Michael Miloro · G. E. Ghali ·
Peter E. Larsen · Peter Waite *Editors*

Peterson's Principles of Oral and Maxillofacial Surgery

Fourth Edition

Springer

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Michael Miloro • G. E. Ghali • Peter E. Larsen • Peter Waite
Editors

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ISBN 978-3-030-91919-1 ISBN 978-3-030-91920-7 (eBook)
https://doi.org/10.1007/978-3-030-91920-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Beth and Macy, and my family, for their love and support, and my parents for always being there for me. To my students and residents of oral and maxillofacial surgery for teaching me and making me realize every day that I made the right career choice. To Pete Peterson, who I think about quite often even though it has been 20 years since his death; thank you for being such an excellent mentor – I would not be here if you had not come into my life in 1994.

Michael Miloro

This book is dedicated to my wife, Hope, and our wonderful children, Gregor, Gracie, Gabrielle, and Garrisyn. Thanks for always reminding me of the important things in life. To my students, residents, fellows, and staff, who always keep it relevant and enjoyable for me.

G. E. Ghali

To my wife Patty, and my sons, Michael, Matthew, and Mark, for reminding me that my most important role is that of father and husband. To my father, who inspired me to enter medicine, and to my mother, who convinced me that I could accomplish whatever I put my mind to. To my residents, many of whom have become close friends. I am proud of the fine surgeons they have become. Lastly, to the many faculties with whom I have had the great privilege to work with throughout my career.

Peter E. Larsen

To my wife Sallie and our three children, Allison, Eric, and Jonny for giving me the time to follow my surgical and teaching ambitions. To my father, Daniel E. Waite, Professor and Chair of OMS, for his love and commitment to the specialty still today continues to inspire me. Thanks to my mentors, colleagues, and residents who continue to challenge me every day.

Peter Waite

Preface

Nearly 30 years ago in 1992, Dr. Larry J. "Pete" Peterson published the first edition of *Principles of Oral and Maxillofacial Surgery* when he was Professor and Chairman of Oral and Maxillofacial Surgery at The Ohio State University in Columbus, Ohio. In his preface for that book, he recognized that "(t)he specialty of Oral and Maxillofacial Surgery has advanced dramatically over the last 15 years [1977–1992]." Over the next 10 years (1992–2002), Pete certainly experienced some of the advancements in our specialty until his premature death in 2002. Yet, I wonder how he would see the subsequent expansion of the scope of the specialty, as well as the significant and explosive technological advances that have occurred over the past 20 years and have shaped the manner in which we practice medicine, dentistry, and specialty care today. I am certain that he would have had restrained enthusiasm, and would have reserved judgment until the published studies had validated the efficacy of these advances in improving patient care while maintaining a favorable cost-to-benefit ratio; Pete was never one to "jump on the bandwagon," and evidence-based practice was mandatory. Dr. Peterson also recognized "…that much of the surgery that the individual practitioner is called on to do today was learned *after* formal residency training." Most surgeons would agree, and this basic premise served as his impetus to have a complete and comprehensive reference textbook for the practicing surgeon. Dr. Peterson's intention was that the first edition "…emphasizes new and innovative methods and techniques," and it certainly accomplished that goal within the constraints of the technological limitations of the time.

With similar themes in mind from 1992, in 2021 we have created the fourth edition of *Peterson's Principles of Oral and Maxillofacial Surgery* to reflect the significant changes in clinical practice, and contain contemporary, state-of-the-art knowledge and clinical techniques for the oral and maxillofacial surgeon, both in training and in practice. We have sought to assemble an excellent authorship composed of both experienced surgeons and young surgeons to collaborate on the specific chapters in order to include both historical and experienced points of view combined with a fresh perspective on each chapter topic. The clear purpose of this fourth edition is to provide an authoritative textbook that is concise, easy to read, contemporarily referenced, and that contains the requisite information that the competent oral and maxillofacial surgeon should possess. Throughout the prior three editions, this textbook has been used as a *required* resource for residency training programs in the USA and abroad, and it has served well those residents in training and candidates for board certification well as a resource for didactic conference preparation, clinical and operating room preparation, and examination preparation.

Unfortunately, many who will benefit from this fourth edition, and future editions, would have never met Dr. Peterson, but those who knew Pete Peterson as the *teacher* would know how important it would have been for him to see his *teachings* continue through this textbook.

Peterson's Principles of Oral and Maxillofacial Surgery is, without a doubt, *the* authoritative textbook for the specialty of oral and maxillofacial Surgery.

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Contents

I Medicine, Surgery, and Anesthesia

1 **Wound Healing** 3
Vivek Shetty and Charles N. Bertolami

2 **Medical Management and Preoperative Patient Assessment** 19
Steven M. Roser and Gary F. Bouloux

3 **Pharmacology of Outpatient Anesthesia Medications** 53
Kyle J. Kramer and Steven I. Ganzberg

4 **Outpatient Anesthesia** 81
Jeffrey Bennett, Kevin Butterfield, and Kyle J.Kramer

II Dentoalveolar and Implant Surgery

5 **Impacted Teeth** 131
Gregory M. Ness, George H. Blakey, and Ben L. Hechler

6 **Pre-Prosthetic Surgery** 171
Joseph E. Cillo Jr.

7 **Pediatric Dentoalveolar Surgery** 191
Carl Bouchard, Maria J. Troulis, and Leonard B. Kaban

8 **Utilization of Three-Dimensional Imaging Technology to Enhance Maxillofacial Surgical Applications** 211
Scott D. Ganz

9 **Dynamic Navigation for Dental Implants** 239
Robert W. Emery III and Armando Retana

10 **Implant Prosthodontics** 273
Olivia M. Muller and Thomas J. Salinas

11 **The Science of Osseointegrated Implant Reconstruction** 311
Michael Block

12 **Comprehensive Implant Site Preparation: Mandible** 371
Ole T. Jensen and Jared Cottam

13 **A Graft-less Approach for Treatment of the Edentulous Maxilla: Contemporary Considerations for Treatment Planning, Biomechanical Principles, and Surgical Protocol** 389
Edmond Bedrossian, E. Armand Bedrossian, and Lawrence E. Brecht

14 **Soft Tissue Management in Implant Therapy** 409
Anthony G. Sclar

15 **Craniofacial Implant Surgery** 433
Douglas Sinn, Danielle Gill, Edmond Bedrossian, and Allison Vest

III Maxillofacial Trauma

16 **Initial Management of the Trauma Patient** 473
J. Blake Calcei, Michael P. Powers, Shawn Clark, and John R. Gusz

17 **Soft Tissue Injuries** 515
Alan S. Herford, G. E. Ghali, and Paul Jung

18 **Rigid Versus Nonrigid Fixation** 539
Edward Ellis III

19 **Dentoalveolar and Intraoral Soft Tissue Trauma** 555
Colonya C. Calhoun, Eric R. Crum, and Briana Burris

20 **Contemporary Management of Mandibular Fractures** 581
R. Bryan Bell, Lance Thompson, and Melissa Amundson

21 **Fractures of the Mandibular Condyle** 649
Hany A. Emam and Courtney Jatana

22 **Management of Maxillary Fractures** 671
Melvyn Yeoh, Ali Mohammad, and Larry Cunningham

23 **Management of Zygomatic Complex Fractures** 689
Ashley E. Manlove and Jonathan S. Bailey

24 **Orbital and Ocular Trauma** 707
Hany A. Emam and Deepak G. Krishnan

25 **Management of Frontal Sinus and Naso-orbitoethmoid Complex Fractures** 751
Mariusz K. Wrzosek and Stephen P. R. MacLeod

26 **Nasal Fractures** 775
Tirbod Fattahi and Salam O. Salman

27 **Maxillofacial Firearm Injuries** 785
David B. Powers and Jon Holmes

28 **Pediatric Facial Trauma** 813
Bruce B. Horswell and Daniel J. Meara

29 **Management of Panfacial Fractures** 849
Patrick Louis and Earl Peter Park

IV Maxillofacial Pathology/Infections

30 **Differential Diagnosis of Oral Disease** 873
John R. Kalmar and Kristin K. McNamara

31 **Odontogenic Cysts and Tumors** 891
Eric R. Carlson and Thomas P. Schlieve

32 **Benign Nonodontogenic Lesions of the Jaws** 935
Brett L. Ferguson and M. Anthony Pogrel

33 **Oral Cancer: Classification, Diagnosis, and Staging** 965
Michael R. Markiewicz, Nicholas Callahan, and Anthony Morlandt

34 **Oral Cancer Management** 1009
Andrew T. Meram and Brian M. Woo

35 **Lip Cancer** 1057
Stavan Y. Patel and G. E. Ghali

36 **Head and Neck Skin Cancer** 1081
Roderick Y. Kim, Brent B. Ward, and Michael F. Zide

37 **Salivary Gland Disease** 1115
Antonia Kolokythas and Robert A. Ord

38 **Mucosal and Related Dermatologic Diseases** 1137
John M. Wright, Paras Patel, and Yi-Shing Lisa Cheng

39 **Pediatric Maxillofacial Pathology** 1169
Antonia Kolokythas

40 **Odontogenic Infections** 1193
Rabie M. Shanti and Thomas R. Flynn

41 **Osteomyelitis, Osteoradionecrosis (ORN), and Medication-Related Osteonecrosis of the Jaws (MRONJ)** 1221
George M. Kushner and Robert L. Flint

V Maxillofacial Reconstruction

42 **Local and Regional Flaps** 1245
Alan S. Herford and G. E. Ghali

43 **Nonvascularized Reconstruction** 1269
Dale Baur and Maximillian Beushausen

44 **Vascularized Reconstruction** 1291
D. David Kim and Rui Fernandes

45 **Microneurosurgery** 1313
Michael Miloro

46 **Comprehensive Management of Facial Clefts** 1345
Bernard J. Costello, Ramon L. Ruiz, and Suganya Appugounder

47 **Alveolar Cleft Reconstruction** 1373
Kelly Kennedy and Peter E. Larsen

48 **Nonsyndromic Craniosynostosis** 1389
Jennifer E. Woerner and G. E. Ghali

49 **Craniofacial Dysostosis Syndromes: Evaluation and Treatment of the Skeletal Deformities** 1415
Paul S. Tiwana, Jeffrey C. Posnick, and Ramon L. Ruiz

50 **Technology in Oral and Maxillofacial Reconstruction** 1455
Michael R. Markiewicz, Brian Farrell, and Rabie M. Shanti

VI Temporomandibular Joint Disease

51 **Anatomy and Pathophysiology of the Temporomandibular Joint** 1535
Michael D. Han and Stuart E. Lieblich

52 **Nonsurgical Management of Temporomandibular Disorders** 1551
Vasiliki Karlis, Alexandra G. Glickman, and Robert Glickman

53 **Arthroscopy and Arthrocentesis of the Temporomandibular Joint** 1569
Joseph P. McCain, Jose Montero, David Y. Ahn, and Mohamed A. Hakim

54 **Internal Derangement of the Temporomandibular Joint** 1625
Luis G. Vega

55 **Hypomobility and Hypermobility Disorders of the Temporomandibular Joint** 1663
David Y. Ahn, Mohamed A. Hakim, Meredith August, Leonard B. Kaban, and Maria J. Troulis

56 **Pediatric Temporomandibular Disorders: Juvenile Idiopathic Arthritis** 1693
Cory M. Resnick and Peter Waite

57 **End-Stage Temporomandibular Joint Disease** 1705
Louis G. Mercuri and Eric J. Granquist

VII Orthognathic Surgery

58 **Craniofacial Growth and Development** 1729
Shankar Rengasamy Venugopalan and Veerasathpurush Allareddy

59 **Digital Data Acquisition and Treatment Planning in Orthognathic Surgery** 1767
Marco Caminiti and Michael D. Han

60 **Orthodontics for Orthognathic Surgery** 1801
Larry M. Wolford

61 **Model Surgery and Computer-Aided Surgical Simulation for Orthognathic Surgery** 1825
Martin B. Steed, H. Alexander Crisp, Vincent J. Perciaccante, and Robert A. Bays

62 **Mandibular Orthognathic Surgery** 1851
Dale S. Bloomquist, Jessica J. Lee, and Steven M. Sullivan

63 **Maxillary Orthognathic Surgery** 1909
Deepak G. Krishnan and Vincent J. Perciaccante

64 **Sequencing in Orthognathic Surgery** 1945
Zachary Brown, Daniel Perez, and Edward Ellis III

65 **Concomitant Orthognathic and Temporomandibular Joint Surgery** 1969
Pushkar Mehra and Charles Henry

66 **Facial Asymmetry** 1989
Peter Waite and Chung How Kau

67 **Soft Tissue Changes and Prediction with Orthognathic Surgery** 2019
Rishi Jay Gupta and Stephen Schendel

68 **Complications in Orthognathic Surgery** 2039
Joseph Van Sickels and Salam O. Salman

69 **Cleft Orthognathic Surgery** 2071
Kevin S. Smith

70 **Distraction Osteogenesis of the Craniomaxillofacial Skeleton** 2089
Michael R. Markiewicz, Michael Miloro, and David Yates

71 **Surgical and Nonsurgical Manssagement of Obstructive Sleep Apnea** 2135
Yedeh Ying and Peter Waite

VIII Facial Esthetic Surgery

72 **Blepharoplasty** 2163
Tirbod Fattahi and Armando Retana

73 **Basic Principles of Rhinoplasty** 2181
James Koehler and Peter Waite

74 **Rhytidectomy** 2209
Faisal A. Quereshy and Josh Coffey

75 **Forehead and Brow Procedures** 2227
Angelo Cuzalina, Faisal A. Quereshy, and Andrei Marechek

76 **Otoplastic Surgery for the Protruding Ear** 2259
Todd G. Owsley

77 **Adjunctive Facial Cosmetic Procedures** 2273
Ryan M. Diepenbrock and Joe Niamtu III

Supplementary Information
Index 2303

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Medicine, Surgery, and Anesthesia

Contents

Chapter 1 **Wound Healing – 3**
Vivek Shetty and Charles N. Bertolami

Chapter 2 **Medical Management and Preoperative Patient Assessment – 19**
Steven M. Roser and Gary F. Bouloux

Chapter 3 **Pharmacology of Outpatient Anesthesia Medications – 53**
Kyle J. Kramer and Steven I. Ganzberg

Chapter 4 **Outpatient Anesthesia – 81**
Jeffrey Bennett, Kevin Butterfield, and Kyle J.Kramer

Wound Healing

Vivek Shetty and Charles N. Bertolami

Contents

1.1 Introduction – 4

1.2 The Healing Process – 4

1.3 Wound Healing Response – 4
1.3.1 Inflammatory Phase – 4
1.3.2 Proliferative Phase – 6
1.3.3 Remodeling Phase – 7

1.4 Specialized Healing – 7
1.4.1 Nerve – 7
1.4.2 Bone – 8
1.4.3 Extraction Wounds – 9
1.4.4 Skin Grafts – 10

1.5 Wound Healing Complications – 10
1.5.1 Wound Infection – 10
1.5.2 Wound Dehiscence – 11
1.5.3 Proliferative Scarring – 11

1.6 Optimizing Wound Healing – 11
1.6.1 Tissue Trauma – 11
1.6.2 Hemostasis and Wound Debridement – 12
1.6.3 Tissue Perfusion – 12
1.6.4 Diabetes – 12
1.6.5 Immunocompromise – 13
1.6.6 Radiation Injury – 13
1.6.7 Hyperbaric Oxygen (HBO) Therapy – 14
1.6.8 Age – 14
1.6.9 Nutrition – 14

1.7 Advances in Wound Healing – 15
1.7.1 Growth Factors – 15
1.7.2 Gene Therapy – 16
1.7.3 Dermal and Mucosal Substitutes – 16

References – 17

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1

Learning Aims

1. Wound healing restores tissue integrity and function through a coordinated series of cellular events.
2. Healing continuum consists of overlapping inflammatory, proliferative, and remodeling phases.
3. Quality of healing depends on wound and tissue type.
4. Multiple local and systemic factors can cause wound healing complications.
5. Healing may be modulated spatiotemporally with growth factors, gene therapy, and biologic scaffolds.

1.1 Introduction

The healing wound is an overt expression of an intricate and tightly choreographed sequence of cellular and biochemical responses directed toward restoring tissue integrity and functional capacity following injury. Although healing in the orofacial region culminates uneventfully in most instances, a variety of intrinsic and extrinsic factors can hamper or facilitate the process. Understanding wound healing at multiple levels – biochemical, physiologic, cellular, and molecular – provides the surgeon with a framework for basing clinical decisions aimed at optimizing the healing response. Equally important, it allows the surgeon to critically evaluate and selectively use the growing collection of biologic approaches that seek to assist healing by favorably modulating the wound microenvironment.

1.2 The Healing Process

The restoration of tissue integrity, whether initiated by trauma or surgery, is a phylogenetically primitive but essential defense response. Injured organisms survive only if they can repair themselves quickly and effectively. The healing response depends primarily on the type of tissue involved and the nature of the tissue disruption. When restitution occurs through tissue that is structurally and functionally indistinguishable from native tissue, *regeneration* has taken place. However, if tissue integrity is reestablished primarily through the formation of scar tissue, then *repair* has occurred. Repair by scarring is the body's version of a spot weld and the replacement tissue is coarse and has lower cellular content than native tissue. Except for bone and liver, tissue disruption invariably results in repair rather than regeneration.

At the cellular level, the rate and quality of tissue healing depend on whether the constitutive cells are labile, stable, or permanent. Labile cells, including the keratinocytes of the epidermis and epithelial cells of the oral mucosa, divide throughout their life span. Stable cells such as fibroblasts exhibit a low rate of duplication but can undergo rapid proliferation in response to injury. For example, bone injury causes pluripotent mesenchymal cells to speedily differentiate into osteoblasts and osteoclasts. On the other hand, permanent cells such as specialized nerve cells do not divide in postnatal life. The surgeon's expectation of "normal healing" should be correspondingly realistic and based on the inherent capabilities of the injured tissue. Whereas a fibrous scar is normal for skin wounds, it is suboptimal in the context of bone healing.

At a more macro level, the quality of the healing response is influenced by the nature of the tissue disruption and the circumstances surrounding wound closure. Healing by first intention occurs when a clean laceration or surgical incision is closed primarily with sutures or other means and healing proceeds rapidly with no dehiscence and minimal scar formation. If conditions are less favorable, wound healing is more complicated and occurs through a protracted filling of the tissue defect with granulation and connective tissue. This process is called healing by second intention and is commonly associated with avulsion injury, local infection, or inadequate closure of the wound. For more complex wounds, the surgeon may attempt healing by third intention through a staged procedure that combines secondary healing with delayed primary closure. The avulsion or contaminated wound is debrided and allowed to granulate and heal by second intention for 5–7 days. Once adequate granulation tissue has formed and the risk of infection appears minimal, the wound is sutured close to heal by first intention.

1.3 Wound Healing Response

Injury of any kind sets into motion a complex series of synchronized and temporally overlapping processes directed toward restoring the integrity of the involved tissue. Reparative processes are most commonly modeled in skin [1]; however, similar patterns of biochemical and cellular events occur in virtually every other tissue [2]. To facilitate description, the healing continuum of coagulation, inflammation, reepithelialization, granulation tissue, and matrix and tissue remodeling is typically broken down into three distinct overlapping phases: inflammatory, proliferative, and remodeling [3, 4].

1.3.1 Inflammatory Phase

The inflammatory phase presages the body's reparative response and usually lasts for 3–5 days. Vasoconstriction of the injured vasculature is the spontaneous tissue reac-

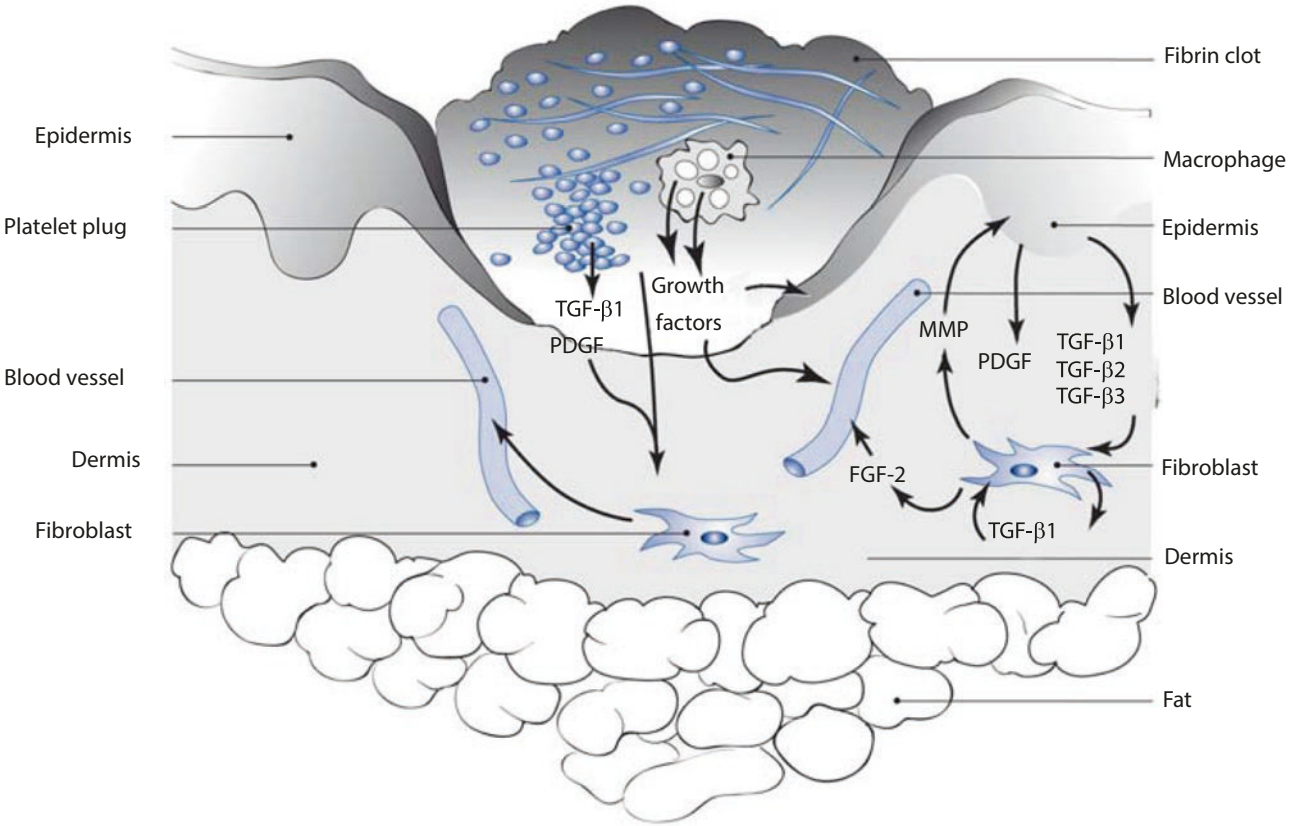

Fig. 1.1 Immediately following wounding, platelets facilitate the formation of a blood clot that secures hemostasis and provides a temporary matrix for cell migration. Cytokines released by activated macrophages and fibroblasts initiate the formation of granulation tissue by degrading extracellular matrix and promoting development of new blood vessels. Cellular interactions are potentiated by reciprocal signaling between the epidermis and dermal fibroblasts through growth factors, MMPs, and members of the TGF-β family. FGF fibroblast growth factor, MMP matrix metalloproteinase, PDGF platelet-derived growth factor, TGF-β transforming growth factor beta. (Adapted with permission from Bissell MJ and Radisky D[70])

tion to stop bleeding. Tissue trauma and local bleeding activate factor XII (Hageman factor), which initiates the various effectors of the healing cascade including the complement, plasminogen, kinin, and clotting systems. Circulating platelets (thrombocytes) rapidly aggregate at the injury site and adhere to each other and the exposed vascular subendothelial collagen to form a primary platelet plug organized within a fibrin matrix. The clot secures hemostasis and provides a provisional matrix through which cells can migrate during the repair process. Additionally, the clot serves as a reservoir of cytokines and growth factors that are released as activated platelets degranulate (Fig. 1.1). The bolus of secreted proteins, including interleukins, transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), maintains the wound milieu and regulates subsequent healing.

Once hemostasis is secured, the reactive vasoconstriction is replaced by a more persistent period of vasodilation that is mediated by histamine, prostaglandins, kinins, and leukotrienes. Increasing vascular permeability allows blood plasma, leucocytes, and other cellular mediators of healing to pass through the vessel walls (diapedesis) and populate the extravascular space. Parallel clinical manifestations include swelling, redness, heat, and pain. Cytokines released into the wound provide the chemotactic cues that sequentially recruit the neutrophils and monocytes to the site of injury. Neutrophils normally begin arriving at the wound site within minutes of injury and rapidly establish themselves as the predominant cells. Migrating through the scaffolding provided by the fibrin-enriched clot, the short-lived neutrophils flood the site with proteases and cytokines that help cleanse the wound of contaminating bacteria, devitalized tissue, and degraded matrix components. Neutrophil activity is accentuated by opsonic antibodies leaking into the wound from the altered vasculature. Unless a wound is grossly infected, neutrophil infiltration ceases after a few days. However, the proinflammatory cytokines released by perishing neutrophils, including tumor necrosis factor α (TNF-α) and interleu-

kins (IL-1a, IL-1b), continue to stimulate the inflammatory response for extended periods [5].

The initial levels of neutrophils begin to taper over the next 24–72 h with an increasing deployment of blood-borne monocytes to the site of injury. Activated monocytes, now termed macrophages, continue with the process of wound microdebridement initiated by the neutrophils. The macrophages secrete collagenases and elastases to break down injured tissue and phagocytose bacteria and cell debris. Beyond their scavenging role, the macrophages also serve as the primary source of healing mediators. Once activated, macrophages release a battery of growth factors and cytokines (TGF-α, TGF-β1, PDGF, insulin-like growth factor [IGF]-I and -II, TNF-α, and IL-1) at the wound site, further amplifying and perpetuating the action of the chemical and cellular mediators released previously by degranulating platelets and neutrophils. Macrophages influence all phases of early wound healing by regulating local tissue remodeling through proteolytic enzymes (e.g., matrix metalloproteases and collagenases), inducing the formation of new extracellular matrix, and modulating angiogenesis and fibroplasia through local production of cytokines such as thrombospondin-1 and IL-1b [6]. The centrality of macrophage function to early wound healing is underscored by the consistent finding that macrophage-depleted animal wounds demonstrate diminished fibroplasia and defective repair. Although the numbers and activity of the macrophages taper off by the fifth post-injury day, they continue to modulate the wound healing process until repair is complete.

1.3.2 Proliferative Phase

The cytokines and growth factors secreted during the inflammatory phase stimulate the succeeding proliferative phase (Fig. 1.2) [7]. Starting as early as day 3 post-injury and lasting up to 3 weeks, the proliferative phase is distinguished by the formation of pink granular tissue (granulation tissue) containing inflammatory cells, fibroblasts, and budding vasculature enclosed in a loose matrix [8]. An essential first step is the establishment of a local microcirculation to supply the oxygen

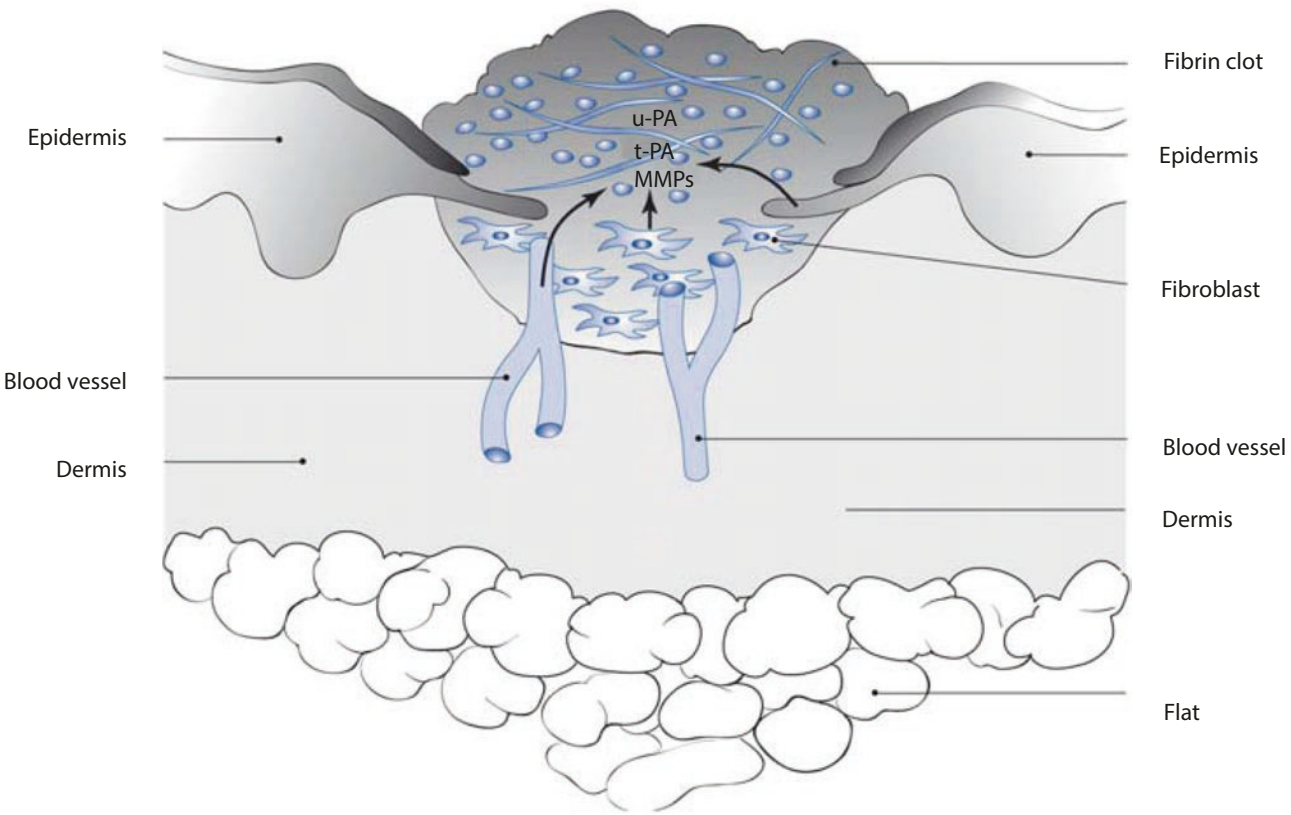

Fig. 1.2 The cytokine cascade mediates the succedent proliferative phase. This phase is distinguished by the establishment of local microcirculation and formation of extracellular matrix and immature collagen. Epidermal cells migrate laterally below the fibrin clot, and granulation tissue begins to organize below the epithelium. MMPs matrix metalloproteinases, t-PA tissue plasminogen activator, u-PA urinary plasminogen activator. (Adapted with permission from Bissell MJ and Radisky D[70])

and nutrients necessary for the elevated metabolic needs of regenerating tissues. The generation of new capillary blood vessels (angiogenesis) from the interrupted vasculature is driven by wound hypoxia as well as with native growth factors, particularly VEGF, fibroblast growth factor 2 (FGF-2), and TNF-β. Around the same time, matrix-generating fibroblasts migrate into the wound in response to the cytokines and growth factors released by inflammatory cells and wounded tissue. The fibroblasts start synthesizing new extracellular matrix (ECM) and immature collagen (Type III). The scaffold of collagen fibers serves to support the newly formed blood vessels supplying the wound. Stimulated fibroblasts also secrete a range of growth factors, thereby producing a feedback loop and sustaining the repair process. Collagen deposition rapidly increases the tensile strength of the wound and decreases the reliance on closure material to hold the wound edges together. Once adequate collagen and ECM have been generated, matrix synthesis dissipates, evidencing the highly precise spatial and temporal regulation of normal healing.

At the surface of the dermal wound, new epithelium forms to seal off the denuded wound surface. Epidermal cells originating from the wound margins undergo a proliferative burst and begin to resurface the wound above the basement membrane. The process of reepithelialization progresses more rapidly in oral mucosal wounds in contrast to skin. In a mucosal wound, the epithelial cells migrate directly onto the moist exposed surface of the fibrin clot instead of under the dry exudate (scab) of the dermis. Once the epithelial edges meet, contact inhibition halts further lateral proliferation. Reepithelialization is facilitated by underlying contractile connective tissue, which shrinks in size to draw the wound margins toward one another. Wound contraction is driven by a subset of the fibroblasts that transform into myofibroblasts and generate strong contractile forces. The extent of wound contraction depends on the depth of the wound and its location. In some extraoral instances, the forces of wound contracture are capable of deforming osseous structures.

1.3.3 Remodeling Phase

After week 3 post-injury, the proliferative phase is progressively replaced by an extended period of remodeling and strengthening of the immature scar tissue. The remodeling/maturation phase in dermis can last for several years and involves a finely choreographed balance between matrix degradation and formation. As the metabolic demands of the healing wound decrease, the rich network of capillaries begins to regress. Under the general direction of the cytokines and growth factors, the collagenous matrix is continually degraded, resynthesized, reorganized, and stabilized by molecular cross-linking into a scar. The fibroblasts start to disappear and the collagen Type III deposited during the granulation phase is gradually replaced by stronger Type I collagen. Correspondingly, the tensile strength of the scar tissue gradually increases and eventually approaches about 80% of the original strength. Homeostasis of scar collagen and ECM is regulated to a large extent by serine proteases and matrix metalloproteinases (MMPs) under the control of the regulatory cytokines. Tissue inhibitors afford a natural counterbalance to the MMPs and provide tight control of proteolytic activity within the scar. Any disruption of this orderly balance can lead to excess or inadequate matrix degradation and result in either an exuberant scar or wound dehiscence.

1.4 Specialized Healing

1.4.1 Nerve

Injury to the nerves innervating the orofacial region may range from simple contusion to complete interruption of the nerve. The healing response depends on injury severity and extent of the injury [9, 10]. Neuropraxia represents the mildest form of nerve injury and is a transient interruption of nerve conduction without loss of axonal continuity. The continuity of the epineural sheath and the axons is maintained and morphologic alterations are minor. Recovery of the functional deficit is spontaneous and usually complete within 3–4 weeks. If there is a physical disruption of one or more axons without injury to stromal tissue, the injury is described as axonotmesis. Here, the individual axons are severed but the investing Schwann cells and connective tissue elements remain intact. The nature and extent of the ensuing sensory or motor deficit relates to the number and type of injured axons. Morphologic changes are manifest as degeneration of the axoplasm and associated structures distal to the site of injury and partly proximal to the injury. Recovery of the functional deficit depends on the degree of the damage.

Complete transection of the nerve trunk is referred to as neurotmesis and spontaneous recovery from this type of injury is rare. Histologically, changes of degeneration are evident in all axons adjacent to the site of injury [11]. Shortly after nerve severance, the investing Schwann cells begin to undergo a series of cellular changes called Wallerian degeneration. The degeneration is evident in all axons of the distal nerve segment and in a few nodes of the proximal segment. Within 78 h, injured axons start breaking up and are phagocytosed by adjacent Schwann cells and by macrophages

that migrate into the zone of injury. Once the axonal debris has been cleared, Schwann cell outgrowths attempt to connect the proximal stump with the distal nerve stump. Surviving Schwann cells proliferate to form a band (Büngner's band) that will accept regenerating axonal sprouts from the proximal stump. The proliferating Schwann cells also promote nerve regeneration by secreting numerous neurotrophic factors that coordinate cellular repair as well as cell adhesion molecules that direct axonal growth. In the absence of surgical realignment or approximation of the nerve stumps, proliferating Schwann cells and outgrowing axonal sprouts may align within the randomly organized fibrin clot to form a disorganized mass termed *neuroma.*

The rate and extent of nerve regeneration depend on several factors including type of injury, age, state of tissue nutrition, and the nerves involved. Although the regeneration rate for peripheral nerves varies considerably, it is generally considered to approximate 1 mm/day. The regeneration phase lasts up to 3 months and ends on contact with the end-organ by a thin myelinated axon. In the concluding maturation phase, both the diameter and performance of the regenerating nerve fiber increase.

1.4.2 Bone

The process of bone healing after a fracture has many features similar to that of skin healing except that it also involves calcification of the connective tissue matrix. Bone is a biologically privileged tissue in that it heals by regeneration rather than repair. Left alone, fractured bone is capable of restoring itself spontaneously through sequential tissue formation and differentiation, a process also referred to as *indirect healing.* As in skin, the interfragmentary thrombus that forms shortly after injury staunches bleeding from ruptured vessels in the haversian canals, marrow, and periosteum. Necrotic material at the fracture site provokes an immediate and intense acute inflammatory response which attracts the polymorphonuclear leukocytes and subsequently, macrophages to the fracture site. The organizing hematoma serves as a fibrin scaffold over which reparative cells can migrate and perform their function. Invading inflammatory cells and the succeeding pluripotent mesenchymal cells begin to rapidly produce a soft fracture callus that fills up interfragmentary gaps. Comprised of fibrous tissue, cartilage, and young immature fiber bone, the soft and compliant callus acts as a biologic splint by binding the severed bone segments and damping interfragmentary motion. An orderly progression of tissue differentiation and maturation eventually leads to fracture consolidation and restoration of bone continuity.

More commonly, the surgeon chooses to facilitate an abbreviated callus-free bone healing termed *direct healing* (Fig. 1.3). The displaced bone segments are surgically manipulated into an acceptable alignment and rigidly stabilized through the use of internal fixation devices. The resulting anatomic reduction is usually a combination of small interfragmentary gaps separated by contact areas. Ingrowth of mesenchymal cells and blood vessels starts shortly thereafter, and activated osteoblasts start depositing osteoid on the surface of the fragment ends. In contact zones where the fracture ends are closely apposed, the fracture line is filled concentrically by lamellar bone. Larger gaps are filled through a succession of fibrous tissue, fibrocartilage, and woven

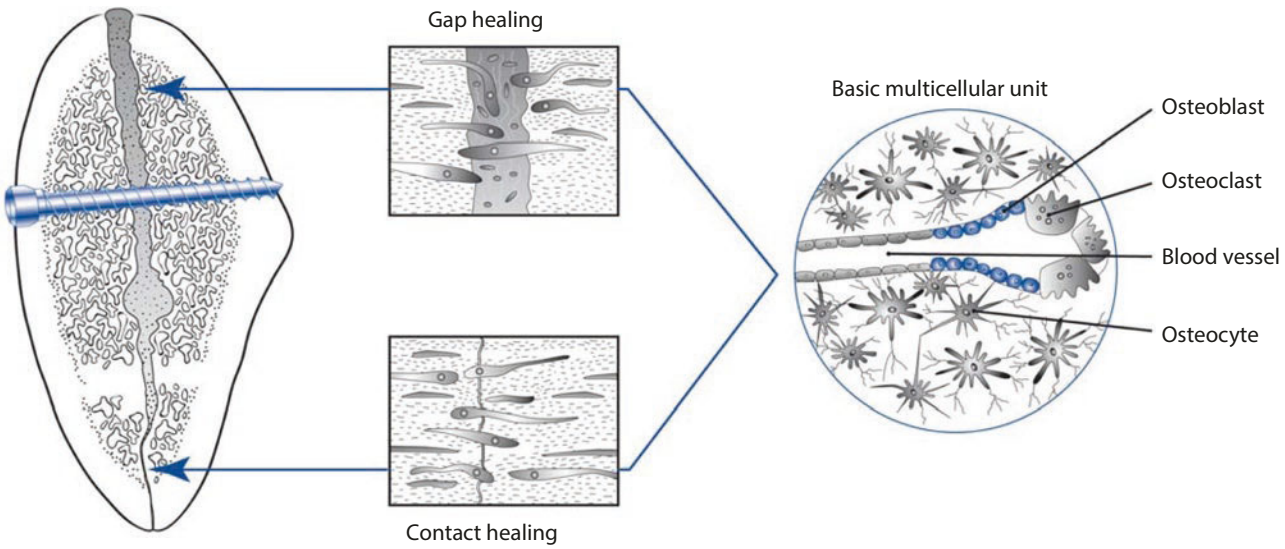

Fig. 1.3 Direct bone healing facilitated by internal fixation. The fracture site shows both gap healing and contact healing. The internal architecture of bone is restored eventually by the action of basic multicellular units

bone. In the absence of any microinstability at the fracture site, direct healing takes place without any callus formation.

Subsequent bone remodeling eventually restores the original shape and internal architecture of the fractured bone. Functional sculpting and remodeling of the primitive bone tissue is carried out by a temporary team of juxtaposed osteoclasts and osteoblasts called the basic multicellular unit (BMU). The osteoblasts develop from pluripotent mesenchymal stem cells, whereas multicellular osteoclasts arise from a monocyte/macrophage lineage [12, 13]. The development and differentiation of the BMUs are controlled by locally secreted growth factors, cytokines, and mechanical signals. As osteoclasts at the leading edge of the BMUs excavate bone through proteolytic digestion, active osteoblasts move in, secreting layers of osteoid and slowly refilling the cavity. The osteoid begins to mineralize when it is about 6 μm thick. Osteoclasts reaching the end of their lifespan of 2 weeks die and are removed by phagocytes. The majority (up to 65%) of the remodeling osteoblasts also die within 3 months and the remainder are entombed inside the mineralized matrix as osteocytes.

While the primitive bone mineralizes, remodeling BMUs cut their way through the reparative tissue and replace it with mature bone. The "grain" of the new bone tissue starts paralleling local compression and tension strains. Consequently, the shape and strength of the reparative bone tissue changes to accommodate greater functional loading. Tissue-level strains produced by functional loading play an important role in the remodeling of the regenerate bone. Whereas low levels of tissue strain (~2000 microstrains) are considered physiologic and necessary for cell differentiation and callus remodeling, high strain levels (>2000 microstrains) begin to adversely affect osteoblastic differentiation and bone matrix formation [14]. If there is excess interfragmentary motion, bone regenerates primarily through endochondral ossification or the formation of a cartilaginous callus that is gradually replaced by new bone. In contrast, osseous healing across stabilized fracture segments occurs primarily through intramembranous ossification. Major factors determining the mechanical milieu of a healing fracture include the fracture configuration, the exactness of fracture reduction, the stability afforded by the selected bone stabilization approach, and the degree and nature of microstrains provoked by function. If a fracture fixation device is incapable of stabilizing the fracture, the interfragmentary microinstability provokes osteoclastic resorption of the fracture surfaces and results in a widening of the fracture gap. Although bone union may be ultimately achieved through secondary healing by callus production and endochondral ossification, the healing is protracted. Fibrous healing and nonunions are clinical manifestations of excessive microstrains interfering with the cellular healing process.

The healing at dental implant interfaces follows a similar pattern. Following the seating of an endosseous implant, a blood clot forms in the interstices between the implant grooves and the osseous bed. The clot is rapidly infiltrated by granulocytes and macrophages. Eventually, fibroblastic progenitor cells migrate into the provisional matrix, allowing formation of succedent granulation tissue. The granulation tissue is vascularized by endothelial cell migration and the cells in the granulation tissue begin to differentiate into osteoblasts and create bone [15]. The bone formation starts within a few days after dental implant placement and most of the bone–implant contact is achieved by 3 months. Depending on the mechanical stress caused by occlusal forces, notable bone remodeling around the dental implant can persist for at least 1 year. Mechanical loading by occlusal forces can stimulate peri-implant bone but excessive micromotion can compromise osseointegration and lead to implant failure [16].

1.4.3 Extraction Wounds

The healing of an extraction socket is a specialized example of healing by second intention [17]. Immediately after the removal of the tooth from the socket, blood fills the extraction site. Both intrinsic and extrinsic pathways of the clotting cascade are activated. The resultant fibrin meshwork, which contains entrapped red blood cells, seals off the torn blood vessels and reduces the size of the extraction wound. Organization of the clot begins within the first 24–48 h, with engorgement and dilation of blood vessels within the periodontal ligament remnants, followed by leukocytic migration and formation of a fibrin layer. In the first week, the clot forms a temporary scaffold upon which inflammatory cells migrate. Epithelium at the wound periphery grows over the surface of the organizing clot. Osteoclasts accumulate along the alveolar bone crest and set the stage for active crestal resorption. Angiogenesis proceeds in the remnants of the periodontal ligaments. In the second week, the clot continues to get organized through fibroplasia and new blood vessels begin to penetrate toward the center of the clot. Trabeculae of osteoid slowly extend into the clot from the alveolus, and osteoclastic resorption of the cortical margin of the alveolar socket is more distinct. By the third week, the extraction socket is filled with granulation tissue and poorly calcified bone forms at the wound perimeter. The surface of the wound is completely reepithelialized with minimal or no scar formation.

Active bone remodeling by deposition and resorption continues for several more weeks. Reorganization and maturation of the alveolar site may continue up to 1 year after the extraction, but most of the dimensional changes evident clinically take place in the first 3 months [18]. The rate of bone makeover is extremely variable between individuals with complete remodeling of the precursor woven bone into lamellar bone and bone marrow taking from several months to years [19].

Occasionally, the blood clot fails to form or may disintegrate, causing a localized alveolar osteitis. When this happens, the healing is delayed considerably and the socket fills gradually. In the absence of a healthy granulation tissue matrix, the apposition of regenerate bone to the remaining alveolar bone takes place at a much slower rate. Compared to a normal socket, the infected socket remains open or partially covered with hyperplastic epithelium for extended periods.

1.4.4 Skin Grafts

Skin grafts may be either full-thickness or split-thickness [20]. A full-thickness graft is composed of epidermis and the entire dermis; a split-thickness graft is composed of the epidermis and varying amounts of dermis. Depending on the amount of underlying dermis included, split-thickness grafts are described as thin, intermediate, or thick [21]. Following grafting, nutritional support for a free skin graft is initially provided by plasma that exudes from the dilated capillaries of the host bed. A fibrin clot forms at the graft–host interface, fixing the graft to the host bed. Host leukocytes infiltrate into the graft through the lower layers of the graft. Graft survival depends on the ingrowth of blood vessels from the host into the graft (neovascularization) and direct anastomoses between the graft and the host vasculature (inosculation). Endothelial capillary buds from the host site invade the graft, reaching the dermoepidermal junction by 48 h. Concomitantly, vascular connections are established between host and graft vessels. However, only a few of the ingrowing capillaries succeed in developing a functional anastomosis. The formation of vascular connections between the recipient bed and transplant is signaled by the pink appearance of the graft, which appears between the third and fifth day postgrafting. Fibroblasts from the recipient bed begin to invade the layer of fibrin and leukocytes by the fourth day after transplantation. The fibrin clot is slowly resorbed and organized as fibroblastic infiltration continues. By the ninth day, the new blood vessels and fibroblasts have achieved a firm union, anchoring the deep layers of the graft to the host bed.

Re-innervation of the skin graft occurs by nerve fibers entering the graft through its base and sides. The fibers follow the vacated neurilemmal cell sheaths to reconstruct the innervation pattern of the donor skin. Recovery of sensation usually begins within 2 months after transplantation. Grafts rarely attain the sensory qualities of normal skin, because the extent of re-innervation depends on how accessible the neurilemmal sheaths are to the entering nerve fibers. The clinical performance of the grafts depends on their relative thickness. As split-thickness grafts are thinner than full-thickness grafts, they are more susceptible to trauma and undergo considerable contraction; however, they have greater survival rates clinically. Full-thickness skin grafts do not "take" as well and are slow to revascularize. However, full-thickness grafts are less susceptible to trauma and undergo minimal shrinkage.

1.5 Wound Healing Complications

Healing in the orofacial region is often considered a natural and uneventful process and seldom intrudes into the surgeon's consciousness. However, this changes when complications arise and hamper the wound healing continuum. Most wound healing complications are evident in the early postsurgical period but some may manifest much later. The two problems most commonly encountered in the orofacial region are wound infection and dehiscence; proliferative healing is less typical.

1.5.1 Wound Infection

Infections complicating surgical outcomes usually result from gross bacterial contamination of susceptible wounds. All wounds are intrinsically contaminated by bacteria; however, this must be distinguished from true wound infection where the bacterial burden of replicating microorganisms actually impairs healing [22, 23]. Experimental studies have demonstrated that, regardless of the type of infecting microorganism, wound infection occurs when there are more than 1×10^5 organisms per gram of tissue [24]. Beyond relative numbers, the pathogenicity of the infecting microorganisms as well as host response factors also determines whether wound healing is impaired.

The continual presence of a bacterial infection stimulates the host immune defenses leading to the production of inflammatory mediators, such as prostaglandins and thromboxane. Neutrophils migrating into the wound release cytotoxic enzymes and free oxygen radicals. Thrombosis and vasoconstrictive metabolites cause

wound hypoxia, leading to enhanced bacterial proliferation and continued tissue damage. Bacteria destroyed by host defense mechanisms provoke varying degrees of inflammation by releasing neutrophil proteases and endotoxins. Newly formed cells and their collagen matrix are vulnerable to these breakdown products of wound infection, and the resulting cell and collagen lysis contribute to impaired healing. Clinical manifestations of wound infection include the classic signs and symptoms of local infection: erythema, warmth, swelling, pain, and accompanying odor and pus.

Inadequate tissue perfusion and oxygenation of the wound further compromise healing by allowing bacteria to proliferate and establish infection. Failure to follow aseptic technique is a frequent reason for the introduction of infectious microorganisms into the wound. Transformation of contaminated wounds into infected wounds is also facilitated by excessive tissue trauma, remnant necrotic tissue, foreign bodies, or compromised host defenses. The most important factor in minimizing the risk of infection is meticulous surgical technique, including thorough debridement, adequate hemostasis, and elimination of any dead space. Careful technique must be augmented by proper postoperative care, with an emphasis on keeping the wound site clean and protecting it from trauma.

1.5.2 Wound Dehiscence

Partial or total separation of the wound margins may manifest within the first week after surgery. Most instances of wound dehiscence result from tissue failure rather than improper suturing techniques. The dehisced wound may be closed again or left to heal by secondary intention, depending upon the location, extent of the disruption, and the surgeon's assessment of the clinical situation.

1.5.3 Proliferative Scarring

Some patients may go on to develop aberrant scar tissue at the site of their skin injury. The two common forms of hyper-proliferative healing, hypertrophic scars and keloids, are characterized by hyper-vascularity and hyper-cellularity. Distinctive features include excessive scarring, persistent inflammation, and an overproduction of extracellular matrix components, including glycosaminoglycans and collagen Type I [25]. Despite their overt resemblance, hypertrophic scars and keloids do have some clinical dissimilarities. In general, hypertrophic scars arise shortly after the injury, tend to be circumscribed within the boundaries of the wound, and eventually recede. Keloids, on the other hand, manifest months after the injury, grow beyond the wound boundaries, and rarely subside. There is a clear familial and racial predilection for keloid formation, and susceptible individuals usually develop keloids on their face, ear lobes, and anterior chest.

Although processes leading to hypertrophic scar and keloid formation are not yet clarified, altered apoptotic behavior is believed to be a significant factor. Ordinarily, apoptosis or programmed cell death is responsible for the removal of inflammatory cells as healing proceeds and for the maturation of granulation tissue into scar. Dysregulation in apoptosis results in excessive scarring, inflammation, and an overproduction of extracellular matrix components. Both keloids and hypertrophic scars demonstrate sustained elevation of growth factors including TGF-β, platelet-derived growth factor, IL-1, and IGF-I [25]. The growth factors, in turn, increase the numbers of local fibroblasts and prompt excessive production of collagen and extracellular matrix. Additionally, proliferative scar tissue exhibits increased numbers of neoangiogenesis-promoting vasoactive mediators as well as histamine-secreting mast cells capable of stimulating fibrous tissue growth. Although there is no effective therapy for keloids, the more common methods for preventing or treating these lesions focus on inhibiting protein synthesis. These agents, primarily corticosteroids, are injected into the scar to decrease fibroblast proliferation, decrease angiogenesis, and inhibit collagen synthesis and extracellular matrix protein synthesis.

1.6 Optimizing Wound Healing

At its very essence, the wound represents an extreme disruption of the cellular microenvironment. Restoration of constant internal conditions or homeostasis at the cellular level is a constant undertow of the healing response. A variety of local and systemic factors can impede healing, and the informed surgeon can anticipate and, where possible, proactively address these barriers to healing so that wound repair can progress normally [26, 27].

1.6.1 Tissue Trauma

Minimizing trauma to the tissues helps promote faster healing and should be a central consideration at every stage of the surgical procedure, from placement of the incision to suturing of the wound. Properly planned, the surgical incision is just long enough to allow optimum exposure and adequate operating space. The incision

should be made with one clean consistent stroke of evenly applied pressure. Sharp tissue dissection and carefully placed retractors further minimize tissue injury. Sutures are useful for holding the severed tissues in apposition until the wound has healed enough. However, sutures should be used judiciously as they can add to the risk of infection and are capable of strangulating the tissues if applied too tightly.

1.6.2 Hemostasis and Wound Debridement

Bleeding from a transected vessel or diffuse oozing from the denuded surfaces interfere with the surgeon's view of underlying structures. Achieving complete hemostasis before wound closure helps prevent the formation of a hematoma postoperatively. The collection of blood or serum at the wound site provides an ideal medium for the growth of microorganisms that cause infection. Additionally, hematomas can result in necrosis of overlying flaps. However, hemostatic techniques must not be used too aggressively during surgery as the resulting tissue damage can prolong healing time. Postoperatively, the surgeon may insert a drain or apply a pressure dressing to help eliminate dead space in the wound.

Devitalized tissue and foreign bodies in a healing wound act as a haven for bacteria and shield them from the body's defenses. The dead cells and cellular debris of necrotic tissue have been shown to reduce host immune defenses and encourage active infection. A necrotic burden allowed to persist in the wound can prolong the inflammatory response, mechanically obstruct the process of wound healing, and impede reepithelialization. Dirt and tar located in traumatic wounds not only jeopardize healing but may result in a "tattoo" deformity. By removing dead and devitalized tissue, and any foreign material from a wound, debridement helps reduce the number of microbes, toxins, and other substances that inhibit healing. The surgeon should also keep in mind that prosthetic grafts and implants, despite refinements in biocompatibility, can stimulate varying degrees of foreign body reaction and adversely impact the healing process.

1.6.3 Tissue Perfusion

Poor tissue perfusion is one of the main barriers to healing since tissue oxygen tension drives the healing response [28, 29]. Oxygen is necessary for hydroxylation of proline and lysine, the polymerization and cross-linking of procollagen strands, collagen transport, fibroblast and endothelial cell replication, effective leukocyte killing, angiogenesis, and many other processes related to wound healing. Relative hypoxia in the region of injury is useful to the extent that it stimulates a fibroblastic response and helps mobilize other cellular elements of repair [30]. However, very low oxygen levels act together with the lactic acid produced by infecting bacteria to lower tissue pH and contribute to tissue breakdown. Cell lysis follows, with releases of proteases and glycosidases and subsequent digestion of extracellular matrix. Impaired local circulation also hinders the delivery of nutrients, oxygen, and antibodies to the wound. Neutrophils are affected because they require a minimal level of oxygen tension to exert their bactericidal effect. Delayed movement of neutrophils, opsonins, and the other mediators of inflammation to the wound site further diminishes the effectiveness of the phagocytic defense system and allows colonizing bacteria to proliferate. Collagen synthesis is dependent on oxygen delivery to the site, which in turn affects wound tensile strength. Most healing problems associated with diabetes mellitus, irradiation, small vessel atherosclerosis, chronic infection, and altered cardiopulmonary status can be attributed to local tissue ischemia.

Wound microcirculation after surgery determines the wound's ability to resist the inevitable bacterial contamination [30]. Tissue rendered ischemic by rough handling, or desiccated by cautery or prolonged air drying, tends to be poorly perfused and susceptible to infection. Similarly, tissue ischemia produced by tight or improperly placed sutures, poorly designed flaps, hypovolemia, anemia, and peripheral vascular disease all adversely affect wound healing. Smoking is a common contributor to decreased tissue oxygenation [31]. The peripheral vasoconstriction produced by smoking a cigarette can last up to an hour; thus, a pack-a-day smoker remains tissue hypoxic for the most of each day. Smoking also increases carboxyhemoglobin, increases platelet aggregation, increases blood viscosity, decreases collagen deposition, and decreases prostacyclin formation, all of which negatively affect wound healing. Patient optimization, in the case of smokers, may require that the patient abstain from smoking for a minimum of 1 week before and after surgical procedures. Another way of improving tissue oxygenation is the use of systemic hyperbaric oxygen (HBO) therapy to induce the growth of new blood vessels and facilitate increased flow of oxygenated blood to the wound.

1.6.4 Diabetes

Studies have demonstrated that the higher incidence of wound infection associated with diabetes has less to do with the patient having diabetes and more to do with hyperglycemia [32]. Simply put, a patient with well-

controlled diabetes may not be at a greater risk for wound healing problems than a nondiabetic patient. Tissue hyperglycemia impacts every aspect of wound healing by adversely affecting the immune system including neutrophil and lymphocyte function, chemotaxis, and phagocytosis [33]. Uncontrolled blood glucose hinders red blood cell permeability and impairs blood flow through the critical small vessels at the wound surface. The hemoglobin release of oxygen is impaired, resulting in oxygen and nutrient deficiency in the healing wound. Wound ischemia and impaired recruitment of cells resulting from the small vessel occlusive disease render the wound vulnerable to bacterial and fungal infections.

1.6.5 Immunocompromise

The immune response directs the healing response and protects the wound from infection. In the absence of an adequate immune response, surgical outcomes are often compromised. An important assessment parameter is total lymphocyte count. A mild deficit is a lymphocytic level between 1200 and 1800, and levels below 800 are considered severe total lymphocyte deficits. Patients with debilitated immune response include human immunodeficiency virus (HIV)-infected patients in advanced disease stages, patients on immunosuppressive therapy, and those taking high-dose steroids for extended periods. Studies indicate that HIV-infected patients with CD4 counts of less than 50 cells/mm^3 are at significant risk of poor wound outcome [34]. Although newer immunosuppressive drugs, such as cyclosporine, have no apparent effect on wound healing, other medications can retard the healing process, both in rate and quality, by altering the inflammatory reaction and the cell metabolism.

The use of steroids, such as prednisone, is a typical example of how suppression of the innate inflammatory process also increases wound healing complications. Exogenous corticosteroids diminish prolyl hydroxylase and lysyl oxidase activity, depressing fibroplasias, collagen formation, and neovascularity. Fibroblasts reach the site in a delayed fashion and wound strength is decreased by as much as 30%. Epithelialization and wound contraction are also impaired. The inhibitory effects of glucocorticosteroids can be attenuated to some extent by vitamin A given concurrently.

Most antineoplastic agents exert their cytotoxic effect by interfering with DNA or RNA production. The reduction in protein synthesis or cell division reveals itself as impaired proliferation of fibroblasts and collagen formation. Attendant neutropenia also predisposes to wound infection by prolonging the inflammatory phase of wound healing. Because of their deleterious effect on wound healing, administration of antineoplastic drugs should be restricted, when possible, until such time that the potential for healing complications has passed.

1.6.6 Radiation Injury

Therapeutic radiation for head and neck tumors inevitably produces collateral damage in adjacent tissue and reduces its capacity for regeneration and repair. The pathologic processes of radiation injury start right away; however, the clinical and histologic features may not become apparent for weeks, months, or even years after treatment [35]. The use of radiation therapy to treat cancer inevitably involves exposure of normal tissues. As a result, patients may experience symptoms associated with damage to normal tissue during the course of therapy for a few weeks after therapy or months or years later. Symptoms may be due to cell death or wound healing initiated within irradiated tissue and may be precipitated by exposure to further injury or trauma. Many factors contribute to risk and severity of normal tissue reactions; these factors are site specific and vary with time after treatment. Treatments that reduce the risk or severity of damage to normal tissue or that facilitate the healing of radiation injury are being developed. These could greatly improve the quality of life of patients treated for cancer [36]. The cellular and molecular responses to tissue irradiation are immediate, are dose dependent, and can cause both early and late consequences [37]. DNA damage from ionizing radiation leads to mitotic cell death in the first cell division after irradiation or within the first few divisions. Early acute changes are observed within a few weeks of treatment and primarily involve cells with a high turnover rate. The common symptoms of oral mucositis and dermatitis result from loss of functional cells and temporary lack of replacement from the pools of rapidly proliferating cells. The inflammatory response is largely mediated by cytokines activated by the radiation injury. Overall, the response has the features of wound healing; waves of cytokines are produced in an attempt to heal the radiation injury. The cytokines lead to an adaptive response in the surrounding tissue, cause cellular infiltration, and promote collagen deposition. Damage to local vasculature is exacerbated by leukocyte adhesion to endothelial cells and the formation of thrombi that block the vascular lumen, further depriving the cells that depend on the vessels.

The acute symptoms eventually start to subside as the constitutive cells gradually recover their proliferative abilities. However, these early symptoms may not be

apparent in some tissues such as bone, where the cumulative progressive effects of radiation can precipitate acute breakdown of tissue many years after therapy. The late effects of radiation are permanent and directly related to higher doses. Collagen hyalinizes and the tissues become increasingly fibrotic and hypoxic due to obliterative vasculitis, and the tissue susceptibility to infection increases correspondingly. Once these changes occur, they are irreversible and do not change with time. Hence, the surgeon must always anticipate the possibility of a complicated healing following surgery or traumatic injury in irradiated tissue. Wound dehiscence is common and the wound heals slowly or incompletely. Even minor trauma may result in ulceration and colonization by opportunistic bacteria. If the patient cannot mount an effective inflammatory response, progressive necrosis of the tissues may follow. Healing can be achieved only by excising all nonvital tissue and covering the bed with a well-vascularized graft. Due to the relative hypoxia at the irradiated site, tissue with intact blood supply needs to be brought in to provide both oxygen and cells necessary for inflammation and healing. The progressive obliteration of blood vessels makes bone particularly vulnerable. Following trauma or disintegration of the soft tissue cover due to inflammatory reaction, healing does not occur because irradiated marrow cannot form granulation tissue. In such instances, the avascular bone needs to be removed down to the healthy portion to allow healing to proceed.

1.6.7 Hyperbaric Oxygen (HBO) Therapy

HBO therapy is based on the concept that low tissue oxygen tension, typically a partial pressure of oxygen (Po_2) of 5–20 mm Hg, leads to anaerobic cellular metabolism, increase in tissue lactate, and a decrease in pH, all of which inhibit wound healing [38]. HBO therapy requires that the patient recline in a hyperbaric chamber and breath 100% oxygen at 2.0–2.4 atmospheres for 1–2 h. The HBO therapy is repeated daily for 3–10 weeks. HBO increases the quantity of dissolved oxygen and the driving pressure for oxygen diffusion into the tissue. Correspondingly, the oxygen diffusion distance is increased threefold to fourfold, and wound Po_2 ultimately reaches 800–1100 mm Hg. The therapy stimulates the growth of fibroblasts and vascular endothelial cells, increases tissue vascularization, enhances the killing ability of leukocytes, and is lethal for anaerobic bacteria. Clinical studies suggest that HBO therapy can be an effective adjunct in the management of diabetic wounds [39]. Animal studies indicate that HBO therapy could be beneficial in the treatment of osteomyelitis and soft tissue infections [39, 40]. Adverse effects of HBO therapy are barotraumas of the ear, seizure, and pulmonary oxygen toxicity. However, in the absence of controlled scientific studies with well-defined end points, HBO therapy remains a controversial aspect of surgical practice [41, 42].

1.6.8 Age

In general, wound healing is faster in the young and protracted in the elderly. The decline in healing response results from the gradual reduction of tissue metabolism as one ages, which may itself be a manifestation of decreased circulatory efficiency. The major components of the healing response in aging skin or mucosa are deficient or damaged with progressive injuries [43]. As a result, free oxidative radicals continue to accumulate and are harmful to the dermal enzymes responsible for the integrity of the dermal or mucosal composition. In addition, the regional vascular support may be subjected to extrinsic deterioration and systemic disease decompensation, resulting in poor perfusion capability. However, in the absence of compromising systemic conditions, differences in healing as a function of age seem to be small.

1.6.9 Nutrition

Adequate nutrition is important for normal repair [44]. In malnourished patients, fibroplasia is delayed, angiogenesis decreased, and wound healing and remodeling prolonged. Dietary protein has received special emphasis with respect to healing. Amino acids are critical for wound healing with methionine, histidine, and arginine playing important roles. Nutritional deficiencies severe enough to lower serum albumin to <2 g/dL are associated with a prolonged inflammatory phase, decreased fibroplasia, and impaired neovascularization, collagen synthesis, and wound remodeling. As long as a state of protein catabolism exists, the wound will be very slow to heal. Methionine appears to be the key amino acid in wound healing. It is metabolized to cysteine, which plays a vital role in the inflammatory, proliferative, and remodeling phases of wound healing.

Serum prealbumin is commonly used as an assessment parameter for protein [45, 46]. Contrary to serum albumin, which has a very long half-life of about 20 days, prealbumin has a shorter half-life of only 2 days. As such, it provides a more rapid assessment ability. Normal serum prealbumin is about 22.5 mg/dL, a level below 17 mg/dL is considered a mild deficit, and a severe defi-

cit would be below 11 mg/dL. As part of the perioperative optimization process, malnourished patients may be provided with solutions that have been supplemented with amino acids such as glutamine to promote improved mucosal structure and function and to enhance whole-body nitrogen kinetics. An absence of essential building blocks obviously thwarts normal repair, but the reverse is not necessarily true. Whereas a minimum protein intake is important for healing, a high protein diet does not shorten the time required for healing.

Several vitamins and trace minerals play a significant role in wound healing [47]. Vitamin A stimulates fibroplasia, collagen cross-linking, and epithelialization and will restimulate these processes in the steroid-retarded wound. Vitamin C deficiency impairs collagen synthesis by fibroblasts, because it is an important cofactor, along with α-ketoglutarate and ferrous iron, in the hydroxylation process of proline and lysine. Healing wounds appear to be more sensitive to ascorbate deficiency than uninjured tissue. Increased rates of collagen turnover persist for a long time, and healed wounds may rupture when the individual becomes scorbutic. Local antibacterial defenses are also impaired because ascorbic acid is also necessary for neutrophil superoxide production. The B-complex vitamins and cobalt are essential cofactors in antibody formation, white blood cell function, and bacterial resistance. Depleted serum levels of micronutrients, including magnesium, copper, calcium, iron, and zinc, affect collagen synthesis. ^{43}Copper is essential for covalent cross-linking of collagen, whereas calcium is required for the normal function of granulocyte collagenase and other collagenases at the wound milieu. Zinc deficiency retards both fibroplasia and reepithelialization; cells migrate normally but do not undergo mitosis [48]. Numerous enzymes are zinc dependent, particularly DNA polymerase and reverse transcriptase. On the other hand, exceeding the zinc levels can exert a distinctly harmful effect on healing by inhibiting macrophage migration and interfering with collagen cross-linking.

1.7 Advances in Wound Healing

A better understanding of the wound healing processes has increased interest in manipulating the wound microenvironment to facilitate healing. Traditional passive ways of treating surgical wounds are rapidly giving way to approaches that actively modulate wound healing. Therapeutic interventions range from treatments that selectively jump-start the wound into the healing cascade, to methods that mechanically protect the wound or increase oxygenation and perfusion of the local tissues [49, 50].

1.7.1 Growth Factors

Through their ability to orchestrate the various cellular activities that underscore inflammation and healing, cytokines have profound effects on cell proliferation, migration, and ECM synthesis. Accordingly, newer interventions seek to control or modulate the wound healing process by selectively inhibiting or enhancing the tissue levels of the appropriate cytokines.

The more common clinical approach has been to apply exogenous growth factors, such as PGDF, angiogenesis factor, epidermal growth factor (EGF), TGF, basic fibroblast growth factor (bFGF), and IL-1, directly to the wound. However, the potential of these extrinsic agents has not yet been realized clinically and may relate to figuring out which growth factors to put into the wound, when to apply, and at what dose. Becaplermin (recombinant human platelet-derived growth factor-BB [rhPDGF]; Regranex, 0.01% gel; Ortho-McNeil Pharmaceutical Inc., Raritan, New Jersey) was one of the first US Food and Drug Administration-approved recombinant growth factor products introduced to promote growth of soft tissue granulation tissue in treating cutaneous wounds. The recombinant PDGF increases fibroblast replication and induces fibroblasts to produce collagenase, which is important for connective tissue remodeling. In addition, rhPDGF increases the production of other connective tissue matrix components including glycosaminoglycans and proteoglycans. Notwithstanding its clinical efficacy, becaplermin has not found broad application due to its high costs [51, 52]. Within the fibroblast growth factor family (FGF), some members including FGF-2, FGF-7, and FGF-10 are essential to wound healing. The recombinant human keratinocyte growth factor 2 (KGF-2) enhanced both the formation of granulation tissue in rabbits and wound closure of the human meshed skin graft explanted on athymic nude rats [53, 54].

Growth factors also have potential in facilitating peripheral nerve healing and several belonging to the neurotrophin family have been implicated in the maintenance and repair of nerves. Nerve growth factor (NGF), synthesized by Schwann cells distal to the site of injury, aids in the survival and development of sensory nerves. This finding has led some investigators to suggest that exogenous NGF application may assist in peripheral nerve regeneration following injury [55]. Newer neurotrophins such as brain-derived neurotrophic factor and neurotrophin-3 as well as ciliary neurotrophic factor appear to support the growth of sensory, sympathetic, and motor neurons in vitro [56]. Insulin-like growth factors have demonstrated similar neurotrophic properties [57]. Although most of the

investigations until now have been experimental, increasing sophistication in the dosing, combinations, and delivery of neurotropic growth factors will lead eventually to greater clinical application.

Osteoinductive growth factors hold special appeal to surgeons conducting bone grafting procedures as they can promote the formation of new bone and avoid harvesting autogenous bone with its associated complications. Of the multiple osteoinductive cytokines, the bone morphogenetic proteins (BMPs) belonging to the TGF-β superfamily have received the greatest attention [58, 59]. These cytokines stimulate chondrocyte and osteoblast proliferation, promote the osteoblastic differentiation of mesenchymal stem cells, and increase production of extracellular matrix. Advances in recombinant DNA techniques now allow the production of these biomolecules in quantities large enough for routine clinical applications. In particular, recombinant human bone morphogenetic protein-2 (rhBMP-2) and rhBMP-7 have been studied extensively for their ability to induce undifferentiated mesenchymal cells to differentiate into osteoblasts (osteoinduction). Other cell signaling proteins tested for their osteogenic and angiogenic modulation of bone healing include fibroblast growth factors (FGFs), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) [60]. FGFs, particularly FGF-2 or bFGF, can stimulate mesenchymal cell, osteoblast, and chondrocyte proliferation and also boost tissue growth due to their angiogenic properties.

Because impaired wound healing represents an environment where so many factors are deficient and dysregulated, it is unlikely that any one "master regulator" would be able to rescue the wound phenotype. This realization has led wound researchers to propose the use of a cocktail of growth factors to optimize and balance the healing process [61]. The intent is to promote the sequential phases of wound healing by delivering various growth factors to the wound site in different concentrations to influence the key cells involved (e.g., macrophages, fibroblasts, endothelial cells, etc.) in each phase. An attendant challenge is the need to apply supraphysiological levels due to the rapid inactivation and clearance of the exogenous growth factors. This greatly increases the costs of treatment as well as the risk for adverse side effects [62]. These issues have motivated the development of biomaterial technologies that allow better control of biomolecule delivery [63]. The growth factors are physically or chemically conjugated with polymeric matrices/gels or liposome carriers that allow their gradual and controlled release [64]. The composite scaffolds retain the biomolecules at the wound site for extended periods and induce the spatiotemporal delivery of multiple growth factors that recruit endogenous stem cells from adjacent tissues and modulate their differentiation.

1.7.2 Gene Therapy

The application of gene therapy to wound healing has been driven by the desire to selectively express a growth factor for controlled periods of time at the site of tissue injury [65]. Unlike the diffuse effects of a bolus of exogenously applied growth factor, gene transfer permits targeted, consistent, local delivery of peptides in high concentrations to the wound environment [66]. Genes encoding for select growth factors are delivered to the site of injury using a variety of viral, chemical, electrical, or mechanical methods. Cellular expression of the proteins encoded by the nucleic acids helps modulate healing by regulating local events such as cell proliferation, cell migration, and the formation of extracellular matrix. The more popular methods for transfecting wounds involve the in vivo use of adenoviral vectors. Existing gene therapy technology is capable of expressing several modulatory proteins at the physiologic or supraphysiologic range for up to 2 weeks.

Numerous experimental studies have demonstrated the efficacy of gene therapy in stimulating bone formation and regeneration. Mesenchymal cells transfected with adenovirus-hBMP-2 cDNA have been shown to be capable of forming bone when injected intramuscularly in the thighs of rodents [67, 68]. Similarly bone marrow cells transfected ex vivo with hBMP-2 cDNA have been shown to heal femoral defects [69]. Using osteoprogenitor cells for the expression of bone-promoting osteogenic factors enables the cells to not only produce bone growth promoting factors but also to respond, differentiate, and participate in the bone formation process. These early studies suggest that advances in gene therapy technology can be used to facilitate healing of bone and other tissues and may lead to better and less invasive reconstructive procedures in the near future.

1.7.3 Dermal and Mucosal Substitutes

Immediate wound coverage is critical for accelerated wound healing. The coverage protects the wound from water loss, drying, and mechanical injury. Although autologous grafts remain the standard for replacing dermal mucosal surfaces, several bioengineered substitutes are finding their way into mainstream surgical practice. Available human skin substitutes are grouped into three major types and serve as excellent alternatives to autografts. The first type consists of grafts of cultured epidermal cells with no dermal components. The second type has only dermal components. The third type consists of a bilayer of both dermal and epidermal elements. An example of bioengineered skin substitutes is Apligraf®, an allogeneic living epidermal and dermal skin derived from cultured neonatal foreskin

(Organogenesis, Canton, Massachusetts) [70]. This bioengineered, full-thickness skin product consists of a living permanent bilayer skin graft with active cellular and growth factor components. It does not elicit an immune response because its Langerhans cells have been extracted. Currently, Apligraf® is FDA approved for covering venous and diabetic foot ulcers. The chief effect of most skin replacements is to promote wound healing by stimulating the recipient host to produce a variety of wound healing cytokines. The use of cultured skin to cover wounds is particularly attractive inasmuch as the living cells already know how to produce growth factors at the right time and in the right amounts. Thus, the ultimate goal of bioengineers is to develop engineered skin that contains all of the components necessary to modulate healing and allow for wound healing with a surrogate that replicates native tissue and limits scar formation.

Conclusion

Wound healing is an intricate, tightly choreographed continuum of overlapping inflammatory, proliferative, and remodeling phases. With distinctive variations, all tissues including skin, bone, and nerve underdo similar pathways to tissue repair or regeneration. Many local and general factors can affect wound healing, and an improved understanding of modifiable risk factors will help the surgeon optimize the healing process and outcomes. A growing assortment of biologics and scaffolds hold promise in restoring innate repair mechanisms when healing is impaired.

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Medical Management and Preoperative Patient Assessment

Steven M. Roser and Gary F. Bouloux

Contents

2.1 Introduction – 21

2.2 Cardiovascular Assessment and Disease – 22
2.2.1 Coronary Artery Disease – 23
2.2.2 Congestive Heart Failure – 23
2.2.3 Valvular Heart Disease – 24
2.2.4 Prosthetic Valve Replacement – 25
2.2.5 Arrhythmias – 25
2.2.6 Hypertension – 26
2.2.7 Automatic Implantable Cardioverter Defibrillators and Pacemakers – 27

2.3 Respiratory Disease – 28
2.3.1 Asthma – 29
2.3.2 Chronic Obstructive Pulmonary Disease – 29
2.3.3 Pneumonia – 30
2.3.4 Pulmonary Embolus – 31
2.3.5 Atelectasis – 31
2.3.6 Pulmonary Edema – 31
2.3.7 Airway – 31

2.4 Renal Disease – 32

2.5 Liver Disease – 33

2.6 Blood Disorders – 34
2.6.1 Anemia – 34
2.6.2 Myeloproliferative Disease – 35
2.6.3 Leukemia – 35
2.6.4 Lymphoma and Multiple Myeloma – 36
2.6.5 Thrombocytopenia – 36
2.6.6 Coagulopathy – 36

M. Miloro et al. (eds.), *Peterson's Principles of Oral and Maxillofacial Surgery*,
https://doi.org/10.1007/978-3-030-91920-7_2

2.6.7 Hemophilia A and B – 37
2.6.8 Warfarin Therapy – 37
2.6.9 Hypercoagulable Diseases – 38

2.7 Endocrinology – 38
2.7.1 Diabetes Mellitus – 38
2.7.2 Thyroid – 40
2.7.3 Adrenal – 41
2.7.4 Pituitary Disease – 41

2.8 Neurologic Disease – 42
2.8.1 Trauma – 42
2.8.2 Seizures – 42
2.8.3 Cerebrovascular Accident – 43
2.8.4 Myasthenia Gravis – 43

2.9 Other Conditions – 43
2.9.1 Malignant Hyperthermia – 43
2.9.2 Autoimmune Disease – 44
2.9.3 Immunodeficiencies – 45
2.9.4 Substance Abuse – 46
2.9.5 Obesity – 47
2.9.6 Geriatric Patients – 47
2.9.7 Pediatric Patients – 48
2.9.8 Pregnancy – 48

References – 50

Learning Aim

Optimizing outcome of all surgical procedures can only be accomplished when the surgeon has a thorough understanding of all concomitant systemic diseases and have a management plan to effectively deal with these conditions. The aim of this chapter is to familiarize the surgeon with the common systemic diseases and their management in the surgical patient.

2.1 Introduction

Patients who undergo oral and maxillofacial surgery are often young and relatively healthy. Medical complications are uncommon in this patient population. However, medical conditions may be present in any patient and may lead to increased morbidity and mortality unless these conditions are sought in those with a history of disease and recognized in those without such a history. A thorough medical and social history will elicit medical comorbidities when known and provide clear guidelines regarding management in most patients. A thorough physical examination will often confirm the presence of systemic disease or identify it in those without a prior history. A thorough knowledge of medical comorbidities before any surgical procedure will allow patients to be stratified according to surgical risk and managed in an optimal fashion. Preoperative patient assessment is best completed by the surgeon who has a vested interest in the patient's well-being. When medical conditions and comorbidities are recognized preoperatively, appropriate workup or referral is easily organized. The involvement of other medical and surgical subspecialties should be readily sought when indicated.

A systematic approach to preoperative patient assessment is required. This requires a didactic approach to a patient interview. This mandates obtaining a chief complaint; history of the chief complaint; other complaints; a medical history with review of all systems, allergies, medications, social history, family history, surgical history; and functional status. The sensitivity of a thorough history to identify a previously unrecognized medical condition should not be underestimated.

The physical examination should also be standardized to include all systems. The examination is, however, often focused based on the chief complaint and a thorough history. In addition to identifying the need for oral and maxillofacial surgery, the primary purpose of the physical examination is to identify pertinent positive and negative findings. The history and physical examination will then enable the surgeon to request additional investigations and medical referrals that allow risk stratification.

Table 2.1 American Society of Anesthesiology physical status classification

Classification	Description
I	Healthy patient
II	Mild systemic disease with no functional limitation
III	Severe systemic disease with functional limitation
IV	Severe systemic disease that is a threat to life
V	Moribund patient
VI	Brain-dead patient awaiting organ transplantation

Adapted from American Society of Anesthesiologists [53]

The ultimate goal of the preoperative evaluation is to identify medical concerns and provide for the most efficacious perioperative treatment algorithm that minimizes patient morbidity. The risk assessment for each patient undergoing surgery requires an understanding of the surgical stress and the patient's medical condition. Head and neck surgery is considered to be intermediate in perioperative risk. Oral and maxillofacial procedures performed in an ambulatory setting would be considered low risk. The patient's medical conditions impart additional risk factors that are best evaluated using a combination of the American Society of Anesthesiologists (ASA) classification (Table 2.1) and an assessment of functional status.

Additional classification systems may be appropriate for risk stratification for specific organ systems depending on the medical disease present. The Duke Activity Status Index is particularly useful to classify patients according to functional status [1] (Table 2.2). Age itself is a poor surrogate risk indicator but serves to further assess patients for surgical risk.

Frailty has also been shown to correlate with postoperative complications, increased length of stay, and discharge to other than home. There are a number of frailty indices. They are commonly based on weight loss, weakness and exhaustion, low physical activity, and slow gait [2]. Similarly, cognitive dysfunction, functional dependence, increased comorbidities, low albumin, and hemoglobin were correlated with an increase in postoperative mortality in a 6-month period following elective surgery [3].

Table 2.2 Duke Activity Status Index

Activity	METs	Functional capacity
Walk around house	1.75	Poor
Walk two blocks on level ground	2.75	Poor
Activities of daily living	2.75	Poor
Light house work (dishwashing)	2.7	Poor
Moderate housework (vacuuming)	3.5	Poor
Yard work	4.5	Moderate
Sexual relations	5.25	Moderate
Climb stairs	5.5	Moderate
Golf	6	Moderate
Swimming, basketball	7.5	Excellent
Running	8.0	Excellent

Adapted from Hlatky et al. [1]
MET metabolic equivalent (1 MET = 3.5 mL/kg/min O_2 use)

2.2 Cardiovascular Assessment and Disease

Cardiovascular disease is a heterogeneous group of diseases that correlate with perioperative risk. It is crucial that the presence of cardiovascular disease be sought in the history and physical examination. Risk factors for cardiovascular disease may also provide insight into a patient's likelihood of cardiac complications. A multitude of cardiac indices have been put forward to help classify patients. The ACC/AHA released guidelines in 2002 stating that there are three satisfactory tools for evaluating perioperative cardiac risk for noncardiac surgery. These include the Revised Cardiac Risk Index (RCRI)*, National Surgical Quality Improvement Program Myocardial Infarction & Cardiac Arrest (NSQIP MICA)*, and the National Surgical Quality Improvement Program Risk Calculator (NSQIP RC)* [4]. The RCRI includes six clinical risk predictors. Patients with a score of 0 have a 0.4% risk of a major adverse cardiac event (MACE), a score of 1 has 0.9% risk of MACE, a score of 2 has a 6.6% risk of MACE, and a score of 3 or more has an 11% risk of MACE [5, 6] (Table 2.3).

The NSQIP MICA model simply uses the type of surgery, ASA classification, functional status, creatinine >1.5 mg/dL, and increasing age. The NSQIP Risk Calculator is an online tool that calculates risk based on the planned surgical procedure (CPT code) as well as 21 patient-specific variables. It has the advantage of calculating the risk of multiple system complications in addition to myocardial infarction and cardiac arrest. The tool is easily accessed at ▶ https://riskcalculator.facs.org/.

Table 2.3 Revised Cardiac Risk Index

Condition	No (0) or yes (1)
Coronary artery disease	
Congestive heart failure	
Cerebrovascular disease	
Insulin-dependent diabetes mellitus	
Renal insufficiency and creatinine >2 mg/dL	
High-risk surgery	

Adapted from: Lee et al. [5]

Noninvasive cardiac testing typically involves a stress test using specific exercise protocol with age-related heart rate requirement and real-time ECG monitoring. The sensitivity of the stress test is low depending in part on how many vessels are stenosed. More sensitive noncardiac testing is typically more appropriate in some patients. The tests include exercise echocardiography, dobutamine stress echocardiography, and dipyridamole thallium stress testing. Any patient identified as high risk through this testing should proceed to coronary angiography before any noncardiac surgery.

Myocardial work is primarily determined by four factors related to myocardial oxygen demand: heart rate, preload, afterload, and contractility. *Heart rate* is influenced by a number of factors including oxygen demand, physical activity, and hormonal and neurogenic mechanisms. *Preload* represents all factors that contribute to passive ventricular wall stress at the end of diastole. It approximates the end-diastolic ventricular pressure. Volume status significantly influences preload. An accurate determination of preload requires a central line to measure central venous pressure or pulmonary capillary wedge pressure. *Afterload* represents all factors that contribute to the ventricular wall stress during systole. The total peripheral resistance has the most influence on afterload, although intrathoracic pressure may also influence afterload as is the case with mechanical ventilation. *Contractility* refers to the ability of the myocardium to contract. The opportunity to influence myocardial work and oxygen demand exists through modulation of any of these four factors.

2.2.1 Coronary Artery Disease

Patients with coronary artery disease (CAD) are often identified during the history and physical examination. When identified preoperatively, CAD should prompt risk stratification following the ACC/AHA algorithm. Patients with acute coronary syndromes should not undergo noncardiac surgery. Tests to consider include:

- Chest radiograph to evaluate for cardiomegaly, pulmonary edema, or pleural effusion.
- ECG to evaluate for left ventricular hypertrophy, ST segment changes, inverted T waves, Q waves, and arrhythmias.
- Transthoracic Doppler echocardiography for wall motion abnormalities, ejection fraction, and chamber pressures.
- Stress test to assess for functional cardiac ischemia. This can be combined with echocardiography.
- Perfusion nuclear imaging to assess cardiac perfusion at rest and with function.
- Cardiac angiography.

Asymptomatic patients with CAD may, however, develop symptoms in the perioperative period. Risk factors for CAD are DM, HTN, smoking, hypercholesterolemia, and a family history. CAD may result in stable angina or one of the acute coronary syndromes (ACSs). Stable angina often presents with precordial pain radiating to the left arm, neck, and jaw upon exertion. It is relieved by rest or the use of sublingual nitroglycerin. ACSs include unstable angina, non-ST-elevated MI, and ST-elevated MI. Symptoms are similar to stable angina but occur with less exertion than is usual, or at rest, and do not abate with further rest. The history surrounding the onset of chest pain has a diagnostic sensitivity of 90% when the symptoms are classic. An ECG may show ST segment depression or inverted T waves indicating ischemia. ST segment elevation indicates frank MI. The treatment of any patient suspected of having ACS begins with the correct diagnosis. The diagnosis can be confirmed with:

- A 12-lead ECG (ST elevation, inverted T waves, Q waves)
- Cardiac enzymes (CK-MB [MB isoenzyme of creatine kinase], troponins)

The initial treatment for suspected ACS or MI has traditionally been morphine, oxygen, nitrates, and aspirin (MONA). Current evidence supports the use of aspirin which has been shown to reduce mortality. Morphine remains the drug of choice for pain but it has not been shown to reduce mortality. Oxygen should be used when oxygen saturation is less than 90% on room air as it has been shown to increase the infarct size [7]. The advent of anti-platelet drugs, fibrinolytics, and percutaneous coronary angioplasty (PCA) has reduced the mortality from MI to 3%.

The use of perioperative beta blockers has been shown to reduce the likelihood of cardiac events including MI. Patients with a recent MI may be at risk for reinfarction following the initial infarct. The ACC recommends waiting a minimum period of 6 weeks after an MI before proceeding with elective surgery [8]. Furthermore, the longer the time period from the MI to the elective surgery, the greater the risk reduction.

Patients who have had PCA and are typically treated with dual anti-platelet therapy (DAPT). This typically involves the use of aspirin and a glycoprotein IIb/IIIa inhibitor (e.g., abciximab or eptifibatide) or an ADP antagonist (e.g., clopidogrel, etc.). It is recommended that in the event that a patient requires noncardiac surgery, the aspirin should be continued. The glycoprotein IIb/IIIa inhibitor or ADP antagonist should be continued for a minimum period of 14 days, 30 days, and 3 months for balloon angioplasty, bare metal stents, and drug eluting stents, respectively [9, 10].

2.2.2 Congestive Heart Failure

CHF is a result of inadequate cardiac output. Compensated CHF is considered an intermediate clinical predictor, whereas decompensated CHF is considered a major clinical predictor within the ACC/AHA algorithm and a contraindication to elective surgery. The New York Heart Association (NYHA) classification may also be used to help stratify surgical patients (Table 2.4).

The risk of surgical patients with CHF decompensating depends on their class, with NYHA class I patients having a 3% risk and class IV patients having a 25% risk [11]. Causes of CHF include MI, valvular heart disease, HTN, anemia, pulmonary embolism (PE),

Table 2.4 New York Heart Association Classification

Class	Symptoms
I	Asymptomatic
II	Symptomatic with moderate activity, comfortable at rest
III	Symptomatic with minimal activity, comfortable at rest
IV	Symptomatic at rest

cardiomyopathy, thyrotoxicosis, and endocarditis. Heart failure can be left-sided, right-sided, or both. Left-sided failure presents with exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cardiomegaly, rales, and a third heart sound (S_3) gallop. Right-sided heart failure results in elevated jugular venous pressure, peripheral edema (especially lower extremities), and atrial fibrillation (AF). The diagnosis is best made with a transthoracic echocardiogram, although the measurement of brain natriuretic peptide (BNP) can be used to help diagnose and monitor CHF progression. Posteroanterior and lateral chest radiography will often reveal cardiomegaly and may show pulmonary edema and plural effusions if decompensated. Treatment is primarily aimed at reducing afterload and increasing the cardiac contractility. Treatment may include:

- Angiotensin-converting enzyme inhibitor (ACEI; e.g., captopril, lisinopril, ramipril)
- Diuretic (e.g., furosemide or hydrochlorothiazide)
- Beta blocker (metoprolol or carvedilol)
- Digoxin

Patients with CHF should have their regular medications maintained in the perioperative setting. Particular attention to fluid and electrolyte balance is crucial. Potassium should be monitored closely because hypokalemia may be present secondary to the use of non–potassium-sparing diuretics or renal hypoperfusion. This may require correction with 10–40 mEq of oral or parenteral potassium. Parenteral replacement should be done carefully with no more than a 10 mEq/h. Digitalis is often used to increase contractility in patients with CHF. Patients taking digitalis are at risk for fluctuating digitalis blood levels secondary to interactions with other drugs. This can lead to digitalis toxicity. In addition, reducing the preload can reduce cardiac output just as much as excessive preload can precipitate decompensation. Fluid replacement must be judicious and is often assisted by a central line so that central venous pressure can be monitored.

2.2.3 Valvular Heart Disease

Valvular heart disease is recognized through a thorough history and physical examination. Although the requirements for antibiotic prophylaxis have changed, the potential for valvular abnormalities to affect cardiovascular parameters must be recognized. As with most systemic diseases, functional status serves as a wonderful barometer with which to evaluate the severity of the valvular abnormality. Perioperative changes in cardiac rate, rhythm, blood pressure, preload, afterload, and contractility secondary to anesthesia and surgery may have profound influences on cardiovascular stability and morbidity.

Aortic stenosis (AS) may be congenital or secondary to rheumatic fever or dystrophic calcification. It may also be a result of obstructive hypertrophic subaortic stenosis. The classic presentation is syncope, angina, and exertional dyspnea. Patients are intolerant to changes in heart rate and peripheral vascular resistance. Auscultation of a high-pitched midsystolic crescendo-decrescendo murmur at the right upper sternal border is consistent with AS. Critical AS is an independent risk factor for perioperative morbidity and mortality [11]. *Critical stenosis* is defined as an aortic valve area of less than 0.75 cm^2 and/or a valvular pressure gradient of 50 mmHg. A transthoracic echocardiogram is required to quantitate disease severity. As a result of the increased ventricular systolic pressures, left ventricular hypertrophy (LVH) develops with increased myocardial oxygen demand and a propensity for ischemia even without preexisting CAD. LVH may be identified on the ECG as well as with auscultation of the cardiac apex where a fourth heart sound (S_4) gallop may be appreciated. Patients with AS cannot tolerate heart rate increases or a reduction in peripheral resistance that further decreases coronary perfusion.

Aortic regurgitation (AR) may be secondary to rheumatic heart disease, bicuspid aortic valve, endocarditis, or aortic root disease. It may present with pulmonary edema, hypotension, and CHF. Auscultation of a diastolic decrescendo murmur, a high-pitched crescendo decrescendo murmur, and diastolic rumble are consistent with AR. The ECG will often reveal LVH, whereas a chest x-ray will reveal left ventricular and aortic root enlargement. Treatment of patients often aims to reduce total peripheral resistance with calcium channel blockers or ACEIs. Beta blockers are best avoided because they increase the regurgitation by prolonging diastole.

Mitral stenosis (MS) is often due to preexisting rheumatic heart disease. It may present with dyspnea, orthopnea, pulmonary edema, AF, and a right ventricular heave. Auscultation of an opening snap and a mid-diastolic low-pitched rumble at the apex are consistent with MS. An ECG may reveal notched or enlarged P waves when atrial enlargement has developed. AF may be the final outcome. As with AS, increases in heart rate are not well tolerated owing to the potential for acute increases in pulmonary pressures and reduced cardiac output. Mitral regurgitation (MR) may be secondary to MS, mitral valve prolapse (MVP), rheumatic heart disease, endocarditis, or MI. It may present with pulmonary edema, hypotension, dyspnea on exertion, and a holosystolic high-pitched murmur at the cardiac apex.

2.2.4 Prosthetic Valve Replacement

Prosthetic valves can be alloplastic or biologic. A biologic valve can be a heterograft or a xenograft. Valve function is best evaluated with an assessment of the functional capacity of the patient and a transthoracic echocardiograph. Mechanical valves always require anticoagulation, whereas biologic valves may not require anticoagulation after 3 months, although this depends on other risk factors. Patients with prosthetic valves are susceptible to endocarditis, valve failure, red cell destruction, and thromboemboli formation. Patients should have their warfarin discontinued before surgery if bleeding is likely to be a problem. The risk for thromboembolism and CVA is high if anticoagulation is discontinued and, accordingly, patients may need to be bridged with low-molecular-weight heparin (LMWH) as an outpatient or unfractionated heparin (UFH) as an inpatient. The adequacy of the warfarin anticoagulation should be measured with the prothrombin time or international normalized ratio (INR). The therapeutic value of the INR is typically between 2.5 and 3.5. Adequacy of anticoagulation with UFH is measured with the partial thromboplastin time (PTT), which should be between 50 and 90 s. When LMWH is used to bridge the patient, the adequacy of anticoagulation is typically not measured, although an assay for Factor Xa can be used to measure anticoagulation for both UFH and LMWH. The half-life of UFH is 1–2 h, which necessitates cessation 6 h before a surgical procedure. LMWH has a longer half-life, which requires cessation the night before the procedure.

Antibiotic prophylaxis is required in patients with prosthetic heart valves or those with a history of endocarditis, unrepaired cyanotic congenital heart disease, or repaired congenital heart disease during the first 6 postoperative months. The antibiotic of choice is amoxicillin 2 g or clindamycin 600 mg (if penicillin allergic) orally 1 h before the procedure. When antibiotics are to be given parenterally, ampicillin 2 g or clindamycin 600 mg (if penicillin allergic) should be administered within 1 h of the procedure start time.

2.2.5 Arrhythmias

Patients with diagnosed or occult arrhythmia present a management challenge to the surgeon and anesthesiologist. Arrhythmias typically compromise cardiac output to some degree. The distinction between supraventricular and ventricular arrhythmias must be made early. The latter requires prompt attention and due concern. Anesthesia and surgery are capable of unmasking occult arrhythmias through stress-mediated physiologic change, proarrhythmic drugs, and hypoxia. The evaluation of patients with arrhythmias includes an ECG. When the arrhythmia is intermittent in nature, the ECG may fail to identify the rhythm. In this situation, it may be prudent to obtain a 24-h continuous monitoring record that can be analyzed to identify the abnormal rhythm.

Common supraventricular arrhythmias include supraventricular tachycardia (SVT) (also known as paroxysmal atrial tachycardia), atrial flutter, and AF. SVT is benign but results in heart rates of 150 beats per minute (bpm) or greater in an adult. The net result may be a reduction in cardiac output and blood pressure. It is typically due to a reentrant conduction abnormality and may precipitate myocardial ischemia. SVT may be initiated by premature atrial contractions (PACs), which are otherwise considered very common. Beta blockers and calcium channel blockers are often used to reduce the frequency of SVT. Recalcitrant SVT may require electrophysiologic ablation of the reentrant pathway [12]. Cardiac stimulants such as alcohol and coffee should be limited. Exogenous and endogenous epinephrine may also precipitate this arrhythmia. When SVT develops in the perioperative setting, it demands treatment. Carotid massage may be used in patients without carotid bruits or stenosis. This results in stimulation of the carotid sinus with an increase in vagal tone. In addition, a Valsalva maneuver can be performed, which also acts through vagal stimulation. Failure to correct the SVT in a timely fashion or the development of angina or unstable vital signs demands more aggressive treatment with intravenous adenosine or electrical cardioversion in a monitored setting in which acute cardiac life support measures can be instigated.

Atrial flutter is characterized by an atrial rate approaching 300 bpm. There is often a rapid ventricular response (RVR) depending on how many of the atrial contractions are conducted through to the atrioventricular (AV) node. This often presents as a 2:1 or 3:1 block and a ventricular rate of 100–150 bpm. Mortality in patients with atrial flutter who undergo surgery is higher. Treatment often requires calcium channel blockers or amiodarone to control the RVR.

Atrial fibrillation (AF) is an exceedingly common arrhythmia. The ventricular rate varies and is irregular giving rise to the term "irregularly irregular" to describe the pulse. Cardiac output is reduced owing to the lack of an atrial "kick," which often produces fatigue in older patients. Atrial enlargement, thyrotoxicosis, CAD, and stimulants such as alcohol, caffeine, cocaine, and nicotine can precipitate AF. AF predisposes the myocardium to mural thrombi and embolic events. Paroxysmal or chronic AF usually requires long-term anticoagulation with warfarin to reduce this risk. The treatment of AF

usually requires chemical cardioversion with digitalis or amiodarone. The latter may also be used to prevent the recurrence of AF [13]. Calcium channel blockers or beta blockers may be used to help manage the RVR. Electrical cardioversion remains an effective treatment modality for acute-onset AF when chemical cardioversion is unsuccessful or vital signs dictate a more urgent restoration of sinus rhythm.

Ventricular arrhythmias are generally more concerning than atrial arrhythmias, given the potential for some to deteriorate into a nonperfusing rhythm. Premature ventricular contractions (PVCs) are common in healthy patients but may also be associated with fever, hypoxia, inhalational anesthetics, Swan-Ganz catheters, electrolyte disturbances, or myocardial ischemia. Isolated PVCs are often not pathologic, but three or more consecutive PVCs are considered ventricular tachycardia. The discovery of excessive PVC activity on a preoperative ECG mandates referral to a cardiologist for workup. The onset of PVCs in the perioperative period is more worrisome and may reflect myocardial ischemia, MI, or electrolyte abnormalities [14, 15].

Ventricular tachycardia may be perfusing or nonperfusing. When nonperfusing, the advanced cardiac life support (ACLS) protocol is adopted. This requires basic life support and early electrical cardioversion. Additional drugs that may be of benefit are amiodarone and magnesium. Elective surgery should be deferred in all patients with ventricular dysrhythmias. Long-term therapy may involve the use of antiarrhythmic drugs, radiofrequency ablation, or implantable cardiac defibrillators.

Heart blocks arise from an abnormality in conduction from the sinoatrial node to the AV node. This slows cardiac conduction leading to PR intervals that are longer than 0.2 s. Heart blocks can be divided into four categories. *First-degree blocks* are associated with a prolonged PR interval, but all atrial impulses are conducted through to the AV node with a corresponding ventricular contraction. First-degree blocks are usually not symptomatic and require no treatment. When the heart rate is excessively slow, they may require atropine. *Second-degree blocks* are divided into Mobitz I and Mobitz II variants. The Mobitz I variant involves a progressive increase in the PR interval over several beats until one atrial impulse fails to be conducted through the AV node, resulting in the lack of a ventricular contraction. This type of heart block is generally asymptomatic and requires no treatment. An excessively slow heart rate may again require atropine. The Mobitz II variant involves a constant but prolonged PR interval with the loss of conduction through the AV node after several beats. This results in the loss of a ventricular contraction at a regular time period, usually every third or fourth beat. *Third-degree heart block* has no conduction through the AV node with atria and ventricles contracting independently. The heart rate is often in the 30s and this produces symptoms due to a reduction in cardiac output and blood pressure. Treatment of a second-degree heart block Mobitz II or third-degree heart block often requires external or internal pacing to maintain a satisfactory heart rate. Long-term management involves implantation of a pacemaker. The occurrence of any heart block in the perioperative period requires further investigation to determine causes, particularly electrolyte abnormalities, drug toxicity, and myocardial ischemia. The development of second-degree Mobitz II and third-degree heart block will most often require perioperative pacing [16].

2.2.6 Hypertension

HTN is one of the most common diseases, and a large number of surgical patients will have HTN. HTN is defined as a systolic blood pressure in excess of 140 mmHg or a diastolic blood pressure in excess of 90 mmHg measured on two separate occasions (Table 2.5). It is one of the most common reasons for postponing elective surgery. Most HTN is of unknown etiology and is referred to as "essential hypertension." Secondary HTN is a result of known pathology including renal disease, Cushing's syndrome, Conn's syndrome, pheochromocytoma, hyperthyroidism, aortic regurgitation, and medication induced. Blood pressure can be classified based on the systolic and the diastolic blood pressures.

Hypertensive urgency requires referral to a primary care physician or internist as soon as possible and preferably within 24 h to avoid the potential for hypertensive emergency and end-organ damage including CVA, acute renal failure, and myocardial ischemia. *Hypertensive emergency* is defined by any elevated blood pressure

Table 2.5 Hypertension

Class	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Pre-HTN	120–139	80–89
Stage I HTN	140–159	90–99
Stage II HTN	160–179	100–109
Hypertensive urgency	>180	>110

Adapted from Chobanian et al. [54]
HTN hypertension

associated with end-organ damage including encephalopathy, heart failure, pulmonary edema, and renal failure. Hypertensive emergency requires immediate transport to an emergency room for blood pressure control. Elective surgery should be postponed for hypertensive urgency and emergency [17].

Major risk factors for HTN include smoking, hyperlipidemia, DM, age older than 60 years, gender, and family history. If untreated, it commonly causes CAD, cardiomegaly, left ventricular dysfunction, CHF, renal disease, retinopathy, and CVA.

The diagnosis of HTN should not be made for the first time in the postoperative setting because many perioperative factors, including pain, may elevate blood pressure in an otherwise nonhypertensive patient. All patients with a history of HTN should be maintained on their usual blood pressure medication in the perioperative period. However, several antihypertensive medications reduce the patient's ability to compensate for anesthesia-induced hypotension. It may be necessary in some patients to reduce the antihypertensive medication dose on the morning of surgery. Beta blockers, calcium channel blockers, and clonidine should be continued in the perioperative period. Diuretics, ACEIs, and angiotensin-receptor blockers may be held the morning of surgery if anesthesia-induced hypotension is likely to be a problem. The choice of anesthetic agents for a general anesthesia may also be modified if there are concerns for blood pressure lability. Most of the inhalational anesthetics will reduce blood pressure to some degree. The intravenous agents such as propofol may also produce a similar blood pressure reduction. Induction with etomidate should be considered if there is a need to maintain blood pressure.

The signs and symptoms of HTN are subtle unless hypertensive emergency develops. An S_4 gallop is often present owing to the LVH that may also be evident on the ECG. The treatment of hypertensive emergency may include nonselective beta blockers such as labetalol which is an alpha 1, beta 1, and beta 2 receptor antagonist. It will reduce both the heart rate and peripheral resistance to decrease blood pressure. Esmolol is a selective beta 1 blocker that can also be used, but this requires a continuous intravenous infusion because the half-life of the drug is less than 5 min. ACEIs can also be used to reduce peripheral resistance, although only enalaprilat is available for intravenous administration. Hydralazine is a selective alpha 1 antagonist that can reduce peripheral resistance and lower blood pressure very quickly, but caution should be exercised in the elderly because it produces a reflex tachycardia that can exacerbate myocardial ischemia.

The most recent guidelines from the Joint National Committee (JNC8) recommend initiating treatment for those greater than 60 years when systolic blood pressure (SBP) >150 mmHg or diastolic blood pressure (DBP) >90 mmHg. Individuals under age 60 and those with chronic kidney disease or diabetes mellitus should begin antihypertensive medication when SBP >140 mmHg or DBP >90 mmHg [18]. The treatment of patients with stage I and stage II HTN includes numerous classes of medications. Medication is often added over time and titrated to effect. Many patients will require multiple medications to control blood pressure. Weight loss, exercise, and reduced dietary sodium consumption are also important to help manage blood pressure. Patients who develop HTN in the perioperative setting or those with a history of controlled HTN who are difficult to maintain in a normotensive range may benefit from treatment. Unless significantly elevated, it is generally not ideal to diagnose HTN in the immediate perioperative setting because many physical and emotional factors may influence the blood pressure. Inadequate pain control is often responsible for an elevated blood pressure and is best addressed by increasing analgesia. Simply asking patients to rate their pain on a visual analogue scale will often identify whether pain is a significant issue and a likely etiology of the HTN. When treatment is thought to be necessary, a stepwise approach is required and, although most patients will have essential HTN, consideration of secondary causes is warranted. A diuretic such as hydrochlorothiazide is an excellent first-choice medication. It results in potassium wasting and elevated serum calcium so electrolytes should be monitored in the long term. A selective beta 1 blocker such as metoprolol is also a good initial or subsequent choice. This is particularly useful in patients with a history of MI. An ACEI such as captopril is a reasonable third choice. Once an appropriate dose is found, it can be changed to another longer-acting ACEI such as lisinopril or ramipril, which require only once-a-day dosing. ACEIs are ideal for patients with DM owing to the renal protection that these drugs provide. Angiotensin-receptor blockers and calcium channel blockers are additional choices for medications.

2.2.7 Automatic Implantable Cardioverter Defibrillators and Pacemakers

A growing number of patients who present for surgery will have an automatic implantable cardioverter-defibrillator (AICD) or cardiac pacemaker. These devices are able to monitor cardiac rhythm, pace, and

defibrillate. Some devices have the ability to sense oxygen saturation, right ventricular pressures, temperature, and body movement. Patients with an AICD or pacemaker who require surgery will have a cardiac history that should be determined. An ECG will indicate whether the AICD or pacemaker is pacing the myocardium as evident by the pacing spike and subsequent QRS complex. The decision to reset the AICD or pacemaker immediately before the surgical procedure should be made only in consultation with the cardiologist and anesthesiologist. This requires a magnetic key and knowledge of exactly which device (brand and model number) has been implanted. Defibrillators should be turned off to prevent accidental discharge or damage to the device. The AICD can have the defibrillator turned off and the pacer left on for surgery. Monopolar electrocautery should be avoided in all patients with an AICD or pacemaker. The current generated can damage an AICD or pacemaker even when turned off and it will be sensed by the device if the device is left on, which could result in inappropriate activity. Bipolar electrocautery can also affect the AICD, although this is less likely. If electrocautery was used during surgery, the device should be assessed immediately upon completion of the procedure to ensure that the device is functioning normally. All patients with an AICD should have an external means of pacing and defibrillating available throughout the surgery in case a cardiac dysrhythmia develops.

2.3 Respiratory Disease

All patients require a thorough history and physical examination to identify respiratory disease. Furthermore, the very nature of oral and maxillofacial surgery dictates that the potential for upper airway obstruction is a potential concern with many procedures. The functional status of the patient, as with most systemic diseases, provides significant insight into the disease severity and the potential for perioperative complications. Much can also be learned by simply watching the patient in terms of the respiratory rate and work of breathing. Smoking tobacco should always be considered in all patients. Postoperative respiratory complications are more common in those who smoke [19]. The risk declines by 50% after only 8 weeks of smoking cessation, although patients who stop smoking for less than 8 weeks before surgery have a higher risk for complications than those who continue to smoke [20]. Cigarette smoke also results in elevated levels of carboxyhemoglobin (CoHb), which predisposes the patient to perioperative hypoxia. Pulse oximetry cannot detect CoHb and the displayed saturation level will, therefore, be incorrectly elevated. An arterial blood gas (ABG) is required to measure the CoHb. CoHb and nicotine both increase the potential for cardiac complications including ventricular fibrillation [21]. This additional risk can be eliminated with smoking cessation for 24 h.

The need for additional preoperative pulmonary testing is dictated by the history, physical examination, functional status, smoking history, and age. The most common screening tool continues to be the history. The chest x-ray, although the yield is relatively low unless diffuse parenchymal disease, pulmonary edema, pneumonia, or advanced chronic obstructive pulmonary disease (COPD) is present, should be considered as a baseline in patients with known pulmonary disease. Pulmonary peak flow can be easily measured with an office peak flowmeter. This can help quantitate obstructive airway disease and identify those patients who are having an exacerbation of preexisting disease or whose disease is progressing. Pulmonary function testing (PFT) is the gold standard in evaluating pulmonary function. PFT measures lung volumes and lung dynamics including flow rates throughout the respiratory cycle. The forced expiratory volume in 1 s (FEV_1) and its relationship to the forced vital capacity (FVC) are particularly useful to quantitate disease severity and stratify patients. The measurement of the ABG is typically done in conjunction with the PFTs. The effects of a bronchodilator on pulmonary function are routinely measured as part of the PFT protocol. Knowing the improvement in lung function, if any, after the administration of the bronchodilator can better prepare the surgical/anesthesia team to handle a respiratory emergency. The measurement of the partial pressures of oxygen and carbon dioxide, pH, and base excess allows the net effect of pulmonary disease on oxygenation to be seen. For a patient with known respiratory disease, previous PFTS, a history, examination, office PEFR measure, and chest x-ray are all that is needed for a preoperative assessment.

Respiratory disease is a common diagnosis among surgical patients. The net result of most respiratory diseases is hypoxemia that, in broad terms, may develop from one of four mechanisms: hypoventilation, diffusion impairment, ventilation-perfusion mismatching, and shunting. *Hypoventilation* as defined by a decrease in respiratory rate or vital capacity that can be due to asthma, chronic COPD, obstructive sleep apnea, pneumonia, chest trauma, narcotics, neurologic disease, and idiopathic pulmonary fibrosis. *Diffusion impairment* may be due to idiopathic pulmonary fibrosis or acute respiratory distress syndrome. *Ventilation-perfusion mismatching* can be the result of many processes including PE, whereas *shunting* is often seen with pulmonary edema, pneumonia, atelectasis, cardiac septal defects, and chronic liver disease.

The perioperative management of a patient in respiratory distress with hypoxemia and increased work of breathing requires intervention. The management of these patients entails a general initial approach while the cause for the hypoxemia is sought. Treatment involves the administration of oxygen using one of several methods, all of which increase the fractional concentration of inspired oxygen (FiO_2). The effect of varying the method of oxygen delivery on the FiO_2 should not be underestimated.

- Nasal cannula (1 L/min increases the FiO_2 by 4% to a maximum of 40% at 6 L/min)
- Rebreathing facemask (increases the FiO_2 to 60% at 10 L/min)
- Non-rebreathing facemask (increases the FiO_2 to 90% at 10 L/min)
- CPAP/BiPAP (continuous positive airway pressure/bilevel positive airway pressure) with positive pressure (increases the FiO_2 to 80%)
- Intubate/tracheostomy (increases the FiO_2 to 100%)

Several diseases should be considered in any patient with signs or symptoms of disordered respiration. The diagnosis, and ultimately the treatment, depends on a good history, physical examination, and appropriate studies.

2.3.1 Asthma

Asthma is classically defined by bronchial hyperresponsiveness and reversible bronchoconstriction due to smooth muscle contraction leading to reduced minute ventilation and hypoxemia. Signs and symptoms of asthma include episodic dyspnea, shortness of breath, nocturnal awakenings, limitation in activity, wheezing that is predominantly expiratory, cough, chest tightness, chest pain, and status asthmaticus. The likelihood of an asthma exacerbation in the perioperative period is dependent on many factors including the occurrence of pain, stress, aspiration during induction, and the presence of an unrecognized preoperative upper respiratory tract infection. The frequency, severity, duration, and response to therapy of recent asthma attacks are useful predictors. Furthermore, a history of emergency room visits and the need for intubation should be reasons for concern. Requirements for multiple asthma medications including inhaled steroids should also raise suspicion of severe disease. Patients with significant asthma as evident by these indicators are probably ASA class III patients and are probably not good candidates for office-based sedation or general anesthesia. Whereas well-controlled asthma poses minimal risk to patients, an exacerbation can occur in any asthmatic. Bronchospasm that heralds an asthma attack can occur rapidly and be difficult to manage even with positive-pressure ventilation and intubation. This is in part due to the combined effect of smooth muscle contraction, edema, and mucus plugging.

The diagnosis of asthma can be made with an appropriate history of asthma-like symptoms and PFT that indicates a reduction in FEV_1, normal vital capacity, reduced FEV_1/FVC (proportional to severity), and an increase in FEV_1 by 10% with bronchodilator treatment. Peak expiratory flow rate is best used to monitor asthma over time and identify potential exacerbations. A decline in the peak flow rate to less than 80% of baseline would suggest exacerbation, and elective surgery should be postponed until the patient can be stabilized and optimized.

The goal of asthma management is to maintain all preoperative medications. The choice of medication is usually determined by classifying asthma as intermittent, mild persistent, moderate persistent, or severe persistent. The frequency and severity of symptoms, FEV_1, and peak flow are all used to categorize patients into one of these groups. The choice of medication is individualized but often progresses through an algorithm that includes:

- Short-acting beta agonist (SABA) such as albuterol
- Inhaled corticosteroids such as fluticasone
- Anticholinergic medications such as ipratropium or tiotropium
- Long-acting beta agonists (LABAs) such as salmeterol or formoterol
  - Combination inhalers that include LABA and inhaled steroids

Other useful agents include:

- Leukotriene receptor antagonists such as montelukast and zafirlukast
- Cromolyn
- Theophylline

Perioperative exacerbations may occur despite adequate control with medication. The treatment of exacerbations often requires that a SABA be administered by metered-dose inhaler (MDI) or nebulizer every 2 h as needed. Continuous nebulized treatment may be beneficial in children. Anticholinergic medication can also be administered by MDI or nebulizer every 6 h as needed. A short course of oral or parenteral corticosteroid over a week may also be needed [22].

2.3.2 Chronic Obstructive Pulmonary Disease

Emphysema and chronic bronchitis are the two major respiratory diseases within COPD. Emphysema is characterized by dilated and collapsed small airways with alveolar destruction secondary to smoking or alpha 1

antitrypsin deficiency, a congenital deficiency. Chronic bronchitis is characterized by increased airway secretions and mucus production, often secondary to smoking. A patient with emphysema is often described as a "pink puffer," whereas a patient with chronic bronchitis is often described as a "blue bloater." The net result of both diseases is retention of carbon dioxide and eventually hypoxemia.

The symptoms and signs of COPD include chronic cough, sputum production, shortness of breath, decreased functional status, wheezing, and a barrel-shaped chest. As disease advances, patients may begin to expire with pursed lips, which increases intrathoracic pressure to help stent their airways open. The diagnosis of COPD can be made with an appropriate history supplemented with additional tests. PFTs reveal a reduction in FEV_1, no change in vital capacity, and a reduction in the FEV_1/FVC. ABGs are particularly helpful and reveal an increase in the partial pressure of carbon dioxide, a decrease in the partial pressure of oxygen, and respiratory acidosis. The chest x-ray reveals a loss of lung markings, hyperinflation, and a flattened diaphragm.

COPD should be optimized before surgery. Smoking cessation should have occurred concurrently with the initial diagnosis of COPD, but if patients continue to smoke, complications will be higher. Smoking cessation should occur longer than 8 weeks before the planned surgical procedure. Elective surgery in the face of a COPD exacerbation or a URI is contraindicated. The patient may require a course of inhaled steroids or systemic steroids as part of the optimization program [23].

The perioperative management of patients with COPD aims to maintain the preoperative medication regime that is typically determined by classifying COPD as mild, moderate, severe, and very severe. All patients should be well hydrated and use humidified oxygen when needed to reduce the inspissation of secretions. Patients with mucopurulent sputum are best treated with a course of antibiotics such as azithromycin, trimethoprim/sulfamethoxazole, or amoxicillin [24]. This is best completed before the planned surgery. In addition the patient should be instructed on how to perform postoperative lung expansion maneuvers. If the patient has been on long-term systemic corticosteroid therapy, pre-op stress dosing is indicated and either puffs of the inhaler or a nebulized SABA treatment should be delivered in the preoperative holding area.

Complications in patients with COPD undergoing surgery can be perioperative or frequently postoperative. The perioperative concerns are typically anesthesia related. Nitrous oxide is best avoided due to its blood/gas coefficient and the potential to accumulate within the multiple bullae associated with COPD, which can rupture. Ventilator plateau pressures should be kept to a moderate level to further reduce this risk. Peak flow pressures will typically be increased to allow for a short inspiratory and prolonged expiratory time. The latter is crucial to reduce the likelihood of auto-PEEP (auto-positive end-expiratory pressure). Despite maintaining normal preoperative medications, patients with COPD may experience postoperative exacerbations that require further treatment. This usually includes the administration of the following:

- Oxygen delivery with nasal cannula or facemask.
- SABA such as an albuterol MDI or nebulizer as needed.
- Anticholinergic medication such as an ipratropium MDI or nebulizer as needed.
- Corticosteroid burst given orally or intravenously over 5 days (prednisolone 1 mg/kg/day).
- The need to intubate patients who are doing poorly should be considered early.

The potential concern of administering oxygen to COPD patients who rely on a hypoxic respiratory drive is more theoretical than real. Any patient with COPD who is hypoxemic as a result of the disease should be treated aggressively with oxygen.

2.3.3 Pneumonia

Nosocomial pneumonia may occur in the postoperative period. It may be associated with the use of mechanical ventilation, at which time it is referred to as "ventilator-associated pneumonia." The development of pneumonia may be influenced by the use of perioperative antibiotics, the placement of nasogastric feeding tubes, and the propensity for aspiration. The most common causative organisms associated with nosocomial pneumonia are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* species, and occasionally, anaerobic organisms. The net result is hypoxemia and sepsis. Signs and symptoms include dyspnea, shortness of breath, fever, chest pain, decreased breath sounds, and fremitus. The diagnosis should be considered in any patient on a ventilator who develops fever and the need for increased ventilatory support including inspired oxygen pressure and PEEP. The peak pressures are often also elevated secondary to reduced lung compliance. Additional findings are a chest x-ray or computed tomography (CT) scan indicating infiltration or consolidation of lung parenchyma and parapneumonic pleural effusion, a bronchoalveolar lavage with cultured organisms, positive blood culture, and an increased white blood cell count. The treatment of pneumonia includes the use of parenteral antibiotics, which may involve either monotherapy or combination therapy depending on the organisms identified. The need to convert patients from an endotracheal tube to a

tracheotomy and the timing of this continue to be controversial [25].

2.3.4 Pulmonary Embolus

More than 95% of PEs are from the deep veins of the legs. These travel to the lungs, leading to respiratory and cardiovascular compromise. Most emboli are clinically silent owing to their small size. Risk factors include smoking, contraceptives, pregnancy, advance age, malignancy, abdominal and orthopedic surgery, and hereditary coagulation disorders such as antithrombin III deficiency, Factor V Leiden, and protein C and S deficiency. Prevention with sequential calf compressors, thromboembolic deterrent stockings, and perioperative UFH or LMWH is important. All patients who undergo surgery should be considered at risk for PE. In addition to the risk factors listed previously, general anesthesia and surgery produce a prothrombotic state that is compounded by bed rest. Early ambulation and appropriate preventive measures afford the best opportunity to reduce the risk of PE.

Signs and symptoms include chest pain, shortness of breath, dyspnea, sinus tachycardia, hemoptysis, a swollen and painful leg, and pain on dorsiflexion of the foot (Homan's sign). The workup of possible PE may involve several investigations. An initial ABG with a large alveolar-arterial (A-a) gradient would be suspicious for PE. A CT scan of the chest with contrast (PE protocol) can identify subsegmental pulmonary arteries and emboli within them. This has largely replaced the ventilation-perfusion scanning. A duplex ultrasound of the leg veins should also be obtained. The sensitivity of this scan is highest for deep venous thrombosis (DVT) between the knee and the groin. The D-dimer assay is a relatively simple blood test that measures the level of fibrin degradation products. A positive D-dimer may be due to a multitude of conditions, whereas a negative D-dimer virtually excludes DVT/PE, reflecting the high negative predictive value. An ECG most often reveals a nonspecific sinus tachycardia, although the classic pattern of an S wave in lead I and a Q wave and inverted T wave in lead III may be seen, reflecting right ventricular strain. Pulmonary angiography remains the gold standard but is infrequently used because it is invasive.

The treatment of PE may include an initial heparin bolus followed by a heparin drip. Alternatively, enoxaparin or fondaparinux can be administered subcutaneously. Long-term anticoagulation should also be simultaneously initiated with warfarin with a goal INR of 2.5–3. Massive PE leading to right ventricular strain may require chemical thrombolysis or surgical thrombectomy. Patients unable to be anticoagulated and patients with recurrent PE despite anticoagulation are candidates for inferior vena cava filters to prevent the development of PEs. The filters may be permanent or temporary and are themselves at risk for obstruction.

2.3.5 Atelectasis

Atelectasis is a common postoperative outcome characterized by the segmental collapse of lung alveoli. It leads to a progressive decline in lung compliance, impaired segmental ventilation, retained secretions, and a decrease in functional residual capacity. The signs and symptoms of atelectasis include decreased breath sounds, inspiratory crackles at the bases, increased work of breathing, and a low-grade fever. The diagnosis is based on the clinical picture and temporal relationship to the immediate postoperative period supported when indicated by chest x-ray. Treatment includes incentive spirometry and early ambulation.

2.3.6 Pulmonary Edema

Pulmonary edema can develop from cardiac and noncardiac causes. In the setting of normal cardiac function, it may be the result of fluid overload or it can follow extubation as a result of upper airway obstruction leading to negative-pressure pulmonary edema (NPPE). The latter is more common in young males. The net result is significant alveolar transudation and hypoxemia. Risk factors include obesity, obstructive sleep apnea, and maxillofacial surgical procedures. Signs and symptoms include increased work of breathing, dyspnea, shortness of breath, decreased breath sounds, and bilateral crackles. The diagnosis is based on the clinical suspicion, the development in the immediate postoperative period, and chest x-ray with diffuse infiltrates.

Treatment usually requires supplemental oxygen, support of the airway, and possible re-intubation and a short period of mechanical ventilation with PEEP. Diuretics may be used to facilitate fluid removal in more severe cases.

2.3.7 Airway

A preoperative assessment of the airway is mandatory, and the oral and maxillofacial surgeon is in a unique position to provide this evaluation. Complications related to establishing an airway and maintaining ventilation continue to be a source of significant patient morbidity and mortality. The oral and maxillofacial surgeon must carefully assess the potential for airway difficulty

and must be in a position to appropriately prevent it when possible and manage it when it develops during sedation or general anesthesia.

A thorough evaluation of the patient's airway begins with the patient's history. A history of prior sedation or general anesthesia that presented with a difficult airway or complication should be sought. This may require obtaining anesthesia records to verify the nature of the difficulty and the management rendered. The physical examination should address several airway-related issues. The patient's weight and body mass index should be obtained. Obese individuals present potentially difficult airways and, due to their weight, have a reduced functional residual capacity, making early oxygen desaturation likely. Pregnancy will produce an identical picture. A decrease in cervical range of motion, a decrease in the maximum incisal opening, or the presence of a retrognathic mandible all portend to a potentially difficult airway. Additional patients that may present with a difficult airway include those with congenital conditions such as Pierre Robin, Treacher Collins, Goldenhar, Klippel-Feil, and Down syndromes; those with oropharyngeal infections and oropharyngeal tumors; radiotherapy patients; and patients with temporomandibular joint ankylosis. In all patients, the oral cavity and oropharynx should be examined and classified using the Mallampati scheme [26] (Table 2.6).

The difficulty of direct laryngoscopy and intubation correlates with advancing Mallampati class. In all patients undergoing sedation or general anesthesia, the Mallampati classification should be determined and used to predict the likelihood of a difficult airway. Supplemental measures to obtain and secure an airway should always be immediately available. For office-based procedures, the ability to support the airway with jaw lift, oral airway, nasal airway, and positive-pressure bag-valve-mask ventilation is mandatory. There will always be a small percentage of difficult airway patients who cannot be ventilated with these techniques. One or more additional techniques are needed. The surgeon should be proficient in the insertion of a laryngeal mask or endotracheal tube and the performance of a cricothyroidotomy. Patients who present with potentially difficult airways might be better candidates for hospital-based procedures. This has the advantage of a more controlled environment where the possibility of using indirect laryngoscopes, fiberoptic intubation, or emergent tracheostomy can be readily performed [27, 28]. Furthermore, additional well-trained personnel are typically available and able to assist in an emergency. Ultimately, it is the responsibility of the surgeon and anesthesiologist to provide a secure airway and one or more backup plans should the unexpected difficult airway be encountered.

Table 2.6 Mallampati classification

Class	Anatomy
I	Visualized entire tonsillar pillars, uvula, soft palate, hard palate
II	Visualized upper tonsillar pillars, base of uvula, soft palate, hard palate
III	Visualized base of uvula, soft palate, hard palate
IV	Visualized hard palate

2.4 Renal Disease

Renal disease and renal failure correlate directly with surgical morbidity and mortality [29]. HTN, DM, polycystic kidney disease, pyelonephritis, and autoimmune kidney disease can all result in diminished renal function. The normal glomerular filtration rate (GFR) is approximately 120 mL/min. Generally, the GFR needs to decrease to about 30 mL/min before a rise in serum creatinine or urea is seen. This represents a 75% loss in renal function before a significant increase in serum creatinine occurs. As renal disease progresses, the normal urine production declines from 0.5 to 1 mL/kg/h until the patient eventually becomes oliguric or anuric. As the renal function decline continues, the patient will develop anemia, hypoalbuminemia, and electrolyte abnormalities of sodium, potassium, calcium, magnesium, and phosphorus. Furthermore, the ability to regulate acid-base homeostasis is impaired because the kidney can no longer effectively excrete hydrogen ions or conserve bicarbonate. The effective removal of metabolic waste products and urea is also impaired, resulting in azotemia and uremia, respectively. Renal disease also results in extrarenal disease including bone marrow suppression, thrombasthenia, pericardial effusion, and immunosuppression. The basic assessment of the patient with renal disease should include urine output, serum creatinine, serum electrolytes, bicarbonate, and hematocrit.

Urine output depends on the level of hydration and patient age. Typically, urine output approximates 1 mL/kg/h in a young adult. Serum creatinine and urea provide indirect evidence of renal function by correlating only roughly with the GFR owing to active renal secretion of the former and active renal resorption of the latter. The GFR can be calculated by the Cockcroft-Gault formula, which requires the patient's age, sex, weight, and serum creatinine. More accurate methods to calculate GFR are available but these require a 24-h urine collection and the administration of a compound like inulin

that is filtered but neither secreted nor reabsorbed. Urinalysis with microscopy is only useful in the initial diagnosis of renal disease when the presence of protein, red blood cells (RBCs), white blood cells, casts, and crystals can be identified. Urinalysis can be used to monitor renal disease progression in certain diseases such as DM.

Perioperative renal impairment can occur in a patient with preexisting renal disease or in otherwise healthy patients. Abnormalities in renal function should be classified as prerenal, renal, or postrenal. Prerenal causes of renal failure include hypovolemia, shock, hypotension, and heart failure. Renal causes of renal failure include glomerulonephritis (GN), acute tubular necrosis (ATN), interstitial nephritis (IN), and pyelonephritis. GN may be secondary to autoimmune disease, DM, human immunodeficiency virus (HIV), and amyloidosis. ATN may be secondary to renal ischemia, hypotension, rhabdomyolysis, drugs, and intravenous contrast media. IN is most often drug related. GN is readily identified by RBC casts in the urine, ATN by muddy brown casts, and IN by eosinophiluria. Postrenal causes of renal failure are usually obstructive in nature secondary to prostate hypertrophy, malignancy, and renal stones.

The initial diagnosis of acute renal failure may be made when urine output begins to decline, serum creatinine increases, and serum electrolyte abnormalities develop. The assessment for a patient with new-onset renal failure should include serum creatinine and urea, serum electrolytes, urinalysis with microscopy, and the fractional excretion of sodium (FENa). The latter helps to distinguish prerenal, renal, and postrenal causes of renal failure. Urine osmolality, urine sodium, and the blood urea nitrogen (BUN)-to-creatinine ratio can also be used to help distinguish among the three broad causes of renal failure. The FENa is calculated as follows:

$$\text{FENa} = \frac{[\text{Urine Na}]/[\text{Plasma Na}]}{[\text{Urine Cr}]/[\text{Plasma Cr}]}$$

A FENa less than 1% is consistent with prerenal causes, a FENa above 2% is consistent with renal causes, and a FENa above 4% is consistent with postrenal causes.

Perioperative management of the patient with renal disease should focus on volume status because patients may become fluid overloaded quickly. The use of intravenous fluid replacement should be done conservatively and without the addition of potassium. Clinically significant anemia should be managed acutely with packed cells, although the potential for significant fluid shifts exists. Chronic management usually mandates erythropoietin subcutaneously or intravenously. Long-term iron supplementation is also appropriate. Electrolyte abnormalities especially hyperkalemia can develop quickly and can result in severe cardiac arrhythmias. Hyperkalemia above 5.5 mEq/L mandates an ECG. A wide QRS complex, loss of P waves, and peaked T waves require urgent treatment with calcium gluconate to stabilize the cardiac membrane, kayexalate to bind gastrointestinal potassium, and dextrose/insulin to drive the intracellular movement of potassium. Dialysis may be needed when the hyperkalemia is excessively high or ventricular cardiac arrhythmias develop.

Many medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and some antibiotics require discontinuation if they are nephrotoxic. Many other medications need to be renally dosed if they are renally excreted. This typically means a reduced frequency of drug administration rather than a reduced dose and early consultation with a pharmacist or nephrologist is indicated.

Patients with end-stage renal disease require dialysis, which is typically performed three times a week as an outpatient. Patients with acute renal failure or those with end-stage renal disease who are inpatients may also be managed with continuous renal dialysis, which is typical with patients in the intensive care unit. Less frequently, patients with renal disease receive peritoneal dialysis. Surgery should be performed the day after dialysis so that electrolytes are optimized and fluid shifts minimized. All medications should be renally dosed and the diet modified to ensure that it is consistent with the needs of the patient. This typically means a low-salt and low-protein diet.

2.5 Liver Disease

Liver disease can have a significant impact in the perioperative period. A careful history will often reveal patients who are at risk for liver disease including those with alcoholism, substance abuse, prior transfusions, hepatitis, tattoos, and sexual promiscuity. Signs and symptoms may be conspicuous by their absence, although fatigue, pruritus, jaundice, palmar erythema, spider telangiectasia, splenomegaly, gynecomastia, testicular atrophy, and increased abdominal girth are all suggestive. Screening for liver disease in an otherwise healthy patient is of little benefit. The end stage of liver disease is cirrhosis, which results in portal hypertension with esophageal varices and hemorrhoids with the inherent potential for severe gastroesophageal bleeding. Perioperative morbidity and mortality are significantly higher in this patient population. Surgery is generally contraindicated in patients with acute or fulminant hepatitis, alcoholic hepatitis, or severe chronic hepatitis. Furthermore, the 30-day mortality rate for nonmajor head and neck surgery increases substantially with advancing liver disease

with a tenfold increased risk for death with advanced lover disease.

The liver is an important organ for the metabolism of many drugs, and liver disease can adversely affect drug metabolism. Liver disease also influences mechanical ventilation owing to the respiratory compromise it produces through hepatopulmonary syndrome, pleural effusions, and pulmonary HTN. Liver disease also predisposes patients to excessive bleeding owing to the impaired synthesis of the vitamin K-dependent Factors II, VII, IX, and X.

Patients with cirrhosis have typically been risk stratified according to the Child's classification, but the model for end-stage liver disease (MELD) system may be superior [30]. There is growing evidence that MELD can be used to predict risk in head and neck surgery. The MELD score is determined from an equation that includes the serum creatinine, serum bilirubin, and INR. Several modifications to this system have been suggested with the goal of more accurately predicting survival in patients with end-stage liver disease. An online calculator for determining a patient's MELD score can be found on the United Network for Organ Sharing website (► www.unos.org/resources/meldpeldcalculator.asp). Patients with a MELD score less than 10 can undergo elective surgery, those with a MELD score of 10–15 may undergo elective surgery with caution, and those with a MELD score greater than 15 should not undergo elective surgery.

Liver function can also be easily assessed using simple blood tests including:

- Liver enzymes alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltranspeptidase.
- Bilirubin.
- Prothrombin time, INR, PTT.
- Serologic markers for hepatitis (A, B, or C) are of limited value unless in the setting of acute hepatitis or when establishing exposure or carrier status.

Recently the aspartate amino transferase to platelet ratio (APRI) has been found to be relatively sensitive and specific in identifying hepatic fibrosis [31]. A ratio >0.7 suggests the presence of liver disease.

The perioperative goals of the patient with liver disease are multiple and depend to some degree on what the surgical procedure is and whether it is being performed under local anesthesia, sedation, or a general anesthesia. The elevated prothrombin time and INR can be corrected with vitamin K if time allows, although it may take 12 h for the vitamin K-dependent factors to be synthesized in sufficient quantities to significantly decrease the INR. Alternatively, fresh frozen plasma (FFP) or activated Factor VII can be administered with an immediate improvement in the INR. Desmopressin (DDAVP) can also be administered to increase von Willebrand's factor (vWF), which is normally produced in endothelium, megakaryocytes, and the liver. This results in increased platelet function through enhanced platelet binding. Ascites should be managed with diuretics, beta blockers, and the removal of excessive peritoneal fluid. Intravenous fluid should be limited, as should total sodium intake. Electrolyte abnormalities such as hypokalemia must also be addressed with cautious supplementation. When present, elevated plasma ammonia levels should be managed with lactulose and dietary modification. Antibiotic prophylaxis to reduce the risk of peritoneal infection secondary to bacterial translocation should be considered. Fluid balance can remain a challenge, and careful management of blood volume, cardiac output, and urine production is required. The potential for severe and life-threatening gastroesophageal bleeding exists in all patients with liver disease, and consideration to reducing this risk with histamine (H_2) antagonists is warranted.

2.6 Blood Disorders

2.6.1 Anemia

Patients may present with a history of anemia or it may be suspected based on nonspecific symptoms of fatigue and tiredness. Occasionally, patients may report blood loss in the stool or emesis or from menorrhagia. Anemia is an absolute or relative reduction in the hemoglobin concentration or hematocrit. The net result is hypoxemia due to a lack of oxygen-carrying capacity. Anemia may be due to a decrease in RBC production or an increase in RBC destruction. Patients with anemia require a diagnosis, and elective surgical procedures should be delayed if the anemia is significant. No absolute value can be used to decide what is significant, although when the anemia is symptomatic, this should be considered important. Females with a history of heavy menstrual bleeding and breakthrough bleeding have a reason to be anemic, and referral to a gynecologist is needed. Female patients with gastrointestinal losses and all males with anemia require appropriate workup to identify the source of bleeding.

Anemia is diagnosed with a complete blood count (CBC), which will reveal a reduced red cell number, reduced hemoglobin, and a reduced hematocrit. RBC indices will also be available as part of the CBC and include the mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). The initial approach to a patient with anemia begins with determining whether it is a result of decreased production or increased destruction. The reticulocyte count can distinguish the two, with hypoproliferative disorders

associated with a reduction in the reticulocyte count, and anemia due to an increased red cell destruction would be associated with an increased reticulocyte count. Decreased RBC production can be divided into microcytic, normocytic, and macrocytic anemia. All have the common feature of decreased RBC production with a decreased reticulocyte count below 2%. Microcytic anemia is defined by an MCV less than 80 fL and may be the result of iron deficiency, thalassemia, sideroblastic anemia, or sickle cell disease. Additional tests are required to distinguish among the four entities. *Iron deficiency* is the most common and easily recognized by a decrease in serum iron and serum ferritin and an increase in total iron-binding capacity (TIBC). *Thalassemia* typically has a positive family history and diagnosis requires gel electrophoresis. *Sideroblastic anemia* is uncommon and associated with an increase in serum iron and ferritin, although diagnosis requires bone marrow biopsy. *Sickle cell trait/disease* also typically provides a positive family history and can be confirmed with a blood smear or genetic testing.

Normocytic anemia is defined by an MCV of 80–100 fL and may be the result of renal failure, chronic disease, or aplastic anemia. Macrocytic anemia is defined by an MCV greater than 100 fL and is most often due to vitamin B_{12} or folic acid deficiency. The serum vitamin B_{12}, folic acid, methylmalonic acid, and homocysteine can be used to distinguish the two.

Anemia due to increased RBC destruction is associated with an increased reticulocyte count above 2% and may be due to hereditary spherocytosis, autoimmune hemolysis, cold agglutinin disease, or mechanical destruction. A blood smear and direct and indirect Coombs' test can be used to identify the cause. The presence of schistocytes in the blood smear can be the result of disseminated intravascular coagulation (DIC), prosthetic heart valve, thrombotic thrombocytopenic purpura (TTP), or hemolytic-uremic syndrome (HUS).

The general workup of the anemic patient should include a CBC, peripheral smear, MCV, and reticulocyte count. Additional tests should be requested based on the initial results and may include serum iron, ferritin, TIBC, vitamin B_{12}, folate, Coombs' test (direct and indirect), methylmalonic acid, homocysteine, and a bone marrow biopsy.

Iron-deficiency anemia may be treated with iron supplements, whereas megaloblastic anemias should be treated with vitamin B_{12} or folate depending on the deficiency. Dietary change should also be instigated in all cases except pernicious anemia because a lack of intrinsic factor renders dietary vitamin B_{12} ineffective. Megaloblastic anemia can be seen in vegetarians and those who avoid leafy green vegetables. Dietary inadequacy may also be seen in chronic alcoholics.

Sickle cell anemia deserves special mention because it is seen frequently in African Americans. Sickle cell trait is heterozygous and of minor clinical significance. Sickle cell disease is homozygous and clinically important. Deoxygenated RBCs polymerize and sickle. This leads to vaso-occlusive crises causing pain, cardiomyopathy, and infarcts of bone, lungs, and kidneys. Most patients undergo autosplenectomy owing to the progressive splenic infarction. Intravascular hemolysis also leads to gallstones in young patients. The treatment of sickle cell patients requires:

- Hydration
- Supplemental oxygen
- Hydroxyurea to decrease the incidence and severity of pain crises
- Narcotic pain medication during crises
- Aggressive treatment of infection
- Vaccination as a result of the autosplenectomy

2.6.2 Myeloproliferative Disease

This is a group of disorders characterized by a clonal proliferation of myeloid cells. All of these entities have the potential to transform into acute leukemias, although this occurs slowly. Myeloproliferative diseases may be suspected based on symptoms but may be identified from routine blood screening in otherwise asymptomatic patients. Myeloproliferative diseases can be classified according to the cell line responsible. Although bone marrow biopsy is the most sensitive diagnostic test, a CBC and smear are often suggestive. The four categories of myeloproliferative diseases include polycythemia vera, essential thrombocytosis, myelofibrosis, and chronic myelogenous leukemia. *Polycythemia vera* is an elevated RBC count and may present with headache, CVA, angina, pruritus, amaurosis, claudication, and splenomegaly as a result of the hyperviscosity syndrome. *Essential thrombocytosis* is an elevated platelet count and presents with symptoms similar to those of polycythemia vera. *Myelofibrosis* is defined by an increase in bone marrow fibrous tissue and is associated with fatigue, weight loss, extramedullary hematopoiesis, and massive splenomegaly. *Chronic myelogenous leukemia* is discussed in the next section.

2.6.3 Leukemia

The leukemias are a group of malignant diseases of lymphocytes or myeloid cells. They are mentioned for completeness. The leukemias are classified according to cell type: acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and chronic

lymphocytic leukemia. All leukemias tend to present with similar perioperative concerns. Anemia, thrombocytopenia, and ineffective leukocytosis present multiple surgical challenges. Infections are more common and should be treated aggressively. The medical management of leukemia causes further immunocompromise, increasing patient morbidity.

2.6.4 Lymphoma and Multiple Myeloma

Lymphoma is a malignancy of lymphoid tissue that resides predominantly within lymphoid tissue. It can be classified as Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL) depending on the presence of Reed-Sternberg cells, which are present in the former. Waldenström's macroglobulinemia is a low-grade form of NHL that secretes immunoglobulin leading to a hyperviscosity syndrome, peripheral neuropathy, and Raynaud's phenomenon.

Multiple myeloma (MM) is a malignant proliferation of plasma cells that produce a monoclonal antibody (M component). The disease progresses slowly but can lead to anemia, bone pain, hypercalcemia, renal disease, nephrotic syndrome, and hyperviscosity syndrome.

The treatment of lymphoma and MM includes chemotherapy and occasionally radiotherapy. The additional use of bisphosphonates in MM to reduce lytic lesions and bone pain has greatly improved the quality of life but has resulted in the development of bisphosphonate-related osteonecrosis of the jaws (BRONJ) in a proportion of patients.

2.6.5 Thrombocytopenia

Thrombocytopenia is due to decreased platelet production, increased destruction, or splenic sequestration. The net result is bleeding episodes that occur spontaneously or with minimal trauma when the platelet count falls below 50,000 cells/mm^3. The causes of thrombocytopenia are multiple but the surgeon should be aware of idiopathic thrombocytopenic purpura (ITP), TTP, HUS, and DIC. ITP is an autoimmune disorder that can follow an upper respiratory infection and is treated with steroids or splenectomy. Although often self-limiting, persistent mild perioperative thrombocytopenia may require steroids to increase the platelet count depending on the number and the nature of the planned procedure. TTP and HUS are characterized by hemolytic anemia, thrombocytopenia, and renal failure, although the former is also associated with seizures. DIC may be seen in the perioperative period, particularly the multitrauma and septic patient. Patients are at risk for significant perioperative bleeding. All patients with thrombocytopenia should be optimized before any surgical procedure. This entails managing the underlying condition and increasing the platelet count, which may necessitate platelet transfusion. Patients with DIC should not be considered surgical candidates.

2.6.6 Coagulopathy

Abnormalities of platelets, the intrinsic clotting pathway, and the extrinsic clotting pathway are all causes of coagulopathy. A personal or family history of a bleeding diathesis or a history of excessive bleeding with prior surgical procedures or extractions is a sensitive means of assessing potential bleeding problems. The propensity for bleeding is best assessed with a CBC to evaluate the platelet count; platelet aggregation tests to assess platelet function; and the prothrombin time (PT), INR, and PTT to evaluate the coagulation cascade. Routine screening in an asymptomatic patient without a history of bleeding is not recommended, however [32–37].

Thrombasthenia may be due to inherited defects as seen with Bernard-Soulier thrombasthenia, Glanzmann's thrombasthenia, or von Willebrand's disease (vWD). The latter is a common autosomal disease associated with a decrease in vWF and Factor VIII. There are several types of vWD that are classified depending on whether the vWF defect is quantitative or qualitative. When the defect is quantitative, treatment with the vasopressin analogue (DDAVP) will increase the vWF and Factor VIII level. The preoperative platelet count and the nature of the surgery will determine whether this increase is sufficient for the planned procedure. When the platelet count is particularly low or the defect qualitative, Factor VIII concentrate, recombinant vWF, or cryoprecipitate will be necessary. A hematologist should be involved early in the patient's management to optimize the treatment. Platelet defects may also be acquired. This is very common and the potential impact should not be underestimated. A recent history of NSAIDs, clopidogrel, ticlopidine, or platelet IIb/IIIa inhibitors should be sought. Many patients will fail to report the use of aspirin unless specifically asked. Lastly, patients with end-stage renal disease may present with uremia, which may reduce platelet function significantly.

The general aim with surgical patients is to achieve a platelet count above 100,000 cells/mm^3. In addition, platelet function may be abnormal and should be assessed and corrected if possible. The use of clopidogrel and ticlopidine is not usually problematic for minor surgery, but the potential for bleeding exists and this needs to be considered before any major surgery. In the case of expected major blood loss at surgery, consultation with the patient's internist and subsequent discontinuation of clopidogrel and ticlopidine is recommended

1 week before the procedure. Platelet replacement may be required for patients with either thrombocytopenia or thrombasthenia. It should be remembered that the development of autoantibodies to prior platelet transfusions may result in a less than predictable response to subsequent platelet transfusions.

2.6.7 Hemophilia A and B

Hemophilia A is an X-linked recessive inherited disorder characterized by a deficiency in Factor VIII. Males are affected, although females may be carriers and can have hemophilia if they are homozygous. Factor VIII is a key coagulation factor in the extrinsic cascade and any deficiency can be measured with the PTT. The Factor VIII level can also be measured to quantitate disease severity. Hemophilia A can be classified based on the Factor VIII level:

- Mild hemophilia with Factor VIII level of 5–25%
- Moderate hemophilia with Factor VIII level 1–5%
- Severe hemophilia with Factor VIII level lower than 1%

The treatment of hemophilia A depends on the Factor VIII level and the nature of the proposed surgical procedure. Minor surgical procedures may require only modest elevations in Factor VIII level to 50% of the normal value. Major surgical procedures usually dictate that the level be restored to a normal level. The most common treatment involves replacement with recombinant Factor VIII. DDAVP can be used in mild cases and results in a mild increase in Factor VIII level through endothelial cell release. Cryoprecipitate can also be used but carries the risk of disease transmission because it is obtained from pooled human donors. If antibodies have developed prior to Factor VIII replacement therapy, then activated Factor VII may be required. With a half-life of 12 h, Factor VIII replacement needs to be given twice a day. Despite an improvement in the PTT or factor, local measures at the time of surgery are also of paramount importance in helping to reduce the risk of postoperative bleeding. Antifibrinolytics should also be considered in this patient population. Epsilon-aminocaproic acid (EACA) and tranexamic acid can be administered systemically or applied topically as a mouthwash/gargle and have been shown to reduce the number of postoperative bleeding episodes. A growing number of patients are maintained on home therapy and learn to self-administer Factor VIII when necessary or have a family member do so. These patients can have minor surgery performed on an ambulatory basis. They should be instructed in conjunction with their hematologist/hemophilia nurse to administer the appropriate number of units at home preoperatively and postoperatively.

Hemophilia B (Christmas disease) is less common that hemophilia A and is autosomal recessive in the mode of inheritance. It is due to a deficiency in Factor IX. The half-life of Factor IX is 18 h, and, accordingly, replacement is required every 18 h. Distinguishing between hemophilia A and B can initially be difficult because they both present with an elevated PTT. A Factor IX assay is required to make the diagnosis of hemophilia B. Treatment is with Factor IX replacement, which should increase the Factor IX level and normalize the PTT.

2.6.8 Warfarin Therapy

Many patients present who are anticoagulated with warfarin. They may have a history of AF, prosthetic heart valve, peripheral vascular disease, DVT, or PE. The adequacy of treatment is measured by evaluating the PT or the INR. The actual therapeutic level required is determined more by the medical condition necessitating the anticoagulation. Warfarin is a potent inhibitor of the vitamin K-dependent proteins II, VII, IX, X, C, and S. Proteins C and S are involved in the fibrinolytic pathway, and, as such, a deficiency of these proteins tends to promote coagulation. The type of surgery planned, the INR, and the underlying medical need for warfarin will dictate whether to discontinue it before surgery, although considerable controversy exists. For minor surgery, such as extractions and the surgical removal of teeth, maintaining warfarin with an INR of less than 3.0 or 3.5 seems appropriate, given the potential for significant embolic complications in those who discontinue warfarin. Local hemostatic measures during surgery are paramount and should be combined with postoperative tranexamic acid or EACA [38].

Major surgery dictates a different approach. Several options exist and should be tailored to the patient. Early discussion and treatment planning with the patient's treating physician is needed before any decision making.

- Stop warfarin 4 days before the procedure and resume after surgery (if medically appropriate to discontinue).
- Stop warfarin 4 days before the procedure. Bridge with enoxaparin 1 mg/kg subcutaneously twice a day and resume warfarin after surgery. Hold enoxaparin the night before and the morning of the procedure and resume the evening of the procedure.
- Stop warfarin 4 days before the procedure. Bridge with UFH infusion and resume warfarin dose after surgery. Hold heparin 6 h before the procedure and resume 6 h after surgery.
- Use local hemostatic measures during surgery.
- Administer tranexamic acid or EACA orally or topically.

Active bleeding or the emergent need for surgery dictates a different approach. Warfarin can be reversed with the administration of vitamin K, although it typically takes 10–12 h for the reversal to occur. It also has a short half-life and may need to be redosed every 6 h. Acute bleeding necessitates immediate treatment and replacement of clotting factors with FFP.

2.6.9 Hypercoagulable Diseases

There are multiple inherited and acquired conditions that predispose patients to thrombosis. The acquired states include antithrombin III deficiency, protein C and S deficiency, Factor V Leiden deficiency, and Factor II mutation. Acquired states include prolonged immobilization, pregnancy, oral contraceptives, malignancy, smoking, nephritic syndrome, and systemic lupus erythematosus. Acquired causes should be eliminated whenever possible. Patients may be receiving warfarin, and this may influence the perioperative management. Additional perioperative steps that can reduce the risk for DVT and PE should be instituted.

- Encourage ambulation as soon as possible.
- Use sequential calf compressors.
- Use thromboembolic deterrent stockings (TEDS).
- Use UFH at 5000 units subcutaneously every 8 h or enoxaparin 30 mg subcutaneously every 12 h.

DVT should be suspected if leg pain, leg swelling, lower extremity pitting edema, pain on dorsiflexion (Homan's sign), chest pain, shortness of breath, unexplained sinus tachycardia, or an elevated A-a oxygen gradient is noted. Appropriate workup should include a duplex ultrasound of the lower extremity, D-dimer assay, and spiral CT of the chest if PE is suspected. Appropriate management requires heparin anticoagulation and long-term warfarin treatment. Patients who cannot tolerate warfarin or who develop additional episodes of DVT on warfarin sodium (Coumadin) may require an inferior vena cava filter.

2.7 Endocrinology

2.7.1 Diabetes Mellitus

DM affects a significant proportion of the population and is characterized by autoimmune destruction of the pancreatic islet cells or the development of insulin resistance. Elevated blood glucose level and the by-products of glucose metabolism result in multiple negative physiological and end-organ changes (Table 2.7).

Table 2.7 Complications of diabetes mellitus

Complication	Perioperative implication
Cardiovascular disease Myocardial ischemia Myocardial infarction Cerebrovascular accident Heart failure	Perioperative morbidity and mortality
Autonomic neuropathy Cardiovascular Cystopathy Gastroparesis	Arrhythmia Urinary retention, UTI Delayed gastric emptying, GERD
Hypoglycemia	Glucose monitoring
Nephropathy	Avoid IV contrast Avoid nephrotoxic drugs Attention to hydration
Peripheral neuropathy	Cutaneous ulcers Gait disturbance
Retinopathy	Acute visual changes with blood loss
Cheiroarthropathy	Difficult intubation, positioning, and IV access
Reduced neutrophil activity and tissue perfusion	Surgical site infection

Adapted from Miller and Richman [55]
UTI urinary tract infection, *GERD* gastroesophageal reflux disease, *IV* intravenous

Signs and symptoms of DM include polyphagia, polydipsia, polyuria, acanthosis nigricans, peripheral skin pigmentation/ulcers, peripheral neuropathy, decreased visual acuity, nonketotic hyperosmolar coma, diabetic ketoacidosis (DKA), altered mental status, and electrolyte abnormalities.

The diagnosis of DM can be established using a number of methods. A random blood glucose above 200 mg/dL is suggestive of DM. A fasting blood glucose between 100 and 125 mg/dL is considered to represent a prediabetic state. A fasting blood glucose above 126 mg/dL is diagnostic of DM. If the random or fasting blood glucose levels are inconclusive, then the oral glucose tolerance test can be used. This requires the ingestion of 75 mg of glucose after an 8-h fast. A post blood glucose is then measured at 2 h with a blood glucose level of 140–199 mg/dL considered to represent impaired glucose tolerance and a blood glucose of greater than 200 mg/dL diagnostic of DM.

A significant number of patients with DM will require surgical procedures. For diabetic patients undergoing procedures under local anesthesia, no change in their medication regime is warranted, provided that they

Table 2.8 Guidelines for managing diabetes mellitus medications before surgery

Class	Nonfasting period	Surgery before 10 am	Surgery after 10 am
Oral medications and noninsulin injectables	Continue medications and diet Withhold metformin	Hold morning dose Hold second-generation sulfonylureas 1 day before surgery Hold chlorpropamide 2 days before surgery Hold SGLT2 inhibitors 3 days before surgery	Hold morning dose Hold second-generation sulfonylureas 1 day before surgery Hold chlorpropamide 2 days before surgery Hold SGLT2 inhibitors 3 days before surgery
NPH	Half normal dose Normal diet Monitor BSL	Half normal dose	Half normal dose
Detemir or glargine	Half normal dose Normal diet Monitor BSL	Normal dose	Half the usual dose
Oral medications and noninsulin injectables and long-acting insulin	Normal diet Normal oral medications Half normal insulin dose	NPH – half dose Detemir or glargine take normal dose Withhold oral medications and noninsulin injectables	Half long-acting insulin dose Withhold oral medications and noninsulin injectables
Rapid-acting insulin	Half normal dose Normal diet Monitor BSL	Hold	Hold
NPH and rapid-acting insulin	Half normal dose Normal diet Monitor BSL	NPH half dose Hold rapid-acting dose	NPH half dose Hold rapid-acting dose
Detemir or glargine and rapid-acting insulin	Half normal dose Normal diet Monitor BSL	Detemir or glargine take normal dose Hold rapid-acting dose	Detemir or glargine take normal dose Hold rapid-acting dose
Insulin pump	Normal dose Normal diet Monitor BSL	Continue basal rate Hold morning bolus	Continue basal rate Hold morning bolus
Premixed insulin	Half normal dose Normal diet Monitor BSL	Hold	Hold

Adapted from Aniskevich et al. [56]

will resume a normal diet postoperatively. Diabetic patients undergoing a general anesthesia or intravenous sedation will be fasting and require a change to their normal regime. Management of the diabetic patient can be divided into the preoperative and postoperative periods. Furthermore, management depends on whether the patient is treated with insulin or oral hypoglycemic agents.

2.7.1.1 Preoperative

The general goal is to avoid excessive hyperglycemia and hypoglycemia. This generally represents maintaining the blood glucose between 80 and 140 mg/dL. Adjustments to a patient's insulin and/or oral hypoglycemic medications will need to be made and depend on the what type of insulin or oral hypoglycemic the patient is taking (Table 2.8).

The sliding scale for insulin administration is derived from individuals with relatively normal insulin sensitivity and should be used to adjust the blood sugar level in the perioperative period. Patients who respond poorly to the calculated insulin dose may have reduced insulin sensitivity and adjustment to the formula is needed or consideration of changing to a CII. SSI requires that blood glucose be measured every 6 h. Regular insulin is then administered subcutaneously according to the formula:

$$\text{Units regular insulin} = \frac{\text{Blood Sugar Level} - 140}{40}$$

The glucose control in the preoperative period can be estimated by measuring the hemoglobin A1c (HbA1c). The latter measures the amount of glycosylated hemoglobin over the prior 3 months, which reflects the average glucose level over that time. It is an independent predictor of morbidity. A hemoglobin A1c ≥ 8% suggests poor preoperative glucose control and the patient will likely benefit from delaying elective surgical procedures until the HbA1c can be reduced.

DKA can occur in insulin-dependent diabetics, usually as a result of inadequate insulin, infection, or drug use. It is associated with severe hyperglycemia and ketosis. There is a 1% mortality rate even when treated appropriately. The clinical manifestations include polyuria, polydipsia, dehydration, hypotension, nausea, emesis, abdominal pain, altered mental status, and Kussmaul's respiration. The diagnosis is supported by the presence of an anion gap metabolic acidosis, hyperglycemia, pseudohyponatremia, and ketoacidosis (acetoacetate and β-hydroxybutyrate) in serum and urine. The treatment of DKA requires aggressive intravenous hydration with normal saline, intravenous regular insulin as an initial bolus and infusion, potassium replacement, and bicarbonate when severe acidosis or cardiac instability is present. The latter is typically defined by a pH of less than 7. The fluid used for hydration should be changed to a dextrose-containing fluid such as D_5½NS when the glucose level reaches 250 mg/dL. DKA may take many hours to treat because the hourly reduction in the glucose level with this regime should not exceed approximately 100 mg/dL/h.

Nonketotic hyperosmolar hyperglycemic coma can occur in older non–insulin-dependent diabetics. Precipitating factors are the same as for DKA. The mortality rate is higher than DKA owing in part to the older patients. The key clinical features are severe dehydration and altered mental status. Significant hyperglycemia and an increase in serum osmolality (>350 mOsm/L) are typical. The treatment includes aggressive rehydration with normal saline. This should be accompanied by the administration of regular insulin as a bolus and infusion.

2.7.2 Thyroid

Surgical patients may present with a history of hypothyroidism or hyperthyroidism. Hypothyroidism is typically characterized by the progressive destruction of thyroid tissue. It occurs in Hashimoto's thyroiditis in which an autoimmune lymphocytic infiltrate develops with antithyroid peroxidase antibodies. Subacute thyroiditis is also autoimmune and often follows a flu-like illness and presents with jaw pain but is usually self-limiting and resolves in a few months. Hypothyroidism may also be iatrogenic, resulting from the medical treatment of hyperthyroidism. The signs and symptoms of hypothyroidism include fatigue, weight gain, cold intolerance, constipation, facial edema, delayed deep tendon reflexes, and altered mental status. The diagnosis is usually established by observing a decreased free thyroxin (T_4) and elevated thyroid-stimulating hormone (TSH) level. Mild hypothyroidism is not a contraindication to surgery [39]. The treatment of hypothyroidism requires levothyroxine. The adequacy of treatment can be measured through TSH levels, which should approach normal. Myxedema is the only emergent hypothyroid condition that can develop as a result of infection, surgery, medications, or any other stressful event. The diagnosis of acute myxedema is based on a history of hypothyroidism and the development of altered mental status, seizures, or hypotension. Treatment requires immediate intravenous levothyroxine and corticosteroids. Patients in a myxedema coma also require intravenous liothyronine. Any patient who presents with acute myxedema preoperatively requires postponement of the surgery until appropriate treatment has been rendered and the patient made euthyroid.

Hyperthyroidism is most often due to Graves' disease, an autoimmune disease characterized by the presence of thyroid-stimulating antibodies. There is the potential for thyroid storm with fever, cardiac arrhythmias, high-output cardiac failure, coma, and death. The signs and symptoms of hyperthyroidism include tachycardia, anxiety, tremors, heat intolerance, weight loss, AF, diarrhea, elevated systolic blood pressure, exophthalmos, and pretibial myxedema. The diagnosis can be established by the presence of an increased free T_4, decreased TSH, and the presence of thyroid-stimulating antibodies. The treatment of hyperthyroidism may require several approaches, although the development of thyroid storm mandates a rapid and aggressive approach. Many patients with hyperthyroidism will have been treated with radioactive iodine or thyroidectomy, which should render them euthyroid or even hypothyroid [40, 41]. These patients provide no additional perioperative risk. Others may have mild hyperthyroidism that requires beta blockers and either propylthiouracil (PTU) or methimazole to reduce thyroxin secretion in the perioperative period. A significant concern for any patient with a history of hyperthyroidism is the potential for thyroid storm. It can develop quickly with fever, tachycardia, hypertension, cardiac failure, altered mental status, and death. Treatment requires a prompt diagnosis and the sequential administration of beta blockers, PTU or methimazole, and sodium iodide. One problem is that the signs and symptoms that present may be confused with malignant hyperthermia (MH), neuroleptic malignant syndrome, or pheochromocytoma. Additional treatment includes hyperventilation to help manage the

hypercarbia secondary to the hypermetabolic state and rapid cooling to manage the increasing body temperature. Decreasing ambient temperature, cool intravenous fluids, and cooling blankets may also be needed. For either hypothyroidism or hyperthyroidism, elective surgery should be delayed until the treatment makes the patient euthyroid as determined by thyroid hormone levels. Emergent or urgent procedures should be undertaken without delay and the patients should be monitored closely. The potential need to supplement patients with thyroid hormone, corticosteroids, and cardiovascular support or the need to block the production and effects of excess thyroid hormone should be recognized early.

2.7.3 Adrenal

Patients with adrenal disease may present with excessive adrenal function or adrenal insufficiency. Cushing's syndrome is characterized by excessive plasma cortisol levels. It can be secondary to adrenal hyperplasia, pituitary adenoma, ectopic adrenocorticotropic hormone (ACTH) production, or exogenous corticosteroid administration. Patients present with truncal obesity, moon facies, abdominal striae, hirsutism, hyperglycemia, HTN, and purpura. The diagnosis is confirmed with a 24-h urine-free cortisol level, high dexamethasone suppression test, and abnormal ACTH level. Conn's syndrome is characterized by excessive aldosterone levels. This is usually secondary to adrenal hyperplasia or adenoma of the zona glomerulosa but can occur as a result of renal disease and increased serum renin. Patients present with HTN, hypernatremia, hypokalemia, hyperchloremia, and alkalosis. The diagnosis is confirmed with elevated serum aldosterone levels. The perioperative concerns relate primarily to fluid balance, electrolytes, and glucose level, all of which require appropriate correction as needed.

Adrenal insufficiency may be primary or secondary. Primary adrenal insufficiency is due to destruction of the adrenal glands from autoimmune disease, infection, or infarction and is referred to as *Addison's disease.* Secondary adrenal insufficiency is due to a lack of ACTH due to pituitary failure. Primary and secondary adrenal insufficiency can be distinguished based on the presence of hyperpigmentation, ACTH level, and the cosyntropin stimulation test. The inadequate levels of adrenal cortisol place the patient at risk for an acute adrenal crisis when stressed with surgery or any infection. Acute adrenal crisis is characterized by nausea, emesis, abdominal pain, fever, lethargy, severe hypotension, altered mental status, and electrolyte abnormalities. Patients with adrenal insufficiency are usually managed with prednisolone replacement therapy. The steroid administration, while providing adequate replacement for daily physiologic needs, is insufficient to manage the patient's requirements in the perioperative period. This requires a significant increase in the perioperative steroid dose. Occasionally, patients may also be receiving mineralocorticoid replacement (fludrocortisone) if the adrenal insufficiency has resulted in decreased aldosterone production. For minor procedures such as extractions, the patient should double the usual corticosteroid dose on the morning of the procedure. Blood pressure should be monitored during and after the procedure. Hypotension should be treated with intravenous hydrocortisone (100 mg) or an equipotent dose of another steroid. For major procedures, the patient should receive intravenous corticosteroids in the perioperative period. Doses should be equivalent to or greater than 300 mg of cortisol per day, which represents the normal physiologic endogenous steroid production in the face of major surgical stress. Hydrocortisone can be administered every 6 h and the dose or frequency increased to maintain blood pressure. Alternatively, a more potent steroid with a longer half-life such as dexamethasone can be administered. Patients with primary adrenal insufficiency may also have fluid and electrolyte abnormalities from the relative lack of aldosterone. Judicious fluid replacement and management of hyponatremia and hyperkalemia are required.

2.7.4 Pituitary Disease

Diabetes insipidus (DI) can occur as a result of a decrease in pituitary antidiuretic hormone (ADH) production or as a result of renal insensitivity to ADH. These two disorders are referred to as *central* and *nephrogenic* DI, respectively. They present with severe polyuria, polydipsia, increased serum osmolality (>300 mmol), and mild hypernatremia. The diagnosis of DI can be made with the water deprivation test in which inappropriate urine production occurs in the face of restricted water intake. The continued urinary loss of free water results in the increased serum osmolality and hypernatremia. The distinction between central and nephrogenic DI is made by administering DDAVP. Central DI responds to DDAVP with an appropriate decrease in free water urinary loss and a corresponding correction of the serum osmolality and hypernatremia. The long-term management of central DI is nasally administered DDAVP, whereas nephrogenic DI is treated with sodium restriction and liberal water intake. The perioperative management of the surgical patient with DI revolves around fluid and electrolyte balance.

2.8 Neurologic Disease

2.8.1 Trauma

2

The spectrum of neurologic disease is wide with some patients presenting significant perioperative challenges. Acute neurologic deterioration in the setting of trauma is a special circumstance that also demands particular attention. The initial management of the trauma patient requires a systematic approach. The primary survey is designed to identify and correct life-threatening conditions and entails an assessment of the airway, breathing, circulation, and disability. The latter is a neurologic assessment that can be influenced by many factors including the airway, breathing, and circulation. The assessment of the neurologic status continues with the use of the Glasgow Coma Scale (GCS), which helps determine severity, treatment, and prognosis of head-injured patients (Table 2.9) [42].

Injury may be classified as mild, moderate, or severe based on the score. Severe injury as determined by a GCS of 8 or less typically mandates intubation, although less severe injuries may also require a secure airway. The nature of the neurologic injury will depend in part on the mechanism of injury. Gunshot wounds are typically associated with penetrating and avulsion injuries, whereas motor vehicle crashes, sporting injuries, and domestic violence are more likely to result in extradural, subdural, subarachnoid, and parenchymal hemorrhage or diffuse axonal damage. Early involvement of the neurosurgical team to manage and treat the injury is paramount. Generalized goals of treatment are to limit further damage by controlling hemorrhage, minimizing cerebral edema, and maintaining cerebral perfusion. The role of the maxillofacial surgeon is limited, but the importance of securing the airway is critical and may necessitate intubation or an emergent airway.

Table 2.9 Glasgow Coma Scale

Action	Score
Eye opening	
Spontaneously	4
To speech	3
To pain	2
No response	1
Verbal response	
Orientated	5
Confused	4
Inappropriate words	3
Incomprehensible	2
No response	1
Motor response	
Obeys commands	6
Localizes pain	5
Withdraws to pain	4
Flexes to pain	3
Extends to pain	2
No response	1

2.8.2 Seizures

Seizures can occur in the perioperative period in healthy patients and those with a known seizure disorder such as epilepsy. Seizures can be classified as partial and generalized. Unremitting generalized seizure activity is termed *status epilepticus*. The potential causes of seizure are many. Epilepsy is a frequent cause of seizures, and a careful history regarding the frequency and severity of seizure activity should be sought. This will enable the surgeon to determine whether local anesthesia, sedation, or a hospital-based procedure is appropriate. Patients with well-controlled seizures can generally undergo anesthesia and surgery in the office or hospital. Irrespective of the procedure location, seizure medication should always be maintained. A multitude of medications are currently available to control seizures. Traditional medications such as phenytoin, valproic acid, carbamazepine, ethosuximide, and phenobarbital are used less frequently owing to the side effects including sedation. Bone marrow suppression with carbamazepine and liver enzyme inhibition with valproic acid may also occur. Newer drugs such as gabapentin, pregabalin, lamotrigine, topiramate, and tiagabine are becoming more popular owing to their efficacy and side effect profile.

Additional potential causes of seizure activity include anesthesia-related drugs, drug and alcohol withdrawal, degenerative central nervous system disease, head trauma, CVA, and metabolic derangements. Two particular anesthetic drugs that can reduce the seizure threshold are local anesthetics and meperidine. Local anesthetic overdose can suppress inhibitory neurons and increase seizure activity. Meperidine has an active metabolite, normeperidine, that can promote seizure activity particularly in the face of renal insufficiency. Benzodiazepine, barbiturate, and alcohol withdrawal can also promote seizures owing to loss in neuronal

inhibition from these drugs. Head injury can also promote seizures from raised intracranial pressure, extravascular blood, and diffuse axonal injury. Metabolic derangements may be encountered in relatively healthy surgical patients, and this may also lead to seizures. Sodium, calcium, magnesium, glucose, urea, and ammonia are particularly important in this regard. Fluid and electrolyte balance is paramount, and all abnormalities should be corrected promptly.

New-onset seizures require treatment as well as a search for the cause. Signs and symptoms of seizure include altered mental status, confusion, loss of consciousness, and abnormal movement. The diagnosis of seizure may require an electroencephalogram (EEG). The initial treatment of perioperative seizures may require intravenous loading and maintenance with phenytoin. Fosphenytoin may be preferred owing to the more predictable bioavailability. Benzodiazepines may also be used to terminate a seizure but play no role in the long-term management of recurrent seizure activity. The transition to oral seizure medications is best managed in conjunction with neurology.

2.8.3 Cerebrovascular Accident

Atherosclerosis of the carotid and cerebral blood vessels places patients at risk for CVA and transient ischemic attacks (TIAs) in the perioperative period. Carotid atherosclerosis may be suspected based on the presence of a carotid bruit. A carotid duplex ultrasound is typically used to better define the severity of the stenosis. Occasionally, angiography, CT angiography, or magnetic resonance angiography may be used. Stenosis greater than 70% may benefit from endarterectomy before any elective surgical procedure [43]. CVA may be the result of thromboembolic events or hemorrhage, whereas TIA is typically a result of the former. AF also increases the risk for CVA owing to atrial thrombosis and subsequent embolic events. Thrombosis of the lower extremity veins can also lead to CVA or TIA in the presence of atrial or ventricular septal defects. Patients with AF who are typically on warfarin should continue the medication in the perioperative period whenever possible. Patients with a history of TIA or thromboembolic CVA are often treated with aspirin or ticlopidine, which should be continued in the perioperative period if the nature of the planned surgical procedure allows. Surgical patients with a history of hemorrhagic CVA need to have their blood pressure well controlled. They may also have a history of HTN. Excessive elevations or reductions in blood pressure may also predispose to either CVA or TIA.

2.8.4 Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease characterized by the development of antibodies against the acetylcholine (Ach) receptor. It is often the result of thymus hyperplasia or a thymoma. Stressors including surgery, infections, and certain medications such as aminoglycosides, phenytoin, and meperidine may predispose patients to a myasthenic crisis. The signs and symptoms of a myasthenia crisis may include weakness, fatigue, ptosis, diplopia, dysarthria, dysphonia, dysphagia, respiratory distress, or failure to wean from the ventilator. Patients who present with a history of MG present challenges mostly related to their ventilatory status. This has an impact on their ability to undergo sedation, general anesthesia, and ventilator separation. Close collaboration with the neurologist managing the MG is strongly recommended. The diagnosis of an MG requires repetitive muscle activity with demonstrative progressive weakness, an electromyogram with decreased amplitude on repetitive nerve stimulation, and the edrophonium test, during which there is a rapid but transient improvement in symptoms due to increased Ach at the motor endplate. The diagnosis can also be supported by the presence of anti-Ach receptor antibody and a thymoma on CT or magnetic resonance imaging of the chest. The perioperative treatment of MG may involve anticholinesterase medication such as pyridostigmine, intravenous immunoglobulin (IVIG), and plasmapheresis.

2.9 Other Conditions

2.9.1 Malignant Hyperthermia

MH is a serious, life-threatening condition characterized by a state of hypermetabolism leading to hyperthermia and massive rhabdomyolysis. It is an autosomal dominant genetic defect of one of several receptors within the sarcoplasmic reticulum. A mutation in the ryanodine receptor accounts for most cases, although several other receptors such as the CACNA 1S calcium channel receptor are involved in some patients. Certain anesthetic drugs including all volatile agents and succinylcholine can cause the rapid accumulation of calcium within the sarcoplasmic reticulum within skeletal muscle. The patient with a history suspicious of MH would benefit from a definitive diagnosis before any future anesthesia. This typically requires a skeletal muscle biopsy and the caffeine halothane contraction test, which has a sensitivity and specificity of 97% and 75%, respectively [44]. Genetic susceptibility testing is cur-

rently available for the ryanodine and CACNA 1S receptor mutations [45]. More often than not, the diagnosis is made only after the rapid development of MH.

One of the earliest features of developing MH is hypercarbia as seen through an increase in end-tidal carbon dioxide. This is followed by tachycardia, muscle rigidity, metabolic acidosis, and hyperthermia. Massive rhabdomyolysis with renal failure, electrolyte abnormalities including hyperkalemia, cardiovascular collapse, and death ensues unless treated aggressively.

The treatment of MH mandates immediate cessation of the volatile anesthetic agent or succinylcholine followed by hyperventilation to eliminate any volatile agent and reduce end-tidal CO_2, This should then be followed by the administration of dantrolene (2.5 mg/kg) and fluid resuscitation. Dantrolene is available as Dantrium® or Revonto® is available as a 20 mg vial with each vial requiring 60 mL of sterile water for reconstitution. A 100 kg patient would therefore require 12.5 vials or reconstituted dantrolene which can be time consuming in a emergent situation. Dantrolene is also available as Ryanodex® with each vial containing 250 mg and requiring only 5 mL or sterile water for reconstitution. Doses in excess of 2.5 mg/kg may be needed.

An arterial or venous blood gas should be obtained to determine the degree of metabolic acidosis followed by the administration of bicarbonate (1–2 mEq/kg) and cooling. Hyperkalemia above 5.9 will require calcium chloride (10 mg/kg) for myocardial stabilization followed by glucose/insulin (50 mL 50% dextrose and 10 units of regular insulin).

2.9.2 Autoimmune Disease

There are a multitude of autoimmune diseases that are likely to affect surgical patients. These include rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, scleroderma, ankylosing spondylitis, mixed connective tissue disease, Sjögren's syndrome, polyarteritis nodosa, and polymyositis. The autoimmune disease as well as the medical treatment of the disease results in suppression of the immune system and increases the likelihood of perioperative complications. In addition, organ systems may be the target of the disease resulting in airway, pulmonary, cardiovascular, musculoskeletal, renal, hematologic, and neurologic difficulties. Wound healing may also be impaired in many of these patients and surgical infections are more common.

Three autoimmune diseases worth elaborating on are rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis. Surgical patients with one of these diseases are likely to be encountered. Rheumatoid arthritis, despite the name, is a multisystem disease. In addition to the classic symmetrical involvement of the joints, nonarticular involvement can include the pericardium, pleura, lung, blood vessels, muscle, bone marrow, and skin. This can result in pericarditis, pleuritis, pneumonitis, vasculitis, myopathy, bone marrow suppression, and ulcers. Anemia of chronic disease is also often present. Rheumatoid factor may or may not be present in patients. Temporomandibular joint involvement may occur and result in limited opening, arthralgia, degenerative joint disease, and apertognathia. Cervical involvement may limit neck extension, further complicating anesthesia. The patient with limited opening may present anesthetic challenges, and planning for a difficult airway is essential. Many of the medications used to treat rheumatoid arthritis result in complications themselves. NSAIDs reduce platelet function; glucocorticoids result in adrenal insufficiency and Cushing's syndrome; and the slow-acting antirheumatic drugs (SAARDs), disease-modifying anti-rheumatic drugs (DMARDs), and anticytokine drugs are all immunosuppressive. SAARDS and DMARDS include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide. Anticytokine drugs continue to grow in number. Several categories of drugs exist including the interleukin 1 receptor antagonist anakinra, B cell-depleting agent rituximab, T cell costimulator blocking agent abatacept, and the tumor necrosis factor inhibitors etanercept, adalimumab, and infliximab. Ideally, patients with rheumatoid arthritis should have their disease control maximized before an elective surgical procedure. However, cessation of anticytokine medication before an elective procedure may be appropriate, given the potential for infection in this group, and this should be discussed with the rheumatologist. Cessation of medication typically requires 1 week before and after the surgical procedure.

Systemic lupus erythematosus is another autoimmune disease with multisystem involvement. Features may include anemia, thrombocytopenia, rash, polyarthritis, photosensitivity, uveitis, coagulopathy, neurologic manifestations, psychosis, and renal disease. Perioperative concerns relate primarily to anemia, renal disease, adrenal suppression, and risk for DVT. Care should be exercised in the use of radiographic contrast media and drugs may need to be renally dosed. Appropriate risk reduction for DVT mandates sequential calf compressors in the perioperative period, early mobilization, and heparin or enoxaparin prophylaxis. Additional steroids to compensate for adrenal suppression are likely, but this will depend on the nature of the surgical procedure and the usual daily steroid dose.

Ankylosing spondylitis is an autoimmune disease characterized by progressing spondylosis and immobility. Kyphosis develops insidiously and results in a rigid cervical spine that provides significant challenge for anesthesia. This is often combined with temporoman-

dibular joint involvement and limited opening. Sedation is generally contraindicated in this group owing to the inability to secure an airway should it become necessary. General anesthesia is also problematic and often requires fiberoptic intubation or an awake tracheostomy. The kyphosis also reduces pulmonary compliance and functional residual capacity.

2.9.3 Immunodeficiencies

Deficiencies in cell-mediated immunity predispose patients to infection from bacteria, mycobacteria, viruses, fungi, and parasites. Cell-mediated immunity can be assessed by observation of the prototypical cell-mediated response of the delayed-type hypersensitivity reaction. This is classically seen with the Mantoux test, in which an intradermal injection of tuberculin is given. A more predictable method of evaluating cell-mediated immunity is by measuring the ratio of CD4 helper T cells to the CD8 suppressor cells. This provides quantitative information but might not necessarily correlate with normal function. One of the most common causes of reduced cell-mediated immunity is HIV. However, the advent of highly active antiretroviral treatment (HAART) has significantly reduced morbidity and mortality by reducing the viral load and increasing the CD4 count in most patients.

Deficiencies in humoral immunity also predispose patients to infection. Humoral immunity is best assessed by measuring the serum level of the five classes of immunoglobulin. Prior vaccination may also lead to the development of circulating antibody, which can be readily measured to determine the adequacy of the humoral system.

Deficiencies in the nonspecific immune pathway often present with abnormalities of neutrophil function. This predisposes patients to bacterial and fungal infections. Although the absolute neutrophil count can be measured, neutrophil function should also be evaluated. An absolute neutrophil count below 500 cells/mL requires patient isolation and prophylactic antibiotic and antifungal treatment. Deficiencies in complement also predispose patients to bacterial infections. Individual complement factors can be measured as can the entire complement cascade function through the CH50 assay.

Immunocompromised patients should have a thorough history to ascertain whether there is a history of recurrent infections, opportunistic infections, generalized lymphadenopathy, or weight loss. A thorough understanding of any identified autoimmune disease or immunodeficiency is necessary to further appreciate the effect on organ systems. The clinical examination should identify signs of immunodeficiency, which manifest as opportunistic infections. Of particular importance are oral and esophageal candidiasis, gingivitis and periodontitis, oral ulceration, diarrhea, and persistent cough and shortness of breath. Laboratory investigations may include a CBC with differential, CD4/CD8 ratio, serum immunoglobulins (IgG, IgM, IgE, IgD, and IgA), functional assays for neutrophil and complement function, and a chest x-ray.

Immunocompromised patients need to be aggressively treated when infections occur. This includes early surgical intervention and broad-spectrum antibiotics. The use of perioperative and postoperative antibiotics should be considered in all but the simplest elective surgical procedures. Optimizing the immune status is also critical, although difficult to do in the short term. Treatment of the underlying cause of immunodeficiency is paramount. This is particularly true for HIV. HAART has no role in the acute setting but should be implemented as soon as possible. Optimizing blood glucose control reduces patient morbidity and should be the goal in all patients. Consideration should also be given to reducing or eliminating perioperative steroids, which will further suppress the inflammatory response and immune system.

Patients who have lost their spleen through surgery or sickle cell disease are a special group. They are at risk for bacterial infections, particularly from bacteria with polysaccharide capsules such as *Pneumococcus*, *Meningococcus*, and *Haemophilus.* These patients should be vaccinated against these organisms. Early and aggressive treatment of infections is appropriate.

A significant number of patients take immunosuppressive agents to modulate autoimmune disease, treat malignancy, or suppress organ transplant rejection. A multitude of drugs are used, and these can result in neutropenia and lymphopenia. This places patients at risk for poor wound healing, infection, and overwhelming sepsis. Treatment of the underlying autoimmune disease should be optimized before any elective surgery. The judicious discontinuation of certain medications in the perioperative period should be discussed with the patient's rheumatologist or internal medicine specialist. Perioperative antibiotics should be considered in most patients, and any infections that do develop should be treated aggressively.

HIX affects more than one million Americans and results in the progressive destruction of CD4 helper T cells. This may lead to acquired immunodeficiency syndrome (AIDS) with opportunistic infections. Infection with HIV should be considered in any patient with signs and symptoms of opportunistic infections. The diagnosis of HIV infection requires a screening enzyme-linked immunosorbent assay (ELISA) test and a confirmatory Western blot. The CD4 count is used to assess disease progression and is often combined with polymerase

chain reaction (PCR) to evaluate viral load and response to HAART. There are four broad drug categories in HAART. These include nucleoside/tide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors. The CD4 count should be known before all surgical procedures. This allows for risk stratification and appropriate prophylaxis against opportunistic infections. Every organ system can be affected by HIV/AIDS, and management of these patients can be challenging.

For a CD4 count below 200 cells/mL, *Pneumocystis jiroveci* pneumonia (formerly known as *Pneumocystis carinii* pneumonia; PCP) prophylaxis with trimethoprim/sulfamethoxazole, dapsone, atovaquone, or pentamidine is needed. As the CD4 count declines below 100 cells/mL, prophylaxis against toxoplasmosis becomes important with trimethoprim/sulfamethoxazole as the first choice. When the CD4 count falls below 50 cells/mL, the potential for *Mycobacterium avium* complex (MAC) necessitates prophylaxis with a macrolide antibiotic. Patients with HIV who will require surgery may benefit from receiving prophylactic treatment in the perioperative period even if currently not receiving such medication.

2.9.4 Substance Abuse

The oral and maxillofacial surgery patient may present with a problem related to substance abuse. This may include alcohol, opioids, or illicit drugs. A thorough understanding of the substance abuse will allow appropriate social and surgical management of the patient. In general terms, a distinction should be made between patients who abuse drugs and those who are dependent on them. *Abuse* is best defined as an individual who continues to use a drug despite social, interpersonal, and legal consequences. *Drug dependence* has the same features of abuse as well as ongoing physical harm. Patients with dependence are at risk of withdrawal when drugs are discontinued. Withdrawal is invariably emotionally and physically painful but, in addition, can be life-threatening depending on the drug involved.

Alcohol withdrawal is much more concerning than opioid withdrawal. The "CAGE" questionnaire is a simple means of screening for alcohol abuse and potential dependency [46]. The four questions that are asked are "Have you ever felt the need to **c**ut down?", "Have you ever felt **a**ngry at someone's criticism of your drinking?", "Have you ever felt **g**uilty about your drinking?", and "Have you ever had an **e**ye opener?". Two or more positive answers correlate with a high likelihood of alcohol abuse. Alcohol withdrawal may be characterized by a state of neuronal excitability. This may lead to severe syndrome of delirium tremens (DTs) with associated hallucinations, autonomic instability, hypertension, seizures, and coma [47]. Alcohol withdrawal can be avoided by continuing to provide alcohol in the perioperative period or by providing an alternative sedative medication. Benzodiazepines are the most appropriate medications to consider. Chlordiazepoxide and lorazepam are two common agents. Chlordiazepoxide can be given preemptively as a 4-day tapered oral regime beginning with 50 mg every 4 h on day 1, 50 mg every 6 h on day 2, 25 mg every 4 h on day 3, and 25 mg every 6 h on day 4. Most surgeons prefer to carefully evaluate potential patients and treat when the first signs of central nervous system excitation are seen. Early signs include restlessness, agitation, and tremulousness. Lorazepam can then be administered orally, intramuscularly, or intravenously every 6–8 h. Additional areas of concern in patients with alcohol dependence include liver disease, anemia, and nutritional deficiency. Patients are often deficient in folate and thiamine, and these should be repleted.

Opioid-related deaths in the United States have reached epidemic proportions with 47,600 deaths in 2017. Deaths from prescription-related opioid abuse account for 35% (16,600) of these deaths. Patients may be taking opioids for either acute or chronic pain. Those patients receiving opioids for chronic pain will typically be under the care of a pain specialist. Despite the legitimate use of opioids for acute or chronic pain, the potential for adverse events (AE), tolerance, and adverse drug-related behavior (ADRB) including abuse, misuse, and addiction. It is estimated that there were more than 16,000 prescription opioid-related deaths in the US in 2017. It remains critical to minimize opioid exposure by adopting a systematic approach to pain management for all patients. This should include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and gabapentinoids as first-line analgesics. The use of opioids should be the last resort beginning with weak, moderate, and finally strong opioids when needed. Prescriptions should be for the minimum time period possible and must comply with state-run prescription drug monitoring programs (PDMP).

The risk for ADRB in opioid naive patients can be calculated with a moderate sensitivity using the Opioid Risk Tool (ORT) [48] or the Revised Screener and Opioid Assessment for Patients in Pain (Revised SOAPP) [49]. A positive from the ORT or SOAPP is associated with a relative risk (RR) for ADRB of 14.3 and 2.5, respectively. Patients who are already receiving opioids can be evaluated for the risk of ADRB by completing the Current Opioid Misuse Measure (COMM) which has a RR of 2.7 when positive [50].

Table 2.10 Body mass index

Category	BMI range
Severely underweight	<16.5
Underweight	16.5–18.4
Normal	18.4–24.9
Overweight	25.0–30.0
Obese class I	30.1–35.0
Obese class II	35.1–40.0
Obese class III	>40.0

2.9.5 Obesity

Patients with obesity present many challenges in addition to the actual surgical procedure. Obesity is best measured by calculating the body mass index (BMI; Table 2.10). This is calculated by dividing the mass in kilograms by the square of the height in meters. The BMI allows patients to be risk stratified.

Surgical risks increase exponentially with the BMI once obesity is reached. The most common perioperative complications tend to be pulmonary. Obesity results in a restrictive pattern of lung disease due to decreased chest compliance and a superiorly displaced diaphragm, especially in the supine patient. Additional complications include a reduced functional residual capacity and the propensity to desaturate rapidly, airway obstruction, bronchospasm, atelectasis, PE, and pneumonia. Obese patients are also likely to suffer from obstructive sleep apnea (OSA), which potentially increases the likelihood of comorbid conditions such as HTN, coronary artery disease, and CVA. Office procedures under local anesthesia eliminate potential airway concerns. Intravenous sedation is more problematic and may not be appropriate for the obese and morbidly obese patient because the ability to secure an airway may be very challenging or not possible in the emergent setting. When sedation is chosen, the level should be light enough for the patient to maintain his or her own airway and respirations. Patients undergoing hospital-based procedures will still provide significant perioperative challenges, but these are more readily managed in this setting. The potential immediate postoperative need for CPAP in this group, particularly with a history of OSA, should not be underestimated. ASA recommends that any patient with OSA be carefully screened to determine whether they are candidates for ambulatory surgery. Factors that need to be considered include the severity of the OSA, coexisting disease, type of surgery, type of anesthesia, postoperative opioid needs, and the post-discharge observation [51]. A growing number of hospitals and anesthesia services are requiring patients with a proven diagnosis of OSA to be planned for overnight hospital admission with continuous pulse oximetry to monitor oxygen saturation.

Drug pharmacokinetics are also different in the obese patient, particularly for lipid-soluble drugs. The redistribution of lipid-soluble drugs to large body stores increases the volume of distribution, which significantly delays emergence from anesthesia.

Postoperatively, patients should be encouraged to rest with an elevated head of bed, ambulate as soon as possible, use incentive spirometry, and receive subcutaneous heparin for DVT prophylaxis.

2.9.6 Geriatric Patients

Elderly patients can provide significant challenges in the perioperative period. Those challenges depend on their general health status, comorbidities, and age. Advancing age is itself not considered a predictor of complications, but medical conditions such as HTN and coronary artery disease are more common in this age group. Furthermore, physiologic changes ensure that the compensatory mechanisms are less able to accommodate anesthetic and surgical stresses. The medical history, current medications, and an assessment of the functional capacity are still reasonably sensitive tools to detect potential problems. Common complications that can occur in the elderly include atelectasis, pneumonia, MI, DVT, PE, CHF, and altered mental status.

Pulmonary function typically declines and is seen as a reduced lung compliance, vital capacity, and functional residual capacity. The A-a oxygen gradient also increases with age. There is roughly a 5-mmHg reduction in the arterial partial pressure of oxygen for each decade of life. A healthy 20-year-old would, therefore, have a partial pressure of oxygen of 100 mmHg on room air, whereas a 70-year-old would have a partial pressure of 75 mmHg. Furthermore, the elderly patient's response to hypoxia and hypercarbia is blunted. The potential to desaturate rapidly or become apneic is high. Pulmonary vascular changes also ensure that ventilation-perfusion mismatching increases, further reducing pulmonary function.

Cardiac function also declines with a reduction in the maximal heart rate. This reduces a significant compensatory mechanism that would otherwise allow cardiac output to increase. The development of CAD is ubiquitous, and even without a prior history, MI, acute coronary syndrome, or angina, the presence of CAD should be suspected. HTN is also often present to some

degree and is likely to have reduced ventricular compliance through LVH. This may be recognized as an additional S_4 on auscultation or with an ECG. This further reduces the heart's ability to increase cardiac output. Autonomic dysfunction, arteriosclerosis, and dystrophic calcification may also lead to postural hypotension, carotid stenosis, and aortic valve stenosis, respectively.

Renal function declines insidiously, and, although there may be no clinical symptoms or signs of renal disease, the GFR is reduced. This is best assessed with the creatinine clearance. Serum creatinine is an indirect measure of creatinine clearance but may remain relatively normal owing to the reduced muscle mass. The most clinically important renal concerns in the elderly patient are related to fluid and electrolyte balance. Judicious fluid administration and appropriate monitoring of fluid balance are important. Urinary retention, particularly in males, may also be problematic secondary to benign prostatic hypertrophy or prostate cancer.

Elderly patients often fail to exhibit the classic signs of infection. Pyrexia and an elevated white cell count may be conspicuous by their absence. The signs may be subtle and deterioration rapid. Fatigue, malaise, and altered mental status may be early indicators of infection, electrolyte abnormality, MI, or PE. The ability to make the appropriate diagnosis relies on a strong index of suspicion.

The preoperative evaluation of the elderly patient requires a thorough history, physical examination, and ancillary studies as needed. The latter depends on the history, physical examination, nature of the planned procedure, and the type of anesthesia proposed. Additional studies may include a CBC, chemistries, ECG, chest x-ray, carotid or cardiac ultrasound, and PFTs. Other healthcare providers who are managing the patient's medical conditions may need to be contacted to further clarify the severity of systemic diseases and the patient's suitability for the planned anesthesia and surgical procedure. Perioperative and postoperative medications should be chosen carefully and used judiciously to avoid unwanted responses. Dose reduction should be the rule for most medications [52]. Generally, the fewer the medications introduced, the less likely the patient is to develop side effects.

2.9.7 Pediatric Patients

The pediatric patient provides significant challenges just as does the geriatric patient. The physiology and anatomy of pediatric patients dictate a unique approach to their management. The airway presents challenges in that the mouth is small, the tongue large, the epiglottis large and floppy, and the vocal cords more anterior. Intubation can, therefore, be more difficult and the use of a Miller blade for direct laryngoscopy may be more appropriate. The functional residual capacity is reduced, and the predisposition to rapid and early desaturation is always present. Cardiac output is proportional to heart rate because the pediatric patient has little capacity to increase stroke volume. Blood volume is higher than in adults at approximately 80 mL/kg. Fluid administration and resuscitation need to be carefully administered and are weight based. Urine output is higher than adults and may approximate 2–3 mL/kg/h in infants and toddlers. This declines with increasing age. Children also have large surface areas and can rapidly develop hypothermia. This mandates appropriate techniques to keep them warm including warming blankets and fluid warmers. Drugs should be administered based on weight and should be checked to ensure that they are appropriate for the pediatric patient. Certain NSAIDs such as aspirin should be avoided owing to the potential for developing Reye's syndrome, whereas certain antibiotics such as the tetracyclines and fluoroquinolones should also be avoided owing to their adsorption into mineralizing tissue such as teeth, bones, and cartilage.

2.9.8 Pregnancy

Pregnancy results in many maternal physiologic changes. Cardiac output, minute ventilation, and renal perfusion increase. There is a relative anemia due to dilution. Pulmonary function declines largely due to the reduction in functional residual capacity with the gravid uterus. As the pregnancy progresses, compression of the inferior vena cava while supine reduces cardiac filling with a reduction in cardiac output and blood pressure. Second- and third-trimester pregnancies, therefore, require a lateral decubitus position when supine to avoid this problem. The gravid uterus also increases intra-abdominal pressure, resulting in delayed gastric emptying and increased gastroesophageal reflux disease. The potential for aspiration is, therefore, increased. When general anesthesia is needed, this necessitates a rapid induction with cricoid pressure to help reduce the risk. Nausea and emesis, if present, typically improve as the pregnancy progresses but can further compound the risk of aspiration. The frequency of urination also increases over time as the bladder is compressed by the enlarging uterus. Additional complications that may develop include preeclampsia, eclampsia, and the HELLP syndrome. *Preeclampsia* is characterized by HTN, proteinuria, headache, and edema. The onset of tonic-clonic seizures heralds *eclampsia.* The HELLP syndrome can accompany either preeclampsia or eclampsia and is characterized by hemolysis, elevated liver enzymes, and

low platelets. These are serious and potentially life-threatening conditions that mandate early and aggressive intervention by the obstetrician and gynecologist.

Any drug administered to the mother should be considered capable of crossing the placenta and entering the fetal circulation. Different plasma protein concentrations in the fetus may further compound maternal drug administration by leading to fetal trapping of those drugs. Teratogenic drugs are most problematic in the first trimester during fetal organogenesis. The US Food and Drug Administration (FDA) introduced a classification system for drugs and pregnancy that guides the choice of drugs (Table 2.11).

It would be ideal to use only category A drugs during pregnancy, but most drugs fall into category B or C as defined by the FDA. The decision should be individualized for the patient. Category D and X drugs are contraindicated in pregnancy. Even after childbirth, maternal drugs may result in potential harm to the infant through breastfeeding. Many drugs are present in breast milk, and precautions should be taken that may include choice of another drug that is not present in breast milk, a safer drug, or avoidance of breast feeding for a period of time.

Table 2.11 Drug classification in pregnancy

Class A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy
Class B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
Class C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Class D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
Class X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits

Key Points

- The risk of cardiac complications during noncardiac surgery can be determined by history, functional classification, and the invasiveness of the surgery. Consultation with the team caring for the patient's cardiac disease is always recommended. Cardiac conditions including recent MI, decompensated CHF, ventricular dysrhythmias, and aortic stenosis require additional concerns.
- Pulmonary complications are the most common perioperative complications. Many patients with chronic pulmonary disease are not optimized for surgery leading to unnecessary morbidity and mortality. Pulmonary embolism is a common and serious postoperative pulmonary complication. The occurrence can be significantly decreased with proper management.
- Patients with underlying renal disease who sustain acute kidney injury (AKI) often require continuous renal replacement therapy and may progress to end-stage renal failure. Radiograph contrast dye and nephrotoxic medications can precipitate AKI in the surgical patient. Electrolyte imbalances can lead to fatal dysrhythmias. Fluid overload can precipitate cardiac failure in patients with renal and cardiac disease. Careful perioperative management and understanding the fragility of these patients will prevent and minimize the morbidity and mortality in these patients.
- The impact of liver failure on clotting, drug metabolism and on cardiac and renal function must be assessed. Patients require care for the anesthetic management, operative bleeding and blood loss, and postoperative pain management protocols.
- The surgeon must have a management plan in place for patients with coagulation disorders before elective surgical procedures. Close collaboration with the patient's hematology team is almost always required. Major surgical procedures can be undertaken in these patients with these management plans in place.
- Diabetes affects a significant number of people globally. Surgeons must take into consideration the end-organ damage in the diabetic patients as well as perioperative glucose control.
- Identification of neurological injuries patients with maxillofacial trauma is paramount to prevent further neurological injury during the management of the facial trauma. For the elective patients with neurological disease, careful anesthetic management and seizure control will minimize potential life-threatening perioperative complications.
- Special considerations in the perioperative period need to be taken for patients with a history of malignant hyperthermia, immune deficiencies, obesity, pregnancy, and pediatric patients.

Conclusion

For the oral and maxillofacial surgeon regardless of what procedure they are performing in addition to performing a thorough history and focused physical examination for every patient, it is essential to have an understanding of the common systemic disease and how to manage these patients in the perioperative period. The outcome of the patients' surgery is the responsibility of the surgeon. Optimizing the patient preoperatively and careful management of the patient postoperatively cannot be left to the patients' medical team alone but should be a collaborative effort with the surgeon.

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