous injuries, joint instability, and joint stiffness.

32.1 Vascular Injuries

Vascular injury can occur in the involved extremity because the joint is forcibly displaced from its anatomic location. The medical literature contains reports of 200 cases of vascular injury after shoulder dislocations [1]. Most of these cases involved elderly patients, whose vessels are stiffer and more fragile. The axillary artery consists of three sections that lie medial to, behind, and lateral to the pectoralis minor muscle. The second section of the artery is most commonly injured when the thoracoacromial trunk is avulsed, and the third section is most commonly injured when the subscapular and circumflex branches are avulsed [2]. The mechanism of injury is believed to be the forced abduction and external rotation of the shoulder. Because the humeral head dislocates anteriorly, the artery becomes taut and is displaced forward. Because the artery is relatively fixed at the lateral margin of the pectoralis minor muscle, this forward displacement causes the pectoralis minor muscle to act as a fulcrum over which the artery is deformed and ruptured. Patients with axillary artery injuries resulting from shoulder dislocation experience pain, an expanding hematoma, pulse deficit, peripheral cyanosis, pallor, and neurologic dysfunction. Treatment requires emergent vascular repair.

Vascular injuries have also been reported after elbow dislocations. Approximately 30 cases of brachial artery disruption have been reported after elbow dislocations [3]. Brachial artery injury occurs most often with open dislocations and in the presence of associated fractures.

The most common dislocation resulting in vascular injury is dislocation of the knee (Figure 32.1). Green and Allen, in a review of 245 knee dislocations, found a 32% incidence of popliteal artery injury in association with traumatic dislocation of the tibiofemoral joint [4]. Anatomically, the popliteal artery is tethered proximally to the femur in the adductor hiatus and distally to the fibula by the fibrous bands of the soleus fascia. This tethering of the artery explains the high incidence of vascular injury in association with disruption and subsequent displacement of the knee joint (Figure 32.2). Posterior dislocations (posterior displacement of the tibia) can result in complete transection of the artery because the vessel impacts the posterior rim of the tibial plateau. Anterior dislocations (anterior displacement of

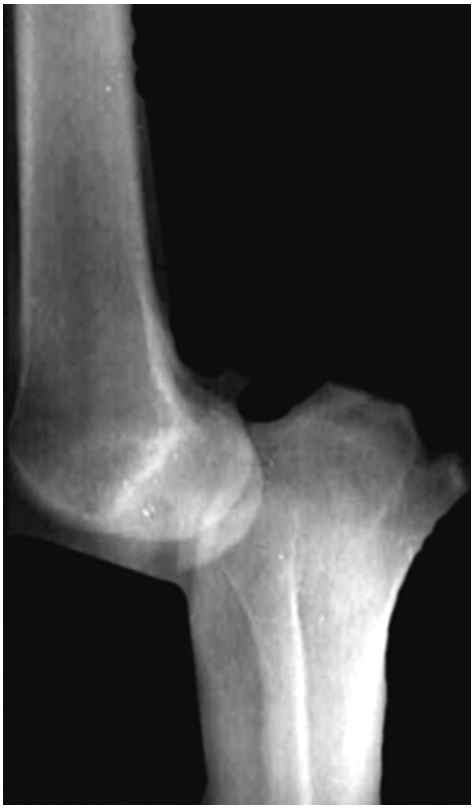
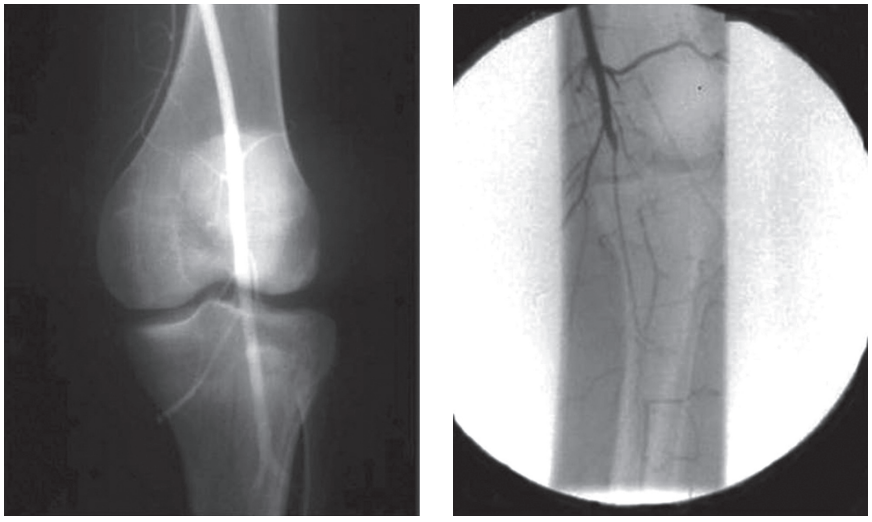


FIGURE 32.1
Posterior dislocation of a knee. The direction of the dislocation is determined by the position of the tibia relative to that of the femur.

the tibia) typically cause a contusion of the vessel with intimal injury. Diagnosis of arterial injury associated with knee dislocation can be reliably and rapidly made noninvasively with the use of the ankle brachial index (ABI). Mills et al. reported a 100% sensitivity, specificity, and positive predictive value for an ABI value below 0.90 in the diagnosis of vascular injury associated with knee dislocation. Furthermore, they were not able to support routine arteriography as a diagnostic tool in the setting of these acute injuries [20]. Popliteal artery injuries are a surgical emergency requiring immediate repair. Consensus exists among traumatologists that circulation to the extremity needs to be restored within 6–8 h if the risk of amputation is to be minimized because an amputation rate of 85% has been reported for cases in which the popliteal artery injury was left untreated or was not repaired within 8 h [5].

32.2 Neural Injuries

In the event of the joint being dislocated, the surrounding neural structures can be contused, stretched, or even lacerated. The sciatic nerve, specifically the peroneal component, is injured in 8%–19% of patients who sustain a posterior dislocation of the hip [6]. Epstein et al. [7] postulated that one of the most important factors in the production of sciatic nerve injury is the marked internal rotation of the hip that occurs at the time of dislocation. The internal rotation causes a winding and tightening of the sciatic



(a) (b)

FIGURE 32.2
Angiogram of a knee after dislocation. Note the beading of the vessel just proximal to the knee joint. This finding indicates intimal damage to the popliteal artery. (a) Normal angiogram of the popliteal artery at the knee and (b) angiogram after knee dislocation with popliteal injury.

nerve. As the hip dislocates posteriorly, it directly contuses or entraps the nerve, and this contusion or entrapment often results in peroneal nerve palsy. These nerve injuries must be recognized early because nerve tissue does not tolerate pressure well and permanent ischemic changes occur quickly. Treatment again involves a thorough physical and radiographic examination followed by a prompt reduction. Most reports of series of patients show that 60%–70% of patients with sciatic nerve palsy eventually experience functional recovery [8].

The axillary nerve is the neural structure most commonly injured in association with shoulder dislocations. Axillary nerve injury has been reported to occur with 5%–33% of all shoulder dislocations; it is most common among elderly patients, after high-energy trauma, and in association with long-standing dislocations [9]. The axillary nerve lies directly across the anterior surface of the subscapularis muscle. As the humeral head displaces the subscapularis muscle and tendon forward and anterior in glenohumeral dislocations, traction and direct pressure are produced on the axillary nerve and result in injury to the neural structures. The diagnosis of nerve injury is made on the basis of neurologic signs such as weakness or numbness after dislocation. Blom and Dahlback demonstrated that the usual sensory testing of the axillary nerve on the skin of the lateral arm just above the deltoid insertion yields unreliable diagnostic findings [10]. Most axillary nerve injuries are traction neuropraxias and will recover completely.

Common peroneal nerve palsies can result after knee dislocations. Typically, 20%–40% of knee dislocations, primarily those involving lateral and posterolateral dislocations of the tibia, result in peroneal nerve palsies [11]. Approximately half of these palsies are permanent. Treatment involves symptomatic care with the use of assistive ambulation devices, possible surgical exploration, tendon transfers, or nerve grafting.

32.3 Avascular Necrosis

Avascular necrosis of the femoral head is a well-recognized complication after posterior dislocation of the hip. The incidence of avascular necrosis varies from 6% to 40% after posterior dislocation of the hip [12]. The cause of the avascular change is believed to be ischemia, caused by damage to the vessels of the ligamentum teres and the retinaculum of Weitbrecht. Both the degree of initial trauma and the time during which the hip remains dislocated have been found to directly correlate with the likelihood of avascular necrosis. Hougaard and Thomsen reported that reduction within 6 h of injury substantially decreased the incidence of avascular necrosis [13]. Therefore, prompt reduction is mandated in all cases of hip dislocation. Avascular necrosis has been reported to occur as long as 2–5 years after posterior dislocation of the hip. Thus, careful monitoring and follow-up must be maintained after reduction if possible avascular changes are to be detected. If avascular necrosis is not diagnosed early, femoral head collapse and traumatic arthritis will result.

32.4 Heterotopic Bone Formation

Heterotopic ossification of the surrounding soft tissue can occur as a result of traumatic joint dislocation. This condition is most frequently noted after elbow dislocation and occurs in as many as 75% of cases [14]. The most common sites of periarticular calcification are the anterior elbow region and the collateral ligaments. Ectopic bone formation is associated with delayed surgical intervention, closed head injury, and aggressive passive elbow joint manipulation after dislocation. If heterotopic bone formation is limiting joint motion, resection of the involved bone should be delayed until the ossification appears mature on plain radiographs, typically 6 months after the initial trauma. Radiographic maturation is characterized by well-defined cortical margins with linear trabeculations.

Ectopic bone formation has also been reported after hip dislocation (Figure 32.3). Epstein reported a 2% incidence of myositis ossificans after hip dislocation [15]. The ectopic bone formation is believed to result from the

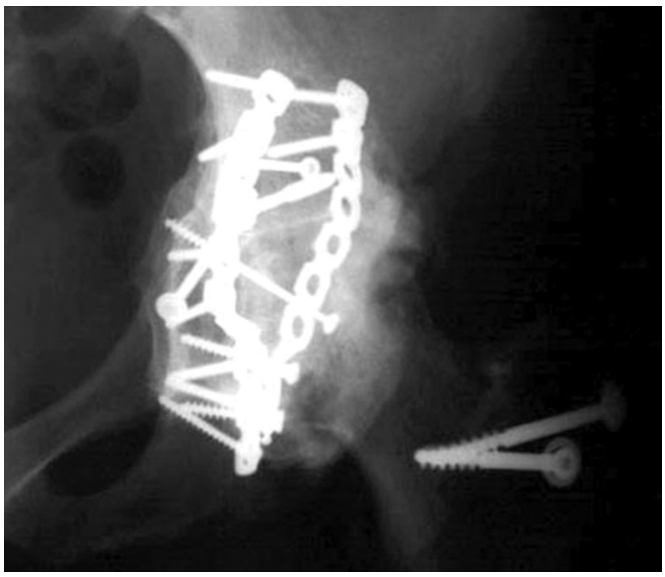


FIGURE 32.3
Heterotopic ossification of the soft tissues surrounding the hip joint after posterior dislocation of the hip.

initial muscle damage, the formation of hematoma, and the influx of inflammatory mediators. The severity of the traumatic dislocation seems to be the best predicator of the occurrence of bone formation in the surrounding tissue. Restriction of motion is not common; therefore, treatment is based on symptoms and the recommended excision time of the extraosseous tissue correlates with the maturity of the ectopic bone.

32.5 Posttraumatic Arthritis

The traumatic process of a joint dislocation can permanently and irreversibly injure the articular cartilage lining of the involved joint. This injury to the cartilage can lead to the development of osteoarthritis. The severity of the initial trauma and the structural damage to the articular surface are the primary factors in determining the later development of posttraumatic arthritis. Hip and ankle dislocations are most commonly associated with the later development of arthritic changes.

32.6 Musculotendinous Injury

Dislocation may disrupt surrounding muscles and tendons and cause a functional disability. Anterior and inferior glenohumeral dislocations can injure the rotator cuff of the shoulder. Tijmes et al. [16] reported rotator cuff tears in association with 28% of anterior dislocations. The frequency of this complication increases with the age of the patient. Thirty percent of patients older than 40 years and 80% of patients older than 60 years typically sustain rotator cuff tears with dislocations [16]. Injury to the rotator cuff causes pain and weakness with external rotation and abduction of the shoulder. Treatment involves appropriate radiographic studies to assess the extent of the rotator cuff tear, conservative therapy, and possibly surgical repair.

32.7 Instability

Traumatic dislocations can seriously injure the supportive structures of the joint, thus rendering it unstable during physiologic motion. This instability is most common after glenohumeral dislocations in young patients. McLaughlin and MacLellan [17] observed recurrence of 95% of 181 primary traumatic dislocations of the shoulder in teenagers. Most of the secondary dislocations occurred within 2 years of the initial traumatic dislocation. This increased rate of instability is linked to the high incidence of disruption of the labral attachment of the anterior–inferior glenohumeral ligament and of fracture of the anterior–inferior glenoid rim (Bankart lesion) after dislocations. Disruption of the anterior–inferior glenohumeral ligament, which is the primary static restraint to anterior shoulder dislocation, increases the patient's susceptibility to repeated dislocation during abduction and external rotation. Treatment involves sling immobilization and possibly surgical intervention.

Hip dislocation can also result in persistent joint instability. Lutter reported the occurrence of repeated dislocations after approximately 1% of hip dislocations [18]. Instability is believed to be linked to repeated injury, a shallow acetabulum or deficient posterior rim, and massive soft-tissue injury. Treatment typically involves some form of capsular plication.

After traumatic elbow dislocation, insufficiency of the lateral elbow ligaments can lead to elbow instability. Injury to the ulnar lateral collateral ligament is primarily responsible for this lack of stability. With injury to the ulnar collateral ligament, the elbow subluxates with elbow supination and flexion. Typically, nonoperative treatment with elbow immobilization is adequate to allow regaining the stability of the joint.

Most dislocations of the knee involve tears of the central pivot, including both the posterior cruciate ligament and the anterior cruciate ligament. The collateral ligaments are also frequently disrupted in dislocations of the tibiofemoral joint. Incompetence of these ligaments—which are the primary stabilizers to anterior, posterior, varus, and valgus stresses—makes the knee quite unstable and severely limits the patient's ability to ambulate. Current treatment guidelines recommend early (within 1–2 weeks) surgical reconstruction or repair of all involved ligamentous structures so that stability and mobility of the knee can be maximized.

32.8 Joint Stiffness

Stiffness of the elbow joint is very common after traumatic dislocation. Most patients will lose the terminal 10°–15° of elbow extension after elbow dislocation. The stiffness is frequently caused by thickening and fibrosis of the anterior joint capsule. Early active mobilization, usually within 2 weeks of injury, is necessary if this complication is to be minimized. Elbow capsular release can be considered if an elbow contracture of more than 30° persists after 6 months of therapy.

How to Avoid Complications of Dislocations

Complications	Methods of Avoidance	Comments
Vascular injuries	Prompt reduction, rapid transfer to trauma center, restoration of normal circulation	Must restore circulation within 6–8 h to minimize risk for amputation [5]; effective treatment can be administered without a preoperative angiogram [16]
Neural injuries	Prompt reduction	Avoid use of tourniquet during subsequent surgical repair of joint in the presence of known neural injury to prevent second ischemic insult [17]
Avascular necrosis	Prompt reduction, close follow-up	Reduction of hip joint within 6 h decreases incidence; close follow-up of the patient is needed to detect the development of a vascular necrosis early
Heterotopic bone formation	Recognize patients at risk; treat with indomethacin or radiation therapy	Radiation after acute elbow trauma may increase nonunion rates [18]
Posttraumatic arthritis	Anatomic surgical reduction of joint surface, restoring joint stability	Ankle is at greater risk of developing post-traumatic osteoarthritis than the knee, therefore restoration of articular congruity of the tibiotalar joint is critical [19]
Musculotendinous injury	Early recognition and advanced diagnostic imaging	Rotator cuff injury rate with anterior dislocations increases with age (Tijmes et al. [16] from original chapter)
Instability	Recognition of at-risk patients, appropriate early surgical and therapy protocols	Teenagers have increased rate of shoulder re-dislocation (McLaughlin and MacLellan [17] from original chapter); presence of a shallow acetabulum or deficient posterior rim can predispose to hip re-dislocation
Joint stiffness	Early active mobilization of elbow	Mobilize elbow within 2 weeks of injury, consider elbow contractural release if contracture of more than 30° persists after 6 months of therapy

Incidence Rates and Complications Associated with Joint Dislocations

Joint	Rate per 1000-Member Years [1]	Complications
Sternoclavicular [2]	0.002	Nonoperative: Anterior dislocations—cosmetic deformity, instability, late DJD and pain; Posterior dislocations—great vessel compromise, tracheal or esophageal injury, brachial plexus compression, dysphagia, voice changes; Operative: migration of transfixion pins, infection, limited shoulder mobility due to resection of medial clavicle, posterior spurring
Acromioclavicular [2]	0.108	Nonoperative: DJD-70% (Type I), 75% (Type II); pain-36% (Type I), 48% (Type II); distal clavicle osteolysis; operative: pin migration, hardware failure, clavicle erosion, recalcification of distal clavicle resection
Scapulothoracic [3]	0.007	Death (11%), amputation (24%), flail upper extremity (39%), ischemic complications (<10%), exsanguination (6%) brachial plexus avulsions (complete vs. incomplete)
Shoulder [4]	0.131	Associated fractures (30%–55%) including Hill–Sachs lesion (68%) and greater tuberosity (12%–15%), neurologic injury (21%–65%), vascular injury (rare)
Elbow [5]	0.076	Brachial artery disruption (rare), ulnar nerve injury (rare), stiffness, heterotopic ossification (75%), DRUJ instability, instability to valgus stress (100%), instability to varus stress (25%–50%)
Wrist [6]	0.007	Loss of 30%–40% total arc wrist motion, post-traumatic arthritis, chronic instability, hardware irritation
Hip [7]	0.012	Ipsilateral knee soft tissue injury (89%), sciatic nerve injury (10%–15%), osteonecrosis (11%–34%), posttraumatic arthritis (16%)
Patella [8,9]	0.567	Osteochondral fracture (52%–76%), loose body (22%), recurrent dislocation (17%)
Knee [10,11]	0.017	Popliteal artery injury (32%–45%), neurologic damage (16%–40%), inability to return to high-demand sports, DVT
Ankle [12,13]	0.01	Posttraumatic arthritis subtalar joint (63%) and midfoot (72%), bone lesions (47%–64%), talar osteonecrosis (10%–29%), talar joint stiffness
Tarsometatarsal [14,15]	0.034	Posttraumatic arthritis (26%), broken hardware (2%–25%), late fracture displacement (<4%), decreased ROM

References

1. Gugenheim S, Sanders RJ. Axillary artery rupture caused by shoulder dislocation. *Surgery.* 1984; 95:55–58.
2. Beeson M. Complications of shoulder dislocation. *Am J Emerg Med*. 1999; 17:288–295.
3. Cohen MS, Hastings H II. Acute elbow dislocation: Evaluation and management. *J Am Acad Orthop Surg*. 1998; 6:15–23.

   This review paper provides a complete and inclusive discussion on the evaluation and management of acute elbow dislocation. Of note, most elbow dislocations are stable after closed reduction. Treatment with early range-of-motion exercises leads to favorable results including low rates of late elbow instability and stiffness.
4. Green NE, Allen BL. Vascular injuries associated with dislocation of the knee. *J Bone Joint Surg Am*. 1977; 59:236–239.
5. Good L, Johnson RJ. The dislocated knee. *J Am Acad Orthop Surg*. 1995; 3:284–292.
6. Stewart MJ, McCarroll HR Jr., Mulhollan JS. Fracture-dislocation of the hip. *Acta Orthop Scand*. 1975; 46:507–525.
7. Epstein HC, Wiss DA, Cozen L. Posterior fracture dislocation of the hip with fractures of the femoral head. *Clin Orthop*. 1985; 201:9–17.
8. Epstein HC. *Traumatic Dislocation of the Hip*. Baltimore, MD: Williams & Wilkins, 1980: pp. 172–215.
9. Rockwood C, Wirth M. Subluxations and dislocations about the glenohumeral joint. In: RW Bucholz, JD Heckman, eds. *Rockwood and Green's Fractures in Adults*. Vol. 2. 5th edn. Philadelphia, PA: Lippincott-Raven Publishers, 2001: pp. 1109–1201.
10. Blom S, Dahlback LO. Nerve injuries in dislocations of the shoulder joint and fractures of the neck of the humerus. A clinical and electromyographical study. *Acta Chir Scand*. 1970; 136:461–466.
11. Siliski JM, Plancher K. Dislocation of the knee. Presented at the *Annual Meeting of the American Academy of Orthopedic Surgeons, 1989. Proceedings of the American Academy of Orthopedic Surgeons*, Las Vegas, NV, 1989.
12. Upadhyay SS, Moulton A. The long-term results of traumatic posterior dislocation of the hip. *J Bone Joint Surg Br*. 1981; 63:548–551.
13. Hougaard K, Thomsen PB. Coxarthrosis following traumatic posterior dislocation of the hip. *J Bone Joint Surg Am*. 1987; 69:679–683.
14. Josefsson PO, Johnell O, Gentz CF. Long-term sequelae of simple dislocation of the elbow. *J Bone Joint Surg Am*. 1984; 66:927–930.
15. Epstein HC. Traumatic dislocations of the hip. *Clin Orthop*. 1973; 92:116–142.
16. Tijmes J, Loyd HM, Tullos HS. Arthrography in acute shoulder dislocations. *South Med J*. 1979; 72:564–567.
17. McLaughlin HL, MacLellan DI. Recurrent anterior dislocation of the shoulder. II. A comparative study. *J Trauma.* 1967; 7:191–201.
18. Lutter LD. Post-traumatic hip redislocation. *J Bone Joint Surg Am*. 1973; 55:391–394.
19. Brinker MR, O'Connor DP. The incidence of fractures and dislocations referred for orthopaedic services in a capitated population. *J Bone Joint Surg Am*. 2004; 86-A(2):290–297.

    This paper provides a guideline as to the overall incidence of fractures and dislocations. The gender-specific and age-specific incidence rates of fractures and dislocation referred for orthopedic service were recorded prospectively from an average of 135,333 patients who were enrolled in a given capitated insurance program over a 3 year period.
20. Mills WJ, Barei DP, McNair P. The value of the ankle-brachial index for diagnosing arterial injury after knee dislocation: A prospective study. *J Trauma.* 2004;56(6):1261–1265.

    The sensitivity, specificity, and positive predictive value of an ankle-brachial index value lower than 0.90 was 100%, and the negative predictive value of an ankle-brachial index of 0.90 or higher was 100%.

33

Complications of Amputations

Boulos Toursarkissian

CONTENTS

33.1 Introduction

Indications for and complications from amputation have changed over time. Early amputations in the history of mankind were mostly from trauma and associated with hemorrhage as the major complication, followed closely by infection. While both of these have improved, mortality remains a major complication today, mostly because of advancing age and debility of patients undergoing amputation today. Peripheral vascular disease is responsible for approximately 60%–70% of extremity amputations nowadays, diabetes mellitus for 10%–20%, and trauma for another 10%–20% [1].

Complications from amputation can be divided into (1) local issues such as wound necrosis and nonhealing, infection, bleeding and hematomas, contractures, as well as incisional and phantom pain and (2) systemic complications such as mortality, cardiac or pulmonary issues, and venous thromboembolism.

33.2 Local Wound Complications

These are the most common complications following amputation surgery. A recent review of a large national database found a wound occurrence rate of 10.4% for below-the-knee amputations (BKA) and 7.2% for above-the-knee amputations (AKA) [2]. These numbers represent some of the better ones reported in the literature, with most series reporting much higher rates of wound complications for both BKA and AKA.

Conditions that interfere with wound healing, such as diabetes mellitus, malnutrition, or steroid treatment, are associated with a higher rate of wound infections, dehiscence, and repeated amputation [3]. Prior radiation in the case of amputation for malignancy also increases the risk of complications. Patients with uncontrolled infections also have a higher rate of complications. The general incidence of wound infection is 10%–30% but may be as high as 60% when the limb is infected [4]. Smokers also have a higher rate of infection than nonsmokers (42% vs. 22%) [5]. Nicotine induces the release of catecholamines, which reduce cutaneous blood flow. Patients with chronic renal failure have a higher complication rate (61% vs. 9%) than patients without renal failure [6]. A number of studies have also shown that prolonged delay of needed amputation is associated with increased risk of complications such as wound problems in addition to increased risk of deep venous thrombosis (DVT), phantom pain, and delirium [7,8]. It is still not very clear as to whether a failed prior open vascular reconstruction increases the risk of local complications following amputation. A prospective study of

234 amputations determined that patients who had a previous bypass had a higher rate of stump infection and required, in general, higher-level amputations than patients without prior bypass [9]. In the case of traumatic amputations, it is important that all devitalized tissues be appropriately debrided and irrigated to decrease the risk of infection.

Diabetic control and nutritional status should be optimized as much as possible. Any infection should be grossly controlled prior to definitive amputation closure; debridements and prior open amputations may be required beforehand. In extreme situations, in which severe infection requires an emergent amputation, an open guillotine procedure may be performed first, followed by definitive higher amputation several days later. Anaerobic and mixed flora infections should be covered with broad-spectrum intravenous antibiotics in diabetics. Even in noninfected cases, prophylactic antibiotics should be considered in the perioperative period. The use of prophylactic antibiotics has been found to reduce the rates of wound infection and repeated amputation by as much as 50% [10]. Ideally, smoking cessation should take place a week or more before elective amputation. Amputation should be performed expeditiously. If the patient is critically ill and the limb has wet gangrene or severe acute ischemia, a physiologic bedside cryoamputation using dry ice limb immersion and tourniquets can be considered as a temporizing measure to control sepsis and allow physiologic stabilization [11]. When cryoamputation is performed, formal surgical amputation may be deferred for 24–48 h and may reduce mortality in critically ill patients.

Failure to heal is not uncommon in limbs with ischemic issues. Some studies have reported nonhealing rates around 20% [12]. In those limbs, more distal amputations have a higher risk of nonhealing [2]. Paradoxically, for BKA, younger patients seem more prone to wound problems possibly because of more aggressive vascular disease [2]. For AKA, an increased body mass index has been associated with increased wound complications. The most common reason for failure to heal is low oxygen delivery to the wound because of primary vascular insufficiency related to an incorrect choice of the level of amputation. The more distal the amputation level, the more limited the oxygen delivery to the tissues and greater the likelihood of wound breakdown. Other reasons for healing failure are increased pressure in the wound caused by undrained hematoma or short flaps, sutures that are too tight, infection, an excessively long fibula, inadequate beveling of the tibia, and/or immunosuppressive medications. Drains are still controversial but used occasionally to prevent hematomas that may affect subsequent healing. Some studies suggest a higher risk of infection with drain use [13].

Meticulous surgical technique is important to minimize the risk of complications. For instance, usage of cautery at the skin edges should be avoided, sutures should be left in place for about 3 weeks before removal, and perioperative low-dose anticoagulation should be used to minimize stump vessel thrombosis.

A more distal amputation increases the rehabilitation potential at a cost of increased wound complications and nonhealing. A nonambulatory or neurologically debilitated patient or one with a joint contracture is likely best served by a more proximal amputation. For example, a chronically bed-bound patient with gangrene of the foot may have a more optimal outcome and reduced hospital length of stay when treated with prompt AKA, even though BKA would have initially sufficed for control of sepsis.

There have been several methods proposed to try predict optimal amputation levels. Transcutaneous oxygen measurements (TcPO2) are often used and values greater than 30 mmHg are recommended. A palpable distal pulse is also a good prognostic indicator [14]. Intraoperatively, the muscle should appear viable with arterial bleeding and contraction with electric stimulation. Adequate but not excessive muscle coverage should be available.

33.3 Pain Issues

Neuroma of the stump can cause severe deep and dull localized pain that persists for months after amputation. A neuroma will form after nerve transection but normally does not cause discomfort unless the area is subjected to excessive pressure or is not covered by sufficient soft tissue. The best strategy for minimizing the clinical manifestations of neuroma is cutting the nerve deep in the muscle tissue and allowing it to retract during the primary operation. Opinions vary as to whether ligating the nerve helps prevent or promote pathologic neuroma formation. Coverage of the nerve stump with adequate soft tissue to avoid trauma from the prosthesis seems intuitive.

The most common postamputation pain syndrome is phantom pain. Almost all amputees experience phantom limb sensation, which is the feeling that the missing limb is still present. In some, however, this sensation presents as a poorly localized pain. Its incidence is at least 30%–50% [1]. Three major characteristics define this syndrome: (1) pain that lasts for some time after the wound has healed; (2) pain elicited by

the activation of trigger zones; and (3) pain that resembles the pain experienced preoperatively [16]. A high level of pre-amputation pain in the limb may predispose to phantom limb pain [17]. Furthermore, the likelihood of phantom pain is correlated with the site of the amputation; the higher the level of amputation, the more likely the phantom pain. Phantom pain is more likely after upper-extremity amputations than after lower-extremity amputations. The etiology is very complex and treatment methods included narcotics, gabapentin, sensory discrimination training, and the use of more functional prosthesis and aggressive rehabilitation [18]. A recent prospective trial has suggested that optimized perioperative analgesia, in terms of maximal use of narcotics and gabapentin agonists, reduces chronic phantom limb pain [19].

The third pain syndrome seen after amputations is causalgia or reflex sympathetic dystrophy (RSD). It is more often seen after traumatic amputations. It presents with a burning pain, hyperesthesias, and edema. In its chronic stage, skin mottling and contraction will happen. Sympathectomy can be helpful treatment when done in the acute phase.

33.4 Prosthesis Problems

Failure of primary fitting of the prosthesis is usually related to inadequate shaping of the stump, or to flexion contracture of the proximal joint (more than 9° at the hip or 15° at the knee). Contracture in turn can be due to failure to maintain the proper postoperative position of the stump, or due to failure to provide adequate physical therapy. The use of a cast postoperatively can help prevent contractures; a cast must be carefully padded, however, to prevent pressure necrosis, especially at the patella in dysvascular limbs. Inadequate shaping of a stump is sometimes related to a stump being too short or too close to a joint; appropriate preoperative planning is most helpful to avoid this.

Failure of fitting after initial successful fitting is usually due to progressive stump shrinkage. Other causes can be the development of calluses or ulcers, persistent neuropathic pain or progression of peripheral arterial disease with ischemic pains, formation of bone spurs, or overgrowth. Orthopedic problems in the proximal joints can also interfere with successful prosthetic use. Refitting with a new prosthesis may be required. Bursitis can sometimes develop when there is increased friction or pressure on a moving part; revision of the prosthesis is usually needed to recess the area of increased pressure.

33.5 Long-Term Dermatologic Complications

Dermatologic problems on the stump can affect 15%–40% of cases, depending on the definition. The prevalence is higher if one includes wounds and abscesses [20]. The combination of pressure and friction within the prosthesis socket can cause epidermoid cysts, which may become infected and are very likely to recur, even after surgical removal. The most dramatic skin complication is verrucous hyperplasia. Proximal constriction in the socket without adequate distal tissue support causes extreme skin edema with wart-like appearance and occasional exudation. Surgical reshaping of the distal stump will gradually correct this problem. Prosthetic revision is also likely to be required.

33.6 Mobility Complications and Return to Function

Ambulating with a prosthesis requires increased energy. A patient with a unilateral BKA needs at least 10% more energy for ambulation than a nonamputee of similar age. The energy requirement for ambulation is increased by 50% for unilateral AKA [21]. Many elderly patients who undergo amputation are debilitated or have very limited cardiopulmonary reserve and cannot meet the increased energy requirements for ambulation. Any postoperative complication also decreases the likelihood of successful ambulation. Psychological factors such as depression or anxiety also decrease the likelihood of successful rehabilitation [22]. Finally, in 40%–50% of cases, the patient will require a contralateral amputation within 2 years [23], further decreasing the likelihood of successful mobility. Successful fitting of prosthesis can be expected after 75% of BKA and after 50% of AKA [24]. However, this does not necessarily equate with successful ambulation. About 60% of those patients will still be able to use a prosthesis 3 years after amputation [25]. More recent studies looking at patient-centered measures found that only 37% were able to return to or exceed the baseline mobility level they had before amputation [22]. Early aggressive physical therapy likely increases rehabilitation potential.

Return to work is often not an issue in amputees secondary to arterial disease, given advanced age and comorbidities. However, even in younger patients with traumatic amputations, return to work is not uniform. Recent studies in war veterans have suggested that individuals with higher degree of education are more likely to return to employment than those with lesser

degrees of education [26,27]. Those who return to work are more likely in turn to experience worthwhile use of the prosthesis. Depression is very common after amputation, especially in younger individuals, and may persist for longer than a year. Successful rehabilitation decreases the incidence of depression.

33.7 DVT and Other Systemic Complications

Patients undergoing amputation are often elderly with many comorbidities. Therefore, cardiac and pulmonary complications should be anticipated and appropriate measures taken. Cardiac complications are the most common systemic complications (5%–10%), with heart failure being the most common and MI (myocardial infarction) the next most common [28,29]. Beta-blockers should be continued whenever possible. Pulmonary complications happen in about 5% of cases [29]. Incentive spirometry should be encouraged. Urinary catheters should be removed early while providing measures to avoid contamination of the stump dressings. Mobility is often impaired and appropriate use of unfractionated or low-molecular-weight heparins (LMWH) for DVT prophylaxis should be encouraged. Without prophylaxis, DVT will happen in at least half the patients [30,31]. LMWH use will decrease the incidence of DVT to about 10% [32]. Postoperative stroke occurs in about 1% of patients after amputation [33].

33.8 Mortality

Mortality rates after amputation remain high, especially in patients with peripheral arterial disease, a likely reflection of associated comorbidities like atherosclerosis. Mortality rates are even higher with more proximal amputations. This reflects a selection bias, in that patients undergoing more proximal amputation have a higher burden of atherosclerotic disease. Overall, the perioperative mortality rate has been reported at 10%–30% [34], although some series have reported lesser degrees of mortality—[35] 2% for BKA and 9% for AKA. The amputation associated with the highest mortality is hip disarticulation. The mortality rate associated with this procedure is as high as 60% when it is required after trauma, probably because the victim has sustained a devastating amount of energy transfer in the initial trauma [36]. Patients with chronic renal failure have a higher mortality rate (24% vs. 7%) and a higher complication rate (61% vs. 9%) than patients without renal failure [33]. The mortality rate after AKA that followed a failed BKA is 21%, emphasizing again the need for proper level selection for initial amputation.

A recent study looking at the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database reported a 7.6% 30-day mortality and risk factors included advanced age, dialysis, low albumin, impaired sensorium, alcohol abuse, recent weight loss, dyspnea, and increased bilirubin [37]. Unfortunately, most of those conditions are beyond the surgeon's control.

Long-term survival is also decreased. The estimation is that one-third of patients who undergo lower-limb amputation will die by the second postoperative year and two-thirds will die within 5 years [34,38]. Long-term cardiovascular complications are also increased [38].

33.9 Upper-Extremity Amputations

Upper-extremity amputations are less common than lower-extremity ones, are typically related to trauma and therefore, occur in younger individuals. Systemic complications including mortality are therefore less frequent and will mostly relate to complications of trauma, including possibly infections. Excluding amputations from vascular disease, upper-extremity amputations have a lower risk of flap necrosis and nonhealing as compared to lower-extremity amputations. Long-term phantom pain will occur in at least a third of patients. Psychosocial disability is more frequent with upper-extremity amputations compared with lower-extremity ones. Return to work is more difficult even with just digital or hand amputations. In general, every effort should be made to preserve as much length to the limb as possible even if this requires the use of grafts or flaps. Longer stumps correlate with increased postoperative function. Through the joint amputations should therefore be used more frequently. Technically, for upper-extremity amputations, referral to subspecialists is important, as there are many techniques being developed to allow selective muscle reinnervation, which then allow the use of specialized myoelectrically controlled prostheses [39].

33.10 Summary

A high rate of postoperative complications can be anticipated after amputations. The surgeon must often make

a difficult choice between the procedure that provides the best chance for rehabilitation and the procedure that carries the lowest complication rate.

Incidence of Common Complications

Complications	Incidence (%)	References
Delayed wound healing	7–10	[2]
Wound infection	10–30	[3,4]
Phantom limb pain	30–50	[15]
Dermatologic complications	15–40	[20]
Lack of mobility	At least 50	[22,25]
Mortality	10–30	[26,29]

Measures to Prevent or Decrease Complications

Delayed healing	Careful selection of amputation level; minimize cautery at wound edges; low-dose anticoagulation; leave skin sutures for 3 weeks; control edema with wraps or elevation; smoking cessation; nutritional support; hyperbaric oxygen treatment postoperatively
Wound infection	Prophylactic antibiotics; careful debridement of devitalized tissues; staging of amputations in cases of severe foot infection; diabetic control
Pain	Adequate coverage of nerve stump; use of gabapentin; aggressive rehabilitation; sympathectomy for causalgia
Prosthetic difficulties	Create a stump of adequate length; adequate but not excessive soft tissue padding
Dermatologic problems	Adequate fitting of prosthesis; no excess soft tissue at the stump
Mobility problems	Do amputation as distally as safely possible; control psychological issues; aggressive rehabilitation and medical management; carefully monitor contralateral extremity
Mortality	General medical management

References

1. Hansson J. The leg amputee. A clinical follow-up study. *Acta Orthop Scand*. 1964; 10(Suppl 69):1–104.
2. Hasanadka R, McLafferty RB, Moore CJ, Hood DB, Ramsey DE, Hodgson KJ. Predictors of wound complications following major amputation for critical limb ischemia. *J Vasc Surg*. 2011; 54: 1374–1382.

   A current review of predictors of complications focusing mostly on patients with peripheral arterial disease.
3. Weiss GN, Gorton TA, Read RC, Neal LA. Outcomes of lower extremity amputations. *J Am Geriatr Soc*. 1990; 38:877–883.
4. Desai Y, Robbs JV, Keenan JP. Staged below-knee amputations for septic peripheral lesions due to ischemia. *Br J Surg*. 1986; 73:392–394.
5. Lind J, Kramhoft M, Bodtker S.The influence of smoking on complications after primary amputations of the lower extremity. *Clin Orthop*. 1991; 267:211–217.
6. Dossa CD, Shepard AD, Amos AM et al. Results of lower extremity amputations in patients with end-stage renal disease. *J Vasc Surg*. 1994; 20:14–19.
7. Weiss GN, Gorton TA, Read RC, Neal LA. Outcomes of lower extremity amputations. *J Am Geriatr Soc*. 1990; 38:877–883.
8. Rosenberg N, Adiarte E, Bujdoso L, Backwinkel KD. Mortality factors in major limb amputations for vascular disease: A study of 176 procedures. *Surgery.* 1970; 67:437–441.
9. Van Niekerk LJ, Stewart CP, Jain AS. Major lower limb amputation following failed infrainguinal vascular bypass surgery: A prospective study on amputation levels and stump complications. *Prosthet Orthot Int*. 2001; 25:29–33.
10. Norlin R, Fryden A, Nilsson L, Ansehn S. Short-term cefotaxime prophylaxis reduces the failure rate in lower limb amputations. *Acta Orthop Scand*. 1990; 61:460–462.
11. Bunt TJ. Physiologic amputation for acute pedal sepsis. *Am Surg*. 1990; 56(9):530–532..
12. Clyne CA. Selection of level for lower limb amputation in patients with severe peripheral vascular disease. *Ann R Coll Surg Engl*. 1991; 73:148–151.
13. Coulston JE, Tuff V, Twine CP, Chester JF, Eyers PS, Stewart AH. Surgical factors in the prevention of infection following major lower limb amputation. *Eur J Vasc Endovasc Surg*. 2012; 43(5):556–560.
14. van den Broek TA, Dwars BJ, Rauwerda JA, Bakker FC. A multivariate analysis of determinants of wound healing in patients after amputation for peripheral vascular disease. *Eur J Vasc Surg*. 1990; 4:291–295.
15. Melzack R. Sherman RA, Sherman CJ, Parker L. Chronic phantom and stump pain among American veterans: Results of a survey. *Pain.* 1984; 18:83–95.
16. Melzack R. Phantom limb pain: Implications for treatment of pathological pain. *Anesthesiology.* 1971; 35:409–419.
17. Foell J, Bekrater-Bodmann R, Flor H, Cole J. Phantom limb pain after lower limb trauma: Origins and treatments. *Int J Low Extrem Wounds.* 2011; 10(4):224–245.
18. Malone JM, Moore WS, Leal JM, Childers SJ. Rehabilitation for lower extremity amputation. *Arch Surg*. 1981; 116:93–98.
19. Karanikolas M, Aretha D, Tsolakis I, Monantera G, Kiekkas P, Papadoulas S, Swarm RA, Filos KS. Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence and frequency. *Anesthesiology.* 2011; 114:1144–1154.
20. Bui KM, Raugi GJ, Nguyen VQ, Reiber GE. Skin problems in individuals with lower limb loss: Literature review and proposed classification system. *J Rehab Res Dev*. 2009; 46:1085–1090.
21. Huang CT, Jackson JR, Moore NB et al. Amputation: Energy cost of ambulation. *Arch Phys Med Rehabil*. 1979; 60:18–24.
22. Norvell DC, Turner AP, Williams RM, Hakimi KN, Czerniecki JM. Defining successful mobility after lower extremity amputation for complications of peripheral vascular disease and diabetes. *J Vasc Surg*. 2011; 54:412–419.

23. Bodily RC, Burgess EM. Contralateral limb and patient survival after leg amputation. *Am J Surg*. 1983; 146:280–282.
24. Steinberg FU, Sunwoo I, Roettger F. Prosthetic rehabilitation of geriatric amputee patients: A follow-up study. *Arch Phys Med Rehabil*. 1985; 66:742–745.
25. De Luccia N, Pinto MA, Guedes JP, Albers MT. Rehabilitation after amputation for vascular disease: A follow-up study. *Prosthet Orthot Int*. 1992; 16:124–128.
26. Frank RG, Kashani JH, Kashani SR et al. Psychological response to amputation as a function of age and time since amputation. *Br J Psychiatry.* 1984; 144:493.
27. Weed R, Kirkscey M, Mullins G et al. Return to work rates in case of amputation. *J Rehabil Outcomes Meas*. 1997; 1:35–39.
28. Nehler MR, Coll JR, Hiatt WR et al. Functional outcome in a contemporary series of major lower extremity amputations. *J Vasc Surg*. 2003; 38:7–14.
29. Aulivola B, Hile CN, Hamdan AD et al. Major lower extremity amputation: Outcome of a modern series. *Arch Surg*. 2004; 139:395–399.
30. Huang ME, Johns JS, White J, Sanford K. Venous thromboembolism in a rehabilitation setting after major lower-extremity amputation. *Arch Phys Med Rehabil*. 2005; 86:73–78.
31. Burke B, Kumar R, Vickers V et al. Deep vein thrombosis after lower limb amputation. *Am J Phys Med Rehabil*. 2000; 79:145–149.
32. Lastória S, Rollo HA, Yoshida WB et al. Prophylaxis of deep-vein thrombosis after lower extremity amputation: Comparison of low molecular weight heparin with unfractionated heparin. *Acta Cir Bras*. 2006; 21:184–186.
33. Nowygrod R, Egorova N, Greco G et al. Trends, complications, and mortality in peripheral vascular surgery. *J Vasc Surg*. 2006; 43:205–216.
34. Kristensen MT, Holm G, Kirketerp-Moller K, Krasheninnikoff M, Gebuhr P. Very low survival after non traumatic lower limb amputation in a consecutive series: What to do? *Interact Cardiovasc Thorac Surg*. 2012; 14:543–547.
35. Kald A, Carlsson R, Nilsson E. Major amputation in a defined population: Incidence, mortality and results of treatment. *Br J Surg*. 1989; 76:308–310.
36. Endean ED, Schwarcz TH, Barker DE, Munfakh NA, Wilson-Neely R, Hyde GL. Hip disarticulation: Factors affecting outcome. *J Vasc Surg*. 1991; 14:398–404.
37. Davenport DL, Ritchie JD, Xenos ES. Incidence and risk factors for 30 day postdischarge mortality in patients with vascular disease undergoing major lower extremity amputation. *Ann Vasc Surg*. 2012; 26:219–224.

    A recent review of a large national database based on ACS NSQIP data.
38. Abola MTB, Bhatt DL, Duval S, Cacoub PP, Baumgartner I, Keo H, Creager MA, Brennan DM, Steg PhG, Hirsch AT. Fate of individuals with ischemic amputations in the REACH registry: Three year cardiovascular and limb related outcomes. *Atherosclerosis.* 2012; 221:527–535.
39. Kuiken TA, Miller LA, Lipschutz R et al. Targeted reinnervation for enhanced prosthetic arm function in woman with a proximal amputation. *Lancet.* 2007; 369:371–380.

34

Complications of Treatment of the Hand

John Stanton

CONTENTS

The most common complication of any hand injury is stiffness, which results from the collaborative effects of inflammation, swelling, and immobility. Attempts at preventing stiffness are much more effective and worthwhile than later attempts at correcting established stiffness [1].

34.1 Complications of Fracture Care

Optimum bone and joint reconstruction goals are prompt anatomic reduction of injury and stable skeletal fixation with the least amount of additional soft-tissue disruption. Tight casts may result in local pressure sores, discomfort, and, in the worst scenario, vascular compromise and compartment syndrome. The risk of complications is highest when circumferential casts are applied after closed reduction of an elbow or forearm fracture on the day of injury. In this situation, the risk may be reduced by splitting ("bivalving") the cast into two separate longitudinal sections immediately after application.

34.1.1 Radius and Ulna

Distal radius fractures account for about one of every six fractures and three of four forearm fractures seen in the emergency room. They are most common in children of both sexes between the ages of 6 and 10 years and in women between the ages of 60 and 69 years.

Operative treatments include external fixation, percutaneous pinning, open reduction, and any combination of these. Poor final outcome is more likely when the fracture is initially very displaced, when the distal radioulnar joint is involved, when the radiocarpal joint is comminuted, when there is residual shortening of >2 mm, or when there is dorsal angulation of >15°. Redisplacement will occur with about one of three closed reductions, and the final outcome when redisplacement occurs and repeated closed manipulations are required will be good or excellent for only one of three fractures [2]. This is due to dorsal comminution in which there is no supporting posterior cortex. Pinning, plating, and posterior grafting can help prevent recurrent dorsal tilt (apex volar angulation).

Malunion should be avoided because secondary surgery for distal radius malunion is successful in only three of four cases [3]. Nonunion is uncommon. Complex regional pain syndrome and finger stiffness occur to some degree in as many as one of three patients. Loss of motion is also common with loss of full supination and extension. Tendon rupture [4] may occur early or late, with either open or closed reduction, and may be related to fracture displacement, hardware irritation [5], or ulnar head prominence. Median or ulnar nerve compression may develop early or late after this fracture.

Distal radius malunions are common after closed reduction of an unstable fracture pattern, resulting in dorsal or volar angulation, shortening, and loss of radial inclination. Functional outcome correlates poorly with radiographic changes.

Posttraumatic arthritis is most common among young adults and is seen on radiographs of two out of three young patients, years after injury. Fortunately many of these patients have no symptoms.

Distal radius nonunions are uncommon, but usually symptomatic due to progress of angulation and symptoms from distal radioulnar joint disruption.

Radial shortening (relative to the distal ulna) results in an "ulnar plus" situation that causes impingement against the distally placed triangular fibrocartilage complex (TFCC). This complex comprises stabilizing ligaments and a meniscoid cartilage between the distal ulna and the carpus.

A relatively long ulna can result in damage to the intervening cartilage, loss of ulnar deviation, cosmetic deformity, and pain.

Treatment includes ulnar shortening, distal ulna resection, and/or radial lengthening if bracing is unacceptable.

34.1.2 Scaphoid

34.1.2.1 Vascular Supply

Scaphoid fractures are prone to healing problems because of the combination of poor perfusion of the proximal fracture fragment and strong forces across the fracture site because of normal wrist mechanics. The scaphoid receives its blood supply through a single artery that enters the distal pole and works its way proximally. The result is often limited vascularity to the fracture site as well as disvascularity to the proximal fragment. Scaphoid fractures may heal in malunion ("humpback deformity"), but delayed union and nonunion are much more common and are difficult problems. Left untreated, scaphoid nonunions naturally progress to a characteristic pattern of collapse followed by wrist arthritis, initially involving the radioscaphoid and capitolunate joints. Unstable, displaced, or proximal fractures are prone to nonunion even with prolonged casting and should be considered for early open reduction.

34.1.2.2 Collapse and SNAC

Scaphoid fractures usually occur as an isolated fracture but may be part of a larger injury complex. Oblique, comminuted, and proximal fracture lines are prone to nonunion. Nonunion may be radiographically subtle, cystic, or hypertrophic. The majority of scaphoid nonunions progress to a pattern of radioscaphoid and midcarpal arthritis referred to as scaphoid nonunion advanced collapse or "SNAC wrist."

34.1.2.3 Arthritis

Scaphoid nonunion eventually leads to progressive wrist arthritis in many patients and loss of ROM.

34.1.2.4 Scapholunate Injury

Injuries to the scapholunate ligament result from the same mechanism of injury as scaphoid fractures. Left untreated, scapholunate dissociation naturally progresses to a characteristic pattern of wrist arthritis, initially involving the radioscaphoid and capitolunate joints, referred to as scapholunate advanced collapse, or "SLAC wrist" [6]. Treatment options include partial wrist fusion, proximal row carpectomy, and a variety of soft-tissue ligament reconstruction procedures.

Scapholunate dissociation may require dynamic stress views to demonstrate. The tear of the scapholunate ligament allows the scaphoid to drop and the lunate to tilt dorsally, since the two bones are no longer connected. On a lateral x-ray, the result is that the angle between the axis of the scaphoid and a line across the upper lunate drops from 47° to 10°–15°. Furthermore, the capitate and metacarpals (MCs) shift dorsally and are no longer in line with the radius. This is a dorsal intercalated segmental instability (DISI). AP views may show a gap or space between the scaphoid and lunate. With time and progression the capitate may drop down into the scapholunate interval with a shortened, widened carpus.

Most carpal and hand injuries in children are treated nonsurgically. However, surgical treatment is often required for certain clinical situations. Complications resulting from pediatric hand fractures, dislocations, and soft-tissue injuries are most commonly caused by a failure to identify and treat an injury requiring surgery [7].

34.1.2.5 Metacarpal Fractures

Metacarpal (MC) fractures may result from a direct blow—or, more commonly, from striking a blow with a fist against a stationary, solid, innocent object. Impact against the distal fifth MC can result in an impacted or angulated distal MC fracture, a midshaft fracture, or a proximal dislocation. Distal angular fractures of the fifth are better tolerated because of the mobility of the fourth and fifth MCs compared to the relatively immobile second and third MCs.

Shortening and overlap of third and fourth midshaft MC fractures is somewhat limited due to the suspensory natatory ligaments found between the MC heads.

Fractures need to heal in anatomic position, and the soft tissues must be supple so that the fingers can move through a useful range of motion [8]. Rotational deformity is more a result of incorrect fixation than a direct result of the fracture itself. In flexion, the fingertips converge toward a common point in the proximal palm, approximately the distal pole of the scaphoid. This can be helpful in quickly assessing for rotational malalignment of a MC or phalangeal fracture. Rotational malalignment of MC fractures may not be apparent with the fingers in extension. Reduction of rotational malalignment should be checked in the acute setting (and during surgery for internal fixation) by placing the fingers in full flexion.

Diaphyseal fractures of the MCs and phalanges are common injuries that can lead to impairment of hand function. The fracture pattern and soft-tissue injury vary with the mechanism of injury. The imbalance of the flexor and extensor forces created by displaced fractures will often produce a secondary angulatory deformity. Nonoperative treatment is indicated for reducible and stable fracture configurations. Irreducible or unstable fracture patterns require open or closed reduction and fixation. MC fractures are prone to angulation and shortening and often fail closed treatment with splinting or casting. Surgical options include closed reduction

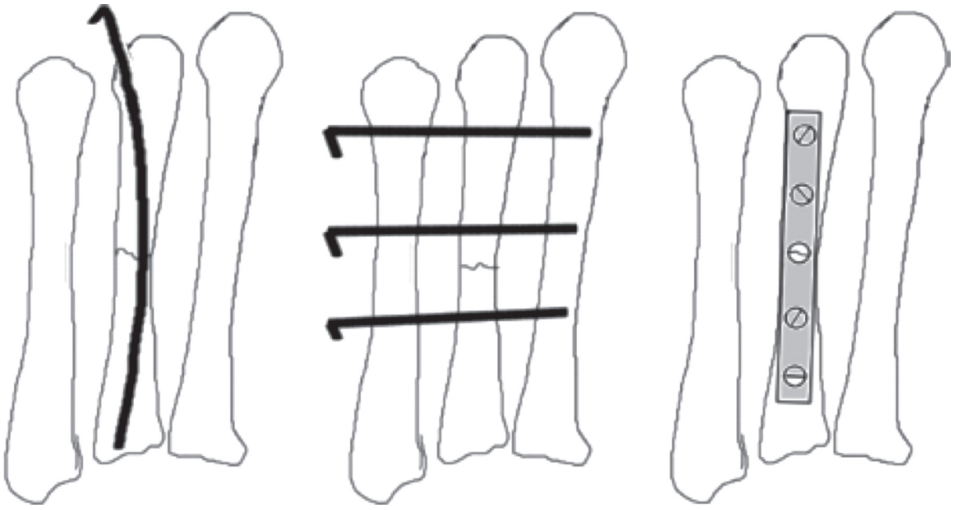


FIGURE 34.1
Treatment options for unstable diaphyseal metacarpal fractures include (a) closed reduction and (b) percutaneous pinning (CRPP) or (c) open reduction and plate fixation (ORIF).

and pinning with transverse pins or with a single longitudinal intramedullary pin. Open reduction and plating reduce the risk of rotational deformity and pin tract infections, but may require another surgery for hardware removal (Figure 34.1).

34.1.2.6 Complications of Finger Immobilization

Splints and other supportive dressings maintain a posture that may be helpful or detrimental. Often, splints fabricated for comfort in the emergency room restrain joints in positions that promote stiffness.

The generic "safe position" for hand immobilization is intended to prevent the usual pattern of stiffness after hand disuse. The three features are maintenance of interphalangeal joint (IPJ) extension, metacarpophalangeal (MCP) joint flexion, and first web-space span (Figures 34.2 and 34.3).

Treatment of fractures of the proximal phalanx and MCs is based on the presentation of the fracture, degree of displacement, and difficulty in maintaining fracture reduction. A wide array of treatment options exists for the variation in fracture patterns observed. Inherently stable fractures do not require surgical treatment; all other fractures should be considered for additional stabilization. In general, of the many combinations of internal fixation possible, Kirschner wires and screw-and-plate fixation predominate. Transverse and short oblique proximal phalanx fractures generally are treated with Kirschner wires, although a stable short oblique transverse shaft fracture can be managed with an intrinsic plus splint or Cobra cast (Figure 34.3). Hand fractures are common injuries and most do not require open surgical treatment [9] (Figure 34.4).

34.1.2.7 Distal Phalanx Fractures

Displaced fractures of the distal phalanx may give rise to nonunion if they are not reduced and provided with adequate internal fixation. Typically, these cannot be pinned if comminuted or often asymptomatic if left untreated.

Mallet deformity is a drooping of the distal phalanx due to an incompetent extensor mechanism. Often the result of a blow directed against an extended finger, the extensor tendon may be stretched or torn or may avulse its boney attachment.

Tendon rupture should be repaired open with a stabilizing pin across the DIP joint. Attempts at splinting are often unsuccessful due to noncompliance.

A tendon stretch injury will not respond to splinting, and again requires open tendon plication and a protective pin across the joint.

34.1.2.8 Mallet fx

Mallet fracture dislocations of the distal IPJ should be distinguished from simple stable displaced mallet fractures because outcome after conservative management of such dislocations is poor as the result of joint incongruity (Figures 34.5 and 34.6).

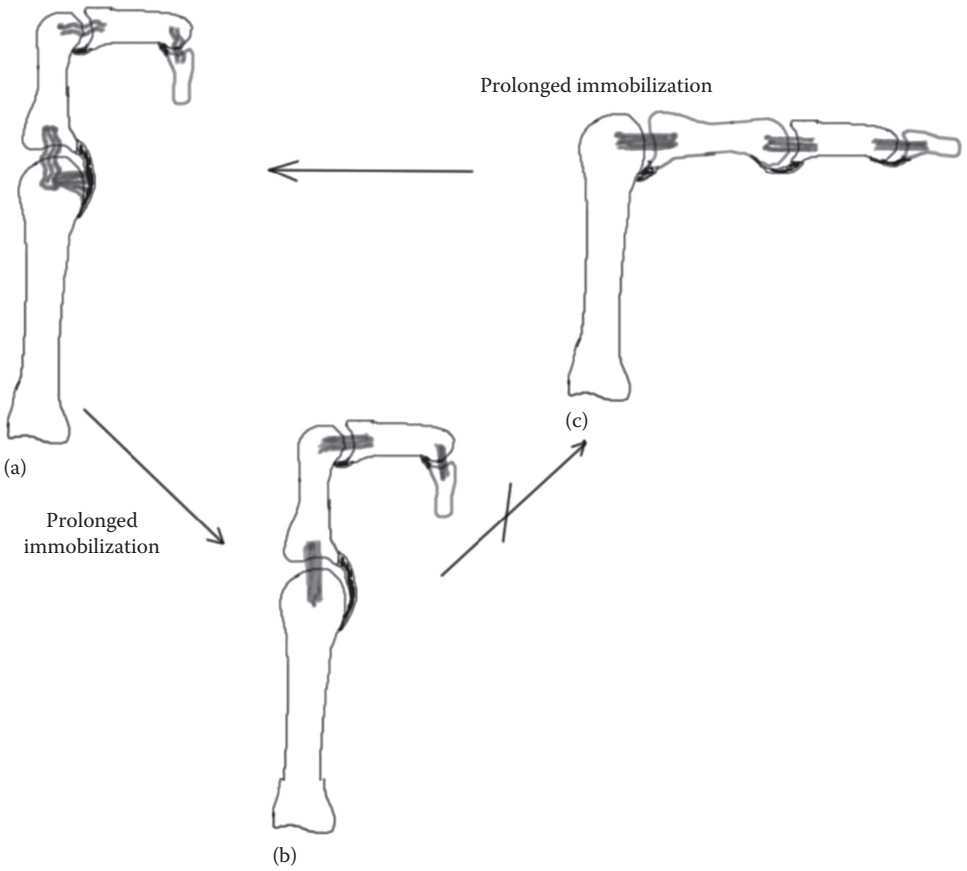


FIGURE 34.2
Prolonged positioning of the fingers can result in significant stiffness if immobilized in the wrong position. (a) shows the positioning in which the direct collateral ligaments are the loosest. (c) shows the positioning in which they are tight. In normal daily activity, the hand will alternate between the two positions. If the fingers are immobilized in position (a) for a prolonged period, the collaterals will tighten as seen in (b) and resist shifting to position (c). If immobilized in the tight position (c) (the "safe position"), then the fingers can shift to the loosened position (a) with much less problem.

34.1.2.9 Intra-articular Injuries at PIP and MP Joints

Most fractures of the phalanges or MCs are amenable to closed treatment, with favorable outcomes. However, two groups of complex fractures are difficult to diagnose and treat. The first group includes unicondylar and bicondylar fractures, fracture dislocations, and fracture-related instability of the proximal IPJ. Fracture dislocations can be treated with splinting or surgical intervention. The second group includes displaced diaphyseal fractures associated with a soft-tissue injury, instability, or multiple fracturing. Articular fractures and fracture dislocations at the base of the MC can also be difficult to diagnose and treat [10]. Displaced articular fractures should be anatomically reduced and fixed whenever possible.

Poor functional outcome is common with phalangeal fractures that are open, comminuted, or associated with either significant soft-tissue injury or periosteal stripping. Angulation causes a zigzag posture because of tendon imbalance, which results in joint contracture to a degree similar to the degree of proximal angulation.

Intra-articular injuries may lead to joint subluxation or dislocation and must be identified in a timely manner to limit loss of motion, degenerative changes, and impaired function [11]. Fracture dislocations of the proximal IPJ are usually dorsal with a small volar-plate avulsion fracture. These dislocations are usually stable if the volar fracture fragment comprises less than one-third of the articular surface.

In contrast, dorsal fracture dislocations in which the palmar fragment involves more than one-third of the joint surface, palmar fracture dislocations, and combined dorsal and palmar fractures ("pilon fractures") are intrinsically unstable. These injuries range from those requiring minimal intervention to obtain an excellent outcome to those that are challenging to the most experienced surgeon. The treatment options include extension-block splinting, percutaneous pinning, traction, external

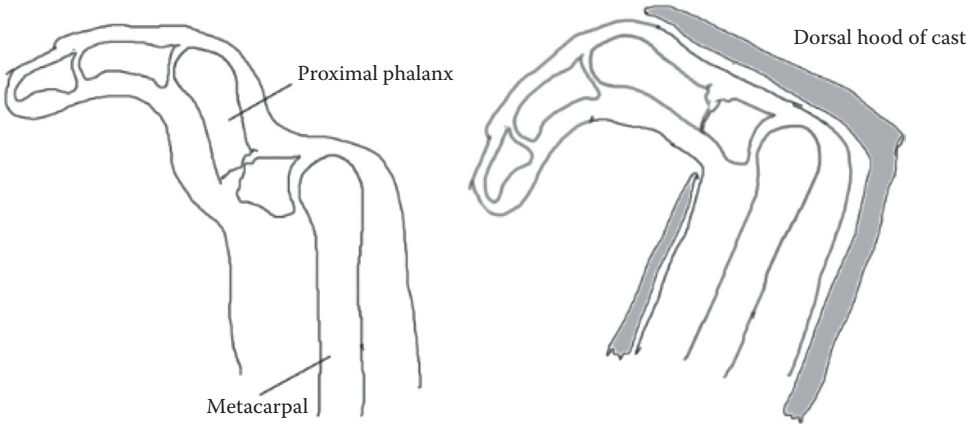


FIGURE 34.3
Unstable phalangeal fractures follow a predictable course regarding three complications. First, dorsal-palmar angulation of midshaft phalangeal fractures occurs due to asymmetric pull of muscle tendon units. Proximal phalanx fractures typically fall into a dorsal concave ("apex volar") angulation. Second, failure of reduction often results in complete recurrence of fracture deformity. Third, tendon imbalance due to malunion in angulation results in joint contractures distal to the fracture equal in magnitude and opposite in direction as the malunion. This type of fracture can be treated with a "Cobra cast" in which the wrist is extended 30°–40° and a dorsal cap holds the reduced proximal phalanx at 90°. The proximal fragment cannot flex >90°; so the distal fragment is brought down to it. This technique allows early ROM of the DIP and PIP joints.

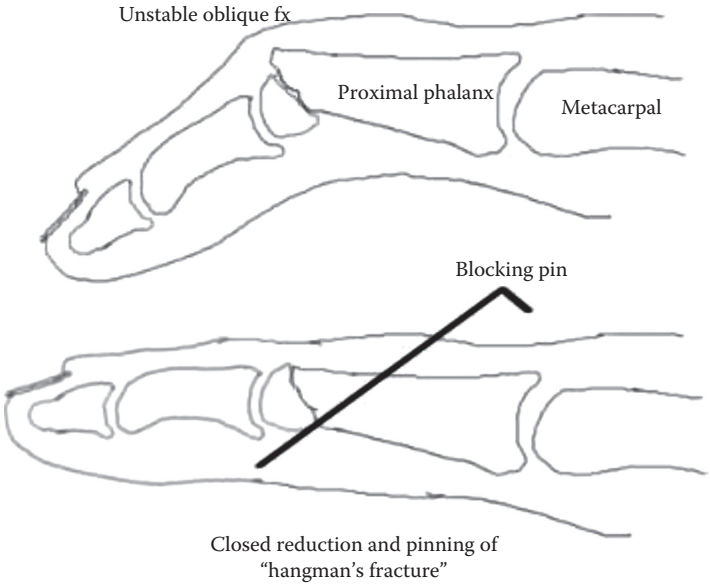


FIGURE 34.4
Phalangeal neck fractures are sometimes referred to as "hangman's fracture," either because the break is through the "neck" of the bone, or more importantly because posterior–anterior x-rays may be deceptively normal but lateral x-rays show an unstable fracture especially if oblique. If caught early, a blocking pin can be placed percutaneous just proximal to the fracture while held reduced. The tendon tolerates a transfixing pin much better than an open procedure.

fixation, open reduction and internal fixation, and volar-plate arthroplasty [11].

34.1.2.10 IPJ Dislocations

Pure dislocations of the proximal IPJ are most commonly dorsal, are usually stable after reduction, and carry about the same outlook as a bad sprain of this joint. These fractures often follow a hyperextension injury and may be open with the head of the proximal phalanx protruding through a volar skin tear. The flexor tendon is subluxed to the side and is usually intact. The exposed bone should be cleaned before reduction, as the wound will close following reduction.

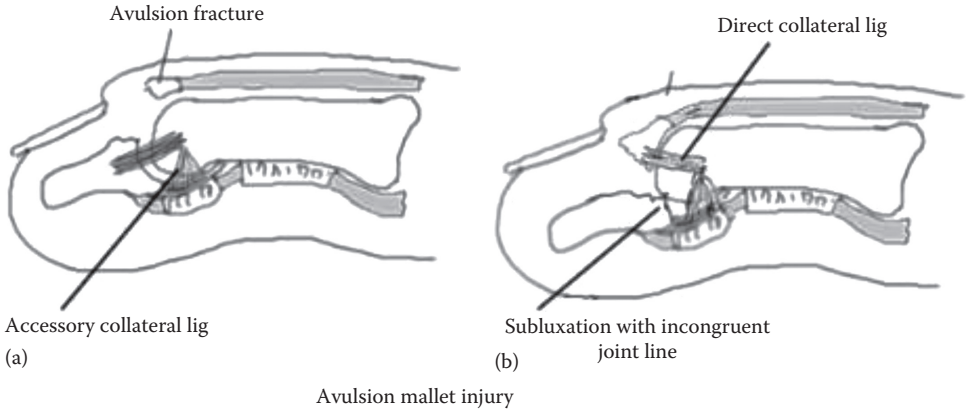


FIGURE 34.5
Mallet fractures in which the smaller fracture fragment includes half or more of the joint surface may be unstable, resulting in palmar subluxation of the distal phalanx (b). This is a consequence of the direct collateral no longer attached to the distal phalanx and results in an incongruent joint line. However, this is not always the case, and the joint may remain stable with a smaller avulsion fragment (a).

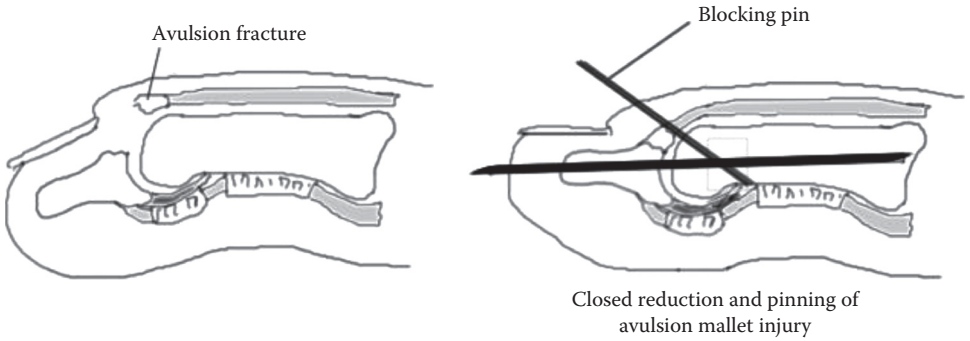


FIGURE 34.6
Mallet deformity due to avulsion fx can be treated with closed reduction and pinning. The distal phalanx is flexed and a blocking pin is placed through the extensor tendon just behind the avulsed fragment. The DIP is then brought out to extension, and the DIP is held in extension with the fracture reduced by a second transfixing pin.

In contrast, palmar dislocations or dislocations with a lateral component are frequently unstable after reduction and are more prone to progressive contractures, angulation, and degenerative joint changes. These dislocations often tear the central slip of the extensor tendon and result in a Bouttoneirre deformity if not followed closely (Figure 34.7).

34.2 Amputations

Trauma is the most common reason for amputation of the upper extremity [12]. Hand injuries involving traumatic amputation most often affect the fingers. The associated nerve injury always forms a neuroma, and the treating surgeon should trim the digital nerve ends away from the distal wound so as to lessen the chance of disabling scar tenderness.

34.2.1 Distal Amputations

Fingertip amputations are no less problematic than more proximal amputations, particularly when the critical contact areas used in pinching and fine manipulation are involved.

34.2.2 Transverse, Oblique, and Skiving

Fingertip injuries that involve the "critical contact areas" of the thumb, index, and middle fingers pose particularly difficult challenges for reconstruction. Rotating blade saws commonly result in combined injuries, impairing the ability to use the hand for fine manipulation.

Conservative treatment of tip amputations includes protective bandaging while the skin grows in from the periphery (centripetally). This can take several weeks to gain coverage and may result in a rather thin skin cover. Additionally, there will often be a thin subcutaneous layer over prominent bone that can result in hypersensitivity. As a result, skin flaps or skin advancement

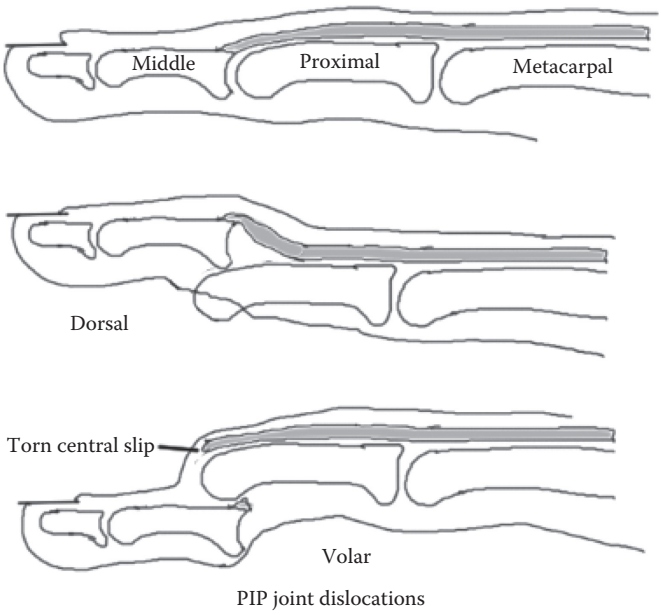


FIGURE 34.7
Proximal interphalangeal (PIP) joint "simple" dislocations are usually dorsal and may be reduced by extending the finger to reproduce the deformity and then dorsal pressure on the base of the middle phalanx. These are usually stable following reduction. Volar dislocations represent a more serious injury, are less commonly easily reduced, and are more commonly unstable following reduction. Although often passed off as a "jammed finger," PIP dislocations commonly result in 6–12 months of swelling, PIP flexion contracture, and permanent joint enlargement.

techniques are recommended to speed the healing process and obtain better tissue coverage. Examples are the Cutler V-Y advancement flap which can be used on one side of the finger to close a skiving injury—or on both sides to close a distal transverse amputation. A long volar flap can be used to close a distal volar-directed skiving injury.

Lateral oblique/skiving tip amputations can be treated with the "Cutler V-Y" advancement flap. A proximally based, "V"-shaped, full-thickness graft with neurovascular supply is created from a dorsal midaxial incision and a second volar-directed incision made down to the bone with care to avoid damaging the neurovascular bundle. The graft is then mobilized and can be advanced 10–12 mm to give good coverage of exposed bone.

As mentioned, transverse amputation can be treated with a flap from both sides that meet in the middle.

A volar skiving amputation can be treated by creating a long volar flap from bilateral midaxial incisions back to the PIP joint or farther if needed. The volar skin and neurovascular bundles are lifted from the flexor tendon sheath and advanced forward with the finger held flexed. The graft is attached distally to the tip and then attached laterally. The skin will stretch with time to allow full extension.

34.2.3 Hypersensitivity

Dysesthesia is common, and all patients should be provided with an early desensitization program that can be performed at home. Sensitivity to or intolerance of cold is a problem for most patients, but this condition usually improves after the first year. Complex regional pain syndrome may be triggered and then maintained by tender finger stumps.

34.2.4 Nail Deformity

Fingernail deformities are common after lacerations and crush injuries in the area of the nail bed. The most common problems are split nail resulting from nail bed injury and hook nail deformity resulting from loss of the tuft of the distal phalanx by a fingertip amputation.

When more than the distal third of the phalanx is lost, a hook nail deformity will result. This is due to the fact that the nail bed is not fully supported by the distal phalanx when a portion has been removed or if there is a nonunion of a tuft fracture. If there is only a small residual nail bed after an amputation of the tip, abnormalities of the retained nail remnant may be avoided by careful total excision of the entire germinal matrix when the amputation is closed.

Once established, fingernail deformities may be difficult or impossible to correct.

34.2.5 Amputations at IPJ

Amputations at the level of an IPJ can result in abnormal positioning of the residual digit due to tendon imbalance. Care must also be taken to round off the boney prominences on either side of the distal end of the phalanx to avoid skin irritation and thinning.

Amputations through the proximal phalanx often result in extensor habitus. Extensor habitus refers to the tendency for the injured index finger or small finger to be held in extension. This unconscious posturing is powered by the independent extensor of the finger and is best treated by early recognition and, if possible, buddy taping.

34.2.6 Metacarpal-Phalangeal Amputations

MCP joint disarticulation of the index or small finger results in an easily traumatized and visibly prominent MC head. MCP joint disarticulation of the middle or ring finger results in a "hole in the hand," through which small objects held in the cupped palm can fall. Treatment of either of these scenarios with removal of a MC replaces the original problem with a narrowed palm and reduced torque grip strength.

A better option may be resection of the distal half of the residual ring finger MC followed by transfer of the distal half of the fifth MC and small finger to close the gap. Similarly, the index finger can be transferred onto the proximal half of the third MC in cases of a middle finger MP joint amputation. These transfers close the "hole in the hand" and maintain palm width.

34.2.7 Amputation with Reimplantation

Inadequate blood supply is the single most likely explanation for complications of delayed healing, fibrosis, and infection. Adequate blood supply is achieved by aggressive debridement, revascularization, and the use of vascularized flaps.

Order of repair. The ideal order of repair of the severely injured upper extremity is debridement, skeletal stabilization, musculotendinous repairs, nerve repairs, and then vascular repairs, all under tourniquet control. Such an approach minimizes hemorrhage and allows the most precise primary repairs.

34.2.8 Complications of Replantation

All complications of complex hand wounds can occur after replantation, including tendon adhesions, tendon rupture, neuroma, and delayed healing. In addition, however, replantation carries the risk of a number of additional problems. Early vascular failure of replantation is influenced by the mechanism of injury and patient selection. Early failure is more common among smokers [13], when replantation occurs at a more distal level, and when the injury has involved crush or avulsion [14]. After successful revascularization, venous problems are more likely than arterial thrombosis to result in loss of the replanted extremity [15,16]. The crucial time for failure or successful salvage is the first four postoperative days [16].

The most common complication of successful replantation is stiffness due to tendon adhesions [15]. Cold intolerance is uncommon after pediatric replantation but occurs after most adult replantations [15]. Aesthetically disturbing fingertip atrophy occurs with nearly half of all replanted digits [15] because of the effects of incomplete reinnervation and, in some cases, the late effects of prolonged ischemia. Lack of sensory recovery is more common when the patient is an adult, when both arteries have not been repaired [17], and when the injury involves avulsion [14]. As with any other vascular repair, replantation may be associated with local vascular complications such as pseudoaneurysm [18], arteriovenous fistula [19], stricture, and late thrombosis. Delayed union, nonunion, or avascular necrosis may occur, particularly when the replantation is performed at the level of the phalangeal neck [20]. Functional outcome is significantly worse when replantation involves prolonged ischemia or injury in flexor tendon Zone II [13].

34.3 Wounds

Complex hand wounds are an unfortunate consequence of conflict. Increased battlefield survival rates have resulted in an evolving range of ballistic hand trauma encountered by deployed surgical teams, requiring increased knowledge and understanding of these injuries. In the civilian setting, the combined threats of gun crime and acts of terrorism warrant appreciation for such injury among all surgeons [21].

Wounds should be closed and covered with mobile, well-vascularized soft tissue as quickly as possible. In the hand, stiffness, difficulty with use, and ultimate disability are directly related to the length of time required for wound healing.

Edema indicates inadequate lymphatic circulation and has the same ultimate effects as inadequate blood supply. Edema is best treated with elevation and active range-of-motion exercises, when possible.

Infection. Unchecked surface growth produces such high concentrations of organisms that the skin is invaded directly, producing maceration dermatitis. This condition may progress to cellulitis, but it can be stopped in the early stages by increasing the frequency of dressing changes and allowing the affected skin to dry.

34.3.1 Scar Contracture

Contractures resulting from skin scarring are more likely to be a problem if the scars extend longitudinally across the flexor surface of a joint. In severe cases, scar contractures may develop over the first few weeks after injury, but in many cases they progress over the course of months. In the growing child, scar contractures may lead to progressive growth disturbances. Stiffness and contractures due to mechanical changes in joints and tendons, as discussed earlier, may develop independently.

34.3.1.1 Devascularized Wounds

Crush and avulsion wounds typically have combined effects of indeterminate or inadequate vascularity and widespread contamination. Infection following such wounds is due to inadequate debridement, and primary wound closure increases the chance of marginal wound necrosis.

34.3.1.2 Foreign Debris: Rust, Wood, and Fibers

Severe contamination is common with missed complex wounds of the hand because the hand is so often physically exposed to contaminated mechanisms of injury.

Soft-tissue gas is a frequent benign finding accompanying open wounds immediately after injury, but in the presence of infection should always be assumed to be due to gas-forming organisms.

Removal of foreign bodies that are lodged entirely beneath the surface of the skin should be performed with tourniquet control and surgical anesthesia. Foreign bodies are most likely to give rise to problems when they are composed either of organic materials (wood, plant thorn, etc.) or of highly contaminated materials.

Atypical infections [22] may involve subcutaneous tissues or, more commonly, tendon sheath spaces. Mycobacteria species, most commonly *Mycobacterium marinum*, produce slowly progressing hand infections.

Diabetic hand infections, particularly in patients with diabetic chronic renal failure, are common, are frequently severe, and often result in tissue loss. Hand infections among such patients are frequently more severe than clinical examination indicates, and the surgeon must consider early extensive surgical debridement of the entire zone of inflammation. Gram-negative infections are common, and amputation is a common consequence.

34.3.1.3 Determination of Tetanus Status

Horseshoe abscess is an infection spreading from the thumb to the small finger on the palmar surface. The flexor sheath of the thumb, which extends into the wrist, lies next to and in contact with the ulnar bursa which encapsulates the flexor tendons at the wrist and extends up into the small finger. Interestingly, the index, middle, and ring finger are spared since their tendon sheaths do not extend into the palm or to the wrist.

If the zone of injury can be determined with reasonable certainty, severe wounds should be radically debrided with anticipation of the potential need for complex flap closure. Debridement should remove severely contaminated tissues and all ischemic tissues that cannot be revascularized, including crushed flaps, distally based flaps with a length-to-width ratio of more than one to two, and flaps that are obviously ischemic. Initial debridement should be performed under tourniquet control. The skin of the palm has a primarily perpendicular rather than tangential vascular pattern, and traumatic palmar flaps should be considered for primary excision and alternate resurfacing because their vascularity is quite unreliable. Crush injuries are prone to delayed wound healing and stiffness with standard open reduction and internal fixation techniques.

34.3.2 Poor Timing of Wound Closure

Traditionally, the timing of closure of severe hand wounds has been classified as primary (immediate), delayed primary (within 2 weeks), and secondary (after 2 weeks). Delayed primary closure is still appropriate when the only available wound closure technique is direct closure or closure with local flaps. Wounds that require flap closure are associated with the lowest complication rate when closure is performed during the acute phase (first 2 weeks), and with the highest complication rate when surgery is performed during the subacute (after 2 weeks) phase [23–28].

34.3.2.1 Reflex Sympathetic Dystrophy

Complex regional pain syndrome—previously known as reflex sympathetic dystrophy (RSD), algodystrophy, sympathetic maintained pain, and Sudeck's atrophy—may develop after any hand injury, but is particularly common in association with nerve injury or irritation. This problem may occur spontaneously after major or minor injury. It may cause spontaneous burning pain, hyperalgesia, swelling, vasomotor disturbances, and disuse, and it may be exacerbated by movement. Although there may be spontaneous resolution, most patients experience some degree of chronic symptoms such as pain, stiffness, and difficulty with normal use of the hand, despite all available treatments [29]. The best treatment results require early recognition, aggressive medical therapy, and elimination of triggering phenomena. Medical therapy may involve sympathetic nerve blocks, gabapentin, pregaba or other nerve desensitizing medications, and biofeedback. Additionally, physical or hand therapy can treat with contrast baths, desensitization, and grip strengthening.

Triggers known to aggravate the condition include peripheral nerve irritation due to neuroma or compressive neuropathy, aggressive passive range-of-motion therapy, and dynamic hand splinting. The effects of complex regional pain syndrome may be far more disabling than the initial injury.

RSD usually results in swelling, stiffness, disuse, and color and temperature changes. The entire hand is usually affected, less commonly a single digit. Dupuytren's type contractures are common. This may follow elective surgery, but is most often seen after injury, such as a crush injury, amputation, or distal radius fracture.

34.3.3 Animal Bite Injuries

Animal bites to the hand are most often dog or cat bites. These bites can lead to prolonged morbidity, particularly when there is a delay between injury and initial treatment [30]. Dog bites are associated with soft-tissue

crush injury and fractures. Cat bites are particularly dangerous in hand because the cat's needlelike teeth can easily penetrate into joint spaces, tendon sheaths, and other deep compartments of the hand through a relatively innocuous skin wound. A common pathogen is *Pasturella multiceda* which can be treated with penicillin derivatives or cephalosporins.

34.3.4 Human Bite Injuries

Human bite injuries to the hand most often occur as clenched-fist bite injuries, sustained when the fist strikes the mouth of another person during an altercation. The most common constellation of injuries is a skin laceration at the level of the MC head accompanied by injury to the extensor tendon and the MC head. This injury is usually sustained when the hand is in a clenched-fist position, but the patient frequently does not present for treatment until the MCP joint is pulled into extension by dorsal hand swelling. This change in positioning places the soft-tissue and bone injuries at an offset, giving the appearance that the injury is more superficial than it is. Treatment requires a high level of suspicion, aggressive debridement, and intravenous antibiotics appropriate for a bite injury. Clenched-fist bite injuries of the MC head or proximal phalanx are highly contaminated, often deeply penetrating wounds with bone involvement. They are at particular risk for the development of septic arthritis and osteomyelitis.

Unsatisfactory results are more likely when hand infections involve anaerobes or *Eikenella corrodens*, and when the tooth crushes and devitalizes tissue.

34.3.5 Spider Bites—Insect Bites

Bites to the hand from insects such as brown recluse spiders may cause painful, slow-healing wounds, resulting in chronic functional deficits. The initial bite injury may be painless. A swollen red finger or hand often results from the combination of devitalized tissue (from the venom) and bacteria introduced at the time of the bite. When fluctuance is obvious, incision and drainage should be performed. Cultures can be obtained and necrotic tissue removed. When surgical excision is indicated for localized necrosis, the results appear to be better when surgery is delayed until after the acute inflammatory process has subsided [29].

34.3.6 High-Pressure Injection Injuries

High-pressure injection of paint, sand, lubricating fluid, or water can lead to severe infection/inflammation. Typically, the patient has briefly placed the hand or fingertip over a pressure spray nozzle, thereby sustaining an injection of material into the soft tissues. Under pressure, this material tracks up tissue planes next to flexor tendons, nerves, and arteries and through the named bursae and compartments of the hand and arm. Debris may be driven from the fingertip to the chest wall. The examiner may be misled by a small visible wound and the patient may be discharged only to return within 24 h because of worsening symptoms. Radiographs may show the presence of air, particulate debris, or pigment (in certain types of paint) in soft tissues.

Treatment is emergency radical debridement [31]. The pressure-injected material tends to track through the loose areolar tissue along longitudinal structures, and only careful debridement may allow preservation of all vital structures.

In contrast, late surgical treatment may require en bloc tumor-like excision of contaminated zones, or even amputation. Late results are worst when the injected material is either a petroleum-based solvent or a particulate material (sandblasting), when the tendon sheath is involved, and when there is wide proximal spread of the injected material. The injected material is not sterile and prophylactic antibiotic treatment is indicated. Injection of pressurized aerosol fluorocarbon liquids such as that used in refrigerants may also result in deep frostbite injury.

34.3.6.1 Flexor Tendon Sheath Infection

Flexor tendon infection from puncture wounds, pressure injection, bites, etc. involve the entire tendon sheath. In the small finger and thumb, this sheath may extend into the wrist. As the sheath swells and fills, pain and loss of motion ensues.

Knavel described signs of sheath infection: finger-held flexed, pain with attempted extension, a sausage-shaped finger, and pain along the entire course of the flexor sheath.

Treatment includes I&D at both ends of the sheath and wash-through of the sheath with a catheter placed into one end of the tendon sheath while irrigant flows out the other end. Complications include persistent or recurrent infection, stiffness, loss of tendon excursion, and possible need for finger amputation.

34.3.6.2 Compartment Syndrome

34.3.6.2.1 Cause

Finger dressings made from tubular gauze may produce ischemic pressure complications. Even minimally tight elastic dressings applied as part of a circumferential bandage may lead to progressive swelling. Tight casts may result in local pressure sores, discomfort, and, in the worst scenario, vascular compromise and compartment syndrome. The risk of complications is highest when circumferential casts are applied after

closed reduction of an elbow or forearm fracture on the day of injury. In this situation, the risk may be reduced by splitting ("bivalving") the cast into two separate longitudinal sections immediately after application.

Compartment syndrome of the hand may develop after crush injury, reperfusion after fracture-related ischemia, intravenous injections, crush or blast injury [32], bleeding after fracture, arterial cannulation or regional surgery, or prolonged pressure on the hand or arm. Heparin-induced thrombocytopenia (HIT) has been known to cause clot formation throughout the small vessels of the hand resulting in compartment syndrome of the interossei and even necessitating digit amputation. Surgery for compartment syndrome of the intrinsics can be performed through two or three longitudinally placed incisions on the dorsum of the hand.

The forearm is the most common site of compartment syndrome in the upper extremity. Compartment syndrome of the upper extremity is more likely to develop among patients with obtundation. Seriously ill children who receive multiple venous and arterial injections are also at particular risk. Treatment requires prompt recognition and decompression of intrinsic muscle compartments, as well as carpal tunnel release in selected cases. The late consequence of compartment syndrome of the upper extremity is Volkmann's contracture [19,33], which involves both muscle contracture and local ischemic neuropathy. Ischemic muscle contractures respond poorly to nonoperative measures such as splinting; this condition requires an aggressive surgical approach using muscle slides, tendon lengthening, and tendon transfers similar to those used in the treatment of upper extremity spasticity.

34.3.6.2.2 Sequelae

Intrinsic contractures produce MCP joint flexion contractures, first web space contracture, and extension contractures of the interphalangeal joints. Secondary swan-neck deformity of the fingers is also common.

34.4 Nerve Injury

34.4.1 Complications of Common Nerve Injuries

Nerve injuries in the hand can lead to complications such as tender neuroma, paralysis, and incomplete sensory recovery. In addition, upper extremity nerve injuries usually produce some degree of cold intolerance and are a common trigger of complex regional pain syndrome. Dysesthesia and disuse of the hand may occur and are best treated with an aggressive desensitization and sensory re-education program under the supervision of a hand therapist.

34.4.1.1 Median Nerve Injury

Median nerve injuries result in a greater loss of hand function than ulnar nerve injuries because the critical contact areas of the hand are affected. If median nerve palsy is left untreated, a contracture of the first web space and thenar atrophy will result.

The median nerve is a mixed nerve in the wrist with both sensory and motor function. Acute injury can occur from deep central wrist laceration or penetrating trauma, as well as compression from a volar-displaced lunate dislocation or from a severely angulated distal radius fracture.

Findings include diminished sensation to the palm and volar thumb, index and middle fingers, as well as weakened thumb opposition.

34.4.1.2 Ulnar Nerve

Ulnar nerve palsy will result in proximal IPJ contractures of the ring and small fingers.

Palsy of the ulnar nerve due to ulnar neuropathy at the level of the elbow is a recognized but poorly understood complication of surgery involving general anesthesia [34]. Use of elbow pads—and avoidance of abduction, pronation, and elbow flexion—may reduce the incidence of this complication. When the ulnar nerve is injured above the wrist, there will be diminished sensation to the dorsal as well as volar small finger.

Involvement distal to Guyon's canal, in contrast, involves only the volar small finger. In either case, the intrinsic, thumb adductor and the lateral lumbricals to small and ring fingers are weakened. Atrophy and fixed clawing of the hand may result.

34.4.1.3 Neuroma

Treatment of a sensitive, prominent neuroma preferably is accomplished through nerve repair. This directs the regenerative nerve tissue down the nerve sheath to revitalize the denervated area. Other options include burying the sensitive nerve tissue beneath nearby muscle, or into the protection of a bone through a small cortical window.

34.5 Tendon Injury/Repair

34.5.1 Partial Tendon Lacerations

Partial tendon lacerations should be suspected after penetrating wound injury when the muscle tendon unit functions with pain, or when there is pain when attempting motion against resistance. Missed partial tendon

injuries may result in triggering, loss of motion from tendon adhesions, weakness or delayed tendon rupture.

Complete transaction of a tendon is often, but not always, obvious with loss of wrist or finger extension or flexion.

34.5.1.1 Redundancy

Injuries to the extensor tendon of the dorsal hand may be missed because they often cause little initial functional deficit, either because of the action of adjacent tendinous junctures or because only one of two (proprius and communis) tendons in the index or small fingers have been cut. Extensor pollicis longus tendon injuries may be missed because of trick motion through the action of the thumb intrinsic muscles on the thumb extensor mechanism; this action may allow IPJ extension to neutral despite a divided extensor pollicis longus tendon.

34.6 Flexor Zones of Injury/Repair

34.6.1 Flexor Tendon Injuries

A flexor tendon injury is often the result of trauma involving laceration or avulsion of the flexor digitorum profundus (FDP) or flexor digitorum superficialis (FDS). Pathological ruptures are rare. Diagnosis of a flexor tendon injury is based on an evaluation of the subjective patient history and a thorough clinical assessment. The flexor tendons are encased in a sheath comprised of annular (A) pulleys and cruciate (C) pulleys. A1, A3, and A5 attach to each side of the volar plates at MP, PIP, and DIP joints, respectively. The A2 and A4 pulleys attach to the sides of the proximal and middle phalanges, respectively. The cruciate bands lie between the annular ones (Figures 34.8 and 34.9).

The Kessler repair utilizes a running suture that grasps the palmar aspect of the tendon on each side of the injury with a transverse segment placed so as to avoid the vascular supply which lies on the osseous side of the tendon. This transverse segment of the suture resists pullout or pull through the tendon fibers. A disadvantage is that once the suture has been placed on one side, it cannot be easily tightened. An epitendinous suture runs around and captures loose fibers at the anastomosis [35].

A new technique is described which uses one or more cloverleaf sutures placed transversely on each side of the injury to capture and prevent pullout. The suture is placed with the knot on the osseous side. The closing sutures pass up through the tendon, around the transverse sutures and then pass to the other side. Multiple sutures may be placed and when tighten effect the closure of the injury gap. An epitendinous suture may be used.

This technique can be used to pull the cut tendon end through a pulley, especially if the sublimus has been sacrificed. With care, sutures may be placed around the base of the distal phalanx, and avoid use of suture anchors.

34.7 Complications of Repair

The worst results of flexor tendon injuries occur when the injuries are located in the flexor tendon sheath extending from the MC head to the middle portion of the middle phalanx, referred to as "Zone II" or "no man's land." Even with ideal treatment, only about half of the patients with injuries at this level recover to experience good-to-excellent function. Quadrigia syndrome, or limited excursion of the middle, ring, and small fingers, occurs because of tethering connections between the profundus tendons of these fingers.

Adhesions are the most common problem after tendon repair. Rupture of a flexor tendon repair occurs in at least 4% of cases after primary flexor tendon repair in Zone II with postoperative controlled passive motion [36]. Stiffness may be due to either adhesions or rupture, and it may be impossible to determine the nature of loss of motion, even with magnetic resonance imaging.

The worst results of extensor tendon injuries occur when the injuries are located over the dorsum of the proximal phalanx or the proximal IPJ. Loss of proximal IPJ motion may take the form of a fixed contracture, a swan-neck deformity, or a Boutonniere finger.

34.7.1 Complications of Missed Repair

34.7.1.1 Missed Injuries to the Extensor Mechanism of the Finger

Terminal tendon injuries at the distal IPJ and central slip injuries at the proximal IPJ should be suspected when the patient has suffered a regional injury and has pain upon attempted extension against resistance, even if the patient has full, active motion without resistance (Figure 34.10).

Boutonniere finger deformity is characterized by proximal interphalangeal (PIP) joint flexion, distal interphalangeal (DIP) joint extension, and hyperextension of the MCP joint, with volar subluxation of the lateral bands. The deformity is common in patients with rheumatoid arthritis; however, it is not specific to this disorder and may occur following trauma or other inflammatory arthritides. A variety of surgical procedures are available

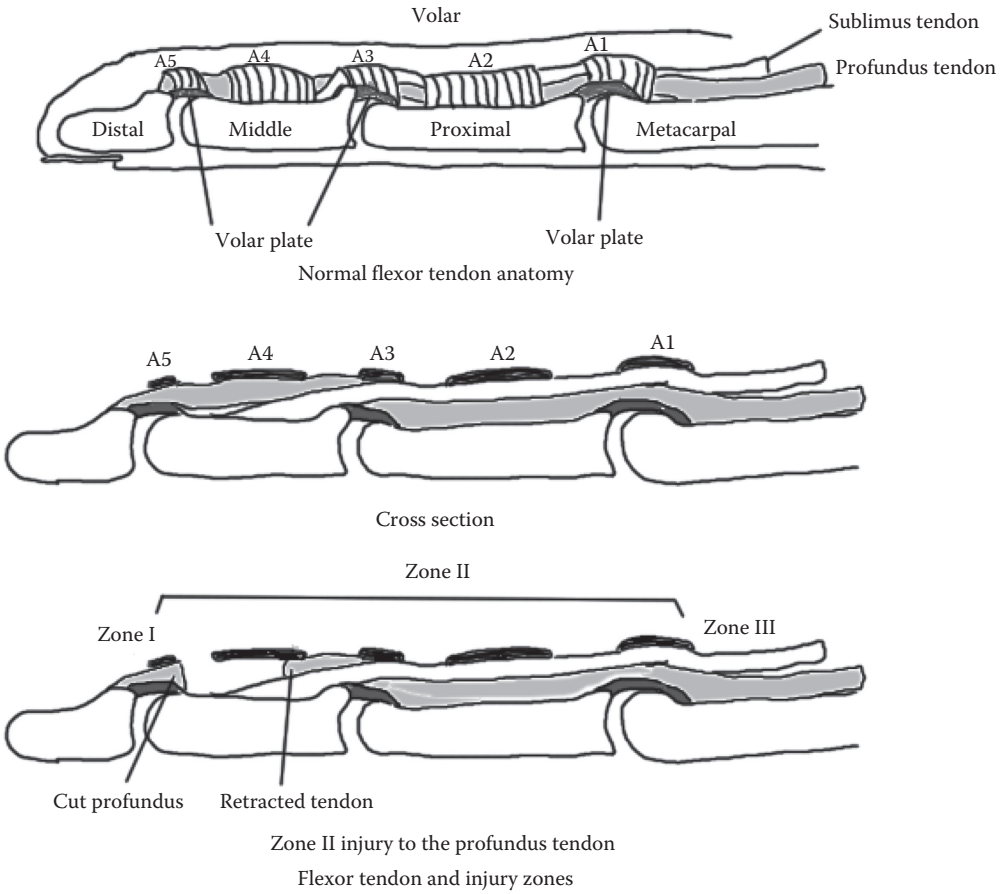


FIGURE 34.8
The portion of the flexor sheath between A1 and A5 is considered Zone II or "no man's land" based on difficulty of tendon repair and poor excursion of the healed tendon due to scar adhesions to the sheath or bulkiness of the repair site, which prevent gliding under the pulleys. Zone I is at flexor profundus insertion. Zone III is located in the palm while Zone IV is the area considered the carpal tunnel, beneath the transverse carpal ligament. Zone V is the tendon in the distal forearm.

for Boutonniere finger deformity, including tenotomy of the terminal extensor tendon and reconstruction of the central slip. The choice of surgical treatment is based on the flexibility of the PIP joint and the status of the articular cartilage [37].

34.8 Flexor Tendon

A complication of missed flexor tendon repair is collapse of the sheath. This can occur after only 7–10 days and prevent passage of the tendon end back through the sheath. More complicated reconstruction techniques are then required, such as reforming the sheath with a two-stage procedure. A scilastic "Hunter" rod is used to induce a scar-like sheath, and then replaced with a tendon graft (the original tendon is usually shortened and will not allow a primary repair).

34.9 Complications of Selected Surgeries

34.9.1 De Quervain's

De Quervain's tenosynovitis involves the tendons of the first extensor compartment of the wrist. The extensor pollicis brevis and abductor policis longus pass beneath a retinaculum over the radial styloid. Surgical release is usually quite effective.

Complications of the procedure include incomplete release and radial nerve injury. The abductor policis may pass through a separate sheath, or there may be an anomalous tendon passing through an additional sheath. Incomplete release can lead to persistent pain.

The dorsal branch of the radial nerve passes over or near to the radial styloid. Injury to the nerve can lead to a tender, prominent neuroma, and numbness to the dorsum of the thumb, index, and middle fingers.

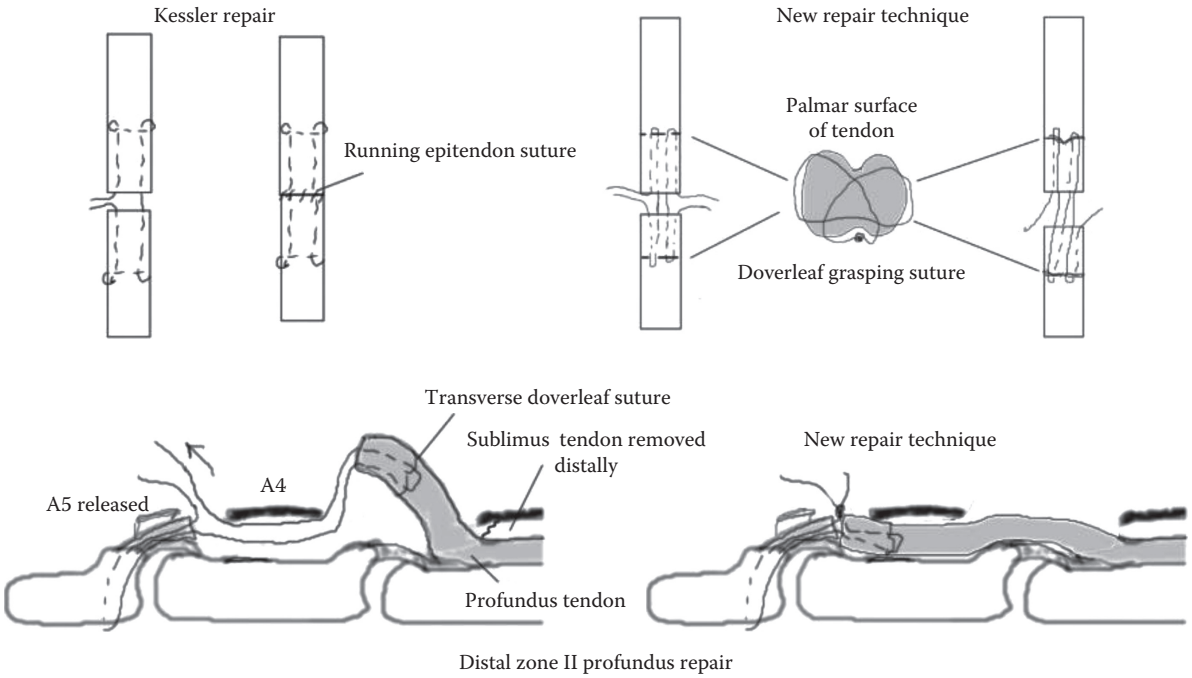


FIGURE 34.9
A drawing comparing traditional Kessler and a new technique for tendon repair.

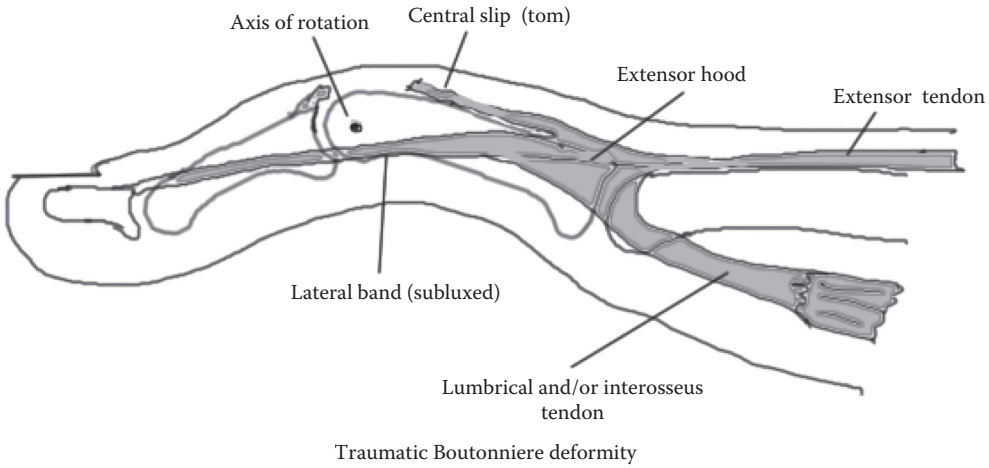


FIGURE 34.10
A complication of missed extensor injury, either due to transaction of the central slip from a cut, or a stretch injury from a dislocation, is the Boutonniere deformity. If the PIP joint is allowed to remain flexed, the lateral bands of the extensor hood will sublux below the center of rotation of the PIP joint, shorten, and prevent PIP extension. Further, the DIP will be pulled into extension and resist flexion.

Numbness or tingling lasting more than a day may indicate partial nerve injury and should lead to consideration of early exploration. Treatment options for chronic cases are the same as for any cutaneous neuroma and lingering symptoms are common.

34.9.2 Dupuytren's

Duypuytren's contractures in the palm result from contracture of myofibroblastic type tissue in the superficial palmar fascia. These fibers run longitudinally just beneath the skin and may extend from the proximal palm out to the volar midphalanx of one or several fingers.

Resection of this tissue may result in skin necrosis if the skin is too thin, button-holed, or if corners of a zigzag incision are at too acute of an angle. Recurrence is the most frequent complication, even if the cord has reached maturity. Removal of a cord during an active, painful stage may result in persistent pain or even RSD.

A well-established cord may leave a joint that cannot fully extend due to a tight volar plate, tight collaterals, and tight volar skin. Finally, damage to the small finger ulnar digital nerve may occur during resection if it is wrapped around the Dupuytren's cord.

34.9.3 Thumb Arthroplasty

Arthroplasty at or about the carpal MC (CMC) joint of the thumb is a good example of treatment options for carpal arthritis, carpal instability, and carpal collapse. There are multiple surgical procedures, and each has its own set of complications.

Trapezial resection, interpositional arthroplasty w/ rolled tendon and MC suspension, is a good primary or salvage procedure for CMC arthritis and subluxation. Use of abductor policis longus tendon avoids the risks of a contaminated graft, but a small tendon may not be sufficient to suspend the thumb MC to the index MC and still leave enough to use as a filler for the removed trapezium. For this reason, an allograft is often used.

CMC fusion answers the problem of subluxation and instability of the proximal thumb MC, but can severely limit thumb abduction and grasp. Further, there is the ever-present risk of nonunion at the fusion site.

The Orthosphere™ implant is a smooth ceramic sphere interposed into the CMC joint and held in recesses fashioned into the upper trapezium and proximal MC articular surfaces. In the appropriate patient the joint capsule is retensioned, subluxation is controlled, and motion is maintained.

If the trapezium is too eroded or flattened, or if the recesses are placed too far laterally, the implant may displace and present itself under the skin. Even a well-placed implant can dislodge and the peripheral bone can fracture if the patient falls onto the thumb.

Silicon implants were popular in the 1980s and early 1990s as a substitute for a degenerative trapezium. Their use has mostly ceased due to risks of implant fracture, implant displacement, and silicon particle–induced synovitis.

34.9.4 CTR

Even the commonly performed carpal tunnel release has attendant risks. Recurrent or persistent symptomatology may be the result of an incomplete release through a too small incision. Unreleased fibers of the distal transverse carpal ligament or of the distal forearm fascia may be the culprit. The recurrent nerves to the thenar muscles may exit through the transverse ligament rather than beyond its fibers. Poor visualization may result in nerve injury during the release. The palmar cutaneous nerve proximally and the arterial arch distally also must be avoided.

Complications by Category

Complications	Nonoperative	Operative
Fracture	Nonunion	Infection
	Malunion	Implant irritation
	Shortened	Nerve/tendon
	Angulated	Skin
	Rotated	
	Arthritis	
	Stiffness from immobilization	
	AVN (scaphoid)	Compartment syndrome
Amputation	Delayed healing	Tendon imbalance
	Bony prominence	Nail deformity
	Hypersensitivity	Graft/transfer necrosis
		"Hole in hand"
Wounds	Flap necrosis	Persistent infection
	Tetanus	Stiffness
	Foreign body—infection	Swelling
	Dissecting abscess	Stiffness
	Skin necrosis	
	Tendon sheath infection	
Nerve injury	Neuroma	
	Missed partial injury	
Tendon injury	Late rupture	Repair failure
	Contracture/imbalance	Tendon stretch/drooping
	Boutonniere deformity	Adhesions/scar
	Mallet deformity	Loss of ROM/triggering infection
Implant surgery		Nerve injury
		Loosening of implant
		Dislocation of implant
		Periprosthetic fracture
		Silicon toxicity/synovitis
		Scar/stiffness

Avoidance Techniques for Common Complications

Infection	Stiffness
Antibiotics	Proper positioning
Thorough debridement	Careful tissue handling
Wash/irrigate	Stable fixation/early ROM
Delayed closure	
Malunion	Hypersensitivity
Assess reduction with x-ray	Scar massage
Check ROM and alignment intra-op	Early return to work
Use correct positioning in cast	PT/OT

References

1. Eaton C, The Hand Center, Jupiter, FL.
2. Leung F, Ozkan M, and Chow SP. Conservative treatment of intra-articular fractures of the distal radius—Factors affecting functional outcome. *Hand Surg* 2000; 5(2):145–153.

3. Flinkkila T, Raatikainen T, Kaarela O, and Hamalainen M. Corrective osteotomy for malunion of the distal radius. *Arch Orthop Trauma Surg* 2000; 120(1–2):23–26.
4. Bonatz E, Kramer TD, and Masear VR. Rupture of the extensor pollicis longus tendon. *Am J Orthop* 1996; 25(2):118–122.
5. Bell JS, Wollstein R, and Citron ND. Rupture of flexor pollicis longus tendon: A complication of volar plating of the distal radius. *J Bone Joint Surg Br* 1998; 80(2):225–226.
6. Watson HK and Ballet FL. The SLAC wrist: Scapholunate advanced collapse pattern of degenerative arthritis. *J Hand Surg (Am)* 1984; 9(3):358–365.
7. Engles D, Diao E, Seiler JG III, and Taras JS. Surgical treatment of carpal and hand injuries in children. *Instructional Course Lectures* 2009.
8. Leversedge FJ, Ditsios K, Owsley BJ, and Boyer MI. Posttraumatic reconstruction in the hand. *Orthopaedic Knowledge Online J* 2004.

   The complex anatomy of the hand means that injuries result in substantial loss of function. Evaluation and management of malunion, nonunion, bone loss, and stiff fingers are important factors in posttraumatic reconstruction of the hand.
9. Strauch RJ and Olson PR. Hand fractures: Current concepts. *Orthopaedic Knowledge Online J* 2012.

   Hand fractures are common injuries, and most do not require surgical treatment. Even with modern techniques of surgical fixation, the best results are often obtained with closed treatment. Regardless of the method of treatment, most fractures heal adequately enough to allow gentle range of motion by 3 to 4 weeks. If the patient is not progressing on a timeline to achieve full digital range of motion by 6 to 8 weeks postinjury, formal hand therapy should be initiated. Current concepts for the management of fractures of the MCs and phalanges are discussed.
10. Waters PM. The treatment of complex fractures and fracture dislocations of the hand. *Instructional Course Lectures* 2008.

    Microscrews and condylar plates have added considerably to the ability to securely fix small articular fractures and fracture dislocations about the proximal IPJ. Some unstable fracture-dislocations are characterized by loss of the volar aspect of the articular surface of the base of the middle phalanx; they can be treated by using a sculpted osseous articular graft from the dorsal hamate.
11. Blazar PE and Steinberg DR. *J AAOS*. 2000.
12. Eardley MWGP and Stewart CMPM. Traumatic and trauma-related amputations: Part II: Upper extremity and future directions. *J AAOS* 2010.

    The morphological and functional distinctions between the upper and lower extremities render the surgical techniques and decision making different in many key respects. Careful management of the peripheral nerves is critical to minimize painful neuroma formation while preserving options for possible future utilization in targeted muscle reinnervation and use of a myoelectric prosthesis.
13. Waikakul S, Sakkarnkosol S, Vanadurongwan V, and Unnanuntana A. Results of 1018 digital replantations in 552 patients. *Injury* 2000; 31(1):33–40.
14. Aziz W, Noojin F, Arakaki A, and Kutz JE. Avulsion injuries of the thumb: Survival factors and functional results of replantation. *Orthopedics* 1998; 21(10):1113–1117.
15. Schwabegger AH, Hussl H, Ninkovic MM, and Anderl H. Replantation in childhood and adolescence. Long-term outcome. *Unfallchirurg* 1997; 100(8):652–657.
16. Janezic TF, Arnez ZM, Solinc M, and Zaletel-Kragelj L. One hundred sixty-seven thumb replantations and revascularisations: Early microvascular results. *Microsurgery* 1996; 17(5):259–263.
17. Adani R, Busa R, Castagnetti C, Castagnini L, and Caroli A. Replantation of degloved skin of the hand. *Plast Reconstr Surg* 1998; 101(6):1544–1551.
18. Gerard F, Obert L, Garbuio P, and Tropet Y. An unusual complication of reimplantation of the hand: A false aneurysm of the radial artery anastomosis. Apropos of a treated case. *Chir Main* 1999; 18(2):149–152.
19. Matsubara J, Seko T, Ohta T et al. Arterio-venous fistula formation after hand replantation. *Jpn J Surg* 1983; 13(3):207–210.
20. Snelling CF and Hendel PM. Avascular necrosis of bone following revascularization of the thumb. *Ann Plast Surg* 1979; 3(1):77–87.
21. Jupiter JB, Hastings H II, and Capo JT. Early management of ballistic hand trauma. *Instructional Course Lectures* 2010.

    Surgeons often have to relearn the management of ballistic hand trauma and other aspects of war surgery under difficult circumstances because the experiences of their predecessors may be forgotten. Current evidence regarding these injuries is scarce. Minimal, accurate debridement, and decompression with early stability are crucial. Delayed primary closure and an awareness of future reconstructive options are fundamental.
22. Dellinger EP, Wertz MJ, Miller SD, and Coyle MB. Hand infections. Bacteriology and treatment: A prospective study. *Arch Surg* 1988; 123(6):745–750.
23. Stanec Z, Skrbic S, Dzepina I et al. High-energy war wounds: Flap reconstruction. *Ann Plast Surg* 1993; 31(2):97–102.
24. Schwabegger AH, Anderl H, Hussl H, and Ninkovic MM. Complex hand injuries. Importance of primary repair with free flaps. *Unfallchirurg* 1999; 102(4):292–297.
25. Godina M. Early microsurgical reconstruction of complex trauma of the extremities. *Plast Reconstr Surg* 1986; 78(3):285–292.
26. Melissinos EG and Parks DH. Post-trauma reconstruction with free tissue transfer—Analysis of 442 consecutive cases. *J Trauma* 1989; 29(8):1095–1102 (discussion 1102–1103).
27. Arnez ZM. Immediate reconstruction of the lower extremity—An update. *Clin Plast Surg* 1991; 18(3):449–457.
28. Scheker LR, Langley SJ, Martin DL, and Julliard KN. Primary extensor tendon reconstruction in dorsal hand defects requiring free flaps. *J Hand Surg Br* 1993; 18(5):568–575.
29. Zyluk A. The sequelae of reflex sympathetic dystrophy. *J Hand Surg Br* 2001; 26(2):151–154.
30. Grant I and Belcher HJ. Injuries to the hand from dog bites. *J Hand Surg Br* 2000; 25(1):26–28.

31. Zyluk A and Walaszek I. Results of treatment for high-pressure injection hand injuries. *Chir Narzadow Ruchu Ortop Pol* 2000; 65(4):367–374.
32. Naidu SH and Heppenstall RB. Compartment syndrome of the forearm and hand. *Hand Clin* 1994; 10(1):13–27.
33. Lanz U and Felderhoff J. Ischemic contractures of the forearm and hand. *Handchir Mikrochir Plast Chir* 2000; 32(1):6–25.
34. Stahl S, Norman D, and Zinman C. Postoperative ulnar nerve palsy of the elbow. *Harefuah* 1997; 133(11): 533–535, 590.
35. Leversedge FJ, Ditsios K, Owsley BJ, and Boyer MI. Zone II flexor tendon repair. *Orthopaedic Knowledge Online J* 2004.

    Demonstrates the Zone II flexor tendon repair, including tendon retrieval, core suture method, and epitendinous method.
36. Strickland JW. Results of flexor tendon surgery in zone II. *Hand Clin* 1985; 1(1):167–179.
37. Erickson JM, Jebson PJL, and Murray PM. Boutenierre deformities. *Orthopaedic Knowledge Online J* 2008.

Section VIII

Neurologic

35

Complications of Postoperative Pain and Pain Management

Amit A. Shah and Raymond S. Sinatra

CONTENTS

35.1 Introduction

Poorly managed pain is associated with pathophysiological responses that negatively impact key organ systems and delay postoperative recovery. Despite the introduction of new analgesics and novel analgesic delivery systems, pain management practices remain suboptimal. Opioids and intravenous patient-controlled analgesia (IV-PCA), the current standards of postoperative pain management, are associated with significant complications that reduce analgesic effectiveness and overall safety. This chapter will outline complications associated with poorly controlled postoperative pain and discuss adverse events (AEs) associated with commonly prescribed analgesics and analgesic techniques. It will then present methods to improve pain control by identifying barriers to effective analgesic control and presenting new approaches to management.

35.2 Undermedication of Surgical and Trauma-Related Pain

Pain following surgery is among the most common of patient complaints encountered by healthcare professionals and remains a major cause of patient dissatisfaction, morbidity, and delayed hospital discharge. Severe acute pain is the most common reason for admission to the emergency department (ED), and a large proportion of patients presenting with surgical or trauma-related problems report pain of severe to very severe intensity [1,2]. According to the National Center for Health Statistics, an estimated 29.0 million inpatient and 43.6 million ambulatory surgeries were performed in 2011 with a majority associated with moderate to very severe postoperative pain [3].

Despite the availability of effective treatment, introduction of pain management services, and development of novel analgesics and analgesic techniques, moderate to severe pain can persist for many days following hospital discharge from surgery [1,2,4,5]. In a large study of ambulatory surgical patients, McGrath et al. [2] reported that over 30% of patients reported moderate to severe pain scores (6.3 cm) on a 0–10 cm visual analog scale (VAS) on postoperative day 1, and pain intensity decreased only slightly (5.6 cm) by postoperative day 3. Beauregard et al. [1] assessed pain in patients recovering from ambulatory surgery and found that 40% of patients reported moderate to severe pain during the first 24 h after discharge; pain decreased over time but was severe enough to interfere with daily activities and return to work for several days to weeks after surgery.

Several epidemiological investigations performed in teaching or community hospitals have employed telephone questionnaires and patient surveys to assess postoperative pain intensity and satisfaction with therapy. Warfield and Kahn [5] found that ~75% of patients experienced pain after surgery; 80% of those rated their pain as moderate to extreme. In a follow-up study 9 years later, Apfelbaum et al. [4] similarly found 80% of patients experienced pain during the 2-week period after surgery. The majority (86%) of these patients classified their pain as moderate, severe, or extreme [4]. The lack of pain intensity differences between two similar trials performed 9 years apart is strikingly similar (Figure 35.2). Follow-up epidemiological surveys have yet to be performed; however, it is highly unlikely that pain intensity and patient satisfaction have improved to any great extent during the decade following these reports [6,7]. The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) conducted two 1-year studies of 3765 hospitals and found that the average satisfaction score for pain management was only 68/100 [8].

The rationale for improving pain management is summarized in Box 35.1. Optimal pain management is a basic human right, and there is a critical need for

BOX 35.1 WHY SHOULD CAREGIVERS BE CONCERNED ABOUT POSTOPERATIVE PAIN?

1. There is always a humanitarian need to reduce pain and suffering.
2. Poor pain control can adversely effect outcome in elderly and high-risk patients.
3. Joint Commission and American Pain Society mandates underscore the importance of optimal pain management (pain as the "Fifth Vital Sign").
4. Patients have become increasingly knowledgeable about new forms of therapy. Hospitals are being ranked on how well or how poorly they and their surgical staff manage pain.
5. Hospitals and caregivers are increasingly liable for patient complaints of pain and suffering.
6. Hospitals are ranked according to the quality of pain management they provide. Maintenance of future reimbursement will depend upon meeting or exceeding national averages.

improvement particularly for elderly and high-risk patients, as well as those recovering from extremely painful procedures. In recent years, caregivers and national societies have become increasingly aware of the importance of pain management. The American Pain Society has declared the 10 year period beginning in 2001 as the "Decade of Pain" [6]. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO or Joint Commission) has mandated that pain intensity be measured regularly as the "fifth vital sign," and that complaints of inadequate relief be treated promptly [9]. The Agency for Healthcare Research and Quality (AHRQ) and the Joint Commission have suggested that hospital performance standards include reductions in the incidence and severity of postoperative pain as well as improvements in patient satisfaction and comfort [9]. The Center for Medicare and Medicaid Services (CMS), as per the Affordable Healthcare Act of 2010, will start measuring and penalize poor performers based upon 30 day readmission rates [9]. Hospitals will continue to be ranked based upon postoperative pain control and percentage reimbursement will be based upon these results.

35.3 Pathophysiology of Acute Pain

The American Pain Society describes pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [6]. Pain can be classified based upon patient complaint, or quality (i.e., burning, sharp, etc.), intensity, duration (e.g., acute, rehabilitative, chronic), and mechanism [10]. Nociceptive pain is the primary mechanism of pain in the postsurgical or traumatic setting. Surgery involves minor to highly invasive trespass of the human body in an effort to correct or control disease states and pathological processes. Tissue dissection and associated inflammatory responses generate intense noxious stimulation, which, if poorly controlled, can result in hemodynamic instability, pulmonary dysfunction, impaired rehabilitation, and development of persistent pain [11]. Therefore, in addition to the humanitarian reasons for reducing discomfort, there is increased scientific understanding that poorly controlled postsurgical suffering can lead to pathological changes in pain pathways and perception [11–14].

Nociception (or pain detection) follows cell damage and activation of nerve fiber endings by local inflammatory responses and secondary responses to humoral mediators. Pain perception requires transmission of nociceptive signals to the spinal cord and then on to higher cortical centers. The pathological changes that occur in these pathways provide some survival benefits but can cause significant morbidity in high-risk patients (Table 35.1). They include (1) *hyperalgesia* from peripheral and central sensitization, (2) *sympathoadrenal activation*, (3) *neuroendocrine responses*, and (4) *development of chronic pain*.

TABLE 35.1

Acute Injury Response: Potential Benefits versus Disadvantages in Postsurgical Settings

Beneficial Effects after Severe Injury	Adverse Effects in Elderly and High-Risk Patients
1. Maintenance of intravascular volume and MAP	1. Hypertension, hypervolemia, risk of hemorrhage and stroke
2. Maintenance of cardiac output and cerebral perfusion	2. Tachycardia, arrhythmias, myocardial ischemia, CHF
3. Enhanced hemostasis	3. Hypercoagulable state, risk of arterial and DVT
4. Immobilization, minimizing further tissue injury	4. Deconditioning, splinting/hypoxia, pneumonia
5. Substrate mobilization, enhanced energy production	5. Hyperglycemia, negative nitrogen balance
6. Learned avoidance	6. Anxiety, fear, demoralization, prolonged convalescence
7. Nerve plasticity promotes regeneration	7. Nerve plasticity leading to chronic pain

35.3.1 Neuroendocrine Responses

Nociceptive impulses are capable of activating hypothalamic centers, adrenal cortex, and medulla, thus initiating a neuroendocrine stress response [15,16]. This response consists of the secretion of cortisol, glucagon, growth hormone, catecholamines, and the inhibition of insulin and testosterone. Thus, acute pain precipitates a catabolic response of substrate mobilization, hyperglycemia, and a negative nitrogen balance [12]. The catabolic response to acute pain can be beneficial in the short term by increasing available energy. When acute pain is poorly controlled and protracted, these normal responses can negatively impact patient outcome by resulting in muscle wasting, impaired immune response, and decreased resistance to infection [11].

35.3.2 Sympathoadrenal Activation

Surgical injury is associated with marked increases in plasma epinephrine and norepinephrine concentrations [16]. Nociceptive impulses favor and increase sympathetic tone by stimulating sympathetic cells in the hypothalamus and preganglionic neurons anterior

lateral horn of the spinal cord. Poorly controlled acute pain can lead to pathophysiological changes and deleterious patient outcomes mediated through increased sympathetic tone. These changes include the following:

- Increased incidence of postsurgical hypertension by 5%–50% (varying by severity of surgery) [12].
- Increased risk of perioperative myocardial ischemia in patients with poorly compensated coronary artery disease [17]. Severe pain is commonly associated with an impaired ability to ambulate and with decreased venous blood flow.
- Catecholamines, angiotensin, and other factors associated with surgical stress increase platelet–fibrinogen activation, while surgery, trauma, or even surgical positioning can impede venous return from the lower extremities. These factors underlie Virchow's triad of venous stasis, hypercoagulability, and endothelial injury, increasing the risk of clot formation, deep venous thrombosis (DVT), and pulmonary embolism [11,18,19].

35.3.3 Peripheral and Central Sensitization

A process termed "sensitization" increases pain intensity at the incision and in areas adjacent to the surgical injury. Sensitization can occur at peripheral and central sites along the pain pathway and predisposes to hyperalgesia (increased pain sensitivity to noxious stimuli) and allodynia (pain in response to normally non-noxious stimulation) [20].

Peripheral sensitization occurs when the threshold for nociceptive firing is amplified by prostaglandins and other peripheral noxious mediators. In settings of intense inflammation, nerve fibers at the injury site demonstrate exaggerated firing and pain sensation, often out of proportion to the size of the incision and the degree of wound site stimulation. This enhancement in pain signaling to the spinal cord and eventually the sensory cortex is termed primary hyperalgesia [20].

Central sensitization occurs at the level of the spinal cord. Poorly controlled acute pain facilitates pain signaling in the dorsal horn, resulting in the "windup" and firing of nociceptor specific and wide dynamic range (WDR) neurons independent of stimuli [21,22]. Central sensitization leads to secondary hyperalgesia, which results in increased pain at dermatomes above and below the injury site, muscle spasm, and exaggerated discomfort in response to non-noxious stimulation [21–23].

Hyperalgesia and allodynia can result in prolonged discomfort and impaired rehabilitation [21]. Increased incident ("effort-dependent") pain can markedly impair ambulation, incentive spirometry, and physical therapy. For example, hyperalgesia and splinting after upper abdominal and thoracic surgery generally interfere with a patient's ability to cough, clear secretions, and take deep inspirations. This predisposes patients to atelectasis, pneumonia, and hypoxia, particularly those who are elderly or have underlying pulmonary disease [24].

Extreme forms of central sensitization and secondary hyperalgesia can lead to persisting pain, which after a period of 3–6 months is considered chronic pain [12,23–26]. Poorly controlled and protracted postoperative pain leads to plasticity changes, such as apoptosis and nerve fiber sprouting in the central nervous system (CNS). Such changes maintain exaggerated pain perception at the healed surgical site and cannot be reversed. There is a strong correlation between the intensity of acute postoperative pain and the risk of pain persistence 1 year after surgery [27]. An estimated 10%–50% of patients undergoing operations such as leg amputation, coronary artery bypass grafting (CABG), breast surgery, and groin hernia repair report persistent pain 1 year after surgery [25,26,28]. The incidence of chronic pain following routine surgical procedures is presented in Table 35.2. Surgeons may not be aware of these complaints as they rarely see patients after 2 months unless complications arise. An overview of causal factors associated with the development of chronic postoperative pain is presented in Figure 35.1. Pathophysiological responses to poorly controlled pain and their impact on key target organs are outlined in Figure 35.2.

TABLE 35.2

Estimated Incidence of Chronic Postoperative Pain and Disability after Selected Surgical Procedures

	% of Patients		
	Estimated Incidence of Chronic Pain	Estimated Chronic Severe (Disabling) Pain (>5 out of 10)	US Surgical Volumes (1000s)
Amputation	30–50	5–10	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy)	20–30	5–10	479
Thoracotomy	30–40	10	Unknown
Inguinal hernia repair	10	2–4	609
Coronary artery bypass	30–50	5–10	598
Caesarean section	10	4	220

Source: Modified from Kehlet, H. et al., *Lancet*, 367(9522), 1618, 2006.

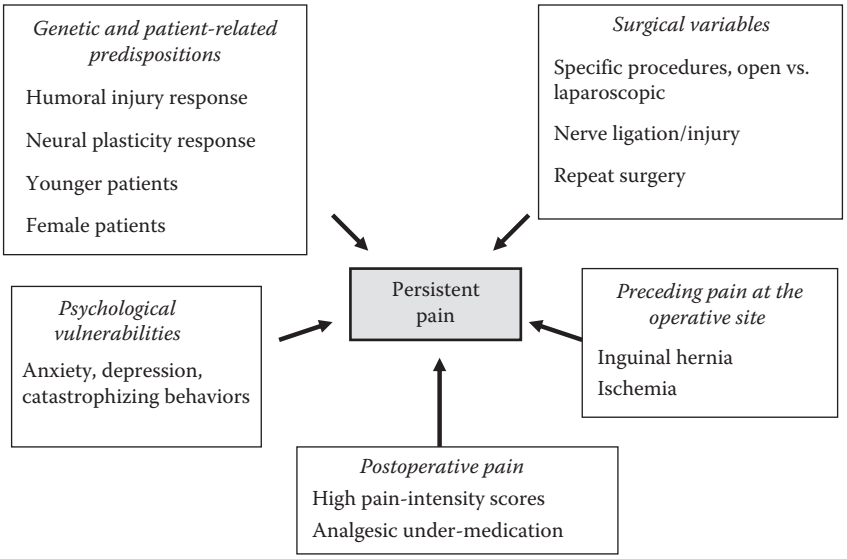


FIGURE 35.1
Risk factors for persistent pain following surgery.

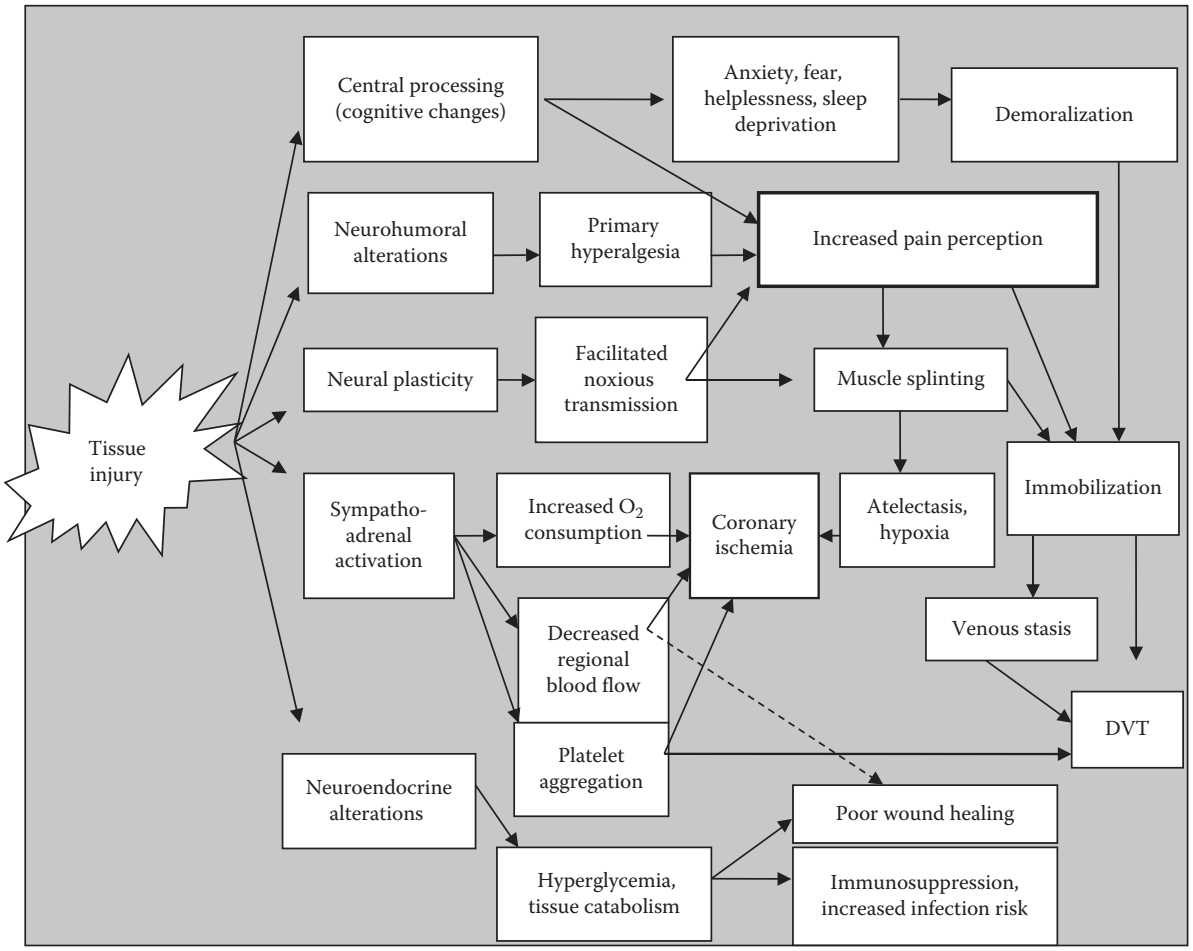


FIGURE 35.2
Pathophysiology of pain.

35.4 Deficiencies in Postsurgical Pain Management

Surgical caregivers and hospital administrators have expressed both surprise and dismay that despite the introduction of new analgesics and novel analgesic delivery systems, postoperative pain remains suboptimally controlled [4,5]. Many ask, why are we not doing a better job? A number of factors appear to be responsible for inadequate pain management (Box 35.2).

35.4.1 Educational Deficits

Physician misconceptions regarding analgesic therapy are often the result of educational deficits and misinformation gained during medical training [29]. Medical school and postgraduate training programs have historically placed a low educational emphasis on pain management. Common educational deficits include the following. (1) Nonrecognition of pain-related pathophysiological responses and associated perioperative morbidity, particularly in elderly, obese, and high-risk populations [11,14]. (2) Negative caregiver and patient attitudes toward opioids and exaggerated addiction concerns, resulting in a reluctance to prescribe or take them particularly in certain age and racial populations [29].

BOX 35.2 FACTORS RESPONSIBLE FOR THE LACK OF IMPROVEMENTS IN POSTSURGICAL PAIN MANAGEMENT

1. Educational deficits (uninformed, misinformed caregivers)
2. Patient misinformation (unrealistic expectations, overconcern regarding addiction risks)
3. Lack of "pain service" supervision (dedicated anesthesiology, surgical or nurse-directed protocol development, and 24 h coverage)
4. Analgesic gaps (pain developing in PACU, following transition in therapy and following hospital discharge)
5. Technology failures (IV infiltration, pump misprogramming, epidural or nerve block catheter dislodgement)
6. Opioid "monotherapy" (overreliance on IV and oral opioids)
7. Opioid dependency (not recognizing or adjusting therapy for opioid-tolerant and hyperalgesic patients)

In reality, opioids administered under proper physician supervision are associated with very low rates of opioid misuse or dependency. Surgeons can educate and correct patient misconceptions and inappropriate expectations, thereby preparing them to better cope with postsurgical pain. Patients receiving realistic, nonbiased pain management education prior to total hip arthroplasty were found to be significantly less anxious just before surgery than noninformed patients. They experienced less pain following surgery and were able to participate in rehabilitation sooner [30].

35.4.2 Undermedication of Pain

Although opioids are generally considered the foundation of analgesic therapy and treatment of choice for moderate to severe postsurgical pain, a relatively low proportion of patients actually receive prescriptions adequate to control their discomfort. Surgeons withhold opioids because of confusion regarding addiction, regulation of controlled substances, and an exaggerated fear of legal liability and regulatory scrutiny [29]. A study by Orgill et al. [31] showed that surgeons ordered opioids to inpatients with moderate to severe pain following total laryngectomy. To make matters worse, nurses administered significantly lower doses than prescribed, and no patient received the recommended minimum daily dose of morphine for adequate management of moderate–severe pain.

Dose-dependent opioid adverse effects often prevent dosing to maximal efficacy and can be a contributing factor to patients' discontinuation of therapy. Many patients may choose to cope with pain rather than continuing to experience intolerable opioid side effects [32–34]. This attitude was observed in pre- and postoperative interviews of 50 patients undergoing abdominal surgery, in which patients were asked to choose from among several hypothetical treatments with different characteristics reflecting the balance between analgesia and side effects [33]. Overall, the severity of side effects was considered a more important consideration for satisfaction with therapy than the degree of pain relief, and many patients were willing to "trade" analgesic efficacy for a reduction in side effects [32,33].

35.4.3 Analgesic Gaps

Analgesic gaps are specific time periods during postsurgical recovery when pain is unrelieved [29]. For example, a patient following major surgery may be extremely comfortable for many hours; however, a sudden change in analgesic delivery or change in patient activity may lead to dramatic increases in pain intensity. When patients are surveyed prior to

BOX 35.3 ANALGESIC GAPS: SPECIFIC TIME PERIODS WHEN PAIN IS UNRELIEVED

1. Pain in PACU (intraoperative analgesic deficiency)
2. Pain during transport to and from procedures
3. Technology failures (IV infiltration, pump misprogramming, epidural or peripheral nerve infusion catheter dislodgement)
4. Transition from regional/neuraxial or IV patient-controlled analgesia to oral analgesics
5. Inadequate analgesic prescriptions for home discharge

hospital discharge, they remember these short, yet highly uncomfortable intervals, and rank overall pain relief and satisfaction lower than it could have been if the "gap" had not occurred. Common causes of analgesic gaps include, technology failures, pain following transition from an interventional technique to oral analgesics, and pain following hospital discharge (Box 35.3). Patients experiencing severe pain in the PACU are the result of "anesthetic gaps" in which opioids or neural blockade is either withheld or administered in subtherapeutic doses. It may take many minutes to hours of opioid loading by PACU nurses to overcome this analgesic deficiency which patients recall all to vividly.

Analgesic delivery systems that are complex, invasive, or involve multiple steps for dose administration have more frequent system-related events (SREs), or problems that must be addressed by healthcare providers. For IV-PCA opioids, infiltration of the IV line is a frequently reported SRE that results in an ineffective subcutaneous deposition of drug, and increasing pain and discomfort. In this regard, the average patient may need to have their IV restarted 2.3 times just to maintain a site for PCA.

Technology failures with epidural and peripheral nerve catheters are also responsible for analgesic gaps. "The success rate of epidural catheters is about 70%, which means that the inherent potential failure of epidural technology is about 30%" [35]. Inadequate analgesia may be related to catheter dislodgement following turning, physical therapy, or ambulation. Epidural analgesic solutions are very dilute and rapidly become subtherapeutic if the catheter is no longer in the epidural space. The surgeon and nursing staff should contact anesthesiology caregivers immediately to evaluate any interventional technique that is not providing effective pain relief. Adjustments in catheter position and bolusing of drug can often reestablish analgesia. Although in some situations, catheters may need to be replaced or an alternative analgesic technique provided.

Inappropriate or inadequate transitions between interventional techniques and oral medications also contribute to analgesic gaps [36]. Anesthesiology-managed epidural and peripheral neural infusions are usually replaced by surgical orders for "as-needed" doses of hydrocodone or oxycodone. This transition may only provide 3 or 4 h of relief and less optimal analgesia. Reliance on short-acting opioids may create a cycle in which patients request doses frequently and may experience periods of inadequate analgesia over and over again.

35.4.4 Overreliance on Opioid Monotherapy

In contrast to those who under prescribe opioids, a growing number of surgeons rely almost exclusively on this analgesic class for acute pain management, and many prescribe relatively large doses despite fears of respiratory depression and other AEs. Many of these caregivers prescribe opioids as monotherapy, that is opioids for mild pain, more for moderate pain, and even more for severe pain. Monotherapeutic dosing protocols generally fail as patients suffer increasing AEs and intolerability in relation to increasing exposure and elevations in CNS levels of drug [32,34].

The overall effectiveness of any form of analgesic therapy consists of a balance between efficacy and overall tolerability. High opioid dose exposure or opioid "burden" is the key factor responsible for annoying side effects and occur in a large proportion of patients prescribed IV-PCA or oral opioids [32–34]. Symptoms may become so intolerable that many patients refrain from prescribed dosing and choose to suffer moderate to severe discomfort rather than experience dose-related AEs. These patients suffer in silence rather than alerting the surgical office or "offending" their surgeons with complaints related to analgesic choice and dosing regimen. Gastrointestinal (GI) and CNS side effects associated with opioids are often but not always dose-dependent, and can be so troublesome that patients refuse additional dosing [34,37].

In surveys of patients undergoing abdominal surgery, the severity of side effects was considered a more important consideration for therapy than the degree of pain relief [37,38]. Many patients are willing to "trade" analgesic efficacy for reductions in side effect severity (Figure 35.2). Thus, surgeons and patients alike share a difficult dilemma in that subtherapeutic opioid doses may be better tolerated yet provide inadequate pain relief, while prescription of higher, more effective doses

often elicits an increased incidence of AEs, and suboptimal pain relief if additional doses are refused. The answer may reside in the use of analgesic regimens reduce the opioid burden and improve tolerability while still maintaining analgesic efficacy.

35.4.5 Misdosing Opioids

Several factors increase risk for opioid under medication and intolerance. Many surgeons prescribe opioids according to standardized protocols despite marked patient variability in age, weight, and drug tolerance/dependency. This "one dose size fits all" dosing philosophy can lead to overdose and intolerance in a frail elderly patients or subtherapeutic dosing in vigorous adults. Age appears to be one of the most important variables determining opioid dose response [33,39]. Therapy should always be individualized for age-related differences in drug clearance and elimination, as well as effects on the CNS. A common example of overstandardization is seen with IV-PCA morphine or hydromorphone order sets. Surgical orders often specify the same loading dose, bolus dose, lockout interval, and 4 h limits for 30 year old and 70 year old patients and for less invasive versus highly invasive procedures.

Analgesic dosing should also be based upon the intensity of operative pain as determined by the site, extent, and duration of surgery [40]. Thoracotomy, upper abdominal, and flank procedures require the most painful incisions, while laparoscopic, breast, and pelvic surgery are associated with lower pain intensity. Ankle surgery, total knee replacement, and spinal fusion are among the most painful forms of orthopedic surgery [29].

A patient's baseline health should also be considered with analgesic dosing. Declining levels of cardiac, hepatic, and renal function are often associated with notable alterations in the volume of distribution, clearance, and excretion of most analgesic agents. For analgesics with high hepatic uptake and clearance, reductions in hepatic blood flow are accompanied by proportional decrements in the overall extraction rate and prolonged pharmacological effects. Agents that undergo biotransformation or are eliminated by the kidneys can produce serious AEs in patients with renal failure unless dose adjustments are made.

Finally, it should be recognized that an increasing number of surgical procedures are being performed in patients with chronic opioid dependencies. Postsurgical IV-PCA orders for these patients are rarely adjusted or increased to compensate for opioid tolerance, and again the same bolus dose given to a naïve individual is prescribed to a patient taking oxycodone 100 mg daily for chronic pain [41].

35.5 Pharmacoeconomic Consequences of Poorly Controlled Pain

35.5.1 Impaired Patient Functionality

Poorly controlled postoperative pain negatively impacts patient recovery and functionality during and beyond the immediate postoperative period. Dihle et al. [6] found that patients with high pain intensity scores following major orthopedic surgery experienced impaired functionality and greater sleep disturbances postoperatively. These impairments included reductions in walking, general activity, social interactions, and mood. Another study by Morrison et al. [42] evaluated 411 patients undergoing repair of hip fracture and found that patients with poorly controlled pain had a significantly longer length of hospital stay, were less likely to be ambulating by postoperative day 3, and took significantly longer to ambulate further than a bedside chair. Because of these early setbacks, they also had significantly lower locomotion scores at 6 months.

35.5.2 Economic Impact

Poorly controlled postoperative pain can add a significant burden to healthcare resources and cost. Coley et al. [43] followed 20,817 ambulatory surgery patients and found that 38% of those who returned complained primarily of pain. They also found that the cost per patient readmission due to pain was $1869.

35.5.3 Quality Markers

Despite reductions in functionality and increased costs associated with poorly controlled pain, many surgeons continue to question the need for improvement, suggesting that acute pain is a necessary physiological response to traumatic injury that will progressively diminish in intensity and eventually resolve. Most hospital administrators and reviewing organizations disagree, stating that optimal pain relief is a patient right and that under medication of pain is associated with significant morbidity and delay in return to baseline functionality.

Data collected from local and regional patient satisfaction surveys including information sent to The Hospital Consumer Assessment of Healthcare providers and Systems (HCAHPS) are increasingly being utilized to develop hospital performance standards for healthcare facilities [13,14]. The overall quality pain management provided at each facility and by medical and surgical specialists affiliated with those institutions has become a key performance marker. Surveys focused on patient satisfaction with pain management may be used to rank healthcare facilities as best or worst depending upon how well their pain was controlled. Facilities where pain was

"sometimes" or "never" well controlled have been ranked as worst. These rankings are presently published online or by US World Report rankings of hospital performance. It is no surprise that some hospitals are ranked far superior to others. Patients are increasingly making decisions to select one facility over a nearby competitor. Superiority in providing pain management may influence their choice. In the future, it is not inconceivable that government and private payers may base rates of reimbursement in proportion to pain and other performance rankings.

35.5.4 Opioid-Related Adverse Drug Event Costs

Data also show that opioid-related adverse drug events (ADEs) have a significant impact on cost. Moleski et al. found that patients with greatest length of stay and cost had an equivalent of two times the opioid consumption of the control group, and significantly more respiratory and GI-related opioid-related ADEs [44]. Adamson et al. [45] examined a large national database and found that patients coded for postoperative ileus (POI) had on average an additional 6 days length of stay and an additional $9417 in hospital costs. A different study by Iyer et al. [46] evaluated a large series of patients recovering from colectomy and found that patients who experienced opioid-related POI had significant increases in length of hospital stay (1.86 days) and in total hospital costs ($4786).

35.6 Analgesic-Related Complications and Adverse Events

In addition to adverse effects from poorly controlled acute pain, additional ADEs are associated with analgesics. Analgesic-related AEs are summarized in Table 35.3.

35.6.1 Opioid Adverse Events

Opioid analgesics, whether given by enteral, IV, IV-PCA, or epidural routes, are associated with a significant incidence of AEs and occasional life-threatening complications (Table 35.4). Oderda et al. [33] examined 324,568

TABLE 35.3

Analgesic-Related Adverse Events and Complications

Agent	Mechanism of Action	Adverse Effects
Opioids (morphine, hydromorphone, oxycodone, hydrocodone, fentanyl)	Mu receptor–mediated inhibition of pain transmission	Nausea, vomiting, ileus, sedation, cognitive changes, respiratory depression
NSAIDs (toradol, ibuprofen, naproxen)	COX-2 inhibition	Wound site bleeding, GI bleeding, renal toxicity
Acetaminophen	GABA interaction, serotonergic	Hepatotoxicity
α-Agonists (clonidine)	Enhanced monoamine-mediated analgesia	Hypotension, bradycardia
Ketamine (Ketalar)	Nonselective NMDA antagonism	Hallucinations, confusion
Gabapentinoids (gabapentin, Neurontin)	α-2 Delta channel blockade	Sedation
Local anesthetics (bupivacaine, ropivacaine, lidocaine, Exparel)	Nerve conduction blockade, infiltration	Neurotoxicity, cardiotoxicity
Tricyclic antidepressants	Norepinephrine reuptake inhibitor	Dry mouth, arrhythmias, drowsiness
Dual-acting analgesics (tapentadol)	Mu-opioid agonist and norepinephrine reuptake inhibition	Sedation

TABLE 35.4

Incidence of Side Effects by Route—Summary Data from Randomized Controlled Trials

Adverse Event	Epidural (%)	IV-PCA (%)	IV (%)	IM (%)	TransDerm (%)	Total (%)
Respiratory	12/635 (1.9)	8/442 (2)	4/164 (2)	17/154 (11)	17/154 (11)	44/1596 (2)
Pruritus	149/636 (23)	82/557 (14)	7/40 (18)	27/194 (14)	27/194 (14)	291/1589 (18)
GI	158/688 (23)	282/761 (37)	71/252 (28)	88/144 (61)	88/144 (61)	630/2034 (31)
Urinary	36/138 (26)	36/220 (16)	32/90 (35.6)	4/97 (4)	4/95 (4)	112/640 (17)
CNS	79/447 (18)	132/389 (34)	11/60 (18)	104/137 (76)	6/64 (9.4)	332/1097 (30)

Source: Modified from *The Journal of Pain*, 3(3), Wheeler, M., Oderda, G.M., Ashburn, M.A., and Lipman, A.G., Adverse effects associated with postoperative opioid analgesia: a systematic review, 159–180, Copyright 2002, with permission from Elsevier.

Note: GI, gastrointestinal; Urinary, urinary retention; CNS, central nervous system effects; IV, intravenous; IM, intramuscular; TransDerm, transdermal.

patients recovering from inpatient surgery and found that at least 20% experienced an opioid-related ADE during their hospital course. GI AEs, including nausea, vomiting, constipation, and ileus, were the most common. Sedation and somnolence are the most commonly reported CNS effects (30.3%). Respiratory depression is a rare CNS adverse effect, but potentially the most catastrophic.

Opioids are also known to induce postoperative delirium (POD), particularly in elderly populations. POD is associated with an increased risk of morbidity, mortality, LOS, and likelihood of nursing home placement [45]. Predictors of POD include age >70 years, preexisting cognitive impairment, history of alcohol abuse, depression, dehydration, visual impairment, and preoperative use of opiates, as well as postoperative pain and the use of anticholinergic and benzodiazepines [45,47].

Respiratory depression associated with opioid use is thought, from observational studies, to occur in the range of 0.01%–3.0%. Respiratory events are most common in elderly patients, those with comorbidities (obesity, sleep apnea, pulmonary disease) and when opioids are administered with other CNS depressants or concomitantly via different routes (neuraxial plus parenteral) [45,47].

35.6.2 Nonsteroidal Anti-Inflammatory Drug Adverse Events

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed as monotherapy for mild pain and as analgesic adjuvants for moderate to severe pain. Their primary mechanism of effect is via inhibition of the arachidonic acid–cyclooxygenase (COX) pathways. The COX cascade consists of two distinct pathways: COX-1 and COX-2. The analgesic and anti-inflammatory effects of NSAIDS are attributable to inhibition of COX-2, while their detrimental effects (e.g., renal dysfunction, GI mucosal compromise, platelet inhibition) are mediated by inhibition of the COX-1 [48,49]. By reducing prostaglandin synthesis, NSAIDs can result in decreased inflammation, hyperalgesia, and allodynia. NSAIDs also decrease the recruitment of leukocytes and the production of leukocyte-derived inflammatory mediators.

Ketorolac tromethamine is an IV NSAID widely employed for the short-term (≤5 days) management of moderately severe acute postoperative pain. Of note, ketorolac has far greater inhibitory effect on COX-1 than on COX-2 (300:1). Thus, IV ketorolac is contraindicated for use in patients with renal insufficiency, which is particularly prevalent in elderly populations, or for patients with a history of GI bleeding. The potent effect of ketorolac on COX-1 also inhibits platelet function, which can increase the risk for bleeding in the perioperative setting. Indeed, postoperative use of ketorolac has been associated with hematomas and other signs of wound bleeding. As such, the prescribing information for IV ketorolac contains a black box warning against its use as a prophylactic analgesic before any major surgery. To minimize bleeding and GI risks, ketorolac doses should be reduced to 15 mg every 6 h and for no more than 3–5 days [50].

35.6.3 Local Anesthetic Adverse Events

Local anesthetics are associated with several disadvantages. Patchy or incomplete blockade may ensue if the surgeon uses too limited a dose or does not infiltrate all surgical planes of the wound site. All local anesthetics have some degree of neurotoxicity, which is dose- and exposure duration–dependent. Rapidly metabolized agents such as chloroprocaine are less toxic. Large doses of local anesthetic injected into highly vascular tissues are more rapidly absorbed and can quickly reach toxic levels. Toxicity is a concern with either unintentional IV administration or rapid vascular uptake from tissue. Some agents are reasonably benign such as lidocaine or chloroprocaine, but others such as bupivicaine and ropivacaine can result in seizures or fatal ventricular arrhythmias. Depending on the agent, dosage, and injection location, treatment of toxicity may be necessary. Required supportive care may rapidly require airway and ventilatory support, seizure treatment, blood pressure support, and arrhythmia control. In cases of systemic toxicity due to bupivicaine, advanced life support and IV administration of a fat emulsion are effective [51].

35.6.4 Acetaminophen-Related Adverse Events

Acetaminophen is widely prescribed for surgical pain management and fever, and is contained in a large number of preparations and opioid compounds. Accidental or intentional acetaminophen overdose (7.5–10 g in adults; >150 mg/kg in children) can cause hepatotoxicity, which is the most common cause of acute liver failure in United States [52]. Toxicity from acetaminophen is not from the drug itself but from one of its metabolites, *N*-acetyl-*p*-benzoquinone imine (NAPQI). Normally this metabolite undergoes conjugation with glutathione, but at toxic doses conjugation depletes glutathione, leading to hepatic cell necrosis. Symptoms related to NAPQI hepatotoxicity including anorexia, nausea, vomiting, right upper quadrant pain, diaphoresis, jaundice, and hypoglycemia may develop over 1–5 days [52]. Treatment of acetaminophen overdose includes administration of oral-activated charcoal to decrease absorption of acetaminophen and *N*-acetyl cysteine—as an antidote, which act as a precursor for glutathione. Acetaminophen is absolutely contraindicated in

patients in fulminant hepatic failure, and restricted for use in chronic alcohol abusers. Acetaminophen should be used with caution in patients with severe hepatic impairment, although hepatotoxicity has not been shown to occur at the recommended doses. In patients with severe renal impairment, the minimum interval redosing of the drug should be increased to 6 h [53,54].

35.7 Improving Surgical Pain Management

35.7.1 Multimodal Analgesia

Complete abolition of postoperative pain (pain prevention) is difficult to achieve with a single drug or analgesic technique [55–57]. In an effort to improve postoperative pain management, The American Society of Anesthesiology has developed practice guidelines for "balanced" or multimodal analgesia. Multimodal analgesia provides several potential benefits. First, the use of agents with different mechanisms of action can provide analgesic synergy and greater reduction in opioid dose requirements. Second, analgesic synergism may reduce dose requirements of each respective agent, thereby limiting AEs [55,56]. The concept of multimodal analgesia versus monotherapy is presented in Figure 35.3.

Unless contraindicated, all patients without contraindications should receive consideration of an around-the-clock regimen of NSAIDs, COX-2 inhibitors, or acetaminophen, as well as neural blockade with local anesthetics. Furthermore, the availability of an IV analgesic is critical in the immediate postoperative period. As compared to oral formulations, IV medications tend to have improved bioavailability, an earlier onset of analgesic effect, and are not dependent on an enteral route, as oral intake may be compromised by postoperative nausea and vomiting or the nature of the surgery [58]. Among IV agents used in multimodal analgesia are opioids, NSAIDs, acetaminophen, α_2-agonists (e.g., clonidine), and *N*-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine.

35.7.2 Preventive Analgesia

A second pain management strategy that has gained renewed attention is the administration of analgesics prior to surgical incision, or preventive analgesia. Investigators have found that preemptive administration of NSAIDs and local anesthetics can effectively block nociceptor activation, release of inflammatory mediators, and transmission of noxious stimuli [59,60]. By reducing the cascade of events that lead to peripheral and central sensitization, preventive analgesia may improve pain control, rehabilitation, functionality, and a variety of other outcome measures.

35.7.3 NSAIDs and COX-2 Inhibitors

Several NSAIDs with safety margins superior to ketorolac may be considered for augmentation of perioperative analgesia. Celecoxib and meloxicam are oral formulations of COX-2-selective agents. An intravenous formulation of ibuprofen (Caldolor®) was approved for management of mild to moderate pain, and as an adjunct to opioid analgesics for management of moderate to severe pain. When compared with ketorolac, IV ibuprofen has more "balanced" affinity for the COX isoenzymes, which translates into a lower risk for COX-1-related AEs [61,62]. Published data indicates that IV ibuprofen had even greater efficacy when used as a preemptive analgesic [61,63]. Preoperative dosing followed by doses every 6 h reduced pain intensity scores and PCA morphine requirements by 33% in patients recovering from major orthopedic surgery and was not associated with bleeding, renal toxicity, or other AEs [63].

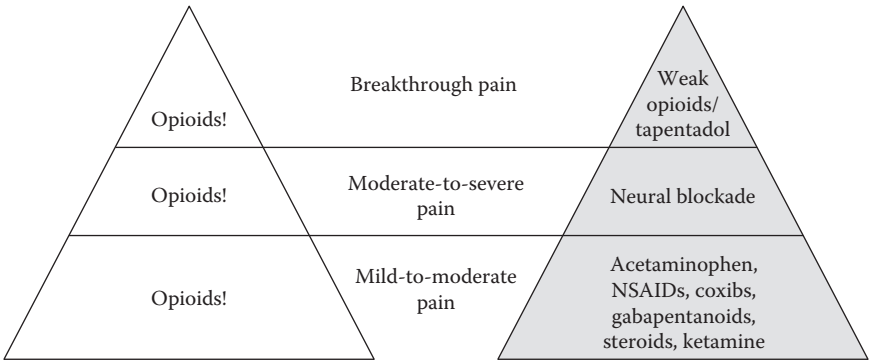


FIGURE 35.3
Opioid monotherapy versus multimodal analgesia.

35.7.4 Epidural and Spinal Analgesia

An ideal target for suppression of noxious signaling is the synapse between the primary pain fiber and the second-order cell in the spinal cord. Analgesics administered via spinal and epidural needles or catheters as well as parenteral and oral routes can bind to endogenous receptors and enhance local and descending inhibitory mechanisms. The anesthetist can be asked to add small doses (0.15–0.5 mg) of preservative-free morphine (Duramorph, Astramorph) to the spinal anesthetic [50,64]. This small dose can provide up to 24 h of pain relief and significantly reduce the need for parenteral or oral opioids. Continuous epidural infusions of fentanyl or hydromorphone can be maintained for up to 96 h [65]. The addition of ultradilute concentrations of bupivacaine (0.02%) or ropivacaine (0.1%) to the infusion provides spinal neural blockade and additional analgesic benefits. While catheter placement is invasive, epidural infusions of opioid plus local anesthetic provide efficient and effective form of pain control for thoracic and abdominal surgeries including colectomy, as well as for orthopedic total knee replacement. Unfortunately, low-molecular-weight heparin must be held for a period of time around the insertion and removal of epidural catheters, but epidural catheters can be maintained in patients receiving aspirin or subcutaneous unfractionated heparin [66].

35.7.5 Peripheral Neural Blockade

Local anesthetics may be used to effectively block noxious signaling in peripheral nerves, thereby reducing pain intensity and opioid requirements. Anesthesiologists and surgeons can employ ultrasound to more reliably administer either boluses doses of local anesthetic or to guide catheter placement for continuous infusions. Continuous neural blockade with bupivacaine or ropivacaine can provide prolonged pain relief but requires placement of a catheter. Following catheter placement, infusions can be maintained for up to 96 h to control pain associated with hand, arm, shoulder, knee, and ankle procedures [50,58,67,68]. In some institutions, selected patients may be discharged home or to rehabilitation facilities with catheters in place and infusions maintained with pressure powered pumps [69]. Infusate solutions of bupivacaine and ropivacaine may be diluted as low as 0.2%–0.25% to selectively block small pain fibers while sparing the larger sensory and motor fibers. In patients recovering from total knee replacement surgery, continuous femoral nerve block with bupivacaine 0.25% provides superior pain relief, and functionality (greater knee flexion), with fewer AEs than IV-PCA morphine [67,68].

Infiltration of local anesthetic into the wound can also provide effective analgesia; however, the duration is often limited to 6–8 h unless a catheter and infusion pumps are employed to maintain the block. A novel local anesthetic preparation of liposomally encapsulated bupivacaine (Exparel™) has recently been approved by the FDA for surgical wound infiltration [69]. A single infiltration can provide an extremely prolonged duration of analgesia ranging up to 72 h. This preparation is expected to play a major role in surgeon-managed multimodal analgesia particularly for colorectal and orthopedic surgery and "fast-track" opioid reduction treatment plans.

35.7.6 Intravenous Acetaminophen

Intravenous acetaminophen (IV-APAP) is a synthetic, nonopiate, centrally acting analgesic and antipyretic. It is recommended as a first-line analgesic for mild to moderate acute pain states and is effective in combination with other analgesics for more severe pain. Intravenous acetaminophen is the preferred preparation for use in perioperative settings since most patients are unable to tolerate oral medications and/or may have unpredictable GI function following surgery [54,70,71]. It is available as a 1 g/250 mL vial that should be administered over 15 min, every 6 h with a maximum daily dose of 4 g. When compared to oral and rectal formulations, IV-APAP achieves more predictable and effective plasma levels in a shorter interval of time [70,71]. It is comparable to other IV ketorolac 30 mg for the treatment of moderate postoperative pain. It can reduce the amount of opiates required for postoperative pain by 33%, and possibly reduce narcotic-related adverse effects [70,71]. IV acetaminophen has an excellent safety profile as it is not associated with sedation, respiratory depression, nausea, vomiting, ileus, or pruritus observed with opioids, or the renal, GI, and platelet effects observed with NSAIDs.

35.7.7 Novel Opioid Preparations

Since surgical pain has a constant component with periods of exacerbation, orthopedic and general surgeons often prescribe sustained release opioids as a continuous approach to pain management. While not specifically indicated for postoperative pain, controlled release opioids, including morphine (MS), contin, and oxycontin, are increasingly employed in this setting. Controlled release preparations are ideally suited for patients suffering prolonged discomfort during rehabilitation and those with chronic pain. They provide 8–12 h of pain relief, avoid frequent peak and trough plasma levels, and provide greater analgesic reliability and uniformity [72].

Tapentadol is a mu-opioid, central-acting analgesic recently approved for postoperative pain management that offers equivalent analgesia to commonly used opioid, oxycodone but with a reduced incidence of GI AEs. Tapentadol blocks the norepinephrine reuptake protein on terminal endings of descending axons, thereby increasing concentrations of norepinephrine and enhancing α-adrenergic-mediated pain suppression. Clinical studies indicate that tapentadol (50–75 mg) provides analgesia comparable to oxycodone (10 mg) with significantly less nausea, vomiting, constipation, and pruritus [73]. Tapentadol may be useful for patients with history of opioid GI intolerance who are recovering from procedures with moderate to severe pain.

35.7.8 Central-Acting Drugs

α-Adrenergic blockers such as clonidine bind to endogenous α-adrenergic receptor and enhance endogenous analgesia. Clonidine (Catapress™) transdermal patch offers a noninvasive convenient way to administer drug at a rate of 0.2 mg/24 h. Its analgesic benefits are useful in patients intolerant of opioids and are best appreciated when the patch is applied prior to surgery [74,75]. Other drugs that can be used to enhance spinal and supraspinal α-adrenergic analgesia include tricyclic antidepressants (TCAs), and serotonin–norepinephrine reuptake inhibitors (SNRIs). These agents provide antineuropathic effects and are useful in patients with a nerve injury component (thoracotomy, mastectomy, amputation) to their postsurgical pain [76]. They also improve sleep and provide antidepressant benefits for patients unable to cope with severe pain, or those with poor outcomes following oncological surgery. In contrast to the delayed onset of antidepressant activity, the onset of TCA-based analgesia is fairly rapid (24 h). Since TCAs can be sedating, they are best administered prior to sleep. Doses should be given at night to improve sleep while reducing complaints of sedation and blurred vision.

35.7.9 Muscle Relaxants

Hyperalgesic spinal motor responses to peripheral injury increase skeletal muscle tone in dermatomes at and adjacent to the site of trauma. Increasing muscle spasm and accumulation of lactic acid result in increased sensitization and pain. Opioids have minimal effect on hyperalgesic muscular spasm but can diminish associated pain. Administration of skeletal muscle relaxants, including judicious doses of diazepam and lorazepam, can inhibit muscle spindle activity and reduce pathological spasm. By breaking the cycle of pain causing muscle spasm and increasing spasm causing increasing pain, patients benefit from greater comfort and reduced opioid dose. It should be remembered that coadministration of benzodiazepines and other muscle relaxants will increase central sedation; therefore doses of other central-acting agents, particularly opioids, should be reduced [77].

35.7.10 Central-Acting Analgesics

Nonopioid pain modulators such as ketamine, gabapentin, and pregabalin are increasingly prescribed for postoperative pain management. In clinical trials, these agents provide measurable opioid-sparing effects, reduce pain intensity scores, and reduce wound site hyperalgesia. Ketamine is nonselective NMDA receptor antagonist that can suppress the sensitization of second-order spinal neurons [78]. Low-dose IV ketamine infusions (0.1–2 mg/kg/h) are generally well tolerated and are not associated with hallucinations and dysphoria seen with high-dose administration of ketamine. Ketamine infusions provide significant opioid-sparing effects and are particularly useful in patients who are intolerant to opioids and others who have significant pulmonary disease. They are also effective for reestablishing effective analgesia in patients with high-grade opioid tolerance and diminished opioid effect (opioid hyperalgesia) [79]. In contrast to opioids, ketamine supports airway reflexes and maintains respiratory rate [78].

Anticonvulsant agents approved for chronic neuropathic pain have been advocated for use as postoperative analgesic adjuvants [80]. Pre- and postoperative dose of gabapentin (900 mg) and pregabalin (150 mg) has been shown to significantly reduce opioid consumption in several postoperative models. These analgesics do not provide significant reductions in pain intensity or opioid requirements; however, perioperative dosing has been shown to reduce peripheral and central sensitization and the risk of persistent pain.

35.7.11 Improved Patient and Provider Relationships

The patient–provider relationship can also impact the quality of postoperative analgesia. For example, one study demonstrated that patients receiving realistic, unbiased pain management education prior to total hip arthroplasty experience less pain following surgery and were able to stand sooner than those who did not [22]. This relationship may be improved if the provider is better able to understand the patient's perspective.

Understanding a patient's emotional coping mechanisms may help the provider optimize analgesia. Reaction to pain is a conditioned behavior that reflects cultural values and can be divided into two broad categories. Stoic patients and cognitively impaired may express minimal discomfort vocally, and emotive

TABLE 35.5

Improving Postoperative Analgesia

Attitudes and Educational Barriers	
Nonrecognition of pain-related pathophysiological responses and their impact on perioperative morbidity	
Reluctance to prescribe opioids because of exaggerated negative concerns over opioids and addiction	Close supervision does not increase addiction risk
Patients receiving realistic, unbiased pain management; education prior to THA experience; less pain following surgery; and were able to stand sooner	
Studies have shown that many patients receive significantly lower doses of opioids than necessary to affect pain control	Age, dose response, site, extent, and duration of surgery are the most important factors
Education	Provide realistic expectations of postoperative pain
Approach to analgesia	
Opioid-related ADEs	Risk is increased with increasing dose, consider CR opioids and tapentadol
Analgesic gaps	IVPCA and controlled-release opioids; more uniform pain control
Use multimodal therapy	Mild-to-moderate pain: acetaminophen, NSAIDs, coxibs, gabapentanoids Moderate-to-severe pain: consider adding neural blockade Severe breakthrough: opioids, ketamine

patients are quite vocal. Highly aggressive and angry patients tend to consume more medications than do patients whose coping styles are more passive.

Surgeons can educate and positively influence patient expectations, thereby preparing them to better cope with postsurgical pain. Patients receiving realistic, nonbiased pain management education and simple breathing exercises prior to surgery are generally less anxious and functional than noninformed patients [81]. Analgesics and educational techniques that may be employed to improve postoperative pain and increase patient satisfaction are presented in Table 35.5.

35.8 Conclusion

Poorly controlled pain is associated with significant pathophysiological responses, poor patient satisfaction, impaired rehabilitation, delayed hospital discharge, and an increased risk for developing chronic pain. Inadequate control of postoperative pain is related to educational deficiencies, analgesic undermedication, and AEs related to opioid monotherapy. A stepwise, multimodal analgesic approach offers improved analgesic efficacy while minimizing adverse effects. The increased availability of injectable nonopioid analgesics and improvement in regional analgesia have dramatically increased interest and application of multimodal analgesia. A significant body of positive evidence has been published [56,82] indicating that multimodal analgesia is safe, effective, and can improve patient outcomes and hospital costs related to opioid overuse.

References

1. Beauregard L, Pomp A, and Choiniere M. Severity and impact of pain after day-surgery. *Can J Anaesth* 1998;45:304–311.
2. McGrath B, Elgendy H, Chung F, Kamming D, Curti B, and King S. Thirty percent of patients have moderate to severe pain 24 hr after ambulatory surgery: A survey of 5,703 patients. *Can J Anaesth* 2004;51:886–891.
3. Bian J and Morrisey MA. Free-standing ambulatory surgery centers and hospital surgery volume. *Inquiry* 2007;44:200–210.
4. Apfelbaum JL, Chen C, Mehta SS, and Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003;97:534–540.
   Highlights the prevalance of poorly controlled acute pain as a common problem.
5. Warfield CA and Kahn CH. Acute pain management. Programs in U.S. hospitals and experiences and attitudes among U.S. adults. *Anesthesiology* 1995;83:1090–1094.
6. Dihle A, Helseth S, Kongsgaard UE, Paul SM, and Miaskowski C. Using the American Pain Society's patient outcome questionnaire to evaluate the quality of postoperative pain management in a sample of Norwegian patients. *J Pain* 2006;7:272–280.
7. Strassels S, McNicol E, Wagner A, Rogers W, Gouveia W, and Carr D. Persistent postoperative pain, health-related quality of life, and functioning 1 month after hospital discharge. *Acute Pain* 2004;6:95–104.
8. US Department of Health and Human Services CfMaM. HCAHPS: Patients' Perspectives of Care Survey. In: Medicaid CfMa, ed., 2010.
9. Comprehensive Accreditation Manual for Hospitals: Joint Commission Resources, 2012.
10. Bonica J. *Management of Pain*, 2nd edn. Philadelphia, PA: Lea & Febiger, 1990.
11. Ghori M, Zhang Y, and Sinatra R. Pathophysiology of acute pain. In: Sinatra R, ed. *Acute Pain Management*. Cambridge, NY: Cambridge University Press, 2009.
    Discusses in-depth pathophysiology of acute pain.

12. Cousins M. Acute pain and the injury response: Immediate and prolonged effects. *Reg Anesth* 1989;14: 162–179.
13. Hume DM and Egdahl RH. The importance of the brain in the endocrine response to injury. *Ann Surg* 1959;150:697–712.
14. Vanderah T. Pathophysiology of pain. *Med Clin North Am* 2007;91:1–12.
15. Basali A, Mascha EJ, Kalfas I, and Schubert A. Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. *Anesthesiology* 2000;93:48–54.
16. Breslow M. Neuroendocrine responses to surgery. In: Breslow M, Miller C, and Rogers M, eds. *Perioperative Management*. St. Louis, MO: Mosby, 1990:180–193.
17. Beattie WS, Buckley DN, and Forrest JB. Epidural morphine reduces the risk of postoperative myocardial ischaemia in patients with cardiac risk factors. *Can J Anaesth* 1993;40:532–541.
18. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000;85:109–117.
19. Kehlet H and Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001;87:62–72.
20. LaMotte RH, Thalhammer JG, and Robinson CJ. Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: A comparison of neural events in monkey with sensory judgments in human. *J Neurophysiol* 1983;50:1–26.
21. Woolf CJ. Central sensitization: Uncovering the relation between pain and plasticity. *Anesthesiology* 2007;106:864–867.
22. Woolf CJ and Chong MS. Preemptive analgesia—Treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993;77:362–379.
23. Coderre TJ, Katz J, Vaccarino AL, and Melzack R. Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. *Pain* 1993;52:259–285.
24. Ali J, Weisel R, Layug A, Kripke B, and Hechtman H. Consequences of postoperative alterations in respiratory mechanics. *Am J Surg* 1974;128:376–382.
25. Kehlet H, Jensen TS, and Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006;367(9522):1618–1625.
26. Perkins FM and Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 2000;93:1123–1133.
27. Pluijms WA, Steegers MAH, Verhagen AFTM, Scheffer GJ, and Wilder-Smith OHG. Chronic post-thoracotomy pain: A retrospective study. *Acta Anaesthesiol Scand* 2006;50:804–808.
28. Bach S, Noreng MF, and Tjéllden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988;33:297–301.
29. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain Med* 2010;11:1859–1871.
    Highlights key causes and consequences of the inadequate management of acute pain.
30. Giraudet-Le Quintrec J-S, Coste J, Vastel L, Pacault V, Jeanne L, Lamas J-P, Kerboull L, Fougeray M, Conseiller C, Kahan A, and Courpied J-P. Positive effect of patient education for hip surgery: A randomized trial. *Clin Orthop Relat Res* 2003:112–120.
31. Orgill R, Krempl GA, and Medina JE. Acute pain management following laryngectomy. *Arch Otolaryngol Head Neck Surg* 2002;128:829–832.
32. Eckstrand JA, Habib AS, Williamson A, Horvath MM, Gattis KG, Cozart H, and Ferranti J. Computerized surveillance of opioid-related adverse drug events in perioperative care: A cross-sectional study. *Patient Saf Surg* 2009;3:18.
33. Oderda GM, Evans RS, Lloyd J, Lipman A, Chen C, Ashburn M, Burke J, and Samore M. Cost of opioid-related adverse drug events in surgical patients. *J Pain Symptom Manage* 2003;25:276–283.
    Highlights key complications and costs associated with the use of opioid analgesia.
34. Wheeler M, Oderda GM, Ashburn MA, and Lipman AG. Adverse events associated with postoperative opioid analgesia: A systematic review. *J Pain* 2002;3(3):159–180.
35. Ready LB. Acute pain: Lessons learned from 25,000 patients. *Reg Anesth Pain Med* 1999;24:499–505.
36. Chen PP, Chui PT, Ma M, and Gin T. A prospective survey of patients after cessation of patient-controlled analgesia. *Anesth Analg* 2001;92:224–227.
37. Eberhart LHJ, Morin AM, Wulf H, and Geldner G. Patient preferences for immediate postoperative recovery. *Br J Anaesth* 2002;89:760–761.
38. Gan TJ, Lubarsky DA, Flood EM, Thanh T, Mauskopf J, Mayne T, and Chen C. Patient preferences for acute pain treatment. *Br J Anaesth* 2004;92:681–688.
39. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, and Strom BL. Side effects of opioids during short-term administration: Effect of age, gender, and race. *Clin Pharmacol Ther* 2003;74:102–112.
40. Fleming MF, Balousek SL, Klessig CL, Mundt MP, and Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain* 2007;8:573–582.
41. Mitra S and Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. *Anesthesiology* 2004;101:212–227.
42. Morrison RS, Magaziner J, McLaughlin MA, Orosz G, Silberzweig SB, Koval KJ, and Siu AL. The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003;103:303–311.
43. Coley KC, Williams BA, DaPos SV, Chen C, and Smith RB. Retrospective evaluation of unanticipated admissions and readmissions after same day surgery and associated costs. *J Clin Anesth* 2002;14:349–353.
44. Moleski R, Adamson R, and Lew I. Cost and quality implications of opioid-based post surgical pain control in total abdominal hysterectomy: A study of cost outliers and opioid related adverse events. *46th ASHP Midyear Clinical Meeting and Exhibition*, New Orleans, LA, 2011.
45. Adamson RT, Lew I, Beyzarov E, Amara S, and Reitan J. Clinical and economic implications of postsurgical use of opioid therapy. *Hosp Pharm* 2011;46:S4–S11.

46. Iyer S, Saunders WB, and Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. *J Manag Care Pharm* 2009;15:485–494.
47. Hutchison R, Chon EP, Tucker W, Gilder R, Moss J, and Daniel P. A comparison of a fentanyl, morphine, and hydromorphone patient-controlled intravenous delivery for acute postoperative analgesia: A multicenter study of opioid-induced adverse reactions. *Hosp Pharm* 2006;41:659–663.
48. Cashman JN. The mechanisms of action of NSAIDs in analgesia. *Drugs* 1996;52 (Suppl 5):13–23.
49. Vane JR and Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104:8.
50. Sinatra RS, Torres J, and Bustos AM. Pain management after major orthopaedic surgery: Current strategies and new concepts. *J Am Acad Orthop Surg* 2002;10:117–129.
51. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, and Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* 2006;105:217–218.
52. Jahr JS, Donkor KN, and Sinatra RS. Nonselective nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, and acetaminophen in acute perioperative pain. In: Sinatra RS, de Leon-Cassasola OA, Ginsberg B, and Viscusi ER, eds. *Acute Pain Management*. New York: Cambridge University Press, 2009:332–365.
53. Romsing J, Moiniche S, and Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. *Br J Anaesth* 2002;88:215–226.
54. Toms L, McQuay HJ, Derry S, and Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev* 2008;(4):CD004602.
55. Kehlet H and Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993;77:1048–1056.
56. Kehlet H and Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002;183:630–641.
57. Wall PD. The prevention of postoperative pain. *Pain* 1988;33:289–290.
58. Peters CL, Shirley B, and Erickson J. The effect of a new multimodal perioperative anesthetic regimen on postoperative pain, side effects, rehabilitation, and length of hospital stay after total joint arthroplasty. *J Arthroplasty* 2006;21:132–138.
59. Duellman TJ, Gaffigan C, Milbrandt JC, and Allan DG. Multi-modal, pre-emptive analgesia decreases the length of hospital stay following total joint arthroplasty. *Orthopedics* 2009;32:167.
60. Liu SS, Carpenter RL, Mackey DC, Thirlby RC, Rupp SM, Shine TS, Feinglass NG, Metzger PP, Fulmer JT, and Smith SL. Effects of perioperative analgesic technique on rate of recovery after colon surgery. *Anesthesiology* 1995;83:757–765.
61. Elia N, Lysakowski C, and Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology* 2005;103:1296–1304.
62. Pham K and Hirschberg R. Global safety of coxibs and NSAIDs. *Curr Top Med Chem* 2005;5:465–473.
63. Singla N, Rock A, and Pavliv L. A multi-center, randomized, double-blind placebo-controlled trial of intravenous-ibuprofen (IV-ibuprofen) for treatment of pain in post-operative orthopedic adult patients. *Pain Med* 2010;11:1284–1293.
64. Boezaart AP, Eksteen JA, Spuy GV, Rossouw P, and Knipe M. Intrathecal morphine. Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. *Spine (Phila Pa 1976)* 1999;24:1131–1137.
65. Grass JA. Fentanyl: Clinical use as postoperative analgesic—Epidural/intrathecal route. *J Pain Symptom Manage* 1992;7:419–430.
66. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, and Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence Based Guidelines. *Regional Anes Pain Med* 2010;35:64–101.
67. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, and d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999;91:8–15.
68. Hebl JR, Dilger JA, Byer DE, Kopp SL, Stevens SR, Pagnano MW, Hanssen AD, and Horlocker TT. A preemptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery. *Reg Anesth Pain Med* 2008;33:510–517.
69. Ilfeld BM, Morey TE, Wang RD, and Enneking FK. Continuous popliteal sciatic nerve block for postoperative pain control at home: A randomized, double-blinded, placebo-controlled study. *Anesthesiology* 2002;97:959–965.
70. Remy C, Marret E, and Bonnet F. State of the art of paracetamol in acute pain therapy. *Curr Opin Anaesthesiol* 2006;19:562–565.
71. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, and Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* 2005;102:822–831.
72. Portenoy RK, Farrar JT, Backonja M-M, Cleeland CS, Yang K, Friedman M, Colucci SV, and Richards P. Long-term use of controlled-release oxycodone for noncancer pain: Results of a 3-year registry study. *Clin J Pain* 2007;23:287–299.
73. Hartrick C, Van Hove I, Stegmann J-U, Oh C, and Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: A 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clin Ther* 2009;31:260–271.
74. Jeffs SA, Hall JE, and Morris S. Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia. *Br J Anaesth* 2002;89:424–427.

75. Segal IS, Jarvis DJ, Duncan SR, White PF, and Maze M. Clinical efficacy of oral-transdermal clonidine combinations during the perioperative period. *Anesthesiology* 1991;74:220–225.
76. O'Connor AB, Noyes K, and Holloway RG. A cost-effectiveness comparison of desipramine, gabapentin, and pregabalin for treating postherapeutic neuralgia. *J Am Geriatr Soc* 2007;55:1176–1184.
77. Chou R, Peterson K, and Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: A systematic review. *J Pain Symptom Manage* 2004;28:140–175.
78. Elia N and Tramer MR. Ketamine and postoperative pain—A quantitative systematic review of randomised trials. *Pain* 2005;113:61–70.
79. Angst M and Clark D. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology* 2006;104:570–587.
80. Tiippana EM, Hamunen K, Kontinen VK, and Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007;104:1545–1556.
81. Culp WC and Beyer EA. Preoperative inspiratory muscle training and postoperative complications. *JAMA* 2007;297:697–698.
82. Gottschalk A and Smith DS. New concepts in acute pain therapy: Preemptive analgesia. *Am Fam Physician* 2001;63:1979–1984.

36

Complications after Craniotomy

Johnny Delashaw, Frank P. Hsu, and Joshua Kras

CONTENTS

36.1 Introduction

Acute care of neurosurgical patients can be extremely complicated and challenging. The entire team comprising neurosurgeons, trauma surgeons, intensivists, and the nursing staff must have a thorough background in managing complications associated with these patients and work together to afford the patient the best possible chance of a successful outcome. This chapter will serve as a broad overview of a multitude of complications following craniotomy that should be understood by the team and recognized in a timely fashion to decrease the overall morbidity of this unique patient population.

36.2 Intracranial Hemorrhage

Before patients undergo craniotomy, a thorough history should be obtained to evaluate for any history of clotting abnormalities and a thorough review of medications should be obtained. Preoperative laboratory testing including prothrombin time, partial thromboplastin, international normalized ratio, and platelet levels should be assessed. Those patients receiving aspirin, Plavix, Coumadin, heparin, Pradaxa, and Lovenox are at an increased risk for postoperative complications, and appropriate treatment prior to or during surgery should ensue [1,2] (Table 36.1). However, prevention of these complications can be best achieved by meticulous hemostasis at the time of the operation and tight blood pressure control during the perioperative period.

Despite all best efforts both intraoperative and postoperative, complications still occur. Following surgery, patients may suffer from bleeding and the development of a hematoma in several different compartments around and inside the brain. These include epidural, subdural, intraparenchymal, and intraventricular [3,4]. The clinical presentation of these lesions is not specific; the practitioner responsible for these patients should

TABLE 36.1

Management of Antiplatelet, Antithrombotic, and Anticoagulation Agents

Medication	Pharmacology	Laboratory Testing	Treatment	Dosage
Acetylsalicylic acid (i.e., Aspirin)	Half-life 2–4.5 h; inhibits platelet function for 7–10 days	Platelet function assay (PFA) and bleeding time	Platelet transfusion	
Clopidogrel (i.e., Plavix)	Half-life 7–10 h; inhibits platelet function for 7–10 days	Platelet function assay (PFA) and bleeding time	Platelet transfusion	1 apharesis unit (4–6 pooled units of platelets) raises platelet count by 30×10^9/L; goal functioning platelet count $>100 \times 10^9$/L
Heparin	Half-life 1–2 h	Partial thromboplastin time (PTT)	Protamine sulfate	1 mg/90–100 units of heparin given in previous 2–3 h
Enoxaparin sodium (i.e., Lovenox)	Half-life 4.5 h	No reliable test	Protamine sulfate	1 mg/1 mg enoxaparin in previous 8 h
Dabigatran etexilate (i.e., Pradaxa)	Half-life 12–14 h, prolonged with renal impairment	Thrombin time (TT), activated partial thromboplastin time (aPTT), ecarin clotting time (ECT)	Hemodialysis	
Warfarin sodium (i.e., Coumadin)	Inhibits vitamin K–dependent clotting factors; Half-lives: Factor II—60 h, VII—4–6 h, IX—24 h, and X—48–72 h Protein C—8 h, Protein S—30 h	International normalized ratio (INR)	Vitamin K, fresh frozen plasma (FFP), factor VIIa	Vitamin K—5–10 mg IV q12 h × 3 doses; FFP—10–30 mL/kg (1 unit = 250 mL); factor VIIa—15–90 units/kg

be well versed in the neurological examination and have a high index of suspicion to prevent delays in care that severely affect the morbidity and mortality of this patient population. Patients who become increasingly lethargic and exhibit focal signs such as hemiparesis, aphasia, cranial nerve palsy, or seizure are at significant risk [5]. Changes in vital signs, such as Cushing's triad (hypertension, bradycardia, and abnormal respiratory pattern), may reflect increasing intracranial pressure (ICP) signifying imminent herniation [6,7]. Identification of any of the earlier signs or symptoms warrants emergent computed tomography (CT) scanning as the initial test of choice [8].

Treatment for these lesions surrounds the principle of relieving increased ICP and is dependent on the exact location and size of the insult [9]. General measures include maintaining the head of bed at 30°, keeping the head neutral to allow adequate venous drainage, and loosening cervical collars as to not compress venous outflow. Medical management may include the use of mannitol, hypertonic saline (i.e., 23.4%), or temporary hyperventilation.

Mannitol is an effective osmotic agent and will rapidly decrease ICP. Dosing is 1–1.5 g/kg given as a bolus; subsequent dosing of 0.5 g/kg every 4 h may help sustain the effects. Measuring serum osmolarity is important to avoid a hyperosmolar state with the potential for severe metabolic derangements and acute renal failure; mannitol should be discontinued if the serum osmolarity reaches 320 mOsm [10–19].

The 23.4% hypertonic saline is equally as effective as mannitol and is given as a 30 cc bolus. Following serum sodium levels every 4–6 h, if the serum sodium level exceeds 155 meq/L, hypertonic saline should be discontinued to prevent renal damage [20,21].

Patients whose neurological condition is deteriorating and whose level of consciousness is depressed require intubation, not only for airway protection but also for allowing temporary hyperventilation. Monitoring arterial blood gases is essential and the ventilator settings should be adjusted to reach a goal CO_2 of 30–35 torr [10,13,22–27].

Ultimately the patient may best be served by evacuation of the offending lesion in the case of an epidural, subdural, or intraparenchymal lesion. In the event of intraventricular hemorrhage, an external ventricular drain may be placed to prevent obstructive hydrocephalus.

36.3 Hydrocephalus

Hydrocephalus may cause symptoms resembling those caused by focal, expanding mass lesions and occurs when the drainage pathway from one ventricle to another becomes blocked. This most commonly occurs between the lateral and third ventricles and less commonly between the third and fourth ventricles. In the postoperative period, the most common cause of obstruction is blockage from blood within the ventricular system. This may require placement of a ventriculostomy to allow an outlet for the accumulation of cerebrospinal fluid (CSF). Another common cause could be from compression

of the ventricular system by a blood clot or developing edema. In the event of a blood clot, the offending hemorrhage may need to be evacuated to open the blockage. If edema is present, the patient could benefit from medical therapy with either mannitol or hypertonic saline. The use of decadron may be helpful in patients suffering from edema caused by a neoplastic process.

The patient will become lethargic and demonstrate progressive signs associated with the exact location of the inciting insult. The first and most sensitive diagnostic tool to evaluate patients with hydrocephalus is a noncontrast CT scan.

There are two primary types of hydrocephalus: communicating and noncommunicating. Communicating hydrocephalus blocks the reabsorption of CSF downstream from the foramen of Luschka to its point of reabsorption through the arachnoid villi into the major venous sinuses. The point of obstruction may be at the tentorial incisures as the result of scarring from meningitis or damage to the arachnoid granulations. The most common cause of communicating hydrocephalus in the postoperative period is the blockage of absorption pathways by subarachnoid blood. Communicating hydrocephalus causes the patient's condition to deteriorate slowly, generally over a period of days. Typically there are no focal signs; however, the patient may exhibit gait ataxia, memory difficulty, urinary incontinence, lethargy, and increased headache. A CT scan shows universal dilation of the entire ventricular system. Lumbar puncture may demonstrate a high opening pressure. The CSF may be xanthochromic with a high protein level, indicating the viscous nature of the fluid and the potential problem in filtering it through the arachnoid villi. Serial lumbar punctures may be performed as a temporizing measure to diagnose and treat communicating hydrocephalus versus the placement of a ventriculostomy with continuous drainage of CSF. If the patient's neurological condition improves, definitive treatment in the form of a shunt may be required.

Noncommunicating hydrocephalus usually causes rapid deterioration of the patient's condition [28]. The patient may at first be agitated but then enters a comatose state. Sedating a patient who is agitated after craniotomy without first ruling out hydrocephalus as the cause of this alteration in mental status is a common fatal mistake because sedation masks the increase in ICP and the eventual herniation. Therefore, patients at risk of blockage of CSF flow, such as those who have recently undergone surgery to the posterior fossa or those with intraventricular hemorrhage, require more careful, anticipatory observation for the signs of deterioration caused by acute hydrocephalus (Figure 36.1). A ventriculostomy kit should be placed at the bedside of the patient; so immediate decompression can be provided if necessary. Similar to communicating hydrocephalus, permanent shunt placement may become necessary and is the definitive treatment for obstructive hydrocephalus.

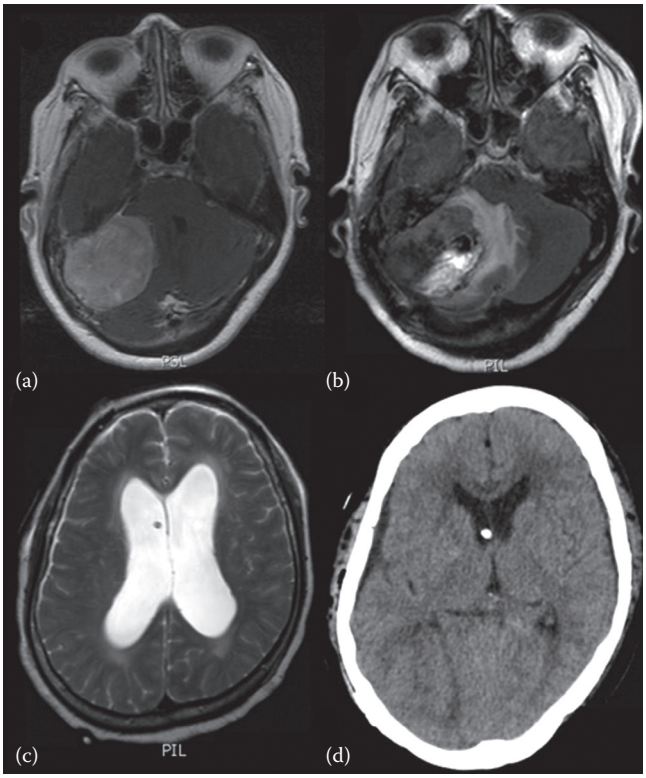


FIGURE 36.1
(a) Axial T1W MRI with contrast showing large right cerebellopontine angle meningioma. (b) Postoperative axial flair MRI showing edema and fourth ventricular obstruction. (c) Postoperative axial T2W MRI showing hydrocephalus and ventriculostomy placement. (d) Axial CT showing resolution of hydrocephalus following ventriculostomy.

36.4 Pneumocephalus

Pneumocephalus is the accumulation of air in the intracranial compartment. It commonly occurs after craniotomy if the air is not completely evacuated before the bone flap is replaced or if there is communication with an air-filled sinus. It may also occur after a traumatic basilar skull fracture when air is introduced into the subarachnoid space by communication with the exterior environment, usually through the ethmoid, sphenoid, mastoid, or frontal sinuses [29]. Pneumocephalus may cause a patient to become lethargic and confused. A CT scan may confirm the accumulation of air beneath the bone flap or communication with one of the sinuses. Most cases of pneumocephalus are asymptomatic and require no treatment. In the event the patient is symptomatic, the patient may be given 100% oxygen by a

nonrebreather mask and kept flat in bed. Tension pneumocephalus, marked by an enlarging accumulation of air causing mass effect, including midline shift, sulcal effacement, or both, demands more aggressive and invasive intervention to alleviate the pressure. Emergent reopening of the craniotomy or needle aspiration may be necessary in life-threatening situations.

Pneumocephalus indicates communication between the exterior environment and the intracranial cavity [30]. This condition can be a precursor of CSF leakage. CSF may drain through the ethmoid or sphenoid sinus complex, causing rhinorrhea, or through the mastoid air cells, causing otorrhea. Although pneumocephalus indicates a tear in the dura, a CSF leak indicates a relatively large dural tear allowing a stream of CSF to flow. CSF may also leak from the scalp suture line; the flow of CSF to the external environment should stop after a watertight closure has been established by oversewing the suture line. When rhinorrhea or otorrhea occurs postoperatively, it should be treated conservatively with placement of a lumbar drain. The drain should be opened and the height adjusted to allow 10–15 cc/h for 3–5 days. Before removal of the lumbar drain, it should be clamped and the patient monitored for 24 h to assess for any further drainage. If a seal is not accomplished after conservative treatment, surgical intervention may become necessary. The use of antibiotics to treat pneumocephalus alone or in combination with CSF leakage is controversial. Treatment with antibiotics should not be initiated unless signs and symptoms of CSF infection develop. Prophylactic treatment with antibiotics should be initiated only if the patient has significant sinusitis.

36.5 Postoperative Edema

Brain edema [31] during the postoperative period can be caused by excessive intraoperative retraction, intraoperative trauma, arterial or venous occlusion, and associated with a neoplastic process [32]. On further evaluation with CT scanning, edema will appear as an area of decreased density and may be associated with sulcal effacement or brain shift. Brain edema is commonly associated with intracerebral hemorrhage and contusion. Edema associated with cerebral infarction generally indicates severe stroke and may lead to herniation. All of these causes may be seen during the postoperative period (Figure 36.1). When accompanying a neoplastic process, the most typical cause is a metastatic lesion; however, primary brain tumors such as glioblastoma and meningioma may also cause significant edema following resection.

The treatment of edema depends on the underlying cause of the lesion. When edema is associated with a neoplastic process or inflammation (i.e., vasogenic edema), steroids play an important role. The role of steroids in the setting of trauma, infarction, or anoxia (i.e., cytotoxic edema) has proven not to be beneficial and even harmful, leading to septic complications and gastrointestinal hemorrhage [33–36]. In the setting of both types of edema, there is a role for mannitol, hypertonic saline, and in emergent cases hyperventilation. The latter has a limited role and should only be used as a temporizing measure until further medical or surgical treatment can be added to the treatment regimen. Mannitol can be given as an initial IV bolus of 1 g/kg followed by a maintenance dose of 0.5 mg/kg given every 4 h. Serum osmolarity and serum sodium should be checked every 4 h [37]. To prevent renal dysfunction, mannitol should be discontinued if the serum osmolarity reaches 320 mOsm. More recently, 23.4% hypertonic saline has been used to treat acute situations. The dosing is an IV bolus of 30 cc. Three percent of hypertonic saline can also be used as a continuous infusion with a goal serum sodium of 145–155 meq/L.

36.6 Infarctions

36.6.1 Arterial Infarcts

Infarctions resulting from occlusion of arterial vascular supply are most commonly associated with atherosclerotic disease. Arterial infarct is a rare complication after craniotomy but may occur if there has been substantial intraoperative manipulation of cerebral vessels [7,13,38–40]. Intraoperative coagulation or ligation of bleeding vessels in patients without good collateral circulation leads to postoperative infarction. A CT scan performed in the immediate postoperative period may not show areas of infarct; however, a second CT scan 24–48 h later will show areas of hypodensity representing infarct [41]. Clinically, the patient will usually exhibit focal neurological deficits. If a large area or bilateral areas of the brain are involved, the patient may experience a global decrease in level of consciousness and more extensive neurological deficits. If the stroke is detected early, and attempt to save the penumbra should be made by improving blood flow through collateral vessels by keeping the patient euvolemic, slightly hypertensive, in certain situations the consideration of anticoagulation may be considered.

Any involvement of the arteries serving the cerebellum may lead to a cerebellar infarct; thus, immediate neurosurgical attention is necessary. Cerebellar infarction places the patient at a high risk of obstructive

hydrocephalus as the cerebellar swelling continues to deform and occlude the fourth ventricle. In the conscious patient, there is an orderly progression of clinical signs and symptoms. Symptoms and signs related to cerebellar dysfunction, such as dizziness, vertigo, nausea, vomiting, truncal ataxia, nystagmus, and dysarthria, appear first. Next, the patient may suffer from the onset of hydrocephalus with symptoms of headaches, agitation, and finally obtundation. In these situations, the patient may benefit from ventriculostomy placement and potential urgent decompression of the posterior fossa.

36.6.2 Venous Infarcts

Venous infarcts are generally seen after craniotomy, especially if the venous sinuses are involved in the surgical field. Repair of dural sinus lacerations or prolonged compression of a sinus by an extrinsic force (i.e., retractors) places the patient at a risk of venous sinus thrombosis and postoperative infarction [42,43] (Figure 36.2).

In the conscious patient, thrombosis results in symptoms that include headache, nausea, vomiting, and seizures. Cerebral venous thrombosis and/or dural sinus thrombosis can lead to venous infarction [44]. Venous infarction has a predilection to convert into a hemorrhagic lesion and often involves subcortical white matter and traverses the typical arteriovascular boundaries seen on CT scan. In the absence of hemorrhage, the patient should be kept euvolemic to hypervolemic to prevent further exacerbation of thrombosis in the dehydrated state. In certain situations, anticoagulation may be necessary to prevent further propagation of clot in the venous sinuses and an exacerbation of the venous infarct.

The component of hemorrhage or significant mass effect resulting from edema may become a neurosurgical emergency. Evacuation of the clot may be necessary, as may decompressive craniectomy to reduce the increase of ICP in a patient whose condition is deteriorating.

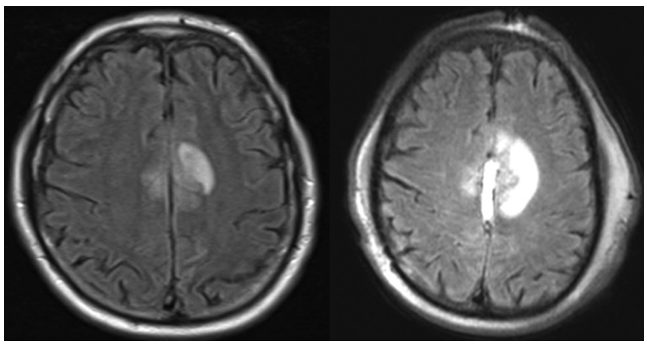


FIGURE 36.2
Preoperative (left) and postoperative (right) axial flair MRI images showing venous infarction.

36.7 Infection

36.7.1 Meningitis

Meningitis is an infection of the leptomeninges (the pia and the arachnoid) and thus of the subarachnoid space [45]. This space is continuous from the hemispheric convexities to the lumbosacral space. Infection of the subarachnoid space is typically diagnosed by a lumbar puncture. Infection localized to the subdural space (subdural empyema) may leave the ventricular and lumbar fluids sterile with little more than a parameningeal reaction or reactive pleocytosis. The same is true of cerebritis and brain abscess, unless there is erosion into the ventricular system or the subarachnoid space.

Meningitis typically causes high fever, meningismus, positive Kernig's and Brudzinski's signs, headache, a depressed level of consciousness, seizures, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, and severe advanced cases, diabetes insipidus (DI). Meningitis may occur as late as 4 weeks after surgery because violation of the mastoid air cells in the face of CSF leak. After craniotomy, the patient's preoperative depressed level of consciousness may persist, rendering the patient unable to complain of headaches; the patient may also be predisposed to seizures or meningeal irritation as the result of blood in the subarachnoid spaces after the surgical procedure. Unfortunately, after craniotomy the patient may exhibit all of the clinical signs of an aseptic meningitis, including fever; therefore, the diagnosis may depend entirely upon examination of CSF and careful observation.

The manifestations of postoperative meningitis are often much more subtle than those of the typical pneumococcal or meningococcal variety. If signs of meningeal irritation should occur in isolation or in association with any other changes, neurological or metabolic, examination of the CSF is mandatory before antibiotics are administered. Because cell count, glucose concentrations, and protein concentration are abnormal after craniotomy, an absolute diagnosis must await the result of CSF culture or the demonstration of bacteria on Gram stain. Empiric treatment with broad-spectrum intravenous antibiotics should be started while the results of the culture are awaited. Therapy directed at Gram-positive cocci and Gram-negative organisms must be instituted. The antibiotic regimen should then be tailored once the final culture results and sensitivities have been obtained.

36.7.2 Ventriculitis

The clinical picture of ventriculitis differs little from that of meningitis, although the presentation is usually

much more subtle. Meningeal symptoms may be minimal and fever variable, whereas alteration in mental status and neurological function predominates. Diagnosis requires careful observation; the only diagnostic test is CSF sampling of ventricular fluid.

Both meningitis and ventriculitis tend to occur in the postoperative period >3 days after violation and contamination of the subarachnoid or ventricular space. The usual postoperative effects of operative trauma and brain edema begin to resolve during this period. Any reversal in this pattern of healing should alert the clinician to infection in one of these spaces. Both meningitis and ventriculitis may be associated with elevated ICP, and infection should be considered in a patient with increasing ICP, especially if the elevation has no clear or reasonable cause and if no mass effect is visible on CT scan. Again, selecting a treatment regimen depends on the results of CSF cultures and sensitivities. In the meantime, the intrathecal administration of antibiotics may be considered so as to provide broad-spectrum coverage. The antibiotic can be tailored once the results of final cultures and sensitivities have been obtained.

36.7.3 Abscess

Brain abscess [46], or its immediate precursor, cerebritis, is relatively rare in the postoperative period (Figure 36.3). The development of meningeal signs or infected CSF in the face of focal deficits suggests that this process must be ruled out. The absence of focal deficits does not rule out the presence of abscess.

If an abscess does not communicate with the ventricular or subarachnoid space, meningeal signs will usually be absent. In up to 95% of cases of cerebral abscesses, the CSF may be completely normal and the patient can be afebrile. As is the case with meningitis and ventriculitis, steroids may suppress or delay neurological change in the developing abscess; therefore, abscess must be considered when a patient's condition worsens after discontinuation of steroids.

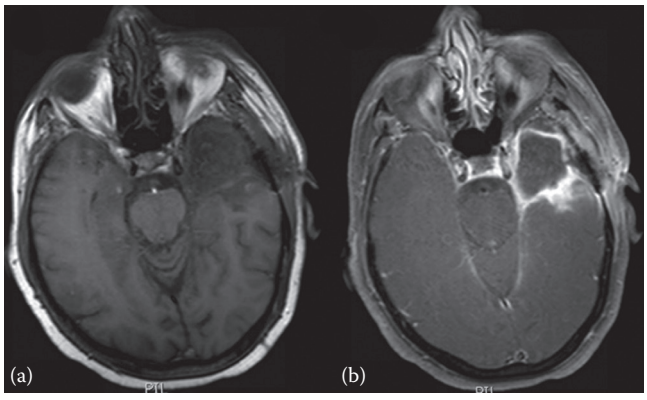


FIGURE 36.3
Postoperative axial MRI (a) without contrast and (b) with contrast showing ring enhancement, consistent with cerebral abscess.

The treatment of brain abscess is the same as that of any other abscess: incision and drainage [46]. This procedure is also diagnostic. Needle aspiration combined with the administration of high-dose antibiotics will clear approximately 80%–85% of abscesses. The remainder will require craniotomy for complete cure. If infection also involves the bone flap, then reoperation, bone flap removal, and drainage of the abscess should be considered to allow maximal resolution of the infection. The increased use of intraventricular antibiotics in the past decade has provided an effective means of treating certain forms of infection, especially meningitis and ventriculitis caused by highly resistant Gram-positive and Gram-negative organisms.

36.7.4 Subdural Empyema

Subdural empyema is a specific form of abscess [47,48]. This entity is also marked by neurological deterioration, with the development of focal signs of hemiparesis, seizures, or both. The seizures associated with subdural empyema tend to begin focally, become generalized, and then quickly progress to status epilepticus. These neurological findings are related to mass effect from edema. Unlike subdural hematomas, subdural empyemas are associated with edema that is out of proportion to the volume of fluid in the subdural space.

Subdural empyema is rare after craniotomy but may follow burr hole drainage of chronic subdural hematomas. Most subdural empyemas are associated with chronic sinusitis in adults or with middle ear infections in young children and infants.

Diagnosis by CT scan may be difficult and a high index of suspicion is required. However, a parafalcine subdural collection, which can be seen on CT scan, is pathognomonic of subdural abscess. Inflammatory effects are predominant and treatment with drainage and antibiotics is the gold standard. The choice of antibiotic and dose are the same as those for meningitis, which may also be present. Drainage may also be accomplished by reoperation or burr hole drainage; some surgeons recommend placing subdural catheters for irrigation of this space with antibiotic solutions.

36.8 Metabolic Imbalances

36.8.1 Hyponatremia

Sodium imbalance is the most common metabolic disturbance experienced by a neurosurgical patient. Electrolyte levels should be checked daily after craniotomy until

the levels are stable. Sodium concentrations outside the normal physiological range lead to decreased level of consciousness, disorientation, seizures, and global encephalopathy. After craniotomy, low sodium concentrations may be attributable to cerebral salt wasting (CSW) or SIADH [49].

CSW is a condition in which an unknown mechanism, currently believed to be a signal for overproduction of atrial natriuretic protein (ANP), causes natriuresis or overexcretion of sodium into the urine. This condition causes the body to respond to hypovolemia by increasing the secretion of antidiuretic hormone (ADH). Water is reabsorbed from the effects of ADH, whereas sodium continues to be excreted under the influence of ANP, thus resulting in a hyponatremic state. In contrast, SIADH causes water to be reabsorbed despite a euvolemic or hypervolemic state, thus also resulting in hyponatremia [7,10].

It is important to differentiate between the two mechanisms of hyponatremia because they require different treatments. CSW causes the urine electrolytes to show an inappropriately high content of sodium. The patient may have clinical signs and symptoms of dehydration, along with a high serum osmolality. Treatment of this condition involves a combination of fluid restriction and replacement of intravascular volume with a colloid solution high in sodium content, most commonly albumin. Replacing the intravascular volume with colloid breaks the viscous cycle of ADH secretion. SIADH causes a hypervolemic state and may produce clinical signs and symptoms of low serum osmolality. Urine electrolyte levels will show a high sodium concentration, but not as high as that seen with CSW. The treatment is strict restriction of parenterally and enterally administered fluids.

The use of hypertonic saline should be considered for cases in which hyponatremia continues to progress despite initiation of fluid restriction, the infusion of colloid, or cases in which the exact cause cannot be determined despite appropriate review of all relevant laboratory values. If hypertonic saline is administered, sodium levels should be checked on a frequent basis. A too rapid correction of sodium levels may lead to the devastating complication of central pontine myelinolysis, especially in patients who have chronic hyponatremia.

Hyponatremia after craniotomy is usually temporary. It is important to support the patient until the physiological mechanism of dealing with sodium balance returns to full function.

36.8.2 Hypernatremia

After craniotomy, hypernatremia frequently occurs with dysfunction of the hypothalamic or pituitary axis resulting from manipulation of these areas during surgery. This dysfunction results in DI, which causes too much water to be lost in the urine and produces a high serum sodium concentration as the result of inadequate production of ADH. Postoperatively, DI [50] may be diagnosed by using three criteria: (1) urine output of >250 cc/h for two consecutive hours, (2) an increasing serum sodium concentration of higher than 145 mEq/L, and (3) urine specific gravity below 1.005. Continued DI should be managed by administering a hypotonic saline solution delivered at a rate higher than that used for maintenance of intravenous fluids. The urine output should be replaced cubic centimeter to cubic centimeter hourly up to a maximum of 250 cc. A conscious patient should be allowed to drink water in an amount equal to that of the urine output.

If the DI is refractory to intravenous fluid therapy or the patient cannot ingest enough fluid to keep up with the demand, aqueous pitressin should be administered. A one-time subcutaneous injection of five units of aqueous pitressin should be administered with continued close monitoring of sodium concentrations and urine output. If the DI continues, another injection of aqueous pitressin may be administered. The goal is a slow, gradual correction of the serum concentration. Correcting hypernatremia too rapidly may result in lethal brain edema.

After craniotomy, patients are expected to experience only a temporary problem with hypernatremia unless the pituitary stalk or posterior lobe of the pituitary gland has been severely damaged. Once the stunned pituitary recovers function, the hypernatremia is expected to resolve.

36.8.3 Cerebrospinal Fluid Leak

Following craniotomy, there may be significant involvement of the air sinuses (primarily frontal sinus), mastoid air cells, and several other sites of possible CSF leakage. As transnasal endoscopic procedures are gaining popularity, these cases have a high affinity for developing CSF fistula. In these instances, if not properly identified and dealt with patients will be at increased risk of developing complications. Increased risk of pneumocephalus and meningitis may be encountered if leaking occurs. By waxing all bony edges around the craniotomy site, exoneration of the frontal sinus with packing of the nasofrontal duct, and meticulous harvesting of a nasoseptal flap for transnasal cases, these complications can be kept to a minimum. If encountered, the use of a lumbar drain or ventriculostomy as an outlet for CSF drainage while scarring of the leak site takes place will lessen overall morbidity. In certain instances, it may be necessary to explore the site and repair primarily.

Complications and Incidence

Complication	Incidence	References
Intracranial hemorrhage	1.1%	[1–27]
Pneumocephalus	[a]	[29,30]
Hydrocephalus	[a]	[28]
Postoperative edema	[a]	[31–37]
Arterial infarction	[a]	[7,13,38–41]
Venous infarction	[a]	[42–44]
Infection	2%	[45–48]
Metabolic imbalances	[a]	[7,10,49,50]
Cerebrospinal fluid leak	[a]	—

[a] Due to the difficulty in studying these problems, there is no conclusive study regarding the incidence of these complications.

Complication Avoidance

- Intracranial hemorrhage
  - Identification and correction of coagulopathy and drug-induced bleeding tendencies
  - Strict postoperative blood pressure control (SBP <140)
- Pneumocephalus
  - Filling the operative cavity with fluid and watertight dural closure
  - Waxing of air cells and exoneration of sinus cavities in direct communication with the intracranial space
- Hydrocephalus
  - Placement of a ventriculostomy prophylactically in cases with high likelihood of developing hydrocephalus
  - Limiting/removal of blood products in the ventricular system
- Postoperative edema
  - Limit manipulation and retraction of brain parenchyma
  - Liberal use of steroids in the immediate perioperative period (1–3 days)
- Arterial infarction
  - Careful manipulation of vessels
  - Preventing hypotension throughout the perioperative period
- Venous infarction
  - Prevention of dehydration and maintenance of euvolemia throughout perioperative period
  - Gentle use of retractors and limiting amount of time compressing brain
- Infection (i.e., meningitis, ventriculitis, abscess, subdural empyema)
  - Meticulous sterile technique
  - Removal of drains (i.e., ventriculostomy) as soon as is safe
  - Routine use of pre/postoperative prophylactic antibiotics
  - Postoperative wound care
- Hyponatremia
  - No method of prevention has been found useful
  - Urgent identification in the postoperative period and adequate correction
- Hypernatremia
  - Gentle manipulation of the hypothalamus, pituitary gland, and stalk
- Cerebrospinal fluid leak
  - Watertight dural closure
  - Exoneration of sinuses and waxing of air cells
  - Appropriate use of ventriculostomy and lumbar drains in high-risk cases

References

1. Clark, JA, Finelli RE, and Netsky MG. Disseminated intra-vascular coagulation following cranial trauma. Case report. *J Neurosurg* 1980; 52:266–269.
2. Pitts LH. Comment on "The incidence and significance of hemostatic abnormalities in patients with head injuries." *Neurosurgery* 1989; 14:832.
3. Ribas GC and Jane JA. Traumatic contusions and intracerebral hematomas. *J Neurotrauma* 1992; 9:S265–S278.
4. Miller JD, Murray LS, and Teasdale GM. Development of a traumatic intracerebral hematoma after a "minor" head injury. *Neurosurgery* 1990; 27:669–673.
5. Marshall LF, Barba D, Toold BM, and Bowers SA. The oval pupil: Clinical significance and relationship to intracranial hypertension. *J Neurosurg* 1983; 58:566–568.
6. Savitz SI. Cushing's contributions to neuroscience, part 1: Through the looking glass. *Neuroscientist* 2000; 6:411–414.
7. Savitz SI. Cushing's contributions to neuroscience, part 2: Cushing and several dwarfs. *Neuroscientist* 2001; 7:469–473.
8. Wilberger JE Jr, Rothfus WE, Tabas J, Goldberg AL, and Deeb ZL. Acute tissue tear hemorrhages of the brain: Computed tomography and clinicopathological correlations. *Neurosurgery* 1990; 27:208–213.
9. Woster PS and LeBlanc KL. Management of elevated intracranial pressure. *Clin Pharm* 1990; 9:762–772.
   Excellent overview of pharmacological management of the treatment of increased intracranial pressure.
10. Miller SM. Management of central nervous system injuries. In: Turndorf H, Capan LM, and Miller SM, eds. *Trauma: Anesthesia and Intensive Care*. Philadelphia, PA: JB Lippincott Co., 1991: pp. 321–355.
11. Muizelaar JP, Lutz HA, and Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head injured patients. *J Neurosurg* 1984; 61:700–706.
12. Rosner MJ and Daughton S. Cerebral perfusion pressure management in head injury. *J Trauma* 1990; 30:933–940.
13. Rosner MJ and Coley I. Cerebral perfusion pressure: A hemodynamic mechanism of mannitol and postmannitol hemogram. *Neurosurgery* 1987; 21:147–156.
14. Bouma GJ, Muizelaar JP, Bandoh K, and Marmarou A. Blood pressure and intracranial pressure–volume dynamic in severe head injury: Relationship with cerebral blood flow. *J Neurosurg* 1992; 77:15–19.
15. Cruz J, Minoja G, Okuchi K, and Facco E. Successful use of the new high-dose mannitol treatment in patients with Glasgow Coma Scale scores of 3 and bilateral abnormal pupillary widening: A randomized trial. *J Neurosurg* 2004; 100:376–383.
16. Muizelaar JP, Wei EP, Kantos HA, and Becker DP. Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. *J Neurosurg* 1983; 59:822–828.
17. Schrot RJ and Muizelaar JP. Mannitol in acute traumatic brain injury. *Lancet* 2002; 359:1633–1634.
18. Burke AM, Quest DO, Chien S, and Cerri C. The effects of mannitol on blood viscosity. *J Neurosurg* 1981; 55:550–553.

19. Marshall LF, Smith RW, Rauscher LA, and Shapiro HM. Mannitol dose requirements in brain-injured patients. *J Neurosurg* 1978; 48:169–172.
20. Qureshi AI, Suarez JI, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF, Ulatowski JA. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: Effect on intracranial pressure and lateral displacement of the brain. *Crit Care Med* 1998; 26:440–446.
21. Kerwin AJ, Schinco MA, Tepas JJ, Renfro WH, Vitarbo EA, Muehlberger M. The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: A pilot study. *J Trauma* 2009; 67:277–282.
22. Diringer MN, Videen TO, Yundt K, Zazulia AR, Aiyagari V, Dacey RG Jr., Grubb RL, Powers WJ. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. *J Neurosurg* 2002; 96:103–108.
23. Fessler RD and Diaz FG. The management of cerebral perfusion pressure and intracranial pressure after severe head injury. *Ann Emerg Med* 1993; 22:998–1003.
24. Oertel M, Kelly DF, Lee JH, McArthur DL, Glenn TC, Vespa P, Boscardin WJ, Hovda DA, Martin NA. Efficacy of hyperventilation, blood pressure elevation, and metabolic suppression therapy in controlling intracranial pressure after head injury. *J Neurosurg* 2002; 97:1045–1053.
25. Lee JH, Kelly DF, Oertel M, McArthur DL, Glenn TC, Vespa P, Boscardin WJ, Martin NA. Carbon dioxide reactivity, pressure autoregulation, and metabolic suppression reactivity after head injury: A transcranial Doppler study. *J Neurosurg* 2001; 95:222–232.
26. Artru AA. Reduction of cerebrospinal fluid pressure by hypocapnia: Changes in cerebral blood volume, cerebrospinal fluid volume, and brain tissue water and electrolytes. *J Cereb Blood Flow Metab* 1987; 7:471–479.
27. Newell DW, Weber JP, Watson R, Aaslid R, and Winn HR. Effect of transient moderate hyperventilation on dynamic cerebral autoregulation after severe head injury. *Neurosurgery* 1996; 39:35–43.
28. Duong DH, O'malley S, Sekhar LN, and Wright DG. Postoperative hydrocephalus in cranial base surgery. *Skull Base Surg* 2000; 10:197–200.

    This study validates the need for close follow-up and continued monitoring following craniotomy to evaluate for hydrocephalus and the implications of this postoperative problem.
29. Osborn AG, Daines JH, Wing SD, and Anderson RE. Intracranial air on computerized tomography. *J Neurosurg* 1978; 48:355–359.
30. Reasoner DK, Todd MM, Scamman FL, and Warner DS. The incidence of pneumocephalus after supratentorial craniotomy. Observations on the disappearance of intracranial air. *Anesthesiology* 1994; 80:1008–1012.
31. Durward QJ, Del Maestro RF, Amacher A, and Farrar JK. The influence of systemic arterial pressure and intracranial pressure on the development of cerebral vasogenic edema. *J Neurosurg* 1983; 59:803–809.
32. Yoshino E, Yamaki T, Higuchi T, Horikawa Y, and Hirakawa K. Acute brain edema in fatal head injury: Analysis by dynamic CT scanning. *J Neurosurg* 1985; 63:830–839.
33. Gudeman SK, Miller JD, and Becker DP. Failure of high dose steroid therapy to influence intracranial pressure in patients with severe head injury. *J Neurosurg* 1979; 51:301–306.
34. Dearden NM, Gibson JS, MacDowall DG, Gibson RM, and Cameron MM. Effect of high dose dexamethasone on outcome from severe head injury. *J Neurosurg* 1986; 64:81–88.
35. Braakman R, Schouten HJ, Blaauw-van Dishoeck M, and Mindehoud JM. Megadose steroid in severe head injury. Results of a prospective double-blind trial. *J Neurosurg* 1983; 58:326–330.
36. Giannotta, SL, Weiss H, Apuzzo ML, and Martin E. High dose glucocorticoids in the management of severe head injury. *Neurosurgery* 1984; 15:497–501.
37. Miller JD and Leech P. Effects of mannitol and steroid therapy on intracranial volume–pressure relationships in patients. *J Neurosurg* 1975; 42:274–281.
38. Matin NA, Doberstein C, Zane C, Caron MJ, Thomas K, and Becker DP. Posttraumatic cerebral arterial spasm: Transcranial Doppler ultrasound, cerebral flow, and angiographic findings. *J Neurosurg* 1992; 77:575–583.
39. Hoh BL, Topcuoglu MA, Singhal AB, Pryor JC, Rabinov JD, Rordorf GA, Carter BS, Ogilivy CS. Effect of clipping, craniotomy, or intravascular coiling or cerebral vasospasm and patient outcome after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2004; 55: 779–786.
40. Suwanwela C and Suwanwela N. Intracranial arterial narrowing and spasm in acute head injury. *J Neurosurg* 1972; 36:314–323.
41. Krause GS, White BC, Aust SD, Nayini NR, and Kumar K. Brain cell death after ischemia and reperfusion: A proposed biomechanical consequence. *Crit Care Med* 1998; 16:714–726.
42. Ferrera PC, Pauze DR, and Chan L. Sagittal sinus thrombosis after closed head injury. *Am J Emerg Med* 1998; 16:382–385.
43. Tsutsumi K, Shiokawa Y, Sakai T, Aoki N, Kubota M, Saito I. Venous infarction following the interhemispheric approach in patients with acute subarachnoid hemorrhage. *J Neurosurg* 1991; 74:715–729.
44. Stefini R, Latronico N, Cornali C, Rasulo F, and Bollati A. Emergent decompressive craniectomy in patients with fixed dilated pupils due to cerebral venous and dural sinus thrombosis: Report of three cases. *Neurosurgery* 1999; 45:626–629.
45. Baltas I, Tsoulfa S, Sakellariou P, Vogas V, Fylaktakis M, and Kondodimou A. Posttraumatic meningitis: Bacteriology, hydrocephalus, and outcome. *Neurosurgery* 1994; 35:422–427.

    Thorough study discussing causes, risk factors, and treatment of patients with meningitis following craniotomy and cranial trauma.
46. Stephanov S. Surgical treatment of brain abscess. *Neurosurgery* 1988; 22:724–730.

    Informative article on appropriate treatment for brain abscess.
47. Kubik CS and Adams RD. Subdural empyema. *Brain* 1943; 66:18–42.

48. Dill SR, Cobbs CG, and McDonald CK. Subdural empyema: Analysis of 32 cases and review. *Clin Infect Dis* 1995; 20:372–386.
49. Palmer BF. Hyponatremia in patients with central nervous system disease: SIADH versus CSW. *Trends Endocrinol Metab* 2003; 14(4):182–187.

Discussion of the importance of identifying the cause of hyponatremia and determining the appropriate treatment regimen.

50. Griffin JM, Hartley JH Jr, Crow RW, and Schatten WE. Diabetes insipidus caused by craniofacial trauma. *J Trauma* 1976; 16:979–984.

37

Complications after Spinal Cord Injury

Michael Y. Wang and Barth A. Green

CONTENTS

37.1 Historical Context

Accounts of spinal cord injury (SCI) date back over four millennia to the Edwin Smith Papyrus [1,2]. In the record of a case by Imhotep, physician to Pharaoh Zoser III, incontinence, paralysis, and loss of sensation were described. The recommendation by Imhotep that cervical spine injuries were "an ailment not to be treated" persisted until the last half-century. Until the advent of modern nursing care and antibiotics, even young patients were quick to succumb to pneumonia, sepsis, and thromboembolism. Indeed, as recently as 1924, the British Medical Council stated "the paraplegic may live a few years in a state of more or less ill-health [3]."

Sir Ludwig Guttman established the Spinal Injuries Centre of Stoke Mandevile Hospital in 1944. This center was in part a response to the devastating casualties of World War II and focused on aggressive medical care for paraplegic patients. Physical therapy, occupational therapy, and nursing services targeted at returning these patients to independent living were successful in prolonging the life expectancy and improving the quality of life for these patients [3]. The proliferation of SCI centers, particularly in the Veterans Administration Hospitals in America, has since drastically improved the outlook for paraplegic and quadriplegic patients. Now the SCI patient has a life expectancy approximating that of normal adults.

The past half-century has seen remarkable advances in spinal instrumentation technology. Restoring spinal stability through internal fixation has obviated the need for prolonged immobilization, reducing the risk of medical complications. The increasing safety of general anesthesia and improvements in microsurgical technique have also made possible urgent spinal cord decompression, and new clinical evidence is emerging to show that emergent surgery to relieve compressed neural structures may be beneficial in improving neurological function. Finally, advances in neuroprotective and regenerative interventions are offering hope in mitigating the disastrous effects of traumatic SCI.

37.2 Epidemiology

Traumatic SCI is a major public health problem in North America. Each year an estimated 11,000 new cases occur in the United States, but the tragedy of SCI lies in its devastating effect on predominantly young healthy adults between 15 and 35 years of age [4]. Due to improvements in prehospital care and posttrauma medical and surgical management, survival from even severe injuries is commonplace. As a consequence, it is estimated that over 250,000 SCI patients are currently alive in United States at a financial cost of roughly 4 billion dollars/year [3].

Motor vehicle accidents are the most common injury mechanism (55%) followed by occupation-related trauma (22%), sports injuries (18%), and assault 5% [4]. The majority of injuries are due to blunt trauma resulting in fracture, dislocation, or subluxation of the vertebrae, although penetrating injuries from gunshots and stabbings do occur. Transitional regions of the spine at the junction where a more mobile segment meets a less mobile one (i.e., craniovertebral, cervicothoracic, and thoracolumbar regions) are the usual sites of injury.

The cervical spine is the most commonly affected region followed by thoracic and lumbar injuries [5]. Considering all spinal levels, a fracture or dislocation of the vertebral column carries a 14% chance of neural injury. However, the spinal level of involvement will influence the likelihood of neurological impairment: 40% in the cervical region, 10% in the thoracic region, 35% in the thoracolumbar area, and 3% with lumbar involvement (Figure 37.1).

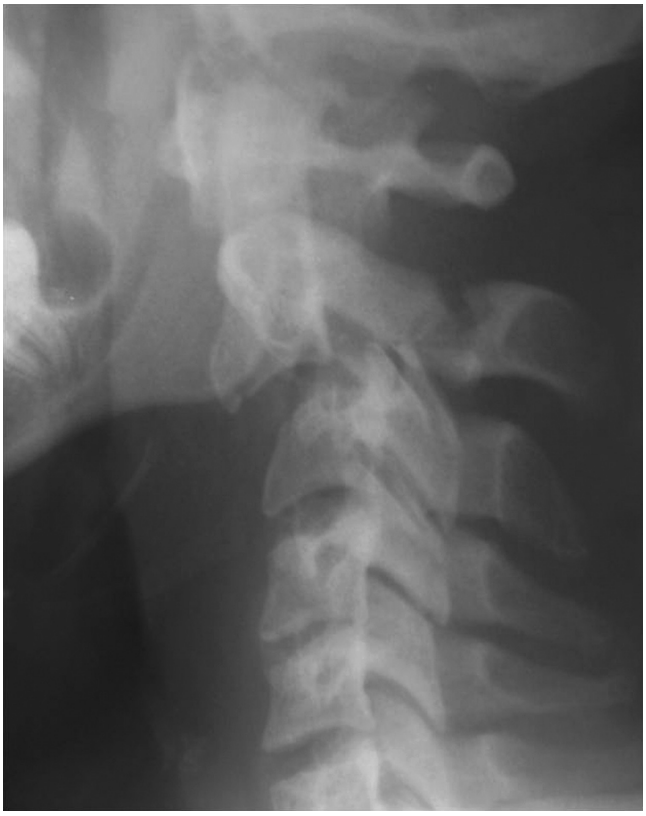


FIGURE 37.1
X-ray of a C2 hangman's fracture resulting from extension and distraction as seen with traditional judicial hangings. The fracture enlarges the spinal canal. While biomechanically unstable, neurological function can be preserved.

37.3 Biomechanics of Injury

The neural and musculoskeletal components of the human spine are intimately associated. Thus any discussion regarding blunt traumatic SCI requires an understanding of the vertebral column. Motion occurs between the 25 distinct vertebrae, and while these motion segments are stereotyped, variabilities exist in each spinal region. Rotatory motion in the axial plane occurs primarily at the occipitocervical and thoracic regions. Flexion and extension in the sagittal plane occur at the cervical and lumbar levels. The orientation and configuration of the facet joints determine to a large extent the degree of mobility at each motion segment. The thoracic spine is also made less mobile because of its articulations with the rib cage.

Concepts of stability in the vertebral column are complex and frequently confusing. The vertebral column serves to transmit loads, permit motion, and protect the spinal cord. Instability of the spinal column may then be defined as its failure to perform any of these functions under physiological levels of mechanical loading. This failure may occur either acutely or in a progressive, delayed manner. In cases of traumatic SCI, the vertebral column acutely fails to shield the neural elements from external forces as a result of being stressed beyond its mechanical tolerances.

Numerous classification schemes have been devised to predict if the spine is unstable. The most common of these is the three-column theory introduced by Denis [6]. Although this was originally based upon studies of thoracolumbar fractures, these principles have also been applied to other regions of the spine. This classification system divides the spine into anterior, middle, and posterior columns. The anterior column consists of the anterior half of the vertebral body, the anterior half of the intervertebral disk, and the anterior longitudinal ligament. The middle column consists of the posterior half of vertebral body, the posterior half of the intervertebral disk, and the posterior longitudinal ligament. The posterior column consists of the posterior arch, the facet joint complex, the interspinous ligament, the supraspinous ligament, and

the ligament flavum. The diagnosis of instability is made if two or more of the columns are compromised.

External forces placed upon the spine include axial compression, distraction, flexion, extension, and translation. Axial compression in the cervical spine results in disruptions of the ring of C1 and burst fractures of the remaining vertebrae. Axial compression in the thoracolumbar spine typically results in burst fractures. When compressive forces are applied anterior to the spinal column and result in a component of flexion, anterior compression fractures result. Severe flexion is the most common injury mechanism in the cervical spine. This can cause odontoid fractures, teardrop fractures of the vertebral bodies, dislocations of the vertebral bodies, and jumped facets. In the thoracolumbar spine, severe flexion results in compression of the anterior vertebral body. If the fulcrum of force is anterior to the vertebral column, as occurs when a seat-belted passenger is involved in a motor vehicle accident, a flexion-distraction injury of the thoracolumbar junction may result.

37.4 Pathophysiology

The pathological outcome of trauma to the spinal cord is related to a "primary" mechanical injury at the epicenter of the damage. Direct crush, stretch, and shear injury to neurons and axons within the spinal cord lead to immediate cell death. However, delayed cascades of cellular and molecular events known as "secondary" SCI occur in the hours to days after the traumatic event and lead to further cell death. The release of excitotoxic amino acids such as glutamate disturbs ionic homeostasis in neural tissues. The resulting increases in intracellular calcium ions, cellular energy failure, and accumulation of free radicals lead to local cell death in a delayed fashion [7,8].

Because spinal cord–injured patients frequently suffer polytrauma, they are susceptible to derangements of systemic homeostasis. Cardiovascular and pulmonary compromise may affect perfusion and oxygen delivery to the spinal cord, exacerbating the damage and therefore worsening secondary SCI. Vasoactive substances released by injured cells and endothelin released from damaged capillaries may also disrupt the spinal cord microcirculation. Ischemia may thus cause neurological deficits to extend rostrally beyond the initially injured area [9,10]. Because cell death due to secondary injury and ischemia occurs after the patient has reached a medical treatment facility, it is hoped that early pharmacological intervention and maintenance of adequate tissue perfusion can salvage these neurons.

The window of secondary injury also provides an opportunity for clinical intervention. Neuroprotective measures, minimization of additional mechanical trauma, and hemodynamic support can all lead to improved clinical outcomes and enhance the recovery potential for the SCI patient.

37.5 Clinical Features

The neurological examination is of paramount importance for localizing the probable site of injury. Particular attention should be paid to the motor, sensory, reflex, and rectal examinations. Based upon the degree of functional impairment, the American Spinal Injury Association (ASIA) has proposed an easily used scoring system (Figure 37.2). This score, in conjunction with the lowest normal segmental level, defines in simple terms the neurological injury. In this classification scheme, a grade "A" denotes a complete injury, and grades "B" through "D" are incomplete injuries [11]. Complete recovery of function after an ASIA "A" injury is exceedingly rare; however, improvement of one or two ASIA grades is seen in over 10% of patients. Recovery is most likely to occur in grade "D" injuries [12].

Neural compression typically results from acute displacement of bone fragments, ligaments, and herniated disk. Delayed spinal cord compression may also develop from a hematoma within the spinal canal or movement of bone or prolapsed disk in a spine that is not properly immobilized. The characteristic clinical picture is of a patient presenting without neurological deficits or an incomplete injury who then develops complete paralysis, particularly after intubation or transportation. Deterioration can also occur in the chronic setting weeks to months after injury. Posttraumatic syringomyelia and progressive bony deformity are the most frequent etiologies. Overall, loss of neurological function when compared to admission occurs in roughly 3% of patients [12].

Specific neurological syndromes have been described for particular partial cord injuries. The *anterior cord syndrome* is characterized by complete paralysis and hypalgesia (anterior and anterolateral column function) below the level of injury with preservation of position sense, vibration, and light touch (posterior column function). This syndrome occurs most commonly after ischemia in the territory supplied by the anterior spinal artery which supplies the corticospinal and spinothalamic tracts. The *central cord syndrome* is characterized by motor dysfunction more pronounced in the distal upper extremities accompanied by varying degrees of sensory loss and bladder dysfunction. This injury occurs characteristically following a hyperextension injury in an elderly patient and can be seen in the absence of any clear radiographic disruption of the bones or ligaments.

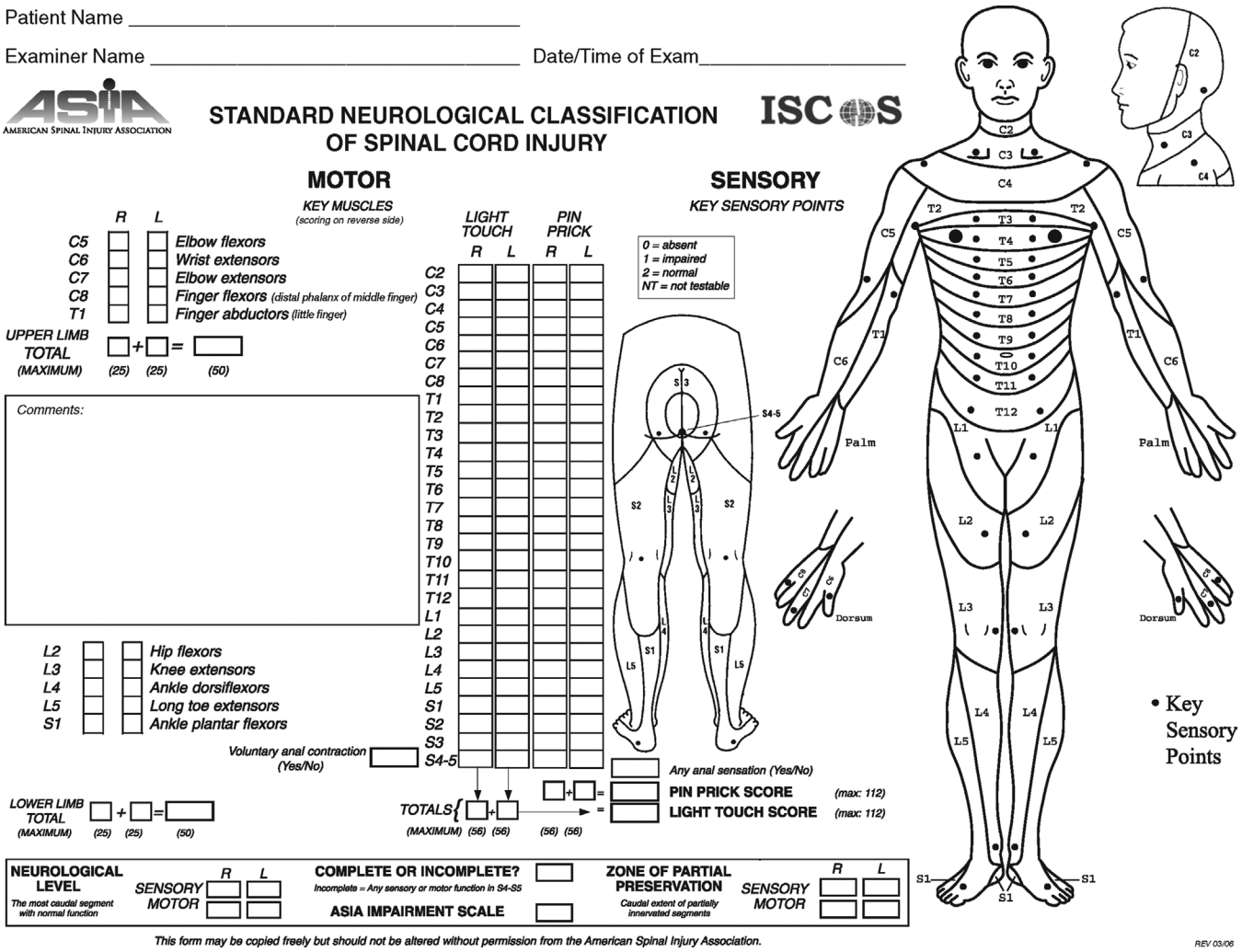


FIGURE 37.2
American Spinal Injury Association (ASIA) grading scale for SCI.

Most patients recover the ability to walk, with partial restoration of upper extremity strength. The *posterior cord syndrome* is an uncommon presentation where position and vibration are impaired due to injury to the dorsal columns. The *Brown–Sequard syndrome*, or hemisection cord syndrome, presents with ipsilateral paresis and loss of proprioception below the level of the lesion and contralateral loss of pain and temperature sensation. This can be the result of penetrating injuries or tumor compression and is usually not seen in a pure form. The *conus medullaris syndrome* occurs with injuries at the thoracolumbar junction. This syndrome has components of both spinal cord and nerve root injury due to the dense population of lower nerve roots emerging from the caudal end of the spinal cord. Symmetrical lower extremity motor impairment and anesthesia with bowel and bladder dysfunction are typically seen. Recovery from this syndrome is unlikely, unlike the *cauda equina syndrome* where partial recovery is possible with early decompression. Cauda equina injuries occur at spinal levels below the termination of the cord at L1 or L2.

Cord concussions present with fleeting neurological symptoms followed by rapid resolution. These injuries, also called "stingers," are seen most commonly in athletes with low-velocity hyperflexion or extension injuries of the cervical spine. Complete recovery is the rule; however, patients should be evaluated meticulously for occult spinal instability and intraspinal hematomas.

37.6 Evaluation of Suspected Injury

The current medicolegal environment in the United States is intolerant of missed spinal injuries. Indeed, failure to detect spinal instability can cause delayed loss of neurological function. In the most extreme case,

a patient who is not paralyzed due to the traumatic event may become quadriplegic after inappropriate mobilization by the medical team. Thus, it is not surprising that tremendous resources and efforts are directed at detecting spinal injuries.

The diagnosis of a spinal column injury is based upon the clinical examination and radiological investigations. In an awake, nonintoxicated patient, the absence of pain along the spinal axis is useful to rule out injury. It is essential that radiographic evidence of spinal column injury be correlated with the clinical examination as 10% of patients will have injuries at multiple spinal segments. X-ray, computed tomography (CT), and magnetic resonance imaging (MRI) investigations are needed in patients who are not able to fully cooperate with the neurological examination.

Radiographs are useful not only for the detection but also for the classification injuries. The fracture type, as well as the degree of cord compression, are particularly important aspects of the injury that will determine the management strategy. For the cervical spine, plain lateral x-rays must include the C7–T1 junction, as 31% of injuries occur between C6 and T1. In large, bulky patients, downward traction on the shoulders, a swimmer's view, or CT scan may be needed to properly visualize the cervicothoracic junction. Lateral x-rays allow evaluation of vertebral alignment, canal diameter (normal is >12 mm in adults), angulation of the intervertebral space (normal is <110), interspinous gap, and the atlanto-dental interval (the distance between anterior margin of the dens and closest point on the anterior arch of C1 should be ≤3 mm in adults). Soft tissue swelling in the prevertebral space is an indirect indicator of cervical spine injury (maximum prevertebral space in adults at C1 is 10 mm, C2–C4 is 5–7 mm, and C5–C7 is 22 mm).

In the thoracic and lumbar spine, anterior compression fractures and fracture dislocations are usually clearly visible on lateral x-rays. Splaying of the interspinous ligaments is indicative of disruption of the posterior tension band, comprised of the spinous processes and the interspinous ligament. Burst fractures may be difficult to detect on a lateral x-ray but are evident from an abnormally increased interpedicular space when compared to adjacent levels. CT is particularly useful in burst fractures for assessing the degree of canal compromise by retropulsed bone fragments from the vertebral body.

37.7 Acute Management

Care of the spinal injury patient begins in the field with Emergency Medical Services personnel. Attention to maintaining a patent airway and the management of shock takes precedence. The patient is immobilized with a rigid cervical collar and backboard for transportation to a trauma center. Intubation and helmet removal should be attempted only with strict attention to maintaining neck alignment. This is particularly important in unresponsive patients as 3%–5% of comatose patients have a cervical spine injury.

In the trauma center, the priority remains the maintenance of tissue oxygenation and perfusion, with particular attention to maintaining an adequate mean arterial blood pressure. However, mechanical respiratory efforts may be minimal when the injury level is C5 or higher. In these patients, muscular expansion of the rib cage is absent and diaphragmatic breathing may be weakened. Thus, intubation with in-line stabilization using two physicians may be the only option to quickly establish airway control and ventilation. Caution should be exercised in suctioning the oropharynx as this may stimulate autonomic reflex arcs causing profound bradycardia and even cardiac arrest.

Cervical and high thoracic injuries may result in neurogenic shock, which can severely complicate the management of a patient already in hypovolemic shock. Neurogenic shock results from the loss of sympathetic vasoregulatory tone. The clinical picture is hypotension with an associated bradycardia. Treatment is with mild fluid resuscitation and continuous intravenous inotropic infusions possessing α-adrenergic properties to increase the heart rate, cardiac output, and vasomotor tone. Dopamine, because of its mixed α- and β-adrenergic effects, is a useful medication to treat neurogenic shock. Acutely symptomatic bradycardia should be treated with intravenous atropine.

Associated extraspinal injuries that are common must also be ruled out. Because spinal column injuries are typically the result of severe traumatic mechanisms, the incidence of cranial, thoracic, abdominal, and orthopedic injuries is high. Priority must be given to the most life-threatening injuries.

Cervical traction using either a halo frame or Gardner–Wells tongs may be utilized to restore alignment of the spine and reduce neural compression. However, traction must be initiated with caution as neurological deterioration can occur from overdistraction or movement of acutely herniated disk material [13]. Before traction is initiated, a full set of x-rays and an MRI scan help to reduce the likelihood of worsening deficits. In the subaxial spine, it is prudent to begin with 10 lb and add weight until either reduction is achieved or a total of 5 lb per cervical level has been used. Serial lateral x-rays or fluoroscopic images should be taken after each addition of weight to ensure that the neck has not been overdistracted.

37.8 Pharmacological Therapy for Spinal Cord Injury

Animal models of SCI have offered the hope that damage caused by secondary injury can be mitigated by early pharmacological intervention. Three large, randomized, multicenter clinical trials have investigated the utility of high-dose methylprednisolone for SCI [14]. These studies (NASCIS I–III) found that a bolus dose of 30 mg/kg followed by 5.4 mg/kg/h mildly improved the functional outcome in some patients with either complete or incomplete injuries. If steroid is administered within 4 h of injury, the infusion should be continued for 24 h; if it is administered within 4–8 h after injury, then the infusion is continued for 48 h [15]. High-dose steroids are not likely to be useful in penetrating SCIs, and the systemic effects on polytraumatized and pediatric patients have not been fully assessed. Significant controversy surrounds the efficacy of high-dose methylprednisolone administration. While there may be some benefit from high-dose steroids, an increase in the incidence of complications, such as pneumonia and skin problems, is well documented [16,37].

Trials of other pharmacological interventions for SCI are currently underway. Initial studies of GM-1 gangliosides and the 21-aminosteroid tirilazad are promising, but the results are preliminary [17]. Opiate antagonists, NMDA receptor blockers, calcium channel blockers, and antioxidants have all shown promise in animal models of SCI but remain unproven in humans.

37.9 Surgical Management

Radiologically proven compression of the spinal cord and nerve roots mandates surgical intervention for decompression and stabilization in the patient with incomplete SCI (e.g., ASIA grades B–D). Surgery for patients with complete loss of neurological function remains controversial. Early surgical stabilization within the first 24 h after injury has more recently become popular because of the increasing safety of general anesthesia. Early stabilization allows for safe mobilization of the patient, physical and occupational therapy, and improved pulmonary toilet. Surgery for patients who have suffered severe injuries to vital organs surgery may have to be delayed. In these cases, maintenance of spinal precautions with a cervical collar and strict "log rolling" for nursing care should prevent any neurological deterioration.

Whether or not emergent surgery to decompress the spinal cord will improve the neurological outcome remains controversial [18]. To date, studies showing that early surgery or traction reduction of the spine improves neurological outcome all fall within Class III levels of evidence [13]. In contrast, three Class II studies have demonstrated no advantage with early surgery. No definitive studies to resolve this issue have been performed [13]. However, recent data from prospective nonrandomized studies have shown trends for neurological improvement [19]. This strategy is logical as a subset of patients will likely benefit from removal of local compression in a timely manner. In the cervical spine, urgent surgery is typically not problematic. Emergency surgery for thoracolumbar fractures can prove more problematic as anterior compression is often best treated through a thoracotomy approach, making surgical decompression more morbid. Thoracolumbar injuries are also associated with a higher rate of hollow viscous, pulmonary, and cardiovascular injuries.

Another recent advance has been the development of criteria to help the clinician determine the need for surgery. While patients with neurological deficits will typically be candidates for surgery (to decompress the neural elements and stabilize the vertebral column), surgical management of many thoracolumbar fractures are controversial. A recently developed classification system for thoracolumbar injures has been developed in an effort to guide the need for surgical management due to skeletal instability (Figure 37.3) [20].

37.10 Prevention of Complications

37.10.1 Cutaneous and Musculoskeletal

Pressure ulcers occur in 25%–30% of SCI patients [21]. Because of transport on hard backboards, prolonged immobilization, and loss of cutaneous sensation, these patients are at extremely high risk for developing skin breakdown. The most common sites of involvement are the sacrum, heels, ischium, and occiput (Figure 37.4).

Prevention of pressure ulcers begins in the emergency room. During the secondary trauma survey, all of the patient's clothes should be removed to inspect the body for bruising and abrasion. The patient should be removed from the backboard as soon as possible as pressure necrosis of the skin can occur in as little as 1 h on hard surfaces. In the acute care setting, the patient should be turned in a "log-roll" fashion every 2 h until the spine is either proven to be stable or stabilized surgically. An alternative to this is the use of an electrically driven kinetic bed such as the Roto-Rest (Midmark Corporation, Versailles, Ohio) [22].

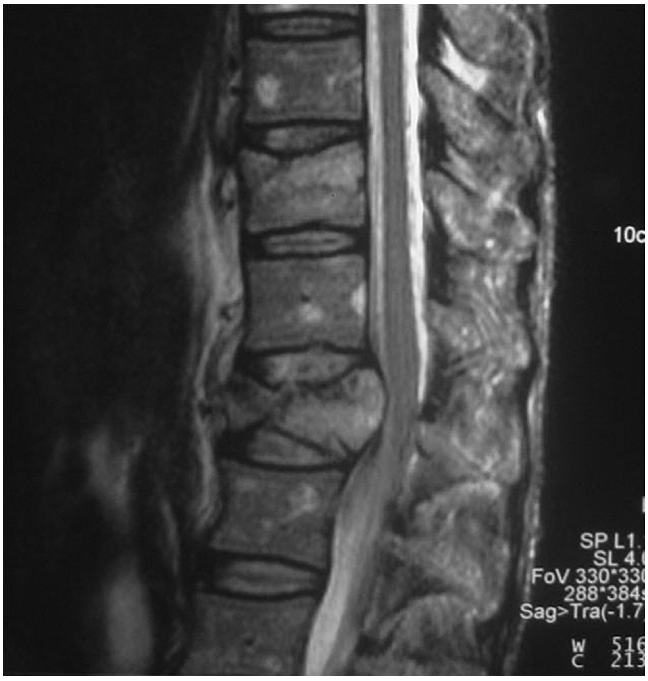


FIGURE 37.3
Burst fracture of the T12 vertebra after a 20 ft fall resulting in complete loss of neurological function (grade A injury). Sagittal MRI showing compression of the spinal cord by bone fragments.

The best treatment for pressure and decubitus ulcers remains prevention and early detection. Stage I lesions can be managed with aggressive mobilization and adhesive barrier dressings. However, once the dermis has been compromised daily sterile dressing changes may be needed for wound debridement. Deeper lesions may require debridement and skin grafting or rotational flaps in the operating room. Proper management of even mild lesions will prevent devastating late sequelae such as sepsis from infected ulcers.

In the subacute and chronic setting, muscle denervation leads to atrophy, spasticity, and contracture formation. Passive range of motioning and splinting forestall the formation of deformities and contracture. Etidronate sodium and increasing mobility may reduce heterotopic ossifications [23].

37.10.2 Thromboembolism

Paralyzed patients are at high risk of developing deep venous thrombosis and pulmonary embolism. The incidence of lower extremity venous thrombosis is as high as 79% if fibrinogen scanning, impedance plethysmography, and venography are utilized [24,25]. Pulmonary embolism occurs in 2%–3% of patients and is responsible for roughly 10% of all deaths after spinal cord trauma [5]. This risk of thromboembolism peaks 2–3 weeks after injury.

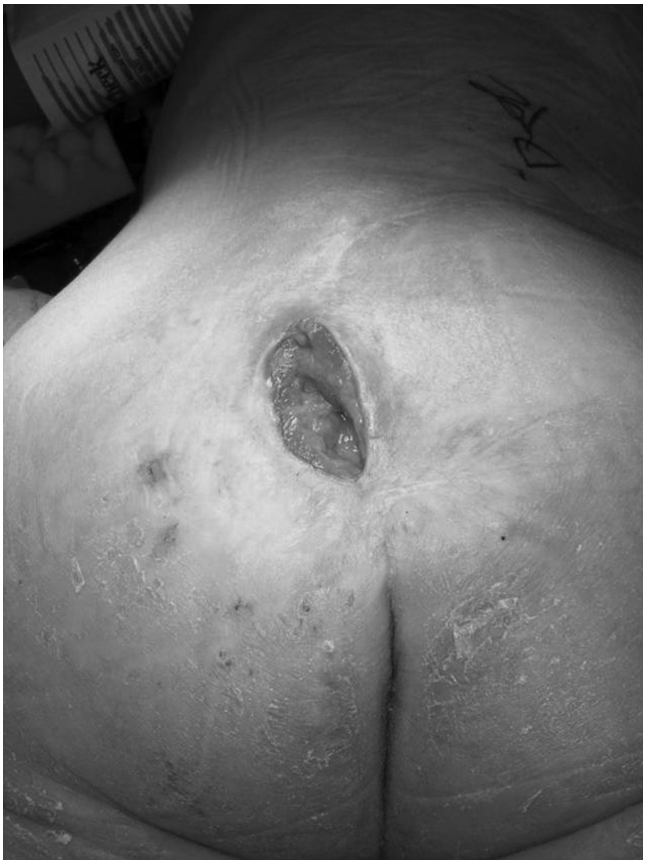


FIGURE 37.4
Typical decubitus ulcer refractory to a previous local musculocutaneous flap. The sore results from chronic local compression and ischemia in a patient lacking the protective sensation that would be present in a neurologically intact patient.

The early use of pneumatic compression devices and subcutaneous heparin can reduce the risk of thromboembolism [26]. In the absence of any medical or surgical contraindication to anticoagulation, 5000 units of subcutaneous heparin should be administered twice a day starting within the first 2 days of injury. Low-molecular-weight heparins can also be used for anticoagulation and are associated with a low incidence of hemorrhagic side effects [27].

37.10.3 Genitourinary and Lower Gastrointestinal Complications

The aim of bladder management is to preserve renal function and prevent urinary tract infections. Immediately after a complete SCI, the bladder is acontractile. Indwelling catheterization will allow bladder drainage and measurements of fluid balance. Intermittent catheterization every 4–6 h should commence as soon as possible under strict aseptic technique, and in paraplegic patients self-catheterization can be taught as soon as the patient is able to sit up.

Urinary tract infections are common and should be treated aggressively to prevent urosepsis. Urea-splitting bacteria such as *Proteus* are associated with high incidence of renal calculus formation and should be vigorously treated. Renal calculi are found in ~1% of patients [21].

Following severe spinal injury, rectal tone is flaccid. Constipation can easily occur unless manual evacuation is carried out on a regular basis. The judicious use of rectal suppositories stimulates bowel emptying, and regular doses of stool softener should also be used.

37.10.4 Upper Gastrointestinal Complications

Posttraumatic ileus is common in this patient population and a nasogastric tube should be placed to suction drainage in the emergency room. This will help prevent the aspiration of any regurgitated stomach contents and minimizes the distension from ileus. Nutritional support is critical after trauma. The caloric requirement in SCI is roughly 150% of basal levels, and special attention must also be directed at meeting increased protein requirements. Proper nutritional support prevents catabolism, supplements wound healing, and maximizes immune protection [28]. Parenteral nutrition is appropriate until the ileus resolves, but tube feeding should begin as early as possible. Even low rates of enteral feeding may reduce the risk of sepsis through enterocyte nutrition.

Peptic ulceration is common in SCI patients, and this risk is increased with the use of high-dose methylprednisolone. Gastrointestinal hemorrhage is less common and occurs in 3% of patients [21]. H_2 blockers, proton pump inhibitors, and sucralfate appear to be similarly effective in reducing the risk of gastrointestinal hemorrhage. Pancreatitis and acalculous cholecystitis can also occur, especially if parenteral nutrition is utilized for prolonged periods of time. These disorders can be diagnosed by elevated amylase and bilirubin levels, respectively. Early recognition of these disorders lies upon a heightened level of suspicion.

37.10.5 Pulmonary Complications

Respiratory diseases account for 28% of deaths and are the leading cause of mortality in the first year following SCI [5]. Spinal injury patients are at high risk for pulmonary infection for a number of reasons. Prolonged mechanical ventilation, poor pulmonary toilet, an inability to clear upper airway secretions, poor respiratory capacity, nosocomial exposure, weakened immune responses, and any accompanying chest trauma all increase the risk of pneumonia. The judicious use of aggressive suctioning, chest physiotherapy, bronchodilators, positive pressure ventilation, and bronchoscopic airway clearance helps prevent infection. Severe atelectasis can also cause respiratory distress in the absence of infection.

The risk of pulmonary complications clearly increases with higher-level injuries. For patients with injuries at C1–C4, tracheostomy and prolonged mechanical ventilation will probably be required. However, in patients with lower-level injuries, successful weaning from mechanical ventilation without tracheostomy should be aggressively pursued.

37.11 Spinal Cord Injury in Children

By adolescence the spine is well developed and the patterns of injury resemble those of adults. Perhaps because of the increased mobility of the developing spine, pediatric SCIs are rare [29]. However, because of the greater proportional mass of the head children are more susceptible to atlanto-occipital injuries. The hypermobility of the pediatric spine also accounts for cases of SCI without radiographic abnormality (SCIWORA). SCIWORA represents 15%–20% of all pediatric SCIs [30].

The principles in managing pediatric SCIs are similar to adults. However, because children cannot cooperate fully with the physical examination, it is important to recognize subtle physical and radiological signs, and an increased reliance must often be placed on radiographic studies. Many of the standard measurements used to evaluate cervical x-rays need to be adjusted for the pediatric spine.

In young children, the increased relative size of the head compared to body will result in neck flexion when placed on a rigid backboard. This malalignment can accentuate deformity in cervical spine and should be avoided. Equipment tailored for pediatric spine immobilization should be used whenever possible. Unlike adults, the majority of these injuries can be treated nonsurgically with bracing [31].

37.12 Future Advances

Future advances in the science of SCI will provide this population of patients with the hope of an improved quality of life. The past decade has already seen an explosion of knowledge about the mechanisms that underlie primary and secondary SCI. Numerous drugs

have shown promise in limiting nerve cell death from secondary injury in the laboratory setting. A randomized trial of the orally administered drug riluzole, a sodium channel blocker showing promise as a neuroprotectant, began in 2010 [32]. A starting dose of 50 mg by mouth given within 12 h of injury is continued every 12 h for 14 days and is intended to reduce secondary neuronal injury. The results of the study should be available in 2013.

At our institution, we have been utilizing moderate intravascular hypothermia as a neuroprotectant. SCI patients with a complete injury (AIS Grade A) who present within 6 h without exclusionary criteria are cooled to 33°C for 48 h [33,34]. Pilot data from the first 35 patients treated in this manner revealed complication rates similar to historical cohorts. There were no cases of neurological worsening, and at 1 year follow-up 15 of 35 patients (42.8%) had converted from AIS A to an incomplete SCI (Figure 37.2). This compares favorably to historical series of SCI. Conversion rates from a complete to incomplete injury in previous studies have been lower (Sygen® Trial = 12.5% [797 patients] [35], MSCIS = 16% [2025 patients] [12], and the European Multicenter Study of Human SCI = 26.1% [273 patients] [36]).

Advances will also come from other related fields of medicine. The specialty of intensive care medicine continues to make strides in preventing and treating the complications of prolonged hospitalization. SCI patients will no doubt benefit from decreased risks of pneumonia, infection, wound breakdown, and thromboembolism. Improvements in imaging science will enable treating physicians to detect instability quickly and reliably. Rehabilitation of the SCI patient will integrate robotic technology that will give the plegic patient increased mobility.

The holy grail of SCI is neural restoration. Whether through the transplantation of stem cells, molecular manipulation using transfection techniques, or modulation of the local cytokine milieu, the hope is to restore function to cells and axons that have already been destroyed. Because reinnervation of the spinal cord is the only way to restore neurological function, research in this area remains a primary goal of a number of laboratories throughout the world. At our institution, there is currently an FDA-approved pilot study of autologous Schwann cell transplantation in SCI.

Despite all of the advances forthcoming in the field of SCI, prevention of injury remains a top priority. Programs such as the Think First initiative in Florida have already dramatically reduced the incidence of diving-related cervical spine injuries. Physicians, who are most acutely aware of the devastating consequence of SCI, must assume a key role in educating the public on how to avoid these catastrophic injuries.

Complications in Spinal Cord Injury

Complications	Incidence (%)	References	Comments
Pneumonia	40–70	[38]	
Deep venous thrombosis	1.9	[39]	
Pulmonary embolism	2–4	[38]	
Decubitus ulcers	10–20	[40]	For stage II ulcer
Neurological worsening	2–10	[10]	
Urinary tract infection	5–20	[41]	In the acute setting, cumulative incidence is much higher
Death	5–50	[42]	Dependent on age, other injuries, and degree of neurological impairment

How to Avoid Complications in SCI

Complications	Method of Avoidance
Pneumonia	• Frequent suctioning • Aggressive pulmonary toilet • Incentive spirometry • Minimization of time on mechanical ventilation • Rapid mobilization
Deep venous thrombosis and pulmonary embolism	• Mechanical thrombosis prophylaxis • Prophylactic anticoagulants • Early detection with close clinical monitoring
Decubitus ulcers	• Early mobilization • Minimizing time on hard backboards • Use of specialized mattresses to redistribute dependent skin pressure • Log rolling every 2 h • Monitoring and early treatment for early-stage ulcers
Neurological worsening	• Proper neural decompression and stabilization with halo traction and surgery • Maintenance of mean arterial blood pressure ≥85 mm Hg
Urinary tract infection	• Early transition to intermittent catheterization • Use of sterile technique for catheterization

References

1. Breasted, J., *The Edwin Smith Papyrus*. Chicago, IL: Chicago University Press, 1930.
2. Elsberg, C., The Edwin Smith surgical papyrus and the diagnosis and treatment of injuries to the skull. *Ann Med Hist*, 1931, 3: 271–279.

3. Guttman, L., *Spinal Cord Injuries: Comprehensive Management and Research*. Oxford: Blackwell Scientific, 1973.
4. Nobunaga, A., B. Go, and R. Karunas, Recent demographic and injury trends in people served by the model spinal cord injury care systems. *Arch Phys Med Rehab*, 1999, 80: 1372–1382.
5. DeVivo, M., J. Krause, and D. Lammertse, Recent trends in mortality and causes of death among persons with spinal cord injury. *Arch Phys Med Rehab*, 1999, 80: 1411–1419.
6. Denis, F., The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. *Spine*, 1983, 8: 817–831.
7. Amar, A., Surgical controversies in the management of spinal cord injury. *J Am Coll Surg*, 1999, 188: 550–566.
8. Atici, T. et al., Results of surgical treatment for kyphotic deformity of the spine secondary to trauma or Scheuermann's disease. *Acta Orthop Belg*, 2004, 70(4): 344–348.
9. Tator, C. and M. Fehlings, Review of the secondary injury theory of acute spinal cord injury with emphasis on vascular mechanisms. *J Neurosurg*, 1991, 75: 15–26.
10. Harrop, J. et al., The cause of neurologic deterioration after acute cervical spinal cord injury. *Spine*, 2001, 26: 340–346.

    Review of causes of neurological deterioration and how to prevent them.
11. Maynard, F. et al., International standards for neurological and functional classification of spinal cord injury. *Spinal Cord*, 1997, 35: 266–274.

    Provides key information for the practitioner wishing to grade SCI patients.
12. Marino, R. et al., Neurologic recovery after traumatic spinal cord injury: Data from the Model Spinal Cord Injury Systems. *Arch Phys Med Rehab*, 1999, 80: 1391–1396.
13. Fehlings, M. and C. Tator, An evidence-based review of decompressive surgery in acute spinal cord injury: Rationale, indications, and timing based on experimental and clinical studies. *J Neurosurg*, 1999, 91(Suppl): 1–11.
14. Bracken, M. et al., Methylprednisolone or naloxone treatment after acute spinal cord injury. *J Neurosurg*, 1992, 76: 23–31.
15. Bracken, M. et al., Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. *JAMA*, 1997, 277: 1597–1604.

    Original article leading to the use of high-dose steroids for acute SCI, a practice that has been abandoned by many practitioners due to higher risk and little perceived benefit.
16. Hurlbert, R., The role of steroids in acute spinal cord injury: An evidence-based analysis. *Spine*, 2001, 26: S55.
17. Geisler, F., F. Dorsey, and W. Coleman, Recovery of motor function after spinal cord injury—A randomized placebo controlled trial with GM-1 ganglioside. *N Engl J Med*, 1991, 324: 1829–1838.
18. Waters, R. et al., Emergency, acute, and surgical management of spine trauma. *Arch Phys Med Rehab*, 1999, 80: 1383–1390.
19. Fehlings, M. et al., Early versus delayed decompression for traumatic cervical spinal cord injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS One*, 2012, 7(2): Epub February 23, 2012.

    Key paper on the use of early (<24 h) surgery to treat SCI.
20. Rampersaud, Y. et al., Agreement between orthopedic surgeons and neurosurgeons regarding a new algorithm for the treatment of thoracolumbar injuries. *J Spinal Disord Tech*, 2006, 19: 477–482.
21. Chen, D. et al., Medical complications during acute rehabilitation following spinal cord injury—Current experience of the Model Systems. *Arch Phys Med Rehab*, 1999, 80: 1397–1401.
22. Green, B., K. Green, and K. Klose, Kinetic nursing for acute spinal cord injury patients. *Paraplegia*, 1980, 18: 181.
23. Stover, S., Heterotopic ossification, in *Management of Spinal Cord Injuries*, R. Block and M. Basbaum, Editors. Williams & Wilkins, Baltimore, MD, 1986, p. 127.
24. Weingarten, S., Deep venous thrombosis in spinal cord injury. *Chest*, 1992, 102: 636s–639s.
25. Harris, S., D. Chen, and D. Green, Enoxaparin for thromboembolism prophylaxis in spinal injury. *Am J Phys Med Rehab*, 1996, 75: 326–327.
26. Nicolasides, A., J. Fernandez, and A. Pollock, Intermittent sequential pneumatic compression of the legs in the prevention of venous stasis and deep venous thrombosis. *Surgery*, 1980, 87: 69.
27. Deep, K. et al., Prophylaxis of thromboembolism in spinal injuries—Results of enoxaparin used in 276 patients. *Spinal Cord*, 2001, 39: 88–91.
28. Apelgren, K. and D. Wilmore, Nutritional care of the critically ill patient. *Surg Clin North Am*, 1983, 63: 497.
29. Durkin, M. et al., The epidemiology of urban pediatric neurological trauma: Evaluation of, and implication for, injury prevention programs. *Neurosurgery*, 1998, 42: 300–310.
30. Grabb, P. and D. Pang, Magnetic resonance imaging in the evaluation of spinal cord injury without radiographic abnormality in children. *Neurosurgery*, 1994, 35: 406–414.
31. Eleraky, M. et al., Pediatric cervical spine injuries: Report of 102 cases and review of the literature. *J Neurosurg*, 2000, 92(Suppl): 12–17.
32. Fehlings, M. et al., Riluzole for the treatment of acute traumatic spinal cord injury: Rationale for and design of the NACTN Phase I clinical trial. *J Neurosurg: Spine*, 2012, (1 Suppl): 151–156.
33. Levi A, Green BA, Wang MY, Brindle T, Vanni S, Casella G, Elhammady G, Jagid JJ. Clinical application of modest hypothermia after spinal cord injury. *J Neurotrauma,* 2009;26(3):407–415.
34. Levi, A. et al., Clinical application of modest hypothermia after spinal cord injury. *J Neurotrauma*, 2008, 26: 407–415.
35. Geisler, F. et al., The Sygen multicenter acute spinal cord injury study. *Spine*, 2001, 26: S87–S98.
36. von Middendorp, J. et al., ASIA impairment scale conversion in traumatic SCI: Is it related with the ability to walk? A descriptive comparison with functional ambulation outcome measures in 273 patients. *Spinal Cord*, 2009, 47: 555–560.

37. Hall, E. and J. Springer, Neuroprotection and acute spinal cord injury: A reappraisal. *NeuroRx*, 2004, 1(1): 80–100.
38. Aarabi, B. et al., Predictors of pulmonary complications in blunt traumatic spinal cord injury. *J Neurosurg: Spine*, 2012, 17(1 Suppl): 38–45.
39. McKinley, W. et al., Long-term medical complications after traumatic spinal cord injury: A regional model systems analysis. *Arch Phys Med Rehab*, 1999, 80(11): 1402–1410.
40. Chen, Y., M. DeVivo, and A. Jackson, Pressure ulcer prevalence in people with spinal cord injury: Age–period–duration effects. *Arch Phys Med Rehab*, 2005–1213, 86: 1208.
41. Cardenas, D. et al., Intermittent catheterization with a hydrophilic-coated catheter delays urinary tract infections in acute spinal cord injury: A prospective, randomized, multicenter trial. *PM R*, 2011, 3(5): 408–417.
42. Fassett, D. et al., Mortality rates in geriatric patients with spinal cord injuries. *J Neurosurg: Spine*, 2007, 7(3): 277–281.

    Paper illustrating the changing demographics of SCI, with many older patients now suffering from this injury.

38

Complications of Nerve Injury and Repair

Matthew Bindewald and Howard Wang

CONTENTS

Because of its proximity to tendons, bones, and neurovascular structures, the peripheral nervous system is vulnerable to injury due to trauma or to complications of surgical procedures. Prevention or early recognition of these nerve injuries is vital for optimal outcome. Unfortunately, many patients with nerve injuries experience only limited recovery, even when the injuries are promptly diagnosed and treated.

Most injuries to major peripheral nerves result from trauma. The prevalence of major peripheral nerve injuries among trauma patients at one institution was 2.8%, and 54% of these patients required surgery for these injuries [1]. However, iatrogenic injuries also account for a substantial number of nerve injuries. A study of a series of 2000 major nerve injuries at two hospitals found that 10% of the injuries were the result of medical treatment [2].

38.1 Diagnosis of Nerve Injuries

Nerve injuries can be diagnosed by an adequate neurological examination. Because nerve damage is possible among patients with fractures, lacerations, and other forms of trauma, a neurological examination of the extremity should be performed as soon as possible after the injury. Simple soft-tissue lacerations are frequently repaired without neurological examination, and in such cases, a nerve injury may not be detected. Missing an injury may result in a delay in treatment and may sometimes preclude the possibility of primary repair because the nerve ends retract. Long delays adversely affect the outcome of nerve injuries.

Detailed neurological examinations are often impractical for patients with multiple traumatic or life-threatening injuries. An attempt should be made to examine at least the distal sensation and motor function of the extremities. Assessing distal function is a quick way to determine whether an injury to the nerve has occurred. Physicians at all levels of training should be familiar with and adept at performing these examinations. In the upper extremity, the median, radial, and ulnar nerves can be evaluated quickly and simply. Motor function of all three nerves can be tested by asking the patient to extend the thumb ("hitch-hiking" or "thumbs-up" maneuver), which tests the radial nerve, to separate the index and long fingers (the "peace sign"), which tests the ulnar nerve, and to touch the tip of the thumb with the tip of the small finger, which tests the median nerve. Sensation can be tested at three autonomous sensory areas: the tip of the index

finger (median), the tip of the small finger (ulnar), and the dorsal web space between the thumb and index fingers (radial). The two-point discrimination can be assessed at these areas using both the static and moving maneuvers. For the lower extremity, flexing and extending the great toe tests the motor component of the terminal portions of the tibial and peroneal nerves. Sensory innervation by these nerves can be assessed on the plantar surface and in the first web space of the foot, respectively.

When patients have signs of nerve injury due to penetrating trauma, immediate exploration and repair are indicated. Repairing nerve injuries shortly after they occur has been shown to improve outcome [3]. When patients are believed to have a nerve injury as the result of closed trauma, electromyography (EMG) should be performed if complete recovery has not occurred after 3–4 weeks. Such testing will help to confirm the diagnosis, localize the lesion, and provide a baseline for monitoring recovery. EMG should be repeated 3 months later if recovery is not yet complete. By this time, reinnervation can often be detected. If EMG shows no recovery of the nerve, surgery for neurolysis or excision of the damaged nerve with repair or grafting should be considered.

38.2 Anatomy

Knowledge of the general anatomy of peripheral nerves is important for understanding of nerve injuries and their potential for regeneration. The epineurium is the connective tissue that forms the outer layer of the nerve and runs around and between the nerve fascicles. It forms a dense layer around the periphery of the nerve to protect and support the fascicles. The perineurium is the connective tissue layer that surrounds each fascicle and gives the nerve most of its tensile strength. The endoneurium is the loose connective tissue within the fascicle. Each fascicle contains numerous axons surrounded by Schwann cells and their myelin sheath.

The primary vascular supply to each nerve runs longitudinally in the epineurium. These vessels interconnect with the vessels of the perineurium and endoneurium, forming a rich anastomotic plexus.

38.3 Classification of Nerve Injuries

Sunderland developed the most commonly used system for classifying nerve injuries [3]. This system describes lesions that fall into "pure" categories, in which all parts of the nerve undergo the same level of injury; unfortunately, most nerve injuries fall into a mixed category. Nevertheless, the system works fairly well in explaining why lesions differ in regeneration potential.

According to the Sunderland classification, a type 1 injury, also called neuropraxia, is characterized by local myelin damage; the axons remain in continuity. These lesions are usually caused by nerve compression. Because the axons remain in continuity, complete recovery occurs, although it may take weeks to months.

In Sunderland type 2 (axonotmesis) injuries, the axons are physiologically disrupted, but all of the supporting tissues are intact. Because these tissues remain intact, the axons are guided along their normal course and full recovery can be expected. When the axons are disrupted, the distal ends undergo degeneration and the axon must regrow toward its target. Recovery from such lesions often takes many months, and the time taken for recovery depends on the level of the injury.

Because each additional connective tissue layer is damaged, the Sunderland grade goes up. For example, in Sunderland type 3 injuries, the axons and the endoneurium are disrupted but the perineurium and epineurium remain intact. When the endoneurium is damaged, axonal regeneration is blocked by intrafascicular fibrosis and recovery is incomplete.

In Sunderland type 4 injuries, only the epineurium is intact. Increased damage within the nerve leads to increased scarring. Very little useful recovery can be expected and surgical excision with repair or grafting is required. Complete disruption of the nerve is a type 5 injury (neurotmesis), from which spontaneous recovery is rarely seen.

More recently, a sixth injury category was added that included these mixed injury types and has been categorized as neuroma in situ. This type of injury is important to consider in that more than one type of injury may be present in the course of the nerve. Some areas may improve over time particularly type 1 through 3 segments. However, attempts to repair areas blocked by type 4 injuries may cause inadvertent damage to less damaged areas of neuropraxia and axonotmesis that may recover with time [3,4].

38.4 Complications of Nerve Repair

Most nerve injuries leave nerves in gross continuity. The most common causes of such injuries are compression, blunt trauma, and traction. The main problem in treating these injuries is deciding when to intervene operatively. When nerve injuries fail to resolve within 3 months, disruption of the axons has most likely occurred. With proximal nerve injuries, clinical recovery of even lower

grade injuries may not be evident for up to 3 months because of the distance of axons from the distal target. EMG is useful in these situations to confirm whether recovery is occurring. Four main factors have consistently been shown to adversely affect the results of nerve repair: gaps greater than 5 cm between axons, delay of repair for >3 months, the patient's age being >20 years, and blunt (as opposed to penetrating) injury [5].

After nerve transection or resection of a nerve lesion in continuity, the nerve must be sutured; the surgeon whose task is to repair injured nerves may encounter a number of pitfalls. These problems may include failure to recognize the extent of the nerve injury, excessive tension on the repair, failure of sutures, malalignment of the repair, and suture of the nerve to a nonneural structure.

One of the most common problems associated with nerve repair is failing to recognize the extent of injury to the nerve and attempting to repair unhealthy nerve ends. Unless a patient has sharp lacerations in the acute setting, it is often difficult to assess the full extent of nerve injury. When nerve injuries result from blunt force or gunshot wounds, the architecture of the internal nerve is often disrupted beyond the obvious severed ends of the nerve. Intraneural scarring increases and leads to poor axonal regeneration. When a nerve lesion in continuity is resected, the same problems can be encountered and a neuroma can form. A longer nerve graft is more likely to succeed than a shorter graft between two scarred nerve ends. Therefore, it is of the utmost necessity to assure that the ends of the nerves being repaired are healthy. This means debriding them back outside the zone of injury. This may mean that grafting may be needed rather than primary repair. Hints that viable nerve has been reached may include the finding of bulging fascicles and abrupt tachycardia when the nerve is cut under lightened anesthesia [3].

Nerve repair may also fail if there is too much tension on the repair site. Tension can cause gaps that may fill in with scar tissue, thereby blocking axonal regeneration. Even in the absence of gapping, excess tension at the repair site can impede nerve healing by reducing intraneural circulation. When the nerve length is increased by 15%, the blood flow to the nerve decreases by ~80%, with little recovery over time [6]. When a gap exists between the nerve ends, some mobilization of the nerve ends can help reduce tension, but excessive dissection may further strip the nerve of blood supply. If the gap is too large, a nerve graft should be performed. However, in most situations, a repair under modest tension is more likely to recover than is a nerve graft [7]. It is of course important to passively range the area over which the repair or graft spans prior to closure in order to assure that motion will not cause undue tension that may cause the repair to fail.

With lesions in continuity, the decision to perform neurolysis or excision with repair, grafting, or both may be a difficult one. Sparing of intact or regenerating portions of the nerve is ideal but is often technically demanding. A nerve stimulator may be of help, but relatively spared portions of the nerve may still be resected [8].

Other problems associated with nerve grafting are poor harvesting technique, graft-size mismatch, graft tension, graft necrosis, and failure to recognize multilevel nerve injury.

Alternatives to nerve grafting include the use of nerve conduits, distal nerve transfers, or tendon transfers. Each procedure is associated with its own risks and benefits. Nerve conduits may be biological or synthesized in that they may consist of vein grafts or commercially available materials. In general, the use of nerve conduits should only be used for noncritical sensory nerve repairs in that they are not as effective as autogenous nerve grafts. The benefit of nerve conduits is that they are readily available and require no harvest procedure with their attendant morbidity [3].

Nerve transfers may be of benefit in the setting of proximal nerve injury such as a brachial plexus injury where the distance to the end organ precludes nerve grafting. In this situation, the nerves to functioning redundant muscles may be transferred to denervated muscle or nerve distal to the zone of injury. The benefit of this strategy is that function may be restored in a more timely fashion than with nerve grafting, the dissection and reapproximation of the involved nerves take place outside of the zone of injury, and the involved nerves may be easier to reapproximate primarily without the use of nerve grafting [3,4].

It is also important to remember the great many adjunctive treatment options that may be beneficial regardless of whether or not operative repair is to be undertaken. These of course include a multitude of medications including antidepressants such as amitriptyline, anti-inflammatory medications, gabapentin, sympatholytics such as clonidine, and anticonvulsants. Additional procedures such as sympathetic blocks and stimulator implants may also be beneficial in patients with complex regional pain syndromes. Neuroma excision may be a palliative step even in the absence of repair. And physical and occupational therapy is important in regaining function not only in the postoperative patient, but also in the patient who is not a candidate for repair [3].

38.5 Injuries Associated with Nerve Injuries

Because of the proximity of nerves to bones and blood vessels, nerve trauma often accompanies injuries to these structures; therefore, patients with such

injuries should always be evaluated for nerve injuries. Depending on the regional anatomy, each fracture or dislocation is associated with a unique pattern of potential nerve injuries. Shoulder girdle injuries are often associated with brachial plexus lesions. Patients with shoulder dislocations should be evaluated for axillary nerve injuries because of the high incidence of traumatic dysfunction [9].

Approximately 10% of humeral shaft fractures are associated with injury to the radial nerve in the spiral groove [10]. Elbow injuries, especially dislocations and displaced fractures of the distal humerus, frequently involve the ulnar nerve, the median nerve, or both [11]. Wrist fractures can be accompanied by injuries to the median nerve; acute carpal tunnel syndrome occurs in as many as 17% of patients with such injuries [12]. Ten percent of fractures or dislocations of the hip are accompanied by nerve injuries, usually to the peroneal branch of the sciatic nerve [13]. Knee dislocations and fractures of the fibular head can injure the peroneal nerve. Open fractures and high-energy fractures are more likely than other injuries to be associated with nerve damage. The callus of a healing fracture can also entrap or compress nerves; such compression can cause progressive gradual loss of function.

Soft-tissue swelling resulting from fractures can cause nerves to be secondarily entrapped in fixed positions. The ulnar nerve can be compressed in the cubital tunnel; this nerve should be transposed during surgical procedures for most severe fractures of the distal humerus or proximal ulna. Acute carpal tunnel syndrome or compression of the ulnar nerve in Guyon's canal at the wrist can occur after wrist fractures, even when there has been no direct trauma to the nerve; division of the transverse carpal ligament should be strongly considered.

Vascular injuries are also common in association with nerve trauma. One published study found that 40% of patients with traumatic vascular injuries also had nerve damage [14]. Vessel injuries are often associated with aneurysms, arteriovenous fistulae, and bleeding, all of which can lead to nerve compression. Injury to the axillary artery or the subclavian artery may result in aneurysms that can compress the brachial plexus. Hematoma formation in a confined space can cause progressive neurological deterioration even without direct neural injury.

Patients with traumatic brain injuries have been found to have a 10%–34% incidence of peripheral nerve injuries [15]. Because the patients often do not complain of problems associated with the nerve injury, physicians caring for them should have a high index of suspicion for nerve lesions. Thorough neurological examination with EMG can be helpful in diagnosing these injuries. As many as 10% of patients with traumatic brain injuries will also have brachial plexus lesions [15]. Thus, in addition to brain injury, patients with brachial plexus palsy may also have injuries to the cervical spine, clavicle, scapula, or proximal humerus.

Compartment syndrome of the extremity is another important cause of neurological loss, even without intrinsic nerve injury. Acute compartment syndrome can be caused by a number of different conditions that affect local blood flow, such as fractures, shock, crush injuries, tight dressings, vascular injuries, severe swelling, or bleeding into a compartment. The local blood flow to the tissues is diminished by a decrease in arterial inflow pressure, an increase in venous pressure, or a combination of both. Pain with passive stretch and pain out of proportion to the patient's injury are the most important clinical findings in the conscious patient with suspected compartment syndrome. Splitting of casts or other circumferential dressings down to the skin has been shown to significantly decrease compartment pressure [16]. Circumferential casts should not be used for obtunded patients because the conditions of these patients cannot be reliably monitored. The diagnosis can be confirmed by measuring compartmental pressures with intravenous tubing attached to an arterial line transducer, a handheld pressure monitor, or another technique. When intracompartmental pressures are higher than 30 mm Hg, decompressive fasciotomy is indicated. Prompt recognition of compartment syndrome is essential because permanent damage may occur after no more than 3–4 h, and certainly after 6–8 h, of prolonged muscle ischemia [17].

Volkmann's ischemic contracture occurs when an acute compartment syndrome is left untreated. Nerve dysfunction occurs for two main reasons. The initial nerve problem results from nerve ischemia. Later, the nerves are entrapped by tight, constricting bands of fibrotic muscle that had been injured by ischemia in the initial phase of the compartment syndrome. Volkmann's contracture can be devastating, with loss of function of the muscles, joint contractures, and diminished sensation. In general, this problem can be avoided by prompt diagnosis and treatment of compartment syndromes [18].

38.6 Injuries to Nerves from Operations or Other Medical Procedures

As stated previously, as many as 10% of nerve injuries are iatrogenic. Although most of these injuries will resolve spontaneously, deficits will occasionally linger and may require surgery. Every effort should be made to prevent potentially avoidable lesions and to minimize complications when a nerve injury has occurred.

38.6.1 Lower Cranial Nerves and Cervical Nerves

The vagus nerve and its branches are susceptible to injury when neck surgery is performed; these injuries are most often associated with carotid endarterectomy (CEA) or cardiac surgery. The reported incidence of nerve injury is ~1% for primary CEA and as high as 12% for repeat CEA [19]. After coronary artery bypass grafting (CABG), vocal cord dysfunction is seen in 1.9%–7.8% of patients [20]. Injury to the vagus nerve or its branches may cause hoarseness or dysphagia and can lead to aspiration. Diagnosis is made by laryngoscopy. More than 90% of these injuries will resolve with time, although some patients will require treatments such as Teflon injection into the vocal cords to obtain a satisfactory result [21].

The hypoglossal nerve can also be damaged during surgery to the neck; damage to this nerve has been reported with CEA and with anterior cervical spine surgery [19]. Most of these lesions will resolve spontaneously.

The spinal accessory nerve is the sole motor innervation of the trapezius muscle. Damage to this nerve causes weakness of the trapezius, drooping of the shoulder, and even winging of the scapula. Spinal accessory nerve palsies are not common, but ~10% of these injuries are accounted for by iatrogenic injury [22]. The nerve is most susceptible to injury in the posterior triangle of the neck, where it lies in a superficial position. Injury can be caused by a wide variety of surgical procedures, including radical neck dissection, lymph node biopsy, and CEA, and can also result from irradiation or even from prolonged use of a sling [23]. Occasionally, the spinal accessory nerve is deliberately cut and used in nerve transfer to treat severe brachial plexus injuries. Patients who experience complete nerve palsies after surgery or penetrating trauma should be treated with neurolysis, nerve repair, or grafting.

The phrenic nerve arises from the third, fourth, and fifth cervical nerve roots, travels through the neck and chest, and innervates the diaphragm. The nerve may be injured at any level along its course, but intrathoracic lesions are most common. The left phrenic nerve is more frequently affected because of its close association with the pericardium. Cases of bilateral damage are rare. Although any thoracic surgical procedure may damage the phrenic nerve, injuries are most common after open heart surgery. Two mechanisms by which the nerve can be damaged may play a role alone or in combination: topical myocardial cooling and phrenic ischemia after dissection of the internal mammary artery (IMA). Topical hypothermia is routine during cardiac surgery, and because of the proximity of the phrenic nerve to myocardial tissue, the nerve also undergoes substantial cooling. The other proposed mechanism of injury to the phrenic nerve is damage to the nerve's vascular supply during IMA dissection; ligation of the pericardiophrenic artery may potentiate the effects of hypothermic damage. There is no gold standard for the diagnosis of phrenic nerve dysfunction. The most commonly used tests at present are phrenic nerve conduction studies, fluoroscopy, and ultrasonography [24]. Symptoms may range from none to difficulty in weaning from mechanical ventilation and may vary according to the patient's underlying pulmonary function. Most phrenic nerve injuries resolve within 3–6 months. Pediatric patients do not recover as well from phrenic nerve paralysis as do adult patients, and they are also more likely to experience difficulty in weaning from mechanical ventilation [24]. When the effects of phrenic nerve dysfunction are severe, treatment with diaphragmatic plication is sometimes performed.

The long thoracic nerve provides the only innervation of the serratus anterior muscle; damage to this nerve leads to winging of the scapula. Exploration with early neurolysis, repair, or grafting should be considered for patients with iatrogenic injuries or penetrating trauma, but few published studies have documented the results of this treatment [25]. Patients with persistent winging of the scapula after prolonged conservative treatment or failure of surgery may be candidates for transfer of the sternal portion of the pectoralis major to the scapula [25].

38.6.2 Brachial Plexus and Shoulder Level

Brachial plexus injuries are among the most common iatrogenic injuries to the peripheral nervous system. Postoperative brachial plexopathy is associated with median sternotomy, transaxillary first-rib resection, radical mastectomy, surgery for shoulder instability, shoulder arthroscopy, injuries from regional anesthesia, and poor positioning [24,26]. The brachial plexus may also be injured by irradiation, usually after surgery for breast cancer.

The incidence of postoperative brachial plexus palsy in association with open heart surgery ranges from 2.7% to 10% [27]. Key factors associated with brachial plexopathy after median sternotomy are sternal retraction and IMA dissection. With sternal retraction, the first rib rotates superiorly and the clavicle pushes into the retroclavicular space, thereby stretching the brachial plexus. Fracture of the posterior first rib by sternal retraction can cause direct injury to the plexus; neurological complaints are associated with the fracture site of the first rib. Vander Salm et al. found that a more caudal placement of the sternal retractor decreased the incidence of first-rib fracture, and they also recommended that the retractor be opened as little

as possible to decrease the likelihood of rib fractures [28]. Brachial plexus lesions have also been associated with dissection of the IMA for use as a graft. In a prospective study of 1000 patients, Vahl et al. found that the incidence of neuropathies was 1% for patients who had not received IMA grafts but 10.6% for those who had received IMA grafts [27]. It is believed that these lesions are caused by the asymmetric sternal retraction required for harvesting the graft.

The only patient characteristic associated with increased risk of postoperative brachial plexopathy is advanced age [28]. Other characteristics such as diabetes mellitus, sex, height, weight, and smoking status are not significant risk factors [29].

The lower roots of the brachial plexus (C8–T1) are most commonly affected by plexopathies after sternotomy. Patients typically exhibit symptoms in the distribution of the ulnar nerve. Ulnar nerve dysfunction at the elbow can coexist with brachial plexopathies; this dysfunction may be a preexisting but subclinical condition or may be related to positioning during surgery [30]. Thorough physical examination can often help to determine whether a lesion exists and its severity because the muscles innervated by the C8 to T1 contributions of the median (flexor pollicis longus) and radial nerves (extensor pollicis longus) will also be affected. EMG may also be useful in localizing the lesion [30]. Fortunately, only ~1% of patients will have symptoms that persist for more than 3–4 months [27,29].

The infraclavicular portions of the brachial plexus (cords and terminal branches) are at risk during surgical procedures to the shoulder and axilla. Complete transection of the brachial plexus has been seen in association with axillary dissection during radical mastectomy. Injuries to several nerves about the shoulder, most commonly to branches of the axillary nerve, have been reported after shoulder arthroscopy. The incidence of nerve injury after anterior reconstruction for glenohumeral instability has been reported to be ~8% [31]. Eighty-seven percent of patients with these lesions experienced full recovery within 6 months, and all were believed to have traction-type lesions. The musculocutaneous nerve was most frequently involved.

Radiation-induced brachial plexus injuries can be a devastating complication of radiation therapy after mastectomy for breast cancer. Symptoms usually develop months to years after treatment; symptoms usually begin with sensory loss but may progress to complete plexopathy with a flaccid, insensate arm. Pathologically, the nerves are often entrapped in dense scar tissue, but damage to the vasculature of the nerves probably plays an important role in nerve damage [32]. Unfortunately, there is no effective treatment for this type of lesion [26].

38.6.3 Arm and Forearm Level

Using tourniquets during surgery to the extremities causes nerve injuries in ~1 in 5000 cases [33]. The usual clinical picture is involvement of all major nerves in the extremity, with greater involvement of motor nerves than sensory nerves. Conservative treatment is the rule because nearly all patients will experience a complete recovery.

Ulnar nerve injuries at the elbow have been reported as a complication of surgical repair of elbow fractures and of ulnar nerve transposition. Displaced fractures of the distal humerus in children are usually treated with closed reduction and percutaneous pinning of the fracture. Postoperative ulnar nerve palsy develops in ~5% of patients after crossed pinning [34]. Although some authors recommend observation alone for this problem, others advocate pin removal with exploration of the nerve because of the possibility of direct penetration of the nerve by the pin [35]. Whether treated surgically or not, most patients with ulnar nerve palsy will experience complete recovery, although resolution may take several months. Patients who suffer malunion of the distal humerus with progressive deformity may also experience late ulnar nerve palsy.

The median nerve is most often injured at either the elbow or the wrist. Injuries around the elbow are usually due to venipuncture or arterial catheterization. At the wrist level, the median nerve is most frequently injured during carpal tunnel release. Both the endoscopic and the open technique have been reported to be associated with lacerations of the main trunk of the median nerve, the palmar cutaneous branch, the median motor branch, the common and proper digital nerves, the main trunk of the ulnar nerve, or the motor branch of the ulnar nerve [36]. By far, the most common nerve lesion is neuropraxia, which is self-limited and resolves completely. The median nerve may also be injured during corticosteroid injections to treat carpal tunnel syndrome if these injections are inadvertently administered intraneurally. There are also several reported cases of mistaken removal of the median nerve during attempts to harvest the palmaris longus tendon for use as a graft. This mistake is often not recognized until it is too late, and the nerve must be reconstructed with nerve grafting.

The radial nerve can be injured during surgical treatment of fractures or nonunions of the humeral shaft, during surgical approaches to the elbow (anterior or lateral approaches), by the placement of external fixation pins, by surgery for de Quervain's tenosynovitis, or by surgical procedures on the radial artery. Awareness of neurological complications resulting from harvesting the radial artery for CABG has increased. A survey of patients who underwent such harvesting showed

that 30% subsequently reported some type of neurological complaint (sensation abnormality or thumb weakness) [37]. Because of the nature of this study, it is difficult to determine whether the median nerve, the radial nerve, or both were involved or whether the problems were due to nerve traction or insufficient vascularity.

38.6.4 Pelvis and Hip Level

Injuries to the ilioinguinal, iliohypogastric, and genitofemoral nerves can cause pain in the inguinal region. These nerves are most commonly injured during inguinal herniorrhaphy but can also be damaged during inguinal lymph node dissection, abdominal hysterectomy, abdominoplasty, and harvest of iliac crest bone grafts [38]. The best results of surgical treatment were achieved for patients with lesions of the ilioinguinal nerve or the iliohypogastric nerve, and the worst results were in patients with injuries to the genitofemoral nerve [39].

The lateral femoral cutaneous nerve (LFCN) is vulnerable to injuries during herniorrhaphy, during surgical procedures to the pelvis, especially those using the ilioinguinal approach, and during spine surgery. Injury to this nerve causes pain, numbness, or both to the anterolateral thigh; such injury is also called neuralgia paresthetica. During spine surgery, placing the patient on the Hall–Relton frame may cause external pressure on the nerve at the anterior superior iliac spine [40]. The nerve can also be injured by retroperitoneal hematoma or during harvest of iliac crest bone grafts [40]. Almost 90% of patients experienced complete recovery within 3 months, and >90% of those requiring surgical decompression experienced good to excellent outcomes [40].

The femoral nerve forms within the substance of the psoas muscle, emerging along the lateral border to run between the psoas and iliacus muscles. It then enters the thigh after passing beneath the inguinal ligament, branches out to supply motor input to the quadriceps, and continues as the saphenous nerve. The nerve can be injured in either its intrapelvic portions or its extrapelvic portions. Symptoms range from mild paresthesias to profound motor and sensory deficits. Motor weakness is usually manifested by buckling of the knee as the result of weakness of the quadriceps. Most femoral nerve lesions are iatrogenic. Causes include compression from self-retaining retractors, transection or suture during herniorrhaphy, infrainguinal vascular procedures, ischemia, cement entrapment in hip arthroplasty, traction, and positioning. Probably the most common cause is compression by self-retaining retractors, most often during pelvic surgery. The reported incidence of femoral nerve lesions in association with total abdominal hysterectomy is 11% [41]. The lateral blade of the retractor can directly compress the nerve or can trap the nerve and the psoas muscle between the retractor and the pelvic wall. Most authors recommend using smaller blades on the self-retaining retractors to prevent this problem [41,42].

The saphenous nerve is the sensory continuation of the femoral nerve; it provides sensory supply to the anteromedial aspect of the leg and the medial side of the foot. Patients can experience anesthesia, hyperesthesia, or pain in its distribution when the nerve is damaged. The nerve is commonly injured during harvest of vein grafts for CABG. One study showed that 90% of patients experienced some anesthesia after vein harvest, and 72% were still experiencing these symptoms 20 months after harvest [43].

Because of its proximity to the hip joint, the sciatic nerve is most commonly injured during hip arthroplasty. The incidence of such injuries in association with primary hip arthroplasty is 1% and increases to 3% in association with revision surgery [44]. Although intraoperative traction of the nerve is believed to be the most common cause of injury, the nerve may also be injured by postoperative dislocation, by heat damage from cement, or by nerve laceration. The prognosis is best for patients who can walk immediately after surgery or who regain motor function within 2 weeks. Whether patients undergo neurolysis, nerve repair or grafting, or conservative treatment, recovery is more likely in the tibial nerve distribution than in the peroneal division of the nerve [45]. Other causes of iatrogenic sciatic injury include ischemia after prolonged intra-aortic balloon pump therapy, improper patient positioning during surgical procedures, and injection injuries.

The peroneal nerve is susceptible to injury because it winds around the posterolateral corner of the knee joint. Damage to this nerve causes foot drop, a weakness of dorsiflexion of the ankle. Peroneal nerve palsies have been reported as a complication of knee arthroplasty, tibial osteotomy, knee arthroscopy, lower-extremity casts, positioning during surgery, and the use of pneumatic compression devices. As with most iatrogenic nerve lesions, most injuries to the peroneal nerve will resolve with time. If surgery is performed, only 40% of patients will recover sufficient strength to prevent foot drop, and approximately half will regain protective sensation in the foot [46].

38.6.5 Injection and Catheterization Injuries

Peripheral nerves are at risk of injury during all invasive procedures, including intramuscular injections, arterial and venous catheterization, and even routine venipuncture. A review of sciatic nerve injuries at the level of the buttocks reported that more than half were the result of misplaced gluteal muscle injections. Not all injection palsies resolve spontaneously [45]. Published reports

have described brachial plexus neuropathy after subclavian vein catheterization [47]. Many reports describe peripheral nerve injury leading to complex regional pain syndrome after routine venipuncture [48].

38.6.6 Anesthesia-Related Nerve Injuries

Peripheral nerve damage associated with anesthesia may result from injury to the nerves themselves by administration of regional anesthesia or may be related to patient positioning. Regional anesthesia for upper-extremity surgery is associated with a number of serious neurological complications, although most of these complications are minor and transient [49]. Injury may result from direct needle trauma to nerves or from hematomas that form after transarterial techniques.

Although in this chapter injuries related to patient positioning are treated as anesthesia-related complications, it is imperative that every surgeon be aware of these complications and know how to avoid them. Analysis of the American Society of Anesthesiologists Closed Claims Database showed that 16% of claims were for anesthesia-related nerve injuries and that nearly 30% of those claims were for injuries to the ulnar nerve [50]. The most commonly affected nerves are the ulnar nerve and the peroneal nerve, probably because of their superficial course in the extremities. The ulnar nerve can be injured by compression against the operating table or by excessive flexion of the elbow. The peroneal nerve is vulnerable to injury because it winds around the fibular head, and it may be compressed against the lithotomy pole or by placing the patient in the lateral position. If the patient's arm rests on a hard edge, the radial nerve can be compressed against the posterior part of the humerus. The sciatic nerve is at risk of compression when patients are thin; other risk factors are lengthy procedures and hard tables. The nerve can also suffer traction injury when patients are placed in the lithotomy position with the hip flexed and in maximal external rotation. The lithotomy position can also cause femoral nerve palsies by entrapping the nerve against the inguinal ligament when the hip is hyperflexed. The brachial plexus can also undergo traction injury as the result of positioning, particularly when the arms are placed in abduction with external rotation and posterior shoulder displacement.

38.7 Conclusion

Peripheral nerve injuries are a cause of significant morbidity. Many types of traumatic injuries can be associated with nerve injury. Recognition of these injuries in a timely manner is essential in improving their outcome. It is also important to note that many peripheral nerve injuries may be iatrogenic. Knowledge of how common surgeries and procedures can lead to nerve injury is essential in their prevention. Finally when surgical repair is indicated, it is important to recognize the variety of tools that are available from direct repair to nerve grafting and nerve conduits.

Complications of Nerve Injury and Repair

Complications	Incidence	Comments	References
Traumatic injury	2.8% of trauma patients had injury to at least one major peripheral nerve	Up to 54% required an operative intervention	[1]
Peripheral nerve injury in CNS trauma	10%–34% associated peripheral nerve injury in patients with CNS injury	10% association with brachial plexus injury	[15]
Radial nerve injury	10% of humeral shaft fractures		[10]
Median nerve injury	17% of wrist injuries	May require urgent carpal tunnel release	[12]
Peroneal nerve injury	10% of hip fracture/dislocations		[13]
Iatrogenic injury	10% of peripheral nerve injuries are associated with medical treatment		[2]
Brachial plexus injury	2.7%–10% following open heart surgery		[27]
Ulnar nerve injury	5% in cross pinning of the humerus in children		[34]
Radial/median nerve palsy	30% had thumb weakness or sensory changes after radial artery harvest for CABG	Injury to the radial and/or median nerves	[37]
Femoral nerve palsy	11% following abdominal hysterectomy	Associated with retraction	[41]
Saphenous nerve injury	Up to 90% following vein harvest for CABG had sensory changes	72% still had deficits at 20 months post op	[43]
Sciatic nerve injury	1% following hip arthroplasty	3% with revision arthroplasty	[44]

Avoidance of Complications in Nerve Injury and Repair

Complications	Method of Avoidance	References
Traumatic injury	Recognizing the possibility of injury given the mechanism and knowledge of the involved anatomy. Timely neurological examination and repair when indicated.	[1,3]
Peripheral nerve injury in CNS trauma	Repeated neurological examination with a high index of suspicion in the patient with CNS injury.	[15]
Radial nerve injury in distal humerus fractures	Recognizing of the possibility of injury, timely radiographs, and clear understanding of the anatomy involved.	[10]
Median nerve injury in wrist injuries	Careful neurological examination. Prophylactic carpal tunnel release.	[12]
Peroneal nerve injury in hip fractures	Recognizing the possibility of injury and careful neurological examination.	[13]
Volkmann's contracture	High index of suspicion. Neurological examination and compartment pressure measurements. Timely fasciotomy when indicated.	[18]
Iatrogenic injuries	Comprehensive knowledge of the involved anatomy. Proper positioning, retraction, and intraoperative padding.	[2]
Brachial plexopathy	Understanding the anatomy involved in sternotomy and retraction. Limiting the extent of sternal retraction.	[24,26,27]
Ulnar nerve palsy	Understanding the anatomy of the ulnar nerve prior to cross pining.	[34]
Nerve palsy following graft harvests for CABG	Understanding the anatomy of the radial artery and saphenous veins prior to harvest.	[37,43]
Femoral nerve palsy	Limiting the extent of the retraction and using smaller blades to avoid femoral nerve compression.	[41,42]
Sciatic nerve palsy	Understanding the anatomy of the sciatic nerve and the peroneal branch. Proper intraoperative padding and avoidance of traction on the sciatic nerve.	[44–46]
Increased tension on the repair	Recognition of the extent of the injury. Tension-free repair with extended neurolysis or transposition and the judicious use of nerve grafts. Up to 70% recovery with direct tension-free repair and 50% with grafts <3 cm.	[6,8]

Acknowledgment

Dr. Patrick W. Owens was the author of the first edition chapter on which this chapter is based.

References

1. Noble J, Munro CA, Prasad VS, and Midha R. Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. *J Trauma* 1998; 45(1):116–122.
2. Birch R, Bonney G, Dowell J, and Hollingdale J. Iatrogenic injuries of peripheral nerves. *J Bone Joint Surg Br* 1991; 73:280–282.
3. Fox IK and Mackinnon SE. Adult peripheral nerve disorders: Nerve entrapment, repair, transfer and brachial plexus disorders. *Plastic Reconstruct Surg* 2011; 127:105e–118e.
   Recent review regarding the classification of nerve injury, diagnostic workup, and methods of repair.
4. Myckatyn TM and Mackinnon SE. Microsurgical repair of peripheral nerves and nerve grafts. In: Thorne CH, Beasley RW, Aston SJ, Bartlett SP, Gurtner GC, Spear SL, eds. *Grabb and Smith's Plastic Surgery*. Philadelphia, PA: Lippincott Williams & Wilkins, 2007: pp. 73–83.
5. Frykman GK and Gramyk K. Results of nerve grafting. In: Gelberman RH, ed. *Operative Nerve Repair and Reconstruction*. Philadelphia, PA: JB Lippincott, 1991: pp. 553–567.
6. Clark WL, Trumble TE, Swiontkowski MF, and Tencer AF. Nerve tension and blood flow in a rat model of immediate and delayed repairs. *J Hand Surg [Am]* 1992; 17(4):677–687.
7. Hentz VR, Rosen JM, Xiao SJ, McGill KC, and Abraham G. The nerve gap dilemma: A comparison of nerves repaired end to end under tension with nerve grafts in a primate model. *J Hand Surg [Am]* 1993; 18:417–425.
8. Spinner RJ and Kline DG. Surgery for peripheral nerve and brachial plexus injuries or other nerve lesions. *Muscle Nerve* 2000; 23(5):680–695.
   A review of electrodiagnostic diagnostics and methods of repair of peripheral nerve and brachial plexus injuries.
9. Visser CP, Coene LN, Brand R, and Tavy DL. The incidence of nerve injury in anterior dislocation of the shoulder and its influence on functional recovery. A prospective clinical and EMG study. *J Bone Joint Surg Br* 1999; 81(4):679–685.
10. Samardzic M, Grujicic D, and Milinkovic ZB. Radial nerve lesions associated with fractures of the humeral shaft. *Injury* 1990; 21:220–222.
11. Galbraith KA and McCullough CJ. Acute nerve injury as a complication of closed fractures or dislocations of the elbow. *Injury* 1979; 11(2):159–164.

12. Stewart HD, Innes AR, and Burke FD. The hand complications of Colles' fractures. *J Hand Surg [Br]* 1985; 10:103–106.
13. Cornwall R and Radomisli TE. Nerve injury in traumatic dislocation of the hip. *Clin Orthop* 2000; 377:84–91.
14. Pillai L, Luchette FA, Romano KS, and Ricotta JJ. Upper-extremity arterial injury. *Am Surg* 1997; 63(3): 224–227.
15. Stone L and Keenan MA. Peripheral nerve injuries in the adult with traumatic brain injury. *Clin Orthop* 1988; 233:136–144.
16. Garfin SR, Mubarak SJ, Evans KL, Hargens AR, and Akeson WH. Quantification of intracompartmental pressure and volume under plaster casts. *J Bone Joint Surg Am* 1981; 63:449–453.
17. Trumble TE. Compartment syndrome and Volkmann's contracture. In: Trumble TE, ed. *Principles of Hand Surgery and Therapy*. Philadelphia, PA: WB Saunders, 2000: pp. 179–191.
18. Hovius SE and Ultee J. Volkmann's ischemic contracture. Prevention and treatment. *Hand Clin* 2000; 16(4):647–657.
19. AbuRahma AF and Choueiri MA. Cranial and cervical nerve injuries after repeat carotid endarterectomy. *J Vasc Surg* 2000; 32:649–654.
    A prospective study of repeat carotid endarterectomy focusing on the risks of cranial and cervical nerve injury.
20. Shafei H, el-Kholy A, Azmy S, Ebrahim M, and Al-Ebrahim K. Vocal cord dysfunction after cardiac surgery: An overlooked complication. *Eur J Cardiothorac Surg* 1997; 11:564–566.
21. AbuRahma AF and Lim RY. Management of vagus nerve injury after carotid endarterectomy. *Surgery* 1996; 119(3):245–247.
22. Kim D, Cho YJ, Tiel RL, and Kline DG. Surgical outcomes of 111 spinal accessory nerve injuries. *Neurosurgery* 2003; 53(5):1106–1112.
23. Wiater JM and Bigliani LU. Spinal accessory nerve injury. *Clin Orthop* 1999; 368:5–16.
24. Sharma AD, Parmley CL, Sreeram G, and Grocott HP. Peripheral nerve injuries during cardiac surgery: Risk factors, diagnosis, prognosis, and prevention. *Anesth Analg* 2000; 91:1358–1369.
    A review focusing on the diagnosis and prevention of neuropathies of the brachial plexus, phrenic, recurrent laryngeal, and saphenous nerves encountered in cardiac surgery.
25. Wiater JM and Flatow EL. Long thoracic nerve injury. *Clin Orthop* 1999; 368:17–27.
26. Wilbourn AJ. Iatrogenic nerve injuries. *Neurol Clin* 1998; 16(1):55–82.
27. Vahl CF, Carl I, Muller-Vahl H, and Struck E. Brachial plexus injury after cardiac surgery. The role of internal mammary artery preparation: A prospective study on 1000 consecutive patients. *J Thorac Cardiovasc Surg* 1991; 102(5):724–729.
28. Vander Salm TJ, Cutler BS, and Okike ON. Brachial plexus injury following median sternotomy. Part II. *J Thorac Cardiovasc Surg* 1982; 83(6):914–917.
29. Hanson MR, Breuer AC, Furlan AJ, Lederman RJ, Wilbourn AJ, Cosgrove DM, Loop FD, Estafanous FG. Mechanism and frequency of brachial plexus injury in open-heart surgery: A prospective analysis. *Ann Thorac Surg* 1983; 36(6):675–679.
30. Morin JE, Long R, Elleker MG, Eisen AA, Wynands E, and Ralphs-Thibodeau S. Upper extremity neuropathies following median sternotomy. *Ann Thorac Surg* 1982; 34(2):181–185.
31. Ho E, Cofield RH, Balm MR, Hattrup SJ, and Rowland CM. Neurologic complications of surgery for anterior shoulder instability. *J Shoulder Elbow Surg* 1999; 8(3):266–270.
32. Vujaskovic Z. Structural and physiological properties of peripheral nerves after intraoperative irradiation. *J Peripher Nerv Syst* 1997; 2(4):343–349.
33. Landi A, Saracino A, Pinelli M, Caserta G, and Facchini MC. Tourniquet paralysis in microsurgery. *Ann Acad Med Singapore* 1995; 24(Suppl 4):89–93.
34. Lyons JP, Ashley E, and Hoffer MM. Ulnar nerve palsies after percutaneous cross-pinning of supracondylar fractures in children's elbows. *J Pediatr Orthop* 1998; 18(1):43–45.
35. Rasool MN. Ulnar nerve injury after K-wire fixation of supracondylar humerus fractures in children. *J Pediatr Orthop* 1998; 18(5):686–690.
36. Palmer AK and Toivonen DA. Complications of endoscopic and open carpal tunnel release. *J Hand Surg [Am]* 1999; 24(3):561–565.
37. Denton TA, Trento L, Cohen M, Kass RM, Blanche C, Raissi S, Cheng W, Fontana GP, and Trento A. Radial artery harvesting for coronary bypass operations: Neurologic complications and their potential mechanisms. *J Thorac Cardiovasc Surg* 2001; 121(5):951–956.
38. Nahabedian MY and Dellon AL. Outcome of the operative management of nerve injuries in the ilioinguinal region. *J Am Coll Surg* 1997; 184(3):265–268.
39. Lee CH and Dellon AL. Surgical management of groin pain of neural origin. *J Am Coll Surg* 2000; 191(2): 137–142.
    A retrospective review focused on the evaluation and treatment of groin pain and outcomes of associated surgical treatment.
40. Mirovsky Y and Neuwirth M. Injuries to the lateral femoral cutaneous nerve during spine surgery. *Spine* 2000; 25(10):1266–1269.
41. Kvist-Poulsen H and Borel J. Iatrogenic femoral neuropathy subsequent to abdominal hysterectomy: Incidence and prevention. *Obstet Gynecol* 1982; 60(4):516–520.
42. Dillavou ED, Anderson LR, Bernert RA, Mularski RA, Hunter GC, Fiser SM, and Rappaport WD. Lower extremity iatrogenic nerve injury due to compression during intraabdominal surgery. *Am J Surg* 1997; 173(6):504–508.
43. Mountney J and Wilkinson GA. Saphenous neuralgia after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 1999; 16(4):440–443.
44. Schmalzried TP, Amstutz HC, and Dorey FJ. Nerve palsy associated with total hip replacement. Risk factors and prognosis. *J Bone Joint Surg Am* 1991; 73(7):1074–1080.

45. Kline DG, Kim D, Midha R, Harsh C, and Tiel R. Management and results of sciatic nerve injuries: A 24-year experience. *J Neurosurg* 1998; 89(1):13–23.
A retrospective study analyzing the causes and providing guidelines for the repair of sciatic nerve injuries.
46. Wilkinson MC and Birch R. Repair of the common peroneal nerve. *J Bone Joint Surg Br* 1995; 77(3):501–503.
47. Trentman TL, Rome JD, and Messick JM, Jr. Brachial plexus neuropathy following attempt at subclavian vein catheterization. Case report. *Reg Anesth* 1996; 21(2):163–165.
48. Horowitz SH. Venipuncture-induced causalgia: Anatomic relations of upper extremity superficial veins and nerves, and clinical considerations. *Transfusion* 2000; 40(9):1036–1040.
49. Stark RH. Neurologic injury from axillary block anesthesia. *J Hand Surg [Am]* 1996; 21(3):391–396.
50. Cheney FW, Domino KB, Caplan RA, and Posner KL. Nerve injury associated with anesthesia: A closed claims analysis. *Anesthesiology* 1999; 90(4):1062–1069.

39

Psychological and Behavioral Complications of Trauma

Gillian Hotz and Deborah M. Little

CONTENTS

39.1 Introduction

If complications of trauma are to be approached comprehensively, the cognitive, emotional, and behavioral domains must be considered. In addition to the more overt changes in level of consciousness or behavior, which can result from moderate to severe brain injury, physical trauma to the head can also lead to more subtle alterations of cognition and mood that nonetheless can have a profound impact on functioning and quality of life. A diagnosis of traumatic brain injury (TBI) in either the acute or chronic patient raises one example that highlights the interrelationship between central nervous system injury and associated behavioral and psychological sequelae. Although such factors can affect virtually all types of trauma, traumatic injury to the brain, for which damage is by definition tied to alterations in brain function and behavior, provides an extreme case where primary injury and psychological sequelae must be examined as co-occurring conditions. We take the approach herein to examine the most common co-occurring and/or comorbid psychological considerations from the time of injury (survival) forward into recovery with an emphasis on depression and posttraumatic stress disorder (PTSD). We also begin our discussion with a very brief overview of cognitive impairments secondary to TBI as it appears mood and anxiety disorders may increase these deficits.

39.2 Traumatic Brain Injury

39.2.1 Incidence, Prevalence, and Cost

Trauma is a common cause of brain injury, and TBI is a leading cause of death and disability in the United States. Each year, an estimated 1.5 million Americans sustain a TBI. Of these, 50,000 die; 230,000 are hospitalized and survive; and approximately 80,000–90,000 experience long-term disability [1]. Advances in prehospital care, classifications of injury severity and outcome, imaging, critical care, and rehabilitation have contributed to a reduction in mortality and to improved outcomes for patients with TBI [2–4]. The healthcare costs of TBI are estimated at approximately US $35 billion per year [5]. In veteran populations,

such costs are difficult to assess and bring significant controversy but range from an estimated $11,700 per patient in the first year of care (non-polytrauma setting, without PTSD) to $136,000 for those TBI patients with more significant injuries requiring specialized polytrauma care. Given the numbers of deployed service members, the estimated care over the lifetime of a patient with TBI is significant. Unlike the rates identified earlier, sports concussion alone is estimated to occur at a range between 1.6 and 3.8 million annually. In clinical studies, the short- and long-term effects of concussion have been reported to be serious and occasionally fatal. Sports-related injuries are second to motor vehicle accidents as the leading cause of TBI for young people between 15 and 24 years old [6]. At present, there are no estimated "costs" per se, but this is a topic that warrants further investigation.

39.2.2 Severity and Prognostic Indicators

Computed tomography (CT) has revolutionized the early diagnosis and treatment of patients with moderate to severe TBI. The immediate detection of intracranial mass lesions has made a significant difference in the outcome of patients with brain injury. Indications for intracranial pressure monitoring, the role of glucocorticoids, the role of prophylactic antiseizure medications, the use of hyperventilation, and the importance of cerebral perfusion pressure in the care of patients with severe TBI have all made an impact. In 1996, the Guidelines for the Management of Severe Head Injury [7] were distributed throughout the United States and Canada. The document provided evidence-based standards, guidelines, or options regarding the role of neurosurgeons in trauma systems. Several other elements of the treatment of patients with head injury were also included. With these guidelines, the management of severe TBI and its outcomes is now more consistent across North America. Unfortunately, and as supported in a recent report to the United States Congress, noninvasive imaging methods including both CT and magnetic resonance imaging (MRI) have to date not had an impact on assessment of milder injuries for which lesions and microbleeds are uncommon. The reader is directed to this report for a comprehensive review on this topic that is outside the scope of this chapter. It is hopeful that the push for TBI Common Data Elements (CDE) providing the foundation for some standardization across sites, as with neurosurgical guidelines, may change the future role of MRI and CT.

In order to develop the TBI CDE standards, a variety of cosponsoring federal agencies led a scientific initiative to develop the core set of recommended variables to include and collect in TBI studies. Scientific experts were invited in 2009 to participate in a working group to develop recommendations for specific topic-driven CDE. Without a common set of data elements (which include variable definitions and recommended measures), comparison of findings across studies was difficult. This is one major challenge for the reader in determining such things as treatment efficacy. Without CDEs to characterize a very heterogeneous sample, we are left with small studies that do not generalize across sites. Currently, Version 2.0 of the TBI CDEs are available at www.commondataelements.ninds.nih.gov/tbi. Briefly, the CDEs are organized according to type of study including those focused on concussion and mild TBI, acute hospital-based studies, those focused on moderate to severe TBI, rehabilitation, and larger-scale epidemiology studies.

The Version 2.0 CDEs are classified according to the following definitions:

- *Core*—Small set of data elements that are relevant to all TBI clinical studies.
- *Basic*—Small set of data elements, beyond the core, that are recommended for inclusion in studies of concussion/mild TBI, acute hospitalized, moderate/severe TBI, rehabilitation, or epidemiology.
- *Supplemental*—Additional recommended data elements where inclusion depends upon the particulars of the study.

Therefore, researchers working on acute hospitalized, concussion or mild TBI, rehabilitation of moderate or severe TBI, and epidemiology studies can use these classifications as guidelines to find customized sets of elements that they can incorporate into their studies hopefully leading to greater generalizability.

The duration of coma and the period of posttraumatic amnesia (PTA) are important predictors of outcome. The patient's condition during the first few hours after injury is an important early index of severity and is most commonly measured by the Glasgow Coma Scale (GCS) [2], which serves as an objective measure of level of consciousness. This scale allows for the best assessment of verbal, motor, and visual response with a corresponding classification of brain injury as mild (GCS score, 13–15), moderate (GCS score, 9–12), or severe (GCS score, 3–8). The period of PTA was first described by Russell [8] and refers to the duration of time from the point of injury to until the patient has continuous memory of ongoing events and is able to retain new information. Cognitive function during PTA is highly variable and difficult to evaluate. Those patients who remain in coma longer and experience longer periods of PTA suffer significant neurological and behavioral deficits that are often irreversible. The effect of age at the time of injury to the brain is also an important variable that should

not be ignored. Many clinicians assume that because of brain plasticity, children will have a better prognosis for neurobehavioral recovery after TBI than will adults [9]. Studies have reported that an early injury to the brain in younger children may limit the brain's ability to develop normally or may interfere with the timing of neural development [10]. In addition, new deficits may emerge at later stages after injury. Therefore, from the mildest of injuries to the most catastrophic injury, patients may demonstrate different severities of brain injury, which results in different types of cognitive and behavioral impairments.

The fastest growing segment of the population in terms of head injury prevalence are persons over the age of 65 years. This further complicates the understanding of recovery and impairment in healthy older populations as well as those with neurodegenerative diseases which may contribute to fall risk. However, although this is the fastest growing segment of the TBI population, very little is known about the confounding effects of increased age on injury severity and outcomes. This lack of information is of significance in this discussion given the rates of geriatric depression that, independent of TBI, provide treatment challenges.

39.2.3 Pathophysiology

An understanding of cognitive and behavioral deficits first requires an understanding of the neuropathology of diffuse and focal injuries and the different patterns of recovery associated with them. Historically, damage to the frontal and temporal lobes is considered to be responsible for most of the cognitive and behavioral deficits associated with civilian TBI including such injury mechanisms as motor vehicle–associated accidents, sports-related concussions, assaults, and falls. The pathophysiology of head trauma includes both the immediate impact (primary injury) and delayed brain injury (secondary injury). The result of mechanical forces applied to the skull and transmitted to the brain is focal brain damage, diffuse brain damage, or both. Focal lesions result from a direct blow to the head and include brain laceration, contusion, intracerebral hemorrhage, subarachnoid or subdural hemorrhage, epidural hematoma, and ischemic infarct. The mechanism of injury involves a rapid acceleration and deceleration of the head, such as that typically produced by motor vehicle crashes or falls. The areas most commonly affected are the orbitofrontal area and the temporal area [11]. Also, the differential motion of the brain within the skull causes shearing and stretching of axons [12]. The widespread spectrum of injuries, ranging from brief physiological disruption to widespread axonal tearing, is called diffuse axonal injury [13]. Generally, this overall description of the pathophysiology is consistent across injury mechanism. However, it is becoming increasingly important to note that there may be injury mechanism–specific pathophysiology that may also affect outcomes. For example, preliminary and initial studies investigating TBI due to improvised explosive devices (blast TBI) in the theater of war appear to indicate a much heavier injury burden represented by widespread white matter lesions generally occurring at the gray–white junction. Such an observation has face validity in that simple exposure to a blast can result in alterations in intracranial pressure as well as direct shear and strain injury due to mechanical forces, and similar to acceleration–deceleration type TBI, blast TBI is associated with damage to axons, cerebral edema, and small hemorrhages in white matter, the cerebellum, and brain stem [14].

In addition to damage occurring at the time of impact, secondary damage may occur during the recovery period. Secondary damage can be caused by hypoxia, hypotension, severe anemia, metabolic abnormalities, infection, hydrocephalus, intracranial hypertension, fat embolism, and subarachnoid hemorrhage. Other delayed effects include release of excitatory amino acids, production of oxidative free radicals, release of arachidonic acid metabolites, and disruption of neurotransmitters such as monoamines and serotonin [15].

Over the last few years, increased media attention and research has been on mild TBI and concussion. Concussion is a type of brain injury caused by a blow to the head. A concussion can occur with or without a loss of consciousness. Damage to the brain is theoretically caused by biomechanical forces that lead to shear and strain injury. The pathophysiology, as discussed earlier, can cause short- and/or long-term cognitive, physical, psychological, and academic issues. A general overview of the most common cognitive impairments and alterations is discussed later. Less often discussed are the alarming rates of postconcussive psychiatric illness, with mood and anxiety disorders being the most common. These are also discussed later.

Concussion in sports has become a national public health issue with local, state, and federal legislation being created and enforced. Daily reports are released concerning the prolonged, negative effects of concussions in athletes. Professional athletes have publicly suffered injuries highlighting the importance of proper concussion management. Current research indicates that the most serious effects of concussion can be avoided if the athlete's injury is immediately identified and properly managed. Over the last few years, more research is being reported about chronic traumatic encephalopathy (CTE), a progressive degenerative disease of the brain found in athletes (and others) with a history of repetitive brain trauma. This kind of trauma, which includes multiple concussions, triggers progressive degeneration

of the brain tissue, including the buildup of an abnormal protein called *tau*. The brain degeneration is associated with memory loss, confusion, impaired judgment, paranoia, impulse control problems, aggression, depression, and eventually progressive dementia. There have been many cases of retired football and hockey players, boxers, and wrestlers with reported evidence of CTE at autopsy [16].

Typically after mild TBI, most deficits resolve within 3 months [17]. The most common postconcussive complaints are headaches, dizziness, fatigue, irritability, anxiety, insomnia, memory problems, and noise sensitivity. These symptoms usually follow mild TBI, but are also seen after all other degrees of TBI. After moderate or severe TBI, patients are left with a combination of physical, cognitive, and behavioral deficits that may persist for months or years after the injury. These deficits are best treated by a multidisciplinary team of experts that includes a physician with expertise in brain injury rehabilitation, nurses, a physical therapist, an occupational therapist, a speech pathologist, a neuropsychologist, a recreational therapist, a dietician, a social worker, and the patient's family.

39.2.4 Behavioral Sequelae: Cognitive Impairment

Cognition is defined by Neisser as the processes by which sensory input is transformed, reduced, elaborated, stored, recovered, and used [18]. Cognitive deficits are caused by the effects of focal and diffuse brain damage. Despite the variability in the severity of brain injury and the cognitive deficits associated with it, certain common patterns exist because of the typical damage to the frontal and temporal lobes (gray matter), the midbrain, and the corpus callosum (white matter). Cognitive outcome depends on a number of factors, including degree of diffuse axonal injury, age, duration of loss of consciousness, duration of PTA, brain stem dysfunction at the time of injury, and presence and size of focal injury.

The cognitive disorders typically experienced by patients with TBI include impairment of arousal, attention, concentration, memory, language, visuospatial and perceptual function, and executive function [19]. Deficits in attention and memory are among the most commonly reported disorders after TBI. Attention is not a single entity, but is rather a finite set of brain processes that interact with other brain processes in the performance of different perceptual, cognitive, and motor tasks. Components of attention include vigilance (attending to a task over time), selection (attending to different targets), and executive attention (planning and coordination of multiple tasks). Attention is the basis for information processing, learning, and execution of the activities of daily living.

Memory is a complex process that includes the ability to encode (analyze and restructure information into storable forms), store (maintain stored memories), and retrieve (locate stored information and return it to awareness) information [18]. Patients with head injury demonstrate a combination of retrograde (inability to recall events preceding the injury) and anterograde (difficulty in acquiring new information) amnesia, caused by damage to the medial temporal lobes and the hippocampus or to portions of the thalamus.

Disorders of communication and language may take many forms depending on the site and extent of the lesion. It has been reported that language disorders associated with TBI are a manifestation of underlying cognitive disorganization. Patients demonstrate reduced word fluency, impaired visual naming, impaired auditory comprehension, anomia, paraphasias, and problems with reading and writing. The most commonly reported deficit is anomia, or problems with finding words or naming objects. Anomia is described as the inability to generate names on visual confrontation or in spontaneous speech, with damage to the dominant parietal area [14]. Executive function problems include poor planning, organizing, sequencing, and set-shifting abilities, with impaired judgment and impulse control (for a general review of language disorders in TBI, see [20]).

Visuospatial and perceptual deficits are not as common as other deficits because the posterior areas of the brain are less often damaged than the frontal and temporal areas. Prosopagnosia (inability to recognize familiar faces) is associated with lesions of the right inferior occipitotemporal region. Other visuospatial deficits include problems with neglect, motor planning, perception of forms, spatial relations, color, and figure–ground relationships. In more severe TBI, hemispatial neglect is more common with patients having significant difficulty with attending to either the right or the left half of space. These visuospatial deficits have significant functional consequences for independent living over the lifetime of the patient with no "good" treatment available. It is important to screen patients during the acute phase of brain injury to assess a wide range of cognitive, memory, and language deficits that are first seen in the early stages of recovery. In the acute stage, the patient is usually disoriented and confused. The Galveston Orientation Amnesia Test should be administered daily to track the patients' progress through PTA [21].

A full neuropsychological assessment should be administered to patients during the rehabilitation phase. A scale commonly used to follow a patient's progress through cognitive recovery is the Rancho Los Amigos Scale [22], which describes the patient's current level of cognitive functioning. The scale ranges

from Level I (no response) to Level VIII (purposeful, appropriate). Various treatment techniques have been developed and used at different stages of recovery. Patients recover at different rates depending on the severity of the brain injury. Complicating the cognitive assessment is the common absence of gross neuropsychological deficits in milder TBI populations where it is common to have patient self-reported deficits in attention and memory but with performance that falls within standardized norms. Further, given the proposed association between lifetime history of multiple–mild TBIs and later dementia such screenings will likely be required in high-risk patients (i.e., boxers) as cognitive symptoms increase with age.

The rehabilitation of cognitive deficits may be referred to as cognitive retraining, cognitive remediation, or cognitive rehabilitation. Cognitive rehabilitation is a set of therapies used to help improve damaged intellectual, perceptual, psychomotor, and behavioral skills. Approaches may vary from the use of computer programs to paper-and-pencil and traditional therapy tasks, may focus on single components of cognition or on cognitive aspects embedded in functional tasks, or may be aimed directly at improving impaired cognitive processes or at developing compensatory strategies. Cognitive retraining involves using techniques to retrain the patient in specific cognitive domains by providing a series and a hierarchy of mental stimuli, tests, and activities. This therapy consists of task repetition and assistance provided by cueing techniques [23]. Therapeutic strategies of cognitive rehabilitation have been classified in the literature as either restorative (repetitive exercise with the goal of restoring lost function) or compensatory (development of internal strategies or external prosthetic assistance for dysfunction). At present, there are a number of funded studies examining efficacy of such treatments but as with most fields within TBI, controlled double-blind studies are still missing.

In mild TBI, the deficits noted earlier are rarely observed to degrees that would allow definition of clinical impairment. However, across multiple studies decreased mental flexibility, trouble shifting sets, and impaired attention are observed in mild TBI even if they do not reach clinical impairment [19]. Also often complaints about by mild TBI patients and their families are poor planning, lack of organization, problems with sequencing, impaired judgment, deficits in verbal fluency, problems with working memory, as well as impulsivity errors [19].

Neuropharmacological management involving psychostimulants and other dopaminergic agents has been reported to be beneficial in improving deficits of arousal, poor attention, concentration, and memory. Recently, the use of cholinergic agents has been reported to be promising in treating these deficits [24]. However, as with all patients, use of these agents must be considered with respect to noncognitive behavioral sequelae including aggression and agitation.

39.2.5 Behavioral Sequelae: Mood and Anxiety Disorders

Frequently reported behavioral sequelae after TBI include agitation, disinhibition, depression, apathy, mania, and psychosis. These behavioral problems have been mostly associated with injury to the frontal and temporal lobes. It is also important for the reader to note that many of the available studies evaluating pharmacological interventions for such behavioral sequelae must be interpreted with an eye for sample size, inclusion criteria, and appropriate control groups. Pharmacological studies in TBI are historically challenging given the wide array of clinical presentations, acuity of treatment relative to injury, and other common comorbidities that can confound the common behavioral sequelae such as sleep disturbance. We focus herein on depression and PTSD. However, we direct the reader to Table 39.1 which includes the best estimates for prevalence of other observed psychological sequelae including agitation, apathy, mania, and psychosis.

39.2.6 Depression

Depressive symptoms frequently occur following TBI, and estimates of prevalence extend to greater than 50% in some studies [25]. The lifetime risk of developing depression after TBI is increased relative to the general population [26]. A 2007 study of professional athletes in the National Football League showed that those players who had had at least three concussions were three times as likely to develop depression [5]. However, depression is often poorly conceptualized following TBI and as such is likely underrecognized and undertreated in acute care and rehabilitation models [27]. There are likely multiple etiologic pathways that converge to a common clinical presentation of disturbed mood with a myriad of features [12].

Due to the frequency and potential consequences if left untreated, it is important to assess for underlying mood disorders in this population. Importantly, mood disturbances following TBI may not necessarily meet traditional psychiatric criteria for major depressive disorder. The presentation may be more consistent with a dysregulated mood (i.e., showing features of several types of mood disorders) rather than fitting neatly into any one diagnostic category. Mood symptoms may be subtle and may manifest as primary behavioral changes including irritability, uncooperativeness, apathy, or failure to thrive. For example, the presence of aggression

TABLE 39.1

Most Prevalent Comorbid and Co-occurring Neurobehavioral Outcomes Following TBI

Complications	Incidence (%)	References	Comments
Cognitive impairment (mild TBI)	5–10	[17,42–44]	The incidences in moderate to severe TBI are too variable to document consistently given the measurement variability.
Depression	10–50	[5,12,25–27]	Rates depend on severity of injury, preinjury, psychiatric illness, mechanism of injury, number of lifetime injuries.
Agitation	25	[45]	The numbers are with reference to more severe injury and in the acute phase. Rates are unknown in chronic TBI and in mild TBI.
Apathy	60	[46]	These numbers include those patients with any depressive symptoms so should be considered with that as a reference.
Mania	5–9	[47,48]	This is heavily biased by characterization in severe TBI.
Psychosis	7–10	[49]	This is heavily biased by characterization in severe TBI. Rates are not published in mild to moderate TBI.
PTSD	11–18	[29,31,50,51]	Based upon combat veterans who presented to the ED and civilian motor vehicle accident patient studies.

has been consistently correlated with depression in TBI. Emphasized previously, TBI commonly results in disturbances in mood and in changes in cognition and behavior. Additionally, other issues, such as chronic pain (e.g., headaches), which are relatively common in TBI, can play a significant interactive role in the extent of neurobehavioral symptoms. As such, these other factors must also be characterized and addressed. The presence of depression also appears to have a negative effect upon both subjective and objective cognitive deficits following TBI. Severity of depression symptoms have been shown to exacerbate problems with cognition [27,28]. Other studies have noted similar effects of depression following TBI in areas of working memory, verbal memory, processing speed, and executive function [28]. Not surprisingly, depression has also been associated with decreased social function at both 6 and 12 months following injury [27]. These findings are consistent with current knowledge of cognitive effects associated with major depressive disorder [27]. Neuroanatomic studies have identified a relationship between depression in TBI with reduced prefrontal gray matter volumes [29,30]. Although not causal, this finding does strengthen the link between the neurological consequence of injury and resultant depression.

Additional risk factors for poor outcomes for untreated depression in TBI include impaired cognitive functioning, exacerbation of existing neurological deficits, and diminished motivation which can affect recovery and rehabilitation. Additionally, as with other types of trauma, premorbid depression and other psychiatric illness apparently increase postinjury risk for mood and anxiety disorders.

In terms of treatment and management, there are some limited studies that demonstrate a better response post-TBI to serotonergic agents. There are no studies of significant enough scale to assess the effects of other agents [31]. Also worth discussion but not otherwise well studied is how depression in the TBI patient affects family support and community reintegration both of which are critical for functioning post-TBI.

39.2.7 Anxiety Disorders: Posttraumatic Stress Disorder

Anxiety disorders in TBI are the most prevalent and have a significant impact on function. Many kinds of anxiety disorders have been reported after TBI, such as generalized anxiety disorder, panic disorder, phobic disorders, PTSD, and obsessive–compulsive disorder. Patients with TBI often experience anxiety associated with persistent worry, tension, and fearfulness [32]. Increased activity of the aminergic system and decreased activity of the γ-amino butyric acid (GABA) inhibitory network are the proposed mechanisms for the clinical manifestation of anxiety. Right-hemispheric lesions are more often associated with anxiety disorder than are left-hemispheric lesions [33]. Treatment includes antidepressants such as SSRIs, opioid antagonists (such as naltrexone), and buspirone. Benzodiazepines and antipsychotic agents should be avoided because they can cause memory impairment, disinhibition, and delayed neuronal recovery [34]. Behavioral therapy and psychotherapy are also important in the treatment of anxiety.

39.3 Posttraumatic Stress Disorder

39.3.1 Prevalence

With the current conflicts in Iraq and Afghanistan, additional attention has been focused on comorbid TBI and PTSD. However, the co-occurrence of TBI and PTSD is not novel nor it is isolated to injuries and exposure in combat. As one might expect, PTSD is more common in certain high-risk populations including combat Veterans. Rates of PTSD in Operation Iraqi Freedom/Operation Enduring Freedom veterans vary from study to study but are generally reported to range from 8% to 16%. Approximately, 15% of veterans presenting to VA hospitals meet diagnostic criteria for PTSD [35]. Independent of TBI, more than half of the adults in the United States have undergone experiences that would be "potentially traumatic events." These are events that would meet the first criteria required for diagnosis of PTSD according to the Diagnostic and Statistics Manual of the American Psychiatric Association, namely, experiencing or witnessing an event "that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others." From this estimated 50% (based upon this one study), 8% are reported to actually meet diagnostic criteria. This means that those 8% not only experienced a "potentially traumatic event" but also had a response that "involved intense fear, helplessness, or horror" [36]. Factors that lead to risk (development of PTSD) or resilience (those who are exposed but do not meet PTSD) caseness is outside the realm of this chapter. However, the current suggestion offered by some in explaining the increased incidence in veterans is that TBI may increase the risk of progression to PTSD similar to the risk for depression secondary to TBI. In civilians, with comorbid PTSD and TBI secondary to motor vehicle accidents the rates appear in the 10%–38% range [37]. As a comparison, the rates of PTSD in combat veterans with TBI are reported at 11%–44% [38]. It is, however, critical to understand that such rates in combat samples are highly variable and likely do not represent the true base rates due to significant issues with screening, reporting, and follow-up.

PTSD requires three main components including reexperiencing the trauma, avoidance and emotional numbing, and symptoms of heightened arousal. Of relevance herein is the need to address and treat PTSD as quickly as possible in the TBI population. Once PTSD becomes chronic, it is much more treatment resistant.

Part of the challenge in understanding true base rates is that, behaviorally, symptoms between PTSD and postconcussive syndrome overlap to include anxiety, insomnia, irritability, trouble concentrating, fatigue, hyperarousal, and avoidance. But there are clear symptoms that do not overlap and include the key feature of reexperiencing the traumatic event, shame, and guilt in the case of PTSD and posttraumatic headache, sensitivity to light and sound, and objective memory impairments in TBI. Many of the neuropsychological deficits are common among the two making the need to have clear, quantitative studies of neuropathology more important. On the surface, one would hypothesize that PTSD would not alter the cerebral and brain stem white matter microstructure in the same way as TBI. In fact, although TBI has a clear cause in physical trauma resulting in shear and strain injury, PTSD also has a cerebral pathophysiology that is known to affect the cerebral white matter microstructure and as such must be considered. Traditionally, PTSD and anxiety disorders are known to affect temporal lobe structures including the hippocampus, parahippocampal gyri, and amygdala and even alter blood flow to these same regions [39].

Although the gold standard is still the structured interview, the validation and widespread use of screening measures and checklists have increased for both civilian and military populations. Still lacking in terms of brief screening measures are appropriate validated tools for pediatric and adolescent patients.

39.3.2 Risk Factors for Posttraumatic Stress Disorder

Although there appears to be uncertainty with regard to genetic risk factors for PTSD, there are behavioral and experiential risk factors that seem fairly stable. First, severity of traumatic exposure (with greater severity or risk to self, increasing the exposure) increases risk for progression to PTSD caseness [40]. Second, history of sexual assault appears to increase risk for PTSD later in life. This is a topic that requires consideration given the increased role of women in combat and rates of sexual assault in the military [40]. Third, combat exposure including number of deployments is associated with increased lifetime risk. However, it is also important to understand that the latter observation likely reflects all at-risk population to include first responders.

Importantly, with the exception of history of sexual assault, all other risk factors for PTSD are also associated with risk of TBI. Regardless, there is very little published on early intervention and almost no literature on how to reduce risk for development of PTSD in a TBI population.

39.3.3 Therapeutic Approaches to Posttraumatic Stress Disorder

Recently, substantial advances have been made in the understanding of how to treat PTSD optimally. These advances form the basis of the first comprehensive and authoritative set of recently published treatment

guidelines for the disorder [41]. Interventions may be psychotherapeutic or pharmacological. Among the available psychotherapies, cognitive-behavioral therapy (CBT) has the best-established effectiveness. One effective form of CBT, prolonged exposure, includes sessions during which the memory of the traumatic experience is recounted in the first person, in as much detail as possible, over multiple sessions. Related strategies can incorporate cognitive restructuring and anxiety-management techniques. When successful, these approaches facilitate "emotional processing," which allows the person to habituate to the fear-inducing aspect of a trauma memory and to develop a more adaptive set of associations and beliefs.

Medications are also established therapeutic options for PTSD. Sertraline, an antidepressant medication from the SSRI class, is the first and so far the only medication to be specifically approved for the indication of PTSD by labeling from the Food and Drug Administration. Sertraline and other SSRIs have been well studied for the treatment of PTSD in randomized, controlled clinical trials, in which most but not all of the results have supported effectiveness. Other psychotropic medications, although less established, are often used to treat PTSD because of intolerance, partial response, or lack of response to SSRIs, or because of the need to target various comorbid conditions. Categories of agents include other types of antidepressants, mood stabilizers, noradrenergic blocking agents, and novel types of antipsychotic medications. However, the clinician must also consider that in a comorbid population such as TBI and PTSD one should consider the effects of all medications on recovery from TBI. For example, given the high rates of chronic pain and sleep disturbance one would expect a number of medications that can affect functional recovery.

39.3.4 Considerations for Care

Synthesis of the information given earlier presents dilemmas in conceptualizing optimal care systems with respect to managing PTSD issues in the setting of acute trauma care. PTSD will develop in a substantial minority of severely injured patients and in significant numbers of high-risk patients with milder injury. When PTSD develops and persists, it compromises functional recovery and quality of life and becomes increasingly difficult to treat over time. Thus, the acute trauma setting would seem to present an important opportunity for preventive intervention. As discussed, there are limitations to the current state of knowledge with regard to early identification of cases at risk and effectiveness of early interventions. These limitations being acknowledged, we do know enough to make some sensible recommendations that can be refined as the field progresses.

Providers in acute trauma settings should have a general awareness of issues related to PTSD so that they can optimally assess and manage risks for complications of injury. Although there is not sufficient information to predict later PTSD in the chronic stage based upon acute data, it is important for continuity of care for providers at all stages to understand the significant risk of behavioral sequelae and engage in patient education when appropriate. However, the burden of identification of co-occurring behavioral conditions in TBI falls on providers in the subacute and chronic stage for virtually all cases given the strong association between TBI and mood and anxiety disorders. Knowledge of the behavioral overlap between persisting postconcussive symptoms and these disorders will be helpful in triaging care to optimize function. Untreated mood and anxiety disorders can affect recovery and function in significant ways as described earlier. Additionally, and especially in the chronic setting, the clinical must also consider other common comorbidities that may affect function in a TBI population that extend beyond the behavioral sequelae identified earlier that may complicate recovery from injury and treatment of the injury and psychological comorbidities. These are now believed to include significant sleep disorders, chronic pain, growth hormone deficiency, and hypopituitarism.

References

1. Thurman, D. et al., Traumatic brain injury in the United States: A public health perspective. *J Head Trauma Rehabil*, 1999, 14(6): 602–615.
2. Teasdale, G. and B. Jennett, Assessment of coma and impaired consciousness. *Lancet*, 1974, 2: 81–84.
3. Marshall, L. et al., The diagnosis of head injury requires a classification based on computed axial tomography. *J Neurotrauma*, 1991, 9(Suppl 1): S287–S292.
4. Jennett, B. and M.J. Bond, Assessment of outcome after severe brain damage: A practical scale. *Lancet*, 1975, 1: 480–484.
5. Guskiewicz, K. et al., Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*, 2007, 39(6): 903–909.
6. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: Emergency department visits, hospitalizations, and deaths. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010.
7. Brain Trauma Foundation, A.A.o.N.S., Joint Section on Neurotrauma and Critical Care, Guidelines for the management of severe head injury. *J Neurotrauma*, 1996, 13: 641–734.
8. Russell, W., Cerebral involvement in head injury. *Brain*, 1932, 35: 549–603.

9. Buchwald, J., Comparison of plasticity in sensory and cognitive processing systems. *Clin Perinatol*, 1990, 17: 57–66.
10. Dennis, M. and M. Barnes, Developmental aspects of neuropsychology: Childhood. *Handbook of Perception and Cognition*, D. Zaidel, ed. New York: Academic Press, 1994.
11. Gennarelli, T.A., The pathobiology of traumatic brain injury. *Neuroscientist*, 1997, 3(1): 73–81.
12. McAllister, T.W., Neuropsychiatric sequelae of head injuries. *Psychiatr Clin North Am*, 1992, 15(2): 395–413.
13. Gennarelli, T.A., L.E. Thibault, and D.I. Graham, Diffuse axonal injury: An important form of traumatic brain damage. *Neuroscientist*, 1998, 4(3): 202–215.
14. Moore, E. et al., Blast physics and central nervous system injury. *Future Neurol*, 2008, 3(3): 1–8.
15. Auerbach, S., The pathophysiology of traumatic brain injury. In *Physical Medicine and Rehabilitation: State of the Art Review, Traumatic Brain Injury*, L. Horn and D. Cope, eds. Philadelphia, PA: Hanley & Belfus, 1989, pp. 1–11.
16. McKee, A. et al., Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repeated head injury. *J Neuropathol Exp Neurol*, 2009, 68(7): 709–735.

    This article discusses the cause and findings of CTE in athletes. Also the concern about repeated concussions over many years to cause CTE.
17. Levin, H. et al., Neurobehavioral outcome following minor head injury: A three center study. *J Neurosurg*, 1987, 66: 234–243.
18. Neisser, U., *Cognitive Psychology*. New York: Appleton-Century-Crofts, 1967.
19. Levin, H.S. and M.F. Kraus, The frontal lobes and traumatic brain injury. *J Neuropsychiatry Clin Neurosci*, 1994, 6(4): 443–454.

    This group of researchers has been involved in neurotrauma research for many years. This discussion of frontal lobe injuries discusses the neuropathology and sequelae.
20. Hagen, C., *Language Disorders in Head Trauma*. San Diego, CA: College Hill Press, 1983.
21. Levin, H., V. O'Donnell, and R. Grossman, The Galveston Orientation and Amnesia Test: A practical scale to assess cognition after head injury. *J Nerv Ment Dis*, 1979, 167: 675–684.
22. Malkmus, D., B. Booth, and C. Kodimer, Rehabilitation of the head-injured adult: Comprehensive cognitive management, 1980, Professional Staff Association of Ranch Los Amigos Hospital, Downey, CA.
23. Wilson, B., Cognitive rehabilitation: How it is and how it might be. *J Int Neuropsychol Soc*, 1997, 3: 487–496.
24. Taverni, J., G. Seliger, and S. Lichtman, Donepezil-mediated memory improvement in traumatic brain injury during post-acute rehabilitation. *Brain Inj*, 1998, 12: 77–80.
25. Dikmen, S.S. et al., Natural history of depression in traumatic brain injury. *Arch Phys Med Rehabil*, 2004, 85(9): 1457–1464.
26. Holsinger, T. et al., Head injury in early adulthood and the lifetime risk of depression. *Arch Gen Psychiatry*, 2002, 59(1): 17–22.
27. National Institute of Medicine, The numbers count: Mental disorders in America: A summary of statistics describing the prevalence of mental disorders in America, 2001.
28. Chamelian, L. and A. Feinstein, The effect of major depression on subjective and objective cognitive deficits in mild to moderate traumatic brain injury. *J Neuropsychiatry Clin Neurosci*, 2006, 18(1): 33–38.
29. Jorge, R.E. et al., Major depression following traumatic brain injury. *Arch Gen Psychiatry*, 2004, 61(1): 42–50.
30. Levin, H.S. et al., Predicting depression following mild traumatic brain injury. *Arch Gen Psychiatry*, 2005, 62(5): 523–528.
31. Fedoroff, J.P. et al., Depression in patients with acute traumatic brain injury. *Am J Psychiatry*, 1992, 149: 918–923.
32. Lewis, L. and S. Rosenberg, Psychoanalytic psychotherapy with brain-injured adult psychiatric patients. *J Nerv Ment Dis*, 1990, 178: 69–77.
33. Paul, S., Anxiety and depression: A common neurobiological substrate? *J Clin Psychiatry*, 1988, 49(Suppl): 13–16.
34. Preston, G.C. et al., Effects of lorazepam on memory attention and sedation in man: Antagonism by Ro 15-1788. *Psychopharmacology (Berl)*, 1989, 91: 222–227.
35. Stein, M. and T.W. McAllister, Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *Am J Psychiatry*, 2009, 166(7): 768–776.

    This article discusses two very important issues: PTSD and mild traumatic brain injury. The paper brings out the way the two are related and assessed.
36. Kessler, R.C. et al., Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*, 1995, 52: 1048–1060.
37. Ursano, R., C. Fullerton, and R. Epstein, Acute and chronic posttraumatic stress disorder in motor vehicle accident victims. *Am J Psychiatry*, 1999, 156(4): 589–595.
38. Schneiderman, A., E. Braver, and H. Kang, Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: Persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol*, 2008, 167: 1446–1452.
39. Lee, Y. et al., Decreased blood flow of temporal regions of the brain in subjects with panic disorder. *J Psychiatric Res*, 2006, 40: 528–534.
40. Breslau, N. et al., Trauma and posttraumatic stress disorder in the community: The 1996 Detroit Area Survey of Trauma. *Arch Gen Psychiatry*, 1998, 55(7): 626–632.
41. Friedman, M. et al., Pharmacotherapy. In *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies*, E.B. Foa, T.M. Keane, and M.J. Friedman, eds. New York: Guilford Press, 2000, pp. 245–268.

    The importance of this paper presented by a group of experts was developed in order to publish Practice Guideline for effective treatments of PTSD.
42. Capruso, D.X. and H.S. Levin, Cognitive impairment following closed head-injury. *Neurol Clin*, 1992, 10(4): 879–893.

43. Goldstein, F.C. et al., Neurobehavioral consequences of closed-head injury in older adults. *J Neurol Neurosurg Psychiatry*, 1994, 57(8): 961–966.

    This article is a good review of the many neurobehavioral deficits following a traumatic brain injury in adults. Discusses the kind of cognitive and behavioral issues that are typically seen in this patient population.
44. Levin, H.S., Neurobehavioral outcome of closed-head injury: Implications for clinical trials. *J Neurotrauma*, 1995, 12(4): 601–610.
45. Nott, M., C. Chapparo, and I. Baguley, Agitation following traumatic brain injury: An Australian sample. *Brain Inj*, 2006, 20(11): 1175–1182.
46. Kant, R., J. Duffy, and A. Pivovarnik, Prevalence of apathy following head injury. *Brain Inj*, 1998, 12: 87–92.
47. Jorge, R.E., R.G. Robinson, and S. Starkstein, Manic syndromes following traumatic brain injury. *Am J Psychiatry*, 1993, 150(6): 916–921.
48. Jorge, R.E. et al., Secondary mania following traumatic brain injury. *Am J Psychiatry*, 1993, 150(6): 916–921.
49. Davison, K. and C. Bagley, Schizophrenia-like psychosis associated with organic disorder of the CNS. *Br J Psychiatry*, 1969, 4: 113–184.
50. Jorge, R. and R.G. Robinson, Mood disorders following traumatic brain injury. *Int Rev Psychiatry*, 2003, 15(4): 317–327.
51. Jorge, R. et al., Comparison between acute- and delayed-onset depression following traumatic brain injury. *J Neuropsychiatry*, 1993, 5(1): 43–49.

Section IX

Burns and Wound Healing

40

Wound and Soft Tissue Complications: Complications of Wound Repair

Callie M. Thompson, Nicole S. Gibran, and F. Frank Isik

CONTENTS

> For truly, if a man had a dangerous wound, the longer he waited to cure himself the more would it fester and hasten him toward his death; and also the wound would be but the harder to heal.
>
> **Geoffrey Chaucer (*Canterbury Tales, The Parson's Tale*; ~1400)**

Wound repair is a common theme for all surgical subspecialties. The principles of wound closure and tissue handling that are practiced by a plastic surgeon should be no different from those practiced by a cardiac or minimally invasive surgeon. In spite of years of research in areas of both deficient wound repair in chronic nonhealing wounds and excessive fibroproliferation in hypertrophic scars and keloids, we still know very little about the cellular and molecular processes required for normal wound repair and have not yet succeeded in controlling responses to injury. As surgeons, we must use clinical judgment and good technique to optimize our patients' results. This chapter presents a brief outline of what is known about concepts related to normal wound healing and addresses a few of the complications and failures associated with the repair processes.

40.1 Continuum of Normal Wound Repair Processes

Tissue repair begins immediately after injury. The immediate hemostatic response involves microvasculature constriction coupled with coagulation. Extrinsic and intrinsic coagulation pathways combine with platelet accumulation to complete hemostasis and to provide the provisional matrix scaffolding for cellular migration.

The coagulation cascade, initiated by tissue factors, culminates in thrombin-mediated cleavage of fibrinogen to fibrin, which forms the structure for a clot. Factor XIII, the enzyme known to cross-link fibrin and other matrix molecules, stabilizes this provisional wound matrix [1,2]. The activated enzymes of the plasminogen system, secreted by inflammatory and resident cells in the wound, cleave plasminogen to plasmin. Plasminogen activator inhibitors regulate the plasminogen system and assure that the clot is not resolved too rapidly. Exogenous plasminogen activator may promote the conversion of the zone of stasis in an acute burn wound to a zone of hyperemia [3].

Vasodilation and capillary leak with neutrophil infiltration into the tissue follow the transient vascular constriction. Neuropeptides derived from sensory nerves contribute to microvascular dilatation and capillary leak. Neuropeptides indirectly induce mast cell degranulation of histamine [4], induction of cytokines and adhesion molecules by keratinocytes and endothelial cells, chemotaxis of neutrophils, and proliferation of fibroblasts [5]. Serotonin, histamine, bradykinin, and the arachidonic acid–pathway products (prostacyclin and leukotrienes) prolong vasodilation and capillary permeability [6].

Endogenous cells are important contributors to cutaneous inflammation. "Skin-associated lymphoid tissue" includes bone marrow–derived cells, such as Langerhans cells, dermal dendrocytes, keratinocytes, and microvascular endothelial cells [7]. Keratinocytes, the major cells comprising the epidermis, synthesize cytokines, including interleukin-1, interleukin-8, interleukin-6, monocyte chemoattractant protein-1, and tumor necrosis factor (TNF). Dermal microvascular endothelial cells not only synthesize interleukin-6 and monocyte chemoattractant protein-1 but also regulate neutrophil migration by increasing the production of cell surface adhesion molecules ICAM-1, VCAM, and E-selectin. These adhesion molecules bind to circulating neutrophils and facilitate neutrophil margination into the wound.

Prior to margination into the extravascular space, neutrophils plug the capillaries, thereby increasing inflammation and potential tissue ischemia. In burn wounds, neutrophil-mediated reperfusion injury may cause the zone of stasis to convert to a zone of coagulation, which will not heal.

The interaction of inflammatory mediators after tissue injury is at best complicated. The arachidonic acid pathway, the kinin system, the complement system, and oxidative processes potentiate microvascular permeability, activate neutrophils, and contribute to matrix degradation. Oxidative byproducts and TNF contribute to the antimicrobial activity at wound sites. Whereas attempts to modulate these pathways in *in vitro* studies and animal studies have been promising, disappointing results of clinical trials attest to the complexity and probable redundancy in the inflammatory web.

A growing body of evidence suggests the therapeutic potential of multipotent mesenchymal stem/stromal cells (MSCs) in the treatment of acute and chronic wounds [8]. These cells are typically defined as plastic-adherent cells of fibroblast-like morphology with the capacity for multipotent differentiation *in vitro*. Whereas their contribution to tissue repair by both differentiation and paracrine signaling is possible, the latter is thought to be the predominant mechanism as MSCs have low engraftment efficiency, and MSC-conditioned medium has similar effects on wound repair as MSCs.

Angiogenesis is widely thought to be mandatory for normal wound repair. Granulation tissue provides clinical evidence that a wound is healthy and is ready for closure. However, no study has demonstrated that angiogenesis is necessary; two reports suggest that angioinhibition does not prevent excisional wound closure [9,10]. Conversely, increasing angiogenesis has been shown to decrease healing times as well as decrease wound size in a murine model [11]. Grafts and tissue flaps require angiogenesis for engraftment. The delivery of oxygen and nutrients to the wound occurs for a few days by imbibition—or diffusion; however, graft take requires neovascularization, which occurs by connection between existent capillaries in the graft and in the wound bed—a process known as inosculation. Soluble growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF)-BB, and transforming growth factor (TGF)-α, induce endothelial cell proliferation and migration. Growth factor receptors are tightly regulated and may be influenced by endothelial cell interactions with extracellular matrix molecules.

Wound closure is defined as complete restoration of the epithelial layer. Epithelialization restores the protective barrier with fluid maintenance, temperature regulation, and prevention of microbial invasion. It probably represents a transition in the inflammatory state of the wound. Many studies have demonstrated that epidermal–dermal interactions regulate morphogenetic processes such as fetal skin development and wound repair [12,13]. The epidermis responds to mesenchyme-derived mediators [14], and migrating keratinocytes in the advancing epidermal tongue appear to promote dermal inflammation by secreting cytokines and growth factors. Evidence for an epidermal influence on the inflammatory response includes not only experimental data about keratinocyte biology in culture and in wound models [15] but also clinical observations that partial-thickness wound coverage with a viable biological dressing, such as allograft, eliminates granulation tissue formation and promotes healing [16].

Clinicians know that full-thickness wounds heal from the edges and that partial thickness wounds heal from the remnants of epidermal appendages in the wound bed. The advancing epithelial tongue migrates for approximately 1 cm before it stops migrating and heaps up at the edge of the wound. Keratinocyte migration is dependent on the underlying matrix, which may promote cell migration or anchorage. Compton et al. have determined that cultured epithelial grafts display poorly formed anchoring fibers comprising immature collagen VII fibrils for approximately 12 months after grafting [17], which correlated with the time that the patient stopped blistering. Therefore, manipulation of the underlying matrix or keratinocyte receptors may constitute a treatment approach to a long-term rehabilitative problem.

The application of exogenous PDGF, FGF, and TGF-α increases epithelialization in diabetic mice with abnormal healing responses. However, the administration of exogenous growth factors to chronic wounds in human clinical trials has had limited success [18]. Studies about the temporal and spatial relationships of growth factors and growth factor receptors in normal and impaired wounds are essential before we can ethically treat human burns with costly recombinant growth factors.

Whereas an epithelialized wound is considered to be "healed," fibrogenesis, critical for long-term wound appearance and strength, continues for much longer. From the time of the initial injury, the dermal mesenchyme undergoes constant change. Remodeling occurs as a continuum in healing wounds—beginning with dissolution of the fibrin clot and ending with the mature wound, 12–24 months later. The provisional matrix molecules fibrin, thrombin, fibronectin, and vitronectin promote cellular migration and proliferation for angiogenesis and fibrogenesis in the early wound. As fibroblasts migrate into the wound from the margins, they synthesize collagen. The deposition of collagen III and subsequently collagen I results in a basket-weave distribution that typifies dermal scar [19]. As the wound matures, collagen I fibrils are cross-linked into cables, thereby increasing the dermal breaking strength. Regardless, the tensile strength of a wound never meets that of uninjured skin.

Centrifugal forces in the center of the wound cause wound contraction, which significantly contributes to wound closure. Myofibroblasts—highly differentiated fibroblasts characterized by intracellular smooth muscle actin filaments—are involved in the contractile mechanism [20]. The extreme of wound contraction is contracture—an abnormal scarring process that negatively impacts joint motion. Even with constant attention to stretching, exercising, and splinting diminishes contracture development, surgical release to restore normal function may be necessary.

With scar maturation, the epidermis also continues to undergo changes. Melanocytes migrate from the wound edge and from the epidermal appendages soon after the keratinocytes. Repigmentation can be unpredictable and may result in either increased or decreased melanin in partial-thickness wounds. Clinicians must advise patients that exposure to ultraviolet rays may exacerbate pigmentation changes in the wound and that topical bleaching agents may cause chemical burns to the recently injured skin.

Patients with healing partial-thickness wounds complain of pruritus even 5 and 10 years after injury [21]. Hypertrophic scars, which are classically very pruritic, have increased numbers of sensory nerves compared to normal scars and uninjured skin as well as higher levels of substance P, a neuropeptide that stimulates histamine release by mast cells [22].

40.2 Types of Wounds

Incisional wounds or lacerations involve linear separation of the epidermis, the dermis, and sometimes the subcutaneous tissue. Primary closure of these wounds can generally be performed surgically. In the event of a traumatic stellate laceration, the wound edges may need to be trimmed; the wound should then be closely inspected for foreign bodies and irrigated liberally.

Partial-thickness wounds involve removal of the epithelium and the superficial dermis (papillary dermis). Most of the dermis and the epithelial appendages remain in the wound bed. Wound closure occurs by epithelial proliferation and migration from the hair follicles and sweat glands. Examples of partial-thickness wounds are scald burns and donor sites for split-thickness skin grafts.

Full-thickness wounds involve the destruction of all layers of the skin. These wounds close by contraction and by epithelial proliferation and migration from the wound edge. An advancing epithelial tongue generally can migrate 1 cm; thus, a quarter-sized wound is roughly the largest wound that can heal by epithelialization alone. Examples of full-thickness wounds include avulsion injuries, necrotizing soft tissue skin infections, and electrical injuries.

Chronic nonhealing wounds are those that do not heal within 3 months after injury. They usually involve impairment in epithelial migration coupled with poor dermal regeneration. Epithelial cell proliferation appears to be adequate in many chronic wounds because the epithelial tongue at the wound edge heaps up with a raised rim of epithelium. Furthermore, pro-inflammatory cytokines are highly upregulated in chronic wounds, leading to a constant state of inflammation. Whereas no single cause of the impaired healing response has been identified, infection, impaired vascular supply, and inadequate oxygen delivery have been implicated.

Additionally, bacterial biofilms may represent a source for persistent inflammation in chronic wounds. Potential mechanisms include a biofilm generating excessive amounts of receptor substrate, thereby overwhelming the receptor and leading to increased expression of the pro-inflammatory cytokines as well as upregulation of protease activity leading to tissue destruction [23].

40.3 Wound Closure and Coverage

Whether a wound can be closed by suturing or requires alternative wound coverage depends on the type of wound, the level of contamination, and the size of the wound.

Primary wound closure involves surgical wound closure with direct approximation of the wound edges using sutures, staples, glue, or tape soon after the wound has been created. Wounds amenable to primary closure

include most surgical incisions and fresh lacerations. Lacerations on the face can be safely closed primarily within 6 h after injury. Lacerations in other anatomic sites with less vascular supply should be closed sooner.

Delayed primary wound closure involves surgical closure of a wound 1–5 days after injury. Indications for delayed primary closure include grossly contaminated surgical wounds (abdominal wounds with intraoperative fecal spillage) and lacerations contaminated with foreign matter or bacteria. The closure of human bite wounds should be delayed unless the wounds are on the face. Wound Vac® therapy is frequently used in the treatment of wounds without a definitive reason for its effectiveness. The question of cost benefit is still unclear in spite of reduced nursing care and likely increased patent comfort related to decreased frequency of dressing changes. A recent Cochrane review found no evidence as to the effectiveness of negative-pressure therapy on wound closure for wounds that would otherwise be expected to heal by primary intention. They also noted, as a point of caution, the high incidence of fracture blisters when negative-pressure therapy was used following orthopedic surgery [24]. This negative-pressure system promotes cellular ingrowth into the deeper wound and reduces tissue edema. It has also been shown to increase expression of VEGF and FGF-2 in a murine model. The sponge attached to a vacuum pump can be applied to a granulating deep wound to promote closure of dead spaces; it can also be applied directly to a skin graft to increase graft adherence to the wound bed [25].

Closure by secondary intention involves spontaneous healing of the wound without surgical closure. Generally, the wound granulates and contracts with limited epithelialization; a skin graft is often required. Infected abdominal wounds with dehiscence of the rectus abdominus fascia and evisceration of the bowel benefit from closure of the fascia with secondary skin closure, often involving skin grafting secondary skin closure often involving skin grafting.

40.4 Surgical Technical Principles

Incision orientation should follow the natural skin creases to minimize tension on the scar. Incisions along tension lines subsequently minimize contracture and are hidden in the natural body contours. This concept also applies to skin graft placement. The outcome of grafts can be superior when the junctures are placed parallel to the skin lines rather than at angles to the lines; placement at angles accentuates the appearance of an abnormal surface marking. Incisions on the extremities should zigzag across a joint to break up a linear scar and avoid joint contracture.

Hemostasis must be meticulous to prevent the development of hematomas, which increase the likelihood of healing complications by increasing the risk of infection and causing a fibroplastic reaction. Hematomas prevent vascularization of flaps or skin by mechanically separating the wound bed from the graft.

Biological dressings and skin substitutes are important means of closing wounds that will not epithelialize. Different types of permanent or temporary dressings exist; several are discussed later.

Autograft, a sheet of the patient's own skin, is the gold standard for coverage of a nonhealing wound. For burns, early excision and autografting of deep dermal or full-thickness burns decrease hospital length of stay and time away from work or school; this procedure also reduces scarring [26]. Thicker grafts contract less and are more durable than thinner grafts but do not "take" as well. The optimal thickness of the graft and the need for meshing to expand the size of the graft depend on the site of the wound. Whereas thicker grafts may be ideal, they are not always practical because of lack of donor sites or donor site complications. Planning a surgical approach to wound coverage must include deciding when covering the wound is important enough to risk donor site complications. Like other wounds, deep donor sites result in deep dermal injury, which can lead to scarring complications. Wounds on the palm are ideally treated with full-thickness grafts. Likewise, wounds on the face or the dorsal side of the hands benefit from full- or partial-thickness sheet grafts. Sites that are cosmetically or functionally less important can be treated with thinner grafts.

Allograft or homograft is a graft from one person to another. This "cadaver skin" is harvested just as are other tissues from organ donors. In general, allograft is available as frozen sheet grafts. Because the sheets have been frozen, cellular viability is limited [27]. The tissue is viable enough to engraft, but the keratinocytes do not proliferate or migrate across a wound bed. Because the grafts do "take," they undergo rejection, which leads to a substantial inflammatory response. Indications for the use of allograft include temporary wound coverage until a donor site can be found and testing a wound bed to determine whether an autograft would engraft.

Xenograft is harvested from a different species. In the United States, the most commonly used xenograft is pigskin, which is available as frozen sheet grafts. Xenograft adheres to the wound but does not engraft. Xenograft can be successfully used to test wound bed viability and as an overlay over widely meshed autograft. Xenograft also provides an excellent biological coverage for uniformly shallow wounds in patients with toxic epidermolysis necrosis; as the wound epithelializes, the xenograft lifts off the surface of the wound.

Integra® is a commercially available dermal substitute with a temporary outer silastic layer that "closes" the wound while autologous fibroblasts migrate into the matrix formed by synthetic collagen I and chondroitin-6-sulfate. Once the dermal layer has vascularized, the silastic layer can be removed and an ultrathin autograft can be applied. The advantages of Integra are the creation of a pliable neodermis and the use of thinner grafts; these thinner grafts result in shallower donor sites that heal quickly and scar less [28]. Use of Integra compared to cadaveric dermal substitutes in pediatric burn patients has been shown to attenuate the hypermetabolic state seen postinjury and result in aesthetically improved scars at 12 and 24 months postinjury [29]. Integra requires fastidious surgical excision and perioperative wound care. As familiarity with the product has grown, the use for scar revisions and reconstruction has expanded.

AlloDerm® (BMI, FL) is a commercially available dermal substitute derived from allografts that have been processed to remove the epidermis at the basement membrane and to remove all dermal cells to prevent rejection and graft failure. Because this material is composed of uninjured human dermis, it is conceptually attractive. The use of AlloDerm requires simultaneous application of a thin skin graft or cultured epithelial cells. AlloDerm is commonly used in postmastectomy breast reconstruction and complex abdominal wall reconstruction.

Apligraf® (Organogenesis, Inc., Canton, MA) is a construct of collagen I with allogeneic human neonatal foreskin keratinocytes and fibroblasts. The fibroblasts are interspersed into prealigned collagen fibrils to create a dermis-like synthetic layer. Keratinocytes are seeded on the surface of the graft to create a multilayered skin substitute. Apligraf has been primarily marketed and successfully used for the treatment of nonhealing venous stasis and diabetic ulcers.

Tissue transfer of vascularized tissue may be necessary to cover deep tissue defects that will not take a skin graft because of exposed, poorly vascularized vital structures—such as nerves, tendons, vessels, or bones—and that are not amenable to other closure techniques. The ability to transfer complex and vascularized tissues, whether skin, fat, fascia, muscle, or bone, singly or in various combinations, allows for optimal tissue restoration. The size and location of the defect dictate the source of the tissue, which should have form and function similar to those of the missing tissue. When the donor tissue is available adjacent to the wound, advancement or rotation flaps provide a reliable method of closing both the defect and the donor site. When local tissue availability is limited, as in the head and neck, or when the defect is large, as with the extirpation of large recurrent cancers, distant tissues must be used. In the past two decades, numerous free flaps containing combinations of skin, fascia, fat, muscle, and bone have been created; the territories of these flaps can be completely perfused by a single artery and vein. The transfer is accomplished by microsurgical anastomosis of pedicle arteries and veins that may be 1–2 mm in diameter. The use of local and distant free flaps has favorably affected the treatment of patients with chronic wounds and has facilitated reconstruction after trauma and extirpative surgery.

40.5 Risk Factors for Abnormal Wound Repair

Every medical student learns the acronym "FRIEND" with regard to nonclosing fistulas. The words whose initial letters comprise this term also apply in some respects to wound complications: foreign body, radiation, inflammation, epithelialization, neoplasia, and distal obstruction (although for cutaneous wounds, "diabetes mellitus" might be a more appropriate term).

Foreign bodies, whether small (glass fragments) or large (sutures and drains), disrupt wound closure (Figure 40.1a). Removal of large foreign bodies (such as bullets) in the deep tissue may be contraindicated if the dissection would cause excessive injury to the tissues. On the other hand, aggressive efforts should be made to remove superficial dirt or tar from skin abrasions because these foreign bodies can cause infections or permanent pigmented tattoos in the healed wounds.

Radiation kills the rapidly proliferating cells that repopulate the wound bed; killing these cells leads to an impaired response to injury. Decreased angiogenesis results in tissue ischemia, and reduced keratinocyte proliferation and migration lead to inadequate epithelialization. Dense collagen production, combined with decreased cellular proliferation, results in a hard yet fragile wound that is easily disrupted. Incisional wound strength is markedly diminished, and secondary closure of an open wound may be delayed or may lead to a chronic wound. Patients with rectal cancers that have been treated with preoperative radiation followed by abdominoperineal resection are at a particularly high risk of chronic draining perineal wounds. A study by Chessin and colleagues showed benefit from tissue transfer of viable rectus abdominus muscle flaps into the wound bed [30].

Infection complicates healing of preexisting wounds such as burn wounds or donor sites or can be the direct cause of wounds such as carbuncles and hidradenitis. Bacteria colonize the skin under normal conditions. To guide clinical management, surgeons have traditionally classified wounds as clean (surgical incisions and simple

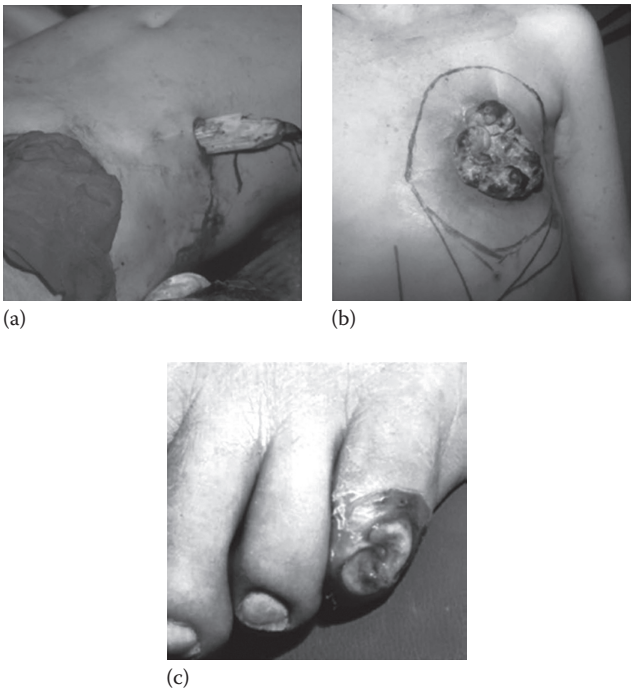


FIGURE 40.1
Risk factors for wound complications: (a) Foreign bodies protruding through the skin not only prevent healing of the entrance site but also constitute a risk for infection. Intraoperative removal of foreign bodies should involve not only evaluation of the deep tissues but also aggressive irrigation and debridement of the wound track. This wound should not be closed primarily. (b) Neglected breast cancer may present as a fungating, open, draining wound. The debridement of a chronic wound should include pathologic evaluation of the tissue to rule out a neoplasm. (c) Diabetic ulcers have multifactorial causes, including microangiopathy and neuropathy. Twenty percent of patients with these chronic nonhealing wounds undergo amputation of the extremity.

lacerations), contaminated (bites, bowel injuries, and open fractures), or dirty (abscesses). Whereas quantitative bacterial counts less than 10^5 bacterial colonies per gram of tissue do not affect the response to acute injury, higher counts will invariably lead to wound breakdown [31]. Intra-abdominal infection is associated with fascial dehiscence, a disease process that increases both the morbidity and mortality of the original operation and results in an abdominal wall hernia. Osteomyelitis, or bony infection, following traumatic injury such as open fractures of the tibia or fibula causes substantial morbidity. After cardiac bypass surgery, sternal osteomyelitis can complicate surgical results when the left internal mammary artery is used to vascularize the heart. In 2%–4% of the population, this condition results in inadequate vascular supply to the remaining inferior sternum. Without bacterial seeding, the result is limited to sterile nonunion of the sternal wound. However, bacterial infection of the wound results in life-threatening mediastinitis, which requires immediate debridement of the devitalized sternum followed by coverage with healthy vascularized tissue.

Neoplasia should always be suspected when there is no known cause for chronic nonhealing wounds. The debridement of chronic wound should include pathologic evaluation to rule out neoplasm. Marjolin's ulcer in an old burn wound is the classic example of an aggressive squamous cell cancer in a nonhealing wound. Alternatively, neglected breast cancer or squamous cell cancer can result in fungating, open, draining wounds (Figure 40.1b).

Diabetes mellitus is an important risk factor for wound healing. Sensory neuropathy and microangiopathy increase the incidence of nonhealing wounds in the lower extremities (Figure 40.1c), and hyperglycemia also increases the risk of wound infection, which contributes to wound breakdown.

In addition to these commonly recognized causes of delayed healing, other important risk factors and comorbidities can affect the response to injury. Details about these factors should be collected during the initial history taking and physical examination.

Nutrition can often be overlooked because so many persons eat well-balanced diets. According to the Centers for Disease Control and Prevention, the incidence of rickets increased in the United States in 2001 because of vitamin D deficiency; therefore, we need to remain cognizant of our patients' nutritional status. Additionally, with our current obesity epidemic in the United States, clinicians must remember that obese patients frequently present with micronutrient deficiencies despite appearing well fed [32,33]. Essentially, all vitamins, minerals, and trace elements play an essential cellular or enzymatic role, crucial for normal wound healing. Vitamin C deficiency leads to dermal scar degeneration during the remodeling stage because prolyl hydroxylation, a necessary step in collagen synthesis, is dependent on vitamin C. Vitamin A is involved in collagen synthesis and is essential for keratinocyte differentiation. Vitamin E deficiency leads to immune dysfunction. Vitamin K deficiency should be suspected in patients with fat malabsorption because deficiency can lead to bleeding and wound hematomas. Zinc deficiency leads to delayed epithelialization, reduced tensile strength, and increased infection.

Vascularity is crucial insofar as oxygen delivery is necessary for normal wound healing. Revascularization can aid and abet the closure of wounds on ischemic limbs. Recent studies have observed normal wound closure in the face of angioinhibition [9,10]; thus, the ultimate role of wound microvascularity may require reevaluation. Increased vascularity in granulation tissue probably contributes to excessive scar formation. One caveat is that granulation tissue, a hallmark of a healing wound, is replete with bacterial contamination and inflammatory

proteases that can reduce graft take. Granulation tissue is also a precursor of hypertrophic scaring.

Genetic conditions are rare but should be considered when patients have fragile skin, poor wound strength, easy wound disruption, or spontaneous large-vessel nonatherosclerotic aneurysms. The most common genetic disturbances that alter dermal response to injury are the seven distinct variants of Ehlers–Danlos syndrome and Marfan's syndrome. Patients with Ehlers–Danlos syndrome have very thin skin with marked diminution of the dermis; extra caution must be taken with these patients to ensure careful tissue handling and wound closure. Proper testing should be undertaken if there is any clinical suspicion of a previously undiagnosed genetic connective tissue disorder. Blistering disorders such as epidermolysis bullosa may be more clinically obvious, and special attention should be paid to wound care.

Genetic variants have also been implicated as risk factors for the development of abnormal scar patterns and poor healing. Unlike the aforementioned syndromes, these DNA mutations, which are relatively common in the general population, have not been shown to be causative. Rather, they have been shown to be present in greater percentages among those patients with specific scarring or healing phenotypes. Examples include single nucleotide polymorphisms (SNPs) that have been associated with the development of keloids [34,35] as well as several SNPs that have been associated with increased risk of chronic venous leg ulcers [36]. Conversely, one study identified a variant associated with shorter healing time in venous ulcers following superficial venous surgery [37].

Advanced age has been found to be associated with impaired wound healing, specifically a delay in wound repair response [38]. Exercise has been found to improve wound healing in elderly mice and humans though the mechanism for this observation has not been elucidated [39]. Hormones have been implicated in the age-related delay in healing. Hardman and Ashcroft found that gene expression differences between wounds in elderly and young males were almost exclusively regulated by estrogen [40]. Both systemic and topical application of estrogen has been found to accelerate healing in both elderly men and women by reducing the inflammatory response [41,42]. Conversely, castration in wounded elderly mice accelerated healing as did androgen receptor blockade in elderly humans by directly inhibiting TNF-α expression by macrophages [43].

Pressure and other mechanical forces such as shear and friction frequently compromise skin integrity for patients with neuropathy, including diabetes mellitus, spinal cord injuries, and head injuries. Education to both patients and caregivers about the methods to avoid pressure ulcers, such as frequent repositioning, and the catastrophic consequences of lesions are essential preventative measures.

Pharmacologic agents are also notorious for altering the response to injury.

Corticosteroids inhibit the inflammatory response that is crucial for normal wound repair. Corticosteroids also repress the action of the enzyme prolyl hydroxylase; this repression leads to decreased collagen cross-linking and weaker incisional wounds. Corticosteroids have been found to decrease the levels of type III and type I tropocollagen as well as decrease the concentrations of collagenase [44].

Colchicine, a common anti-rheumatologic agent known for its anti-inflammatory effects, decreases wound contraction and wound strength. Clinical reports of delayed healing in patients treated with colchicine abound [45]. This agent has been touted as an effective treatment for keloids; a prospective randomized study of keloid treatments demonstrated that postoperative colchicine prevented recurrence in 32% of cases [46]. Recognized effects of this agent include inhibition of cell proliferation and migration, microtubule disruption, and altered collagen synthesis. At best, our knowledge about the effects of colchicine on collagen metabolism is muddy. Most findings support the idea that colchicine suppresses the production of type I collagen but stimulates the production of collagenase [47]. Conversely, colchicine has been found to decrease the production of macrophage-derived collagenase. The direct effects of colchicine on wound repair processes must be clarified.

Anticoagulants can often be associated with the formation of postoperative hematomas, a formidable and easily preventable complication. Patients taking therapeutic Coumadin® are especially at risk of perioperative bleeding because the effect of Coumadin is not quickly reversible. These patients should be switched to heparin therapy preoperatively to facilitate correction of the coagulation diathesis in the event of perioperative bleeding. Other agents that interfere with platelet adhesion include aspirin, nonsteroidal anti-inflammatory drugs, and the long-chain carbohydrates such as dextran, which are commonly used by microvascular surgeons for tissue transfers.

Naturopathic agents present an increasingly confounding variable in treating patients [48]. Whereas surgeons routinely obtain a list of the medications their patients are taking before surgery and instruct patients to hold medications that may interfere with hemostasis, nonprescription drugs may not be captured in the history. Knowing that a patient takes naturopathic medications such as *Gingko biloba* may be essential. *Gingko biloba* ranks as the fourth most commonly used herbal therapy in the United States [49]. This particular medication, which is used to treat a wide variety of symptoms including dementia, memory loss, headache, sexual dysfunction,

depression, and premenstrual syndrome, has been associated with spontaneous [49] and perioperative bleeding [50], possibly because of inhibition of platelet-activating factor and reduced platelet aggregation.

40.6 Surgical Tissue Injury

Crush injury should be avoided during surgical procedures by gentle tissue handling and the use of noncrushing instruments. To avoid ischemia of the outer layer of the skin, the surgeon should take care to pick up the subcutaneous tissue or the dermis rather than the epidermal layer.

Tension can be excessive, especially when running sutures are used. The temptation to pull tightly on the suture to approximate the wound edges will probably result in tissue ischemia and may lead to wound dehiscence, especially on fascia closures. An appropriate motto should be "approximate, do not strangulate" [51]. Sutures or staples left in for too long lead to permanent scarring because of both the crushing effect and the tension on the skin.

Dog ears, often encountered when elliptical incisions are being closed, result from excess skin and subcutaneous fat at the two edges of the closure. Removal involves upward traction with a single skin hook perpendicular to the skin at the end of the incision. In upward traction, a semicircular incision (180°) is made around the base of the excess skin down to the subcutaneous fat. The cut skin margin is rotated and pulled away from the initial incision at a 90° angle, until the dog-ear deformity has been resolved. The remaining upper edge of the excess skin is transected to provide optimal resection of the dog ear. Removal of a dog ear leads to a longer final incision but an overall more appealing cosmetic result.

Scar revision should not be undertaken earlier than 1 year after the injury. The reason for this delay derives from the observation that tissue remodeling occurs for as long as 1–2 years after closure of the wound. Often, the incision looks worst (raised and hyperemic) 2–3 months after closure. With time, most of these raised and red wounds recede and fade without intervention. Whereas waiting for a wound to mature is the widely used therapeutic approach for normally healing wounds, early scar revision may be justified if patients are miserable because of wound pruritus and cosmetic unsightliness, especially after deep dermal wounds. For hypertrophic scars, intralesional excision and primary closure are widely performed.

Z-plasty wound closure is one method of lengthening shortened, contracted scars. When linear scars contract, shortening of skin and subcutaneous tissues may limit motion, especially across joints such as the volar aspect of a digit. The Z-plasty requires the presence of adjacent mobile unscarred tissue to advance into the scar; this procedure lengthens the wound proportionate to the amount of advanced tissue (Figure 40.2). A second objective in the use of a Z-plasty is to reorient a scar so that it is in the lines of skin tension; such reorientation will render the scar less noticeable and often narrower.

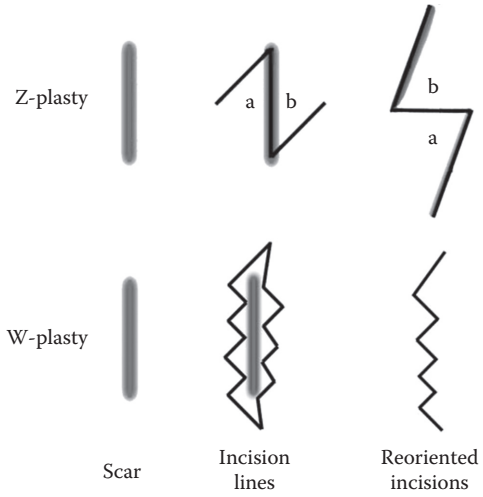


FIGURE 40.2
Scar revisions can be used either to lengthen a contracted incision (Z-plasty) or to break up the appearance of an unsightly scar (W-plasty).

W-plasty reorients and breaks up a scar to minimize contraction. Unlike Z-plasty, W-plasty does not lengthen a scar. A long linear scar that runs perpendicular to the lines of skin tension may be quite visible and wide and can be revised by using a small, repeating up-and-down pattern, hence the name W-plasty (Figure 40.2).

40.7 Specific Examples of Wound Complications

Keloids are scars that extend beyond the boundaries of the original wound with an excessive amount of dermal collagen. These cauliflower-like wounds tend to be increased in more darkly pigmented individuals and are commonly located on earlobes and presternal skin. No treatment is uniformly successful for all patients. Some therapeutic choices include intralesional steroid injection, pressure therapy, or surgical debulking with or without postoperative radiation.

Hypertrophic scars resemble keloids clinically, but they never extend beyond the boundaries of the original wound and they often resolve over a period of 12–24 months without intervention. They are raised scars

characterized by pruritus, hyperemia, and warmth. Years of research has found that hypertrophic scars are associated with extracellular matrix molecules, growth factors, and enzymes, but no cellular or molecular cause of this undesirable response to injury has been identified. Hypertrophic scars occur at the same body sites where contraction prevails, such as the presternal skin. Hypertrophic scars uniformly develop in deep dermal wounds that take a long time to heal; this fact suggests that the deep dermis or subcutaneous tissue may hold the answer to the cause of this scarring. As is true for keloids, therapeutic options often provide unsatisfactory results.

Pearls for Avoiding Wound Complications
Preoperative management
Optimize nutrition
Review all medications
Control serum glucose concentrations
Verify adequate vascularity
Intraoperative management
Use skin lines to plan incisions
Avoid surgical tissue injury or excessive tension
Debride all nonviable tissue
Achieve hemostasis
Postoperative management
Avoid pressure from casts and dressings
Diagnose and treat infection early

References

1. Sane DC, Moser TL, Pippen AM, Parker CJ, Achyuthan KE, Greenberg CS. Vitronectin is a substrate for transglutaminases. *Biochem Biophys Res Commun*. 1988; 157(1):115–120.
2. Prince CW, Dickie D, Krumdieck CL. Osteopontin, a substrate for transglutaminase and factor XIII activity. *Biochem Biophys Res Commun*. 1991;177(3):1205–1210.
3. Isik S, Sahin U, Ilgan S, Guler M, Gunalp B, Selmanpakoglu N. Saving the zone of stasis in burns with recombinant tissue-type plasminogen activator (r-tPA): An experimental study in rats. *Burns*. 1998;24(3):217–223.
4. Payan DG, Levine JD, Goetzl EJ. Modulation of immunity and hypersensitivity by sensory neuropeptides. *J Immunol*. 1984;132(4):1601–1604.
5. Ansel JC, Kaynard AH, Armstrong CA, Olerud J, Bunnett N, Payan D. Skin-nervous system interactions. *J Invest Dermatol*. 1996;106(1):198–204.
6. Arturson G. Pathophysiology of the burn wound. *Ann Chir Gynaecol*. 1980;69(5):178–190.
7. Streilein JW. Skin-associated lymphoid tissues (SALT): Origins and functions. *J Invest Dermatol*. 1983;80 Suppl:12s–16s.
8. Hocking AM, Gibran NS. Mesenchymal stem cells: Paracrine signaling and differentiation during cutaneous wound repair. *Exp Cell Res*. 2010;316(14):2213–2219.
9. Jang YC, Arumugam S, Gibran NS, Isik FF. Role of alpha(v) integrins and angiogenesis during wound repair. *Wound Repair Regen*. 1999;7(5):375–380.
10. Bloch W, Huggel K, Sasaki T, Grose R, Bugnon P, Addicks K et al. The angiogenesis inhibitor endostatin impairs blood vessel maturation during wound healing. *FASEB J*. 2000;14(15):2373–2376.
11. Shome S, Rana T, Ganguly S, Basu B, Chaki Choudhury S, Sarkar C et al. Dopamine regulates angiogenesis in normal dermal wound tissues. *PLoS One*. 2011;6(9):e25215.
12. Wu L, Pierce GF, Galiano RD, Mustoe TA. Keratinocyte growth factor induces granulation tissue in ischemic dermal wounds. Importance of epithelial-mesenchymal cell interactions. *Arch Surg*. 1996;131(6):660–666.
13. Kaplan ED, Holbrook KA. Dynamic expression patterns of tenascin, proteoglycans, and cell adhesion molecules during human hair follicle morphogenesis. *Dev Dyn*. 1994;199(2):141–155.
14. Bohnert A, Hornung J, Mackenzie IC, Fusenig NE. Epithelial-mesenchymal interactions control basement membrane production and differentiation in cultured and transplanted mouse keratinocytes. *Cell Tissue Res*. 1986;244(2):413–429.
15. Detmar M, Yeo KT, Nagy JA, Van de Water L, Brown LF, Berse B et al. Keratinocyte-derived vascular permeability factor (vascular endothelial growth factor) is a potent mitogen for dermal microvascular endothelial cells. *J Invest Dermatol*. 1995;105(1):44–50.
16. Kirsner RS, Falanga V, Eaglstein WH. The biology of skin grafts. Skin grafts as pharmacologic agents. *Arch Dermatol*. 1993;129(4):481–483.
17. Compton CC, Gill JM, Bradford DA, Regauer S, Gallico GG, O'Connor NE. Skin regenerated from cultured epithelial autografts on full-thickness burn wounds from 6 days to 5 years after grafting. A light, electron microscopic and immunohistochemical study. *Lab Invest*. 1989;60(5):600–612.
18. Steed DL. The role of growth factors in wound healing. *Surg Clin North Am*. 1997;77(3):575–586.
19. Ashcroft GS, Horan MA, Ferguson MW. Aging is associated with reduced deposition of specific extracellular matrix components, an upregulation of angiogenesis, and an altered inflammatory response in a murine incisional wound healing model. *J Invest Dermatol*. 1997;108(4):430–437.
20. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol*. 2002;3(5): 349–363.
21. Carrougher GJ, Martinez EM, McMullen KS, Fauerbach JA, Holavanahalli RK, Herndon DN et al. Pruritus in adult burn survivors: Postburn prevalence and risk factors associated with increased intensity. *J Burn Care Res*. 2013 Jan-Feb;34(1):94–101.

    This recent publication based on a multi center study of functional outcomes following burn injury underscores how little the medical community understands of the chronicity of symptoms following a wound.
22. Scott JR, Tamura RN, Muangman P, Isik FF, Xie C, Gibran NS. Topical substance P increases inflammatory cell density in genetically diabetic murine wounds. *Wound Repair Regen*. 2008;16(4):529–533.

23. Wolcott RD, Rhoads DD, Dowd SE. Biofilms and chronic wound inflammation. *J Wound Care*. 2008;17(8):333–341.
24. Webster J, Scuffham P, Sherriff KL, Stankiewicz M, Chaboyer WP. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. *Cochrane Database Syst Rev*. 2012;4:CD009261.
25. Blackburn JH, 2nd, Boemi L, Hall WW, Jeffords K, Hauck RM, Banducci DR et al. Negative-pressure dressings as a bolster for skin grafts. *Ann Plast Surg*. 1998; 40(5):453–457.
26. Engrav LH, Heimbach DM, Reus JL, Harnar TJ, Marvin JA. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: A randomized prospective study. *J Trauma*. 1983;23(11):1001–1004.

    The introduction of early excision and grafting of burns represents the single therapeutic innovation in the 20th century that changed survival and functional recovery after burn injury.
27. Bravo D, Rigley TH, Gibran N, Strong DM, Newman-Gage H. Effect of storage and preservation methods on viability in transplantable human skin allografts. *Burns*. 2000;26(4):367–378.
28. Heimbach D, Luterman A, Burke J, Cram A, Herndon D, Hunt J et al. Artificial dermis for major burns. A multi-center randomized clinical trial. *Ann Surg*. 1988;208(3):313–320.
29. Branski LK, Herndon DN, Pereira C, Mlcak RP, Celis MM, Lee JO et al. Longitudinal assessment of Integra in primary burn management: A randomized pediatric clinical trial. *Crit Care Med*. 2007;35(11):2615–2623.
30. Chessin DB, Hartley J, Cohen AM, Mazumdar M, Cordeiro P, Disa J et al. Rectus flap reconstruction decreases perineal wound complications after pelvic chemoradiation and surgery: A cohort study. *Ann Surg Oncol*. 2005;12(2):104–110.
31. Robson MC, Heggers JP. Delayed wound closure based on bacterial counts. *J Surg Oncol*. 1970;2(4):379–383.
32. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: A new form of malnutrition? Part A: Vitamins. *Obes Surg*. 2008;18(7):870–876.
33. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: A new form of malnutrition? Part B: Minerals. *Obes Surg*. 2008;18(8):1028–1034.
34. Shih B, Bayat A. Genetics of keloid scarring. *Arch Dermatol Res*. 2010;302(5):319–339.
35. Brown JJ, Ollier WE, Thomson W, Bayat A. Positive association of HLA-DRB1*15 with keloid disease in Caucasians. *Int J Immunogenet*. 2008;35(4–5):303–307.
36. Gemmati D, Federici F, Catozzi L, Gianesini S, Tacconi G, Scapoli GL et al. DNA-array of gene variants in venous leg ulcers: Detection of prognostic indicators. *J Vasc Surg*. 2009;50(6):1444–1451.

    This manuscript underscores our collective need to explore new etiologies and epidemiologies of reasons for complications in wound repair.
37. Gemmati D, Tognazzo S, Catozzi L, Federici F, De Palma M, Gianesini S et al. Influence of gene polymorphisms in ulcer healing process after superficial venous surgery. *J Vasc Surg*. 2006;44(3):554–562.
38. Gosain A, DiPietro LA. Aging and wound healing. *World J Surg*. 2004;28(3):321–326.

    This article nicely outlines the effect of aging on wound healing and its potential to increase wound healing complications.
39. Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Frid DJ. Exercise accelerates wound healing among healthy older adults: A preliminary investigation. *J Gerontol A Biol Sci Med Sci*. 2005;60(11):1432–1436.
40. Ashworth JJ, Smyth JV, Pendleton N, Horan M, Payton A, Worthington J et al. Polymorphisms spanning the 0N exon and promoter of the estrogen receptor-beta (ERbeta) gene ESR2 are associated with venous ulceration. *Clin Genet*. 2008;73(1):55–61.
41. Ashcroft GS, Dodsworth J, van Boxtel E, Tarnuzzer RW, Horan MA, Schultz GS et al. Estrogen accelerates cutaneous wound healing associated with an increase in TGF-beta1 levels. *Nat Med*. 1997;3(11):1209–1215.
42. Ashcroft GS, Greenwell-Wild T, Horan MA, Wahl SM, Ferguson MW. Topical estrogen accelerates cutaneous wound healing in aged humans associated with an altered inflammatory response. *Am J Pathol*. 1999;155(4):1137–1146.
43. Ashcroft GS, Mills SJ. Androgen receptor-mediated inhibition of cutaneous wound healing. *J Clin Invest*. 2002;110(5):615–624.
44. Oishi Y, Fu ZW, Ohnuki Y, Kato H, Noguchi T. Molecular basis of the alteration in skin collagen metabolism in response to in vivo dexamethasone treatment: Effects on the synthesis of collagen type I and III, collagenase, and tissue inhibitors of metalloproteinases. *Br J Dermatol*. 2002;147(5):859–868.
45. Alster Y, Varssano D, Loewenstein A, Lazar M. Delay of corneal wound healing in patients treated with colchicine. *Ophthalmology*. 1997;104(1):118–119.
46. Lawrence WT. In search of the optimal treatment of keloids: Report of a series and a review of the literature. *Ann Plast Surg*. 1991;27(2):164–178.
47. Chung KY, Kang DS. Regulation of type I collagen and interstitial collagenase mRNA expression in human dermal fibroblasts by colchicine and D-penicillamine. *Yonsei Med J*. 1999;40(5):490–495.
48. Tsen LC, Segal S, Pothier M, Bader AM. Alternative medicine use in presurgical patients. *Anesthesiology*. 2000;93(1):148–151.
49. Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with ginkgo biloba: A case report and systematic review of the literature: A case report and systematic review of the literature. *J Gen Intern Med*. 2005;20(7):657–661.
50. Fessenden JM, Wittenborn W, Clarke L. Gingko biloba: A case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy. *Am Surg*. 2001;67(1):33–35.
51. Mullikan J. Management of wounds. In: May H, ed. *Emergency Medicine*. New York: John Wiley & Sons; 1984:283–298.

    This chapter outlines the basic tenets of surgical management of wounds that is not emphasized in surgical training as it once was.

41

Complications of Thermal Injuries

Mark Cockburn, Edgar J. Pierre, and Mark G. McKenney

CONTENTS

Burn injuries present great metabolic, immunologic, and mechanical challenges to the human body. Additionally, burn injuries are associated with a variety of complications. In this chapter, we will discuss the prevention, diagnosis, and treatment of many of these associated complications.

41.1 Complications of Burn Injuries

41.1.1 Definitions

Burns are categorized by the depth of injury. Burns involving only the epidermis are first-degree burns and require no specific therapy. Burns involving part of but not the entire thickness of the dermis are second-degree burns. There is a high degree of variability within the class of second-degree burns. Superficial second-degree burns can be expected to heal spontaneously in as little as a few days or in as much as 2–3 weeks, with minimal risk of hypertrophic scarring or functional disability. Deeper second-degree burns can also close spontaneously over longer periods of time but can be expected to be associated with significant hypertrophic scarring and unstable overlying epithelium, which is prone to blisters and injuries from minor trauma. Indeterminate second-degree burns are those whose appearance defies classification by the trained observer or those that are of mixed depth and require longer periods of observation before the wounds can be clearly defined as deep or superficial burns. Burns involving the entire thickness of the dermis are classified as third-degree or full-thickness burns. All of the dermal elements are destroyed and the wound can close only by contraction from its perimeter. This type of closure may be acceptable when the burns are very small, depending on their location, but when such burns occur in important functional or cosmetic areas, closure by contraction leads to unacceptable functional outcomes and cosmetic deformities. Excision and grafting are generally required for the treatment of third-degree burns. Burns involving the muscle fascia and deeper structures are sometimes referred to as fourth-degree burns, but this is not a widely used term.

41.1.2 Immediate Complications

The risk of complications begins at the time of burning. Maneuvers performed to extinguish flames, such as rolling on the ground or immersing the wound in

standing water, may contaminate the wound. *Aeromonas* infection can occur when the wound is immersed in a natural body of water. If water or ice is applied to large burns, systemic hypothermia can occur. For this reason, cooling maneuvers are recommended only for small burns. Efforts to neutralize chemical burns can lead to further injury due to the neutralizing agent. However, the conventional belief that neutralization is an exothermic reaction that will cause further burning has recently been challenged in animal studies (unpublished data). Failure to recognize the depth of burning can lead either to incorrect triage or to delay of appropriate therapy. Immersion burns may have a moist red appearance suggestive of a superficial scald; careful observation will reveal that these wounds do not blanch and that the redness is caused by fixed hemoglobin in a deep wound. Some deep-contact burns may have an intact epidermis that can easily be rubbed away to reveal the deep underlying dermal burn. If this epidermis is left undisturbed, the presence of the burn may be unappreciated. If medical care is not obtained within 24 h after burning, the burns may have a coat of proteinaceous exudates, which can confound the determination of burn depth.

Burn wounds exist in three dimensions. The area of direct exposure to heat will contain the zone of coagulation, that is, the area of the burn that has undergone coagulation necrosis. Surrounding this zone in every direction is the zone of stasis, a zone of variable protein coagulation and impaired circulation that results from endothelial injury. This zone is at risk of becoming part of the zone of coagulation if the patient is inadequately resuscitated or if the wound becomes infected [1].

Commonly, burn patients suffer unnecessarily because of inadequate pain control. Effective relief of burn pain generally requires opioids; commonly prescribed non-narcotic analgesics are generally inadequate. Inadequate pain control may prevent the patient from performing adequate wound care and participating in rehabilitation.

Both early under-resuscitation and over-resuscitation are common complications for burn patients. The Advanced Burn Life Support (ABLS) program of the American College of Surgeons recommends resuscitation with 2–4 mL of fluid/kg body weight times the percentage of the body surface area that is burned; this amount of fluid should be administered over a 24 h period, half during the first 8 h. Those unfamiliar with burns may not appreciate the large volumes of fluid required to resuscitate a burn patient, and this lack of knowledge can lead to under-resuscitation and its consequences of renal failure and multiple organ system failure. Conversely, those loosely familiar with the need for fluid resuscitation of burn patients are likely to injudiciously over-resuscitate, and this problem leads to unnecessary degrees of edema that can cause local tissue hypoxia in the edematous areas or airway obstruction in severe cases.

41.1.3 Infectious Complications

The burn patient is at risk of infection because of impaired mechanical, cellular, and humoral host defenses. This break in the defensive barrier, coupled with contamination, nutritional difficulties, and gut effects (bacterial translocation through an already compromised, hypoxic mucosal barrier) [2], accounts for the incidence of infectious complications.

Both cell-mediated and humoral responses [2] are adversely affected in the burn patient. It is thought that defects in the lysosomal enzymes and a decrease in the production of oxygen radicals account for the decrease in the intracellular bacterial killing capacity of neutrophils despite normal phagocytic ability [3,4]. The activation of the complement system also creates a condition of relative immunosuppression in burn patients [5]. The levels of certain cytokines, interleukin-1-beta, interteukin-6, interleukin-10, and tumor necrosis factor alpha, are elevated in severely burned patients. These changes appear to increase susceptibility to infection.

Historically, gram-positive organisms (Streptococci and Staphylococci spp.) have been most frequently associated with septic death among burn patients. Since the advent of penicillin antibiotics and the use of topical antimicrobial agents, these organisms are rarely the cause of death. However, when Streptococci cause burn-wound infection, there is an increase in pain, erythema, and induration [2]. Classically, in these cases, erythema originates at the burn-wound margin, and progression of the infection to the lymphatics may occur. Penicillin is the antibiotic of choice for Streptococcal cellulitis. A dreaded complication of Streptococcal infection is the conversion of skin graft donor sites to full-thickness injury. Streptococcal infection can also result in skin graft loss [2]. Staphylococcal infection of burn wounds has also been treated with nafcillin, oxacillin, or methicillin. Recent years have seen the development of infection due to methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin is the drug of choice for treating this infection [2]. The development of toxic shock syndrome, although rare, requires aggressive management with antibiotics, intravenous human immunoglobulin, and circulatory support. Clostridial infections are rare but must be watched for in patients with deep-tissue injury. Intravenous antibiotics and early aggressive debridement of nonviable tissue are the mainstays of infection management.

More recently, the cause of burn-wound infections has been predominantly gram-negative bacteria. One of the primary pathogens involved in these infections is *Pseudomonas aeruginosa*; these bacteria can invade

the burn wound locally and cause sepsis. Early infection with *Pseudomonas* can be detected by the classic fruity smell of the wound and its dressing and by the characteristic green pigment produced by the bacteria. Visualization of fluorescence under a Wood's lamp can also be helpful. Subeschar clysis of antibiotics has been used in the past to treat invasive burn-wound sepsis, but this procedure is rarely used currently in the developed world, where proper antisepsis, topical antimicrobial agents, and early excision of the burn wounds make burn-wound sepsis a preventable complication. The keys to early recognition of pathogens and the use of appropriate antibiotics are the microbial prevalence patterns and the antibiotic susceptibility reports of individual burn units and centers.

The emergence and increasing incidence of fungal infections among burn patients have resulted from the increasing use of systemic antibacterial agents and effective topical antibacterial burn-wound regimens [2]. Although silver sulfadiazine (SSD) is effective against *Candida*, another commonly used topical agent, mafenide acetate, allows *Candida* to overgrow the margins of the burn wound [6]. *Candida* species are the most common fungal organisms causing burn-wound infections [2]. Commonly, *Candida* may be a wound contaminant, but when *Candida* causes a local wound infection, nystatin can be used locally. When systemic infection with *Candida* organisms occurs, systemic antifungal therapy is necessary. The administration of systemic antibacterial agents should be discontinued if possible. Early aggressive surgical debridement with rapid coverage has also been beneficial in controlling systemic fungal infections [2].

Early burn-wound excision, occurring within the first few days after burn injury, aims primarily at removal of the dead tissue that stimulates a systemic inflammatory response syndrome and prevention of infection by temporary or permanent closure of the burn wound [7].

41.1.4 Complications of Topical Antimicrobials

A number of topical agents are used in the care of burn patients. By controlling infection, effective topical antimicrobial therapy decreases the conversion of partial-thickness to full-thickness wounds, but its use is adjunctive to early excision therapy. Some of these agents are used in wound-cleansing procedures and others as part of the wound dressing. Certain complications are related to the use of these agents.

Silver nitrate can cause hyponatremia and hypochloremia, and thus serum electrolyte levels must be carefully monitored while this agent is being administered. This occurs because the silver ion in the silver nitrate binds to elemental chlorine ions causing the electrolyte imbalance when there is repeated or large-surface application of this solution [8,9].

SSD 1% cream, formulated in 1967, has excellent activity against *P. aeruginosa*, *S. aureus*, and other organisms, including yeast. The silver ion binds to the microorganism's nucleic acid, releasing the sulfadiazine that interferes with the metabolism of the microbe [10]. Mild cutaneous hypersensitivity reactions may occur in fewer than 5% of patients [11,12]. A transient leukopenia may occur, typically within 2–3 days after the institution of therapy; however, no increased susceptibility to infectious complications has been identified [6]. Some bacteria, such as all *Enterobacter cloacae* strains and some *Pseudomonas* strains, are not susceptible to SSD (Silvadene®, King Pharmaceuticals, Inc., Bristol, TN).

Sulfamylon® (mafenide acetate 0.5% cream), introduced in the mid-1960s, is readily absorbed through burn eschar. It is available in both a 10% water-soluble cream and a 5% solution. It has a wide antibacterial spectrum against most gram-positive bacteria, including *Clostridia*, and most gram-negative bacteria [6,11]. Cutaneous hypersensitivity reactions may be seen in as many as 50% of patients. Mafenide is a potent carbonic anhydrase inhibitor, and its use can result in metabolic acidosis. A compensatory hyperventilation may occur; minute ventilation as high as 50 L has been reported [9]. Consequently, when mafenide is used, the patient's respiratory status, pH levels, and blood gases must be frequently monitored. In burn patients with inhalation injury and concomitant respiratory acidosis, the use of mafenide acetate over a large burn surface area or repeated application of this compound can be fatal [7]. Mafenide acetate also decreases the breaking strength of healed wounds and delays healing [13]. Because of its ability to inhibit human keratinocytes and fibroblasts in vitro and to suppress the activity of polymorphonuclear leukocytes (PMNs) and lymphocytes, mafenide inhibits re-epithelialization more than SSD does [11].

Cerium nitrate–SSD was developed by adding the lanthanide salt cerium nitrate to SSD. This agent has excellent bacteriostatic activity on wounds. Methemoglobinemia has occurred in some patients treated with this agent and is caused by the absorption of reduced nitrates. No other electrolyte abnormalities have been noted when cerium nitrate–SSD is used [6]. This agent has been shown to reduce the inflammatory response to burn injury, decrease bacterial colonization, and provide a firm eschar for easier wound management [14].

Povidone-iodine, as a 10% ointment, has a wide spectrum of antibacterial and antifungal activity and is effective against protozoa. Its systemic absorption through the wound is associated with decreased renal function or renal failure. Patients using povidone-iodine dressings for prolonged periods of time should

be monitored for symptoms of iodine toxicity, which include hypercalcemic metabolic acidosis, cardiovascular instability (bradycardia, hypertension), elevation of hepatic enzymes, and central nervous system and progressive renal dysfunction [15]. This agent is no longer extensively used.

Dakin's solution (sodium hypochlorite 0.5% or 0.25% solution) is bactericidal, fungicidal, and virucidal. It is effective against MRSA, methicillin-resistant *Staphylococcus epidermidis*, and *Enterococci* [6]. Sodium hypochlorite dissolves clots and may cause bleeding. At concentrations higher than 0.025%, it is toxic to fibroblasts, keratinocytes, and PMNs [11].

The aforementioned complications of topical antimicrobial agents, of course, can be eliminated if these agents are not used. It is possible not to use them in some circumstances, if an occlusive wound dressing can be applied. Types of these dressings include simple clear adhesive dressings for small wounds and Biobrane® (UDL Laboratories, Inc., Rockford, IL), xenograft, and allograft for larger wounds. These dressings can be left in place, thereby obviating the need for frequent painful dressing changes and avoiding the complications that may accompany the use of topical antimicrobial agents. However, the occlusive dressings introduce their own complications. Primary among these is the chance that definitive treatment of the wound may be delayed. Such delay may occur if the depth of the wound was underestimated when the dressing was applied, particularly if the dressing remains adherent and the underlying wound is not examined. Acticoat® and other silver-containing occlusive dressings combine the advantages of the topical antimicrobial agents and those of the occlusive dressings. These dressings have potent antibacterial activity against most aerobic gram-negatives, including *Pseudomonas aeruginosa* and antibiotic-resistant members of the family Enterobacteriaceae, as well as aerobic gram-positive bacteria, including MRSA and vancomycin-resistant enterococci [16–18]. However, Acticoat can cause a burning sensation on application and can temporarily limit range of motion if allowed to desiccate.

The complications associated with the topical antimicrobial agents and the occlusive dressings can be avoided with early definitive excision and grafting. Pediatric patients treated with immediate excision and grafting have experienced less blood loss and shorter hospital stays than similar patients who were not treated in this way [19,20].

41.1.5 Pulmonary Complications

Historically, wound infection was the most common infection suffered by burn patients. Since the development of topical antimicrobials and intravenous antibiotics, however, the infection most frequently suffered by burn patients is pneumonia [21]. In fact, for burn patients, the leading cause of death is respiratory failure. Early diagnosis with sputum assessment and chest radiographs is necessary when respiratory failure occurs. The results of cultures should guide the use of antibiotic therapy, and aggressive pulmonary toilet should be instituted. Before culture results are ready, empiric therapy against the organisms that predominate in the unit should be used.

Some patients who suffer thermal injury experience inhalation injury. Inhalation injury is a chemical tracheobronchitis and acute pneumonitis caused by inhalation of smoke and other irritative products of incomplete combustion. The mortality rates for burn patients with inhalation injury are greater overall than that for patients with burns of similar size but with no inhalation injury [22]. Chest radiography is insensitive in making the diagnosis [23]; fiberoptic bronchoscopy (FOB) and xenon-133 scans are more reliable. FOB evidence of mucosal inflammation or ulceration and deposition of carbon particles indicate inhalation injury. Therapy depends on the severity of the injury. For mild cases, humidified oxygen–enriched air and incentive spirometry may be the only treatment required. However, for impaired mucociliary function, repeated FOB may be necessary. For the patient with progressive respiratory difficulty, endotracheal intubation and mechanical ventilation must be undertaken [24]. Because of the increased mortality rates associated with inhalation injury, the appearance of a new infiltrate on the chest radiograph of a patient with progressive respiratory difficulty should prompt the clinician to obtain endobronchial cultures and to begin treatment with intravenously administered antibiotics for presumptive bronchopneumonia.

Patients with inhalation injury are at a significant risk of carbon monoxide poisoning as a result of incomplete combustion of organic materials, particularly if they are burned in an enclosed space. Treatment involves endotracheal intubation (in cases of severe respiratory distress) and administration of oxygen-enriched air mixtures. On room air, the half-life of carboxyhemoglobin (COHb) is about 5 h whereas 100% oxygen delivered through a nonrebreather mask can reduce the half-life of COHb to about 1 h [25]. Many patients suffer prolonged neurologic sequelae (PNS) for months or years after exposure to CO, even when appropriate therapy is promptly delivered. The pathophysiology of this PNS is poorly understood and several small in vitro and in vivo animal studies seem to indicate that inhibition of the cytochrome oxidase system persists even when COHb levels drop to undetectable levels [25–27]. Current theory is that hyperbaric oxygen therapy can somehow overcome this inhibition reducing delayed neuronal death [25]. Hyperbaric oxygen therapy can be

used, especially for those patients who are comatose and have carbon monoxide poisoning [22].

Cyanide (CN) gas can also be produced as a direct result of the combustion of synthetic materials as well as natural materials such as silk and wool. CN can contribute independently and markedly to illness and death in smoke inhalation [28,29]. CN reversibly binds to the cytochrome oxidase (a3) within the mitochondria causing intracellular hypoxia affecting aerobic cell metabolism. CN completely stops oxidative phosphorylation in the cell by binding to the ferric ion at the terminal enzyme in the Krebs cycle [28]. The cell is unable to produce ATP because the electron transport chain is halted [29]. The cell's metabolism shifts to anaerobic metabolism resulting in lactate formation and ultimately a high anion gap metabolic acidosis [28,30]. The inability of the cells to use oxygen results in the accumulation of oxygen in the venous supply, and therefore, while arterial blood gases may be normal, a venous blood gas will show abnormally elevated oxygen levels resulting in a reduced arteriovenous oxygen saturation difference (<10 mmHg) [29]. CN also binds to the ferric form of hemoglobin making this type of hemoglobin incapable of transporting oxygen [28]. The CN antidote kit (amyl nitrite, sodium nitrite, and sodium thiosulfate) has been used in the United States for acute CN poisoning. The nitrites oxidize the iron in hemoglobin to form methemoglobin [30]. CN binds preferentially to the ferric ion of methemoglobin rather than to the ferric ion of the cytochrome oxidase (a3) in the mitochondrial membrane. CN is reversibly bound to cytochrome oxidase and as a result methemoglobin is able to extract CN from the mitochondria and reverse its toxic effects on the electron transport chain. Cells can then generate ATP. The third drug in the CN antidote kit, sodium thiosulfate, is then given intravenously over 30 min and acts as a sulfhydryl donor [30]. The sulfhydryl group of the thiosulfate ion will bind to any unbound, extracellular CN forming thiocyanate, which is then excreted by the kidneys [30]. The two nitrites must be administered first. The Food and Drug Administration (FDA) approved the use of hydroxocobalamin for the treatment of acute CN poisoning in December 2006 [31]. The starting dose of hydroxocobalamin for adults is 5 g (both 2.5 g vials) administered intravenously over 15 min. Depending on the clinical response and the severity of the poisoning, a second dose of 5 g may be given: total dose 10 g. Each 2.5 g vial of hydroxocobalamin is reconstituted with 100 mL of diluents (not in Cyanokit). Hydroxocobalamin works by binding with CN to form nontoxic cyanocobalamin (vitamin B12), which can be excreted by the kidneys. Cyanocobalamin can also release CN in the liver to allow hepatic rhodanese to convert it to thiocyanate, which can be excreted by the kidneys [32]. Like methemoglobin, CN has a greater affinity for hydroxocobalamin than for the cytochrome oxidase (a3) within the mitochondria. However, since hydroxocobalamin does not form methemoglobin, it can be safely used without compromising the oxygen-carrying capacity of hemoglobin [28]. The most common side effects are reddening of the skin and urine [33].

Both severe pneumonia and inhalation injury can lead to the development of acute respiratory distress syndrome. Patients with this disease may require prolonged mechanical ventilatory assistance, and the use of this treatment further increases the incidence of ventilator-associated pneumonia. In a murine model of cotton smoke inhalation injury and intranasal infection with *Pseudomonas aeruginosa*, smoke inhalation alone had a 90% survival rate, whereas smoke inhalation with a bacterial infection had a 10% survival rate, implying that combined lung injury and infection markedly increase mortality risk [34].

41.1.6 Gastrointestinal Complications

Patients sustaining burns over more than 25% of the body are likely to experience paralytic ileus. With adequate resuscitation, the return of gastrointestinal (GI) motility occurs around the third to fifth postburn day. Thus, the initiation of enteral nutrition is delayed. Because of this delay and the development of focal ischemia (which can occur as early as 3–5 h after the burn), there is a great risk of mucosal ulcerations and perforation [22]. The burn patient with sepsis is also at an increased risk of mucosal ulceration, which can result in GI bleeding. Histamine-2 receptor antagonists (H2RA) have been shown to be more effective than sucralfate in preventing gastric mucosal ulceration among critically ill patients without burns [35]. Additionally, antacids are effective and are used at some institutions in an effort to prevent erosive gastritis (Curling's ulcer). The 2008 Surviving Sepsis Campaign guidelines included a statement on stress ulcer prophylaxis where they recommended the use of either an H2RA or a proton pump inhibitor (PPI). In those guidelines, H2RAs were given a higher evidence grade (1A versus 1B) [36]. Two large recent meta-analyses showed a lower incidence of upper GI bleeding with PPIs compared with H2RAs [37,38]. In the 2010 meta-analysis, this difference was not significantly significant, while it was significant in the 2012 meta-analysis. Vitamin A supplementation may help prevent ulceration by assisting in mucin production. Cholestyramine can be used to prevent bile reflux gastritis. Today, we rarely see massive hemorrhage from mucosal ulcers, but when they occur the patient's likelihood of mortality is increased. It is unclear whether very sick patients with an already poor prognosis are more likely to experience these massive GI bleeds or

whether the massive hemorrhage by itself increases the patient's likelihood of mortality.

41.1.7 Renal Complications

The development of acute kidney injury (AKI) in critically ill burn patients has long been recognized as an ominous sign with a reported mortality as high as 50%–100% [39,40]. Adequate fluid resuscitation of burn patients cannot be sufficiently stressed. Of concern is the fact that, as the patient's blood pressure falls, there is progressive vasoconstriction of the afferent arterioles. The efferent arterioles may also undergo vasoconstriction as the result of the administration of norepinephrine and angiotensin. The net result is hypoxia at the level of the glomerulus and the tubules. The potential for muscle necrosis with resulting myoglobinuria or hemoglobinuria, coupled with a decrease in blood flow to the tubules, further potentiates the acute tubular necrosis. When myoglobinuria is suspected, alkalinization of the urine [41] by adding sodium bicarbonate to the intravenous fluid and maintenance of urine output of l00 cc/h or greater are recommended. Over-resuscitation of burn patients, however, can lead to many severe untoward consequences, which include abdominal compartment syndrome (ACS), airway obstruction, extremity compartment syndromes, and pulmonary edema [42,43]. ACS results in decreased renal blood flow and subsequent renal failure. When ACS develops, decompressive laparotomy must be performed to prevent progression to multiorgan failure and death.

41.1.8 Complications of Reconstruction

Skin grafting has shortened recovery time and has decreased the rate of infectious complications among burn patients [19,44]. However, skin grafting is also associated with complications. Of particular importance is the contraction of skin grafts. It has been noted that full-thickness skin grafts suffer less contraction than split-thickness skin grafts. In addition, the interval of time between the initial release of contraction and subsequent releases was longer with full-thickness grafts than with split-thickness grafts [45]. Pentoxifylline has been shown to decrease cell proliferation in hypertrophic scars. In one prospective study, pentoxifylline was administered to patients with burn hypertrophic peribuccal scarring and resulted in improved mouth opening and dental distance during the 38 days of treatment [46].

"Graft take" is affected by infection and may be delayed in the malnourished patient. Thus, various degrees of graft loss can be experienced. Sponge deformity is a complication of skin grafting that usually occurs around the periphery of the excised area where the excision was shallower or with thicker skin grafts [47]. It may be that the bed beneath the graft epithelializes from residual epithelial elements before vascularization of the autograft develops [41].

41.1.9 Psychological Complications

Victims of burn injuries suffer from a variety of psychological disorders. The equivocal findings of some studies suggest a relationship between total body surface area of the burn and the incidence of post-traumatic stress disorder (PTSD) [48]. However, other studies suggest a correlation between the occurrence of PTSD and previous psychological adjustment, preburn affective disorder, delirium or severe pain during acute treatment, and weaker perceptions of social support [49]. It has been noted that patients are at risk of PTSD both at the time of hospitalization and after discharge. Thus, it is important for clinicians to provide all patients with education and psychological intervention during hospitalization and with aggressive follow-up after discharge [44]. Some patients experience anticipatory anxiety as a result of unavoidable, painful wound dressing changes [50]. Adequate premedication before dressing changes can minimize the likelihood that aversion reactions will occur. Depressive symptoms may develop as the result of changes in body image and excessive pain. One would expect that the degree of disfigurement would correlate with the degree of depressive symptoms. However, no such correlation has been shown in previous studies. In one study of 70 burn survivors in western Australia, personality assessments were made using personality inventory scores. Twenty-nine patients developed depressive symptoms following burn injury. Neuroticism and avoidant coping were the personality traits most linked to the development of depressive symptoms [51]. The authors concluded that patients at risk for depression following a burn injury could be identified early by personality assessments.

41.1.10 Heterotopic Ossification

Heterotopic ossification (HO) can be a sequela of burn injury and is clinically devastating [52], often leading to restricted joint mobility, severe pain, and even nerve entrapment [53]. When HO develops in a burn patient, physical rehabilitation must be stopped, which can result in a significant delay in functional progress. Studies report a 1%–3% incidence of HO in burn patients, but a 60% incidence is observed in patients with severe burns [54]. HO often occurs secondary to deep-tissue burns, usually in >20% TBSA or full-thickness burns [54]. Mesenchymal stem cells (MSCs) may play a role in both HO and prevention of HO through their immunomodulatory properties. MSCs are known to secrete

potent cytokines that may regulate the wound environment, and these paracrine interactions may also drive HO formation. MSCs have also been shown to produce the receptor activator of nuclear factor-κβ ligand, which stimulates the formation of bone-resorbing osteoclasts [55]. It remains unclear how exogenously delivered and/or genetically engineered MSCs will play a therapeutic role in patients with HO.

41.2 Complications of Electrical Injuries

Electrical injuries depend on the source of the current, the voltage, the amperage, the duration of contact, and the surface area through which the current flows. Certainly, the greater the voltage and amperage and the greater the duration of contact [56], the more energy delivered to the victim and the more severe the potential injury. The complications can be categorized as acute or early, ongoing, and late. Low-voltage electricity is defined as less than 1000 V and supplies power in our homes, work places, and areas of recreational activities.

41.2.1 Early Complications

Neurological sequelae, when they occur, can be early or late and can affect both the central and the peripheral nervous systems. Up to 70% of patients who sustain a high-voltage injury are rendered unconscious [57], particularly if current passes through the head. All patients who have not sustained a fatal injury regain consciousness. Patients who fall after being electrocuted can experience closed head injuries, which must be managed in much the same way as they are managed in the regular trauma setting. The tetanic contractions that occur at the time of electrocution can produce vertebral fractures that can result in paralysis and other neurological deficits [58]. Thus, maintaining spinal precautions when examining the electrocuted victims and completely evaluating these patients for associated injuries are very important.

Ventricular fibrillation can occur with electrical injury and can be fatal. However, sinus tachycardia and nonspecific S-T segment changes are the most common cardiac findings [59,60]. Most of these disturbances resolve spontaneously within a few hours. Patients who are burned by either low-voltage current or high-voltage current but who reach the emergency room without evidence of cardiac abnormalities rarely experience these abnormalities later. If the patient suffers arrhythmia or demonstrates electrocardiogram evidence of acute myocardial infarction, then cardiac monitoring is necessary. These are key points because such patients usually require multiple surgical procedures, which should not be delayed because of questionable findings [61].

Patients who are apneic at the time of injury should undergo full cardiopulmonary resuscitation and support. Chest radiographs of patients who have fallen should be obtained and examined for evidence of pneumothorax or hemothorax. Effusions and pneumonitis may occur near entrance and exit wounds. Effusions can be treated by tube thoracostomy.

41.2.2 Ongoing Complications

The fluid requirements of patients with thermal burns can be estimated more accurately than can those of the electrically burned patient. Because current has passed through the tissue between the entrance and exit sites, it is difficult to gauge the fluid requirement strictly by outward evidence of injury. Thus, one must be hypervigilant so that ongoing injuries and consequent fluid requirements are not overlooked. Adequate urine output can still be used as a guide to resuscitation. Muscle tissue can become edematous when injured. The muscles lie within fascial compartments, and as the muscle swells the pressure within the compartment increases. At a certain critical value, the blood flow to the muscle decreases, and further muscle damage is produced. The five symptoms of pain, pallor, paresthesias, paralysis, and pulselessness are all evidences of compartment syndrome. However, the earliest sign of this syndrome is paresthesia. The consequences of muscle injury include limb loss with the need for extensive rehabilitation and acute renal failure caused by myoglobin deposition within the renal tubules.

Determining the extent of tissue damage and viability is difficult. The resistance of bone is high; thus, heat is produced deep within the limb [56]. Consequently, the superficial muscles may be viable although the deeper muscles are necrotic. There is no good test to determine the viability of the muscles short of exploring the compartments to determine whether the muscle bleeds or contracts [62]. The problem caused by failure to detect necrotic muscle is that this tissue provides a focus for the development of infection and sepsis. When necrotic muscle is detected, debridement is mandatory. Subsequent re-exploration and additional debridement may be required.

When rhabdomyolysis is suspected, the urinary output should be maintained at 100 mL/h. Mannitol has been used to enhance excretion of hemochromogens. Alkalinization of the urine may be helpful in preventing crystallization of myoglobin within the renal tubules [48]. Because of the large fluid shifts that take place, shock can occur. It is essential to administer large volumes of fluid because under-resuscitation is the most common cause of acute renal failure among these patients.

The direct passage of current through the abdominal wall may injure both the wall and the underlying intestines. Injury to intra-abdominal viscera can occur even when the entrance and exit sites are not on the abdomen. A high index of suspicion is necessary to make the diagnosis, particularly if patients have other severe injuries. Bowel perforation [63], pancreatitis, and gallbladder necrosis [64] have been reported. Exploratory laparotomy may be necessary when suspicion is high. Curling ulcers may also occur [56]. This complication was discussed earlier under GI complications of thermal injuries.

41.2.3 Late Complications

Fibrosis and scarring of locally damaged tissue in and around peripheral nerves may result in late nerve compression and decreased conductance. The perineural tissue may undergo vascular inflammation, thrombosis, or fibrosis. Causalgia, motor weakness, paresthesias, and hyperesthesia have been reported. With regard to the central nervous system, cortical encephalopathy, hemiplegia with or without aphasia, striatal syndrome, and brain stem dysfunction can occur [65]. Seizure disorders can also occur late. Spinal cord symptoms similar to those of progressive muscular atrophy, amyotrophic lateral sclerosis, or transverse myelitis may develop later [66].

Cataracts may occur in 5%–7% of patients and frequently are bilateral [50]. The onset of blurred vision usually begins about 6 months after injury [67]. Because of the possibility of such a devastating complication, patients should undergo ophthalmologic examination as part of their acute care and should be made aware of the potential for cataracts [59].

Complications of thermal injuries clearly can involve any of the body's systems. Although prevention is the goal, knowledge of the potential pitfalls may help to mitigate the detrimental effects of the complications when they do occur. Careful attention and a high index of vigilance can help to prevent some, but not all, of these complications.

Overview of Complications of Thermal Injuries

Complication	Incidence	References
Immediate complications:		
Contamination		
Infection		
Immune suppression		
Cellulitis		
Burn-wound infection		
Hypothermia		
Misdiagnosis/mistriage		
Inadequate pain relief		
Under-resuscitation/over-resuscitation		
Complications of topical antimicrobial agents:		
Silver nitrate solution 0.5%		
Hyponatremia		
Hypochloremia		
Hypothermia	0.5%	
Silver sulfadiazine		
Cutaneous hypersensitivity	<5%	[11,12]
Transient leukopenia	5%–15%	[68]
Mafenide acetate		
Cutaneous hypersensitivity	≈50%	[9]
Metabolic acidosis		
Pulmonary complications		
Pneumonia	Up to 65%	[69]
ARDS		
Tracheobronchitis		
Gastrointestinal complications		
Paralytic ileus		
Mucosal ulceration		
Perforation		
Renal complications		
Acute tubular necrosis	0.5%–30%	[70]
Renal failure secondary to myoglobinuria		
Complications of reconstruction		
Donor site conversion to full-thickness injury		
Skin graft loss		
Graft contraction		
Sponge deformity		
Contracture across joints		
Psychological complications		
Post-traumatic stress disorder		
Anxiety		
Depression		
Complications of electrical injury	Cataracts in 6.2%	[71]
Neurologic complications		
Loss of consciousness		
Paresthesia		
Cardiac complications		
Ventricular fibrillation		
S-T segment changes		
Sinus tachycardia		
Musculoskeletal complications		
Compartment syndrome		
Post-tetanic fractures		

Abbreviation: ARDS, acute respiratory distress syndrome.

Avoiding Complications of Thermal Injury
Use aseptic technique at all times
Maintain warm environment
Titrate fluids carefully
Control pain adequately
Wean patients from ventilator as rapidly as is safely possible
Administer enteral feedings early, but stop feeding if tolerance is in question
Err on the side of grafting in areas where contractures are a concern. Remain cognizant of concomitant injury and the potential for compartment syndrome
Provide emotional and psychological support

References

1. Jackson DM. The diagnosis of the depth of burning. *Br J Surg* 1953; 40:588–596.
2. Treat RC. Infectious complications. In: Maull KI, ed. *Complications in Trauma and Critical Care*. Philadelphia, PA: Saunders, 1996: pp. 505–512.
3. Cole WQ, Cook JJ, and Grogan JB. In vitro neutrophil function and lysosomal enzyme levels in patients with sepsis. *Surg Forum* 1975; 26:79–81.
4. Curreri PW, Heck EL, Browne L, and Baxter CR. Stimulated nitroblue tetrazolium test to assess neutrophil antibacterial function: Prediction of wound sepsis in burned patients. *Surgery* 1973; 74(1):6–13.
5. Gelfand JA. How do complement components and fragments affect cellular immunological function? *J Trauma* 1984; 24(9 suppl):S118–S124.
6. Heggers J, Linares HA, Edgar P, Villareal C, and Herndon DN. Treatment of infections in burns. In: Herndon DN, ed. *Total Burn Care*. Philadelphia, PA: Saunders, 1997: pp. 120–169.
7. Church D, Elsayed S, Reid O, Winston B, and Lindsay R. Burn wound infections. *Clin Micro Reviews* April 2006; 19(2):403–434.
8. Heggers JP, Hawkins H, Edgar P, Villareal C, and Herndon DN. Treatment of infections in burns. In: Herndon DN, ed. *Total Burn Care*. London, U.K.: Saunders, 2002: pp. 120–169.
9. Monafo WW and West MA. Current treatment recommendations for topical burn therapy. *Drugs* 1990; 40:364–373.
10. Lansdown AB. Silver. 1. Its antimicrobial properties and mechanism of action. *J. Wound Care* 2002; 11:125–130.
11. Ward RS and Saffle JR. Topical agents in burn and wound care. *Phys Ther* 1995; 75(6):525–538.
12. Kaye ET. Topical antibacterial agents. *Infect Dis Clin North Am* 2000; 14(2):321–339.
13. Boyce ST, Supp AP, Swope VB, and Warden GD. Topical sulfamylon reduces engraftment of cultured skin substitutes on athymic mice. *J Burn Care Rehab* 1999; 20:33–36.
14. Garner JP and Heppell PS. Cerium nitrate in the management of burns. *Burns* 2005; 31:539–547.
15. Burks RI. Povidone-iodine solution in wound treatment. *Phys Ther* 1998; 78(2):212–218.
16. Dunn K and Edwards-Jones V. The role of Acticoat with nanocrystalline siver in the management of burns. *Burns* 2004; 30(suppl. 1):S1–S9.
17. Heggers JR, Goodheart RE, Washington J, McCoy L, Carino E, Dang T, Edgar P, Maness C, and Chinkes D. Therapeutic efficacy of three silver dressings in an infected animal model. *J Burn Care Rehabil* 2005; 26:53–56.
18. Yin HQ, Langford R, and Burrell RE. Comparative evaluation of the antimicrobial activity of ACTICOAT antimicrobial barriers dressing. *J Burn Care Rehabil* 1999; 20:195–200.
19. Xiao-Wu W, Herndon DN, Spies M, Sanford AP, and Wolf SE. Effects of delayed wound excision and grafting in severely burned children. *Arch Surg* 2002; 137(9): 1049–1054.
20. Desai MH, Herndon DN, Broemeling L, Barrow RE, Nichols RJ Jr., and Rutan RL. Early burn wound excision significantly reduces blood loss. *Ann Surg* 1990; 211(6): 753–762.
21. Pruitt BA Jr. Infection and the burn patient. *Br J Surg* 1990; 77(10):1081–1082.
22. Shirani KZ, Pruitt BA Jr., and Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg* 1987; 205:82–87.

    Article stresses the importance and impact of inhalation injury in the mortality of burn patients.
23. Clark WR, Bonaventura M, and Myers W. Smoke inhalation and airway management at a regional burn unit: 1974–1983: Part I. Diagnosis and consequences of smoke inhalation. *J Burn Care Rehabil* 1989; 10:52–62.
24. Wolf SE and Herndon DN. Burns. In: Townsend CM, ed. Sabiston, *Textbook of Surgery*. Philadelphia, PA: Saunders, 2001: pp. 345–363.
25. Buckley N, Juurlink D, Isbister G, Bennett M, and Lavonas E. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev* 2011:CD002041.
26. Zhang J and Piantadosi CA. Mitochondrial oxidative stress after carbon monoxide hypoxia in the rat brain. *J Clin Invest* 1992: 90;1193–1199.
27. Thom SR. Deshydrogenase conversion to oxidase and lipid peroxidation in brain after carbon monoxide poisoning. *J Appl Physiol* 1992; 73:1584–1589.
28. Hall AH, Dart R, and Bogdan G. Sodium thiosulfate or hydroxocobalamin for the empiric treatment of cyanide poisoning? *Ann Emerg Med* 2007; 49:806–813.
29. Smith D, Cairns B, Ramadan F et al. Effect of inhalation injury, burn size, and age on mortality: A study of 1447 consecutive burn patients. *J Trauma* 1994; 37:655–659.

    Article highlights three factors that impact mortality in burn injuries specifically the impact of inhalation injury, which needs to be promptly considered and treated.
30. Shepard G and Velez L. Role of hydroxocobalamin in acute cyanide poisoning. *Ann Pharmacoth* 2008; 42:661–669.
31. US Food and Drug Administration. FDA news: FDA approves drug to treat cyanide poisoning. US Food and Drug Administration Web site. Available from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108807.htm; accessed May 6, 2011.

32. DesLauriers CA, Burda AM, and Wahl M. Hydroxocobalamin as a cyanide antidote. *Am J Ther* 2006; 13:161–165.

    It is important to recognize the possibility of cyanide gas poisoning in indoor fire and know how to treat it. The antidote is safe and efficacious.

33. Uhl W, Nolting A, Golor G, Rost KL, and Kovar A. Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study. *Clin Toxicol (Phila)* 2006; 44(Suppl 1):17–28.
34. Lange M, Hamahata A, Traber DL et al. A murine model of sepsis following smoke inhalation injury. *Biochem Biophys Res Commun* 2010; 391:1555–1560.
35. Cook D, Guyatt G, Marshall J et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998; 338(12):791–797.
36. Dellinger RP, Levy MM, Carlet JM et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock:2008. *Crit Care Med* 2008; 36(1):296–327.
37. Lin PC, Chang CH, Hsu PI, Tseng PL, and Huang YB. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: A meta-analysis. *Crit Care Med* 2010; 38(4):1197–1205.
38. Barkun AN, Bardou M, and Martel M. Proton pump inhibitors vs histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: A meta-analysis. *Am J Gastroenterol* 2012; 107:507–520.

    In critically ill patients at risk for the development of SRMB, PPI prophylaxis significantly decreased rates of clinically significant bleeding compared with H2RA, without affecting the development of nosocomial pneumonia or mortality rates.

39. Chung KK, Lundy JB, Matson JR et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: A cohort study. *Crit Care* 2009; 13:R62.
40. Mustonen KM and Vuola J. Acute renal failure in intensive care burn patients (ARF in burn patients). *J Burn Care Res* 2008; 29:227–237.
41. Ron D, Taitelman U, Michaelson M, Bar-Joseph G, Bursztin S, and Better OS. Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med* 1984; 144:277–280.
42. Ivy ME, Atweh NA, Palmer J et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma* 2000; 49:387–391.
43. Zak AL, Harrington DT, Barillo DJ et al. Acute respiratory failure that complicates the resuscitation of pediatric patients with scald injuries. *J Burn Care Rehabil* 1999; 20:391–399.
44. Echinard CE, Sajdel-Sulkowska E, Burke PA, andBurke JF. The beneficial effect of early excision on clinical response and thymic activity after burn injury. *J Trauma* 1982; 22:560–565.
45. Iwuagwu FC, Wilson D, and Bailie F. The use of skin grafts in postburn contracture release: A 10-year review. *Plast Reconstr Surg* 1999; 103:1198–1204.
46. Isaac C, Carvalho VF, Paggiaro AO, de Maio M, and Ferreira MC. Intralesional pentoxifylline as an adjuvant treatment for perioral post-burn hypertrophic scars. *Burns* 2010; 36:831–835.
47. Engrav LH, Gottlieb JR, Walkinshaw MD, Heimbach DM, and Grube B. The "sponge deformity" after tangential excision and grafting of burns. *Plast Reconstr Surg* 1989; 83:468–470.
48. Baur KM, Hardy PE, and Van Dorsten B. Posttraumatic stress disorder in burn populations: A critical review of the literature. *J Burn Care Rehabil* 1998; 19(3):230–234.
49. Yu BH and Dimsdale JE. Posttraumatic stress disorder in patient with burn injuries. *J Burn Care Rehabil* 1999; 20(5):426–433.
50. Taal LA and Faber AW. Posttraumatic stress and maladjustment among adult burn survivors 1–2 years postburn. *Burns* 1998; 24:285–292.
51. Andrews RM, Browne AL, Drummond PD, and Wood FM. The impact of personality and coping on the development of depressive symptoms in adult burns survivors. *Burns* 2010; 36:29–37.
52. Olmsted-Davis E, Gannon FH, Ozen M et al. Hypoxic adipocytes pattern early heterotopic bone formation. *Am J Pathol* 2007; 170:620–632.
53. Shore EM and Kaplan FS. Role of altered signal transduction in heterotopic ossification and fibrodysplasia ossificans progressiva. *Curr Osteoporos Rep* 2011; 9:83–88.
54. Shafer DM, Bay C, Caruso DM, and Foster KN. The use of eidronate disodium in the prevention of heterotopic ossification in burn patients. *Burns* 2008; 34:355–360.
55. Djouad F, Bouffi C, Ghannam S, Noel D, and Jorgensen C. Mesenchymal stem cells: Innovative therapeutic tools for rheumatic diseases. *Nat Rev Rheumatolo* 2009; 5:392–399.
56. Briggs SM. Electrical complications. In: Maull KI, ed. *Complications in Trauma and Critical Care*. Philadelphia, PA: Saunders, 1996: pp. 521–528.
57. Skoog T. Electrical injuries. *J Trauma* 1970; 10:816–830.
58. Warden GD and Heimbach DM. Burns. In: Schwartz SI, ed. *Principles of Surgery*. New York: McGraw-Hill, 1998: pp. 223–262.
59. Baxter CR. Present concepts in the management of major electrical injury. *Surg Clin North Am* 1970; 50:1401–1418.
60. Hartford CE and Ziffren SE. Electrical injury. *J Trauma* 1971; 11:331–336.
61. Housinger TA, Green L, Shahangian S, Saffle JR, and Warden GD. A prospective study of myocardial damage in electrical injuries. *J Trauma* 1985; 25: 122–124.
62. Robson MC and Smith DJ. Care of the thermally injured victim. In: Jurkwicz MJ, Krize TJ, Mathes SJ, Ariyan S, eds. *Plastic Surgery: Principles and Practice*. St. Louis, MO: CV Mosby Company, 1990: pp. 1355–1410.
63. Frank DH and Fisher JC. Complications of electrical injury. In: Greenfield LJ, ed. *Complication in Surgery and Trauma*. Philadelphia, PA: Lippincott, 1990: pp. 26–36.
64. Smith J and Rank BK. A case of severe electrical burns with an unusual sequence of complications. *Br J Surg* 1946; 33:365–368.
65. Christensen JA, Sherman RT, Balis GA, and Waumett JD. Delayed neurologic injury secondary to high-voltage current, with recovery. *J Trauma* 1980; 20:166–168.

66. Farrell DFand Starr A. Delayed neurological sequelae of electrical injuries. *Neurology* 1968; 18:601–606.
67. Monafo WW and Freedman BM. Electrical and lightning injury. In: Boswick JA, ed. *The Art and Science of Burn Care*. Rockville, MD: Aspen Publishers Inc., 1987: pp. 241–254.
68. Choban PS and Marshall WJ. Leukopenia secondary to silver sulfadiazine: Frequency, characteristics and clinical consequences. *Am Surg* 1987;53(9):515–517.
69. Wurtz R, Karajovic M, Dacumos E et al. Nosocomial infections in a burn intensive care unit. *Burns* 1995; 21:181–184.
70. Schiavon M, DiLandro D, Baldo M et al. A study of renal damage in seriously burned patients. *Burns Incl Thermal Inj* 1988;14(2):107–114.
71. Saffle JR, Crandall A: Cataracts a long term complication of electrical injury. *J Trauma* January 1985;25(1):17–21.

42

Complications of Reconstructive Surgery

Deepak Narayan and Joseph H. Shin

CONTENTS

Reconstructive surgery attempts to restore both form and function. Because many postsurgical and traumatic conditions result in loss of tissue, restoration of form and function frequently requires replacement of the lost tissue, preferably in kind. Two general categories of tissue may be used in reconstruction: flaps and grafts. Grafts may be composed of any kind of tissue (skin, cartilage, fat, bone, or nerve), but all are devoid of an active, functioning blood supply. Flaps, in contrast, carry their own blood supply and therefore have the advantage of bringing tissue and blood supply to an area that is deficient in both. In cases of significant loss of tissue or volume or lack of donor sites, implants may be used for restoration of volume or scaffolding and possibly to maintain stability, such as in breast reconstruction. All of these are associated with the potential for specific complications and attendant failure.

Depending on the anatomical components they contain, flaps may be cutaneous, fasciocutaneous, muscular, or osteomyocutaneous. Cutaneous or fasciocutaneous flaps may be oriented to incorporate a blood vessel running along their length (the so-called axial-pattern flap) or may depend entirely on the richly anastomosing network of dermal circulation (the random-pattern flap). The absence of a defined blood vessel renders random-pattern flaps more prone to complications than axial-pattern flaps. To paraphrase Sir Harold Gilles, we might state that surgical procedures involving flaps face a constant struggle between blood supply and coverage; the loss of blood supply is responsible for many of the complications that ensue after such procedures.

Flaps may also be described as "pedicled," which retain their original blood supply, or "free," which are completely detached from their native source of circulation and are later anastomosed to a feeding vessel by means of microsurgical techniques. Of these two types of flaps, pedicled flaps are easier to create, allow shorter operative procedures, and, unlike free flaps, are not subject to a myriad of complications related to surgical technique. Free flaps (those requiring microvascular surgery), however, have greatly increased the number of reconstructive techniques available to plastic surgeons. When coupled with advances in technology and patient care, free-flap reconstructions are now considered the standard of care in many situations.

Flaps may be seen as a panacea for infected wounds, which they are not. Debridement, treatment of related host factors in wound healing, and provision of an adequate blood supply are crucial for the success of procedures involving flaps. Antibiotic therapy may be an important adjunct in the setting of significant infections, such as osteomyelitis. Persistent infections despite flap coverage, therefore, should not be construed as a failure of the flap but may instead be associated with a failure to adhere to the crucial principles enumerated earlier.

The reconstructive surgeon's goal of completely restoring preinjury form and function may be achieved but can be fraught with significant problems related to the reconstructive surgery itself. Realistic expectations on the part of the patient and the surgeon are necessary in the most challenging cases.

42.1 Skin Grafts

Skin grafts are at once the simplest technical procedures to perform but often amongst the most difficult to get a consistent result with regard to healing. The skin graft is an ancient procedure. It is important that it provides immediate coverage of a wound with a resultant donor site that is relatively benign, except for appearance. While advantageous for reasons of ease of procurement, the most common complication is graft loss. The factors are multivariate but include infection, poor recipient bed, hematoma or seroma preventing graft adherence, and technical factors including movement and lack of proper immobilization.

Proper wound bed debridement, either immediately prior to or some time prior to graft placement, is critical to ensure graft survival. Presence of a contaminated wound, especially in the setting of a chronic wound, is a known factor leading to graft loss.

If the graft bed has been properly prepared and a graft has been harvested well, securing the graft with a bolster or some pressure dressing is critical to ensure that the graft gets immediate nourishment to maintain metabolic functioning of the skin cells. The processes of imbibition, inosculation, and eventual graft take can be best facilitated with a bolster or negative pressure dressing. This prevents the three factors associated with graft loss: (1) shear, (2) hematoma, and (3) seroma. Graft stabilization and immobilization can be best ascertained with a proper bolster and dressing and, in such cases, can provide the necessary conditions for graft take.

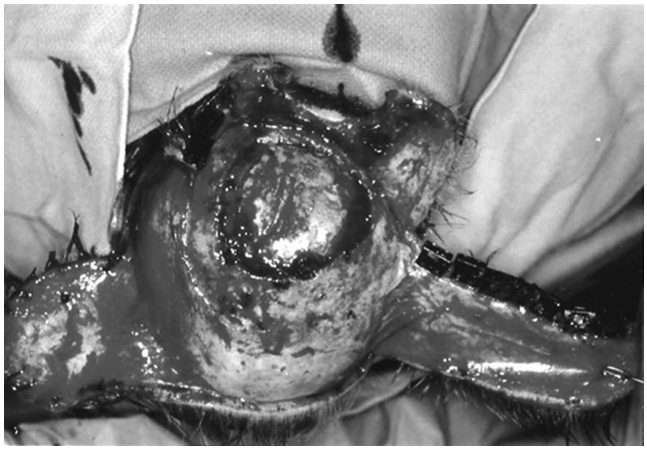


FIGURE 42.1
A 75-year-old woman was injured in a fall; the injury resulted in exposed hardware (placed for calvarial replacement after resection of a meningioma) on the vertex of the skull. Shown here is the defect (center of the picture) with scalp flaps raised circumferentially. (Courtesy of Thomson, J.C., Yale University, New Haven, CT.)

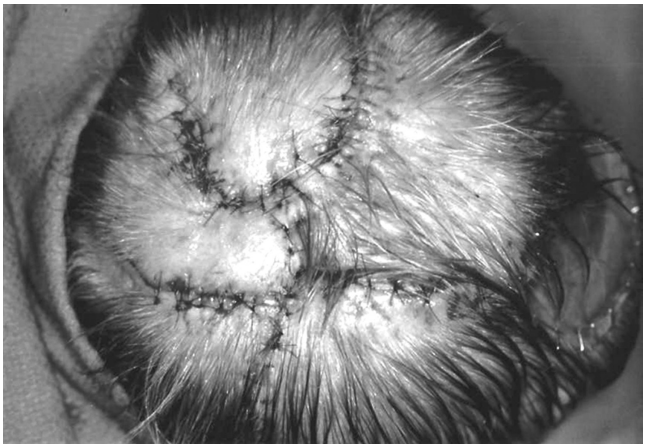


FIGURE 42.2
Immediate postoperative result with coverage of hardware. (Courtesy of Thomson, J.C., Yale University, New Haven, CT.)

42.2 Cutaneous Flaps

Cutaneous flaps are termed advancement, rotation, and rhomboid. The principal advantage of these local flaps is the ability to cover "like with like," that is, the ability to match the color, thickness, and texture of the surrounding tissue by reconstructing the defect with neighboring skin. Cutaneous flaps may be subject to a variety of mishaps: poor design, inability to cover the defect, tension on the flap with subsequent ischemic necrosis, etc. (Figures 42.1 through 42.4). These complications can be magnified by the use of flaps in aesthetically sensitive areas such as the face. The "pin cushion" or "trap-door deformity" results when the flap tissue bunches up because of a circular scar line at its base; this deformity can be obviated by the use of transposition flaps that are angulated such as the rhomboid flap. A random skin flap is much more prone to complications when the patient is a smoker, presumably because of the ischemic complications induced by nicotine and carbon monoxide [1,2].

On the whole though, these cutaneous flaps are associated with a high degree of success and failure is rare. Complications are almost always associated with identifiable host factors, such as infection or prior radiation

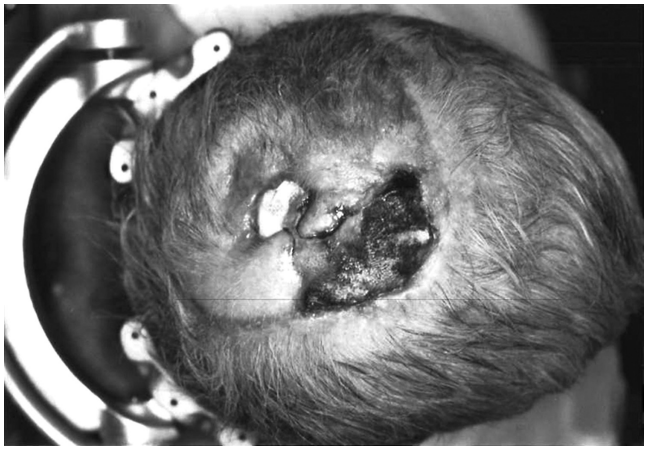


FIGURE 42.3
Ischemic necrosis of flaps with reexposure of hardware. (Courtesy of Thomson, J.C., Yale University, New Haven, CT.)

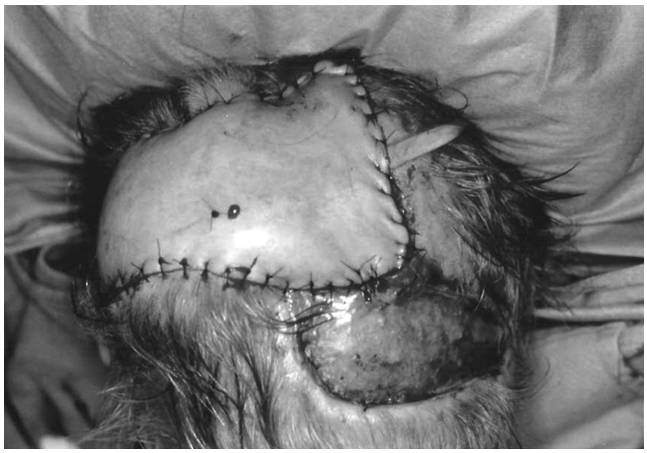


FIGURE 42.4
The wound was debrided, and a lateral arm flap was harvested (because the results of Allen's tests on both arms precluded the use of a radial forearm flap) to provide coverage. Here we see the lateral arm flap covering the defect. (Courtesy of Thomson, J.C., Yale University, New Haven, CT.)

limiting vascular supply. They are for the most part straightforward and provide durable and consistent results. They are limited though in their ability to cover larger regional or distant defects.

42.3 Pedicled Muscle or Myocutaneous Flaps

Because many of the complications of muscle or myocutaneous flap surgery are related to vascularity, the vascular anatomy associated with these flaps has been categorized to facilitate their design prior to surgery.

TABLE 42.1

Types and Examples of Muscle Flaps According to the Mathes–Nahai Classification Scheme

Type	Description	Example
1	Muscle with single dominant pedicle	Tensor fascia lata, gastrocnemius (each head)
2	Muscle with single dominant and minor pedicle(s)	Gracilis
3	Muscle with two dominant pedicles	Rectus abdominis
4	Muscle with segmental blood supply	Sartorius
5	Muscle with one main and multiple segmental branches	Latissimus dorsi

The Mathes–Nahai classification is one such paradigm in general use; it describes the vascular anatomy of muscles in a manner that can be correlated with their potential clinical use. This classification scheme defines five primary types of flaps (Table 42.1).

This classification scheme has practical applications in the consideration of complications associated with the flap and its surgical execution. The vast majority of complications with these flaps are related to the vascularity or are technical factors associated with "raising" these flaps. These complications are associated with the failure of the vascular supply to fully nourish the bulk of the muscle or the cutaneous paddle. For example, a Type-4 muscle such as the sartorius muscle has a limited arc of rotation (and, hence, limited transferability) because its blood supply is segmental. The limitations hence will result in limitations for its use such as coverage of the infected groin wound resulting from vascular repairs of the femoral artery or exposure of the femoral vessels in cancer resections.

The blood vessel orientation of the medial head of the gastrocnemius (Type 1), in contrast, is much more axial and therefore allows a wider arc, as long as the main pedicle is not compromised. This allows the muscle to be rotated or transposed along a much further distance to cover the medial knee in the event of coverage of exposed hardware following knee surgery or tibial injuries. The two dominant blood vessels in the rectus abdominis muscle (the superior and inferior epigastric arteries), each of which can nourish the entire muscle and its overlying fasciocutaneous unit, allow either vessel to be divided for pedicled transfer. Dividing the inferior epigastric artery allows the transverse rectus abdominis muscle (TRAM) flap to be inset into the chest wall with connection to the superior epigastric artery alone.

Examples of such muscle and the associated complications follow.

42.3.1 Gracilis Muscle Flap

The pedicled gracilis muscle, along with its overlying skin paddle, is often used for vaginal reconstruction and anal rectal complications following abdominoperineal resections. This is often necessary if the resultant surgical defect happens in the setting of prior or anticipated radiation. The muscle alone has been used to reconstruct the rectal sphincter. Abdominal, perineal, as well groin wounds may also be covered with flaps composed of this muscle and its associated skin paddle, termed the myocutaneous flap.

Lying between the adductor longus anteriorly and the semimembranosus posteriorly is the thin, flat gracilis, which is supplied predominantly by the ascending branch of the medial circumflex femoral artery, a branch of the profunda femoris. The distal end of the skin paddle, however, is not as a general rule reliable, and the so-called delay procedure prior to raising the flap some weeks prior has been used in an effort to avert avascular necrosis. The sartorius muscle (also thin and flat) is sometimes mistaken for the gracilis, especially in limbs with long-standing paralysis. Shearing off the skin paddle from the underlying muscle, which is nourished by the perforating vessels during overly aggressive attempts to tunnel the flap, can also contribute to the loss of the accompanying skin paddle. Tunneling the muscle under unyielding skin, resultant venous outflow obstruction, or placement of undue tension on the pedicle may also result in vascular compromise and partial or complete flap necrosis.

42.3.2 Gastrocnemius

The gastrocnemius is conveniently divided into two heads, each with its own blood supply. This muscle is particularly robust and is useful for covering defects around the knee joint or tibia in the case of infections, exposed hardware following fracture fixation, or possibly in tumor resections. Contour donor defects can result if the muscle is used with a skin paddle. Therefore, the muscle is usually transferred without the overlying skin and is often covered by a split-thickness skin graft. Damage to surrounding structures such as to the tibial and peroneal nerves can result during dissection of the popliteal fossa. Sural artery occlusion due to kinking of the pedicle may compromise the vascularity of the flap; a preoperative angiogram can identify this arterial anatomy and may help prevent this mishap. Lower-extremity deep vein thrombosis is a relative contraindication to the use of this flap. To preserve plantar flexion, the medial or lateral gastrocnemius muscle flap should not be used if the opposite head of the gastrocnemius and the soleus muscles are not functional.

42.4 Free Microvascular Flaps

Free flaps are considerably more technically demanding than local or pedicled flaps. A free flap involves detaching a unit of tissue (which may contain skin, fascia, fat, muscle, bone, or various combinations of all of these tissues) with its blood supply and anastomosing this unit to a new blood supply by using microvascular techniques. The main complication, flap loss, results from vascular compromise of either arterial or the venous in nature (Table 42.2).

Technical factors are clearly the most important consideration, and many of these factors are interlinked. As the microvascular anastomosis is done under either loupe magnification or the microscope, technical complications consistent with all vascular surgeries, such as "backwalling" and improper suturing or rotation of the artery or vein and resultant kinking of the vessel, may result in immediate or delayed thrombosis. Inadequate pain control may lead to excessive movement, which may lead to the mechanical shearing of the graft or disruption of the microvascular anastomosis. Venous engorgement may produce thrombosis of the vessels in the graft, eventually causing ischemic damage. In particular, constrictive dressings may compromise both venous outflow and arterial inflow, resulting in flap loss. Hypothermia may lead to vasospasm of the inflow vessel, as may the use of vasopressors. Hourly monitoring for the first few hours to days is critical to the success of any microsurgery as flap salvage is dependent upon the time to identification of critical flap ischemia.

A few commonly used free flaps and the attendant complications associated with them are described in the following sections.

42.4.1 Radial Forearm Free Flap

The radial forearm free flap, usually constructed in its fasciocutaneous form, is applicable in diverse situations

TABLE 42.2

Sources of Complications Affecting Free-Flap Reconstruction

1. Technical factors
   a. Surgical skill
   b. Position of the anastomosis
   c. Tension of the pedicle
   d. Redundant pedicle
2. Poor inflow (below stenotic lesions, use of vasoconstrictors)
3. Poor outflow (venous engorgement)
4. Inadequate immobilization
5. Poor pain control
6. Hypothermia
7. Constrictive dressings

Source: Kilaru, S. et al. *J. Am. Coll. Surg.*, 193, 538, 2001.

such as lower-extremity coverage, resurfacing of the floor of the mouth, pharyngeal reconstruction, penile reconstruction, or upper extremity (hand and elbow) reconstruction. A preoperative Allen's test is mandatory to ascertain the patency of the radial and ulnar arteries in all cases to prevent the devastating complications of an ischemic hand, brought about by removing the dominant (or rarely the only) vessel of the hand. The ulnar artery trap, which includes the anatomic anomaly of a superficial ulnar artery in addition to the radial artery, can lead to the same problem [3]. Donor-site complications may include exposed tendons and their subsequent rupture, cold intolerance, and damage to the radial sensory nerve, which causes painful paresthesias. Harvesting the radius muscle in the form of an osteomyocutaneous flap may result in fracture of the radius. This complication can be avoided by harvesting less than 40% of the cross-sectional area of the radius.

The skin graft used to cover the donor site is usually of a poor color match and does not address the contour defect in the more heavyset patient. The flap is usually taken from the nondominant hand so that functional deficits can be minimized.

42.4.2 Fibula Free Flap

Since its original description by Taylor et al. [4], the fibula free flap has been adapted by plastic surgeons to become the workhorse of mandibular reconstruction. The specific advantages of this flap for mandibular reconstruction include the long length of available bone, the flap's ability to undergo segmental osteotomies (hence improving its malleability), the ready incorporation of dental implants, and the easily tolerated donor-site defect. The flap has also been used in this form to replace long-bone defects resulting from either trauma or tumor ablation or occasionally in those cases of maxillary reconstruction requiring segmental reconstruction.

Assessment of the vascularity of the leg preoperatively by either angiography or magnetic resonance angiography (MRA) will help avert the consequences of critical limb ischemia. Thorough knowledge of the regional anatomy is a prerequisite for harvesting this flap, which is among the most demanding of flap procedures. The vascularity of the associated skin paddle incorporated in an osteomyocutaneous fibula flap may be unreliable because it relies on a few and sometimes diminutive septocutaneous perforators. Incorporating a cuff of muscle from the lateral and anterior compartment muscles helps preserve the periosteum and, consequently, the blood supply to the bone.

Damage to the peroneal artery during osteotomy can compromise the viability of the flap. During flap harvest, care must be taken to avoid the peroneal nerve where it curves around the neck of the fibula. Similarly, leaving approximately 8 cm of the bone at the lower end of the fibula helps maintain the stability of the ankle mortise.

42.4.3 Rectus Abdominis Free Flap

This long, strap-like muscle is particularly useful in providing coverage for large defects, and it can be harvested with its overlying skin paddle if necessary. It can be used as a pedicled flap and is extremely versatile in this use. As a free flap, the muscle is usually harvested with the deep inferior epigastric artery; this procedure provides the advantages of a long pedicle and a large-diameter vessel, thus considerably easing the task of anastomosis. A slipped tie from this pedicle, however, can result in substantial yet initially "silent" retroperitoneal blood loss. Prosthetic mesh may be used to prevent the complications of hernia resulting from the harvest of muscle.

A variant of the rectus abdominis flap is the free TRAM flap, which has been widely used for breast reconstruction. The complications associated with the pedicled TRAM flap, such as ventral hernia or abdominal wall weakness, can be minimized with the free-flap transfer of a more limited segmental harvest of the rectus muscle. The free TRAM flap generally has a better blood supply than the pedicled TRAM flap; this advantage results in a lower incidence of fat necrosis because it is not necessary to include the blood flow, thus limiting mesh of vessels connecting the deep superior and inferior epigastric arterial systems. The procedure, however, requires a steep learning curve, in part because of the difficulty in performing a microvascular anastomosis to the thoracodorsal vessels deep in the axilla or to the internal mammary artery. Total flap loss, although uncommon when the surgeon is experienced, is more likely than when the pedicled form of the flap is used.

42.4.4 Latissimus Dorsi Free Flap

The large mass (area) of the latissimus dorsi muscle makes this muscle ideal for covering very large defects in any region of the body. Like the rectus abdominis flap, the latissimus dorsi flap is hardy and can be easily harvested with a skin paddle. Skin necrosis is unusual. Seromas at the donor site are a common problem when latissimus dorsi flaps are used, but reports indicate that using sharp dissection instead of electrocautery can reduce the incidence of this complication by half. More muscle mass can be harvested by including the serratus anterior muscle in the dissection. This procedure, however, increases the likelihood of injury to the long thoracic nerve and the debilitating "winged scapula."

Using this flap to treat patients who are wheel-chair bound can lead to a loss of strength in stabilization and

in extending the shoulder. This condition may negatively affect the patients' ability to transfer to and from the wheelchair, thus decreasing their quality of life.

42.4.5 Jejunal Free Flap

Currently, the jejunal free flap is most commonly used to reconstruct the upper digestive tract after ablative resection of cancerous growths. Jejunal flaps are much more susceptible to ischemia than the flaps described earlier and therefore demand greater technical proficiency of the surgeon performing the anastomosis. Complications associated with jejunal flaps include anastomotic strictures; problems at the donor site, such as abdominal wound infection, dehiscence, and bowel obstruction due to adhesions; and volvulus. Necrosis of the jejunal segment used for esophageal reconstruction could lead to fistulae, abscess, and mediastinitis.

42.5 Complications of Reconstructive Surgery: Maxillofacial Surgery

Reconstructive surgery for patients who have suffered serious facial injuries has improved greatly over the past several decades. Early intervention and rehabilitation, as well as advancements in bony fixation, have reduced the long-term sequelae of such injuries. Despite these improvements, surgical procedures can still cause complications, which fall into two broad categories: soft-tissue complications and skeletal complications.

Traumatic soft-tissue injuries to the head and face may result in a wide variety of secondary complications. The extent of these complications depends on the exact nature of both the inciting traumatic event and the specific tissue injured. Lacerations and abrasions should be thoroughly cleansed and vigorously debrided of foreign bodies because of the risk of substantial scarring and tattooing. However, overzealous debridement or removal of tissue may result in significant loss of tissue that is not easily replaced, such as that of the eyelid. Every effort should be made to meticulously remove foreign bodies and devitalized tissue, but maximal preservation of vital structures is standard. Scarring is generally inevitable in most cases of significant lacerations, but early closure with fine suture materials and meticulous wound care can minimize the extent of scarring and the need for surgical revision. Early removal of sutures may help the scar appearance by preventing the so-called railroad track marks.

Soft-tissue injuries may affect additional structures of the head and face, which are crucial to function. Because of its course and superficial location, the facial nerve is easily damaged by a number of mechanisms of trauma to the face. Early intervention and repair of such injuries are important to assure the long-term function of the facial muscles. Once significant scarring and muscle atrophy have occurred, return of function is less than optimal. Injuries to the orbital and ocular region may cause substantial long-term complications. Such injuries may include unrecognized injuries to the lacrimal system, corneal abrasions with residual scarring, and orbital malposition or entrapment of the globe or the extraocular muscle with subsequent enophthalmos and diplopia. If recognized early, most of these injuries can be successfully treated with a minimum number of residual long-term complications. Traumatic ectropion is exceedingly difficult to correct if not addressed early. Late repair of such problems is generally less satisfactory because scar formation in such delicate tissues may compromise function. Additional complications may involve neuropraxia to the sensory nerves, especially the infraorbital and inferior alveolar nerve. Proper alignment of fractures in the maxilla and mandible is generally sufficient to help restore function, if the nerve has not been lacerated. With blunt injury, however, chronic pain or complete loss of sensation may yield substantial morbidity.

Fractures of the facial skeleton are extremely common. The pattern of injury is generally reproducible related to the type and nature of the trauma. The likelihood of complications after repair of facial fractures has been greatly reduced as a result of early intervention and the use of vastly improved techniques of exposure and fixation. Although it was previously believed that repair of facial skeletal injuries should be delayed to allow soft-tissue swelling to decrease, subsequent studies have demonstrated that early intervention within 24–48 h is beneficial in allowing more precise alignment of the bony segments because the ingrowth of fibroblasts and the process of scar healing will not yet have commenced. This will allow more precise alignment and thus better fixation.

Additionally, early fixation with the use or rigid miniplate and microplate fixation will allow the patient to begin all aspects of rehabilitation and mastication, thereby accelerating healing. The use of rigid fixation has improved not only early fixation but also long-term results. Traditional complications associated with fracture fixation in the facial skeleton include malunion, nonunion, and, as a consequence in some cases, infection and even rarely osteomyelitis.

Of particular concern in the repair of facial fractures is proper maintenance of occlusion. Malunion or failure of fixation may result in nonunion of the maxilla or mandible and hence malocclusion, which can be devastating for the patient. Significant attempts at reconstruction may be required to correct this postoperative

complication. All efforts should be expended preoperatively to ascertain proper occlusal contact. The liberal use of intermaxillary fixation with either wires or intermaxillary fixation screws should be incorporated to establish the proper occlusion and occlusal contact prior to any reduction or fixation. Injuries to the temporomandibular joint (TMJ) and the condyle, if inadequately addressed, may result in ankylosis of the TMJ. Early range of motion as a result of proper rigid fixation may assist in prevention of ankylosis by allowing the jaw to move. This also has the salubrious effect of allowing proper nutrition, as opposed to those patients who are "wired shut."

Proper evaluation of such injuries with early mobilization of the jaw may improve functional outcome. The removal of teeth in line of the fractures may be required to make sure that the likelihood of odontogenic infections is limited. Maxillary sinusitis may occur after fracture repair, especially if there is obstruction of various drainage routes for the sinuses such as the meatuses of the maxillary sinus. Care should be taken to remove bone fragments and blood from the fractured sinus. Frontal sinus fractures may result in dural injuries and obstruction of the frontal sinus drainage. In such cases, care should be taken to properly address the frontal sinus fracture, and cranialization of the sinus may be required in certain cases. Patency of the frontal sinus duct should be ascertained. Complications may include cerebrospinal fluid leakage or late formation of mucocele.

In summary, reconstructive surgery provides substantial relief to patients suffering from loss of tissue from either trauma or ablative surgery for cancer resections. The majority of the complications are related to a variety of host factors but are more typically related to technical problems in either planning or execution of the surgery. Advances in the understanding of the anatomy with improved radiologic techniques and understanding of segmental and regional blood supply have vastly improved our ability to avoid more common complications.

References

1. Sanders WE. Principles of microvascular surgery. In: Green DP, Pederson WC, Campert R, eds. *Green's Operative Hand Surgery*. 4th edn. New York: Elsevier Science, 1998, pp. 1094–1138.
2. Kilaru S, Frangos SG, Chen AH et al. Nicotine: A review of its role in atherosclerosis. *J Am Coll Surg* 2001; 193: 538–546.
3. Fatah MF, Nancarrow JD, Murray DS. Raising the radial artery forearm flap: The superficial ulnar artery "trap". *Br J Plast Surg* 1985; 38:394–395.
4. Taylor GI, Miler G, Ham FJ. The free vascularized bone graft. A clinical extension of microvascular techniques. *Plast Reconstr Surg* 1975; 55:533–544.

Further Readings

Mathes SJ, Nahai F. *Reconstructive Surgery: Principles, Anatomy and Technique*. New York: Elsevier Science, 1999.

Strauch B, Vasconez L, Findlay-Hall E, eds. *Grabb's Encyclopedia of Flaps*. 2nd edn. New York: Lippincott Williams & Wilkins, 1998.

Section X

Genitourinary

43

Complications in Gynecologic Surgery

Constance A. Young and Susan J. Gross

CONTENTS

The female reproductive tract exists in close proximity to a number of organ systems. Whether the surgery is abdominal, vaginal, or minimally invasive, the gynecologic surgeon must always be aware of key structures in the gastrointestinal (GI), urologic, neurologic, and vascular systems. An intimate knowledge of pelvic and abdominal anatomy as well as technical skills appropriate to the planned procedure are vital in preventing, recognizing, and managing complications of the procedure.

43.1 Preoperative Period

History: Prevention of complications begins in the preoperative period. An appropriately detailed history, particularly aimed at identifying previous abdominal surgeries and outcomes, will aid in determining the method of entry into the pelvis. A history of inflammatory conditions in the abdomen and pelvis, such as pelvic inflammatory disease, diverticulitis, inflammatory bowel disease, or endometriosis, all should raise the possibility of pelvic adhesions, changes in the normal anatomic landmarks, and increased risk of injury during surgery. Recognizing that smoking, obesity, and diabetes are risk factors for postoperative surgical site infections can allow the surgeon to be proactive in choosing the duration of prophylactic antibiotics or using vacuum technology for wound closure. A history of thrombotic events will help determine the intensity of interventions to prevent deep venous thrombosis and pulmonary embolus.

Physical exam: Physical exam should note any existing abdominal scars, their locations, and the mobility of the underlying pelvic organs. If the patient's history does not adequately explain the scars, additional history must be obtained prior to surgery. Any masses palpated should be evaluated with imaging studies; pelvic and transvaginal ultrasound may be sufficient, but if the nature of the mass remains unclear, computed tomographic (CT) scan or magnetic resonance imaging (MRI) are sometimes indicated. Barium enema and/or colonoscopy may be necessary if inflammatory or neoplastic bowel conditions are entertained in the diagnosis.

Preoperative testing and evaluation: Preoperative testing and evaluation should be appropriate to the patient's age, medical comorbidities, planned surgery, and potential complications. Preexisting medical conditions should be optimized, and cervical cytology, endometrial biopsy, and tumor markers should be obtained if indicated. Mammography and colonoscopy screening may be warranted depending on the patient's age. Preoperative bowel preparation, antithromboembolic prophylaxis, and antibiotic prophylaxis may be indicated for some procedures.

This chapter will review complications of gynecologic surgery relevant to the various organ systems of the pelvis and abdomen. Strategies for preventing, recognizing, and treating injury to nerves, vascular structures, the genitourinary system, and the GI system will be presented.

43.2 Neurologic Complications of Gynecologic Surgery

Neurologic injury in gynecologic surgery can usually be attributed to one or more of three factors: positioning, retraction, or direct surgical injury. Contributing factors include prolonged surgery, radical dissections, patient weight, and patient anatomy. Most neurologic complications are minor, transient, and resolve spontaneously. In rare instances, the injury is permanent, with significant alterations in patients' quality of life.

Upper extremity: Neurologic injury to the upper extremity is almost entirely due to positioning issues. The brachial plexus (C5 to T1) is susceptible to stretch or compression injuries. The use of shoulder braces for women undergoing laparoscopic surgery with the use of steep Trendelenburg can be associated with stretch injuries when the brace is placed too far laterally and compression injuries when placed too medially. Alternatives to shoulder braces include the use of bean bags or gel pads. Also of value is the use of an egg crate mattress against the patient's bare back, which creates a drag coefficient and prevents slippage during deep Trendelenburg positioning.[1] Brachial plexus injury is also seen when the arms are secured on arm boards and abducted to greater than 90° from the patient's body. These injuries can be avoided by checking the arm position before the drapes are placed to ensure the angle is less than 90° or by tucking the arms by the patient's side. Signs of brachial plexus injury can include wrist drop, inability to move the arm, or milder symptoms of numbness and/or tingling.[1] Ulnar neuropathy, also due to positioning injury, presents with paresthesia of the fourth and fifth digit and the lateral hand. During laparotomy, the ulnar nerve can be compromised if the arm is secured on an arm board in the pronated position. Supination of the forearm and placement of padding around the elbow is an effective way to prevent this complication.[1] Ulnar injury has also been reported following laparoscopy if the arm is supinated before tucking it by the patient's side or if the arm loosens from its restraints and falls onto the metal rails of the surgical table.

Neurologic complications in the pelvis are generally a result of damage to the lumbosacral nerve complex, which arises from nerve roots from T12 to S4. The major nerves involved are the iliohypogastric, ilioinguinal, genitofemoral, lateral femoral cutaneous, femoral, obturator, pudendal, and sciatic nerves.

Ilioinguinal/iliohypogastric nerve damage can occur during laparoscopic procedures or laparotomy performed through a low transverse abdominal incision. The nerves run laterally through the head of the psoas muscle, then through the transversus abdominis muscle, and terminate in the lower lateral aspect of the anterior abdominal wall.[2] Nerve damage in these instances can be the result of direct injury, incorporation into a suture, or late formation of scar tissue and presents as pain and burning at the incision sites, labia, mons, or inner thigh. If recognized, most injuries are reversible with removal of the sutures.[3]

Obturator nerve injuries are seen most frequently following extensive retroperitoneal dissections, particularly those done for endometriosis or pelvic malignancy. Symptoms include sensory loss in the upper medial thigh and motor weakness in the hip abductors.[2] The likelihood of nerve injury can be reduced by retracting the external iliac vessels to maximize exposure of the obturator space. If transection of the obturator nerve is noted intraoperatively, it should be repaired with microsurgical techniques.[2] Obturator nerve injuries respond well to postoperative physical therapy, and complete recovery is common.

Femoral nerve injury associated with abdominal hysterectomy has a reported incidence as high as 12%.[1] Patients with femoral nerve injury have difficulty getting out of bed and climbing stairs, typically present with inability to flex the hip or bend the knee on the affected side and may have paresthesias of the thigh.[1] The femoral nerve runs between the psoas and iliacus muscles, passes under the inguinal ligament, and enters the thigh and is therefore vulnerable to injury from self-retaining retractors both when the retractor pulls the psoas laterally and when the retractor rests directly on the psoas. Positioning the patient in candy cane stirrups during vaginal surgery can result in excessive hip flexion, external rotation, or abduction

with compression of the femoral nerve against the inguinal ligament.

Genitofemoral neuropathy is primarily seen following oncologic surgery. The genitofemoral nerve runs along the ventral surface of the psoas and lies lateral to the external iliac artery where it is vulnerable to injury during pelvic node dissection or the removal of a large mass adherent to the pelvic sidewall. Nerve injury results in paresthesia of the ipsilateral mons, labia majorum, and skin over the femoral triangle.[2]

Sciatic nerve injury and damage to its peroneal branch are infrequently seen following vaginal surgery. Like the femoral nerve injury discussed earlier, the sciatic nerve can be damaged when the patient is positioned in lithotomy and there is an angle approaching 180° between the knee and thigh (i.e., the legs are nearly straight) or when there is excessive external rotation or abduction of the thighs at the hip.[4] Sciatic nerve injuries result in weakness of the hamstring muscles.[5]

Peroneal nerve injuries can be sustained via compression at the lateral fibular head.[2] This injury commonly results in the inability to abduct and evert the foot, accompanied by numbness of the lateral leg and dorsum of the foot.[5]

Lateral femoral cutaneous nerve injury is due to excessive flexion of the hip in lithotomy position (1) or during laparotomy as a result of compression by the lateral blades of self-retaining retractors as it courses over the iliacus muscle and runs under the inguinal ligament. Postoperatively patients experience paresthesia and pain in the anterior and posterior lateral thigh, from the inguinal ligament to the knee, a condition also known as meralgia paresthetica.[3]

The pudendal nerve (S2–S4) exits the pelvis via the infrapiriform or greater sciatic foramen, runs behind the lateral third of the sacrospinous ligament, and reenters the pelvis through the lesser sciatic foramen. Damage to the pudendal nerve can occur during vaginal surgery, especially during sacrospinous ligament fixation for vaginal vault prolapse.[3] A suture placed through the sacrospinous ligament can quite easily incorporate the pudendal nerve as well. It has also been reported following a transobturator inside-out tension-free tape procedure.[6] The incorporation of the pudendal nerve in a suture or placement of a transobturator tape more caudally than recommended can result in pudendal neuralgia, which presents as gluteal/perineal pain or paresthesia. The suture or tape may need to be removed in order to obtain relief of symptoms.

43.2.1 Minimizing the Risk of Nerve Injuries

The vast majority of nerve injuries in gynecologic surgeries are due to one or more of the following: improper positioning of the patient, improper placement of retractors, extensive retroperitoneal dissection, improper trocar placement, and improper incision. Nerve injury will be avoided if the following steps are followed:

1. Minimize use of self-retaining retractors particularly in thin patients. Most benign cases can be done without them. If a self-retaining retractor is necessary, use the shallowest blades possible and cushion with lap pads.
2. Position patients so the arms are abducted less than 90° from the body. If arms are tucked, cushion the posteromedial aspect of the elbow. Avoid shoulder braces if at all possible.
3. If patients are in lithotomy, avoid candy cane stirrups if at all possible in favor of stirrups that support the knee and calf. Position patients with moderate flexion at hip and knee, minimal abduction, and minimal external rotation of the hip. Check the lateral fibular head and pad if necessary.
4. Place lateral trocars at least 2 cm medial and 2 cm superior to the anterior superior iliac spine.
5. If using a Pfannenstiel incision, do not cut the rectus fascia beyond the lateral border of the rectus.
6. Know what your assistants are doing. It is all too easy to perch on a patient's arm or lean on a patient's thigh during lengthy procedures, with a neurologic injury as the outcome.
7. If performing a retroperitoneal dissection or removing a pelvic sidewall tumor, identify the obturator nerve if possible. Retracting the external iliac vessels can be helpful.

43.3 Vascular Complications of Gynecologic Surgery

43.3.1 Anterior Abdominal Wall

Injury to the vessels of the anterior abdominal wall is a recognized complication of both laparoscopy and laparotomy. The inferior epigastric vessels arise from the external iliacs, run just medial to the round ligament as it passes through the deep inguinal ring, then proceed obliquely and superiorly through the transversalis fascia, then between the rectus muscle and its posterior sheath, and ultimately anastomosing with the superior epigastric vessels. The vessels follow a line from the middle of the inguinal ligament toward the umbilicus,

but shortly after this line crosses the linea semilunaris, the direction changes and the vessels proceed directly upward in the line of junction of the inner third with the outer two-thirds of the rectus muscle.[7]

Laparoscopy: Laparoscopic injury to the inferior epigastric vessel is usually related to placement of lateral or secondary ports. Secondary trocars are usually placed 5 cm above the symphysis and 8 cm lateral to the midline in order to avoid the inferior epigastric vessels.[8] In addition, the laparoscope can be used to transilluminate the anterior abdominal wall in the area of a planned trocar insertion; in patients of slender or normal build, this technique will clearly show vascular densities and allow their avoidance. Both of these techniques can fail in the following circumstances: (1) the patient is obese, (2) the trocars are inserted in the skin appropriately but allowed to meander toward the patient's midline during insertion, (3) intraperitoneal adhesions prevent optimum lateral trocar placement, and (4) reinsertion of a secondary trocar especially when the pneumoperitoneum has been lost.[9]

Laparotomy: Rarely, the inferior epigastric artery can be damaged during laparotomy. At a point 2 cm above the symphysis pubis, the inferior epigastrics are lateral to the lateral border of the rectus muscles. This area, Hasselbach's triangle, is bounded medially by the lateral border of the rectus abdominis muscles, laterally by the inferior epigastric vessels, and inferiorly by the medial half of the inguinal ligament. Low transverse fascial incisions that begin 2 cm above the symphysis are often curved upward in order to avoid transecting the iliohypogastric or ilioinguinal nerve, placing the inferior epigastric vessels at risk. As with laparoscopic injuries, this is easily recognized and treated by suturing or cauterizing the bleeding vessels. The prevention of this type of injury is easily attained by placing the fascial incision 4 cm or more above the symphysis.

43.3.2 Major Vessels of the Pelvis

Major vessels at risk during gynecologic surgery include the aorta; the common, external, and internal iliac arteries; the vena cava; and the common, external, and internal iliac veins.

Laparoscopy: Vascular complications of laparoscopy involving the major vessels of the pelvis are uncommon, occurring in approximately 0.04% of cases,[10] and have been reported involving each of the vessels mentioned earlier. In most cases, vessel injury occurs in the initial stages of the operation while inserting either the Veress needle or trocars through the anterior abdominal wall.[10] The aorta and vena cava are particularly vulnerable to Veress needle injury when the Veress is inserted at a 90° angle to the patient's anterior abdominal wall; the insertion of the needle at 45° into the umbilicus and angling toward the pelvis has a protective effect. Unfortunately, in even moderately obese patients, a 90° angle is often necessary to access the peritoneal cavity; in these cases, control of the depth and speed of needle insertion and elevation of the anterior abdominal wall with sharp towel clamps can protect the major vessels from injury. Open entry techniques have been proposed to reduce such complications. However, while an open entry technique does limit the incidence of failed entry, the literature does not support the prevention of major vascular or visceral complications.[11] Avoidance of the umbilical area altogether in primary trocar insertion should clearly impact the risk of major pelvic vascular injury. Entry at Palmer's point, in the left upper quadrant, midclavicular line immediately inferior to the costal margin, provides a safe alternative to umbilical entry. As this is not a common entry site in gynecologic surgery, the risk of vascular injury is uncertain but should be considered as an alternative when the patient is felt to be at increased risk.

Laparotomy: Vascular injury at laparotomy is rarely seen during procedures for benign disease and is primarily a complication of surgery for advanced malignancy or for diseases requiring significant retroperitoneal dissection.

43.3.3 Identification and Treatment

Signs of a vessel injury include (1) copious blood from the Veress needle or trocar site in the case of laparoscopy; (2) brisk intraperitoneal bleeding; (3) a rapidly expanding retroperitoneal hematoma; and (4) signs of hemodynamic instability including hypotension, tachycardia, or both. It is especially important to avoid blindly clamping areas of bleeding as this may result in the incorporation of the ureter into the clamp. The wisest approach is to apply pressure to the area while gaining appropriate exposure with retractors or by enlarging the existing incision. Once the area is visualized, the packing is removed in a controlled fashion, with bleeding vessels cauterized, repaired, or ligated. Hemostatic agents may be helpful. Bilateral hypogastric artery ligation can be useful, as can pelvic artery embolization using interventional radiology techniques. If all else fails, packing the area with multiple lap pads and closing the abdomen[12] can be an effective temporizing measure while the patient is stabilized with blood products. Usually the pads are removed during laparotomy 12–48 h later, depending on the patient's hemodynamic status. Techniques to control bleeding from the epigastric vessels include direct suturing, with or without extension of the involved port site; compression with a Foley catheter inserted through the trocar sleeve; and bipolar coagulation of the vessel intraperitoneally.

43.4 Urologic Complications of Gynecologic Surgery

The degree of morbidity due to a urologic injury is often directly related to the time of diagnosis, with immediate recognition often requiring little or no additional hospitalization. Conversely, delayed diagnosis can be a cause of significant morbidity and may require additional surgery, hospitalization, or diversion of the urinary stream for a prolonged period of time with ongoing major repercussions. It was estimated in a Canadian study that the risk of litigation increases over 90-fold in the setting of a urinary tract injury compared with other complications of gynecologic surgery.[13] The incidence of injury to bladder and ureter ranges from less than one injury per 1000 for subtotal hysterectomy up to 13 injuries per 1000 surgeries for laparoscopic hysterectomy and for other gynecologic and urologic surgeries.[14] Ureteral injuries alone have been estimated to range from 2% to 11% among women undergoing advanced surgeries for prolapse or incontinence such as sacrospinous fixation, vaginal vault suspension, sacrocolpopexy, urethropexy, and bladder neck suspensions.[15]

43.4.1 Ureteric Injury

Iatrogenic injury to the ureter occurs somewhat more frequently than bladder injury. Risk factors include a history of previous pelvic surgery, endometriosis, pelvic inflammatory disease, inflammatory bowel disease, extensive neoplasm, or extensive adhesions, often leading to preoperative stent placement. Hence, the majority of injuries to the ureter occur in patients without significant risk factors.[16] Anatomically, the ureter runs retroperitoneally, entering the pelvis by crossing the bifurcation of the common iliac vessels, running medial to the hypogastric artery, and tracking down the lateral aspect of the uterosacral ligament to enter the cardinal ligament. It passes beneath the uterine artery approximately 1.5 cm lateral to the cervix and then passes medially to enter the bladder trigone.

Ureteral injuries can be divided into two groups. One group seldom requires surgical repair and involves kinking or partial obstruction of a ureter without compromise of ureteral patency. These patients usually have undergone abdominal hysterectomy with inclusion of the ureter in a sutured pedicle at the level of the cardinal ligaments. Patients in this group may have colicky pain, hydroureter and hydronephrosis on imaging, but have partial flow and can usually be managed by removal of the suture (if the injury is recognized promptly) or placement of a retrograde stent into the affected ureter. The second group of patients has ureteral injuries that will require surgical repair. The ureter has been either crushed, transected, or ligated, is nonpatent, and patency cannot be reestablished with stenting. In addition, use of the newer energy-based vessel sealing devices in close proximity to the ureter can cause a cautery injury that may not manifest itself until days or weeks after the surgery. The ureter is most vulnerable to injury at three sites in the pelvis: (1) at the pelvic brim where it rests in close proximity to the infundibulopelvic ligament, (2) at the lower uterine segment where it passes beneath the uterine vessels, and (3) at the level of the uterosacral ligaments.

43.4.2 Identification and Treatment of Ureteric Injury

Intraoperative: A complete ureteral transection may be apparent during abdominal or laparoscopic surgery if urine is noted in the pelvis during surgery or if indigo carmine has been given in preparation for cystoscopy and blue dye is seen to extravasate into the pelvis. It may also be obvious if cystoscopy is undertaken and no ureteral jet is noted from one orifice. In this setting ureteral repair should be immediately undertaken by an individual expert in urologic surgery. Gynecologic oncologists and urogynecologists in general are comfortable repairing transected ureters; generalists are typically not well prepared to handle these surgeries without assistance from a urologist, who should be called into the operating room if needed. The ureter can either be stented and reimplanted into the bladder or directly reanastomosed over a stent. The placement of a pelvic drain to assess any pelvic fluid collections and evaluate postoperative leaking of urine from the anastomosis is a key to successful repair. Ureteroureterostomy with stent placement is the preferred repair for injuries to the proximal one-third ureter (the area from the ureteropelvic junction to the upper border of the sacroiliac joint). Success rates are over 90% in most series[17] and are dependent on creation of tension-free anastomoses over a stent, with good vascular supply to both ends of the anastomosis. In cases of long segments of compromised proximal ureter use of an ileal conduit, Boari flap or psoas hitch can be helpful in reestablishing patency but should best be undertaken by an individual with experience in these procedures. The middle third of the ureter is that part that courses over the sacrum. If a tension-free anastomosis is possible, this area is also appropriate for a ureteroureterostomy with stent. Otherwise, the bladder is mobilized using a psoas hitch, and a ureteroneocystostomy is performed over a stent.[17] A Boari flap can be used for injuries involving a large part of the middle third. The distal one-third of the ureter passes from the inferior border of the sacroiliac joint to the bladder and accounts for 91% of ureteral injuries.[17,18] Ureteroneocystostomy, with or without bladder mobilization/Boari flap, is the

treatment for distal ureteral injuries.[17] In all of the aforementioned repairs, prolonged catheterization of the bladder for 1–2 weeks is generally recommended.

Postoperative: Ureteral injuries not recognized at the time of surgery will usually become apparent in the first few weeks postoperatively. Symptoms are quite variable, but may include fever, ileus, nausea, vomiting, pain or distention, anuria/oliguria/hematuria, unilateral flank pain, or frank drainage of urine from the vagina or abdominal incision. The leakage of urine into the peritoneal cavity may result in urinary ascites, usually accompanied by an elevated serum blood urea nitrogen (BUN) and creatinine; retroperitoneal urine collection will result in a urinoma. Imaging studies such as ultrasound and CT scan and retrograde pyelogram may be necessary. The diagnosis of injury, treatment of infection, ending urine leakage, and protection of the involved kidney are the most important aspects of care following a ureteral injury. Cystoscopy with stent placement should be attempted if there is some ureteral patency. The placement of a temporary nephrostomy tube may be necessary if the damaged ureter cannot be stented or if the patient is not medically stable to undergo additional surgery.

43.4.3 Bladder Injury

The rate of reported bladder injuries in gynecologic surgery is greatly dependent on whether or not identification using cystoscopy is performed at the time of surgery, ranging from 3 to 129 per 1000 surgeries.[14] Injuries to the bladder can result from any pelvic surgery including trocar insertion at laparoscopy. Patients with a history of previous surgery, including caesarian section, malignancy, pelvic adhesions, and pelvic radiation, are at increased risk. Similar to ureteral injuries, bladder injuries can be grouped into those that require surgical repair and those that do not. Bladder abrasions or placement of transmural sutures generally do not require surgical treatment. Small cystotomies that occur in the dome of the bladder and are under 1 cm in diameter will often close with only prolonged bladder decompression with a catheter. Large cystotomies, especially those near the trigone, require surgical repair.

43.4.4 Identification and Treatment of Bladder Injury

Intraoperative: Urine leaking into the operative field or the finding of blue dye from indigo carmine administration may be clear-cut signs of a bladder injury, usually accompanied by reduction in urine output from the bladder catheter. Bladder injuries recognized intraoperatively should be immediately assessed and repaired if necessary.

Postoperative: Signs of a delayed bladder injury generally present early in the postoperative period and include pain, ileus, abdominal distention, urinary ascites, urine draining from the surgical incision or vagina, and elevated BUN and creatinine due to reabsorption from the peritoneal cavity. Such injuries are usually diagnosed using a retrograde cystogram. Delayed bladder injuries can also present as colovesical or enterovesical fistula.[17,19,20] Symptoms include gross hematuria, frequency, irritative voiding, and the identification of feculent material in the urine. The diagnosis is generally confirmed using CT with oral and rectal contrast.

Treatment: Bladder repair is aimed at reconstituting integrity of the bladder wall and ensuring patency of the ureters. As noted earlier, cystotomies under 1 cm in diameter involving the dome of the bladder can be managed conservatively with catheter drainage for 1–2 weeks followed by a retrograde cystogram to insure integrity of the bladder. Large cystotomies in the bladder that are not in proximity to the ureteral orifices are generally closed using a two-layer closure. The first layer closes the mucosa in a running fashion using a 2–0 or 3–0 delayed absorbable suture. The second layer is used to reapproximate the seromuscular layer. A 2–0 or 3–0 delayed absorbable suture can be used in a running fashion. The bladder is then filled in a retrograde fashion with sterile milk or saline with indigo carmine to demonstrate that closure is complete. Bladder injuries that involve the trigone or are in close proximity to the ureters require a more complex approach. Closure should be done following a cystotomy so the ureteral orifices are under direct visualization, and ureteral stenting may be required. Closure is accomplished from the inside of the bladder—closing the seromuscular layer first with a 2-0 or 3-0 delayed absorbable suture and closing the mucosal layer next with the same suture. Such closures, because they are more advanced than cystotomies in the dome, should be undertaken by trained individuals. Urinary catheterization should be continuous for 2 weeks following any of the aforementioned.

43.4.5 Minimizing the Risk of Injury to the Urinary Tract

Common iatrogenic injuries to the bladder and ureters are usually due to one of the following: transection, ligation, or energy based. Avoiding injury to the ureter is best achieved by identifying the course of the ureter throughout the pelvis. This can be accomplished by entering the retroperitoneal space lateral to the infundibulopelvic ligament and identifying the ureter on the medial leaf of the broad ligament. In clinical settings where the path of the ureter is distorted by scarring, endometriosis, or other conditions, the placement of

ureteral stents can help identify injury as the surgeon can palpate the ureter throughout the surgical procedure. Lighted stents provide a visual cue as well. The prevention of bladder injuries requires identifying the bladder, sometimes a challenge in cases of significant pelvic adhesions. Filling the bladder with saline under direct observation can help the surgeon identify the borders of the bladder in relationship to the lower uterine segment and can be helpful in both minimally invasive and open surgeries.

If in doubt, cystoscope. Cystoscopy is routinely performed after some surgical procedures are performed (1) to treat urinary stress incontinence and anterior vaginal prolapse, such as Burch colposuspension, paravaginal defect repair, pubovaginal sling procedures, and tension-free vaginal tape procedures (TVT); (2) to rule out intravesical placement of sutures or mesh; and (3) to verify ureteral patency.[16] Intraoperative bladder perforation occurs in 3%–9% of cases involving TVT and other mid-urethral sling procedures that pass through the retropubic space[21,22]; hence, cystoscopy is especially necessary following these procedures. In general, the decision on whether or not to perform cystoscopy after other gynecologic procedures is left to the discretion of the operating surgeon; if there is any question as to the integrity of the urinary tract, cystoscopy preceded by intravenous indigo carmine can answer a number of questions quickly.

43.5 Gastrointestinal Complications of Gynecologic Surgery

It has been estimated that injury to the GI tract occurs in 0.05%–0.33% of cases, with a mortality rate as high as 3.6%.[23] Injury from the stomach to the rectum can occur from any number of etiologies, including Veress needle placement, laparoscopic trocar placement, suture injury, lysis of adhesions, or dissection of tumor nodules. The mechanism of injury can be penetration, crush injury, devascularization, or energy based. The morbidity from a GI injury is directly related to timing; patients in whom the injury is recognized intraoperatively can usually undergo primary repair of the involved segment and do well postoperatively. Patients in whom the injury is not recognized at the time of surgery typically present with secondary symptoms of sepsis, peritonitis, and fistula formation. Morbidity in this group is significantly increased; septic sequelae are more severe, and treatment often involves diversion of the fecal stream with colostomy or ileostomy when injury involves the large intestine. Risk factors for intestinal injury are those conditions that are likely to cause adhesions and distort anatomy. These would include a history of endometriosis, diverticular or inflammatory bowel disease, pelvic inflammatory disease, previous laparotomy, previous intestinal resection, pelvic malignancy, and pelvic or abdominal radiation treatment.

43.5.1 Identification and Treatment of Gastrointestinal Injury

If there is any question about a bowel injury, careful inspection is important to evaluate the entirety of the GI tract. The small intestine can be examined either laparoscopically or via laparotomy, from the ligament of Treitz to the cecum. Similarly, the colon can be inspected along its length. If a sigmoid injury is suspected, the sigmoid can be gently cross-clamped, insufflated using a proctosigmoidoscope, and the pelvis filled with saline to detect any escaping gas. When an injury to the stomach, small intestine, or large intestine is recognized intraoperatively, it should be repaired by an individual skilled in such repairs. When the surgeon is a gynecologic oncologist, the repair often falls within the skills of the operating surgeon; currently, most gynecologists in general practice or other subspecialities will lack the skill set to perform this repair and should yield to a general surgeon or other trained individual.

In general, small puncture wounds to the stomach can be irrigated and will heal without suturing; larger defects will require repair in one or two layers using either delayed absorbable or permanent sutures.[24] Injuries to the small intestine if small are repaired perpendicular to the long axis of the intestine in one or two layers, using either delayed absorbable or permanent sutures. If the injury is greater than half the circumference of the segment, or if the repair causes a stricture of the lumen to less than 1–2 cm, then segmental resection and anastomosis are indicated.[25] Thermal injuries are generally best treated with resection and anastomosis as well, as the extent of the injury is often not obvious at the time it occurs. Any damaged area of small intestine that has suffered vascular compromise should also be treated by segmental resection and anastomosis. In addition, areas of small intestine in a patient who has been previously irradiated can be safely reanastomosed only if the areas in question were outside the radiated field; otherwise, a diverting procedure may be necessary.[26]

The management of colonic injuries depends on the size, location, and presence or absence of mesentery involvement. Injuries involving the serosa and small full-thickness injuries can usually be closed primarily with copious irrigation of the pelvis.[23] Large injuries and those involving the mesentery should be treated with segmental resection and reanastomosis in hemodynamically stable patients, while delayed injuries may

require diversion. As with injuries to other structures discussed in this chapter, prompt repair usually results in minimal or no morbidity to the patient. Cases of delayed intestinal perforation often cause much greater morbidity and mortality as the patients present with significant peritonitis and sepsis. One study found that one in five cases of delayed diagnosis of bowel injury resulted in death.[27] Delayed repairs often require diversion of the fecal stream, a procedure that carries with it significant quality of life issues for patients even if subsequently reversed.

43.5.2 Minimizing the Risk of Injury to the Gastrointestinal Tract

In laparoscopic cases, especially those done for benign disease, preventative measures include using an alternative primary entry point such as the left upper quadrant, midclavicular line, or Palmer's point, which allows the surgeon to visualize periumbilical and pelvic adhesions and dictates secondary trocar placement. Laparotomy incisions can be performed in a paramedial position or supraumbilically if necessary to minimize the risk of enterotomy during entry into the peritoneal cavity. Using sharp dissection to free bowel adhesions and avoiding the use of energy near intestine can also play an important role in prevention. The use of a nasogastric or orogastric tube prior to laparoscopy will reduce likelihood of gastric injury by trocar or Veress needle. The role of mechanical preoperative bowel preparation, once believed mandatory for primary bowel anastomosis, is uncertain. A recent review of 18 trials involving over 5800 participants found no statistically significant evidence that patients benefit from mechanical bowel preparation in elective colon surgery.[28]

In summary, even with the utmost preparation, optimal outcome ultimately depends on the gynecologist's knowledge of pelvic anatomy, meticulous technique, and appropriate index of suspicion regarding possible intraoperative complications.

Complications in Gynecologic Surgery

Complications	Incidence (%)	References	Comments
Neurologic—lumbosacral	1.9	Bradshaw and Advincula[1]	
Neurologic—iliohypogastric/ilioinguinal	4.9	Hyun Shin and Howard[3]	
Neurologic—femoral nerve	12	Bradshaw and Advincula[1]	Data from abdominal hysterectomies
Sciatic and peroneal nerve	0.2	Pickett et al.[10]	Data from vaginal surgery
Vascular complications, laparoscopy	0.04	Pickett et al.[10]	
Inferior epigastric vessel injury			
Ureter injury	2–11	Kim et al.[15]	Surgery for incontinence or prolapse
Ureter and bladder injury	0.01 0.13	Gilmour et al.[14]	Subtotal hysterectomy, laparoscopic hysterectomy, other
Bladder perforation	3–9	Ward and Hilton[21] Tamussino[22]	TVT and other midurethral sling procedures
Injury to GI tract	0.05–0.33	Sharp and Swenson[23]	

How to Avoid Complications in Gynecologic Surgery

Complications	Method of Avoidance	Comments
Upper extremity neuropathy	Avoid shoulder braces, cushion arms, pad elbows, and all bony prominences Avoid abduction greater than 90° from body	Generally self-limited Responds to physical therapy
Ilioinguinal/ iliohypogastric neuropathy	Place lateral trocars at least 2 cm medial and superior to anterior superior iliac spine Incise fascia only to external border of rectus muscle	Release suture
Obturator nerve injury	Retract external iliac vessels to maximize exposure If transected, repair	Generally responds to physical therapy
Femoral neuropathy	Avoid self-retaining retractors. If used, use shallow blades and cushion blades In lithotomy, avoid excessive hip flexion, extreme external rotation of thighs	Generally responds to physical therapy
Sciatic and peroneal nerve injury	In lithotomy, maintain a 90° angle between thigh, leg, and abdomen. Avoid extreme external rotation/abduction of thighs	Generally responds to physical therapy

Complication	Method of Avoidance	Comments
Vascular injuries		
Inferior epigastric vessels	Laparoscopy: transilluminate Place lateral trocars 5 cm above symphysis and 8 cm lateral to midline Laparotomy: place fascial incision 4 cm above symphysis	Suture Tamponade with foley Cauterize
Major pelvic vessels	Laparoscopy: insert trocars at 45° angle Avoid Trendelenburg Control insertion depth Laparotomy: identify anatomy	Rapid laparotomy Identification of vessel Suture or hemostatic agent Packing Bilateral hypogastric ligation Interventional radiology embolization
Urologic injuries		
Ureter injuries	Identify, dissect free of broad ligament. Stent. Cystoscope after indigo carmine to confirm patency	Repair approximately 1/3 with ureteroureterostomy over stent. Distal 1/3 with ureteroneocystostomy over stent
Bladder injuries	Backfill with saline to identify boundaries of the bladder	Cystoscope Injuries of less than 1 cm close spontaneously
GI injuries		
Stomach	NGT or orogastric tube (OGT) prior to laparoscopy	Veress needle injury seldom requires suturing
Small intestine	Use sharp dissection for adhesiolysis Entry point distal from adhesions, Palmer's point for laparoscopy, supraumbilical/paraumbilical for laparotomy	Run bowel from cecum to ligament of Treitz
Large intestine	Use sharp dissection for adhesiolysis Consider mechanical bowel preparation	Test patency by clamping off, filling pelvis with saline, and insufflating with CO_2 via sigmoidoscope

References

1. Bradshaw A, Advincula A, Postoperative neuropathy in gynecologic surgery. *Obstet Gynecol Clin North Am* 2010;37:451–459.

   Dr Bradshaw and Advincula use clinical cases to describe various postoperative neurological injuries. They detail avoidance techniques and neurologic sequelae.
2. Irvin W, Andersen W, Taylor P et al., Minimizing the risk of neurologic injury in gynecologic surgery. *Obstet Gynecol* 2004;103(2):374–382.

   Drs Irwin, Andersen et al report results of a MEDLINE search using the index terms neurological injury and gynecologic surgery from 1960 to 2003. They review mechanisms of injury to various components of the lumbosacral nerve plexus along with risk reduction strategies.
3. Hyun Shin J, Howard F, Abdominal wall nerve injury during laparoscopic gynecologic surgery: Incidence, risk factors, and treatment outcomes. *J. Minimally Invasive Gynecol* 2012;19(4):448–453.
4. McQuarrie HG, Harris JW et al., Sciatic neuropathy complicating vaginal hysterectomy. *Am J Obstet Gynecol* 1972;113:223–232.
5. Burkhart F, Daly J, Sciatic and peroneal nerve injury: a complication of vaginal operations. *Obstet Gynecol* 1966;28(1):99–102.
6. Masata J, Hubka P, Martan A, Pudendal neuralgia following transobturator inside-out tape procedure (TVT-O)—Case report and anatomical study. *Int Urogynecol J* 2012;23:505–507.
7. Gray, Henry, *Anatomy, Descriptive and Surgical*. Philadelphia, PA: Running Press, 1974: pp. 570–572.
8. Hurd WW, Bude RO, DeLancey JO et al., The location of abdominal wall blood vessels in relationship to abdominal landmarks apparent at laparoscopy. *Am J Obstet Gynecol* 1994;171:642–646.
9. Bhoyrul S, Vierra MA, Nezhat CT et al., Trocar injuries in laparoscopic surgery. *J Am Coll Surg* 2001;192:677–683.
10. Pickett S, Rodewald K, Billow MR et al., Avoiding major vessel injury during laparoscopic instrument insertion. *Obstet Gynecol Clin North Am* 2010;37:387–397.

    The authors review the anatomic relationships between landmarks of the anterior abdominal wall and the retroperitoneal vessels. They discuss methods of avoiding injury to major blood vessels during laparoscopic entry.
11. Ahmad G, O'Flynn H, Duff JMN et al., Laparoscopic entry techniques. *Cochrane Database Syst Rev* 2012; Issue 2:74–98.
12. Stany M, Farly J, Complications of gynecologic surgery. *Surg Clin North Am* 2008;88:343–359.

    Drs Stany and Farley review intraoperative complications involving the urinary, GI and vascular systems along with methods of recognition and avoidance. They then dis-

cuss postoperative complications including bowel obstruction, hernia, infection, vaginal cuff dehiscence, neuropathy, and systemic complications such as pulmonary embolus.

13. Gilmour DT, Baskett TR, Disability and litigation from urinary tract injuries at benign gynecologic surgery in Canada. *Obstet Gynecol* 2005;105:109–114.
14. Gilmour DT, Das S, Flowerdew G, Rates of urinary tract injury from gynecologic surgery and the role of intraoperative cystoscopy. *Obstet Gynecol* 2006; 107(6):1366–1372.

    Drs Gilmour, Das and Flowerdew use a MEDLINE search for urinary tract injuries at gynecologic surgery from 1998–2004 along with a systemic review of the same injuries from 1996 to 1998. They compare detection rates of injury to the urinary tract with and without the aid of intraoperative cystoscopy.
15. Kim J, Moore C et al., Management of ureteral injuries associated with vaginal surgery for pelvic organ prolapse. *Int Urogynecol J* 2006;17:531–535.
16. St Lezin MA, Stoller ML, Surgical ureteral injuries. *Urology* 1991;38(6); 497–506.
17. Delacroix S, Winters JC, Urinary tract injuries: Recognition and management. *Clin Colon Rectal Surg* 2010;23(2): 104–112.

    Drs Delacroix and Winters review iatrogenic injuries to the ureter, bladder and urethra. They review the anatomy, discuss methods of prevention and early identification, and surgical repair. Although intended for colorectal surgeons this article provides general surgical care applicable to all abdominal surgeries.
18. Selzman AA, Spirnak JP, Iatrogenic ureteral injuries; A 20 year experience in treating 165 injuries. *J Urol* 1996;155(3):878–881.
19. Jarrett TW, Vaughan ED Jr, Accuracy of computerized tomography in the diagnosis of colovesical fistula secondary to diverticular disease. *J Urol* 1995;153(1):44–46.
20. Kwon EO, Armenakas NA, Scharf SC et al., The poppy seed test for colovesical fistula; big bang, little bucks! *J Urol* 2008;179(4):1425–1427.
21. Ward K, Hilton P, Prospective multicenter randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. United Kingdom and Ireland Tension Free Vaginal Tape Trial Group. *BMJ* 2002;325:67–70.
22. Tamussino KF, Hanzal E, Kolle D et al. Tension-free vaginal tape operation: results of the Austrian Registry. Austrian Urogynecology Working Group. *Obstet Gynecol* 2001;98:732–736.
23. Sharp HT, Swenson C. Hollow viscus injury during surgery. *Obstet Gynecol Clin North Am* 2010;37(3):461–467.
24. Spinelli P, Di Felice G, Pizzetti P et al., Laparoscopic repair of full-thickness stomach injury. *Surg Endoscopy* 1991:5:156–157.
25. Uzzi L, Bellati F, Zullo MA et al., Mechanical bowel preparation before gynecologic laparoscopy: A randomized, single-blind, controlled trial. *Fertil Steril* 2006;85(3):689–693.
26. Mendez LE, Iatrogenic injuries in gynecologic cancer surgery. *Surg Clin North Am* 2001;81(4):897–923.
27. Brosens I, Gordon A, Campo R et al., Bowel injury in gynecologic laparoscopy. *J Am Assoc Gynecol Laparosc* 2003;10:9–13.
28. Guenaga KK, Matos D, Wille-Jorgenson P, Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* 2011;Issue 9:12–24.

Section XI

Pediatric

44

Complications in Pediatric Surgery

Shannon W. Longshore and Gerald Gollin

CONTENTS

44.1 Introduction

Complications in pediatric surgery generally mirror those encountered in the adult population that are described elsewhere in this text. This chapter reviews complications resulting from some of the surgical disorders that are unique to infants and children. Specifically, it focuses upon complications of esophageal atresia, congenital diaphragmatic hernia, Hirschsprung disease, anorectal malformations, and pyloric stenosis. With all of these disorders, complications can result directly from operative management, but the pathophysiology of most of them is characterized by elements that are not completely solved by an operation and therefore contribute to short- and long-term morbidity.

44.2 Esophageal Atresia

Esophageal atresia, including several variants of tracheoesophageal fistulas, has an incidence of approximately 1 in 3000 live births [1]. In about 64% of cases, infants with esophageal atresia and tracheoesophageal fistula have an associated anomaly [2]. Congenital cardiac defects are the most common of these and are found in about 35%. Esophageal atresia also has an association with trisomies 13, 18, and 21. When a baby is diagnosed with esophageal atresia, it is essential to evaluate for anomalies consistent with the VACTERL (vertebral anomalies, anorectal malformation, cardiac defect, tracheoesophageal fistula, renal defect, limb deformity) syndrome [3].

Gross described five variations of esophageal atresia and tracheoesophageal fistula. Type C (86%) is the most

common and is an esophageal atresia with a distal tracheoesophageal fistula. Type A (7%) is an esophageal atresia without a tracheoesophageal fistula and Type E is an H-type fistula without atresia [4].

The diagnosis of esophageal atresia can be suggested in utero with a demonstration of polyhydramnios and/or a small stomach on ultrasound [5]. Neonates usually present with coughing or choking with feedings. The diagnosis is made when a suction catheter is seen to coil in the proximal esophagus. If the abdomen is persistently gasless, this suggests a pure esophageal atresia without a fistula.

The overall survival rate of neonates with esophageal atresia is 97%. Spitz identified two risk factors for poor outcome: birth weight less than 1500 g and major, congenital cardiac malformations. Survival for neonates with esophageal atresia and a birth weight under 1500 g drops to 60%. If a baby has both a cardiac malformation and a birth weight of less than 1500 g, their survival is only 27% [6].

44.2.1 Preoperative Complications

Appropriate preoperative management is essential in infants with esophageal atresia in order to prevent respiratory and gastrointestinal complications. It is important to decompress the esophageal pouch with a Replogle tube as soon as the diagnosis is made. This helps to avoid aspiration of pooled secretions. These babies should also have the head of their bed elevated to 30°–45° in order to prevent reflux of gastric contents into the airway through the tracheoesophageal fistula.

Endotracheal intubation should generally be avoided in esophageal atresia. If neonates are in respiratory distress and needs to be intubated, they can be difficult to manage because the path of least resistance for air is the fistula, and positive pressure will preferentially fill the stomach and intestine instead of the lungs. If excessive air accumulates in the stomach, it can lead to perforation [7]. Options for the management of gastric perforation include needle decompression of the abdomen and initiation of high-frequency ventilation on the way to the operating room followed by obtaining rapid access to the abdomen and occluding the gastroesophageal (GE) junction, placement of a gastrostomy tube to water seal, bronchoscopy to occlude the fistula with a Fogarty catheter, transgastric fistula occlusion, passage of a cuffed endotracheal tube distal to the fistula, or an emergency transpleural ligation of the fistula [8].

44.2.2 Operative Complications

The operative management of esophageal atresia with a tracheoesophageal fistula can be open or thoracoscopic. The open approach is through a right posterolateral thoracotomy, unless the patient has a right-sided aortic arch. An extra-pleural approach is used to expose the esophagus. The fundamental steps of the operation are identification and division of the tracheoesophageal fistula and construction of an esophagoesophagostomy. Intraoperative maintenance of oxygenation may be difficult as positive pressure ventilation is avoided until the fistula is ligated, in order to avoid gastric distension. Hypoxia is managed by allowing for intermittent expansion of the right lung during dissection of the fistula.

The H-type fistula is approached via a right neck incision, and the pure esophageal atresia, which is associated with a long gap, is usually approached with a staged operation with initial placement of a gastrostomy.

The most common complications of esophageal atresia repair are anastomotic leak and stricture. Factors that predispose to stricture and leak are a long distance between the proximal pouch and the distal fistula, excessive tension across the suture line, and aggressive mobilization of the distal fistula.

Anastomotic leaks occur in about 15% of cases. Most are managed nonoperatively with chest tube drainage and seal within 4 weeks [9]. The use of fibrin glue over the anastomosis is reported to decrease the incidence of leak [10]. Only 5% of leaks require operative exploration, usually because of sepsis or hydropneumothorax. An attempt at another repair is only undertaken if there is minimal contamination and the ends of the esophagus appear healthy and viable. Most will require a segmental esophagectomy with a cervical esophagostomy and drainage of the pleural space and mediastinum. These cases will later require reconstruction of the esophagus.

Esophageal stricture (Figure 44.1) is reported to occur in 37%–49% of cases [9]. The factors that predispose to stricture include a two-layered anastomosis, anastomotic tension, use of silk suture, anastomotic leak, and acid reflux. More than 80% of strictures respond to fewer than four dilations. Pneumatic balloon dilation is preferable to bougienage, but esophageal perforation may occur with any method [11].

A missed or recurrent fistula complicates about 10%–15% of cases during the first year, typically presenting with persistent respiratory compromise. The incidence of recurrent fistula is greater in those infants with an end to side anastomosis or an early leak [12].

Recurrent laryngeal nerve palsy has been reported in as many as 20% of cases [13]. Vagus nerve injury has been described, but it is unclear whether the nerve is compromised during the esophageal dissection or may be congenitally anomalous. Almost all patients with esophageal atresia have esophageal dysmotility and gastroesophageal reflux, which can lead to failure to thrive.

The thoracoscopic approach is transpleural, but the steps of the operation are the same. It is difficult to accomplish

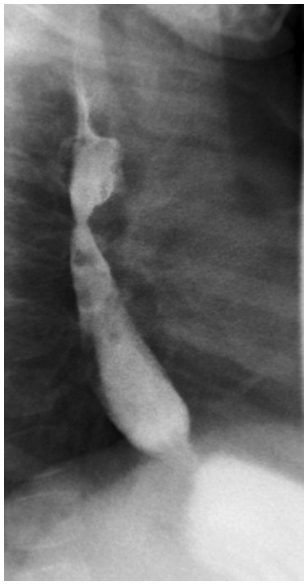


FIGURE 44.1
An esophagram in a 9-month-old girl demonstrates an esophageal anastomotic stricture.

in infants that weigh less than 2 kg or in those that have lung disease. The purported advantage of the thoracoscopic operation is prevention of winged scapula and scoliosis, which can occur after a thoracotomy in which the serratus anterior and latissimus dorsi muscles are divided with an incidence of 8%. With a muscle-sparing thoracostomy, these complications can be avoided.

Thoracoscopic esophageal atresia repair has been reported to have a leak rate of 7.6% and at least one dilation is required in 31.7%. A recurrent fistula occurs in about 2% [14].

44.3 Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) occurs in 1 in 2000–5000 births [15,16]. The overall survival of infants born alive with a CDH is approximately 60%, but reported survival ranges from 25% to 83% [16], based upon the variable severity of cases that present to particular centers. These statistics do not account for as much as one-third of fetuses with CDH who are stillborn [17]. Approximately one-third of neonates with CDH require extracorporeal membrane oxygenation [18], indicating the severe physiological derangement that is frequently associated with CDH.

Complications attributable to CDH are due much more to the pulmonary hypoplasia and pulmonary hypertension that accompany the malformation than to the medical and surgical treatment.

44.3.1 Respiratory Complications

Pulmonary hypoplasia and corresponding pulmonary hypertension are of central importance in neonates with CDH. Pulmonary hypoplasia may, in fact, precede abnormal formation of the diaphragm in the pathogenesis of the disease [19]. Short- and long-term outcomes in CDH depend primarily upon the severity and progression of lung impairment.

The pulmonary hypoplasia that accompanies CDH is probably not due merely to compression from herniated abdominal viscera. Pulmonary hypoplasia is bilateral and characterized by fewer airway generations, thickened alveolar septae, decreased type 2 pneumocytes, and fewer and abnormally muscularized small pulmonary arteries.

The lung–head ratio (LHR) on ultrasound is used as a prenatal metric to classify the degree of pulmonary hypoplasia. When the LHR is less than 0.6, mortality approaches 100% [20]. At birth, there is no definitive indicator of pulmonary hypoplasia that is incompatible with long-term survival, although one study has suggested that failure to achieve a preductal pO_2 that exceeds the pCO_2 is a predictor of poor outcome [21].

The long-term outcome from pulmonary hypoplasia in children with CDH is variable. While most adolescents with a history of CDH have minimal pulmonary morbidity [22], more than half of those who required extracorporeal membrane oxygenation (ECMO) have chronic lung disease that requires bronchodilators, supplementary oxygen, or ventilator support [23].

Pulmonary hypertension results from anatomically and functionally abnormal small pulmonary arteries. In infants with pulmonary hypertension, there is arterial oxygen desaturation accompanied by a pre- to postductal oxygen gradient due to right-to-left shunting through the ductus arteriosus and echocardiographic evidence of elevated pulmonary vascular resistance. The onset of severe pulmonary hypertension may be delayed until the second day of life. The pulmonary arterial circulation in infants with pulmonary hypertension is exquisitely reactive to pain, cold, and other stressors, which makes early repair of CDH particularly hazardous.

The management of pulmonary hypertension consists of conventional mechanical ventilation and early escalation to high-frequency ventilation and ECMO, if necessary. Although nitric oxide is very effective in infants with pulmonary hypertension associated with other conditions such as meconium aspiration, it is only effective in about 10% of infants with CDH [24].

44.3.2 Operative Complications

44.3.2.1 ECMO

ECMO is required in about one-third of newborns with a CDH; therefore, its complications contribute to those

of CDH. Among the significant complications of ECMO are bleeding, cardiovascular collapse, and cerebral ischemia.

Cannula site bleeding occurs in approximately 6.5% of cases and can usually be managed with direct pressure, adjustment of the heparin infusion, or exploration of the wound.

Hemorrhage at other sites that may have otherwise been clinically irrelevant may be exacerbated by heparinization. In particular, dramatic thoracic bleeding may result from placement of a chest tube in an infant on ECMO due to lung or intercostal vessel injury. Therefore, chest tube placement should rarely if ever be performed on ECMO. Devastating intracranial hemorrhage can occur, and this risk mandates that a head ultrasound be performed prior to cannulation to rule out subclinical choroid plexus bleeding. The risk for intracranial hemorrhage is one of the reasons why premature infants are not candidates for ECMO. When significant hemorrhage occurs at any site, ECMO usually must be discontinued.

Systemic hypotension is common on ECMO and can lead to intracranial hemorrhage if not treated with vasopressors. Pericardial tamponade may result from atrial injury by the venous cannula tip. A narrowed pulse pressure might be the initial manifestation, and diagnosis would be confirmed by ultrasound.

Intracranial infarction has been demonstrated in 8.3% of neonates undergoing ECMO. Seizures occur in a similar proportion, and 50% of those affected will have long-term developmental morbidity [25]. The incidence of cerebral ischemia is less when venovenous ECMO is used [26] as the carotid artery is left intact. Repair of the carotid artery after venoarterial ECMO has not been shown to improve neurological outcomes.

44.3.3 CDH Repair

Repair of a CDH does little to improve respiratory physiology but can exacerbate pulmonary hypertension if medium size pulmonary arteries remain reactive. Therefore, it is important that infants be on minimal supplementary oxygen, require no vasopressors, and have no ultrasonic evidence of pulmonary hypertension prior to CDH repair.

Intraoperative bleeding can occur during repair, particularly when repair is done while heparinized on ECMO. Aminocaproic acid is administered in this setting, and dissection of the posterior rim of the diaphragm is avoided in order to reduce hemorrhage. This usually necessitates the placement of a patch.

When a significant proportion of the abdominal contents are herniated into the chest, reduction into the peritoneal cavity may precipitate abdominal compartment syndrome. If abdominal closure results in increased airway pressures, a staged closure may be indicated using vacuum-assisted closure or a patch closure of the fascia in order to avoid compartment syndrome in the postoperative period.

Infrequently, a chylothorax develops pre- or postoperatively either ipsilateral or contralateral to the CDH repair. The etiology of chylothorax is not completely understood. Some believe that it results from injury to the thoracic duct in the course of patch placement, but this does not explain the occurrence of a chylothorax prior to CDH repair. Central venous thrombosis secondary to ECMO may contribute to a chylothorax by preventing drainage from the thoracic duct into the venous circulation. A unifying explanation is that CDH can be associated with lymphatic malformations that prevent normal lymphatic flow. A chylothorax is diagnosed by elevated thoracic fluid triglycerides and a lymphocyte count over 90%. Treatment consists of making the patient NPO (nil per os) or transitioning to a medium-chain triglyceride formula, administration of octreotide, and, if conservative measures are unsuccessful, pleurectomy and pleurodesis [27].

Patch closure of the diaphragmatic defect is indicated when the diaphragm cannot be closed without tension. Whether a patch is composed of a prosthetic material like Gortex® or a collagen matrix, hernia recurrence rate is about 40% [28]. Recurrent hernias may not become apparent for several years. The diagnosis is typically suggested by respiratory symptoms or intestinal obstruction. If a chest radiograph does not demonstrate a recurrent hernia (Figure 44.2), a CT scan with oral contrast may be more sensitive, particularly for small defects. Options for managing a recurrent CDH include

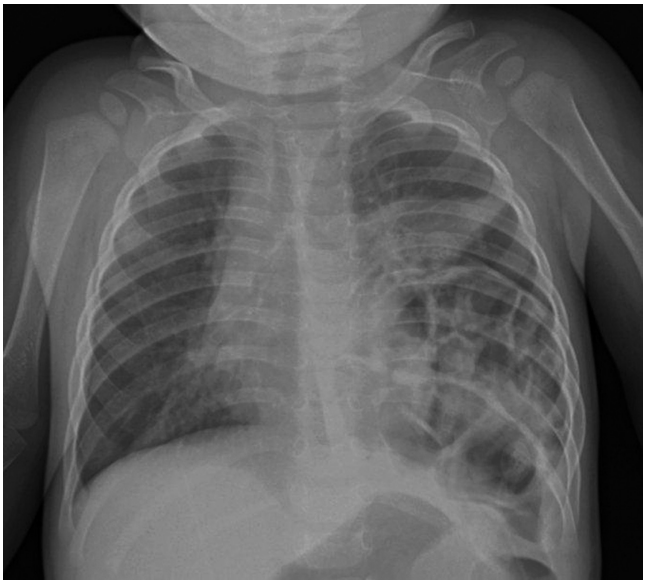


FIGURE 44.2
Chest x-ray shows a recurrent congenital diaphragmatic hernia in a 3-year-old boy. Smaller hernias may only be apparent on CT scan.

replacement or augmentation of the original patch and, in some cases, latissimus dorsi muscle flap closure.

Thoracoscopic repair of CDH is an alternative to open transabdominal repair in infants without any respiratory instability. Retrospective comparisons with open repair have shown higher recurrence rates with thoracoscopic repair [29]. Because of the difficulty in mobilizing the posterior rim of the diaphragm with this approach, repairs have been more likely to be under tension than when an open approach is used, likely leading to more frequent recurrence. A more liberal use of patch closures in thoracoscopic repairs may bring the incidence of recurrence more in line with open repair.

44.4 Anorectal Malformations

Anorectal malformations occur as a wide spectrum of anatomical disorders, each of which carries particular risks for complications due to both their underlying pathophysiology and the corrective procedures that are performed, which include posterior sagittal anorectoplasty (PSARP) and laparoscopic-assisted pull-through. The management of these malformations has been revolutionized over the last three decades, and improvements in the understanding of their gross and functional anatomy have led to much improved outcomes [30]. Nonetheless, many patients with anorectal malformations suffer complications that dramatically impact their overall health and quality of life. Meticulous evaluation, operative technique, and postoperative management can reduce the incidence and severity of adverse outcomes in this complicated population of patients, although abnormal sphincter muscle and innervation limit the potential for normal function in many and emphasize the importance of supportive care.

Anorectal malformations progress in severity from perineal fistula to persistent cloaca. Even the most apparently straightforward lesions can be complicated in the short and long term if diagnosis and management are flawed. Complications associated with anorectal malformations can be reviewed in the context of diagnosis and evaluation, operation, and long-term postoperative management.

44.4.1 Diagnosis and Evaluation

Accurate diagnosis of anorectal malformations is essential for reducing the incidence of complications.

Although any malformation should be identifiable on routine newborn examination, perineal fistulas are occasionally missed and are not identified until a child presents with constipation. By this point, a megarectum, which can exacerbate constipation following an anoplasty, is likely to have developed.

The diagnosis of girls with a persistent cloaca might be more difficult for those not familiar with the perineal anatomy of infants. Without careful identification of a normal urethral meatus, a persistent cloaca might be misdiagnosed as a recto-vestibular fistula, and identification and treatment of the hydrocolpos that can occur in cloacal malformations might be neglected [31]. As untreated hydrocolpos can lead to urethral obstruction and subsequent renal injury, diagnostic accuracy in girls with anorectal malformations is particularly important.

Anorectal malformations are frequently part of the VACTERL association, and comprehensive evaluation for these disorders is essential [32]. In particular, an echocardiogram must be performed prior to any operative intervention to avoid cardiovascular decompensation. In addition, a spinal ultrasound should be obtained in the neonatal period in order to identify a tethered spinal cord, which can contribute to future incontinence.

44.4.2 Operation

Except in cases with a perineal fistula, infants with anorectal malformations frequently undergo colostomy prior to a staged, definitive repair. Potential complications of colostomy in this setting include prolapse, overflow of stool into the distal rectum, compromise of the length of the rectum necessary for the ultimate pull-through, and metabolic acidosis secondary to urine reabsorption from a urethral fistula. The incidence of these complications can mostly be prevented by placement of an end-descending colostomy with a separated mucus fistula [33].

A sigmoid or transverse colostomy may be most convenient to construct, but carries a greater risk for prolapse than an end-descending colostomy, which is held in place by retroperitoneal attachments. A sigmoid colostomy can compromise a subsequent pull-through by limiting the available length of rectum. Alternatively, a transverse colostomy leaves a long segment of distal colon potentially exposed to urine, which can result in metabolic acidosis.

The construction of a loop colostomy risks stool overflow into the distal rectum and fecaloma formation, which can compromise a subsequent PSARP or laparoscopic-assisted pull-through and result in a megarectum. Access to the distal rectum is important, but is best accomplished with the placement of a mucus fistula 15 mm from the colostomy.

Accurate definition of the muscle complex, which mediates continence, using electrical stimulation is essential, whichever operative approach is used. When the rectum is placed outside of the muscle complex, constipation and/or incontinence will result, depending

upon the underlying anatomy. Magnetic resonance imaging (MRI) is useful for evaluating the location of the rectum, and when misplacement is identified, a revision of the anoplasty may be indicated [34]. In the past, the "cutback" anoplasty was frequently used for perineal fistulas, but this may increase the incidence of wound dehiscence, constipation, and incontinence.

The mismanagement of the urethra can result in urinary leakage or fistula. If a recto-bulbar urethral fistula is not recognized, a persistent fistula will result. This emphasizes the importance of a preoperative colostogram for identifying congenital fistulas of the urethra. A recurrent fistula may result from incomplete control of the urethral fistula or from anterior dehiscence of anoplasty due to excessive tension. Finally, if a urethral catheter is not placed, urethral injury during an operation for a perineal fistula might occur more easily and, if unrecognized, result in recto-urethral fistula [35].

A urethral diverticulum may result when a recto-urethral fistula is not divided flush with the urethra and a portion of rectum is retained in continuity with the urethra. This is particularly likely during a laparoscopic-assisted pull-through [36]. This complication may present in a delayed fashion with urinary dribbling, urinary tract infection, or even adenocarcinoma.

Significant rectal prolapse following PSARP occurs with an incidence of 3%, although it is perhaps more frequent after laparoscopic-assisted procedures [37]. While prolapse can negatively affect the lifestyle of the patient and parent, it can also compromise functional results in terms of continence and constipation. Children with anorectal malformations are at particular risk for prolapse because sphincter muscles are weak. During PSARP, it is important to secure the rectum to the deep component of the muscle complex. Since laparoscopic-assisted procedures do not involve deep dissection in the perineum, the rectum should be sutured to the pelvic sidewall in order to decrease the incidence of prolapse.

Stricture of the anoplasty following any pull-through procedure is nearly inevitable if routine, postoperative dilations are not performed [38]. Typically, daily dilations are started 2 weeks after the operation and continued for 4–8 weeks, until a 12–15 mm dilator can be passed. If the end of the rectum is ischemic or under excessive tension, a stricture may develop that is resistant to dilation and a revision of the pull-through may be necessary.

44.4.3 Long-Term Postoperative Management

Despite meticulous diagnosis and operative technique, children with anorectal malformations are at significant risk for long-term incontinence and/or constipation, based upon their anatomy.

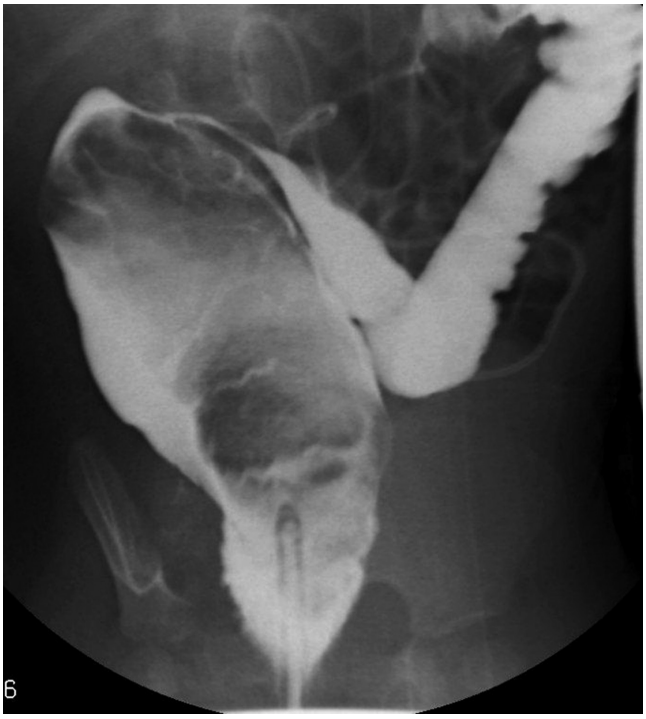


FIGURE 44.3
A barium enema in a 3-year-old girl with constipation and a history of posterior sagittal anorectoplasty for a recto-vestibular fistula demonstrates a megarectum.

The incidence of incontinence after a pull-through for anorectal malformation ranges from nearly zero for perineal fistulas to greater than 80% for recto-bladder neck fisutulae and is inversely proportional to the degree of development of the muscle complex and innervation [39].

In some cases, pseudoincontinence can occur when liquid stool passes impacted stool in the setting of constipation and a megarectum (Figure 44.3). And, as discussed earlier, when the rectum is not placed within the muscle complex, incontinence may occur even if the muscle is adequate. This situation can be diagnosed with MRI and may indicate a revision of the pull-through. However, most children with frequent soiling or a complete lack of sensation for stool in the rectum have a neuromuscular etiology.

The central focus of the management of long-term, postoperative incontinence is bowel management. With a combination of enemas and constipating agents, children can avoid diapers and attend school without concern for accidents. Specifically, patients with true incontinence and a tendency toward constipation are given large-volume saline enemas. Those with more diarrheal stool are given smaller volume enemas, in combination with a constipating diet, pectin, and loperamide [40]. As children age, transanal enemas become difficult and a continent appendicostomy can be constructed as a route for

the administration of nightly, antegrade enemas [41]. Even children less than 10 years old can administer these independently.

Constipation frequently accompanies anorectal malformations that are presented with a perineal fistula. Although more acceptable than incontinence, constipation can be debilitating and mandates aggressive treatment to improve lifestyle as well as to prevent the development of a megarectum, which can exacerbate constipation [42].

The evaluation of constipation should include digital rectal exam to assure that there is no stricture at the anoplasty. A contrast enema is useful to assess for a megarectum, which might be managed with resection or tapering.

The management of those with true, functional constipation involves a combination of intermittent disimpaction, occasional enemas, and daily laxative therapy. Senna laxatives are particularly effective and their dose can be titrated as necessary to produce stool every 1–2 days.

44.5 Hirschsprung Disease

Hirschsprung disease is a functional intestinal obstruction that results from incomplete aboral migration of ganglion cells. In a majority of cases, aganglionosis begins in the rectosigmoid, although in some the entire colon or even the small intestine is aganglionic. The disease typically presents with constipation in the newborn period and a failure to pass meconium within the first day of life, although a significant proportion of cases are not diagnosed until months or even years later.

The underlying principles of the operative management of Hirschsprung disease are exclusion of the aganglionic segment of bowel and anastomosis of ganglionic bowel to a point near the dentate line. The surgical management of Hirschsprung disease has evolved over the last 20 years from routine leveling colostomy followed by a later, open pull-through procedure to a strategy of an early, one-stage, minimally invasive procedure [43].

The principal operations used in Hirschsprung disease are the Swenson [44], Soave [45], and Duhamel [46] procedures. All involve resection of aganglionic colon, as necessary, but differ in their management of the rectum. The Swenson operation is a very low anterior resection of the rectum. In the Soave procedure, a rectal mucosectomy is performed in conjunction with a posterior split of the remaining muscular cuff. In the Duhamel operation, the extraperitoneal rectum is left intact and ganglionic bowel is brought posteriorly and anastomosed to it in a side-to-side fashion.

The short- and long-term complications that follow these procedures are both general and specific to the individual operations. Some of these adverse outcomes can be traced to technical issues while others are persistent manifestations of Hirschsprung disease.

44.5.1 Short-Term Complications

Short-term complications related to operations for Hirschsprung disease can be septic or obstructive. In addition, failure to anticipate the possibility of total colonic aganglionosis can negatively impact care.

Anastomotic leaks are infrequent if meticulous technique is used. Ischemia at the anastomosis is unusual unless a long segment of colonic blood supply is compromised [47]. It is important to administer a mechanical and antibiotic bowel preparation prior to any of the definitive operations for Hirschsprung disease as they all involve an intrapelvic dissection and anastomosis. Because of the underlying functional colonic obstruction, a mechanical bowel preparation may be incomplete and recto-colonic irrigations should be performed on-table prior to the initiation of the operation if there is doubt as to the adequacy of the antegrade bowel preparation. In addition, the operative field should be thoroughly irrigated prior to construction of the anastomosis. With these measures, the incidence of cuff abscess is only about 3% following procedures for Hirschsprung disease [48]. While persistent, postoperative fever and leukocytosis might also indicate enterocolitis, as discussed in a subsequent section, this would also accompany pelvic infection from leak or intraoperative contamination and would indicate assessment with a CT scan. A pelvic collection could initially be managed with percutaneous drainage, but if rapid improvement did not occur, operative irrigation, drainage, and proximal diversion would be required.

In most cases, laparoscopic, seromuscular biopsies are obtained and sent for frozen-section analysis prior to initiating a pelvic dissection in order to define the level of aganglionosis. If an unrecognized mucosal injury occurs during a biopsy and this segment of bowel is left in place at the end of the operation, a pelvic abscess or free passage of stool into the peritoneal cavity could result. This would be indicated by a pneumoperitoneum far in excess of what would be expected within 1–2 days of laparoscopic insufflation with carbon dioxide.

In most cases, stool is passed within 1–2 days of the operation. When early obstruction occurs, the surgeon must suspect that the colon was twisted as it was pulled through the pelvis [49]. Although an entirely transanal pull-through is feasible, assuring that the colon did not twist within the pelvis, as well as histologically confirming the transition zone, is a compelling indication for laparoscopy, particularly in the Soave operation.

In the setting of delayed stool passage and a significantly dilated colon, examination of the pull-through segment under anesthesia would be indicated.

Although it is usually possible to accurately define the ganglion cell transition zone by contrast enema, in rare cases this can be misleading and a patient believed to have a recto-sigmoid transition zone will be found to have total colonic aganglionosis when intraoperative biopsies are obtained [50]. This is of particular concern in newborns, who may not have developed significant colonic dilation proximal to the aganglionic bowel. Some surgeons advocate an ileo-anal pull-through in the setting of a newborn with total colonic Hirschsprung disease, but most recommend an immediate leveling ileostomy with the definitive pull-through delayed for 1–3 years. If a surgeon performing a Soave operation proceeds with a transanal dissection and subsequently finds no colonic ganglion cells, it will be necessary to proceed with an immediate ileo-anal anastomosis as the mucosectomy has already been completed. Without proximal diversion, this could lead to morbidity from continuous passage of liquid stool.

44.5.2 Late Complications

Late complications after a definitive pull-through for Hirschsprung disease can result from errors in operative technique, but more frequently are due to manifestations of the disease itself. Children who have undergone an operation for aganglionosis can suffer from mechanical and functional obstructions, incontinence, and enterocolitis.

Ischemic strictures may develop at the colo-anal anastomosis, particularly following the Soave or Swenson operation [47]. Although the colon has a relatively robust blood supply, extensive devascularization of the pull-through segment can lead to ischemia and resultant stricture. Although serial dilations may be sufficient to manage an ischemic stricture, a revision of the pull-through or a Duhamel procedure may be necessary.

Patients who have undergone the Duhamel procedure can develop a mechanical obstruction from kinking at the top of the side-to-side colo-rectal anastomosis. In addition, the procedure routinely leaves a spur of native rectum intact superior to the anastomosis. Over time, this segment of rectum can lengthen and distend to the extent that it obstructs the colon proximal to the anastomosis by a mass effect. It is not unusual for children who have undergone the Duhamel operation to require resection of the retained spur of rectum [51].

The objective of definitive operations for Hirschsprung disease is to bring bowel with ganglion cells to the anus. In some cases, the distal end of the pull-through segment may be completely or partially devoid of ganglion cells at the time of the anastomosis, and in others, ganglion cells may disappear over time.

Prior to the anastomosis during any of the operations for Hirschsprung disease, it is essential that the presence of ganglion cells be confirmed in the distal bowel by frozen-section analysis. Occasionally, a pathologist with limited experience in pediatric cases may identify ganglion cells when, in fact, they are absent. If this is not detected on subsequent permanent sections, symptoms should indicate a postoperative rectal biopsy and revision of the pull-through.

Ganglion cells migrate aborally in a manner similar to dripping paint. When only a part of the circumference of the end of the pull-through segment is subjected to frozen-section analysis for ganglion cells, a transition zone pull-through may result, in which some part of the anastomosis is aganglionic [52]. Obstructive symptoms correlate with the percentage of the bowel circumference that is aganglionic and an effort should be made to assess the entire circumference histologically prior to an anastomosis [53].

Ganglion cells present at the time of operation may disappear over time, possibly due to ischemia. Some of these cases may represent transition zone pull-throughs, but revision of the operation may be necessary.

Although Hirschsprung disease is relatively well defined as an absence of ganglion cells in the submucosal and intermyenteric plexuses, other neuroenteric disorders have yet to be clearly delineated histologically. Some of these, including intestinal neuronal dysplasia, in which there are giant ganglion cells that may be heterotopic, coexist in some patients with Hirschsprung disease and can lead to dysmotility, even after an appropriate operation [54]. In the setting of constipation following a pull-through procedure, the workup should include physical and imaging evaluations for mechanical obstruction followed by rectal biopsy to assure that ganglion cells are present at the anastomosis. If these are unrevealing, laparoscopic, seromuscular biopsies may be indicated to identify intestinal neuronal dysplasia. In rare cases, focal involvement may indicate a repeat pull-through.

There are several etiologies for fecal incontinence after a pull-through procedure. The most common cause would be constipation with overflow incontinence. The diagnosis and management of this situation would be as described previously in the section regarding dysmotility. Sphincter injury may occur due to retraction during an endorectal pull-through and this may result in incontinence. Finally, if the anastomosis is made at a level below the dentate line, the loss of transitional epithelium may result in a sensory deficit and incontinence. Anal manometry may be valuable in this situation [47].

The enterocolitis associated with Hirschsprung disease is due, at least in part, to abnormalities in the mucosal barrier function of the ganglionated bowel [55]. Although it can be exacerbated by distal obstruction preoperatively, enterocolitis occurs in as many as 17%–50% of children following a pull-through procedure.

Enterocolitis typically presents with bloody diarrhea, abdominal distension, emesis, and fever. There are no absolute diagnostic criteria, which may contribute to the wide variation in the reported incidence, but there should be a high index of suspicion for postoperative enterocolitis and treatment should be rapidly instituted. Treatment consists of intravenous antibiotics, nasogastric drainage, and rectal irrigation. Multiple episodes of enterocolitis should lead to concern for persistent aganglionosis, and rectal biopsies should be done [56].

There is reasonable evidence that the incidence of postoperative enterocolitis can be reduced by the administration of daily rectal irrigations and anastomotic dilations for 3 months following a pull-through [57].

44.6 Pyloric Stenosis

Hypertrophic pyloric stenosis classically presents as non-bilious, projectile vomiting after feedings in infants. It is more common in boys than in girls and usually occurs at 2–8 weeks of age. The prevalence of pyloric stenosis ranges from 2 to 4 per 1000 live births [58].

The diagnosis can be made by physical examination in 75% of cases, but this requires nasogastric decompression and a quieted infant. Five percent dextrose water may be given to the infant while right upper abdomen palpation is performed and often a rolling "olive" can be felt, although most physicians now depend on ultrasound to make the diagnosis. A pylorus longer than 15 mm with a wall thickness of greater than 3–4 mm is considered diagnostic [59].

Pyloric stenosis does not require an emergency operation. Adequate fluid and electrolyte resuscitation should occur prior to an operation. Many of these patients have been vomiting for days, if not weeks, and will present with a hypochloremic, hypokalemic, metabolic alkalosis. If left untreated, this contraction alkalosis will predispose to perioperative apnea or respiratory arrest.

There are several operative approaches to pyloromyotomy, all of which have the objective of splitting the thickened muscle fibers to alleviate obstruction. In the traditional open approach, a right upper quadrant incision is used to deliver the pylorus and perform the myotomy. A variation on this approach is to make a more cosmetically appealing transumbilical incision and deliver the pylorus though the umbilicus. A third approach is the laparoscopic pyloromyotomy, which is done through an infraumbilical port and two stab incisions, with the myotomy performed intracorporeally. Prior to induction, the anesthesia team should thoroughly decompress the stomach to prevent aspiration [60].

The overall complication rate for a pyloromyotomy is reported as 3% [61]. Most complications occur when an overly aggressive myotomy causes a mucosal perforation or when an inadequate myotomy leaves the patient with persistent obstruction. Incisional hernias and wound infections are also described for this operation.

It is not uncommon for patients to vomit for 24–48 h after surgery due to the transient gastric dysfunction. When persistent vomiting occurs for more than 7 days, one must suspect an incomplete myotomy. The surgeon tries to avoid this complication by making sure there is independent motion of the superior and inferior edges of the myotomy. The incidence of incomplete myotomy is 1.4%–6% for the laparoscopic approach and less than 0.5% for open pyloromyotomies [62].

Mucosal perforation occurs when the myotomy is extended through the mucosa. If unrecognized at the time of injury, this can become a potentially fatal complication. Most perforations are recognized at the time of injury by direct visualization, leaking gastric content, or during insufflation of the stomach at the end of the procedure. If recognized at the time, it should be repaired and a new myotomy performed. The incidence of perforation is about the same with either the laparoscopic or open approach: 0.4%–2.3% versus 2%–3.6% [62–64].

Manipulation and grasping of the duodenum may result in a partial deserosalization or a full-thickness perforation. During the laparoscopic approach, this can be avoided by taking a large bite across the duodenum with an atraumatic grasper. A small bite of the thin duodenal wall can lead to a perforation. In the open operation, this injury can be avoided by making a large enough incision, so the pylorus can be delivered without a struggle. The incidence of duodenal injury is about 1% [64].

Incisional hernias are reported with both the laparoscopic and open approach with an incidence of about 2%. The fascia at the infraumbilical port site should be approximated to prevent omental evisceration after laparoscopic pyloromyotomy.

Preoperative antibiotics are not usually given for a pyloromyotomy. The incidence of wound infection is about 2%, which is appropriate for a clean case. Antibiotics are advocated for the open, transumbilical approach because the incidence of infection without antibiotics is 7%, as compared to 2.3% when they are given [65].

Selected Complications of Esophageal Atresia and Tracheoesophageal Fistula

Complications	Prevention	Diagnosis	Management
Preoperative pneumonia	Continuous suctioning of proximal pouch, elevation of head of bed, expeditious ligation of tracheoesophageal fistula	Respiratory decompensation	Pulmonary toilet, antibiotics
Gastric perforation	Avoidance of positive pressure ventilation prior to fistula ligation	Pneumoperitoneum, respiratory decompensation	Temporary needle aspiration, control esophagus at GE junction
Anastomotic leak	Avoidance of tension, careful technique	Saliva in chest tube, contrast esophagram	Chest tube drainage, rare reexploration
Anastomotic stricture	Avoidance of tension and devascularization of distal segment, gastric acid blockade	Feeding intolerance, contrast esophagram	Balloon esophageal dilation and acid suppression, rare revision of anastomosis
Recurrent fistula	Careful closure of fistula, avoidance of leak	Cough or pneumonia, contrast esophagram, and/or bronchoscopy	Reexploration and ligation
Scoliosis	Muscle-sparing thoracotomy or thoracoscopic repair	Back pain, physical examination	Spinal instrumentation in severe cases

Selected Complications of Congenital Diaphragmatic Hernia

Complications	Prevention	Diagnosis	Management
Pulmonary hypertension	Prenatal tracheal plugging in selected cases, avoidance of pain and stress	Echocardiogram, pre- to postductal oxygen gradient	High-frequency ventilation, nitric oxide (rarely effective), ECMO
Bleeding on ECMO	Patient selection, avoidance of chest tubes, aminocaproic acid for repair on ECMO	Cranial ultrasound	Limitation of heparinization, direct pressure, discontinuation of ECMO
Compartment syndrome	Silo or patch placement	Respiratory compromise, hypotension, anuria	Decompressive laparotomy
Chylothorax	None	Elevated fluid triglycerides, lymphocytes	Medium-chain triglyceride diet, NPO, octreotide, pleurectomy with pleurodesis
Recurrent hernia	Avoid closure under tension, liberal patch use with thoracoscopic approach	Chest radiograph, CT scan	Redo CDH repair

Selected Complications of Anorectal Malformations

Complications	Prevention	Manifestations	Management
Diagnostic errors	Careful examination of perineum	Megarectum (missed perineal fistula), hydrocolpos (missed cloaca)	Rectal resection (megarectum), vesicostomy (hydrocolpos)
Errors of colostomy construction	Use end-descending colostomy with separate mucus fistula	Metabolic acidosis (transverse colostomy), overflow to distal rectum (loop), limited mobility for anoplasty (sigmoid colostomy)	Revision of colostomy as necessary
Urinary tract problems	Accurate definition of anatomy, urinary catheter, divide fistula on urethra	Recurrent fistula, urethral diverticulum	Redo operation
Stricture of anoplasty	Avoid ischemia in rectum, careful dilation	Constipation	Dilation, revision of anoplasty
Incontinence	Precise placement of rectum within muscle complex, mostly due to neuromuscular deficits	Social compromise	Redo anoplasty in selected cases, bowel management
Constipation	Avoidance of stricture or megarectum, frequently inherent to low defects	Pain, failure to thrive	Laxatives, dilation, rectal resection in selected cases

Selected Complications of Hirschsprung Disease

Complications	Prevention	Diagnosis	Management
Anastomotic leak	Avoidance of ischemia, meticulous technique	Fever and leukocytosis, CT scan	Percutaneous drainage, antibiotics, possible diversion
Anastomotic stricture	Avoidance of extensive devascularization	Infrequent, small-volume stools	Dilation or revision, if resistant
Twisted pull-through	Monitor pull-through with laparoscopy	Failure to pass stool, rectal examination	Revision of pull-through
Transition zone pull-through	Intraoperative assessment of the specimen for circumferential ganglion cells	Persistent constipation, suction rectal biopsies	Revision of pull-through
Incontinence	Avoidance of overstretching anal canal or anastomosis below dentate line	History and possibly anal manometry	Bowel management
Enterocolitis	3 months of daily, postoperative rectal irrigations and dilations	Fever, vomiting, diarrhea, distension	Antibiotics, gastric decompression, rectal irrigations. Rectal biopsy if persistent

References

1. Crisera CA, Connelly PR, Marmureanu AR et al. Esophageal atresia with tracheoesophageal fistula: Suggested mechanism in faulty organogenesis. *J Pediatr Surg* 1999;34:204–208.
2. Engum SA, Grosfeld JL, West KW et al. Analysis of morbidity and mortality in 227 cases of esophageal atresia and or tracheoesophageal fistula over two decades. *Arch Surg* 1995;130:502–509.
3. Keckler SJ, St. Peter SD, Valusek PA et al. VACTERL anomalies in patients with esophageal atresia: An updated delineation of the spectrum and review of the literature. *Pediatr Surg Int* 2007;23:309–313.
4. Gross R. *The Surgery of Infancy and Childhood*. Philadelphia, PA: WB Saunders, 1953.
5. Langer JC, Hussain H, Khan A et al. Prenatal diagnosis of esophageal atresia using sonography and magnetic resonance imaging. *J Pediatr Surg* 2001;36:804–807.
6. Spitz L, Kiely EM, Morecroft JA et al. Oesophageal atresia: At-risk groups for the 1990s. *J Pediatr Surg* 1994;29:723–725.
7. Templeton JM, Templeton JJ, Schnaufer L et al. Management of esophageal atresia and tracheoesophageal fistula in the neonate with severe respiratory distress syndrome. *J Pediatr Surg* 1985;20:394–397.
8. Domanjnko B, Drugans GT, Pegoli W. Temporary occlusion of the gastroesophageal junction: A modified technique for stabilization of the neonate with esophageal atresia and tracheoesophageal fistula requiring mechanical ventilation. *Pediatr Surg Int* 2007;23:1127–1129.
9. Okada A, Usui N, Inoue M et al. Esophageal atresia in Osaka: A review of 39 years' experience. *J Pediatr Surg* 1997;32:1570–1574.
10. Upadhyaya VD, Gopal SC, Gangopadhyaya AN et al. Role of fibrin glue as a sealant to esophageal anastomosis in cases of congenital esophageal atresia with tracheoesophageal fistula. *World J Surg* 2007:31:2412–2415.
11. Chittmittrapap S, Spitz L, Kiely EM et al. Anastomotic stricture following repair of esophageal atresia. *J Pediatr Surg* 1990;25:508–511.
    A description of the incidence of anastomotic stricture and risk factors for its occurrence.
12. Myers NA, Beasley SW, Auldist AW. Secondary esophageal surgery following repair of esophageal atresia with distal tracheoesophageal fistula. *J Pediatr Surg* 1990; 25:773–777.
13. Bargy F, Manach Y, Helardot PG et al. Risk of recurrent laryngeal nerve palsy in surgery of esophageal atresia. *Chir Pediatr* 1983;24:130–132.
14. Holcomb GW, Rothenberg SS, Bax KM et al. Thoracoscopic repair of esophageal atresia and tracheoesophageal fistula. *Ann Surg* 2005;242:422–430.
15. Dott MM, Wong LY, Rasmussen SA. Population-based study of congenital diaphragmatic hernia: Risk factors and survival in metropolitan Atlanta, 1968–1999. *Birth Defects Res A Clin Mol Teratol* 2003;67:261–267.
16. Langham MR, Kays DW, Ledbetter DJ et al. Congenital diaphragmatic hernia. Epidemiology and outcome. *Clin Perinatol* 1996;23:671–688.
17. Harrison MR, Bjordal RI, Langmark F et al. Congenital diaphragmatic hernia: The hidden mortality. *J Pediatr Surg* 1978;13:227–230.
18. Lally KP. Extracorporeal membrane oxygenation in patients with congenital diaphragmatic hernia. *Semin Pediatr Surg* 1996;5:249–255.
19. Jesudason EC. Challenging embryological theories on congenital diaphragmatic hernia: Future therapeutic implications for paediatric surgery. *Ann R Coll Surg Engl* 2002;84:252–259.
20. Metkus AP, Filly RA, Stringer MD et al. Sonographic predictors of survival in fetal diaphragmatic hernia. *J Pediatr Surg* 1996;31:148–152.
21. Schultz CM, DiGeronimo RJ, Yoder BA et al. Congenital diaphragmatic hernia: A simplified postnatal predictor of outcome. *J Pediatr Surg* 2007;42:510–516.

22. Chiu PP, Sauer C, Mihailovic A et al. The price of success in the management of congenital diaphragmatic hernia: Is improved survival accompanied by an increase in long-term morbidity? *J Pediatr Surg* 2006;41:888–892.
A good review of the long-term morbidity of CDH.
23. D'Agostino JA, Bernbaum JC, Gerdes M et al. Outcome for infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: The first year. *J Pediatr Surg* 1995;30:10–15.
24. Kinsella JP, Parker TA, Ivy DD et al. Noninvasive delivery of inhaled nitric oxide therapy for late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia. *J Pediatr* 2003;142:397–401.
25. ELSO Data Registry Report: International Summary. Ann Arbor, MI, January 2007.
26. Zwischenberger JB, Nguyen TT, Upp JR et al. Complications of neonatal extracorporeal membrane oxygenation: Collective experience from the Extracorporeal Life Support Organization. *J Thorac Cardiovasc Surg* 1994; 107:838–848.
27. Gonzalez R, Bryner BS Teitelbaum DH et al. Chylothorax after congenital diaphragmatic hernia repair. *J Pediatr Surg* 2009;44:1181–1185.
28. Grethel EJ, Cortes RA, Wagner AJ et al. Prosthetic patches for congenital diaphragmatic hernia repair: Surgisis vs. Gore-Tex. *J Pediatr Surg* 2006;41:29–33.
29. Gander JW, Fisher JC, Gross ER et al. Early recurrence of congenital diaphragmatic hernia is higher after thoracoscopic than open repair: A single institution study. *J Pediatr Surg 2011;*46;1303–1308.
30. Pena A. Posterior sagittal anorectoplasty: Results in the management of 322 cases of anorectal malformations. *Pediatr Surg Int* 1988;3:94–104.
31. Bischoff A, Levitt MA, Breech L et al. Hydrocolpos in cloacal malformations. *J Pediatr Surg* 2010;45:1241–1245.
32. Nora AH, Nora JJ. A syndrome of multiple congenital anomalies associated with teratogenic exposure. *Arch Environ Health* 1975;30:17–21.
33. Pena A, Migotto-Krieger M, Levitt MA. Colostomy in anorectal malformations: A procedure with serious but preventable complications. *J Pediatr Surg* 2006;41:748–756.
34. Pena A, Grasshoff S, Levitt M. Reoperations in anorectal malformations. *J Pediatr Surg* 2007;42:318–325.
35. Hong AR, Acuna MF, Pena A et al. Urologic injuries associated with repair of anorectal malformations in male patients. *J Pediatr Surg* 2002;37:339–344.
36. Uchida H, Iwanaka T, Kitano Y et al. Residual fistula after a laparoscopically assisted anorectoplasty: Is it a rare problem? *J Pediatr Surg* 2009;44:278–281.
37. Bischoff A, Levitt MA, Pena A. Laparoscopy and its use in the repair of anorectal malformations. *J Pediatr Surg* 2011;46:1609–1617.
38. Bischoff A, Levitt MA, Pena A. Reoperations for anorectal malformations. *J Pediatr Surg* 2007;42:318–325.
39. Pena A. Anorectal malformations. *Semin Pediatr Surg* 1995;4:35–47.
40. Bischoff A, Levitt MA, Bauer C et al. Treatment of fecal incontinence with a comprehensive bowel management program. *J Pediatr Surg* 2009;44:1278–1284.
A comprehensive review of bowel management for incontinence and constipation in patients with anorectal malformations.
41. Levitt MA, Soffer SZ, Pena A. Continent appendicostomy in the bowel management of fecally incontinent children. *J Pediatr Surg* 1997;32:1630–1633.
42. Levitt MA, Kant A, Pena A. The morbidity of constipation in patients with anorectal malformation. *J Pediatr Surg* 2010;45:1228–1233.
43. Somme S, Langer JC. Primary vs staged pull-through for the treatment of Hirschsprung disease. *Semin Pediatr Surg* 2004;13:249–255.
44. Swenson O, Bill AH. Resection of rectum and rectosigmoid with preservation of the sphincter for benign spastic lesions producing megacolon. *Surgery* 1948;24:212–230.
45. Duhamel B. A new operation for the treatment of Hirschsprung's disease. *Surgery* 1960;35:38–39.
46. Soave F. A new surgical technique for treatment of Hirschsprung's disease. *Surgery* 1964;56:1007–1014.
47. Little DC, Snyder CL. Early and late complications following operative repair of Hirschsprung's disease. In: Holschneider AM, Puri P, ed. *Hirschsprung's Disease and Allied Disorders*, 3rd ed. New York: Springer; 2008: pp. 375–385.
48. Pratap A, Gupta DK, Shakya VC et al. Analysis of problems, complications, avoidance and management with transanal pull-through for Hirschsprung disease. *J Pediatr Surg* 2007;42:1869–1876.
49. Langer JC, Seifert M, Minkes RK. One-stage Soave pull-through for Hirschsprung's disease: A comparison of the transanal and open approaches. *J Pediatr Surg* 2000;35:820–822.
50. Proctor ML, Traubici J, Langer JC et al. Correlation between radiographic transition zone and level of aganglionosis in Hirschsprung's disease: Implications for surgical approach. *J Pediatr Surg* 2003;38:775–778.
51. Minford JL, Ram A, Turnock RR et al. Comparison of functional outcomes of Duhamel and transanal endorectal coloanal anastomosis for Hirschsprung's disease. *J Pediatr Surg* 2004;39:161–165.
52. Friedmacjer F, Puri P. Residual aganglionosis after pull-through operation for Hirschsprung's disease: A systematic review and meta-analysis. *Pediatr Surg Int* 2011; 27:1053–1057.
53. Coe A, Collins MH, Lawai T et al. Reoperation for Hirschsprung disease: Pathology of the resected problematic distal pull-through. *Pediatr Dev Pathol* 2012;15:30–38.
54. Kobayashi H, Miyano T, Yamataka A et al. Use of synaptophysin polyclonal antibody for the rapid intraoperative immunohistochemical evaluation of functional bowel disorders. *J Pediatr Surg* 1997;32:38–40.
55. Austin KM. The pathogenesis of Hirschsprung's disease-associated enterocolitis. *Semin Pediatr Surg* 2012;21:319–327.
56. Frykman PK, Short SS. Hirschsprung-associated enterocolitis: Prevention and therapy. *Semin Pediatr Surg* 2012;21:328–335.

57. Marty TL, Seo T, Sullivan JJ et al. Rectal irrigations for the prevention of postoperative enterocolitis in Hirschsprung's disease. *J Pediatr Surg* 1995;30:652–654.
A description of a protocol to reduce the incidence of postoperative enterocolitis in Hirschsprung disease.
58. Mitchell LE, Risch N. The genetics of infantile hypertrophic pyloric stenosis. *Am J Dis Child* 1993;147:1203.
59. Haider N, Spicer R, Grier D et al. Ultrasound diagnosis of infantile hypertrophic pyloric stenosis: Determinants of pyloric length and the effect of prematurity. *Clin Radiol* 2002;57:136–139.
60. Cook-Sather SD, Tulloch HV, Liacouras CA et al. Gastric fluid volume in infants for pyloromyotomy. *Can J Anaesth* 1997;44:278–283.
61. Safford SD, Pietrobon R, Safford KM et al. A study of 11,003 patients with hypertrophic pyloric stenosis and the association between surgeon and hospital volume and outcomes. *J Pediatr Surg* 2005;40(6):967–972.
62. Adibe OO, Nichol PF, Flake AW, Mattei P. Comparison of outcomes after laparoscopic and open pyloromyotomy at a high-volume pediatric teaching hospital. *J. Pediatr Surg* 2006;41:1676–1678.
63. Leclair MD, Plattner V, Mirallie E, Lejus C, Nguyen JM, Podevin G, and Helaury Y. Laparoscopic pyloromyotomy for hypertrophic pyloric stenosis: A prospective, randomized controlled trial. *J Pediatr Surg* 2007; 42:692–698.
64. Yagmurlu A, Barnhart DC, Vernon A, Georgeson KE, and Harmon CM. Comparison of the incidence of complications in open and laparoscopic pyloromyotomy: A concurrent single institution series. *J Pediatr Surg* 2004;39:292–296.
65. Ladd AP, Nemeth SA, Kirincich AN et al. Supraumbilical pyloromyotomy: A unique indication for antimicrobial prophylaxis. *J Pediatr Surg* 2005;40:974–977.

Section XII

Transplantation

45

Complications of Immunosuppression in Solid Organ Transplantation

Obi Ekwenna and Akin Tekin

CONTENTS

45.1 Overview of Immunosuppression

The development of transplantation has dramatically changed the fate of individuals presenting with end-organ failure. The collaboration of scientists and surgeons has led to greater understanding of the complexities of immune response and paved the way to the discovery of agents that improve allograft survival. Fundamental knowledge of the immune response is paramount in understanding the pharmacological and physiological effects of drugs used to prevent organ rejection. In this chapter, we review the basics of transplantation immunity and mechanism of action of immunosuppressive agents and complications and strategies of prevention and management.

45.1.1 Basics of Immune Response

Immune response is classified broadly as *innate* and *acquired*; both having evolved over millions of years to offer protection against pathogens and prevent the development of disease. The innate and acquired immune systems work in a concerted fashion to optimize immune response to pathogens [1]. The innate response recognizes the general characteristics of pathogens or noxious stimuli, conferring a nonspecific defense to the host [2]. In general, the innate immune response acts as a barrier to infection, helps recruit immune cells to sites of infection, activates the complement cascade to identify and clear bacteria, identifies and removes any possible antigens present within the host, and activates the adaptive immune system.

Conversely, the acquired immune response recognizes specific structural aspects of nonself substances in the form of peptides, carbohydrate moieties, and specific receptors. The complex mechanism of immunity is an integrated system that acts in concert to achieve optimal overall response.

45.1.2 History of Immunosuppression

Seminal experiments by Medawar [3] illustrated the immunologic basis of graft rejection, and it was recognized that for successful organ transplantation immunosuppression is required. Initially, transplant pioneers used radiation and chemicals as nonselective immunosuppressive agents [4,5]; although the results were dismal for long-term survival, the science of rejection and immunosuppression developed. Slowly, the advent of cyclosporine and prednisone combination for immunosuppression in the 1980s began the modern era of organ

transplantation. During this time, overall survival has increased. This is attributed to technical advances, improved safety of surgical procedures, efficacy, and safety of immunosuppression. While cyclosporine became the first drug that "selectively" inhibited specific adaptive immunity, "sparing" nonspecific host defenses, many more have come to the forefront making immunosuppression less dangerous. Thus, transplantation has become the accepted treatment modality for end-stage organ dysfunction.

45.2 Mechanism of Action of Immunosuppressants

To maintain allograft function and survival, transplant recipients must use pharmaceutical agents to prevent rejection. Clear understanding by surgeons and clinicians of the mechanistic action of the common agents used in transplantation and the complications associated with immunosuppression is important in the management of the growing population of transplant patients. We will now explore the various types of immunosuppression and associated complications.

45.2.1 Types of Immunosuppression

Despite the tremendous advances made in transplantation over the last half century, agents used for immunosuppression remain nonspecific in action. Multiple agents are usually needed to control normal immune response necessitated by the redundancy of the immune system. Although we know that all patients do not have the same risk for rejection or propensity for complications, most transplant centers are not "patient-centered" in their utility of immunosuppressive agents. Inevitably, patients are exposed to the risk of "protocol-driven" immunosuppression. While immunosuppression can broadly be categorized into *induction, maintenance,* and *antirejection therapy*, these agents/regimens are used interchangeably:

1. *Induction therapy* [6]*:* During the immediate posttransplant period, an induction regimen is introduced to establish an adequate level of immunosuppression. This initial conditioning of the recipient's immune system is important for complete depletion of T-cell response and is tolerated for a brief period of time without lethal consequences. Due to the heightened state of inflammation during the first few days to months posttransplantation and increased exposure to various risk factors, some argue that it necessitates use of prophylactic induction immunosuppression in the early postoperative period. Although controversial, most transplant centers continue to use induction therapy in the form of steroids and various antibody infusion therapies (see Table 45.1).
2. *Maintenance therapy:* Short- and long-term regimens of *maintenance therapy* are necessary to combat the high risk of acute rejection during the first months after transplantation. The goal of the short-term *maintenance therapy* is to avert early acute rejection episodes, the occurrence of which appears to increase the risk of eventual graft loss [8]. Cyclosporine/tacrolimus may be administered alone, in combination with corticosteroids, or in a triple-drug combination with azathioprine or mycophenolate mofetil in long-term maintenance therapy. Long-term maintenance immunosuppression regimens are calcineurin inhibitor (CNI) based and include steroids, with or without an additional maintenance agent (see Table 45.1).
3. *Antirejection therapy:* Although immune tolerance can develop, immunosuppression is required for the functional life of the graft. The discontinuation of immunosuppression decades after transplantation may lead to rejection. The majority of transplant failure is a result of rejection. There is significant pathologic consequence of excessive immunosuppression required for rejection therapy; the key issue in treating rejection is *definitive diagnosis*. Transplant centers and physicians may initiate empirical treatment of rejection; however, most prefer histological confirmation. Antirejection medications consist of *rescue agents* (see Table 45.1), which are generally the same agents used for induction therapy.

45.3 Complications Associated with Immunosuppression

By suppressing the body's defensive immune functions, all immunosuppressive regimens can lead to increased rates of systemic or localized *infections* and increased risk of *malignancy*. Normal cell function is altered on the molecular level, which results in undesired, *nonimmune side effects*, including direct organ toxicity and injury. In discussing the complications associated with transplant recipients in both bone marrow transplantation (BMT) and solid organ transplantation (SOT), an emphasis will be on SOT in this chapter with the caveat that both

TABLE 45.1

Immunosuppressive Agents and Their Side Effects

Category	Agent/Drug	Mechanism of Action	Common Side Effects/Comments
Induction	Corticosteroids (hydrocortisone, prednisone, prednisolone, methylprednisolone)	Suppress antibody and complement binding, upregulate IL-10 expression, downregulate IL-2, IL-6, and interferon gamma synthesis by T cells (Vacca et al. 1992, Ray et al. 1990, Verhoef 1999)	Diabetes Weight gain Impaired wound healing Adrenal insufficiency osteoporosis Gastrointestinal ulcers
	Antithymocyte globulin (ATGAM, RATG)	Polyclonal antibody against T-cell epitopes, leads to T-cell depletion via complement-mediated lysis and opsonization, interferes with T-cell receptor signaling (Merion et al. 1998)	Cytokine release syndrome (premedication indicated) Thrombocytopenia Leukopenia
	Muromonab-CD3 (OKT3)	Monoclonal antibody directed against CD3–T-cell receptor complex, causes depletion of T cells	Severe cytokine release syndrome (premedication indicated) Pulmonary edema Renal insufficiency Neurological dysfunction
	Basiliximab (Simulect®)	Chimeric monoclonal anti-IL2 receptor antibody with high-affinity binding to CD25 on T cells, thereby inhibiting proliferation of T cells	Allergic reaction (premedication may be indicated)
	Daclizumab[a] (Zenapax®)	Chimeric monoclonal anti-IL2 receptor antibody with high-affinity binding to CD25 on T cells, thereby inhibiting proliferation of T cells	Allergic reaction (premedication may be indicated)
	Rituximab[b]	Chimeric antibody against CD20 on B cells, facilitates B-cell depletion	Hypersensitivity/allergic reaction (premedication may be indicated)
	Alemtuzumab (Campath-1H®)	Monoclonal chimeric antibody against CD52 on both T and B cells. CD52 is present on mature lymphocytes, monocytes, and B cells	Bone marrow suppression Thyroid disease Cytokine release syndrome Autoimmune idiopathic thrombocytopenia and autoimmune hemolytic anemia Infusion reactions Severe infections
	Intravenous immunoglobulin[b]	Works via several mechanisms: neutralization of circulating autoantibodies and alloantibodies, down regulation of Fc-mediated mechanisms	
Maintenance	Corticosteroids	See above	
	Azathioprine (Imuran®)	Prodrug (purine analogue) converted to 6-mercaptopurine and other metabolites, which inhibit DNA synthesis in rapidly dividing cells	
	Mycophenolate mofetil (MMF®, Cellcept®) Mycophenolate sodium (Myfortic®)	Prodrug converted to mycophenolic acid (MPA). MPA inhibits inosine monophosphate dehydrogenase, prevents GMP formation, and leads to selective inhibition of B- and T-cell proliferation	Diarrhea/colitis neutropenia Anemia
	Leflunomide (Arava®)	Antimetabolite prodrug, which inhibits tyrosine phosphorylation and dihydro-orotate dehydrogenase, used in pyrimidine synthesis	See above MMF Diarrhea Alopecia Asymptomatic liver transaminase elevation
	Cyclosporine	Derived from fungus, *Cylindrocarpon lucidum*, inhibits T-cell activation by binding intracellular cyclophin, reduces calcineurin activation	Hypertension Nephrotoxicity Neurotoxicity Gingival hyperplasia Hirsutism New onset diabetes Hyperlipidemia

(*continued*)

TABLE 45.1 (continued)

Immunosuppressive Agents and Their Side Effects

Category	Agent/Drug	Mechanism of Action	Common Side Effects/Comments
	Tacrolimus	A macrolide isolated from *Streptomyces tsukubaensis* inhibits IL-2 and interferon gamma by binding FKBP12, which inhibits calcineurin and T-cell activation	Hypertension Diabetes Hyperlipidemia Neurotoxicity (tremors) Gingival hyperplasia
	Sirolimus (Rapamune®)	A macrolide isolated from *Streptomyces hygroscopicus* binds to FKBP12, the complex inhibits mammalian target of rapamycin and IL-2-dependent T-cell proliferation	Poor wound healing Increased cholesterol Thrombocytopenia Ulcers Pneumonitis
	Everolimus	Semi-synthetic form of sirolimus that binds to FKBP12, the complex inhibits target of rapamycin and IL-2-dependent T-cell proliferation	Same as above
	Belatacept	Fusion protein of CD152 (CTLA-4) and IgG1 that binds CD80/86 on APC, prevents interaction with CD28 on T cell, thereby impairs costimulation and T-cell activation	Not recommended to liver transplant patients Increased risk of PTLD Neutropenia
	Fingolimod	Derived from fungus *Isaria sinclairii*, an analogue of sphingosine. Antagonist of sphingosine that leads to sequestration of lymphocytes in lymphoid tissue	Reversible bradycardia Gastrointestinal symptoms; diarrhea, nausea, vomiting Increased liver enzymes
	Deoxyspergualin	Derivative of antitumor antibiotic spergualin. Unclear mechanism, involved in modulation of APC	Investigational drug[c] Leukopenia Dysgeusia
Antirejection	Corticosteroids	See above	
	Muromonab-CD3	See above	
	Antithymocyte globulin	See above	
	Intravenous immunoglobulin[b]	See above	

Source: Kirk, A.D., *Transplantation*, 82(5), 593, September 15, 2006; Marcen, R., *Drugs*, 69(16), 2227, November 12, 2009.

[a] No longer available in the United States.

[b] Used for highly sensitized transplant recipients undergoing kidney transplantation and ABO incompatible pairings. APC-antigen presenting cell. FKBP12-FK-binding protein.

patient populations have similar manifestations of the complications associated with immunosuppression. BMT recipients tend to have additional infectious risk due to the ablative therapy and compromised anatomic barriers and long-term immune depression.

Infections: The most frequent complication after transplantation is infection. Viral, respiratory, and urinary tract infections are common in the first months after transplantation [9–11]. Infection risk stratification in transplant patients is determined by a "semiquantitative relationship" between two factors: the epidemiologic exposures of the individual and the "net state of immunosuppression" [12].

The epidemiologic factors are determined by a detailed history by a clinician of potential encounters with a variety of pathogens. According to Fishman et al. [11], *epidemiologic factors* are divided into *donor-derived infections, recipient-derived infections, nosocomial infections,* and *community infections*. With the initiation of immunosuppression, latent pathogens are frequently reactivated. The importance of prior exposure varies based on the immunological deficit in the recipient. Bacterial and fungal infections are common culprits in the setting of neutropenia, while viral (CMV) and intracellular pathogens such as tuberculosis (TB) are common in T-cell depleted states [13]:

a. *Community-acquired pathogens* (*CAPs*) are organisms that a recipient is in contact with within a community. CAPs include common bacterial pathogens such as *Mycoplasma*, *Streptococcus pneumoniae*, *Legionella*, *Listeria monocytogenes*, and *Salmonella*. Common respiratory viruses (respiratory syncytial virus [RSV], influenza, parainfluenza, adenovirus, and others) can cause marked morbidity in transplant recipients. Although there is reduced efficacy in immunocompromised patients [14], vaccinations for

influenza virus and pneumococcus are recommended. The frequency of multiple simultaneous pathologies distinguishes a transplant recipient from the normal individual. As such, common pathogens seen in the "normal population" are also culprits in the transplant population. Endemic pathogens in various geographic locations when exposed to recipients can cause severe morbidity. These include endemic fungi (*Histoplasma capsulatum*, *Coccidioides* spp., *Blastomyces dermatitidis*, and *Cryptococcus gattii*) and other environmental pathogens such as *Cryptococcus neoformans*, *Aspergillus* spp., *Nocardia* spp., and *Cryptosporidium* spp. [13].

b. *Donor-derived infection* (*DDI*) is derived from the donor organs or tissues, which then subsequently get activated in the recipient [15,16]. Although organ donors are screened to avoid transmission of infections to transplant recipients, transmission of infection from donor to recipient still occurs. Latent pathogens in transplanted tissues and unrecognized donor infection are important determinants of DDIs in recipients. Cadaveric donor–associated infection of human immunodeficiency virus (HIV), West Nile virus, rabies, and Chagas disease have been reported in the literature [17–21]. Morbidity associated with these infections in immunocompetent patients can be self-limited with strong immune response. However, transplant recipients with these infections deteriorate rapidly with severe neurologic damage, rapid progression, and death due to immunosuppressive therapy. Presently, routine screening of donors using serology is not definitive in making a diagnosis in an infected donor organ, because seroconversion may not occur initially and detection can be missed [22]. It is therefore inevitable that an organ inhabited by pathogen will be transplanted, and accelerated infectious process will ensue in the recipient by immunosuppression. Specific screening of endemic pathogens in various geographical locations (e.g., West Nile virus, Chagas disease) is recommended. In addition, enhanced donor screening with improved assays by organ procurement organizations will help curb the transplantation of donor-infected organs. Specific prophylaxis can be provided to recipients for seropositive donors; similarly organs from donors infected with various viruses, for example, hepatitis B and C (HBV and HCV), can now under certain protocols be considered for transplantation in specific recipient population with known exposure [23–27], thereby averting known catastrophe. The importance of informed consent cannot be overemphasized in such situations. Potential donors with unknown infectious process, fever of unknown origin, or encephalitis can be avoided to eliminate the risk of implanting an infected organ. See Table 45.2 for a list of important transplant pathogens.

c. *Recipient-derived infections* commonly encountered are TB, certain parasites (e.g., *Strongyloides stercoralis* and *Trypanosoma cruzi*), viruses (e.g., varicella zoster virus, HBV, HCV, and HIV), and endemic fungi (e.g., *Histoplasma capsulatum*, *Coccidioides immitis*, and *Paracoccidioides brasiliensis*) [12]. Similar strategies for screening, prevention, and management are employed for these pathogens as described for DDIs. The important goal of pretransplant evaluation is to identify latent infections so as to develop a preventive strategy for each.

d. *Nosocomial infections* in transplant recipients are particularly ominous in the early posttransplant period. Patients with prolonged hospitalizations or who require mechanical ventilation are at highest risk for exposure. Common examples of nosocomial pathogens are Gram-negative bacilli (*Pseudomonas aeruginosa*, *Legionella* spp., *Klebsiella pneumoniae*, *E. coli faecalis*), Gram-positives (both vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* [MRSA]), fungi such as *Aspergillus* spp. and nonalbicans or azole-resistant *Candida* species, and *Clostridium difficile* that causes colitis [28,29].

45.4 Risk of Infection in Transplant Recipients

The essential determinants of risk of infection are the dose, duration, and sequence of immunosuppression therapies. The totality of factors such as immunosuppressive therapy, previous therapies (chemotherapy, antimicrobial therapy, blood transfusions), presence of catheters or drains, neutropenia, lymphopenia, underlying immunodeficiencies (e.g., hypogammaglobulinemia, systemic lupus erythematosus), metabolic conditions (e.g., uremia, malnutrition, diabetes, cirrhosis), and viral infections (e.g., CMV, HCV, HBV, HIV) all refer to the *net state of immunodeficiency* [11]. The identification and correction of any modifiable risk factor are essential for the prevention and treatment of the infection.

Immunosuppression regimens vary from center to center, with the organ transplanted and patient population.

TABLE 45.2

Important Infections, Predisposed Transplant Organ Recipients, Prevention and Management, and Comments

Pathogen	Organ Recipients/Infection/ Associations				Comments
Viruses [54]		***Predisposed organ***	***Prevention/Prophylaxis***	***Management***	
1. CMV	• Kidney–Pancreas ~ 50% • Heart–Lung ~ 40% • Liver ~ 30% • Heart ~ 25% • Intestine ~ 25–55% • Kidney ~ 8%–10%	• Pancreas • Lung • Liver • Heart • Intestine • Kidney	Passive immunization CMV-IG[a] Acyclovir Ganciclovir Valganciclovir	PO/IV Ganciclovir	CMV seronegative recipients at highest risk for CMV disease EBV seronegative recipients at highest risk for primary EBV infection Chronic prophylaxis with antiviral agents causes bone marrow suppression, which exacerbates infection. Renal toxicity and neurological side effects are common
2. EBV	80% of PTLD associated with EBV in all organ types Kidney/kidney–pancreas recipients ~ 1% PTLD Liver recipients ~ 3% Heart recipients ~ 3.5%–4% Lung recipients ~ 8% Heart–lung recipients 9.4%			Reduction of immunosuppression Passive immunity Antiviral	EBV linked to PTLD [41] in >80% of cases Increased titers of EBV in transplant recipients correlated with increased risk of PTLD
Bacteria Common bacteria associated with transplant recipients (from most commonly isolated and prevalent to least)	***Heart–lung recipients*** Encapsulated bacteria *Streptococcus pneumoniae* *Hemophilus pneumoniae* *Klebsiella pneumonia* *Streptococcus pyogenes* ***Intravenous catheter–associated infection*** *Staphylococcus aureus* (MRSA) *Staphylococcus* spp., coagulase-negative *Enterococcus* spp. (VRE) *Streptococcus* spp., viridians group *Pseudomonas* spp. Enterobacteriaceae	***Heart recipients*** Enterobacteriaceae (*E. coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia*) ***Kidney transplant patients*** Enterobacteriaceae spp. *Enterococcus* spp. ***Postsplenectomy patients*** *Streptococcus pneumoniae* *H. influenza* *Neisseria meningitidis* *Klebsiella pneumoniae*	*Streptococcus pneumoniae* vaccination Standard surgical prophylaxis for all transplant patients	Culture specific Antimicrobial	Variable incidence. However, most common isolates are listed Antibiotic prophylaxis protocols are center specific: Based upon the susceptibility patterns of the organism most frequently recovered from the center Colonized patients need to be covered with broad spectrum antibiotics Overutilization of antibiotics predisposes patients to superinfection with resistant fungal organism and *C. difficile colitis.*

Fungi [28] Important opportunistic pathogens	***Percentage of isolated fungi in transplant recipients*** *Candida* spp. Up to 76% of fungal infections *Aspergillus* spp. 39% of fungal infections *Cryptococcus neoformans* 30% of fungal infections	***Incidence of most common fungal infections*** Heart–lung recipients *Aspergillus* ~ 10%–30% Kidney–pancreas recipients *Candida* spp. 0%–38% Liver transplant *Candida* spp. ~ 4%–42%	Reducing the risk of fungal infection in transplant patients consists of elimination and reduction of risk factors and exposure and optimization of hospital care Azole derivatives or amphotericin B are considered for prophylaxis	Antifungal therapy Surgical intervention	High mortality associated with invasive fungal infection 5%–100% [28] Antifungal prophylaxis does not reduce mortality Fluconazole is safe in liver transplant patients Patients with the following should receive prophylaxis: Prolonged intensive care unit stay Retransplantation and reoperated Prior fungal infection Prior antimicrobial use Prolonged total parental nutrition Kidney and liver dysfunction

Sources: Fischer, S.A. et al., *N. Engl. J. Med.*, 354(21), 2235, May 25, 2006; Kotton, C.N. et al., *Transplantation,* 89(7), 779, April 15, 2012.

For example, in deceased donor kidney transplantation induction therapy with include Antithymocyte globulin (ATGAM) or muromonab-CD3 (OKT3), steroids and another agent while living donor kidney transplantation may not require induction. There is consideration in some HCV patients to minimize induction therapy prior to liver transplantation. Some centers aggressively wean steroids prior to patient discharge; others keep patients on low-dose steroids in combination with other immunosuppressants. Alteration in the type or intensity of immune suppression will alter the risk of infection [30]. Specific adverse effects of immunosuppressive agents are enumerated in Table 45.1.

The posttransplantation period can be divided into time intervals, which correlate with risk of specific pathogen and infection: the *early period* (less than 1 month), the *intermediate period* (1–6 months), and the *late period* (more than 6 months) [11,15]; this changing timetable of infection allows for predictability and stratification of risks. In *the early period*, infections derived from donor or recipient, transplant surgery, and hospitalization are the most characteristic. The infections associated with surgery are the typical common postoperative complications: urinary tract infections, surgical site infections, line sepsis, or pneumonitis. Unique to transplant patients are *superinfections* of ischemic or injured graft tissues (i.e., anastomotic suture lines), fluid collections (hematomas, lymphoceles, effusions, urinomas), and indwelling vascular access catheters, urinary catheters, and surgical drains. Particular attention should be given to nosocomial-derived infections in patients requiring prolonged support prior to transplantation, and individuals with delayed graft function or those requiring early re-exploration or retransplantation are also at increased risk for infection. Especially, notable during this period are fungi and bacteria with antimicrobial resistance.

The nature of common pathogens changes during the *intermediate period* and is characterized by local (geographical and institutional variation) epidemiology, anecdotal immunosuppressive strategies, and use of antimicrobial prophylaxis. Prophylactic antimicrobial strategies are based on our understanding of the pathogens of this period. Major infections of this period include opportunistic pathogens: PCP, CMV, HBV, HCV, BK polyomavirus, HHV-6, -7, -8, RSV, influenza virus, parainfluenza virus, adenovirus, TB, nontuberculous mycobacteria, and endemic fungi (*Histoplasma*, *Coccidioides*, *Cryptococcus*, *Blastomyces*) and latent infections such as toxoplasmosis, leishmaniasis, and Chagas disease [16,21,28,31,32].

During the *late period* (after 6 months), most transplant patients are stable and are at reduced levels of immunosuppression; thus, the risk of infection typically decreases. Transplant patients are subject to community-acquired pneumonia, urinary tract infections, opportunistic infections (*Aspergillus*, atypical molds, *Nocardia*, cryptococcosis, PCP), and viral infections (CMV colitis, retinitis, Epstein–Barr virus [EBV], HCV, and HBV). Viruses exert their effect directly by causing fever and neutropenia (CMV), cholangitis, varicella zoster virus (VZV) infections, encephalitis (HSV, Jakob–Creutzfeldt [JC] virus), hepatitis (HBV, HCV), esophagitis, gastritis, colitis, retinitis, pancreatitis, myocarditis, and to a lesser extent vasculitis and adrenalitis (adrenal insufficiency). Indirect effects of viruses also manifest during this period, for example, *Aspergillus* after influenza infection, PCP with CMV infection, EBV associated with lymphoma, HHV-8 associated with Kaposi's sarcoma, recurrent infections, graft rejection associated with CMV reactivation, and BK virus associated nephropathy, to name a few [33].

As a general principle in transplantation, *unexplained early signs of infection* in patients, such as hepatitis, pneumonitis, encephalitis, rash, and leukopenia, may be donor derived. Viral pathogens and allograft rejection are responsible for the majority of febrile episodes that occur during the intermediate period after transplantation. Although the risk of infection during the late posttransplantation period decreases, transplant recipients are persistently at increased risk for CAPs, and chronic viral infections cause allograft dysfunction (e.g., HCV in liver transplant patients, BK virus in renal patients, RSV in lung transplant patients with bronchiolitis obliterans, accelerated vasculopathy in heart transplant patients with CMV) [11]. The timeline for a given patient is reset with each episode of rejection or intensification of immunosuppression (e.g., with a bolus of steroids or infusion of induction therapy), with an increased risk of opportunistic infection. Therefore, diagnostic testing (tissue histopathology), prevention (see prevention strategies mentioned later), and management (prophylaxis, aggressive surgical intervention when indicated) of infection in transplant recipient must be guided by a dynamic assessment of the risk of infection and stratification of patients into low- and high-risk groups.

Low-risk patients are characterized by immunologic tolerance, good HLA matching, technically successful surgery, good graft function, appropriate surgical antibiotic prophylaxis, effective antiviral prophylaxis, PCP prophylaxis, and appropriate vaccinations. *High-risk patients* are characterized by induction therapy with T-cell depletion, pulsed-dose corticosteroids, plasmapheresis, high risk of rejection, early rejection, graft dysfunction, active and latent infection (donor or recipient derived), technical complications (bleeding, wound infection, prolonged intubation, anastomotic leak), prolonged urinary catheterization, and prolonged intubation [11].

Fortunately, patterns of infections after transplantation have been altered by the use of routine antimicrobial prophylaxis. Transplant centers use various

prophylactic regimens: pneumococcal vaccine, hepatitis B vaccine, trimethoprim-sulfamethoxazole for pneumocystis pneumonia and urinary tract infections, ganciclovir or valganciclovir for CMV, and clotrimazole troche or nystatin for oral and esophageal fungal infections. The evolution of strategies has led to an increase in allograft and patient overall survival and the discovery of other challenges (BK virus–associated nephropathy/ureteral obstruction and JC virus–associated progressive multifocal leukoencephalopathy).

As a general principle, after SOT, it is important that a multidisciplinary approach be instituted in the management of posttransplantation complications including infections in transplant recipients. This ensures that all potential aspects of risk stratification are addressed and the patient receives quality care and appropriate management.

45.4.1 Immunosuppression and Malignancy

The immune system is very important in defending against pathogens as seen with infections; it also plays a critical role in the surveillance and detection of cancer. As newer immunosuppressive and potent regimens have steadily decreased the incidence of rejection extending both graft and patient survival, many reports indicate cancer may now surpass cardiovascular complications as the leading cause of death in transplant patients [34–36]. Posttransplantation malignancy has become an important cause of mortality. The etiology of posttransplantation malignancy is multifactorial, involving impaired immunosurveillance of neoplastic cells as well as depressed antiviral immune activity (as seen with viral-associated Kaposi's sarcoma and posttransplant lymphoproliferative disorder or PTLD). According to Engels et al. [34], there is an increased risk of a wide range of cancers associated with SOT. In this extensive study, the authors found infection-related and infection-unrelated malignancies in all types of organ transplantation. Non-Hodgkin lymphoma and cancers corresponding to kidney, liver, and lung transplants comprised 43% of all cancer cases in transplant recipients compared to 21% in the general US population [34]. To illustrate that immunosuppression is the primary culprit in the development of malignancy in transplant recipients, Grulich et al. [37] showed that there was similarity in the pattern of increased risk of cancer in HIV/AIDS patients and transplant patients, with the common denominator being immunosuppression. The exact impact of immunosuppression is unknown. Wimmer et al. [38] found progressive increase in the incidence of malignancy from the azathioprine era to the most modern immunosuppressive regimens, suggesting a correlation with potency of immunosuppression and increased incidence of malignancy.

Induction therapy or antirejection treatment with polyclonal or monoclonal antibodies increases the incidence of malignancies, especially lymphoproliferative disorders [39–44]. This adverse effect is linked to aberrant production of cytokines that regulate processes promoting tumor growth, metastasis, and angiogenesis [45,46]. Prior studies looking at cyclosporine showed increased risk of malignancy when compared to patients receiving azathioprine and corticosteroids, which is believed to be dose dependent. Tacrolimus has similar malignancy risk as azathioprine [47]. Some conflicting data have found that mycophenolate mofetil is not associated with an increased risk of malignancy and may even be associated with a lower risk in some populations. Data from the Organ Procurement and Transplantation Network (OPTN) show that patients treated with belatacept (long-term data pending), sirolimus, and everolimus without CNIs have a lower incidence of malignancy than those receiving cyclosporine or tacrolimus [48]. Additionally, the conversion to sirolimus or everolimus along with CNI withdrawal has led to regression of both cutaneous and Kaposi's sarcoma, as described by Stallone et al. [49].

45.4.1.1 Prevention Strategies and Management of Immunosuppression-Associated Malignancy

1. *Reduction or cessation of immunosuppressive therapy:* This is useful primarily for patients who have undergone renal transplantation, since loss of the graft to rejection is not a fatal event in these patients. Such measures may result in tumor regression in some cases of lymphoma, some skin cancers, and Kaposi's sarcoma, in which reducing the CNI exposure may be particularly important.
2. In situ anogenital cancers can be treated with laser therapy, electrocautery, or topical fluorouracil. Topical imiquimod, which is available for the treatment of anogenital warts, has not been systematically studied in transplant recipients. Tapering the immunosuppressive regimen is beneficial and may lead to resolution of in situ carcinomas.
3. *Immunosuppressive agent substitution:* Despite the association of the CNIs with increased TGF-beta levels and the risk of malignancy, the first approach is to discontinue antimetabolite agents. This is because rejection is less likely to occur with double therapy with a CNI and prednisone than the combination of an antimetabolite with prednisone. However, some clinicians would substitute sirolimus for the CNI and antimetabolite.

4. Visceral malignancies are treated by standard surgical, radiotherapeutic, or chemotherapeutic modalities. If chemotherapy is needed, azathioprine should be discontinued to avoid additive myelosuppression. The course of these malignancies appears to be more aggressive in transplant recipients, and the outcome is importantly determined by the stage at which the tumor is discovered.
5. *Screening:* The incidence of breast cancer is less than what was previously expected in transplant recipients. This may be due in part to increased screening. Yearly breast exams in women over the age of 40 pre- and posttransplant are typically recommended. Prostate, colon, skin, and cervical cancer screening should be continued as per accepted guidelines.
6. *PTLD:* The management of PTLDs involves multiple approaches for prevention and treatment. The prevention of PTLD largely relies on limiting patient exposure to aggressive immunosuppressive regimens, aggressive withdrawal and tapering of agents required for graft acceptance, and antiviral prophylaxis. Many transplant centers have incorporated EBV monitoring into the routine evaluation of patients at high risk for PTLD and preemptive treatment of PTLD at the time of viral reactivation with rituximab or reduced immunosuppression or antiviral therapy. The management of PTLD varies significantly according to the type of lymphoproliferative disease present, as well as from institution to institution. Immunosuppression reduction is the cornerstone of therapy. Additional therapies include immunotherapy with the CD20 monoclonal antibody rituximab or chemotherapy, radiation therapy, or a combination of these. Other treatments, such as adoptive immunotherapy with EBV-specific cytotoxic T cells, are generally reserved for persistent disease despite initial therapy. Detailed management is beyond the scope of this chapter.
7. *Other cancers:* For tumor of donor origin, reduction of immunosuppression may theoretically lead to rejection of the tumor. Although this has been effective in PTLDs, there is little evidence that this is effective in other tumors. A number of options are available in the management of renal cell carcinoma that emerges from a transplanted kidney. In those without metastatic disease, total transplant nephrectomy may be curative, although a return to dialysis is required. Some have suggested that consideration may be given to nephron-sparing surgery in those with nonmetastatic renal cell carcinoma that is less than 4 cm in size and located peripherally. This approach has been reported thus far in only a few cases. Metastatic disease should be treated with cessation of immunosuppression, transplant nephrectomy, and immune therapy.

45.5 Other Important Complications Associated with Immunosuppression

It is well established that cardiovascular disease is a common cause of mortality in the general population. In the transplant patient, cardiovascular disease remains a frequent cause of death. US Renal Data Systems have identified immunosuppressive therapy as the significant risk factor for cardiovascular disease and severity. Retrospective studies have shown that cyclosporine is associated with increased incidence of hypertension as compared to azathioprine. In multicenter trials, tacrolimus- and cyclosporine-treated patients have similar incidence of hypertension, which ranges from 75% to 90% of patients [50]. The control of hypertension helps reduce the adverse risk of cardiovascular disease and increases patient survival. Moreover, according to Marcen et al. [7], lowering blood pressure after 3 years improved 10-year graft survival, and the risk of cardiovascular death paralleled the changes in systolic BP.

New onset diabetes mellitus (NODM) occurs in 5%–20% of transplant recipients within the first year posttransplantation and approaches 25%–30% in the second year. This is an important problem, particularly in those patients receiving tacrolimus or steroids. The diabetogenic effect of tacrolimus has been demonstrated in multiple randomized controlled trials and confers a significantly higher risk of death [51]. In this study, NODM posttransplantation, impaired fasting glucose, and the incidence of treated diabetes were significantly lower in the cyclosporine group compared to tacrolimus-based regimen at 6 months. Some studies have shown that patients treated with sirolimus in combination with cyclosporine, tacrolimus, or an antimetabolite have an increased risk of NODM compared with patients treated with cyclosporine plus mycophenolate mofetil (MMF) or azathioprine [52]. In addition to NODM, hypertension, and cardiovascular complications, immunosuppressive therapy can lead to hypercholesterolemia. Incidence ranges between 60% and 70% in patients on CNIs. As hypercholesterolemia is

associated with increased prevalence of cardiovascular disease, blood cholesterol should be maintained in the range recommended by practice guidelines, and statins should be initiated as indicated.

In a meta-analysis of available data by Pengel et al. [53], higher wound incidence of wound complications and lymphoceles after kidney transplantation and a higher incidence of wound complications after heart transplantation were observed for immunosuppressive regimens that included mTOR inhibitors versus regimens that did not include mTOR inhibitors from the time of transplantation. Wound complications (incisional hernia, infections, and dehiscence) and lymphoceles typically appear within the first few months; therefore, mTOR inhibitors should be avoided during the first 3 months. It is well known that due to the anti-inflammatory effect of steroids, poor wound healing can occur. Late steroid withdrawal compared with early withdrawal has been associated with poor wound healing, lymphoceles, and complications.

45.6 Summary

Short-term patient survival rates have progressively improved with the introduction of new immunosuppressive drugs to the levels where it is difficult to establish differences in survival among the immunosuppressive agents used. Long-term studies are required to confirm the short-term results. Corticosteroids and cyclosporine have stronger impact on blood pressure and lipid profile than tacrolimus. Tacrolimus is associated with higher incidence of NODM. Steroid withdrawal and CNI withdrawal improve cardiovascular risk profile; however, studies have not shown that this strategy decreases mortality from cardiovascular events. Malignancies and infections still remain important causes of morbidity and mortality. Clearly, there is a pressing clinical need to develop novel immunosuppressive agents that are more specific yet less toxic. In addition, research and discovery on ways to induce immune tolerance will help reduce the need for lifelong immunosuppression and help decrease the incidence of rejection, cancers, and infections.

It is imperative that surgeons and clinicians understand the mechanism of immunosuppressive agents and the implications of the rapidly evolving field of transplant immunology and immunosuppression, antiviral and antimicrobial prophylaxis, and their impact on the growing population of transplant recipients in order to provide excellent and evidence-based care.

References

1. Dempsey PW, Vaidya SA, Cheng G. The art of war: Innate and adaptive immune responses. *Cellular and Molecular Life Sciences*. December 2003;60(12):2604–2621. PubMed PMID: 14685686.
2. Murphy K, Travers P, Walport M, Janeway C. *Janeway's Immunobiology*. 8th ed. New York: Garland Science; 2012. xix, 868pp.
   Fundamental Concepts in Immunology; Innate and Adaptive Immunity.
3. Ortega F. Organ transplantation in the 21th century. *Advances in Experimental Medicine and Biology*. 2012;741:13–26. PubMed PMID: 22457100.
4. Murray JE, Merrill JP, Dammin GJ, Dealy JB, Jr., Walter CW, Brooke MS et al. Study on transplantation immunity after total body irradiation: clinical and experimental investigation. *Surgery*. July 1960;48:272–284. PubMed PMID: 14425430.
5. Hamburger J. The artificial kidney. *El Dia Medico*. August 3, 1959;31:1471–1472. PubMed PMID: 14399218.
6. Kirk AD. Induction immunosuppression. *Transplantation*. September 15, 2006;82(5):593–602. PubMed PMID: 16969280.
7. Marcen R. Immunosuppressive drugs in kidney transplantation: Impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. *Drugs*. November 12, 2009;69(16):2227–2243. PubMed PMID: 19852526.2009.
8. Montandon A, Wegmueller E, Hodler J. Early rejection crises and prognosis of the renal graft. *Nephrologie*. 1985;6(2):59–63. PubMed PMID: 3895011.
   Crises de rejet precoces et pronostic de la greffe renale.
9. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *The New England Journal of Medicine*. June 11, 1998;338(24):1741–1751. PubMed PMID: 9624195.
10. Alangaden GJ, Thyagarajan R, Gruber SA, Morawski K, Garnick J, El-Amm JM et al. Infectious complications after kidney transplantation: Current epidemiology and associated risk factors. *Clinical Transplantation*. July–August 2006 ;20(4):401–409. PubMed PMID: 16842513.
11. Fishman JA. Infection in solid-organ transplant recipients. *The New England Journal of Medicine*. December 20, 2007;357(25):2601–2614. PubMed PMID: 18094380.
12. Fishman JA, Practice ASTIDCo. Introduction: Infection in solid organ transplant recipients. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. December 2009;9 (Suppl 4):S3–S6. PubMed PMID: 20070692.
13. Fishman JA, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. Infectious disease clinics of North America. June 2010;24(2):273–83. PubMed PMID: 20466270.
14. Avery RK. Prophylactic strategies before solid-organ transplantation. *Current Opinion in Infectious Diseases*. August 2004;17(4):353–356. PubMed PMID: 15241081.

15. Fishman JA, Greenwald MA, Grossi PA. Transmission of infection with human allografts: Essential considerations in donor screening. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. September 2012;55(5):720–727. PubMed PMID: 22670038.
16. Morris MI, Fischer SA, Ison MG. Infections transmitted by transplantation. Infectious disease clinics of North America. June 2010;24(2):497–514. PubMed PMID: 20466280.

    Overview of Infections Transmitted by Transplantation and Management Strategies of Donor-Derived Infections.
17. Fischer SA, Graham MB, Kuehnert MJ, Kotton CN, Srinivasan A, Marty FM et al. Transmission of lymphocytic choriomeningitis virus by organ transplantation. *The New England Journal of Medicine*. May 25, 2006;354(21):2235–2249. PubMed PMID: 16723615.
18. Burton EC, Burns DK, Opatowsky MJ, El-Feky WH, Fischbach B, Melton L et al. Rabies encephalomyelitis: Clinical, neuroradiological, and pathological findings in 4 transplant recipients. *Archives of Neurology*. June 2005;62(6):873–882. PubMed PMID: 15956158.
19. Srinivasan A, Burton EC, Kuehnert MJ, Rupprecht C, Sutker WL, Ksiazek TG et al. Transmission of rabies virus from an organ donor to four transplant recipients. *The New England Journal of Medicine*. March 17, 2005;352(11):1103–1111. PubMed PMID: 15784663.
20. Iwamoto M, Jernigan DB, Guasch A, Trepka MJ, Blackmore CG, Hellinger WC et al. Transmission of West Nile virus from an organ donor to four transplant recipients. *The New England Journal of Medicine*. May 29, 2003;348(22):2196–2203. PubMed PMID: 12773646.
21. Centers for Disease C, Prevention. Chagas disease after organ transplantation—United States, 2001. *Morbidity and Mortality Weekly Report*. March 15, 2002;51(10):210–212. PubMed PMID: 11922190.
22. Centers for Disease C, Prevention. Notes from the field: Transplant-transmitted hepatitis B virus—United States, 2010. *Morbidity and Mortality Weekly Report*. August 19, 2011;60(32):1087. PubMed PMID: 21849966.
23. D'Albuquerque LA, Gonzalez AM, Filho HL, Copstein JL, Larrea FI, Mansero JM et al. Liver transplantation from deceased donors serologically positive for Chagas disease. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. March 2007;7(3):680–684. PubMed PMID: 17217440.
24. Seehofer D, Berg T. Prevention of hepatitis B recurrence after liver transplantation. *Transplantation*. September 27, 2005;80(1 Suppl):S120–S1204. PubMed PMID: 16286888.
25. Everhart JE, Wei Y, Eng H, Charlton MR, Persing DH, Wiesner RH et al. Recurrent and new hepatitis C virus infection after liver transplantation. *Hepatology*. April 1999;29(4):1220–1226. PubMed PMID: 10094968.
26. Dominguez-Gil B, Andres A, Campistol JM, Morales JM. Should we be using kidneys from hepatitis C virus-infected donors? *Current Opinion in Nephrology and Hypertension*. November 2011;20(6):599–604. PubMed PMID: 21946162.
27. Lonze BE, Dagher NN, Liu M, Kucirka LM, Simpkins CE, Locke JE et al. Outcomes of renal transplants from Centers for Disease Control and Prevention high-risk donors with prospective recipient viral testing: A single-center experience. *Archives of Surgery*. November 2011;146(11):1261–1266. PubMed PMID: 22106317.
28. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. April 15, 2010;50(8):1101–1111. PubMed PMID: 20218876.
29. Dubberke ER, Riddle DJ, Practice ASTIDCo. Clostridium difficile in solid organ transplant recipients. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. December 2009;9 (Suppl 4):S35–S40. PubMed PMID: 20070693.
30. Rostaing L, Guilbeau-Frugier C, Kamar N. Rituximab for humoral rejection after kidney transplantation: An update. *Transplantation*. April 27, 2009;87(8):1261. PubMed PMID: 19384176.
31. Fernandez-Sabe N, Cervera C, Farinas MC, Bodro M, Munoz P, Gurgui M et al. Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: A matched case-control study. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. February 1, 2012;54(3):355–361. PubMed PMID: 22075795.
32. Doucette K, Fishman JA. Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. May 15, 2004;38(10):1428–1439. PubMed PMID: 15156482.
33. Rubin RH. The indirect effects of cytomegalovirus infection on the outcome of organ transplantation. *The Journal of the American Medical Association*. June 23–30, 1989;261(24):3607–3609. PubMed PMID: 2542634.
34. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ et al. Spectrum of cancer risk among US solid organ transplant recipients. *The Journal of the American Medical Association*. November 2, 2011;306(17):1891–1901. PubMed PMID: 22045767. Pubmed Central PMCID: 3310893.

    Compared with the General Population, Recipients of a Kidney, Liver, Heart, or Lung Transplant have an Increased Risk for Diverse Infection-Related and Unrelated Cancers.
35. Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. *Transplantation*. October 15, 2005; 80(2 Suppl):S254–S264. PubMed PMID: 16251858.
36. Chang SH, Russ GR, Chadban SJ, Campbell SB, McDonald SP. Trends in kidney transplantation in Australia and New Zealand, 1993–2004. *Transplantation*. September 15, 2007;84(5):611–618. PubMed PMID: 17876274.

37. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. *Lancet*. July 7, 2007;370(9581):59–67. PubMed PMID: 17617273.

    The Incidence Cancer in Pharmacologically Immunosuppressed Transplant Recipients Compared to Immunosuppressed Patients with HIV/AIDS.

38. Wimmer CD, Rentsch M, Crispin A, Illner WD, Arbogast H, Graeb C et al. The janus face of immunosuppression—De novo malignancy after renal transplantation: The experience of the Transplantation Center Munich. *Kidney International*. June 2007;71(12):1271–1278. PubMed PMID: 17332737.
39. Bustami RT, Ojo AO, Wolfe RA, Merion RM, Bennett WM, McDiarmid SV et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. January 2004;4(1):87–93. PubMed PMID: 14678038.
40. Pedotti P, Cardillo M, Rossini G, Arcuri V, Boschiero L, Caldara R et al. Incidence of cancer after kidney transplant: Results from the North Italy transplant program. *Transplantation*. November 27, 2003;76(10):1448–1451. PubMed PMID: 14657684.
41. Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, Hanto DW. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. *Transplantation*. November 15, 2003;76(9):1289–1293. PubMed PMID: 14627905.
42. Opelz G, Naujokat C, Daniel V, Terness P, Dohler B. Disassociation between risk of graft loss and risk of non-Hodgkin lymphoma with induction agents in renal transplant recipients. *Transplantation*. May 15, 2006;81(9):1227–1233. PubMed PMID: 16699447.
43. Robson R, Cecka JM, Opelz G, Budde M, Sacks S. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. December 2005;5(12):2954–2960. PubMed PMID: 16303010.
44. Opelz G, Dohler B. Lymphomas after solid organ transplantation: A collaborative transplant study report. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. February 2004;4(2):222–230. PubMed PMID: 14974943.
45. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation*. June 27, 2004;77(12):1777–1782. PubMed PMID: 15223891.
46. Koehl GE, Andrassy J, Guba M, Richter S, Kroemer A, Scherer MN et al. Rapamycin protects allografts from rejection while simultaneously attacking tumors in immunosuppressed mice. *Transplantation*. May 15, 2004;77(9):1319–1326. PubMed PMID: 15167584.
47. Cowlrick I, Delventhal H, Kaipainen K, Krcmar C, Petan J, Schleibner S. Three-year follow-up of malignancies in tacrolimus-treated renal recipients—An analysis of European multicentre studies. *Clinical Transplantation*. May–June 2008;22(3):372–377. PubMed PMID: 18279418.
48. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation*. October 15, 2005;80(7):883–889. PubMed PMID: 16249734.
49. Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *The New England Journal of Medicine*. March 31, 2005;352(13):1317–1323. PubMed PMID: 15800227.
50. Kasiske BL, Anjum S, Shah R, Skogen J, Kandaswamy C, Danielson B et al. Hypertension after kidney transplantation. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*. June 2004;43(6):1071–1081. PubMed PMID: 15168388.
51. Cole EH, Johnston O, Rose CL, Gill JS. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. *Clinical Journal of the American Society of Nephrology*. May 2008;3(3):814–821. PubMed PMID: 18322046. Pubmed Central PMCID: 2386715.
52. Vincenti F, Mendez R, Pescovitz M, Rajagopalan PR, Wilkinson AH, Butt K et al. A phase I/II randomized open-label multicenter trial of efalizumab, a humanized anti-CD11a, anti-LFA-1 in renal transplantation. *American Journal of Transplantation: Official Journal of The American Society of Transplantation and the American Society of Transplant Surgeons*. July 2007;7(7):1770–1777. PubMed PMID: 17564637.
53. Pengel LH, Liu LQ, Morris PJ. Do wound complications or lymphoceles occur more often in solid organ transplant recipients on mTOR inhibitors? A systematic review of randomized controlled trials. *Transplant International: Official Journal of the European Society for Organ Transplantation*. December 2011;24(12):1216–1230. PubMed PMID: 21955006.
54. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Snydman DR et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation*. April 15, 2012;89(7):779–795. PubMed PMID: 20224515.

    Expert Panel Consensus on the Management of Cytomegalovirus in Solid Organ Transplantation.

46

Surgical Complications of Kidney and Pancreas Transplantation

Gaetano Ciancio, Junichiro Sageshima, Linda Chen, Jonathan A. Fridell, and George W. Burke

CONTENTS

Combined pancreas and kidney transplantation, performed either simultaneously (SPK) or sequentially if a living donor is identified for the kidney (PAK), has become one of the standard treatment options for patients with type 1 diabetes (T1D) and end-stage renal disease (ESRD). More effective immunosuppression protocols, improvements in surgical techniques, and a better understanding of postoperative complications have made SPK transplantation the procedure of choice [1–3].

Currently, pancreas transplantation is offered to patients if they are candidates for renal transplantation and there are no absolute contraindications to the procedure.

46.1 Pancreas Transplantation

46.1.1 Donor Operation

The standard donor operation generally includes procurement of the liver, both kidneys, the whole pancreas with the duodenum, and less often the small intestine. A nasogastric tube is advanced into the duodenum of the donor and is irrigated with 25 mL of 1% povidone-iodine solution followed by 50 mL of cold saline solution. The duodenum is then irrigated with an antibiotic solution that includes amphotericin B. The nasogastric tube is subsequently pulled back into the stomach, the duodenal contents are gently milked out of the duodenal segments, and the proximal and distal segments are staple divided. Care is taken to ensure that there is no distention. The portal vein is divided at the superior border of the pancreas. The superior mesenteric artery (SMA) and splenic artery (SA) are divided. A Y vascular graft, composed of the donor's common, external, and internal iliac arteries or the brachiocephalic trunk [4], is stored in a separate container of University of Wisconsin (UW) solution on the back table. The composite pancreas graft is then taken to the back table for further dissection [5].

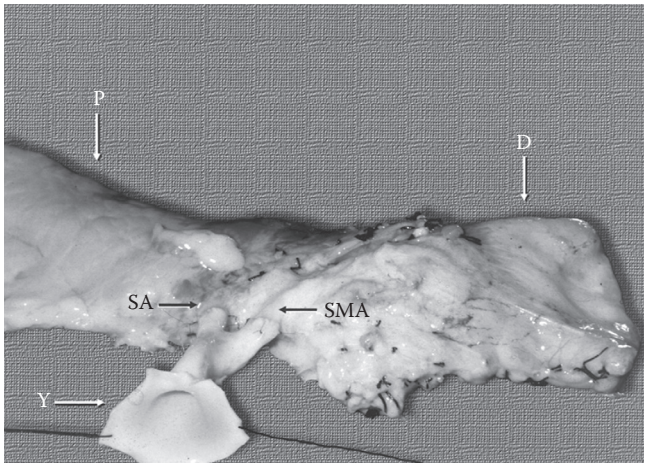


FIGURE 46.1
The composite pancreas and duodenal graft, demonstrating the brachiocephalic Y graft. The portal vein has been dissected free of the pancreatic bed. Y, brachiocephalic trunk anastomosed to the splenic artery and the superior mesenteric artery of the pancreaticoduodenal graft; P, pancreas; D, duodenum; SA, splenic artery; and SMA, superior mesenteric artery.

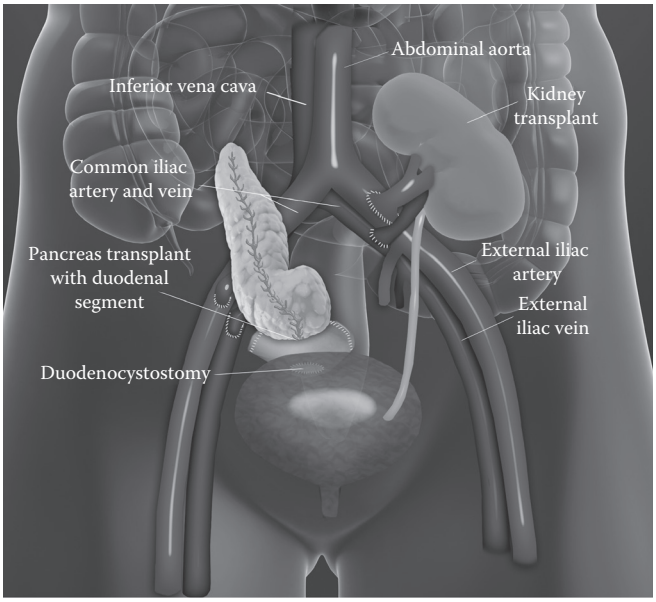


FIGURE 46.2
Surgical technique of simultaneous pancreas–kidney transplantation with bladder drainage through a midline intraperitoneal approach. The donor kidney is revascularized on the left side by anastomosing the renal vein to the external iliac vein and the renal artery to the external iliac artery. The dome of the bladder is shown with the ureteroneocystostomy and pancreaticoduodenocystostomy anastomoses. The pancreas–duodenal allograft is revascularized on the right side by anastomosing the portal vein to the external iliac vein and the common iliac artery of the Y graft to the recipient external iliac artery.

The back-table preparation is as follows: Splenectomy is performed, and for bladder-drained recipient operations, the duodenal segment is shortened; only the second portion of the duodenum is kept. Staple lines are not opened. For enteric-drained recipient operations, the distal duodenum is included. Both the proximal end and the distal end are divided with staples and oversewn with interrupted nonabsorbable stitches. Finally, the Y graft is fashioned, the internal iliac artery is anastomosed to the donor SA, and the external iliac artery is anastomosed to the donor SMA. The portal vein is then dissected free from the pancreatic bed (Figure 46.1).

46.1.2 Recipient Operation

1. *For bladder drainage of the pancreas–duodenal transplant*. The recipient operation begins with a midline incision. The pancreas–duodenal allograft is revascularized on the right side. The external iliac vein and common iliac vein are fully mobilized with division of all the internal iliac venous branches. The portal vein is anastomosed to the external iliac vein, and the common iliac artery of the Y graft is anastomosed to the recipient's external or common iliac artery. The duodenum is opened to allow drainage and prevent distention; a pancreatic duodenocystostomy (PDC) is then performed with a two-layered hand-sewn technique. No external drains are used, and a Foley catheter is left in place for 7–10 days. The kidney is then implanted on the left side by anastomosing the renal vein to the common or external iliac vein and the renal artery to the common or external iliac artery. The ureteroneocystostomy anastomosis is performed with an extravesicular submucosal tunnel (Figure 46.2).
2. *For the enteric drainage of the pancreas–duodenal transplant*. Enteric drainage is currently the most common exocrine drainage procedure performed at most US centers. The anastomosis is accomplished as a two-layered hand-sewn enteric anastomosis between the donor duodenum and recipient small intestine. Many variations of the technique have been described with important differences including orientation of the head of the pancreas toward the upper abdomen, inclusion of a roux-en-Y limb, stapled enteric anastomosis, and location in the small intestine in the proximal or the distal bowel [6] (Figure 46.3).

A recent modification of these procedures is the ipsilateral placement of the pancreas and the kidney on the right side [7]. For enteric drainage, the pancreas–duodenum is placed first and proximally using IVC/CIV and CIA for vascular anastomoses. The kidney is then placed distally (Figure 46.4). For bladder drainage of the

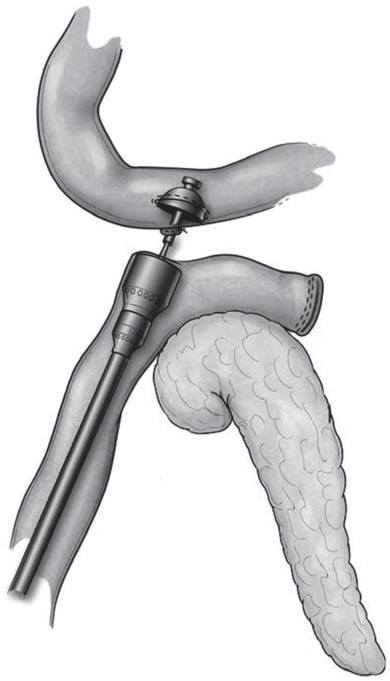


FIGURE 46.3
Use of circular stapler for donor duodenum to recipient bowel anastomosis.

pancreas–duodenal transplant, the kidney is revascularized first and proximally. The pancreas–duodenum is placed next and distally.

46.1.2.1 Portal Venous Drainage

The portal vein of the pancreas transplant may be drained into the systemic or the mesenteric circulation. The former bypasses the liver and, consequently, results in higher levels of systemic c-peptide. The latter is more physiologic and results in normal c-peptide levels. Both are considered acceptable options.

46.1.2.2 Arterial Anastomoses

Patients with T1D and ESRD often have considerable degrees of arterial atherosclerosis. This may present a significant technical challenge at the time of surgery for the creation of arterial inflow into the pancreas transplant. A number of options have been developed, including the following: dissection to include internal iliac artery, common iliac artery, and/or distal aorta; replacement of a severely diseased external iliac artery with (healthy) donor external iliac artery; placement of both transplants on one side (vide supra); endarterectomy; use of a long Carrel arterial patch; common arterial conduit for kidney and pancreas; and jump graft from the distal SMA of the pancreas transplant to the renal artery of the kidney transplant [8–10].

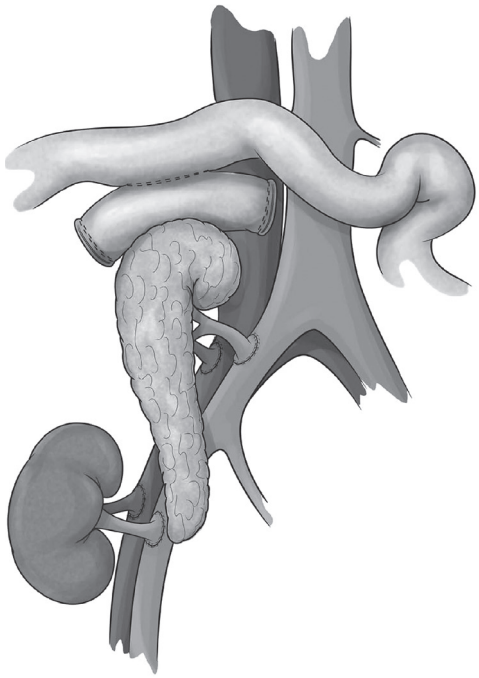


FIGURE 46.4
Ipsilateral placement of pancreas–duodenum (proximal) and kidney (distal) transplant with enteric drainage of pancreas–duodenum.

46.2 Surgical Complications after Pancreas Transplantation

Surgical complications are more common after pancreas transplantation than after kidney transplantation. Nonimmunological complications of pancreas transplantation account for graft losses in 5%–10% of cases. These complications usually occur within 6 months after the transplantation; their impact on loss of the pancreas graft is the same as that of acute rejection [11].

46.2.1 Thrombosis

Vascular thrombosis is a very early complication that typically occurs no later than 48 h and usually within 24 h after transplantation. Of all potential causes of technical failure, graft thrombosis is the most common; its incidence in association with SPK transplantation is 5.5% [12].

It may be difficult to determine precisely which risk factor is implicated in the pathogenesis of graft thrombosis because many causal factors have been described.

These include preterminal donor hypoperfusion, poor preservation, technical or mechanical issues, immunologic problems, sepsis, or hypercoagulable states. In addition, graft thrombosis has been attributed to the hemodynamic changes in blood flow from a high-flow to a low-flow state after ligation of the distal splenic vessels, the superior mesenteric vessels, and all nonpancreatic branches.

Graft salvage is unlikely after thrombosis and can occur only when parenchymal damage is minimal. For this reason, some surgeons have attempted to develop surgical techniques for preventing vascular thrombosis. Some have suggested creating a distal arteriovenous fistula (AVF) so that SA flow is increased [13]. Another alternative is transplanting the pancreas with the spleen so that physiological hemodynamic flow can be maintained [14]. The disadvantage of this procedure is the risk of the potentially lethal complication of graft-versus-host disease [15]. None of these techniques have consistently prevented early graft thrombosis, perhaps because graft perfusion probably remains unchanged despite attempts to increase flow through the larger vessels.

46.2.2 Partial Venous Thrombosis

We retrospectively reviewed our experience with the outcome and treatment options associated with partial venous thrombosis of pancreas allografts. From July 1994 to April 1997, 66 patients scheduled for SPK transplantation underwent antilymphocyte induction therapy with a monoclonal anti-CD3 preparation (OKT3) and oral or intravenous tacrolimus in the operating room. None of these patients experienced partial venous thrombosis. In contrast, from May 1997 to June 1999, 48 patients underwent induction therapy with intravenous tacrolimus alone or in conjunction with humanized monoclonal antibody to the interleukin (IL)-2 receptor (IL2-rmAb; Daclizumab®) [16]. Of these 48 patients, 14 (29%) experienced partial venous thrombosis, which was detected during routine color Doppler ultrasonography. Twelve of these patients had thrombosis of the splenic vein (SpV), one had thrombosis of the superior mesenteric vein (SMV), and one had partial thrombosis of the splenic and SMVs. We administered tacrolimus intravenously so that we could ensure sufficient concentrations early in the posttransplantation period to avoid acute rejection [17–20].

Microvascular changes associated with pancreatic transplantation may also predispose patients to venous thrombosis. Prostacyclin (PGI_2) and thromboxane A_2 (TXA_2), prostanoid derivatives of eicosapolyenoic fatty acids with opposing actions on vascular smooth muscle tone and platelet aggregation, provide a homeostatic mechanism for maintaining the integrity of the circulation [21]. TXA_2 promotes platelet aggregation and causes vasospasm, whereas PGI_2 opposes these actions, inhibiting platelet aggregation and causing vasodilation. Experimental studies noted an increase in the production of TXA_2 by the pancreas and a decrease in the ratio of PGI_2 to TXA_2 after cold ischemia and reperfusion of the pancreas [22]. Others have noted that the change in the ratio of these prostaglandins may result from the stasis of the blood flow in the splenic vessels. Tacrolimus may contribute to this problem by inducing vasospasm and causing microvascular injury. Alternatively, it may cause endothelial injury and thrombosis because of alterations in the ratio of TXA_2 to prostaglandin PGI_2 or because of the release of endothelin [23]. The potential for increased adhesion of T cells that express IL-2 receptors bound by daclizumab, combined with the known low-flow state of the SpV, may provide the setting for venous thrombosis when the endothelial toxic effects of tacrolimus are added to the mix.

Microvascular changes occurring late in the course of oral tacrolimus-based immunosuppression therapy have been reported. Corry et al. [24] reported that 9 of their 123 patients experienced pancreatic thrombosis while receiving intravenous tacrolimus, but the authors attributed the thrombosis to ischemia and reperfusion injury rather than to the use of intravenous tacrolimus. We have also described microangiopathy among recipients of kidney transplants or SPK transplants, who were treated with tacrolimus within 2–4 weeks after transplantation [23]. In each case, the intravenous administration of tacrolimus was discontinued, and immunosuppression was maintained successfully with oral tacrolimus, steroids, and mycophenolate mofetil.

Partial venous thrombosis of the pancreas transplant can be difficult to diagnose (Figure 46.6A). No clinical symptoms of thrombosis, such as graft tenderness, decreased or absent urinary amylase activity, sudden-onset hyperglycemia, hematuria, thrombocytopenia, leukocytosis, or intra-abdominal bleeding, are seen. Nor is there any change in clinical parameters. Superior mesenteric or SpV thrombosis is typically detected incidentally during routine Doppler ultrasonography. Sonography, computed tomography (CT), magnetic resonance imaging, and nuclear medicine scanning have been used to diagnose pancreatic graft thrombosis. We have found color Doppler ultrasonography to be helpful and cost-effective in diagnosing and assessing venous thrombosis of the pancreatic allograft.

Six patients with partial thrombosis of the SpV were treated with aspirin and followed up with serial Doppler ultrasonography. None of the partial thromboses progressed to complete SpV or pancreatic graft thrombosis. It is possible that partial SpV thrombosis is a self-limited process and does not require heparinization. The administration of aspirin may be sufficient [25].

46.2.3 Complete Venous Thrombosis

When partial thrombosis has progressed to complete venous thrombosis (Figure 46.5A and B), attempts at salvaging the thrombosed pancreas graft have been disappointing, but graft salvage rates can be as high as 45% if the problem is addressed immediately [26,27]. Urgent reoperation has also been advised so that life-threatening sequelae related to the necrotic pancreas or from pulmonary emboli can be avoided. Thrombectomy can be performed through a previous portal anastomosis or through a longitudinal or transverse venotomy in the portal vein [26]. Another approach is resection of the thrombosed segment of the pancreas graft. Immediate retransplantation of a new donor pancreas has also been described in cases of graft thrombosis either simultaneously or within the first few weeks of allograft pancreatectomy [28].

46.2.4 Arterial Thrombosis

Arterial thrombosis is less common than venous thrombosis and is usually associated with anastomoses of atherosclerotic vessels. In our series, one patient experienced thrombosis of the SMA. Diagnosis was made by routine Doppler ultrasonography of the pancreas (Figure 46.6B). Surgical thrombectomy was performed successfully through the distal SMA in the head of the pancreas allograft. We placed loops around the recipient iliac artery and the Y arterial graft, but did not occlude inflow; thus, we were able to avoid further ischemic injury to the pancreatic graft.

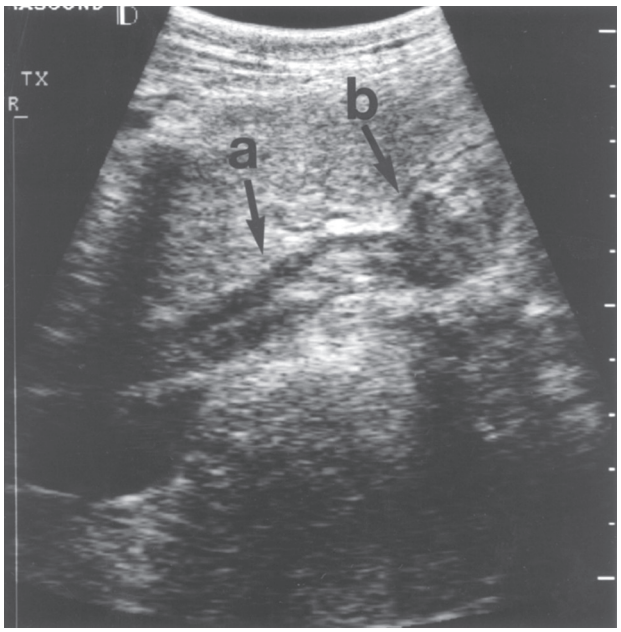
Another patient experienced late thrombosis of the Y graft, although the function of the pancreas allograft persisted. It is possible that pancreatic function was maintained by collateral flow or neovascularization between the donor graft and the recipient vessels. This patient required no treatment [29].

46.2.5 Prophylaxis of Graft Thrombosis

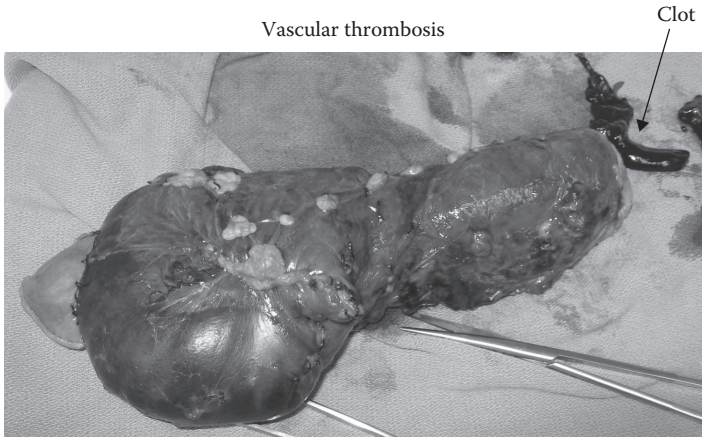
Thrombocytosis has been seen after pancreas transplantation without obvious pathophysiological explanations. Because multiple factors predispose the vessels of the pancreas graft to thrombosis, platelet inhibitors should be administered during the first 2 postoperative months. Another option for preventing graft thrombosis is the use of prophylactic anticoagulant therapy.

Various transplant centers use different therapeutic protocols in an attempt to prevent thrombosis [30]. These include the use of low-molecular-weight dextran, followed by intravenous heparin and antithrombin III supplementation in combination with long-term administration of acetylsalicylic acid. Another approach is the use of dextran followed by low-dose aspirin or a combination of aspirin and dipyridamole.

The routine use of systemic anticoagulation has been controversial. Systemic anticoagulation is

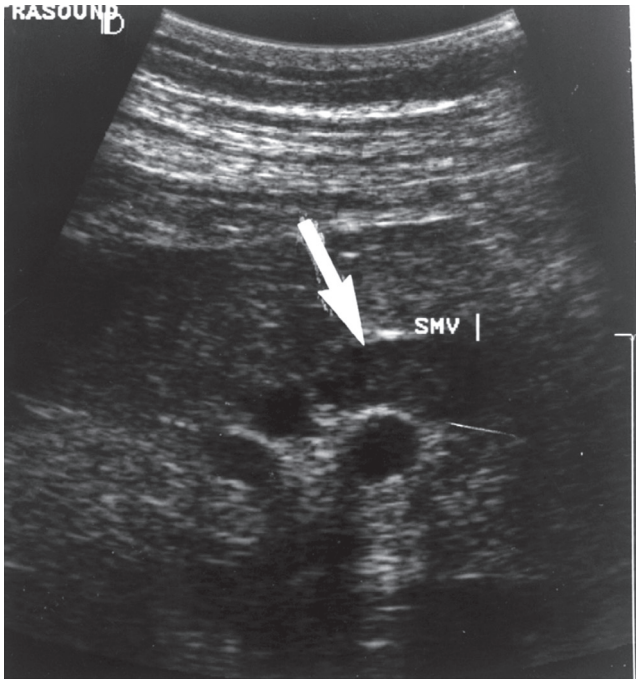


(A)

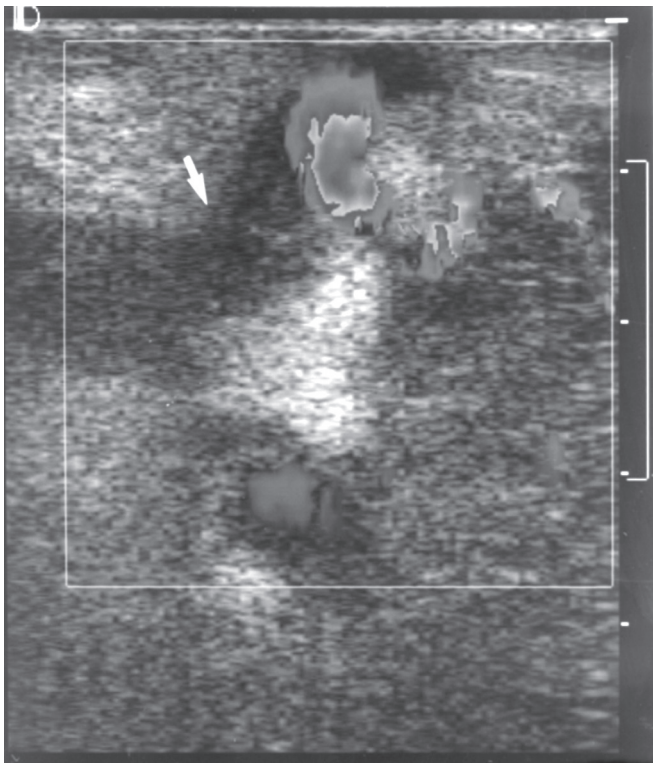


(B)

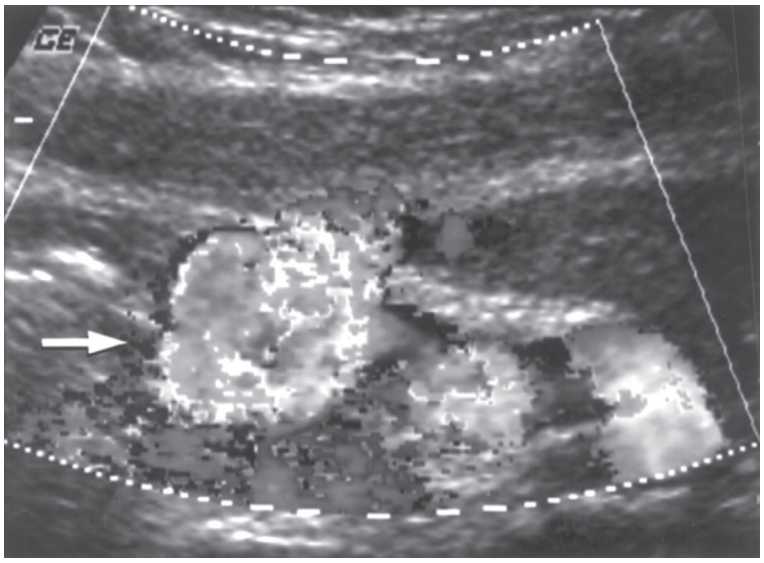
FIGURE 46.5
(A) Doppler ultrasonogram showing complete venous thrombosis of the pancreas allograft, including (a) the SpV and (b) the SMV. (B) Pancreas transplant (explants) following complete venous thrombosis, with clot demonstrated.



(A)



(B)



(C)

FIGURE 46.6
(A) Partial thrombosis (arrow) of the SMV detected by routine color Doppler ultrasonography. (B) Doppler ultrasonogram of the pancreas allograft, showing thrombosis of the superior mesenteric artery (arrow). (C) Doppler ultrasonogram of the pancreas allograft, showing increased pulsatile flow within the area of the body of the pancreas (arrow), a finding diagnostic of an arteriovenous fistula.

accepted therapy when SpV thrombosis has been documented, when SPK grafts have come from live donors, and when only the pancreas has been transplanted [25,30,31]. However, Sollinger has suggested that the use of systemic anticoagulation does not reduce the incidence of vascular graft thrombosis and may increase the likelihood of postoperative bleeding, which may in turn cause venous compression, thereby actually increasing the risk of graft thrombosis [32].

46.2.5.1 University of Miami Approach to Prevention of Pancreas Transplant Thrombosis

Our approach at the University of Miami has been to evaluate the following commonly obtained laboratory values: hemoglobin/hematocrit (Hb/Hct), prothrombin time (PT)/INR, partial thromboplastin time (PTT), platelet count, fibrinogen, and platelet function tests for their rheologic impact. We have found that high levels of Hb/Hct, platelet count, and fibrinogen or low PT/INR are often associated with a hypercoagulable state. An intraoperative thromboelastogram (TEG) is performed that allows confirmation of the hypercoagulable state [33]. If the operative field remains dry, then a bolus of heparin (2000–5000 units) is given intravenously (IV), prior to the placement of vascular clamps. If, after reperfusion of the pancreas transplant, and later after the kidney transplant, the operative field remains dry, then IV heparin is continued. The target PTT is 45–55. This approach has lead to minimizing both pancreas transplant thrombosis and postoperative bleeding. If, after heparinization, the operative field becomes oozy, then no further heparin is used, and, depending on the degree of oozing, either low-molecular-weight dextran or no further anticoagulant is used. This approach has also been used to effectively evaluate and treat recipients of kidney transplants alone.

The prevalence of hypercoagulability noted in SPK recipients (T1D/ESRD) helps to explain the higher incidence of thrombosis seen in pancreas transplantation than for any other solid organ transplant. The pancreas transplant (without the spleen and small bowel), furthermore, has large, high capacitance veins—specifically the SpV and the SMV—that no longer receive the high blood flow for which they were designed. Thus, both veins are subject to venous stasis, with only the low flow through the pancreas to maintain patency. Combined with the endothelial cell damage that occurs in every solid organ transplant (warm/cold ischemia), the hypercoagulable state and venous stasis of the pancreas transplant fulfill Virchow's triad for the development of venous thrombosis and offer a plausible explanation for the higher rate of thrombosis that occurs in pancreas transplants [33].

46.2.6 Arteriovenous Fistula

AVF is a recognized complication of pancreas transplantation. AVF may cause pancreatic endocrine insufficiency, hematuria, or a bruit over the graft. The causes of this abnormality include congenital malformation, needle injury during procurement, injury during the back-table preparation, and injury during reperfusion hemostasis in the recipient. Doppler ultrasonography is indicated if endocrine function suddenly deteriorates or if the patient experiences hematuria and pain over the graft. The diagnosis is confirmed by abnormal flow in the pancreatic head (Figure 46.6C). In our series of patients, four have experienced AVF. Two were treated with surgical correction; the other two were treated with angiography and embolization. Pancreatic endocrine function has been preserved in all four patients [29,34].

46.2.6.1 Vascular Catastrophes

Among the most devastating and potentially graft and life threatening of technical complications are those involving the arterial vascular anastomosis [35]. To date, there have been individual reports of arterial pseudoaneurysms, mycotic aneurysms, and arteriovesical and arterioenteric arterial fistulae.

In terms of pseudoaneurysm formation, the majority of cases occur in the setting of intra-abdominal fluid collections that involve the area of the arterial anastomosis. In fact, following percutaneous drainage of a fluid collection, any bleeding in the drainage fluid should be considered a herald bleed from a pseudoaneurysm unless this is excluded by arteriography. An alternate etiology for pseudoaneurysm is a technical error. The most important reason to specifically clarify the etiology of a pseudoaneurysm involving the arterial anastomosis of an allograft is because surgical repair of a pseudoaneurysm has been described with allograft salvage, but in the case of pseudoaneurysm specifically developing in the background of infection or a fluid collection, attempts at graft salvage are not recommended.

Alternatively, chronic pancreas allograft rejection likely plays an important role in the etiology of arterioenteric fistula. As the allograft fibroses and decreases in size until it is barely detectable, the bowel anastomosis is pulled toward the area of the vascular anastomosis, setting up a configuration where a communication between the artery and the native intestine may develop. It is for this reason that we would recommend that immunosuppression not be completely discontinued following graft failure in pancreas transplant recipients. Alternatively, strong consideration should be given to allograft pancreatectomy if immunosuppression discontinuation is deemed necessary or desirable. Variety of approaches to these situations have been described, most commonly involving a direct operative approach with either repair of the vascular anomaly or urgent allograft pancreatectomy and endovascular approaches such as stenting or coil embolization.

It is extremely important that one have a very low index of suspicion for arterioenteric fistula and arterial pseudoaneurysm in order to make the diagnosis and manage either of these complications in a timely fashion. The diagnosis of arterioenteric fistula is frequently

evasive as upper gastrointestinal endoscopy is often noncontributory due to poor visualization from excessive amounts of blood clot or poor timing during a period between a sentinel bleed and further hemorrhage. Urgent angiography is likely the procedure of choice in order to confirm the diagnosis and to control the bleeding. A common clinical error in the setting of gastrointestinal bleeding from arterioenteric fistula is to perform visceral angiography, which will fail to identify the source of bleeding. It is very helpful, in these situations, to specifically communicate the origin of the arterial anastomosis to the radiologist in order to ensure that the iliac arteries are well visualized and to minimize the amount of intravenous contrast required.

In cases of either pseudoaneurysm or arterioenteric fistula, primary endovascular intervention, in particular with covered stenting of the native artery across the origin of the allograft artery, is possibly the procedure of choice because it provides immediate vascular control without the loss of tamponade or uncontrolled bleeding that are characteristic of surgical exploration [35]. If further surgical intervention is warranted, this will greatly reduce the patients' subsequent transfusion requirements and will render that procedure technically much simpler as arterial control is already established.

46.2.7 Transplant Pancreatitis

Graft thrombosis may occur after the development of reperfusion-induced graft pancreatitis, which is caused when pancreatic blood flow is reduced to a critical level. Multiple factors may be involved in graft pancreatitis including the following [36]. Donor risk factors include hemodynamic instability, brain injury, and vasopressor administration; procurement injury may be due to excessive intraoperative manipulation. Perfusion injury may also occur when excessive flush volumes or perfusion pressures are used. Also, total cold and warm ischemia times may have an effect on preservation and the occurrence of reperfusion injury. Grewal et al. [37] demonstrated that postoperative treatment of the recipient with calcium-channel blockers, combined with the administration of steroids to the donor at the time of procurement, protects against the development of pancreatitis.

Animal models of pancreatitis demonstrate that the microcirculation is impaired as pancreatitis progresses, and this impairment leads to necrosis and thrombosis of the pancreas [38]. Although these findings do not necessarily reflect allograft pancreatitis as associated with transplantation, they could explain some of the events that occur in association with pancreatic graft edema. With the introduction of UW (or Belzer) solution as a perfusate for pancreatic transplantation, pancreatic graft edema after reperfusion is less pronounced. The introduction of this solution was a pivotal contribution to the reduction of graft loss due to thrombosis during the early postoperative period [39].

Reduced preservation time may also help reduce the incidence and the severity of reperfusion injury and edema of the pancreas allograft; however, other large studies have not found that cold ischemia time affects graft survival [36]. The incidence of allograft pancreatitis during the postoperative period has decreased because of improvements in procurement techniques that use the spleen and duodenum as handles that avoid pancreatic manipulation, the introduction of Belzer preservation solution, decompression of the portal system during in situ flushing, and intraperitoneal transplantation of the whole organ with appropriate exocrine drainage. However, allograft pancreatitis is still an important cause of morbidity.

When pancreatitis persists after transplantation, a thorough evaluation is necessary so that its cause can be determined [40,41]. Reflux pancreatitis, high postvoid residual volumes, peripancreatic fluid collections, infectious pancreatitis, and leaks from the duodenal segment may cause hyperamylasemia. For bladder-drained pancreas transplants, a Foley catheter should be placed so that postvoid residual volumes can be checked, and urodynamic studies should be performed so that high postvoid residual volumes and pressures can be detected [42]. In addition, abdominal ultrasonography, CT of the abdomen, and cystography should be performed so that the cause of the pancreatitis can be determined. Urine amylase measurement can provide a helpful diagnostic adjunct. In the presence of falling urine amylase, if no leak is demonstrated, then acute rejection is a likely possibility. If the results of the workup are nondiagnostic, a biopsy of the pancreas should be performed so that rejection can be ruled out as a cause of hyperamylasemia.

46.2.7.1 Small-Bowel Obstruction

Small-bowel obstruction can complicate any laparotomy. In addition to adhesions, there are two etiologies that are specific to pancreas transplantation. First of all, in cases where an enteric anastomosis is selected and particularly when the pancreas is oriented with the head upward, an internal hernia defect is created that is prone to incarceration and intestinal volvulus if not specifically closed at the time of transplantation. Second, the anterior surface of the pancreas in the retroperitoneum presents a raw surface that is prone to adhesion formation. One practice is to cover the pancreas with a sheet of adhesion barrier at the end of the operation. Similarly, the intraperitoneal renal allograft should be covered with colon in order to prevent contact with the small intestine.

46.2.8 Complications Associated with Bladder-Drained Pancreas Transplantation

Bladder-drained pancreas transplantation is associated with multiple urologic [42,43] and metabolic complications. Published reports have shown that 14%–50% of patients require enteric conversion. In our experience at the University of Miami, approximately 8% of our SPK patients required enteric conversion.

Hematuria occurs very frequently and may be caused by the formation of a bladder stone on the staple or suture line. Approximately 30% of patients will require interventions such as Foley catheter placement, irrigation, and cystoscopy for evacuation of clots.

Urinary tract infections are common; they occur in as many as half of all cases and are probably responsible for the irritating effect of the exocrine secretion on the bladder mucosa. Although the urinary pH is generally alkalotic (pH between 7 and 9) and will maintain proenzymes in an inactive state, a urinary tract infection may reduce the pH enough to activate these digestive enzymes. In addition, enterokinase in the brush border of the duodenal mucosa may activate the proenzyme trypsinogen and thereby initiate the pancreatic enzyme–activation cascade. Other proteases, such as plasmin, thrombin, and fibrinolysin, as well as bacterial enzymes, may also activate the conversion of trypsinogen to trypsin. The severe burning and dysuria caused by the resultant urethritis are attributed to urethral autodigestion by the activated pancreatic enzymes, trypsin and chymotrypsin. If untreated, these symptoms may progress to urethral disruption or stricture. Treatment of urethral complications requires both enteric conversion and urological expertise [44]. Fortunately, this complication has become less common during the last 15 years.

Metabolic acidosis is caused by the excretion of large quantities of alkaline pancreatic secretions from the bladder. Most patients require supplemental oral sodium bicarbonate once oral intake is tolerated; this treatment will minimize the degree of acidosis. With time, most of these patients are able to decrease their need for oral sodium bicarbonate.

Fluid management can become problematic for these patients because of the potential for relatively large volume losses. Patients are at risk for dehydration, which can be exacerbated by poor oral intake as the result of gastric-motility problems (gastroparesis) commonly associated with T1D. The symptoms from dehydration can be further increased when patients with diabetes have preexisting orthostatic hypotension because of autonomic neuropathy. Fluid balance can be improved in most patients by the postoperative administration of fludrocortisone.

Urine leaks due to breakdown of the duodenal segment may occur years after transplantation, but this complication is usually encountered within the first 2 or 3 postoperative months. The causes of early urine leaks are technical in nature and usually require surgical correction with prolonged Foley catheter drainage. Late leaks (Figure 46.7) can be caused by high pressure in the duodenum during urination. The onset of abdominal pain with elevated serum amylase activity, which can mimic reflux pancreatitis or acute rejection, is a typical presentation. Supporting imaging studies using cystography or CT may be necessary for confirming the diagnosis. Operative intervention may be required and includes reanastomosis to the bladder. Late leaks may develop as the result of rejection and can be treated successfully with Foley catheter drainage.

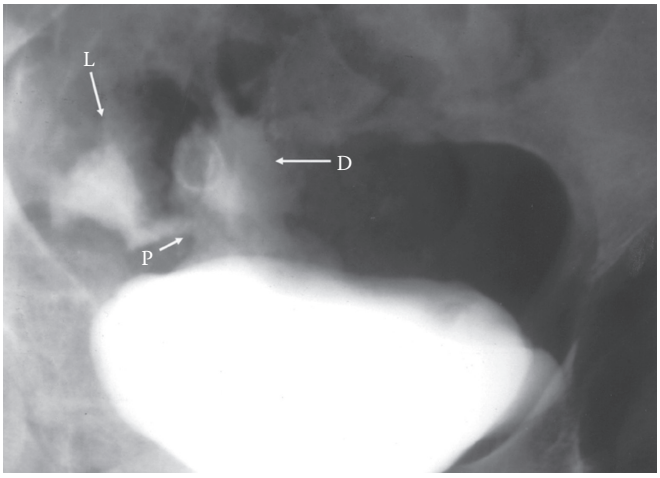


FIGURE 46.7
Cystogram showing a late leak from the duodenum of the pancreas allograft. L, leak; D, duodenum; P, perforation.

Two patients have experienced early postoperative leaks. One patient experienced a disruption of the PDC during cystoscopy for hematuria 2 weeks postoperatively. Another patient experienced a leak as the result of an episode of biopsy-proven acute rejection 6 weeks after transplantation. Both patients required operative treatment that included a revision of the PDC. Another of our patients experienced a late leak during an episode of rejection; this leak was successfully treated with Foley catheter drainage and treatment of rejection.

Despite these complications, bladder drainage of the pancreatic graft has many advantages. Early and late complications may cause morbidity; however, these complications are most often amenable to surgical correction.

Another advantage of bladder drainage is the ability to monitor the patient for graft rejection. The technique also allows cystoscopic access for biopsy of the duodenal or pancreatic graft and easy access to pancreatic fluid. An immediate decrease in urine amylase activity after pancreas transplantation signals early acute

rejection. Six months after transplantation, a decrease in urinary amylase activity may signal late acute rejection. The decrease in urinary amylase activity may be the only clinical indication of a problem, with no change in the serum concentrations of creatinine or glucose or of serum amylase or lipase. A biopsy of the pancreas should be performed for confirming the diagnosis of rejection.

After the administration of rejection therapy with steroids, the need for repeat pancreatic biopsy can be determined by measuring urine amylase activity. If low urine amylase activity persists after rejection therapy, pancreatic biopsy is indicated. In contrast, if urine amylase activity returns to baseline and the blood-glucose concentration remains high after therapy, the causative factor is steroid therapy rather than rejection, and pancreatic biopsy is not necessary.

46.2.9 Complications Associated with Enteric-Drained Pancreas Transplantation

When pancreas transplantation was first performed in the early 1970s, the results of enteric-drainage methods were poor. The small-bowel drainage procedure fell into disfavor because anastomotic leaks with abscess formation and sepsis caused high rates of morbidity and mortality. Recently, more centers are experiencing success with enteric drainage because of improvements in donor management, optimized surgical techniques during organ procurement, better preservation solutions, advances in the implantation procedure, and new immunosuppressive drugs [45–48]. Enteric-drainage techniques vary in bowel arrangement, the level of anastomosis, the site of the recipient small bowel, and the choice of either a stapled or a hand-sewn anastomosis. The most serious complication of enteric-drained pancreas transplantation is a leak at the anastomotic site. This serious problem occurs 1–6 months after transplantation and causes fever, abdominal discomfort, and leukocytosis. CT scans are helpful in diagnosing the problem. The mandatory treatment is surgical exploration and repair of the enteric leak.

Gastrointestinal bleeding may occur at the duodenoenteric suture line. If the enteric anastomosis is created to the proximal jejunum, the recipient is a candidate for push enteroscopy management of this complication with endoscopic clipping, cauterization, or epinephrine injection of the bleeding site. It is highly advisable to intubate the patient for airway control if this is performed in the early posttransplant period. If nonoperative management is inadequate, then re-exploration is required [49].

Enteric drainage has advantages that balance the risk of serious complications associated with this procedure. First, because metabolic acidosis and dehydration do not occur, bicarbonate supplementation is not needed. Second, this procedure is obviously not associated with urological complications such as urinary infections, hematuria, bladder stones, and urinary leaks. Third, fewer laboratory tests are required because there is no reason to monitor urinary activity. However, the diagnosis of rejection episodes therefore relies exclusively on the presence of symptoms and the detection of changes in serum amylase and lipase and may progress undiagnosed before treatment is started, and this delay increases the possibility of allograft loss.

46.3 Summary

The primary goal of therapy for patients with T1D and ESRD is the restoration of normal glucose metabolism and renal function. Many of the technical problems associated with kidney–pancreas transplantation have been resolved, the incidence of associated thrombosis has diminished, and the management of exocrine secretions with bladder and enteric drainage now provides good results. Immunosuppression therapy aimed at preventing rejection has also improved with the availability of tacrolimus, mycophenolate mofetil, rapamycin, monoclonal anti-CD25, and thymoglobulin [20,50]. These drugs, when used in specific combinations, have been highly effective in decreasing the incidence of rejection and prolong graft survival among patients who undergo kidney–pancreas transplantation [51,52].

References

1. Burke G, Ciancio G, Alejandro R et al. Cholesterol control: long-term benefit of pancreas-kidney transplantation with FK506 immunosuppression. *Transplant Proc* 1998;30:513–514.
2. Burke GW, Ciancio G. The renal and pancreatic allograft recipient. In: Kirby RR, Taylor RW, Civetta JM, eds. *Handbook of Critical Care*. 3rd edn. Philadelphia, PA: Lippincott, 1997: pp. 1311–1315.
3. Burke GW, Ciancio G, Olson L, Roth D, Miller J. Ten-year survival after simultaneous pancreas/kidney transplantation with bladder drainage and tacrolimus-based immunosuppression. *Transplant Proc* 2001;33:1681–1683.
4. Ciancio G, Olson L, Burke GW. The use of the brachiocephalic trunk for arterial reconstruction of the whole pancreas allograft for transplantation. *J Am Coll Surg* 1995;181(1):79–80.

5. Fridell JA, Powelson JA, Sanders CE, Ciancio G, Burke GW, 3rd, Stratta RJ. Preparation of the pancreas allograft for transplantation. *Clin Transplant*, 2011;25(2):E103–E112.
6. Fridell JA, Milgrom ML, Henson S, Pescovitz MD. Use of the end-to-end anastomotic circular stapler for creation of the duodenoenterostomy for enteric drainage of the pancreas allograft (corrected). *J Am Coll Surg* 2004;198(3):495–497.
7. Fridell JA, Shah A, Milgrom ML, Goggins WC, Leapman SB, Pescovitz MD. Ipsilateral placement of simultaneous pancreas and kidney allografts. *Transplantation* 2004;78(7):1074–1076.
8. Fridell JA, Gage E, Goggins WC, Powelson JA. Complex arterial reconstruction for pancreas transplantation in recipients with advanced arteriosclerosis. *Transplantation* 2007;83(10):1385–1388.

   Surgical options for operating on severely atherosclerotic T1D arteries for SPK recipients.
9. Moon JI, Ciancio G, Burke GW. Arterial reconstruction with donor iliac vessels during pancreas transplantation: an intraoperative approach to arterial injury or inadequate flow. *Clin Transplant* 2005;19(2):286–290.
10. Gorin MA, Garcia-Roig M, Burke GW 3rd, Ciancio G. Emergent renal revascularization of a simultaneous pancreas-kidney transplant recipient. *Transplantation* 2012; 93(4):e16–e17.
11. Ciancio G, Burke GW, Viciana AL et al. Destructive allo-graft fungal arteritis following simultaneous pancreas-kidney transplantation. *Transplantation* 1996;61:1172–1175.
12. Gruessner RW, Burke GW, Stratta R et al. A multi-center analysis of the first experience with FK506 for induction and rescue therapy after pancreas transplantation. *Transplantation* 1996;61:261–273.
13. Duron JJ, Roux JM, Imbaud P et al. The arteriovenous fistula in segmental pancreatic transplantation in dogs—A hemodynamic study. *Transplantation* 1987;44:600–601.
14. Starzl TE, Iwatsuki S, Shaw BW Jr. et al. Pancreaticoduodenal transplantation in humans. *Surg Gynecol Obstet* 1984;159:265–272.
15. Deierhoi MH, Sollinger HW, Bozdech MJ, Belzer FO. Lethal graft-versus-host disease in a recipient of a pancreas-spleen transplant. *Transplantation* 1986;41:544–546.
16. Ciancio G, Cespedes M, Olson L, Miller J, Burke GW. Partial venous thrombosis of the pancreatic allograft after simultaneous pancreas-kidney transplantation. *Clin Transplant* 2000;14:464–471.
17. Ciancio G, Lo Monte A, Buscemi G, Miller J, Burke GW. Use of tacrolimus and mycophenolate mofetil as induction and maintenance in simultaneous pancreas-kidney transplantation. *Transpl Int* 2000;13:S191–S194.
18. Ciancio G, Burke G, Viciana A et al. Use of intravenous tacrolimus to reverse vascular rejection in kidney and simultaneous kidney-pancreas transplantation. *Transplant Proc* 1998;30:1536–1537.
19. Ciancio G, Burke GW, Roth D, Miller J. Use of intravenous FK506 to treat acute rejection in simultaneous pancreas-kidney transplant recipients on maintenance oral FK506. *Transplantation* 1997; 63:785–788.
20. Burke GW, Ciancio G, Alejandro R et al. Use of tacrolimus and mycophenolate mofetil for pancreas-kidney transplantation with or without OKT3 induction. *Transplant Proc* 1998;30:1544–1545.
21. Moncada S, Vane JR. Arachidonic acid metabolites and interactions between platelets and blood-vessel walls. *N Engl J Med* 1979;300:1142–1147.
22. Johnson BF, Thomas G, Wiley KN et al. Thromboxane and prostacyclin synthesis in experimental pancreas transplantation. Changes in parenchymal and vascular prostanoids. *Transplantation* 1993;56:1447–1453.
23. Burke GW, Ciancio G, Cirocco R et al. Microangiopathy in kidney and simultaneous pancreas/kidney recipients treated with tacrolimus: evidence of endothelin and cytokine involvement. *Transplantation* 1999; 68:1336–1342.
24. Corry RJ, Egidi MF, Shapiro R et al. Tacrolimus without antilymphocyte induction therapy prevents pancreas loss from rejection in 123 consecutive patients. *Transplant Proc* 1998;30:521.
25. Kuo PC, Wong J, Schweitzer EJ, Johnson LB, Lim JW, Bartlett ST. Outcome after splenic vein thrombosis in the pancreas allograft. *Transplantation* 1997;64:933–935.
26. Ciancio G, Julian JF, Fernandez L, Miller J, Burke GW. Successful surgical salvage of pancreas allografts after complete venous thrombosis. *Transplantation* 2000;70:126–131.
27. Fridell JA, Mangus RS, Mull AB et al. Early reexploration for suspected thrombosis after pancreas transplantation. *Transplantation* 2011;91(8):902–907.
28. Hollinger EF, Powelson JA, Mangus RS et al. Immediate retransplantation for pancreas allograft thrombosis. *Am J Transplant* 2009;9(4):740–745.
29. Ciancio G, Lo Monte A, Julian JF, Romano M, Miller J, Burke GW. Vascular complications following bladder drained simultaneous pancreas-kidney transplantation; the University of Miami experience. *Transpl Int* 2000;13(suppl 1):S187–S190.
30. Farney AC, Rogers J, Stratta RJ. Pancreas graft thrombosis: causes, prevention, diagnosis, and intervention. *Curr Opin Organ Transplant* 2012;17(1):87–92.

   Surgical options for operating on severely atherosclerotic T1D arteries for SPK recipients.
31. Gruessner RW, Kendall DM, Drangstveit MB, Gruessner AC, Sutherland DE. Simultaneous pancreas-kidney transplantation from live donors. *Ann Surg* 1997;226:471–482.
32. Sollinger HW. Pancreatic transplantation and vascular graft thrombosis. *J Am Coll Surg* 1996;182:362–363.
33. Burke III George W, Ciancio G, Figueiro J et al. Hypercoagulable state associated with kidney-pancreas transplantation. Thromboelastogram-directed anticoagulation and implications for future therapy. *Clin Transplant* 2004;18:423–428.

   Guidelines to assess hypercoagulabilityin patients with T1D/ESRD undergoing SPK transplantation.
34. Khan TF, Ciancio G, Burke GW III, Sfakianakis GN, Miller J. Pseudoaneurysm of the superior mesenteric artery with an arteriovenous fistula after simultaneous kidney-pancreas transplantation. *Clin Transplant* 1999;13:277–279.

35. Fridell JA, Johnson MS, Goggins WC et al. Vascular catastrophes following pancreas transplantation: An evolution in strategy at a single center. *Clin Transplant* 2012;26(1):164–172.

Approach to diagnose and treat difficult vascular complications following enteric-drained pancreas transplants.

36. Troppmann C, Gruessner AC, Benedetti E et al. Vascular graft thrombosis after pancreatic transplantation: univariate and multivariate operative and operative risk factor analysis. *J Am Coll Surg* 1996;182:285–316.
37. Grewal HP, Garland L, Novak K, Gaber L, Tolley EA, Gaber AO. Risk factors for postimplantation pancreatitis and pancreatic thrombosis in pancreas transplant recipients. *Transplantation* 1993;56:609–612.
38. Klar E, Messmer K, Warshaw AL, Herfarth C. Pancreatic ischaemia in experimental acute pancreatitis: mechanism, significance and therapy. *Br J Surg* 1990; 77:1205–1210.
39. D'Alessandro AM, Kalayoglu M, Sollinger HW, Pirsch JD, Southard JH, Belzer FO. Current status of organ preservation with University of Wisconsin solution. *Arch Pathol Lab Med* 1991;115:306–310.
40. Ciancio G, Burke GW, Roth D, Luque CD, Coker D, Miller J. Reflux pancreatitis after simultaneous pancreas-kidney transplantation treated by a-1 blocker. *Transplantation* 1995;60:760–761.
41. Ciancio G, Montalvo B, Roth D, Miller J, Burke GW. Allograft pancreatic duct dilatation following bladder drained simultaneous pancreas-kidney transplantation: clinical significance. *JOP* 2000;1:4–12.
42. Ciancio G, Burke G, Lynne C et al. Urodynamic findings following bladder-drained simultaneous pancreas-kidney transplantation. *Transplant Proc* 1997;29:2912–2913.
43. Ciancio G, Burke GW, Nery J et al. Urologic complications following simultaneous pancreas-kidney transplantation. *Transplant Proc* 1995; 27:3125–3126.
44. Ciancio G, Burke GW, Nery JR, Coker D, Miller J. Urethritis/dysuria after simultaneous pancreas-kidney transplantation. *Clin Transplant* 1996;10:67–70.
45. Ciancio G, Burke G, Roth D, Miller J. Tacrolimus. *Curr Opin Transplant* 1997;2:62–67.
46. Zucker K, Rosen A, Tsaroucha A et al. Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous in vitro findings. *Transpl Immunol* 1997;5:225–232.
47. Ciancio G, Burke GW, Miller J. Current treatment practices in immunosuppression. *Expert Opin Pharcother* 2000;1:1307–1330.
48. Ciancio G, Burke GW, Roth D et al. Tacrolimus and Mycophenolate Mofetil as primary immunosuppression for renal allograft recipients. In: Racusen LC, Solez K, Burdick JF, eds. *Kidney Transplant Rejection: Diagnosis and Treatment*. New York: Marcel Dekker, 1998:519–529.
49. Ciancio G, Burke G, Roth D, Tzakis AG, Miller J. Update in transplantation 1997. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants*, 1997. Los Angeles, CA: UCLA Tissue Typing Laboratory, 1998: pp. 241–264.
50. Ciancio G, Miller J, Burke GW. The use of intravenous tacrolimus and mycophenolate mofetil as induction and maintenance immunosuppression in simultaneous pancreas-kidney recipients with previous transplants. *Clin Transplant* 2001;15:142–145.
51. Kandula P, Fridell J, Taber TE et al. Impact of tacrolimus-sirolimus maintenance immunosuppression on proteinuria and kidney function in pancreas transplant alone recipients. *Transplantation* 2012;94(9):940–946.
52. Ciancio G, Sageshima J, Chen L et al. Advantage of rapamycin over mycophenolate mofetil when used with tacrolimus for simultaneous pancreas kidney transplants: randomized, single center trial at 10 years. *Am J Transplant* 2012;12:3363–3376.

Ten year randomized, prospective study demonstrating the feasibility of successful immunosupppression with low dose tacrolimus and rapamycin in SPK recipients.

47

Complications of Liver Transplantation

David M. Levi, Gennaro Selvaggi, and Andreas G. Tzakis

CONTENTS

47.1 Introduction

Liver transplantation is the most effective treatment for fulminant hepatic failure, end-stage liver disease, some rare, inherited metabolic disorders, and in selected cases of hepatobiliary malignancy. Advanced surgical techniques and sophisticated immunosuppressive regimens have yielded improvements in patient and graft survival [1]. Success has led to a broadening of the indications for the procedure and an exacerbation of the shortage of grafts available for liver transplantation. The shortage of liver grafts impacts the possibility of complications in several ways. The pressure to transplant more patients has required the consideration and often the utilization of organs from marginal donors. Patients who wait a prolonged period of time for an acceptable graft may be sicker at the time of transplant, increasing the risk of complications [2].

Many factors contribute to possibility of complications during or following liver transplantation. The patient's general condition, performance status, comorbid conditions, degree of hepatic decompensation, and even psychosocial factors may impact the risk of complications [1]. Also, potential technical complications, the requirement for immunosuppression, the possibility of recurrent disease, donor variables, and the possibility of disease transmission from donor to recipient make liver transplantation vastly different from nontransplant hepatobiliary surgery.

In this chapter, complications related to liver transplant are presented and are stratified according to whether they originate as liver graft or systemic/extrahepatic problems. Pretransplant-related complications

from disease progression, patient deconditioning, etc., certainly impact patient outcome but are not the focus of this chapter. Intraoperative complications are often technical in nature but may result from poor recipient or donor selection. Characteristically, certain complications are more common at particular times in reference to the time of transplant. Early complications (those occurring within 3 months of the transplant) are often technical in nature, related to recipient preoperative condition or to early rejection or infection. Complications that develop after 3 or more months are often related to immunosuppression (infection, rejection, drug toxicity, malignant neoplastic disease) or recurrence of the patient's original disease affecting the liver graft.

Ultimately, excellent results following liver transplantation require a team approach; careful recipient selection, pretransplant patient optimization, donor selection, meticulous surgical technique, excellent postoperative management, and long-term follow-up are all imperative for avoiding complications when possible and minimizing their impact when they do occur.

47.2 Extrahepatic/Systemic Complications

47.2.1 Pulmonary

Pulmonary complications are common in the early postoperative course ranging from atelectasis and pleural effusions to pneumonia [3]. Respiratory failure (with or without pneumonia) requiring prolonged mechanical ventilation can result from recipient deconditioning, underlying parenchymal lung disease, or hepatopulmonary syndrome. Injury to the right phrenic nerve during the native liver hepatectomy can lead to right hemidiaphragmatic paralysis. Pulmonary embolism is relatively uncommon in liver transplant recipients in the early postoperative period. Pulmonary edema is often a consequence of renal dysfunction and is usually managed by fluid restriction and diuretics administration; in cases of severe renal impairment, hemodialysis may be necessary. Bacterial or fungal pneumonia occurs most often in the first 30 days posttransplantation [4]. Patients at highest risk for pneumonia are those that are debilitated, malnourished, and/or have been hospitalized prior to transplant; those that are administered more immunosuppression to treat or avoid early rejection; and those that develop other complications that lengthen their time of mechanical ventilation in the intensive care unit.

Acute respiratory distress syndrome (ARDS) that develops after liver transplantation is usually triggered by sepsis. It develops in 5%–17% of posttransplant patients and is associated with intra-abdominal infections, acute cellular rejection (ACR), pancreatitis, and hepatic artery thrombosis (HAT) with resulting hepatic necrosis [5]. It is diagnosed by excluding other etiologies of respiratory failure, primarily pneumonia. Portopulmonary hypertension is present in 2%–4% of patients with end-stage liver disease, and it remains a contraindication to liver transplant [6]. The pathophysiology of the disease is not clear, but it is related to portal hypertension. In patients with severely elevated pulmonary pressures and increased pulmonary vascular resistance, implantation and reperfusion of the liver during the transplant procedure results in acute right heart failure and is usually fatal. Careful screening for portopulmonary hypertension is a routine part of the pretransplant evaluation. An elevated estimated systolic pulmonary artery (PA) pressure determined by transthoracic echocardiography is confirmed by direct measurement with right heart catheterization. A mean PA pressure of >35 mmHg and/or a PA systolic pressure of >50 mmHg in the absence of volume overload (normal pulmonary capillary wedge pressure) mandates treatment and correction prior to transplant. Medical therapy has improved with the advent of potent vasodilatory agents [7,8]. Some patients are successfully treated and can undergo liver transplant.

Hepatopulmonary syndrome is a rare form of pulmonary insufficiency, which manifests with hypoxemia [9]. It is present in 1%–2% of cirrhotic patients and is characterized by arterial hypoxemia and pulmonary vasodilatation in the absence of intrinsic cardiopulmonary disease. The pathophysiology of the disease is due to intrapulmonary, arteriovenous shunting, resulting in a significant ventilation–perfusion mismatch. In contradistinction to portopulmonary hypertension, hepatopulmonary physiology usually gradually resolves after hepatic transplantation.

47.2.2 Renal

Renal insufficiency is common after liver transplantation, especially in patients with preexisting intrinsic kidney disease and/or in those with acute kidney injury or hepatorenal syndrome immediately prior to transplantation [10]. Acute kidney injury due to multiple factors including transient hypotension, blood loss, and fluid shifts during the transplant procedure is common with liver transplantation. Some 10% of patients will experience renal failure necessitating hemodialysis in the early postoperative period. Most recover within days to weeks. Hepatorenal syndrome, characterized by decreased urinary output, low urinary sodium, and high blood urea nitrogen during end-stage liver disease, has a complex pathophysiology resulting in decreased renal cortical perfusion [11]. It is reversible with liver transplant, but most recipients experience a transient rise

in serum creatinine in the early postoperative period. Importantly, blood urea nitrogen and creatinine may be misleading indicators of renal function in decompensated cirrhotics owing to malnutrition and muscle mass loss. Oliguria is a better indicator of renal function impairment in these patients. Immunosuppressive medications, specifically the calcineurin inhibitors tacrolimus and cyclosporine, cause arteriolar vasoconstriction and renal tubular injury [12]. Early on, this effect is usually reversible by dose reduction. Invariably, however, long-term use leads to chronic renal function impairment. End-stage renal failure necessitating chronic hemodialysis or kidney transplant occurs in 10%–20% of adult liver transplant recipients within 5 years, due in large part to calcineurin toxicity [13]. Plasma levels of calcineurin inhibitors are monitored closely to minimize the potential for associated renal injury. Monitoring of serum creatinine, especially in the first months after liver transplant, is key; early toxicity is a strong predictor of late renal failure. Sirolimus (rapamycin) has emerged as an alternative immunosuppressive agent for some recipients with renal dysfunction.

47.2.3 Hematologic

Coagulopathy is the most common hematologic disorder encountered in the posttransplant patient. It is caused by the deficiency in the liver-produced components of the coagulation cascade including the vitamin K–dependent factors (II, VII, IX, and X) and fibrinogen. An important indicator of early liver graft function is the rapid correction of the prothrombin time and fibrinogen level. In addition to early liver graft dysfunction, biliary obstruction can impede the absorption of vitamin K in the ileum resulting in a coagulopathy. Thrombocytopenia is very common prior to liver transplantation and is due to portal hypertension, splenomegaly, and platelet sequestration. After liver transplant, platelet counts usually fall to a nadir around postoperative day 4–5 and recover subsequently to pretransplant levels within a week [14].

47.2.4 Endocrine/Metabolic

In the early posttransplant period, hyperglycemia is common due to high-dose corticosteroid administration during the induction phase of immunosuppressive therapy. Many patients will require insulin for short-term glycemic control and up to 20% will develop diabetes mellitus [15]. Hyperlipidemia affects nearly 30% of liver transplant recipients. Many with hyperlipidemia have metabolic syndrome and nonalcoholic steatohepatitis as the underlying cause of liver disease. Corticosteroid and calcineurin inhibitor use contribute to hyperlipidemia after transplant. Cholesterol and triglyceride level monitoring and appropriate treatment through diet, exercise, and medications are warranted to avoid late cardiovascular complications [16]. Osteoporosis can be a debilitating complication following liver transplantation. It is a common problem in patients with cholestatic liver disease (primary biliary cirrhosis, sclerosing cholangitis) caused by malnutrition and impaired vitamin D absorption [17]. After liver transplant, administration of corticosteroids can exacerbate the situation. Pathologic fractures, especially of the vertebral column, are painful and can impair a patient's rehabilitation after transplant.

47.2.5 Neurologic

Early after transplantation, alteration in the mental status of the patient can be due to resolving hepatic encephalopathy (which can be monitored by the decline in the ammonia level), but it can also be a consequence of the immunosuppressive therapy, delirium, and sleep deprivation in the intensive care unit and can manifest with disorientation and psychosis. These "metabolic" causes resolve with improving hepatic function, reduction of the immunosuppressive therapy, and transfer of the patient to a non-ICU bed. Seizures can occur in the early postoperative period and are usually associated with electrolyte abnormalities (hypomagnesemia, hypokalemia) or toxic effect of the immunosuppressive medications administered (tacrolimus or cyclosporine toxicity) [18]. Anticonvulsants may be necessary, but many alter the metabolism of concomitantly given immunosuppressive agents. Close monitoring of drug levels is indicated. In patients with fulminant liver failure, cerebral edema may progress during the liver transplant procedure before it subsides. Intraoperative intracranial pressure monitoring and aggressive intracranial pressure management may help prevent death from cerebral edema. Central pontine myelinolysis is a devastating complication seen primarily in patients with severe hyponatremia at the time of transplant [19]. Rapid correction of chronic hyponatremia intraoperatively can provoke this complication. Although some patients recover, many are left with a permanent and profound neurologic impairment.

47.2.6 Gastrointestinal/Abdominal

When biliary reconstruction is performed with a Roux-en-Y limb of jejunum, patients are at risk of intestinal anastomotic leak or from the biliary anastomosis itself (discussed later). In addition, bowel perforation or obstruction can complicate the postoperative course. Intra-abdominal bleeding complicates 7%–15% of liver transplants, requiring re-exploration in about half of these patients [20]. Surgical site infection, fascial dehiscence, and late incisional hernia formation are not uncommon; while these are not

unique to liver transplant, wound healing impairment due to preexisting malnutrition and the need for immunosuppression makes these complications more common and potentially more serious.

Ascites, often a problem before liver transplant in cirrhotics with portal hypertension, may persist or develop after transplant. Dissection and lymphatic disruption during the procedure, as well as malnutrition and hypoalbuminemia typical in patients with chronic liver disease, may slow the resolution of ascites after transplant, even though portal hypertension is eliminated with orthotopic liver replacement. After liver transplant, portal vein or hepatic venous outflow obstruction or late recurrent cirrhosis can manifest in ascites [21].

47.2.7 Infections

Liver transplant recipients are at a high risk for developing infections because of the immunosuppressive regimens that are required to avoid and treat rejection. The most common infections are bacterial in origin, followed by fungal and viral infections [22,23]. Depending on the time from transplant, a pattern of types of infections and causative agents can be observed. In the first month after transplant, the majority are bacterial infections related to central venous catheters, pneumonia, the surgical site, urinary tract, or intra-abdominal source. Debilitated patients are at more risk for bacterial infections, and those with prior hospitalizations are at most risk for infections due to multidrug resistant organisms. Fungal infections are at their highest incidence in the first 2 months following transplantation [24]. The spectrum of clinical disease ranges from oral candidiasis to fulminant often lethal fungemia. The most common form of fungal infection is oral and esophageal candidiasis; fungal urinary tract system is also common. Fungal pneumonia or fungal infection from an intra-abdominal source are significant causes of morbidity and mortality, especially in the immunosuppressed liver transplant recipient. Liver transplant for fulminant hepatic failure, transplantation, and cases where massive transfusion volumes are given are associated with a higher incidence of fungal infection. These cases may warrant antifungal prophylaxis. Viral infections are more commonly seen after the first month posttransplant with a peak incidence during the second and third month. Most commonly encountered pathologic viruses in this period are cytomegalovirus (CMV) and Epstein–Barr virus (EBV) [25,26]. Infection by CMV was more common before the implementation of antiviral prophylaxis (ganciclovir) in high-risk recipients, that is, in a CMV seronegative recipient of an organ from a CMV seropositive donor. The spectrum of disease varies from viremia and nonspecific symptoms of malaise, arthralgias, and fever to severe infection from pneumonitis, hepatitis, retinitis, bone marrow involvement, or gastroenteritis. Epstein–Barr viral infection can present in the early postoperative period as mononucleosis syndrome with flu-like symptoms or with hepatitis. Like CMV, EBV infection can present as reactivation in a seropositive patient or as new infection from a seropositive donor [27]. For both, treatment consists of antiviral medications and a reduction in immunosuppression. EBV is associated with posttransplant lymphoproliferative disorder (PTLD).

47.2.8 Malignancies

The use of medications to suppress the immune system and avoid rejection exposes patients to the development of malignant disease. Some of these malignancies are unique to the transplant recipient population, specifically the spectrum of PTLD. Typically, PTLD occurs within 2 years of liver transplant. The disease is related to infection by EBV and its capacity of mutating the proliferation patterns of the lymphoid cell populations it infects [28]. Immunosuppression, required to prevent rejection, impairs the T-cell population responsible for clearing the virus. Often, the discontinuation of immunosuppression leads to disease remission. The most common type of PTLD is a B-cell lymphoma, but the spectrum of disease varies greatly both in terms of the affected tumor cell lines and in terms of the clinical presentation and course. The mildest form of PTLD results from polyclonal cell line expression and disease localized to primary lymphoid beds (tonsils, Peyer's patches of the intestine, spleen, mediastinal and retroperitoneal lymph nodes). More severe disease is monoclonal in nature, is often more diffuse and can involve the bone marrow, and can behave clinically like a frank malignant lymphoma. Diagnosis requires careful immunopathologic analysis of biopsy specimens. For these cases, the cessation of immunosuppression plus specific monoclonal antibody therapy and/or cytotoxic chemotherapy is indicated [29].

The most common sites of non-PTLD malignancies encountered after liver transplant are the skin (Kaposi's sarcoma, squamous cell), oropharyngeal and gastrointestinal tracts (stomach, colon), and genitourinary tract (renal, bladder, cervical) [30]. Skin cancers are the most common nonlymphoid malignancies that develop in posttransplant patients. Multiple factors including recipient age, sun exposure, race, and viral infection have been implicated. Specifically, human papillomavirus infection has been linked to the development of cervical cancers and squamous cell carcinoma. Kaposi's sarcoma is very often associated with human herpes virus 8 infections [31]. Colon cancer is more common in recipients with a history of inflammatory bowel disease. Interestingly, the rate of incidence of breast cancer

in patients posttransplant is lower than in the normal population.

As more patients are undergoing liver transplant for early, unresectable hepatocellular carcinoma (HCC), recurrent HCC is being seen with increasing frequency [32]. While rarely curable, early detection and treatment of localized recurrence can prolong patient survival [33].

47.2.9 Cardiovascular

Cardiovascular complications have emerged as a major long-term cause of morbidity and mortality after liver transplant [34]. Immunosuppressive agents commonly used cause hypertension and hyperlipidemia and are diabetogenic. Renal dysfunction can contribute as well. Treatment consists of lifestyle modification, exercise, proper nutrition, weight loss, and medical treatment of hypertension and hyperglycemia.

47.3 Graft-Related Complications

47.3.1 Primary Graft Nonfunction

Primary nonfunction of the hepatic graft is defined as early graft failure (<30 days after transplant) unrelated to surgical technical factors or rejection. It is the most common cause of graft loss in the early postoperative period, with an incidence of 1%–5% of cases [35]. It is characterized by absent bile production, marked coagulopathy, encephalopathy, ascites, markedly elevated liver enzymes, and progressive renal and multiorgan failure. The major causative factor is ischemia-reperfusion injury with massive hepatocyte necrosis. Donor-related factors such as age, degree of graft steatosis, especially macrovesicular steatosis, severe acidosis and electrolyte imbalances (hypernatremia), and prolonged ischemia time all impact the risk of primary nonfunction [36]. HAT must be excluded to confirm the diagnosis. The only potentially successful treatment for primary nonfunction is urgent transplantation.

47.3.2 Vascular—Arterial

HAT is among the most dreaded complications of liver transplant [37,38]. When it occurs within the first month of transplant, it is a technical complication causing liver graft necrosis and often a biliary anastomotic leak. It occurs in 1%–3% of cases and usually results in graft loss and mandates urgent transplantation. When it occurs later, its etiology is less clear but is likely related to neointimal hyperplasia and/or atherosclerosis at the arterial anastomosis site. Late stenosis or thrombosis of the hepatic artery is associated with biliary complications including strictures, bilomas, jaundice, and cholangitis [39]. Occasionally, late HAT is clinically silent owing to the development of arterial collaterals to the liver and biliary tree. Risk factors for the development of HAT include small vessel size as in pediatric cases, the use of an arterial graft for reconstruction, or recipient hypercoagulable state. Early detection and surgical intervention may result in graft salvage; most centers have a protocol for surveillance with Doppler ultrasound in the first days after liver transplant [40].

47.3.3 Vascular—Portal Vein

Portal vein thrombosis after liver transplant is uncommon [41]. When it occurs early, within the first postoperative month or two, it can cause significant liver dysfunction and portal hypertension-related problems including ascites and variceal hemorrhage. It is considered a technical complication occurring because of an anastomotic problem or poor portal flow. Prior portal vein thrombosis, the existence of large portosystemic collaterals, and hypercoagulability may be associated with posttransplant portal vein thrombosis. When it occurs late, portal venous thrombosis may be discovered as an asymptomatic, incidental finding. Occasionally, if diagnosed early, it can be addressed surgically or via an interventional radiologic approach.

47.3.4 Vascular—Hepatic Veins

Hepatic venous outflow obstruction is also an uncommon complication of liver transplant [41,42]. It may occur in both conventional cases (caval excision) and those where the "piggy-back" technique (caval preservation) is used. With the latter, it is rare if all three recipient hepatic veins are used. Patients who are transplanted for Budd–Chiari syndrome often continue to have a hypercoagulable state after transplant and are at increased risk for rethrombosis and outflow obstruction. Hepatic venous outflow obstruction after transplant can present with a spectrum of problems including liver dysfunction or failure, ascites, and variceal hemorrhage depending on the degree and rate of onset of the outflow obstruction. As with portal vein complications, outflow obstruction can be addressed either surgically or increasingly via an interventional radiologic approach with dilatation and stent placement. Anticoagulation is indicated for patients with hypercoagulable states.

47.3.5 Biliary

The biliary reconstruction has been considered the Achilles' heel of the liver transplant procedure. Because delays in diagnosis are frequent and the association

with cholangitis and sepsis is common, the morbidity and mortality due to these complications remains high. Biliary complications are common, occurring in 10%–20% of recipients [43,44]. They usually occur within the first 6 months after transplant and can be broadly classified in bile leaks and biliary strictures. Early bile leak is a technical complication resulting from dehiscence of the anastomosis. The incidence of the problem is similar regardless of the method of reconstruction or whether the anastomosis is to the recipient common bile duct or a jejunal limb. The morbidity related to the latter, a bilioenteric anastomotic leak, is greater because of associated intra-abdominal sepsis. Adequate arterial supply to the donor bile duct is essential for avoiding bile leak and biliary strictures. Late biliary strictures are often due to ischemic injury related to severe preservation injury at the time of transplant or hepatic artery stenosis or thrombosis [45]. Patients with biliary complications frequently present with fevers, chills, jaundice, elevated liver enzymes, and hyperbilirubinemia. Cholangitis and intra-abdominal sepsis are usually from gram-negative bacteria and require appropriate antibiotics, biliary drainage, and drainage of any infected intra-abdominal fluid collections. Any time a biliary complication is suspected or diagnosed, Doppler ultrasound interrogation of the hepatic artery is warranted to identify a possible concomitant arterial problem such as HAT. Biliary strictures are addressed with techniques similar to those used in nontransplant patients. With increasing frequency, short segment anastomotic strictures can be dilated and stented via endoscopic retrograde cholangiopancreatography (ERCP) or a percutaneous transhepatic route rather than open surgical reconstruction. Bile leaks resulting in intra-abdominal sepsis may require exploration and anastomotic revision; in this circumstance, a duct-to-duct reconstruction is usually converted to a Roux-en-Y choledochojejunostomy. Hepatic artery patency is a key determinant of the likelihood that a particular intervention will correct the problem and ultimately allow for graft salvage. Diffuse, multifocal strictures caused by ischemic cholangiopathy (preservation injury), HAT or, uncommonly, recurrent sclerosing cholangitis may require transplantation.

47.3.6 Rejection

Hyperacute rejection due to preformed circulating antibodies against epitopes of the donor graft is rare in liver transplant. The most common form of rejection in the immediate postoperative course after liver transplantation is ACR [46].

The mechanism of rejection involves the recognition of specific donor antigens on the surface of endothelial and parenchymal cells by the circulating recipient T lymphocytes. Engagement and recognition can follow two pathways referred to as direct and indirect presentation. The direct presentation of an antigen is mediated by donor-derived antigen presenting cells (APCs) that carry their own antigenic epitopes within the human leukocyte antigen (HLA) class II molecules present on their cell surface. Recipient T lymphocytes recognize the antigen–APC complex and activate an allogeneic immune response. In indirect presentation, recipient-derived APC process antigen from the donor and expose antigen fragments in the class II molecule groove to be recognized by recipient T lymphocytes. The final pathway is the activation of the specific lymphocyte by interleukin-2 (IL-2) and the proliferation of clones of T cells that infiltrate the graft and mediate injury.

ACR may occur at any time after transplant, but it is most common within the first 6 weeks with up to 50% of recipients experiencing at least one episode of increased liver enzymes and pathological evidence of cellular infiltrates during that time. Mild episodes of ACR are asymptomatic and are detected only by the elevation in the liver enzymes; more aggressive forms lead to hyperbilirubinemia and transaminitis. Risk factors for the development of ACR are low level of immunosuppression, young age of the recipients, and significant HLA–DR mismatch. Conversely, rejection is seen less often in debilitated, elderly, or malnourished patients, in those with comorbidities like renal failure, or during episodes of sepsis.

Diagnosis is confirmed by liver biopsy. Microscopic examination reveals mixed periportal cellular infiltrate with predominantly lymphocytes and eosinophils. Key features include ductal inflammation (ductulitis), endotheliitis (swollen endothelial cells with cellular infiltrates), and occasionally centrilobular vein infiltration (central venulitis).

Therapy consists in increase in immunosuppression. Most cases are managed by a pulse of intravenous corticosteroids followed by a tapering schedule, with an increase in baseline immunosuppression. More severe cases may require the administration of an antilymphocyte preparation, usually a monoclonal or polyclonal antibody.

Chronic rejection, also described as "ductopenic" rejection, presents more than 6 months after liver transplant [47]. The clinical course is often insidious until the development of jaundice. A disproportionate elevation of the canalicular enzymes is often present. The confirmation of the diagnosis requires liver biopsy. The microscopic features of chronic rejection are cellular infiltrates in the periportal spaces, with predominantly macrophages, and periductal lymphocyte infiltration. Bile duct loss is present in the interlobular areas of the hepatic parenchyma; ductopenia in more than 50% of the visualized portal tracts confirms the diagnosis.

The vasculopathy often present is obliterative in nature affecting large- and medium-sized arteries, compounding the injury to the bile ductules. Standard therapy for ACR usually is not successful for chronic rejection; it often requires transplantation if the patient is a suitable candidate.

47.3.7 Graft versus Host Disease

Graft versus host disease (GVHD) is a rare but potentially lethal complication of liver transplant. It is mediated by the transfer of immunologically competent cells contained within the liver graft to the recipient [48]. These lymphocytes recognize recipient antigens as foreign and mount a cytotoxic response to recipient tissues and organs. The clinical presentation of GVHD can be limited to a humoral reaction with transient hemolysis. The more common (and more dangerous) presentation occurs when T lymphocytes mediate recipient tissue and organ destruction. Disseminated GVHD is associated with a mortality rate of up to 50%. The diagnosis of GVHD is based on the clinical presentation, histological findings, and HLA evidence of donor leukocytes in the recipient blood and affected organs and tissues. GVHD can occur as early as 1 week after transplant, more commonly in the first months. The typical organ targets for GVHD are the skin, gastrointestinal tract, lung, and bone marrow. Death usually occurs because of secondary infectious complications. The treatment of GVHD involves increasing immunosuppression, T-cell depleting protocols, and, rarely, radiation therapy or phototherapy for skin involvement.

47.3.8 Recurrent Disease

The recurrence of the original disease in the liver graft is a significant cause of morbidity and mortality after liver transplant. Hepatitis C recurrence is almost universal in those patients who were unable to achieve viral clearance pretransplant [49]. Up to 25% of recipients with hepatitis C will have cirrhosis within 5 years of transplant. High levels of immunosuppression and a history of multiple rejection episodes treated with corticosteroids are factors associated with early and aggressive hepatitis C recurrence. Retransplantation for recurrent hepatitis C is rarely successful. In contrast, modern antiviral therapy has made cirrhosis due to recurrent hepatitis B infection an avoidable complication. Recurrent HCC after liver transplant is uncommon but is associated with a high mortality rate. By selecting patients with early, unresectable HCC, liver transplant is associated with an 84% 5-year recurrence-free survival in large series [50]. Few patients are transplanted for cholangiocarcinoma or metastatic neuroendocrine tumors because tumor recurrence is common. Recurrent autoimmune hepatitis, cholestatic liver disease (primary biliary cirrhosis and sclerosing cholangitis), nonalcoholic fatty liver disease, and Budd–Chiari disease have all been reported. Recurrent liver disease due to alcohol recidivism is uncommon due to careful patient selection prior to transplant, but unfortunately does occur.

Finally, clinical transplantation's requirement for human organs from living and deceased donors is accompanied with an array of unique risks. Immunologic differences between donor and recipient are the basis of allograft rejection and GVHD. Despite careful screening and testing of potential organ donors, disease transmission (infection or malignancy) from donor to recipient does occur and can be a source of morbidity and mortality. Finally, the critical shortage of organs available for transplant means that physiologically impaired or otherwise imperfect organs are often utilized. The risk of complications when using "marginal" organs from these "extended criteria donors" must be weighed on an individual basis with the risk of morbidity and mortality from the patient's underlying liver disease.

47.4 Conclusion

With improvements in surgical technique, immunosuppressive therapy, liver graft monitoring, and patient management, liver transplant has become safer with better outcomes. Yet, the pressure to use "marginal" grafts to facilitate liver transplant for a broader group of (often "sicker") patients has consequences and patients are subject to complications. Attention to detail, meticulous technique, and careful follow-up help avoid complications; early recognition and treatment of complications help mitigate their impact when they do occur. Many liver transplant-related complications occur or are made worse by the requirement for immunosuppression. As the field of transplant immunology advances, it is hoped that we will see fewer and less severe complications.

Incidence of Liver Transplant–Associated Complications

Complications	Incidence (%)	References
Intra-abdominal bleeding	7–15	[20]
Primary graft nonfunction	1–5	[35]
Hepatic artery thrombosis	1–3	[37]
Biliary complications	10–20	[43]
Acute cellular rejection	~50	[46]
Hepatitis C recurrence	~100	[49]
Recurrent HCC	~15	[50]
Renal failure within 5 years	10–20	[13]

References

1. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pellettier SJ. Liver transplantation in the Unites States, 1990–2008. *Am J Transplant* 2010; 10:1003–1019.
   This review summarizes the evolution of liver transplant in the US over nearly two decades.
2. Brown RS Jr, Ascher NL, Lake JR, Emond JC, Bacchetti P, Randall HB, Roberts JP. The impact of surgical complications after liver transplantation on resource utilization. *Arch Surg* 1997; 132:1098–1103.
3. Afessa B, Gay PC, Plevak DJ, Swensen SJ, Patel HG, Krowka MJ. Pulmonary complications of orthotopic liver transplantation. *Mayo Clin Proc* 1993; 68:427–434.
4. Patel G, Huprikar S. Infectious complications after orthotopic liver transplantation. *Seminar Resp Crit Care Med* 2012; 33:111–124.
   This paper is a good summary of the topic.
5. Plevak DJ. Forum on critical care issues in liver transplantation: Fluids, electrolytes, and renal disease in the perioperative liver transplant recipient. *Liver Transplant* 1996; 21:69–86.
6. Kuo PC, Plotkin JS, Gaine S, Schroeder RA, Rustgi VK, Rubin LJ, Johnson LB. Portopulmonary hypertension and the liver transplant candidate. *Transplantation* 1999; 67:1087–1093.
7. Fishman AP. Pulmonary hypertension—beyond vasodilator therapy. *N Engl J Med* 1998; 338:321–322.
8. Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. *Liver Transplant* 2012;18:881–891.
9. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome—A liver-induced lung vascular disorder. *N Engl J Med* 2008; 359:2378–2387.
   These two papers (8 and 9) are excellent reviews on the two noninfectious pulmonary diseases associated with advanced liver disease.
10. Gonwa TA, Morris CA, Goldstein RM, Husberg BS, Klintmalm GB. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome—Experience in 300 patients. *Transplantation* 1991; 51:428–430.
11. Wong F. Recent advances in our understanding of hepatorenal syndrome. *Nat Rev Gastroenterol Hepatol* 2012; 9:382–391.
12. McCauley J. The nephrotoxicity of FK506 as compared with cyclosporine. *Curr Opin Nephrol Hypertens* 1993; 2:662–669.
13. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; 349:931–940.
   This paper illustrates the problem of late renal failure after liver transplant.
14. Chatzipetrou MA, Tsaroucha AK, Weppler D, Pappas PA, Kenyon NS, Nery JR, Khan MF, Kato T, Pinna AD, O'Brien C, Vinciana A, Ricordi C, Tzakis AG. Thrombocytopenia after liver transplantation. *Transplantation* 1999; 67(5):702–706.
15. Dong M, Parsaik AK, Eberhardt NL, Basu A, Cosio FG, Kudva YC. Cellular and physiological mechanisms of new-onset diabetes mellitus after solid organ transplantation. *Diabet Med* 2012; 29:1–12.
16. Siddiqui MS, Sterling RK. Posttransplant metabolic syndrome. *Int J Hepatol* 2012; 2012:891516. doi: 10.1155/2012/891516. Epub November 27, 2012.
17. Kulak CA, Cochenski Borba VZ, Kulak J, Ribeiro Custodio M. Osteoporosis after solid organ transplantation. *Minerva Endocrinol* 2012; 37:221–231.
18. Wszolek ZK, Fulgham JR. Neurologic complications of liver transplantation. In: Maddrey WC, Sorrell MF, Schiff ER, eds. *Transplantation of the Liver*. Philadelphia, PA: Lippincott Williams and Wilkins, 2001: pp. 297–317.
19. Lee Em, Kang JK, Yun SC, Kim KH, Kim SJ, Hwang KS, Lee SG. Risk factors for central pontine and extrapontine myelinolysis following orthotopic liver transplantation. *Eur Neurol* 2009; 62:362–368.
20. Ozaki CF, Katz SM, Monsour HP Jr, Dyer CH, Wood RP. Surgical complications of liver transplantation. *Surg Clin North Am* 1994; 74:1155–1167.
21. Nishida S, Gaynor JJ, Nakamura N, Butt F, Illanes HG, Kadono J, Neff GW, Levi DM, Moon JI, Selvaggi G, Kato T, Ruiz P, Tzakis AG, Madariaga JR. Refractory ascites after liver transplantation: An analysis of 1058 liver transplant patients at a single center. *Am J Transplant* 2006; 6:140–149.
22. Winston DJ, Emmanouilides C, Busuttil RW. Infections in liver transplant recipients. *Clin Infect Dis* 1995; 21:1077–1091.
23. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998; 338:1741–1751.
   A well-written, classic paper on the topic.
24. Patterson TF. Approaches to fungal diagnosis in transplantation. *Transplant Infect Dis* 1999; 1:262–272.
25. Rubin RH. Importance of CMV in the transplant population. *Transplant Infect Dis* 1999; 1 (Suppl 1):3–7.
26. Straus SE, Cohen JI, Tosato G, Mejer J. NIH conference. Epstein-Barr virus infections: Biology, pathogenesis, and management. *Ann Intern Med* 1993; 118:45–58.
27. Gane E, Saliba F, Valdecasas GJ, O'Grady J, Pescovitz MD, Lyman S, Robinson CA. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group. *Lancet* 1997; 350:1729–1733.
28. Kamdar KY, Rooney Cm, Heslop HE. Posttransplant lymphoproliferative disease following liver transplantation. *Curr Opin Organ Transplant* 2011; 16:274–280.
   A good review of the complication of PTLD in liver transplantation.
29. Green M. Management of Epstein-Barr virus-induced post-transplant lymphoproliferative disease in recipients of solid organ transplantation. *Am J Transplant* 2001; 1:103–108.
30. Fung JJ, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B. De novo malignancies after liver transplantation: a major cause of late death. *Liver Transplant* 2001; 7:S109–S118.

31. Di Benedeto F, Di Sandro S, De Ruvo N, Berretta M, Masetti M, Montalti R, Ballarin R, Cocchi S, Potenza L, Luppi M, Gerunda GE. Kaposi's sarcoma after liver transplantation. *J Cancer Res Clin Oncol* 2008; 134:653–658.
32. Rubin J, Ayoub N, Kaldas, F, Saab S. Management of recurrent hepatocellular carcinoma in liver transplant recipients: a systematic review. *Exp Clin Transplant* 2012; 10:531–543.
33. Davis E, Wiesner R, Valdecasas J, Kita Y, Rossi M, Schwartz M. Treatment of recurrent hepatocellular carcinoma after liver transplantation. *Liver Transplant* 2011; 17:S162–S166.
34. Ripoli C, Yotti R, Bernejo J, Banares R. The heart in liver transplantation. *J Hepatol* 2011; 54:810–822.
35. Bzeizi KI, Jalan R, Plevris JN, Hayes PC. Primary graft dysfunction after liver transplantation: From pathogenesis to prevention. *Liver Transplant Surg* 1997; 3:137–148.
36. Quiroga J, Colina I, Demetris AJ, Starzl TE, Van Thiel DH. Cause and timing of first allograft failure in orthotopic liver transplantation: a study of 177 consecutive patients. *Hepatology* 1991; 14:1054–1062.
37. Langnas AN, Marujo W, Stratta RJ, Wood RP, Shaw BW Jr. Vascular complications after liver transplantation. *Am J Surg* 1991; 161:76–83.
38. Marujo WC, Langnas AN, Wood RP, Stratta RJ, Li S, Shaw BW Jr. Vascular complications following orthotopic liver transplantation: outcome and the role of urgent revascularization. *Transplant Proc* 1991; 23:1484–1486.
39. Tzakis AG. The dearterialized liver graft. *Semin Liver Dis* 1985; 5:375–376.

    The seminal description of HAT in liver transplantation.
40. Nishida S, Kato T, Levi D, Naveen M, Thierry B, Vianna R, Selvaggi G, Buitrago E, Al-Niami A, Nakamura N, Vaidya A, Nery J, Tzakis A. Effect of protocol Doppler ultrasonography and urgent revascularization on early hepatic artery thrombosis after pediatric liver transplantation. *Arch Surg* 2002; 137(11):1279–1283.
41. Lerut J, Tzakis AG, Bron K, Gordon RD, Iwatsuki S, Esquivel CO, Makowka L, Todo S, Starzl TE. Complications of venous reconstruction in human orthotopic liver transplantation. *Ann Surg* 1987; 205:404–414.
42. Orons PD, Hari Ak, Zajko AB, Marsh JW. Thrombolysis and endovascular stent placement for inferior vena cava thrombosis in a liver transplant recipient. *Transplantation* 1997; 64:1357–1361.
43. O'Connor TP, Lewis WD, Jenkins RL. Biliary tract complications after liver transplantation. *Arch Surg* 1995; 130:312–317.
44. Greif F, Bronsther OL, Van Thiel DH, Casavilla A, Iwatsuki S, Tzakis A, Todo S, Fung JJ, Starzl TE. The incidence, timing, and management of biliary tract complications after orthotopic liver transplantation. *Ann Surg* 1994; 219:40–45.

    A thorough review on biliary tract complications.
45. Fisher A, Miller CH. Ischemic-type biliary strictures in liver allografts: the Achilles heel revisited? *Hepatology* 1995; 21:589–591.
46. Wiesner RH, Demetris AJ, Belle SH, Seaberg EC, Lake JR, Zetterman RK, Everhart J, Detre KM. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. *Hepatology* 1998; 28:638–645.

    Rejection remains an important complication after liver transplant, and this paper continues to be a relevant primer on the topic.
47. Desai M, Neuberger J. Chronic liver allograft dysfunction. *Transplant Proc* 2009; 41:773–776.
48. Smith DM, Agura E, Netto G, Collins R, Levy M, Goldstein R, Christensen L et al. Liver transplant-associated graft-versus-host disease. *Transplantation*. January 15, 2003; 75(1):118–126.
49. Everson GT. Impact of immunosuppressive therapy on recurrence of hepatitis C. *Liver Transplant* 2002; 8:S19–S27.
50. Levi DM, Tzakis AG, Martin P, Nishida S, Island E, Moon J, Selvaggi G et al. Liver transplantation for HCC in the MELD era. *JACS* 2010; 210:727–736.

48

Complications of Cardiac and Lung Transplantation

Jay D. Pal, Daniel T. DeArmond, Hao Pan, and Scott B. Johnson

CONTENTS

Cardiac transplantation is the gold-standard treatment for patients with advanced heart failure. Despite an increasingly higher-risk recipient population, as well as the more prevalent use of mechanical support bridging to transplant, the overall survival after cardiac transplantation continues to improve. However, as with any complex operation in patients with end-stage organ dysfunction, perioperative and postoperative complications are frequently encountered. These complications can be classified as immediate, early, or late and whether they are related to the toxic effects of immunosuppressive medications. This chapter will address the common complications encountered after cardiac transplantation.

48.1 Complication of Cardiac Transplantation

48.1.1 Indications for Cardiac Transplantation

Orthotopic cardiac transplantation is indicated for patients with advanced heart failure that is refractory to medical therapies and/or conventional surgical treatments. The specific indications and criteria have been well described [1,2] and have evolved in recent years to include older recipients, as well as those with additional comorbidities [1,3,4]. Similarly, relative contraindications for transplant, such as renal dysfunction, pulmonary hypertension, and hepatic dysfunction, are being treated with mechanical circulatory support or combined organ transplants [5–8]. This has led to a wider application of heart transplantation as a treatment for advanced heart failure.

The conventional indications for heart transplantation include systolic heart failure, ischemic heart disease with intractable angina not amenable to revascularization, intractable dysrhythmias, hypertrophic cardiomyopathy not amenable to surgical or percutaneous therapies, congenital heart disease with diminished ventricular function, and isolated cardiac tumors [1,9]. Absolute contraindications to cardiac transplantation are those factors that diminish survival or graft function, namely, fixed pulmonary hypertension or systemic illnesses such as malignancy, irreversible renal or hepatic function, systemic lupus erythematosus with multisystem involvement, or other processes likely to recur in the transplanted heart. Relative contraindications are evolving, but include distant malignancy, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, diverticulitis, peptic ulcer disease, recent pulmonary embolism, obesity or cachexia, alcohol or drug use, lack of psychosocial support, and history of noncompliance.

48.1.2 Operative Technique

The most commonly used technique for orthotopic cardiac transplantation is the bicaval technique, which is a modification of the biatrial technique described by Shumway and Lower in 1966 [10]. The current method of bicaval anastomosis allows for complete excision of the recipient's right atrium and is associated with a lower incidence of sinus node dysfunction and tricuspid regurgitation [11]. In this method, the pulmonary veins drain into a left atrial cuff, which is anastomosed to the prepared left atrium of the donor graft. The pulmonary artery and aorta are anastomosed in an end-to-end fashion. The inferior and superior vena cava are then sewn individually. The caval anastomoses can be performed with the heart reperfused to minimize donor ischemic time.

48.1.3 Immunosuppression

Since the development of the surgical technique to permit orthotopic cardiac transplantation, the single most profound effect on posttransplant survival has been the widespread use of cyclosporine as an immunosuppressant [12]. Changes in immunosuppressive therapy have had a significant impact in improving survival, as illustrated by the decreasing likelihood of graft failure due to rejection in recent years.

Currently, most centers prescribe posttransplant immunosuppression as an induction phase followed by a tapered maintenance phase [13]. The induction phase may involve cytolytic therapy with antilymphocyte antibodies to rapidly deplete the recipient's T lymphocytes. Alternatively, some centers employ higher levels of maintenance immunosuppression during the induction phase. Maintenance immunosuppression typically consists of a calcineurin inhibitor (tacrolimus or cyclosporine), an antiproliferative agent (mycophenolate mofetil or azathioprine), and a corticosteroid. Calcineurin inhibitors block the activity of the calcium- and calmodulin-dependent phosphatase calcineurin, which is required for T-cell activation and interleukin-2 (IL-2) formation. Mycophenolate mofetil and azathioprine block the synthesis of purines in activated lymphocytes. Corticosteroids inhibit lymphocyte proliferation by inhibiting the production of IL-1 and IL-6.

A newer agent finding increasingly common use is rapamycin (sirolimus), which functions as an IL-2 receptor antagonist. Although rapamycin binds FK-binding protein (as does tacrolimus), it inhibits mammalian target of rapamycin (mTOR) proteins rather than calcineurin. This leads to the destruction of activated lymphocytes expressing IL-2 receptors. Immunosuppression regimens employing rapamycin are associated with

decreased frequency of acute rejection episodes in the first year posttransplant, as well as decreased cardiac allograft vasculopathy [14].

48.1.4 Immediate Perioperative Complications

48.1.4.1 Primary Graft Failure

Primary graft failure is an uncommon but devastating event after heart transplantation that occurs in up to one-quarter of patients. The published rate of primary graft dysfunction varies by definition: 2.3% (death or re-transplant) to 27% (prolonged need for inotropes) [15–19]. The etiology of primary graft failure is typically multifactorial, with donor ischemic time, poor donor preservation, and recipient pulmonary hypertension as frequently associated conditions. The treatment of myocardial dysfunction is supportive, with intravenous inotropes, mechanical circulatory support, or re-transplantation. Most patients will improve with appropriate support; however, this complication will account for 20%–40% of early deaths after heart transplantation [13].

48.1.4.2 Right Ventricular Dysfunction

Right ventricular dysfunction most frequently occurs after cardiac transplantation in recipients with pulmonary hypertension [20]. In addition, excessive volume resuscitation (particularly blood transfusions) is associated with right ventricular failure. Recipient pulmonary vascular resistance (PVR) should be evaluated preoperatively in all patients, and levels above 6 Wood units or transpulmonary gradient >15 mm Hg are relative contraindications to transplantation. These patients should undergo further testing to ensure reversibility of pulmonary hypertension and/or be supported with inotropes or mechanical circulatory support to allow for resolution of elevated PVR. Perioperative care of the right ventricular failure includes maintaining sinus rhythm at 90–100 beats per minute, use of inhaled nitric oxide, and relative hypocapnia to prevent hypoxic pulmonary vasoconstriction.

48.1.4.3 Hyperacute Rejection

Hyperacute rejection occurs due to the presence of preformed antibodies to the donor graft. The incidence of hyperacute rejection has decreased with careful ABO matching, and determination of a recipient's panel reactive antibody allows for risk stratification for rejection episodes. The widespread use of virtual crossmatch, which employs flow cytometry to determine incompatible antigens in potential donors, has also reduced the likelihood of hyperacute rejection episodes. Consequences of hyperacute rejection include microvascular thrombosis with biventricular failure. Treatment is supportive with mechanical circulatory support and cytolytic immunosuppression with plasmapheresis [15,17]. Despite all aggressive measures, mortality remains high for this devastating complication.

48.1.4.4 Hemorrhage

Perioperative hemorrhage occurs in <5% of patients after heart transplantation [4]. Risk factors include recipient right heart dysfunction with hepatic congestion, preoperative anticoagulant use, and prolonged cardiopulmonary bypass duration. Blood transfusion is associated with right ventricular dysfunction, but also found to decrease the incidence of rejection episodes [21]. Strategies to decrease transfusion requirement include preoperative normalization of clotting parameters, judicious administration of blood products, and meticulous surgical technique.

48.1.5 Early Postoperative Complications

48.1.5.1 Acute Cellular Rejection

Acute cellular rejection is a frequent complication after orthotopic heart transplantation, with as many as 30% of patients experiencing at least one rejection episode in the first posttransplant year [13]. Each episode is associated with a mortality risk, as well as a cumulative increase in the risk of cardiac allograft vasculopathy. Most episodes of acute cellular rejection are mild, and not clinically appreciable; therefore, frequent endomyocardial biopsies are employed for surveillance. Most centers employ a prescribed schedule with weekly biopsies in the first 3 weeks posttransplant, with increasing intervals between biopsies as long as no rejection is found. The presence of 1R/2R rejection generally does not warrant treatment, as long as other clinical indicators and pathologic findings are stable. 3R and greater rejection is treated with pulse dose steroids. Endomyocardial biopsy is performed 7–10 days after treatment to ensure resolution. Lack of improvement warrants a second pulse of steroids or cytolytic therapy.

48.1.5.2 Antibody-Mediated Rejection

Antibody-mediated rejection (AMR) is due to anti-HLA donor-specific antibodies in the recipient. AMR is more commonly associated with graft dysfunction requiring inotropic support and is a major cause of graft failure [22]. Patients with AMR are also at higher risk for developing cardiac allograft vasculopathy. The diagnosis of

AMR remains in flux, given the complex underlying pathophysiology. Unlike acute cellular rejection, the diagnosis includes clinical criteria as well as pathologic findings [23,24]. The treatment of AMR is variable amongst centers, but typically includes hemodynamic support, plasmapheresis, intravenous immunoglobulin, cytolytic therapy, and steroid administration.

48.1.5.3 Acute Renal Failure

Acute renal failure is a common finding after cardiac transplantation and usually associated with diminished preoperative renal function, calcineurin inhibitors, prolonged cardiopulmonary bypass duration, and postoperative hypotension. This syndrome is manifested by oliguria and laboratory findings of prerenal azotemia. Most patients will have resolution of renal dysfunction, but a small percentage will require renal replacement therapy. Some centers employ cytolytic therapy during the induction phase to delay the administration of calcineurin inhibitors.

48.1.5.4 Dysrhythmias

The denervated status of the transplanted heart results in lack of autonomic control of heart rate and response to external stimuli. Parasympathetic denervation results in a resting heart rate of 90–110 beats per minute and renders the chronotropic effects of certain medications, such as atropine and digoxin, ineffective. Loss of sympathetic innervation attenuates the stress response of the sinoatrial node, typically leading to a decreased maximum heart rate with exercise and orthostasis.

Sinus or junctional bradycardia occurs in up to half of all cardiac transplant recipients and is associated with prolonged ischemia, biatrial anastomosis, and rejection [25,26]. The infusion of isoproterenol or epicardial pacing is usually supportive and allows resolution of sinus node dysfunction. Tachyarrhythmias such as atrial fibrillation or flutter are seen in up to 30% of patients after transplantation [27]. Treatment is similar to nontransplant patients, with the caveat of increased potency of many antiarrhythmic medications. The finding of any new dysrhythmia or persistent dysrhythmia should prompt a thorough investigation of potential causes, including acute rejection and cardiac allograft vasculopathy.

48.1.5.5 Infection

Due to chronic immunosuppression, transplant recipients are at increased risk for systemic infections, which are the leading cause of morbidity and mortality in this patient population [16]. Infectious complications are most common in the early postoperative period due to the higher levels of immunosuppression. These infections usually present as pneumonia, urinary tract infections, and line infections. Common pathogens are *Pseudomonas*, *Staphylococcus* species, *Enterobacter*, and enterococci. Late infections by opportunistic pathogens such as viruses, protozoa, and fungi are typically associated with increases in immunosuppression.

Viral infections such a cytomegalovirus, hepatitis B and C, and HIV are well described. Appropriate treatment is careful screening of the donor, as well universal precautions in the postoperative period. Viral immunizations and prophylaxis with ganciclovir should be administered to all patients preoperatively barring specific contraindications. Opportunistic protozoal infections by *Pneumocystis* and *Toxoplasmosis* are rare, but well documented. Prophylaxis with sulfa and trimethoprim is routinely provided to all patients. Fungal infections are also rare, but can cause significant morbidity in endemic areas. *Candida* and *Aspergillus* species are most commonly found, and treatment is with typical antifungal therapies.

48.1.6 Late Postoperative Complications

48.1.6.1 Chronic Rejection

Chronic rejection presents in the transplanted heart as cardiac allograft vasculopathy. The disease process results in interstitial fibrosis and diffuse atherosclerotic changes of coronary arteries and small vessels. This accelerated form of coronary artery disease is manifested by concentric fibrous neointimal hyperplasia [28]. This intimal hyperplasia is due to a proliferation of smooth muscle cells into the media in response to immune-mediated and alloantigenic-independent processes. In addition, graft ischemic time, ischemia–reperfusion injury, CMV infection, hyperlipidemia, and diabetes mellitus have also been implicated in the pathogenesis of CAV. The clinical presentation of CAV can involve dysrhythmias, myocardial infarction, or heart failure. Typical anginal symptoms are uncommon. The aggressive management of risk factors and CMV prophylaxis is protective; diltiazem and statin medications have been shown to reduce the incidence of CAV [29]. Treatment options for extensive CAV are limited, as the diffuse nature of the disease usually precludes percutaneous intervention or coronary artery bypass grafting. In appropriate patients, re-transplantation is the only effective treatment.

48.1.6.2 Tricuspid Regurgitation

The incidence of tricuspid regurgitation after heart transplantation has been reported to be as high as 20%, but only 5% develop symptomatic, moderate-to-severe regurgitation. The etiology of posttransplant tricuspid regurgitation is typically related to distortion of the tricuspid annulus by biatrial anastomosis, ischemic injury,

and biopsy-related injury of the leaflets [30]. While most patients will remain asymptomatic, progressive worsening of tricuspid valve function can result in symptoms of right heart failure. Medical treatment with diuresis is the preferred management; however, refractory cases of annular dilation will require annuloplasty [31]. Biopsy-induced TR requires valve replacement, typically with a bioprosthetic valve.

48.1.6.3 Malignancy

Maintenance immunosuppression after cardiac transplantation is associated with an increased incidence of all malignancies. Current ISHLT data suggest that 20% of patients will develop some malignancy in 5 years and that malignancy is responsible for 18.5% of deaths within the same time period [13]. Skin cancers and EBV-associated lymphoproliferative disorders are the most common malignancies found in posttransplant patients. In addition, the administration of antilymphoctye antibody therapy is associated with a higher incidence of lymphoproliferative disorders. Treatment options are limited and associated with high risk and limited success.

48.1.7 Conclusion

Cardiac transplantation is now the gold-standard treatment for patients with advanced heart failure. For appropriate patients, transplantation yields significantly improved survival and quality of life. However, the incidence of complications remains high and requires vigilant surveillance of myocardial function, immunosuppression levels, and infectious complications. Advances in immunosuppressive medications have resulted in fewer complications without increasing the incidence of rejection. Future research on the development of tolerance and the prevention of cardiac allograft vasculopathy may lead to improved graft function and survival in this particularly complex patient population.

48.2 Complications of Lung Transplantation

Lung transplantation is performed in selected patients with end-stage pulmonary disease with the goal of extending life expectancy and improving dyspnea. The technical aspects of lung transplant have been well established over the last few decades. Continuing limitations to lung transplant include the small donor pool and the long-term complication of chronic rejection leading to graft failure.

Currently worldwide, over 3,200 lung transplants are performed per year and this number continues to grow. The main limitation to increasing the number of lung transplants continues to be a limited number of donors; of all donors only approximately 20%–25% will be appropriate for lung donation. Lung transplant is performed for a number of pathologic lung conditions, the most common being (in order of frequency) emphysema/chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), idiopathic pulmonary arterial hypertension (IPAH), and alpha-1 antitrypsin deficiency (A1AT) [33]. The goals of lung transplant are to extend life expectancy of patients with advanced pulmonary disease based on poor life expectancy without lung transplant and to improve quality of life through the relief of dyspnea. Long-term graft survival after lung transplantation continues to be limited by chronic rejection as manifested by bronchiolitis obliterans [33–35].

48.2.1 Indications

48.2.1.1 Chronic Obstructive Pulmonary Disease

COPD is the most common indication for lung transplantation and is reserved for patients who show clinical deterioration despite maximal medical therapy including smoking cessation, bronchodilator therapy, pulmonary rehabilitation, long-term oxygen therapy, and surgical lung volume reduction. Not all patients with COPD will experience a survival advantage after lung transplant, and careful patient selection is critical with a focus on clinical characteristics associated with decreased survival. Conditions considered to be indications for transplant referral include a history of hospitalization for COPD exacerbation with arterial blood gas demonstrating a partial pressure of carbon dioxide greater than 50 mm Hg (associated with median survival of approximately 3 years); pulmonary hypertension, cor pulmonale, or both, despite oxygen therapy; forced expiratory volume in 1 s (FEV1) <20% and diffusing capacity of the lung for carbon monoxide (DLCO) <20%; and homogeneous distribution of emphysema by lung imaging. The BODE index is an important tool in assessing predicted survival in patients with COPD based on the four parameters of body mass index, forced expiratory volume in 1 s, dyspnea score, and 6-min walk distance. Each parameter is scored 0–3 with higher scores given with increasing disease severity; a BODE score of 7–10 is associated with a median survival of approximately 3 years and as such represents an indication for transplant referral. While patients with lower BODE scores may not benefit from transplantation, they may be candidates for early lung transplant consultation.

48.2.1.2 Interstitial Pulmonary Fibrosis

IPF is the second most common diagnosis of patients undergoing lung transplant after COPD. Patients with IPF show the highest mortality on transplant waiting lists. Survival of patients with IPF is highly dependent

on the histology of the disease noted on bronchoscopic or thoracoscopic biopsy: usual interstitial pneumonia (UIP) portends a median survival of 2.5–3.5 years, while with nonspecific interstitial pneumonia survival is more variable. Indications for lung transplant in IPF include UIP histology and any of the following: DLCO less than 39% predicted, 10% decrease in forced vital capacity (FVC) over 6 months, O_2 saturation less than 88% during a 6-min walk, honeycombing on high-resolution computed tomography (HRCT), and development of secondary pulmonary hypertension.

48.2.1.3 Cystic Fibrosis

CF patients have the potential for the greatest benefit from lung transplant though referrals are often delayed due to the young age of these patients. Indications for lung transplantation in patients with CF include FEV1 <30% of predicted, rapidly declining lung function, and/or any of the following: increasing oxygen requirements, hypercapnia, or pulmonary hypertension. Female patients and patients <18 years of age have poorer prognosis and may be candidates for earlier listing. CF patients have frequent respiratory infections and bacterial colonization, which have the potential to adversely impact posttransplant survival. Patients with pulmonary infections due to *Burkholderia cepacia* have been observed to have a 1-year survival of 50%–67% compared with 80%–93% survival at 1 year in CF patients without this organism, which may affect the decision to proceed with transplantation in these patients; *B. cenocepacia* and *B. gladioli* infections also portend a poorer survival after lung transplant in patients with CF. The presence of *Mycobacterium abscessus* in bronchial cultures is considered by some centers as a relative contraindication to lung transplantation. *Aspergillus* species are present in the respiratory cultures of up to 50% of CF patients and though this presents an increased risk of *Aspergillus* anastomotic infections or pneumonia, it is not a contraindication of lung transplant nor is panresistant *Pseudomonas*, which is also commonly cultured in the respiratory tract of CF patients.

48.2.1.4 Lung Allocation Score and Contraindications to Lung Transplant

All patients listed for lung transplant are given a lung allocation score (LAS) to determine their place on the transplant list based on the severity of their disease. Parameters considered in factoring the LAS score include predictors of waiting list mortality (spirometry assessment of forced vital capacity, pulmonary artery systolic pressure, supplemental oxygen requirements, age, body mass index, New York Heart Association status, diagnosis, 6-min walk distance, diabetes, need for ventilatory support) and predictors of posttransplant survival (mean pulmonary arterial pressure, serum creatinine). Contraindications to lung transplantation include recent malignancy (other than nonmelanoma skin cancer), infection with human immunodeficiency virus, infection with hepatitis B or C with histologic evidence of cirrhosis, active or recent cigarette smoking, drug or alcohol abuse, severe psychiatric illness, documented noncompliance with medical care, or absence of reliable social support network. Relative contraindications include age greater than 70 and body mass index greater than 30.

48.2.1.5 Donor Selection Criteria

Donor assessment is directed at identifying donor organs that can reasonably be expected to perform adequate gas exchange in the recipient and do not harbor infection or undue tissue trauma. Donor pulmonary arterial partial pressure of oxygen to fraction of inspired oxygen ratio (P_aO_2/F_iO_2) must be greater than 3, chest radiographs must be clear of infiltrates, and bronchoscopic assessment must be free of purulent secretions. Donors over 55 years of age or with a greater than 20 pack-year smoking history may be considered for selected recipients. Potential donors that initially appear not to meet the aforementioned criteria may undergo alveolar recruitment with ventilatory maneuvers and diuresis in addition to hemodynamic support with vasopressors with the result that pulmonary infiltrates may resolve and oxygenation may improve to meet donor selection criteria. Donor lung size is carefully compared to the recipient thorax size; significant donor to recipient mismatch may result in anastomotic stenosis or graft nonfunction.

48.2.1.6 Surgical Approach

Through the 1980s and 1990s, single lung transplant was performed more often than double lung transplant, but currently over two-thirds of lung transplants performed are double lung transplants. Double lung transplant is most commonly performed via a transverse sternotomy, which allows for excellent exposure of bilateral pulmonary hila as well as heart and great vessels; median sternotomy and bilateral thoracotomy without sternotomy are alternatives. Single lung transplant is performed via posterolateral or anterior thoracotomy incisions. Cardiopulmonary bypass may be employed or operations may be performed off pump. If the cardiopulmonary bypass circuit is not used, placement of a double-lumen endotracheal tube is required to achieve selective lung isolation. Cardiopulmonary bypass cannulation via sternotomy or right thoracotomy is in the ascending aorta and right atrial appendage; in the case of single lung transplant through a left thoracotomy incision requiring bypass, cannulation of the

descending aorta and proximal left pulmonary artery may be performed. Alternatively, regardless of the choice of incision, the femoral vessels may be used for arteriovenous cardiopulmonary bypass cannulation for lung transplantation. Novel cannulation techniques are currently being adopted that allow for the performance of veno-venous extracorporeal membrane oxygenation via a single cannula introduced via the right internal jugular vein. The advantage of the use of cardiopulmonary bypass is the ability to discontinue ventilation and more freely retract the heart for improved exposure of the hilar structures during dissection and anastomosis. The main disadvantage of the use of cardiopulmonary bypass is the risk of coagulopathy requiring high-volume blood transfusion at the conclusion of the operation.

For double lung transplant, graft implantation is performed sequentially; usually, the lung with less function as indicated by the preoperative lung perfusion scan is transplanted first. The sequence with which anastomoses are performed proceeds from posterior to anterior structures: bronchus first, pulmonary venous cuff second, and pulmonary artery third. De-airing maneuvers are carried out prior to unclamping the pulmonary vessels. Bronchial anastomotic patency is confirmed by bronchoscopy and vascular anastomotic patency is confirmed by transesophageal echocardiography.

With respect to the donor operation, infusion of prostaglandin E1 into the main pulmonary artery just prior to aortic cross-clamp results in pulmonary vasodilatation, which facilitates the infusion of cold crystalloid preservative solution (Perfadex) into the pulmonary vascular bed. Donor lungs are transported fully inflated at 4°C.

48.2.2 Complications

48.2.2.1 Rejection

Three subtypes of rejection in lung transplant are recognized: hyperacute rejection, acute rejection, and chronic rejection.

Hyperacute rejection has become a rare phenomenon as understanding of donor–recipient human leukocyte antigen mismatch and immunosuppressive techniques have improved [46]. Hyperacute rejection occurs in the minutes to hours after lung transplant and manifests as immediate overwhelming graft nonfunction with marked pulmonary edema and dense pulmonary infiltrates as seen on chest imaging [46]. Refractory hypoxia and hypercarbia may be present. Pathologic examination reveals widespread intravascular thrombosis and parenchymal infarction. These patients generally require support with extracorporeal membrane oxygenation and immediate re-transplantation as a life-saving measure; even with re-transplantation the prognosis for this condition is almost uniformly poor.

Acute rejection may occur in the days to weeks following lung transplant and becomes less of a concern by 3–4 months after surgery. The diagnosis of acute rejection is challenging in that it may clinically mimic the development of pneumonia with fever, dyspnea, hypoxia, and the appearance of pulmonary infiltrates by chest imaging. Differentiating rejection from infection is crucial in that the treatment for rejection is increased immunosuppression while the treatment for pneumonia is decreased immunosuppression and antibiotics. It has been suggested that positron emission tomography (PET) may help to distinguish between rejection and pneumonia in lung transplant in that pneumonia represents a neutrophil-driven process marked by PET-avid lung infiltrates, while rejection is a T-lymphocyte-driven process that does not produce PET-avid lesions. Ultimately, bronchoscopy with lung biopsy is still required for diagnosis with pathology showing perivascular and intra-alveolar mononuclear infiltration [35]. The treatment is generally a short course of intravenous steroids followed by an increase in maintenance oral steroids [35].

Chronic rejection occurs in the months to years after lung transplantation and is the major limitation to long-term graft survival in lung transplantation. The incidence and severity of chronic rejection is higher than in other solid organs for unclear reasons, possibly due to the direct exposure of the graft to the environment via inhaled air, which differs from other transplanted organs. Chronic rejection manifests in the lungs as bronchiolitis obliterans, which has characteristic chest computed tomography findings of bronchiectasis, mucous plugging, airway wall thickening, mosaic pattern, and air trapping. Functionally, progressive decrease in the forced expiratory volume in 1 s by pulmonary function testing is observed along with graft failure and ultimately recipient demise [34]. Radiographic as well as clinical findings of chronic rejection in the current era affect up to 70% of lung transplant recipients who survive for 5 years.

48.2.2.2 Ischemia–Reperfusion Injury

The ischemic period for the lung allograft begins after donor aortic cross-clamp and ends after implantation of the allograft into the recipient with removal of the pulmonary arterial clamp and restoration of pulmonary arterial blood flow to the implanted lung. In general, the principal of minimizing ischemic time to less than 6 h is adhered to in lung transplant. Regardless of the ischemic time, tissue injury due to the deprivation of nutrients and oxygen may occur in the allograft during the ischemic period; this tissue injury is exacerbated by reperfusion under the influence of the recipient inflammatory response to injured tissue [44,47]. Following

lung transplantation, mechanical ventilator support is discontinued within 48 h. *Ischemia–reperfusion injury* (IRI) manifests in the first 72 h after lung transplant as failure to be able to wean from ventilator support, relative hypoxia by arterial blood gas assessment, and centrilobular infiltrates on chest radiograph. IRI may be subclinical, mild, or severe. Subclinical IRI results in the presence of lung infiltrates by chest radiographs, which nonetheless minimally impacts oxygenation and does not appreciably delay weaning from mechanical ventilatory support. Mild IRI may result in short-lived hypoxia, which delays extubation by 5–7 days; depending on the severity, patients may undergo tracheostomy placement to facilitate weaning from ventilator support. Severe IRI results in an acute respiratory distress syndrome–like presentation with severe refractory hypoxia, which may require extracorporeal membrane oxygenation [43,44]. Differentiation from infection or vascular anastomotic stenosis is paramount and relies on bronchoscopy with bronchial washings to rule out infection and echocardiogram to rule out critical vascular anastomotic gradients. The treatment is generally supportive with the use of diuretics to relieve pulmonary edema; in more severe cases, re-transplantation may be considered.

48.2.2.3 Primary Graft Failure

Primary graft failure represents profound acute lung injury that occurs in the initial days after lung transplantation. The condition is likely multifactorial and related to limitations inherent to current lung transplantation practice including limitations of organ procurement from brain-dead donors, organ preservation techniques, prolonged ischemia due to organ transport times, reperfusion, and rejection [37]. Primary graft failure manifests as massive pulmonary edema of a noncardiac origin and profound hypoxia that may be refractory to maximal ventilatory support and may progress to a need for extracorporeal membrane oxygenation [43]. Reports of successful immediate re-transplantation are extant in the literature.

48.2.2.4 Anastomotic Complications

Early in the history of lung transplantation, bronchial anastomotic dehiscence represented a not unsubstantial cause of graft failure. The bronchial arteries are small and the inability to restore bronchial arterial continuity results in bronchial ischemia. Bronchial anastomotic dehiscence is mitigated by performance of a telescoped anastomosis, usually of the donor bronchus into the recipient bronchus [42]. Regardless of the anastomotic technique employed, bronchial mucosal ischemia as identified on postoperative bronchoscopy is commonplace but does not usually manifest clinically. Bronchial anastomotic dehiscence, though rare, usually presents in the first week after lung transplant and may result in massive air leak; surgical intervention with repair is most often required in these cases [42]. Bronchial ischemia may alternatively present as anastomotic stenosis usually several weeks after transplant; this is usually approached by endobronchial intervention with balloon dilatation of strictured sites with or without the need for bronchial stent placement [42].

48.2.2.5 Complications Related to the Native Lung in Single Lung Transplant

In the case of single lung transplant, the unreplaced native lung may be the source of long-term morbidity and mortality. In patients with COPD, the unreplaced native lung may progress in hyperexpansion such that it crosses the midline of the thorax anterior to the heart to encroach on the transplanted lung, severely limiting its functionality. If the native lung harbors significant septic disease due to the underlying pulmonary pathology present, infection can be passed to the transplanted lung endobronchially leading to graft failure [40]. Additionally, in patients with pulmonary hypertension, the hypertensive pulmonary vascular bed of a native lung may cause nearly all cardiac output to be diverted to the transplanted lung, resulting in pulmonary edema of the transplanted lung [40]. Over the last decade, there has been a shift favoring the performance of double over single lung transplant due to these factors.

48.2.2.6 Infection

Infection is a clinically significant and major cause of morbidity and mortality in the first year after lung transplant. As a result of systemic immunosuppression, infection may occur in any organ but pulmonary infections predominate. The incidence of posttransplantation organisms is segregated into bacterial (46%–63%), viral (23%–31%), and fungal (4%–10%) [48]. Aspergillus and cytomegalovirus are frequently encountered pathogens; cytomegalovirus status of the donor and recipient is an important consideration [33,48,49]. Treatment is centered around antimicrobial therapy directed by bronchoalveolar lavage specimens for microbiological analysis.

48.2.2.7 Renal Failure

Calcineurin inhibitor (cyclosporine and tacrolimus) therapy carries with it the risk of nephrotoxicity. Because of the higher risk of rejection in lung allografts compared to other solid organ transplants, higher

serum levels of calcineurin inhibitors are maintained in lung transplant recipients. This leads to a higher risk of chronic renal insufficiency in lung transplant recipients. Lowering calcineurin inhibitor serum levels along with diuresis may be attempted to avoid chronic renal insufficiency. But in many cases, progression to requirement of renal dialysis ensues, which has been associated with increased hazard for mortality [45].

48.2.3 Conclusion

Appropriate donor and recipient selection is key to successful lung transplantation. A high degree of diagnostic acumen is necessary in both the short- and long-term care of lung transplant recipients to contend with the potential complications inherent in organ procurement from brain-dead donors and current immunosuppressive therapy.

Incidence of Common Complications Following Cardiac Transplantation

Complications	Incidence (%)	References
Primary graft dysfunction	2.3 (circulatory collapse) to 27 (need for prolonged inotropes)	[3,15,17–19]
Right ventricular failure	5–20	[20,13]
Hyperacute rejection	Rare	[22,32]
Bleeding	3–4	[32]
Dysrhythmias	5 (requiring pacemaker) to 50 (junctional bradycardia)	[25–27]
Infection	15–20	[13]
Acute cellular rejection	30	[13]
Antibody-mediated rejection	10–20	[22–24]
Renal failure	20 (within 5 years)	[13]
Cardiac allograft vasculopathy	30 (within 5 years)	[13]
Tricuspid regurgitation	20	[30,31]
Malignancy	20 (within 5 years)	[13]

Prevention and Treatment of Common Complications Following Cardiac Transplantation

Complications	Prevention
Primary graft dysfunction	Prevent extended donor ischemic period Appropriate donor preservation Treat recipient pulmonary hypertension
Right ventricular failure	Treat recipient pulmonary hypertension Ensure pulmonary artery anastomosis is intact Use of inhaled nitric oxide Relative hyperventilation to induce mild hypocapnia Vasodilators
Hyperacute rejection	Proper ABO matching Cross-matching of donor lymphocytes with recipient serum
Bleeding	Use of heparin-bonded CPB circuits Meticulous surgical technique Reversal of preoperative anticoagulation
Dysrhythmias	Prevent extended donor ischemic period Bicaval anastomosis superior to sinoatrial node
Infection	Appropriate perioperative antibiotics Removal of preoperative lines and catheters Strict provider infectious precautions Strict patient infectious precautions CMV prophylaxis Protozoa prophylaxis
Acute cellular rejection	Routine posttransplant surveillance protocol Adjustment of immunosuppressive regimen
Antibody-mediated rejection	Virtual/prospective cross-match Monitor donor-specific antibodies
Renal failure	Prevent elevated levels of calcineurin inhibitors Induction therapy
Cardiac allograft vasculopathy	CMV prophylaxis Aggressive treatment of acute cellular rejection and AMR Treat hyperlipidemia/diabetes mellitus
Tricuspid regurgitation	Meticulous endomyocardial biopsy technique Prophylactic tricuspid annuloplasty Noninvasive surveillance for rejection
Malignancy	Prevent excessive immunosuppression Screen for EBV Routine surveillance for skin cancers

Incidence of Complications Following Lung Transplantation

Complications	Incidence (%)	References
Infection	42.8	[36]
Rejection	10	[36]
Primary graft failure	15–19.8	[37,38]
Chronic rejection	50	[35–39]
Complications related to the native lung	33–50	[40,41]
Anastomotic complications	15	[42]
Ischemic reperfusion injury	15–22.6	[43,44]
Renal failure requiring dialysis	5.4–7.8	[36,45]

Prevention and Treatment of Common Complications Following Lung Transplantation

Complications	Prevention
Rejection	Proper ABO matching Immunosuppressive medications
Ischemia reperfusion injury	Proper allograft preservation techniques Minimizing ischemic time
Primary graft failure	Ventilatory support Extracorporeal membrane oxygenation Immediate retransplantation

Complications	Prevention
Anastomotic complications	Telescoped anastomosis Proper donor to recipient size matching
Complications related to native lung	Avoidance of single lung transplant with anticipation of hyperexpansion or septic complications of native lung Perform double lung transplant preferably over single
Infection	Appropriate perioperative antibiotics Removal of preoperative lines and catheters Strict provider infectious precautions Strict patient infectious precautions Bronchoscopy with bronchial cultures with directed antibiotic therapy Temporary lowering of immunosuppression CMV prophylaxis Protozoa prophylaxis

References

1. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. *Circulation*. July 13, 2010;122(2):173–183.
   Current selection criteria for patients with advanced heart failure undergoing evaluation for heart transplantation.
2. Nwakanma LU, Shah AS, Conte JV, Baumgartner WA. Heart transplantation. In: Cohn LH, ed. *Cardiac Surgery in the Adult*. New York: McGraw-Hill, January 1, vol. 3, 2008, pp. 1539.
3. Lima B, Rajagopal K, Petersen RP, Shah AS, Soule B, Felker GM et al. Marginal cardiac allografts do not have increased primary graft dysfunction in alternate list transplantation. *Circulation*. July 4, 2006;114(1 Suppl):I27–I32.
4. Blanche C, Blanche DA, Kearney B, Sandhu M, Czer LS, Kamlot A et al. Heart transplantation in patients seventy years of age and older: A comparative analysis of outcome. *J. Thorac. Cardiovasc. Surg*. March 2001;121(3):532–541.
5. Pal JD, Piacentino V, Cuevas AD, Depp T, Daneshmand MA, Hernandez AF et al. Impact of left ventricular assist device bridging on posttransplant outcomes. *Ann. Thorac. Surg*. November 2009;88(5):1457–1461; discussion 1461.
6. Daneshmand MA, Rajagopal K, Lima B, Khorram N, Blue LJ, Lodge AJ et al. Left ventricular assist device destination therapy versus extended criteria cardiac transplant. *Ann. Thorac. Surg*. April 2010;89(4):1205–1209; discussion 1210.
7. Tazbir JS, Cronin DC 2nd. Indications, evaluations, and postoperative care of the combined liver-heart transplant recipient. *AACN Clin. Issues*. May 1999;10(2):240–252.
8. Blanche C, Kamlot A, Blanche DA, Kearney B, Wong AV, Czer LS et al. Combined heart-kidney transplantation with single-donor allografts. *J. Thorac. Cardiovasc. Surg*. September 2001;122(3):495–500.
9. Jarvik R. Transplant or VAD? *Cardiol. Clin*. November 2011;29(4):585–595.
10. Shumway NE, Lower RR, Stofer RC. Transplantation of the heart. *Adv. Surg*. 1966;2:265–284.
    The landmark description of the feasibility of orthotopic heart transplantation.
11. Sarsam MA, Campbell CS, Yonan NA, Deiraniya AK, Rahman AN. An alternative surgical technique in orthotopic cardiac transplantation. *J. Card. Surg*. May 1993;8(3):344–349.
12. Sarris GE, Moore KA, Schroeder JS, Hunt SA, Fowler MB, Valantine HB et al. Cardiac transplantation: The Stanford experience in the cyclosporine era. *J. Thorac. Cardiovasc. Surg*. August 1, 1994;108(2):240–252.
13. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI et al. The registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report—2012. *J. Heart Lung Transplant*. October 2012;31(10):1052–1064.
    The largest registry of heart and lung transplantation with annual reports on outcomes, complications, etc.
14. Mancini D, Pinney S, Burkhoff D, LaManca J, Itescu S, Burke E et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. *Circulation*. July 8, 2003;108(1):48–53.
15. Marasco SF, Esmore DS, Negri J, Rowland M, Newcomb A, Rosenfeldt FL et al. Early institution of mechanical support improves outcomes in primary cardiac allograft failure. *J. Heart Lung Transplant*. December 2005;24(12):2037–2042.
16. Hoffman FM. Outcomes and complications after heart transplantation: A review. *J. Cardiovasc. Nurs*. October 2005;20(5 Suppl):S31–S42.
17. D'Alessandro C, Golmard J-L, Barreda E, Laali M, Makris R, Luyt C-E et al. Predictive risk factors for primary graft failure requiring temporary extra-corporeal membrane oxygenation support after cardiac transplantation in adults. *Eur. J. Cardiothorac. Surg*. October 2011;40(4):962–969.
18. Iyer A, Kumarasinghe G, Hicks M, Watson A, Gao L, Doyle A et al. Primary graft failure after heart transplantation. *J. Transplant*. 2011;2011:1–9.
19. D'Ancona G, Santise G, Falletta C, Pirone F, Sciacca S, Turrisi M et al. Primary graft failure after heart transplantation: The importance of donor pharmacological management. *Transplant. Proc*. 2010;42(3):710–712.
20. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. *J. Am. Coll. Cardiol*. October 1, 2001;38(4):923–931.
21. Fernández FG, Jaramillo A, Ewald G, Rogers J, Pasque MK, Mohanakumar T et al. Blood transfusions decrease the incidence of acute rejection in cardiac allograft recipients. *J. Heart Lung Transplant*. July 2005;24(7 Suppl):S255–S261.
22. Michaels PJ, Espejo ML, Kobashigawa J, Alejos JC, Burch C, Takemoto S et al. Humoral rejection in cardiac transplantation: Risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. *J. Heart Lung Transplant*. January 2003; 22(1):58–69.

23. Lones MA, Czer LS, Trento A, Harasty D, Miller JM, Fishbein MC. Clinical-pathologic features of humoral rejection in cardiac allografts: A study in 81 consecutive patients. *J. Heart Lung Transplant*. February 1995; 14(1 Pt 1):151–162.
24. Chih S, Chruscinski A, Ross HJ, Tinckam K, Butany J, Rao V. Antibody-mediated rejection: An evolving entity in heart transplantation. *J. Transplant*. 2012;2012:210210.
25. Blanche C, Czer LS, Trento A, Fishbein MC, Doan D, Jordan S et al. Bradyarrhythmias requiring pacemaker implantation after orthotopic heart transplantation: Association with rejection. *J. Heart Lung Transplant*. June 1992;11(3 Pt 1):446–452.
26. Rothman SA, Jeevanandam V, Combs WG, Furukawa S, Hsia HH, Eisen HJ et al. Eliminating bradyarrhythmias after orthotopic heart transplantation. *Circulation*. November 1, 1996;94(9 Suppl):II278–II282.
27. Stecker EC, Strelich KR, Chugh SS, Crispell K, McAnulty JH. Arrhythmias after orthotopic heart transplantation. *J. Card. Fail*. August 2005;11(6):464–472.
28. Avery RK. Cardiac-allograft vasculopathy. *N. Engl. J. Med*. August 28, 2003;349(9):829–830.
29. Mehra MR, Ventura HO, Smart FW, Stapleton DD. Impact of converting enzyme inhibitors and calcium entry blockers on cardiac allograft vasculopathy: From bench to bedside. *J. Heart Lung Transplant*. December 1995;14(6 Pt 2):S246–S249.
30. Nguyen V, Cantarovich M, Cecere R, Giannetti N. Tricuspid regurgitation after cardiac transplantation: How many biopsies are too many? *J. Heart Lung Transplant*. July 2005;24(7):S227–S231.
31. Filsoufi F, Salzberg SP, Anderson CA, Couper GS, Cohn LH, Adams DH. Optimal surgical management of severe tricuspid regurgitation in cardiac transplant patients. *J. Heart Lung Transplant*. March 2006;25(3):289–293.
32. Little AG. *Complications in Cardiothoracic Surgery: Avoidance and Treatment*. 1st edn. London, U.K.: Wiley-Blackwell;2004.
33. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *J. Heart Lung Transplant*. October 2012;31(10):1073–1086.
34. Todd JL, Palmer SM. Bronchiolitis obliterans syndrome: The final frontier for lung transplantation. *Chest*. August 2011;140(2):502–508.
35. Hachem RR. Lung allograft rejection: Diagnosis and management. *Curr. Opin. Organ Transplant*. October 2009; 14(5):477–482.
36. Kilic A, George TJ, Beaty CA, Merlo CA, Conte JV, Shah AS. The effect of center volume on the incidence of postoperative complications and their impact on survival after lung transplantation. *J. Thoracic Cardiovasc. Surg*. December 2012;144(6):1502–1509.
37. Samano MN, Fernandes LM, Baranauskas JCB, Correia AT, Afonso JE Jr, Teixeira RHOB et al. Risk factors and survival impact of primary graft dysfunction after lung transplantation in a single institution. *Transplant. Proc*. October 2012;44(8):2462–2488.
38. Christie JD, Bavaria JE, Palevsky HI, Litzky L, Blumenthal NP, Kaiser LR et al. Primary graft failure following lung transplantation. *Chest*. July 1, 1998;114(1):51–60.
39. Hertz MI, Aurora P, Benden C, Christie JD, Dobbels F, Edwards LB et al. Scientific Registry of the International Society for Heart and Lung Transplantation: Introduction to the 2011 annual reports. *J. Heart Lung Transplant*. October 2011;30(10):1071–1077.
40. Venuta F, Boehler A, Rendina EA, Giacomo TD, Speich R, Schmid R et al. Complications in the native lung after single lung transplantation. *Eur. J. Cardiothorac. Surg*. July 1, 1999;16(1):54–58.
41. Frost AE, Keller CA, Noon GP, Short HD, Cagle PT. Outcome of the native lung after single lung transplant. Multiorgan Transplant Group. *Chest*. April 1995;107(4):981–984.
42. Kshettry M, Kroshus M, Hertz M, Hunter M, Shumway M, Bolman MI. Early and late airway complications after lung transplantation: Incidence and management. *Ann. Thorac. Surg*. June 1997;63(6):1576–1583.
43. Meyers BF, Sundt TM 3rd, Henry S, Trulock EP, Guthrie T, Cooper JD et al. Selective use of extracorporeal membrane oxygenation is warranted after lung transplantation. *J. Thorac. Cardiovasc. Surg*. July 2000;120(1):20–26.
44. Ailawadi G, Lau CL, Smith PW, Swenson BR, Hennessy SA, Kuhn CJ et al. Does reperfusion injury still cause significant mortality after lung transplantation? *J. Thorac. Cardiovasc. Surg*. March 1, 2009;137(3):688–694.
45. Rocha PN, Rocha AT, Palmer SM, Davis RD, Smith SR. Acute renal failure after lung transplantation: Incidence, predictors and impact on perioperative morbidity and mortality. *Am. J. Transplant*. June 2005;5(6):1469–1476.
46. Frost AE, Jammal CT, Cagle PT. Hyperacute rejection following lung transplantation. *Chest*. August 1996;110(2):559–562.
47. Perrot M de, Liu M, Waddell TK, Keshavjee S. Ischemia–reperfusion–induced lung injury. *Am. J. Respir. Crit. Care Med*. February 15, 2003;167(4):490–511.
48. Alexander BD, Tapson VF. Infectious complications of lung transplantation. *Transpl. Infect. Dis*. September 2001;3(3):128–137.
49. Lease ED, Zaas DW. Update on infectious complications following lung transplantation. *Curr. Opin. Pulm. Med*. 2011 May;17(3):206–209.

MEDICINE

Complications in Surgery and Trauma, Second Edition provides practical information on the incidence, management, and avoidance of complications encountered during and after surgical procedures.

The book offers detailed guidance and techniques for recognizing and controlling complications in the operating room, emergency ward, or intensive care unit. It spans the vast array of complications related to preoperative, intra-operative, and postoperative events. The coverage is comprehensive and includes many surgical sub-specialties including critical care, endocrine, cardiothoracic, vascular, burns and wound healing, orthopedic, pediatric, and transplant.

A key feature of this new edition is the addition of succinct summary tables that list the most common complications related to each area of surgery or trauma and how to avoid them. Nine new chapters are included, and all previous chapters have been updated, making it a completely up-to-date reference for surgical residents, general surgeons, critical care surgeons, and those in training.

Stephen M. Cohn, MD, FACS, Professor of Surgery, University of Texas Health Science Center, San Antonio, TX, USA

Matthew O. Dolich, MD, FACS, Professor of Surgery, University of California, Irvine Medical Center, Orange, CA, USA

CRC Press
Taylor & Francis Group
an **informa** business
www.crcpress.com

6000 Broken Sound Parkway, NW
Suite 300, Boca Raton, FL 33487
711 Third Avenue
New York, NY 10017
2 Park Square, Milton Park
Abingdon, Oxon OX14 4RN, UK

K21608
ISBN-13: 978-1-4822-0886-3
90000
9 781482 208863