Christopher C. Chang
Gary A. Incaudo
M. Eric Gershwin
Editors

Diseases of the Sinuses

A Comprehensive Textbook of Diagnosis and Treatment

Second Edition

Springer

Diseases of the Sinuses

Christopher C. Chang • Gary A. Incaudo • M. Eric Gershwin
Editors

Diseases of the Sinuses

A Comprehensive Textbook of Diagnosis and Treatment

Second Edition

Springer

Editors
Christopher C. Chang, MD, PhD, MBA, FAAAAI, FACAAI
Division of Allergy and Immunology
Department of Pediatrics
Thomas Jefferson University
Wilmington, DE
USA

Gary A. Incaudo, MD, FAAAAI, FACAAI
Division of Rheumatology, Allergy and Clinical Immunology
University of California School of Medicine
Davis, CA
USA

M. Eric Gershwin, MD, MACP, MACR, FAAAAI
The Jack and Donald Chia Distinguished Professor of Medicine
Division of Rheumatology, Allergy and Clinical Immunology
University of California School of Medicine
Davis, CA
USA

ISBN 978-1-4939-0264-4 ISBN 978-1-4939-0265-1 (eBook)
DOI 10.1007/978-1-4939-0265-1
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014940551

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Even a single drop of water will eventually hollow out a stone. We hope this text will be such a drop for sufferers of disease and especially victims of upper airway pathology.

CC, GI, and MEG

Preface

The study of sinus diseases crosses the boundaries of many specialties, but it is primarily the domain of allergists and otolaryngologists. Other disciplines that care for patients with sinus disease include pulmonology, infectious disease, and rheumatology. Since the publication of our first edition, our understanding of sinus disease has changed dramatically, mainly as a result of recent developments and new discoveries in the field of immunology. New immunologic concepts relating to both the innate and adaptive immune systems have helped us to recognize that sinus disease may be more of an inflammatory rather than an infectious process. Since the first edition, pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and their receptors known as pattern recognition receptors (PRRs) have been discovered, and the signaling pathways that lead to chronic inflammation have been refined. New cytokines have been discovered, and the role of IL-17 in chronic inflammation is now being investigated for its role in sinusitis. Other ongoing research concerns the role of other cells including T regulatory cells, dendritic cells, and neutrophils and the pathways that lead to their proliferation, recruitment, and activity. New concepts such as biofilms and their role in chronic sinusitis have afforded us a greater understanding of the pathogenic mechanisms behind the disease. The concept of the unified airway has helped to direct new therapeutic strategies in the treatment of sinusitis, and the mechanism behind the activity of leukotriene and prostaglandin pathways in aspirin-exacerbated respiratory disease and the related sinus disease is of great interest to clinicians and scientists.

This textbook is divided into sections addressing separately the pathogenesis, clinical presentation, and medical and surgical management of acute and chronic rhinosinusitis. Special entities such as autoimmune-related sinusitis, allergy and sinusitis, and aspirin-exacerbated respiratory disease are discussed in separate chapters. The role of immunodeficiency is also addressed. The management section has been updated from the previous edition to incorporate new medical modalities and surgical procedures.

While sinus problems are extremely common, there is very little organized teaching in medical schools. It is the goal of this textbook to provide a comprehensive source of information regarding the basic science of the sinuses and the clinical approach to sinusitis. Sinusitis is not just one disease, and the etiologic factors are likely multifactorial. The authors of this textbook are experts in their field from all over the world and share their expertise and insights from years of collective experience in treating sinus diseases.

The book will appeal to anyone who has an interest in sinus disease, including both physicians and allied health professionals. Internists, pediatricians, allergists, otolaryngologists, and infectious disease specialists will find the book to be a comprehensive source of knowledge. Physician assistants and nurse practitioners who work with specialists who treat sinus disease would also benefit from the book.

We are hopeful that this comprehensive textbook on sinus disease from many experts in the field will provide the reader with different perspectives on how various medical professions or specialties approach the diverse array of sinus problems experienced by our patients.

Philadelphia, PA — Christopher C. Chang, MD, PhD, MBA, FAAAAI, FACAAI
Davis, CA — Gary A. Incaudo, MD, FAAAAI, FACAAI
Davis, CA — M. Eric Gershwin, MD, MACP, MACR

Acknowledgments

The editors of this book would like to thank all the authors for their tireless contribution to their respective chapters. We would also like to thank our administrative coordinator, Dolores DiStefano, for her communications with all the authors during the preparation phase. The editors would also like to thank their families for their sacrifices in order that we may work on this book during weekends and holidays. Finally, we would like to thank our publisher, Richard Lansing, and his staff for their assistance in bringing this textbook to fruition.

Contents

Contributors

Nithin D. Adappa, MD Division of Rhinology and Skull Base, Department of Otorhinolaryngology – Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA, USA

Mohammad O. Aloulah, MBBS, KSUF Department of Otolaryngology, Head and Neck Surgery, King Abdulaziz University Hospital, King Saud University, Riyadh, Saudi Arabia

Peter James Andrews, MBBS, BSc (hons), FRCS (ORL-HNS) University College London Hospital, Royal National Throat Nose and Ear Hospital, London, UK

Marcelo B. Antunes, MD Department of Otorhinolaryngology: Head and Neck Surgery, Perelman School of Medicine of the University of Pennsylvania, University of Pennsylvania Medical Center, Philadelphia, PA, USA

Michael S. Benninger, MD Department of Head and Neck Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

Jonathan A. Bernstein, MD Division of Immunology, Department of Internal Medicine, Allergy Section, University of Cincinnati, Cincinnati, OH, USA

Peter J. Catalano, MD, FACS, FARS Department of Otolaryngology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA

Christopher C. Chang, MD, PhD, MBA, FAAAAI, FACAAI Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, Wilmington, DE, USA

Jinny E. Chang, MD Department of Allergy, Asthma and Immunology, Sansum Clinic, Santa Barbara, CA, USA

Bradley N. Delman, MD Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Gregory P. DeMuri, MD Department of Pediatrics, American Family Children's Hospital/University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Anton R. Dotson, MD Allergy Associates, Chico, CA, USA

Mark S. Dykewicz, MD Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, MI, USA

Nikdokht Farid, MD Division of Neuroradiology, Division of Head and Neck Radiology, Department of Radiology, University of California San Diego, San Diego, CA, USA

Samuel L. Friedlander, MD Department of Allergy/Immunology and Sleep Medicine, University Hospitals of Cleveland, Solon, OH, USA

Jamie L. Funamura, MD Department of Otolaryngology – Head and Neck Surgery, University of California Davis Medical Center, Sacramento, CA, USA

Volker Gudziol, MD, PhD Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Carl Gustav Carus, Dresden, Germany

Rahul C. Gupta, MD Department of Otolaryngology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA

Daniel L. Hamilos, MD Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Brendan C. Hanna, MB, BCh, FRCSI, PhD Department of Surgery-Otolaryngology Head and Neck Surgery, University of Adelaide, Adelaide, Australia

Ng Yuk Hui, MBBS, FAMS Department of Otolaryngology, Singapore General Hospital, Singapore

Gary A. Incaudo, MD, FAAAAI, FACAAI Division of Rheumatology, Allergy and Clinical Immunology, University of California School of Medicine, Davis, CA, USA

Samuel Jayaraj, MBBS, FRCS(Eng), FRCS(ORL-HNS) Barts Health NHS Trust, Whipps Cross University Hospital, London, UK

Douglas R. Johnston, MD Department of Otolaryngology, A.I. duPont Hospital for Children, Thomas Jefferson University, Wilmington, DE, USA

Jan Kastner, MD Department of Otorhinolaryngology and Head and Neck Surgery, Motol Hospital, 1st Medical Faculty of Charles University, Prague, Czech Republic

Jan Kastner Sr., MD Department of Neuroradiology, Medical Faculty in Pilsen, Charles University, Prague, Czech Republic

David W. Kennedy, MD, FACS, FRCSI Department of Otorhinolaryngology: Head and Neck Surgery, Perelman School of Medicine of the University of Pennsylvania, University of Pennsylvania Medical Center, Philadelphia, PA, USA

Todd T. Kingdom, MD Departments of Otolaryngology-Head and Neck Surgery, University of Colorado, Aurora, CO, USA

Jeffrey T. Laitman, PhD, DMedSc(Hon), FAAAS, FAAA, FALA Center for Anatomy and Functional Morphology, Departments of Otolaryngology and Medical Education, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Andrew P. Lane, MD Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins Medical Institutions, Baltimore, MD, USA

William Lawson, MD, DDS, FACS Department of Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Jessica R. Levi, MD Department of Otolaryngology Head and Neck Surgery and the Department of Pediatrics, Boston University/Boston Medical Center, Boston, MA, USA

Jonathan Liang, MD Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins School of Medicine, Baltimore, MD, USA

Wei Yen Lim, MBBS, Master of Radiology Department of Radiology, ANOC Neuroscience and Orthopaedic Center, Kuala Lumpur, Malaysia

Quang Luu, MD Department of Otolaryngology – Head and Neck Surgery, University of California Davis Medical Center, Sacramento, CA, USA

Mahmood F. Mafee, MD, FACR Division of Neuroradiology, Division of Head and Neck Radiology, Department of Radiology, University of California San Diego, San Diego, CA, USA

Michael J. Marmura, MD Department of Neurology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Samuel Márquez, PhD Departments of Cell Biology and Otolaryngology, SUNY Downstate Medical Center, Brooklyn, NY, USA

Stephen J. McGeady, MD Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA, USA

Stanley M. Naguwa, MD Division of Rheumatology, Allergy and Clinical Immunology, University of California, Davis School of Medicine, Davis, CA, USA

David Netuka, MD, PhD Department of Neurosurgery, Central Military Hospital, 1st Medical Faculty of Charles University, Prague, Czech Republic

Richard R. Orlandi, MD Department of Otolaryngology-Head and Neck Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA

Anthony S. Pagano, MPhil Center for Anatomy and Functional Morphology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

James N. Palmer, MD Department of Otorhinolaryngology – Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA, USA

Michael Papaxanthos, MD, DEA Department of Ent and Face and Neck Surgery, Center of Palais Gallien/Clinique Tourny, Palais Ent and Face and Neck Surgery Center, Bordeaux, France

Murugappan Ramanathan Jr., MD Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins Medical Institutions, Baltimore, MD, USA

Vijay R. Ramakrishnan, MD Department of Otolaryngology-Head and Neck Surgery, University of Colorado, Aurora, CO, USA

Nathan Richards, MD Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA, USA

Aaron D. Robinson, MD Department of Otolaryngology – Head and Neck Surgery, University of California Davis Medical Center, Sacramento, CA, USA

Jonathan Romeo, DO Section of Pulmonary, Critical Care, and Allergic and Immunologic Diseases, Wake Forest University School of Medicine, Winston-Salem, NC, USA

Marc R. Rosen, MD Department of Otolaryngology Head and Neck Surgery, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Matthew W. Ryan, MD Department of Otolaryngology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Carmine Taglialatela Scafati, MD, FEBOMFS Servizio di Chirurgia Maxillo-Facciale, Ospedale Santa Maria delle Grazie, Pozzuoli, Naples, Italy

Salvatore Taglialatela Scafati, MD Servizio di Chirurgia Maxillo-Facciale, Ospedale Santa Maria delle Grazie, Pozzuoli, Naples, Italy

Steven D. Schaefer, MD, FACS Department of Otolaryngology, Lenox Hill Hospital, New York, NY, USA

Richard Schmidt, MD Department of Surgery, Nemours duPont Hospital for Children, Wilmington, DE, USA

Craig W. Senders, MD, FACS Department of Otolaryngology – Head and Neck Surgery, University of California Davis Medical Center, Sacramento, CA, USA

Stephen D. Silberstein, MD Department of Neurology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Daniel Simmen, MD, PhD ORL-Zentrum, Center for Rhinology, Skull Base Surgery and Facial Plastic Surgery, The Hirslanden Clinic, Zurich, Switzerland

Ronald A. Simon, MD Division of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, CA, USA

Andrew M. Smith, MD, MS Division of Immunology, Allergy, and Rheumatology, Cincinnati VA Medical Center, University of Cincinnati, Cincinnati, OH, USA

Shannon Doyle Tiedeken, MD Department of Pediatrics, Alfred I. duPont Hospital for Children, Wilmington, DE, USA

Ellen R. Wald, MD Department of Pediatrics, American Family Children's Hospital/University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Meir Warman, MD Department of Otolaryngology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA

Andrew A. White, MD Division of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, CA, USA

Rohan C. Wijewickrama, MD Department of Otolaryngology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA

Troy D. Woodard, MD Department of Head and Neck Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

Peter-John Wormald, MD, FACS, FCS(SA), FRCS(ed), MBChB Department of Otolaryngology, Head and Neck Surgery, Queen Elizabeth Hospital, The University of Adelaide, Woodville South, SA, Australia

Part I
Anatomy and Physiology

Chapter 1
Anatomy of the Nose and Paranasal Sinuses

Samuel Márquez, William Lawson, Steven D. Schaefer, Anthony S. Pagano, Michael Papaxanthos, Bradley N. Delman, and Jeffrey T. Laitman

Anatomy of the Nose and Paranasal Sinuses

Introduction

As a full description of the history, development, and functional anatomy of the nasal complex – nose and paranasal sinuses would require a treatise in itself; this chapter will focus upon those features of gross structure and development most relevant to surgical procedures. In order to fully understand the nature and underlying biology of the nose and paranasal sinus system, multiple approaches were employed here drawing from the diverse backgrounds of the authors (comparative evolutionary anatomists, radiologist, and ENT surgeons from France and the USA who have a combined clinical experience of 120 years of surgical practice). Methods include CT and endoscopic nasal imaging of living humans, examination of dry cranial material, fresh tissue anatomical dissections, and three-dimensional volume-rendering methods that allow digitizing the spaces of the nasal complex for graphical examination. This chapter also addresses issues regarding inconsistencies and vagaries in terminology, as these have often been a major source of confusion among those studying or operating upon the sinuses. For example, the frontal recess, ethmoid infundibulum, and hiatus semilunaris are key anatomical components of the ethmoid region that are defined, described, and explained here as well as being comprehensively illustrated. In addition, an exhaustive 2000-year literature search identified original sources of nomenclature in order to help clarify the persistent confusions found in the literature. This clarification of nomenclature will permit better communication in addition to eliminating redundant terminology. The combination of anatomical, evolutionary, and clinical perspectives provides an important strategy for gaining insight into the complexity of these sinuses.

S. Márquez, PhD (✉)
Departments of Cell Biology and Otolaryngology, SUNY Downstate Medical Center, 450 Clarkson Ave, 5, Brooklyn, NY 11203, USA
e-mail: samuel.marquez@downstate.edu

W. Lawson, MD, DDS, FACS
Department of Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

S.D. Schaefer, MD, FACS
Department of Otolaryngology, Lenox Hill Hospital, New York, NY, USA

A.S. Pagano, MPhil
Center for Anatomy and Functional Morphology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

M. Papaxanthos, MD, DEA
Department of Ent and Face and Neck Surgery, Center of Palais Gallien/Clinique Tourny, Palais Ent and Face and Neck Surgery Center, 68, rue du Palais Gallien, 54, rue Huguerie, Bordeaux 330000, France
e-mail: michael.papaxanthos.orl@wanadoo.fr

B.N. Delman, MD
Department of Radiology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, 1234, New York, NY 10029-6574, USA
e-mail: bradley.delman@mountsinai.org

J.T. Laitman, PhD, DMedSc(Hon), FAAAS, FAAA, FALA
Center for Anatomy and Functional Morphology, Departments of Otolaryngology and Medical Education, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, 1007, New York, NY, USA

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_1,

Defining Paranasal Sinuses on the Basis of Development

The paranasal sinuses are gaseous-filled pockets of bone surrounding the nasal cavity proper that develop from a two-step process of primary and secondary pneumatization. The former process begins prenatally, with each sinus derived from its primordium on the wall of the developing nasal capsule cartilage. These primordia emerge as evaginations of ciliated, pseudostratified, columnar epithelium that invades into the splanchnocranium. At birth, these recesses are generally well defined on the osseous nasal cavity walls and will expand into the surrounding bony elements. Full secondary pneumatization may require 20 postnatal years with extensions to multiple osseous elements in an extramural fashion. At completion of this process, a highly variable collection of spaces, all lined with nasal respiratory mucosa, forms a lifelong communication network with the nasal cavity [1]. Cave [2] next defined a paranasal sinus as (1) having its embryonic respiratory diverticulum expand from the nasal cavity, with which it maintains communication; (2) growth from a specific meatus on the nasal cavity wall; and (3) having a natural ostium that permanently remains associated with its meatus via a patent duct. On this basis, some authors exclude the ethmoid sinus as a true paranasal sinus [3].

Smith and colleagues [4, 5] tracked the fate of cartilages in the lateral nasal capsules of nonhuman primates. In a study of fetal, perinatal, and adult specimens of *Saguinus geoffroyi* (a New World monkey species), they found that ossification of the pars intermedia (middle part of the nasal capsule wall) has begun by the time of birth and produces islands of capsular cartilage in the lateral wall of the nasal cavity [4]. Chondroclasts were detected along the borders of these postnatal cartilages in both *Saguinus* and *Leontopithecus* (two New World monkey taxa that develop extensive paranasal sinuses) and suggest that they serve as an important precursor to the process of pneumatization by the local action of osteoclasts [5]. Other nonhuman primates that do not develop paranasal sinuses exhibit greater continuity of these lateral nasal cavity cartilages.

Clinical Implications

The normal function of the paranasal sinuses is dependent upon both proper drainage and ventilation [6]. During the process of pneumatization, each sinus develops a pattern of drainage, extending through intricate clefts or chambers until it empties into a conjoined space within the lateral wall of the nasal cavity (e.g., ethmoid infundibulum and superior meatus) before reaching the nasopharynx. This confluence of sinus drainage pathways has clinical implications in that infections can spread readily from one sinus to another. Accordingly, knowledge of paranasal sinus development and anatomy is essential to understanding the pathogenesis and spread of sinus infections.

An Overview of the History of Paranasal Sinus Study

Despite a long history of study, the function and development of the paranasal sinuses have remained unclear. The first mention of the sinuses may date back to Hippocrates in 400 B.C.E. who described the nose as a drainage reservoir for fluids produced by the brain. In the second century C.E., Claudius Galen (the great anatomist and personal physician to Roman emperor Marcus Aurelius) described sinuses such as the ethmoid without naming them [7]. No major subsequent contributions to the study of paranasal sinuses were made until 1489 when Leonardo da Vinci illustrated the frontal and maxillary sinuses and further described the latter structure [8] (see Table 1.1 for an overview of the earliest known investigators of the paranasal sinuses) [10–16]. Da Vinci's work was perhaps the first detailed illustrations of human dissections up until this point in history. This development was followed in 1521 by Berengario da Carpi's initial descriptions of the sphenoid and frontal sinuses [16]. He wrote of the frontal bone as containing "two tables within which there is a notable vacuity so as to not weigh down the body." However, the frontal sinus was fully described in 1573 by Volcher Coiter in his *Externarum et Internarum Principalium Humani Corporis Partium Tabulae*, leading some to credit him with its earliest study [12].

Andreas Vesalius, known broadly for his deviation from Gallenic canon, published a discussion of the maxillary sinus in 1543 in his *De Humanis Corporis Fabrica*. By 1615, Peter Paaw published a detailed description of maxillary sinus anatomy in his *Succenturiatus anatomicus* [17]. However, this space is sometimes referred to as the Antrum of Highmore in recognition of the British anatomist Nathaniel Highmore whose 1651 work *Corporis Humani Disquisitio Anatomica in qua Sanguinis Circulationem* described and illustrated the maxillary sinus [18]. Highmore's book, however, describes and illustrates the circulatory system of various systemic regions of the human body (note the complete title of his book), undoubtedly due to his admiration and close association to his mentor William Harvey.[1] Notwithstanding this historical footnote, the maxillary

[1] During 1642, while conducting studies on the embryonic development of the chick, Highmore and William Harvey became close colleagues. Highmore's 1651 treatise was the first anatomical textbook to accept Harvey's theory on the circulation of the blood.

Table 1.1 Paranasal sinus anatomy history

Paranasal sinus	Eponyms	First described	Studies
Maxillary sinus	Antrum of Highmore	Leonardo da Vinci, 1489	da Vinci, 1489 [8]
Sphenoid sinus		Giacomo Berengario da Carpi, 1521	da Carpi, 1521 [16]
Tillaux [25][a]			
Frontal sinus		Volcher Coiter (1534–1576)	Cited in Libersa et al., 1981 [12
		Basilius	Cited in Douglass, 1906 [11]
Ethmoid sinus		Galen (131–201 A.D.)	Galen

Reprinted from Márquez [9]. With permission from John Wiley & Sons, Inc

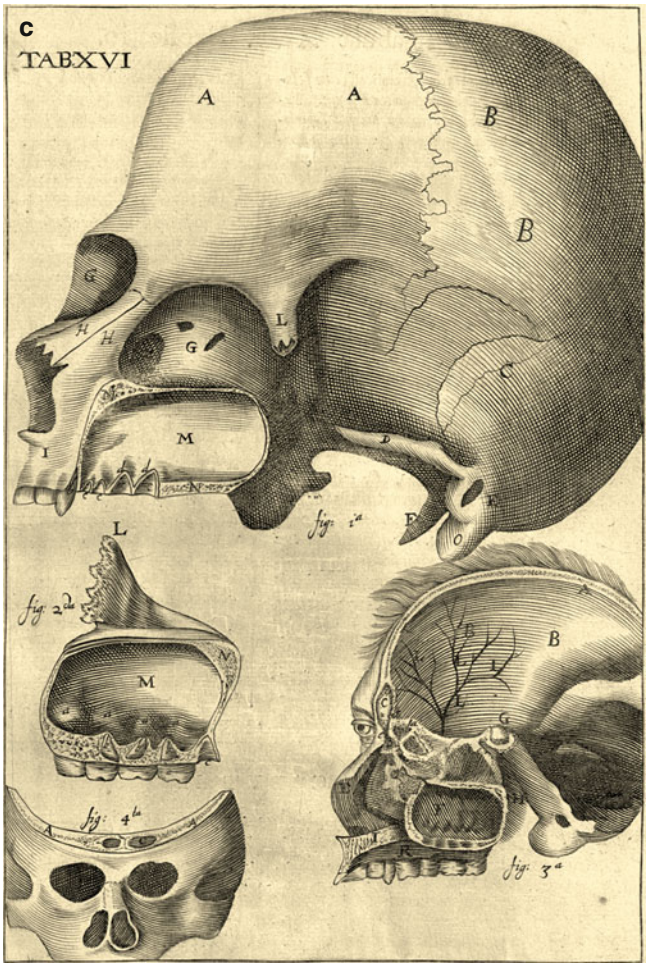
[a]Tillaux was the first to suggest that the sphenoidal sinus was part of the facial sinuses although Johann Riolan (the younger) in 1649 was the first to recognize the paranasal sinuses as an entity [10]

[b]According to Douglass (p. 21) [11], Basilius was the first to describe of the frontal sinus but offers no citation as does Libersa et al. [12] which cites Coiter as the first to describe this sinus

Fig. 1.1 (**a**) The original Title Plate of Nathaniel Highmore's book as it begins "Discussion of the Human Body Anatomy and of the Blood Circulation." This work was printed by the English bookseller Samuel Brown in 1651. (Courtesy of the New York Academy of Medicine Library). (**b**) The magnificent and detailed frontispiece of Highmore's book which includes drawings of Hippocrates, the Father of Medicine and the great anatomist Galen of Pergamon, whose non-human animal dissections became unquestioned doctrine for 1,000 years. As a tribute, Highmore puts the portrait of his mentor William Harvey (bottom right) on this page. Note the central drawing, which likens the human blood circulation to the water flowing from a mountain, with the various tributaries nourishing the surrounding land. (Courtesy of the New York Academy of Medicine Library). (**c**) The original illustration of Highmore's description of the maxillary sinus as it appears on page 227 in his 1651 "Discussion of the Human Body Anatomy and of the Blood Circulation". Note Highmore recognizes the existence of the frontal sinus as illustrated in fig 3 and fig 4. Letters on figures denote the name of the skull bones. (Courtesy from the New York Academy of Medicine Library)

sinus is the anatomical entity for which Highmore is best remembered (Fig. 1.1). Some clinical texts (e.g., Anon and colleagues [19]) continue to erroneously attribute the earliest description of the maxillary sinus to Highmore instead of da Vinci who illustrated and described this sinus in 1489 (see Laitman [20] for the chronology of da Vinci's work).

Fig. 1.1 (continued)



Up until the seventeenth and eighteenth centuries, the paranasal sinuses were included in broader anatomical treatises and usually given brief mention. It was not until the seventeenth and eighteenth centuries that studies began to focus upon the sinuses themselves. Most of these works, however, were focused on theoretical questions addressing functional explanations for the existence of these "hollow" spaces in the cranium [21, 22]. Such anatomical observations were not usually done for systematic assessment of structures, but rather appear to have promoted their own hypotheses on respiratory function [10]. It was only in the nineteenth century that anatomists such as Bosworth [23] and Turner [24] again focused on the functional anatomy of the sinuses. Among them, Tillaux [25] was the earliest to include the sphenoid sinus as part of the paranasal sinus complex in 1862. He was followed by the great Austrian anatomist Emil Zuckerkandl who published the first, detailed, and systematic anatomical and pathologic description of the paranasal sinuses [26–28]. Indeed, his observations and illustrations were so precise and meticulous that they form the foundation for much present-day knowledge, and Zuckerkandl himself is regarded as the "father" of modern sinus anatomy [10, 29].

Today the functional role(s) of the paranasal sinuses remain elusive (see Márquez [9] for discussion). Table 1.2 provides a summary of the many functions ascribed to these sinuses over the last two thousand years. The various putative reasons for the existence of the sinuses can be grouped into three categories: architectural, physiological, and nonfunctional. It should be noted that the concept of function is best approached with caution. The functional role of a feature is its action or how the feature works [95]. Any aspect of purpose, or of design, should be avoided. Function may include the physical and chemical properties of the feature distinct from the biological role it has or had in life. Many workers in functional anatomy have utilized both potential meanings as absolute equals, when in fact they are not [95].

During the pre-antibiotic era, in the early part of the twentieth century, anatomical studies focused upon descriptions, which could improve procedures for cannulation or drainage of pathologic sinuses [96–101]. It became apparent that after treatment, sinus infection would often recur in the same treated sinus and would often spread and infect the other nontreated sinuses. These secondary infections were explained by the close and intimate relationships seen in the anatomy of the

Table 1.2 Historical overview of hypothesized functions ascribed to the paranasal sinuses

Theoretical function 2	Authors
Structural role	
Skull lightening	Blanton [7], Cleland [30]; Paulli [31], Schoennemann [32], Onodi [33], Nemours [34], Shea [35], Moller [36], Buhler [37, 38], Crelin [39], Schummer et al. [40], Davis et al. [41]
Assist in facial growth and architecture	Eckley [42], Dieulafé [43], Moss and Young [44], Enlow [45], Blaney [46, 47], Moore and Persaud [48], Davis et al. [41]
Part of normal skull pneumatization	Witmer [49–52]
Function as pillars for dispersal of masticatory forces	O'Malley [53], Badoux [54], Enlow [45], Preuschoft et al. [55]
Allow functional decoupling of inner and outer tables by occupying intervening space	Paulli [31], Weidenreich [56, 57], Moller [36], Buhler [37, 38]
Occupies space between the mechanical bony pillars	DuBrul [58], Sicher [59]
Provide protection for the brain	Rui et al. [60], Geist [61], Schaffer and Reed [62], Davis et al. [41]
Provide thermal insulation for CNS and sense organs	Bignon [63], Bremer [64], Proetz [65]
Widens the skull base for the support of the large palate to accommodate the permanent dentition	Keith [66, 67], Underwood [68]
Physiological role	
Aid in storing a medullary substance	Bartholin [12]
Serves to increase surface area of olfactory mucosa	Braune and Clasen [69]
Provides even distribution of inspired air, which aids in olfaction	Strickland [70]
Serves as an adjunct in air conditioning of inspired air	O'Malley [53], Eckert-Mobius [71], Sato [72], Proetz [73, 74], Gannon et al. [75]
Imparts resonance to the voice	Cleland [30], Bignon [63], Zuckerkandl [27], Dieulafé [43], Hartz [76], Underwood [68], Mosher [77], O'Malley [53], Eckert-Mobius [71], Wegner [78], Dyce et al. [79], Leakey and Walker [80]
Assists in regulating intranasal pressure	Coffin [81], Neumayer [82], Frers [83], Suarez [84], Del Cañizo [85], Rice and Gluckman [86]
Serves as respiratory reservoirs for mucus secretions	Alger [87]
Assist in flotation at some point in time in its phylogenetic heritage	Bignon [63], Proetz [65], Wegner [78], Rhys Evan [88]
Produces nitric oxide gas	Lundberg et al. [89]
Nonfunctional role	
Exists as evolutionary remains of useless air spaces	Ingersoll [90, 91], Negus [1, 92], Takahashi [93], Lund [94]

Reprinted from Márquez [9]. With permission from John Wiley & Sons, Inc

paranasal sinuses. At this time, the importance of understanding prenatal development as a vehicle to understand sinus surgery became more fully appreciated [102]. Later, technological advances saw the development of endoscopic and external sinus procedures. Having a knowledge of development, surgeons practicing endoscopic sinus surgery today primarily focus attention on the role of the ethmoid sinus in recurrent paranasal sinus infection [103]. We are reminded that recurrent frontal or maxillary sinusitis was recognized earlier this century by Schaeffer [96], who stated that "the maxillary sinus is often a cesspool for infectious material from the sinus frontalis and certain of an anterior group of cellulae ethmoidales." Such is an example of knowledge lost, only to be rediscovered when new interest in the sinuses arose following advances in imaging modalities, instrument technology, and the work of modern sinus surgeons [104, 105].

Ethmoid Sinus

Development and Functional Anatomy

The ethmoid sinus is distinct from the other paranasal sinuses both in the extent of its pneumatization and its embryologic origin in the wall of the cartilaginous nasal capsule differing from all the other sinuses which develop from its primordia [3]. Additionally, the ethmoid sinus does not meet Cave's criteria for classification as a paranasal sinus (see above) [2], and it has been proposed by the French otolaryngologist Roger Jankowski that it is derived phylogenetically from the

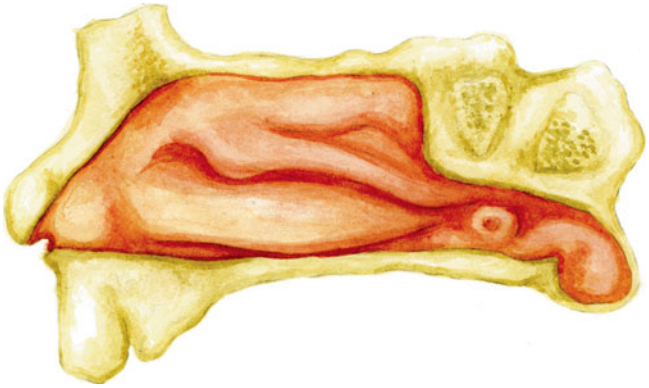


Fig. 1.2 Parasagittal view showing mucosal swellings and evaginations of the future concha of the lateral nasal cavity wall in a 190-day-old fetus. Note the rudimentary nature of the superior nasal conchae (Courtesy of Samuel Márquez, PhD & Bridget Thomas McKnight [American Museum of Natural History])

olfactory system, with a partitioning of the olfactory cleft and ethmoid sinuses occurring during the course of human evolution [106, 107]. The ethmoid bone has been called the "keystone in the sinus system" [108] as all the paranasal sinus drainage pathways are either through or adjacent to its lateral wall. Morphologically, descriptions of the ethmoid bone shape have ranged from ethmoidal "bloc" [109], to pyramidal shape, to a trapezoidal "box" [41]. Ritter [110] believed the ethmoid sinus to be the principal support for the anterior cranial fossa, while others proposed that its primary roles are to both maximize the surface area of the mucosa and absorb the energy of trauma by permitting it to collapse to protect the eyes and the brain [41].

The extensive fetal developmental studies of Schaeffer [102, 111–113] showed no morphological changes on the lateral nasal wall until the 38th to 40th day of prenatal growth when two shallow grooves are observed above and below the region where the inferior nasal conchae or maxilloturbinal eventually develops (Fig. 1.2). Once mesenchymal differentiation in the area of the inferior nasal conchae ensues, it has the effect of producing a more prominent fold of the conchae and aids in accentuating the depth of these grooves or furrows. The developing folds are considered the primitive step for conchal formation, whereas these furrows constitute the future inferior and middle meatus. By the 63rd to 70th day of prenatal development, six major furrows develop along with their corresponding ridges or folds called the ethmoturbinals (i.e., turbinates arising from the ethmoid). Stammberger [115] divides these folds into two anatomical components: an anterior ascending portion (i.e., the ramus ascendens) and a posteroinferior descending more horizontal portion (i.e., ramus descendens). However, not all of these folds and furrows persist during the development of the fetus. For example, from the 7th month to term, one could find three to five ethmoidal conchae with a corresponding number of intervening meatus, but after birth, due to either fusion [22] or obliteration [114], only two or three ethmoidal conchae may persist (e.g., middle, superior, or supreme ethmoidal conchae – see ref. [102]). Although Santorini [115] was the first anatomist to describe all three ethmoidal conchae, the following commentary by Schaeffer [111] illustrates the confusion revealed in the literature regarding the "typical" number of conchae found present at birth:

> Books generally describe and picture two ethmoidal conchae as the typical number, and apparently would have us think that three ethmoidal conchae are rather exceptional. (p. 614)

In a large series of cadaver material, both Schaeffer [111] and Van Alyea [116] have shown that a supreme concha was present in 62.5 and 67 % of their subjects studied, while Zuckerkandl [99] recorded a supreme concha in 80 % of his 120 subjects. However, Lang and Sakals [117] reported only 17 % of their subjects as having a supreme concha, and Bingham et al. [118] found no supreme conchae in their samples. This suggests variable nomenclature or application thereof among investigators. Today still, the issue regarding the typical number of ethmoidal conchae present remains unclear.

The first primary furrow of the lateral nasal wall is located between the first and second ethmoturbinals, sometimes referred to as the first interturbinal furrow. The first ethmoturbinal (Fig. 1.3) is regarded by most authors as the equivalent of the nasoturbinal found in higher mammals, including New World monkeys (e.g., howler monkey) and the lesser and great apes (e.g., gibbons and orangutans) [2, 102, 114, 119, 120]. In humans, the nasoturbinal regresses during later development and never fully develops into a permanent turbinate. However, of anatomical and clinical interest, the ramus descendens of this "failed" first ethmoturbinal becomes the uncinate process while the ramus ascendens becomes the agger nasi, both of which are important landmarks and will be discussed later. The appearance of the first furrow is also an important developmental stage because its descending anterior region will become the ethmoid infundibulum, while the superiorly ascending region becomes the frontal recess. The former is an important region where a number of the paranasal sinuses will eventually drain into and through to the nasal cavity. The frontal recess, on the other hand, undergoes further development with additional furrows appearing, or what Kasper [99] termed "pits," which are outgrowths of epithelium that

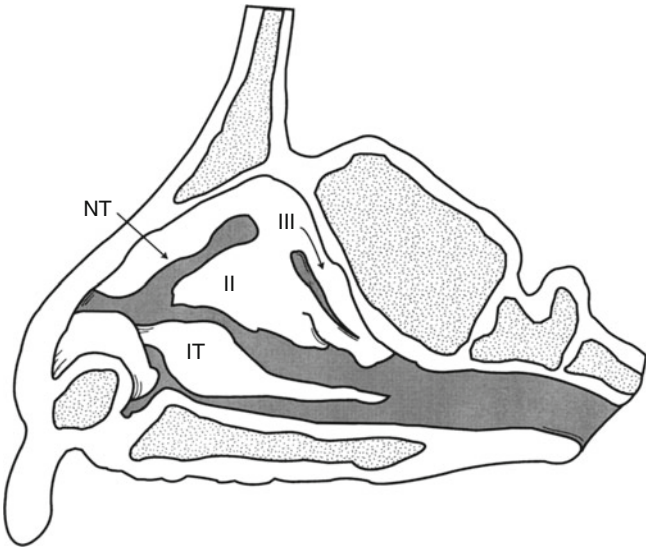


Fig. 1.3 Parasagittal schematic drawing of the lateral nasal cavity wall of an Old World monkey showing inferior turbinate (*IT*), the nasoturbinal (*NT*), middle turbinate (*II*), and superior turbinate (*III*) (Courtesy of Samuel Márquez, PhD & Bridget Thomas McKnight [American Museum of Natural History])

appear as spherically shaped excavations in this region. Pneumatic invasion of the frontal bone originating from one of these pits in the frontal recess results in the development of the frontal sinus (see Frontal Sinus section for further discussion).

At birth, the ethmoid sinus consists of an anterior and posterior division. At this time, the fluid-filled ethmoids are difficult to recognize on routine radiography [121]. However, Spaeth et al. report that CT imaging reveals non-pneumatized ethmoid cells in at least 94 % of newborns [122]. Wolf et al. [123] reported the dimensions of the newborn's ethmoid sinus system to be 8–12 mm in anterior-posterior length, 1–5 mm in superior-inferior height, and 1–3 mm in medial-lateral width. They also found the anterior and posterior ethmoid air cells to be complete in number, although not in terms of adult size. Other studies have confirmed their findings [124]. By ages 1–4 years, the ethmoid has rapidly expanded to 12–21 mm in length, 8–16 mm in height, and 5–11 mm in width. The ethmoid labyrinth may be visualized consistently by plain film radiography only after the first year postpartum and only if the air-filled divisions of the ethmoid sinus are well developed [125]. At ages 4–8 years, the ethmoid sinus system is 18–24 mm in length, 10–15 mm in height, and 9–13 mm in width [106]. By the 12th year, the ethmoids have reached nearly adult size, with expansion during puberty primarily involving the bones outside the ethmoid capsule [126].

The designation of two divisions for the ethmoid sinus is best understood when reviewing the "architecture" of the ethmoid labyrinth (see discussion in Shambaugh [127]). During development, the attachments of the various bony structures arising from the ethmoid (i.e., conchae, uncinate process) to the lateral wall are formed by one of several ground plates or *basal lamellae* (Figs. 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, and 1.10). While the lateral attachments of these lamellae end abruptly, their medial aspects project beyond the labyrinth and form prominences, which extend into the nasal cavity. The most anterior of these lamellae is the lateral extension of the uncinate process. The *second lamella* is referred to as the plate of the bulla because its extension into the nasal cavity forms the bulla ethmoidales, while the third lamella serves as the attachment of the middle turbinate. The *third lamella* is an important anatomical structure, demarcating the division between the anterior ethmoid cells from the posterior cells and so, essentially, dictating the drainage patterns of these air cells into the middle and superior meatus, respectively. It is also clinically significant as it is considered a natural boundary to the spread of infection into the posterior ethmoid, and it is the posterior landmark in anterior ethmoidectomy (Fig. 1.11) [128]. As seen in Figs. 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, and 1.12, this third lamella can be divided into three segments characterized by the anterior one third having a horizontal orientation and attaching superiorly, by the middle third considering the vertical portion coursing posteriorly and obliquely, and by the posterior one third assuming an inferior horizontal position attaching laterally. The physical attachment of this basal lamella in three different planes (i.e., superior, vertical, and horizontal) provides much of the structural support of the middle turbinate [129]. However, when this bony plate is removed during posterior ethmoidectomy, the turbinate loses its stability. Note that this lamella is not always structurally fixed and that the developing ethmoid air cells have a tendency to expand to all available space, which Seydel [128] called "the struggle for space of the ethmoid." This results in air cells impinging and perhaps distorting the osseous barrier, but the lamella always remains intact and prevents intermingling of cells (Fig. 1.13) [114, 116].

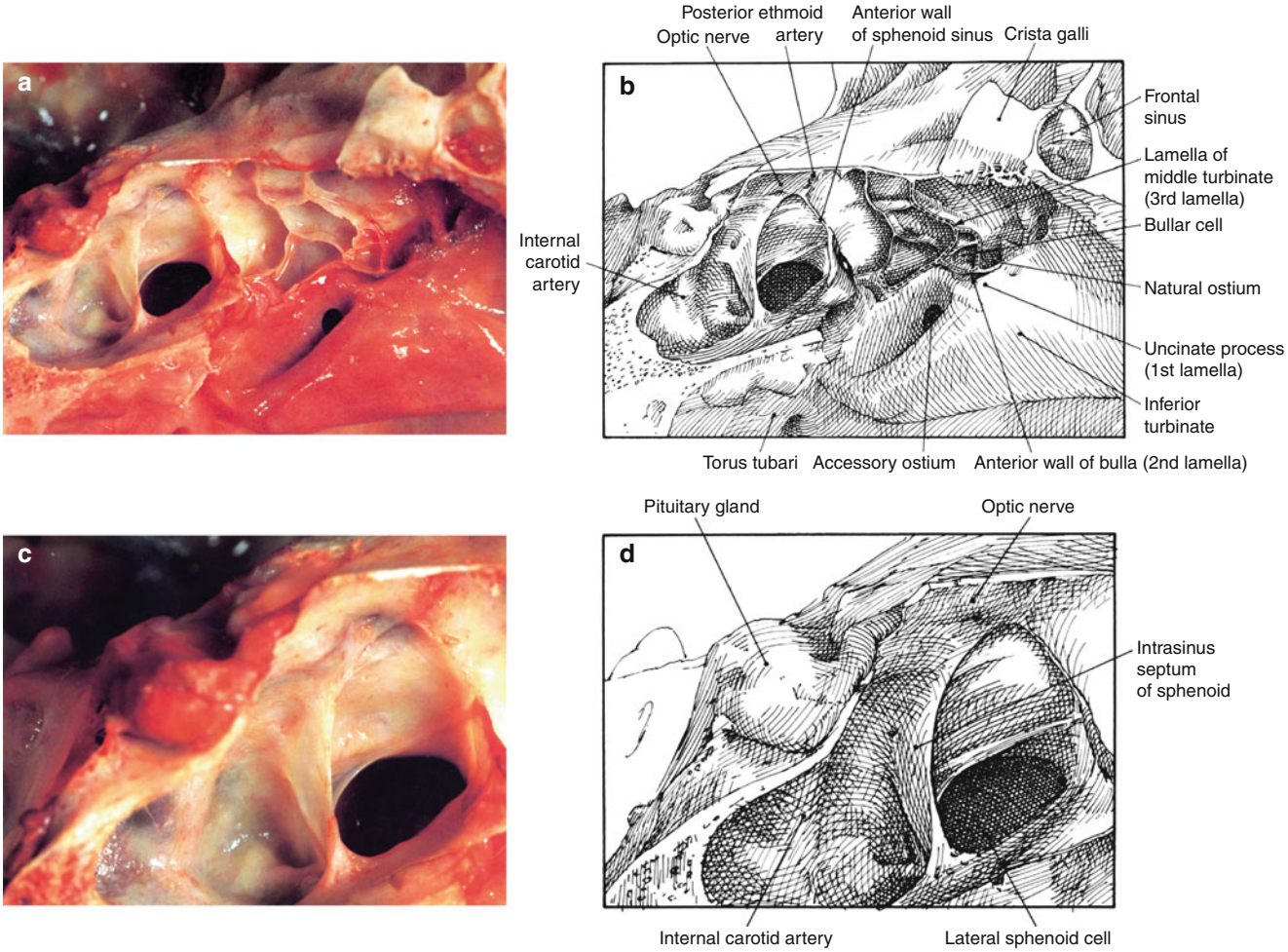


Fig. 1.4 (**a**) Extensively pneumatized sphenoid and ethmoid sinuses. (**b**) Several basal lamellae are demonstrated along with both natural and accessory ostia of maxillary sinus. (**c**) Enlargement of (a) showing sphenoid and ethmoid sinuses. Medial aspect of optic nerve is exposed by ethmoid cells (similar to Onodi cell), and internal carotid artery is transversing the lateral wall of the sinus. (**d**) Extensive pneumatization of the ethmoid bone and extension of posterior ethmoid cells into the sphenoid bone is well demonstrated in this specimen (Courtesy of Steven D. Schaefer, MD)

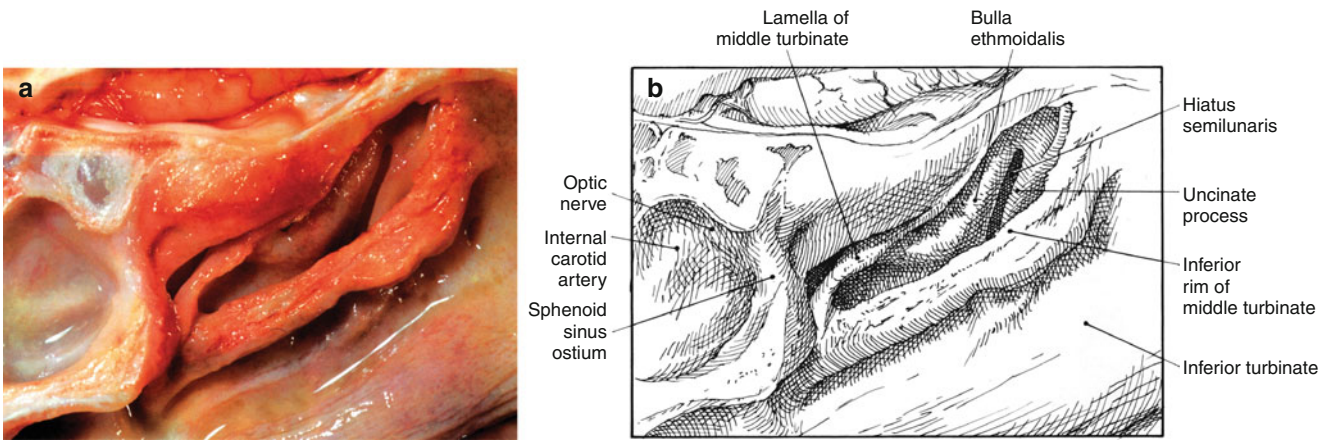


Fig. 1.5 (**a**) Body of middle turbinate has been removed, leaving intact rim of middle turbinate. (**b**) Diagram of (a) shows the course of the third lamella or basal lamella, which supports the middle turbinate. This lamella has three segments, a superior horizontal, an anterosuperior to posteroinferior oblique, and an inferior horizontal segment (Courtesy of Steven D. Schaefer, MD)

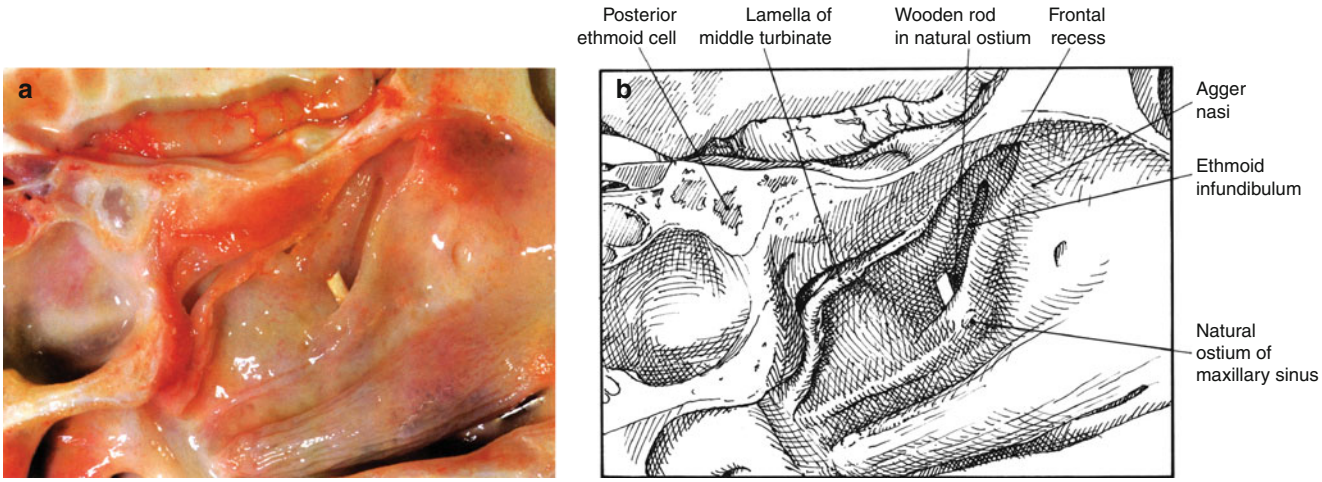


Fig. 1.6 (**a**) Next dissection reveals lateral nasal wall. Ostium of maxillary sinus is cannulated by a wooden rod. (**b**) Diagram of (a) (Courtesy of Steven D. Schaefer, MD)

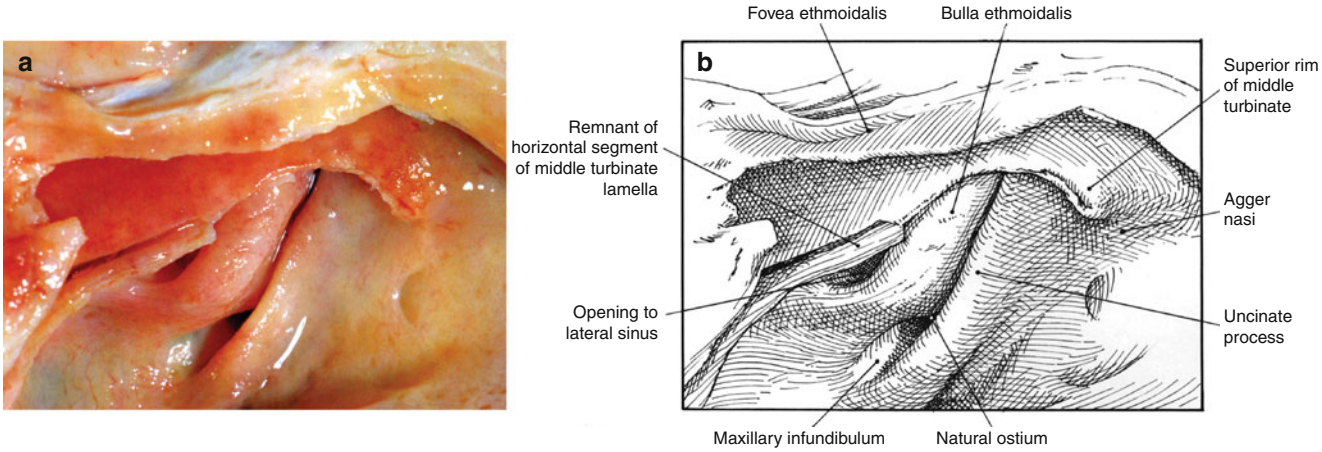


Fig. 1.7 (**a**) Enlargement of Fig. 1.6a. (**b**) Diagram illustrates remnant of posterior horizontal segment of basal lamella of middle turbinate. Also seen is the opening to lateral sinus, which is located between the bullar and posterior ethmoid cells (Courtesy of Steven D. Schaefer, MD)

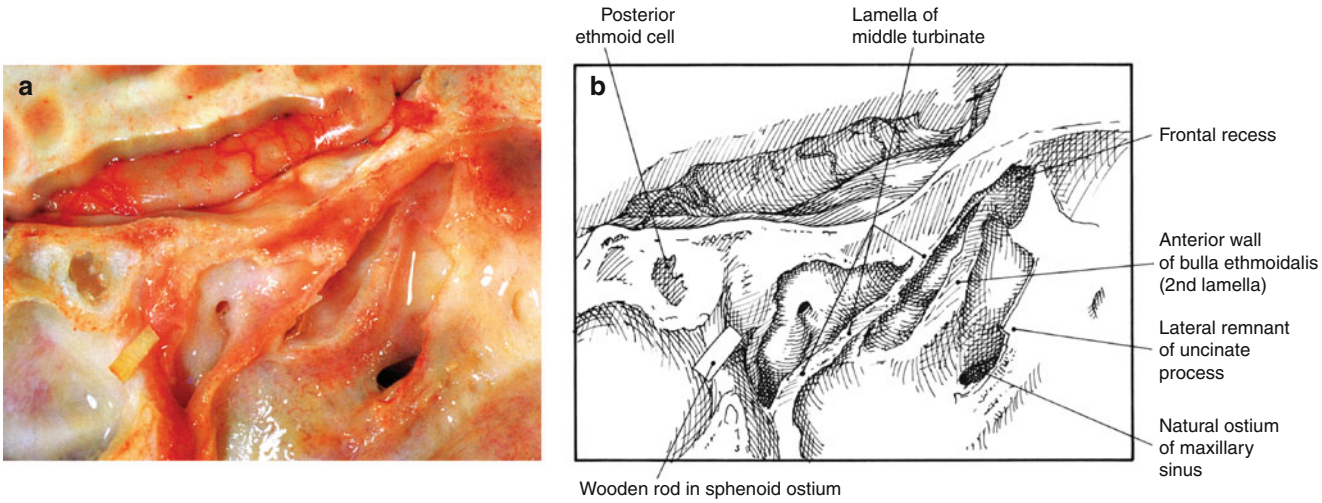


Fig. 1.8 (**a**) Medial aspect of bulla ethmoidalis and uncinate process have been removed to reveal lamella of middle turbinate and natural ostium of the maxillary sinus. (**b**) Three of the lamellae or plates of bone from the lamina papyracea to the lateral nasal wall are shown in illustration. The most anterior lamella is from the uncinate process. The second lamella is the lateral extension of the anterior wall of the bulla. The third or basal (also known as grand) lamella provides the attachment of the middle turbinate to the lamina papyracea (Courtesy of Steven D. Schaefer, MD)

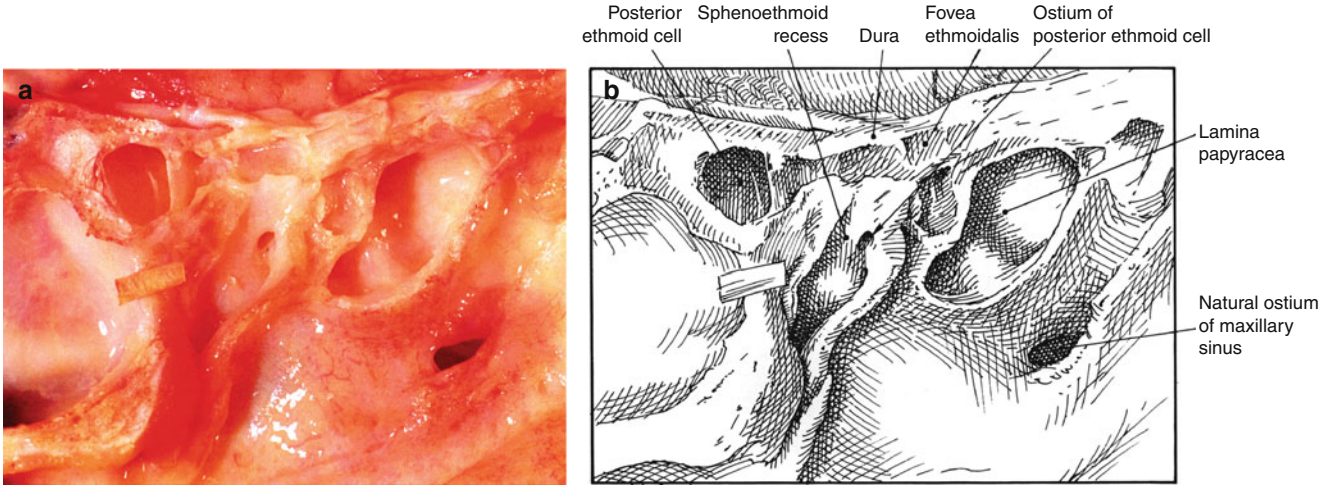


Fig. 1.9 (**a**) Further removal of lateral nasal wall. (**b**) Diagram of (a) (Courtesy of Steven D. Schaefer, MD)

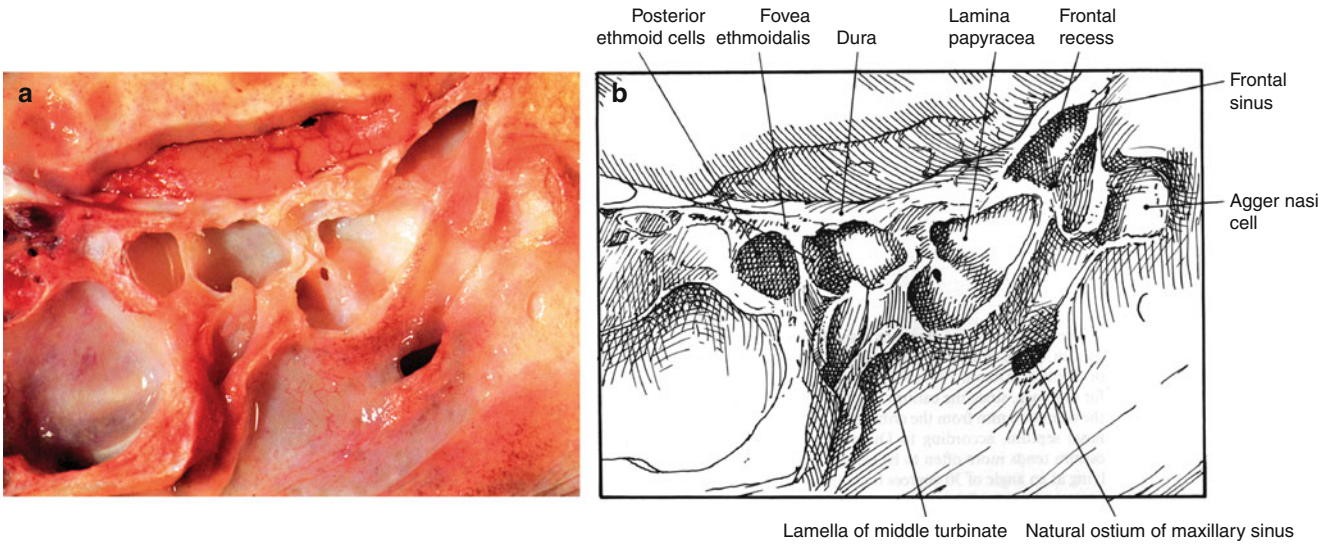


Fig. 1.10 (**a**) All ethmoid cells have been exposed to reveal their location within the ethmoid and adjacent bones. (**b**) Note the relationship of the agger nasi (extramural infundibular cells) to the frontal sinus and the most posterior ethmoid cell to the sphenoid sinus. The latter is important because extramural ethmoid cells may be confused with the sphenoid sinus (Courtesy of Steven D. Schaefer, MD)

Another important variation in ethmoid anatomy is the *lateral sinus*, which forms a space bounded laterally by the lamina papyracea, posteriorly by the lamella of the middle turbinate, anteriorly by the posterior aspect of the bulla ethmoidalis, and superiorly by the fovea ethmoidalis (Figs. 1.7 and 1.11). When the second lamella does not extend to the fovea ethmoidalis, the sinus lateralis continues anteriorly to the frontal recess. This gives rise, above the bulla, to a space known as the *suprabullar furrow* or *suprabullar recess*, which communicates with the middle meatus. The *fourth lamella* is at the attachment of the superior turbinate, and when a supreme turbinate is also present, a *fifth lamella* arises lateral to this turbinate.

Clinical Implications

In the adult, the ethmoid bone viewed in a transverse section forms a pyramid with its blunted apex located anteriorly and the wider base located posteriorly (Fig. 1.14). The entire sinus measures 4–5 cm anteroposteriorly, 2.5 cm inferosuperiorly, 0.5 cm wide anteriorly, and 1.5 cm posteriorly [130]. Various descriptions of the ethmoid roof, such as fovea or foveolae

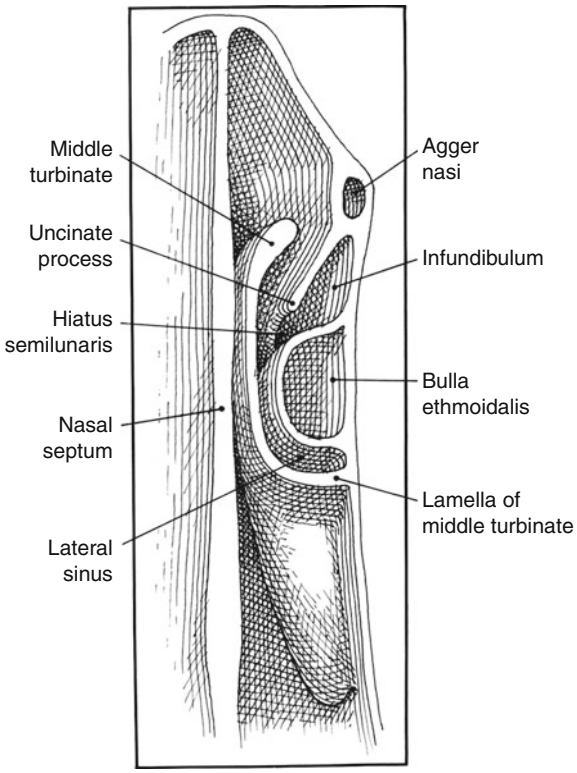


Fig. 1.11 Diagram in axial plane of right lateral nasal wall. Note lateral sinus between posterior aspect of bulla ethmoidalis and third lamella and basal lamella of the middle turbinate (Courtesy of Steven D. Schaefer, MD)

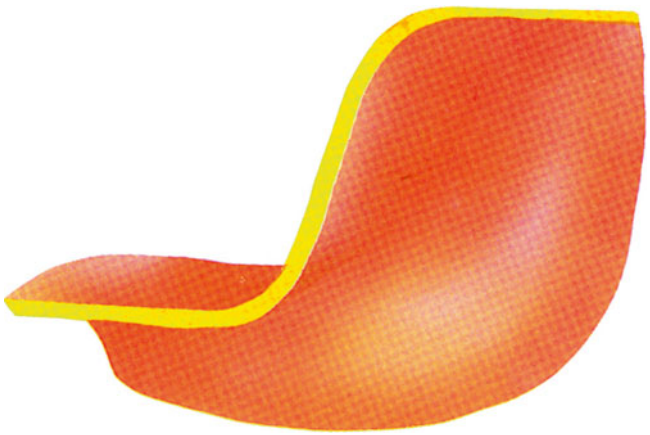


Fig. 1.12 Lateral surface of middle turbinate where yellow border signifies the areas of attachment of the lamella. Note the anterior one third attaches superiorly, the middle third attaches to the lateral wall of nasal cavity in a somewhat vertical manner, and the posterior one third although, also attaching to the lateral wall, does so in a horizontal manner (Reprinted from Stammberger [114])

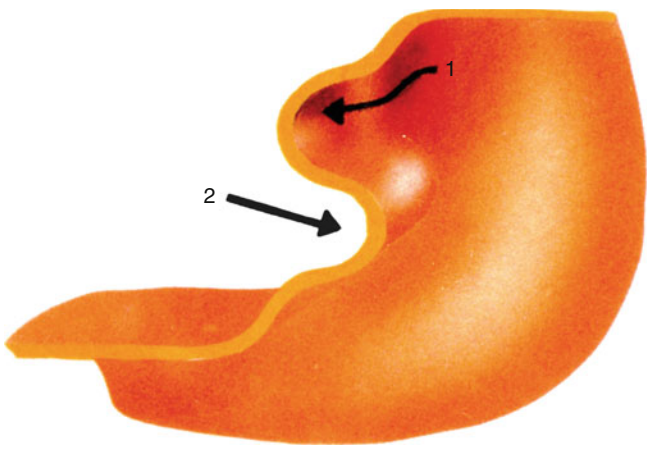


Fig. 1.13 As seen in this illustration, the basal lamella may become somewhat distorted due to the impinging ethmoid air cells (1) representing anterior ethmoid air cell(s) and 2 shows posterior ethmoid air cell(s), but the integrity of the barrier is nevertheless maintained (Reprinted from Stammberger [114])

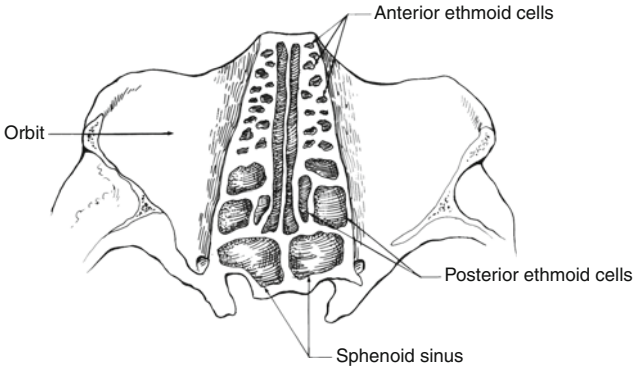


Fig. 1.14 Illustration showing transverse ethmoid (Courtesy of Samuel Márquez, PhD)

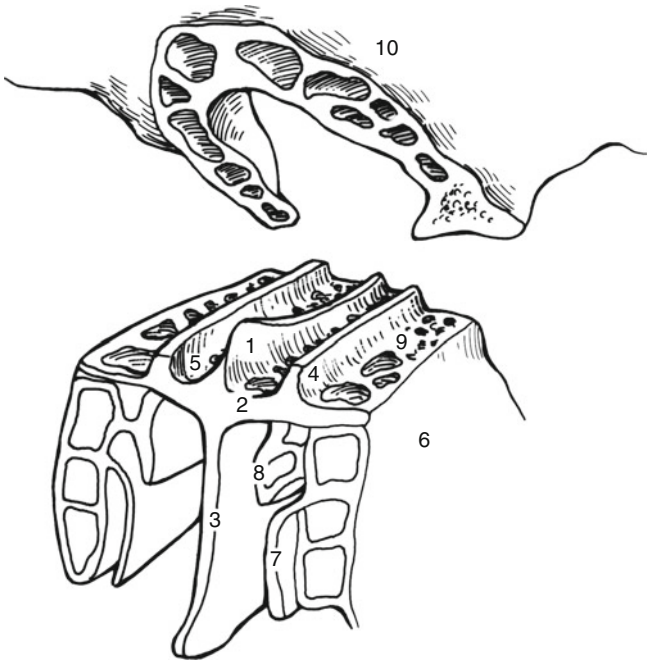


Fig. 1.15 Illustration showing fovea ethmoidalis residing within the frontal bone (*10*). Crista galli (*1*) site of attachment of the falx cerebri; cribiform plate (*2*) through which the olfactory filaments passes through; (*4* and *5*) bony partition between cribiform plate and ethmoid cells; orbital plate (*6*); middle conchae (*7*); superior conchae (*8*) shown here as a pneumatized turbinate or a concha bullosa; (*9*) are the open roofs of the ethmoid cells with (*10*) showing its superior bony cover (Courtesy of Samuel Márquez, PhD)

ethmoidales, have caused considerable confusion over the years. Lateral to the cribriform plate and the insertion of the middle turbinate, numerous ethmoid air cells open superiorly and are closed by the frontal bone. Mosher [132] described this anatomy as follows:

> [U]pon the whole length of the ethmoidal notch of the frontal bone there is a row of little half cells which is matched and completed by a similar row of cells upon the upper surface of the lateral mass of the ethmoid bone. (p. 832)

Since the indentations or foveolae of the frontal bone cover the corresponding clefts and cells of the ethmoid, the frontal bone is anatomically considered the roof of the ethmoid complex (Fig. 1.15) [132]. In addition, the use of the term fovea to describe the entire ethmoid roof does not distinguish between the endonasal view and the endocranial perspective as viewed from the olfactory groove. These air cells are either at or usually above the level of the cribriform plate. Thus, the term fovea or *foveola ethmoidalis*[2] (fovea meaning "pit," rather than roof or tegmen) extends on an average 2–3 mm above the more medial cribriform plate (Fig. 1.16). The plane of the fovea slopes inferomedially, with this bony plate sometimes at an acute angle to the cribriform plate. In such cases, the fovea is particularly vulnerable to penetration along the medial aspect of its anatomy. The lateral wall of the ethmoid bone is the *lamina papyracea* (*orbital plate*), which forms the most constant component.

An analysis of the medial wall of the bony orbit shows the contour of the *lamina ossis ethmoidalis*, or *lamina papyracea*, of the *recessus frontalis* and of the *os lacrimale* (Fig. 1.17). Craniofacial sutures can be clearly identified that include the frontoethmoid, frontolacrimal, frontomaxillary, and frontonasalis sutures (Fig. 1.17). A number of ocular muscles are

[2] Foveolae from the Latin, foveolae ethmoidales ossis frontalis, meaning ethmoid pits of the frontal bone.

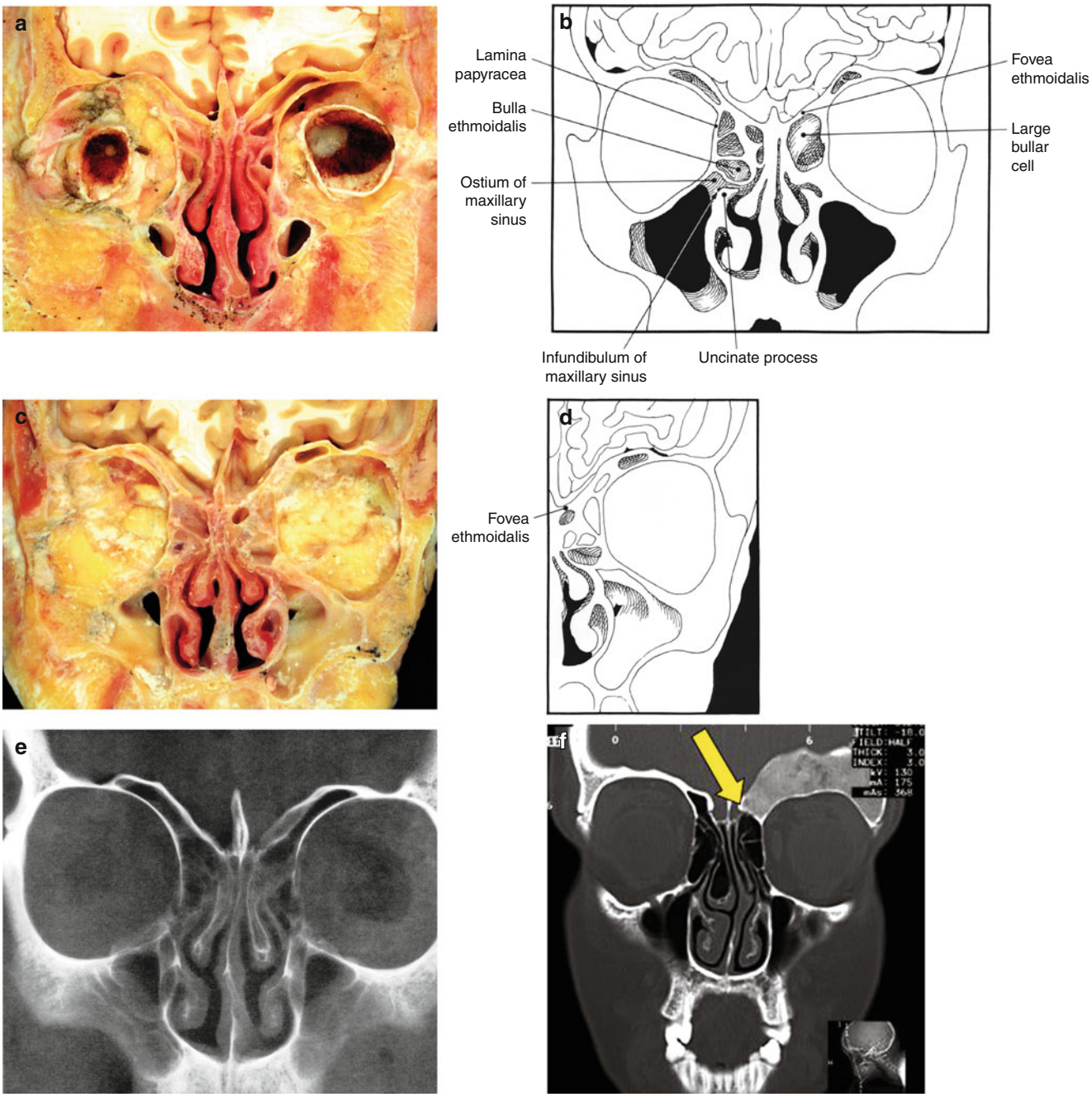


Fig. 1.16 (**a**) The anterior surface of the coronal section contiguous with (c) is shown. It is at the level of the ventral aspect of the maxillary sinus. (**b**) Note the continuation of the infundibular cells. The most constant of these cells is the agger nasi or pneumatization of the lacrimal bone. (**c**) Posterior surface of specimen in (a) is shown, which includes the ventral portion of the maxillary sinus. (**d**) Residual infundibular and supraorbital cells are shown in this section. (**e**) Plain film radiograph of the specimen shown in (a, c) (Courtesy of Steven D. Schaefer, MD). (**f**) Coronal CT scan of patient with fibrous dysplasia of the left frontal bone. As this process involves the entire frontal bone, the image also illustrates that the roof of the ethmoid sinus is the frontal bone (*yellow arrow*). The term *fovea ethmoidalis* refers to the pitlike evagination formed by the migration of the ethmoid cells into the frontal bone. Contrary to common usage, the *fovea ethmoidalis* is not the roof of the ethmoid sinus (Courtesy of William Lawson, MD)

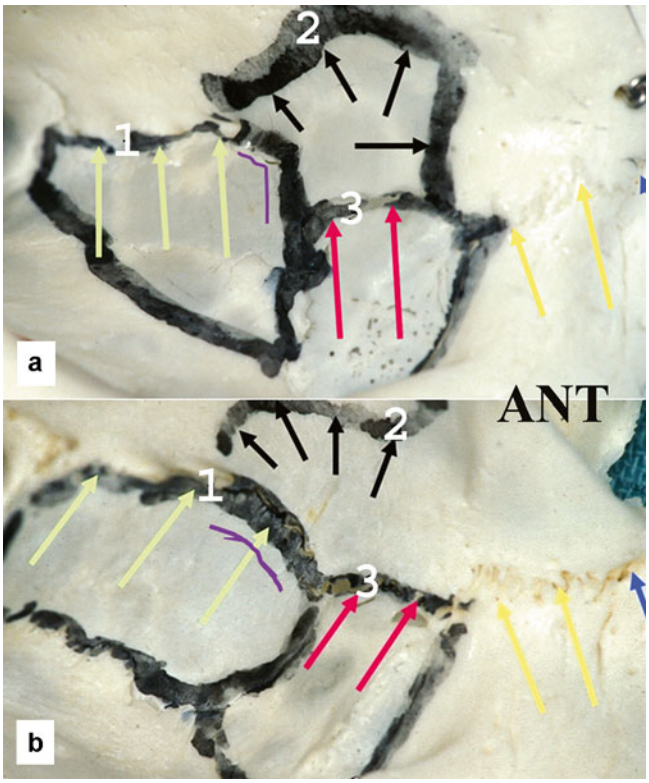


Fig. 1.17 (**a**, **b**) View on medial wall of right orbit. *Thick black lines*: (*1*) Contour of lamina *orbitalis ossis ethmoidalis* (lamina papyracea), (*2*) Contour of *lamina recessus frontalis*, (*3*) Contour of lamina of *os lacrimale. Green arrows*: superior border of lamina papyracea (*sutura frontoethmoidalis*). *Red arrows*: superior border of *os lacrimale (sutura frontolacrimalis*). *Black arrows*: anterosuperior border of frontal recess (in **a**) and superior border only (in **b**). *Yellow arrows*: *sutura frontomaxillaris. Blue arrow*: *sutura frontonasalis*. Note the difference in height between the superior border of the lacrimal and ethmoidal bone! This difference results in a bend (in **a**) or even a notch (in **b**) of the *sutura frontoethmoidalis* (*incisura lamina orbitalis*, *ossis ethmoidalis,* or *lamina papyracea – purple line*), ANT denotes anterior (Courtesy of Samuel Márquez, PhD)

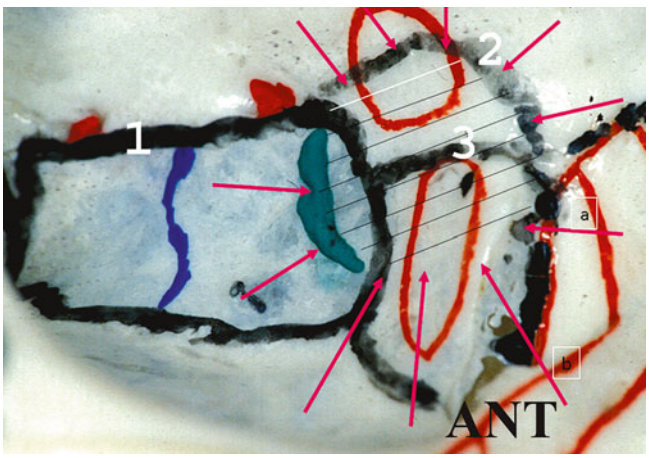


Fig. 1.18 View of medial wall of orbit. Numbers (see Fig. 1.17). *Red lines*: attachment of ocular muscles. *Red arrows* point to shaded plane (lateral wall of frontal recess). *Thick green line*: attachment of lamella *bullae ethmoidalis. Thick blue line*: attachment of basal lamella (*lamella basalis* = frontal part of middle turbinate). Note that only a small part of the lateral wall of the frontal recess is made up by *lamina papyracea* (Courtesy of Samuel Márquez, PhD)

attached on the medial wall of the orbit (Fig. 1.18). The lateral wall of the frontal recess, the area of attachment of the *lamella bullae ethmoidalis*, and the attachment of the *basal lamella* of the middle turbinate can be also observed in the skull (Fig. 1.18). It was documented on this specimen that a small part of the lateral wall of the frontal recess is made up by *lamina papyracea*. The attachment of the middle turbinate can be outlined on the ethmoid bone (Fig. 1.19), and a small *agger nasi cell* can be detected on the lateral wall of the ethmoid (Fig. 1.20). Considerable pneumatization of the *agger nasi* can take place and can be easily observed in CT scans (see Fig. 1.21). The topographical location of the *agger nasi* is considered the anterior limb of the uncinate process, again, markedly reduced during the course of human evolution. Further pneumatization of the agger includes the migration of ethmoid cells into the lacrimal bone, increasing the prominence of this eminence of the lateral nasal wall. Identification of the lacrimal bone is an important landmark because it defines the border between the frontal bone and the frontal process of the maxilla (see Fig. 1.22). When the ethmoid bulla is prominent by CT imaging, the *lamina papyracea* is observed as its lateral border (Fig. 1.22). Further observed in Fig. 1.10 is that the *lamina cranialis* of the frontal bone is the roof of the supraorbital recess.

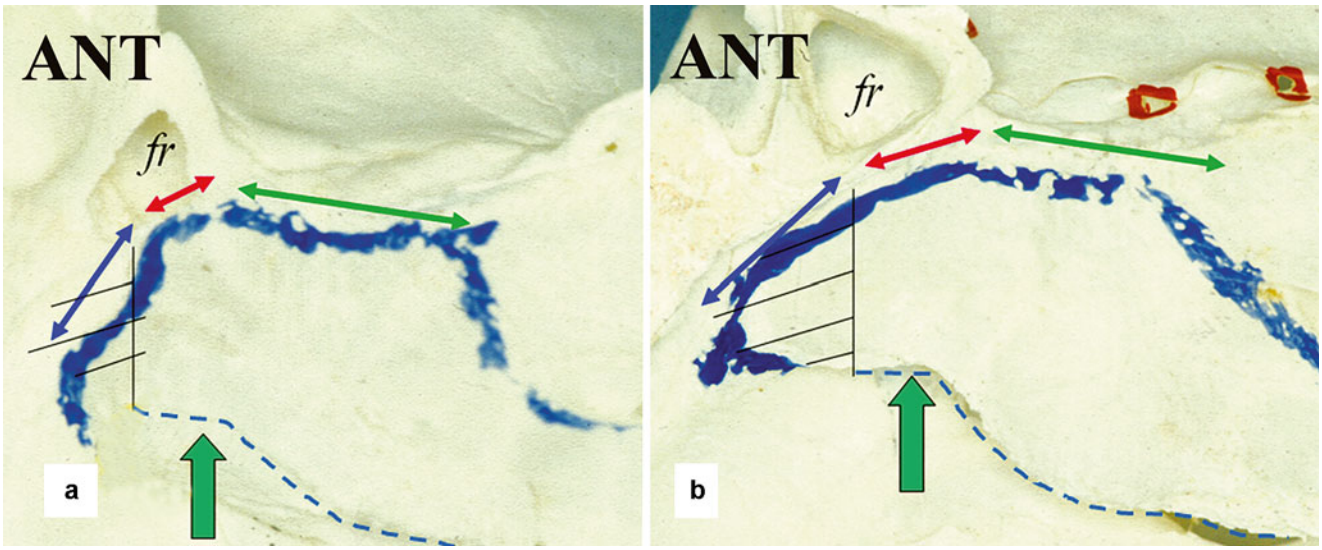


Fig. 1.19 (**a**, **b**) Medial view on sagittal part of middle turbinate in two different cases. *Thick blue line*: attachment of sagittal part of middle turbinate: (**b**) has a well-developed "*agger nasi cell*" while in (**a**) the agger nasi is not very pneumatized resulting in a small "agger nasi cell." *Shaded areas* indicate the site of the agger nasi. *Blue double-headed arrows*: site of insertion of the middle turbinate on frontal process of the maxilla (*crista ethmoidalis ossis maxillaris*). *Red double-headed arrows*: site of insertion of middle turbinate to floor of frontal sinus when frontal recess when the latter is extensively pneumatized medially. *Green double-headed arrows*: part of the middle turbinate that attaches to the skull base. *Thick green arrow* points to a *dashed grey line* (free border of the middle turbinate). Note that (b) has a well-developed *agger nasi cell* (Courtesy of Samuel Márquez, PhD)

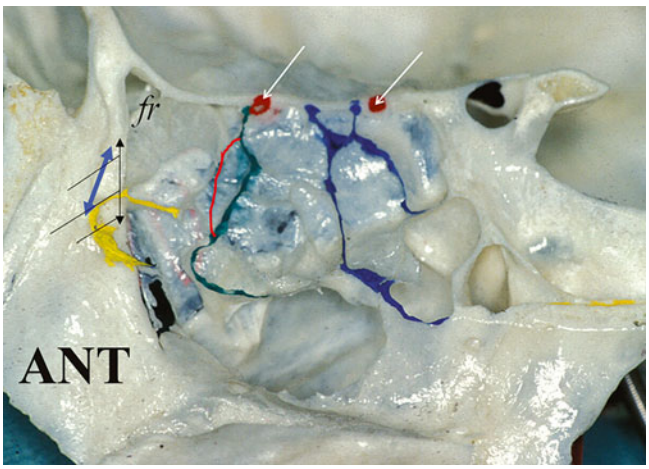


Fig. 1.20 Internal view of the lateral wall of the ethmoid (parasagittal section). *Dashed line* represents the *agger nasi*. In this case, there exists a small *agger nasi cell* in close contact with the *uncinate process* (*yellow line*). *fr* frontal recess. *Black double-headed arrow*: posterior border of *agger nasi. Black arrows*: anterior and posterior ethmoidal artery. *Green line*: attachment of the bulla and *lamina bullae* to *lamina papyracea. Blue line*: attachment of ground or basal lamella (*lamina basalis*) to *lamina papyracea. Red line*: anterior border of *lamina papyracea*. Note small part of lateral wall of the frontal recess that is made up by lamina papyracea (less than 10 % of area is between *red* and *green line*) (Courtesy of Samuel Márquez, PhD)

The actual size of the ethmoid sinus and the number of cells present vary in each reported series (Figs. 1.23, 1.24, and 1.25). Van Alyea [116] examined 100 specimens, finding a range of 4–17 cells and averaging 9 cells per specimen. Schaeffer [133] found the simplest ethmoidal labyrinth to consist of only three cells and the most complex of 16 cells. When only a few cells occupy the ethmoid labyrinth, they become large. However, when there are 12–16 cells "massed" together in the ethmoid region, each cell "struggles for space" resulting in the highly variable and irregularly formed ethmoidal air cells observed. The fact that the sinus is known as the "ethmoid labyrinth" attests to the intricacy of the structure and challenges our understanding of its anatomy [134].

For this discussion, cells are divided into those that are within the ethmoid region or *intramural* and those that are outside the ethmoid or *extramural*. The intramural cells are further divided into the smaller but more numerous anterior cells and the larger posterior cells, with some authors calling the ethmoid bulla the "middle cells" (Figs. 1.26 and 1.27). However, descriptions of a "middle ethmoid" or of "middle ethmoid cells" are considered incorrect since they are not based on developmental, anatomical, or functional grounds [3, 132]. The anterior ethmoid cells can be further subdivided based on their location or that of their ostia [133]. However, cells of a given origin frequently invade the territory usually occupied by cells of another origin, and at least one author favors classification by the location of their ostia (see examples of several classifications in Table 1.3) [135].

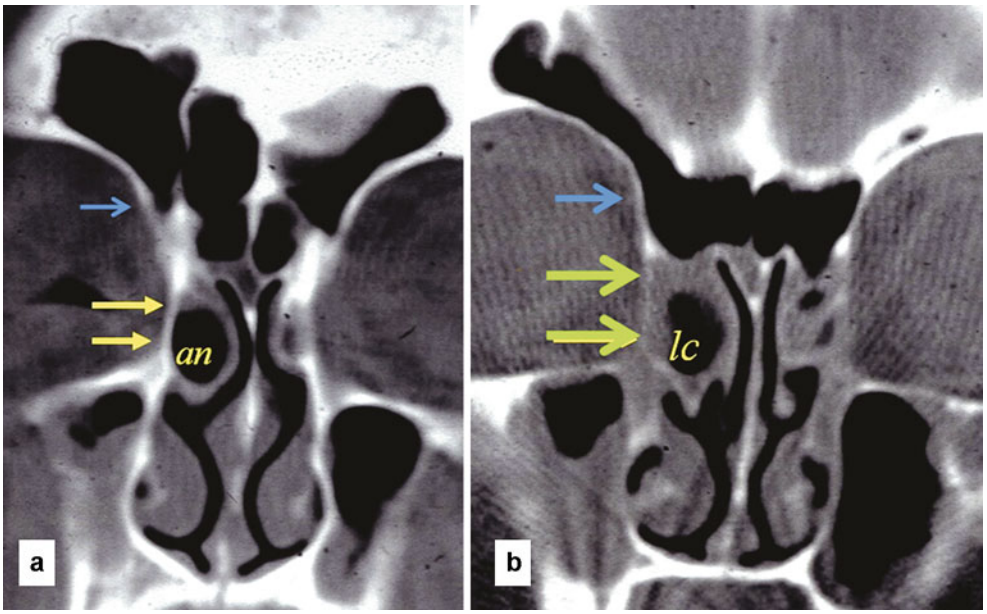


Fig. 1.21 (**a**, **b**) Coronal CT scans. (**a**) A large *agger nasi cell* (note the intimate relation between *agger nasi cell* and *uncinate process*). (**b**) Transition of the *agger nasi* cell into a *lacrimal cell* (note again that the floor of this cell is shaped by the uncinate process that is now more visible). *Yellow arrows*: frontal process of the maxilla. *Blue arrows*: orbital plate of the frontal bone. *Green arrows*: lacrimal bone. Note in (a) the free border of the middle turbinate is not visible or adjacent to the *agger nasi cell*, and the lateral wall of that cell is made up by the frontal recess of the maxilla. This is a true "*agger nasi cell*" because it is located within the surface feature of the lateral nose known as the *agger nasi*. In (b) the lateral wall of this cell is made up by the lacrimal bone, and free border of the middle turbinate begins to become visible. As this cell is posterior to the *agger nasi*, it would be considered a "lacrimal cell" (Courtesy of Samuel Márquez, PhD)

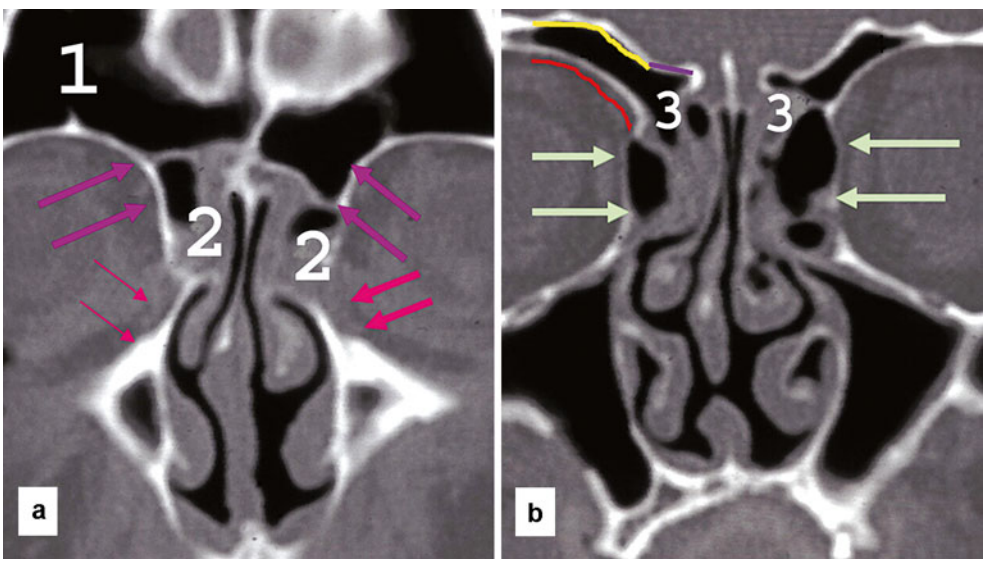


Fig. 1.22 (**a**, **b**) Coronal CT scans. (**a**) *Purple arrows* point to the *lamina orbitalis* of the frontal bone that is always superior to the lacrimal bone (*red arrows*). The lacrimal bone is an easy landmark to define the difference between frontal bone and frontal process of the maxilla. In this CT scan one can see the frontal recess underneath the floor of the frontal sinus. (**b**) *Green arrows*: *lamina papyracea* (lateral wall of the *bulla ethmoidalis*). (*1*) Frontal sinus; (*2*) *frontal recess*; (*3*) *suprabullar recess. Red line*: *lamina orbitalis* of frontal bone. *Yellow line*: lamina cranialis of frontal bone (roof of the supraorbital recess). *Purple line*: roof of the *suprabullar recess* (or *fovea*/frontal bone) (Courtesy of Samuel Márquez, PhD)

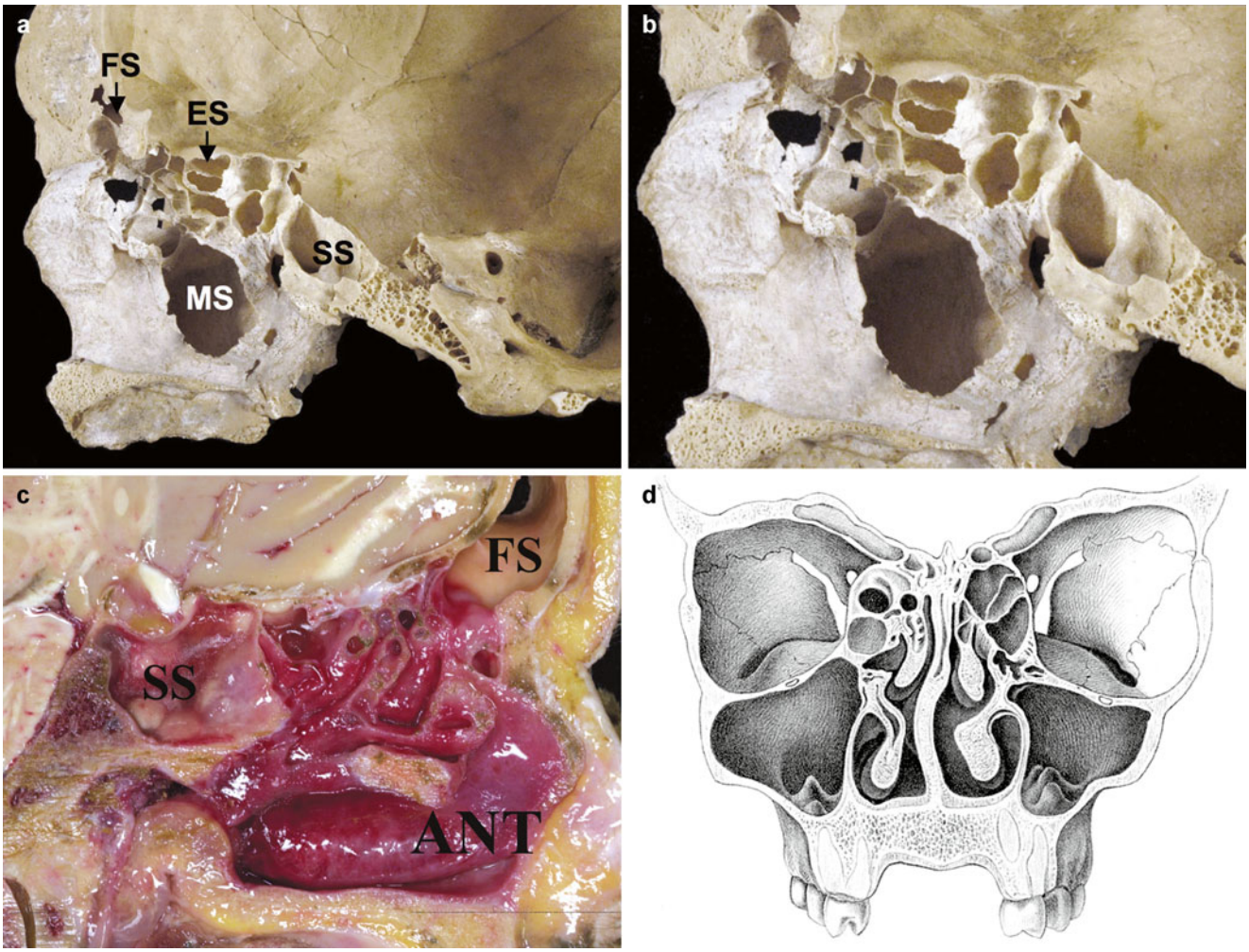


Fig. 1.23 (**a**) Sagittal paramedian section through dried skull. *ES* ethmoid sinus, *FS* frontal sinus, *SS* sphenoid sinus, *MS* maxillary sinus. (**b**) Magnified view of (a) showing thin enchondral bone of ethmoid sinus. (**c**) Sagittal paramedian section through unembalmed cadaver illustrating paranasal sinus anatomy. *SS* sphenoid sinus, *FS* frontal sinus. (**d**) 1882 illustration by Emil Zuckerkandl showing the paranasal sinuses in a coronal plane (**a**–**c**: Courtesy of Samuel Márquez, PhD)

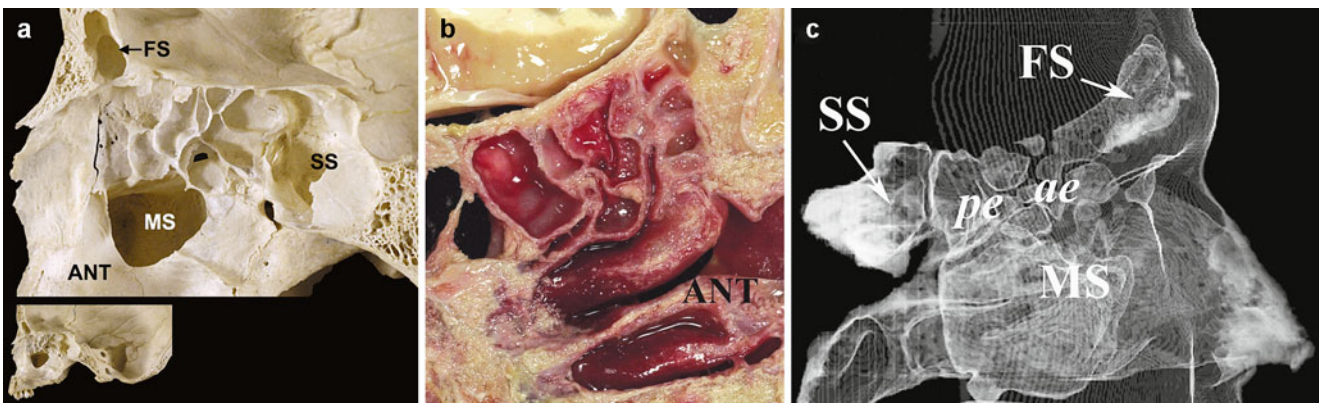


Fig. 1.24 (**a**) Sagittal paramedian section through dried skull in different specimen than Fig. 1.23a, b illustrating variations in ethmoid anatomy. Inset of whole skull provides for orientation. *SS* sphenoid sinus, *MS* maxillary sinus, *FS* frontal sinus. (**b**) Sagittal paramedian section through additional unembalmed cadaver head showing variation in sinus anatomy. (**c**) Paramedian three-dimensional reconstruction of multiple CT images showing complexity of sinus anatomy. *SS* sphenoid sinus, *MS* maxillary sinus, *FS* frontal sinus, *pe* posterior ethmoid sinus, *ae* anterior ethmoid sinus (Courtesy of Samuel Márquez, PhD)

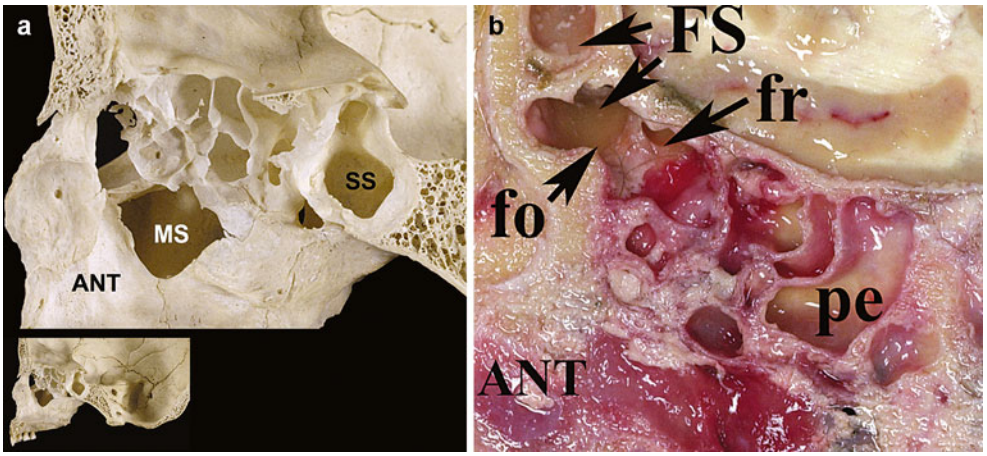


Fig. 1.25 (**a**) Sagittal paramedian section through dried skull in a third specimen, again illustrating the variation in development of the ethmoid sinus. Inset of whole skull provides for orientation. *SS* sphenoid sinus, *MS* maxillary sinus. (**b**) Sagittal paramedian section through unembalmed cadaver other than seen in prior figures showing anatomy of ethmoids, frontal recess, and frontal sinus. *FS* frontal sinus, *fo* frontal ostium or outflow tract, *fr* frontal recess, *pe* posterior ethmoid cell, ANT denotes anterior (Courtesy of Samuel Márquez, PhD)

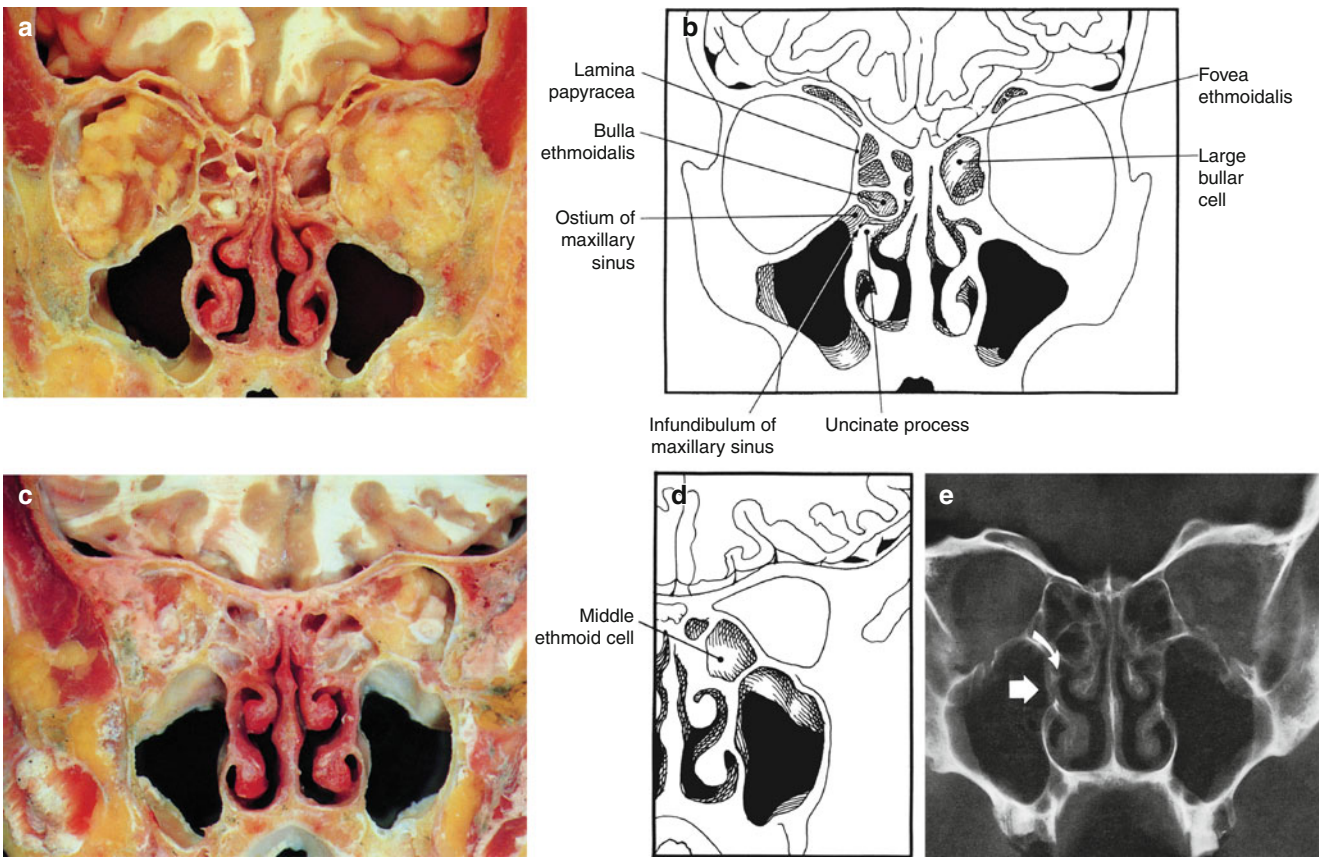


Fig. 1.26 (**a**) Anterior surface of coronal section contiguous with specimen in (c) is shown, which includes the midportion of the maxillary sinus. (**b**) On the right of the specimen are several middle ethmoid cells, including bullar cells. On the left is a large bullar cell. (**c**) Posterior surface of the specimen in (a) is shown, which exposes the middle ethmoid or bullar cells. (**d**) Illustration showing the middle ethmoid cells seen in (c). (**e**) Plain film radiograph of specimen in (a–c). Note the uncinate process projecting several millimeters superiorly (*curved arrow*). The *large arrow* points to membranous meatus (Courtesy of Steven D. Schaefer, MD)

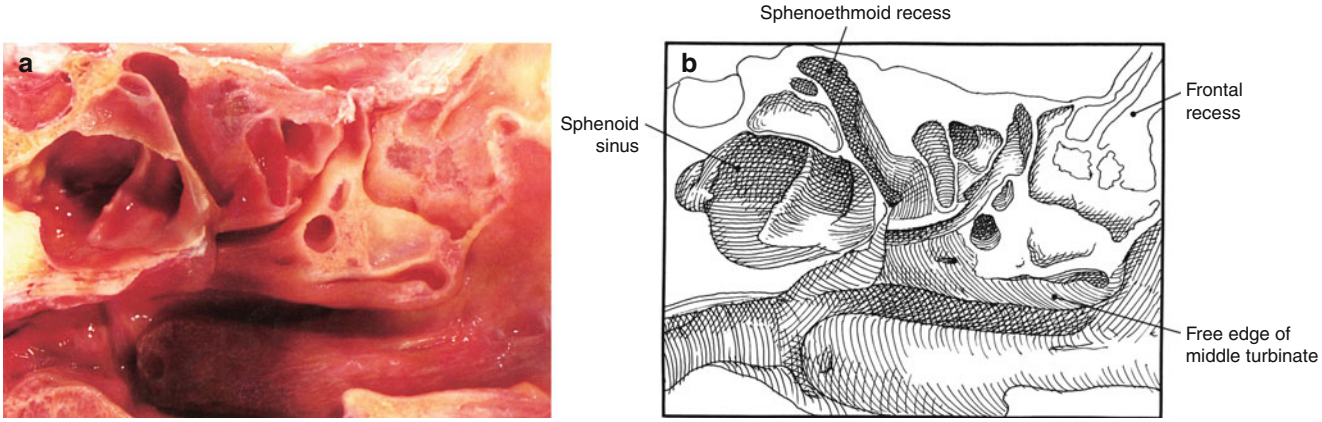


Fig. 1.27 (**a**) Parasagittal section through the middle turbinate is shown. (**b**) Extensive pneumatization of the ethmoid bone is shown, as represented by the anterior and posterior ethmoid sinuses (Courtesy of Steven D. Schaefer, MD)

Table 1.3 Classification of sinus cells

Middle meatus	**Anterior ethmoid cells**	**Anterior ethmoid cells**
Infundibular cells	Fontal recess	Fontal recess
Agger nasi	Infundibular	Infundibular
Terminal	Bullar	Bullar
Suprainfundibular	Conchal	Conchal
Inferior	Extramural (i.e., agger nasi)	Extramural
Superior meatus	**Posterior ethmoid cells**	**Posterior ethmoid cells**
Posterior cells	Intramural	Intramural
	Extramural [110]	Extramural [135]
Supreme meatus		
Postreme cells [116]		

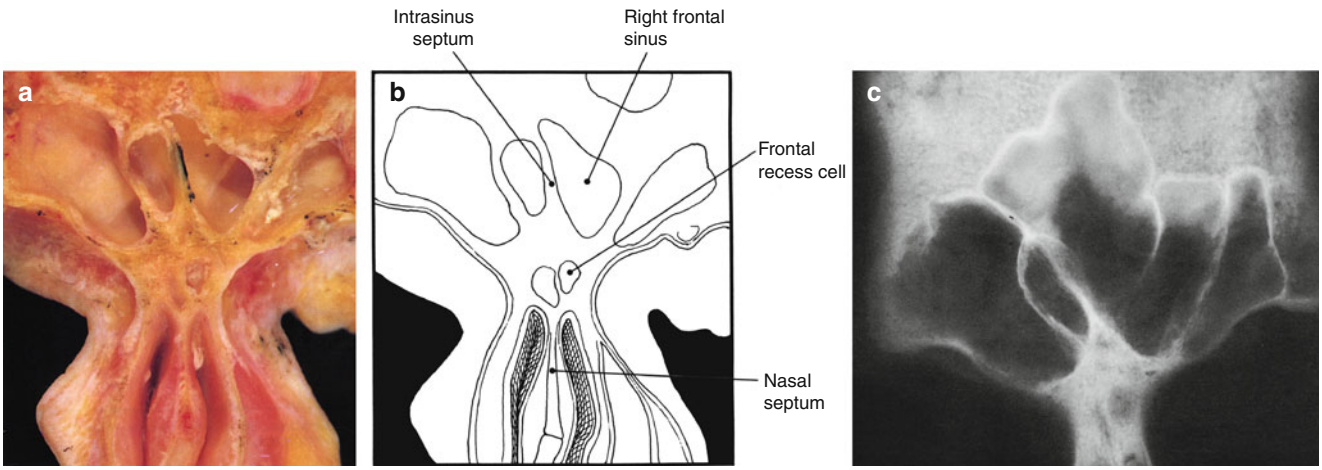


Fig. 1.28 (**a**) Posterior surface of coronal section at the ventral aspect of the frontal sinus is shown. (**b**) This section is sufficiently ventral to the body of the frontal sinus to include only a remnant of the frontal recess cells of the anterior ethmoid. (**c**) Plain film radiograph of the specimen shown in Fig. 1.19a (Courtesy of Steven D. Schaefer, MD)

Among the various classifications proposed, the Ritter nomenclature system conveys most clearly the origin and drainage of the ethmoid cells. Using Ritter's classification, the most anterior cells are the frontal recess cells (range 0–4 cells), which arise from the anterosuperior growth of the ethmoid cells into the frontal bone (Figs. 1.5 and 1.12). These cells may come to rest within the frontal bone by either forming the frontal sinus, giving rise to the *frontal bullae,* bulging into the frontal sinus floor, or forming the *supraorbital ethmoid cells* as they pneumatize the orbit [28, 136]. The inferior expansion of these cells can displace the "nasofrontal duct," resulting in a tortuous or serpentine course of the duct (see Frontal Sinus discussion).

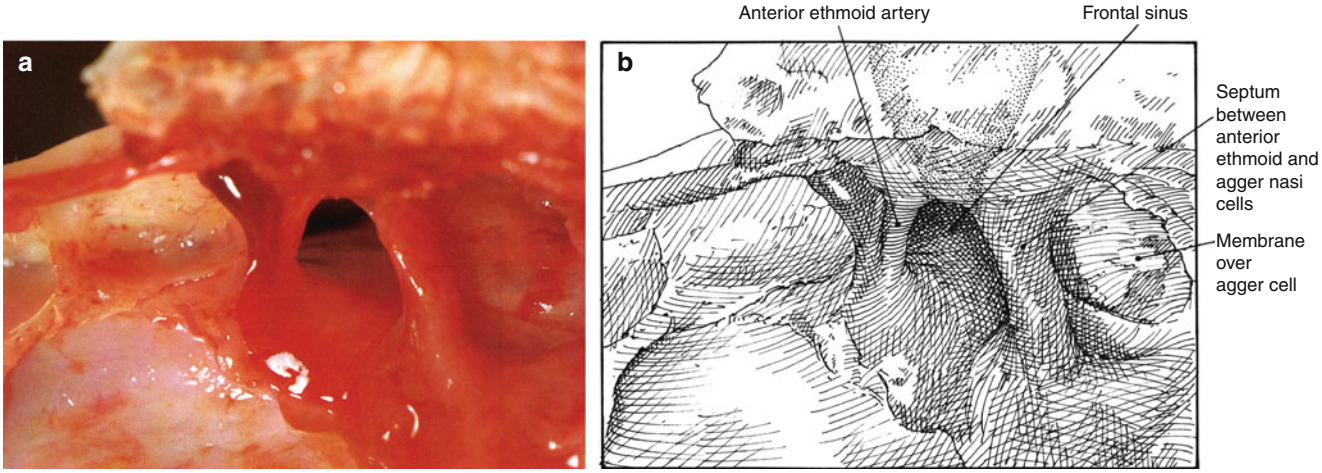


Fig. 1.29 (**a**) Frontal recess of left ethmoid bone. (**b**) Diagram of (a). The relationship of the frontal sinus to the nose may be compared to an hourglass. The upper body of the glass is the frontal sinus, the neck is the ostium, and the lower body is the frontal recess (Courtesy of Steven D. Schaefer, MD)

The infundibular cells (range 1–7 cells) are the second most anterior cells (Figs. 1.28, 1.29, and 1.30). The most constant of these cells form the extramural cells, the *agger nasi*, through the pneumatization of the lacrimal bone [70]. These cells are located on the lateral nasal wall immediately anterior to the middle turbinate and constitute an important landmark in both intranasal procedures and external ethmoidectomy. They drain into the three-dimensional space of the *ethmoid infundibulum*, a pouch or trough that ends superiorly in the frontal recess (Figs. 1.4 and 1.6). In some individuals, the infundibular cells may be the origin of the frontal sinus (Fig. 1.31) [96]. The *ethmoid infundibulum* lies anterior to the bulla ethmoidalis and is bounded medially by the middle turbinate (Figs. 1.5 and 1.6). The infundibulum is also the site of drainage for the frontal sinus and other anterior ethmoid cells involving the adjacent frontal, lacrimal, and nasal bones. Baron Alexis de Boyer is credited to have first coined the term *infundibulum* [Nomina Anatomica] with cells draining into this trough also known as *Boyer's cells* [28].[3] However, the first description of the infundibulum was most probably by Alexander Monro (the elder) in 1797, who described funnel-like openings of irregular cells around the cribriform plate, but did not name them until the second issue of his anatomical text (see discussion in Márquez and colleagues [3]).

The bullar cells (range 1–6 cells) are the most constant of the anterior ethmoid cells and together form a partial sphere lateral or beneath the middle turbinate, the *bulla ethmoidalis* (Figs. 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.17, 1.18, and 1.22) [116]. The term bulla ethmoidalis was first used by Zuckerkandl [28], although Grünwald [209] used the term lateral torus. Lang [137] gave its dimensions as 18 (9–28) mm long and 5.4 (2–13) mm high, whereas Zuckerkandl [28] reported lengths of 20 and 26 mm. By definition, this region of the ethmoid bone would not be called the bulla without pneumatization. A variable number of ethmoid air cells generally develop in the lamella of the bulla, producing the characteristic swelling described as the bulla ethmoidales [131]. Even though the extent of pneumatization of the bulla is highly variable for individuals, a prominence is always detectable endoscopically and radiographically [29]. The bullar cells drain into the middle meatus via crescentic ostia that lie superiorly, posteriorly, and parallel to the much larger semilunar cleft in the lateral nasal wall, the entrance of which Zuckerkandl described as the *hiatus semilunaris* [96, 116]. The hiatus semilunaris forms the curved groove between the bulla ethmoidalis that borders it posteriorly and the uncinate process, a ridge of bone formed by the ramus descendens of the first ethmoturbinal, which borders it anteriorly (Figs. 1.11 and 1.22) [130]. The relationship of the hiatus to the middle turbinate is variable, being noted most commonly 11–20 mm posterior to the anterior aspect of the turbinate [97]. Superiorly, the hiatus communicates with the *ethmoid infundibulum* (Fig. 1.6). The anteroinferior boundary of the hiatus semilunaris is the *uncinate process*, also a semilunar structure, which has an anterosuperior to posteroinferior sagittal orientation. It ranges from nearly flat to 4 mm in height and 14–22 mm in length with its free margin occasionally projecting into the nasal cavity (Figs. 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.31, and 1.32) [97]. The uncinate process being immediately posterior to the agger nasi bone makes its visualization on the lateral nasal wall dependent on the anterior and inferior expansion of the middle turbinate.

The uncinate process is considered one of the most important surgical landmarks of the lateral nasal wall for endonasal sinus surgery. In addition, its medial appendage is strategically located near the osteomeatal complex (OMC) [138].[4] The dynamics of this region are such that any abnormal growth or excessive pneumatization of the uncinate process can potentially narrow and ultimately obstruct the outflow tract of multiple sinuses. Moreover, normal variations in the morphology of

[3] According to Stammberger and colleagues [133], Boyer had named the cleft that Killian would later describe as the frontal recess.

[4] Naumann coined the term OMC to describe the region between the insertions of the inferior and middle conchae where the confluence of the frontal, ethmoid, and maxillary sinuses all drain into before entering the nasal cavity.

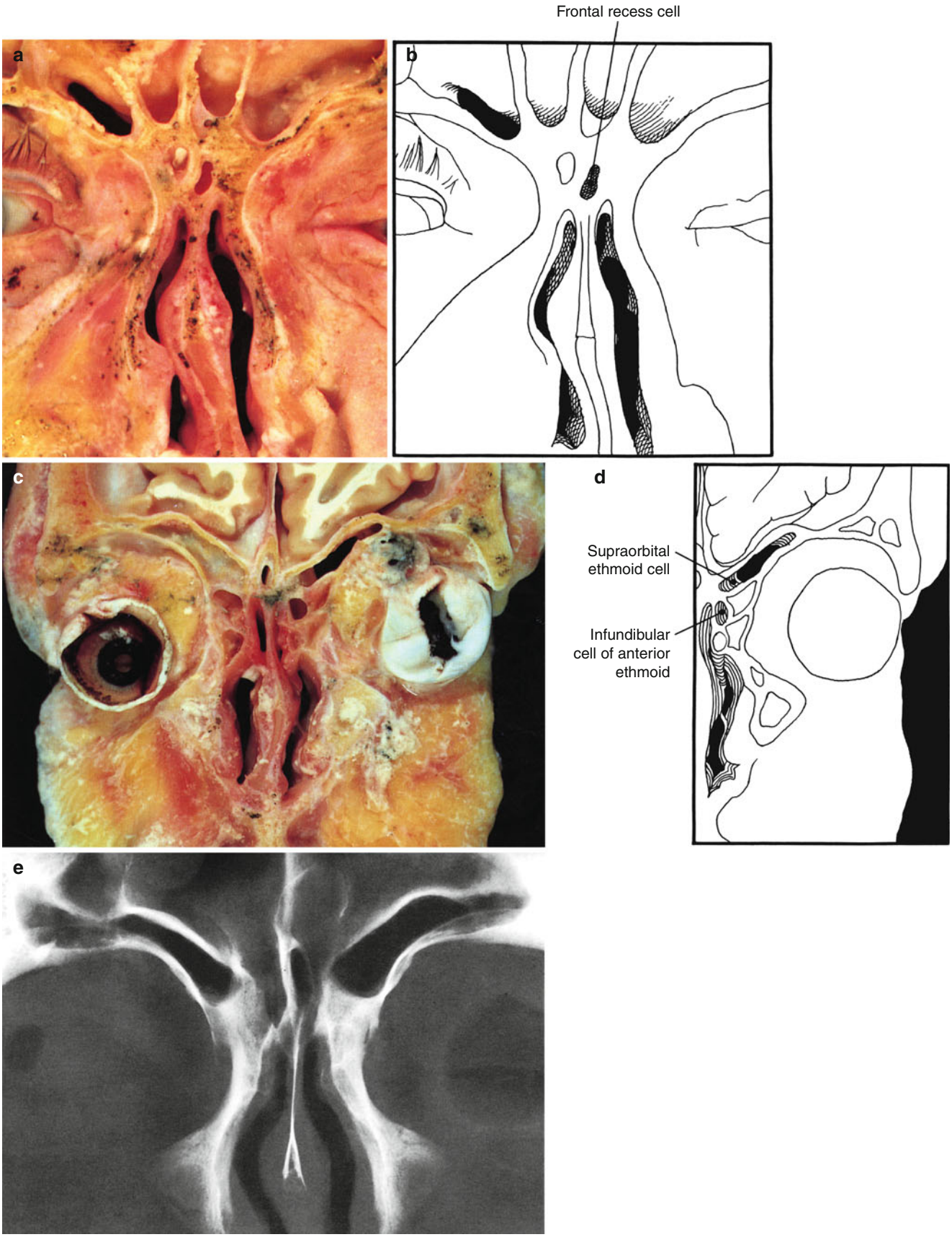


Fig. 1.30 (**a**) Anterior surface of coronal section through frontal sinus contiguous with section in Fig. 1.28a is shown. (**b**) Note frontal recess cells seen in coronal section in (a). These cells are among the several possible origins of the frontal sinus. (**c**) Posterior surface of specimen in (a) is sectioned immediately dorsal to the principal cavity of the frontal sinus. (**d**) Supraorbital ethmoid cells are shown immediately superior to infundibular cells of the anterior ethmoid. The lateral boundary of these cells is the lamina papyracea, which is the most constant structure in the ethmoid bone. (**e**) Plain film radiograph of the specimen shown in (a–c) (Courtesy of Steven D. Schaefer, MD)

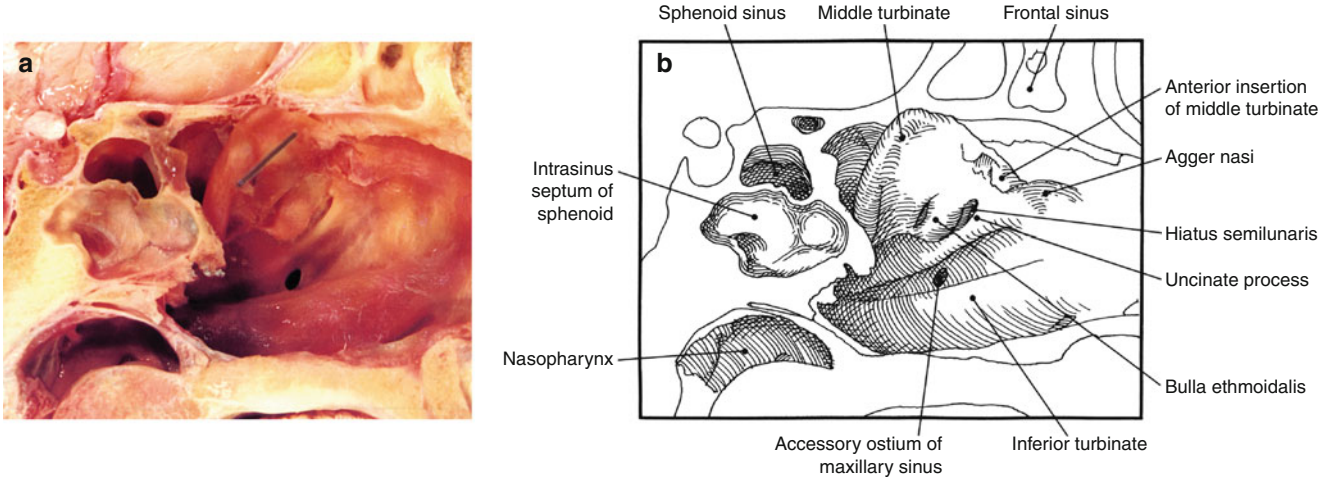


Fig. 1.31 (**a**) Midsagittal section showing anatomy of the lateral nasal wall. Middle turbinate has been deflected superiorly to reveal the surface anatomy of the ethmoid sinus. (**b**) The hiatus semilunaris appears as a depression between the bulla ethmoidalis and the uncinate process. Anterior to the uncinate ridge is the agger nasi, which is formed by the pneumatization of the lacrimal bone by the infundibular cells of the ethmoid. Accessory ostium of maxillary sinus appears above the inferior turbinate (Courtesy of Steven D. Schaefer, MD)

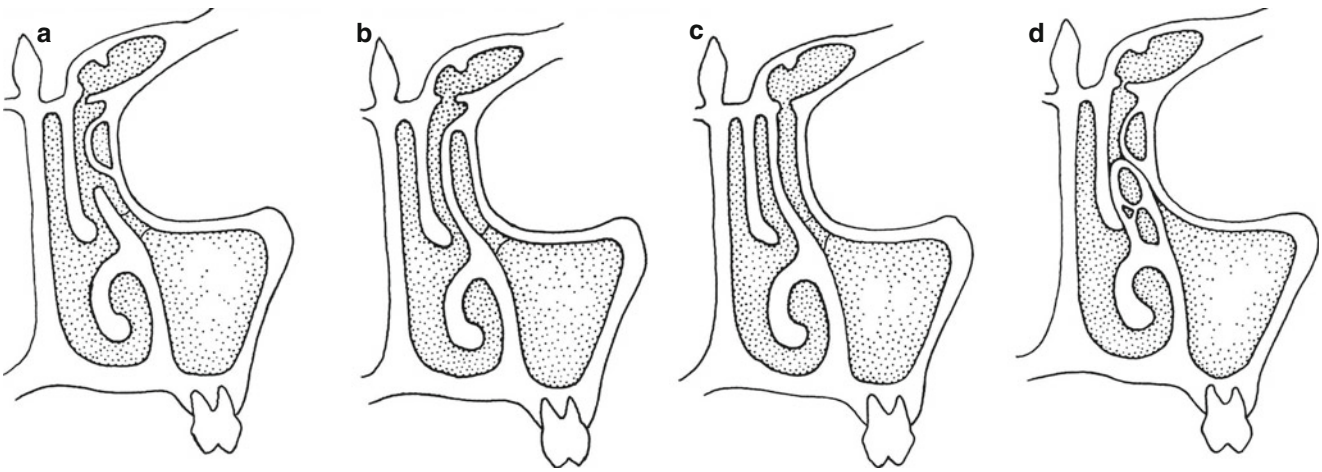


Fig. 1.32 Diagrammatic representation of variations in uncinate process. These include (1) most common appearance of uncinate process giving rise to this structure terminating in the nasal cavity (**a**), (2) uncinate process inserting on the lamina papyracea to form a sinus terminalis (**b**), (3) uncinate process fusing with fovea ethmoidalis (**c**), and (4) extensively pneumatized uncinate process partially obstructing outflow from the ethmoid and maxillary sinuses (**d**) (Courtesy of Steven D. Schaefer, MD)

the uncinate process give rise to several patterns of drainage from the OMC (see discussion in Isobe et al. [139] and Fig. 1.33). The first variation is an uncinate process coursing superolaterally to insert on the lamina papyracea (Fig. 1.32b). This variation leads to closure of the superior aspect of the infundibulum to form a blind pouch known as the *recess terminalis* and results in the communication of the frontal recess with the middle meatus medial to the ethmoid infundibulum. Thus, the frontal sinus drains into the nose medial to the ethmoid infundibulum and lateral to the middle turbinate. A second variation is an uncinate process extending superiorly to insert on or approximate to the fovea ethmoidalis, causing the frontal sinus to drain directly into the ethmoid infundibulum via the frontal recess (Fig. 1.32c). Another variation is extensive pneumatization of the uncinate process, which can potentially obstruct drainage through the infundibulum (Fig. 1.32d).

The terminology regarding the anatomical boundaries of the hiatus semilunaris invites confusion. Some authors prefer to divide the hiatus semilunaris into anterior and posterior portions, while others tend to describe it as extending from the superior terminal of the frontal recess to the posterior aspect of the bulla, thereby substituting the anterosuperior portion of the hiatus for part of the ethmoid infundibulum. Others consider the infundibulum to be the bottom or most lateral region of the hiatus when describing the anterosuperior aspect as the ethmoid infundibulum (e.g., frontal recess to the bulla ethmoidalis)

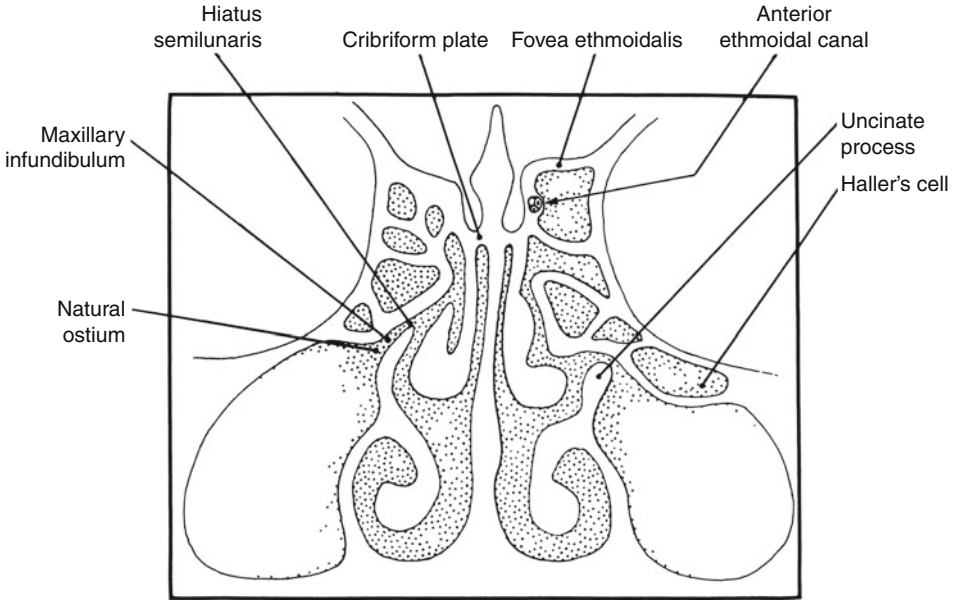


Fig. 1.33 Schematic of relationship of paranasal sinuses to anterior cranial fossa and orbit. The anterior ethmoidal canal varies from 2 mm inferior to 4 mm superior to the cribriform plate, and the posterior canal ranges from 0 to 3.1 mm superior to the cribriform. Pneumatization of inferomedial orbit is known as Haller's cell (Courtesy of Steven D. Schaefer, MD)

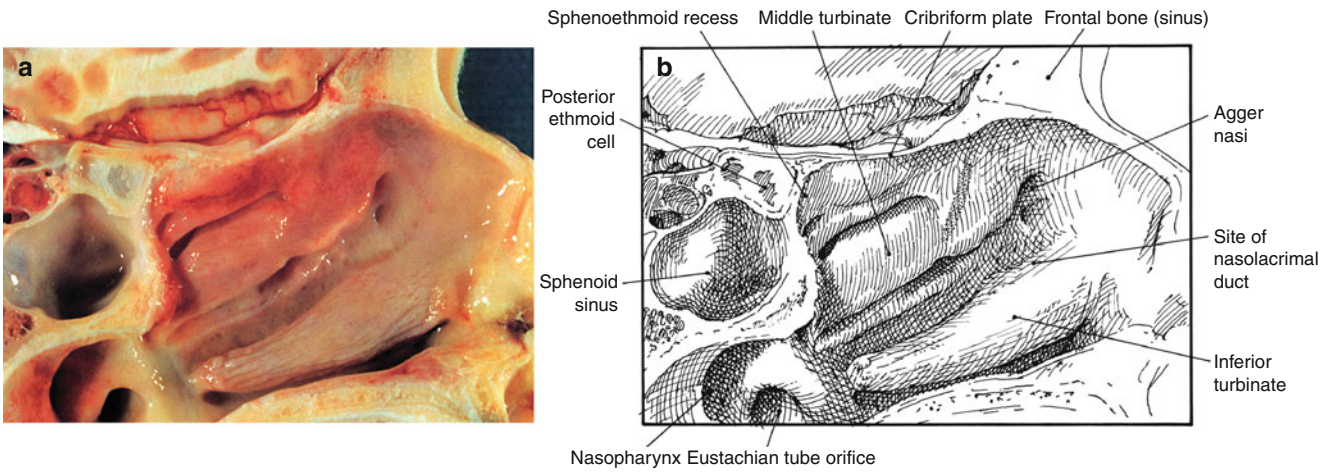


Fig. 1.34 (**a**) Most medial of a series of progressive dissections of left lateral nasal wall. (**b**) Diagram of (a) illustrating surface anatomy (Courtesy of Steven D. Schaefer, MD)

thereby designating that part of the infundibulum which communicates with the natural ostium of the maxillary sinus as the *maxillary infundibulum* (Fig. 1.6) [97, 130]. Various descriptions are given of the hiatus that include part of the infundibulum. The current consensus is that the hiatus should be viewed as a two-dimensional structure, as Zuckerkandl [26] originally described, and should be regarded as the entrance into the infundibulum [132]. Whatever terminology is used, these structures are important landmarks and constitute the route by which secretions can flow from the frontal and anterior ethmoid cells into the ostium of the maxillary sinus [96]. Sometimes a bony process develops from the attachment of the middle turbinate and projects laterally toward the orbit, but this is a rare event. Pneumatization of this process is termed a *Haller's cell* (Fig. 1.33). As this cell is at the inferomedial aspect of the orbital rim, extensive pneumatization can impair outflow of the maxillary sinus, serve as a primary site of ethmoiditis, or increase the vulnerability of the eye to injury during endoscopic ethmoidectomy.

Conchal cells are ethmoid air cells that invade the middle conchae, and when these cells are located in the anterior aspect of the conchae, the condition is referred to as a *concha bullosa* (Fig. 1.27) [28, 140]. The bullosa cells are clinically important because they can be an isolated source of recurrent ethmoiditis or may obstruct the middle meatus. The *middle turbinate*, being a medial appendage of the lateral nasal wall, overhangs the bulla ethmoidalis, the hiatus semilunaris, and the uncinate process (Fig. 1.16). On occasion, both the uncinate process and hiatus semilunaris are not covered by the downward expansion of this 3.5–4 cm long important bony structure. Anteriorly, the middle turbinate is attached superiorly to the cribriform plate, with a 15° slope posteroinferiorly so that the posterior tip lies at, or immediately inferior, to the sphenopalatine foramen (Fig. 1.34) [136].

The *posterior ethmoid cells* (range 1–7 cells), which invade the posterior ethmoid capsule, may also involve the middle turbinate, the sphenoid, the palatine, and the maxillary bones (Figs. 1.4, 1.6, 1.7, 1.26, and 1.27). An important form of the extramural extension of the posterior ethmoid cells is the migration of these cells to the medial aspect of the optic nerve within the sphenoid bone. Such cells located superiorly and inferiorly to the optic nerve are called *Onodi cells* [141]. These cells are clinically important because the optic nerve may be covered by relatively thin bone and vulnerable to injury by dissection posterior to the anterior face of the sphenoid bone (for review on anatomical relationships between optic nerve and paranasal sinuses, see Loeb [142], Fig. 1.4). At the junction of the lamina papyracea and the frontal bone, the posterior ethmoidal artery enters the posterior ethmoids approximately 2–8 mm (average 5 mm) anterior to the optic nerve. The *anterior ethmoidal canal* (Figs. 1.4 and 1.33) containing the artery (AEA) and the nerve of the same name runs between 1 mm inferior and 4 mm superior to the cribriform plate. The extraordinary course of the AEA originates from the orbital region passing through the anterior ethmoidal foramen traversing the anterior ethmoid cells and onto the anterior cranial fossa to finally enter the nasal cavity proper [143]. Among 100 crania studied by Mutalik and colleagues [144], all individuals exhibited an anterior ethmoidal foramen bilaterally, and only two individuals exhibited anterior ethmoidal foramina without having posterior ethmoid foramina. Some individuals also presented with middle and accessory ethmoid foramina. However, Singh et al. [145] and McDonald and colleagues [146] reported 2 and 5 % rates of unilateral expression of the anterior ethmoid foramen. These data suggest that some degree of variability is present in the morphology of the ethmoid foramina and their canals, which is of surgical importance in orbital, sinus, and skull base surgery. Furthermore, a substantial number of individuals will present with a natural dehiscence of the anterior ethmoid canal as it crosses the posterior aspect of the frontal recess at a region called *the dome of the ethmoid* [141, 147]. Injury to the AEA results in bleeding into the nasal cavity that can potentially cause the retraction of the vessel into the orbit, which in turn, leads to intraorbital bleeding and the danger of blindness. The *posterior ethmoidal canal* traverses the ethmoid bone at a plane approximately 1.5 mm above the cribriform plate, and it may also be partially dehiscent of bone.

Maxillary Sinus

Development and Functional Anatomy

The maxillary sinus, universally described as a pyramidal-shaped cavity lying within the body of the maxilla, is the largest and most constant of all four paranasal sinuses [148]. Asymmetries of maxillary sinus size have been reported [149], but differences in the degree of asymmetry have not revealed any clear dominance of one particular side [150]. An overall consensus is lacking regarding its shape, probably due to the high variability in its development [19]. Cullen and Vidic [151] attempted to classify its prenatal morphology as elliptical, triangular, irregular, rectangular, and spherical shaped. Anagnostopoulou et al. [152] classified 119 casts of adult maxillary sinuses from 60 dry skulls as semiellipsoid, paraboloid, hyperboloid, and cone shaped. The maxillary sinus is generally described as being pyramidal shaped [153], although Anon et al. [19] preferred the term "tetrahedral" to represent its morphology in three-dimensional space. Its anterior wall is the facial surface of the maxilla, where the facial vein and artery run, while the posterior wall is the infratemporal fossa, where the maxillary artery[5] and vein are located. The medial wall constitutes the lateral wall of the nasal cavity, where a number of vascular structures are situated (e.g., branches of the sphenopalatine, the septal branch of the superior labial, and ethmoidal arteries). The superior wall or roof of this sinus is the floor of the orbit, and the floor of this sinus is the alveolar process of the maxilla. Evident from its topographical relationship to contiguous structures, infections and tumors of the maxillary sinus can spread in multiple directions, especially to the dentition [154, 155].

Development of the maxillary sinus begins by the 65th day of gestation, making it the first sinus to develop in utero [156]. Various authors have reported different onsets of development. The initial onset of maxillary sinus development reported by Schaeffer [150] was the 70th day; Kallius [157] timed the initial evagination during the middle of the third month; and Brandt and Roper-Hall [158] and Aubert [159] saw the fourteenth week as the beginning of maxillary sinus prenatal development. The initial stage of development of this sinus has been traditionally described as a mucosal evagination (i.e., bud) into the lateral cartilaginous environment of the nasal capsule. However, Wang et al. [160] recently suggested that the

[5] Based on the Nomina Anatomica [NA] adopted in Paris 1955. The maxillary artery, in the older Basle Nomina Anatomica [BNA], was referred to as the "internal maxillary artery" to distinguish it from the "external maxillary artery" which is the "facial artery" in the NA and in the current *Terminologia Anatomica* [TA].

Table 1.4 Embryologic pattern of development

Paranasal sinus	Embryologic appearance	Postnatal appearance	Growth spurt interval
Ethmoid sinus	Development begins in third fetal month	Present at birth	First growth spurt between 1 and 4 years, second growth spurt between 4 and 8 years
Maxillary sinus	65th day of gestation	Present at birth	First growth spurt between birth and 3 years, second between 7 and 12 years
Frontal sinus	Development begins in fourth fetal month	Detected at 7–12 years of age	Adult size is completed by 20 years
Sphenoid sinus	Development begins in third fetal month	Detected at 3–4 years of age	By seventh year, sinus begins to extend posteriorly toward the sella turcica

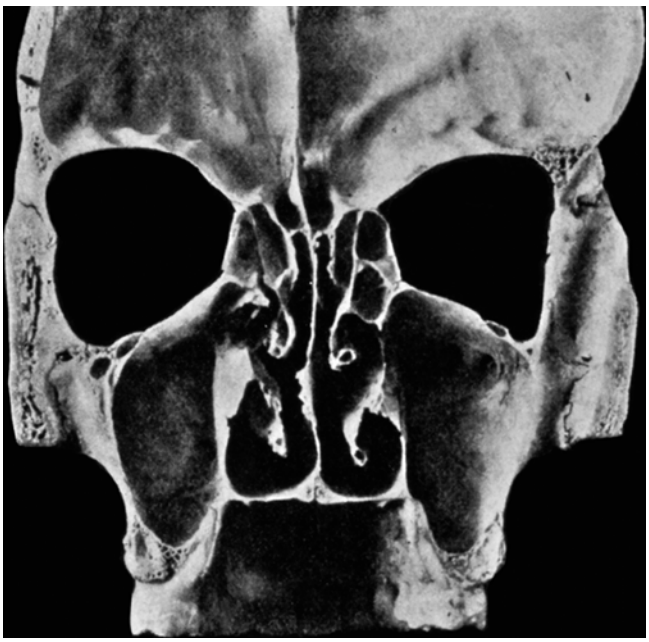


Fig. 1.35 A coronal section of adult human crania shown in dorsal view illustrating the descent of the maxillary sinus floor falling below the level of the nasal cavity floor (Reprinted from Underwood [68])

mucosal evagination or outpouching of the nasal mucous membranes should be considered as a secondary event rather than the primary force. While Schaeffer [150] described this pouch as a minute epithelial sac forming the anlage of the sinus, its presence precedes the appearance of the cartilage that later surrounds it. Wang et al. [160] showed that during the 19th week in utero, the mucosa of the maxillary sinus makes direct contact with the maxillary bone only after the surrounding cartilaginous wall of the maxillary sinus begins to disappear through the degeneration and absorption of its cartilaginous cells. The exact location of this maxillary sinus outpouching stems from the primitive ethmoid infundibulum, also known as the uncibullous groove, which becomes the future uncinate and bulla ethmoidales structures which will demarcate the portal between the ethmoid infundibulum and nasal cavity [150]. This developmental stage explains why any drainage from this sinus will go through the ethmoid infundibulum before reaching the middle meatus.

At birth, the sinus has an average volume of 6–8 ml, but is fluid filled, making interpretation of plain film radiographs difficult [102, 121]. However, Weiglein et al. [161] reported that this sinus is of appreciable size at birth and can be identified on a Caldwell view. A rudimentary maxillary sinus can be seen at birth on CT, either as soft tissue-filled or as a small pneumatized nubbin. The maxillary sinus then undergoes two periods of rapid growth: one between birth and 3 years and the other between 7 and 12 years [102, 150]. Between these two growth periods, at around 4 years of age, the sinus extends laterally past the infraorbital canal [162]. After the second period of rapid growth (see Table 1.4), subsequent expansion involves pneumatization of the alveolar process of the maxilla. Before growth is completed, there is a descent of the maxillary sinus from 4 mm above the floor of the nasal cavity at birth to the same level as the nasal floor at age 8–9 years and then a final drop of 4–5 mm below this level by adulthood (Figs. 1.35 and 1.36) [126]. Since the descent of this sinus coincides with dental eruption, a long-held belief sees an intimate relationship between these two developmental events [107]. Libersa et al. [12] and Márquez et al. [163], however, have demonstrated very poor and statistically insignificant relationships between molar eruption pattern and adult maxillary sinus form and between molar volume and adult sinus size, respectively ($p > 0.05$).

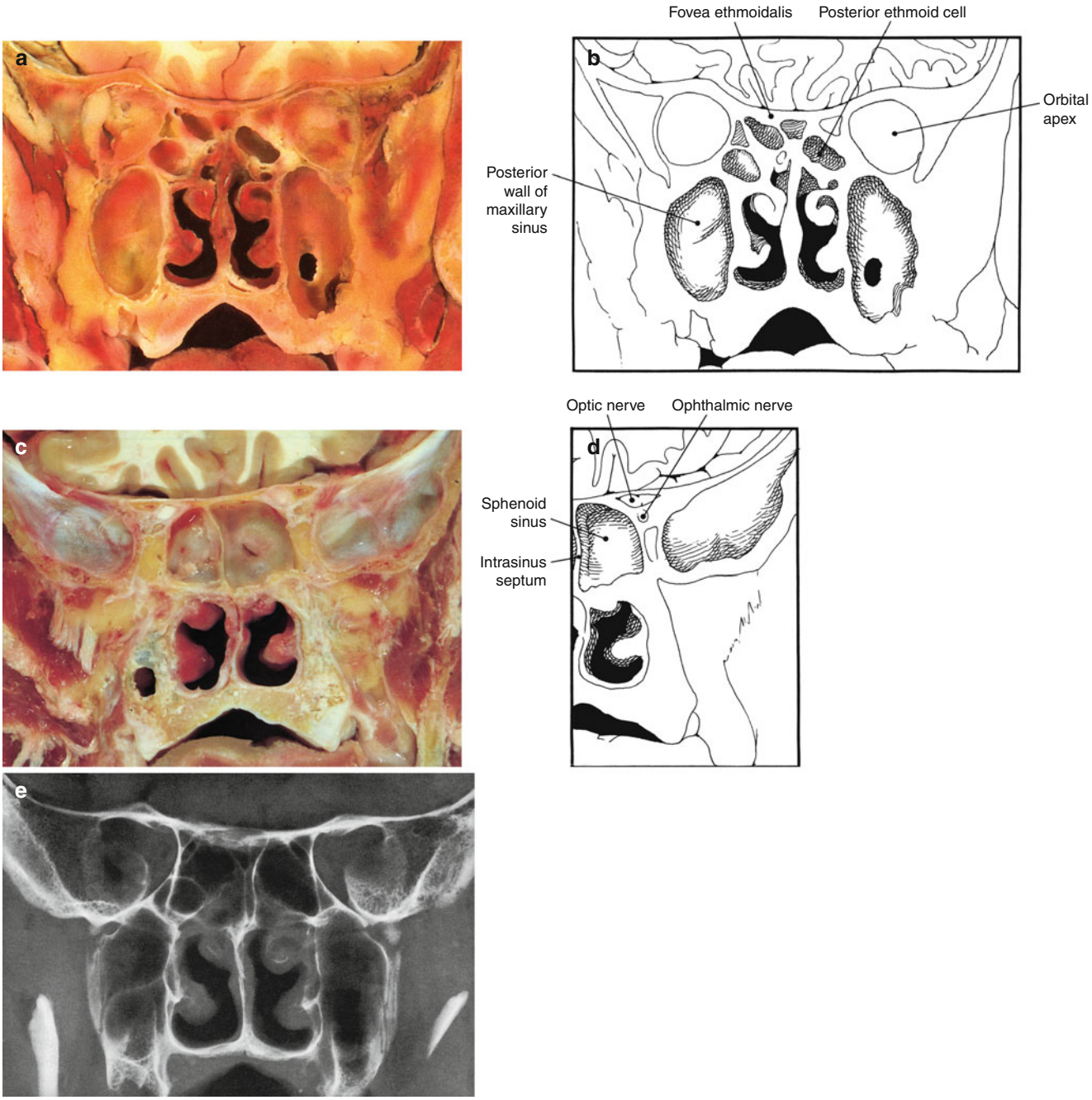


Fig. 1.36 (**a**) A coronal section exposing the posterior wall of the maxillary sinuses is shown from an anterior perspective and as a reference for (c). (**b**) Residual maxillary cavity is shown, along with the adjacent posterior ethmoid cells. Note the fovea ethmoidalis is properly identified. (**c**) The posterior surface of the specimen in (a) is shown. It is immediately dorsal to the maxillary sinus or at the plane of the pterygopalatine space. (**d**) Dorsal surface of the anterior wall of the sphenoid sinus is visualized, along with the nasopharynx. Note the relationship of nerves to the sinus wall. (**e**) Plain film radiograph of the specimen in (a), showing the remnant of the pterygoid plates and the convergence of the posterior ethmoids (a) and the sphenoid sinus (c) (Courtesy of Steven D. Schaefer, MD)

Clinical Implications

In the adult, the maxillary sinus can be roughly described as triangular in shape, measuring 25 mm along the anterior limb of its base, 34 mm in depth, and 33 mm in height [102, 126]. The sinus can be partially compartmentalized by either complete or incomplete septa. Knowledge of the incidence and morphology of maxillary sinus septa has clinical implications especially in sinus lift operations performed preparatory to the placement of dental implants [164]. In rare cases, separate cavities can exist in the posterior part of the sinus, which can be a source of persistent infection [165].

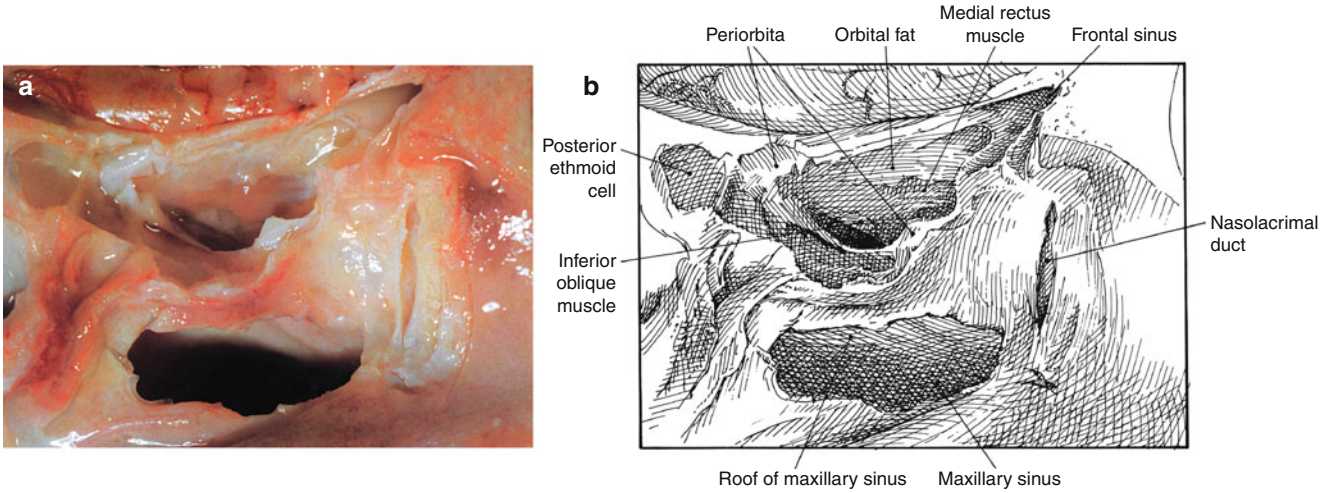


Fig. 1.37 (**a**) The lateral nasal wall has been exenterated to show the medial orbit, maxillary sinus, and nasolacrimal duct. (**b**) The illustrated version of (a) (Courtesy of Steven D. Schaefer, MD)

Lawson et al. [148] showed that enlargement of the sinus is uncommonly encountered and may be produced by air (pneumocele) and mucus (mucocele) entrapment or by benign tumors which have arisen in the sinus or adjacent maxilla and have grown intracavitarily, with the sinus walls expanding and remodeling to accommodate them. Reduction in the size and volume is more frequent. Heredofamilial syndromic conditions reduce sinus size by impaired facial growth centers or obliteration by dense osteosclerosis. *Silent sinus syndrome*, which likely results from resorption of air in an obstructed maxillary sinus leading to negative pressure in the lumen and ultimately initiating inward remodeling of the sinus walls, is a cause of enophthalmos and hypoglobus in some patients. Often the configuration on visual inspection may suggest proptosis on the contralateral (unaffected) side, until CT imaging reveals the true cause of the asymmetry as enophthalmos from an inferiorly bowed orbital floor instead [166]. Irradiation for neoplastic disease in the pediatric population directly suppresses the growth centers or impairs pituitary function. Another iatrogenic cause is by direct surgical intervention (Caldwell-Luc procedure) where the sinus volume and shape is reduced by osteoneogenesis. Midfacial fractures involving the sinus also produce distortion by sclerosis and malpositioning of bone fragments. Systemic disorders such as sickle-cell anemia and osteopetrosis, which diffusely effect medullary bone, do so through either compensatory marrow proliferation or sclerotic new bone formation, thus serving to produce maxillary enlargement and sinus obliteration.

The greatest source of maxillary sinus distortion and destruction are neoplasms. Malignant sinonasal and oral cavity tumors produce bony erosion of the sinus walls, whereas benign odontogenic cysts remain external to the sinuses and compress it as they enlarge. Most odontogenic tumors produce external compression and remodeling. Fibro-osseous disorders similarly produce size and shape distortions by external impingement. Although diverse developmental and pathologic conditions influence maxillary sinus morphology, there is a limited range of biological response.

The primary or *natural ostium* of this sinus is located in the superior aspect of the medial wall of the sinus and drains via its infundibulum into the hiatus semilunaris (Figs. 1.4, 1.6, 1.7, 1.8, 1.9, and 1.10). Despite a marked variation in position, most investigators see the ostia as being in the region of the posterior half of the infundibulum or posterior to the midpoint of the bulla ethmoidalis [97, 100, 102]. Lang and Papke [167] found that the ostium is located 1.3–11.5 mm (average 4 mm) from the nasolacrimal duct (Fig. 1.37), and this proximity of the duct to the natural ostium makes it vulnerable to injury during middle meatus antrostomy. The pneumatization of the ethmoidal bulla and the height (e.g., medial and superior projection) of the uncinate process help to form a canal leading to the maxillary sinus which was incorrectly termed *maxillary infundibulum*.[6] This structure varies in depth (average 5 mm) [150], orientation, and accessibility via the nose [97].

The *natural ostium* tends to be elliptical (Fig. 1.38), measuring from 1 to 20 mm in length [150]. In addition, *accessory maxillary sinus ostia* were found in 15–40 % of subjects examined by various authors (Figs. 1.4 and 1.31) [97, 100, 150]. These ostia may be located in the infundibulum or the membranous region of the medial sinus wall, the latter being only a reduplication of the mucosa of the sinus and the lateral nasal wall. This membranous wall is known as *the membranous meatus or fontanelle*. This region is located inferior to the uncinate process and superior to the insertion of the

[6] The maxillary infundibulum and frontal infundibulum are totally within their respected sinuses appearing as funneling tunnels whose orientation is toward their natural ostia [132].

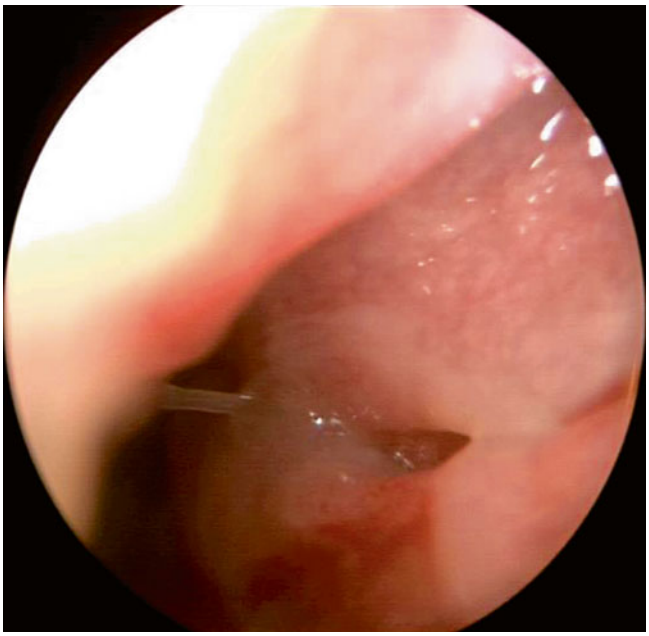


Fig. 1.38 A 30° endoscope image of the left primary maxillary ostium exhibiting its elliptically shaped aperture from which mucus can be seen draining (Courtesy of Michael Papaxanthos, MD)

inferior turbinate. Clinically, this site is particularly important because it may be used as an alternative to open the natural ostium when the latter cannot be found during the performance of a middle meatus or supra-inferior turbinate antrostomy.

During the seventeenth century, antral trephination for suppuration was the most common maxillary sinus operation performed, followed by molar tooth extraction to create an oral-antral fistula for dependent drainage of an infected maxillary sinus [168]. Historically, the next procedure for sinus drainage was an anterior wall approach above the canine fossa which was maintained patent for irrigation procedures. Then came the Caldwell-Luc procedure, which combined the anterior wall approach with an intranasal antrostomy, and after removal of the infected mucosa, the intranasal incision was closed. Presently, endoscopic sinus surgery is performed primarily for treating infected maxillary sinuses [168].

Frontal Sinus

Development and Functional Anatomy

Frontal sinus growth begins during the fourth fetal month in the primordia of the nasofrontal area within the frontal recess [169]. At birth, it has little clinical relevance and is often indistinguishable from the anterior ethmoid cells. Davis [170] tracked the frontal sinus postnatal development of 160 crania ranging from birth to 16 years of age and recorded that an evagination into the vertical portion of the frontal bone occurred during the second year. At 3 years of age, the frontal sinus is observed 3.8 mm above nasion (i.e., a craniometric point defined as the junction between the nasal and frontal bones at the midline) and continues its vertical growth trajectory at an average annual rate of 1.5 mm until the 15th year. Given the length of this growth trajectory, it has been studied as a marker of skeletal age alongside other osseous indicators such as stature and sequence of hand-wrist ossification (e.g., Gagliardi et al. [171]).

Final growth of the frontal sinus is completed before the 20th year, making it the last sinus to develop [126, 162]. Although as many as three sinuses have been reported in the literature (Fig. 1.39) [172], adult frontal sinuses consist generally of a pair which are asymmetrical in nature (Fig. 1.40) [132]. Tilley [173] illustrated the diversity of different frontal sinus morphologies, and he discredited using the prominences of the superciliary ridges as a guide in determining the presence and extent of the sinuses behind them. The potential of diverse initial growth patterns of the frontal sinus means that the adult sinus is highly variable such that each configuration is considered unique to each individual [174]. Indeed, forensic identification of postmortem skeletal material based on the radiography of frontal sinus morphology has been used successfully in criminal investigations (for historical review, see ref. [175] and more recent investigations by Tang and colleagues [176] and da Silva and others [177]). The resulting adult morphology is even variable between monozygotic twins, which may exhibit marked differences in sinus size and shape as a result of secondary pneumatization operating in an opportunistic, epigenetic fashion [178]. Shapiro and Schorr [179] attempted to explain the vast differences observed in pneumatization patterns of the

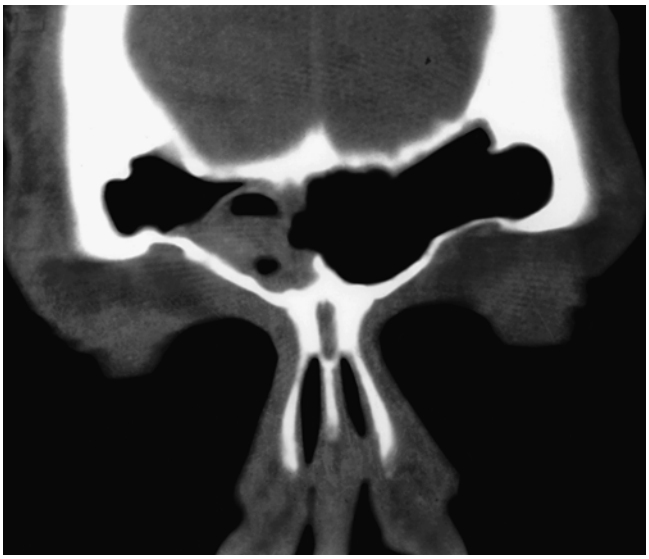


Fig. 1.39 Frontal cell is visible within the right frontal sinus. There is an air-fluid level within the frontal cell (Courtesy Timothy L. Smith, MD, MPH, Medical College of Wisconsin, Milwaukee, Wisconsin)

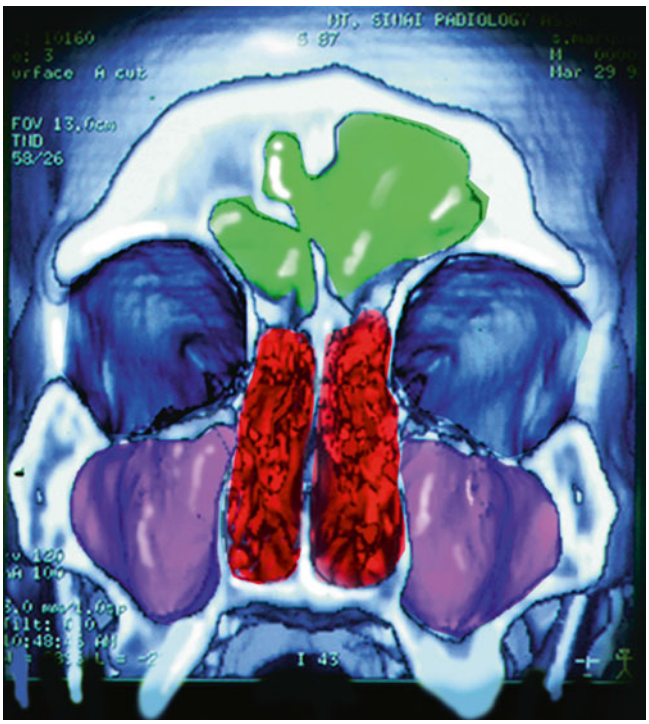


Fig. 1.40 Frontal view of a 3-D CT reconstruction of adult male human head (author SM) showing the topographical relationship between frontal sinus (seen in *green*) and maxillary sinus (seen in *purple*) to the nasal cavity proper (seen in *red*); note the characteristic asymmetry in frontal sinus morphology. The maxillary sinus is the largest of the four paranasal sinuses exhibited by humans and dominates the midfacial architectural space. Sphenoid sinuses are not visible in this coronal plane (Courtesy of Samuel Márquez, PhD)

frontal bone and concluded three factors may be ultimately responsible: (1) craniofacial configuration, (2) thickness of the frontal bone, and (3) hormonal growth factors.

Honig et al. [180] proposed a model in which there were two separate developmental origins for the frontal sinus. They transplanted median sections of the frontal bone into the occipital region of infant pigs before the formation of the frontal sinus via invasion of adjacent ethmoid air cells. The removed occipital bone sections were subsequently used to replace the missing sections of frontal bone. It was found that both the frontal and occipital bone transplants developed sinuses. The transplanted occipital section was invaded laterally by expanding ethmoid air cells that began to approach the median plane (former location of the interfrontal suture). On the transplanted frontal bone section, mucosa-lined sinuses began to form in paramedian planes around the location of the interfrontal suture, which had obliterated. It is proposed that the bone surrounding the interfrontal suture contains pluripotent cells that may assist in both angiogenesis and pneumatization. Honig et al. [180] thus suggest that the frontal sinus has two potential developmental origins.

As the shape of the frontal sinus is extremely variable, so too exists a diversity in patterns of drainage into the middle meatus, which may alter the functional relationships of its boundaries with the lateral nasal wall [181]. In a study of 100 adult specimens and 15 late-termed fetuses, Kasper [99] found the most common origin of the frontal sinus to be pits or furrows

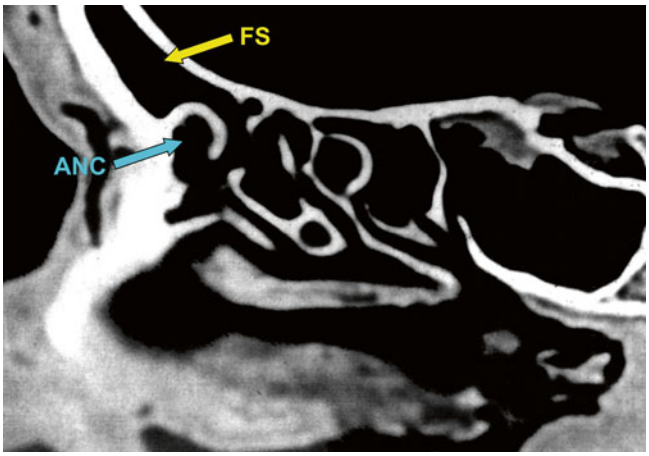


Fig. 1.41 A two-dimensional CT scan reconstruction showing the topographical relationship of the frontal sinus (*FS*) and the agger nasi cell (*ANC*). Note that the roof of the ANC forms part of the floor of the FS. (Courtesy of Steven D. Schaefer, MD)

originating within the frontal recess which are considered rudimentary anterior ethmoid cells (described previously as frontal recess cells). These additional furrows are not to be confused with the previously described furrows that go on to become the meatus. Indeed, Kasper [99] described these nasofrontal structures within the frontal recess as frontal pits due to their "dimple-like" appearance. A lack of clear developmental patterning or constancy in the differentiation of these frontal pits renders standardized description of their developmental anatomy challenging. One individual may exhibit as many as four pits or a total absence of pit formation. In cases of the latter, the frontal recess remains a simple blind outgrowth from the middle meatus without configuration of its lateral wall. Any number of these variably present pits may further develop into a frontal sinus, creating diversity in drainage pattern. For example, the more remote or lateral the location of the pits from the ethmoid infundibulum, the more lateral the resulting frontal sinus will become (as well as its communication with the nasal chamber, which is influenced by the impinging anterior ethmoid cells) [99]. Various developmental patterns are possible when all four pits are present since each pit has the potential to become a frontal sinus [96]. If the most anterior pit (i.e., pit 1) migrates in a ventral direction, it may pneumatize the agger nasi bone becoming an agger nasi cell, while the second most anterior pit (i.e., pit 2) may migrate anterosuperiorly becoming the frontal sinus. Thus, the terms agger nasi (i.e., referring to the mound of bone) and agger nasi cell (i.e., referring to the pneumatization of the agger nasi bone) are not interchangeable, since each represents a distinct anatomical entity. Moreover, a markedly pneumatized agger nasi cell could have potential pathophysiologic consequences in frontal sinus drainage [117]. The relationship between the frontal sinus and its drainage tract to the agger nasi cell is shown in Fig. 1.41. Since the roof of the agger nasi cell is the floor of the frontal sinus, and the posterior wall of the agger nasi cell is the anterior border of the frontal sinus drainage tract, then a markedly inflated cell would theoretically interrupt its normal drainage and ventilation [182]. In fact, Brunner et al. [183] have implicated the agger nasi cell in narrowing the frontal sinus outflow tract as a significant cause for the pathogenesis of frontoethmoid sinus pain and chronic frontal sinusitis. By the end of the second year of life, one of the anterior ethmoid cells will migrate upward into the frontal bone to form the frontal sinus [184]. Another means of frontal sinus formation results if no anterior ethmoid air cells develop in the frontal recess, then ethmoid air cell extension from the ethmoid infundibulum can create a frontal sinus [185].

The following is a summary of the possible developmental patterns of the frontal sinus as a result of a direct outgrowth from the frontal recess region if no frontal pits are present, from one of the frontal pits within the frontal recess when present, and of a direct outgrowth from the ventral portion of the ethmoid infundibulum – either by direct extension or from one of its cellular outgrowths [96]. Lastly, there can be combinations of the possible patterns of development resulting in duplicate and even triplicate sinuses on one side alone [172].

Urken et al. [186] attempted to evaluate whether an overly "large" frontal sinus may actually be abnormally inflated based on linear and derived area measurements as predictors of its "normal" variation. This led to a follow-up study in which Urken et al. [187] proposed three new categories to delineate the degree of excessive pneumatization based on aeration and bony changes of the sinus walls which they termed *hypersinus*, *pneumosinus dilatans*, and *pneumocele*.

Clinical Implications

The adult frontal sinus, when viewed in a transverse section, has been classically described as pyramidal shaped [131]. The base or inferior floor of the pyramid is the orbital nasal portion of the splanchnocranium, the apex extends outward a variable

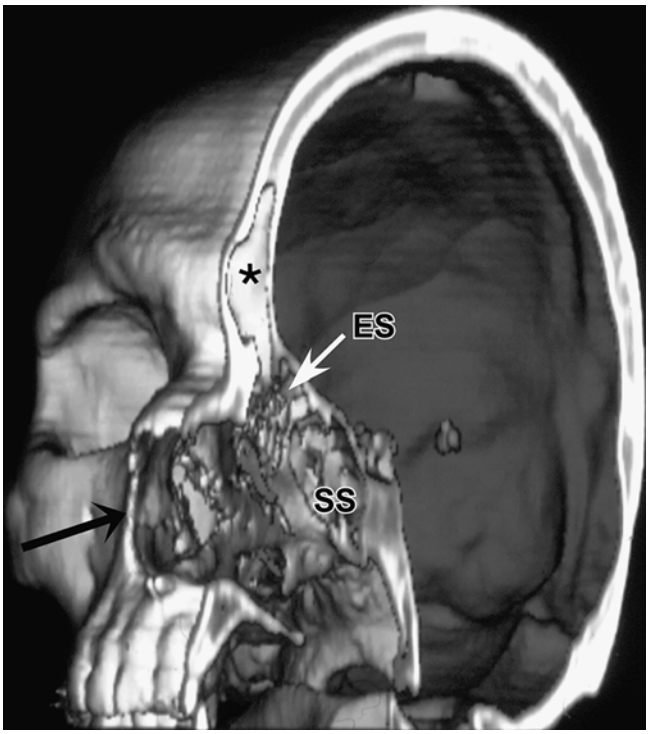


Fig. 1.42 A three-dimensional CT reconstruction of the same individual in Fig. 1.40 shown in oblique parasagittal view where ethmoid (*es*) and sphenoid air sinuses (*ss*) can be viewed. The *black asterisk* indicates the frontal sinus, and the *black arrow* is pointing to the piriform aperture rim where just posterior to it is the site of attachment of the inferior turbinate (Courtesy of Samuel Márquez, PhD)

distance over the orbit, and the anterior wall is subcutaneous while the posterior wall is cerebral. Dimensions of the adult frontal sinus have been reported as measuring 28 mm in height, 27 mm in width, and 17 mm in length [188]. This ideal sinus is a representative average, with the actual size and configuration reflecting the origin of the cavity and the superior development into the squama of the frontal bone [135]. At the inferior aspect in the midsagittal plane, the anterior or outer table of the frontal sinus is approximately twice as thick as the posterior or inner table. The sinus is compartmentalized further by the intrasinus septa and marginated by irregular bone. The loss of definition of the scalloped border, or the intrasinus septa, on radiographic imaging indicates chronic infection [189]. In describing the anatomical relations of the frontal sinus and its connection to the nasal cavity, a number of conflicting terms have caused confusion (Fig. 1.42). For example, while some anatomists have concentrated on the frontal ostium (the "discharge" point), others have concerned themselves with the treatment of frontal sinus disease and the so-called nasofrontal duct [190] (see clinical implication in Frontal Sinus subsection). Historically, the communication of this sinus with the nasal cavity has been described as a distinct nasofrontal duct, although others prefer the term frontal recess. The term nasofrontal duct, which is used to describe the communication of the frontal sinus through the middle meatus and into the nasal cavity, is anatomically and developmentally incorrect. To confuse the issue even further, the terms frontal recess, frontal infundibulum, and nasofrontal duct have also been used interchangeably, when in reality they represent different anatomical structures [132]. Conceptually, drainage of the frontal sinus has been likened to an hourglass with the upper portion being the ostium (varying 2–10 mm in diameter) and the frontal recess representing the lower portion beneath the neck. However, the term frontal recess introduced by Killian [127] is based on the prenatal observation of a space that is the continuation of the ascending branch of the first primary interturbinal furrow, with the descending branch becoming the ethmoid infundibulum. As discussed previously, the frontal sinus and the agger nasi cells are formed by pneumatization superiorly and anteriorly from the frontal recess region [114]. Additionally, cells may develop in the frontal bone adjacent to the frontal sinus, a phenomena that Zuckerkandl [28] called the *bulla frontalis*. The frontal infundibulum was defined by Killian [191] as the superior opening of the frontal sinus drainage tract. Finally, the nasofrontal duct as defined by Lang [137] is any mucosal-lined bony passage greater than 3 mm in length. The developmental variability of the frontal sinus leads to the multiple observed drainage patterns which can be further complicated by the highly variable pneumatization of the adjacent ethmoid air cells and by the position of the uncinate process. As an example, Lothrop [192] reported a direct communication between the frontal sinus and ethmoid infundibulum in 47 % of his 125 cadaver specimens, whereas Van Alyea [181] reported a 12.5 % incidence in 112 cadavers. This has prompted Stammberger [114] to conclude:

> [I]t is senseless to name every recess or inlet that can be seen endoscopically, particularly when pathologic changes are present. (p. 86)

Table 1.5 Important anatomical relationships and their surgical implications

Middle turbinate marks the junction of the roof of nasal cavity and ethmoidal labyrinth
Surgery is performed laterally to avoid cribriform plate injury
Middle turbinate slopes downward along it posterior course
To resect, scissors must be inclined downward; posterior tip of middle turbinate and superior turbinate lie in the plane of the face of the sphenoid
Middle turbinate resection
Superior portion maintained as a landmark; posterior tip may be a source of bleeding and should be electrocauterized
The nasolacrimal duct runs downward at the anterior border of the attachment of the middle and inferior turbinates
Inferior or middle meatus antrostomies must not be carried too far anteriorly to avoid duct injury
The outflow tract of the frontal sinus ("nasofrontal duct") drains into the ethmoid infundibulum or frontal recess cells
It cannot be safely enlarged and the frontal sinus entered intranasally in every case
The natural ostium of the maxillary sinus is generally present 1–2 cm beyond the anterior attachment of the middle turbinate
Dissection anteriorly may injure the nasolacrimal duct; dissection superiorly will penetrate the orbit
Fovea ethmoidalis is generally at a higher level than the cribriform plate
Thickness, yellow color, and sensitivity of bone are not reliable indicators; the higher the fovea, the weaker its medial wall and the more susceptible to fracture and perforation, with intracranial entry
Posterior ethmoidal cells may extend behind the sphenoid face
Dissection behind may produce optic nerve injury or CSF leak
Posterior ethmoidal cells may present superior to sphenoid sinus
Dissection may produce CSF leak
Developmental abnormalities of anterior ethmoidal cells exist
Hypoplasia of the uncinate process may lead to orbital injury on infundibulotomy; hyperplasia of agger nasi cells may block frontal recess or impinge on nasolacrimal duct, making it vulnerable to surgical injury
Ethmoidal labyrinth is placed superior as well as lateral to the middle turbinate in its posterior aspect
Failure to follow cells upward may result in orbital injury
Narrow ethmoid variant (the ethmoid may not widen posteriorly in a small number of cases)
Lateral dissection in a posterior cell my produce optic nerve injury
The lamina papyracea lies superiorly in the plane of the membranous middle meatus
Middle meatus antrostomy must be made on the upper border of the inferior turbinate (supraturbinal) to prevent orbital injury
Sphenoid ostium lies about 7 cm and 30° from the nares
Never blindly perforate into sinus; always cannulate transnasally or transseptally
Sphenoid ostium is 8 mm below cribriform plate
Dissection superiorly carries the risk of intracranial injury; attempted entry should be medially and inferiorly
Sphenoid ostium widening should be performed selectively
Superior widening carries the danger of CSF leak; inferior widening carries the danger of sphenopalatine artery injury
Sphenoid sinus walls may be dehiscent laterally
Instrumentation laterally may cause internal carotid artery injury
Sphenoid sinus may be partially encircled by medially displaced internal carotid arteries
Dissection or fracture superiorly may cause arterial injury

Adapted from Lawson [29]. With permission from John Wiley & Sons, Inc

Clinical Commentary

Serial CT scans are necessary to demonstrate the sinus anatomy in order to gain access to the frontal sinus via the nasal cavity. In following air cells superiorly into the frontal sinus, it is important to dissect as far anterior as possible. As previously discussed, the position of the anterior ethmoid artery, by assisting to identify the frontal recess and preventing an intracranial injury, forms an extremely important anatomical landmark in frontal sinus surgery. The vessel runs in a bony canal along the roof of the ethmoid labyrinth to form the posterior border of the frontal recess. Accordingly, surgery above the level of the canal must be anteriorly to enter the frontal sinus. Surgery posteriorly to it would violate the ethmoidal roof resulting in a dural injury.

Accessing the frontal sinus through the nose may be hazardous because one of the visualized openings may not be the primary drainage of the frontal sinus, and violating the floor of the anterior cranial fossa may lead to an intracranial injury. Moreover, scarring from previous surgery or pathologic conditions can make identification of the frontal recess impossible. This may require trephining the frontal sinus and transilluminating its floor by placement of a light source in the sinus or threading a probe through its ostium into the nasal cavity to guide further surgery. Recently, intraoperative visualization has

been aided by CT-guided visualization of the sinus and its outflow tract by electromagnetic and infrared navigational devices (see Table 1.5 for clinical anatomical concerns).

Sphenoid Sinus

Development and Functional Anatomy

The sphenoid sinus is arguably the most variable cuboidal-shaped sinus of all the paranasal sinuses [193], there being an average of six surfaces in the adult: the anterior, posterior, superior, inferior, medial, and lateral walls. However, in addition to its functional relationship with the nasal cavity, the sinus is strategically located in one of the more complex regions in all of human anatomy by virtue of its location within the sphenoid bone. The endocranial surface of this bone serves as the seat for endocrine activity, as a conduit for cranial nerves responsible for vision, ocular movements, nasal mucosal gland stimulation, and nasal sympathetic innervation and as a major vascular supply for the nasal cavity.

Growth of the usually paired sphenoid sinus is initiated during the third month of intrauterine development [169, 193] while the positions of its main ostia have been noted to undergo growth change as early as the third trimester, when it approaches the adult condition [194]. These two sinuses generally develop asymmetrically where usually one sinus encroaches upon and limits the other's growth to a rudimentary size. The bony partition between the two sinuses has been incorrectly termed "median septum." Congdon [195] suggested the more appropriate term "intersinus septum" since the partition is frequently found more lateral than medial and is the accepted term today. Both complete and partial septation of the sinuses is a frequent occurrence since no clear pattern emerged from a number of studies [195]. The variety of encroachment patterns by the pneumatization of contiguous structures and irregularities of its septa are all considered normal variation [195]. In turn, the sphenoid sinuses themselves may be encroached upon by posterior ethmoid air cells (see discussion of *Onodi cells* by Onodi [196]), a pattern more common among East Asians [197]. Its agenesis is a rarely reported phenomenon (e.g., Orhan et al. [198]).

The sphenoid sinus begins development as an evagination of the nasal mucosa into the posterior portion of the cartilaginous nasal capsule. Van Gilse observed that the inferoposterior expansion forms a pouch-like cavity in the cartilage, the wall of which is called the sphenoid conchae or Bertini's ossicles [199]. At birth, the pyramidal-shaped paired ossicles, whose spines are in contact with the medial pterygoid lamina and whose bases help to form the roof of the nasal cavity, begin to ossify. Around the time of birth, the sphenoid sinus is primarily an evagination of the sphenoethmoid recess, with essentially no growth until age 3 years. It is not until the third year of postnatal life that the sphenoid conchae become attached to the presphenoid and the cavity develops into the definitive sphenoid sinus [200]. After this period, the sinus begins to pneumatize the sphenoid bone, and by the seventh year, the sinus extends posteriorly toward the sella turcica [201]. Based on the prenatal development of the sphenoid bone (e.g., the anterior to posterior arrangement of its ossifications centers), Congdon [195] classified four types of sphenoid sinus pneumatization patterns: conchal, presphenoid, basisphenoid, and occipitosphenoid (i.e., the basilar part of the occipital bone). Based on a sample size of 181 specimens, Congdon [195] classified 5 % as conchal, 4.5 % between conchal and presphenoid types, and 23.5 % presphenoid, and the remaining 67 % included basisphenoid and occipitosphenoid types. Different incidences of these types of sphenoidal pneumatization have been reported over the years. For example, Hammer and Radberg [202] found conchal types in 2.5 % of cases, presellar types (presphenoid) in 11 %, postsellar types (basisphenoid) in 59 %, and mixed types in 27 %. In the most common developmental type, the postsellar, the sinus extends posteriorly toward the sella turcica by age 7 years. Development may continue into adulthood involving the basisphenoid, with arrest in pneumatization accounting for the tremendous variations in the sinus size. Such variations may produce recesses formed by the pneumatization of the sphenoid rostrum, the lesser wing of the sphenoid, and the orbital processes [203–205]. Pneumatization of contiguous bony structures is frequently observed, commonly affecting pterygoid processes in 25–40 % of adults and the anterior clinoid processes in 13 % [162]. Donald [109] reported the occurrence of a septal recess, sometimes called a sphenovomerine bulla, which is pneumatization of the vomer. The tendency to pneumatize contiguous bony structures is not restricted to human development since it is also seen in our own CT-based investigations of African great ape sinus anatomy (Fig. 1.43) [206].

The average adult sinus measures 20 mm in height, 23 mm in length, and 17 mm in width [41]. The volume varies from 0.1 to 30 ml, with the average ranging from 5 to 7.5 ml [41, 176]. As the sinus expands, vessels and nerves in the lateral aspect of the body of the sphenoid bone come to lie as indentations in the wall of the sinus. Thus, Van Alyea [126] found a projection of the internal carotid artery into the lateral sinus wall in 65 specimens ($n = 100$) and the projection being pronounced in 53 of them (Figs. 1.36, 1.44, 1.45, and 1.46). Based on a study of 1,600 skulls, Dixon [193] found that the optic

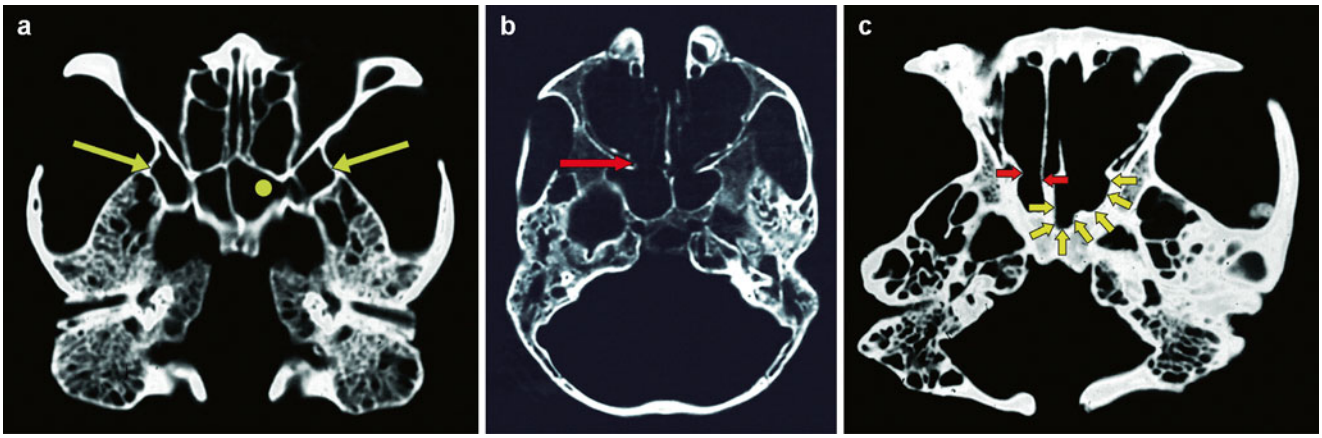


Fig. 1.43 (**a**) An axial scan of an adult gorilla showing the sphenoid sinus (shown in the *yellow dot*) invading and pneumatizing the pterygoid plates shown by the *yellow arrows*. (**b**) An axial scan of a subadult orangutan showing what appears to be a sphenoid sinus but is actually the maxillary sinus invading the sphenoid bone. (**c**) An adult orangutan showing the clearly patent communication between the left maxillary sinus and the evacuated sphenoid bone shown in *yellow*, *red arrow* illustrating the path of the right MS in its encroachment into the sphenoid bone (Courtesy of Samuel Márquez, PhD)

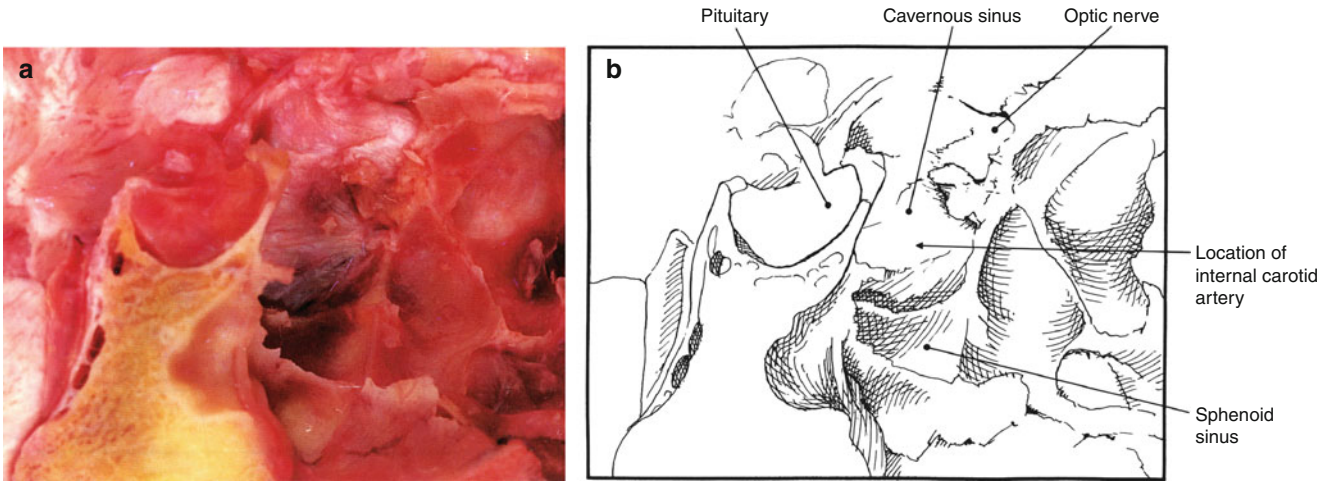


Fig. 1.44 (**a**) Parasagittal section through the sphenoid and posterior ethmoid sinuses. The lateral wall of these sinuses has been removed to expose the cavernous sinus and optic nerve. (**b**) The proximity of the optic nerve and internal carotid artery to the lateral wall of the sphenoid and posterior ethmoid sinuses is illustrated (Courtesy of Steven D. Schaefer, MD)

nerve was present as an indentation in the sinus wall in 8 % of the specimens and the Vidian nerve in 7 % (Figs. 1.36, 1.46, and 1.47). The Vidian nerve may be observed clinically to sit within the sinus entirely displaced from the inferior sinus wall. Dixon also reported that 22 % of the skulls had an intrasinus septum with dehiscence of the septum observed in only five specimens. The primary septum was found in the midline in only one quarter of the subjects. More often than not the septum grows asymmetrically with most of the bony wall coursing to one side, sometimes exhibiting an "S" or "C" shape. Equally important is the thinning of the superior wall, which may separate the sinus from the dura by only 1 mm [118]. Dehiscence of the sella floor is very rare [10], and dehiscence of the lateral wall over the internal carotid artery is also uncommon, but the potential minimal bony covering of this vessel is a clinically important factor to consider (Fig. 1.48).

Clinical Implications

The sphenoid sinus usually drains by a single ostium into the sphenoethmoid recess though it may also sometimes drain into the nasopharynx or posterior ethmoid cells via accessory channels [207]. This ostium, in the clinical setting, is

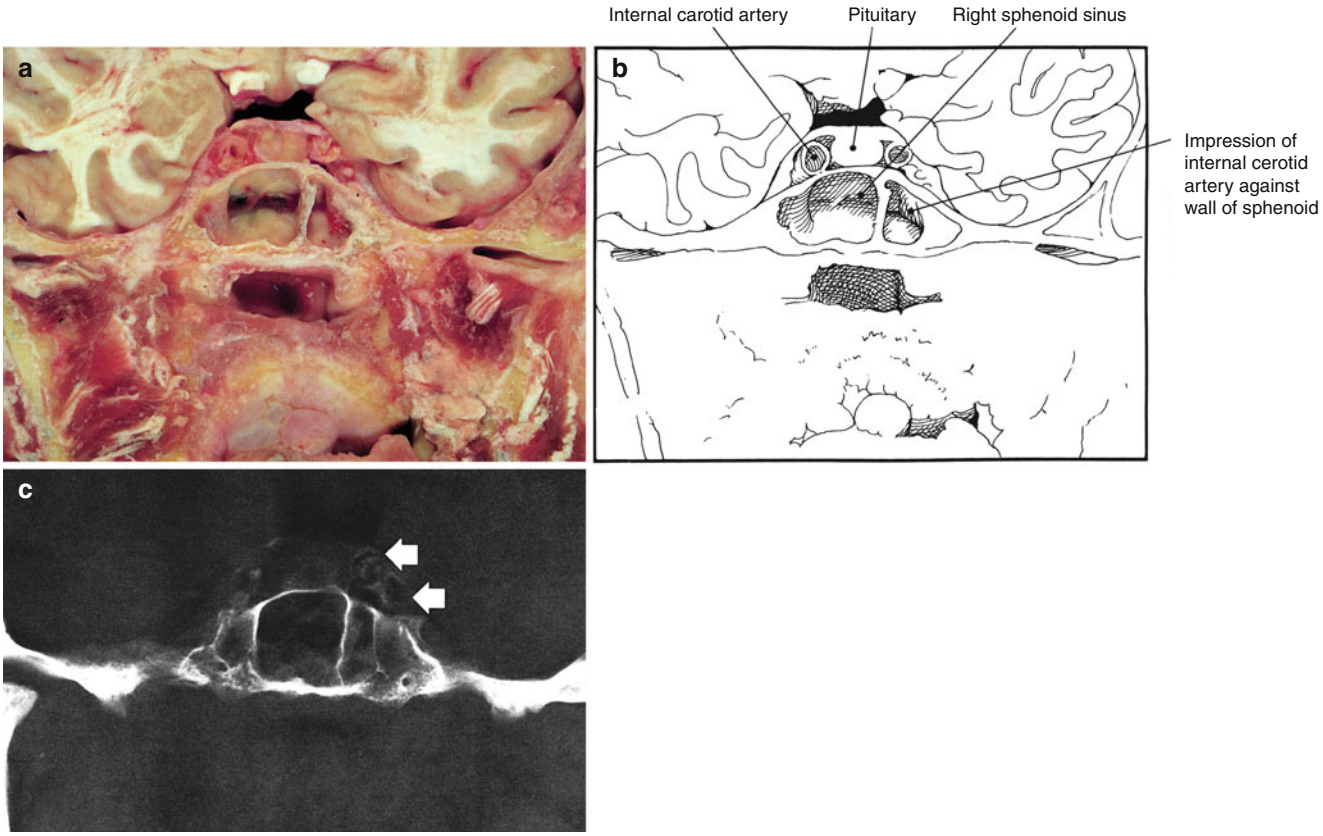


Fig. 1.45 (**a**) Anterior surface of coronal section contiguous with the section in (**c**). Level of the posterior sphenoid sinus. (**b**) Drawing of (a). The drawing emphasizes the close relationship of the sphenoid sinus to the important neurovascular structures. (**c**) Plain film radiograph specimen in (a). The *arrow* points to the internal carotid (Courtesy of Steven D. Schaefer, MD)

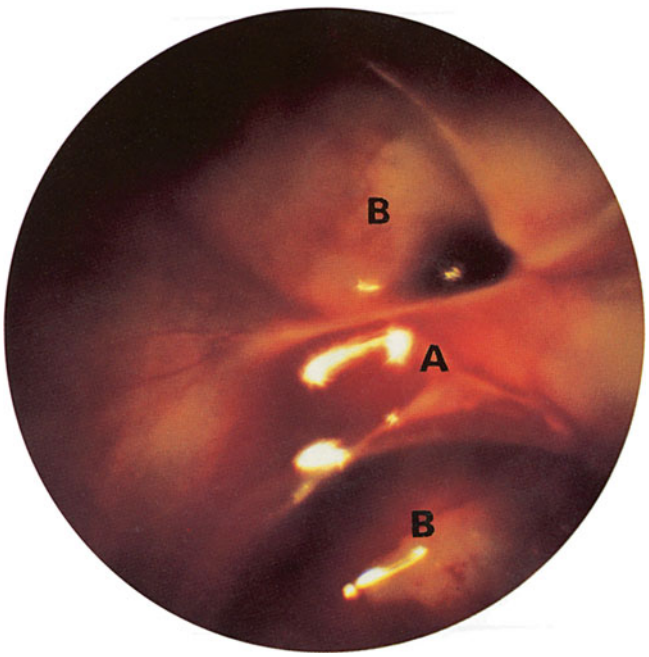


Fig. 1.46 Lateral wall of left sphenoid sinus visualized with a 25° endoscope. Optic nerve (*A*) is horizontally crossing internal carotid artery (*B*) (Courtesy of Steven D. Schaefer, MD)

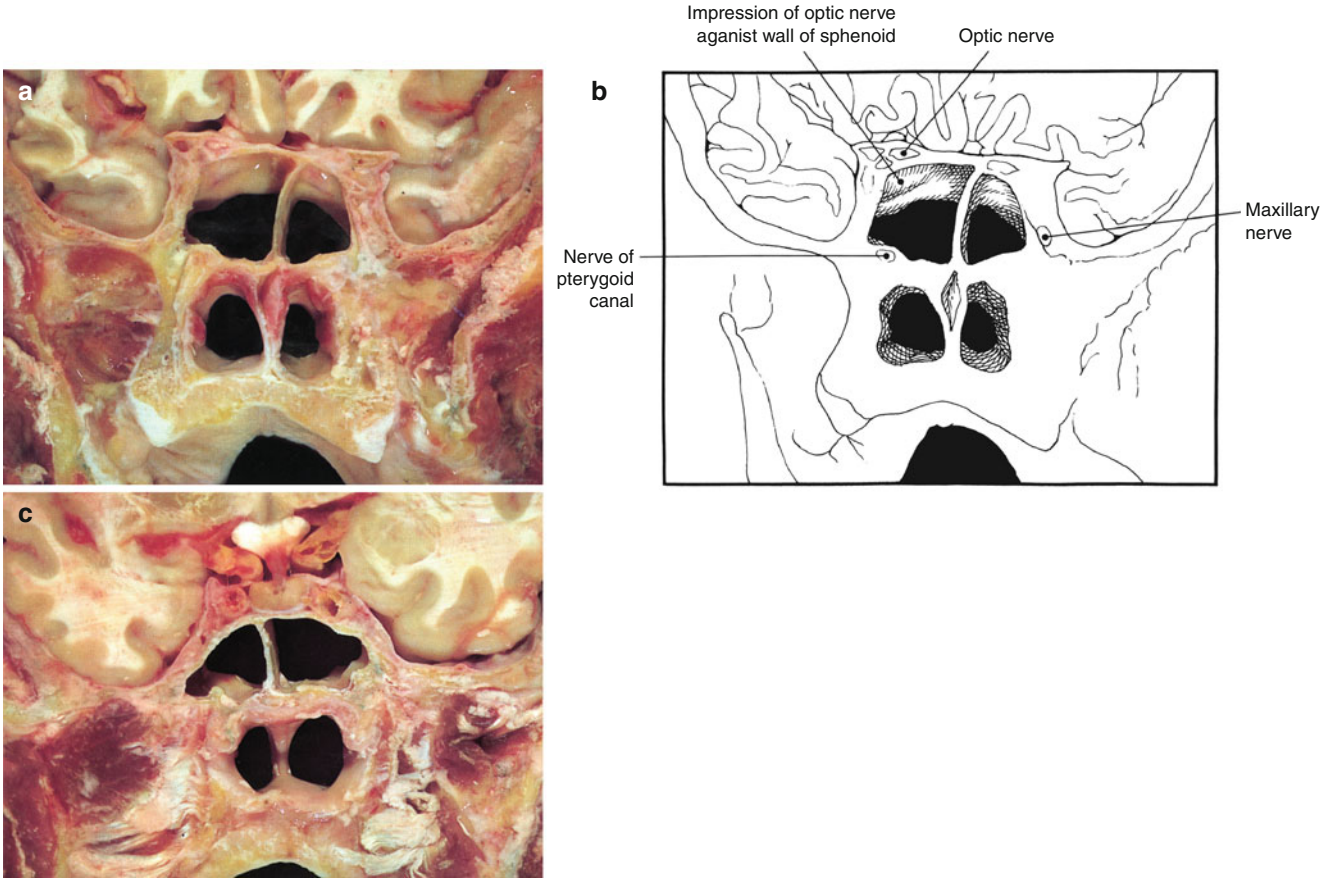


Fig. 1.47 (**a**) Anterior surface of coronal section contiguous with the specimen in (c) or at a plane adjacent to the dorsal aspect of the anterior wall of the sphenoid sinus. (**b**) Diagram of (a) shows the close proximity of the optic nerve to the sphenoid sinus. Inferior to the sphenoid is the posterior choana. (**c**) Posterior surface of the specimen in (a), which encompasses the principal cavity of the sphenoid sinus and the pituitary gland (Courtesy of Steven D. Schaefer, MD)

2–3 mm in diameter and may be either round or elliptical [41, 176]. The sinus depends on mucociliary flow for drainage since the ostium is located typically 10–15 mm superior to the floor of the sinus or 8 mm from the cribriform plate (range 1–15 mm) and 5 mm lateral to the nasal septum [176]. Our own experience suggests that in most cases the ostium tends to be observed more inferior than superior to the average location and generally lies at a 30° angle from the floor of the nose. The pneumatization of the posterior aspect of the middle turbinate may make visualization of this ostium difficult. Because of the importance of such identification in surgery, various measurements have been reported (Figs. 1.31 and 1.34, Table 1.6).

Of the many sinus surgical procedures done today, the sphenoethmoidectomy operation is considered one of the more complex. Schaefer [19] reminds us of the comments offered by the surgeon Harris Mosher, who although was referring to an ethmoidectomy procedure could also be applied here: “one of the easiest operations with which to kill a patient.” The sphenoethmoidectomy operation to be performed safely and effectively is based on the detailed anatomy of the paranasal sinuses. When surgical procedures were performed during the early twentieth century, they usually involved an external approach. Even though the intranasal sphenoethmoidectomy operation was first reported by Yankauer [208] at the Mount Sinai Hospital, the inherent danger of this procedure resulted in very little endonasal sinus surgery being performed until the 1986 introduction of the endoscope to the USA from Europe, where it had already been in use for over a decade. With the advent of more sophisticated cross-sectional imaging techniques and refinements in instrumentation, the sphenoethmoidectomy operation is considered a valuable procedure for surgeons well grounded in the intricate anatomy of the nose and paranasal sinuses.

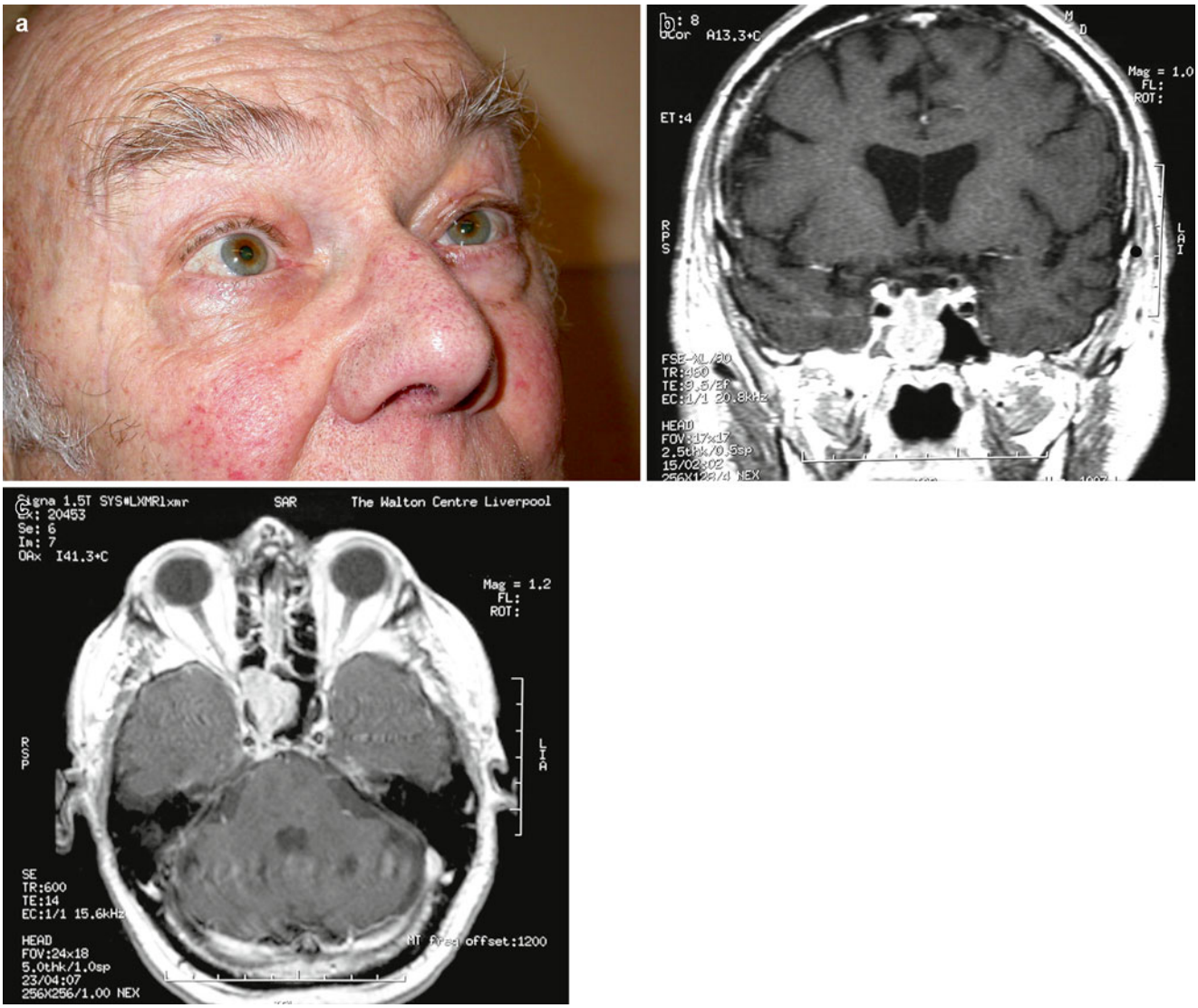


Fig. 1.48 (**a**) A 71-year-old male patient presents his chief complaint as diplopia (double vision) and is suspected of having a sixth nerve palsy. Here, the patient is asked to look to his right and is unable to abduct his right eye. (**b**) This axial MR scan reveals a tumor in his sphenoid sinus encroaching upon his right cavernous sinus. (**c**) The tumor can be clearly seen, in the coronal plane, substantially invading the cavernous sinus causing a right abducent nerve impairment (Courtesy of Mr. Andrew C. Swift, ChM, FRCS, FRCSEd, Consultant ENT Surgeon and Rhinologist, Aintree University Hospital, Liverpool, England)

Table 1.6 Morphometrics of sphenoid sinus anatomy

	Distance from anterior nasal spine	Distance from anterior nasal rim
Sphenoid ostium	7 cm	–
Pituitary fossa	8.5 cm	–
Inferior face of sphenoid	–	5.7 cm
Posterior wall of sphenoid sinus	–	7.6 cm
	Dixon [193] in living subjects	Mosher [130] in cadavers

Conclusions

Knowledge of paranasal sinus anatomy was of critical importance to surgeons in the pre-antibiotic era. Surgical drainage was the most common treatment for relief of the symptoms of infection and prevention of the complications of orbital and intracranial suppuration – which were generally fatal as well as acute and chronic osteomyelitis. External procedures were employed because of difficulties in visualizing and conceptualizing the sinuses intranasally. With technological advances in radiological imaging and the development of innovative instrumentation, there was a resurgence of interest in endonasal sinus surgery. Multiplanar CT and MR imaging now provide three-dimensional reconstruction of sinus anatomy that permit accurate assessment of inflammatory disease and often its differentiation from neoplastic processes. Understanding of sinus morphology through anatomical dissections and radiological imaging has advanced endonasal sinus surgery from speculum rhinoscopy to endoscopic skull base and intracranial surgery. Nevertheless, while the benefits of the new technologies are many, the complexity of sinus morphology requires that regional surgeons be masters of anatomy, with considerable surgical experience to ensure excellent outcomes and minimal morbidity. Indeed, the only aspect of sinus surgery that remains unchanged is a constant striving to better understand the intricate nature of these special spaces. Mastery of sinus anatomy continues to be indispensable for proper and safe sinus surgery.

References

1. Negus V. The comparative anatomy and physiology of the nose and paranasal sinuses. London: E & S Livingstone Ltd.; 1958.
2. Cave AJE, Haines RW. The paranasal sinuses of the anthropoid apes. J Anat. 1940;74:493–523.
3. Márquez S, Tessema B, Clement P, Schaefer SD. Development of the ethmoid sinus and migration of extramural cells: the anatomical basis for this paranasal sinus. Anat Rec. 2008;291:1535–53.
4. Smith TD, Rossie JB, Cocherty BA, Cooper GM, Bonar CJ, Silverior AL, Burrows AM. Fate of the nasal capsular cartilages in prenatal and perinatal Tamarins (*Saguinus geoffroyi*) and extent of secondary pneumatization of maxillary and frontal sinuses. Anat Rec. 2008; 291:1397–413.
5. Smith TD, Rossie JB, Cooper GM, Durham EL, Schmeig RM, Dochertry BA, Bonar CJ, Burrows AM. Microanatomical variation of the nasal capsular cartilage in newborn primates. Anat Rec. 2012;295:950–60.
6. Stammberger H, Hawke M. Essentials of functional endoscopic sinus surgery. St. Louis: Mosby – George Stamathis; 1993.
7. Blanton PL, Biggs NL. Eighteen hundred years of controversy: the paranasal sinuses. Am J Anat. 1969;124:135–48.
8. da Vinci L. Quaderni d'anatomia. I–VI. Fogli della Royal Library di Windsor, pubblicati da C. L. Vangensten, A. Fonahn, H. Hopstock. 6 vols. Christiania, F. Dybwad, 1911–1916; 1489.
9. Márquez S. The paranasal sinuses: the last frontier in craniofacial biology. Anat Rec. 2008;291:1350–61.
10. Stammberger H. History of rhinology: anatomy of the paranasal sinuses. Rhinology. 1989;27:197–210.
11. Douglass B. Nasal sinus surgery with operations on nose and throat. Philadelphia: F. A. Davis Company; 1906.
12. Libersa C, Laude M, Libersa J-C. The pneumatization of the accessory cavities of the nasal fossae during growth. Anat Clin. 1981;2:265–73.
13. Sperber GH. Applied anatomy of the maxillary sinus. J Can Dent Assoc. 1980;6:381–6.
14. Wendler D. Nathanael Highmore (1613–1685) und die Oberkieferhöhle. Anat Anz. 1986;162:375–80.
15. Stoney P, MacKay A, Hawke M. The antrum of Highmore or of Da Vinci? J Otolaryngol. 1991;20:456–8.
16. Berengario da Carpi G. Commentaria cum amplissimis additionibus super anatomia Mundini una cum textu ejusdem in pristinum et verum nitorem redacto. Bononiae, imp. per H. de Benedictis; 1521.
17. Harle F. The history of maxillary sinus surgery – from Leonardo da Vinci until today. Bull Hist Dent. 1992;40:79–84.
18. Highmore N. Corporis humani disquisitio anatomica in qua sanguinis circulationem in quavis corporis particular plurimis typis novis, ac anygmatum medicorum succincta dilucidatione ornatum prosequutus est. Hagae-Comitis, S. Brown; 1651.
19. Anon JB, Rontal M, Zinreich SJ. Anatomy of the paranasal sinuses. Thieme/New York: Thieme Medical Publishers; 1996.
20. Laitman JT. Harnessing the hallowed hollows of the head: the mysterious world of the paranasal sinuses. Anat Rec. 2008;291:1346–9.
21. Bauhin C. Theatrum anatomicum Caspari Bauhini. 2. Auflage von J. Th. De Bry, Basel; 1621.
22. Haller A von. Elementa physiologiae corporis humani. Tumus Quintus: Sensus externi interni. Lausannae, MDCCLXIX; 1769.
23. Bosworth FH. The physiology of the nose. Med News. 1888;53:117–24.
24. Turner L. The accessory sinuses of the nose. Edinburgh: William Green & Sons; 1901.
25. Tillaux P. Rôle des sinus de la face. Paris: Thèse Méd; 1862.
26. Zuckerkandl E. Normale und pathologische Anatomie der Nasenhöhle und ihrere pneumatischen Anhänge. Wien: Braumüller; 1882.
27. Zuckerkandl E. Normale und pathologische Anatomie der Nasenhöhle und ihrere pneumatischen Anhänge. Anatomie der Nasenscheidewand, Bd. II. Wien: Braumüller; 1892.
28. Zuckerkandl E. Normale und pathologische Anatomie der Nasenhöhle und ihrere pneumatischen Anhänge, 2nd ed., Bd. II. Wien: Braumüller; 1893.
29. Lawson W. The intranasal ethmoidectomy: evolution and an assessment of the procedure. Laryngoscope. 1994;104(6 part 2):1–49.
30. Cleland J. On the relations of the vomer, ethmoid, and intermaxillary bones. Phil Trans R Soc Lond. 1862;62:289–321.
31. Paulli S. Über die pneumaticität des Schädels bei den Säugethieren. Eine morphologische Studie III. Über die Morphologie des Siebbeins und Pneumaticität bei den Insectivoren, Hyracoideen, Chiropteren, Carnivoren, Pinnipedien, Edentates, Rodentiern, Prosimien und Primaten. Gegenbaurs Morph Jahrb. 1900;28:483–564.
32. Salinger S. Progress in otolaryngology: the paranasal sinuses. Arch Otolaryngol. 1939;30:442–79.
33. Onodi A. Des rapports entre le nerf optique et le sinus sphénoïdal. La cellule ethmoïdale postérieure en particulier. Rev Hebd Laryngol d'Otol Rhinol. 1903;25:721–40.

34. Nemours PR. A comparison of the accessory nasal sinuses of man with those of lower vertebrates. Trans Am Laryngol Rhinol Otol Soc. 1931; 37:195–9.
35. Shea BT. Eskimo craniofacial morphology, cold stress and the maxillary sinus. Am J Phys Anthropol. 1977;47:289–300.
36. Möller W. Vergleichend-morphologische Unersuchungen an Schädeln höckertragender Anatiden mit einem Beitrag zur Mechanik des Anatidenschädels. III Gegenbaurs Morph Jahr. 1969;113:321–45.
37. Buhler P. Sandwich structures in the skull capsules of various birds – the principle of lightweight structures in organisms. Mitterilungen aus dem Institut für leichte Flächentragwerke (Stuttgart) 1972;4:39–50.
38. Buhler P. Das Vogelskelett – hochentwickelter Knochern-Leichbau. Arcus. 1986;5:221–8.
39. Crelin E. Development of the upper respiratory system. Clin Symp. 1976;28(3):1–30.
40. Schummer A, Nickel R, Sack WO. The viscera of the domestic mammals. 2nd ed. New York: Springer; 1979.
41. Davis WE, Templer J, Parsons DS. Anatomy of the paranasal sinuses. In: Parsons DS, editor. Otolaryngol Clin North Am. 1996;29:57–74.
42. Eckley WT. On the accessory sinuses. Chicago Med Recorder. 1904;26:243–53.
43. Dieulafé L. Morphology and embryology of the nasal fossae of vertebrates. (Translated by Loeb HB. St. Louis: St. Louis University. Reprinted from Ann Otol Rhinol Laryngol 1906).
44. Moss M, Young RL. A functional approach to craniology. Am J Phys Anthropol. 1960;18:281–92, 285.
45. Enlow DH. The human face: an account of the postnatal growth and development of the craniofacial skeleton. New York: Hoeber Medical Division, Harper and Row Publishers; 1968.
46. Blaney SP. An allometric study of the frontal sinus in *Gorilla, Pan and Pongo*. Folia Primatol (Basel). 1986;47:81–96.
47. Blaney SPA. Why paranasal sinuses? J Laryngol Otol. 1990;104:690–3.
48. Moore KL, Persaud TVN. The developing human. 5th ed. Philadelphia: W. B. Saunders; 1993.
49. Witmer LM. Homology of facial structures in extant archosaurs (birds and crocodilians), with special reference to paranasal pneumaticity and nasal conchae. J Morphol. 1995;225:269–327.
50. Witmer LM. The extant phylogenetic bracket and the importance of reconstructing soft tissues in fossils. In: Thomason JJ, editor. Functional morphology in vertebrate paleontology. New York: Cambridge University Press; 1995. p. 19–33.
51. Witmer LM. The evolution of the antorbital cavity of Archosaurs: a study in soft-tissue reconstruction in the fossil record with an analysis of the function of pneumaticity. J Vert Paleontol. 1997;17 Suppl 1:1–65.
52. Witmer LM. The phylogenetic history of the paranasal air sinuses. In: Koppe T, Nagai H, Alt KW, editors. The paranasal sinuses of higher primates. Berlin: Quintessence; 1999. p. 21–34.
53. O'Malley JF. Evolution of the nasal cavities and sinuses in relation to function. J Laryngol Otol. 1924;39:57–64.
54. Badoux DM. Framed structures in the mammalian skull. Acta Morphol Neerl Scand. 1966;6:239–50.
55. Preuschoft H, Witte H, Witzel U. Pneumatized spaces, sinuses and spongy bones in the skulls of primates. Anthropol Anz. 2002;60:67–79.
56. Weidenreich F. Über die pneumatischen Nebenräume des Kopfes. Ein Beitrag zur Kenntnis des Bauprintips des Knochens, des Schädels und des Körpers (Knochenstudien: III. Teil). Z Anat Entwickl Gesch. 1924;72:55–93.
57. Weidenreich F. The brain and its role in the phylogenetic transformation of the human skull. Am Phil Soc. 1941;31:321–442.
58. Du Brul EL. The skull of the lion marmoset *Leontideus rosalia* Linneaus: a study in biomechanical adaptation. Am J Phys Anthropol. 1965; 23:261–76.
59. Sicher H. Oral anatomy. 2nd ed. St. Louis: C. V. Mosby; 1952.
60. Rui R, Den L, Gourlaouen L. Contribution à l'étude du rôle des sinus paraassaux. Rev Laryngol Otol Rhinol. 1960;81:796–839.
61. Geist V. Mountain sheep. Chicago: University of Chicago Press; 1971.
62. Schaffer WM, Reed CA. The co-evolution of social behavior and cranial morphology in sheep and goats (Bovidae, Caprini). Fieldiana Zoo. 1972;61:1–88.
63. Bignon F. Contribution a l'étude de la pneumaticité chez les oiseaux. Les cellules aëriennes cervico-céphalique des oiseaux et leurs rapports avec les os de la tête. Mém Soc Zool France. 1889;2:260–320.
64. Bremer JL. The pneumatization of the head of the common fowl. J Morphol. 1940;67:143–57.
65. Proetz AW. Essays on the applied physiology of the nose. 2nd ed. St. Louis: Annals Publishing; 1953.
66. Keith A. The relationship of the eruption of the permanent molar teeth to the expansion of the maxillary sinus. Br J Dent Sci. 1902; 45:529–44.
67. Keith A. Inflation of the nasal canal in the skulls of adult gorillas and chimpanzees, and the relative development of the sinus maxillaris and inferior meatus in man and apes. J Anat Physiol. 1902;36:47–51.
68. Underwood AS. An inquiry into the anatomy and pathology of the maxillary sinus. J Anat Physiol. 1910;44:354–69.
69. Braune W, Clasen FE. Die Nebenhöhlen der menschlichen Nase in ihre Bedeutung für den Mechanismus des Rieches. Z f Anat. 1877;2:1–28.
70. Strickland GW. Accessory nasal sinus infections in children. J M Soc New Jersey. 1932;29:108–11.
71. Eckert-Mobius A. Comparative study of the nasal sinuses in man and in animals. Arch f OhrenNasen-u Kehlkopfh. 1933;134:287–307.
72. Sato C. Vergleichende Studien über die Morphologie und den Bau der Schleimhaut der Nasennebenhöhlen bei verschiedenen Tieren (Saugetieren, Vogeln und Amphibien.) Mitt. a.d. med. Akad. zu Kioto 1938;22:277.
73. Proetz AW. Observations upon the formation and function of the accessory nasal sinuses and the mastoid cells. Ann Otol Rhinol Laryngol. 1922;31:1083–96.
74. Proetz AW. Applied physiology of the nose. 1st ed. St. Louis: Annals Publishing; 1941.
75. Gannon PJ, Doyle WJ, Ganjian E, Márquez S, Gnoy A, Gabrielle HS, Lawson W. Maxillary sinus mucosal blood flow during nasal vs tracheal respiration. Arch Otolaryngol Head Neck Surg. 1997;123:1336–40.
76. Hartz HJ. Remarks on the physiology and development of the nose and accessory sinuses and nasal reflexes, with special reference to the function and importance of the turbinated bodies. Ann Otol Rhinol Otolaryngol. 1909;18:709–38.
77. Mosher H. Transactions of the 28th Annual Meeting of the American Laryngological, Rhinological and Otological Society, Inc. Held in Washington, D.C. 1922.
78. Wegner RN. Die Nebenhöhlen der Nase bei den Krokodilen. Wissensch Z Ernst Moritz Arndt Univ Greifswald, Germany. 1958;7:1–39.
79. Dyce KM, Sack WO, Wensing CJG. Textbook of veterinary anatomy. Philadelphia: W. B. Saunders; 1987.
80. Leakey M, Walker A. *Afropithecus* – function and phylogeny. In: Begun DR, Ward CV, Rose MD, editors. Function, phylogeny, and fossils. New York: Plenum Press; 1997.

81. Coffin LA. The development of the accessory sinuses of nose. Am J Med Sci. 1905;129:297–312.
82. Neumayer. Ueber den Luftwechsel in den Nebenhohlen. Mon f Ohrenhk S 504;1901.
83. Frers D. Studien über die postembryonale entwickelung der Nebenhöhlen der Nase. Vehr D Vereins Deutscher Lryn S. 191;1909.
84. Suarez ADC. Una nueva teoria sobre la posible function de los senos para-nasales y celdas mastoidaas. Rev Espan Oto-Neuro-Oftal. 1952;11:336.
85. Del Canizo A. Alcum nuovi concetti sulla fisiologia sinusale e delle cellule mastoidee. Arch Ital Otol. 1959;70:20.
86. Rice DH, Gluckman JL. Physiology. In: Donald PJ, Gluckman JL, Rice DH, editors. The sinuses. New York: Raven Press; 1995. p. 49–56.
87. Alger LJ. A new theory of physiology of the sinuses. Lancet. 1943;58:511–12.
88. Rhys Evans PH. The paranasal sinuses and other enigmas: an aquatic evolutionary theory. J Laryngol Otol. 1992;106:214–25.
89. Lundberg JON, Rinder J, Weitzberg E, Lundberg JM, Alving K. Nasally exhaled nitric oxide in humans originates mainly in the paranasal sinuses. Acta Physiol Scand. 1994;152(4):431–2.
90. Ingersoll JM. The function of the accessory cavities of the nose. Ann Otol Rhinol Laryngol. 1906;15:757–70.
91. Ingersoll JM. Some points in the comparative anatomy of the nose and the accessory sinuses which account for the variations in these structures in man. Trans Am Laryngol Rhinol Otol Soc. 1922;28:162–7.
92. Negus V. The function of the paranasal sinuses. AMA Arch Otolaryngol. 1957;66:430–42.
93. Takahashi RYO. The formation of the human paranasal sinuses. Acta Otolaryngol Suppl. 1983;408:2–28.
94. Lund VJ. The maxillary sinus of higher primates. Acta Otolaryngol. 1988;105:163–71.
95. Bock WJ, von Wahlert G. Adaptation and the form-function complex. Evolution. 1965;19:269–99.
96. Schaeffer JP. The genesis, development, and adult anatomy of the nasofrontal region in man. Am J Anat. 1916;20:125–43.
97. Myerson MC. The natural orifice of the maxillary sinus. I. Anatomic studies. Arch Otolaryngol. 1932;15:80–91.
98. Simon E. Anatomy of the opening of the maxillary sinus. Arch Otolaryngol. 1933;29:640–9.
99. Kasper KA. Nasofrontal connections. A study based on one hundred consecutive dissections. Arch Otolaryngol. 1936;23:322–43.
100. Van Alyea OE. The ostium maxillare. anatomic study of it surgical accessibility. Arch Otolaryngol. 1936;24:553–69.
101. Rosenberger HC. The clinical availability of the ostium maxillae: a clinical and cadaver study. Ann Otol Rhinol Laryngol. 1938;47:177–82.
102. Schaeffer JP. The nose, paranasal sinuses, nasolacrimal passageways, and olfactory organ in man. Philadelphia: Blakiston; 1920.
103. Schaefer SD. An anatomic approach to endoscopic intranasal ethmoidectomy. Laryngoscope. 1998;108:1628–34.
104. Wigand ME, Steiner W, Jaumann MP. Endonasal sinus surgery with endoscopical control: from radical operation to rehabilitation of the mucosa. Endoscopy. 1978;10:255–60.
105. Messerklinger W. Endosckopiche Diagnose und Chirugie der rezidivierenden Sinusitis. In: Krajina Z, editor. Advances in nose and sinus surgery. Zagreb: Zagreb University; 1985.
106. Jankowski J. Revisiting human nose anatomy: phylogenic and ontogenic perspectives. Laryngoscope. 2011;121(11):2461–7.
107. Jankowski R. The evo-devo origin of the nose, anterior skull base and midface. Paris: Springer; 2013.
108. Terrier G. Rhinosinusal endoscopy. Diagnosis and surgery. Milano: Zambon; 1991.
109. Donald PJ. Anatomy and histology. In: Donald PJ, Gluckman JL, Rice DH, editors. The sinuses. New York: Raven Press; 1995. p. 25–48.
110. Ritter FN. The middle turbinate and its relationship to the ethmoidal labyrinth and the orbit. Laryngoscope. 1982;92:479–82.
111. Schaeffer JP. The lateral wall of the cavum nasi in man, with especial reference to the various developmental changes. J Morphol. 1910;21:613–707.
112. Schaeffer JP. The genesis and development of the nasolacrimal passages in man. Am J Anat. 1912;13:1–24.
113. Schaeffer JP. Types of ostia nasolacrimalis in man and their genetic significance. Am J Anat. 1912;13:183–92.
114. Stammberger H. Functional endoscopic sinus surgery. In: Hawke M (adapted and edited), Philadelphia: B.C. Decker; 1991.
115. Santorini GD. Observationes Anatomicae. Venetis, apud F. B. Recurti; 1724.
116. Van Alyea OE. Ethmoid labyrinth. Anatomic study, with consideration of the clinical significance of its structural characteristics. Arch Otolaryngol. 1939;29:881–902.
117. Lang J, Sakals E. Über die höhle der Cavitas nasi, die Länge ihres Bodens und Maße sowie Anordnung der Conchae nasales und der Apertura sinus sphenoidalis. Anat Anz. 1981;149:297–318.
118. Bingham B, Wang R-G, Hawke M, Kwok P. The embryonic development of the lateral nasal wall from 8 to 24 weeks. Laryngoscope. 1991;101:992–7.
119. Paulli S. Über die pneumaticität des Schädels bei den Säugethieren. III. Über die morphologie des siebbeins und pneumaticität bei den Insectivoren, Hyracoideen, Chiropteren, Carnivoren, Pinipedien, Edentaten, Rodentiern, Prosimien und Primaten. Morph Jb. 1900;27:483–564.
120. Moore WJ. The mammalian skull. Cambridge: Cambridge University Press; 1981.
121. Wasson WW. Changes in nasal accessory sinuses after birth. Arch Otolaryngol. 1933;17:197–211.
122. Spaeth J, Krügelstein U, Schlöndorff G. The paranasal sinuses in CT-imaging: development from birth to age 25. Int J Pediatr Otorhinolaryngol. 1997;39(1):25–40.
123. Wolf G, Anderhuber W, Kuhn F. Development of the paranasal sinuses in children: implications for paranasal sinus surgery. Ann Otol Rhinol Laryngol. 1993;102:705–11.
124. Pransky SM, Low WS. Pediatric ethmoidectomy. In: Parsons DS, editor. Otolaryngol Clin North Am. 1996;29:131–142.
125. Shapiro R, Jantzen AH. The normal skull: a roentgen study. New York: Paul Be Hoeber; 1960.
126. Van Alyea OE. Nasal sinuses: an anatomic and clinical consideration. 2nd ed. Baltimore: Williams & Wilkins; 1951.
127. Shambaugh GE. The construction of the ethmoid labyrinth. Ann Otol Rhinol Laryngol. 1907;16:771–92.
128. Seydel O. Über die Nasenhöhle der höheren Säugetiere und des Menschen. Gegenbaurs Morphol Jb. 1891;17:44–99.
129. Rice DH. Management of the middle turbinate in endoscopic surgery. In: Friedman M, editor. Oper Tech Otolarygol Head Neck Surg. 1995;6:144–148.
130. Mosher HP. The surgical anatomy of the ethmoidal labyrinth. Ann Otol Rhinol Laryngol. 1929;38:869–901.
131. Mosher HP. The applied anatomy of the frontal sinuses. Laryngoscope. 1904;14:830–55.

132. Stammberger HR, Bolger WE, Clement PAR, Hosemann W, Kuhn FA, Lanza DC, Leopold DA, Ohnishi R, Passàli D, Schaefer SD, Wayoff MR, Zinreich SJ. Paranasal sinuses: anatomic terminology and nomenclature. In: Kennedy DW, editor. International conference on sinus disease: terminology, staging, therapy. Ann Otol Rhinol Laryngol. 1995;104(suppl 167):7–16.
133. Schaeffer JP. The clinical anatomy of the ethmoidal labyrinth. Laryngoscope. 1930;60:627–32.
134. Skillern RH. The catarrhal and suppurative diseases of the accessory sinuses of the nose. Philadelphia: J. B. Lippincott Company, The Washington Square Press; 1923.
135. Hollingshead WH. Anatomy for surgeons: the head and neck. New York: Harper & Row; 1968.
136. Ritter FN. The paranasal sinuses: anatomy and surgical technique. 2nd ed. St. Louis: Mosby; 1978.
137. Lang J. Clinical anatomy of the nose, nasal cavity and paranasal sinuses. New York: Thieme Medical Publishers; 1989.
138. Naumann H. Pathologische Anatomie der chronischen Rhinitis und Sinusitis. In: Proceedings VIII international congress of oto-rhino-laryngology. Amsterdam: Excerpta Medica; 1965.
139. Isobe M, Murakami G, Kataura A. Variations of the uncinate process of the lateral nasal wall with clinical implications. Clin Anat. 1998; 11(5):295–303.
140. Schaeffer JP. On the genesis of air cells in the conchae nasales. Anat Rec. 1910;4:167–80.
141. Lang J, Hass A. Über die Sagittalausdehnung des Sinus frontalis dessen Wanndicke, Abstande zur Lamina cribrosa, die Teife der sogenannten Olfactorious-Rinne und die Cannales ethmoidales. Gegenbaurs Morphol Jb. 1988;134:459–69.
142. Loeb HW. A study of the anatomic relations of the optic nerve to the accessory cavities of the nose. Ann Otol Rhinol Laryngol. 1909; 9:243–76.
143. Kainz J, Stammberger H. The roof of the anterior ethmoid: a place of least resistance in the skull base. Am J Rhinol. 1989;3:191–9.
144. Mutalik A, Kolagi S, Hanji C, Ugale M, Rairam GB. A morphometric anatomical study of the ethmoidal foramina on dry human skulls. J Clin Diagn Res. 2011;51(1):28–30.
145. Singh PR, Ananda MK, Raibagkar CJ. Study of ethmoidal foramen in dry human skull. J Anat Soc India. 2005;54(1):32.
146. McDonald SE, Robinson PJ, Nunez DA. Radiological anatomy of the anterior ethmoidal artery for functional endoscopic sinus surgery. J Laryngol Otol. 2008;122(3):264–7.
147. Kennedy D. Functional endoscopic sinus surgery. Arch Otolaryngol. 1985;111:643–9.
148. Lawson W, Patel ZM, Lin FY. The development and pathologic processes that influence maxillary sinus pneumatization. Anat Rec. 2008;291:1554–63.
149. Hajnis K, Kustra T, Farkas LG, Feiglova B. Sinus maxillaris. Z Morph Anthropol. 1967;59:185–97.
150. Schaeffer JP. The sinus maxillaris and its relations in the embryo, child, and adult man. Am J Anat. 1910;10:313–67.
151. Cullen RL, Vidic B. The dimensions and shape of the human maxillary sinus in the perinatal period. Acta Anat. 1972;83:411–15.
152. Anagnostopoulou S, Venieratos D, Spyropoulous N. Classification of human maxillar sinuses according to their geometric features. Anat Anz. 1991;173:121–30.
153. Alberti PW. Applied surgical anatomy of the maxillary sinus. In: Noyek AM, Zizmor J (guest editors). Otolaryngol Clin North Am. 1976;9:3–20.
154. Almagro AM, Marco JM, Galvis CG, Guiñon IB. Relaciones entre seno maxilar y apófisis alveolar maxilar superior. Estudio anatomotopográfico. Acta Otorrinolaryingol Esp. 1995;46:409–15.
155. Boocock P, Roberts CA, Manchester K. Maxillary sinusitis in medieval Chichester, England. Am J Phys Anthropol. 1995;98:483–95.
156. Amedee RG. Sinus anatomy and function. In: Bailey BJ, editor. Head and neck surgery – otolaryngology. Philadelphia: J. B. Lippincott Co.; 1993. p. 342–9.
157. Kallius E. Sinnesorgane-Erst Abteilung-Geruchsorgan und Geschmacksorgan. Handbuch der Anatomie des Menschen, von Bardelebens, Jena; 1905.
158. Brandt W, Roper-Hall HT. Clinical aspects of the embryonic relations of paranasal sinuses to adjacent structures. Med Press. 1943;209:190–1.
159. Aubert F. Contribution à l'étude embryologique du sinus maxillaire chez l'homme. C R Assoc Anat. 1929;20:571–3.
160. Wang R-G, Jiang S, Gu R. The cartilaginous nasal capsule and embryonic development of human paranasal sinuses. J Otolaryngol. 1994;23:239–43.
161. Weiglein A, Anderhuber W, Wolf G. Radiologic anatomy of the paranasal sinuses in the child. Surg Radiol Anat. 1992;14:335–9.
162. Scuderi AJ, Harnsberger HR, Boyer RS. Pneumatization of the paranasal sinuses: normal features of importance to the accurate interpretation of CT scans and MR Images. Am J Roentgen. 1993;160:1101–4.
163. Márquez S, Gannon PJ, Reidenberg JS, Lawson W, Laitman JT. The role of the primate maxillary sinus: respiratory reservoirs or evolutionary dead spaces? Assoc Res Otolaryngol Abstr. 1998;21:178.
164. Krennmair G, Ulm C, Lugmayr H. Maxillary sinus septa: incidence, morphology and clinical implications. J Cranio-Maxillofac Surg. 1997;25:261–5.
165. Som PM, Sacher M, Lanzier CF, Lawson W, Shuger JM. The hidden antral compartments. Radiology. 1984;152:463–4.
166. Cobb AR, Murthy R, Cousin GC, El-Rasheed A, Toma A, Uddin J, Manisali M. Silent sinus syndrome. Br J Oral Maxillofac Surg. 2011;50(6):e81–5.
167. Lang J, Papke J. Über die klinische Anatomie des Paries inferior orbitae und dessen Nachbarstrukturen. Gengenbaurs Morphol Jb. 1984;130:1–47.
168. Tange RA. Some historical aspects of the surgical treatment of the infected maxillary sinus. Rhinology. 1991;29:155–62.
169. Van Alyea OE. Frontal cells. An anatomic study of these cells with consideration of their clinical significance. Arch Otolaryngol. 1941;34:11–23.
170. Davis WB. Anatomy of the nasal accessory sinuses in infancy and childhood. Ann Otol Rhinol Otolaryngol. 1918;28:940–67.
171. Gagliardi A, Winning T, Kaidonis J, Hughes T, Townsend GC. Association of frontal sinus development with somatic and skeletal maturation in Aboriginal Australians: a longitudinal study. J Comp Hum Biol. 2004;55:39–52.
172. Schaeffer JP. An unusual sinus frontalis. Ann Surg. 1912;60:396–400.

173. Tilley H. An investigation of the frontal sinuses in 120 skulls from a surgical aspect, with cases illustrating methods of treatment of disease in this situation. Lancet. 1896;2:866–70.
174. Schaeffer JP. Further observations on the anatomy of the sinus frontalis in man. Ann Surg. 1916;64:665–71.
175. Ubelaker DH. Positive identification from the radiographic comparisons of frontal sinus patterns. In: Rathbun TA, Buikstra JE, editors. Human identification. Case studies in forensic anthropology. Springfield: Charles C. Thomas; 1985. p. 399–411.
176. Tang JP, Hu DY, Jiang FH, Yu XJ. Assessing forensic applications of the frontal sinus in a Chinese Han population. Forensic Sci Int. 2009;183:104e1–3.
177. da Silva RF, Prado FB, Caputo IGC, Devito KL, Botelho TL, Daruge E. The forensic importance of frontal sinus radiographs. J Forensic Leg Med. 2009;16:18–23.
178. Kjaer I, Pallisgaard C, Brock-Jacobsen MT. Frontal sinus dimensions can differ significantly between individuals within a monozygotic twin pair, indicating environmental influence on sinus size. Acta Otolaryngol. 2012;132:988–94.
179. Shapiro R, Schorr S. A consideration of the systemic factors that influence frontal sinus pneumatization. Invest Radiol. 1980;15:191–202.
180. Honig JF, Merten HA, Schutte R, Grohmann UA, Cassissis A. Experimental study of the frontal sinus development on Goettingen miniature pigs. J Craniofac Surg. 2002;13(3):418–26.
181. Van Alyea OE. Frontal sinus drainage. Ann Otol Rhinol Laryngol. 1946;55:267–77.
182. Talbot AR. Frontal sinus surgery in children. In: Parsons DS, editor. Otolaryngol Clin North Am. 1996;29:143–158.
183. Brunner E, Jacobs JB, Lebowitz RA, Shpizner BA, Holliday RA. Role of the agger nasi cell in chronic sinusitis. Ann Otol Rhinol Laryngol. 1996;105:694–700.
184. Shea JJ. Morphologic characteristics of the sinuses. Arch Otolaryngol. 1936;23:484–7.
185. Brown MJ. Frontal sinusitis. Ann Otol Rhinol Otolaryngol. 1941;50:435–49.
186. Urken ML, Som PM, Lawson W, Edelstein D, McAvay G, Biller HF. The abnormally large frontal sinus. I. A practical method for its determination based upon an analysis of 100 normal patients. Laryngoscope. 1987;97:602–5.
187. Urken ML, Som PM, Lawson W, Edelstein D, Weber AL, Biller HF. Abnormally large frontal sinus. II. Nomenclature, pathology, and symptoms. Laryngoscope. 1987;97:606–11.
188. Maresh MM. Paranasal sinuses from birth to late adolescence. Am J Dis Child. 1940;60:55–78.
189. Wigh R. Mucocelles of the fronto-ethmoid sinuses. Radiology. 1950;54:579–90.
190. Hartmann A. Atlas der Anatomie der Stirnhöhle der vorderen Siebbeinzellen und des Ductus nasofrontalis mit erläuterndem Texte und Bemerkungen über die Behandlung der Stirnhöhleneiterung. Weisbaden: Verlag von J. F. Bergmann; 1900.
191. Killian G. Anatomie der Nase menschilcher Embryonen. Arch Laryngol Rhinol (Berl). 1895;3:17–47.
192. Lothrop HA. The anatomy and surgery of the frontal sinus and anterior ethmoidal cells. Ann Surg. 1898;28:611–765.
193. Dixon FW. A comparative study of the sphenoid. Ann Otol Rhinol Laryngol. 1937;46:687–98.
194. Yilmaz NA, Cicekcibasi AE, Emlik D, Yilmaz MT, Keles B, Salbacak A. Morphometric analysis of the development of nasal cavity in human fetuses: an anatomical and radiological study. Int J Pediatr Otorhinolaryngol. 2010;74:796–802.
195. Congdon ED. The distribution and mode of origin of septa and walls of the sphenoid sinus. Anat Rec. 1920;18:97–123.
196. Onodi A. The optic nerve and the accessory sinuses of the nose: a contribution to the study of canalicular neuritis and atrophy of the optic nerve of nasal origin. New York: William Wood & Company; 1910.
197. Tan HKK, Ong YK, Teo MSK, Fook-Chong SMC. The development of sphenoid sinus in Asian children. Int J Pediatr Otorhinolaryngol. 2003;67:1295–302.
198. Orhan M, Govsa F, Saylam C. A quite rare condition: absence of a sphenoid sinus. Surg Radiol Anat. 2010;32:551–3.
199. Van Gilse PHG. The development of the sphenoidal sinus in Man and its homology in mammals. J Anat 1927;61:153–66.
200. Van Gilse PHG. Investigations of the development of the sphenoidal sinus. J Laryngol Otol. 1926;41(3):137–44.
201. Van Gilse PHG. Zur pneumatisation der Keilbeinhöhle. Z f Hals Nasen Ohren-Heilkunde 1922;III:393–399.
202. Hammer G, Radberg C. Sphenoidal sinus: an anatomical and roentgenological study with reference to transsphenoid hypophysectomy. Acta Radiol (Stockh). 1961;56:401–22.
203. Sluder G. The anatomical and clinical relations of the sphenopalatine (Meckel's) ganglion to the nose and its accessory sinuses. N Y Med J. 1909;90:293–8.
204. Cope VZ. The internal structure of the sphenoid sinus. J Anat (Lond). 1917;51:127–36.
205. Peele JC. Unusual anatomical variations in the sphenoid sinuses. Laryngoscope. 1957;67:208–37.
206. Márquez S, Delson E, Silvers A, Lawson W, Laitman JT. The meaning of emptiness: pneumatization patterns of great ape paranasal sinuses via CT imaging. Am Assoc Phys Anthropol. 1999;28:191.
207. Mann WJ, Toth M, Gouveris H, Amedee RG. The drainage system of the paranasal sinuses: a review with possible implications for balloon catheter dilation. Am J Rhinol Allergy. 2011;25(4):245–8.
208. Yankauer S. The complete spheno-ethmoid operation. Laryngoscope. 1921;31:831–42.
209. Grünwald L. Deskriptive und topograhische Anatomie der Nase und ihrer Nebenhöhlen. In: Denker A, Kahler O, editors. Die Krankheiten der Luftwege und der Mundhöhle, Bd. I. Berlin/Munich: Springer/Bergman; 1925. p. 1–95.

Chapter 2
Physiology and Host Immune Responses of the Nose and Sinuses

Jonathan A. Bernstein and Andrew M. Smith

Introduction

The nose and converging structures have several critical functions that are often trivialized until symptoms persist and interfere with the patient's daily activities. The nose is the body's heating, ventilation, and air conditioning (HVAC) system, as it humidifies, filters, and conditions air. These functions thereby protect the lungs from an influx of aeroallergens, air particulates, and other potentially deleterious air pollutants. The nose is the conduit for several important structures, including the paranasal sinuses and lacrimal duct. When nasal inflammation occurs, these small structures can become obstructed leading to a spectrum of clinical symptoms such as nasal congestion, postnasal drainage, sinus pressure or pain, headache, and ocular lacrimation and itching. In addition, the Eustachian tube also drains into the posterior pharynx. With allergic and/or nonallergic rhinitis, it is not unusual for patients to complain of ear plugging, popping, or pain consistent with Eustachian tube dysfunction. Although intact anatomic structures are essential for the normal functioning of the nose and sinuses, invisible structures buried within the nasal mucosa are equally if not more important for protecting the host from the external environment. This chapter will review the gross and microscopic anatomic and physiologic processes that are essential for normal functioning of the upper respiratory tract.

Phylogeny and Ontogeny of the Nose and Sinuses

The nose and sinuses are considered one organ even though phylogenetically the nose is primarily an olfactory organ, whereas the sinuses are speculated to have evolved as aids to facial growth and structure [1]. Interestingly although the ethmoid sinuses have been considered as part of the paranasal sinuses, the ethmoid bone is actually derived from the cartilaginous nasal capsule, and its main role may have been to protect the olfactory nose [1, 2]. In humans, the ethmoid labyrinth derived from the olfactory labyrinth contains only a very small amount of olfactory mucosa compared to other animal species, which have a much greater dependence on olfaction for their survival. This reduced need for olfaction led to retraction of the nose posteriorly and migration of the orbits anteriorly. These changes resulted in the disconnection of the frontal sinuses from the maxillary sinuses and the repositioning of the ethmoid bone between the paranasal sinuses [1]. The ethmoid bone is considered the most highly conserved region in the skull. Unlike the other paranasal sinuses, the ethmoid sinuses do not have defined walls or a well-defined ostium. They therefore do not meet the criteria of what constitutes a true sinus cavity [2, 3].

J.A. Bernstein, MD (✉)
Division of Immunology, Department of Internal Medicine, Allergy Section, University of Cincinnati, 3255 Eden Ave ML#563 Suite 350, Cincinnati, OH, USA
e-mail: jonathan.bernstein@uc.edu

A.M. Smith, MD, MS
Division of Immunology, Allergy, and Rheumatology, Cincinnati VA Medical Center, University of Cincinnati, 3255 Eden Ave., ML#563, Cincinnati, OH, USA
e-mail: andrew.smith@uc.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_2,

In humans, the olfactory nose develops during week 5 of gestation on the frontal nasal process [1, 4]. By the end of week 6, these structures invaginate to form nasal pits which fuse posteriorly to form a nasal sac separated from the oral cavity by the nasal fin [1, 4]. During week 7, the nasal fin thins to form the oronasal membrane, which then ruptures to form an opening with the oral cavity referred to as the "primitive choanae" [1, 4]. The floor of the nasal fossa subsequently becomes the primary palate [1, 4]. By 6.5 weeks, the cartilaginous nasal capsule develops in connection with the olfactory structures and with the breakdown of the oronasal membrane forms a characteristic "m" shape. This is considered the beginning of the development of the paranasal sinuses [1, 4]. By weeks 9 and 10 of embryogenesis, six major furrows separated by ridges develop that are called the ethmoturbinals. The first ethmoturbinal regresses, leaving as its remnant the uncinate process [1, 4]. The second and third ethmoturbinals develop into the middle and superior turbinates, respectively, whereas the supreme turbinate develops from the fourth and fifth ethmoturbinals [1, 4]. The middle meatus and the hiatus semilunaris evolve from the first primary furrow, the superior meatus from the second furrow, and the supreme meatus from the third furrow [1, 4].

The paranasal sinuses develop after birth. The maxillary, frontal, and sphenoid sinuses evolve from epithelial diverticula that expand from the cartilaginous nasal capsule and become pneumatized [1, 2]. The maxillary sinuses are present at birth and expand throughout childhood. The sphenoid sinuses do not appear until 5 months after birth and then continue to develop throughout childhood [1, 5]. The last to develop are the frontal sinuses, which do not appear until 5–6 years of age and then continue to expand through adolescence [1, 5]. The frontal sinuses are believed to primarily assist in facial growth and architecture [1, 5]. The sizes of the paranasal sinuses vary due to the unpredictable development of the paranasal recesses [1, 5].

Anatomy of the Nose and Sinuses

External Nose

The nose and paranasal sinus complex are the result of fusion of the respiratory nose, the olfactory nose (including the ethmoidal labyrinths and olfactory clefts), and the paranasal sinuses [1]. The external nose is comprised of two nasal bones superiorly and two sets of paired cartilage inferiorly [6]. The respiratory nose is considered a channel. Its inferior wall is the floor of the nasal fossa; the superior wall is comprised of the roof of the rhinopharynx, the inferior edge of the middle turbinate, the tip of the nasal valve, and the vestibule; the lateral wall is made up of the turbinate wall of the maxillary sinus whereas the medial wall is the nasal septum [1]. The respiratory nose is comprised of the nasal vestibule, nasal valve, nasal chamber, and choanae [1].

The olfactory nose is comprised of two medial olfactory clefts and two lateral ethmoid labyrinths [1]. The human olfactory mucosa is limited to the olfactory clefts, but its exact distribution has not been well defined [1, 7–9]. The ethmoid labyrinth, which is devoid of olfactory mucosa, is divided from the olfactory cleft by the turbinate wall of the ethmoid labyrinth (TWEL) [1, 10]. The TWEL is comprised of turbinates, which traverse the entire ethmoid labyrinth and extend laterally to the lamina papyracea and superiorly to the lamina cribrosa (Fig. 2.1) [1, 10]. They are divided by air spaces that are further separated by small transverse septa that form the ethmoidal cells [1, 10]. The olfactory cleft is the narrow air space located below the olfactory groove, medial to the ethmoid labyrinth and lateral to the nasal septum (Fig. 2.1) [1]. The olfactory epithelium is limited to the upper part of the olfactory cleft which is further divided into an upper chamber called the olfactory fossa, which is the sensory cavity and the lower chamber which is called the olfactory vestibule [1]. Airflow is very slow through the olfactory cleft, which allows greater time to facilitate olfactory sensing [1, 11, 12].

Finally, the paranasal sinuses include the frontal, maxillary, and sphenoid sinuses. These are hollow, air-filled cavities, lined by thin respiratory mucosa with minimal to no glands or vascularization [1]. The only contact with the external environment is through the ostia [1]. The air composition in the sinuses remains relatively stable (17.5 % O_2, 2.2 % CO_2, 100 % relative humidity, and 34 ºC) with air exchange occurring between the nose and sinuses likely secondary to passive diffusion [1].

Vestibule

The vestibule is the most important structure of the nose for sensing nasal airflow. It is lined with stratified squamous epithelium, which transitions to pseudostratified columnar epithelium (Fig. 2.2) [6]. Vibrissae are thick hairs without piloerector muscles in the vestibule that filter out large particles [6]. Anterior nasal glands are present at the junction of the squamous and pseudostratified epithelial junction that secrete serous secretions which are atomized with sniffing [6]. In addition, the vestibule also contains thermoreceptors that cause decreased nasal resistance after inspiration of warm air and increased nasal resistance after inspiration of cold air [6, 13, 14].

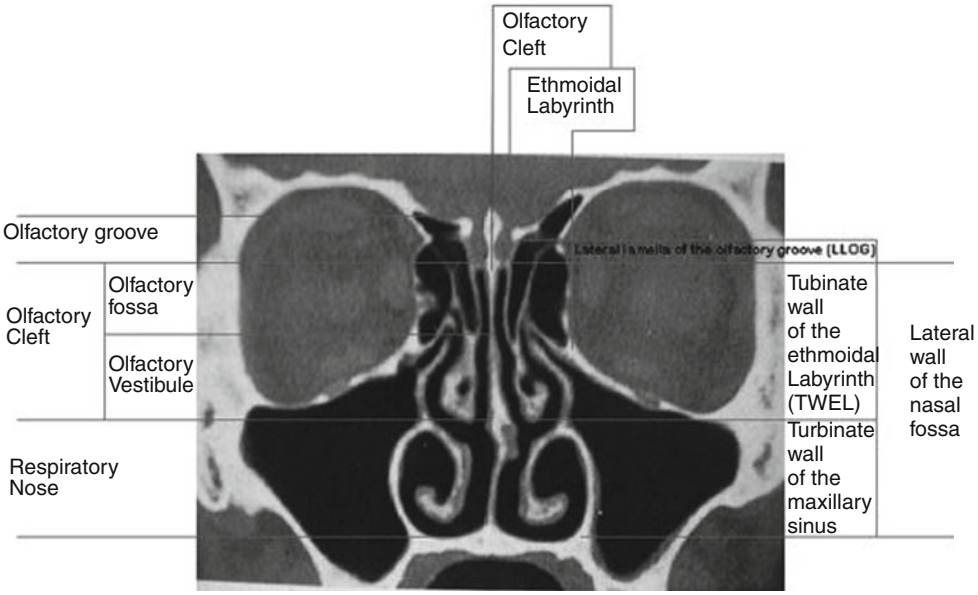


Fig. 2.1 Coronal CT scan of the sinuses (Reprinted from Jankowski [1]. With permission from John Wiley & Sons, Inc.)

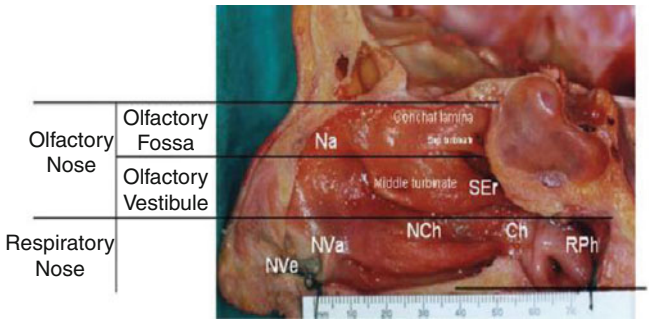


Fig. 2.2 Lateral wall of nasal cavity. *NVe* nasal vestibule, *NVa* nasal valve, *NCh* nasal chamber, *Ch* choana, *RPh* rhinopharynx, *Na* nasal attic, *SEr* sphenoidal ethmoidal recess (Reprinted from Jankowski [1]. With permission from John Wiley & Sons, Inc.)

Nasal Valve and Airflow

The nasal valve, located behind the nasal vestibule, has a cross-sectional area of 40 mm^2 which increases to 150 mm^2 in the nasal cavity (Fig. 2.2). Contraction of the dilator naris muscle leads to increased nasal airflow, manifested as nasal flaring [6, 15, 16]. The nasal valve is responsible for 50–75 % of inspired airflow resistance to the pulmonary alveoli [6, 17]. Airflow through the nasal valve is fastest as it streams through the middle turbinate (18 m/s) and slows significantly as it passes into the main part of the nasal cavity (2–3 m/s) [6, 15]. The slower airflow in the nasal cavity allows for maximal contact with the warmer nasal mucosa, which allows the ambient air to be warmed to 34 °C at resting rates of respiration. The greatest increase in temperature occurs anteriorly in the nasal valve [6, 18]. Relative humidity reaches 100 % in the nasopharynx.

Expiration lasts longer than inspiration and airflow is less laminar. Not surprisingly, the lowest temperatures are measured at the end of inspiration, whereas the highest mucosal temperature is at the end of expiration [6, 19]. Expiratory air cooling occurs primarily in the region of the inferior and middle turbinates [20].

Large volumes of airflow up to 30 L/min occur through the nose, but if larger volumes are necessary, then mouth breathing occurs. However, this can lead to significant loss of water and humidity [6, 21–23]. Physical exercise is the most common cause for increased nasal airflow [21, 22]. While sleeping, nasal airflow causes breathing to increase more in the nose compared to the mouth. Nasal obstruction can lead to abnormal breathing patterns, such as obstructive sleep apnea [24]. Several structural defects, such as septal deviation, enlarged turbinates, and adenoid hypertrophy, can impede nasal airflow which can lead to increased pulmonary resistance.

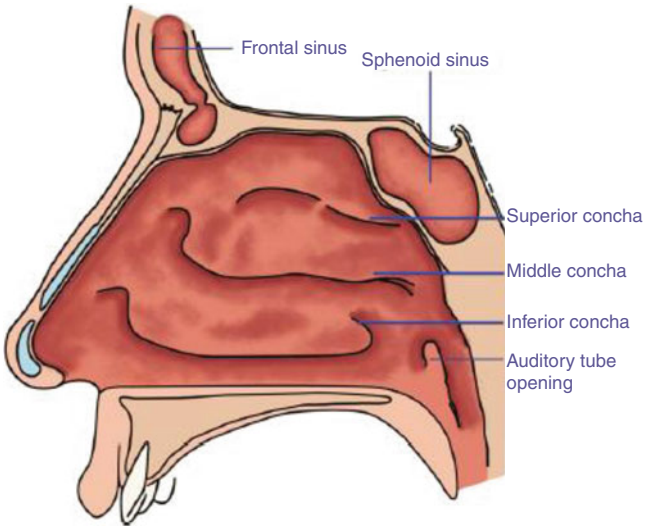


Fig. 2.3 Lateral wall of the nasal cavity illustrating turbinates

Normal individuals have relatively constant nasal airway resistance with alternating airflow in each nasal cavity known as the nasal cycle. The nasal cycle is regulated by the sympathetic nervous system as cervical sympathetic blockades extinguish this sequence [25]. The nasal cycle's pacemaker is believed to be located in the suprachiasmatic nucleus of the hypothalamus [6, 26]. Alternating airflow is the result of increased blood flow to the turbinates and septal tuberculum [6]. Typically, the nasal cycle goes unnoticed if the nasal cavity remains unobstructed, but can become quite apparent with the advent of nasal swelling from structural, infectious, or allergic problems [6, 27].

Nasal Septum and Turbinates

The nasal septum divides the nose into two cavities, thereby increasing the total mucosal surface in the nose (Fig. 2.1) [6]. The anterior tip of the septum is comprised of cartilage. The posterior bony section of the nose is made up of the vomer and the perpendicular ethmoid plate [6]. It is estimated that 90 % of the general public has a septal deviation to some degree or another; a straight septum is twice as common in women compared to men. Small anterior abnormalities can compromise nasal airflow much more dramatically than larger defects in the posterior cavity [6].

The turbinates emanate from the lateral nasal wall (Fig. 2.3). The inferior and middle turbinates are considered to be the functionally most important part of the nose [6]. Turbinates are comprised of a bony frame covered with respiratory epithelium [6]. The inferior turbinate plays an important role in protecting the lungs from the external environment and maintaining the normal physiology of the nose. In addition, several key structures empty under the middle and inferior turbinates. The lacrimal duct empties underneath the inferior turbinate. The anterior ethmoids, maxillary and frontal sinus ostia empty underneath the middle turbinate. Disruption of the middle and inferior turbinates, such as partial turbinectomies, can significantly impair their protective role [6].

Histology of the Nose and Sinuses

The nasal mucosa is lined with pseudostratified columnar epithelium, which contains mucosal secreting goblet cells and ciliated and nonciliated columnar cells with microvilli and scattered mast cells, eosinophils, neutrophils, and lymphocytes (Fig. 2.4) [6, 28]. Ciliated epithelium lines most of the airway from the nose to the respiratory bronchioles as well as the paranasal sinuses, Eustachian tube, and portions of the middle ear [6]. Cilia play an important role in mucous transport and are composed of a shaft (axoneme) made up of microtubules arranged as nine doublets surrounding two central singlets [29]. Each doublet has two dynein arms containing ATPase, which fuels their motion [6, 29].

Goblet cells are arranged perpendicularly to the epithelial surface and are important for secreting a mucosal blanket that protects the nose. The density of goblet cells increases from infancy to childhood. In adults, goblet cells are not found in the

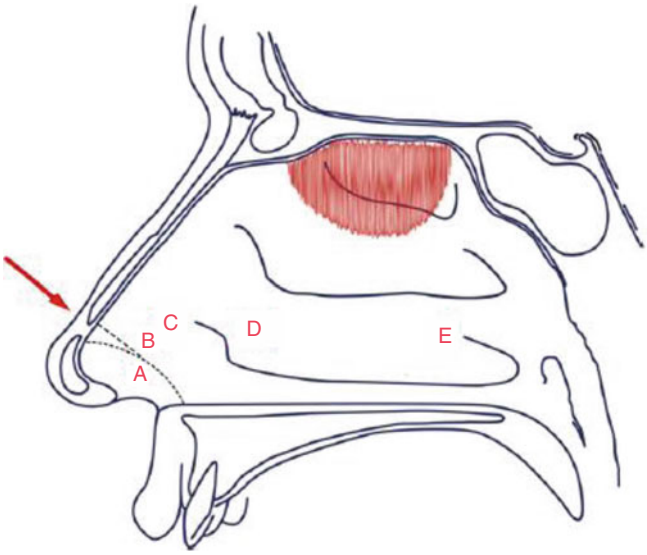


Fig. 2.4 Lateral wall of nose with letters representing histology at specific locations. *A* skin in nostril, *B* squamous epithelium without microvilli, *C* transitional epithelium with short microvilli, *D* pseudostratified columnar epithelium with few ciliated cells, *E* pseudostratified columnar epithelium with ciliated cells

squamous, transitional, or olfactory epithelia but are present in all areas of the pseudostratified columnar epithelium [6, 29]. There is a greater density of goblet cells in the inferior turbinate compared to the middle turbinate and septum. The density of goblet cells in these areas increases from anterior to posterior and inferior to superior. The mucosal barrier produced by goblet mucus-secreting cells provides an important protective layer composed of IgA and other mediators that protect the nose from infection and other external insults [30]. Columnar cells are covered by hundreds of microvilli that are distributed over the entire apical surface epithelium [6, 30]. They promote exchange processes across the epithelium. The microvilli are important for retaining moisture, which is important for ciliary function. Basal cells are important for providing adhesion between cells and anchoring columnar cells to the basement membrane [6]. Previously, studies have reported that basal cells may actually be progenitors for goblet cells, but this has not been reproduced by other investigators and is considered speculative.

The basement membrane separates the epithelium from the lamina propria. The submucosa is comprised of nerves, blood vessels, and glands. The glands in the submucosa produce the greatest amount of nasal secretions. The nasal mucosa does not contain lymphoid aggregates, and therefore, lymphocytes migrate to the nasal mucosa via the blood through tonsillar lymphoid tissue [6]. There are three types of submucosal nasal glands: (1) the anterior serous glands, (2) the seromucinous glands, and (3) the Bowman's glands. The anterior glands are important for moisturizing the nasal mucosa. The seromucinous glands produce the greatest amount of mucus in the nose. Bowman glands are serous glands located in the olfactory region, important for aiding in smell [6].

Mucociliary Clearance

Mucociliary transport is a physiologic mechanism of the nose important for clearing secretions and unwanted particulates. The mucus blanket is composed of secretions from goblet cells and submucosal glands. The mucus layer consists of a sol phase which is a watery periciliary layer and a gel phase which is closest to air (Fig. 2.5) [6]. Particles greater than 3 um are filtered primarily in the nasal valve region. Smaller particles between 0.5 and 3 um are filtered by the nasal mucosa and transported to the nasopharynx by ciliary flow [6]. Intranasal particle deposition occurs during inspiration and expiration [31]. The mucus blanket is also the first line of defense against bacterial and viral infections, largely due to the protective effect of IgA which is the major immunoglobulin in nasal secretions [30, 32]. IgA assists in preventing microorganisms from adhering to the nasal mucosa [6, 30]. Finally, the mucus blanket provides water for humidification [6, 30]. Daily mucus production is approximately 1 liter per day. The gel-like properties of mucus are due to being comprised of high molecular weight glycoproteins named mucin, which is composed of 80–90 % carbohydrate, 20 % protein, and 1–2 % sulfate bound to oligosaccharide side chains, to which water binds to form a matrix that lubricates the mucosa [32]. Mucin genes encode the protein backbones of mucins [33]. More than 16 are found to be expressed in the respiratory tract, but MUC5AC, MUC5B, and MUC2 appear to be the most important gel-forming mucins secreted in the airway [33]. Other components of mucus

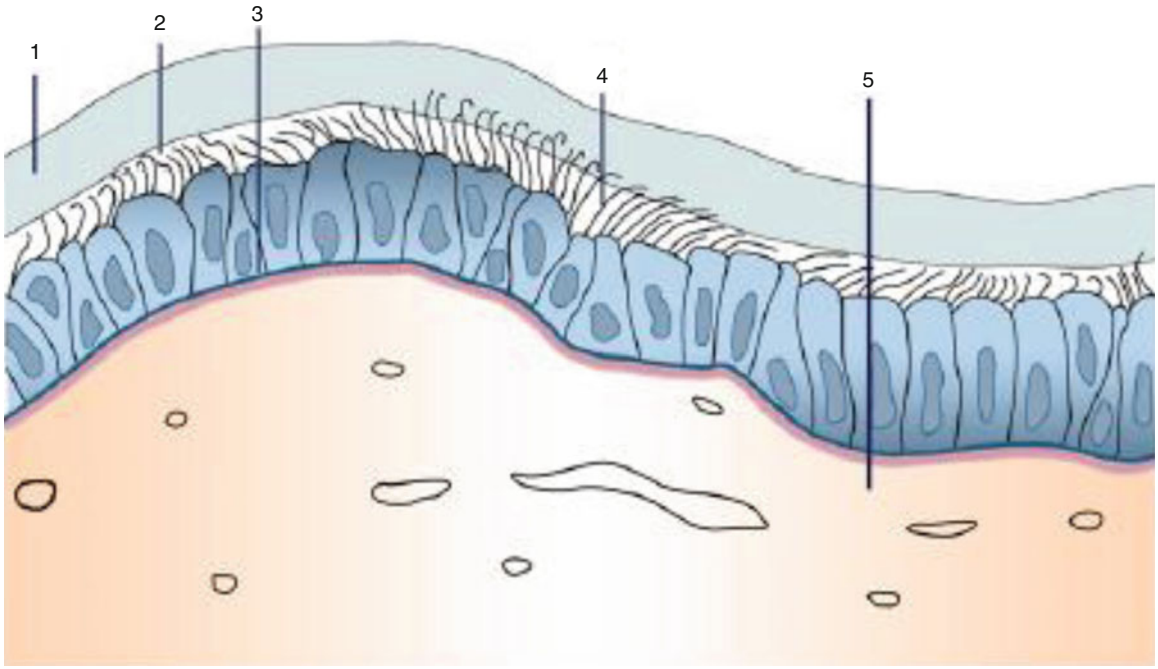


Fig. 2.5 Phases of the nasal airway mucus layer. *1* Gel phase, *2* sol phase, *3* basement membrane, *4* cilia, *5* submucosal layer

include IgG, IgE, albumin, bacteria, lactoferrin, lysozyme, ions, and cellular debris [6, 30]. Mucus moves posteriorly to the nasopharynx, except in the area anterior to the inferior turbinate where transport is anterior [6]. This transport mechanism can clear inhaled particles from the nasal cavity in 10–20 min. Mucociliary transport is increased with nasal irrigation. Clearance of secretions is also enhanced by nasal sniffing, sneezing, and nose blowing [6].

Cilia are all oriented in a similar direction and have a two-stroke pattern. The effector stroke is important for moving mucus. The recovery stroke is when the cilia bend and move in the watery sol phase [6]. Although patients with chronic rhinosinusitis are believed not to have differences in ciliary beat frequency compared to healthy individuals, they do have decreased numbers of ciliated cells and more ciliary disorganization and microtubular abnormalities [6]. Temperatures lower than 32 °C and higher than 40 °C can lead to decreased ciliary beating. Preservatives in nose sprays, such as benzalkonium chloride, can decrease mucociliary transport and cause ciliastasis [6, 34–36]. A number of structural problems in the nose, viral and bacterial infections, and genetic disorders such as cystic fibrosis and immotile cilia syndrome all have impaired mucociliary transport mechanisms leading to increased viscosity of secretions [6].

Vasculature

The nasal cavity blood supply comes from the internal and external carotid arteries. Branches of the internal carotid include the anterior and posterior ethmoid arteries and the ophthalmic artery. The sphenopalatine artery is a branch of the external carotid [6]. These vessels converge with branches of the facial artery and form a large triangle in the septum, which is the most common site of epistaxis in the nose [6, 37]. Veins run next to the arteries and empty into the pterygoid and ophthalmic venous plexi. Some drainage from veins occurs into the cavernous sinus, which can be a potential route for a spread of infection [6]. Arterial branches from the perichondral and periosteal arteries supply the subepithelial and glandular zones. These arteries move forward to the surface, branching off to form a cavernous plexi and ultimately a network of fenestrate capillaries in the subepithelium. These fenestrate capillaries are believed to be an important source of fluid for humidification [6].

Nasal airflow is regulated by alteration in blood flow to the turbinates and septum. Nasal congestion manifests as the result of changes in vascular tone, which leads to vascular engorgement in the sinusoids [6]. Vascular tone is regulated by receptors on blood vessels. When stimulated, the alpha-adrenoceptors cause vasoconstriction; specifically α-2-adrenoceptors are important for contracting nasal veins whereas the α-1-adrenoceptors cause constriction of nasal arteries [6]. A blockade of

cholinergic receptors results in drying nasal secretions. Histamine release, usually from mast cells and basophils in atopic individuals, leads to increase vascular permeability, glandular secretions, sneezing, and itching [6]. Blocking of H1, H2,and H3 receptors can lead to decreases in symptoms related to these physiologic changes [6].

Lymphatics

Lymphatic vessels in the nose drain to the external nose and along facial vessels to the submandibular lymph nodes. In contrast, lymphatics of the nasal fossae drain toward the nasopharynx [6]. Lymphadenopathy associated with rhinosinusitis is rare because the nasal-draining lymph nodes are buried deep along the vertebral bodies and cannot be palpated [6]. Lymphatic drainage in the maxillary sinus is unique in that it drains through the ostia as well as across the sinus wall through bony gaps [6, 38].

Nervous System

Sensory innervation of the nose involves the olfactory, ophthalmic, and maxillary branches of the trigeminal nerve [6]. Depolarized nociceptive C fibers release neuropeptides, including substance P, neurokinin A, and calcitonin gene-related peptide. These neuropeptides are potent vasodilators, resulting in increased vascular permeability [6, 39, 40]. Regulation of neurogenic inflammation occurs in part through chemoreceptors like transient response potential ion channels. These calcium ion channels are co-localized with other receptors like bradykinin-2-receptor, 5-lipoxygenase, and toll-like receptors. The complex interaction of these co-localized receptors can further enhance the parasympathetic response and down-modulate the sympathetic response, resulting in the physiologic responses observed in patients with allergic and nonallergic rhinitis [41, 42].

Sensory nerves regulate several nasal reflexes. The nasonasal reflex occurs when one side of the nasal cavity is stimulated, leading to bilateral efferent reflexes that can be observed in the contralateral nostril [43, 44]. The nasal ocular reflex occurs after chemical or mechanical stimulation of the nasal mucosa resulting in lacrimation [43]. The submersion reflex occurs when there is mucosal irritation, manifested as apnea, glottis closure, bradycardia, and vasoconstriction. The purpose of this reflex is to protect the heart and brain by the redistribution of blood to these organs [6]. Cooling of the skin causes nasal vasoconstriction, whereas heating of the skin causes an increase in nasal temperature [6, 45]. Finally, a nasobronchial reflex has also been described; irritation of the nasal mucosa has been demonstrated to increase lower airway hyperresponsiveness [6]. Treatment of upper airway inflammation has been shown to decrease lower respiratory tract airway hyperresponsiveness [46]. However, the definitive mechanism of this neurogenic reflex connecting the upper and lower respiratory tracts remains elusive.

The parasympathetic nerve supply originates in the midbrain and travels with fibers of the seventh cranial nerve. After synapsing in the sphenopalatine ganglion, they are distributed to mucosal and submucosal branches [6]. Postganglionic branches contain acetylcholine and neuropeptides, including vasoactive intestinal peptide and secretoneurin [6, 47]. Parasympathetic nerve stimulation causes glandular secretion and vasodilation [6, 48].

The sympathetic nerve supply originates in the hypothalamus. They synapse with the superior cervical ganglion and travel to the carotid plexus to join the parasympathetic fibers from the seventh cranial nerve to form the vidian nerve [6]. The sympathetic fibers do not synapse in the sphenopalatine ganglion [6]. Sympathetic responses are mediated by adrenoceptors stimulated by norepinephrine and neuropeptide Y [6, 49]. Stimulation of the sympathetic nervous system leads to vasoconstriction, resulting in decreased nasal airway resistance [6].

The olfactory epithelium is covered by a layer of mucus rich in immunoglobulins, lactoferrin, and lysozyme that protect against infection [6, 50]. The olfactory and trigeminal systems interact to inhibit or activate one another [6]. The field of *olfaction* has dramatically grown with the discovery of a superfamily of approximately 1,000 odorant receptor (OR) genes, located in multiple clusters on all but two of the 24 human chromosomes [51]. These *OR* gene clusters comprise 17 gene families, four of which contain greater than 100 genes each [51, 52]. It has been estimated that the *OR* gene superfamily comprises 1–3 % of the entire genomic complement of genes. It is likely to be the largest gene superfamily in the genome of any species [52]. The OR genes are members of the 7-transmembrane domain G-protein-coupled receptor (GPCR) superfamily [52]. In situ hybridization studies indicate that each *OR* gene is expressed in approximately 1 out of every 1,000 olfactory epithelial (OE) neurons, suggesting that each OE neuron expresses only one OR gene [53]. Interestingly, 63 % of

human OR genes are nonfunctional pseudo-genes, which increase the likelihood for the presence of OR genetic polymorphisms [51, 53].

Odorant-binding proteins help transport odorant molecules through hydrophilic mucus to the olfactory epithelium where they can bind to OR [52]. This binding sends an impulse through axons that pass through the cribriform plate and into the CNS to synapse with the olfactory bulb [52]. Neuronal projections travel from the olfactory bulb to a number of regions in the brain important for olfactory sensory processing [6]. Not surprising, olfaction is not as well developed in humans as it is in animals who depend on smell for survival [6]. In humans, the estimated percent of blood flow to the olfactory region is 10 %. Olfaction can be impaired by a number of conditions, including allergic and nonallergic rhinitis, nasal polyposis, viral infections, vitamin A or thiamin deficiency, or other structural abnormalities resulting from developmental disorders, malignancy, or trauma [6]. Recently, loss of olfaction has been demonstrated to be an early diagnostic indicator for the onset of Parkinson's and Alzheimer's disease [54].

Innate Immune Responses in the Nose

The nasopharynx is colonized with normal flora that act as commensal organisms to prevent colonization of the host with more pathogenic organisms, thereby preventing disease [55]. Gram-positive organisms, including *Streptococci viridians*, *Staphylococcus epidermidis and aureus*, and *Corynebacterium*, and gram-negative organisms, such as *Moraxella* and *Haemophilus* (*influenza and parainfluenza*), can be found in the nasopharynx with some regularity in normal hosts [55]. Colonization of these organisms varies with age [55]. For example, children less than 2 years of age harbor the above organisms more commonly than adolescent-aged children. In contrast, the paranasal sinuses are considered sterile cavities that are protected by anatomic and local mucosal defense mechanisms. These low virulent organisms can paradoxically cause disease when local protective innate immune responses become impaired [55].

There are several natural protective mechanisms in the nose that are part of the innate immune response. Because the nasal epithelium provides a weak protective barrier, innate immunity plays a very important role to prevent infection and other pathologic inflammatory responses [30]. The nasal mucus acts as a protective barrier against the invasion of microorganisms and injury by toxic agents. Mucociliary transport is an essential first line of defense for elimination of microorganisms [30]. Alterations of the viscoelastic properties of the nasal mucous lead to stasis and abnormal mucociliary clearance, increasing the risk of infection [30, 56].

In addition, nasal secretions are rich in lysozyme, which has potent anti-bactericidal or bacteriostatic activity against some gram-positive bacteria and enhances lytic activity of antibody-activated complement on some gram-negative bacteria such as *E. coli* [30, 55]. Lactoferrin is an iron-binding protein in nasal secretions that inhibits bacterial growth of organisms that depend on iron for their metabolism, such as facultative and aerobic gram-positive and -negative bacteria as well as *Candida albicans*, which increases in the presence of secretory IgA [30, 55]. Neither lysozyme and lactoferrin have any effect against viral infections [30]. Lactoperoxidase acts on peroxide and oxidized forms of thiocyanate to form molecules that are toxic to bacteria [55].

Other important molecules include secretory leukoprotease inhibitor, uric acid, peroxidase, aminopeptidase, secretory phospholipase A2, and defensins [30]. Human beta-defensin (hBD)-1 is expressed constitutively in epithelial cells and have broad antibacterial and antifungal activity; hBD-2 and 3 are expressed in response to bacterial and other forms of inflammation [55]. Nitric oxide is present in high concentrations in the nasal cavity and sinuses and also plays an important role in defense [30]. The complement system consists of a network of over 30 proteins that play a critical role in the nasal innate immune response by assisting with opsonization by phagocytes of viruses and bacteria, activation of phagocytic cells, and lysis of bacteria and infected cells [30].

Nonspecific immune responses occur if the above initial defense systems are broken down. These immune responses are manifested as the release of bioactive and chemotactic factors resulting in increased migration of inflammatory cells into the mucosa, increased vascular permeability, and hyperemia [30]. Increased blood flow carries numerous plasma proteins to the nasal mucosa including immunoglobulins, complement, and proteases and helps to rid the nasal cavity of microorganisms [30]. Table 2.1 summarizes the specific and nonspecific mechanical, humoral, and cellular defense mechanisms in the nose.

Toll-like receptors (TLRs) are transmembrane proteins that function as pathogen-recognizing receptors (PRRs) capable of interacting with conserved domains on microorganisms, referred to as pathogenesis-associated molecular patterns (PAMPs) [55]. PAMPs include protein (TLR4, 5), lipid or lipoprotein (TLR1, 2), and nucleic acid (TLR9) motifs [55]. Activation of TLRs results in activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and transcription resulting in subsequent production of a spectrum of proinflammatory cytokines (including IL-1α, IL-6, IL-12, TNFα), anti-inflammatory cytokines (including IL-10, TGF-β), and chemokines (including RANTES, MIP-1, IL-8). These cytokines and chemokines provide nonspecific protection to the host [55].

Table 2.1 Defense mechanisms of the upper airways

Defense	Humoral	Cellular
Mechanical	Mucus	Ciliary epithelium
Nonspecific immune responses	Complement, lysozyme, lactoferrin	Granulocytes, macrophages
Specific immune responses	Immunoglobulins	Lymphocytes

Reprinted from Fokkens and Scheeren [30]. With permission from Elsevier

Bacterial clearance requires recruitment and activation of inflammatory cells such as neutrophils and macrophages at the site of inflammation [30]. Recruitment and activation require a well-coordinated series of events, including increased expression of leukocyte and vascular adhesion molecules and the establishment of chemotactic gradients generated by the release of proinflammatory cytokines and chemokines [30]. Acute inflammation initially manifests as increased neutrophils, which migrate to the site of inflammation within 24 h, followed by the appearance of macrophages and lymphocytes [30]. Neutrophils have toxic granules containing proteolytic enzymes that, when released, can cause oxidative damage of surrounding tissue leading to inflammation [30]. The oxidative burst created by neutrophils, manifested as increased nitric oxide levels, is an important protective mechanism against unwanted invasive microorganisms [30].

Adaptive Immunity

The humoral adaptive immune response plays an important role in combating infection as well as eliciting specific IgE-mediated responses in susceptible individuals. Mucosa-associated lymphoreticular tissue (MALT) is an aggregate collection of lymphoid cells present throughout the nasopharynx, bronchi, and gastrointestinal tract [55]. In the nasopharynx, dendritic cells process foreign antigens for a presentation and activation of T- and B-lymphocytes [55]. Antigen-stimulated B-lymphocytes migrate to mucosal lymphoreticular tissue where they expand and differentiate into specific immunoglobulin-producing plasma cells [55]. Immunoglobulins are formed in response to proteins as well as the polysaccharide bacterial capsules of organisms like *Haemophilus influenza B* and *Streptococcus pneumoniae* [30].

Elicitation of a specific IgE-mediated allergic response in a genetically susceptible person first requires antigen exposure leading to sensitization, followed by a latency period that can be of a variable length of time [57]. Specific IgE antibodies are bound to high affinity IgE receptors (FcεRI) on mast cells. After re-exposure to the sensitizing allergen, the antigen-binding sites of specific IgE antibodies on mast cells recognize the eight to nine amino acid-relevant sensitizing peptides and are cross-linked, leading to mast cell activation and the release of preformed (such as histamine, platelet activating factor) and newly formed (such as leukotrienes, prostaglandins) bioactive mediators. These bioactive mediators cause vascular and neuroreflex responses characteristic of allergy symptoms, including nasal congestion, postnasal drainage, rhinorrhea, nasal and ocular itching, and sneezing [57].

Pathogenesis of Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is a condition characterized by persistent inflammation of the mucosa in the nose and paranasal sinuses [58]. This condition encompasses both polypoid and non-polypoid forms of disease. In a small subset of patients, genetic disorders (such as Kartagener's syndrome and cystic fibrosis) and systemic autoimmune disorders (such as Wegener's granulomatosis and sarcoidosis) account for the underlying inflammation, leading to chronic rhinosinusitis [58]. However, most cases of chronic rhinosinusitis are idiopathic. Proposed mechanisms for CRS included obstruction of the osteomeatal complexes, impaired mucociliary transport, atopy, microbial resistance, and biofilm formation [58, 59]. The *Alternaria* "fungal hypothesis" proposes that *Alternaria*, a common ascomycete fungi genus, is the primary pathogenic trigger of all forms of CRS. In contrast, the *Staphylococcus aureus* "superantigen hypothesis" proposes that colonizing *S. aureus* release superantigenic toxins that can induce direct T and B cell immune responses [58, 60–68]. The primary support for the *Alternaria* hypothesis is the hyperreactivity of peripheral blood mononuclear cells in response to stimulation with supraphysiologic doses of *Alternaria* antigen [58, 69–71]. However, there is little in vitro, in vivo, or clinical evidence to support the fungal hypothesis as the cause of chronic sinus disease [58, 72]. With respect to the superantigen hypothesis, there is currently no evidence to support a role for superantigens causing CRS. Currently, they are considered more a modifier rather than a cause of disease [58, 73].

The immune barrier hypothesis proposes that compromises of the nasal epithelium physical barrier, mucociliary transport, the innate and adaptive immune responses induced by environment irritants, and colonizing and pathogenic organisms lead to chronic inflammation and CRS [58]. Recent evidence supports a role for mutations in genes significant for coding

proteins important for epithelial structure and function in CRS [58, 74, 75]. Evidence for impaired barrier disruption includes decreased tight junction proteins and increased ion permeability in patients with CRS compared to normal controls [58]. This observation is supported by a decrease in SPINK5, a gene that encodes the protease inhibitor LEKT1 (important for maintenance of epithelial barrier function) [58, 74, 75]. A deficiency of this protease inhibitor could lead to increased susceptibility to the intrinsic protease activity of bacteria, fungi, and allergens like dust mites, thereby rendering the host more vulnerable to penetration by foreign proteins and leading to increased inflammation from innate and adaptive immune responses [58, 74, 75]. Similarly, antiproteases like LEKT1 protect epithelial surface receptors (referred to as protease activated receptors or PARS) from exogenous proteases [58, 76]. Protease activity receptor stimulation could lead to increased cytokine and chemokine release and effector cell recruitment to the nose, leading to impaired immune responses [58, 76]. Recent evidence suggests that S100 proteins, which are antimicrobial proteins, are reduced in patients with CRS [58, 77]. CRS has been postulated to be in part caused by a deficiency of these proteins, which are important for antibacterial and antifungal activity, neutrophil and lymphocyte recruitment, and wound healing [58, 74, 75].

Interestingly, toll-like receptor-2 (TLR2) mRNA has been found to be decreased in patients with cystic fibrosis nasal polyps; TLR2 and TLR9 mRNA are decreased in patients with CRS with nasal polyps [58, 78–81]. However, data relating the pathogenic role for TLR and CRS are inconsistent and still remain a theoretical mechanism [58]. IL-22 secreted by Th17 and Th1 cells activates epithelial cells by binding to IL-22R [58, 82, 83]. It has been shown that patients with CRS with nasal polyps have decreased IL-22R and therefore a decreased IL-22 response [58, 84]. This deficiency remains yet another way the innate immune response can be impaired.

Epithelial cells likely play a major role in the pathogenesis of CRS, likely due to their ability to regulate activation of T cells as well as produce cytokines that can activate B cells, dendritic cells, T cells and chemokines that can attract effector cells to the nasal tissue [58, 80]. Epithelial cells also produce and release thymic stromal lymphopoietin (TSLP) in response to viruses such as rhinovirus, which cause T cells to differentiate into Th2 cells. Interestingly, TSLP has been demonstrated to be increased in those individuals who have a deficiency of the protease inhibitor LEK1 [58, 85].

It is clear that numerous immune components and pathways are involved in the pathogenesis of the various forms of rhinosinusitis. These immune mechanisms are discussed in greater detail in Chap. 3.

Conclusions

The upper respiratory tract is a complex anatomic, neurologic, and vascular network that provides structural, physiologic, and immune defense barriers to protect the host from the external environment. When one or more of these processes break down, then many predictable and at times unpredictable medical consequences can occur. Correct diagnosis and appropriate treatment of patients with allergic, nonallergic, or mixed rhinitis to prevent unchecked nasal inflammation will often prevent or ameliorate the progression to chronic rhinosinusitis. Future research investigating the pathogenesis and mechanism(s) of rhinitis subtypes and CRS will provide better opportunities for developing novel therapies to improve our management of this common clinical condition.

References

1. Jankowski R. Revisiting human nose anatomy: phylogenic and ontogenic perspectives. Laryngoscope. 2011;121(11):2461–7.
2. Marquez S, et al. Development of the ethmoid sinus and extramural migration: the anatomical basis of this paranasal sinus. Anat Rec (Hoboken). 2008;291(11):1535–53.
3. Cave AJ. Observations on the platyrrhine nasal fossa. Am J Phys Anthropol. 1967;26(3):277–88.
4. Sander K. Ernst Haeckel's ontogenetic recapitulation: irritation and incentive from 1866 to our time. Ann Anat. 2002;184(6):523–33.
5. Keir J. Why do we have paranasal sinuses? J Laryngol Otol. 2009;123(1):4–8.
6. Sahin-Yilmaz A, Naclerio RM. Anatomy and physiology of the upper airway. Proc Am Thorac Soc. 2011;8(1):31–9.
7. Biedlingmaier JF, et al. Histopathology and CT analysis of partially resected middle turbinates. Laryngoscope. 1996;106(1 Pt 1):102–4.
8. Feron F, et al. New techniques for biopsy and culture of human olfactory epithelial neurons. Arch Otolaryngol Head Neck Surg. 1998;124(8):861–6.
9. Leopold DA, et al. Anterior distribution of human olfactory epithelium. Laryngoscope. 2000;110(3 Pt 1):417–21.
10. Bodino C, et al. Surgical anatomy of the turbinal wall of the ethmoidal labyrinth. Rhinology. 2004;42(2):73–80.
11. Doorly D, et al. Experimental investigation of nasal airflow. Proc Inst Mech Eng H. 2008;222(4):439–53.
12. Doorly DJ, Taylor DJ, Schroter RC. Mechanics of airflow in the human nasal airways. Respir Physiol Neurobiol. 2008;163(1–3):100–10.

13. Clarke RW, Jones AS. Nasal airflow receptors: the relative importance of temperature and tactile stimulation. Clin Otolaryngol Allied Sci. 1992;17(5):388–92.
14. Salman SD, et al. Nasal resistance: description of a method and effect of temperature and humidity changes. Ann Otol Rhinol Laryngol. 1971;80(5):736–43.
15. Cole P. Nasal and oral airflow resistors. Site, function, and assessment. Arch Otolaryngol Head Neck Surg. 1992;118(8):790–3.
16. Latte J, Taverner D. Opening the nasal valve with external dilators reduces congestive symptoms in normal subjects. Am J Rhinol. 2005;19(2): 215–9.
17. Yu S, et al. Influence of nasal structure on the distribution of airflow in nasal cavity. Rhinology. 2008;46(2):137–43.
18. Lindemann J, et al. A numerical simulation of intranasal air temperature during inspiration. Laryngoscope. 2004;114(6):1037–41.
19. Lindemann J, et al. Nasal mucosal temperature during respiration. Clin Otolaryngol Allied Sci. 2002;27(3):135–9.
20. Pless D, et al. Numerical simulation of airflow patterns and air temperature distribution during inspiration in a nose model with septal perforation. Am J Rhinol. 2004;18(6):357–62.
21. Fonseca MT, et al. Effects of physical exercise in nasal volume. Braz J Otorhinolaryngol. 2006;72(2):256–60.
22. Fonseca MT, Voegels RL, Pinto KM. Evaluation of nasal volume by acoustic rhinometry before and after physical exercise. Am J Rhinol. 2006;20(3):269–73.
23. Svensson S, Olin AC, Hellgren J. Increased net water loss by oral compared to nasal expiration in healthy subjects. Rhinology. 2006;44(1): 74–7.
24. McNicholas WT, Coffey M, Boyle T. Effects of nasal airflow on breathing during sleep in normal humans. Am Rev Respir Dis. 1993;147(3): 620–3.
25. Rooker DW, Jackson RT. The effects of certain drugs, cervical sympathetic stimulation and section on nasal patency. Ann Otol Rhinol Laryngol. 1969;78(2):403–14.
26. Mirza N, Kroger H, Doty RL. Influence of age on the 'nasal cycle'. Laryngoscope. 1997;107(1):62–6.
27. Eccles R, Reilly M, Eccles KS. Changes in the amplitude of the nasal cycle associated with symptoms of acute upper respiratory tract infection. Acta Otolaryngol. 1996;116(1):77–81.
28. Jafek BW. Ultrastructure of human nasal mucosa. Laryngoscope. 1983;93(12):1576–99.
29. Cohen NA. Sinonasal mucociliary clearance in health and disease. Ann Otol Rhinol Laryngol Suppl. 2006;196:20–6.
30. Fokkens WJ, Scheeren RA. Upper airway defence mechanisms. Paediatr Respir Rev. 2000;1(4):336–41.
31. Wiesmiller K, et al. The impact of expiration on particle deposition within the nasal cavity. Clin Otolaryngol Allied Sci. 2003;28(4):304–7.
32. Rubin BK. Physiology of airway mucus clearance. Respir Care. 2002;47(7):761–8.
33. Ali MS, Pearson JP. Upper airway mucin gene expression: a review. Laryngoscope. 2007;117(5):932–8.
34. Green A, et al. The effect of temperature on nasal ciliary beat frequency. Clin Otolaryngol Allied Sci. 1995;20(2):178–80.
35. Mallants R, Jorissen M, Augustijns P. Effect of preservatives on ciliary beat frequency in human nasal epithelial cell culture: single versus multiple exposure. Int J Pharm. 2007;338(1–2):64–9.
36. Marple B, Roland P, Benninger M. Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. Otolaryngol Head Neck Surg. 2004;130(1):131–41.
37. Chiu T, Dunn JS. An anatomical study of the arteries of the anterior nasal septum. Otolaryngol Head Neck Surg. 2006;134(1):33–6.
38. Hosemann W, et al. Histochemical detection of lymphatic drainage pathways in the middle nasal meatus. Rhinology. 1998;36(2):50–4.
39. Baraniuk JN, et al. Gastrin-releasing peptide in human nasal mucosa. J Clin Invest. 1990;85(4):998–1005.
40. Sarin S, et al. The role of the nervous system in rhinitis. J Allergy Clin Immunol. 2006;118(5):999–1016.
41. Fernandes ES, Fernandes MA, Keeble JE. The functions of TRPA1 and TRPV1: moving away from sensory nerves. Br J Pharmacol. 2012;166(2):510–21.
42. Keh SM, et al. The menthol and cold sensation receptor TRPM8 in normal human nasal mucosa and rhinitis. Rhinology. 2011;49(4):453–7.
43. Baroody FM, et al. Nasal ocular reflexes and eye symptoms in patients with allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100(3): 194–9.
44. Baroody FM, et al. Nasal challenge with allergen leads to maxillary sinus inflammation. J Allergy Clin Immunol. 2008;121(5):1126–32.e7.
45. Assanasen P, et al. Elevation of the nasal mucosal surface temperature after warming of the feet occurs via a neural reflex. Acta Otolaryngol. 2003;123(5):627–36.
46. Corren J. Allergic rhinitis and asthma: how important is the link? J Allergy Clin Immunol. 1997;99(2):S781–6.
47. Korsgren M, et al. Secretoneurin is released into human airways by topical histamine but not capsaicin. Allergy. 2005;60(4):459–63.
48. Borum P. Nasal methacholine challenge. A test for the measurement of nasal reactivity. J Allergy Clin Immunol. 1979;63(4):253–7.
49. Baraniuk JN, et al. Neuropeptide Y (NPY) in human nasal mucosa. Am J Respir Cell Mol Biol. 1990;3(2):165–73.
50. Mellert TK, et al. Characterization of the immune barrier in human olfactory mucosa. Otolaryngol Head Neck Surg. 1992;106(2):181–8.
51. Bernstein JA, et al. Olfactory receptor gene polymorphisms and nonallergic vasomotor rhinitis. J Asthma. 2008;45(4):287–92.
52. Gaillard I, Rouquier S, Giorgi D. Olfactory receptors. Cell Mol Life Sci. 2004;61(4):456–69.
53. Hasin-Brumshtein Y, Lancet D, Olender T. Human olfaction: from genomic variation to phenotypic diversity. Trends Genet. 2009;25(4): 178–84.
54. Rahayel S, Frasnelli J, Joubert S. The effect of Alzheimer's disease and Parkinson's disease on olfaction: a meta-analysis. Behav Brain Res. 2012;231(1):60–74.
55. Hull MW, Chow AW. Indigenous microflora and innate immunity of the head and neck. Infect Dis Clin North Am. 2007;21(2):265–82, v.
56. Baroody FM. Mucociliary transport in chronic rhinosinusitis. Clin Allergy Immunol. 2007;20:103–19.
57. Bernstein JA. Allergic rhinitis. Helping patients lead an unrestricted life. Postgrad Med. 1993;93(6):124–8, 131–2.
58. Tan BK, Schleimer RP, Kern RC. Perspectives on the etiology of chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2010; 18(1):21–6.
59. Van Cauwenberge P, Van Hoecke H, Bachert C. Pathogenesis of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2006;6(6):487–94.
60. Bachert C, et al. Role of staphylococcal superantigens in airway disease. Chem Immunol Allergy. 2007;93:214–36.

61. Bachert C, et al. Staphylococcus aureus enterotoxins as immune stimulants in chronic rhinosinusitis. Clin Allergy Immunol. 2007;20:163–75.
62. Conley DB, et al. Superantigens and chronic rhinosinusitis: skewing of T-cell receptor V beta-distributions in polyp-derived CD4+ and CD8+ T cells. Am J Rhinol. 2006;20(5):534–9.
63. Conley DB, et al. Superantigens and chronic rhinosinusitis II: analysis of T-cell receptor V beta domains in nasal polyps. Am J Rhinol. 2006;20(4):451–5.
64. Patou J, et al. Staphylococcus aureus enterotoxin B, protein A, and lipoteichoic acid stimulations in nasal polyps. J Allergy Clin Immunol. 2008;121(1):110–5.
65. Seiberling KA, et al. Superantigens and chronic rhinosinusitis: detection of staphylococcal exotoxins in nasal polyps. Laryngoscope. 2005;115(9):1580–5.
66. Seiberling KA, Grammer L, Kern RC. Chronic rhinosinusitis and superantigens. Otolaryngol Clin North Am. 2005;38(6):1215–36, ix.
67. Van Zele T, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. J Allergy Clin Immunol. 2004;114(4):981–3.
68. Van Zele T, et al. Detection of enterotoxin DNA in Staphylococcus aureus strains obtained from the middle meatus in controls and nasal polyp patients. Am J Rhinol. 2008;22(3):223–7.
69. Ponikau JU, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc. 1999;74(9):877–84.
70. Sasama J, et al. New paradigm for the roles of fungi and eosinophils in chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2005;13(1):2–8.
71. Shin SH, et al. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. J Allergy Clin Immunol. 2004;114(6): 1369–75.
72. Ebbens FA, Fokkens WJ. The mold conundrum in chronic rhinosinusitis: where do we stand today? Curr Allergy Asthma Rep. 2008;8(2): 93–101.
73. Kern RC, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. Am J Rhinol. 2008;22(6):549–59.
74. Richer SL, et al. Epithelial genes in chronic rhinosinusitis with and without nasal polyps. Am J Rhinol. 2008;22(3):228–34.
75. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124(1):37–42.
76. Vroling AB, Fokkens WJ, van Drunen CM. How epithelial cells detect danger: aiding the immune response. Allergy. 2008;63(9):1110–23.
77. Eckert RL, et al. S100 proteins in the epidermis. J Invest Dermatol. 2004;123(1):23–33.
78. Claeys S, et al. Human beta-defensins and toll-like receptors in the upper airway. Allergy. 2003;58(8):748–53.
79. Dong Z, Yang Z, Wang C. Expression of TLR2 and TLR4 messenger RNA in the epithelial cells of the nasal airway. Am J Rhinol. 2005;19(3):236–9.
80. Kato A, Schleimer RP. Beyond inflammation: airway epithelial cells are at the interface of innate and adaptive immunity. Curr Opin Immunol. 2007;19(6):711–20.
81. Claeys S, et al. Nasal polyps in patients with and without cystic fibrosis: a differentiation by innate markers and inflammatory mediators. Clin Exp Allergy. 2005;35(4):467–72.
82. Wolk K, et al. IL-22 increases the innate immunity of tissues. Immunity. 2004;21(2):241–54.
83. Wolk K, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. Eur J Immunol. 2006;36(5):1309–23.
84. Ramanathan Jr M, Spannhake EW, Lane AP. Chronic rhinosinusitis with nasal polyps is associated with decreased expression of mucosal interleukin 22 receptor. Laryngoscope. 2007;117(10):1839–43.
85. Briot A, et al. Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. J Exp Med. 2009;206(5):1135–47.

Chapter 3
Immunobiology of Chronic Rhinosinusitis

Gary A. Incaudo and Christopher C. Chang

Introduction

The upper airway plays an important immunologic role as the primary filter of inspired air. As a consequence, the upper airway experiences daily exposure to particulates, gases, antigens, and potential pathogens. Under optimal conditions, the upper airway readily clears larger particulates and some gases using mucous entrapment. Elimination of filtered material follows through the gastrointestinal tract using the mucociliary escalator without involvement of the innate or adaptive immune system. However, if the barrier function of the epithelial layer fails, otherwise filtered materials can penetrate into the submucosa, activate the immune system, and raise the potential for acute and chronic inflammation.

Because inflammation of the nasal cavity and sinuses commonly coexists, the term "rhinosinusitis" has been coined to describe any inflammatory upper airway event. When signs and symptoms are persistent for more than 12 weeks, the term "chronic rhinosinusitis" (CRS) is commonly used. Although one could argue that CRS represents a persistent infection process in a closed space, it is clear that many cases are more complex and involve an aberration in the immune response, particularly if polyposis ensues.

CRS is best viewed as a heterogeneous group of disorders in which the sinonasal mucosa is often abnormally and persistently inflamed and whose etiology and pathogenesis are largely unknown. Abnormalities in the host response to recurrent external insults such as allergens, fungi, bacteria, and virus have been suggested to underlie the persistence of the inflammatory state [1]. As we have seen in earlier chapters, CRS is further divided into two types based upon the absence or presence of nasal polyps (NPs), CRS without NPs (CRSsNP) and CRS with NPs (CRSwNP). Each has a distinctive expression of inflammatory and remodeling mediators. In Western populations, CRSsNP is characterized most commonly by neutrophilic inflammation and prevalent Th1 cytokine profile. In contrast, CRSwNP is mainly characterized by eosinophilic inflammation and prevalent helper T cell type Th2 responses [2]. Eosinophilic inflammation has been found in 65–90 % of involved NP cases among whites and 50 % of Asians suggesting a genetic component [3]. However, it should be emphasized that both the presence and extent of eosinophilia in NPs can be quite variable. Furthermore, a large subset of patients with idiopathic nasal polyposis exists who do not demonstrate predominantly eosinophilia or neutrophilia. These observations support a view that although certain forms of CRS may be more commonly associated with NPs (e.g., NSAID hypersensitivity), polyposis can develop as a complication of any form of CRS and is based on a separate mechanism that may be genetic or epigenetic. Although the exact pathogenesis of each of these disorders remains largely unknown, considerable insight into the immunology has been accomplished over the last decade.

That CRSwNP and CRSsNP are commonly distinct clinical entities is supported by the observations that these two subgroups usually display unique histologic, gene, and protein expression patterns [4, 5]. However, the immunologic patterns seen are not mutually exclusive to subdivide CRS based solely on the presence or absence of NP. These findings suggest that

G.A. Incaudo, MD, FAAAAI, FACAAI (✉)
Division of Rheumatology, Allergy and Clinical Immunology, University of California School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA
e-mail: gincaudo@norcalallergy.com

C.C. Chang, MD, PhD, MBA, FAAAAI, FACAAI
Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: cchang@nemours.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_3,

Table 3.1 Classification of rhinosinusitis

Clinical classification of chronic rhinosinusitis
Chronic infectious sinusitis
Non-eosinophilic sinusitis
Chronic hyperplastic eosinophilic sinusitis
Allergic fungal sinusitis
NSAID hypersensitivity-related or aspirin-exacerbated respiratory disease
Alternate classification systems of rhinosinusitis
Rhinosinusitis
Acute rhinosinusitis
Chronic rhinosinusitis
Chronic rhinosinusitis with nasal polyps
Chronic rhinosinusitis without nasal polyps
Allergic fungal rhinosinusitis
Classification system for fungal rhinosinusitis
Invasive
Acute invasive fungal rhinosinusitis (necrotizing, fulminant)
Chronic invasive fungal rhinosinusitis
Granulomatous invasive fungal rhinosinusitis (indolent)
Noninvasive
Allergic fungal rhinosinusitis
Saprotic fungal infestation
Fungus ball (fungus mycetoma)
Eosinophilic fungal rhinosinusitis

CRS subgroups are more diverse and represent a complex interaction of many factors which, in unison, result in the wNP and sNP categorization. Until distinct immunologic and genetic profiling becomes available to clinicians, health-care providers are left with clinical definitions of CRS as the best approach for directing treatment. The five clinical division of CRS have been proposed as follows [4]: (1) chronic infectious sinusitis, (2) non-eosinophilic sinusitis, (3) chronic hyperplastic eosinophilic sinusitis, (4) allergic fungal sinusitis, and (5) NSAID hypersensitivity-related or aspirin-exacerbated respiratory disease (AERD). This is illustrated in Table 3.1, along with other suggested classification systems for rhinosinusitis.

Chronic hyperplastic eosinophilic sinusitis, allergic fungal rhinosinusitis, and NSAID hypersensitivity are associated with some degree of nasal polyposis. Such a high degree of heterogeneity underscores the variety of therapeutic options open to clinicians depending on the specific format of CRS and extends beyond the presence or absence of polyps. For example, allergic fungal sinusitis can also be treated with antifungal agents and specific antifungal immunotherapy. NSAID hypersensitivity-related or aspirin-exacerbated respiratory disease can also be treated with ASA desensitization for polyp control in addition to other more standard measures used in the treatment of CRS with eosinophilic NP such as topical and systemic corticosteroids and leukotriene antagonists. In general, compared with non-eosinophilic CRSwNP, eosinophilic CRSwNP demonstrates a higher degree of disease severity, greater steroid responsiveness, and a poorer response to surgery.

Still, the question remains whether CRSwNP and CRSsNP represent a disease spectrum that varies over time based upon genetic and epigenetic factors or does CRS represent different diseases that develop separately while maintaining similar immunologic characteristics. It is compelling to consider CRS as a spectrum of disorders in which the level of eosinophilia and propensity for the development of polyposis exists on a continuum based on host genetic and epigenetic factors (Fig. 3.1).

In general, CRS is clearly a complex interplay between host factors, consisting of the innate and adaptive immune responses, barrier function, and environmental factors, including fungal or bacterial colonization, biofilms, superantigens, osteitis, and allergen exposure. The answer to this question will ultimately be found by characterizing host factors on the basis of the expression of inflammatory patterns and genetic profiles. Indeed, defining the role of humoral or innate immune deficiencies, inflammatory cell profiles (eosinophils vs neutrophils), epithelial barrier defects, and identifying the differentiated T-effector cells (Th1, Th2, and Th17) and regulatory T (Treg) cells will ultimately lead to more specific diagnostic subgroups. Such information, when combined with an understanding of the mechanistic imbalance favoring TH1 or TH2 responsiveness and the remodeling processes of fibrosis and/or edema formation, will ultimately provide more targeted therapeutic options in the future. This chapter will review the most important immunologic findings that will improve our knowledge of CRS pathogenesis and lead to a better clinical understanding of this complex disease.

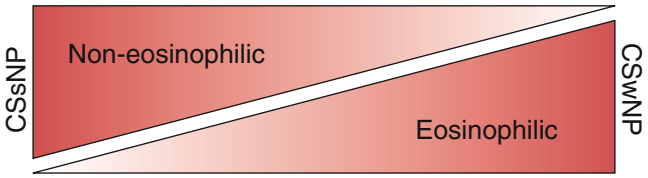


Fig. 3.1 Role of eosinophils in chronic rhinosinusitis. Eosinophilic and non-eosinophilic forms of sinusitis present with distinct pathological features and require distinct clinical approaches. However, in individual patients CS presents along a spectrum in which the level of eosinophilia and predilection for polyposis exists on a continuum. *CSsNP* chronic sinusitis without nasal polyposis, *CSwNP* chronic sinusitis with nasal polyposis (Reprinted from Payne et al. [4]. With Permission from Elsevier)

The Role of Innate Immunity in Chronic Rhinosinusitis

The role of innate immunity in various diseases is becoming more and more appreciated, and chronic rhinosinusitis is no exception. The first line of defense against infectious agents is the mucosal and skin barriers that form a physical defense system by employing a number of different systems. These include clearance mechanisms such as mucus and cilia, tight junctions between cells to keep out invaders, and even regulation of environmental or ambient local conditions such as temperature and humidity. The role of the epithelial barrier is not limited to a physical on. Rather, the epithelium is an active organ that is designed to identify or recognize dangers to the host and generate a multifaceted response to these signals. The role of pattern recognition receptors will also be presented, as will other aspects of innate immunity, including complement and other nonspecific cellular responses.

The Epithelial Cell as an Immune Barrier in CRS

Tight Junctions

The airway mucosa maintains a structural integrity that protects the subepithelial tissue from foreign invasion. An intact barrier function is the first-line defense mechanism of the airway against potential antigens and pathogens. A major component of barrier integrity is the structure of the "tight junctions (TJs)" that hold epithelial cells firmly together. TJs are the gatekeepers of the nasal and sinus mucosa. They are responsible for the regulation of paracellular flux and control epithelial permeability. TJs can prevent foreign particles from entering the subepithelial layers and paradoxically become permeable to promote inflammatory cell discharge into the sinus and nasal cavities. When dysfunctional, TJs can contribute to the aggravation of inflammatory processes and have the capacity to direct an immune response.

Tight junction (TJ) components consist of various scaffold adaptor and transmembrane proteins. Different members of the TJ proteins have been identified. These include occludin, tricellulin, the family of claudins, and junctional adhesion molecules which form intercellular homodimers/heterodimers between neighboring cells. Within the cytoplasm, they bind to the actin cytoskeleton through associated proteins, such as the zonula occludens (ZO) family and cingulin [6, 7]. Their tightness prevents foreign particles, such as irritants and allergens, from entering the subepithelial layers as they act both structurally as a barrier and immunologically through innate toll-like receptors (see below) and secretory IgA transport (Fig. 3.2). On the other hand, TJ permeability can lead to drainage of inflammatory cells into the lumen, promoting resolution of the inflammatory process. It is clear that the epithelial layer of the respiratory tract acts as an important gatekeeper whose function is to prevent, promote, and resolve inflammation.

Dysfunctional TJs can promote inflammation through facilitating the invasion of pathogens and environmental antigens, including allergens, into the submucosal layer. Recent research has defined an increasing number of mucosal-based disorders linked to defective or altered TJs. Schultze et al. described TJ abnormalities in patients with inflammatory bowel diseases, including Crohn's disease [8]. Atopic disorders such atopic dermatitis and asthma have also demonstrated tight junction abnormalities [9–12]. Rhinoviral infection, a notorious trigger of sinusitis and asthma flares, has been shown to disrupt the cytoplasmic actin cytoskeleton further enhancing inflammation from otherwise innocuous inhaled particulates or gases as well as increase binding of bacteria to and promote internalization of bacteria by epithelial cells [13].

Changes in TJ arrangement within the epithelium of the nasal cavity, a region heavily exposed to environmental antigens and infective agents, have only recently been understood in the context of promoting chronic inflammation [1, 14]. In 2002,

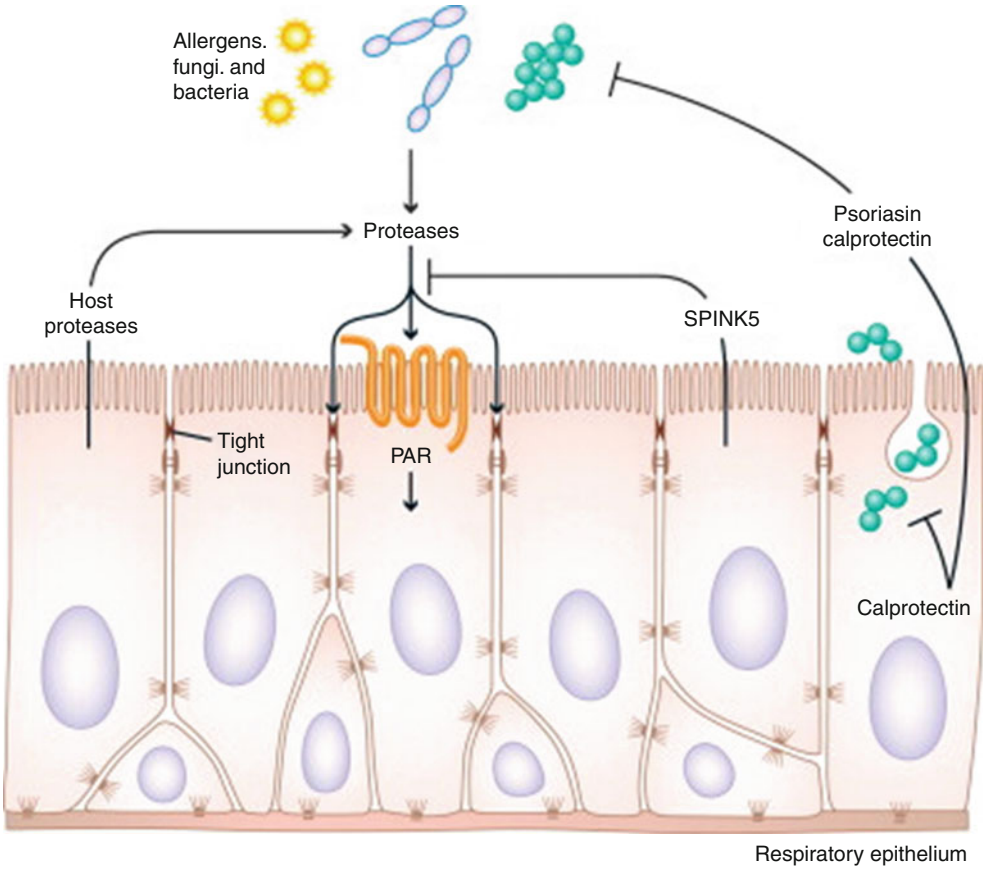


Fig. 3.2 Immune barrier proteins and chronic rhinosinusitis. Potential points of influence of proteases, SPINK5, and S100 proteins on the immune barrier in the upper airways. See text for discussion. *PAR* protease-activated receptor (Reprinted from Tieu et al. [14]. With permission from Elsevier)

ZO-1 was found to be downregulated in nasal polyposis along with epithelial dedifferentiation [15]. Zuckerman et al. was able to demonstrate weakened desmosomal junctions in patients with CRSwNP and suggested that TJ weakening may be the source of polyp formation [16]. Bernstein et al. demonstrated that cultured epithelial cells from nasal polyps manifest a greater absorption of sodium and water than cells from turbinate. These authors propose that the microenvironmental inflammatory response within the respiratory epithelial structure can affect the bioelectrical integrity of the sodium and chloride channels at the luminal surface and promote polyp formation [17].

Further research from Japan supported the concept that sinonasal epithelial cells from patients with CRS express increased rates of ion transport which might be pathophysiologically relevant to disease progression [18, 19]. Soyka et al. took this line of research a step further demonstrating a defective barrier function in patients with CRS in conjunction with a decreased expression of TJ proteins and decreased mRNA levels compared with that seen in normal control subjects [7]. The defective barrier function in this study was most pronounced in patients with CRSwNP when compared to healthy controls and patients with CRSsNP. The changes in TJ function was enhanced by the cytokines IFN-γ and interleukin 4 (IL-4). Of additional interest in this study was the finding that dysfunctional TJs in CRS mucosa could still be demonstrated when the epithelium was cultured in the absence of any inflammatory stimuli suggesting a possible intrinsic (genetic?) defect inherent or induced and persisting in the diseased mucosa. Taken together, these studies suggest that polyp formation begins, in part, with a dysfunctional TJ function within the lining of the upper respiratory tract that is either induced or inherent or both that allows a transepithelial migration of fluid and inflammatory cells into a polypoid mass. Still, a clear and comprehensive comparison of TJs changes from mucosa of normal controls, CRSsNP, and CRSwNP remains lacking. It is still not known whether the defective TJ production and function are a primary source or a secondary result of the inflammatory response in CRS. Nevertheless, these discoveries have underscored the important protection the epithelial layer provides, whether in the airway, intestinal tract, or skin, as it interacts with the environment.

The Immune Barrier as a Mediator of T Cell Function

In addition to a physical barrier, the airway epithelium operates as a mediator of immune defense. Defects in a broad set of epithelial-related genes, in theory, could contribute to a dysfunctional innate and adaptive immune response to environmental

agents entering the upper airways similar to those described in the skin and lungs. The resultant immune differentiation could then serve as the basis for developing CRS heterogeneity. Details of the innate, humoral, and T cell immune function found in CRS are discussed below. There is considerable evidence suggesting that patients with CRS demonstrate enhanced epithelial cell immune activation. CRS appears to generate a wide range of T cell cytokines and chemokines with mixed Th1/Th2/Th17 profiles such as INF-γ, transforming growth factor, IL-3, IL- 4, IL- 5, IL- 13, IL-17, IL-19, IL-32, CCL5 (RANTES), CC chemokine ligand 18, and eotaxins as well as reduction in T regulatory markers such as FOXP3 [7, 20–25]. The broad immunologic diversity of inflammatory markers observed within tissue from patients with CRS stands in stark contrast to the simple CRSsNP and CRSwNP clinical classification and underscores the need for better immunologic phenotyping [26].

Components of innate and humoral immunity such as toll-like receptors on the epithelial surface play a key role in T cell activation and are described below. Other formats of micro-signaling dysregulation from epithelial cells in CRS patients have been recently uncovered. Some authors have suggested that there are epigenetic changes in the sinonasal mucosa signaling in patients with CRS [27]. For example, microRNAs regulate gene expression primarily by translational repression and, as such, represent a fundamental component of the gene-regulatory network in humans. Zhang et al. identified an upregulated expression of a single microRNA miR-125b in patients with CRSwNP. They found that miR-25b can enhance interferon production by suppressing the transcriptional regulator EIF4E-binding protein 1. The authors linked this regulator to mucosal eosinophilia and a Th2 bias by suggesting the suppression can result in increased INF-β mRNA expression [25].

Other Components of Innate Immunity

S100 Protein Genes

Another focus of gene research is the epidermal differentiation complex located on chromosome 1q21. Chromosome 1q21 encodes many genes that are expressed in epidermal cells. A majority of the S100 protein genes are encoded in this region. S100 proteins are small, calcium-binding proteins whose genes are localized in a cluster on human chromosome 1. Through their ability to interact with various protein partners in a calcium-dependent manner, the S100 proteins exert their influence on many vital cellular processes such as cell cycle, cytoskeleton activity, cell motility, cell differentiation, etc. The characteristic feature of S100 proteins is their cell-specific expression, which is frequently up- or downregulated differently in various pathological states. Tieu et al. studied the S100 proteins in the mucosa of patients with CRS [28]. Of particular interest in epithelial barrier function are the proteins S100A7 (Psoriasin) and S100A8/S100A9 (calprotectin), initially found to be overexpressed in psoriasis [29, 30]. Tieu and colleagues found that S100 protein expression was significantly decreased in the epithelium of CRS patients. One of the important S100 proteins, S100A7, has significant chemotactic properties and acts as an attractant for CD4+ lymphocytes and neutrophils and can directly kill bacteria [31]. Tieu speculated that the decrease in S100 protein expression is a form of immune deficiency that could lead to a diminished innate immune response and defective barrier function, setting the stage for the development of CRS and possibly nasal polyps.

Another S100 protein, calprotectin promotes neutrophil migration. Tieu et al also found increased levels of calprotectin in nasal polyp tissue which they speculated may reflect neutrophil recruitment stimulated as a compensatory mechanism to counteract against the immune barrier defect [31]. It is possible that an induced or genetically directed reduction in S100 proteins in patients with CRS represents at least one mechanism that can result in immune dysregulation that results in increased susceptibility to infection by organisms that are directly sensitive to these proteins. The adverse immune response is further enhanced by limiting transepithelial migration of leukocytes attempting to repair of the epithelium (Fig. 3.2). This data provides strong evidence for a direct gene-based induction of an immune barrier defect at the epithelial/mucosal level in patients with CRS that promotes antigenic penetration and triggers an enhanced inflammatory response. Examples of potential triggers of this activation could be colonization with bacteria, viral invasion, or an innate inflammatory response to fungi and other environmental antigens.

Lymphoepithelial Kazal-Type-Related Inhibitor (LEKTI) A.K.A Serine Protease Inhibitor Kazal-Type 5 (SPINK5)

Recently, there has been increasing interest in SPINK5 and thymic stromal lymphopoietin (TSLP), an IL-7-related cytokine that is secreted by epithelial mucosal cells, as potential sources of CRS development. SPINK5 is an epithelial proteinase inhibitor that provides maintenance support for the epithelial barrier in a variety of ways including keratinization. TSLP directs dendritic cells to release a cytokine burst that attracts Th2 cells and promotes T cell activation. The link of SPINK5 and TSLP to CRS begins with the discovery of the key defect underlying a congenital disorder called the

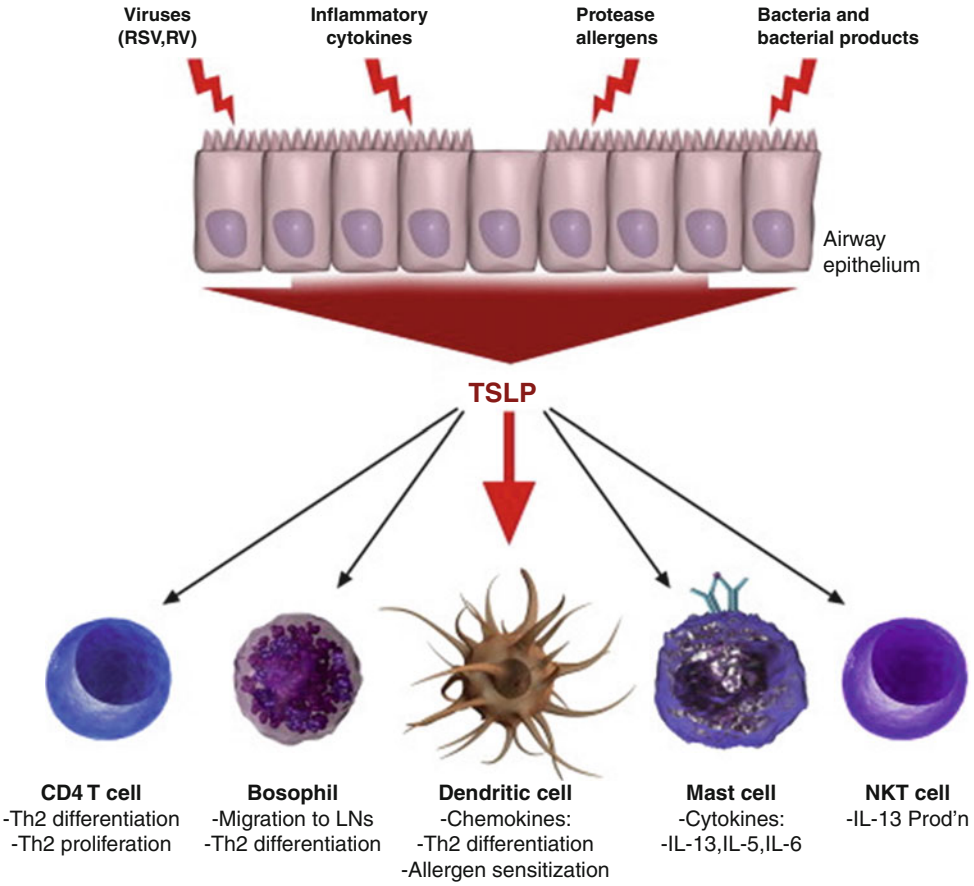


Fig. 3.3 TSLP target cells at mucosal surfaces: schematic representation of TSLP activity at mucosal surfaces. A variety of stimuli are capable of inducing TSLP expression by barrier epithelial cells. TSLP can then activate resident cells, especially DCs, to drive a type 2 response (Reprinted from Ziegler [37]. With permission from Elsevier)

Netherton syndrome. Netherton syndrome is an autosomal recessive disorder marked by severe ichthyosis and a strong Th2 immune bias toward atopic disease development. It has been linked to the lymphoepithelial Kazal-type-related inhibitor (LEKTI) also known as serine protease inhibitor Kazal-type 5 (SPINK5). LEKTI deficiency has also been linked to atopic disease, another component of the Netherton syndrome [32]. Richer et al. extended the effects of LETKI deficiency beyond keratinization and atopy [33]. These authors found decreased SPINK5 expression in the mucosa of patients with both CRSsNP and CRSwNP which suggests that serine protease inhibitor Kazal-type 5 is an important component in mucosal epithelial barrier integrity. Decreased SPINK5 appears to be even more pronounced in CRS/NSAID-associated airway disease further supporting a causative role for this gene product in a subgroup of CRSwNP that tends to be clinically aggressive and highly symptomatic [34].

Thymic Stromal Lymphopoietin (TSLP)

LEKTI deficiency has been connected to the dysregulation of the protease kallikrein 5, which in turn activates protease-activated receptor 2 (PAR-2) [35]. Activated PAR-2 can induce the expression of TSLP, a key inflammatory cytokine from epithelial airway cells [36] (Fig. 3.3). TSLP production from barrier epithelial cells acts as a central component of Th2 expression, primarily through stimulating dendritic cell (DC) OX-40 expression. It is the interaction of DC OX-40 with OX-40 L-CD4 cells that drives Th2 differentiation [37]. A connection between TSLP and CRS with nasal polyps was identified by Liu et al [38]. These authors found high levels of TSLP in nasal epithelial tissue with polyps (with and without allergic rhinitis) and increased TSLP receptors on peripheral dendritic cells in mucosal/polyp tissue, suggesting that DC-TSLP interaction is involved in the pathogenesis of nasal polyps. The influence of TSLP activation on CRS was expanded to include CRSsNP by Boita et al. that same year [39]. It appears likely that epithelial cell dysregulation of SPINK5, primarily through a reduction in regulatory activity, promotes TSLP generation and provides a direct pathway for inflammatory amplification, particularly with a Th2 bias. SPINK5 and TSLP represent yet another defect of barrier epithelium function that can promote the development Th2 activity and CRS with and without polyps in affected individuals and serve as a target for future therapeutics.

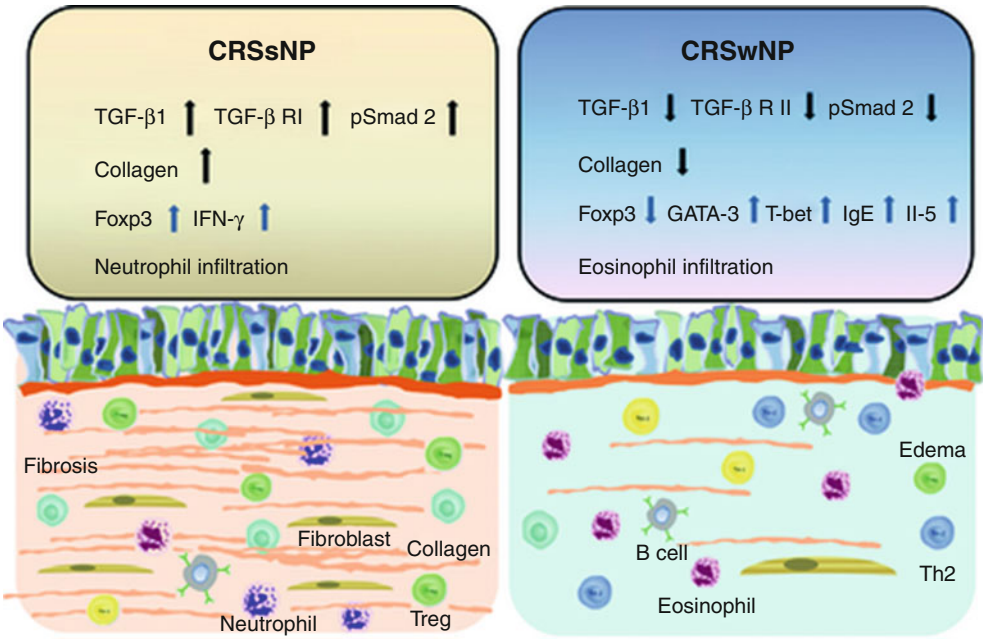


Fig. 3.4 Regulation of TGF-β1 in CRSsNP and CRSwNP from inflammation and remodeling (Reprinted from Yang et al. [101]. With permission from John Wiley & Sons, Inc)

Transforming Growth Factor (TGF)

The mucosal epithelial barrier can be involved in the entire inflammatory process in ways that have yet to be fully defined. Cell proliferation in somatic tissues, specification of cell fate during embryogenesis, differentiation, and cell death are controlled by a multitude of cell–cell signals. Prominent among these regulatory signals is the transforming growth factor-beta (TGF-β) superfamily, which comprises a large and diverse group of polypeptide morphogens with over 33 members. The TGF-β family plays an important role in the development, homeostasis, and repair of most human tissues [40]. All immune cell lineages, including B cell, T cell, and mucosal and dendritic cells as well as macrophages, secrete TGF-β, which negatively regulates their proliferation, differentiation, and activation by other cytokines. Thus, TGF-β is a potent immunosuppressor, and the disturbance of TGF-β signaling is linked to autoimmunity, inflammation, and cancer [41]. Recent evidence suggests that TGF-β1 is involved in very early respiratory disease as well as late persistent respiratory disease and is involved with both the inflammatory and the remodeling processes [42]. It has long been observed that chronic rhinosinusitis with and without nasal polyps, asthma, and chronic obstructive pulmonary disease is similarly characterized by mucosal inflammation and remodeling. TGF-β1 has been demonstrated to be upregulated in both CRSsNP and COPD, upregulated or unchanged in asthma, and downregulated in CRSwNP [40].

Different TGF-β responses are likely the result of varying Treg activity. It has been shown that there is a difference in the presence of Treg cells in CRS. There appears to be a deficit in FoxP3 expression and Treg cell numbers in CRSwNP, but not in CRSsNP. Both the Treg and inflammatory cell dysregulation in CRSwNP are coincident with significant downregulation of TGF-β1 expression, a lack of collagen, and an intense edematous stroma. In contrast, CRSsNP demonstrates no deficit in Treg cell numbers, excessive collagen production, and fibrosis and displays a much less severe inflammatory mucosal reaction [21, 43] (Fig. 3.4). Given its regulatory function in both inflammation and remodeling processes, TGF-β1 represents a future therapeutic target for patients with CRSwNP. The regulation of TGF-β1 itself is discussed later in the chapter in the section on cytokines.

Pattern Recognition Receptors and Pathogen- and Danger-Associated Molecular Patterns

A feature of the immune system of higher organisms is the ability to recognize conserved pathogenic molecular patterns on potentially harmful organisms or substances. These are known as pathogen-associated molecular patterns (PAMPs) when one is referring to infectious agents and danger-associated molecular patterns (DAMPs) when one is referring to other non-infectious agents such as chemicals. The receptors that recognize these molecular patterns and trigger the cascade of signaling pathways that lead to a protective immune response are known as pattern recognition receptors (PRRs). The most well known of the pattern recognition receptors are the toll-like receptors (TLRs), transmembrane receptors found on a variety of

immune cells that were discovered in the late 1990s and are now known to play a significant role not just in infectious diseases, but also in autoimmunity, noninfectious inflammatory diseases, and even in diseases not normally thought to have an immune component. Each TLR is localized to a different part of the cell, some are intracellular and some are membrane bound, signifying different functions. Moreover, each TLR binds to a different set of ligands. As a result, TLR2 and TLR4 may play a role in defenses against fungi, bacterial, and endotoxin. Bacterial lipopolysaccharide (LPS) has been found to be a ligand of TLR4. TLR3 binds to viral double-stranded DNA, but TLR 7 and TLR8 are activated by single-stranded RNA. TLR5 recognizes bacterial flagellin, and TLR9 recognized methylated CpG moieties primarily found in bacteria. These are all illustrations of how the innate immune system distinguishes self from nonself. With regard to CRS, one study reported an absence of TLR2 and TLR4 as well as TLR3 in nasal polyps of patients in whom bacteria were detected in cultures from the nasal vestibule. The clinical significance of this is unknown at this time.

The airway epithelium has already been discussed in detail as to its role as a component of innate immunity and first-line defense against pathogens. The role of airway epithelium in various diseases, including diseases that are now thought to be primarily a function of chronic inflammation, such as asthma and chronic rhinosinusitis, is being increasingly recognized. Nasal fibroblasts have also been found to play a role in nasal polyps. An in vitro study demonstrated that ligands for TLR 2,3,4, and 5 can stimulate nasal fibroblasts to secrete thymus and activation-related cytokine (TARC) leading to the production of IL-4, suggesting an interplay between the innate immune system and the development of a predominantly Th2 response in patients with nasal polyps [44].

Complement and Rhinosinusitis

The complement system is a component of innate immunity, but also serves as a bridge between innate and adaptive immunity in that it facilitates the interaction between cellular elements of adaptive immunity, i.e., B and T cells. There are three pathways of complement, the classical pathway, so named because it was the first discovered, the alternative pathway, and the lectin pathway. The latter two are antibody independent and are therefore more closely linked with innate immunity.

Deficiencies in complement are rare. The most common deficiency is a C3 deficiency. Deficiencies of the latter components, C5 through C9, result in a failure to form a functional membrane attack complex, leaving the host susceptible to pathogenic infectious agents such as *Neisseria*. The clinical significance of deficiencies of the earlier components of the classical pathway is unknown. One study showed that a C4A deficiency was associated with an increased risk of chronic rhinosinusitis. Seppanen et al. demonstrated a strong relationship between CRS and the C4A null allele [45]. A C2 deficiency has also been associated with severe and mild sinus infections [46]. A deficiency of mannose-binding lectin of the lectin pathway has been associated with recurrent infections, although more commonly, the clinical effect of this deficiency is seen in conjunction with other immune system deficiencies. A more detailed discussion of the impact of immune deficiency on chronic rhinosinusitis is available in Chap. 14.

Mannose-binding lectin (MBL) deficiency has been associated with chronic rhinosinusitis. But the association is weak, and in a study of 87 patients, 15 of them, or 17.2 %, showed a complete lack of MBL. But compared with a control group with an MBL deficiency rate of 9.3 %, this was not found to be statistically significant [47]. Moreover, another study actually showed that chronic rhinosinusitis patients with nasal polyps have higher C3 and MBL levels than those without nasal polyps, and both groups have MBL levels higher than the healthy controls [48]. The significance of MBL in chronic rhinosinusitis is therefore still unknown.

Others have suggested that it is not a specific complement deficiency that is related to chronic rhinosinusitis, but an overall functional impairment of the complement pathway [49]. Whether complement function is related to sinus infections alone or if there is a more complex relationship related to inflammation of the nose and paranasal sinuses is unknown at this time.

Staphylococcus Superantigens and Chronic Rhinosinusitis

It is now known that *Staphylococcus aureus* (*S. aureus*) enterotoxins can function as superantigens in chronic rhinosinusitis. This means that enterotoxin can activate T cells independently of the antigen-specific groove, by direct interaction with the T cell receptor variable β-chain. *S. aureus* enterotoxin B can skew the T helper cell paradigm toward a Th2 dominance. This is particularly true in CRS with nasal polyps. *S. aureus* induces an increased expression of Th2 cytokines, including IL-2, IL-4, and IL-5 [50] while reducing the impact of T regulatory cell cytokines such as transforming growth factor β1 and interleukin 10 [51]. The clinical significance of superantigen involvement in chronic rhinosinusitis is that the activation of T cells by superantigen leads to a polyclonal stimulation of B cells, with recruitment of other inflammatory cells such as eosinophils. Besides *S. aureus*, other pyogenic Staphylococcal species such as *S. pyogenes* can also secrete enterotoxins. Concomitant findings in patients with CRSwNP were the increase in IgE antibodies to *S. aureus* in nasal polyp tissue, an increase in IL-5, eotaxin and

eosinophil cationic protein (ECP) [52], and an increase in the number of T cells expressing the variable β-chain which is induced by enterotoxin [53]. A related staphylococcal enterotoxin, toxic shock syndrome toxin (TSST-1), has been found to be able to enhance Th2 responses by inducing expression of costimulatory molecules involved in T and B cell interactions [54].

The Role of Adaptive Immunity in Chronic Rhinosinusitis

Humoral Immunity

Antibody may play a role in certain types of chronic rhinosinusitis. Allergic fungal rhinosinusitis is generally considered to be a noninvasive form of chronic rhinosinusitis. It is a relatively rare disease and certain criteria need to be fulfilled in order to make the diagnosis. The presence of fungal specific IgE and eosinophilic mucus are two of the immunologic criteria. Interestingly, culturing fungus from the sinuses by itself does not make the diagnosis of fungal sinusitis. In other words, the host response may be more important than the infectious agent.

But what about the role of adaptive immunity in non-fungal types of chronic rhinosinusitis, especially chronic rhinosinusitis with nasal polyps? Is this an allergic disease and is this mediated by IgE antibody, thus making a type 1 hypersensitivity disorder?

The Role of T Cells in Chronic Rhinosinusitis

The European position paper (E3POS) published in 2007 on chronic rhinosinusitis states that CRSwNP is primarily a Th2 disease, with characteristics of eosinophilia, as well as a role for Th17 cells [55, 56]. The possibility that CRS is a T cell-driven disease has already been discussed above.

It has been shown that chronic rhinosinusitis may in fact be several different diseases, with different pathophysiologies. For example, CRSwNP is a Th2-mediated disease, whereas in the absence of nasal polyps, Th1 effects predominate. When comparing patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and controls with allergic rhinitis, evidence of local receptor revision and IgE class switching was detected in those patients with CRSwNP, but not in the controls. In the CRSwNP patients, 30 % of plasma cells, B cells, and T cells in the polyp tissue expressed both RAG1 and RAG2. The switch to IgE production, as measured by mRNA concentrations of RAG1 and RAG2 in polyp tissue, correlated with the magnitude of the inflammation as well as the presence in the nasal mucosa of *S. aureus* enterotoxin B-specific IgE [57].

The regulation of T cells and the role of the various forms of T cells in chronic rhinosinusitis are complex. Chronic rhinosinusitis is now believed to be a set of differing diseases (see Table 3.1) in terms of the type of phenotypic characteristics that may result from a predominance of one particular T cell activity. In general, Th1 or Th2 effects predominate in CRSsNP and CRSwNP, respectively, but what about the role of T regulatory cells and Th17 cells? Van Bruaene studied the cytokine profiles in CRSwNP, CRSsNP, and normal controls by examining direct tissue expression of the transcription patterns for Th1, Th2, Th17, and Treg cells. They found that the nasal tissue of patients with CRSwNP had a significantly lower expression of TGF-β and FoxP3, but a higher expression of IL-5, IL-13, T-bet, and Gata-3 when compared to normal controls. The transcription pattern in CRSsNP showed a higher level of expression of TGF-β1 and interferon-γ, but there was no significant difference in FoxP3, Gata-3, RORc, nor T-bet compared to controls [21].

Cytokines and Chemokines in Rhinosinusitis

Cytokines

TNF-α

TNF-α is a proinflammatory cytokine with numerous immunomodulating activities. Local increases in TNF-α production can lead to epithelial damage, disruption of normal pathways of apoptosis of olfactory neurons, and desensitization of odorant-induced signaling in the nasal passages. TNF-α also affects the normal function of cilia and damages respiratory mucosal lining, partly through its inflammatory effects that lead to infiltration of inflammatory cells including neutrophils, lymphocytes, and monocytes. By this mechanism, it is thought that TNF-α has the ability to impair normal olfaction, a defect that is seen in many patients with CRSwNP [58, 59].

TNF-α effects result from the interaction with two different TNF-α receptors. Type I receptors (TNFR-I) are expressed by all human nucleated cells and are responsible for a broad range of activities. Type II receptors (TNFR-II) are detected in acute inflammatory reactions and are expressed only by antigen-presenting cells and lymphocytes. A study of 36 patients with CRSwNP showed an eosinophilic, polymorphonuclear cell, and plasmacyte infiltration into the subepithelial layer of inflamed nasal polyps [60]. The cellular infiltrate was predominantly eosinophilic in 7 of the 36 patients with an absence of biofilm. The specimens, obtained from endoscopic sinus surgery, demonstrated a neutrophilic infiltration of the subepithelial layer that correlated with the presence of biofilms. This was accompanied by an increased expression of TNFR-I and TNFR-II receptors. The upregulation of TNF-α/TNFR-I in cases with biofilm presence indicates a proinflammatory pathophysiology in the formation of biofilms, but the observation that the cellular infiltrate is predominantly neutrophilic, and not eosinophilic, suggests that cases with biofilm formation may not be a result of a Th2 paradigm. It is interesting also to note that in most cases of CRSwNP, IL-4 and IL-5 are upregulated, while interferon-γ and TGF-β are downregulated (see below). Moreover, single-nucleotide polymorphisms in the genes encoding IL-1A, IL-1B, IL-4, and TNF have been detected in patients with CRSwNP and CRSsNP [61, 62].

TNF-α also appears to temporarily stimulate the release of IL-18 (discussed below) from human neutrophils, with a rapid release and peak enhancement at 3 min with a return to baseline at 10 min [63]. Lipopolysaccharide (LPS) led to a much more sustained release of IL-18 from human monocytic THP-1 cells, and the effects of the stimulation could still be seen after 1 day [64].

TGF-β

TGF-β is a cytokine expressed by many cell types, including macrophages, and is known for its role in remodeling of tissues in a wide variety of diseases, including asthma, autoimmune diseases, cancer, and diabetes. It has a role in tissue remodeling as discussed earlier in this chapter. It interacts with many other cytokines in a complex manner. One of its primary roles is the differentiation of fibroblasts into myofibroblasts. TGF-β1, the primary isoform of this cytokine, exists in latent and active forms. Latency-associated peptide (LAP) and latent TGF-β-binding protein (LTBP-1) inhibit TGF-β1 from exerting its biological activity [65, 66]. Normally, only a fraction of TGF-β1 exists in the active form. Studies have shown that this is increased significantly in CRS [67], and is believed to be part of the pathophysiology of the tissue remodeling process.

The regulation of TGF-β1 is under the control of a variety of factors, including integrins and proteases. These molecules play a role in determining how much of the latent form is rendered active. A link between the matrix metalloproteases and TGF-β has been found, suggesting that membrane type-1 MMPs may play a role in this regulation [68, 69]. Other compounds that may regulate TGF-β1 include the aryl hydrocarbon receptor (AhR), which inhibits LTBP-1 transcription and maintains the gene in a suppressed state, thereby preventing the activation of TGF-β1 [70]. The different pathways in CRSwNP versus CRSsNP can possibly be explained by the fact that hypoxia-inducible factor 1α, a positive regulator of AhR, is increased in nasal polyp tissue compared to normal tissues [71]. Thus in CRSwNP, AhR is enhanced, leading to decreased activity of TGF-β1, whereas in CRSsNP, AhR is suppressed, resulting in overexpression of TGF-β1, leading to mucosal fibrosis by the mechanisms explained above [72].

IL-6

IL6 is known to activate Th17 cells. Among some of the other functions are B cell activation and regulation of T cells. IL-6 exerts its effects via STAT3 after binding to the IL-6 receptor, IL-6R, with the resulting complex binding to glycoprotein-130 (gp130), a 130-kd signaling molecule. Alternatively, IL-6R can engage mechanisms of trans-signaling in cells that do not have the IL-6R by binding to soluble IL-6R (sIL-6R) which can then complex with membrane bound gp130.

Il-6 has been studied in chronic rhinosinusitis because of its known role in the pathogenesis of inflammatory diseases. The level of sIL-6R was found to be increased in polyp tissue compared to normal control tissue. There was no difference in the level of expression of IL-6 secreted by epithelial cells from either the uncinate process or inferior turbinate in patients with CRS versus normal controls. Interestingly, the level of STAT3, a key component of the signaling pathway for IL-6, was actually reduced in nasal polypoid tissue compared to normal tissue. The authors concluded that although there are elevated levels of sIL-6R and IL-6 in nasal polyp tissue of patients, this did not seem to influence STAT3-related signaling pathways.

Since there may in fact be a blunting of the STAT3 signaling pathway, it has been hypothesized that this would impair Th17 activity and that this could be the mechanism for increased risk for recurrent infection in patients with CRSwNP. On the other hand, there seems to be conflicting evidence as to whether IL-6 plays a stimulatory role or an inhibitory role in the regulation of inflammation in chronic rhinoconjunctivitis with nasal polyps. In fact, both elevations in proinflammatory molecules and downregulatory molecules have been identified [73].

IL-17

The IL-17 family of cytokines includes IL-17A through F. IL-17A is a major cytokine secreted by Th17 cells that plays a role in many inflammatory and autoimmune diseases. In patients with chronic rhinosinusitis with nasal polyps, IL-17A correlated with the serum levels of the acute phase protein serum amyloid A (SAA) [74]. This protein functions to induce chemotaxis, adhesion, and infiltration of monocytes and polymorphonuclear leukocytes [75–77].

IL18

IL-18 is a proinflammatory cytokine belonging to the IL-1 family. IL-18 has a role in the stimulation of SEB-induced expression of IL-5, IL-13, and IFN-γ. Blocking IL-18 suppresses this stimulation. IL-18 has been detected in the culture supernatants from dispersed nasal polyp cells and uncinate tissue in patients with chronic rhinosinusitis when compared to non-CRS patients. The clinical significance of the observed increase in IL-18 expression was supported, though not conclusively, by the observation of a correlation with local eosinophilia and the severity of the sinusitis as indicated by computed tomography (CT) scan. Immunohistochemical studies indicated that epithelial cells (cykeratin+) and macrophages (CD68+) expressed IL-18. Other cells that expressed IL-18, were CD79a+ B cells and plasma cells, CD4+ cells, and vimentin+ cells (fibroblasts and vascular endothelial cells). Interestingly, cells that did not express IL-18 included eosinophils (EG2+), mast cells (tryptase+), and neutrophils (elastase+) [78]. The release of IL-18 is triggered by exposure to chemical and physical stresses on the nasal epithelium. This activation is thought to be driven by the NLRP3 inflammasome, which activates IL-18 from pro-IL18 via a caspase1-dependent pathway [79].

Because IL-18 appears to be able to induce the expression of the Th2 cytokines IL-5 and IL-13, but also the Th1 cytokine IFN-γ, it is unclear of the predominant influence of IL-18 on Th1/Th2 balance. It is now thought that IL-18 enhances both Th1 and Th2 pathways, but to make this even more complicated, IL-18 also appears to be able to enhance the production of IL-17A in both in vivo and in vitro systems [80, 81].

IL-19

IL-19 belongs to the IL-10 family of cytokines. A study of the role of IL-19 was triggered by the concept of the United Airway discussed in Chap. 11. IL-19 was found to be upregulated in asthma by Asthma Gene Array. Subsequently, IL-19 gene expression was found to be increased in chronic rhinosinusitis with nasal polyps patients over normal controls. IL-19 levels were also found to be elevated in the nasal epithelium of patients with CRSwNP [82]. The role of IL-19 in chronic rhinosinusitis is still not entirely clear. There is some evidence that IL-19 downregulates eotaxin production in patients with allergic rhinitis, by decreasing IL-4 in human nasal fibroblasts. On the other hand, IL-19 has been shown to be a pro-Th1 cytokine by upregulating IL-4 and downregulating interferon-c [83, 84]. Others have proposed that IP-10 and IL-8 can be induced by *S. aureus* enterotoxin B, leading to an increased inflammatory response, and that LPS stimulation increased expression of IL-19 in monocyte cultures via TLR4 and MyD88 signaling [85–88]. Despite its classification as an IL-10 family cytokine, IL-19 does seem to possess proinflammatory activity and is produced by synovial cells, whereupon it can induce IL-6 production and decrease synovial cell apoptosis, resulting in joint inflammation in rheumatoid arthritis [89]. IL-19 expression is increased in patients with CRSwNP, along with IL-5, IL-13, and GATA-3. IL-19 was also able to stimulate nasal epithelial cell proliferation, which was blocked by a tyrosine kinase inhibitor, herbimycin. Finally, it was also demonstrated in the same study that IL-19 highly co-expressed with Ki67 in patients with CRSwNP [22]. Ki67 is a nuclear protein encoded by the *MKI67* gene that is necessary for cell proliferation [90].

IL-32

IL-32 is a proinflammatory cytokine that exists in multiple isoforms. Other functions include regulation of cytokine production and apoptosis. It also has a role in inflammasome-related stimulation of IL-1β production via caspase-1. Like IL-18, IL-32 has been implicated in autoimmune and allergic diseases. In a study of nasal epithelial cells from patients with CRS and control subjects, the level of IL-32 was found to be high in those patients with CRS without nasal polyps compared with those who had nasal polyps. IL-32 is induced by TNF, IFN-γ, and double-stranded RNA. IL-32 was found to be present in the epithelial cells, as well as inflammatory cells in the lamina propria. The precise role of IL-32 in the pathogenesis of chronic rhinosinusitis is not clear, nor is its clinical significance in the disease [91].

Chemokines

CCL18

CCL 18 is also known as pulmonary and activation-regulated cytokine (PARC), as well as AMAC-1, DC-CK1, and MIP-4. CCL18 is a T cell chemokine, attracting Th2 cells, skin-homing memory T cells, and naïve T cells. It is also chemotactic to immature dendritic cells. CCL18 is increased in patients with autoimmune and allergic diseases, and it is expressed in thymus, lymph nodes, and the lung. In one study, CCL18 was found to be increased in patients with chronic rhinosinusitis with nasal polyps. CCL18 in the nasal polyps of these patients was found to co-localize in CD68+/CD163+/macrophage mannose receptor-positive M2 macrophages as well as tryptase-positive mast cells. M2 macrophages are thought to be the primary producer of CCL18 in patients with CRSwNP as CCL18 levels are associated with markers of M2 macrophages [24].

CCL23

In humans, CCL23, also known as myeloid progenitor inhibitory factor 1, chemokine b8, or macrophage inflammatory protein 3, has been found to be a chemoattractant for lymphocytes, monocytes, and dendritic cells. It exerts its activity by interacting with its ligand CCR1. These activities include endothelial cell migration, angiogenesis, and tube formation. CCL23 also suppresses monocyte and granulocyte precursors and has been implicated in allergic diseases such as eczema and autoimmune diseases such as rheumatoid arthritis and systemic sclerosis. The CCL23 level in nasal tissue was also found to be elevated in four patients with eosinophilic chronic rhinosinusitis with nasal polyps [92]. The numbers are small in this study, so it remains to be seen whether this finding is clinically significant, but it suggests that CCL23 may play a role in CRSwNP by recruiting CCR1+ inflammatory cells such as monocytes and macrophages.

Secretoglobins in Rhinosinusitis

There are nine secretoglobins, small dimeric proteins whose function is not clearly understood. Some have been associated in certain cancers, while others have been implicated in the regulation of immune function [93, 94]. Two of these small molecules, the Clara cell 10-kd protein (CC10) and the uteroglobin-related protein 1 (UGRP1), appear to have anti-inflammatory effects on airway inflammation in a mouse model. These two proteins share significant homology and are primarily expressed by secretory epithelium, and expression of CC10 has been associated with asthma and chronic rhinosinusitis [95–98].

The expression of secretoglobins appears to be in part regulated by various cytokines. In a study of nasal mucosa tissue from patients with chronic rhinosinusitis, the mRNA expression of secretoglobins other than CC10 in nasal mucosa could be detected. It was found that the expression of UGRP1 was enhanced by interferon-γ, but inhibited by IL-1β, TNF-α, IL-4, and IL-13 [99]. In both CRSwNP and CRSsNP, UGRP1 expression was decreased compared to "normal" controls, namely, patients without any sinus disease who underwent septoplasty or turbinectomy for obstruction only. This suggests that UGRP1 has an anti-inflammatory effect, as reduction of mRNA expression of UGRP1 seems to correlate inversely with a number of infiltrating cells, symptoms scores, and other measures of disease. The fact that Th2 cytokines inhibit UGRP1 expression is consistent with the significant role of Th2 cytokines in CRSwNP, though not consistent with CRSsNP, which is thought by some investigators to be more of a Th1-mediated disease process.

Conclusion

Despite the many recent discoveries described above, the causative agent or condition that ultimately drives the epithelium to promote leakage and/or proinflammatory cytokine production remains largely unknown. Just as CRS appears to be a heterogeneous group of airway diseases, we have seen that the sources of CRS also demonstrate similar diversity in potential causes. Genetic sources and epigenetic changes defining epithelial integrity are clearly involved and can be found enhancing inflammation. Whatever the trigger, there is ample evidence that a diminished innate immune response and diminished barrier function can have severe consequences. Observations of diminished barrier function, proinflammatory cytokine production, and reduced levels of antimicrobial peptides in CRS might be compatible with the leading theories of the pathogenesis of CRS discussed above [100].

If the immune barrier function is indeed disrupted, then sensitization to ambient fungi such as *Alternaria* or *Aspergillus* species, another subgroup of CRSwNP, would be more likely to occur as a result of increased penetration of fungal allergens. Enhanced penetration would be particularly damaging if genetic-based defects lead to inhibition of fungal or host proteases that activate epithelial cells and increase their permeability. Likewise, reduced levels of key antimicrobial peptides, such as S100A7 and calprotectin mentioned above, could increase the likelihood of bacterial colonization in the upper airways, even if this does not lead to acute sinus disease. We have seen that poor expression of both S100A7 and calprotectin might lead to inadequate innate resistance to diverse strains of extracellular and intracellular bacteria. Increased colonization of the upper airways with bacteria and fungi or increased epithelial permeability and/or permeability by bacteria such as *Staphylococcus* or fungi like *Aspergillus* might explain the exaggerated immune response that is observed in patients with CRS. In future studies, it will be important to determine whether defects in barrier function serve as a primary promoter in the pathogenesis of CRS and/or whether barrier dysfunction renders the host susceptible to colonization by pathogens, setting the stage for a heightened inflammatory response, tissue damage, and, in some circumstances, polyp formation.

The enhanced inflammatory response generated from cytokine release from airway epithelial cells such as TSLP (and Th1/Th2 activation) or lack of TGF-β1 regulatory function can be further amplified though increased access of antigenic material to the submucosal tissue. We now know that multiple cytokines and chemokines influence the cellular infiltrate and local immunologic status of the nose and paranasal sinuses. We also know that the innate and adaptive immune system regulate each other. The relationship between the components of and within these two systems are numerous and complex. A better understanding of these relationships will ultimately improve our treatment of the various forms of rhinosinusitis.

References

1. Kern RC, Conley DB, Walsh W, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. Am J Rhinol. 2008;22:549–59.
2. Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy. 2006;61:1280–9.
3. Cao PP, Li HB, Wang BF, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. J Allergy Clin Immunol. 2009;124:478–84, 84.e1–2.
4. Payne SC, Borish L, Steinke JW. Genetics and phenotyping in chronic sinusitis. J Allergy Clin Immunol. 2011;128:710–20, quiz 21–2.
5. Payne SC, Early SB, Huyett P, Han JK, Borish L, Steinke JW. Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. Laryngoscope. 2011;121:2262–7.
6. Chiba H, Osanai M, Murata M, Kojima T, Sawada N. Transmembrane proteins of tight junctions. Biochim Biophys Acta. 2008;1778:588–600.
7. Soyka MB, Wawrzyniak P, Eiwegger T, et al. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-gamma and IL-4. J Allergy Clin Immunol. 2012;130:1087–96 e10.
8. Schulzke JD, Ploeger S, Amasheh M, et al. Epithelial tight junctions in intestinal inflammation. Ann N Y Acad Sci. 2009;1165:294–300.
9. De Benedetto A, Rafaels NM, McGirt LY, et al. Tight junction defects in patients with atopic dermatitis. J Allergy Clin Immunol. 2011;127:773–86 e1–7.
10. Holgate ST. Epithelium dysfunction in asthma. J Allergy Clin Immunol. 2007;120:1233–44, quiz 45–6.
11. Xiao C, Puddicombe SM, Field S, et al. Defective epithelial barrier function in asthma. J Allergy Clin Immunol. 2011;128:549–56 e1–12.
12. Weidinger S, O'Sullivan M, Illig T, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. J Allergy Clin Immunol. 2008;121:1203–9 e1.
13. Sajjan U, Wang Q, Zhao Y, Gruenert DC, Hershenson MB. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. Am J Respir Crit Care Med. 2008;178:1271–81.
14. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124:37–42.
15. Jang YJ, Kim HG, Koo TW, Chung PS. Localization of ZO-1 and E-cadherin in the nasal polyp epithelium. Eur Arch Otorhinolaryngol. 2002;259:465–9.
16. Zuckerman JD, Lee WY, DelGaudio JM, et al. Pathophysiology of nasal polyposis: the role of desmosomal junctions. Am J Rhinol. 2008;22:589–97.
17. Bernstein JM, Gorfien J, Noble B, Yankaskas JR. Nasal polyposis: immunohistochemistry and bioelectrical findings (a hypothesis for the development of nasal polyps). J Allergy Clin Immunol. 1997;99:165–75.
18. Dejima K, Randell SH, Stutts MJ, Senior BA, Boucher RC. Potential role of abnormal ion transport in the pathogenesis of chronic sinusitis. Arch Otolaryngol Head Neck Surg. 2006;132:1352–62.
19. Yasuda M, Niisato N, Miyazaki H, et al. Epithelial ion transport of human nasal polyp and paranasal sinus mucosa. Am J Respir Cell Mol Biol. 2007;36:466–72.
20. Sejima T, Holtappels G, Kikuchi H, Imayoshi S, Ichimura K, Bachert C. Cytokine profiles in Japanese patients with chronic rhinosinusitis. Allergol Int. 2012;61:115–22.
21. Van Bruaene N, Perez-Novo CA, Basinski TM, et al. T-cell regulation in chronic paranasal sinus disease. J Allergy Clin Immunol. 2008;121:1435–41, 41.e1–3.

22. Pace E, Scafidi V, Di Bona D, et al. Increased expression of IL-19 in the epithelium of patients with chronic rhinosinusitis and nasal polyps. Allergy. 2012;67:878–86.
23. Soyka MB, Treis A, Eiwegger T, et al. Regulation and expression of IL-32 in chronic rhinosinusitis. Allergy. 2012;67:790–8.
24. Peterson S, Poposki JA, Nagarkar DR, et al. Increased expression of CC chemokine ligand 18 in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2012;129:119–27 e1–9.
25. Zhang XH, Zhang YN, Li HB, et al. Overexpression of miR-125b, a novel regulator of innate immunity, in eosinophilic chronic rhinosinusitis with nasal polyps. Am J Respir Crit Care Med. 2012;185:140–51.
26. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. J Allergy Clin Immunol. 2011;128:728–32.
27. Mfuna-Endam L, Zhang Y, Desrosiers MY. Genetics of rhinosinusitis. Curr Allergy Asthma Rep. 2011;11:236–46.
28. Tieu DD, Peters AT, Carter RG, et al. Evidence for diminished levels of epithelial psoriasin and calprotectin in chronic rhinosinusitis. J Allergy Clin Immunol. 2010;125:667–75.
29. Jinquan T, Vorum H, Larsen CG, et al. Psoriasin: a novel chemotactic protein. J Invest Dermatol. 1996;107:5–10.
30. Glaser R, Harder J, Lange H, Bartels J, Christophers E, Schroder JM. Antimicrobial psoriasin (S100A7) protects human skin from Escherichia coli infection. Nat Immunol. 2005;6:57–64.
31. Madsen P, Rasmussen HH, Leffers H, et al. Molecular cloning, occurrence, and expression of a novel partially secreted protein "psoriasin" that is highly up-regulated in psoriatic skin. J Invest Dermatol. 1991;97:701–12.
32. Walley AJ, Chavanas S, Moffatt MF, et al. Gene polymorphism in Netherton and common atopic disease. Nat Genet. 2001;29:175–8.
33. Richer SL, Truong-Tran AQ, Conley DB, et al. Epithelial genes in chronic rhinosinusitis with and without nasal polyps. Am J Rhinol. 2008;22:228–34.
34. Fruth K, Goebel G, Koutsimpelas D, et al. Low SPINK5 expression in chronic rhinosinusitis. Laryngoscope. 2012;122:1198–204.
35. Briot A, Deraison C, Lacroix M, et al. Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. J Exp Med. 2009;206:1135–47.
36. Kouzaki H, O'Grady SM, Lawrence CB, Kita H. Proteases induce production of thymic stromal lymphopoietin by airway epithelial cells through protease-activated receptor-2. J Immunol. 2009;183:1427–34.
37. Ziegler SF. Thymic stromal lymphopoietin and allergic disease. J Allergy Clin Immunol. 2012;130:845–52.
38. Liu T, Li TL, Zhao F, et al. Role of thymic stromal lymphopoietin in the pathogenesis of nasal polyposis. Am J Med Sci. 2011;341:40–7.
39. Boita M, Garzaro M, Raimondo L, et al. The expression of TSLP receptor in chronic rhinosinusitis with and without nasal polyps. Int J Immunopathol Pharmacol. 2011;24:761–8.
40. Kang JS, Liu C, Derynck R. New regulatory mechanisms of TGF-beta receptor function. Trends Cell Biol. 2009;19:385–94.
41. Moustakas A, Pardali K, Gaal A, Heldin CH. Mechanisms of TGF-beta signaling in regulation of cell growth and differentiation. Immunol Lett. 2002;82:85–91.
42. Halwani R, Al-Muhsen S, Al-Jahdali H, Hamid Q. Role of transforming growth factor-beta in airway remodeling in asthma. Am J Respir Cell Mol Biol. 2011;44:127–33.
43. Kim YM, Munoz A, Hwang PH, Nadeau KC. Migration of regulatory T cells toward airway epithelial cells is impaired in chronic rhinosinusitis with nasal polyposis. Clin Immunol. 2010;137:111–21.
44. Nonaka M, Ogihara N, Fukumoto A, Sakanushi A, Pawankar R, Yagi T. Toll-like receptor 2, 3, 4, 5 ligands and interleukin-4 synergistically induce TARC production in nasal polyp fibroblasts. Auris Nasus Larynx. 2008;35:515–20.
45. Seppanen M, Suvilehto J, Lokki ML, et al. Immunoglobulins and complement factor C4 in adult rhinosinusitis. Clin Exp Immunol. 2006;145:219–27.
46. Jonsson G, Truedsson L, Sturfelt G, Oxelius VA, Braconier JH, Sjoholm AG. Hereditary C2 deficiency in Sweden: frequent occurrence of invasive infection, atherosclerosis, and rheumatic disease. Medicine (Baltimore). 2005;84:23–34.
47. Gaunsbaek MQ, Lange B, Kjeldsen AD, et al. Complement defects in patients with chronic rhinosinusitis. PLoS One. 2012;7:e47383.
48. Cui YH, Zhang F, Xiong ZG, You XJ, Gao QX, Liu Z. Increased serum complement component 3 and mannose-binding lectin levels in adult Chinese patients with chronic rhinosinusitis. Rhinology. 2009;47:187–91.
49. Schlosser RJ, Mulligan RM, Casey SE, Varela JC, Harvey RJ, Atkinson C. Alterations in gene expression of complement components in chronic rhinosinusitis. Am J Rhinol Allergy. 2010;24:21–5.
50. Patou J, Gevaert P, Van Zele T, Holtappels G, van Cauwenberge P, Bachert C. Staphylococcus aureus enterotoxin B, protein A, and lipoteichoic acid stimulations in nasal polyps. J Allergy Clin Immunol. 2008;121:110–5.
51. Cardona ID, Goleva E, Ou LS, Leung DY. Staphylococcal enterotoxin B inhibits regulatory T cells by inducing glucocorticoid-induced TNF receptor-related protein ligand on monocytes. J Allergy Clin Immunol. 2006;117:688–95.
52. Van Zele T, Gevaert P, Watelet JB, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. J Allergy Clin Immunol. 2004;114:981–3.
53. Tripathi A, Kern R, Conley DB, et al. Staphylococcal exotoxins and nasal polyposis: analysis of systemic and local responses. Am J Rhinol. 2005;19:327–33.
54. Jabara HH, Geha RS. The superantigen toxic shock syndrome toxin-1 induces CD40 ligand expression and modulates IgE isotype switching. Int Immunol. 1996;8:1503–10.
55. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2007;2007:1–136.
56. Fokkens W, Lund V, Mullol J. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. Rhinology. 2007;45:97–101.
57. Gevaert P, Nouri-Aria KT, Wu H, et al. Local receptor revision and class switching to IgE in chronic rhinosinusitis with nasal polyps. Allergy. 2013;68:55–63.
58. Sultan B, May LA, Lane AP. The role of TNF-alpha in inflammatory olfactory loss. Laryngoscope. 2011;121:2481–6.
59. Turner JH, Liang KL, May L, Lane AP. Tumor necrosis factor alpha inhibits olfactory regeneration in a transgenic model of chronic rhinosinusitis-associated olfactory loss. Am J Rhinol Allergy. 2010;24:336–40.
60. Karosi T, Csomor P, Sziklai I. Tumor necrosis factor-alpha receptor expression correlates with changes and biofilm presence in chronic rhinosinusitis with nasal polyposis. Laryngoscope 2012;122(3):504–10.

61. Mfuna Endam L, Cormier C, Bosse Y, Filali-Mouhim A, Desrosiers M. Association of IL1A, IL1B, and TNF gene polymorphisms with chronic rhinosinusitis with and without nasal polyposis: a replication study. Arch Otolaryngol Head Neck Surg. 2010;136:187–92.
62. Yea SS, Yang YI, Park SK, et al. Interleukin-4C-590 T polymorphism is associated with protection against nasal polyps in a Korean population. Am J Rhinol. 2006;20:550–3.
63. Silliman CC, Kelher MR, Gamboni-Robertson F, et al. Tumor necrosis factor-alpha causes release of cytosolic interleukin-18 from human neutrophils. Am J Physiol Cell Physiol. 2010;298:C714–24.
64. Foster N, Andreadou K, Jamieson L, Preshaw PM, Taylor JJ. VIP inhibits P. gingivalis LPS-induced IL-18 and IL-18BPa in monocytes. J Dent Res. 2007;86:883–7.
65. Rifkin DB. Latent transforming growth factor-beta (TGF-beta) binding proteins: orchestrators of TGF-beta availability. J Biol Chem. 2005;280:7409–12.
66. Hirschberg A, Jokuti A, Darvas Z, Almay K, Repassy G, Falus A. The pathogenesis of nasal polyposis by immunoglobulin E and interleukin-5 is completed by transforming growth factor-beta1. Laryngoscope. 2003;113:120–4.
67. Watelet JB, Claeys C, Perez-Novo C, Gevaert P, Van Cauwenberge P, Bachert C. Transforming growth factor beta1 in nasal remodeling: differences between chronic rhinosinusitis and nasal polyposis. Am J Rhinol. 2004;18:267–72.
68. Van Bruaene N, Derycke L, Perez-Novo CA, et al. TGF-beta signaling and collagen deposition in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124:253–9, 9.e1–2.
69. Lee YM, Kim SS, Kim HA, et al. Eosinophil inflammation of nasal polyp tissue: relationships with matrix metalloproteinases, tissue inhibitor of metalloproteinase-1, and transforming growth factor-beta1. J Korean Med Sci. 2003;18:97–102.
70. Gomez-Duran A, Ballestar E, Carvajal-Gonzalez JM, et al. Recruitment of CREB1 and histone deacetylase 2 (HDAC2) to the mouse Ltbp-1 promoter regulates its constitutive expression in a dioxin receptor-dependent manner. J Mol Biol. 2008;380:1–16.
71. Hsu YC, Kuo WR, Chen YY, Tai CF, Tsai CJ, Wang LF. Increased expression of hypoxia-inducible factor 1alpha in the nasal polyps. Am J Otolaryngol. 2007;28:379–83.
72. Kou W, Hu GH, Yao HB, et al. Regulation of transforming growth factor-beta1 activation and expression in the tissue remodeling involved in chronic rhinosinusitis. ORL J Otorhinolaryngol Relat Spec. 2012;74:172–8.
73. Peters AT, Kato A, Zhang N, et al. Evidence for altered activity of the IL-6 pathway in chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2010;125:397–403 e10.
74. Wang H, Bai J, Ding M, et al. Interleukin-17A contributes to the expression of serum amyloid A in chronic rhinosinusitis with nasal polyps. Eur Arch Otorhinolaryngol. 2013;270:1867–72.
75. Badolato R, Wang JM, Murphy WJ, et al. Serum amyloid A is a chemoattractant: induction of migration, adhesion, and tissue infiltration of monocytes and polymorphonuclear leukocytes. J Exp Med. 1994;180:203–9.
76. Badolato R, Johnston JA, Wang JM, et al. Serum amyloid A induces calcium mobilization and chemotaxis of human monocytes by activating a pertussis toxin-sensitive signaling pathway. J Immunol. 1995;155:4004–10.
77. Xu L, Badolato R, Murphy WJ, et al. A novel biologic function of serum amyloid A. Induction of T lymphocyte migration and adhesion. J Immunol. 1995;155:1184–90.
78. Okano M, Fujiwara T, Makihara S, et al. Characterization of IL-18 expression and release in the pathogenesis of chronic rhinosinusitis. Int Arch Allergy Immunol. 2012;160:275–86.
79. Birrell MA, Eltom S. The role of the NLRP3 inflammasome in the pathogenesis of airway disease. Pharmacol Ther. 2011;130:364–70.
80. Smith PM, Jacque B, Conner JR, Poltorak A, Stadecker MJ. IRAK-2 regulates IL-1-mediated pathogenic Th17 cell development in helminthic infection. PLoS Pathog. 2011;7:e1002272.
81. Smith DE. The biological paths of IL-1 family members IL-18 and IL-33. J Leukoc Biol. 2011;89:383–92.
82. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67:91–8.
83. Liao SC, Cheng YC, Wang YC, et al. IL-19 induced Th2 cytokines and was up-regulated in asthma patients. J Immunol. 2004;173:6712–8.
84. Gallagher G, Eskdale J, Jordan W, et al. Human interleukin-19 and its receptor: a potential role in the induction of Th2 responses. Int Immunopharmacol. 2004;4:615–26.
85. Conti P, Kempuraj D, Frydas S, et al. IL-10 subfamily members: IL-19, IL-20, IL-22, IL-24 and IL-26. Immunol Lett. 2003;88:171–4.
86. Kempuraj D, Frydas S, Kandere K, et al. Interleukin-19 (IL-19) network revisited. Int J Immunopathol Pharmacol. 2003;16:95–7.
87. Azuma YT, Matsuo Y, Nakajima H, et al. Interleukin-19 is a negative regulator of innate immunity and critical for colonic protection. J Pharmacol Sci. 2011;115:105–11.
88. Huvenne W, Callebaut I, Reekmans K, et al. Staphylococcus aureus enterotoxin B augments granulocyte migration and survival via airway epithelial cell activation. Allergy. 2010;65:1013–20.
89. Sakurai N, Kuroiwa T, Ikeuchi H, et al. Expression of IL-19 and its receptors in RA: potential role for synovial hyperplasia formation. Rheumatology (Oxford). 2008;47:815–20.
90. Bullwinkel J, Baron-Luhr B, Ludemann A, Wohlenberg C, Gerdes J, Scholzen T. Ki-67 protein is associated with ribosomal RNA transcription in quiescent and proliferating cells. J Cell Physiol. 2006;206:624–35.
91. Keswani A, Chustz RT, Suh L, et al. Differential expression of interleukin-32 in chronic rhinosinusitis with and without nasal polyps. Allergy. 2012;67:25–32.
92. Poposki JA, Uzzaman A, Nagarkar DR, et al. Increased expression of the chemokine CCL23 in eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2011;128:73–81 e4.
93. Zafrakas M, Petschke B, Donner A, et al. Expression analysis of mammaglobin A (SCGB2A2) and lipophilin B (SCGB1D2) in more than 300 human tumors and matching normal tissues reveals their co-expression in gynecologic malignancies. BMC Cancer. 2006;6:88.
94. Sjodin A, Guo D, Sorhaug S, Bjermer L, Henriksson R, Hedman H. Dysregulated secretoglobin expression in human lung cancers. Lung Cancer. 2003;41:49–56.
95. Liu Z, Kim J, Sypek JP, et al. Gene expression profiles in human nasal polyp tissues studied by means of DNA microarray. J Allergy Clin Immunol. 2004;114:783–90.

96. Liu Z, Lu X, Zhang XH, et al. Clara cell 10-kDa protein expression in chronic rhinosinusitis and its cytokine-driven regulation in sinonasal mucosa. Allergy. 2009;64:149–57.
97. Shijubo N, Itoh Y, Yamaguchi T, et al. Serum levels of Clara cell 10-kDa protein are decreased in patients with asthma. Lung. 1999;177:45–52.
98. Wang H, Long XB, Cao PP, et al. Clara cell 10-kD protein suppresses chitinase 3-like 1 expression associated with eosinophilic chronic rhinosinusitis. Am J Respir Crit Care Med. 2010;181:908–16.
99. Lu X, Wang N, Long XB, You XJ, Cui YH, Liu Z. The cytokine-driven regulation of secretoglobins in normal human upper airway and their expression, particularly that of uteroglobin-related protein 1, in chronic rhinosinusitis. Respir Res. 2011;12:28.
100. Schleimer RP, Kato A, Peters A, et al. Epithelium, inflammation, and immunity in the upper airways of humans: studies in chronic rhinosinusitis. Proc Am Thorac Soc. 2009;6:288–94.
101. Yang YC, Zhang N, Van Crombruggen K, Hu GH, Hong SL, Bachert C. Transforming growth factor-beta 1 in inflammatory airway disease: a key for understanding inflammation and remodeling. Allergy. 2012;67:1193–202.

Chapter 4
Structural Anomalies of the Nose and Sinuses in Patients with Rhinosinusitis

Vijay R. Ramakrishnan, Todd T. Kingdom, and Richard R. Orlandi

Introduction

Acute and chronic rhinosinusitis are different disease processes thought to result from different mechanisms [1]. Acute rhinosinusitis (ARS) is considered primarily an infectious disease, where initial mucosal injury occurs from any number of processes, allowing for subsequent development of an acute viral or bacterial infection. Recurrent episodes of ARS (RARS) and chronic rhinosinusitis (CRS) likely have more etiologic factors that result in more frequent bacterial infections and a chronic inflammatory state.

The anatomy and embryology of the nose and sinuses are fairly consistent, although subtle variations commonly occur. Many of these variations have been considered contributing factors to recurrence and prolonged duration of infections. Alternatively, such anatomic variations can possibly contribute to symptoms related to ARS or CRS, even when active infection is not present. If patient anatomy were the predominant or sole factor in rhinosinusitis, then surgery would be curative. Unfortunately, surgery is rarely *curative*, but in many patients it can be quite helpful for management of symptoms.

When considering anatomic structures that can predispose to rhinosinusitis, the anatomy and physiology of the nasal cavity and paranasal sinuses must be remembered. Ciliated respiratory epithelium lines the nasal cavity and sinuses, and functional mucosa actively directs mucus from the sinuses through narrow drainage pathways into the nasal cavity toward the nasopharynx. Historically, great emphasis has been placed on the osteomeatal complex (OMC) as the site of primary interest for sinonasal pathology causing rhinosinusitis, with anatomic abnormalities in this region as potential contributors to the development of disease. The OMC is a functional unit more than a distinct anatomic structure and is centered on the ethmoid infundibulum, thus affecting the anterior ethmoid and maxillary sinuses and possibly the frontal sinus. Disease at the OMC is perhaps an oversimplified theory of rhinosinusitis pathogenesis, but optimal sinonasal function relies upon patency of these narrow drainage pathways, absence of inflammation, and absence of infection.

In this chapter, we will discuss common anatomic abnormalities that may predispose patients to ARS, RARS, or CRS.

Nasal Septum

Septal deviation has long been thought of as a possible anatomic factor contributing to rhinosinusitis. Septal deviation can lead to alterations in airflow dynamics [2], changes in mucociliary clearance [3], and in severe cases can lead to frank obstruction of the osteomeatal complex (Fig. 4.1). The diagnosis of "deviated septum" actually describes a number of possible configurations that can widely vary in severity. The presence of septal deformity is quite common, with only 21 % of adults having a straight septum [4]. The configuration of a deviated septum may demonstrate a broad deviation, spur, or frank fracture (Figs. 4.2 and 4.3). The location of the deviation and variance from midline may help predict alterations in airflow

V.R. Ramakrishnan, MD • T.T. Kingdom, MD
Department of Otolaryngology-Head and Neck Surgery, University of Colorado, Aurora, CO, USA

R.R. Orlandi, MD (✉)
Department of Otolaryngology-Head and Neck Surgery, University of Utah School of Medicine, 50 North Medical Drive, 3C120, Salt Lake City, UT 84132, USA
e-mail: richard.orlandi@hsc.utah.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_4,

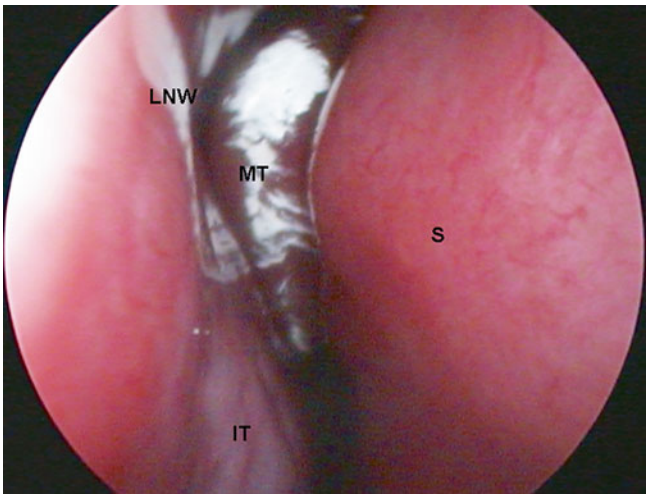


Fig. 4.1 Airflow patterns are illustrated in this endoscopic view of a right nasal cavity immediately after several hours of commercial painting. This shows particulate deposition on the anterior face of the middle turbinate (*MT*) and to a lesser degree on the lateral nasal wall (*LNW*). Septal deviation (*S*) is present and the inferior turbinate (*IT*) is relatively normal in appearance

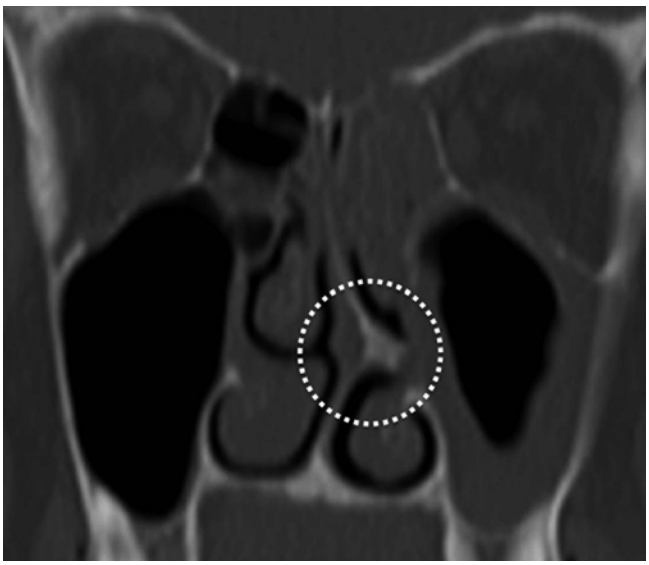


Fig. 4.2 Chronic rhinosinusitis, predominantly on the left side, associated with a deviated septum and prominent septal spur (*dotted circle*)

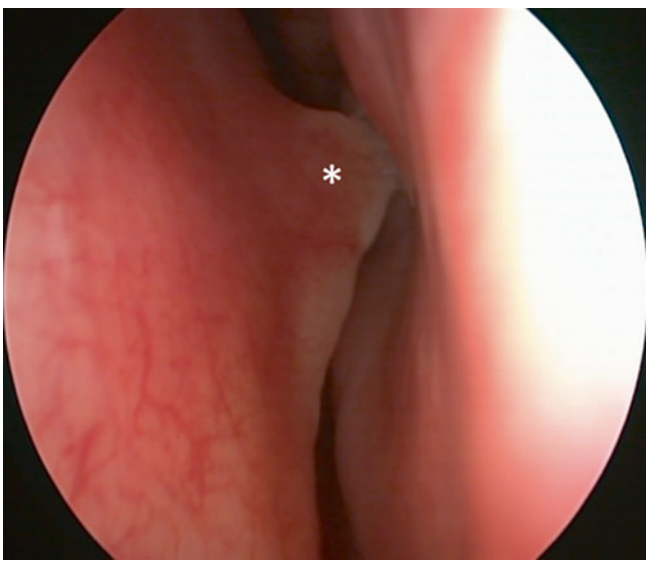


Fig. 4.3 After topical decongestion, the endoscopic view of the left nasal cavity shows a deviated septum with a prominent septal spur (*) impinging upon the inferior turbinate at the attachment of the uncinate process

or potential for narrowing of sinus outflow pathways. Adjacent portions of the septum may deflect to the opposite side, especially in the setting of posttraumatic septal deformity. Not infrequently, the inferior turbinate or middle turbinate is enlarged on the side opposite to the deviation, a finding referred to as compensatory turbinate hypertrophy. This may be a physiologic change resulting from increased airflow through the more open side (Fig. 4.4).

Increasing severity of the septal deformity is statistically more associated with the likelihood of rhinosinusitis, but the degree of correlation is relatively low [5, 6]. Curiously, in these two studies, the prevalence of associated rhinosinusitis was similar on both the concave and convex sides of the deviation. This finding suggests that the mechanism is not simply septal deviation causing OMC obstruction and associated rhinosinusitis. Recently, a systematic review was conducted to determine the effect of septal deviation on the development of rhinosinusitis [7]. Including five studies (1,621 subjects) with similar methods, septal deviation was strongly associated with rhinosinusitis ($p = 0.004$), but the overall effect was relatively low (odds ratio = 1.47).

Septal perforation may be noticed on physical examination, endoscopy, or imaging. Septal perforations are most commonly associated with trauma, prior septal surgery, or intranasal drug use. However, irregular tissue around the perforation or concurrent irregularities of the nasal cavity or sinuses may suggest the possibility of autoimmune vasculitis such as Wegener granulomatosis. In a prospective study of newly diagnosed septal perforations, over half of the patients met criteria for diagnosis of concurrent CRS, but the presence of a septal perforation did not appear to worsen sinonasal symptoms in those patients [8]. If discovered, the clinician should attempt to establish an etiology for the septal perforation, and if none can be identified on history, the need for laboratory workup or biopsy should be entertained (Fig. 4.5).

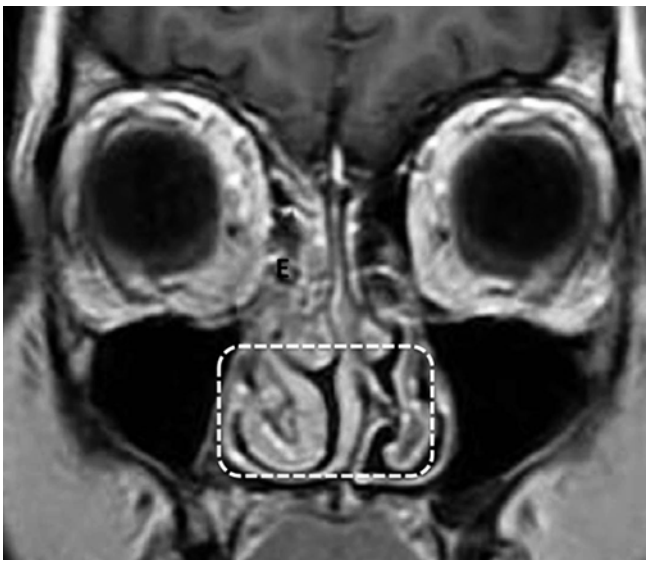


Fig. 4.4 T1-weighted coronal MR showing a left-sided septal deviation and compensatory inferior turbinate hypertrophy on the contralateral side (*dotted box*). There is mild inflammation in the ethmoid sinus (*E*) on the right side as well

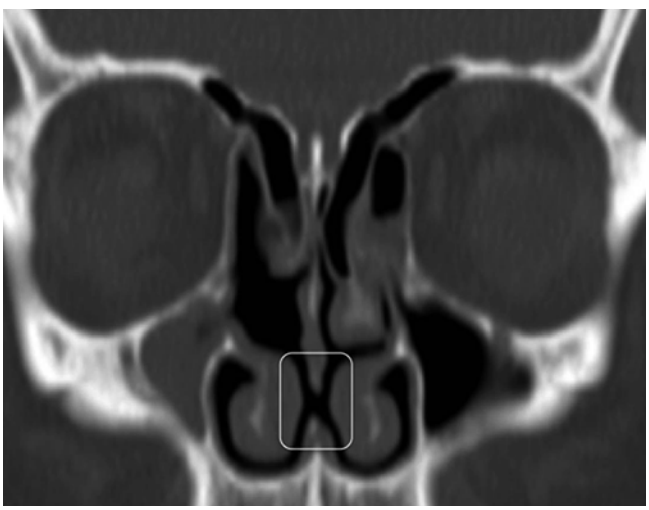


Fig. 4.5 Coronal CT scan of a patient with an asymptomatic perforation related to prior septoplasty and sinus surgery. There is persistent sinus disease unrelated to the septal perforation (*box*)

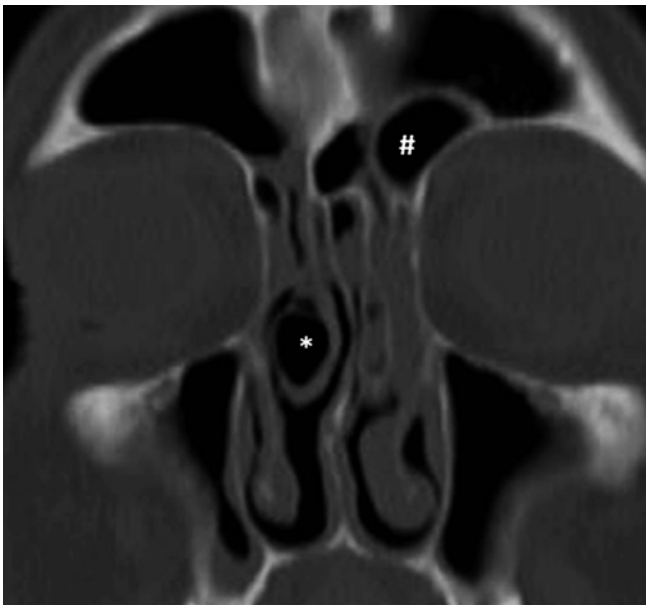


Fig. 4.6 A large concha bullosa (*) is seen on the right in this patient, with associated inflammation in the anterior ethmoid sinus and frontal recess. The left side shows an accessory frontal cell (#) which is associated with mild inflammatory disease

Middle Turbinate Variants

Concha bullosa refers to aeration of the lower bulbous portion of the middle turbinate, although some use it to describe aeration of any portion of the middle turbinate. When the vertical lamella of the middle turbinate is pneumatized, this should be referred to as an interlamellar cell [9]. The interlamellar cell is not thought to have any real effect on sinusitis, although it has not been specifically studied.

As varying definitions have been used for the concha bullosa, its estimated incidence has ranged from 14 to 53 % in the literature depending on the definition used. Concha bullosa has been theorized to develop embryologically as pneumatization of the middle turbinate (third ethmoturbinal) in the presence of a septal deviation, as the two are tightly associated in radiographic study [10]. In this observational study of patients undergoing CT scans of the sinuses, 44 % of 998 patients had at least one concha bullosa, and 21 % had bilateral concha. There was a significant association between dominant concha and contralateral septal deviation ($p < 0.0001$); however, the presence of a dominant concha was not associated with same-sided or general sinus inflammatory disease. In comparing CT scans of 166 CRS patients to 36 healthy controls, Bolger and colleagues noted the presence of a pneumatized middle turbinate to have a greater prevalence in symptomatic patients ($p = 0.042$) [11]. The truth is likely somewhere in between. In total, a concha bullosa deformity may contribute to nasal airway obstruction but appears to have little effect on sinus health. However, large ones may actually contribute to osteomeatal obstruction and associated sinusitis (Fig. 4.6) [12].

The *paradoxical* middle turbinate is one in which the para sagittal anterior third of the turbinate curves in a convex fashion laterally (Fig. 4.7). This configuration can be mildly bothersome surgically, as it narrows the operative corridor, and may potentially be a risk factor for postoperative scarring. It is not known to be associated with sinusitis, although this anatomic finding has not been specifically studied.

Maxillary and Frontal Sinus Drainage Pathways

In theory, narrow drainage pathways could predispose to recurrent or prolonged infections, as mild inflammatory stimuli may result in impaired mucociliary clearance, stagnant secretions, and alterations in the local microenvironment (pH, oxygen tension, etc.) (Fig. 4.8). Functional cilia of the maxillary sinus directly flow toward the natural ostium into the ethmoid infundibulum. This course may be altered by a number of anatomic anomalies such as the infraorbital ethmoid (Haller) cell, or it may be naturally narrow (Fig. 4.9). In a retrospective case-control study comparing control patients to those with RARS, the width of the ethmoid infundibulum was found to be approximately 40 % wider in patients who were free from disease [13].

An additional factor that may compromise normal mucociliary flow from the maxillary sinus is the presence of an accessory ostium. Maxillary sinus fontanelles may be present in the lateral nasal wall. These are defined as areas where no bone

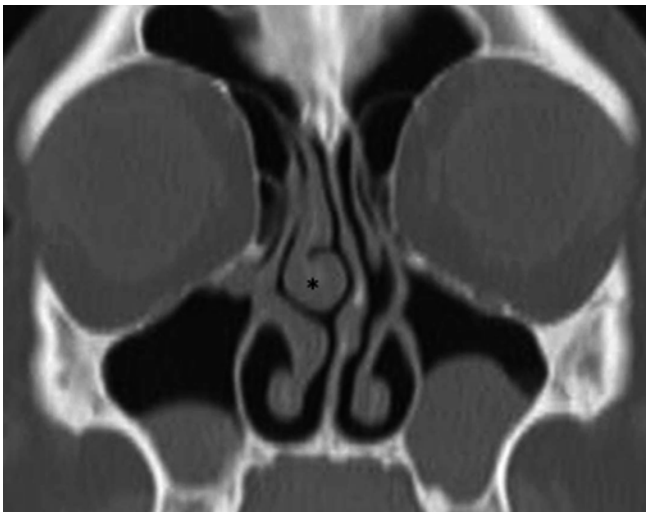


Fig. 4.7 Coronal CT scan showing paradoxic curvature of the right middle turbinate (*). Incidental maxillary sinus mucous retention cysts are seen in the floor of the maxillary sinuses. In general, these are asymptomatic and can be observed

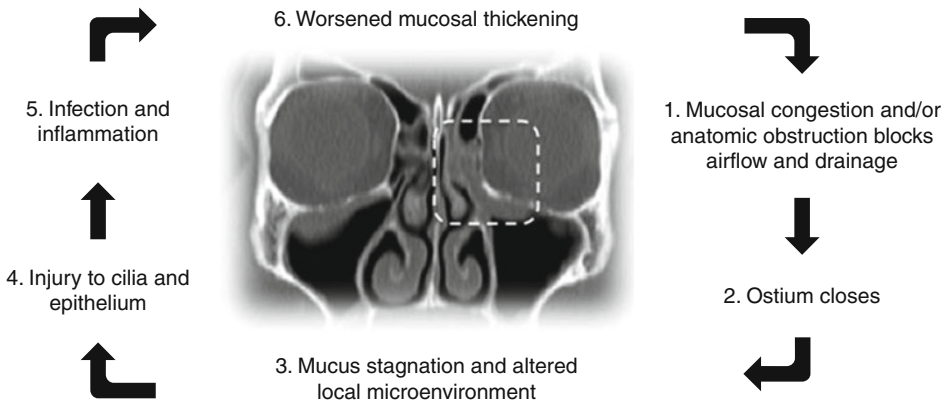


Fig. 4.8 Narrow drainage pathways can predispose to ostial closure, which may lead to a number of downstream effects resulting in acute, recurrent, or chronic rhinosinusitis (Adapted from Gwaltney et al. [34] with permission from *Annals of Otology, Rhinology & Laryngology*)

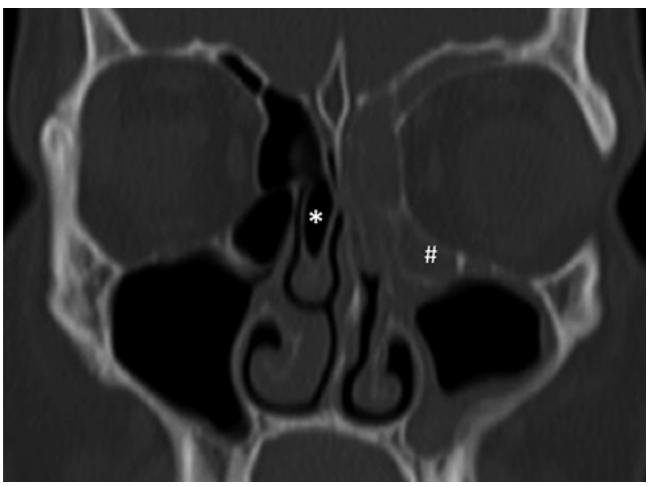


Fig. 4.9 Coronal CT scan demonstrating paranasal sinus inflammation associated with an involved Haller (infraorbital ethmoid) cell (#). There is also a right interlamellar cell (*). This is not truly a concha bullosa, as the inferior aspect of the middle turbinate is not pneumatized

is present, and only a periosteal layer separates the mucosa of the maxillary sinus from the nasal cavity. Accessory ostia can be present at the anterior fontanelle (anterior and inferior to uncinate process) or, more commonly, the posterior fontanelle (superior and posterior to uncinate process) (Figs. 4.10 and 4.11) [9]. Because natural mucociliary flow is directed toward the natural ostium, the presence of these accessory ostia at the fontanelles can result in a recirculation phenomenon or can lead the surgeon to misplace the maxillary antrostomy.

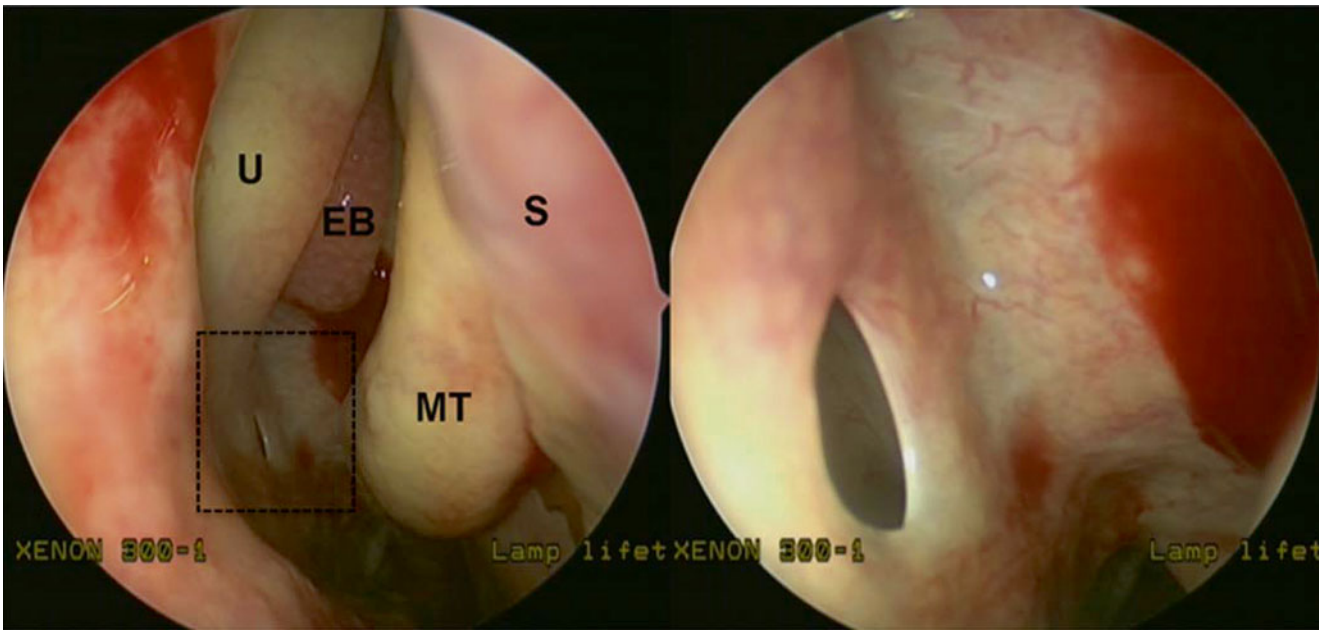


Fig. 4.10 Endoscopic view of right-sided nasal anatomy in an asymptomatic patient. Normal structures are identified (*left*), including the uncinate process (*U*), ethmoid bulla (*EB*), middle turbinate (*MT*), and septum (*S*). There is a posterior fontanelle with an accessory maxillary ostium present, through which the posterior maxillary sinus wall can be seen (*right*, enlargement of box from left photo)

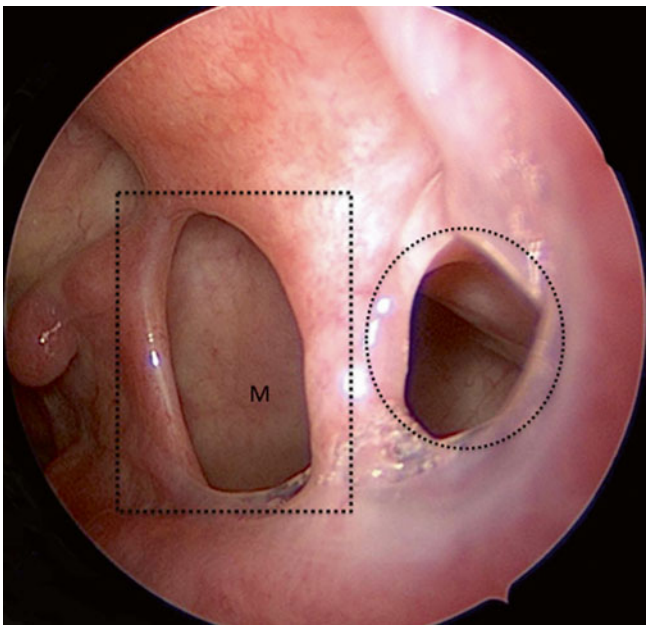


Fig. 4.11 Endoscopic view of the left maxillary sinus (*M*) in a previously operated patient, using an angled telescope. The uncinate process has been removed and residual tissue is noted between the natural ostium of the maxillary sinus (*circle*, anteriorly) and the larger surgical antrostomy (*box*, posteriorly). As mucociliary flow is directed at the natural ostium, it flows back over the surgical opening and can result in a "recirculation phenomenon"

The anatomy of the frontal sinus and its outflow pathway has been extensively studied in anatomic specimens and radiographic review, including three-dimensional modeling. This anatomy can range from fairly simply to quite complex, as the frontal sinus drainage into the ethmoid infundibulum can be narrowed by a number of accessory cells or have a decreased anterior-posterior diameter that results from a prominent nasofrontal beak (Fig. 4.12). Understanding the detailed anatomy of each specific accessory cell (agger nasi, frontal types 1–4, supraorbital, interfrontal sinus, suprabullar, frontobullar) is less imperative in the initial evaluation of sinusitis, but extremely relevant for frontal sinus surgery [14]. The presence and degree of pneumatization of these cells are a potential anatomic risk factor for impaired frontal sinus drainage (Fig. 4.13). In a retrospective study of 179 CT scans obtained for sinus-related complaints, type 1–4 frontal cells were identified in 40 % of sides, and other accessory cells were less frequently identified [15]. Radiographic evidence of frontal sinusitis was seen in 14 % of sides, and 77 % of these had accessory frontal cells. In multivariate analysis, suprabullar and supraorbital ethmoid

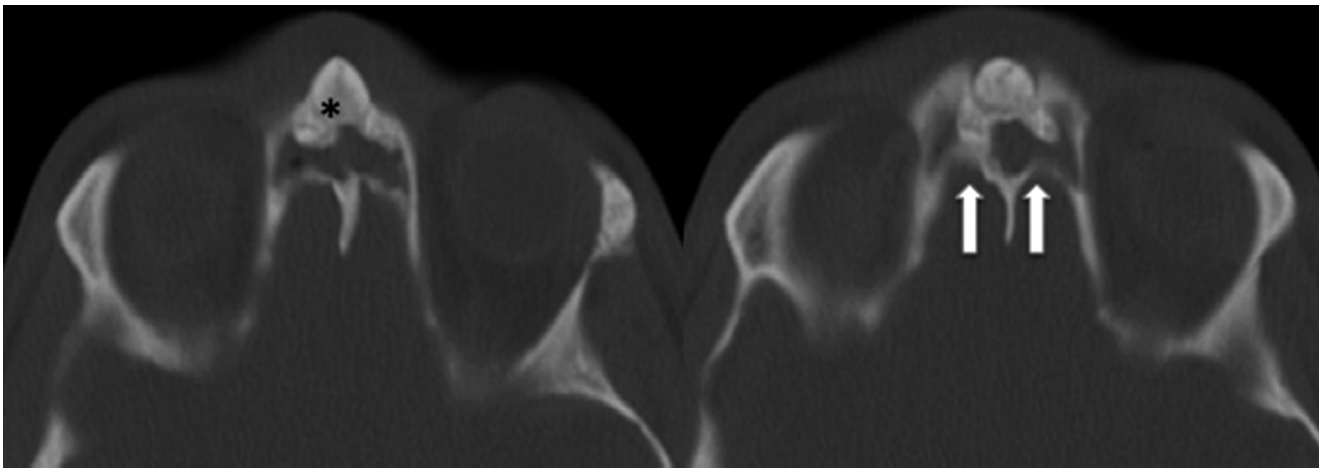


Fig. 4.12 Axial CT scans of a patient with chronic frontal sinusitis. Narrow anterior-posterior diameter is noted and results from a prominent nasofrontal beak (*) and protuberance of the anterior fossa (*arrows*)

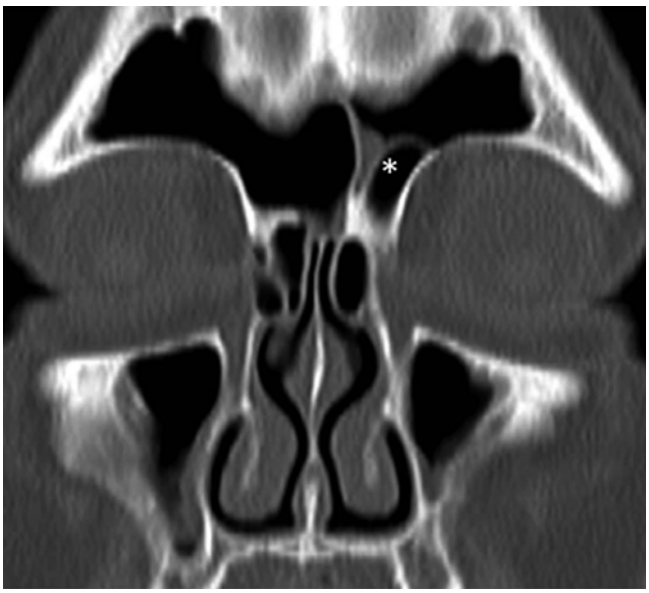


Fig. 4.13 Coronal CT scan of a patient presenting with episodic left frontal barosinusitis. An accessory frontal cell (type 3, *) narrows the frontal outflow tract, and mild mucosal inflammation is noted in this region

cells and the recessus terminalis were findings associated with frontal sinus disease. Additionally, suprabullar and frontobullar cells were found to significantly narrow the anterior-posterior dimension. However, in a second retrospective study of patients undergoing sinus surgery, accessory frontal cells were identified in 33 % of all patients. In this study, their presence was not associated with a higher incidence of radiographic frontal disease, leading the authors to conclude that underlying mucosal inflammation was likely more important than strict bony anatomy [16].

Accessory Ethmoid Cells

The *infraorbital ethmoid cell*, also called the Haller cell after his original description in the eighteenth century [17], is an accessory ethmoid cell that occurs in 10–45 % of patients depending on the exact definition [11, 18]. It originates from the medial floor of the orbit and forms the medial roof of the maxillary sinus. Because of its location at the lateral margin of the ethmoid infundibulum near the natural ostium of the maxillary sinus, its presence can potentially narrow the maxillary outflow tract, contributing to chronic maxillary sinusitis or recurrent acute maxillary sinusitis (Fig. 4.14) [13, 19]. In retrospective reviews of sinus CT scans, a general association of Haller cell presence and maxillary sinusitis is not found, but when closely examined, an association can be identified in medium and large Haller cells when compared with smaller ones [11, 20].

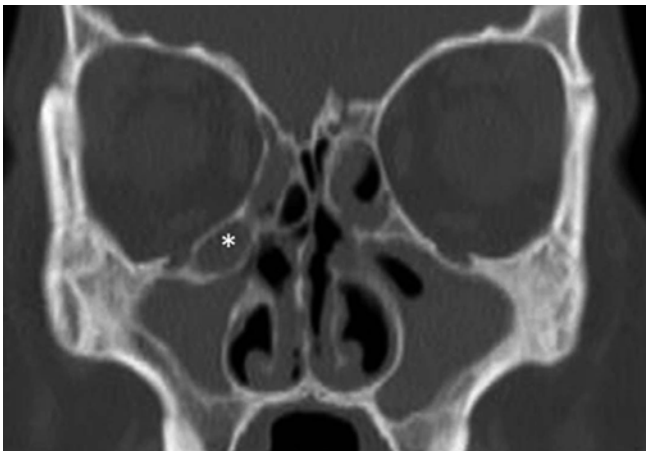


Fig. 4.14 An infraorbital ethmoid cell (Haller cell, *) is seen on the right side in this patient with chronic rhinosinusitis. This cell may be identified on a normal CT scan in patients with RARS

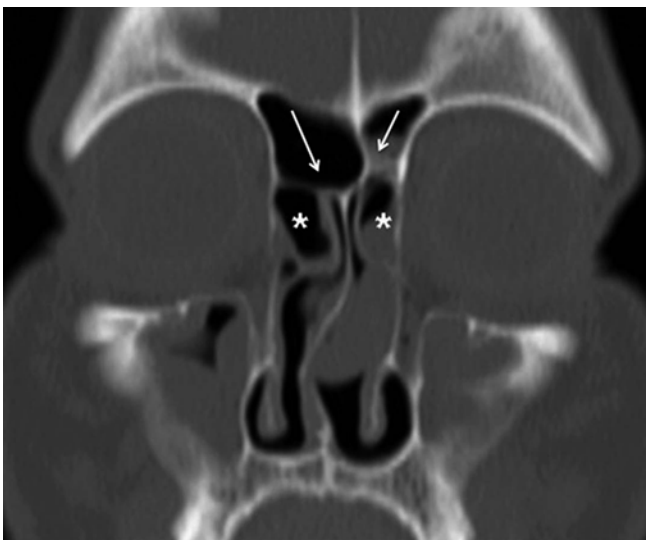


Fig. 4.15 The presence of a large agger nasi cell (*asterisks*) may narrow the frontal outflow pathway (*arrow*)

The *agger nasi* refers to the most superior remnant of the first ethmoturbinal, which forms a mound at the anterior superior insertion of the middle turbinate [9]. It is considered the most consistent ethmoid cell although its size is variable, and on CT scan the agger nasi cell can almost always be identified. A large agger nasi cell can potentially narrow the frontal outflow tract and predispose to recurrent frontal disease similar to other accessory frontal cells (Fig. 4.15). The agger nasi cell is a critical cell to address in frontal sinus surgery, as incomplete removal of this cell is often found in revision frontal surgery procedures [21].

The *sphenoethmoidal cell*, or Onodi cell, is a pneumatized posterior ethmoid cell that extends posteriorly, superiorly, and laterally into the sphenoid sinus (Fig. 4.16). This cell does not particularly affect any physiologic drainage pathway, but is of surgical relevance because of its intimate relationship with the optic nerve and carotid artery. As a result, it is not generally associated with sinusitis but can be associated with major surgical complications when unrecognized [22].

Sinus Pneumatization

The degree of paranasal sinus pneumatization is not known to affect the incidence or degree of sinusitis but may have some level of importance in the management of the disease. Hypoplastic, or poorly pneumatized, sinuses occur infrequently in the normal population and are more often noted in the frontal and sphenoid sinuses rather than the maxillary. Due to the relative infrequency, chronic sinus disease associated with this finding must raise the suspicion of disease processes such as cystic

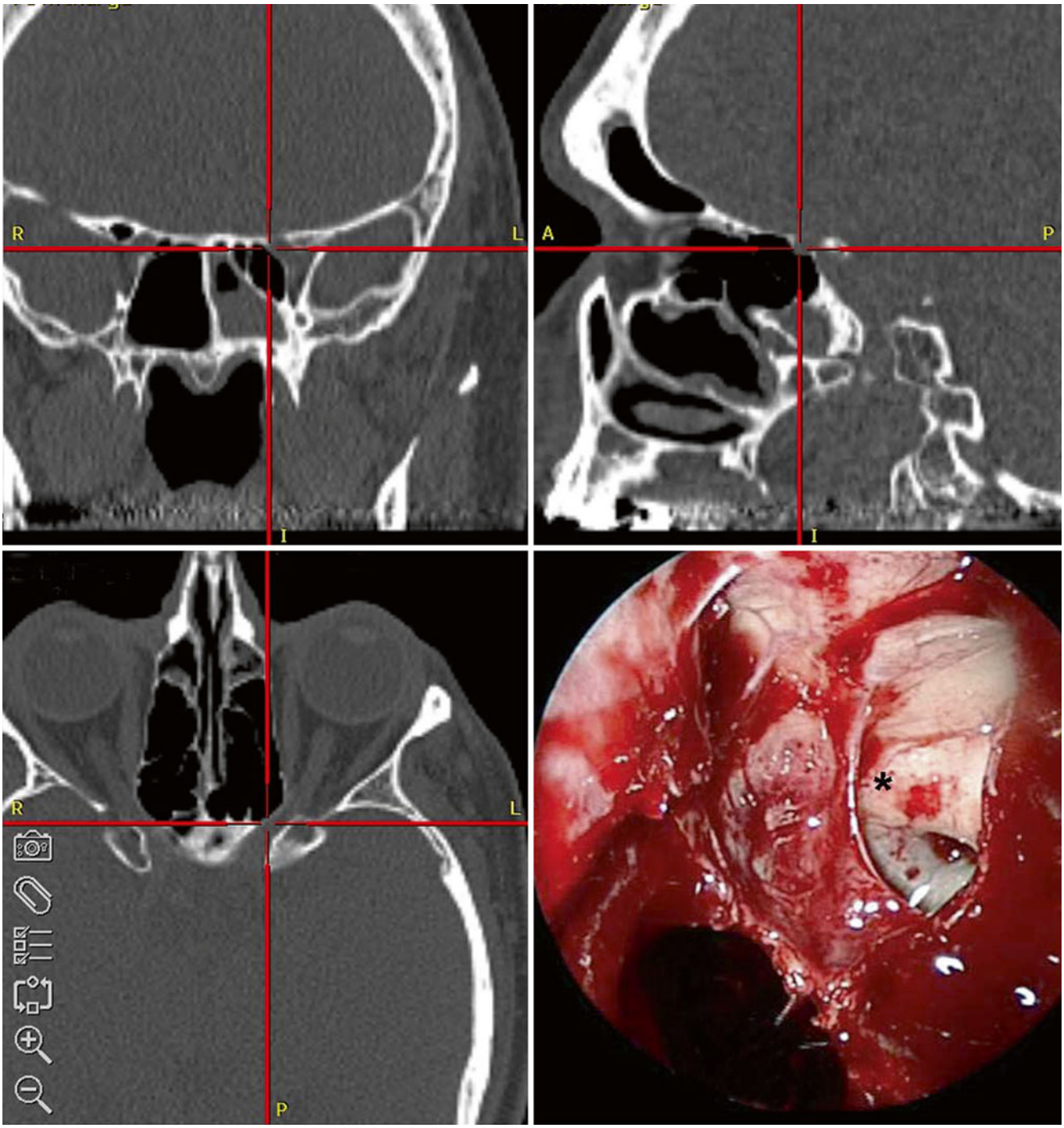


Fig. 4.16 Intraoperative photograph after left Onodi cell has been opened and marsupialized into the sphenoid sinus. The target is at the optic nerve (*)

fibrosis, primary or secondary ciliary dyskinesia, and immunodeficiency syndromes which may have been present during development of the frontal and sphenoid sinuses during adolescence and young adulthood [23]. The majority of frontal and sphenoid sinuses in cystic fibrosis patients are hypoplastic or aplastic, and this finding appears to be common in those patients with more severe genotypes such as delta F508 homozygotes [24, 25]. From a therapeutic standpoint, small or hypoplastic sinuses may be particularly challenging to maintain patency after frontal sinusotomy. This is of particular note in the cystic fibrosis population, where this finding is more frequent and severe chronic inflammatory disease persists after surgical intervention (Fig. 4.17).

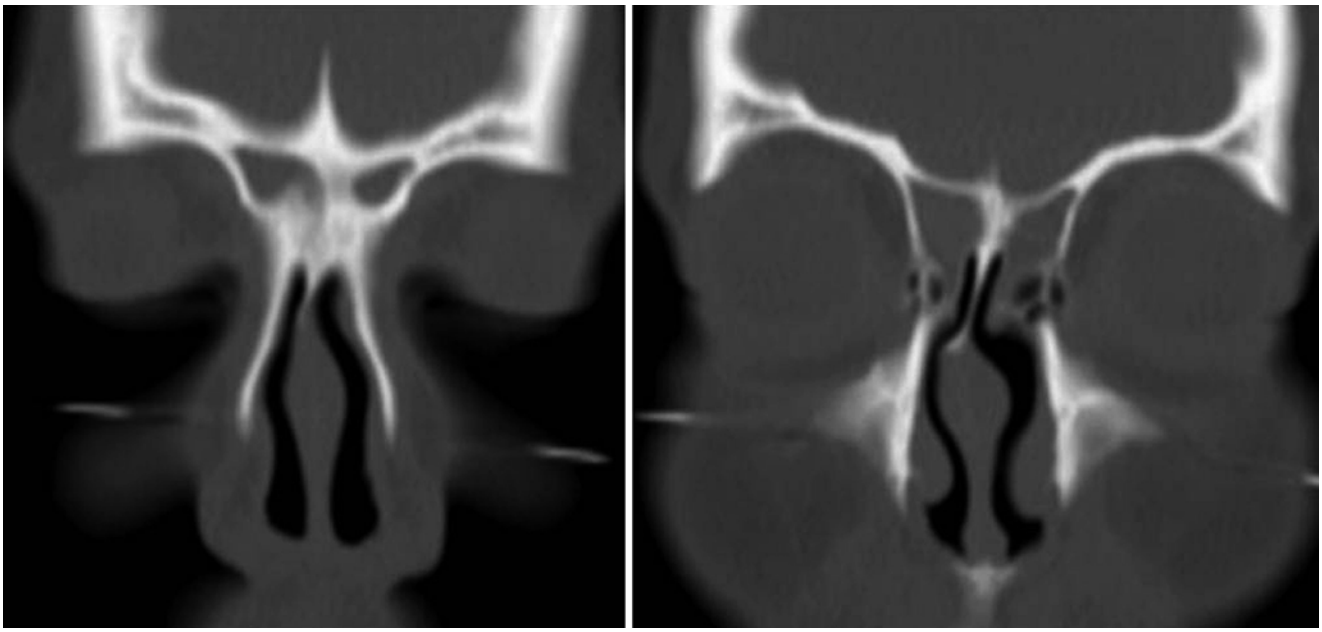


Fig. 4.17 Coronal CT images demonstrating hypoplastic frontal sinuses in a patient with cystic fibrosis

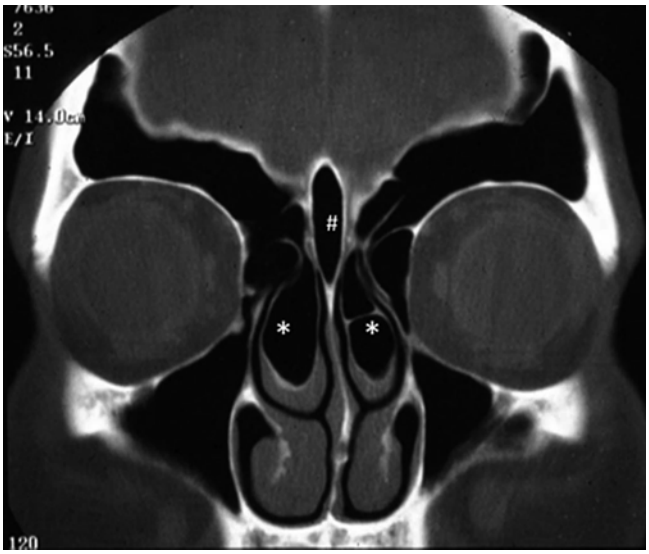


Fig. 4.18 Extreme hyperpneumatization of the sinuses in a patient without sinus disease. Bilateral concha bullosa are present (*), as well as extensive lateral pneumatization of the orbital plate of the frontal bone and the crista galli of the ethmoid bone (#)

In contrast, hyperpneumatization of the paranasal sinuses may also occur (Fig. 4.18). Again, this has not been the subject of formal study, but one would assume that hyperpneumatization of the sinuses does not predispose to rhinosinusitis. However, if infection were to occur, there would be very little anatomic separation of the infectious process to critical orbital or neurovascular structures. Congenital bony dehiscences of the orbit or skull base are rare, but extensive paranasal sinus pneumatization may expose the optic nerve, maxillary branch of the trigeminal nerve (V2), vidian nerve, carotid artery, and cavernous sinus by "skeletonizing" these structures (Fig. 4.19). Though it has been suggested infectious complications such as blindness, meningitis, and cavernous sinus thrombosis may be more common in such situations, there is no concrete data to support this contention (Fig. 4.20).

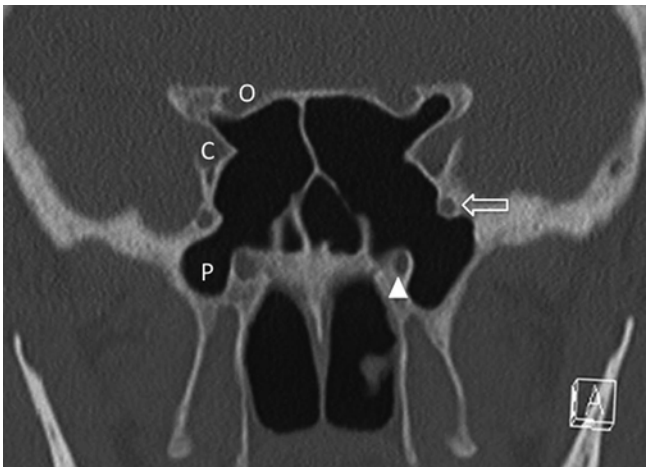


Fig. 4.19 Coronal CT demonstrating hyperpneumatization of the sphenoid sinuses. The anterior clinoid process is pneumatized, creating prominence of the optic nerve and carotid artery. Due to pneumatization of the lateral (pterygoid) process of the sphenoid sinus, the vidian nerve and the maxillary branch of the trigeminal nerve (V2) near the cavernous sinus are exposed (*P* pterygoid process, *O* optic nerve, *C* carotid artery, *arrowhead* vidian nerve, *open arrow* V2)

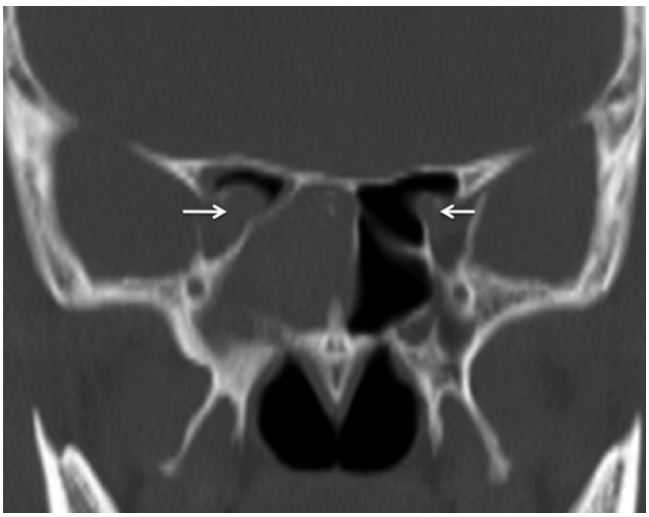


Fig. 4.20 Coronal CT scan of woman presenting with chief complaint of right-sided vision loss. Pneumatization of the Onodi cells into the anterior clinoid process leaves the optic nerves exposed (*arrows*). She was ultimately found to have chronic noninvasive fungal sinusitis

Neighboring Areas

The adenoid may play a role in some patients with ARS, RARS, or CRS, particularly in the pediatric population. This mucosa-lined lymphoid tissue in the nasopharynx may contribute to disease either by obstruction of drainage and airflow or by serving as a biofilm reservoir for recurrent infection (Fig. 4.21). Large adenoids can certainly contribute to nasal obstruction, congestion, and drainage, three of the top five symptoms encountered in adult CRS [1]. Although a large adenoid can contribute to physical obstruction, adenoid size does not appear to correlate with degree of infection, at least in the pediatric population [26, 27]. When examined with regard to microbial presence, the adenoid core had a positive predictive value of 92 % and a negative predictive value of 84 % in forecasting the middle meatal culture result, implying that it may serve as a reservoir for bacteria relevant to sinus disease [28]. In addition to simply harboring bacteria, the adenoid may be colonized with bacterial biofilms in the disease state, irrespective of its size and endoscopic appearance, perhaps serving to explain why adenoidectomy is a potential treatment for CRS in children. According to this hypothesis, bacterial biofilms would be difficult to permanently eradicate from the adenoid and would periodically shed planktonic bacteria leading to recurrent acute infections. In a small study comparing mucosal surface biofilms in adenoids from children with CRS or obstructive sleep apnea (OSA), CRS patients had an average of 94.9 % adenoid surface area biofilm compared to an average of 1.9 % in OSA patients [29]. This is certainly interesting, and as bacterial biofilms appear to be more relevant in otolaryngic diseases such as chronic otitis media, further investigation is required to prove causation rather than association of these findings (Fig. 4.22).

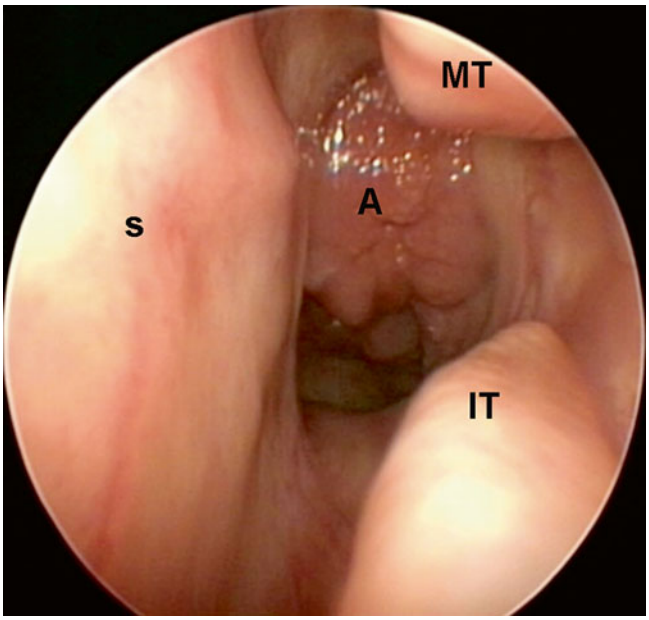


Fig. 4.21 Endoscopic appearance of a prominent adenoid as seen through the left nasal cavity (*S* septum, *A* adenoid, *MT* middle turbinate, *IT* inferior turbinate)

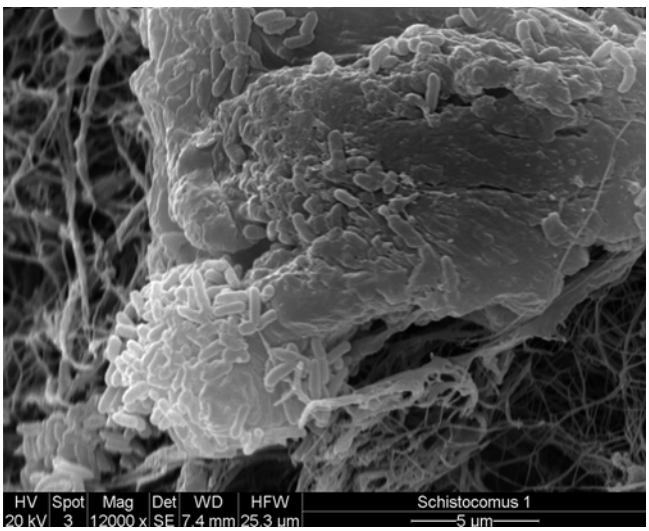


Fig. 4.22 Scanning electron microscopy (SEM) demonstrates biofilm presence on sinonasal mucosa (Courtesy of Noam Cohen, MD, PhD, University of Pennsylvania)

Additionally, adenoiditis—either acute or chronic—can mimic many of the symptoms of rhinosinusitis. The adenoid should therefore be considered in the evaluation of pediatric patients with ARS, RARS, or CRS.

The close proximity of tooth roots to the maxillary sinus may also lead to secondary sinus infections, and as such, dental disease should be suspected in isolated maxillary or unilateral sinus disease. Odontogenic sinusitis is estimated to account for 10–12 % of maxillary sinus infections, and this etiology should be established because the bacteria present will more likely be polymicrobial with a high concentration of anaerobes [30]. Thorough patient history may provide clues to an odontogenic source, including known dental disease, prior oral surgical procedures, or presence of an oroantral fistula. Severe maxillary sinus infections are often associated with oroantral fistula and periodontal disease, and the degree of radiographic opacification correlates with the likelihood of an odontogenic source [31]. Orbital and intracranial infectious complications of sinusitis are fortunately quite rare but commonly demonstrate oral flora on cultures, implying that dental disease may be a risk factor. Interestingly, dental disease is frequently missed on dental X-rays and initial sinus CT reports by radiologists [32]. This is perhaps due to low sensitivity of dental plain film X-rays when compared to CT for examination of the dental roots and periapical space and low index of suspicion from radiologists who may be primarily examining the sinuses [33]. The presence or absence of dental disease is important to identify, because incomplete disease resolution would be expected if only the sinuses are managed and the origin of disease is left untreated (Figs. 4.23 and 4.24).

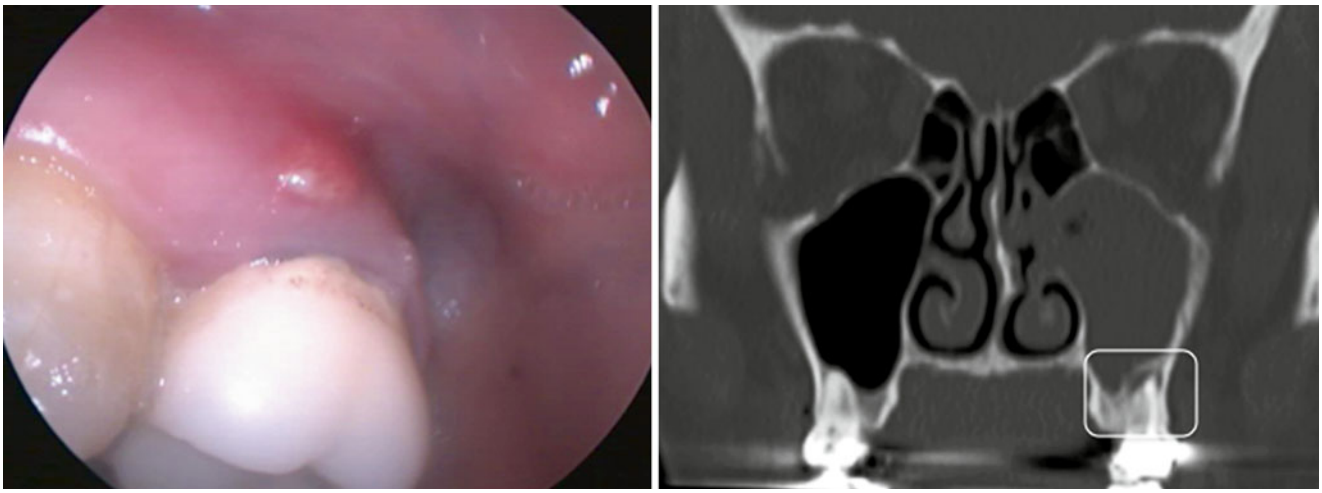


Fig. 4.23 Unilateral maxillary sinusitis associated with periapical abnormality. Oral examination shows a tender pustule at the gingiva overlying diseased 2nd maxillary molar (*left*). The CT scan (*right*) shows a periapical lucency (*box*) after prior root canal, which was not seen on dental X-ray

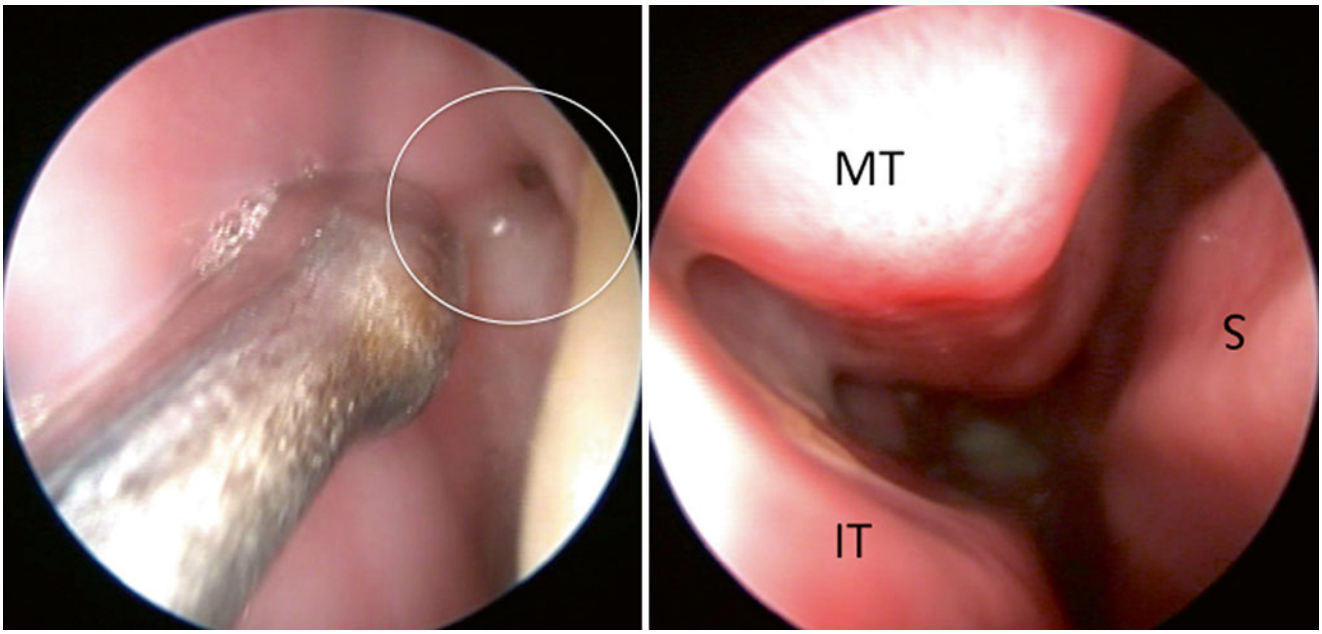


Fig. 4.24 Transoral view of right oroantral fistula found lateral to 2nd molar after dental procedure (*left*), with corresponding endoscopic view demonstrating edema at the middle meatus (*S* septum, *MT* middle turbinate, *IT* inferior turbinate)

Conclusion

Structural abnormalities of the nose and sinuses exist in many patients. A number of anatomic abnormalities or variants can contribute to the development of rhinosinusitis. The overall clinical effect of such variants is relatively mild; however, in many patients identification and treatment may be expected to yield significant improvement. The clinician who treats sinus disease can identify many of these abnormalities with thorough history and physical examination and endoscopy if available. Radiology reports from sinus CT scans may overlook many of these findings, and accordingly the clinician is recommended to personally review images whenever possible. Consideration of the role of structural abnormalities in a given patient with sinusitis will contribute to consistently favorable clinical outcomes.

References

1. Meltzer EO, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. Otolaryngol Head Neck Surg. 2004;131(6):S1–62.
2. Chen XB, Lee HP, Chong VF, de Wang Y. Assessment of septal deviation effects on nasal air flow: a computational fluid dynamics model. Laryngoscope. 2009;119:1730–6.
3. Jang YJ, Myong NH, Park KH, Koo TW, Kim HG. Mucociliary transport and histologic characteristics of the mucosa of deviated nasal septum. Arch Otolaryngol Head Neck Surg. 2002;128:421–4.
4. Gray LP. Deviated nasal septum. Incidence and etiology. Ann Otol Rhinol Laryngol. 1978;87(3 Pt 3 Suppl 50):3–20.
5. Elahi MM, Frenkiel S. Septal deviation and chronic sinus disease. Am J Rhinol. 2000;14:175–9.
6. Yasan H, Dogru H, Baykal B, Doner F, Tuz M. What is the relationship between chronic sinus disease and isolated nasal septal deviation. Otolaryngol Head Neck Surg. 2005;133:190–3.
7. Orlandi RR. A systematic analysis of septal deviation associated with rhinosinusitis. Laryngoscope. 2010;120:1687–95.
8. Bhattacharyya N. Clinical symptomatology and paranasal sinus involvement with nasal septal perforation. Laryngoscope. 2007;117(4):691–4.
9. Stammberger HR, Kennedy DW. Paranasal sinuses: anatomic terminology and nomenclature. The Anatomic Terminology Group. Ann Otol Rhinol Laryngol Suppl. 1995;167:7–16.
10. Stallman JS, Lobo JN, Som PM. The incidence of concha bullosa and its relationship to nasal septal deviation and paranasal sinus disease. AJNR Am J Neuroradiol. 2004;25:1613–8.
11. Bolger WE, Butzin CP, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. Laryngoscope. 1991;101:56–64.
12. Zinreich SJ, Mattox DE, Kennedy DW, Chisholm HL, Diffey DM, Rosenbaum AE. Concha bullosa: CT evaluation. J Comput Assist Tomogr. 1988;12(5):778–84.
13. Alkire BC, Bhattacharyya N. An assessment of sinonasal anatomic variants potentially associated with recurrent acute rhinosinusitis. Laryngoscope. 2010;120:631–4.
14. Lee WT, Kuhn FA, Citardi MJ. 3D computed tomographic analysis of frontal recess anatomy in patients without frontal sinusitis. Otolaryngol Head Neck Surg. 2004;131:164–73.
15. Lien CF, Weng HW, Chang YC, Lin YC, Wang WH. Computed tomographic analysis of frontal recess anatomy and its effect on the development of frontal sinusitis. Laryngoscope. 2010;120:2521–7.
16. Delgaudio JM, Hudgins PA, Venkatraman G, Beningfield A. Multiplanar computed tomographic analysis of frontal recess cells: effect on frontal isthmus size and frontal sinusitis. Arch Otolaryngol Head Neck Surg. 2005;131(3):230–5.
17. von Haller A. First lines of physiology. Cullen W, editor. Edinburgh: Obrabran, Penniman; 1803. p. 223–5.
18. Kennedy DW, Zinreich SJ. Functional endoscopic approach to inflammatory sinus disease: current perspectives and technique modifications. Am J Rhinol. 1988;2:89–96.
19. Stammberger H, Wolf G. Headaches and sinus disease: the endoscopic approach. Ann Otol Rhinol Laryngol. 1988;97 Suppl 134:3–23.
20. Stackpole SA, Edelstein DR. The anatomic relevance of the Haller cell in sinusitis. Am J Rhinol. 1997;11(3):219–23.
21. Wormald PJ. The agger nasi cell: the key to understanding the anatomy of the frontal recess. Otolaryngol Head Neck Surg. 2003;129(5):497–507.
22. Weinberger DG, Anand VK, Al-Rawi M, Cheng HJ, Messina AV. Surgical anatomy and variations of the Onodi cell. Am J Rhinol. 1996;10(6):365–70.
23. Pifferi M, Bush A, Caramella D, Di Cocco M, Zangani M, Chinellato I, Pacchia P, Boner AL. Agenesis of paranasal sinuses and nasal nitric oxide in primary ciliary dyskinesia. Eur Respir J. 2011;37(3):566–71.
24. Orlandi RR, Wiggins 3rd RH. Radiological sinonasal findings in adults with cystic fibrosis. Am J Rhinol Allergy. 2009;23(3):307–11.
25. Woodworth BA, Ahn C, Flume PA, Schlosser RJ. The delta F508 mutation in cystic fibrosis and impact on sinus development. Am J Rhinol. 2007;21(1):122–7.
26. Shin KS, Cho SH, Kim KR, Tae K, Lee SH, Park CW, Jeong JH. The role of adenoids in pediatric rhinosinusitis. Int J Perdiatr Otorhinolaryngol. 2008;72(11):1643–50.
27. Bercin AS, Ural A, Kutluhan A, Yurttas V. Relationship between sinusitis and adenoid size in pediatric age group. Ann Otol Rhinol Laryngol. 2007;116(7):550–3.
28. Elwany S, El-Dine AN, El-Medany A, Omran A, Mandour Z, El-Salam AA. Relationship between bacteriology of the adenoid core and middle meatus in children with sinusitis. J Laryngol Otol. 2011;125(3):279–81.
29. Zuliani G, Carron M, Gurrola J, Coleman C, Haupert M, Berk R, Coticchia J. Identification of adenoid biofilms in chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2006;70(9):1613–7.
30. Brook I. Sinusitis of odontogenic origin. Otolaryngol Head Neck Surg. 2006;135(3):349–55.
31. Bomeli SR, Bransteter 4th BF, Ferguson BJ. Frequency of a dental source for acute maxillary sinusitis. Laryngoscope. 2009;119(3):580–4.
32. Longhini AB, Ferguson BJ. Clinical aspects of odontogenic maxillary sinusitis: a case series. Int Forum Allergy Rhinol. 2011;1(5):409–15.
33. Patel S, Wilson R, Dawood A, Mannocci F. Detection of periapical pathosis using periapical radiography and cone beam computed tomography part 1: pre-operative status. Int Endod J. 2012;45(8):702–10.
34. Gwaltney Jr JM, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on sinus Disease. Ann Otol Rhinol Laryngol Suppl. 1995;167:22–30.

Part II
Microbiology

Chapter 5
Microbiology of Acute, Subacute, and Chronic Rhinosinusitis in Children

Gregory P. DeMuri and Ellen R. Wald

Introduction

An understanding of the microbiology of acute bacterial sinusitis in children is key to making decisions about antimicrobial selection. Most work in this area has focused on acute bacterial sinusitis, with fewer studies addressing subacute and chronic sinusitis in children. Since the routine use of conjugate pneumococcal vaccines in 2000 and the emergence of *Streptococcus pneumoniae* which were highly resistant to penicillin, there has been renewed interest in determining the microbiology and epidemiology of sinusitis. This chapter will focus primarily on the microbiology of acute sinusitis in children. Subacute and chronic sinusitis in children, which have received much less attention in the medical literature, will also be reviewed.

Acute Bacterial Sinusitis

Sinus Aspiration

The challenge in obtaining material for culture is that the sinuses are a closed system accessible only through a mucous membrane that is highly contaminated with respiratory flora. Because of the invasive nature of sinus aspirates, this procedure has not been performed on humans with normal sinuses. The sterility of the sinus cavity has been established in healthy rhesus monkeys that have undergone sinus aspiration [1]. This sterile environment is maintained by the mucociliary apparatus of the sinus and by normal immune function.

Aspiration of the maxillary sinus after sterilization of the mucous membrane of the nasal cavity is the most stringent method for obtaining culture material to avoid contamination. This procedure is performed by anesthetizing and sterilizing the nasal mucosa with a solution of 10 % cocaine (cocaine has antiseptic properties). A culture of the mucosa is performed to test sterility to ensure that effective antisepsis has been achieved. Puncture is performed with a sterile 16-gauge trocar positioned beneath the inferior nasal turbinate; the antral cavity is aspirated. If no material is returned, then the sinus is irrigated with non-bacteriostatic saline which is aspirated and sent for culture. A significant growth of bacteria is considered $\geq 10^4$ colony-forming units per milliliter [2]. Results must be expressed quantitatively to ensure that an organism is present in sufficient number to represent a true pathogen and not a contaminating organism.

The only sinus puncture studies performed in children to establish the microbiology of acute bacterial sinusitis were reported in the 1980s [3, 4] (Table 5.1). Fifty children between the ages of 1 and 16 years who were suspected of having sinusitis were evaluated. Children were entered into the study based on clinical symptoms and abnormal plain radiographs of the maxillary sinuses. Sinus puncture was performed and aspirates were cultured aerobically and anaerobically and a Gram stain prepared. A total of 79 sinus aspirates were performed. At least one sinus had significant growth in 51 of 79

G.P. DeMuri, MD (✉) • E.R. Wald, MD
Department of Pediatrics, American Family Children's Hospital/University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, 4108, Madison, WI 53792, USA
e-mail: demuri@pediatrics.wisc.edu; erwald@pediatrics.wisc.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_5,

Table 5.1 Bacteriology of acute sinusitis in 79 sinus aspirates in 50 children with acute sinusitis based on sinus puncture [3, 4]

Organism	Total number of isolates	% of isolates
S. pneumoniae	22	37
H. influenzae[a]	15	25
M. catarrhalis	15	25
Streptococcus species	4	7
Other[b]	3	5
Total	*59*	*100*

[a]All were non-typable
[b]*Eikenella corrodens*, *Peptostreptococcus*, and *Moraxella* sp.

(65 %) aspirates. The predominant organisms isolated from the maxillary sinuses by puncture, in order of frequency, were *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae*, and *Moraxella catarrhalis*. As in studies of otitis media in this era, *S. pneumoniae* was isolated at about 1.5–2 times the rate of isolation of *H. influenzae* and *M. catarrhalis*. It is notable that 13 % of sinus aspirates grew more than one species of bacteria. Six of the 50 subjects had isolates of bacteria that were beta-lactamase producing. This study was also remarkable in that anaerobic bacteria were only present in one aspirate and there were no isolates of *Staphylococcus aureus*.

Endoscopically Obtained Cultures of the Middle Meatus

Because sinus aspiration is not a routine procedure, may be uncomfortable, may rarely be associated with complications, and should only be performed by a pediatric otolaryngologist, there has been a search for a surface culture of the respiratory mucosa, obtained by less invasive methods, which might correlate with the results of the sinus aspirate. The challenge in any less invasive method is that the nasal mucosa is heavily colonized with normal bacterial flora. Cultures of the middle meatus obtained by the use of an endoscope have been used as a surrogate for sinus aspiration. The maxillary, frontal, and anterior air cells of the ethmoid sinuses drain into the middle meatus via the osteomeatal complex. The endoscope is inserted into the nose, and a sample is obtained from material in the middle meatus via a swab or aspiration. The mucosa of the anterior nares must be disinfected, and meticulous care must be taken to be sure the endoscope does not touch the nasal vestibule and become contaminated. Benninger et al. performed a meta-analysis of studies in a mainly adult population comparing endoscopically obtained cultures of the middle meatus to maxillary sinus puncture [5]. When all bacterial isolates are considered, endoscopically obtained cultures show a sensitivity of 80 %, specificity of 70 %, positive predictive value of 78 %, negative predictive value of 75 %, and an overall accuracy of 76 % when compared with maxillary sinus aspiration. If only the sinus pathogens *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are taken into account, the test performs somewhat better with a sensitivity and specificity of 81 and 83 %, positive and negative predictive value of 91 and 89 %, and overall accuracy of 87 %. Given that the caliber of the nasal passage in children is significantly smaller than adults, one might expect a greater rate of contamination of endoscopically obtained cultures when this procedure is performed in children. Hsin et al. compared endoscopic middle meatal cultures to maxillary sinus puncture in children 2–12 years with subacute and chronic sinusitis [6]. This population of children had failed 30 days or more of antimicrobial therapy. Endoscopic culture performed less well in children than adults with a sensitivity of 75 %, a specificity of 99.9 %, a positive predictive value of 96 %, negative predictive value of 50 %, and an accuracy of 78 %. Overall endoscopic cultures may provide useful information for the treatment of individual adults when interpretation is confined to the three sinus pathogens: *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. However, in epidemiological studies of the etiology of sinusitis, endoscopic cultures are likely to be confounded by normal nasal flora such as alpha-hemolytic streptococci, *Corynebacterium*, and *Staphylococcus* species and, therefore, are of limited usefulness in children.

Surface Cultures

Because of the ease of obtaining a culture of the anterior nose or the nasopharynx, several studies have examined whether the results of these surface cultures corresponded to the results of maxillary sinus aspiration. Axelsson and Brorson studied 472 patients (the age range of the patients was not specified) and found a correlation between the nasal culture and the sinus aspirate only 50 % of the time [7].

In a study done solely in children, nasopharyngeal cultures were taken at the same time as a sinus aspirate was performed [3]. Of 17 subjects who had a predominant organism recovered from the nasopharynx, the same organism was present in the

sinus aspirate in only 4. Thus nasal and nasopharyngeal cultures show a poor correlation with cultures of the sinus performed by aspiration [7]. In contrast, there has been no study to determine if the absence of *S. pneumoniae* on culture of the nasopharynx might have a high negative predictive value regarding the likelihood of *S. pneumoniae* as a cause of sinusitis.

The Role of *Staphylococcus aureus*

In sinus puncture studies, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* have been identified as the major pathogens associated with acute bacterial sinusitis. Recently, some authors have purported that *S. aureus* should also be considered a major pathogen in acute bacterial sinusitis [5, 8, 9]. If this were the case, it would have important implications for empiric antibiotic selection as current guidelines do not include recommendations for the use of agents that are directed at this pathogen [10, 11]. When examined carefully, however, the role of *S. aureus* as an etiological agent of acute bacterial sinusitis is doubtful [12]. In adults, during a period of 15 years of performing sinus aspirates, *S. aureus* was present in only 7 of 226 (3 %) positive specimens obtained from 339 patients [13]. No isolates of staphylococci were detected in significant quantity in the two studies in which maxillary aspirates were performed in 50 children with acute bacterial sinusitis [3, 4].

The majority of studies arguing that *S. aureus* is a sinus pathogen are based on cultures of the middle meatus. To effectively analyze such studies, it is important to understand the microbiology of the nose and middle meatus in healthy individuals. The nasal vestibule is an area that may be heavily colonized with *S. aureus*. In one study of healthy children in a community setting, over 65 % of children harbored *S. aureus* in the anterior nares [14]. Any study of the microbiology of the middle meatus involves passing an endoscope through this highly colonized region. Thus, even with measures such as antisepsis and the use of a sterile nasal specula, contamination is possible.

The middle meatus itself is also an area densely colonized with bacteria. Gordts et al. performed middle meatal cultures on healthy children who were undergoing surgery for reasons unrelated to the head and neck [15]. In this study, a swab was placed through an ear speculum placed in the disinfected nasal vestibule. Cultures were performed from swabs of the middle meatus and revealed *S. pneumoniae* in 50 %, *H. influenzae* in 40 %, *M. catarrhalis* in 34 %, *S. aureus* in 20 %, and *Corynebacterium* in 52 %. In a study of children with recurrent or chronic sinusitis, *S. aureus* was present in the middle meatus in 32 % of samples [16]. These studies indicate that the middle meatus is heavily colonized with pathogenic and nonpathogenic bacteria in healthy children. Thus, identifying any of these organisms from the middle meatus in children with sinusitis may represent normal colonization and not the etiology of the sinus infection.

Payne et al. performed a meta-analysis on studies of sinus aspirate and middle meatal cultures in adults and concluded that *S. aureus* is prevalent in sinus cultures and should be considered a major pathogen [9]. The authors state that *S. aureus* was found in culture from various sinus and nasal sources 10 % of the time overall. There are significant problems with this analysis, however. First, it is notable that this rate of culture positivity is in the range of results seen in cultures of the middle meatus in healthy adults suggesting that cultures may have been contaminated [17]. Also, in middle meatal cultures, *S. aureus* was isolated at nearly twice the rate as cultures of sinus aspirates (14 % vs 7.8 %). One would expect that these two rates would be similar unless the middle meatal cultures were contaminated with normal flora. In addition, studies included in this meta-analysis had serious methodological problems. For example, in one of the studies with the highest (20 %) rate of isolation of *S. aureus* from sinus aspirates, no methods are given for performing the sinus aspirate [18]. It was not indicated whether the nasal mucosa was disinfected before the procedure. In addition, all patients who had *S. aureus* isolated in this study had anatomic abnormalities of the nasal cavity. This raises serious concerns that the culture results for *S. aureus* may represent contamination from normal nasal flora and thus would skew the results of the meta-analysis.

Overall, caution must be exercised in interpreting these recent studies highlighting the role of *S. aureus* as a major pathogen in acute bacterial sinusitis. Studies in children have mainly relied on middle meatal specimens which do not show good correlation with maxillary sinus aspiration. In the studies in adults, there is serious concern that similar studies have a high rate of contamination with normal nasal flora. It appears unlikely that *S. aureus* is a major pathogen in acute bacterial sinusitis. Accordingly, empiric antibiotic choices need not include coverage for this organism.

The Changing Microbiology of Acute Bacterial Sinusitis

No sinus puncture studies in children with acute bacterial sinusitis have been published since 1984 [4]. Knowledge of changes in the microbiology of acute bacterial sinusitis is important in making decisions about antibiotic selection. In the absence of high-quality data from sinus aspirates, important information may be learned from cultures of middle ear aspirates in children with acute otitis media (AOM). AOM may be used as a surrogate for sinusitis as the middle ear is, in fact, a paranasal sinus [19]. The anatomy and physiology of the middle ear are very similar to that of the sinuses. The middle ear

Table 5.2 Rate of isolation of pathogens from middle ear fluid in children with acute otitis media before and after the introduction of 7-valent pneumococcal conjugate vaccine (PCV-7)

	S. pneumoniae		*H. influenzae*		*M. catarrhalis*	
Study	Pre-PCV-7	Post-PCV-7	Pre-PCV-7	Post-PCV-7	Pre-PCV-7	Post-PCV-7
Block, 2004 [20]	48	31	41	56	9	11
Casey, 2004 [21]	48	31	38	57	4	1
Kaur, 2010 [51]	–	25	–	35	–	9

drains via the Eustachian tube into the nasopharynx, analogous to sinus drainage via the osteomeatal complex into the nose. A viral upper respiratory infection is often the predisposing factor for both of these infections causing impairment of drainage with subsequent bacterial growth and inflammation. Like sinusitis, the major pathogens of AOM are *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Examining the changes of the epidemiology of these pathogens in the context of AOM should reflect similar changes that have occurred in acute bacterial sinusitis.

Since the introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7), there has been a shift in the rate of isolation of *S. pneumoniae* from middle ear fluid in children with AOM (Table 5.2). Two studies have compared the relative rates of isolation of otitis pathogens before and after the introduction of PCV-7 in 2000 for universal immunization in the United States. Block et al. performed tympanocentesis on 381 children aged 7–24 months with otitis media in a practice setting in rural Kentucky [20]. After the introduction of PCV-7, the rate of isolation of *S. pneumoniae* decreased significantly from 48 to 21 % of all isolates. Meanwhile, *H. influenzae* was isolated more frequently during this time period, shifting from 41 to 56 % of isolates. The rate of isolation of *Moraxella* was not changed in this study. In the second study, covering the period from 1995 to 2003, Casey et al. cultured middle ear fluid obtained from children who had failed treatment for AOM or had persistent AOM [21]. During this time period, the rate of isolation of *S. pneumoniae* decreased from 48 to 31 %, *H. influenzae* increased from 38 to 57 %, and *Moraxella* did not change. This same group, however, found a near reversal of this trend between 2007 and 2009 (before the introduction of the 13-valent conjugate pneumococcal vaccine in 2010). During this time frame, *S. pneumoniae* and *H. influenzae* were isolated 44 and 41 % of the time from middle ear fluid [22]. This change was primarily due to the emergence of penicillin-resistant serotype 19 of *S. pneumoniae*. Subsequent data, accumulated by Pichichero et al., suggest that increasing use of PCV-13 has truncated this issue, with a dramatic diminution of cases caused by *S. pneumoniae* [23]. Further assessment of this microbiological shift will be important as the use of PCV-13 becomes more widespread. Overall, we can anticipate that the prevalence *of S. pneumoniae* will continue to decrease and *H. influenzae* increase as the causative organism in children with AOM in the United States. It is likely the same phenomenon is occurring with acute bacterial sinusitis, since the source of the pathogens in both diseases is ultimately the nasopharynx. The proportion of cases of sinusitis caused by *H. influenzae* will drive the selection of an appropriate antibiotic that is beta-lactamase stable.

The prevalence of resistance to the common antimicrobial agents used to treat AOM and acute bacterial sinusitis has varied greatly over the past decade. There has been large geographic variation in penicillin and macrolide resistance rates in *S. pneumoniae* and an increase in ampicillin resistance in *H. influenzae* worldwide mediated by beta-lactamase production. Table 5.3 demonstrates that surveys of respiratory isolates in populations have shown great variation over geographic region and time [20, 22, 24–34]. Historically, the proportion of *H. influenzae* from respiratory sources, including middle ear fluid, that have produced beta-lactamase has been 20–30 %. Recently, nasopharyngeal and middle ear isolates of *H. influenzae* in children from Upstate New York have shown rates as high as 50 % [22], and in Asia rates of 60–65 % have been reported [31]. If these high rates of resistance are widespread, then the effectiveness of amoxicillin as first-line treatment for AOM and acute bacterial sinusitis will be significantly limited.

In the post-PCV-7 era, the rates of isolation of penicillin non-susceptible *S. pneumoniae* (PNSP) have also varied greatly depending on the geographic region and the source of the isolates. The overall trend, however, seems to be either a decrease or no change in the rate of isolation of PNSP since the introduction of PCV-7. Penicillin non-susceptibility rates have ranged from 10 to 61 % [22, 29] (Table 5.3). The Active Bacterial Core surveillance program measured rates of invasive disease caused by PNSP in the United States. Among children under 2 years of age, disease caused by penicillin non-susceptible strains decreased by 81 % from 1999 to 2004, concurrent with the introduction of the pneumococcal conjugate vaccine. During the last two decades, the prevalence of macrolide resistance in *S. pneumoniae* has become widespread, limiting the usefulness of azithromycin and clarithromycin in treating AOM and, by inference, acute bacterial sinusitis. [25] In surveys of surface and middle ear isolates from children, one constant is that *M. catarrhalis* produces beta-lactamase nearly 100 % of the time [22].

Several conclusions may be drawn from these epidemiological studies over the past decade. These data have been derived mainly from middle ear and nasopharyngeal isolates but likely apply to acute bacterial sinusitis. (1) There has been a shift in the proportion of isolation of respiratory pathogens with an increase in the rate of isolation of *H. influenzae* and a decrease

Table 5.3 Rates of antimicrobial resistance (%) in *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*

Study	Population	Source	Region	*S. pneumoniae*	*H. influenzae*		*M. catarrhalis*
				PNSP	Macrolide resistant	Beta-lactamase positive	Beta-lactamase positive
Casey, 2010 [22]	Children	Nasopharynx + middle ear	NY, USA	17–61	–	29–50	100
Harrison, 2009 [29]	Children	Respiratory	USA	10.6	37.3	42	95.2
Gotoh, 2008 [31]	Children	Nasopharyngeal	Vietnam	–	–	59.5	–
Fallon, 2008 [27]	Mainly children	Middle ear fluid	USA	19.4	–	45.5	–
Critchey, 2008 [25]	Children	All – most common serotypes	USA	51	45	–	–
Critchey, 2007 [24]	Adults and children	Respiratory	USA	37.9	34.5	27.4	91.6
Tristam, 2007 [30]	Adults and children	Literature review	Worldwide	–	–	3–65	–
McEllistrem, 2005 [33]	Children	Middle ear fluid	USA	59	–	–	–
Garbutt, 2004 [32]	Children	Nasopharynx	St. Louis, USA	19	63	–	–
Block, 2004 [20]	Children	Middle ear fluid	Rural Kentucky	19		36	100
Gordon, 2003 [28]	Adults and children	Respiratory	USA	35	23	24.5	–
Joloba, 2001 [34]	Children	Middle ear	USA	57	43		
Doern, 1999 [26]	Adults and children	All isolates	USA and Canada	–	–	33.5	99.2

in the isolation of *S. pneumoniae*. (2) The rate of beta-lactamase production by *H. influenzae* has increased. (3) The rate of isolation of penicillin non-susceptible *S. pneumoniae* has either decreased or stayed the same. (4) Macrolide resistance in *S. pneumoniae* is widespread. (5) The rate of isolation of *M. catarrhalis* has remained unchanged and nearly all produce beta-lactamase. These shifts in the microbiology limit the usefulness of amoxicillin for the treatment of acute bacterial sinusitis. Therefore, the addition of clavulanate to amoxicillin provides theoretical advantage in therapy.

Role of Viruses

Although viruses have often been implicated in the pathogenesis of acute bacterial sinusitis, the epidemiology and exact role of viruses have not been well defined. In the original sinus aspiration studies in children in the 1980s, traditional viral cell culture methods were used to identify viruses in sinus samples as well as in throat swabs taken from children with sinusitis [4]. Of 45 children tested, only three had viruses identified on culture. Sinus aspirates grew a parainfluenza virus and an adenovirus, and one throat culture grew a coxsackie B virus. Studies in adults have also isolated rhinovirus in viral culture [13]. No studies of the viruses associated with childhood sinusitis have been reported using molecular techniques nor have any tested for recently recognized respiratory viruses such as human metapneumovirus or bocavirus. It is widely believed that a viral URI is often the prescient event that results in the complication of acute bacterial sinusitis. Thus, an understanding of the viral epidemiology of sinusitis may lead to methods to prevent this infection. Once again using the analogy of AOM is useful in understanding what is occurring during episodes of sinusitis. Studies surveying the viruses associated with AOM using PCR techniques have demonstrated the presence of rhinovirus, respiratory syncytial virus, human metapneumovirus, influenza A and B, parainfluenza virus, adenovirus, human bocavirus, enteroviruses, and coronavirus [35, 36]. It is likely that these same viruses also play a role in the development of acute bacterial sinusitis.

Complications

The rate of complications in children who have sinusitis is relatively low. However, they are associated with serious morbidity and occasional mortality. These complications may be categorized as extracranial, intracranial, and those involving the bone of the sinus wall (osteitis). The extracranial complications include orbital cellulitis and abscess, subperiosteal abscess, optic neuritis, and preseptal inflammatory edema. Epidural and subdural empyema, meningitis, brain abscess, and cavernous sinus thrombosis comprise the intracranial complications of acute bacterial sinusitis. Pott's puffy tumor is an osteitis of the wall of the frontal sinus that presents with forehead swelling and tenderness. Since many of these complications of sinusitis

Table 5.4 Microbiology of the orbital and intracranial complications of sinusitis

	Orbital (125 isolates)	Intracranial (142 isolates)
Gram positive		
S. aureus	58	6
S. pneumoniae	2	4
S. anginosus	4	49
S. pyogenes	9	9
Other β-hemolytic streptococci	1	4
Other α-hemolytic streptococci	14	20
Coagulase-negative staphylococci	4	12
Other gram positive		1
Gram negative		
Enteric gram-negative rods	9	5
NTHi	6	2
Other *Haemophilus* spp.	2	1
M. catarrhalis		1
Neisseria spp.	2	
Anaerobes		
Bacteroides spp.	1	6
Eikenella spp.	3	2
Fusobacterium spp.	3	3
Peptostreptococcus	3	6
Prevotella	1	2
Other	3	9

From Refs. [37–45]

are local fluid collections, surgical drainage is necessary. Specimens sent for culture from these sources are likely to represent the actual etiology of the infection.

A summary of the studies that have surveyed the microbiology of the orbital and intracranial complications of sinusitis is shown in Table 5.4 [37–45]. In orbital infections, *Staphylococcus aureus* is the predominant pathogen followed by *Streptococcus pyogenes*, *S. pneumoniae*, other gram positives, *H. influenzae*, enteric gram-negative bacilli, and anaerobes. The importance of methicillin-resistant *S. aureus* in orbital disease has been increasingly recognized [45]. In intracranial complications, the microbiology is similar, though *S. aureus* is isolated less frequently than in orbital infections. Over the past decade, *Streptococcus anginosus* (formerly *S. milleri*) has become the predominant pathogen isolated in many studies.

Subacute and Chronic Sinusitis

Much less attention has been given to the microbiology of subacute and chronic sinusitis in children. This is complicated, in part, by a lack of standard definitions for these conditions. Acute sinusitis has been defined as an infection with a duration of less than 4 weeks. Subacute sinusitis is infection from 4 weeks to 2–3 months. Chronic sinusitis is commonly defined as infection for more than 2–3 months and often years [46]. These definitions, however, are somewhat arbitrary.

Wald studied the microbiology of children with subacute sinusitis. Children aged 2–16 had sinus symptoms for more than 30 but less than 120 days. Maxillary sinus aspirations were performed on 52 sinuses in 40 children with significant bacterial growth found in 58 % of these aspirates. The organisms isolated included *S. pneumoniae* (34 %), *H. influenzae* (31 %), and *M. catarrhalis* (23 %) with the remainder comprised of Group A beta-hemolytic streptococci, viridans streptococci, and a *Moraxella* species. Of the *H. influenzae* isolated, 27 % were beta-lactamase producing and many of the children in the study had recently received antibiotics. Overall, the microbiology of these children with subacute sinusitis was nearly identical to those with acute bacterial sinusitis.

Available microbiologic data from children with chronic sinusitis are limited and confusing because of variable definitions of chronic sinusitis, frequent failure to obtain specimens aseptically, lack of quantitation of results, and concurrent use of antibiotics. In children with chronic sinusitis, multiple species of bacteria have been isolated from sinus aspirates. Brook found anaerobic bacteria such as *Bacteroides*, anaerobic gram-positive cocci, and *Fusobacterium* species predominated among these isolates [47]. Aerobic bacteria were isolated less frequently and included alpha-hemolytic streptococci, *S. aureus*, and *Haemophilus* species. In a separate study of acute exacerbations of chronic sinusitis, multiple species of anaerobes, *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *S. aureus* were present [48]. Hsin performed maxillary sinus

puncture in 21 children who had four or more weeks of sinus symptoms despite antimicrobial therapy [6]. This study was somewhat limited in that there was no quantitation of bacterial growth and no sterility testing of the puncture site. However, 28 sinus aspirate cultures demonstrated *S. pneumoniae* (12 aspirates), *H. influenzae* (7 aspirates), *M. catarrhalis* (1 aspirate), and no growth in 5 aspirates.

In patients with chronic persistent sinusitis (nasal congestion and/or rhinorrhea and/or cough), the role of bacteria is less clear. The persistence of symptoms despite multiple courses of appropriate antimicrobial agents is counter to the notion that bacterial infection is a significant component of chronic sinusitis. All these observations support the hypothesis that bacterial infection has a minor role, if any, in a substantial number of patients with chronic sinusitis.

This disease is now thought to be an inflammatory disorder rather than a primary infectious disease [49]. An alternative hypothesis regarding the importance of bacterial infection in patients with chronic sinusitis relates to the potential role of biofilms (discussed in the Chap. 7). Biofilms are complex colonies of bacterial cells that live within a glycocalyx matrix attached to a moist surface. Biofilms offer important survival advantages to bacteria. They are more resistant to the effects of antibiotics than free-floating planktonic bacteria. This is accomplished by several mechanisms: (1) greater cell-cell contact to facilitate plasmid exchange for the evolution of resistance, (2) production of beta-lactamases, (3) slow bacterial growth resulting in decreased effect of antibiotics that rely on cell growth and turnover for killing effect, and (4) the presence of "persister" cells that reform the biofilm when the antibiotic is discontinued [50]. The appeal of the concept of biofilms is that it might explain the chronic nature of the infection, frequent failure to respond to antibiotics, and acute exacerbations when antibiotics are discontinued in patients who had previously responded. Although biofilms have been demonstrated on the mucosa of patients with chronic sinusitis, their precise role remains to be determined as they are not present in all cases of CRS and limited biofilms are present in some healthy controls.

Conclusion

The microbiology of sinusitis in children is dynamic, having undergone significant changes in the past decade. Although there have been no puncture studies done in children since the 1980s, there is evidence that the prevalence of *H. influenzae* relative to *S. pneumoniae* has been increasing since the introduction of the pneumococcal conjugate vaccine in the United States. In addition, the rate of beta-lactamase production by *H. influenzae* is increasing in many areas. Thus, selecting an antimicrobial that is beta-lactamase stable or has a beta-lactamase inhibitor is important in treating children with sinusitis. Future studies that address methods of noninvasively detecting bacteria in the sinus would be helpful so that changes in the microbiology may be more readily monitored. Furthermore, additional research is needed to explore the role of viruses in the pathogenesis of AOM in children.

References

1. Shapiro ED, Wald ER, Doyle W, Rohn D. Bacteriology of the maxillary sinus of rhesus monkeys. Ann Otol Rhinol Laryngol. 1982; 91:150–1.
2. Evans Jr FO, Sydnor JB, Moore WE, et al. Sinusitis of the maxillary antrum. N Engl J Med. 1975;293:735–9.
3. Wald ER, Milmoe GJ, Bowen A, Ledesma-Medina J, Salamon N, Bluestone CD. Acute maxillary sinusitis in children. N Engl J Med. 1981; 304:749–54.
4. Wald ER, Reilly JS, Casselbrant M, et al. Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. J Pediatr. 1984;104:297–302.
5. Benninger MS, Payne SC, Ferguson BJ, Hadley JA, Ahmad N. Endoscopically directed middle meatal cultures versus maxillary sinus taps in acute bacterial maxillary rhinosinusitis: a meta-analysis. Otolaryngol Head Neck Surg. 2006;134:3–9.
6. Hsin CH, Tsao CH, Su MC, Chou MC, Liu CM. Comparison of maxillary sinus puncture with endoscopic middle meatal culture in pediatric rhinosinusitis. Am J Rhinol. 2008;22:280–4.
7. Benninger MS, Appelbaum PC, Denneny JC, Osguthorpe DJ, Stankiewicz JA. Maxillary sinus puncture and culture in the diagnosis of acute rhinosinusitis: the case for pursuing alternative culture methods. Otolaryngol Head Neck Surg. 2002;127:7–12.
8. Brook I. Methicillin-Resistant Staphylococcus aureus Infections of the Sinuses. Curr Infect Dis Rep. 2008;10:180–1.
9. Payne SC, Benninger MS. Staphylococcus aureus is a major pathogen in acute bacterial rhinosinusitis: a meta-analysis. Clin Infect Dis. 2007;45:e121–7.
10. American Academy of Pediatrics. Sub committee on management of sinusitis and committee on Quality Improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108:798–808.
11. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54:e72–112.

12. Wald ER. Staphylococcus aureus: is it a pathogen of acute bacterial sinusitis in children and adults? Clin Infect Dis. 2012;54:826–31.
13. Gwaltney Jr JM, Scheld WM, Sande MA, Sydnor A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol. 1992;90:457–61; discussion 62.
14. Fritz SA, Krauss MJ, Epplin EK, et al. The natural history of contemporary Staphylococcus aureus nasal colonization in community children. Pediatr Infect Dis J. 2011;30:349–51.
15. Gordts F, Abu Nasser I, Clement PA, Pierard D, Kaufman L. Bacteriology of the middle meatus in children. Int J Pediatr Otorhinolaryngol. 1999;48:163–7.
16. Elwany S, El-Dine AN, El-Medany A, Omran A, Mandour Z, El-Salam AA. Relationship between bacteriology of the adenoid core and middle meatus in children with sinusitis. J Laryngol Otol. 2011;125:279–81.
17. Gordts F, Halewyck S, Pierard D, Kaufman L, Clement PA. Microbiology of the middle meatus: a comparison between normal adults and children. J Laryngol Otol. 2000;114:184–8.
18. Klapan I, Culig J, Oreskovic K, Matrapazovski M, Radosevic S. Azithromycin versus amoxicillin/clavulanate in the treatment of acute sinusitis. Am J Otolaryngol. 1999;20:7–11.
19. Parsons DS, Wald ER. Otitis media and sinusitis: similar diseases. Otolaryngol Clin North Am. 1996;29:11–25.
20. Block SL, Hedrick J, Harrison CJ, et al. Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. Pediatr Infect Dis J. 2004;23:829–33.
21. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995–2003. Pediatr Infect Dis J. 2004;23:824–8.
22. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2010;29:304–9.
23. Pichichero M, Casey J, Center K, et al. Efficacy of PCV13 in prevention of AOM and NP colonization in children: first year of data from the US. In: 8th international symposium of pneumococci and pneumococcal diseases, Iguacu Falls; 2012.
24. Critchley IA, Brown SD, Traczewski MM, Tillotson GS, Janjic N. National and regional assessment of antimicrobial resistance among community-acquired respiratory tract pathogens identified in a 2005–2006 U.S. Faropenem surveillance study. Antimicrob Agents Chemother. 2007;51:4382–9.
25. Critchley IA, Jacobs MR, Brown SD, Traczewski MM, Tillotson GS, Janjic N. Prevalence of serotype 19A Streptococcus pneumoniae among isolates from U.S. children in 2005–2006 and activity of faropenem. Antimicrob Agents Chemother. 2008;52:2639–43.
26. Doern GV, Jones RN, Pfaller MA, Kugler K. Haemophilus influenzae and Moraxella catarrhalis from patients with community-acquired respiratory tract infections: antimicrobial susceptibility patterns from the SENTRY antimicrobial Surveillance Program (United States and Canada, 1997). Antimicrob Agents Chemother. 1999;43:385–9.
27. Fallon RM, Kuti JL, Doern GV, Girotto JE, Nicolau DP. Pharmacodynamic target attainment of oral beta-lactams for the empiric treatment of acute otitis media in children. Paediatr Drugs. 2008;10:329–35.
28. Gordon KA, Biedenbach DJ, Jones RN. Comparison of Streptococcus pneumoniae and Haemophilus influenzae susceptibilities from community-acquired respiratory tract infections and hospitalized patients with pneumonia: five-year results for the SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis. 2003;46:285–9.
29. Harrison CJ, Woods C, Stout G, Martin B, Selvarangan R. Susceptibilities of Haemophilus influenzae, Streptococcus pneumoniae, including serotype 19A, and Moraxella catarrhalis paediatric isolates from 2005 to 2007 to commonly used antibiotics. J Antimicrob Chemother. 2009;63:511–9.
30. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in Haemophilus influenzae. Clin Microbiol Rev. 2007;20:368–89.
31. Gotoh K, Qin L, Watanabe K, et al. Prevalence of Haemophilus influenzae with resistant genes isolated from young children with acute lower respiratory tract infections in Nha Trang, Vietnam. J Infect Chemother. 2008;14:349–53.
32. Garbutt J, St Geme 3rd JW, May A, Storch GA, Shackelford PG. Developing community-specific recommendations for first-line treatment of acute otitis media: is high-dose amoxicillin necessary? Pediatrics. 2004;114:342–7.
33. McEllistrem MC, Adams JM, Patel K, et al. Acute otitis media due to penicillin-nonsusceptible Streptococcus pneumoniae before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis. 2005;40:1738–44.
34. Joloba ML, Windau A, Bajaksouzian S, Appelbaum PC, Hausdorff WP, Jacobs MR. Pneumococcal conjugate vaccine serotypes of Streptococcus pneumoniae isolates and the antimicrobial susceptibility of such isolates in children with otitis media. Clin Infect Dis. 2001;33:1489–94.
35. Chonmaitree T, Revai K, Grady JJ, et al. Viral upper respiratory tract infection and otitis media complication in young children. Clin Infect Dis. 2008;46:815–23.
36. Ruohola A, Meurman O, Nikkari S, et al. Microbiology of acute otitis media in children with tympanostomy tubes: prevalences of bacteria and viruses. Clin Infect Dis. 2006;43:1417–22.
37. Adame N, Hedlund G, Byington CL. Sinogenic intracranial empyema in children. Pediatrics. 2005;116:e461–7.
38. McKinley SH, Yen MT, Miller AM, Yen KG. Microbiology of pediatric orbital cellulitis. Am J Ophthalmol. 2007;144:497–501.
39. Huang SF, Lee TJ, Lee YS, Chen CC, Chin SC, Wang NC. Acute rhinosinusitis-related orbital infection in pediatric patients: a retrospective analysis. Ann Otol Rhinol Laryngol. 2011;120:185–90.
40. Bair-Merritt MH, Shah SS, Zaoutis TE, Bell LM, Feudtner C. Suppurative intracranial complications of sinusitis in previously healthy children. Pediatr Infect Dis J. 2005;24:384–6.
41. Botting AM, McIntosh D, Mahadevan M. Paediatric pre- and post-septal peri-orbital infections are different diseases. A retrospective review of 262 cases. Int J Pediatr Otorhinolaryngol. 2008;72:377–83.
42. Germiller JA, Monin DL, Sparano AM, Tom LW. Intracranial complications of sinusitis in children and adolescents and their outcomes. Arch Otolaryngol Head Neck Surg. 2006;132:969–76.
43. Jones NS, Walker JL, Bassi S, Jones T, Punt J. The intracranial complications of rhinosinusitis: can they be prevented? Laryngoscope. 2002;112:59–63.

44. Kombogiorgas D, Seth R, Athwal R, Modha J, Singh J. Suppurative intracranial complications of sinusitis in adolescence. Single institute experience and review of literature. Br J Neurosurg. 2007;21:603–9.
45. Liao S, Durand ML, Cunningham MJ. Sinogenic orbital and subperiosteal abscesses: microbiology and methicillin-resistant Staphylococcus aureus incidence. Otolaryngol Head Neck Surg. 2010;143:392–6.
46. Wald ER. Microbiology of acute and chronic sinusitis in children and adults. Am J Med Sci. 1998;316:13–20.
47. Brook I. Bacteriologic features of chronic sinusitis in children. JAMA. 1981;246:967–9.
48. Brook I, Foote PA, Frazier EH. Microbiology of acute exacerbation of chronic sinusitis. Ann Otol Rhinol Laryngol. 2005;114:573–6.
49. Silviu-Dan F. Pediatric chronic rhinosinusitis: the old, the new, and the reasonable. Pediatr Ann. 2011;40:213–20.
50. Keir J, Pedelty L, Swift AC. Biofilms in chronic rhinosinusitis: systematic review and suggestions for future research. J Laryngol Otol. 2011;125:331–7.
51. Kaur R, Adlowitz DG, Casey JR, Zeng M, Pichicheso ME. Simultaneous assay for four bacterial species including Alloiococcus otitidis Using multiplex-PCR in children with culture negative acute otitis media. Pediatr Infect Dis J. 2010;29:741–5.

Chapter 6
Microbiology of Acute, Subacute, and Chronic Rhinosinusitis in Adults

Michael S. Benninger and Troy D. Woodard

Introduction

Rhinosinusitis is a term used to describe inflammation of the mucosa of the nose and paranasal sinuses [1]. Although this term encompasses multiple etiologies, some of which are not related to microbial pathogens, for the purposes of this chapter it will be used only in the context of infectious pathogens. Acute bacterial rhinosinusitis (ABRS) is a common upper respiratory infection characterized by inflammation of the mucosa of the nose and paranasal sinuses [1]. Since viruses tend to cause most cases of rhinosinusitis, it has been recommended that ABRS be identified in patients who have worsening symptoms after 5–7 days following the onset of symptoms or persistent symptoms for 7–10 days [2]. Acute bacterial rhinosinusitis has been estimated to effect 3 in every 1,000 people in the United States each year, with some individuals having multiple episodes [3]. It also appears that the incidence of ABRS is increasing [3, 4].

Chronic rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 weeks duration [1]. There are estimates that up to 20 million people in the United States suffer from chronic rhinosinusitis. However, many of these are not diagnosed by objective studies. Subacute rhinosinusitis refers to rhinosinusitis episodes lasting from 4 weeks up to 12 weeks. The prevalence of subacute rhinosinusitis has not been well defined. Although these terms are somewhat arbitrary and there are episodes of overlap, they do help to distinguish both differences in pathogens and also patient symptoms.

Acute Rhinosinusitis

During the first 7–10 days of a respiratory tract infection that involves the nose and sinuses, the predominant organisms are viruses, notably rhinovirus and adenovirus. There is strong evidence that viruses alone can cause inflammation in the sinuses. This has been confirmed by CT scans performed during a viral upper respiratory tract infection [5]. One of the interesting things about these viruses is that they may play a role in the alteration of the host immune system to allow for increased bacterial colonization and aggregation in the lymphoid tissue of the nasopharynx. Adenovirus types 1, 2, 3, and 5 have been shown to upgrade receptors for *Streptococcus pneumonia* which may increase adherence of the bacteria and subsequently increase the risk of infections [6].

Streptococcus pneumoniae (20–45 %) and *Haemophilus influenzae* (22–35 %) are the predominant organisms in ABRS in adults, while *Streptococcus pneumoniae* (30–43 %), *Haemophilus influenzae* (20–28 %), and *Moraxella catarrhalis* (20–28 %) are the predominant organisms as traditionally reported in acute bacterial rhinosinusitis in children [4]. Although *Staphylococcus aureus* has been identified as being cultured in many prospective clinical trials, it was often considered a contaminant. A recent meta-analysis suggests that *Staphylococcus aureus* is a real pathogen in approximately 10 % of cases of ABRS [7] (Fig. 6.1). Although *Moraxella catarrhalis* is frequently cultured in ABRS as well as other upper respiratory

M.S. Benninger, MD (✉) • T.D. Woodard, MD
Head and Neck Institute, Cleveland Clinic Foundation, 9500 Euclid Ave, A-71, Cleveland, OH 44195, USA
e-mail: benninm@ccf.org; woodart@ccf.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_6,

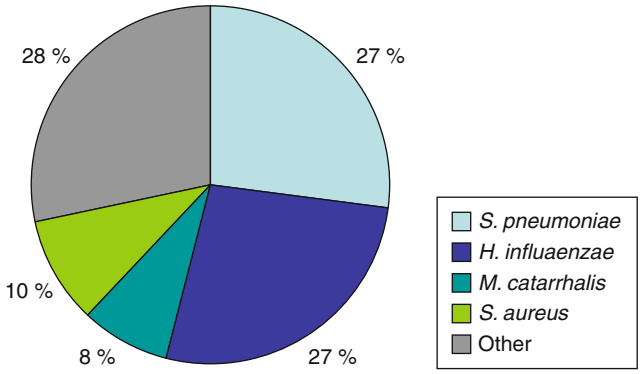


Fig. 6.1 Distribution of pathogens based on maxillary sinus taps and middle meatal cultures (Reprinted from Payne and Benninger [7]. With Permission from Oxford University Press)

tract infections, some researchers feel that it is typically a self-limited infection that does not require antibiotic treatment under most circumstances [7, 8]. Furthermore, disease severity based both on symptoms and radiographic findings is worse for *Streptococcus pneumoniae* than for *Haemophilus influenzae* and *Moraxella catarrhalis* [9].

There has been growing evidence of increasing antibiotic resistance to commonly used antibiotics for the treatment of ABRS [10]. In the 1990s there was evidence of a rapidly increasing resistance rate among common bacterial origins of ABRS and emergence of multidrug-resistant strains [10]. Forty percent of *Streptococcus pneumoniae* isolates have been found to be resistant to two or more of the antibiotics tested, and over 28 % were resistant to three or more antibiotics [10]. Fortunately, over the past few years, there has been a stabilization of these resistant rates [10]. The increased efforts to curb the overuse of antibiotics have led to changes in antibiotic prescribing patterns and may have played a partial role in the flattening of these resistant rates.

Conjugate *Haemophilus influenzae* type b (Hib) vaccines were initiated in 1990 as a routine part of childhood immunizations. This vaccine is nearly universally effective against the typable *H influenzae* strains that were responsible for a number of aggressive diseases such as meningitis and epiglottitis. Hib vaccinations have nearly eliminated the incidence of *Haemophilus influenzae* meningitis among widely vaccinated populations, due to the achievement of herd immunity [11]. Non-typable strains of *Haemophilus influenzae* are still major pathogens in ABRS, acute otitis media (AOM), and lower respiratory tract infections. It appears that rates of non-typable *Haemophilus influenza*, the major etiology of ABRS, are not affected by Hib vaccination and have, in fact, gradually increased in appearance [12, 13].

With *Streptococcus pneumoniae*, over 90 serotypes have been isolated, many of which can cause disease in humans [11]. This differs greatly when compared to *H. influenza,* where one subtype accounted for almost all of the invasive disease and where a single vaccine was effective in dramatically reducing invasive disease states. In the United States, seven serotypes are responsible for over 80 % of the invasive disease caused by *Streptococcus pneumoniae* in young children [11]. Research thus targeted these seven serotypes. A heptavalent conjugate pneumococcal vaccine (PCNV7) was found to be 100 % effective in preventing invasive pneumococcal disease and was approved in the United States in 2000 [11, 14]. Multiple additional studies have supported the efficacy of the vaccine in preventing invasive pneumococcal disease [15–17]. In addition, the beneficial effect has been extended to the adult community as a result of herd immunity [16, 17]. The primary effects of routine vaccination appear to have had an impact on the more common diseases such as ABRS and AOM.

Pathogen Shift

There has been a dramatic shift in the repertoire of pathogenic organisms found in both ABRS and AOM as a result of the widespread use of conjugate pneumococcal vaccines. Brook et al. have shown that there have been measurable changes in the recovery of pathogens in adults with acute maxillary sinusitis. When comparing time points at 4 years prior to and 5 years after the introduction of the conjugate pneumococcal vaccine, *Haemophilus influenzae* increased from an incidence of 36 % prior to vaccine advancements to become the most common pathogen at 43 %. Recovery of *Streptococcus pneumoniae* from sinus aspirates was found to decrease from the most common pathogen at 46 % of isolates to 35 % after the use of the vaccine. There also was a proportionate increase in the cases caused by *Staphylococcus aureus* and *Moraxella catarrhalis* [18].

In another study, nasopharyngeal cultures were obtained in children with acute maxillary sinusitis before and after widespread use of conjugate pneumococcal vaccination. *Streptococcus pneumoniae* decreased from 43 % of isolates to 25 %, while *Haemophilus influenzae* increased from 33 to 41 %. *Moraxella catarrhalis* remained stable 13–14 %, while *Streptococcus pyogenes* increased from 7 to 12 % and *Staphylococcus aureus* increased from 4 to 8 % [18].

With this shift in organism involvement has been a gradual shift in resistance. Ampicillin resistance among *H. influenzae* due to β-lactamase production is now highly prevalent worldwide [19]. The Infectious Disease Society of America, in their guidelines for the treatment of ABRS, recommends a shift in the approach to antibiotic use in ABRS to beta-lactamase-resistant drugs. The recommendation that amoxicillin-clavulanate rather than amoxicillin alone be considered as first-line therapy for ABRS is based on two observations: (a) the increasing incidence of *H. influenzae* in upper respiratory tract infections of children, particularly acute otitis media, since the introduction of conjugated pneumococcal vaccine and (b) the high prevalence of β-lactamase-producing respiratory pathogens in ABRS (particularly *H. influenzae* and *M. catarrhalis*) among recent respiratory tract isolates.

There has also been a change in the serotypes of *Streptococcus pneumoniae* responsible for both ABRS and AOM toward those not found in the vaccine [20–22]. In one study, the number of episodes of AOM that were attributable to serotypes contained in the vaccine has decreased by 51 %, while the number of episodes attributable to other serotypes has increased by 33 % [21].

Pneumococcal Resistance

There is strong evidence from multiple recent studies that there has been a reduction in both the non-susceptible and high-level resistant strains of *Streptococcus pneumoniae* cultured in AOM and to a lesser extent in ABRS [14, 17, 23, 24]. Whitney et al. showed that there was a reduction of 35 % in strains non-susceptible to penicillin [17]. High-level resistance of *Streptococcus pneumoniae* to penicillin also appears to have dropped from 15 to 5 % [14]. There has been an associated increase in the β-lactamase-producing strains of *Haemophilus influenzae* [23]. Ampicillin resistance among *H. influenzae* due to β-lactamase production is highly prevalent worldwide [19].

The impact of vaccination on the incidence of ABRS is somewhat difficult to assess as acute sinusitis, particularly in children, can be caused by a number of pathogens and is often viral [1, 4]. In addition, much of the culture data are based on AOM studies. However, there has been a clear shift in the pathogens associated with both ABRS and AOM, and this shift is consistent between the two groups. This concordance is not unexpected since the pathogenic organisms for ABRS and AOM are commonly the same pathogens [24]. Another interesting phenomenon following the vaccine era has been the apparent increase in the culture rates of *Staphylococcus aureus* [18]. Although there has been some speculation that *Staphylococcus aureus* in ABRS might be a contaminant, a recent meta-analysis of randomized clinical trials of antibiotic therapy in ABRS strongly suggests that *Staphylococcus aureus* is a real pathogen and should be considered in the treatment of ABRS [7] (Fig. 6.1). The emergence of *Staphylococcus aureus* as a recognized pathogen [7], and one which may be increasing [18] in upper respiratory tract infections, may result in changes in therapy in the future. Although the prevalence of *Staphylococcus aureus* remains relatively small, it is important that this organism be watched closely. This is particularly true in the era of increasing rates of community-acquired methicillin-resistant *Staphylococcus aureus*.

If there are concerns about the microorganisms that may be playing a role in ABRS or if there is a poor response to empiric treatment, cultures may be obtained. Traditionally, sinus aspirations were required, particularly since random cultures of the anterior nares or the nasopharynx would often reveal different organisms than were found when cultures were obtained directly from the sinuses. Performing maxillary taps in clinical practice is both cumbersome and uncomfortable for the patient. Endoscopic middle meatal culture is a much better technique and will be discussed later in this Chap. [25].

Subacute Rhinosinusitis

Evaluating the microbiology of subacute rhinosinusitis is difficult since patients tend to either present with acutely symptomatic ABRS or present to a medical provider later when the symptoms have persisted long enough to be classified as chronic. In addition, symptoms of subacute rhinosinusitis are not as acute as seen in ABRS and are very often diagnosed with other disorders, such as allergic rhinitis or chronic rhinitis (which may in fact be occurring concurrently with sinusitis in some cases). Furthermore, in some patients, there may have been a short period of improved symptoms following the acute infection which may make it difficult to determine whether this is another primary acute infection or a subacute inflammatory process. Confusion in the diagnosis of subacute rhinosinusitis can also occur when the patient has been initially treated with an antibiotic and still is symptomatic which raises questions as to whether they were inadequately treated for the initial episode or whether the persistent inflammation is noninfectious.

In most cases, subacute rhinosinusitis has a typical pathogen pattern similar to ABRS with *Streptococcus pneumonia, Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes,* and *Staphylococcus aureus* predominating. There

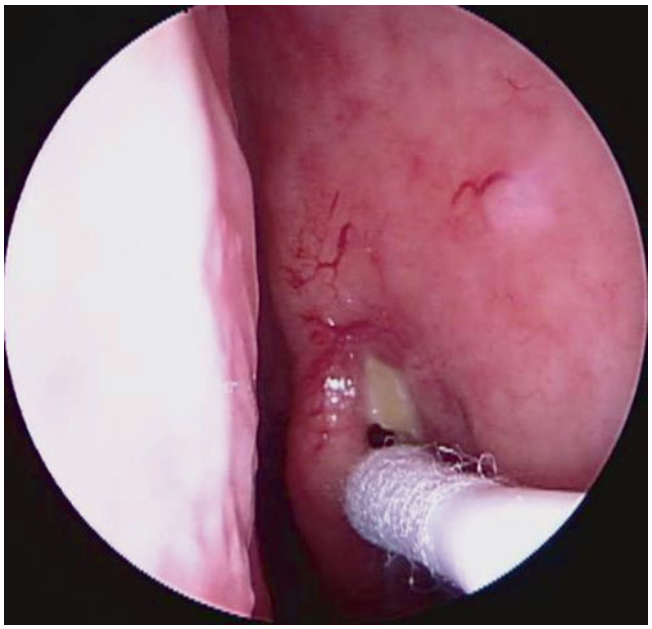


Fig. 6.2 Endoscopic-guided culture of middle meatus

may be some pathogens more typical of CRS, particularly by the third month. If the patient had been treated with an antibiotic during the early phase of the infection, there may also be a shift in pathogens or some selection of more antibiotic-resistant strains.

Chronic Rhinosinusitis

Chronic rhinosinusitis (*CRS*) is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses for at least 12 consecutive weeks' duration [1]. It is a very common illness and reportedly more widespread than arthritis and hypertension, affecting over 31 million Americans [1, 26]. CRS is associated with significant symptoms which result in loss of productivity and negatively impacts quality of life parameters [27]. This complex disorder has many potential etiologies, and the spectrum of disease can vary dramatically from individual to individual. In addition the responsiveness to treatment is often unpredictable. However, for the purpose of this chapter, we will focus on the infectious/microbiologic etiologies of CRS.

Bacteria

Despite the multifactorial nature of CRS, the presence of bacteria within the paranasal sinuses has been well documented and implicated as the cause of inflammation in many individuals [28, 29]. Unlike acute bacterial rhinosinusitis, where the pathogens (*Streptococcus pneumoniae, Haemophilus Influenzae*, and *Moraxella catarrhalis*) are well described, there is much debate on the pathogens associated with CRS. As a result, broad-spectrum antibiotics are most commonly used and have been associated with development of drug-resistant microbes.

The increased incidence of drug-resistant bacteria has prompted many otolaryngologists to initiate culture-directed antibiotic therapy in their practice. Traditionally, the gold standard for obtaining sinus cultures was by maxillary sinus taps (MST) through the canine fossa or inferior meatus. However, this method is not ideal because it is more invasive, associated with increased discomfort, requires local anesthesia, and has a potential small risk of injury to the teeth, infraorbital nerve, and lacrimal apparatus. Advances in endoscopic techniques have allowed for the development of endoscopic-guided aspiration or swab of a variety of sinuses under direct visualization (Fig. 6.2).

Endoscopic-guided cultures have been shown to be well tolerated and as effective as maxillary sinus taps [30–32]. A meta-analysis by Benninger et al. compared the results of endoscopic directed middle meatal (EDMM) cultures and

Table 6.1 Classic pathogens found in sinusitis

	Duration	Viral	Bacterial	Fungal
Acute	Up to 4 weeks			
		Rhinovirus	*Streptococcus pneumoniae*	Aspergillus
		Adenovirus	*Haemophilus influenzae*	Absidia
			Moraxella catarrhalis	Basidiobolus
			Streptococcus pyogenes	Mucor
			Staphylococcus aureus	Rhizopus
Subacute	From 4 to 12 weeks		*Streptococcus pneumoniae*	
			Haemophilus influenzae	
			Moraxella catarrhalis	
			Streptococcus pyogenes	
			Staphylococcus aureus	
Chronic	Greater than 12 weeks		Coagulase-negative staphylococci	Aspergillus
			Staphylococcus aureus	Alternaria
			Corynebacterium diphtheriae	Bipolaris
			Haemophilus influenzae	Mucor
			Streptococcus pneumoniae	Candida
			Pseudomonas aeruginosa	Curvularia
			Anaerobic bacteria spp.	Sporothrix
				Pseudallescheria

maxillary sinus taps in patients with acute bacterial maxillary rhinosinusitis. The meta-analysis demonstrated that EDMM is both highly sensitive and specific (80.9 and 90.5 %, respectively) and is a viable and preferred method of culturing the sinuses of a patient with rhinosinusitis [25].

In contrast to acute sinusitis, there are significant differences in the bacterial pathogens associated with chronic sinusitis (Table 6.1). Brook evaluated the aerobic and anaerobic microbiology of acute and chronic sinusitis in patients with involvement of multiple sinuses. He confirmed the importance of aerobic and facultative bacteria in acute sinusitis. However, he found that there was a predominance of anaerobic bacteria in patients with chronic sinusitis [33]. In another study, Brook et al. analyzed the transition from acute maxillary sinusitis to chronic maxillary sinusitis in five patients that failed antimicrobial therapy. Initial endoscopic aspirations during the acute phase of the sinus infection revealed aerobic or facultative bacteria (*S. Pneumoniae*, *H. influenzae*, and *M. Catarrhalis*). However, as the infection became more chronic, the aerobic and facultative bacteria were eventually replaced by anaerobes [34]. It is proposed that the gradual shift in species is a result of selective pressures placed on the bacteria by both the antimicrobial agents and changes in the environment caused by edema, reduced blood supply, low oxygen tension, and increased acidity within the sinus.

To further illustrate the strong presence of anaerobic bacteria, Brook also evaluated patients with chronic frontal, sphenoid, and ethmoid sinusitis. He found that anaerobic bacteria were found in over two thirds of the patients. The predominant anaerobes were *Prevotella, Peptostreptococcus,* and *Fusobacterium* spp. Aerobic bacteria included mostly gram-negative bacilli, such as H. *influenzae, K. Pneumoniae, E. coli*, and *P. aeruginosa* [35–37].

Many practitioners are unable to duplicate anaerobic bacterial growth in their studies. Factors that may affect this finding include different methods utilized to sample, transport, and cultivate the samples, the patient population, geography, and previous antimicrobial therapy. Doyle and Woodham performed 94 endoscopically guided ethmoid cultures on 50 adults with chronic sinusitis and no anaerobes were found. While coagulase-negative staphylococci were the most common non-classical pathogen found within 71 % off the specimens, *Staphylococcus aureus* predominated as the most frequent classical pathogen (33 %). In addition, *Corynebacterium diphtheriae* (10 %), *Haemophilus influenzae* (4 %), *Pseudomonas aeruginosa* (2 %), and *Streptococcus pneumoniae* (2 %) were also present [38]. Nadel et al. compared 507 endoscopically guided cultures in 265 patients with chronic sinusitis to 50 cultures from healthy volunteers. The aim of the study was to determine the prevalence of bacterial species in recalcitrant sinus disease. Coagulase-negative Staphylococci, *Staphylococcus aureus, Pseudomonas aeruginosa*, and Streptococcus were the most common isolates. *Pseudomonas aeruginosa* was more common in patients taking systemic steroids [39].

Despite the evidence of bacterial growth, some authors question the role that bacteria have in the pathogenesis of CRS. Bhattacharyya performed a controlled paired analysis in 49 patients with unilateral chronic rhinosinusitis. He obtained aerobic, anaerobic, and fungal cultures in these patients and compared it to the non-diseased contralateral side. He was able to recover both aerobic and anaerobic bacteria from both the diseased and contralateral non-diseased side in patients with CRS [40]. These findings cast doubt on the etiologic role of bacteria in CRS and possibly suggest that there are other factors

associated with its development. Similarly, Pandak et al. aimed to identify the bacteria in chronically inflamed sinuses and examined whether the bacteria found were colonizers or whether or not they actually infected the sinus mucosa [41]. Nasopharyngeal and sinus swabs were performed on 65 patients that underwent endoscopic sinus surgery, and a correlation between the cultures was made to determine if the nasopharyngeal swab could be of any significance in determining the antimicrobial therapy of chronic sinusitis. They found that the bacteria from the nasopharyngeal swabs were similar to those isolated from the sinuses and therefore not pathogenic. Because the bacteria were found in both locations and since they did not detect a significant number of leukocytes, they proposed that chronic sinusitis should be thought of as a chronic inflammatory condition rather than an infectious process. In addition, it was recommended that routine antibiotic therapy should be avoided except for cases in which there is an acute exacerbation of chronic sinusitis.

Low bacterial culture rates, lack of response to antibiotic therapy, and lack of correlation between bacteriological findings and clinical features have led many clinicians to favor nonbacterial etiologies of chronic rhinosinusitis. However, over the past few years, there is increasing evidence that bacterial biofilms exist on the mucosa of CRS patients, and this is discussed in depth in another section of this text. The discovery of bacteria existing in alternative forms has led investigators to reexamine the role that bacteria may have in CRS.

Biofilms are surface-associated communities of microorganisms that are encased in a protective extracellular polymeric matrix. Biofilms lack the antibiotic susceptibility of planktonic bacteria and are reportedly up to 1,000 times more resistant to antimicrobials therapy [42]. In addition, the matrix serves to increase bacterial survival by protecting against host antibodies, phagocytosis, complement binding, and antibiotic penetration [42]. Bacteria within biofilms are able to share genetic material via plasmids. This allows for sharing of protective mechanisms and enables the bacteria to mutate and develop antibiotic resistance. Biofilms have been implicated in playing a role in chronic rhinosinusitis resulting in poor disease progression and persistent sinonasal inflammation [43, 44]. Singhal et al. conducted a prospective blinded study on 51 consecutive patients undergoing endoscopic sinus surgery for CRS [43]. Biofilms were found in 71 % of patients. The patients with biofilms had more severe disease preoperatively and persistence of postoperative symptoms, mucosal inflammation, and infections.

Biofilms can be polymicrobial or made of a single species. Consequently, different biofilm species are associated with different disease phenotypes. While, the presence of polymicrobial biofilms is associated with worse preoperative disease severity, it did not affect the postsurgical outcomes [45]. In addition, patients with *H. influenzae* biofilms present with milder sinus disease and have a faster recovery to normal sinus mucosa when compared to patients with *Staphylococcus aureus* biofilms [45, 46]. The importance of biofilms in infection cannot be understated, and there is an entire chapter in this book dedicated to the discussion of the role of biofilms in rhinosinusitis in much greater detail (see Chap. 7).

Fungal

Although bacteria have been implicated as being the culprit in many cases of CRS, fungi may also play a role. There is much debate about the exact function of fungi in the pathogenesis of CRS. The ubiquitous nature of fungi makes it present in both diseased and healthy individuals. While some believe that fungi are innocent bystanders that colonize the nasal and sinus cavities, others postulate that fungi are the primary etiology for CRS.

Fungal rhinosinusitis (FRS) is broadly classified into invasive and noninvasive forms based on histopathological findings. The invasive forms include acute invasive FRS, chronic invasive FRS, and granulomatous invasive FRS. The noninvasive forms include fungal ball, saprophytic, and eosinophilic-related FRS.

Acute invasive FRS is a very aggressive fungal infection that has significant morbidity and a high mortality rate. It generally has a time course less than 4 weeks duration and occurs in immunocompromised and or poorly controlled diabetic patients. Biopsy and histopathological analysis of suspected tissue are critical in making a diagnosis. Histopathology demonstrates hyphal invasion of the nasal mucosa and underlying vasculature resulting in tissue necrosis. This disease has been shown to be caused by a variety of fungal species including Absidia, Aspergillus, Basidiobolus, Mucor, and Rhizopus [47, 48].

In contrast to the acute invasive FRS, chronic invasive FRS has a more protracted course. This chronic condition is diagnosed after being present for more than 12 weeks and generally occurs in patients with a mild immunologic impairment. Similarly to acute invasive FRS, the tissue must be biopsied to verify tissue invasion. Although dense populations of hyphae are identified under histopathological examination, vascular invasion is less likely and only occurs occasionally. While *Aspergillus fumigatus* is the most commonly isolated fungi and is cultured in more than 50 % of cases, Mucor, Alternaria, Curvularia, Bipolaris, Candida, *Sporothrix schenckii*, and *Pseudallescheria boydii* species have been identified [47, 48]. Despite the insidious nature of the disease, the outcome can be fatal. Thus, medical and surgical treatments are required.

Table 6.2 Bent and Kuhn diagnostic criteria for allergic fungal sinusitis

1. Type 1 hypersensitivity
2. Characteristic CT findings
3. Eosinophilic mucin without tissue invasion
4. Positive fungal stain/culture
5. Nasal polyposis

Chronic granulomatous invasive FRS is an extremely rare disease process that has been identified in three cases in the United States as well as in Sudan, India, Pakistan, and Saudi Arabia [47, 48]. Similar to chronic invasive FRS, the symptoms of this disease must be present for at least 12 weeks. Interestingly, infected individuals are usually immunocompetent and present with proptosis. Histopathology reveals fungal invasion with noncaseating granulomas and giant cell formation. Similar to the other invasive forms of fungal sinusitis, this infection can leave the paranasal sinuses and spread to other organs.

Fungal balls represent a form of noninvasive fungal infections. Fungal balls are an accumulation of densely packed fungal hyphae compacted into one sinus cavity, most commonly the maxillary sinus. However, the other sinuses can be affected. A variety of fungal species are capable of developing fungal balls, including *Aspergillus flavus*, *Aspergillus fumigatus*, Alternaria, and Mucor. Criteria for the diagnosis of fungal balls include:

1. No histologic evidence of fungal invasion of mucosa, associated blood vessels, or underlying bone
2. Radiologic evidence of sinus opacification with or without associated calcifications
3. Mucopurulent, cheesy, or clay-like material within a sinus
4. Dense conglomeration of hyphae separate from but adjacent to sinus respiratory mucosa
5. A chronic inflammatory response that does not include a predominance of eosinophils, allergic mucin, or a granulomatous response [49]

While fungal balls are not typically invasive, this is not always the case in an immunocompromised host. Patients with fungal balls usually present with symptoms suggestive of chronic sinusitis.

Another form of noninvasive fungal infection includes saprophytic fungal infections. The ubiquitous nature of fungal spores allows them to be continuously inhaled into the nasal airway. As a result, saprophytic fungal infections occur when fungal spores land and germinate on crust within the nasal cavity, commonly after sinus surgery. Treatment involves removing the crust.

Throughout the past few decades, eosinophilic-related FRS has evolved from just being a component of allergic fungal sinusitis to being considered a separate entity in which there is eosinophilic mucin. The pathogenesis is thought to occur when sensitized individuals are exposed to the fungal allergens. The resulting immune response results in respiratory inflammation and the production of "allergic" mucin. The allergic mucin blocks sinus drainage and traps the fungal particles. This further stimulates the reactive immune reactions leading to the accumulation of eosinophilic mucin and other inflammatory mediators such as major basic protein, tumor necrosis factor B, eosinophil peroxidase, eosinophil-derived neurotoxin, and interleukins 4,5,10, and 13 [48].

Allergic fungal sinusitis affects 8–12 % of patients with CRS [50]. It is diagnosed by the presence of five criteria which include Type I hypersensitivity, nasal polyps, characteristic CT findings, eosinophilic mucin without signs of fungal invasion, and positive fungal stain or culture [51] (Table 6.2). Patients present with signs and symptoms that are recalcitrant to traditional medical and surgical therapy. They also have characteristic allergic fungal mucin, which is a thick, tenacious, eosinophilic secretion with the texture of peanut butter and characteristic histologic findings. CT scans may demonstrate bony erosion and/or expansion and reveal heterogeneous signal intensity thought to be from hemosiderin and deposition of heavy metals such as iron and manganese [52] (Fig. 6.3).

Although fungal detection within the mucin is important, the results should be interpreted with caution because the hyphae may be sparse and difficult to culture. The incidence of fungal microorganisms found within the sinuses varies from study to study. Ponikau et al. was able to obtain positive fungal cultures and allergic mucin in 96 % of patients with CRS, suggesting that the majority of CRS patients may actually have AFS [53]. However, the majority of his patients (58 %) did not demonstrate evidence of allergy or increased levels of IgE to fungus. These results put into question the role of IgE in the pathogenesis of AFS. Consequently, he proposed that the terminology of allergic fungal sinusitis be changed to eosinophilic fungal rhinosinusitis.

This new classification of fungal sinusitis was further defined by Ferguson who performed a literature review and compared 431 allergic fungal sinusitis patients to 69 eosinophilic mucin rhinosinusitis (EMRS) patients [54]. There were significant clinical and immunological differences to distinguish AFS from EMRS. While AFS is an allergic response to fungi in

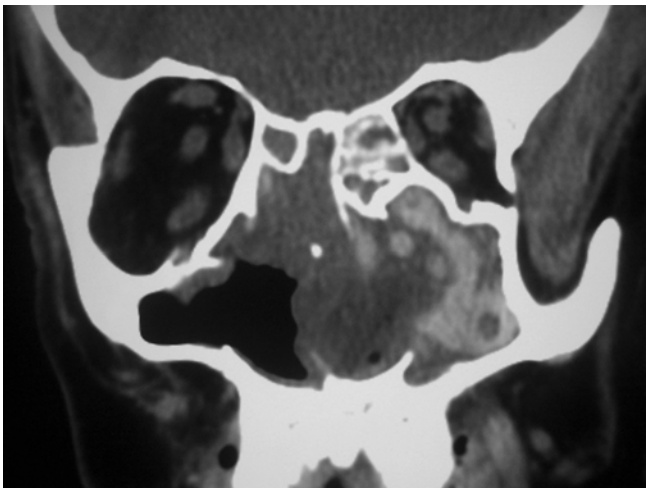


Fig. 6.3 CT scan of patient with AFS. There is heterogeneous signal intensity within the paranasal sinuses and extensive bony expansion and remodeling

predisposed individuals, EMRS occurs because of a systemic immunological dysregulation. EMRS is a systemic disease and presents bilaterally, while the allergic response in AFS may occur unilaterally or bilaterally depending on the antigenic stimulation. In both disorders, medical therapy with steroids and other anti-inflammatory agents, along with surgical extirpation, are the treatments of choice. The treatment of fungal rhinosinusitis is discussed in detail in Chap. 15.

References

1. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg. 2003;129:S1–32.
2. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg. 1997;117:S1–7.
3. Benninger MS, Sedory Holzer SE, Lau J. Diagnosis and treatment of uncomplicated acute bacterial rhinosinusitis: summary of the Agency for Health Care Policy and Research evidence-based report. Otolaryngol Head Neck Surg. 2000;122:1–7.
4. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 2004;130:1–45.
5. Gwaltney JM, Phillips CD, Miller RD, et al. Computed tomographic evaluation of the common cold. N Engl J Med. 1994;330:25–30.
6. Håkansson A, Kidd A, Wadell G, Sabharwal H, Svanborg C. Adenovirus infection enhances in vitro adherence of Streptococcus pneumoniae. Infect Immun. 1994;62:2707–14.
7. Payne SC, Benninger MS. Staphylococcus aureus is a major pathogen in acute bacterial rhinosinusitis: a meta-analysis. J Clin Infect Dis. 2007;45:e121–7.
8. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54:e1–41.
9. Benninger MS, Brook I, Farrell DJ. Disease severity in acute bacterial rhinosinusitis is greater in patients infected with streptococcus pneumoniae than in those infected with haemophilus influenzae. Otolaryngol Head Neck Surg. 2006;135:523–8.
10. Sahm DF, Benninger MS, Evangelista AT, Cheung Yee Y, Thornsbury C. Antimicrobial resistance trends among sinus isolates of Streptococcus pneumoniae from the United States: 2000–2005. Otolaryngol Head Neck Surg. 2007;136:385–9.
11. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J. 2000;19:187–95.
12. Benninger MS. Acute bacterial rhinosinusitis and otitis media: changes in pathogenicity following the widespread use of pneumococcal conjugate vaccine. Otolaryngol Head Neck Surg. 2008;138:274–8.
13. Benninger MS, Manz R. Impact of vaccination on rhinosinusitis and otitis media. Cur Allergy Asthma Rep. 2010;10:411–8.
14. Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in northern California Kaiser Permanente. Pediatr Infect Dis J. 2004;23:485–9.
15. Pelton SI. The decline in invasive pneumococcal disease. Pediatrics. 2004;113:617–8.
16. Shafinoori S, Ginocchio CC, Greenberg AJ, Yeoman E, Cheddie M, Rubin LG. Impact of pneumococcal conjugate vaccine and the severity of winter influenza-like illnesses on invasive pneumococcal infections in children and adults. Pediatr Infect Dis J. 2005;24:10–6.
17. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003;348:1737–46.
18. Brook I, Foote PA, Hausfeld JN. Frequency of recovery of pathogens causing acute maxillary sinusitis in adults before and after introduction of vaccination of children with the 7-valent vaccine. J Med Microbiol. 2006;55:943–6.
19. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in Haemophilus influenzae. Clin Microbiol Rev. 2007;20:368–89.
20. Kilpi T, Ahman H, Jokinen J, et al. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Infect Dis. 2003;37:1155–64.

21. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med. 2001;344:403–9.
22. Hanage WP, Auranen K, Syrjanen R, et al. Ability of pneumococcal serotypes and clones to cause acute otitis media: implications for the prevention of otitis media by conjugate vaccines. Infect Immun. 2004;72:76–81.
23. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995–2003. Pediatr Infect Dis J. 2004;23:824–8.
24. Pichichero ME. Pathogen shifts and changing cure rates for otitis media and tonsillopharyngitis. Clin Pediatr. 2006;45:493–502.
25. Benninger MS, Payne SC, Ferguson BJ, Hadley JA, Ahmad N. Endoscopically directed middle meatal cultures versus maxillary sinus taps in acute bacterial maxillary rhinosinusitis: a meta-analysis. Otolaryngol Head Neck Surg. 2006;134:3–9.
26. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol. 2004;114:155–212.
27. Glicklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg. 1995;113:104–9.
28. Brook I. Microbiology and antimicrobial management of sinusitis. J Laryngol Otol. 2005;119:251–8.
29. Brook I. Microbiology of sinusitis. Proc Am Thorac Soc. 2011;8:90–100.
30. Tantilipikorn P, Fritz M, Tanabodee J, et al. A comparison of endoscopic culture techniques for chronic rhinosinusitis. Am J Rhinol. 2002;2002: 255–60.
31. Araujo E, Palombini BC, Cantarelli V, et al. Microbiology of middle meatus in chronic rhinosinusitis. Am J Rhinol. 2003;17:9–15.
32. Nadel DM, Lanza DC, Kennedy DW. Endoscopically guided sinus cultures in normal subjects. Am J Rhinol. 1999;13:87–90.
33. Brook I. Discrepancies in the recovery of bacteria from multiple sinuses in acute and chronic sinusitis. J Med Microbiol. 2004;53:879–85.
34. Brook I, Frazier EH, Foote PA. Microbiology of the transition from acute to chronic maxillary sinusitis. J Med Microbiol. 1996;45:372–5.
35. Brook I. Bacteriology of acute and chronic sphenoid sinusitis. Ann Otol Rhinol Laryngol. 2002;111:1002–4.
36. Brook I. Bacteriology of acute and chronic frontal sinusitis. Arch Otolaryngol Head Neck Surg. 2002;128:583–5.
37. Brook I. Bacteriology of acute and chronic ethmoid sinusitis. J Clin Microbiol. 2005;43:3479–80.
38. Doyle PW, Woodham JD. Evaluation of the microbiology of chronic ethmoid sinusitis. J Clin Microbiol. 1991;29:2396–400.
39. Nadel DM, Lanza DC, Kennedy DW. Endoscopically guided cultures in chronic sinusitis. Am J Rhinol. 1998;12:233–41.
40. Bhattacharyya N. Bacterial infection in chronic rhinosinusitis: a controlled paired analysis. Am J Rhinol. 2005;19:544–8.
41. Pandak N, Pajić-Penavić I, Sekelj A, et al. Bacterial colonization or infection in chronic sinusitis. Wien Klin Wochenschr. 2011;123:710–3.
42. Suh JD, Ramakrishnan V, Palmer JN. Biofilms. Otolaryngol Clin North Am. 2010;43:521–30.
43. Singhal D, Psaltis AJ, Foreman A, Wormald PJ. The impact of biofilms on outcomes after endoscopic sinus surgery. Am J Rhinol Allergy. 2010;24:169–74.
44. Psaltis AJ, Weitzel EK, Ha KR, Wormald PJ. The effect of bacterial biofilms on post-sinus surgical outcomes. Am J Rhinol. 2008;22:1–6.
45. Foreman A, Wormald PJ. Different biofilms, different disease? A clinical outcomes study. Laryngoscope. 2010;120:1701–6.
46. Singhal D, Foreman A, Bardy JJ, Wormald PJ. Staphylococcus aureus biofilms: nemesis of endoscopic sinus surgery. Laryngoscope. 2011;121: 1578–83.
47. de Shazo RD, O'Brien M, Chapin K, Soto-Aguilar M, Gardner L, Swain R. A new classification and diagnostic criteria for invasive fungal sinusitis. Arch Otolaryngol Head Neck Surg. 1997;123:1181–8.
48. Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. Laryngoscope. 2009;119:1809–18.
49. de Shazo RD, O'Brien M, Chapin K, et al. Criteria for the diagnosis of sinus mycetoma. J Allergy Clin Immunol. 1997;99:475–85.
50. Chan Y, Kuhn FA. An update on the classifications, diagnosis, and treatment of rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2009;17:204–8.
51. Bent JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994;111:580–8.
52. Glass D, Amedee RG. Allergic fungal rhinosinusitis: a review. Ochsner J. 2011;11:271–5.
53. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc. 1999;74:877–84.
54. Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. Laryngoscope. 2000;110:799–813.

Chapter 7
Biofilms in Chronic Rhinosinusitis

Nithin D. Adappa and James N. Palmer

Introduction

Chronic rhinosinusitis (CRS) is one of the most common chronic medical conditions affecting between 14 and 16 % of the US population. Direct health-care costs are estimated to be greater than $5.8 billion per year. According to data from the National Health Interview Survey, rhinosinusitis continues to be one of the ten leading diagnoses of office visits in the United States [1–5]. Patients with CRS consistently demonstrate lower quality-of-life scores than those suffering from chronic obstructive pulmonary disease, congestive heart failure, back pain, or angina [6, 7].

Chronic inflammation appears to be the hallmark of CRS. A number of factors have been implicated in this chronic inflammation including asthma, allergic rhinitis, Gram-positive and Gram-negative infections, aspirin-sensitive asthma, fungus, paranasal osteitis, nasal polyps, and superantigens. Although CRS is likely multifactorial, the common pathophysiologic finding is the development of ineffective paranasal sinus mucociliary clearance which subsequently results in stasis of sinonasal secretions and resultant infections and/or persistent inflammation. Although this is not typical of all CRS, there is a subset of patients that develop chronic inflammation despite maximal medical and surgical therapy. It is among this group of CRS patients that bacterial biofilms may have the greatest impact.

Biofilm Background

It is currently estimated that at least 65 % of all human bacterial infections may involve biofilm formation. These include a diverse range of infectious processes, including dental caries, periodontitis, musculoskeletal infections, osteomyelitis, bacterial prostatitis, endocarditis, and cystic fibrosis pneumonia. In the otolaryngology literature, biofilms have been implicated in multiple areas including otitis media, CRS, chronic tonsillitis, adenoiditis, and device infections such as tympanostomy and tracheostomy tubes [8].

Bacterial biofilms are surface-associated communities of microorganisms encased in a protective extracellular matrix. The life cycle of a bacterial biofilm can be divided into five major components (Fig. 7.1). Biofilms initially develop when free-floating, planktonic bacteria anchor to biologic or inert surfaces. The attached bacteria multiply and develop from a state of monolayer to a microcolony. At some point, they develop into a critical mass, in which interbacterial cross talk occurs, triggering a phenomenon known as “quorum sensing” that leads to the biofilm phenotype.

N.D. Adappa MD (✉)
Division of Rhinology and Skull Base, Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania, 3400 Spruce Street, 5 Ravdin Pavilion, Philadelphia, PA 19104, USA
e-mail: nithin.adappa@uphs.upenn.edu

J.N. Palmer, MD
Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania, 3400 Spruce Street, 5 Ravdin Pavilion, Philadelphia, PA 19072, USA
e-mail: james.palmer@uphs.upenn.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_7,

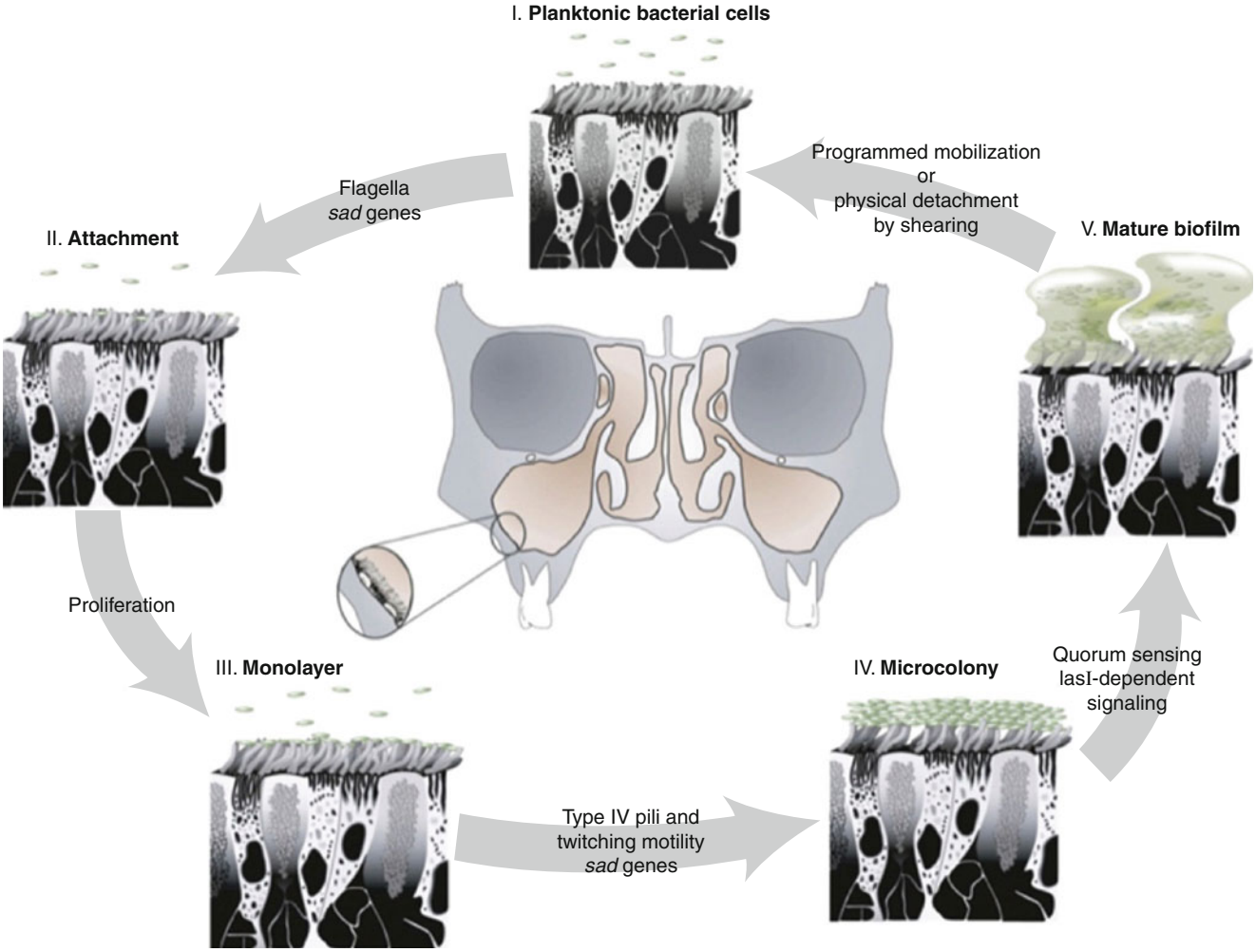


Fig. 7.1 Bacterial biofilm life cycle

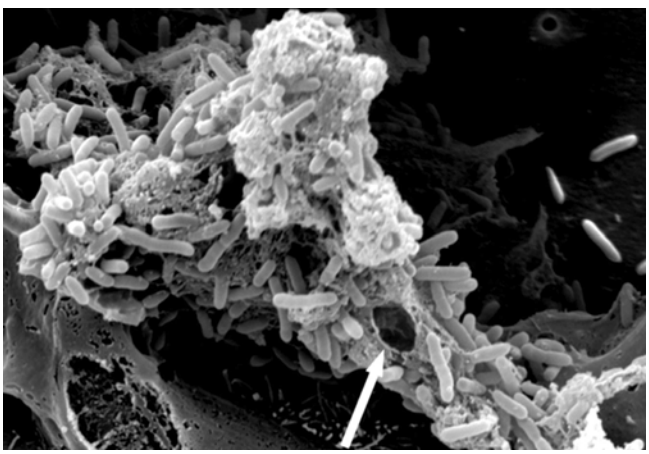


Fig. 7.2 Scanning electron microscopy demonstrating towers of Gram-negative bacteria with interspersed water channels (*arrow*)

The bacteria subsequently respond collectively to express factors that are specific to the biofilm phenotype, which subsequently leads to secretion of an exopolysaccharide matrix. Morphologically, this biofilm phenotype is composed of layers and towers of embedded, live bacteria with interspersed water channels (Fig. 7.2). The exopolysaccharide matrix makes up as much as 90 % of the biofilm [9]. Under the correct environmental conditions, the biofilm releases free-floating bacteria and the cycle continues. Approximately 80 % of the world's microbial biomass resides in the

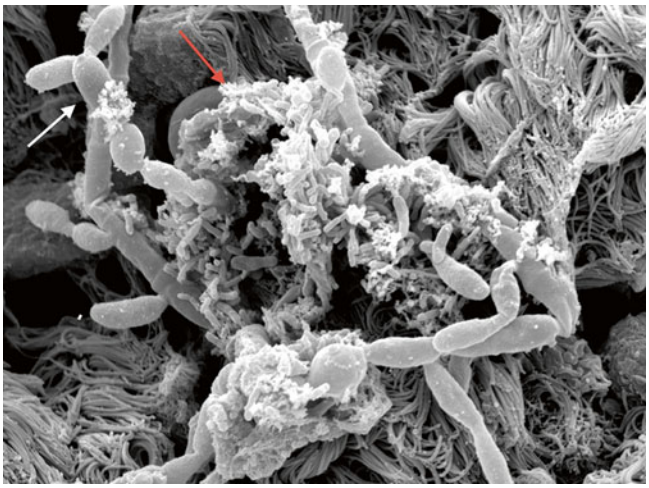


Fig. 7.3 Scanning electron microscopy demonstrating confluence of fungal (*white arrow*) and bacterial (*red arrow*) biofilms in a chronic sinusitis specimen

biofilm state. The National Institute of Health estimates that more than 75 % of the microbial infections that occur in the human body are related to the formation and persistence of biofilms [10, 11].

Microbiology of Bacterial Biofilms

Bacterial biofilm formation has been demonstrated in a plethora of bacteria including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. Prince et al. sampled 157 consecutive patients with CRS over a 4-month period, demonstrating that 28.6 % of samples demonstrated biofilm growth. *P. aeruginosa* and *S. aureus* composed 71 % of the samples that had biofilms [12]. Pseudomonas has also been demonstrated in cystic fibrosis infections [13, 14]. The remainder of the biofilm samples in the study were polymicrobial with and without *P. aeruginosa*, coagulase-negative staphylococci, and *H. influenzae*. Other studies have corroborated this data. Sanderson and colleagues used confocal laser scanning microscopy (CLSM) and fluorescein in situ hybridization (FISH) analyses to examine intraoperative samples taken from 18 patients with CRS undergoing septoplasty [15]. They demonstrated 78 % of the patients had detectable bacterial biofilm formation. Interestingly, they found biofilms on two of their five control patients (no CRS), highlighting the need for a better understanding of the correlation between biofilms and CRS.

Fungal Biofilms

Numerous fungal species have also been shown to form biofilms both in vitro and in vivo [16]. *Candida* spp. are among the most common agents demonstrated in yeast biofilm infections. *Cryptococcus*, *Pneumocystis*, *Aspergillus*, *Coccidioides*, and other fungal species have also been identified in biofilm form. The most common fungal biofilm associated with indwelling medical devices is *Candida albicans*. Chandra et al. demonstrated that *Candida albicans* isolates in biofilm form demonstrated increased resistance to amphotericin B, nystatin, chlorhexidine, and fluconazole when compared to planktonic *Candida* forms [17]. Characterization of fungal biofilms has been challenging, but like their bacterial counterparts, developmental phases have been identified. The main phases of fungal biofilm development include adhesion, filamentation, and hyphal and yeast proliferation with maturation and production of an extracellular matrix. The matrix consists predominantly of proteins, chitins, DNA, and carbohydrates. It acts to cover the biofilm and serves as a protective layer against host immune factors, antifungal agents, and physical disruption of underlying cells. El-Aziz and colleagues demonstrated *Candida* spp. were able to form biofilms by directly attaching to bacteria that have already colonized a surface [18].

Fungal elements have been demonstrated within sinus mucosal biofilms in CRS patients (Fig. 7.3) [18]. It has been theorized that the fungi may contribute to the chronic inflammation or possibly the fungi and bacteria interact in a symbiotic relationship to increase resistance to host defenses and treatment. Foreman et al. identified mixed bacterial-fungal biofilms from intraoperative specimens in patients with CRS [19]. Continued investigation is necessary to determine the effects fungal biofilms have on CRS pathophysiology.

Evidence for Biofilms in the Sinus

As biofilms were implicated in various other chronic diseases including otitis media, osteomyelitis, periodontitis, and others, it was natural to look at the evidence for biofilms in CRS. We originally described bacterial biofilms in the paranasal sinuses. Initially, using scanning electron microscopy (SEM), morphological features characteristic of biofilms, including water channels and the exopolysaccharide matrix, were identified in 6/6 sinus stents removed from CRS patients. The culture demonstrated *Pseudomonas aeruginosa* on all six patients. We subsequently examined sterile stents placed in a Pseudomonas culture media for 48 h and identified identical biofilm structures [20]. These findings were then corroborated in an animal model in which rabbits were inoculated with Pseudomonas for varying time courses (1–3 weeks) and all demonstrated biofilm formation on the epithelium of the infected mucosa compared to lack of biofilm formation on non-inoculated (control) rabbit group [21]. The authors ultimately demonstrated bacterial biofilms on the sinonasal mucosa of 16 recalcitrant CRS patients. Of the 16 patients, they demonstrated signs of infection including loss of cilia in all patients, and 25 % had near total coverage of the apical surface with a slime consisting of biofilm characteristics [22].

Since this time, enormous investigation has been ongoing both in our lab and others regarding biofilms (Table 7.1). Others, using a variety of techniques, including SEM, transmission electron microscopy (TEM), in situ FISH hybridization, and CLSM, have subsequently demonstrated the presence of bacterial biofilms in sinuses (Fig. 7.4) [15, 23, 25].

Table 7.1 Evidence of biofilms in chronic rhinosinusitis patients

Author	Examination method	Biofilm/total patients (%)	Patient characteristics
Cryer et al. [22]	SEM	4/16 (25)	OR revision—FESS specimen or office debridement
Ferguson and Stolz [23]	TEM	2/4 (50)	OR or office biopsy
Bendouah et al. [24]	In vitro formation	16/19 (84)	Office culture from post-FESS patient
Ramadan et al. [25]	SEM	5/5 (100)	OR FESS specimen
Sanderson et al. [15]	FISH	Patients 14/18 (77)	Patients—OR FESS biopsy
		Controls 2/5 (40)	Controls—OR septoplasty biopsy
Sanclement et al. [26]	SEM and TEM	Patients 24/30 (80)	Patients—OR FESS specimen
		Controls 0/4 (0)	Controls—OR septoplasty or CSF leak specimen
Psaltis et al. [27]	CSLM	Patients 17/38 (44)	Patients—OR FESS specimens
		Controls 0/9 (0)	Controls—OR endoscopic TSA specimen
Psaltis et al. [28]	CSLM	20/40 (50)	OR FESS specimens
Prince et al. [12]	In vitro formation	45/157 (28.6)	Office cultures

CLSM confocal laser scanning microscopy, *CSF* cerebrospinal fluid, *FISH* fluorescent in situ hybridization, *OR* operating room, *SEM* scanning electron microscopy, *TEM* transmission electron microscopy, *TSA* transsphenoidal approach for pituitary lesion

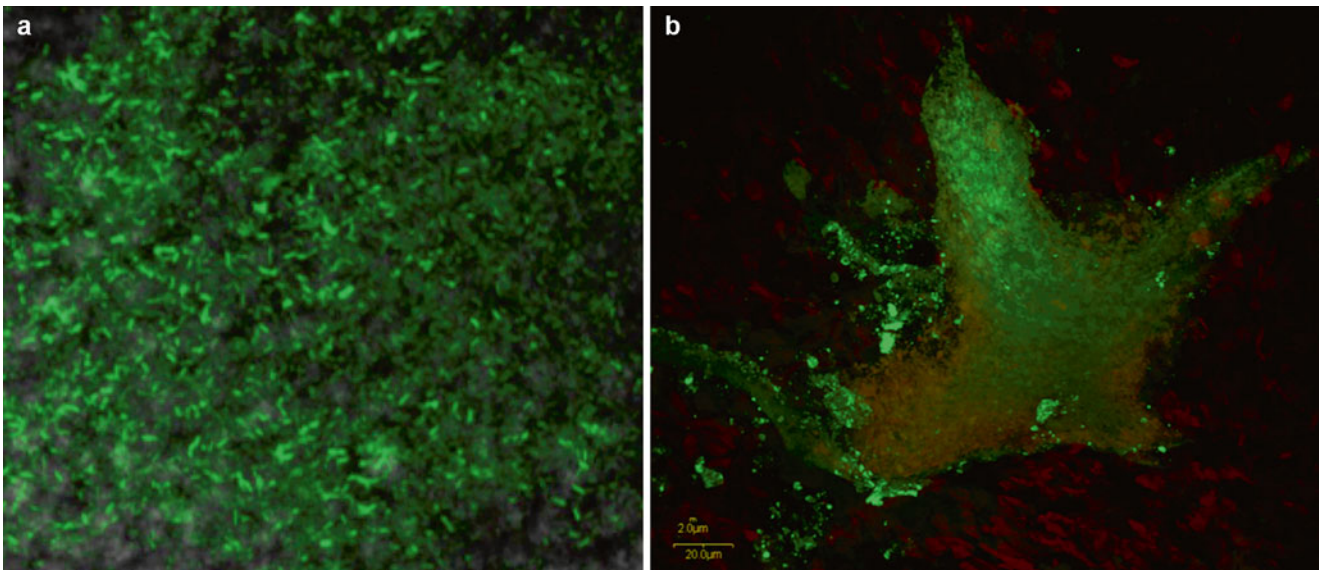


Fig. 7.4 (**a**) Fluorescent in situ hybridization (FISH) demonstrating a pseudomonas biofilm. (**b**) Confocal laser scanning microscopy visualizing biofilm formation

Table 7.2 Techniques for identifying biofilms

Method	Advantage	Disadvantage
SEM	Detailed morphology	Difficult to distinguish between biofilm and clot
TEM	High-power detail of architecture	Two-dimensional image, labor-intensive specimen processing
Live/dead staining with CSLM	Easy processing, with good three-dimensional information	Inability to distinguish microbial species
FISH with CSLM	Three-dimensional information with ability to detect specific microbial species	Mild degradation of image due to permeabilization, and limit of three to four microbial species
CV staining	Inexpensive, high throughput	Does not assess in vivo biofilms

Based on data from Ref. [29]
SEM scanning electron microscopy, *TEM* transmission electron microscopy, *CLSM* confocal laser scanning microscopy, *FISH* fluorescent in situ hybridization, *CV* crystal violet

A study using Calgary biofilm assay later demonstrated the prevalence of 28.6 % of bacterial biofilm formation in swabs collected from patients with CRS [12]. Using a similar method, Bendouah et al. demonstrated that when *Staphylococcus aureus* or *Pseudomonas aeruginosa* recovered from CRS patients are able to form biofilms, they are associated with an unfavorable postoperative course based on nasal endoscopy and quality-of-life scores [24].

Although mounting literature suggests a link between biofilms and CRS in humans, there is no study demonstrating any causal association in the pathophysiology of CRS. Current investigation has not been able to clearly demonstrate which factors determine the persistence and growth of biofilms on the sinonasal mucosa of the host. Part of the challenge of studying biofilms is the difficulty in studying viable tissue cultures even in animals. As previously mentioned, the standard approaches to study biofilms have included SEM and TEM. These techniques provide detailed imaging of the intricate architecture, developmental stages, and polymicrobial nature of biofilms. That said, both of the techniques can be limited in clinical utility due to difficulties in fixation, the presence of artifacts in the fixation process, and the challenge to identify individual bacterial species. SEM has additional limitations in differentiating between mucus, clot, and biofilm, whereas TEM only renders a two-dimensional section of the biofilm [23]. Other techniques including in situ FISH and confocal laser scanning provide three-dimensional biofilm structures and information but carry their own set of limitations (Table 7.2).

With study limitations on biofilms, few investigations have been able to successfully identify interactions between the host and the biofilm. Starner et al., using broncho-epithelial human cells, demonstrated that *H. influenza* biofilms grown on these cell cultures evoked an inflammatory response with an increase of NF-κB, IL-8, TNF-alpha, and MIP-3alpha (macrophage inflammatory protein) [30]. Studies are ongoing to identify and understand the different mechanisms of host-biofilm interaction in the sinonasal mucosa, specifically looking to identify what drives the formation of biofilms in certain patients, and the development and understanding of the humoral and cellular defense responses involved.

Factors Implicated Biofilm Formation in the Paranasal Sinuses

Since the identification of biofilms in the sinonasal mucosa, investigators have been attempting to find risk factors associated with biofilm formation. Zhang et al. provide the largest clinical study to date [31]. They prospectively evaluated 518 patients with CRS to identify for biofilms and subsequently investigate for risk factors. Of the patients, 108 (20.9 %) demonstrated biofilm formation in vitro. They demonstrated that biofilm formation in vitro was not significantly associated with polyps, allergy, Samter's triad, sleep apnea, smoking status, age, or gender. They did find biofilms significantly associated with positive culture results, prior sinus surgeries, and nasal steroid use within the month prior to collection. The data continues to be equivocal. Although there may be an association, it is also possible that patients with biofilms may have more persistent symptoms and inflammation, thus resulting in a greater number of surgeries. On the same note, these patients may be more likely to be placed on nasal steroids to reduce endoscopically evaluated inflammation.

Another study performed at the University of Pennsylvania looked at patient-cultured biofilms to identify effects of smoking [32]. They cultured the biofilms of both smokers and nonsmokers and subsequently introduced smoke exposure to the cultures. What they demonstrated was that patients who smoke had bacterial isolates that were more prone to produce biofilm material in response to additional smoke exposure than nonsmokers. They also found that growth of the bacterial isolates from smokers in the absence of tobacco smoke produced a biofilm formation phenotype characteristic of the bacterial isolates from nonsmokers. This suggests a reversibility of the tobacco effect on active smokers pertaining to biofilm formation. Additionally, these phenotypic switches fostered by tobacco smoke exposure or removal were not identified in a single organism, but rather it was identified in eight different species. The authors went on to speculate that these responses represent a well-conserved, global microbial response to tobacco smoke exposure and could potentially represent a novel therapeutic target.

Table 7.3 Methods for bacterial biofilm resistance to antibiotics

Possible methods for bacterial biofilm resistance to antibiotics
Deactivation or neutralization of antibiotic
Quiescent bacteria (with decreased oxygen and nutritional needs) in biofilm form resist antibiotics that are predominantly eradicating actively dividing bacteria
Decreased penetration of antibiotics into biofilm exopolysaccharide matrix
Decreased porins in the bacterial cell wall that inhibit diffusion of antibiotic

Methods of Antibiotic Resistance

Evolutionarily, biofilm formation is thought to provide a mechanism for enhanced bacterial survival. A hallmark of bacterial biofilms is increased antibiotic resistance. Bacterial biofilms show 10–1,000-fold less sensitivity to antibiotics than bacteria growing in culture [9, 10]. Significant investigation is ongoing to establish the exact mechanism of antibiotic resistance.

At the current time, the antibiotic resistance appears to be multifactorial in etiology (Table 7.3). One method of resistance may be the difficulty in penetration of the biofilm exopolysaccharide alginate coat. This is currently under investigation, as concentration studies demonstrate that antibiotics can, in fact, diffuse efficiently into biofilms, thus contradicting this theory [9]. A large portion of the biofilm is comprised of water, and this allows for diffusion of antibiotics down the water channels into the core regions of the biofilm. Another proposed method of resistance argues that antibiotics may be deactivated or neutralized when the positively charged antibiotics interact with the negatively charged polymers of the biofilm matrix. A third theory suggests that bacteria may be forced into a nongrowing state in the basal layers of the biofilm due to the accrual of waste products and depletion of needed substrates. This results in a state of suspended animation that confers relative resistance to antibiotics as the majority of antibiotics work only on actively dividing bacteria. Alternatively, osmotic forces from changing nutrient gradients could create a stress response that results in fewer porins in the bacterial cell wall, potentially leading to decreased diffusion of antibiotics into the bacterial cytoplasm.

Additionally, the biofilm environment provides an ability for the bacteria to transfer genetic information through plasmids to promote genetic variability and adaptive mutations such as antibiotic resistance. A key component to understanding biofilm host evasion systems is the heterogeneous morphology of biofilms. Essentially, the biofilm phenotype is highly dependent on the surrounding environment. For example, bacterial biofilms that have developed on mucosal surfaces, termed "mucosal biofilms," are bacterial biofilms that have formed in the unique environment of ciliated mucosa. The mucosal biofilms have a unique cascade of gene expression and different microenvironments compared with biofilms that form on inert surfaces because the former will be modified by the host inflammatory response and may incorporate some of the host proteins, waste products, and cellular debris [13]. In the paranasal sinuses, this results in a chronic disease state with intermittent acute infections when the biofilm releases planktonic bacteria, resulting in new implantation and population of additional anatomic locations. Although a number of antibiotic resistance theories are currently under investigation, the reality is it is likely a combination of the aforementioned mechanisms.

Current investigation also has found subtherapeutic doses of certain antibiotics may potentially induce biofilm formation. A recent report by May et al. demonstrates that subinhibitory concentrations of antibiotics trigger biofilm formation in *Escherichia coli* and the induction of antibiotic efflux pumps [33]. The study suggests that subtherapeutic doses of antibiotic treatment can trigger biofilm formation and lead to chronic infection. Similarly, Hoffman and colleagues demonstrated the induction of biofilm formation in *Pseudomonas aeruginosa* and *Escherichia coli* secondary to subtherapeutic concentrations of aminoglycoside antibiotics [34]. Certain Pseudomonas may have a gene, aminoglycoside response regulator (arr), that contributes to this biofilm-specific aminoglycoside resistance. This is potentially a source of bacterial resistance in CRS, especially in individuals undergoing topical aminoglycoside irrigations at subtherapeutic concentrations.

Treatment of Biofilm-Associated CRS

Ongoing investigation into biofilm treatment and management is currently underway. New treatments including surgery, topical antibiotics, surfactant therapy, and disruption of quorum sensing mechanism are being evaluated (Table 7.4).

Surgical intervention is aimed at improving the ventilation of affected sinuses. Surgery is considered to be effective against biofilms by increasing oxygen tension, mechanically disrupting biofilms, and assisting with the host's natural defenses to clear infections. In addition, surgical ventilation allows for improved access for further topical therapy highlighted below. The utilization of topical medications is an alternative method aimed at delivering high concentrations of

Table 7.4 Potential sinonasal biofilm treatment options

Method	Description
Mechanical	Surgery
Surfactant	Baby shampoo irrigation [35]
	Citric acid/zwitterionic surfactant [36]
Antimicrobial	Topical mupirocin irrigations for *S. aureus* [37, 38]
	Honey for *S. aureus* and *P. aeruginosa* biofilm [39]
	Innate immunity proteins [40]
Quorum sensing disruption	Macrolide therapy [41, 42]

antibiotics directly to sinus mucosa and biofilms. Topical antibiotics allow for higher concentrations that can be applied directly to biofilms with potentially lower systemic side effects than parenteral antibiotics. Desrossiers et al. examined mupirocin in vitro against various strains of *S. aureus* to determine the effects on biofilm growth [37]. After 24 h, the mupirocin at concentrations of 7.8–125 ug/ml eradicated 90 % of biofilms in all isolates. The study demonstrated that mupirocin's broad-spectrum activity makes it an attractive treatment option for CRS-related biofilms. A study from the Cleveland Clinic, although not specifically addressing biofilms, demonstrated encouraging data supporting the use of topical mupirocin nasal irrigations as an alternative to intravenous antibiotics in the treatment of acute exacerbations of methicillin-resistant *Staphylococcus aureus* (MRSA)-associated CRS [38]. Patients using mupirocin in sinus irrigations showed improved symptoms and reduced MRSA recovery on follow-up cultures. Alternative topical therapies continue to be investigated. Alandejani et al., for example, demonstrated that honey was effective against *S. aureus* and *P. aeruginosa* biofilms in vitro [39]. They found honey eradicated 73 % of MRSA biofilms and 91 % of pseudomonas biofilms. The clinical utility of honey for patients with biofilm-associated CRS is yet to be established.

Innate immune proteins also have been studied as therapeutic agents. LL-37 is a peptide that is secreted in saliva and sweat and expressed in leukocytes. It is believed to be a part of the innate immune system. Chennupati et al. demonstrated that LL-37 was able to eradicate *Pseudomonas aeruginosa* biofilms in a rabbit model of CRS [40]. In their study, high concentrations of topical tobramycin with 2.5 mg/ml of LL-37 were effective in significantly lowering bacterial counts and biofilm levels. They did, however, identify that high concentrations of LL-37 showed proinflammatory and ciliotoxic effects on sinus mucosa.

Finally, it has been proposed that surfactants can break up biofilms and subsequently allow bacteria and debris to be irrigated from the sinuses. Chiu and colleagues explored the use of baby shampoo as a chemical surfactant to disrupt biofilm integrity [35]. In a prospective, nonrandomized study, post-FESS patients were irrigated with 1 % baby shampoo in saline for 4 weeks. 46.6 % of patients had subjective improvement of sinonasal outcome test scores, and 63 % had improvements in olfaction as determined by the University of Pennsylvania Smell Identification Test (see Chap. 18). In addition, they determined that endoscopic appearance of the cavity after shampoo treatment demonstrated decreased edema and polypoid degeneration. Adappa and colleagues are currently investigating the use of a combination of surfactant and antibiotic therapy in vitro and have demonstrated a synergistic therapeutic effect on both MRSA and *Pseudomonas aeruginosa* biofilms (unpublished data). Further clinical investigation is still necessary, but both studies suggest that surfactant-based therapies may aid in the treatment of biofilm-related CRS.

Long-term macrolide therapy has been shown to improve sinonasal symptoms in select patients with CRS [43]. Investigators have demonstrated that low-dose macrolide therapy, significantly below established minimal inhibitory concentration for *Pseudomonas*, has some success in decreasing biofilm formation. Tre-Hardy et al. showed that the combination of clarithromycin and tobramycin had marked synergistic effects on in vitro biofilms of *P. aeruginosa* than either of the two drugs used alone [41]. In addition, Tateda and colleagues demonstrated azithromycin was shown to decrease quorum sensing in a *P. aeruginosa* wild-type strain [42]. The study shows encouraging results using subminimum inhibitory concentrations of macrolides, which may become a useful adjuvant strategy to treat biofilm-associated CRS in the future.

Future directions for biofilm-associated CRS include treatment at a cellular and molecular level. Specific molecular targets of the biofilm life cycle show promise. Interrupting attachment phases by disrupting the type IV pili of *Pseudomonas* is one such avenue of investigation [44]. Disruption of quorum sensing also demonstrates promise. It is possible to interrupt quorum sensing through a variety of novel mechanisms that affect quorum sensing signaling pathways, including the substitution of furanones and the enzymatic cleavage of acyl-homoserine lactones [45, 46].

Conclusions

Since the initial description of sinonasal biofilms in 2004, significant research has been conducted regarding the implications of biofilms in CRS, as well as treatment modalities. Data continues to mount showing a contributory role of biofilms in recalcitrant CRS. Current investigation is focused on the clinical role of biofilms, genetic predisposition toward biofilm

formation, and inflammatory response to mucosal biofilms. Regardless of the etiology, the primary treatment modality of CRS includes topical and systemic antimicrobial and anti-inflammatory agents with surgical ventilation providing both aeration and improved application of topical therapies. The data so far demonstrates that bacterial biofilms show increased antibacterial resistance. Accordingly, novel therapeutic approaches are under investigation to provide both prophylaxis against biofilm formation as well as eradication of preexisting sinonasal biofilms. Encouraging data demonstrating efficacy of topical antibiotics both alone and in combination with surfactant therapy has been reported, although additional clinical trials are necessary to ultimately confirm the safety of these measures. Although, at this point, surgical intervention is the mainstay of therapy for recalcitrant CRS, improved understanding of the pathophysiology of biofilms will impact the development of improved biofilm treatment modalities.

References

1. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. Vital Health Stat. 2002:1–109.
2. Cherry DK, Woodwell DA. National Ambulatory Medical Care Survey: 2000 summary. Adv Data. 2002:1–32.
3. Ly N, McCaig LF. National Hospital Ambulatory Medical Care Survey: 2000 outpatient department summary. Adv Data. 2002:1–27.
4. Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol. 1999;103:408–14.
5. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg. 2003;129:S1–32.
6. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg. 1995;113: 104–9.
7. Khalid AN, Quraishi SA, Kennedy DW. Long-term quality of life measures after functional endoscopic sinus surgery. Am J Rhinol. 2004;18: 131–6.
8. Solomon DH, Wobb J, Buttaro BA, Truant A, Soliman AM. Characterization of bacterial biofilms on tracheostomy tubes. Laryngoscope. 2009;119:1633–8.
9. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet. 2001;358:135–8.
10. Davies D. Understanding biofilm resistance to antibacterial agents. Nat Rev Drug Discov. 2003;2:114–22.
11. Richards JJ, Melander C. Controlling bacterial biofilms. Chembiochem. 2009;10:2287–94.
12. Prince AA, Steiger JD, Khalid AN, et al. Prevalence of biofilm-forming bacteria in chronic rhinosinusitis. Am J Rhinol. 2008;22:239–45.
13. Parsek MR, Greenberg EP. Quorum sensing signals in development of Pseudomonas aeruginosa biofilms. Methods Enzymol. 1999;310: 43–55.
14. Singh PK, Schaefer AL, Parsek MR, Moninger TO, Welsh MJ, Greenberg EP. Quorum-sensing signals indicate that cystic fibrosis lungs are infected with bacterial biofilms. Nature. 2000;407:762–4.
15. Sanderson AR, Leid JG, Hunsaker D. Bacterial biofilms on the sinus mucosa of human subjects with chronic rhinosinusitis. Laryngoscope. 2006;116:1121–6.
16. Ramage G, Mowat E, Jones B, Williams C, Lopez-Ribot J. Our current understanding of fungal biofilms. Crit Rev Microbiol. 2009;35: 340–55.
17. Whatley WS, Chandra RK, MacDonald CB. Systemic absorption of gentamicin nasal irrigations. Am J Rhinol. 2006;20:251–4.
18. El-Azizi MA, Starks SE, Khardori N. Interactions of Candida albicans with other Candida spp. and bacteria in the biofilms. J Appl Microbiol. 2004;96:1067–73.
19. Foreman A, Psaltis AJ, Tan LW, Wormald PJ. Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. Am J Rhinol Allergy. 2009;23:556–61.
20. Perloff JR, Palmer JN. Evidence of bacterial biofilms on frontal recess stents in patients with chronic rhinosinusitis. Am J Rhinol. 2004; 18:377–80.
21. Perloff JR, Palmer JN. Evidence of bacterial biofilms in a rabbit model of sinusitis. Am J Rhinol. 2005;19:1–6.
22. Cryer J, Schipor I, Perloff JR, Palmer JN. Evidence of bacterial biofilms in human chronic sinusitis. ORL J Otorhinolaryngol Relat Spec. 2004;66:155–8.
23. Ferguson BJ, Stolz DB. Demonstration of biofilm in human bacterial chronic rhinosinusitis. Am J Rhinol. 2005;19:452–7.
24. Bendouah Z, Barbeau J, Hamad WA, Desrosiers M. Biofilm formation by Staphylococcus aureus and Pseudomonas aeruginosa is associated with an unfavorable evolution after surgery for chronic sinusitis and nasal polyposis. Otolaryngol Head Neck Surg. 2006;134:991–6.
25. Ramadan HH, Sanclement JA, Thomas JG. Chronic rhinosinusitis and biofilms. Otolaryngol Head Neck Surg. 2005;132:414–7.
26. Sanclement JA, Webster P, Thomas J, Ramadan HH. Bacterial biofilms in surgical specimens of patients with chronic rhinosinusitis. Laryngoscope. 2005;115:578–82.
27. Psaltis AJ, Ha KR, Beule AG, Tan LW, Wormald PJ. Confocal scanning laser microscopy evidence of biofilms in patients with chronic rhinosinusitis. Laryngoscope. 2007;117:1302–6.
28. Psaltis AJ, Weitzel EK, Ha KR, Wormald PJ. The effect of bacterial biofilms on post-sinus surgical outcomes. Am J Rhinol. 2008;22:1–6.
29. Tamashiro E, Banks CA, Chen B, et al. In vivo effects of citric acid/zwitterionic surfactant cleansing solution on rabbit sinus mucosa. Am J Rhinol Allergy. 2009;23:597–601.
30. Starner TD, Zhang N, Kim G, Apicella MA, McCray Jr PB. Haemophilus influenzae forms biofilms on airway epithelia: implications in cystic fibrosis. Am J Respir Crit Care Med. 2006;174:213–20.

31. Zhang Z, Kofonow JM, Finkelman BS, et al. Clinical factors associated with bacterial biofilm formation in chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2011;144:457–62.
32. Goldstein-Daruech N, Cope EK, Zhao KQ, et al. Tobacco smoke mediated induction of sinonasal microbial biofilms. PLoS One. 2011;6:e15700.
33. May T, Ito A, Okabe S. Induction of multidrug resistance mechanism in Escherichia coli biofilms by interplay between tetracycline and ampicillin resistance genes. Antimicrob Agents Chemother. 2009;53:4628–39.
34. Hoffman LR, D'Argenio DA, MacCoss MJ, Zhang Z, Jones RA, Miller SI. Aminoglycoside antibiotics induce bacterial biofilm formation. Nature. 2005;436:1171–5.
35. Chiu AG, Palmer JN, Woodworth BA, et al. Baby shampoo nasal irrigations for the symptomatic post-functional endoscopic sinus surgery patient. Am J Rhinol. 2008;22:34–7.
36. Desrosiers M, Myntti M, James G. Methods for removing bacterial biofilms: in vitro study using clinical chronic rhinosinusitis specimens. Am J Rhinol. 2007;21:527–32.
37. Desrosiers M, Bendouah Z, Barbeau J. Effectiveness of topical antibiotics on Staphylococcus aureus biofilm in vitro. Am J Rhinol. 2007;21:149–53.
38. Solares CA, Batra PS, Hall GS, Citardi MJ. Treatment of chronic rhinosinusitis exacerbations due to methicillin-resistant Staphylococcus aureus with mupirocin irrigations. Am J Otolaryngol. 2006;27:161–5.
39. Alandejani T, Marsan J, Ferris W, Slinger R, Chan F. Effectiveness of honey on Staphylococcus aureus and Pseudomonas aeruginosa biofilms. Otolaryngol Head Neck Surg. 2009;141:114–8.
40. Chennupati SK, Chiu AG, Tamashiro E, et al. Effects of an LL-37-derived antimicrobial peptide in an animal model of biofilm Pseudomonas sinusitis. Am J Rhinol Allergy. 2009;23:46–51.
41. Tre-Hardy M, Vanderbist F, Traore H, Devleeschouwer MJ. In vitro activity of antibiotic combinations against Pseudomonas aeruginosa biofilm and planktonic cultures. Int J Antimicrob Agents. 2008;31:329–36.
42. Tateda K, Ishii Y, Kimura S, Horikawa M, Miyairi S, Yamaguchi K. Suppression of Pseudomonas aeruginosa quorum-sensing systems by macrolides: a promising strategy or an oriental mystery? J Infect Chemother. 2007;13:357–67.
43. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. 2006;116:189–93.
44. Gallant CV, Daniels C, Leung JM, et al. Common beta-lactamases inhibit bacterial biofilm formation. Mol Microbiol. 2005;58:1012–24.
45. Koch B, Liljefors T, Persson T, Nielsen J, Kjelleberg S, Givskov M. The LuxR receptor: the sites of interaction with quorum-sensing signals and inhibitors. Microbiology. 2005;151:3589–602.
46. Dong YH, Wang LH, Xu JL, Zhang HB, Zhang XF, Zhang LH. Quenching quorum-sensing-dependent bacterial infection by an N-acyl homoserine lactonase. Nature. 2001;411:813–7.

Chapter 8
Fungus in Sinus Disease

Matthew W. Ryan, Ng Yuk Hui, and Mohammad O. Aloulah

Introduction

Fungal rhinosinusitis appears to be more common than in decades past. This apparent increase may be due to greater awareness among healthcare practitioners, an excessive use of antibiotics for upper respiratory symptoms, and a greater population of immunocompromised individuals. Many aspects of fungal rhinosinusitis remain poorly understood, and diagnostic distinction between fungal rhinosinusitis and other forms of rhinosinusitis can be a challenge. However, a revised nomenclature and a clearer understanding of the risk factors, natural history, and prognosis of fungal sinus disease have simplified the diagnosis and treatment approach. The aim of this chapter is to give an overview of the diagnosis and treatment of fungal disease in the sinuses.

Classification of Fungal Sinus Disease

Fungal disease was reported as early as 1791 by Plaignaud. Since that time descriptions of fungal disease focused on the causative organism, leading to terms such as "aspergillosis," "mucormycosis," and "zygomycosis." *Aspergillus* is the most common organism to cause fungal sinusitis. However, it is now clear that aside from selecting an appropriate antifungal agent, the particular organism involved is not salient in the diagnosis or classification of fungal rhinosinusitis. As a result, terms such as "mucormycosis" are not recommended for describing fungal sinus disease.

In 1965 Hora [1] described the clinical and histopathological distinction between invasive and noninvasive fungal infections of the sinuses, highlighting for the first time the importance of differentiating invasion as an indicator of prognosis and need for emergent treatment. We now recognize tissue invasion to be one of the most important factors for determining the appropriate treatment for fungal rhinosinusitis. The host's immunologic response to the fungus is an additional factor in determining the manifestation of fungal rhinosinusitis in a particular patient. Katzenstein et al. [2] described "allergic *Aspergillus* sinusitis," a clinical presentation of fungal disease characterized by type 1 hypersensitivity, polypoid rhinosinusitis, and sinus mucus that resembled the bronchial aspirates of patients with allergic bronchopulmonary aspergillosis (ABPA).

Fungal disease of the sinuses has been classified into five distinct categories [3]. The forms of noninvasive fungal disease are *saprophytic colonization*, *fungus ball*, and *allergic fungal rhinosinusitis* (AFRS). Saprophytic colonization with the growth of fungus on dried mucus secretions is usually asymptomatic, and the condition is detected as an incidental finding.

M.W. Ryan, MD (✉)
Department of Otolaryngology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9035, USA
e-mail: matthew.ryan@utsouthwestern.edu

N.Y. Hui, MBBS, FAMS
Department of Otolaryngology, Singapore General Hospital, Outram Road, 169608, Singapore
e-mail: ng.yuk.hui@sgh.com.sg

M.O. Aloulah, MBBS, KSUF
Department of Otolaryngology, Head and Neck Surgery, King Abdulaziz University Hospital, King Saud University,
Prince saud ibn saud street, Riyadh, 102502, 11685, Saudi Arabia
e-mail: dr_aloulah@hotmail.com

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_8,

Hence, it is not usually considered in the classification of fungal rhinosinusitis. A fungus ball is a collection of dense debris usually found in a single sinus. Histologically, a fungus ball is noninvasive and appears under the microscope as a collection of fungal hyphae. In comparison, allergic fungal rhinosinusitis (AFRS) usually occurs in atopic patients and involves multiple sinuses, and multiple sinuses contain mucus that is filled with eosinophils and fungal elements. Invasive fungal rhinosinusitis can be divided into acute and chronic forms. Acute invasive fungal rhinosinusitis (AIFRS) usually occurs in the immunocompromised host and is associated with rapid progression and poor prognosis. Chronic invasive fungal rhinosinusitis (CIFRS) on the other hand usually occurs in the immune-competent patient. As its name suggests, the clinical course is less aggressive. CIFRS has been further divided into a granulomatous and nongranulomatous form, although they both seem to follow the same clinical course [4].

Fungal rhinosinusitis is relatively uncommon, with a majority of cases being noninvasive. Studies have shown up to 7 % [5] of chronic rhinosinusitis cases taken to surgery have a noninvasive fungal pathology. In comparison, invasive forms of fungal rhinosinusitis are rarer. AIFRS is largely a disease of the immunocompromised and has classically been described in immunocompromised patients with neutropenia or diabetic ketoacidosis. The annual incidence in patients with leukemia has been reported to approach up to 3.4 % [6] in this immunocompromised population. Chronic invasive fungal rhinosinusitis is extremely rare in the United States [4] and is more common in dry desert regions in Sudan and Saudi Arabia [7].

Role of Fungi in Chronic Rhinosinusitis

Chronic rhinosinusitis is a heterogeneous group of disorders with similar symptomatic presentation but without a single unifying etiology. Fungi have traditionally been accorded a small role in causing chronic sinus disease. However, a report in 1999 [8] suggested that most cases of chronic rhinosinusitis are caused by environmental fungi. This report described the presence of fungi in 96 % of patients with CRS (though also in 100 % of "normal" controls) utilizing a novel method of specimen collection and culture to identifying fungi in nasal mucus. Further publications postulated that ubiquitous fungi in the environment evoke an eosinophilic inflammatory response that results in the chronic inflammation of CRS [9]. Subsequent investigation focused on eradicating the fungus in an attempt to treat CRS. In a small randomized double-blind placebo-controlled trial published in 2005 [10], topical treatment with amphotericin B led to a small improvement in CT and endoscopic findings in patients with CRS. Multiple randomized trials of antifungal therapy have now been performed, and reviews [11, 12] from the various subsequent trials showed no benefit of systemic or topical antifungal therapy on patients with CRS. In particular, a Cochrane review [12] of 6 trials on 380 patients showed that patients treated with antifungal therapy actually had worse symptom scores and a higher rate of adverse effects than those treated with placebo.

Limited laboratory data exist to provide support for the "fungal hypothesis" of CRS pathogenesis. Shin et al. [9] showed that exposure of peripheral blood mononuclear cells (PBMCs) of patients with CRS to fungal antigens (especially *Alternaria*) resulted in an increase in IL-5 and IL-13 production, while normal control PBMCs did not. These results lend support to the notion that fungal exposure in CRS patients incites an eosinophilic response that is not seen in normal individuals. However, these results were not replicated in a later study by Orlandi et al. [13] who found both IL-5 and IL-13 production increased in both CRS and normal patients following *Alternaria* exposure. Recent studies have also focused on the presence of fungal biofilms in patients with CRS [14]. In a study of 50 patients with CRS and 10 controls, fungal biofilms were found to be present in 11 of the 50 study subjects and none of the controls. Of the 11 subjects with fungal biofilms, 9 had concomitant bacterial biofilms present. Although the data suggests that biofilms are more prevalent in patients with CRS than controls, there is a lack of definitive evidence suggesting that the presence of the fungal biofilm contributes to the disease process of CRS. Furthermore, there is no evidence that the removal of such these fungal biofilms result in a resolution of CRS. Without a clearly defined pathophysiology and a clear demonstration of cause and effect, the hypothesis that fungi is the cause of CRS has been widely rejected, putting an end to more than a decade of controversy.

Microbiology of Fungi

Fungal classification can be confusing due to the large number of terms and different classification systems that have been developed. On a microscopic level, fungi can appear as a mold or yeast. A mold is distinguished by its multicellular colony with filaments or hyphae (which may appear septated). In comparison, yeast appears as a spherical or ellipsoid unicellular form. Certain fungi are able to grow as yeast or as a mold depending on physical conditions. Fungi are also able to exist in both sexual and asexual forms, each having its own name. The asexual name is most commonly used in the medical

Table 8.1 Common fungal pathogens

Category	Genera
Mucoraceae	*Mucor*
	Rhizopus
	Rhizomucor
	Absidia
Hyaline molds	*Aspergillus*
	Fusarium
	Pseudallescheria
Dematiaceous molds	*Alternaria*
	Bipolaris
	Curvularia
	Exserohilum

literature. Depending on the presence of septations and pigment and branching patterns, these fungi can be broadly classified as mucoraceae, hyaline molds, or dematiaceous molds (Table 8.1). Although the specific genera may cause more than one pathology, certain pathologies are more likely associated with specific fungi. For example, acute invasive fungal rhinosinusitis is commonly associated with *Mucor* or *Aspergillus*, fungus balls are almost commonly caused by A*spergillus*, and allergic fungal rhinosinusitis is commonly associated with *Alternaria*, *Bipolaris*, and other dematiaceous molds.

Diagnostic Tests

The diagnosis of fungal rhinosinusitis requires the demonstration of fungus in tissue or sinus contents. Identification of fungal elements in surgical specimens can be difficult even with special stains. While some molds may stain with the Gram or hematoxylin–eosin stains, special stains like Gomori methenamine silver (GMS) or periodic acid–Schiff (PAS) demonstrate fungi better. Often, potassium hydroxide may be added to dissolve away human cells so that the fungi can be better seen. Fungal cultures may take weeks for results to return, may be affected by bacterial contamination, and are hard to interpret due to their variable yield [15]. Recently, attention has been turned to polymerase chain reaction techniques as well as ELISA identification of fungal specific antigen for rapid diagnosis of invasive fungal conditions [16, 17]. However, these advanced diagnostic tools have not been adequately studied in sinus disease.

Fungus Ball

A fungus ball is the common term used to describe a gross collection of fungal elements within a sinus. The previous terms "mycetoma" or "aspergilloma" have given way to this preferred terminology. A more precise description would also include the site as well as the causative organism [18], for example, "maxillary sinus fungus ball due to *Aspergillus*." A fungus ball may be an incidental finding in patients undergoing endoscopic surgery for chronic rhinosinusitis or incidentally noted on head and neck imaging. When symptomatic, the clinical presentation is similar to other forms of chronic rhinosinusitis with patients reporting symptoms such as nasal obstruction, postnasal drainage, facial pain, and a foul-smelling discharge. These symptoms may wax and wane with associated bacterial infection of the diseased sinus. Patients who develop fungus balls are typically not atopic or immunocompromised and usually belong to the older age group [19]. Fungus balls are usually found in the maxillary or sphenoid sinus but may also occur in the ethmoid and frontal sinuses. Some even involve multiple adjacent sinuses [20].

Computed tomography (CT) imaging usually shows an isolated sinus with heterogeneous opacification due to the presence of fungal debris within the sinus with surrounding mucosal inflammation. In about 65 % of cases, the fungus ball may show apparent calcifications [21] (Fig. 8.1a–c). In chronic cases, there may be thickening of the surrounding bone or bony erosion [22].

Grossly, fungus balls are composed of thick yellowish green, cheesy material. Histological examination of the fungus ball reveals tangles of fungal hyphae that are extramucosal and noninvasive into the sinus tissue (Fig. 8.2). Calcifications and oxalate crystals may also be found within the sinus contents [20]. Despite the gross presence of many apparently viable fungal elements, negative fungal cultures are common [19]. *Aspergillus* is the most common causative organism.

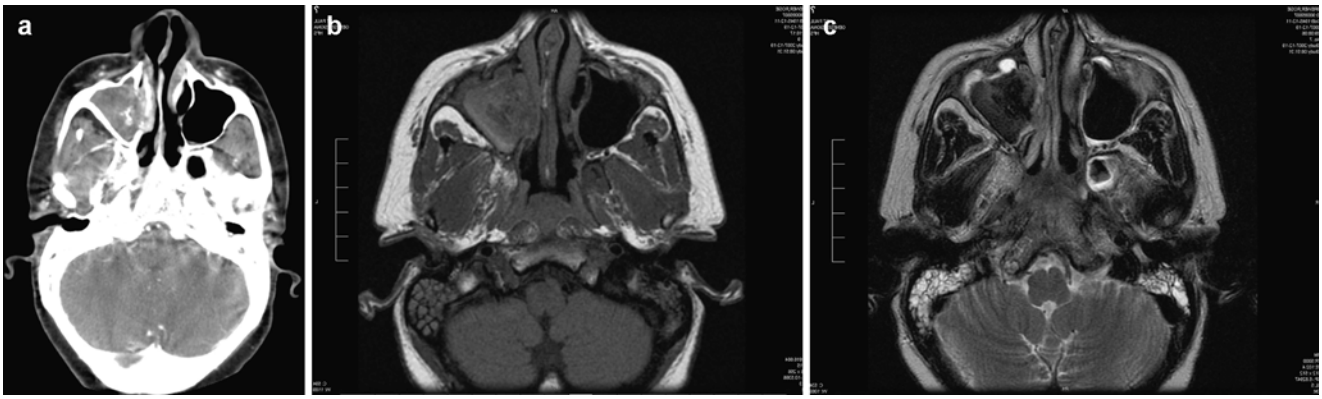


Fig. 8.1 (**a**) CT scan of fungus ball. Axial CT demonstrating the presence of a fungal ball in the maxillary sinus. Note the heterogeneous opacification and presence of calcification. (**b**, **c**) MRI of fungus ball. Corresponding axial MRI T1 (**b**) and T2 images (**c**) of the same patient. Note the presence of surrounding mucosal inflammation and the hypodense appearance of the fungus ball

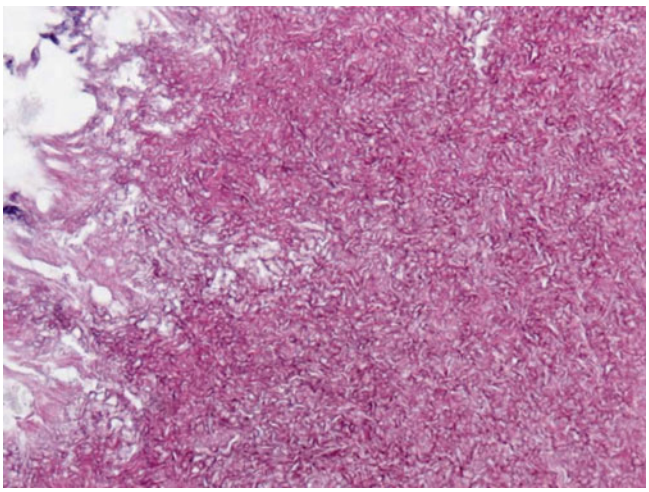


Fig. 8.2 Histopathology of a fungus ball. Large masses of densely packed fungal hyphae with feathered borders. The hyphae are densely packed, and the branching septate hyphae are readily identified under high magnification

The pathogenesis of a fungal ball requires trapping of fungal spores within a sinus followed by proliferation and associated impairment of the normal clearance of mucus from the sinus. Fungus balls grow slowly and if they do not evoke a significant inflammatory response may remain asymptomatic for months to years. If the fungus ball expands in the presence of sinus outflow tract obstruction, a mucocele may form (an expanded opacified sinus). The diseased sinus is susceptible to acute or chronic bacterial infection.

Treatment for a fungus ball aims to remove the fungus and restore normal drainage and aeration of the involved sinus. This is usually achieved through an endoscopic approach [22]. Postoperative management usually consists of saline irrigation. Although microbiological cultures of the extracted fungus ball may harbor aerobic and anaerobic bacteria [23], their significance is not well understood, and symptoms generally resolve without the use of antibiotics or antifungal medications. Recurrences of a fungus ball are rare [19], and these are quite easily managed with endoscopic removal through the surgical sinusotomy.

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis was first described as a distinct clinical entity when it was noticed that the thick, dark, sticky nasal mucus in these patients was similar to the inspissated bronchial mucus of patients with bronchopulmonary aspergillosis. Microscopically, this "eosinophilic mucin" contains eosinophils, lysophospholipase crystals (Charcot–Leyden crystals), and occasional fungal elements. *Aspergillus* was initially thought to be the causative organism giving rise to the term "allergic *Aspergillus* sinusitis." However, as studies showed that dematiaceous fungi [24] were more commonly isolated, the

Table 8.2 Bent and Kuhn criteria

1	Type I hypersensitivity
2	Nasal polyps
3	Characteristic CT features
4	Eosinophilic mucin
5	Positive fungal stain

terminology has shifted to allergic fungal rhinosinusitis (AFRS). Although the type of fungi isolated does not affect the clinical presentation or course of the disease, its presence is important to fulfill the diagnostic criteria of AFRS. AFRS is the commonest form of fungal sinus disease, though epidemiologic data is lacking. This disease usually occurs in the immune-competent, young patient with a history of atopy. It has a particular geographical distribution and seems to be more prevalent in the southern United States [25]. The pathogenesis, while still not resolved, is believed to include a combination of a Gell and Coombs type I and III sensitivity to fungal antigens. This theory is supported by elevated levels of fungi specific IgE and IgG [26] in patients with AFRS. Changes of these levels seem to correspond with symptoms [27], and there is evidence suggesting improved outcomes with fungal desensitization [28].

The original diagnostic criteria for AFRS were described by Bent and Kuhn [29], who based their description on a series of 15 patients. Their criteria included (1) type 1 hypersensitivity as evidenced by serum IgE, skin testing, or clinical history; (2) nasal polyps; (3) characteristic computed tomographic findings of serpiginous areas of high attenuation in affected sinuses; (4) presence of eosinophilic mucus without fungal tissue invasion; and (5) positive fungal smear in the mucus (see Table 8.2). Although alternative diagnostic criteria exist, these are the most widely accepted.

In some patients, fungal elements cannot be identified in the allergic mucin, giving rise to the term "AFS-like syndrome" [30] and "eosinophilic mucin rhinosinusitis" (EMRS) [31]. Yet another group of patients have identifiable fungi but do not show the characteristic IgE-mediated allergy to the fungi [32]. The relationship of these groups of patient with the originally described AFRS is now controversial. These inconsistencies have raised doubts about the role of fungi and allergy in the development of AFRS and demonstrate that the exact pathogenesis of AFRS remains elusive.

Patients with AFRS are typically adolescents or young adults. Older patients with similar presentations are more likely to have "eosinophilic mucin rhinosinusitis." A previous history of allergic rhinitis or asthma is common and the clinical evolution of sinus symptoms usually gradual. Patients commonly present with the typical symptoms of polypoid sinonasal inflammation, often with unilateral symptoms of nasal obstruction, anosmia, postnasal drip, and the production of characteristic thick, dark mucus (Fig. 8.3). In severe cases, there may be diplopia, proptosis, or telecanthus resulting from mucocele impingement on the orbital contents [33]. Such late presentations are not uncommon due to the insidious nature of the disease.

Physical examination in these patients may reveal external physical deformity caused by the expanding mass, raising concern for a neoplastic process. However, sinonasal endoscopic examination reveals typical nasal polyps, often with an asymmetric distribution, and loculations of "eosinophilic mucin." Entrapped by the polyps, the inspissated mucus often appears as thick yellowish, brown collections.

Diagnostic testing is required to establish the diagnosis of AFRS. Skin prick testing or serum antigen specific IgE tests are required to establish the presence of fungal type 1 hypersensitivity. As these patients often demonstrate allergy to both fungal and non-fungal antigens [34], it is common practice to test for region-specific seasonal and perennial allergens together with the fungal allergens. While not necessary from a diagnostic standpoint, total serum IgE levels are dramatically elevated and peripheral eosinophilia is common.

CT imaging is necessary for diagnosis and surgical treatment. The classic findings in AFRS include asymmetric disease with multiple inflamed or opacified sinuses, hyperdense sinus contents, bony erosion, and mucocele formation (Fig. 8.4). Compared to other forms of polypoid chronic rhinosinusitis, there is a greater propensity for bony erosion with up to half of CT scans showing some evidence of skull base or orbital erosion [35]. Magnetic resonance imaging is reserved for cases where there are orbital or intracranial complications. On T2-weighted images, there are central areas of signal void corresponding to the thick eosinophilic mucin, while surrounding inflamed mucosa has a high intensity signal [36]. The T1 signal is often hypo or isotense relative to the brain.

Treatment of AFRS includes a combination of surgical and medical approaches. Due to physical obstruction and the distortion of normal anatomy and sinus drainage pathways, surgery is required to effectively treat this disease. The primary aim is to improve drainage by removing obstructing polyps and sinus septations and to remove the eosinophilic mucin [34]. This is usually accomplished with an endoscopic surgical approach. Due to the distortion of normal bony landmarks and dehiscence of bony barriers to the brain and orbit, the risk of surgery is potentially increased. The consequence of incomplete surgery is often the recurrence of the disease [37], as retained bony lamella may harbor pockets of the eosinophilic mucin

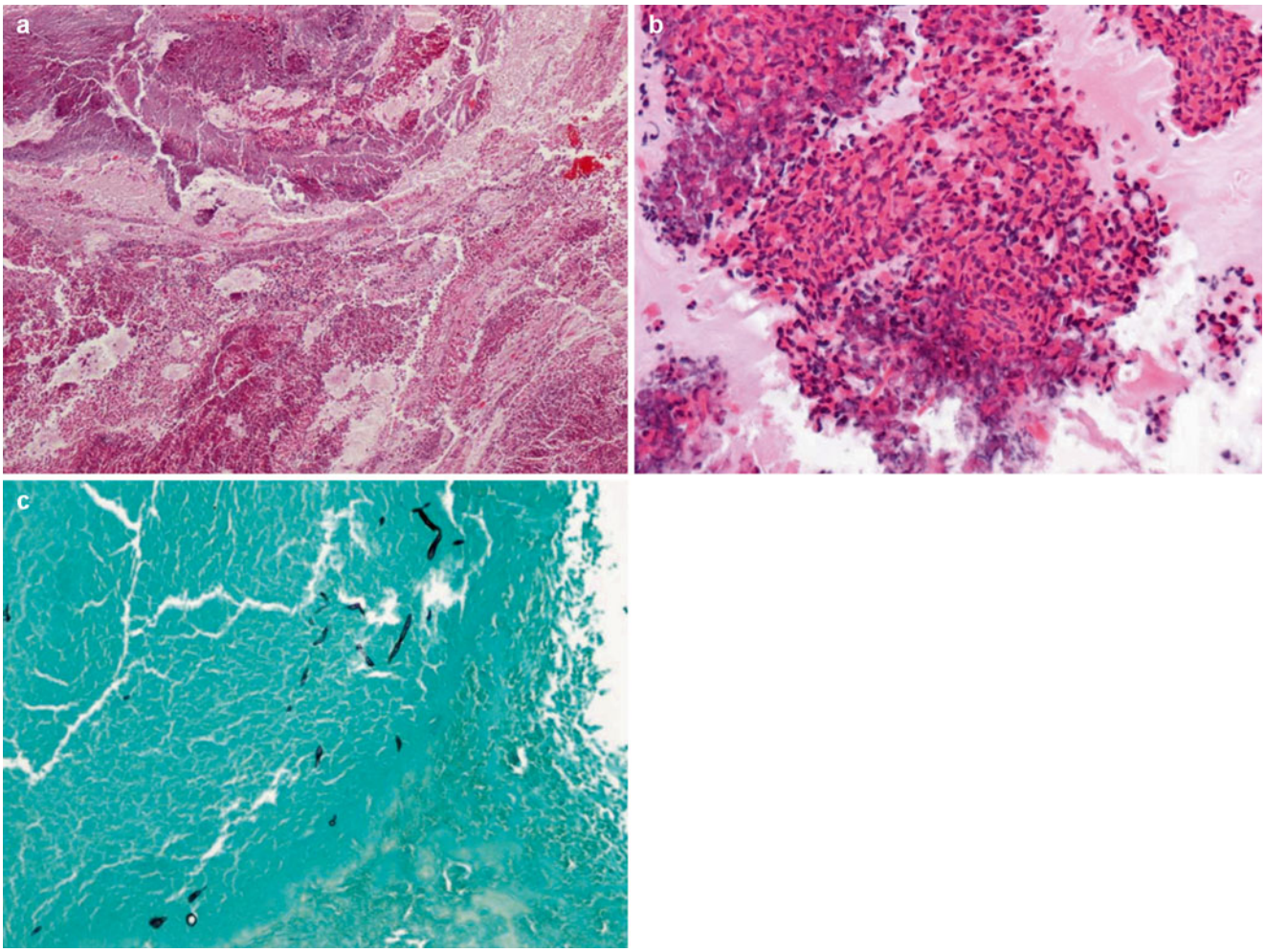


Fig. 8.3 Histopathology of allergic fungal rhinosinusitis. (**a**) Eosinophilic mucin under 40× magnification showing inspissated mucus with eosinophilic material and admixed inflammatory cells (so-called eosinophilic mucus). (**b**) 100× magnification showing amorphous eosinophilic material with eosinophils and scattered neutrophils. (**c**) GMS stain identifies occasional branching septate fungal hyphae

that function as a stimulus for further inflammation. Over the course of the disease, revision surgery is commonly required for recurrences that are resistant to medical therapy or when massive polyposis results in entrapment of mucin within the sinuses. Minimally invasive approaches such as balloon dilation are not appropriate in this disease process.

Comprehensive medical therapy is a crucial component in the long-term management of this disease process [38]. AFRS is an inflammatory disease, not a fungal infection. Systemic and topical corticosteroids are the main forms of medical therapy [39]. Steroids are used perioperatively and for long-term maintenance therapy. The use of steroids has been shown to improve symptoms and increase the time interval between relapses [40]. In severe cases, prolonged treatment with systemic corticosteroids may be necessary to maintain control of inflammation. Due to the potential side effects of prolonged systemic steroid use, it is common practice to confine steroid usage to the immediate postoperative period and in short bursts to treat acute exacerbations or polyp recurrences. Topical steroids have the advantage of targeted delivery of the medication without the side effects of systemic steroids. Topical steroids have demonstrated efficacy for nasal polyps [41], and they are often used at higher doses to improve their efficacy [39]. While high-dose topical steroids have not been adequately studied in polypoid CRS, there is considerable interest in the use of these agents as a means to reduce the use of systemic corticosteroids. In a previous operated patient without a significant polyp burden, topical agents are able to reach the sinus mucosa directly. Budesonide respules, for example, may be applied directly as drops, mixed with a nasal irrigation or sprayed via an atomizer device. Inverted head positioning is required to insure distribution into the frontal, ethmoid, and sphenoid regions. Although these agents are anecdotally effective, topical steroid alone is often insufficient to completely eliminate the need for systemic steroids. Other anti-inflammatory agents such as leukotriene receptor antagonists [42], macrolides, and itraconazole have been recommended; however, none of these agents has been adequately studied. The use of systemic and topical antifungal

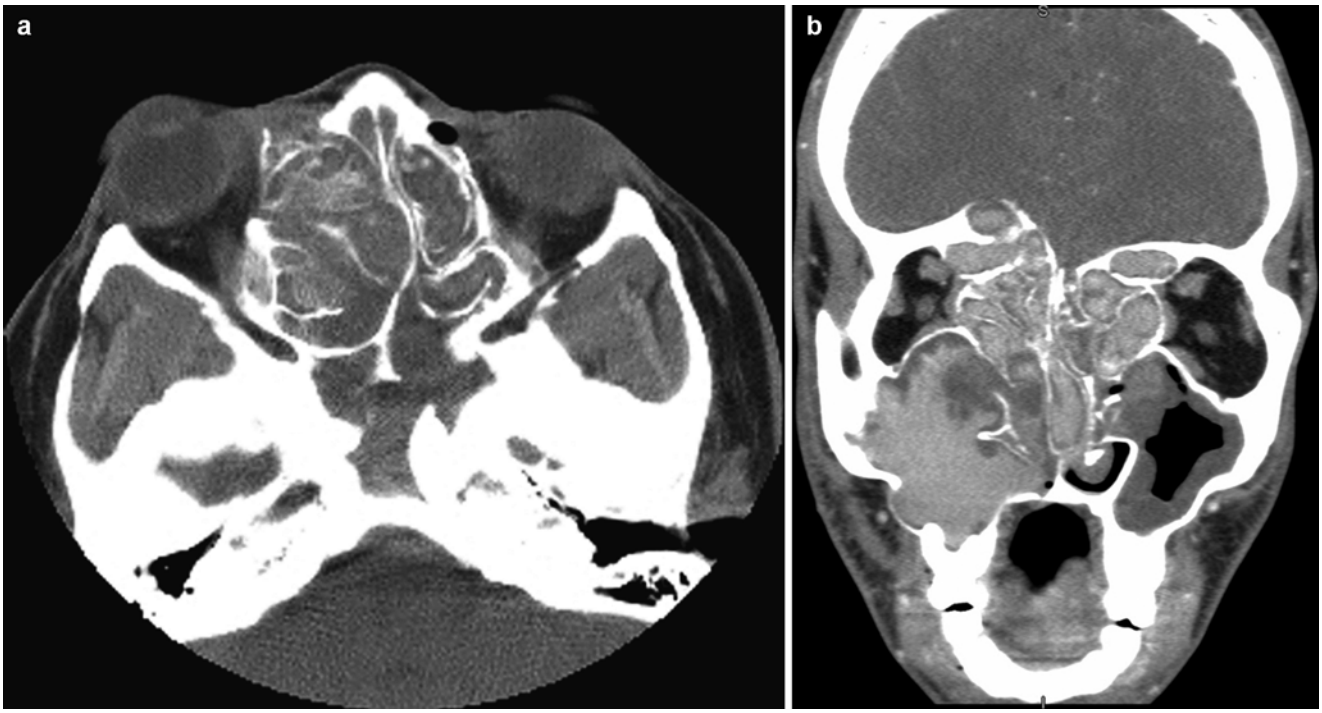


Fig. 8.4 Axial and coronal CT of a patient with AFRS. Axial (**a**) and coronal (**b**) images of a patient with severe allergic fungal rhinosinusitis with extensive mucocele formation. Note the extension into the anterior cranial fossa and right orbit causing proptosis. Eosinophilic mucin has a heterogeneous appearance within the sinuses

therapy has also been described, with the aim to reduce the antigenic load contributed by the fungus [43]; however, these are not commonly employed.

Immunotherapy is another treatment option in the management of AFRS, based on the theory that AFRS is due to allergen-specific IgE-mediated inflammation. Although the role of the type 1 hypersensitivity in AFRS is still unclear, studies have shown that immunotherapy is well tolerated and may be effective in the management of AFRS, reducing recurrences after surgery and decreasing the need for corticosteroids [44]. In a study of 22 patients treated with immunotherapy for AFRS, results at a mean treatment time of 33 months showed better symptoms scores and endoscopic appearance and less reliance on corticosteroids [45]. Given that all of these patients are allergic, it seems reasonable to include immunotherapy as one of the immunomodulating treatment modalities for AFRS.

Despite initial treatment success, some patients with AFRS continue to relapse and may do so at variable times. In a study spanning 7 years, patients with AFRS required an average of two surgeries and three course of systemic steroids per year [46]. It was also noted that serum IgE in these patients also remained high despite resolution of symptoms, suggesting a chronic process with a high propensity for recurrence. Hence, the need for regular endoscopic examination and follow-up of these patients cannot be overemphasized.

Chronic Invasive Fungal Rhinosinusitis

Chronic invasive fungal rhinosinusitis (CIFRS) is a slowly progressing fungal infection of the sinuses that evolves over a time course of >12 weeks. When there is the presence of a granulomatous reaction, the term "granulomatous invasive fungal rhinosinusitis" is used. The latter is differentiated by the presence of noncaseating granulomas with giant cell formation and fewer fungal hyphae. The granulomatous form seems to have a distinct geographical distribution and is more commonly found in the dry desert areas of Sudan [47]. In contrast, the histology of the nongranulomatous variant shows a larger number of fungal hyphae with tissue invasion. Both are largely caused by *Aspergillus*, and due to their similarities in terms of presentation, prognosis, and management, for the purposes of this chapter, they will be discussed as a single entity.

Chronic invasive fungal rhinosinusitis typically manifests in the healthy patient without demonstrable immune defect. However, some may have a mild immune impairment in the form of diabetes mellitus [4]. Symptoms develop slowly and

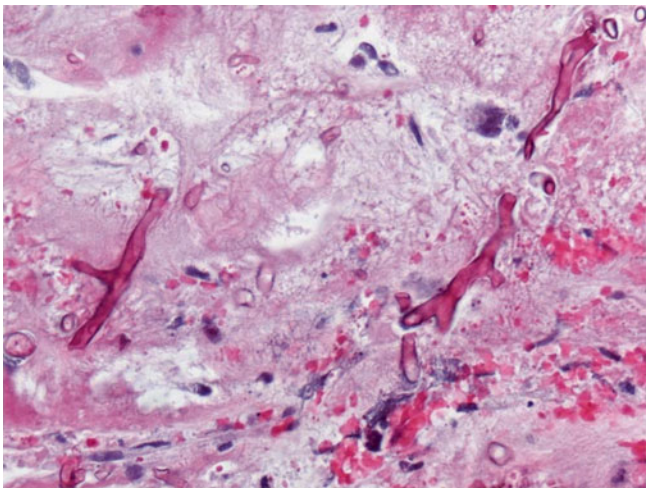


Fig. 8.5 Histopathology of acute invasive fungal rhinosinusitis. 400× magnification image showing broad-based, "ribbonlike" hyphae, consistent with mucoraceae, in a background of necrosis

may evolve over months to years. The clinical presentation may resemble a sinonasal neoplasm. The most common presentation is proptosis resulting from erosion into the orbit. Extensions to other areas may lead to palatal fistulas and neurological deficits. Fatal complications may result from erosions into the internal carotid artery and cavernous sinus thrombosis [48].

Physical examination findings are quite variable depending upon the location and extent of disease. Endoscopic examination shows nasal congestion with occasional nasal polyps. There may be a soft tissue mass or evidence of mucosal ulcerations. A faint yellowish hue of the tissue has also been described [4].

The imaging modality of choice for chronic invasive rhinosinusitis is the CT scan. However, in view of the potential for dural extension and a differential diagnosis of malignancy, MRI is also employed to rule out these processes. Characteristic imaging findings include a homogeneous opacity that is iso- or slightly hyperdense compared to muscle, intermediate signal intensity on T1-weighted MRI, and low signal intensity on T2. Contrasted scans may show extensive tissue involvement outside of the sinuses [49]. Definitive diagnosis, however, relies on histological examination showing fungal invasion (Fig. 8.5).

Management of chronic invasive fungal rhinosinusitis is accomplished with a combination of surgical resection and antifungal therapy. The treatment is based on the principles of management of acute invasive fungal rhinosinusitis. Surgical resection secures tissue for the diagnosis of invasion as well as identification of the offending organism. The second role of surgery is debridement; the extent of surgical resection required is not well defined, but this may range from simple debridement to radical resection of all tissue that is involved with fungus. Most authors would favor an individualized approach with the extent of surgery dependent on the initial extent of disease and response to medical therapy [4].

The antifungal armamentarium for chronic invasive fungal disease includes the use of amphotericin B and the oral triazoles. As with surgical therapy, the intensity and duration of antifungal therapy should be tailored to the patient's circumstances. Some advocate a course of intravenous amphotericin B of up to 2 g followed by a long-term course of oral antifungal therapy [50], while others advocate a more conservative treatment with monitoring of response [51]. The wide variability of treatments, potential side effects of treatment, and variable response highlight the need for individualized treatment and long-term follow-up of this condition.

Acute Invasive Fungal Rhinosinusitis

Acute invasive fungal rhinosinusitis (AIFRS) or fulminant invasive fungal rhinosinusitis is defined as an invasive fungal infection of less than 4 weeks [18]. Left untreated, this condition is rapidly fatal. AIFRS affects mainly the immunocompromised, with prolonged neutropenia being the most important risk factor. Patients with hematological malignancies are especially at risk for developing AIFRS with *Aspergillus* species. The other classic risk factor for AIFRS is diabetic ketoacidosis, and these cases usually involve the mucoraceae. Other risk factors include end-stage AIDS, systemic corticosteroid therapy, and chronic renal failure. Restoration of immune function is considered vital in the treatment of AIFRS.

The initial clinical symptoms of AIFRS may be mild and appear innocuous. However, symptoms such as clear rhinorrhea and nasal congestion may rapidly progress to other more ominous signs and symptoms such as fever, severe facial pain, visual disturbances, facial swelling, palatal and facial necrosis, and cranial nerve palsies [52]. Erosion of the skull base with direct invasion into the brain may lead to altered mental status.

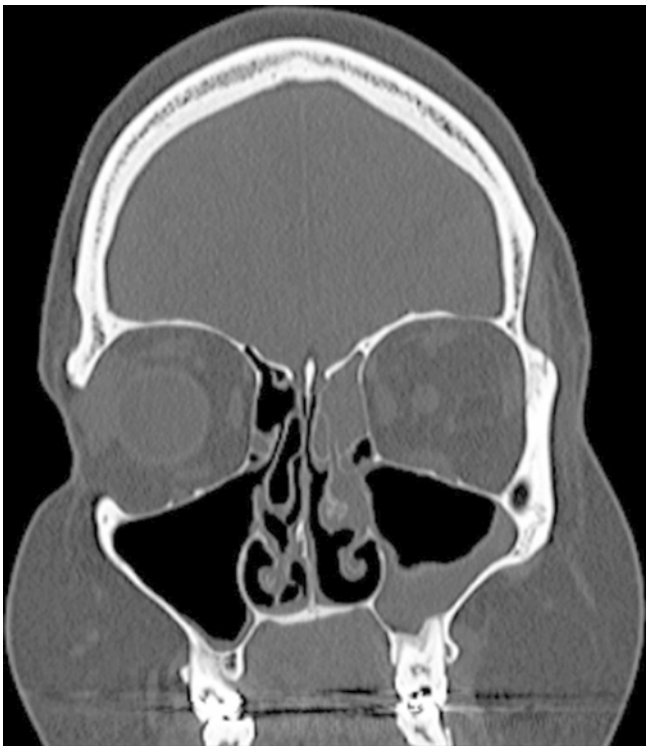


Fig. 8.6 CT Scan of acute invasive fungal rhinosinusitis. Coronal CT scan of acute invasive fungal rhinosinusitis with nonspecific changes of mild opacification of the left ethmoid and bilateral maxillary sinuses. Imaging findings are not benign appearing in the early course of this disease

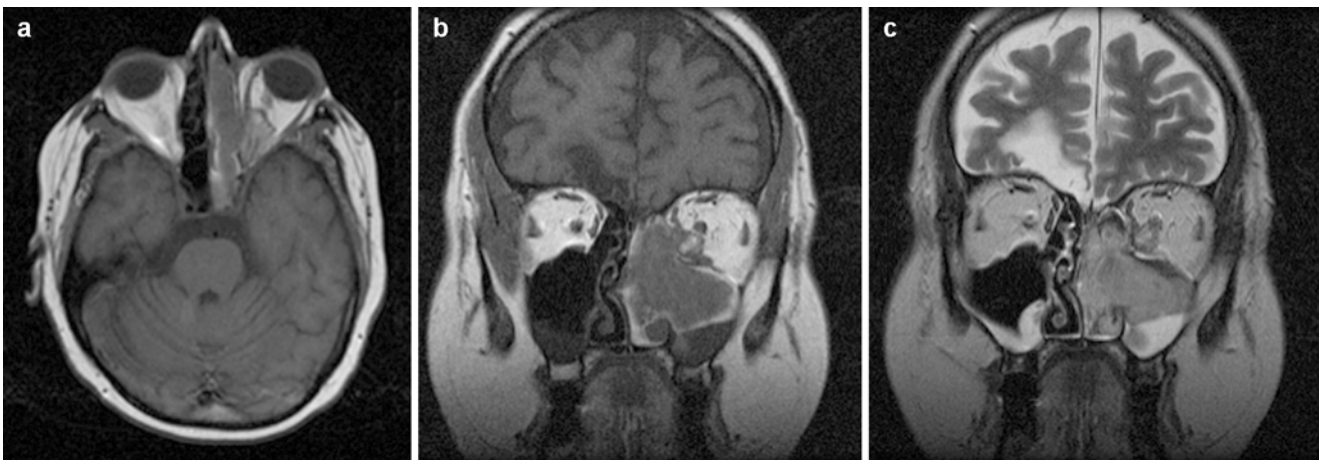


Fig. 8.7 MRI images of acute invasive fungal rhinosinusitis. MRI axial T1 (**a**) and coronal T1(**b**) and T2 (**c**) images. Showing invasive fungal rhinosinusitis with left inferomedial orbital involvement

External physical examination findings are not present until the disease has extended out of the sinonasal cavities. Early diagnosis therefore requires nasal endoscopy. Acute invasive fungal rhinosinusitis causes tissue necrosis that is initially manifest as erythematous or pale mucosa that is insensate to touch. As the disease progresses, these areas become necrotic and the mucosa may take on a dark, dusky appearance. Although these changes may occur anywhere along the nasal mucosa, the most common areas is the mucosa of the middle turbinate [53]. As progression may occur in a matter of hours, it is important to repeat an endoscopic examination if initial findings are inconclusive and there is diagnostic uncertainty.

Imaging of the patient with AIFRS is important for diagnosis as well as to delineate the extent of the disease. A CT scan is the initial imaging study. Early findings may be nonspecific with areas of mucosal thickening or sinus opacification (Fig. 8.6). One large series showed that severe unilateral nasal soft tissue swelling [54] was a common feature of early AIFRS. Late radiological signs include bony erosion and orbital or facial soft tissue invasion. If extra-sinus involvement is suspected, an MRI (Fig. 8.7) may be used to delineate the extent of tissue involvement and may be helpful in guiding the extent of surgical resection.

AIFRS is a disease that is better prevented than treated. By identifying patients that are at risk for immune suppression, for example, as a result of chemotherapeutic drugs or in posttransplant patients, measures to reduce exposure to fungal spores, screening for sinus disease, or even prophylactic antifungal therapy [55] may be implemented to reduce the rate of AIFRS.

Due to a paucity of trials, the ideal treatment regimen for treating AIFRS is unknown. The principles of therapy include reversal of the immunocompromised state, surgical debridement, and the use of antifungal therapy.

Reversal of the immunocompromised state is vital for survival in AIFRS. Depending on the cause, this may necessitate stopping chemotherapeutic agents, aggressively reversing hyperglycemia and ketoacidosis, or the administration of granulocyte-stimulating factors [56]. If the underlying immunocompromise cannot be reversed, the prognosis for survival is poor.

Surgical debridement of patients with AIFRS has been a mainstay of therapy [57]. Surgery also secures a specimen for proper identification of the offending organism, confirms the diagnosis, and clears necrotic tissue [58]. With advancements in surgical techniques, there is a trend toward endoscopic resection of the necrotic tissue as it entails a lower surgical morbidity. Additionally, it is increasingly recognized that AIFRS is primarily a "medical" disease and that surgery is at best an adjunct to antifungal medications and the restoration of immune function. Traditional open surgery is reserved for advanced cases where there is significant orbital or intracranial involvement, and radical facial resections are not common. The contemporary approach to surgical treatment is to remove all tissue that is obviously involved with fungus. Frozen section examination of the resected specimen has been used for the initial diagnosis and to guide the extent of debridement. However, this should be used with care as one study [59] showed that up to 37 % of intraoperative specimens sent for frozen section had false-negative results. Surgery in cases of AIFRS is often fraught with difficulties as these patients are often thrombocytopenic and coagulopathic. As a result, there is significant intraoperative hemorrhage and potential for morbidity.

Antifungal therapy is a critical component of the treatment of AIFRS. It can be administered systemically or in combination with topical therapy, although evidence for the latter is lacking. As most invasive fungal infections are caused by *Aspergillus* or the mucoraceae, amphotericin B is commonly used for empiric therapy. Amphotericin B deoxycholate causes significant infusion related and systemic toxicities that limit its dosing. However, newer lipid formulations have fewer side effects that permit more aggressive dosing [60]. Other antifungal agents include voriconazole or itraconazole, which are effective against *Aspergillus*, and posaconazole, which is typically used as an oral therapy for mucoraceae after initial therapy with amphotericin B. The duration of antifungal therapy required once the disease process is arrested is unclear. Ultimately the duration of therapy should be dependent on the immune status of the patient and clinical evidence of disease recurrence and should be decided in conjunction with an infectious disease specialist.

Conclusions

Fungal rhinosinusitis has a wide variety of clinical presentations. These range from the minimally symptomatic fungus ball to the lethal acute invasive fungal rhinosinusitis (Table 8.3). It appears that the host immune response to the fungus plays an important role in determining the manifestation of the disease. While most rhinosinusitis can be adequately managed with medical therapy alone, all of the subtypes of fungal rhinosinusitis require surgery for diagnosis and treatment. Antifungal medications are only indicated for tissue invasive forms of fungal sinusitis. In allergic fungal rhinosinusitis, long-term

Table 8.3 Summary table of fungal rhinosinusitis

	Fungus ball	AFRS	CIFRS	AIFRS
Pathogen	*Aspergillus*	*Alternaria*, *Bipolaris*, dematiaceous molds	*Aspergillus*	*Mucoraceae*, *Aspergillus*
Patient profile	Normal immunity elderly	History of atopy or allergic rhinitis	Older age group	Immune compromised
		Adolescent, young adult	Diabetes mellitus	
Presentation	Nasal obstruction	Gradual onset	Proptosis	Medical emergency
	Purulent nasal discharge, facial pain	Unilateral symptoms	Facial pain	Nasal congestion, rhinorrhea, facial pain, fever
		Characteristic dark colored mucus		
		Proptosis		Visual disturbance
Treatment	Surgical removal of fungus ball	Surgical drainage	Surgical resection of affected areas	Restore immune function
		Systemic corticosteroids		
	No antifungals needed	Topical steroids	Systemic antifungal therapy	Surgical debridement
		Immunotherapy		Systemic antifungal therapy

anti-inflammatory medication in the form of topical and systemic corticosteroids is required to prevent the recurrence of polyps and the reaccumulation of eosinophilic mucin.

Acknowledgments The authors would like to thank Dr. Jason Mull, M.D., Assistant Professor, Pathology, University of Texas Southwestern Medical Center, for the histopathological figures used in this chapter.

References

1. Hora JF. Primary aspergillosis of the paranasal sinuses and associated areas. Laryngoscope. 1965;75:768–73.
2. Katzenstein AL, Sale SR, Greenberger PA. Allergic Aspergillus rhinosinusitis: a newly recognized form of rhinosinusitis. J Allergy Clin Immunol. 1983;72:89–93.
3. Ferguson BJ. Definitions of fungal rhinosinusitis. Otolaryngol Clin North Am. 2000;33:227–35.
4. Stringer SP, Ryan MW. Chronic invasive fungal rhinosinusitis. Otolaryngol Clin North Am. 2000;33:375–87.
5. Schwietz LA, Gourley DS. Allergic fungal rhinosinusitis. Allergy Proc. 1992;13:3–6.
6. Talbot GH, Huang A, Provencher M. Invasive aspergillus rhinosinusitis in patients with acute leukemia. Rev Infect Dis. 1991;13:219–32.
7. Milosev B, el-Mahgoub S, Aal OA, et al. Primary aspergilloma of paranasal sinuses in the Sudan. A review of seventeen cases. Br J Surg. 1969;56:132–7.
8. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal rhinosinusitis. Mayo Clin Proc. 1999;74:877–84.
9. Shin SH, Ponikau JU, Sherris DA, et al. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. J Allergy Clin Immunol. 2004;114:1369–75.
10. Ponikau JU, Sherris DA, Weaver A, et al. Treatment of chronic rhinosinusitis with intranasal amphotericin B: a randomized, placebo-controlled, double-blind pilot trial. J Allergy Clin Immunol. 2005;115:125–31.
11. Fokkens WJ, van Drunen C, Georgalas C, et al. Role of fungi in pathogenesis of chronic rhinosinusitis: the hypothesis rejected. Curr Opin Otolaryngol Head Neck Surg. 2012;20(1):19–23.
12. Sacks PL, Harvey RJ, Rimmer J, et al. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Cochrane Database Syst Rev. 2011;8:CD008263.
13. Orlandi RR, Marple BF, Georgelas A, et al. Immunologic response to fungus is not universally associated with rhinosinusitis. Otolaryngol Head Neck Surg. 2009;141:750–6.e1–2.
14. Foreman A, Psaltis AJ, Tan LW, et al. Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. Am J Rhinol Allergy. 2009; 23:556–61.
15. Glass D, Amedee RG. Allergic fungal rhinosinusitis: a review. Ochsner J. 2011;11:271–5.
16. Buchheidt D, Hummel M, Schleiermacher D, et al. Current molecular diagnostic approaches to systemic infections with aspergillus species in patients with hematological malignancies. Leuk Lymphoma. 2004;45:463–8.
17. Lass-Florl C, Gunsilius E, Gastl G, et al. Clinical evaluation of Aspergillus-PCR for detection of invasive aspergillosis in immunosuppressed patients. Mycoses. 2005;48 Suppl 1:12–7.
18. Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. Laryngoscope. 2009;119:1809–18.
19. Klossek JM, Serrano E, Peloquin L, et al. Functional endoscopic sinus surgery and 109 mycetomas of paranasal sinuses. Laryngoscope. 1997;107:112–7.
20. Ferreiro JA, Carlson BA, Cody 3rd DT. Paranasal sinus fungus balls. Head Neck. 1997;19:481–6.
21. Seo YJ, Kim J, Kim K, et al. Radiologic characteristics of sinonasal fungus ball: an analysis of 119 cases. Acta Radiol. 2011;52:790–5.
22. Ferguson BJ. Fungus balls of the paranasal sinuses. Otolaryngol Clin North Am. 2000;33:389–98.
23. Brook I. Recovery of aerobic and anaerobic bacteria in sinus fungal ball. Otolaryngol Head Neck Surg. 2011;145:851–2.
24. Manning SC, Schaefer SD, Close LG, et al. Culture-positive allergic fungal rhinosinusitis. Arch Otolaryngol Head Neck Surg. 1991;117:174–8.
25. Ferguson BJ, Barnes L, Bernstein JM, et al. Geographic variation in allergic fungal rhinosinusitis. Otolaryngol Clin North Am. 2000;33:441–9.
26. Stewart AE, Hunsaker DH. Fungus-specific IgG and IgE in allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg. 2002;127:324–32.
27. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal rhinosinusitis. II. Treatment and follow-up. J Allergy Clin Immunol. 1998;102:395–402.
28. Horst M, Hejjaoui A, Horst V, et al. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. J Allergy Clin Immunol. 1990;85:460–72.
29. Bent 3rd JP, Kuhn FA. Diagnosis of allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg. 1994;111:580–8.
30. Allphin AL, Strauss M, Abdul-Karim FW. Allergic fungal rhinosinusitis: problems in diagnosis and treatment. Laryngoscope. 1991;101:815–20.
31. Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. Laryngoscope. 2000;110:799–813.
32. Pant H, Kette FE, Smith WB, et al. Eosinophilic mucus chronic rhinosinusitis: clinical subgroups or a homogeneous pathogenic entity? Laryngoscope. 2006;116:1241–7.
33. McClay JE, Marple B, Kapadia L, et al. Clinical presentation of allergic fungal rhinosinusitis in children. Laryngoscope. 2002;112:565–9.
34. Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. Laryngoscope. 2001;111:1006–19.
35. Ghegan MD, Lee FS, Schlosser RJ. Incidence of skull base and orbital erosion in allergic fungal rhinosinusitis (AFRS) and non-AFRS. Otolaryngol Head Neck Surg. 2006;134:592–5.
36. Manning SC, Merkel M, Kriesel K, et al. Computed tomography and magnetic resonance diagnosis of allergic fungal rhinosinusitis. Laryngoscope. 1997;107:170–6.

37. Marple BF, Mabry RL. Allergic fungal rhinosinusitis: learning from our failures. Am J Rhinol. 2000;14:223–6.
38. Rupa V, Jacob M, Mathews MS, et al. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal rhinosinusitis. Eur Arch Otorhinolaryngol. 2010;267:233–8.
39. Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: a four-year follow-up. Am J Rhinol. 2000;14:149–56.
40. Ryan MW, Marple BF. Allergic fungal rhinosinusitis: diagnosis and management. Curr Opin Otolaryngol Head Neck Surg. 2007;15:18–22.
41. Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2008;139:340–7.
42. Schubert MS. Antileukotriene therapy for allergic fungal rhinosinusitis. J Allergy Clin Immunol. 2001;108:466–7.
43. Jen A, Kacker A, Huang C, et al. Fluconazole nasal spray in the treatment of allergic fungal rhinosinusitis: a pilot study. Ear Nose Throat J. 2004;83(692):94–5.
44. Mabry RL, Marple BF, Folker RJ, et al. Immunotherapy for allergic fungal rhinosinusitis: three years' experience. Otolaryngol Head Neck Surg. 1998;119:648–51.
45. Folker RJ, Marple BF, Mabry RL, et al. Treatment of allergic fungal rhinosinusitis: a comparison trial of postoperative immunotherapy with specific fungal antigens. Laryngoscope. 1998;108:1623–7.
46. Marple B, Newcomer M, Schwade N, et al. Natural history of allergic fungal rhinosinusitis: a 4- to 10-year follow-up. Otolaryngol Head Neck Surg. 2002;127:361–6.
47. Veress B, Malik OA, el-Tayeb AA, et al. Further observations on the primary paranasal aspergillus granuloma in the Sudan: a morphological study of 46 cases. Am J Trop Med Hyg. 1973;22:765–72.
48. Chakrabarti A, Sharma SC, Chandler J. Epidemiology and pathogenesis of paranasal sinus mycoses. Otolaryngol Head Neck Surg. 1992;107:745–50.
49. Reddy CE, Gupta AK, Singh P, et al. Imaging of granulomatous and chronic invasive fungal rhinosinusitis: comparison with allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg. 2010;143:294–300.
50. Washburn RG, Kennedy DW, Begley MG, et al. Chronic fungal rhinosinusitis in apparently normal hosts. Medicine (Baltimore). 1988;67:231–47.
51. Gumaa SA, Mahgoub ES, Hay RJ. Post-operative responses of paranasal Aspergillus granuloma to itraconazole. Trans R Soc Trop Med Hyg. 1992;86:93–4.
52. Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am. 2000;33:349–65.
53. Gillespie MB, Huchton DM, O'Malley BW. Role of middle turbinate biopsy in the diagnosis of fulminant invasive fungal rhinosinusitis. Laryngoscope. 2000;110:1832–6.
54. DelGaudio JM, Swain Jr RE, Kingdom TT, et al. Computed tomographic findings in patients with invasive fungal rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2003;129:236–40.
55. Malani PN, Kauffman CA. Prevention and prophylaxis of invasive fungal rhinosinusitis in the immunocompromised patient. Otolaryngol Clin North Am. 2000;33:301–12.
56. Goering P, Berlinger NT, Weisdorf DJ. Aggressive combined modality treatment of progressive sinonasal fungal infections in immunocompromised patients. Am J Med. 1988;85:619–23.
57. Blitzer A, Lawson W, Meyers BR, et al. Patient survival factors in paranasal sinus mucormycosis. Laryngoscope. 1980;90:635–48.
58. Gillespie MB, O'Malley Jr BW, Francis HW. An approach to fulminant invasive fungal rhinosinusitis in the immunocompromised host. Arch Otolaryngol Head Neck Surg. 1998;124:520–6.
59. Taxy JB, El-Zayaty S, Langerman A. Acute fungal rhinosinusitis: natural history and the role of frozen section. Am J Clin Pathol. 2009;132:86–93.
60. Patterson TS, Barton LL, Shehab ZM, et al. Amphotericin B lipid complex treatment of a leukemic child with disseminated Fusarium solani infection. Clin Pediatr (Phila). 1996;35:257–60.

Part III
The Clinical Spectrum of Sinus Disease

Chapter 9
Differential Diagnosis of Rhinitis and Rhinosinusitis

Jonathan Romeo and Mark S. Dykewicz

Introduction

Both rhinitis and sinusitis (rhinosinusitis) affect millions of people in westernized countries and have significant effects on an individual's quality of life and health-care costs. Although allergic rhinitis is the most common form of rhinitis, many patients have various nonallergic forms of rhinitis that must be considered in the differential diagnosis of patients presenting with nasal symptoms. The term rhinosinusitis recognizes that sinusitis rarely occurs in the absence of rhinitis and the fact that the nose and sinuses are contiguous structures sharing vascular, neuronal, and interconnecting anatomic pathways. As a consequence, rhinitis and rhinosinusitis can overlap in clinical presentation making differentiation between these diagnoses often difficult. In addition, there are a variety of conditions that may mimic rhinitis and rhinosinusitis. As such, it is important to have a methodical and comprehensive approach when evaluating patients who present with nasal symptoms. The primary goal of this chapter is to discuss the differential diagnosis of rhinitis and rhinosinusitis.

The Differential Diagnosis of Rhinitis

Recurrent or chronic rhinitis is one of the most common medical conditions presenting for medical care in developed countries. Recurrent or chronic rhinitis can be subdivided into allergic and nonallergic forms. Allergic rhinitis alone affects approximately 30–60 million people annually in the United States [1–3] of which 10–30 % are adults and up to 40 % are children [4–8]. In contrast, pure nonallergic rhinitis occurs less frequently. Nearly three times as many people suffer from allergic rhinitis compared to pure nonallergic rhinitis. In general, between 44 and 87 % of patients presenting for evaluation of recurrent or chronic rhinitis present a "mixed" combination of both allergic and nonallergic triggers [4, 9].

While some may view rhinitis as a minor disease, there are significant consequences to poor control of this condition. Rhinitis itself can contribute to patient morbidity in relation to decreased quality of life, increased medical costs, and lost time/poor performance at school or work. In addition, rhinitis has been associated with significant comorbidities including conjunctivitis, asthma, sinus disease, otitis media, and sleep apnea.

Clinical Presentation/Characterization

Rhinitis is a condition characterized by a constellation of nasal symptoms. These include one or more of the following: congestion, anterior or posterior rhinorrhea, sneezing, and itching [10]. Allergic rhinitis can frequently be associated with

J. Romeo, DO
Section of Pulmonary, Critical Care, and Allergic and Immunologic Diseases, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA
e-mail: jromeo@wakehealth.edu

M.S. Dykewicz, MD (✉)
Section of Allergy and Immunology, Saint Louis University School of Medicine, 1402 South Grand Boulevard, M157, St. Louis, MI 63104, USA
e-mail: dykewicz@slu.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_9,

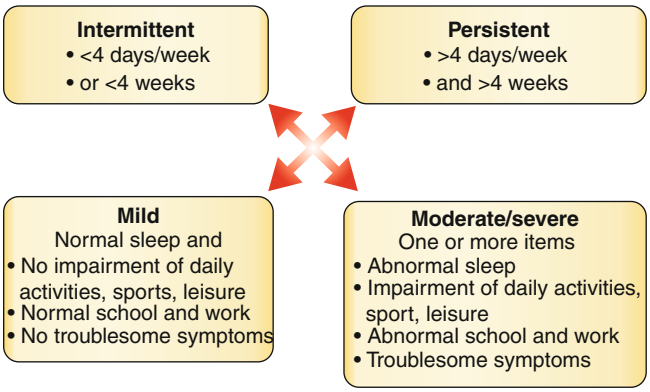


Fig. 9.1 ARIA classification of allergic rhinitis (Reprinted from Bousquet et al. [11]. With permission from John Wiley & Sons, Inc.)

allergic conjunctivitis (conjunctival redness, itching, swelling, and excess lacrimation) [10, 11]. Treatment of underlying allergic rhinitis symptoms helps reduce any associated ocular symptoms. In contrast, eye symptoms are less often associated with nonallergic rhinitis or occur independently.

The frequency of symptoms is also important in defining the types of rhinitis as well as ultimately guiding treatment regimens. While there are several national and international treatment guidelines for rhinitis, two of the most comprehensive are the US Joint Task Force on Practice Parameters (JTF), sponsored by American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; and Joint Council on Allergy, Asthma and Immunology, and the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (produced by an international panel). These two guidelines differ in the nomenclature used to characterize symptom duration.

Consistent with FDA regulatory guidance, the US parameter has defined allergic rhinitis as being either seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR), with recognition that some patients have SAR exacerbations that overlay PAR. Symptoms associated with either SAR or PAR may be infrequent or more frequent (as assessed by the clinician, but not further defined formally in the parameter), with the frequency of symptoms being factored into the selection of recommended therapeutic options. In addition to SAR and PAR, the most recent update of the JTF guidelines uses an additional subcategory of allergic rhinitis, *episodic* (environmental) rhinitis. Episodic rhinitis symptoms are elicited by sporadic exposure to inhalant allergens that are not normally present in someone's daily environment [10].

The ARIA guidelines take an alternative approach to rhinitis nomenclature, using the terms *intermittent* to classify symptoms less than 4 days a week and/or less than 4 weeks duration and *persistent* used to classify patients with symptoms occurring more frequently and/or for longer duration (Fig. 9.1) [11]. The terms intermittent and persistent rhinitis are independent of the traditional terms of SAR and PAR. The ARIA guidelines have discouraged the use of the terms SAR and PAR, noting that seasonal allergens in some geographic regions may be perennial in other regions of the world. However, more recent ARIA updates make limited use of the term SAR in making treatment recommendations [12].

The most recent updates of the ARIA and the Joint Task Force Parameter concur that *mild* allergic rhinitis is the presence of symptoms not troublesome enough to impact quality of life, such as sleep disturbance, or cause impairment of daily activities, leisure, sport, school, or work. ARIA defines moderate and severe rhinitis according to the criteria listed in Fig. 9.1. The US Practice Parameter uses a concept of *more severe* rhinitis (without formally defining a distinction between moderate and severe rhinitis) when symptoms cause impairment of quality of life.

Types of Rhinitis

Allergic Rhinitis

Allergic rhinitis is the result of an immunoglobulin E (IgE) antibody-mediated reaction against inhaled allergens [13] (Table 9.1). Following sensitization to a particular allergen, subsequent exposure will incite IgE-induced mast cell and basophil degranulation and activation. This results in the release of preformed mediators, such as histamine, and de novo generation of mediators including cysteinyl leukotrienes and prostaglandin D2 that are capable of generating a variety of adverse effects. An allergic reaction can have an early or an early- and late-phase response depending upon the character of the mucosal inflammation caused by resident and infiltrating inflammatory cells and their numerous vasoactive and proinflammatory mediators [14–17]. The early-phase response is characterized by acute mucosal edema, mucus secretion,

Table 9.1 Classification of rhinitis

Allergic rhinitis
Seasonal
Perennial
Episodic
Nonallergic rhinitis
Idiopathic/vasomotor rhinitis
Irritant triggered (e.g., chlorine)
Cold air
Exercise
Emotional
Undetermined or poorly defined triggers
NARES
Rhinitis due to food/alcohol
Gustatory rhinitis
Hormonal
Menstrual cycle/others
Pregnancy-induced rhinitis
Drug-induced rhinitis
ASA/NSAIDS
Antihypertensives and cardiovascular agents
Others (e.g., phosphodiesterase-5 selective inhibitors)
Rhinitis medicamentosa
Atrophic rhinitis
Infectious rhinitis
Work-related rhinitis
Work-exacerbated rhinitis
Occupational rhinitis
Rhinitis associated with inflammatory or immunologic disease
Granulomatous infections
Wegener's granulomatosis
Sjogren's syndrome
Sarcoidosis
Churg-Strauss disease
Relapsing polychondritis (RPC)
Amyloidosis
Lethal midline granuloma

Adapted from Wallace et al. [10]. With permission from Elsevier

vascular leak, and stimulation of sensory neurons that occurs within minutes of exposure [17]. The late-phase response occurs over several hours with release of chemotactic factors, such as IL-5, causing an influx of inflammatory cells (especially eosinophils). Symptoms of both early- and late-phase reactions consist of sneezing, congestion, and rhinorrhea; however, nasal congestion appears to predominate in the late-phase response [18].

In most geographic locations, grass, tree, and weed pollens and outdoor molds most commonly cause seasonal allergic rhinitis. The symptom expression is dependent on the degree of individual allergenicity, length of exposure, geographic location, and climactic conditions [19, 20]. As noted earlier, in some countries and geographic regions, certain pollens may be present during most of the year inducing a perennial presentation [11]. In contrast, more typical perennial rhinitis is caused by aeroallergens present consistently year round in most environments, such as dust mites, animal allergens, occupational allergens, and indoor molds

Nonallergic Rhinitis

Nonallergic rhinitis is characterized by perennial or intermittent symptoms of rhinitis that are, by definition, not allergic and, therefore, not IgE mediated [10]. Such a broad definition comprises many different forms of rhinitis that arise from infectious, inflammatory, or noninflammatory mechanisms. Approximately one-third of adults with perennial nasal complaints have forms of nonallergic rhinitis [4, 9]. Table 9.2 differentiates between inflammatory and noninflammatory causes of nonallergic rhinitis.

Table 9.2 Causes of nonallergic rhinitis

Nonallergic, inflammatory
Occupational
Drug induced
Infective
Aspirin sensitive
NARES
Nonallergic, noninflammatory
Emotional
Idiopathic
Atrophic
Gustatory
Vasomotor
Rhinitis medicamentosa
Hormonal

Based on data from Adkinson et al. [125]

Vasomotor (Joint Task Force) or Idiopathic (ARIA-Preferred Term) Rhinitis

This heterogeneous group of disorders refers to rhinitis that does not have an immunologic or infectious basis and is not associated with nasal eosinophilia. The symptoms may be variable, consisting mainly of nasal obstruction or increased secretion. Sneezing and pruritus are less common than in allergic rhinitis. In comparison to allergic rhinitis, associated eye symptoms are infrequently observed or occur as an independent issue. Vasomotor rhinitis is a term sometimes used synonymously with nonallergic rhinitis without eosinophilia. Nasal symptoms of vasomotor or nonallergic rhinitis are typically provoked by nonallergic environmental factors, such as irritants and strong odors (i.e., smoke, perfume, cleaning solutions), changes in temperature (i.e., cold air), alcoholic beverages, emotional factors, and exercise [21–24].

Nonallergic Rhinitis with Eosinophilia Syndrome (NARES)

NARES is characterized by nasal mucosal eosinophils without evidence of specific IgE antibodies demonstrable in the serum or skin. It typically affects middle-aged patients. Symptoms usually are perennial in nature with paroxysmal exacerbations of symptoms that include sneezing, profuse watery rhinorrhea, nasal pruritus, nasal congestion, and occasional hyposmia or anosmia [25–29]. It should be noted, however, that a portion of patients with NARES have or will ultimately develop nasal polyposis and aspirin sensitivity [30]. In addition, patients with NARES are at increased risk for developing sleep apnea [31]. Although the majority of patients with NARES do not have known triggers, some people have worsening of their condition with exposure to weather changes, odors, and irritants.

Rhinitis from Food and Alcohol Ingestion

Rhinitis from food and alcohol occur through a variety of pathways. IgE-mediated food allergy is a very rare cause of rhinitis unless associated with coexisting gastrointestinal, dermatologic, or systemic manifestations. In contrast to an allergic etiology, the ingestion of food can cause primarily anterior rhinorrhea termed gustatory rhinitis. Gustatory rhinitis is a form of nonallergic rhinitis that is associated with symptoms that occur during or shortly after eating. This phenomenon is particularly common with the ingestion of hot and spicy food. However, in some patients, particularly the elderly, it can occur with any meal and sometimes upon arising in the morning. It is felt to be mediated by vagal mechanisms in that it typically responds to topical anticholinergic medications. In contrast, beer, wine, and other alcoholic beverages can also produce nasal symptoms, probably through nasal vasodilation. There are some individuals who develop congestion only upon the ingestion of certain beers or wine whose etiology remains uncertain.

Hormonal Rhinitis

Rhinitis symptoms may be associated with the menstrual cycle, pregnancy, puberty, and specific endocrine disorders such as hypothyroidism and acromegaly. Rhinitis during pregnancy can include all forms of rhinitis such as allergic rhinitis,

Table 9.3 Drugs associated with rhinitis

Analgesics
NSAIDS: aspirin, etc.
Cardiovascular agents
ACE inhibitors
Amiloride
β-blockers
Psychotropics
Risperidone
Chlorpromazine
Amitriptyline
Phosphodiesterase type 5 inhibitors
Sildenafil
Tadalafil
Vardenafil
Others
Cocaine
Gabapentin

Based on data from Adkinson et al. [125]

rhinosinusitis, rhinitis medicamentosa, and nonallergic rhinitis [32–36]. Approximately 1/3 of pregnant patients will have an increase in their rhinitis symptoms during pregnancy, which has been attributed to nasal vascular pooling caused by vascular dilatation and increased blood volume [37, 38]. A type of rhinitis specific to pregnancy, "pregnancy-induced rhinitis" typically occurs in the second or third trimester peaking within the last 6 weeks of pregnancy (34 weeks gestation). Rhinitis of pregnancy spontaneously resolves within 2 weeks of delivery [39]. By definition, pregnancy-induced rhinitis must be without infectious, allergic, or medication-related causes. It can be detrimental to ignore this condition in that snoring caused by pregnancy-induced rhinitis has been associated with preeclampsia [40].

Drug-Induced Rhinitis

Several classes of drugs can induce rhinitis symptoms (Table 9.3). Rhinitis symptoms can be induced by blood pressure medications such as ACE inhibitors and β-blockers. Alpha receptor antagonists used for benign prostatic hypertrophy and phosphodiesterase-5 selective inhibitors used for treatment of erectile dysfunction [41–44] have also been incriminated in rhinitis cases. Contrary to long-standing belief, one study has concluded that oral contraceptive pills do not contribute to nasal symptoms [45]. Aspirin and other NSAIDS can cause increased rhinorrhea as an isolated symptom or as part of aspirin-exacerbated respiratory disease (AERD). AERD, classically known as Samter's triad, is the combination of asthma, hyperplastic rhinosinusitis typically with nasal polyposis, and adverse respiratory reactions to the ingestion of aspirin and other NSAIDs [6, 46]. This topic is discussed in greater detail in another chapter of this text.

Rhinitis Medicamentosa

Rhinitis medicamentosa is a syndrome of rebound nasal congestion associated with prolonged use of intranasal α-adrenergic decongestants or recreational intranasal cocaine [47, 48]. Prolonged use results in tachyphylaxis from the effects of intranasal decongestants (imidazoles such as oxymetazoline or catecholamines such as phenylephrine) resulting in rebound congestion and the resultant need for continuous use to maintain the ability to breath comfortably through the nose. Reduced mucociliary clearance may ultimately occur from the loss of ciliated epithelial cells [49]. Benzalkonium chloride, an excipient used in some formulations of nasal vasoconstrictor sprays, may augment local pathological effects on the nasal mucosa caused by topical decongestants when used for longer than 30 days [50–52]. On exam, nasal mucosa is typically inflamed, appears beefy red, and has areas of punctate bleeding with scant mucus. Rarely, perforation of the nasal septum may occur [10].

Atrophic Rhinitis: Primary and Secondary Forms Occur

Primary (idiopathic) atrophic rhinitis is characterized by progressive atrophy of the nasal mucosa and resorption of the bone and cartilage which leaves the nasal cavities abnormally wide on examination. There is a lack of identifiable turbinates on

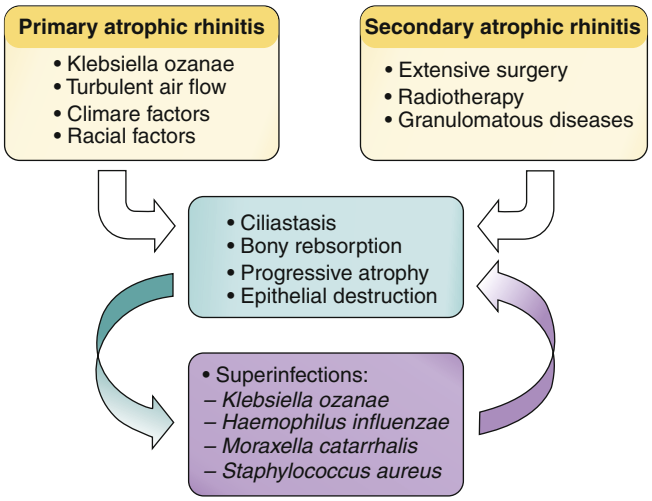


Fig. 9.2 Mechanism of atrophic rhinitis (Reprinted from Adkinson et al. [125]. With permission from Elsevier)

sinus CT (Fig. 9.2). These findings have been commonly referred to as the "empty nose syndrome" [53–55]. Other defining features of atrophic rhinitis include nasal dryness secondary to insufficient glandular cells, ciliary stasis, and ozena. Ozena is the presence of nasal crusting and fetor [53, 54] that results from mucous stasis in this condition.

Primary atrophic rhinitis usually occurs in young to middle-aged adults living in warm climates of developing countries and is frequently associated with sinusitis. Infection of the nasal cavity by *Klebsiella ozaenae* or other bacteria such as *Haemophilus influenzae*, *Moraxella catarrhalis*, *and Staphylococcus aureus* is common [55]. Mucosal biopsy of primary atrophic rhinitis reveals squamous metaplasia, glandular cell atrophy, and loss of pseudostratified epithelium. Patients often complain of a feeling of severe nasal congestion from the dryness, despite the absence of obstructive mucosal tissue.

Secondary atrophic rhinitis can be caused by recurrent or chronic sinusitis, direct trauma, irradiation or excessive surgical removal of the nasal turbinates, and infection with granulomatous diseases [55]. Secondary atrophic rhinitis should not be confused with rhinitis in the elderly, in which structural changes in vasculature and connective tissue due to aging induce rhinitis symptoms [10].

Infectious (e.g., Viral) Rhinitis

Nearly all cases of infectious rhinitis are the result of acute viral upper respiratory infections. Infectious rhinitis may be initially difficult to differentiate from other causes of rhinitis. However, a careful history usually reveals associated constitutional symptoms with peak severity approximately 48 h after onset. There is typically resolution of symptoms within 7–10 days of onset [56, 57]. Because the mucosa of the nose and sinuses form a continuum, a viral infection of the nose is commonly associated with sinus involvement. Differentiating nonallergic rhinitis with a secondary sinus infection from infectious rhinosinusitis of viral origin may be difficult on an initial visit because of symptom overlap (e.g., purulent nasal drainage may be present in noninfectious rhinitis or rhinosinusitis) [56]. However, the knowledge of a local viral epidemic, associated constitutional symptoms including sore throat, fever, and cough particularly in a child, and a history of perhaps other family members being similarly ill soon clarify the picture.

Work-Related or Occupational Rhinitis

This includes a wide spectrum of rhinitis conditions involving immunologic and non-immunologic mechanisms of occupational origin (Fig. 9.3). Occupational or work-exacerbated rhinitis (OR) is defined as rhinitis due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace [58]. *Work-exacerbated rhinitis* is rhinitis that is present concurrently in nonoccupational settings but aggravated by work exposures [59, 60].

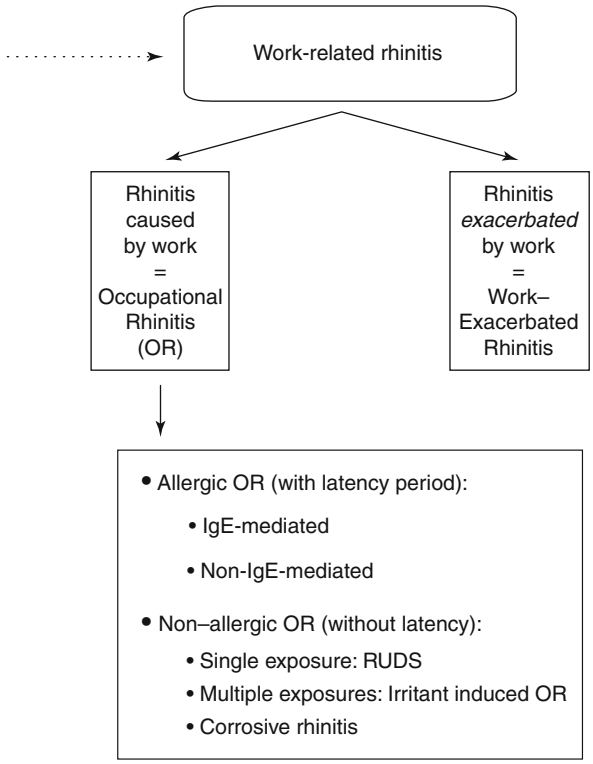


Fig. 9.3 Classification of work-related rhinitis including occupational rhinitis (OR). *RUDS* reactive upper airways dysfunction syndrome (Reprinted from Moscato et al. [58])

Occupational rhinitis can be triggered by nonallergic or allergic mechanisms and frequently precedes or accompanies the development of occupational asthma. *Allergic occupational rhinitis* results from exposure to a sensitizing agent that acts through an IgE antibody- or cell-mediated immunologic mechanism. Sensitizing agents that act through IgE antibody mechanisms include laboratory animal antigens, flour, latex, and psyllium. Rhinitis from some lower molecular weight chemicals (e.g., polyisocyanates in paints) may develop through non-IgE mediated, immunologic mechanisms that are still not fully understood [58]. There is a latency period of weeks to years between initial exposure and symptom onset, during which immunologic sensitization to the causal agent occurs. After sensitization, symptoms recur on reexposure to the sensitizing agent at concentrations not affecting other similarly exposed workers. Symptoms may be intermittent or persistent according to the frequency and intensity of exposure to the causal agent. There is typically a temporal relationship between symptoms and work exposure. As with other forms of rhinitis, a thorough history is very important. Patients with this condition will generally report resolution or improvement of symptoms when away from the workplace for extended periods.

Nonallergic occupational rhinitis develops through irritant, non-immunologic mechanisms in response to exposures to factors such as organic chemicals, grain dust, and ozone. There is often no latency period between exposure and symptom onset. Transient or persistent upper airway symptoms may occur within a few hours after exposure to very high concentrations of irritant compounds, termed the *reactive upper airways dysfunction syndrome* (RUDS). RUDS is analogous to *reactive airways dysfunction syndrome* (RADS) that may affect the bronchi [59–66]. In *multiple exposure irritant-induced occupational rhinitis*, upper airway symptoms may develop in subjects repeatedly exposed at work to irritants (vapors, fumes, smokes, dusts), without any identifiable exposure to high concentration of irritants.

A variety of occupational exposures have been reported to produce this syndrome and include ozone, volatile organic compounds, thermal degradation products of polyurethanes, grain and cotton dust, chlorine, formaldehyde, wood dust, and waste handling [58]. Wright-Giemsa stain of the nasal mucous or mucosa typically reveals a predominantly neutrophilic component. Symptoms can be provoked by long-standing chronic exposure, high exposure, or by exposure to a mixture of several irritants concurrently.

Corrosive rhinitis is the most severe form of persistent irritant-induced occupational rhinitis. Corrosive rhinitis is characterized by the presence of chronic inflammation of the nasal mucosa that may progress to ulcerations and nasal septal perforation. This condition has been reported after persistent or recurrent exposure to corrosive chemicals such as chromium [60, 67, 68].

The diagnosis of occupational rhinitis requires a complete medical and occupational history and nasal examination. Selectively, immunologic tests are helpful in some cases to assess any sensitization to common nonoccupational aeroallergens as well as specific occupational agents if available. Some medical centers have an occupational medicine laboratory which is capable of performing occupational nasal provocation tests. In this circumstance, the patient is exposed to a known quantity of the suspected triggering substance, and the response is assessed by objective measures such as rhinometry, rhinomanometry, and examination of nasal secretions after challenge and compared to a control group [59].

Rhinitis Associated with Underlying Inflammatory/Immunologic Disorders

Rhinitis may present in the context of an underlying inflammatory or immunologic condition. In many cases, symptoms of rhinitis may precede overt systemic manifestations of these conditions. Biopsy is often required for diagnosis of such conditions. Rhinitis associated with underlying inflammatory/immunologic disorders is discussed in greater detail in another chapter of this text. This group of disorders is briefly defined as follows:

Granulomatous Infections

Certain infections can lead to granulomatous nasal lesions. These lesions can be ulcerative with formation of crust that can lead to nasal obstruction or bleeding. In patients who have evidence of ulcerative nasal lesions, infections such as tuberculosis, syphilis, leprosy, sporotrichosis, blastomycosis, histoplasmosis, and coccidioidomycosis must be considered. Rhinoscleroma can present with epistaxis and nasal obstruction. This condition, caused by infection with *Klebsiella rhinoscleromatis*, induces the formation of a polypoid mass, most often within the nasal cavity. *Klebsiella rhinoscleromatis* can also affect the nasopharynx, larynx, trachea, and bronchi. While not as common in the United States, this condition is endemic to areas of Africa, Southeast Asia, Mexico, Central and South America, and Central and Eastern Europe. It should be considered in patients who have immigrated from these areas. Recent studies have found a genetic predisposition to this disease, making family history an important part of the assessment [69].

Wegener Granulomatosis

This is a systemic autoimmune necrotizing vasculitis. It can affect multiple organs, including the heart, lungs, skin, kidneys, and nervous system. In addition, a majority of patients with Wegener granulomatosis have nasal manifestations including congestion, nosebleeds, purulent rhinorrhea, crusting, and, most severely, septal erosion and perforation leading to saddle nose deformity. Anti-neutrophilic cytoplasmic antibody screening (ANCA) is positive in a majority of patients with this condition. The differentiation between p-ANCA and c-ANCA can have prognostic as well as diagnostic significance. In the "Wegener's Granulomatosis Etanercept Trial," ANCA was present in 83 % of those with limited Wegener's granulomatosis as opposed to 96 % of those with active severe disease [69]. Among patients with limited disease, 69 % were c-ANCA positive, while only 11 % were p-ANCA positive [69, 70]. A more detailed discussion of autoimmunity and sinus disease can be found in Chap. 15.

Sjogren's Syndrome

Sjogren's syndrome is a systemic autoimmune syndrome in which there is destruction of the exocrine glands leading to generalized dryness. Effects on the nose can include granuloma formation as well as nasal dryness, epistaxis, a sensation of congestion, and occasionally rhinosinusitis.

Sarcoidosis

Sarcoidosis is a chronic immune-mediated inflammatory disease in which there is formation of noncaseating granulomas. While this is a rare cause of rhinitis in the overall population, up to 18 % of sarcoidosis patients can have upper respiratory tract symptoms, with the nose more commonly affected compared to the sinuses [71]. Sinonasal involvement should be diagnosed using strict criteria including clinical and radiographic features, histologic confirmation, and exclusion of other causes [69, 70]. Criteria have been proposed to help diagnose sarcoidosis of the nose and sinuses (Table 9.4). These criteria

Table 9.4 Proposed criteria for diagnosis of sarcoidosis of the sinuses

1. Mucoperiosteal thickening or opacification of a sinus as detected by plain film, CT, or MRI
2. Histopathological demonstration of noncaseating granulomas in material taken from sinus. Special stains for fungus and mycobacteria must be negative, and no evidence of vasculitis may be present
3. Negative serologic test response for syphilis and negative ANCA test response
4. No evidence on chest radiograph or clinical history of other disease processes associated with granulomatous nasal or sinus inflammation to include tuberculosis, syphilis, Wegener's granulomatosis, fungal infection, or berylliosis

Adapted deShazo et al. [71]. With permission from Elsevier

do not include the classic pulmonary findings of sarcoidosis because nasal/sinus involvement may occur independent of pulmonary findings. The criteria are to be primarily used to distinguish sarcoidosis-induced nasal symptoms from other granulomatous causes of nasal and sinus disease.

Churg-Strauss Syndrome

Churg-Strauss syndrome is a systemic autoimmune vasculitis that affects medium and small vessels. Churg-Strauss is also known as "allergic granulomatosis" and is associated with systemic granuloma formation. Manifestations can include chronic rhinosinusitis, nasal polyposis, asthma (usually presenting manifestation), peripheral blood eosinophilia, cardiomyopathy, neuropathy, and renal involvement. ANCA differentiation is helpful in diagnosing this disease. Approximately 50 % of patients are p-ANCA (with myeloperoxidase specificity) positive, whereas <1 % demonstrate the presence of c-ANCA [69]. According to the American College of Rheumatology, four of the following six criteria must be present to make the diagnosis of Churg-Strauss syndrome: asthma, blood eosinophilia >10 %, presence of mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates, presence of paranasal sinus abnormality, and histologic evidence of extravascular eosinophils [69].

Relapsing Polychondritis (RPC)

RPC is a rare systemic autoimmune disease with highly variable features. The term relapsing polychondritis was first used in 1960 by Pearson et al. to describe a disease causing inflammation of the auricles, nasal septum, peripheral joints, and larynx, with occasional involvement of the middle and inner ears, eyes, costal cartilages, spine, trachea, bronchi, and epiglottis. Currently the diagnosis is clinical and is based on the finding of chondritis in 2 of 3 sites (auricular, nasal, and laryngotracheal) or one of these sites and two other features, including ocular inflammation, audio vestibular damage, or seronegative inflammatory arthritis [72]. Specific nasal manifestations include nasal congestion, crusting, rhinorrhea, epistaxis, and hypogeusia. In severe cases, cartilage destruction can lead to saddle nose deformity. The treatment of this condition is based upon the clinical presentation, though it usually begins with oral corticosteroids.

Amyloidosis

Amyloid deposition in the upper respiratory tract occurs most commonly as localized (not systemic) amyloidosis and is usually a benign phenomenon. It is important to differentiate between the two, however, as systemic amyloidosis carries a much worse prognosis. In either case, amyloid deposition in the nasopharynx may lead to nasal obstruction, epistaxis, postnasal discharge, and ear problems [73]. Unfortunately, radiographic imaging is very nonspecific in diagnosing this condition. Histologic examination of biopsied material with Congo red staining was classically the diagnostic method of choice, although now this has been supplanted by newer immunohistochemical techniques [74].

Lethal Midline Granuloma

The majority of these tumors are malignant and fall under the World Health Organization (WHO) classification of an extranodal NK/T-cell lymphoma-nasal-type (LMG-NTL) disorder. The lesion typically arises in the nasal cavity and presents with symptoms of nasal obstruction, rhinorrhea, epistaxis, and facial swelling. Those affected are more often middle-aged males. There is a strong association of lethal midline granuloma and EBV infection. Most lesions will be limited to the midface,

though a small proportion of patients can have cervical node involvement or systemic disease involving lungs, liver, spleen, skin, GI tract, and bone marrow. Biopsy is usually required for diagnosis, and several samples are needed in the majority of cases. In addition to biopsy, immunohistochemistry can now be used to establish the diagnosis [75]. Staging is according to the Ann Arbor system [75].

Conditions Mimicking Rhinitis

Nasal Polyps

Nasal polyposis is considered an inflammatory condition of the nasal and sinus mucosa and is commonly associated with a history of recurrent or chronic rhinosinusitis. Nasal polyps typically emanate from the sinus cavities and protrude into the middle meatus and choanal region. An exception sometimes seen, particularly in severe allergic nasal disease, is nasal polyps that arise from the middle turbinate and obstruct airflow. The most common presentation is rhinorrhea, although eventually nasal congestion and hyposmia or anosmia develops. Whenever persistent anosmia is present, this should always raise the clinical suspicion of nasal polyp-related disease. There is a prevalence of 2–4 % in the population, including both allergic and nonallergic people and there is no sex predilection [76–78]. Although nasal polyps typically occur in middle age (>40 years age), there are several conditions that frequently present with polyps in children, such as cystic fibrosis and immotile cilia syndrome (discussed later). Childhood polyps associated with CF are typically neutrophilic, whereas adult polyps are more typically eosinophilic. Some subsets of adults with asthma may have associated nasal polyps with or without the presence of aspirin-exacerbated respiratory disease (AERD), discussed earlier under drug-induced rhinitis and in more detail in another chapter of this text. Treatment is often aimed at reducing inflammation, primarily with intranasal or sometimes oral corticosteroids [79–81]. Prognosis is variable with AERD generally having less favorable outcomes [82].

Anatomic Abnormalities

Septal deviation is most commonly asymptomatic and present to some degree in over 90 % of individuals. However, significant septal deviation, particularly when present anteriorly in the nasal passage, can lead to increased congestion. This condition can often be diagnosed with direct visualization with an otoscope speculum, though rhinolaryngoscopy, rhinomanometry, and sinus CT can aid in diagnosis [10, 83]. Deviation can be either unilateral with corresponding unilateral obstruction or bilateral (sigmoid configuration of septum) which can result in bilateral obstruction [10].

Adenoid hyperplasia is the most common cause of nasal obstruction in young children. It is often bilateral and associated with open mouth facies and nocturnal snoring. This condition is most commonly present in children between the ages of 3 and 5 years and spontaneously resolves and the child grows to puberty. Diagnosis is made by visualization with either mirror examination of the nasopharynx, rhinolaryngoscopy, or simply suspected based on the age of the child, history, and the presence of upper airway obstruction despite a patent nasal passage seen during examination of the nose with an otoscope. A soft tissue lateral of the nasopharynx or a CT can also be useful in establishing the diagnosis [84].

Choanal atresia is a congenital anatomic abnormality in which excess tissue causes narrowing or blockage of the nasal passage way. Symptoms present in infancy and include mouth breathing, nasal congestion, and feeding difficulties. Any newborn with this constellation of symptoms should be immediately seen by an otolaryngologist.

Cleft palate is a congenital anatomic abnormality in which the upper roof of the mouth fails to form. This condition can occur with or without a cleft lip. While it may be an isolated occurrence, it can be part of an underlying genetic syndrome. This condition can lead to nasal congestion if the nasal passage is affected [84].

Concha bullosa is a common anatomic variant in which the pneumatization of the middle turbinate occurs. Although often not problematic, when extremely large, it can result in nasal obstruction that is typically unilateral [56]. Inspection of the nose with a rhinoscope reveals the typical anatomical variation. This disorder can also be diagnosed by CT scan [10].

Foreign Body

A lodged foreign body in the nose most typically occurs in young children or in association with developmental/mental disorders. The foreign object is often a small object such as a toy bead, peanut, or pencil eraser. A foreign body in the nose produces unilateral congestion with subsequent foul-smelling, purulent nasal discharge that may lead to sinusitis [85].

CSF Rhinorrhea

The presence of refractory clear rhinorrhea may be the result of a CSF leak [86]. While this most commonly occurs after recent trauma or surgery, it can occur spontaneously [87, 88]. Beta-2-transferrin protein in nasal drainage is a sensitive and specific marker for CSF leakage, as it is not found in normal nasal or ear secretions [89, 90].

Laryngopharyngeal/Pharyngonasal Reflux

Laryngopharyngeal reflux refers to involvement of the upper esophagus, larynx, and/or pharyngeal area. Infants with this condition may present with frequent choking or apneic spells, recurrent pneumonia (because of concomitant gastroesophageal reflux and/or tracheal aspiration), and aspiration of formula leading to secondary chemical/infectious rhinitis [10]. Reflux in this population may result from prematurity, neuromuscular disease, or cleft palate [84].

In adults, GERD has been associated with multiple upper and lower respiratory conditions including nasal congestion, sore throat, and cough. One study showed that patients that had symptomatic GERD along with positive pH probe studies had significantly more upper respiratory symptoms than healthy controls, and the severity of the upper respiratory symptoms correlated with the severity of GERD [91]. GERD should be considered in patients with recalcitrant rhinitis symptoms, particularly if no other diagnosis has been found and there is associated sore throat, cough, and a history of a previous esophagogastroduodenal disorder.

Nasal Tumors

A tumor should always be in the differential when a patient presents with unilateral obstruction, especially when it occurs with bleeding, hyposmia or anosmia, pain, or otalgia [92, 93]. This is discussed in greater detail in another chapter of this text.

Ciliary Dysfunction

Ciliary dyskinesis can occur as either a primary or secondary form. Primary ciliary disease (PCD), also known as immotile cilia syndrome, is a rare genetic disorder [94]. Fifty percent of PCD patients present with situs inversus (Kartagener's syndrome) [10]. Other findings in the history may include recurrent sinusitis, otitis media, rhinitis, and chronic cough/pneumonia from a very young age. Eventually, many of these patients develop nasal polyposis, atypical asthma, and bronchiectasis [95, 96]. Secondary forms of this can occur due to recurrent acute or chronic infections, multiple nasal/sinus surgeries, or chronic irritant rhinitis [97, 98]. Smoking has not been shown to have a significant effect on mucociliary clearance [99].

The Differential Diagnosis of Rhinosinusitis

Rhinosinusitis (RS) is defined as inflammation of the nose and paranasal sinuses. Multiple etiologies contribute to the presence of this condition, including viral or bacterial infection, allergy, and, occasionally, anatomical variations or obstruction. Rhinosinusitis is a serious health problem that has been reported to affect up to 1 in 7 adults [100]. Much like rhinitis, it can have detrimental impact on quality of life, school and workplace productivity, and health-care costs [101–104]. When considering a diagnosis of rhinosinusitis, one must consider a broad differential composed of multiple factors that may be causing or contributing to symptoms including all of the conditions listed above (Table 9.5).

The diagnosis of rhinosinusitis on the basis of history alone is not completely reliable and is not adequate for diagnosis of chronic rhinosinusitis. However, several schemes have been proposed to assess the likelihood of sinusitis being present. One general strategy is based on the presence of certain symptoms with both major and minor symptom criteria defined. Several guidelines [105, 106] endorse an approach that requires the presence of at least 2 major or 1 major and ≥2 minor symptoms to establish a diagnosis of rhinosinusitis (Table 9.6). The EPOS2012 (European Position Paper on Rhinosinusitis and Nasal Polyposis) guidelines state that rhinosinusitis (including nasal polyps) is characterized by two or more symptoms, one of which should be either (a) nasal blockage/obstruction or (b) nasal discharge (anterior/posterior nasal drip). Other symptoms may be (c) facial pain/pressure and/or (d) reduction or loss of smell [57].

Table 9.5 Differential diagnosis of bacterial sinusitis

Infectious rhinitis
Viral upper respiratory tract infections
Allergic rhinitis
Nonallergic rhinitis
Rhinitis medicamentosa
Rhinitis secondary to
Pregnancy
Hypothyroidism
Inflammatory or immunologic disorders
Anatomic abnormalities causing rhinitis
Foreign body
Nasal polyps
Nasal septal deviation
Enlarged tonsils and adenoids
Cleft palate
Choanal atresia
Concha bullosa and other middle turbinate abnormalities
Tumors
CSF rhinorrhea
Vascular headache (migraine)
Gastroesophageal reflux

Adapted from Slavin et al. [56]. With permission from Elsevier

Table 9.6 Major and minor criteria as outlined by Rhinosinusitis Initiative (RI) where diagnosis based on presence of at least 2 major or 1 major and ≥2 minor criteria

Major symptoms	Minor symptoms
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis
Facial congestion or fullness	Dental pain
Facial pain or pressure	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (acute sinusitis only)	Fatigue

Adapted from Meltzer et al. [105]. With permission from Elsevier

Major published guidelines on rhinosinusitis include EPOS2012, those of the Joint Task Force on Practice Parameters (JTFPP), the Clinical Practice Guideline: Adult Sinusitis (CPG: AS), the Rhinosinusitis Initiative (RI), the British Society for Allergy and Clinical Immunology (BSACI), and the Infectious Diseases Society of America (IDSA). These guidelines have many commonalities but have some variation in classification, diagnosis, and treatment recommendations.

For example, EPOS2012 defines acute rhinosinusitis (ARS) as symptoms lasting <12 weeks with complete resolution, noting that it is not uncommon for patients to have recurrent ARS with complete resolution of symptoms between episodes. Three guidelines, including the JTFPP, the RI, and the CPG: AS, define ARS as having a symptom duration of 4 weeks or less. EPOS2012 defines chronic rhinosinusitis (CRS) as symptoms on most days lasting at least 12 weeks without complete resolution of symptoms and duration. Three other guidelines (RI, CPG: AS, and BSACI) also use 12 weeks as the cutoff [105, 107, 108]. In contrast, the JTFPP defines CRS as having a symptom duration lasting longer than 8 weeks. Two guidelines have a third category of *subacute sinusitis*. The JTFPP defines subacute sinusitis by symptom duration lasting between 4 and 8 weeks. CPG: AS defines subacute sinusitis as symptoms lasting between 4 and 12 weeks [56, 108]. Of note, EPOS does not recognize the "subacute" designation, and it remains unclear if this diagnosis deserves a specific designation or represents a milder or early form of chronic rhinosinusitis.

Acute Rhinosinusitis

Diagnosis of this condition is based primarily on clinical history. In most cases, it occurs after a viral URI. Viral URI, often referred to as "the common cold," can occur two to three times per year in adults [57] and more than six times per

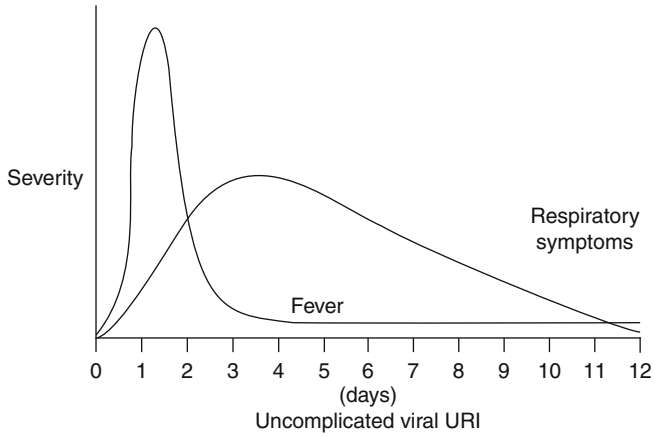


Fig. 9.4 Schematic characterization of the natural history and time course of fever and respiratory symptoms associated with an uncomplicated viral upper respiratory infection (URI) in children (Reprinted from Chow et al. [106]. With permission from Oxford University Press)

year in children [109]. The difficulty is differentiating a viral URI with or without viral sinusitis from the potentially more serious bacterial sinusitis. In the setting of viral sinusitis, symptoms will usually resolve spontaneously (Fig. 9.4), though it will progress to a bacterial sinusitis in approximately 0.5–2 % of cases. Recently published guidelines suggest that the medical provider should consider bacterial rhinosinusitis and, therefore, the need for antibiotics in the case of severe symptoms (fever ≥39 °C and purulent nasal discharge for 3–4 consecutive days at beginning of illness), worsening symptoms after 5–6 days of infection ("double sickening"), or persistent symptoms ≥10 days [105, 106, 110]. Pain in the upper teeth, suggestive of nerve irritation in adjacent tooth roots, can be symptom of maxillary sinusitis. Similarly, an infection in an upper molar or dental manipulation of an upper molar can seed the maxillary antrum, inducing acute bacterial sinusitis. Such a history should be sought in the primary care setting. Otherwise, the presence of purulent drainage by itself in the face of a common viral upper respiratory tract infection does not reliably indicate a bacterial infection unless the infection has been present for ≥10 days, and the origin is clearly the middle meatus or sphenoethmoidal recess.

The most common infectious agents identified in acute bacterial sinusitis have been discussed in other chapters. These are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (most common in children) [111–115]. Other bacterial causes described are other streptococcal species, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and anaerobic species [56]. In the United States, fungal infection has also been found as a rare cause, more commonly reported in the southeastern and southwestern parts of the country [56].

Symptoms or signs highly suggestive of serious complications from bacterial sinusitis should always be kept in mind in evaluating any patient with acute sinus disease. These are facial swelling and/or erythema over an involved sinus, visual changes, abnormal extraocular movements, proptosis, periorbital inflammation/edema, and central nervous system symptoms. The presence of any of these signs or symptoms is a medical emergency and requires immediate referral to a center capable of caring for such comorbidities.

Recurrent Sinusitis

According to EPOS2012 and the JTFPP, *recurrent sinusitis* is defined as ≥3 episodes of ARS per year, with intermittent resolution being the distinguishing factor from CRS [56, 57]. CPG: AS defines recurrent sinusitis as ≥4 episodes in a year with interval resolution of symptoms [108].

Chronic Rhinosinusitis

As mentioned earlier, CRS is generally characterized by persistent inflammation >12 weeks without any intervening acute sinusitis episodes. CRS is a heterogeneous group of inflammatory disorders involving the sinuses. Although bacterial infections can complicate all forms of CRS, CRS should not be viewed as a simple infectious process. CRS is commonly subdivided into three groups: CRS with nasal polyps (CRSwNP), CRS without nasal polyps (CRSsNP), and

allergic fungal sinusitis. According to EPO3S, the clinical diagnosis of CRS should be supplemented with objective evidence of:

- Rhinoscopic/endoscopic findings of:
  - Polyps
  - Mucopurulent discharge
  - Edema/mucosal obstruction
- CT findings of significant mucosal changes within the sinuses

While many of the clinical findings are similar between acute and chronic rhinosinusitis, it should be noted that facial pain is a much less common feature of CRS [116]. Moreover, facial pain and pressure from migraine, tension, and cluster headaches are often incorrectly attributed to chronic rhinosinusitis; facial pain and pressure are not reliable for predicting the presence of objective findings of rhinosinusitis.

One proposed classification scheme for chronic rhinosinusitis is listed in Fig. 9.5 and can be summarized as follows:

- *CRS Without Nasal Polyps* (*CRSsNP*). By far the most common presentation of CRS, this typically presents with persistent symptoms and occasional exacerbations characteristic of ARS episodes [56, 57, 105, 108]. This condition does tend to have more association with infectious etiology in comparison to CRSwNP. Organisms associated with CRSsNP are similar to those implicated in ARS.
- *CRS with Nasal Polyps* (*CRSwNP*). Nasal polyps can be a significant contributing factor to sinusitis by occluding the ostiomeatal complex, which consists of the maxillary sinus ostia, anterior ethmoid cells and their ostia, the ethmoid infundibulum, hiatus semilunaris, and the middle meatus [57]. The presence of nasal polyps in children should raise the suspicion of cystic fibrosis, especially in the presence of *Pseudomonas* colonization. Larger nasal polyps can often be visualized by anterior rhinoscopy but full visualization of nasal polyps requires nasal endoscopy. Infection is less common in CRSwNP than in CRSsNP. As discussed earlier, some patients may present with CRSwNP in conjunction with aspirin-exacerbated respiratory disease (AERD). This history should always be sought and the polyp patient warned of a possible future adverse event upon the ingestion of any NSAID.

The term *chronic hyperplastic eosinophilic sinusitis* is sometimes used to describe patients with sinusitis who have an increased amount of eosinophils with decreased numbers of neutrophils. There is a strong association of asthma and NSAID hypersensitivity with this particular condition [117].

Fungal Sinusitis

Three fungal disorders can involve the sinuses: allergic fungal sinusitis, fungus ball, and invasive fungal sinusitis. Each should be investigated when this diagnosis is being considered. *Allergic fungal sinusitis* typically occurs in immunocompetent atopic patients in association with nasal polyposis and chronic nasal congestion [118]. It is a noninvasive colonization of the mucosal surface that generates a highly symptomatic eosinophilic inflammatory response. Mucus secretions are thick, purulent, often described as having "peanut butter" consistency, ranging in color from light tan to brown to dark green, and contain large amounts of degranulated eosinophils. Fungal hyphae are present in the mucin that does not invade below the mucosal surface. Commonly, there is evidence of IgE-mediated fungal allergy. The most common fungi implicated are *Bipolaris*, *Curvularia*, *Aspergillus*, and *Drechslera* species, though many other fungi have been isolated [56].

Fungus ball typically occurs in the maxillary and sphenoid sinuses and is usually unilateral [119]. It occurs primarily in immunocompetent patients and is considered noninvasive. Patients complain of mucopurulent discharge and usually sinus pain. It can occasionally cause a pressure necrosis if it impinges on surrounding structures. This condition can be differentiated from allergic fungal sinusitis by histologic examination, which shows dense accumulations of hyphae in concentric layers forming a fungus ball [119]. CT or MRI findings of the fungus ball within the sinus cavity are usually diagnostic (see below).

Invasive fungal sinusitis occurs primarily in immunocompromised patients. It is a disseminated disease and patients will often present with fever, headaches, epistaxis, and mental status changes. Physical examination will often reveal insensate nasal ulcers. Aggressive debridement and systemic antifungal therapy are mainstays of treatment [120, 121].

CT scan is a very helpful tool for diagnosis of fungal sinusitis, although a definitive diagnosis requires biopsy. Classic CT findings show a combination of unilateral lesions of one or more sinuses, nodular mucoperiosteal thickening, focal areas of

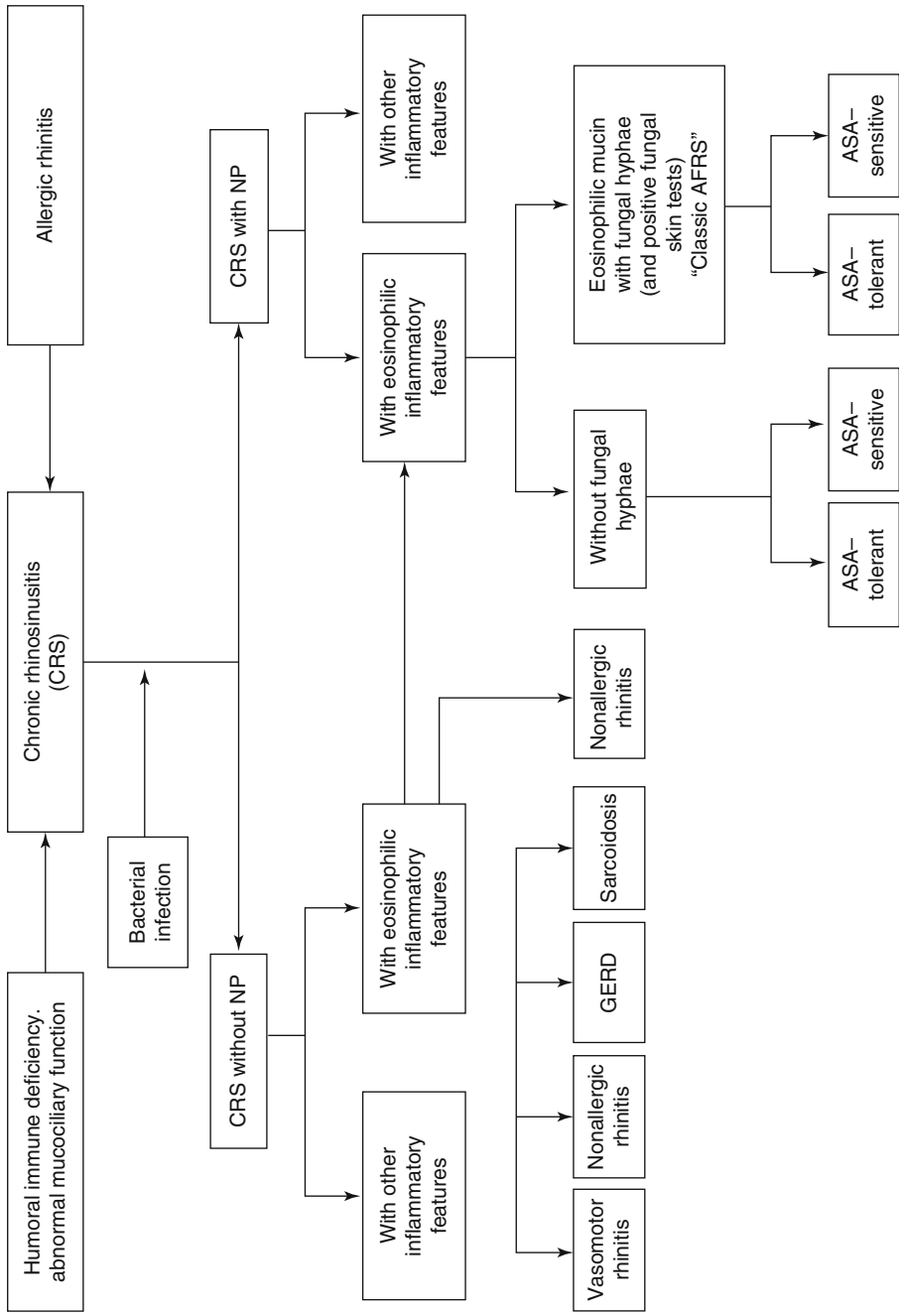


Fig. 9.5 One classification scheme for chronic rhinosinusitis. *AFRS* allergic fungal rhinosinusitis, *ASA* aspirin, *GERD* gastroesophageal reflux disease, *NP* nasal polyposis (Reprinted from Meltzer et al. [105]. With permission from Elsevier)

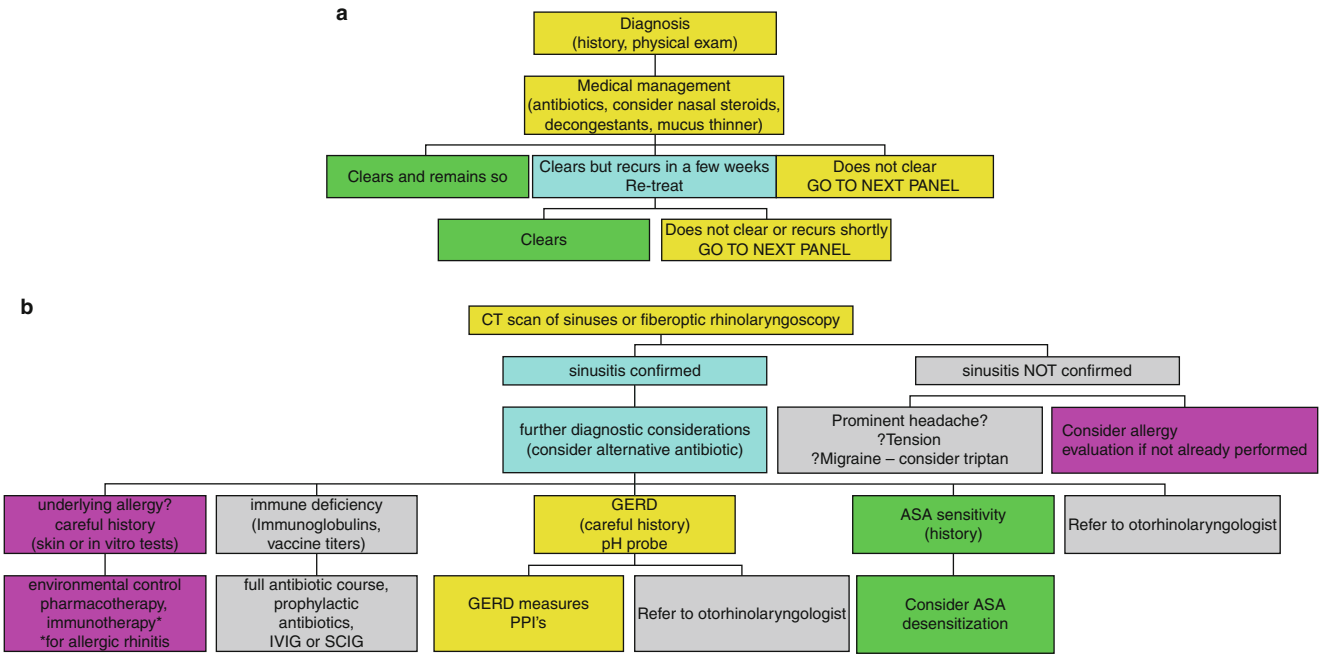


Fig. 9.6 General approach to evaluation and management of rhinosinusitis (**a**, **b**)

bone destruction, and/or dense intrasinus concretions depending on the condition involved [122]. MRI can be of particular value in fungal sinusitis as T2-weighted imaging shows a very low signal intensity (similar to air) as compared to the high signal intensity typically present with viral or bacterial inflammation [123].

The General Approach to the Patient with Rhinitis or Rhinosinusitis

Systematic evaluation of the patient with any form of rhinitis symptoms starts with a history emphasizing the following information: specific nasal and related eye, throat, ear, and lung symptoms; whether nasal symptoms are unilateral or bilateral; chronicity and/or seasonal pattern; and a detailed environmental history that includes work and hobbies and identification of precipitating factors, response to medications, and presence of coexisting conditions.

A family history of any chronic respiratory disorders or atopic conditions is important to help broaden or reduce the probable differential diagnostic possibilities and to support your choice of what diagnostic tests might be needed.

Physical examination of the nose can be accomplished by using an otoscope with nasal adapter, nasal speculum with appropriate lighting, indirect mirror, and/or rigid or flexible nasopharyngoscope, based upon the expertise of the examiner. As with any field of medicine, any case of chronic rhinitis needs a thorough upper airway exam with a decongested nose either with a rhinolaryngoscope or by direct and indirect visualization of the nose and nasopharynx by an experienced medical provider. Although the mucosa of allergic rhinitis is classically described as having a bluish cast, mucosal appearance may not distinguish between allergic and nonallergic rhinitis since both may present with hyperemia, mucosal pallor, or edema. In contrast, the mucosa is usually hyperemic with crusting in the nasal vestibule in infectious rhinitis and in rhinitis medicamentosa. Anterior nasal exam can reveal caudal septal deformity or inferior turbinate hypertrophy as a source of congestion but is not conclusive without ruling out other conditions, particularly atopy. With significant caudal septal deflection, the contralateral inferior turbinate is often enlarged. Application of a topical decongestant to reduce turbinate mucosal edema can assist in differentiating mucosal versus bony hypertrophy as well as pre- and post-rhinomanometry measurements.

A nasopharyngoscope permits better visualization of the middle meatus, posterior septum, sinus ostia, and the nasopharynx. At times, this is the only way of visualizing the presence of nasal polyps or defining mucopurulent material emanating from the middle meatus or sphenoethmoidal recess which is diagnostic of rhinosinusitis.

All patients with chronic rhinitis, particularly those with a family history of atopic disease, should ultimately undergo a screening determination for antigen-specific IgE antibody (sIgE). The most sensitive and cost-effective sIgE determination is by skin testing when performed using standardized antigens by a medical provider experienced in this approach.

Measurement of sIgE in the serum is specific but not as sensitive as prick/puncture skin testing. Measurement of sIgE (by skin testing or in vitro testing) is indicated to confirm or exclude suspected allergic causes, to assess the sensitivity to specific allergens for avoidance measures, and for consideration of allergen immunotherapy.

At this point, a definitive diagnosis of the cause of the rhinitis problem is usually clear. Ancillary office procedures to aide in the diagnosis of rhinitis are described in detail in another chapter of this text. Further clarification can be achieved by the addition of a sinus CT which illustrates the presence or absence of sinus disease and anatomical findings that might be a source of congestion or infection. If chronic rhinosinusitis is suspected or diagnosed at this point, the history should be reviewed again looking for associated factors identified in CRS such as GERD, first- or secondhand cigarette smoke exposure, or primary or secondary immune deficiencies [56, 57]. While a majority of patients with CRS are immune competent, immune deficiency should always be considered in the differential during the initial workup of any patient with CRS [124]. This topic is reviewed in detail in another chapter in this text. These and other considerations have been incorporated in a general algorithm for an approach to the diagnosis of rhinosinusitis, including the use of empiric treatment (Fig. 9.6a, b).

Conclusion

Allergic and nonallergic rhinitis and rhinosinusitis are extremely common conditions that frequently result in decreased quality of life, lost work, decreased work and school productivity, and increased health-care spending. While the diagnosis of rhinitis origins is usually not complicated, the differential diagnosis goes beyond the simplistic diagnosis of allergic versus nonallergic nasal disease. Therefore, the clinician should always consider a systematic approach to the assessment of this group of disorders that includes a variety of conditions that may mimic or complicate any case of rhinitis and rhinosinusitis.

References

1. Fireman P. Allergic rhinitis. In: Fireman P, Slavin R, editors. Atlas of allergies. Philadelphia: JB Lippincott; 1991. p. 9.2–9.18.
2. McMenamin P. Costs of hay fever in the United States in 1990. Ann Allergy. 1994;73:35–9.
3. US Census Bureau. US Census. 2008. Available at: http://www.census.gov/index.html. Accessed 4 July 2008.
4. Settipane RA. Rhinitis: a dose of epidemiological reality. Allergy Asthma Proc. 2003;24:147–54.
5. Druce H. Allergic and nonallergic rhinitis. In: Middleton E, Reed CE, Ellis EF, Adkinson Jr NF, Yunginger JW, Busse WW, editors. Allergy principles and practice. 5th ed. St Louis: Mosby-Year Book; 1998. p. 1005–16.
6. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. Allergy Proc. 1994;15:21–5.
7. Varjonen E, Kalimo K, Lammintausta K, Terho P. Prevalence of atopic disorders among adolescents in Turku, Finland. Allergy. 1992;47:243–8.
8. Smith JM. A five-year prospective survey of rural children with asthma and hay fever. J Allergy. 1971;47:23–30. III.
9. Settipane RA, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. Clin Allergy Immunol. 2007;19:23–34.
10. Wallace DV, Dykewicz MS, Bernstein DI, et al. The Joint Force on Practice Parameters, representing the AAAAI, ACAAI, JCAAI. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008;122:S1–84. PMID: 18662584.
11. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and Aller-Gen). Allergy. 2008;63 Suppl 86:8–160.
12. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466–76.
13. Raphael GD, Baraniuk JN, Kaliner MA. How and why the nose runs. J Allergy Clin Immunol. 1991;87:457–67.
14. Wagenmann M, Schumacher L, Bachert C. The time course of the bilateral release of cytokines and mediators after unilateral nasal allergen challenge. Allergy. 2005;60:1132–8.
15. Okano M, Fujiwara T, Sugata Y, Gotoh D, Masaoka Y, Sogo M, et al. Presence and characterization of prostaglandin D2-related molecules in nasal mucosa of patients with allergic rhinitis. Am J Rhinol. 2006;20:342–8.
16. Peters-Golden M, Gleason MM, Togias A. Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. Clin Exp Allergy. 2006;36:689–703.
17. Heppt W, Dinh QT, Cryer A, Zweng M, Noga O, Peiser C, et al. Phenotypic alteration of neuropeptide-containing nerve fibres in seasonal intermittent allergic rhinitis. Clin Exp Allergy. 2004;34:1105–10.
18. Marinho S, Simpson A, Lowe L, Kissen P, Murray C, Custovic A. Rhinoconjunctivitis in 5-year-old children: a population-based birth cohort study. Allergy. 2007;62:385–93.
19. Galan C, Garcia M, Alcazar H, Dominguez P. Meteorological variation effect on aerobiology: new tools on pollen forecasting. Allerg Immunol (Paris). 2006;38:203–8.
20. Antepara I, Fernandez JC, Gamboa P, Jauregui I, Miguel F. Pollen allergy in the Bilbao area (European Atlantic seaboard climate): pollination forecasting methods. Clin Exp Allergy. 1995;25:133–40.

21. Shusterman D, Balmes J, Murphy MA, Tai CF, Baraniuk J. Chlorine inhalation produces nasal airflow limitation in allergic rhinitic subjects without evidence of neuropeptide release. Neuropeptides. 2004;38:351–8.
22. Cruz AA, Naclerio RM, Proud D, Togias A. Epithelial shedding is associated with nasal reactions to cold, dry air. J Allergy Clin Immunol. 2006;117:1351–8.
23. Silvers WS, Poole JA. Exercise-induced rhinitis: a common disorder that adversely affects allergic and nonallergic athletes. Ann Allergy Asthma Immunol. 2006;96:334–40.
24. Linneberg A, Berg ND, Gonzalez-Quintela A, Vidal C, Elberling J. Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks. Clin Exp Allergy. 2008;38:145–51.
25. Ellis A, Keith P. Nonallergic rhinitis with eosinophilia syndrome. Curr Allergy Asthma Rep. 2006;6:215–20.
26. Schiavino D, Nucera E, Milani A, Della Corte AM, D'Ambrosio C, Pagliari G, et al. Nasal lavage cytometry in the diagnosis of nonallergic rhinitis with eosinophilia syndrome (NARES). Allergy Asthma Proc. 1997;18:363–6.
27. Kirshna M, Mauroleon G, Holgate S. Essentials in allergy. London: Informa Health Care; 2001.
28. Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome): clinical and immunologic presentation. J Allergy Clin Immunol. 1981;67:253–62.
29. Settipane GA, Klein DE. Nonallergic rhinitis: demography of eosinophils in nasal smear, blood total eosinophil counts and IgE levels. N Engl Reg Allergy Proc. 1985;6:363–6.
30. Moneret-Vautrin DA, Hsieh V, Wayoff M, Guyot JL, Mouton C, Maria Y. Nonallergic rhinitis with eosinophilia syndrome a precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. Ann Allergy. 1990;64:513–8.
31. Kramer MF, de la Chaux R, Fintelmann R, Rasp G. NARES: a risk factor for obstructive sleep apnea? Am J Otolaryngol. 2004;25:173–7.
32. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy: safety considerations. Drug Saf. 1999;20:361–75.
33. Blaiss MS. Management of rhinitis and asthma in pregnancy. Ann Allergy Asthma Immunol. 2003;90:16–22.
34. The use of newer asthma and allergy medications during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI). Ann Allergy Asthma Immunol. 2000;84:475–80.
35. Einarson A, Bailey B, Jung G, Spizzirri D, Baillie M, Koren G. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. Ann Allergy Asthma Immunol. 1997;78:183–6.
36. Keles N. Treatment of allergic rhinitis during pregnancy. Am J Rhinol. 2004;18:23–8.
37. Schatz M, Zeiger RS. Diagnosis and management of rhinitis during pregnancy. Allergy Proc. 1988;9:545–54.
38. Toppozada H, Michaels L, Toppozada M, El-Ghazzawi I, Talaat M, Elwany S. The human respiratory nasal mucosa in pregnancy: an electron microscopic and histochemical study. J Laryngol Otol. 1982;96:613–26.
39. Ellegard E, Karlsson G. Nasal congestion during pregnancy. Clin Otolaryngol Allied Sci. 1999;24:307–11.
40. Ellegard EK. Pregnancy rhinitis. Immunol Allergy Clin North Am. 2006;26:119–35.
41. Plosker GL, Goa KL. Terazosin: a pharmacoeconomic evaluation of its use in benign prostatic hyperplasia. Pharmacoeconomics. 1997;11:184–97.
42. Vitezic D, Pelcic JM. Erectile dysfunction: oral pharmacotherapy options. Int J Clin Pharmacol Ther. 2002;40:393–403.
43. Hytonen M, Kanerva L, Malmberg H, Martikainen R, Mutanen P, Toikkanen J. The risk of occupational rhinitis. Int Arch Occup Environ Health. 1997;69:487–90.
44. Lieutier-Colas F, Meyer P, Pons F, Hedelin G, Larsson P, Malmberg P, et al. Prevalence of symptoms, sensitization to rats, and airborne exposure to major rat allergen (Rat n 1) and to endotoxin in rat-exposed workers: a cross-sectional study. Clin Exp Allergy. 2002;32:1424–9.
45. Wolstenholme CR, Philpott CM, Oloto EJ, Murty GE. Does the use of the combined oral contraceptive pill cause changes in the nasal physiology in young women? Am J Rhinol. 2006;20:238–40.
46. Ediger D, Sin BA, Heper A, Anadolu Y, Misirligil Z. Airway inflammation in nasal polyposis: immunopathological aspects of relation to asthma. Clin Exp Allergy. 2005;35:319–26.
47. Ramey JT, Bailen E, Lockey RF. Rhinitis medicamentosa. J Investig Allergol Clin Immunol. 2006;16:148–55.
48. Warner EA. Cocaine abuse. Ann Intern Med. 1993;119:226–35.
49. Graf P, Hallen H. Effect on the nasal mucosa of long-term treatment with oxymetazoline, benzalkonium chloride, and placebo nasal sprays. Laryngoscope. 1996;106:605–9.
50. Hallen H, Graf P. Benzalkonium chloride in nasal decongestive sprays has a long-lasting adverse effect on the nasal mucosa of healthy volunteers. Clin Exp Allergy. 1995;25:401–5.
51. Graf P. Adverse effects of benzalkonium chloride on the nasal mucosa: allergic rhinitis and rhinitis medicamentosa. Clin Ther. 1999;21:1749–55.
52. Knipping S, Holzhausen HJ, Goetze G, Riederer A, Bloching MB. Rhinitis medicamentosa: electron microscopic changes of human nasal mucosa. Otolaryngol Head Neck Surg. 2007;136:57–61.
53. Zohar Y, Talmi YP, Strauss M, Finkelstein Y, Shvilli Y. Ozena revisited. J Otolaryngol. 1990;19:345–9.
54. Bunnag C, Jareoncharsri P, Tansuriyawong P, Bhothisuwan W, Chantarakul N. Characteristics of atrophic rhinitis in Thai patients at the Siriraj Hospital. Rhinology. 1999;37:125–30.
55. Moore EJ, Kern EB. Atrophic rhinitis: a review of 242 cases. Am J Rhinol. 2001;15:355–61.
56. Slavin RG, Spector SL, Bernstein IL, et al; American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6 suppl):S13–47.
57. Fokkens W, Lund V, Mullol J, European Position Paper on Rhinosinusitis and Nasal Polyps Group 2012. European position paper on rhinosinusitis and nasal polyps 2012. Rhinology. 2012;50 Suppl 23:1–298.
58. Moscato G, Vandenplas O, Gerth Van Wijk R, et al. Occupational rhinitis. EAACI Position Paper. Allergy. 2008;63:969–80.
59. Storaas T, Steinsvag SK, Florvaag E, Irgens A, Aasen TB. Occupational rhinitis: diagnostic criteria, relation to lower airway symptoms and IgE sensitization in bakery workers. Acta Otolaryngol. 2005;125:1211–7.
60. Castano R, Theriault G. Defining and classifying occupational rhinitis. J Laryngol Otol. 2006;120:812–7.

61. Chan-Yeung M. Assessment of asthma in the workplace. ACCP consensus statement. American College of Chest Physicians. Chest. 1995;108:1084–117.
62. Meggs WJ, Elsheik T, Metzger WJ, Albernaz M, Bloch RM. Nasal pathology and ultrastructure in patients with chronic airway inflammation (RADS and RUDS) following an irritant exposure. J Toxicol Clin Toxicol. 1996;34:383–96.
63. Leroyer C, Malo JL, Girard D, Dufour JG, Gautrin D. Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine. Occup Environ Med. 1999;56:334–8.
64. Hoffman CD, Henneberger PK, Olin AC, Mehta A, Toren K. Exposure to ozone gases in pulp mills and the onset of rhinitis. Scand J Work Environ Health. 2004;30:445–9.
65. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. Chest. 1985;88:376–84.
66. Meggs WJ. RADS and RUDS – the toxic induction of asthma and rhinitis. J Toxicol Clin Toxicol. 1994;32:487–501.
67. Castano R, Theriault G, Gautrin D. Categorizing nasal septal perforations of occupational origin as cases of corrosive rhinitis. Am J Ind Med. 2007;50:150–3.
68. Slavin RG. Occupational rhinitis. Ann Allergy Asthma Immunol. 2003;90:2–6.
69. Fuchs HA, Tanner SB. Granulomatous disorders of the nose and paranasal sinuses. Curr Opin Otolaryngol Head Neck Surg. 2009;17(1):23–7.
70. Finkielman JD, Lee AS, Hummel AM, et al. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med. 2007;120:643.e9–e14.
71. deShazo RD, O'Brien MM, Justice WK, Pitcock J. Diagnostic criteria for sarcoidosis of the sinuses. J Allergy Clin Immunol. 1999;103(5 Pt 1):789–95.
72. Edrees A. Relapsing polychondritis: a description of a case and review article. Rheumatol Int. 2011;31(6):707–13.
73. Patel A, Pambuccian S, Maisel R. Nasopharyngeal amyloidosis. Am J Otolaryngol. 2001;23(5):308–11.
74. Oluk MA, Murphy J. Nasopharyngeal amyloidosis: an unusual case for epistaxis. J Laryngol Otol. 2010;124(2):209–12.
75. Mendenhall WM, Olivier KR, Lynch Jr JW, Mendenhall NP. Lethal midline granuloma-nasal natural killer/T-cell lymphoma. Am J Clin Oncol. 2006;29(2):202–6.
76. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol. 1999;28:717–22.
77. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde population-based study. Ann Otol Rhinol Laryngol. 2003;112:625–9.
78. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: a cross-sectional, case–control study. Allergy. 2005;60:233–7.
79. Alobid I, Benitez P, Pujols L, Maldonado M, Bernal-Sprekelsen M, Morello A, et al. Severe nasal polyposis and its impact on quality of life: the effect of a short course of oral steroids followed by long-term intranasal steroid treatment. Rhinology. 2006;44:8–13.
80. Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. J Allergy Clin Immunol. 2006;118:128–33.
81. Martinez-Anton A, Debolos C, Garrido M, Roca-Ferrer J, Barranco C, Alobid I, et al. Mucin genes have different expression patterns in healthy and diseased upper airway mucosa. Clin Exp Allergy. 2006;36:448–57.
82. Larsen K. The clinical relationship of nasal polyps to asthma. Allergy Asthma Proc. 1996;17:243–9.
83. Rohr A, Hassner A, Saxon A. Rhinopharyngoscopy for the evaluation of allergic-immunologic disorders. Ann Allergy. 1983;50:380–4.
84. Olnes SQ, Schwartz RH, Bahadori RS. Consultation with the specialist: diagnosis and management of the newborn and young infant who have nasal obstruction. Pediatr Rev. 2000;21:416–20.
85. Zeiger RS. Allergic and nonallergic rhinitis: classification and pathogenesis, part II: non-allergic rhinitis. Am J Rhinology. 1989;3:113–39.
86. Dunn CJ, Alaani A, Johnson AP. Study on spontaneous cerebrospinal fluid rhinorrhoea: its aetiology and management. J Laryngol Otol. 2005;119:12–5.
87. Suryadevara AC, Fattal M, Woods CI. Nontraumatic cerebrospinal fluid rhinorrhea as a result of pseudotumor cerebri. Am J Otolaryngol. 2007;28:242–6.
88. Clark D, Bullock P, Hui T, Firth J. Benign intracranial hypertension: a cause of CSF rhinorrhoea. J Neurol Neurosurg Psychiatry. 1994;57:847–9.
89. Skedros DG, Cass SP, Hirsch BE, Kelly RH. Beta-2 transferrin assay in clinical management of cerebral spinal fluid and perilymphatic fluid leaks. J Otolaryngol. 1993;22:341–4.
90. Nandapalan V, Watson ID, Swift AC. Beta-2-transferrin and cerebrospinal fluid rhinorrhoea. Clin Otolaryngol Allied Sci. 1996;21:259–64.
91. Theodoropoulos DS, Ledford DK, Lockey RF, Pecoraro DL, Rodriguez JA, Johnson MC, et al. Prevalence of upper respiratory symptoms in patients with symptomatic gastroesophageal reflux disease. Am J Respir Crit Care Med. 2001;164(1):72–6.
92. Baumgartner BJ, Ladd T, Esquivel C. Low-grade adenocarcinoma of the nasalcavity – an unusual presentation: case report and review of the literature. Ear Nose Throat J. 2007;86:97–100.
93. Komisar A. Nasal obstruction due to benign and malignant neoplasms. Otolaryngol Clin North Am. 1989;22:351–65.
94. Van's Gravesande KS, Omran H. Primary ciliary dyskinesia: clinical presentation, diagnosis and genetics. Ann Med. 2005;37:439–49.
95. Afzelius BA. Genetics and pulmonary medicine, 6: immotile cilia syndrome: past, present, and prospects for the future. Thorax. 1998;53:894–7.
96. Schidlow DV. Primary ciliary dyskinesia (the immotile cilia syndrome). Ann Allergy. 1994;73:457–68.
97. Alho OP. Nasal airflow, mucociliary clearance, and sinus functioning during viral colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. Am J Rhinol. 2004;18:349–55.
98. Sasaki Y, Togo Y, Wagner Jr HN, Hornick RB, Schwartz AR, Proctor DF. Mucociliary function during experimentally induced rhinovirus infection in man. Ann Otol Rhinol Laryngol. 1973;82:203–11.
99. Stanley PJ, Wilson R, Greenstone MA, MacWilliam L, Cole PJ. Effect of cigarette smoking on nasal mucociliary clearance and ciliary beat frequency. Thorax. 1986;41:519–23.

100. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. Vital Health Stat. 2009;10:1–157.
101. Anand VK. Epidemiology and economic impact of rhinosinusitis. Ann Otol Rhinol Laryngol Suppl. 2004;193:3–5.
102. Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol. 1999;103:408–14.
103. Gill JM, Fleischut P, Haas S, Pellini B, Crawford A, Nash DB. Use of antibiotics for adult upper respiratory infections in outpatient settings: a national ambulatory network study. Fam Med. 2006;38:349–54.
104. Young J, De Sutter A, Merenstein D, et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. Lancet. 2008;371:908–14.
105. Meltzer EO, Hamilos DL, Hadley JA, et al; American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Otolaryngic Allergy (AAOA), the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), the American College of Allergy, Asthma and Immunology (ACAAI), and the American Rhinologic Society (ARS). Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol. 2004;114(6 suppl):S155–212.
106. Chow AN, Benninger MS, Brook I, et al. IDSA clinical practice guidelines for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54:1041–5.
107. Scadding GK, Durham SR, Mirakian R, et al; British Society for Allergy and Clinical Immunology. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. Clin Exp Allergy. 2008;38(2):260–75.
108. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg. 2007;137(3 Suppl):S1–31.
109. Revai K, Dobbs LA, Nair S, Patel JA, Grady JJ, Chonmaitree T. Incidence of acute otitis media and sinusitis complicating upper respiratory tract infection: the effect of age. Pediatrics. 2007;119:e1408–12.
110. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: developing guidance for clinical trials. Otolaryngol Head Neck Surg. 2006;135:S31–80.
111. Gwaltney Jr JM. Acute community-acquired sinusitis. Clin Infect Dis. 1996;23(6):1209–23.
112. Sydnor TA, Kapp EJ, Anthony KE, Lococo JM, Kimm SS, Fowler CL. Open label assessment of levofloxacin for the treatment of acute bacterial sinusitis in adults. Ann Allergy Asthma Immunol. 1998;80:357–62.
113. Wald ER, Milmoe GJ, Bowen AD, Ledesma-Medina J, Salmon N, Bluestone CD. Acute maxillary sinusitis in children. N Engl J Med. 1981;304:749–54. III.
114. Wald ER, Reilly JS, Casselbrant M, et al. Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. J Pediatr. 1984;104:297–302.
115. Hoban D, Felmingham D. The PROTEKT surveillance study: antimicrobial susceptibility of Haemophilus influenzae and Moraxella catarrhalis from community-acquired respiratory tract infections. J Antimicrob Chemother. 2002;50(Suppl S1):49–59.
116. Jones NS, Cooney TR. Facial pain and sinonasal surgery. Rhinology. 2003;41(4):193–200.
117. Hamilos DL. Chronic sinusitis. J Allergy Clin Immunol. 2000;106:213–27.
118. McClay JE, Marple B, Kapadia L, et al. Clinical presentation of allergic fungal sinusitis in children. Laryngoscope. 2002;112:565–9.
119. deShazo RD. Fungal sinusitis. Am J Med Sci. 1998;316:39–45.
120. Rizk SS, Kraus DH, Gerresheim G, Mudan S. Aggressive combination treatment for invasive fungal sinusitis in immunocompromised patients. Ear Nose Throat J. 2000;79:278–85.
121. Washburn RG. Fungal sinusitis. Curr Clin Topics Infect Dis. 1998;18:60–74.
122. Anderson MH, Stafford CT. Comparison of imaging techniques in the diagnosis of sinusitis [abstract]. Ann Allergy. 1991;66:73.
123. Zinreich SJ. Radiologic diagnosis of the nasal cavity and paranasal sinuses. In: Druce HM, editor. Sinusitis: pathophysiology and treatment. New York: Marcel Dekker, Inc.; 1993.
124. Chee L, Graham SM, Carothers DG, et al. Immune dysfunction in refractory sinusitis in a tertiary care setting. Laryngoscope. 2001;111:233–5.
125. Adkinson N, Yunginger J, Busse W, Bochner B, Holgate S, Middleton E, editors. Middleton's allergy: principles and practice. 7th ed. St Louis: Mosby; 2003.

Chapter 10
Diagnosis and Classification of Chronic Rhinosinusitis with and Without Polyposis in Adults and Children

Daniel L. Hamilos

Origin of the Term "Rhinosinusitis" and Evolution of Current Chronic Rhinosinusitis (CRS) Classification System

The term "rhinosinusitis" appeared in the medical literature as early as 1953 with reports of "allergic rhinosinusitis" and "polypoid hyperplastic rhinosinusitis" [1–4]. Several reports in the 1960s and 1970s addressed the issue of "allergic rhinosinusitis" and sensitization to microbial antigens in patients with rhinosinusitis [5]. "Hyperplastic rhinosinusitis" was an established terminology in this time period [6]. Rhinosinusitis polyposis as a symptom of aspirin intolerance was described in 1977 [7].

A classic paper by Messerklinger (the father of "functional endoscopic sinus surgery") in 1987 elegantly states the importance of the nose in the origins of chronic rhinosinusitis [8]:

> In the vast majority of cases infections of the paranasal sinus system are rhinogenic. Usually these spread via the middle nasal meatus and the anterior ethmoid to the dependent larger sinuses, especially to the frontal and/or maxillary sinus. If a sinusitis does not heal or is constantly recurring, a focus of infection has remained in a stenotic cleft of the lateral nasal wall, irritating nasal function and where from infection time and again may spread to the dependent sinuses. These Infection foci may be very circumscribed and limited, and not always must present with the typical triad of sinusitis symptoms: pathological secretion, nasal obstruction and cephalgia. Frequently only one of these symptoms prevails. By the means of nasal endoscopy and polytomography these foci can exactly be localized. After clearing the infection foci, which easily can be achieved under endoscopic guidance, mucosal function usually is restored and the dependent larger sinuses heal without having been touched.

The term "rhinosinusitis" was used in 1990 by Stevenson and colleagues in reference to their long-term experience with aspirin desensitization for "aspirin-sensitive rhinosinusitis-asthma" [9]. Lund and colleagues described the role of functional endoscopic sinus surgery in the management of chronic rhinosinusitis in 1991 [10]. Still, the term "sinusitis" was the more commonly used term in the literature through the late 1990s.

In 1996, the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc. (AAO-HNS) convened a meeting in collaboration with the National Institutes of Allergy and Infectious Disease (NIAID) to identify critical directions for research on sinus disease [11]. In this report, it is stated that "Because the inflammatory process that causes sinusitis is frequently associated with inflammation of the nasal passages, the term rhinosinusitis might more precisely define this disease state."

The Rhinosinusitis Task Force (RSTF) (convened by the AAO-HNS in August, 1996) put forward the term "rhinosinusitis" as "more descriptive of the actual condition" than the term "sinusitis" [12]. Rhinosinusitis in adults was defined as "a condition manifested by an inflammatory response involving the following: the mucous membranes (possibly including the neuroepithelium) of the nasal cavity and paranasal sinuses, fluids within these cavities, and/or underlying bone." The arguments favoring rhinosinusitis over sinusitis were summarized as follows. First, clinical "sinusitis" is often preceded by rhinitis, and sinusitis occurring in the absence of rhinitis is rare. Isolated sinusitis (e.g., dental origin) was acknowledged to occur but not nearly as commonly as the more general rhinosinusitis that usually follows a viral upper respiratory infection. Studies of patients exposed to the common cold virus (rhinovirus) had found that 33 % had magnetic resonance imaging abnormalities of the ethmoid or maxillary sinuses temporally associated with the acute infection [13, 14]. These studies provided

D.L. Hamilos, MD
Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Bulfinch-422, Boston, MA 02114, USA
e-mail: dhamilos@partners.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_10,

compelling evidence for adoption of the term "rhinosinusitis" at least in the context of viral upper respiratory infections, but it could be questioned whether this same association applies to bacterial sinusitis and chronic sinusitis. Certainly from the perspective of symptoms, the answer is yes, since two of the cardinal symptoms of sinusitis, namely, nasal congestion (nasal blockage) and nasal or postnasal drainage, clearly overlap with rhinitis and hyposmia/anosmia. Concomitant allergic or nonallergic rhinitis is also a common comorbid condition with "sinusitis." Adoption of the term "rhinosinusitis" was not intended to downplay the significance of these conditions but rather to highlight their importance as coexisting sources of nasal inflammation that could manifest themselves with similar symptoms and participate in the clinical problem of rhinosinusitis.

Histologically, the nasal passages and the sinus cavities were also felt to have many similarities. The mucous blanket of the sinuses is in continuity with that of the nasal cavity, and all sinus cavities drain into a compartment of the nose [12]. It was also believed that use of the term rhinosinusitis would help educate physicians and the lay public that the nasal passages, as well as the sinuses, are involved with the disorder.

Since the 1997 Task Force document, some evidence has emerged in support of the term rhinosinusitis. Bhattacharyya evaluated paired specimens of nasal septal mucosa and ethmoid sinus mucosa in a prospective cohort of 42 patients undergoing endoscopic sinus surgery for chronic rhinosinusitis [15]. There was histopathologic evidence that rhinitis was associated with chronic sinusitis.

Significant efforts to subclassify and redefine CRS occurred concurrently in the time period 2003–2005. In 2003, another consensus panel endorsed by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), the American Academy of Otolaryngic Allergy (AAOA), the American Rhinologic Society (ARS), and the Sinus and Allergy Health Partnership (SAHP) redefined chronic rhinosinusitis as "a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration." The diagnosis required the presence of 2 major factors or 1 major factor + 2 minor symptoms *or* nasal purulence on examination. Facial pain alone was not regarded as suggestive of CRS in the absence of other nasal symptoms or signs. The consensus panel strongly advocated for the objective confirmation of sinus disease by means of direct visualization or imaging studies [16].

The "Rhinosinusitis Initiative" comprised an expert panel endorsed by the American Academy of Allergy, Asthma, and Immunology; the American Academy of Otolaryngic Allergy; the American Academy of Otolaryngology–Head and Neck Surgery; the American College of Allergy, Asthma, and Immunology; and the American Rhinologic Society [17, 18]. This group convened in 2003 and published a rhinosinusitis definitions document in 2004. Nearly simultaneously, the European Academy of Allergy and Clinical Immunology (EAACI) generated a consensus report [19]. Both groups abandoned the earlier definition based on major and minor criteria and defined rhinosinusitis based on the presence of cardinal symptoms combined with objective evidence of sinus disease by nasal endoscopy or radiographic imaging.

In line with these documents, the American Academy of Otolaryngology–Head and Neck Surgery adopted the term rhinosinusitis on their Web page, citing their preference for this term over sinusitis on the basis of recent literature (AAO-HNS Web site, available at http://www.entnet.org/healthinfo/sinus/allergic_rhinitis.cfm. Accessed July 29, 2005).

Subsequent to the RI and EAACI reports, other groups, including the British Society for Allergy and Clinical Immunology, quickly adopted the term "rhinosinusitis" [20]. However, in the USA, the term rhinosinusitis was adopted by the otolaryngology societies (AAO-HNS, ARS, and AAOA) but not by the allergy societies [21].

The RI and EAACI groups also proposed a new classification scheme for CRS based on subtypes. Thus, chronic rhinosinusitis without nasal polyposis (CRSsNP), chronic rhinosinusitis with nasal polyposis (CRSwNP), and allergic fungal rhinosinusitis (AFRS) were felt to be sufficiently distinct on clinical and/or pathologic grounds to be regarded as distinct subsets of CRS (see section "Subtypes of CRS").

Considering the evolution of thinking and lack of unanimity of opinion regarding disease terminology, it should be kept in mind that most literature prior to 2003 and a substantial fraction of publications since then still use the term "sinusitis" in deference to "rhinosinusitis." In reality, the vast majority of these publications are describing the same condition.

Classification of CRS in Children

Considering the high prevalence and healthcare impact of chronic rhinosinusitis in children, there has been a surprising lack of expert panel reports on its pathogenesis, terminology, or treatment. The RSTF report of 1997 acknowledged that the maturity of the children's immune system affects both their susceptibility to rhinosinusitis and the microbiology of the disease and that children appear to be more susceptible to viral infections and have higher rates of infection through child care facilities [12]. Yet, pediatric chronic rhinosinusitis was not discussed in detail in this or any of the other expert panel reports previously mentioned. Similar definitions of disease based on symptoms and duration of illness were generally regarded as applicable to children as adults.

Table 10.1 Multiple factors contribute to chronic rhinosinusitis in children

High frequency of viral upper respiratory tract infections
Small sinus ostia
Anatomic abnormalities in the sinuses[a]
Immaturity of the pediatric immune system
Biofilm formation in sinus tissue
Enlarged adenoidal pads harboring bacteria that cause CRS
Allergy
Defects in mucociliary clearance (cystic fibrosis, immotile cilia syndrome)

Adapted from [26, 27]
[a]Evidence suggests this makes a relatively small contribution to CRS development

Table 10.2 Summary of similarities and differences in pediatric versus adult CRS

Contributive factor	Pediatric CRS	Adult CRS
Frequent viral URTIs	+	
Small sinus ostia	+	
Anatomic sinus abnormalities	±	±
Immaturity of the humoral immune system	+	
Biofilm formation in sinus tissue	+	+
Enlarged adenoidal pads harboring biofilm	+	
Allergy	+	+
Defects in mucociliary clearance	±	±

+ denotes a factor more common in one form of CRS (pediatric or adult)
± denotes a factor that may contribute to pediatric or adult CRS in selected cases
+ denotes a factor that contributes significantly to both pediatric and adult CRS

Several agencies published guidelines concerning the diagnosis and management of acute bacterial sinusitis, emphasizing the importance of viral infections as the most common cause of rhinosinusitis and that antibiotic treatment of uncomplicated viral upper respiratory tract infections (URTIs) is inappropriate. These guidelines were endorsed by the American Academy of Pediatrics [22].

It is widely acknowledged that adenoid hypertrophy and allergic rhinitis are common in children and that recurrent upper respiratory tract infections lead to most incidences of acute bacterial rhinosinusitis [23]. Furthermore, the histopathology of CRS in children differs from that in adults, being more characteristically lymphocytic and less eosinophilic and showing less evidence of glandular hyperplasia or tissue remodeling [24, 25]. Multiple factors are believed to contribute to CRS in children as summarized in Table 10.1.

The contrasting features of pediatric versus adult CRS are summarized in Tables 10.2 and 10.3 [26]. Typical upper respiratory tract infections (URTI or the "common cold") have been demonstrated within 48–96 h of onset to cause maxillary sinus infundibulum occlusion in 77 % of cases and much more extensive evidence of sinus involvement in many cases that can persist up to 2 weeks [14]. The incidence of the common cold is highest in children <5 years. Children attending school or daycare serve as a large reservoir for URTIs to other children and adults. Children have three to eight viral URTIs per year. Adolescents and adults have two to four URTIs per year, and people older than 60 years have less than one URTI per year. Bacterial rhinosinusitis complicates 2 % of viral URTIs [28].

Small sinus ostia likely contribute to their frequent occlusion by viral URTIs. Likewise, certain anatomic variants, such as septal deviation, Haller cells, paradoxical curvature of the middle turbinate, and agger nasi cells, have been suggested to predispose to obstruction of the ostiomeatal unit, development of CRS, or both. However, there is currently little evidence that these play a role in most cases of chronic sinusitis [29–32]. A recent study in a pediatric population found no correlation between anatomic abnormalities and the extent of CRS on sinus CT scanning [33].

Immaturity of the pediatric immune system is also likely to contribute to the development of CRS. In the study of 61 children with refractory CRS, Shapiro et al. found evidence of low immunoglobulin levels in 6 children and vaccine hyporesponsiveness in 23 children [34]. This is a much higher rate of impaired humoral immunity than found in a study of adult patients with CRS [35].

A schema of the pathogenesis of pediatric CRS that incorporates the distinct features of pediatric versus adult CRS is shown in Fig. 10.1.

Table 10.3 Bacteriologic and pathologic similarities and differences in pediatric versus adult CRS

Contributive factor	Pediatric CRS	Adult CRS
Bacteriology	Similar	Similar
Pathologic features		
Lymphocytes	+	
Eosinophils	Fewer	+
Glandular hyperplasia		+
Tissue remodeling	±	+
Nasal polyps		+

+ denotes a factor more common in one form of CRS (pediatric or adult)
± denotes a factor that may contribute to pediatric or adult CRS in selected cases
+ denotes a factor that contributes significantly to both pediatric and adult CRS

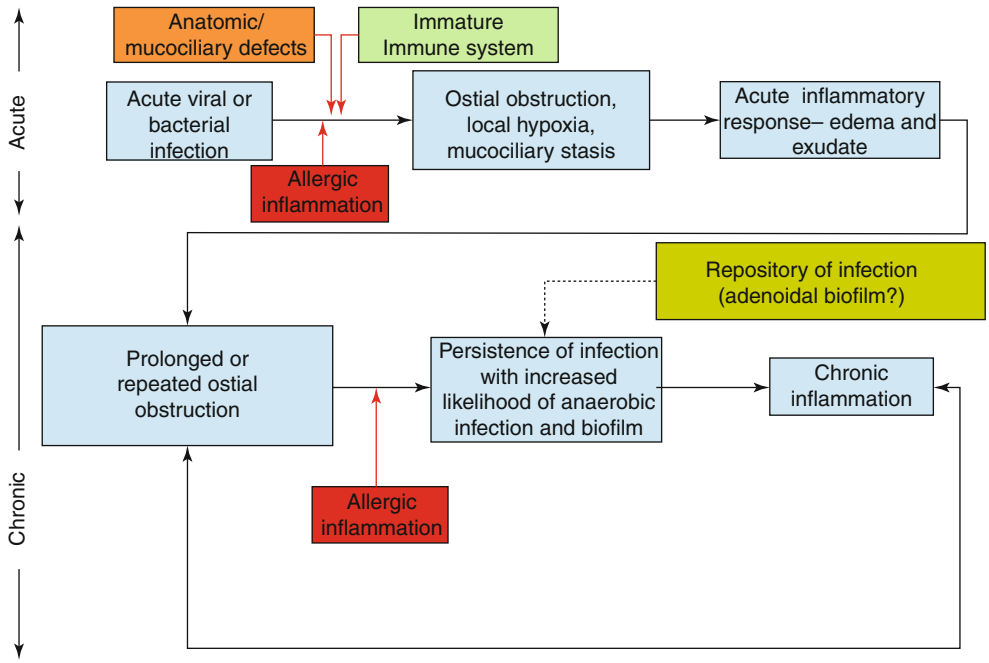


Fig. 10.1 Pathogenesis of pediatric CRS

Subtypes of CRS

The RI and EPOS documents defined three distinct subtypes of CRS (see Fig. 10.2 and Table 10.4). The underlying causes and contributing factors, as well as the response to medical or surgical management, are substantively different among the three conditions:

- CRS with nasal polyposis: 20–33 % of cases
- Allergic fungal rhinosinusitis: 8–12 %
- CRS without nasal polyposis: 60–65 %

The distinct clinical characteristics and pathologic differences between these subtypes are briefly discussed.

CRS Without Nasal Polyposis (CRSsNP): CRSsNP is the most common form of CRS, accounting for 60–65 % of cases [35]. CRSsNP describes the presence of CRS without the other characteristic features that define the other two syndromes (e.g., nasal polyposis or allergic mucin containing fungal hyphae), although the distinction between subtypes is sometimes hazy (see below).

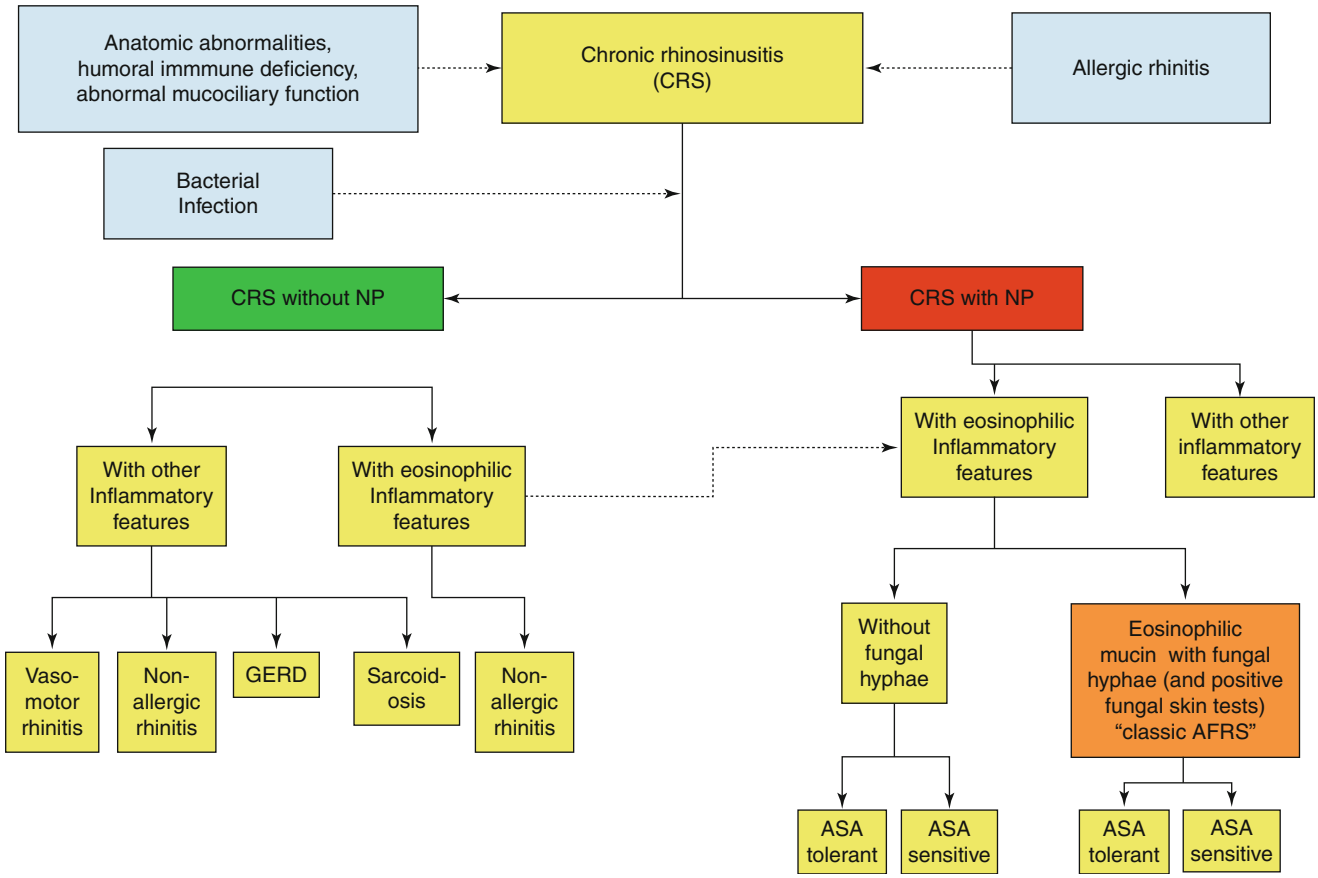


Fig. 10.2 Current classification of CRS (Adapted from Meltzer et al. [17]. With permission from Elsevier)

Table 10.4 Definitions of CRSsNP, CRSwNP, and AFRS as established by the RI and EPOS consensus groups

Summary of recent evidence-based guidelines for the diagnosis of CRS		
Guideline	Criteria for diagnosis	Special assessment recommendations
EP,OS, 2007	≥2 symptoms lasting >12 weeks, 1 of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) ± Facial pain/pressure ± Reduction or loss of smell Objective criteria Endoscopy or rhinoscopy to identify presence/absence of NP CRS with or without NP ≥2 of the following symptoms for ≥12 weeks Anterior and/or posterior mucopurulent drainage Nasal obstruction Facial pain/pressure/fullness (without NP only) Decreased sense of smell (with NP only) Objective criteria Nasal airway examination to confirm or exclude NP and/or to document inflammation Sinus CT not essential but should be strongly considered AFRS ≥1 of the symptoms already listed Objective criteria Endoscopy to document presence of allergic mucin containing fungal hyphae or culturable fungi and inflammation (e.g., edema of middle meatus or ethmoid area, NP) Evidence of fungus-specific IgE (by skin test or in vitro blood test) No histological evidence of invasive fungal disease	Recommended Endoscopy Anterior rhinoscopy, if endoscopy unavailable Allergy testing, if history is suggestive Not recommended CT for primary care Optional CT for ENT specialists Diagnosis of CRS with or without NP Strongly recommended Nasal airway examination, CT (not essential) Diagnosis of AFRS Recommended Skin test or in vitro blood test for fungus-specific IgE Endoscopy Fungal stain of allergic mucin Optional Fungal culture Total serum IgE Imaging by >1 technique (highly suggestive of diagnosis)

Reprinted from Meltzer and Hamilos [36]. With permission from Elsevier

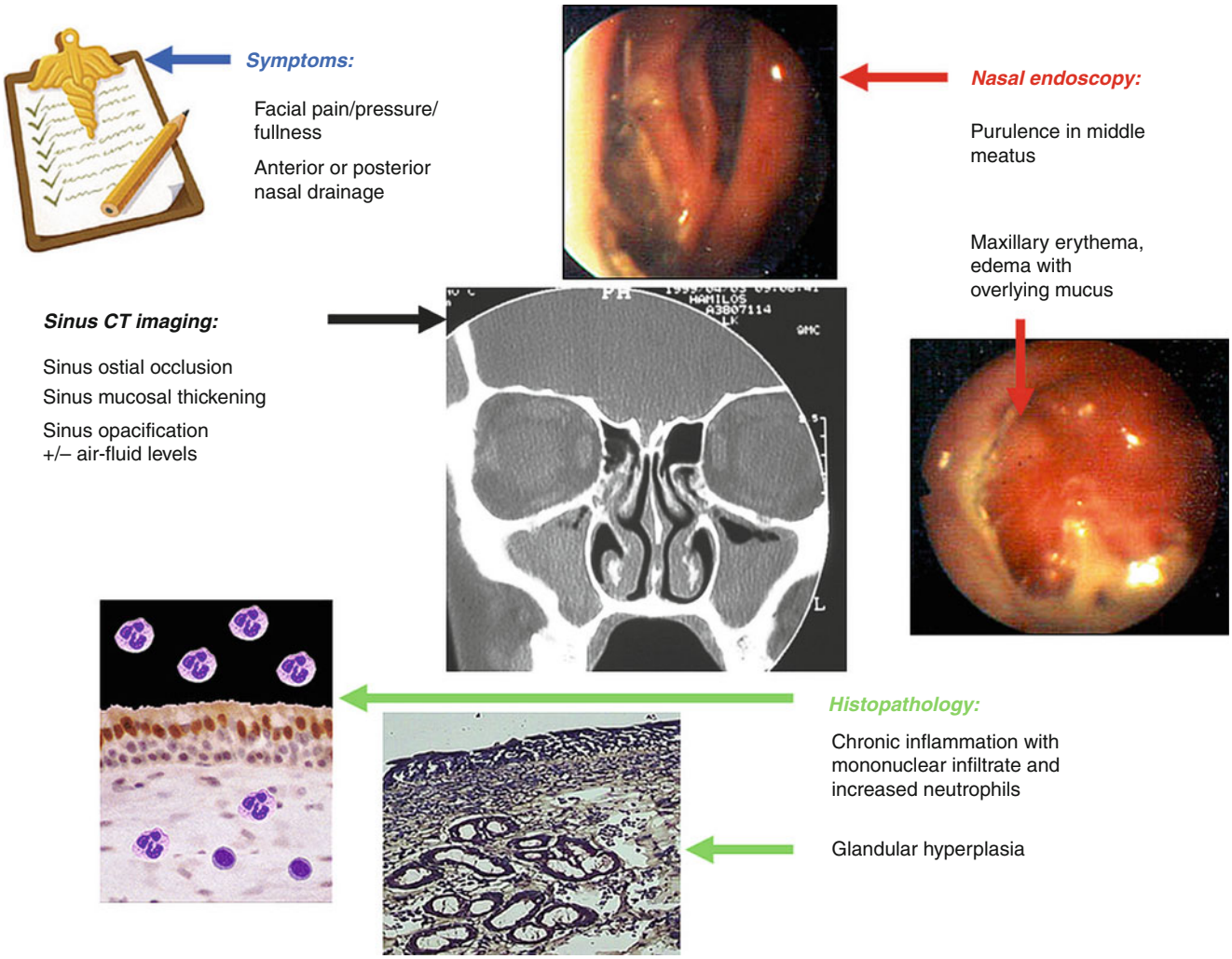


Fig. 10.3 Summary of characteristic features of chronic rhinosinusitis without nasal polyposis (CRSsNP)

CRSsNP is heterogeneous and may include patients with allergic and nonallergic rhinitis, structural abnormalities, and mucociliary defects (e.g., immotile cilia syndrome); patients with gastroesophageal reflux-associated CRS; and patients with immunodeficiency.

Pathophysiology: Sinus ostial obstruction is the well-accepted cause of persistent symptoms and sinus inflammation and is found in the majority of cases [8, 37]. Underlying conditions, such as allergic rhinitis or immunodeficiency, are important contributive factors to the pathogenesis. CRSsNP is characterized by sinus opacification or sinus ostial obstruction with nonpolypoid mucosal thickening of the associated sinus cavity (see Fig. 10.3). Biopsy of mucosal tissue characteristically shows an infiltration of mixed mononuclear cells and neutrophils, with an increase in submucosal glands [38] and stromal fibrosis [39]. Epithelial goblet cell hyperplasia may be present. Eosinophils may be present but generally represent <10 % of the infiltrating inflammatory cells [40] which is another distinguishing feature in comparison to CRSwNP and AFRS. Chronic infection and biofilm formation are likely important components in the pathogenesis of CRSsNP [41].

The sinus mucus from patients with CRSsNP typically shows abundant eosinophils and neutrophils. Allergic mucin is present in some cases without the other characteristic features of AFRS, such as a positive mucus stain for fungi or evidence of fungal-specific IgE by skin tests or in vitro IgE immunoassays (e.g., CAP-RAST tests). Thus, these patients do not fulfill all the criteria of AFRS.

Fungi have been proposed to be involved in the pathogenesis of CRSsNP as well. Although most patients do not produce a classic IgE-mediated response against fungi, eosinophilic inflammation caused by a Th2-type sensitization to colonizing fungi has been proposed [42, 43]. T lymphocytes from a high percentage of CRS patients produce eosinophil-promoting cytokines, including IL-5 and IL-13, when exposed in vitro to certain fungal antigens (e.g., those from Alternaria) [43]. However, the role of fungi in CRSsNP pathogenesis remains controversial [44].

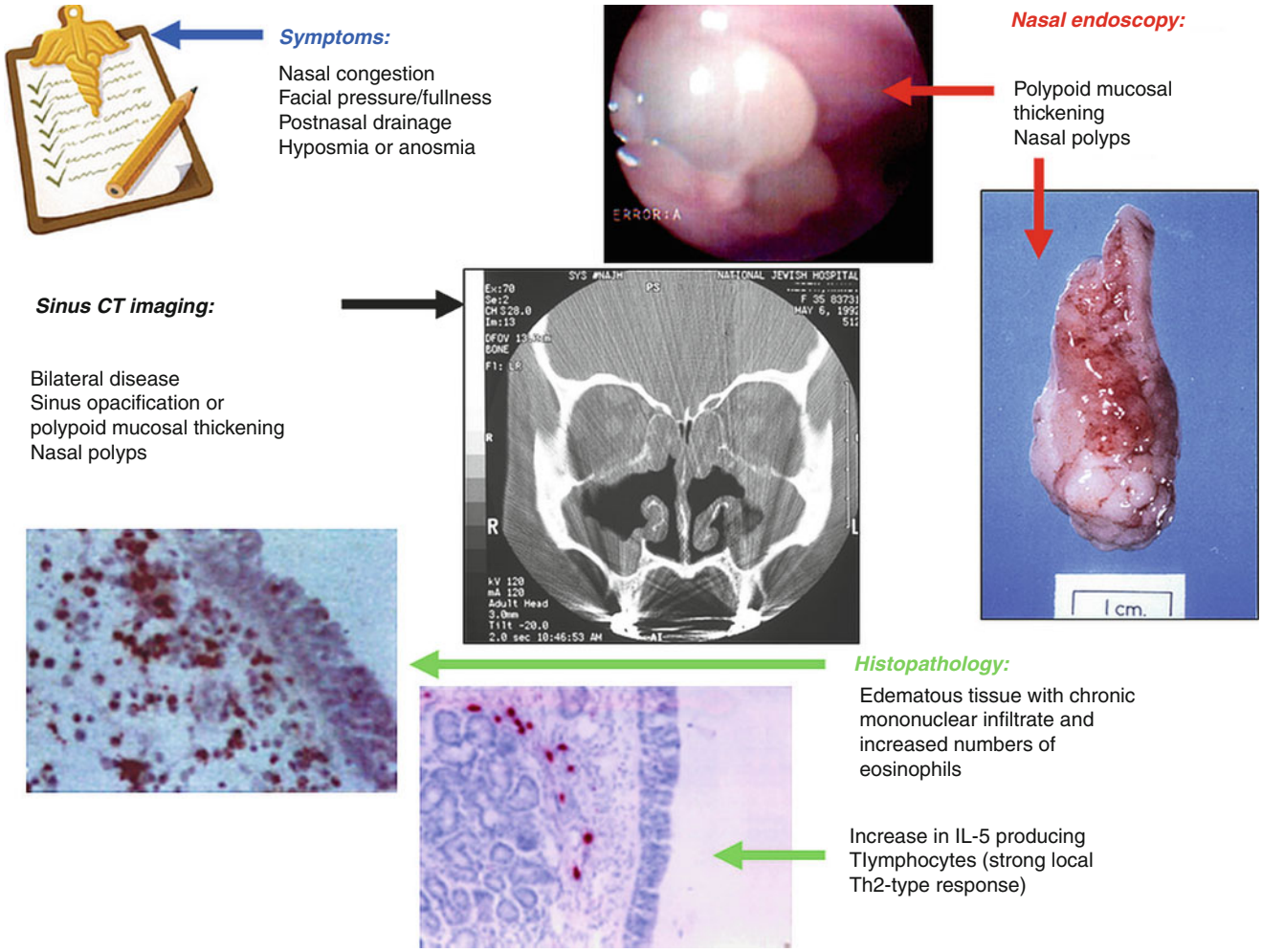


Fig. 10.4 Summary of characteristic features of chronic rhinosinusitis with nasal polyposis (CRSwNP)

Clinical Presentation: The characteristic presentation of CRSsNP is that of persistent symptoms with periodic exacerbations characterized by increased facial pain/pressure and/or increased anterior or posterior drainage. Fatigue is a frequent accompanying symptom. Fever is usually absent or low grade. A subset of patients has recurrent acute rhinosinusitis symptoms, which respond well to antibiotic treatment. These patients have been described as having "recurrent acute rhinosinusitis" or "chronic recurrent rhinosinusitis" [45].

Chronic rhinosinusitis with nasal polyposis (CRSwNP): CRSwNP is characterized by the presence of nasal polyps. Nasal polyps are translucent, yellowish-gray to white, glistening masses filled with gelatinous inflammatory material, which may form in the nasal cavity or paranasal sinuses (see Fig. 10.4). The gray-white color is due to the relatively avascular nature of the polyp tissue. The nasal polyps are characteristically bilateral.

Pathophysiology: Nasal polyps generally begin to form around the ostiomeatal complex, although they may be found through the nasal cavities and sinuses [46]. The initial trigger for their development is probably variable, but experimental evidence in animal models suggests that underlying allergic inflammation and bacterial infection may contribute to their formation [47]. Polyp tissue typically contains a predominance of eosinophils, high levels of the Th2 cytokines interleukin (IL)-5 and IL-13, and high levels of histamine [48].

In CRSwNP, there is evidence for localized allergic hyperresponsiveness to colonizing Staphylococcus aureus, as evidenced by the local production of specific IgE antibodies against staphylococcal enterotoxins [49, 50]. These antibodies can be measured in sinus tissues, although levels in the blood may be undetectable. The enterotoxins act as superantigens and broadly activate T lymphocytes. In contrast, patients with CRSsNP do not appear to produce IgE to staphylococcal enterotoxins [49]. A role for eosinophilic Th2 fungal sensitization has also been suggested, as in CRSsNP (see above).

Clinical Presentation: The characteristic presentation of CRS with NP is gradually worsening nasal congestion/obstruction, sinus fullness and pressure, fatigue, posterior nasal drainage, and hyposmia or anosmia. Fever and severe facial pain are uncommon.

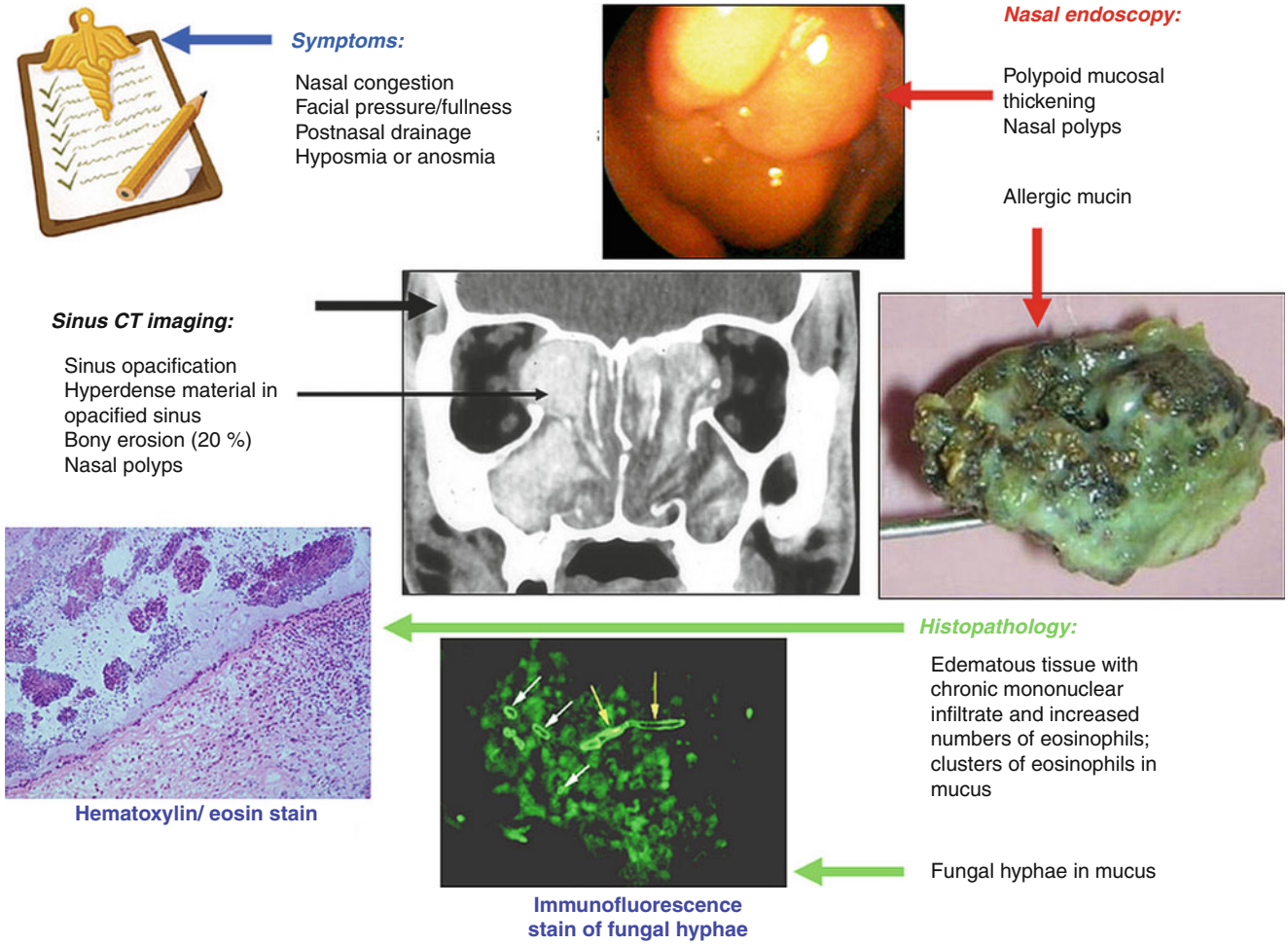


Fig. 10.5 Summary of characteristic features of allergic fungal rhinosinusitis (AFRS) (Reprinted from Ponikau et al. [53]. With permission from Elsevier)

CRSwNP affects immunocompetent patients and is associated with aspirin sensitivity and asthma. Approximately 30–40 % of adult patients with asthma and nasal polyps have aspirin sensitivity [51].

Allergic fungal rhinosinusitis (AFRS): AFRS refers to CRS that is accompanied by sinus opacification with "allergic mucin" or thick, inspissated mucus that ranges in color from light tan to brown to dark green and which contains degranulating eosinophils (see Fig. 10.5). Allergic mucin is generally identified at the time of surgery. Fungal hyphae are demonstrable within the allergic mucin, which suggests fungal colonization rather than invasive fungal disease. In invasive fungal sinusitis, fungal hyphae can be shown histologically to penetrate the underlying mucosa [52].

Over time, patients with AFRS may develop sinus cavity opacification and sometimes local pressure effects on bone. Bony demineralization of the sinus wall may ensue, resulting in expansion of the sinus and possibly mucocele formation. True bone erosion is less common, occurring in 20 % of cases [54].

Patients with AFRS usually have nasal polyposis and are immunocompetent, similar to patients with CRSwNP. However, AFRS patients have evidence of fungal-specific IgE by skin tests or IgE immunoassays (commonly called RAST tests). Thus, AFRS is distinguished from CRSsNP and CRSwNP by the presence of allergic mucin containing viable fungal hyphae (as demonstrated by fungal staining or culture) and evidence of IgE-mediated allergy to one or more fungi [55, 56].

Pathophysiology: The pathophysiology of allergic fungal rhinosinusitis (AFRS) is most consistent with chronic, intense allergic inflammation directed against colonizing fungi. Histologically, allergic mucin demonstrates intense eosinophilic degranulation, mucostasis, and inspissation [57].

Clinical Presentation: AFRS usually presents subtly, with symptoms similar to CRS with NP. Patients may describe semi-solid nasal crusts that are similar in appearance to allergic mucin [17]. Fever is uncommon. In occasional patients, AFRS presents dramatically with complete nasal obstruction, gross distortion of facial features, and/or visual changes.

Cardinal Symptoms of CRS

The cardinal symptoms of CRS, as defined by the RI and EPOS groups, include facial pain/pressure/fullness, anterior and/or posterior nasal drainage ("nasal drip"), nasal obstruction (nasal blockage/congestion), and decrease or loss of sense of smell (also referred to as hyposmia/anosmia). Loss of sense of taste (ageusia) is typically included under disturbance of sense of smell, since taste perception is considered part of olfactory function.

The RI document proposed slightly different symptom criteria based on the diagnosis of ABRS, CRSsNP, CRSwNP, or AFRS. For example, for CRSsNP, only three cardinal symptoms were defined with loss of sense of smell excluded. In contrast, for CRSwNP, only three cardinal symptoms were defined with facial pain/pressure/fullness excluded. Finally, for AFRS, all four cardinal symptoms were defined, but confirmation of the diagnosis required only one symptom, acknowledging that some patients had been found to present with facial disfigurement but minimal nasal symptoms. However, prior to the RI and EPOS documents, the symptom differences between CRSsNP, CRSwNP, and AFRS had not been systematically examined.

Following publication of the RI document, studies by Baraniuk and Maibach [58] and Banerji et al. [59] provided some validation of the symptom differences between CRSsNP and CRSwNP. The Banerji study was based on analysis of data from an outcomes study of CRS conducted at Washington University School of Medicine in St. Louis, MO, from 1999 to 2001. In this study, the Sino-Nasal Outcome Test (SNOT-20), modified to include the symptom of "sense of smell" ("SNOT20+1"), was used for capturing CRS-related symptoms and outcomes of CRS treatment [60]. The most frequent symptoms at presentation included postnasal drainage (96 %), thick nasal discharge (93 %), waking up tired (90 %), and facial pain (86 %). Although the symptom of nasal congestion was not captured, the related symptom of "need to blow nose" was reported with a prevalence of 68 %. Hyposmia/anosmia was the least common of the cardinal CRS symptoms (22 %); however, this symptom was often ranked as the most bothersome on the SNOT20+1.

Banerji further analyzed the data from this study after classifying patients as having CRSsNP (70.2 %), CRSwNP (16.7 %), or "polypoid" CRS (16.5 %) [59]. (In this study, none of the patients were confirmed to have AFRS.) The symptom of facial pain/pressure/fullness was more common in CRSsNP (92 % versus 73 %) ($p = .01$), whereas nasal obstruction (40 % versus 69.5 %) and hyposmia/anosmia (62 % versus 92 %) were more common in CRSwNP ($p = .025$ and .01, respectively).

Since no symptom of CRS is pathognomonic, each symptom must be considered suggestive of rather than diagnostic of CRS. A brief "differential diagnosis" for the cardinal CRS symptoms will be presented along with prevalence data for each symptom in CRS patients.

Facial Pain/Pressure/Fullness and Sinus Headache

The description of facial pain/pressure/headache ranges from vague and poorly localized to sharp and focal, with most patients describing vague discomfort (including "fullness" or "pressure") in the cheeks, above or below the eyes, or across the bridge of the nose. Many patients point to an area on the face that anatomically localizes to the ostiomeatal complex or unit ("OMU") on one or both sides. Patients also frequently report "sinus headaches," but this symptom requires more precise description, since it could signify anything from vague sinus pain/pressure to focal sharp pain or pulsatile vascular-type headaches. Focal and sharp facial pain over one or more sinus area may be rhinogenic in origin but is often unassociated with radiographic evidence of sinus disease and ultimately may be deemed a manifestation of "neurogenic" or "psychogenic" pain without more precise explanation for its cause emerging despite further investigation. Pain in the upper teeth is suggestive of nerve irritation caused by inflammatory process adjacent to tooth roots. In the series reported by Bhattacharyya, facial pressure and headache were both reported by 83 % and dental pain was reported by 50 % of patients [61].

It has been suggested that headaches may be caused by a mucosal "contact point" between the nasal septum and the middle or superior turbinate or between the septum and the medial wall of the ethmoid sinus [62, 63]. However, there is considerable debate over the prevalence of this condition and means to establish it as a cause of headache. Patients may have headaches in the absence of other symptoms of CRS and frequently have other symptoms suggestive of migraine headaches, such as pulsating headaches and photophobia [62].

Facial pain/pressure has been shown to lack specificity with respect to predicting the presence of rhinosinusitis by other objective measures. In one study, headache and facial pain were much less predictive of the presence of sinusitis by nasal endoscopy or sinus CT scan than the symptoms of nasal obstruction or postnasal drip [64]. In another study, patients' cumulative symptoms as recorded with the SNOT-20 instrument were found to lack correlation with sinus CT scoring by the

Lund-Mackay method [65]. Furthermore, endoscopy-negative, sinus CT-negative patients with facial pain were found to be unresponsive to medical treatment for sinusitis [66].

Special Consideration: Distinguishing Rhinogenic from Non-rhinogenic Headaches

Studies analyzing the relationship between headaches and rhinosinusitis have yielded widely disparate results suggesting that the studies themselves suffer from some degree of bias. Thus, in the study by Bhattacharyya [61], an otolaryngologist, 80 % of patients diagnosed with CRS reported headaches, and the clinical impression was that this symptom was reflective of the underlying condition. In contrast, the study of Schreiber et al. [67], which was conducted at multiple primary care sites, 2,991 patients were enrolled if they had experienced at least six episodes of self-described or physician-diagnosed "sinus headaches" in the preceding 6 months. Patients were excluded if they had signs of nasal purulence or postnasal drainage with their self-described "sinus" headaches or if they had radiographic evidence of sinus infection in the previous 6 months. In this study, 80 % of the patients were found to meet International Headache Society criteria for "migraine" headache, and another 8 % met criteria for "migrainous" headaches. Only a minority were felt to have rhinosinusitis. However, the results of the study cannot be generalized to the population of CRS patients, since the study sought to exclude CRS patients at entry and did not thoroughly exclude CRS in the study population. In Tarabichi's study of 82 patients with CRS, 38 % of patients with facial pain plus radiographic and endoscopic evidence of CRS had a persistence of facial pain one year following sinus surgery despite a lack of evidence for persistent sinus disease [68]. The author concluded that roughly one-third of patients with facial pain underwent sinus surgery for a non-sinus indication. Perhaps it would be fairer to say that one-third of patients with facial pain and sinusitis failed to experience relief of facial pain despite surgical correction of their sinusitis.

The author's own experience lies somewhere in between these two extremes. In our Sinusitis Outcomes Study, we found that patients with an initial complaint of facial pain/pressure had a poorer response to medical management compared to patients without this complaint [60]. Facial pain or pressure also correlated poorly with sinus CT scan findings. Of our 91 enrolled patients, 11 had a negative baseline sinus CT scan. Of these, 10 had either facial pain or facial pressure along with other CRS symptoms as part of their presenting symptom complex. Nonetheless, considering our entire patient population, a highly significant improvement in facial pain/pressure was reported by patients after medical treatment for their rhinosinusitis. Therefore, if other symptoms of CRS are present, it is worth considering that the patient's facial pain/pressure/headaches may have a rhinogenic component. If these symptoms fail to improve after treatment, other causes should certainly be sought.

The key point is that facial pain/pressure/headache may have multiple etiologies and is probably the least specific of the cardinal symptoms for CRS.

For this reason, expert panels have recommended that the diagnosis of CRS not be made on the basis of a single major symptom of facial pain/pressure [16]. For the interested reader, a more detailed discussion of the differential diagnosis of facial pain/pressure/fullness and sinus headache has been published [35].

Anterior and/or Posterior Nasal Drainage ("Nasal Drip")

Anterior and/or posterior nasal drainage may be a symptom of seasonal or perennial allergic rhinitis or nonallergic forms of rhinitis. Less common causes include CSF rhinorrhea, nasal and sinus secreting tumors, inverted papilloma, and nasal foreign bodies. Occasionally, the perception of mucus buildup in the throat may be a symptom of gastroesophageal reflux (GERD), particularly laryngopharyngeal reflux (LPR). In this case, other associated symptoms might include heartburn, chronic throat clearing, and hoarseness [69].

Clear, watery rhinorrhea is most typically associated with allergic rhinitis, idiopathic rhinitis, rhinitis medicamentosa, rhinitis associated with medication use, or CSF rhinorrhea. Opaque white or colored drainage is more likely to represent "purulence" and is more likely to be associated with sinus pathology, including acute or chronic infection or chronic noninfectious inflammatory disease, including that seen in association with CRSwNP and AFRS. Thick, yellow, green, or brown mucus may be seen in recurrent acute rhinosinusitis or in refractory CRS cases, including cases of classic AFRS. Thick, crusted, foul-smelling nasal mucus may be a symptom of atrophic rhinitis, a poorly understood chronic infection of the nose [70, 71].

Nasal Obstruction (Nasal Blockage/Congestion)

Nasal congestion is often described by the patient as nasal blockage or stuffiness or less commonly as nasal "fullness." The differential diagnosis of this symptom includes the various forms of rhinitis and "empty nose syndrome." Unilateral nasal congestion/blockage raises the question of a local anatomic problem or tumor, such as an antral choanal cyst.

Decrease or Loss of Sense of Smell (Hyposmia/Anosmia) and Loss of Taste (Ageusia)

Disturbance in sense of smell may be perceived as a reduced or completely absent sense of smell (hyposmia or anosmia, respectively). Patients may also report a reduced ability to taste foods (ageusia). Less commonly, they may experience a reduced taste sensation with preservation in sense of smell.

Correlation of Nasal Endoscopic Findings with CRS Definition

The 1997 Task Force based the definition of chronic rhinosinusitis primarily on history and physical examination findings in order to make it broadly applicable in clinical practice [12]. Nasal endoscopy and radiographic imaging were not required for the initial diagnosis but were acknowledged to be helpful in difficult or recalcitrant cases. The diagnosis was based on a combination of major and minor criteria but was not validated against objective criteria for disease.

To test the validity of this definition, Stankiewicz and Chow performed a study in which 78 adult patients meeting the Task Force definition of CRS were also evaluated with same-day nasal endoscopy and sinus CT imaging [72]. None of the patients had prior surgery, and all evaluations were done prior to the initiation of medical treatment. Patients with obvious nasal polyps, fungus, or purulence on anterior rhinoscopy were excluded from this study. The key finding in this study was that 45 % of patients meeting the Task Force definition of CRS had no objective evidence of disease by nasal endoscopy or sinus CT. Nasal endoscopy was negative in 68 % of patients (53 of 78 patients), but 20 of these patients had findings on sinus CT scan. A total of 41 patients (53 %) had a negative sinus CT scan. Nasal endoscopy was a good predictor of chronic rhinosinusitis only if nasal polyps, purulence, or edematous congested mucosa was present. This study highlighted the limitations of the symptom-based 1997 Task Force definition.

In general, abnormal sinus CT findings correlate better with nasal endoscopic findings, but the correlation is far from 100 % [16, 73]. Both the RI (2004) and EPOS (2005) documents put forth criteria for "clinical" and "research" definitions differing mainly in terms of less stringent requirements for objective documentation needed for the clinical diagnosis. Both groups emphasized the importance of objective documentation of disease to confirm the diagnosis of CRS.

Correlation of Radiographic Findings with CRS Definition

Bhattacharyya et al. compared patient symptoms with sinus CT scanning in 586 patients referred for sinus-related symptoms (58 % chronic and 34 % acute) and sinus CT scanning [65]. In this study, the Sino-Nasal Outcome Test (SNOT-20) was used to collect symptom information. No correlation was found between the SNOT-20 or the individual score on facial pain or pressure and a positive CT scan. Isolated symptoms of facial pain/pressure or headache correlated even less well with CT evidence of sinus disease. In a follow-up study, this group found no correlation between CT scan findings, and symptom severity could be identified using established CT staging systems and patient-based symptom instruments [74].

Other studies have reported a high frequency of incidental abnormalities on sinus MRI in patients imaged for suspected intracranial neurological pathology [75]. In this study, 31.7 % of patients had pathologic findings on MRI defined as $\geq$5 mm, total sinus opacification, or fluid or polyps. "Blocked nose" was the only symptom occurring significantly more often in patients with pathologic changes.

Bhattacharyya and Lee [76] used the Rhinosinusitis Symptom Inventory (RSI) to collect symptom, nasal endoscopic, and imaging data on a group of 202 patients meeting the symptom definition of CRS based on the revised practice guidelines of 2007 [77]. All patients were required to have at least two of the four cardinal CRS symptoms to be included in the study.

Table 10.5 Distribution of patients meeting CRS symptom-based definition who had either positive nasal endoscopy or sinus CT imaging or both in studies by Stankiewicz and Chow [78] and Bhattacharyya and Lee [76]

No. of patients	% Of patients	Positive nasal endoscopy	Positive sinus CT imaging
Stankiewicz and Chow [78]			
35	44.9	–	–
6	7.6	–	+
20	25.6	+	–
17	20.8	+	+
Bhattacharyya and Lee [76]			
90	50.6	–	–
17	9.6	–	+
38	21.3	+	–
33	18.5	+	+

Patients were excluded from the study if they had a history of previous sinus surgery, cystic fibrosis, autoimmune or immunocompromised disorders, or recurrent acute rhinosinusitis. The results of this study were remarkably similar to those of Stankiewicz and Chow [72] as summarized in Table 10.5. The prevalence of CRS based on CT alone was only 39.6 %. For symptom criteria alone, the sensitivity, specificity, positive predictive value, and negative predictive value for CRS were 88.7, 12.3, 39.9, and 62.5 %, respectively. However, the authors found that the addition of endoscopic findings to symptom criteria significantly improved the specificity, predictive value, and negative predictive value to 84.1, 66.0, and 70.3 %.

As mentioned above, the study by Sankiewicz and Chow reported that 53 % of patients meeting the RSTF definition of CRS had a negative sinus CT scan [72]. However, this study excluded patients with obvious nasal polyps, fungus, or purulence on anterior rhinoscopy and therefore underestimated the utility of the definition.

Hwang et al. examined 115 patients with no prior sinus surgery who met the symptom components of the RSTF definition and examined the correlation between symptoms and sinus CT scans [79]. Because patients were not examined, the RSTF criterion "purulence on nasal examination" could not be considered in the analysis, but unlike the Stankiewicz and Chow study, no patients were excluded on the basis of nasal polyps, fungus, or purulence on anterior rhinoscopy. They found that 40 of 115 patients had a negative CT scan. Furthermore, sinus CT abnormalities were found in patients not meeting the RSTF definition. They concluded that the RSTF definition had a high sensitivity for detecting a positive scan (89 %) but very poor specificity (2 %).

In the WUSM Outcomes Study, 94 patients meeting the CRS definition underwent sinus CT imaging at or near the time of enrollment. This study may have been the most "real world" of the studies mentioned, as it collected symptom data, nasal endoscopy, and sinus CT imaging and did not exclude patients based on nasal polyps, fungus, purulence on anterior rhinoscopy, and patients with or without prior sinus surgery [59, 60]. In this study, roughly 8 % of patients had a negative sinus CT. The authors retained these patients in the data analysis. This is consistent with actual clinical practice in which a small percentage of CRS patients have a consistently negative sinus CT scan.

In summary, multiple studies have shown a poor correlation between patient's symptoms of CRS and radiographic findings and indicate that a symptom-based definition is unreliable for the diagnosis of CRS. Some patients who meet a symptom-based definition of CRS will have a negative CT scan or nasal endoscopy, and some patients will be asymptomatic despite objective evidence of sinus disease on CT scan or nasal endoscopy. Nasal endoscopy provides important information in cases where the clinical suspicion of rhinosinusitis pathology is high despite the lack of symptoms or CT findings.

Validation of the Differences Between CRSsNP and CRSwNP

From a clinical perspective, three studies have examined the differences between CRSsNP and CRSwNP.

Baraniuk and Maibach [58] conducted a retrospective review of 99 adult patients meeting the 2004 definition of CRS for clinical and immunologic differences between CRSsNP and CRSwNP. In their population, 49 patients were classified as CRSsNP, and 50 were classified as CRSwNP. Aspirin exacerbated respiratory disease was limited to polyp subjects. An IgE <10 IU/ml was found more commonly in CRSwNP. Immunoglobulin isotype deficiencies were more prevalent in CRSsNP than CRSwNP.

Banerji et al. analyzed data from the WUSM Chronic Rhinosinusitis Outcomes Study [59]. In this study, facial pain/pressure/headache was found to be more prevalent in CRSsNP than CRSwNP, whereas nasal obstruction and hyposmia/anosmia were more prevalent in CRSwNP. Using multivariate analysis, prior surgery, higher sinus CT scan Lund-Mackay scores, and male gender were independent predictors of CRSwNP, whereas allergic status was unrelated to CRS classification.

The author performed a chart review of 100 consecutive patients with CRS seen at Massachusetts General Hospital in Boston, MA [35]. Whereas the WUSM Study excluded patients with known humoral or cellular immune deficiency, cystic

Table 10.6 Demographic, clinical, allergic, immunologic, and microbial differences between CRS without NP (CRSsNP) and CRS with NP (CRSwNP) based on a series of 100 consecutive patients seen at MGH

	Characteristic	CRSsNP	CRSwNP	*P* value for comparison of CRSsNP versus CRSwNP[a]
Demographics[b]	Percent of cases (number)	55	45	
	Sex (% female)	54.5 %	35.6	0.09
	Age	49.8	47.9	0.42
Clinical history	Duration of CRS symptoms	9.0	7.1	0.14
	Antecedent history of SAR	15/55	15/45	0.66
	Ongoing symptoms of SAR	13/55	13/45	0.71
	Previous surgery	52.7 %	77.8 %	0.017
	Avg. # surgeries/patient	.89 ± .15	1.27 ± .16	.09
	Ongoing asthma	21.8 %	51.1 %	.004
	Aspirin sensitivity	1.8 %	17.8 %	.015
	GERD	14.5 %	13.3 %	.91
% Of cases with each symptom	Nasal congestion	72.7 %	80 %	.54
	Anterior or posterior nasal drainage	85.4 %	73.3 %	.21
	Facial pain	50.9 %	9.8 %	<.0001
	Facial pressure	36.4 %	20.0 %	.12
	Headache	29.1 %	11.1 %	.051
	Localized headache	10.9 %	2.2 %	.19
	Chronic cough	18.2 %	20.0 %	.98
	Anosmia	29.1 %	82.2 %	<.0001
	Ageusia	5.4 %	24.4 %	.015
% With medication usage of each type[c]	Antibiotic use >4 x per year	52.7 %	24.4 %	.008
	Use of oral steroids > every 4 months	12.7 %	40.0 %	.004
Pattern of illness	Chronic recurrent infection[d]	11 (20 %)	0	.0017[e]
Unusual bacterial infection	Gram-negative infection	9.1 %	4.4 %	0.62[e]
	Staph. aureus or MRSA	0	4.4 %	0.40[e]
% Of cases with positive allergy skin tests	Pollen allergy	32.7 %	33.3 %	.88
	Dust mite allergy	21.8 %	46.7 %	.016
	Mold allergy	21.8 %	40.0 %	.079
Immune deficiency[f]	IgA or IgM deficiency	5.4 %	0 %	.32
	IgG or IgG subclass deficiency	10.9 %	2.2 %	0.19[e]
	Any hypogamm	12.7 %	2.2 %	.12[e]
Fungal disease	Suspected allergic fungal rhinosinusitis (AFRS)	1.8 %	24.4 %	.001[e]

Reprinted from Hamilos [35]. With permission from Taylor and Francis Group LLC Books

[a]Continuous variables were compared by Student *t*-test. Dichotomous variables were compared using chi-square analysis unless otherwise indicated

[b]The ethnic breakdown of these patients was as follows: Caucasian 91 %, Hispanic/Latino/South American 4 %, Asian 2 %, African-American 1 %, Moroccan 1 %, and Iranian 1 %

[c]Based on information obtained from patients at their initial visit to the clinic

[d]Defined as having ≥4 episodes/year of acute rhinosinusitis exacerbations that respond to antibiotic treatment spaced between periods of wellness

[e]By Fisher exact test

[f]Cystic fibrosis and ciliary dyskinesia syndrome were not represented in this CRS population. Two patients in the CRS without NP group experienced local complications, including one with an oral-antral fistula and one with osteomyelitis of the maxillary sinus. None of the patients had an underlying vasculitis illness (Wegener's, Churg-Strauss syndrome)

fibrosis, and immotile cilia syndrome or those who had undergone a Caldwell-Luc procedure, in the latter study, all patients with CRS were included to give a better appreciation of the frequency of conditions such as hypogammaglobulinemia, gram-negative infection, cystic fibrosis, and oral-antral fistula in a CRS referral population. Patients were classified according to the CRS classification system described above, and the results are summarized in Table 10.6.

In comparing CRSsNP and CRSwNP, several significant differences were noted. As in the WUSM Study, male gender, previous sinus surgery, and hyposmia/anosmia were more common in CRSwNP (although male gender failed to reach statistical significance). Ongoing asthma, aspirin sensitivity, and suspected allergic AFRS were also statistically more prevalent in CRSwNP. As in the WUSM Study, facial pain and headache were more prevalent in CRSsNP.

In terms of medications, antibiotic use >4 x per year was more common in CRSsNP, whereas oral steroid use greater than every 4 months was more frequent in CRSwNP [35]. A pattern of chronic recurrent infection was found in 20 % of the CRSsNP patients but was not found at all in CRSwNP patients. Hypogammaglobulinemia was also more prevalent in CRSsNP, although this did not reach statistical significance. These features suggest that defects in either systemic or local immune function are more clinically relevant in CRSsNP than CRSwNP. In contrast, the prevalence of infection with either a gram-negative bacteria or *Staphylococcus aureus* was not statistically different in these subgroups. The prevalence of pollen allergy was also no different between subgroups, but allergy to house dust mite was more prevalent in patients with CRSwNP.

From a histopathologic perspective, studies comparing CRSsNP and CRSwNP have determined that glandular hyperplasia and submucosal fibrosis are characteristic features of CRSsNP, whereas edematous tissue with sparse glands and little fibrosis is characteristic of CRSwNP [39]. CRSsNP is also characterized by a Th1 cytokine profile and overexpression of TGF-β, whereas CRSwNP are characterized by a Th2 cytokine profile and underexpression of TGF-β [39, 80].

Impact of CRS Phenotype on Response to Surgical or Medical Treatment

Previous reports had also suggested that patients with CRSsNP and CRSwNP respond differently to surgical or medical management. Specifically, Senior et al. found that patients with "advanced mucosal disease" were more likely to show persistence of mucosal disease following functional endoscopic sinus surgery, and these same patients were more likely to undergo revision surgery [81]. Stankiewicz and Deal et al. similarly showed that the presence of nasal polyps or polypoid rhinosinusitis had a negative impact on CRS surgical outcomes [82, 83]. In the latter study of 201 patients, CRSwNP patients had more severe symptoms, higher SNOT-20 scores prior to surgery, less improvement with sinus surgery and higher rate of repeat sinus surgery. Similarly, our group found that symptomatic relapses of CRS following intensive medical treatment occurred sooner in patients with current or past nasal polyps [84]. In that study, patients were assessed for relapses after receiving a combination of oral antibiotics and oral corticosteroids designed to eradicate infection and control mucosal inflammation. Thus, there are important differences in the natural history of patients classified as CRSsNP and CRSwNP with the latter representing the more severe and refractory subtype.

Application of CRS Classification to Clinical Drug Trials

Unfortunately, despite efforts from the RI and EPOS groups to promote application of CRS subtypes to clinical drug trials [85], the term "rhinosinusitis" and the subclassification of CRS into CRSsNP, CRSwNP, and AFRS have not been adopted by the US FDA nor widely adopted for clinical trial design in the USA. For example, in a registration trial of amphotericin B, defined chronic sinusitis did not distinguish patients with CRSsNP versus those with CRSwNP, did not select out patients with AFRS, did not require the presence of a positive fungal stain or culture at entry into the trial, and required "headache" to be a primary outcome variable with complete resolution of headache required to meet the definition of resolution (ClinicalTrials.gov Identifier: NCT00425620).

Application of CRS Classification to Clinical Practice

The application of CRS classification to clinical practice is beyond the scope of this chapter but has been extensively discussed in the EPOS reports [19, 86, 87] and also addressed in a recent review [41].

Potential Future Refinements to CRS Classification

Certain key features of CRS are not well represented in the classification scheme proposed by the RI in 2004 (Fig. 10.2). For instance, the roles of microbial colonization, innate immunity, and allergic ("eosinophilic") inflammation are not clearly described in the context of CRS subtypes. Significant refinements have occurred and should continue to evolve in our understanding of the role of local innate immunity and host-microbial interactions in disease pathogenesis [88] and mechanisms

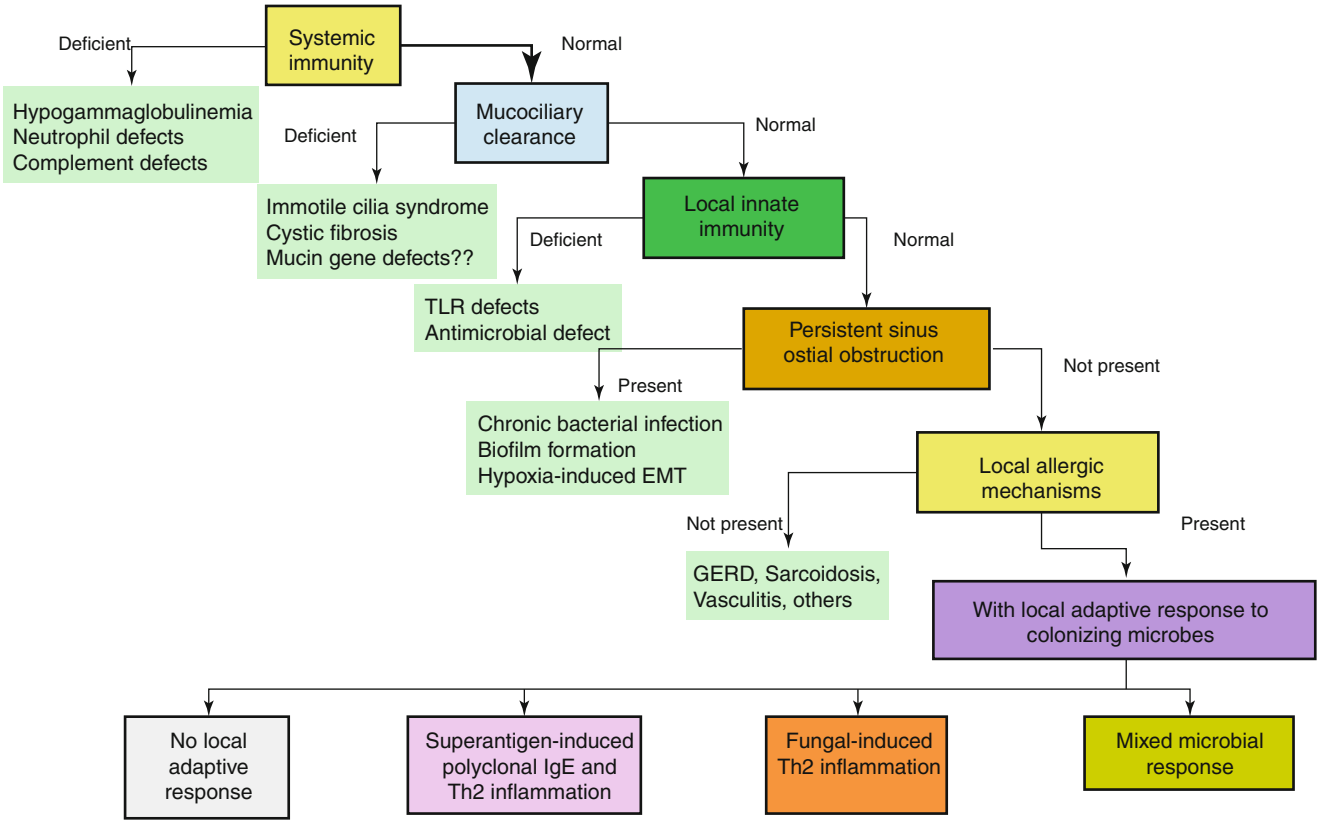


Fig. 10.6 Revised clinicopathologic classification of CRS based on contributive factors (innate/microbial/mucociliary/adaptive) in disease pathogenesis or expression (Note: The contributive factors are not to be considered mutually exclusive)

leading to persistent local adaptive Th2 "allergic" inflammation [89]. For example, biofilm formation on sinonasal mucosal surfaces was first described in 2004 [90] and has now been corroborated in several studies [91, 92]. The presence of bacterial biofilm is associated with more severe preoperative disease (by radiologic and nasal endoscopic scoring) and worse symptoms, endoscopic scores, and persistent mucosal inflammation following endoscopic sinus surgery [93, 94] (Figs. 10.6 and 10.7).

Investigations into host-microbial interactions, innate immunity, and local adaptive Th2 responses are likely to converge in some areas (e.g., uncovering defects in local innate immunity predisposing to bacterial biofilm formation) but diverge in others forcing us to reconsider current paradigms, such as the distinction between CRSsNP and CRSwNP. For example, a subgroup of "polypoid" CRS patients has been described [59], and this subgroup is associated with persistent bacterial infection unlike the low-level bacterial colonization with *Staphylococcus aureus* that typifies CRSwNP (Hamilos, unpublished). It is possible that "polypoid" CRS is more likely to result from a defect in local innate immunity, whereas CRSwNP may be more likely to result from an underlying allergic inflammatory disorder amplified by low-level colonization with superantigen-producing *Staphylococcus aureus*. In support of this, a recently described mouse model of nasal polyp formation is particularly exciting, since it is dependent on local allergic inflammation being amplified by exposure of the mucosal surface to staphylococcal enterotoxin B [47]. Other factors, such as local hypoxia and elaboration of hypoxia-inducing factor-1 alpha (HIF-1α), may also be critical to stimulation of "epithelial-mesenchymal transition" leading to polyp formation [95]. Treatment "recalcitrant" nasal polyposis (CRSwNP) has also been described, and defects in local innate immunity (both congenital and acquired) have been described that may account for this phenotype [96, 97].

Considering the multiplicity of factors that can contribute to the development of CRS, there may be no single paradigm that can adequately embrace all factors and account for overlap between clinical subtypes. Surely, certain clear-cut cases exist. For example, "pure polyp" CRSwNP patients are seen with advanced bilateral polyp disease and no evidence of bacterial infection or fungal colonization. However, other subtypes, such as the "polypoid" subtype, appear to overlap the features of CRSsNP and CRSwNP with repeated sinus infections, microbial colonization, possibly defects in innate immunity, and adaptive Th2 responses all occurring concurrently. Considering the multiplicity of factors that can impact on local mucosal structure and function, perhaps it is best not to be hampered too much by efforts to subclassify CRS until we learn more about its underlying causes.

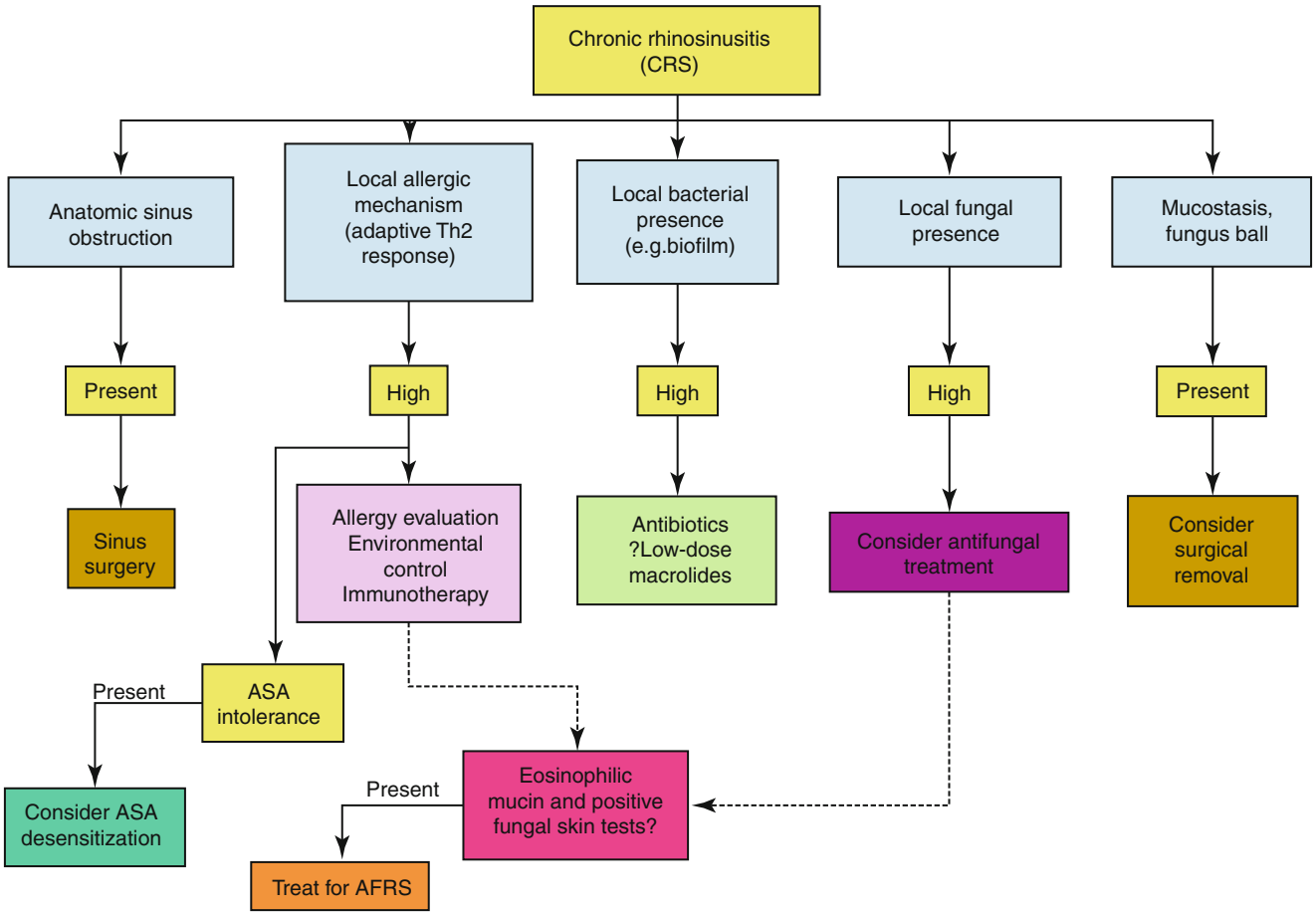


Fig. 10.7 Proposed classification of CRS based on factors most likely to impact on medical or surgical treatment

References

1. Pietrantoni L, Manzini R. Remote results of surgical treatment of polypoid hyperplastic rhinosinusitis. Arch Ital Otol Rinol Laringol. 1953;64 Suppl 13:1–30. Epub 1953/01/01. Esiti a distanza del trattamento chirurgico delle rinosinusiti iperplastiche polipoidi.
2. Clerici E, Leonardelli GB, Pizzetti F. Pathogenesis, histopathology, histochemical and clinical aspects of polypoid hyperplastic rhinosinusitis. Arch Ital Otol Rinol Laringol. 1955;66(6):849–68. Epub 1955/11/01. Patogenesi, istopatologia, istochimica e clinica delle rino-sinusiti iperplastiche polipoidi.
3. Vasconcelos NG. Treatment of rhinosinusitis with specific intravenous vaccines. Arq Bras Med Nav. 1956;17(57):4243–53. Epub 1956/01/01. Tratamento das rinossinusites com vaccinoterapia especifica por via venosa.
4. Baglioni T, Leonardelli GB. Mast cells in chronic polypoid hyperplastic rhinosinusitis. Arch Ital Otol Rinol Laringol. 1956;67(2):214–22. Epub 1956/03/01. Le mastzellen nelle rinosinusiti croniche iperplastiche polipoidi.
5. Begunova TI. Sensitization to microbic allergens in patients with rhinosinusitis by the method of blastotransformation of peripheral blood lymphocytes. Zh Ushn Nos Gorl Bolezn. 1972;32(4):83–8. Epub 1972/07/01. Izuchenie sensibilizatsii k mikrobnym allergenam bol'nykh rinosinusitom metodom blasttransformatsii limfotsitov perifericheskoi krovi.
6. Davison FW. Hyperplastic rhinosinusitis. A twenty year review. Ann Otol Rhinol Laryngol. 1973;82(5):703–8. Epub 1973/09/01.
7. Enzmann H, Kuhn H. Rhinosinusitis polyposa as the only symptom of aspirin intolerance – a rhinorheomanometric diagnosis (author's transl). Laryngol Rhinol Otol. 1977;56(2):151–6. Epub 1977/02/01. Rhinosinusitis polyposa als einziges Symptom einer Aspirin-Intoleranz - eine rhinorheomanometrische Diagnose.
8. Messerklinger W. Role of the lateral nasal wall in the pathogenesis, diagnosis and therapy of recurrent and chronic rhinosinusitis. Laryngol Rhinol Otol. 1987;66(6):293–9. Epub 1987/06/01. Die Rolle der lateralen Nasenwand in der Pathogenese, Diagnose und Therapie der rezidivierenden und chronischen Rhinosinusitis.
9. Sweet JM, Stevenson DD, Simon RA, Mathison DA. Long-term effects of aspirin desensitization–treatment for aspirin-sensitive rhinosinusitis-asthma. J Allergy Clin Immunol. 1990;85(1 Pt 1):59–65. Epub 1990/01/01.
10. Lund VJ, Holmstrom M, Scadding GK. Functional endoscopic sinus surgery in the management of chronic rhinosinusitis. An objective assessment. J Laryngol Otol. 1991;105(10):832–5. Epub 1991/10/01.
11. Kaliner MA, Osguthorpe JD, Fireman P, Anon J, Georgitis J, Davis ML, et al. Sinusitis: bench to bedside. Current findings, future directions. J Allergy Clin Immunol. 1997;99(6 Pt 3):S829–48. Epub 1997/06/01.

12. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg. 1997;117(3 Pt 2):S1–7. Epub 1997/10/23.
13. Turner BW, Cail WS, Hendley JO, Hayden FG, Doyle WJ, Sorrentino JV, et al. Physiologic abnormalities in the paranasal sinuses during experimental rhinovirus colds. J Allergy Clin Immunol. 1992;90(3 Pt 2):474–8. Epub 1992/09/11.
14. Gwaltney Jr JM, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med. 1994;330(1):25–30. Epub 1994/01/06.
15. Bhattacharyya N. Chronic rhinosinusitis: is the nose really involved? Am J Rhinol. 2001;15(3):169–73. Epub 2001/07/17.
16. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg. 2003;129(3 Suppl):S1–32.
17. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol. 2004;114(6 Suppl):155–212. Epub 2004/12/04.
18. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. Otolaryngol Head Neck Surg. 2004;131(6 Suppl):S1–62.
19. Fokkens W, Lund V, Bachert C, Clement P, Helllings P, Holmstrom M, et al. EAACI position paper on rhinosinusitis and nasal polyps executive summary. Allergy. 2005;60(5):583–601. Epub 2005/04/09.
20. Scadding GK, Durham SR, Mirakian R, Jones NS, Drake-Lee AB, Ryan D, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. Clin Exp Allergy. 2008;38(2):260–75. Epub 2008/01/03.
21. Slavin RG, Spector SL, Bernstein IL, Kaliner MA, Kennedy DW, Virant FS, et al. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6 Suppl):S13–47. Epub 2006/01/19.
22. American Academy of Pediatrics Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108(3):798–808. Epub 2001/09/05.
23. Jones NS. Current concepts in the management of paediatric rhinosinusitis. J Laryngol Otol. 1999;113(1):1–9. Epub 1999/05/26.
24. Chan KH, Abzug MJ, Coffinet L, Simoes EA, Cool C, Liu AH. Chronic rhinosinusitis in young children differs from adults: a histopathology study. J Pediatr. 2004;144(2):206–12. Epub 2004/02/05.
25. Coffinet L, Chan KH, Abzug MJ, Simoes EA, Cool C, Liu AH. Immunopathology of chronic rhinosinusitis in young children. J Pediatr. 2009;154(5):754–8. Epub 2009/01/23.
26. Lusk R. Chronic rhinosinusitis: contrasts between children and adult patients. Clin Allergy Immunol. 2007;20:287–98. Epub 2007/05/31.
27. Wald ER. Sinusitis. Pediatr Ann. 1998;27(12):811–8. Epub 1998/12/29.
28. Emedicine/WebMD. Accessed 19 Jan 2009. Centers for Disease Control and Prevention. Nonspecific upper respiratory tract infection. http://www.cdc.gov/getsmart/campaign-materials/info-sheets/adult-nurti.pdf. Accessed 1 Nov 2010.
29. Lusk RP, McAlister B, el Fouley A. Anatomic variation in pediatric chronic sinusitis: a CT study. Otolaryngol Clin North Am. 1996;29(1):75–91. Epub 1996/02/01.
30. Bolger WE, Butzin CA, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. Laryngoscope. 1991;101(1 Pt 1):56–64. Epub 1991/01/01.
31. Jones NS, Strobl A, Holland I. A study of the CT findings in 100 patients with rhinosinusitis and 100 controls. Clin Otolaryngol Allied Sci. 1997;22(1):47–51. Epub 1997/02/01.
32. Danese M, Duvoisin B, Agrifoglio A, Cherpillod J, Krayenbuhl M. Influence of naso-sinusal anatomic variants on recurrent, persistent or chronic sinusitis. X-ray computed tomographic evaluation in 112 patients. J Radiol. 1997;78(9):651–7. Epub 1998/04/16. Influence des variantes anatomiques nasosinusales sur les sinusites recidivantes, persistantes ou chroniques. Evaluation TDM chez 112 patients.
33. Al-Qudah M. The relationship between anatomical variations of the sino-nasal region and chronic sinusitis extension in children. Int J Pediatr Otorhinolaryngol. 2008;72(6):817–21. Epub 2008/04/09.
34. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics. 1991;87(3):311–6. Epub 1991/03/01.
35. Hamilos DL. Chronic rhinosinusitis patterns of illness. In: Hamilos DL, Baroody FM, editors. Chronic rhinosinusitis: pathogenesis and medical management, vol. 20. New York: Informa Healthcare; 2007. p. 1–13.
36. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc. 2011;86(5):427–43. Epub 2011/04/15.
37. Kern EB. Sinusitis. J Allergy Clin Immunol. 1984;73(1 Pt 1):25–31. Epub 1984/01/01.
38. Malekzadeh S, Hamburger MD, Whelan PJ, Biedlingmaier JF, Baraniuk JN. Density of middle turbinate subepithelial mucous glands in patients with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2002;127(3):190–5. Epub 2002/09/26.
39. Watelet JB, Claeys C, Perez-Novo C, Gevaert P, Van Cauwenberge P, Bachert C. Transforming growth factor beta1 in nasal remodeling: differences between chronic rhinosinusitis and nasal polyposis. Am J Rhinol. 2004;18(5):267–72. Epub 2004/12/14.
40. Jankowski R, Bouchoua F, Coffinet L, Vignaud JM. Clinical factors influencing the eosinophil infiltration of nasal polyps. Rhinology. 2002;40(4):173–8. Epub 2003/01/16.
41. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. J Allergy Clin Immunol. 2011;128(4):693–707, quiz 8–9. Epub 2011/09/06.
42. Ponikau JU, Sherris DA, Kern EB, Homburger HA, Frigas E, Gaffey TA, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc. 1999;74(9):877–84. Epub 1999/09/17.
43. Shin SH, Ponikau JU, Sherris DA, Congdon D, Frigas E, Homburger HA, et al. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. J Allergy Clin Immunol. 2004;114(6):1369–75. Epub 2004/12/04.
44. Ling M, Hamilos DL. Are we closer to understanding the pathophysiology of chronic rhinosinusitis? Clin Exp Allergy. 2011;41(2):144–6. Epub 2011/01/15.
45. Bhattacharyya N, Lee KH. Chronic recurrent rhinosinusitis: disease severity and clinical characterization. Laryngoscope. 2005;115(2):306–10. Epub 2005/02/04.
46. Larsen PL, Tos M. Origin of nasal polyps: an endoscopic autopsy study. Laryngoscope. 2004;114(4):710–9. Epub 2004/04/06.
47. Kim DW, Khalmuratova R, Hur DG, Jeon SY, Kim SW, Shin HW, et al. Staphylococcus aureus enterotoxin B contributes to induction of nasal polypoid lesions in an allergic rhinosinusitis murine model. Am J Rhinol Allergy. 2011;25(6):e255–61. Epub 2011/12/22.

48. Drake-Lee AB, McLaughlan P. Clinical symptoms, free histamine and IgE in patients with nasal polyposis. Int Arch Allergy Appl Immunol. 1982;69(3):268–71. Epub 1982/01/01.
49. Van Zele T, Gevaert P, Watelet JB, Claeys G, Holtappels G, Claeys C, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. J Allergy Clin Immunol. 2004;114(4):981–3. Epub 2004/10/14.
50. Bernstein JM, Allen C, Rich G, Dryja D, Bina P, Reiser R, et al. Further observations on the role of Staphylococcus aureus exotoxins and IgE in the pathogenesis of nasal polyposis. Laryngoscope. 2011;121(3):647–55. Epub 2011/02/24.
51. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. J Allergy Clin Immunol. 2006;118(4):773–86, quiz 87–8. Epub 2006/10/13.
52. Taylor MJ, Ponikau JU, Sherris DA, Kern EB, Gaffey TA, Kephart G, et al. Detection of fungal organisms in eosinophilic mucin using a fluorescein-labeled chitin-specific binding protein. Otolaryngol Head Neck Surg. 2002;127(5):377–83. Epub 2002/11/26.
53. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Congdon DJ, Adolphson CR, et al. Striking deposition of toxic eosinophil major basic protein in mucus: implications for chronic rhinosinusitis. J Allergy Clin Immunol. 2005;116(2):362–9. Epub 2005/08/09.
54. Nussenbaum B, Marple BF, Schwade ND. Characteristics of bony erosion in allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg. 2001;124(2):150–4.
55. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal sinusitis. I. Demographics and diagnosis. J Allergy Clin Immunol. 1998;102(3):387–94. Epub 1998/10/13.
56. Hutcheson PS, Schubert MS, Slavin RG. Distinctions between allergic fungal rhinosinusitis and chronic rhinosinusitis. Am J Rhinol Allergy. 2010;24(6):405–8. Epub 2010/12/15.
57. Bent 3rd JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994;111(5):580–8.
58. Baraniuk JN, Maibach H. Pathophysiological classification of chronic rhinosinusitis. Respir Res. 2005;6:149. Epub 2005/12/21.
59. Banerji A, Piccirillo JF, Thawley SE, Levitt RG, Schechtman KB, Kramper MA, et al. Chronic rhinosinusitis patients with polyps or polypoid mucosa have a greater burden of illness. Am J Rhinol. 2007;21(1):19–26. Epub 2007/02/08.
60. Hessler JL, Piccirillo JF, Fang D, Vlahiotis A, Banerji A, Levitt RG, et al. Clinical outcomes of chronic rhinosinusitis in response to medical therapy: results of a prospective study. Am J Rhinol. 2007;21(1):10–8. Epub 2007/02/08.
61. Bhattacharyya N. The economic burden and symptom manifestations of chronic rhinosinusitis. Am J Rhinol. 2003;17(1):27–32. Epub 2003/04/16.
62. Behin F, Behin B, Behin D, Baredes S. Surgical management of contact point headaches. Headache. 2005;45(3):204–10. Epub 2005/04/20.
63. Parsons DS, Batra PS. Functional endoscopic sinus surgical outcomes for contact point headaches. Laryngoscope. 1998;108(5):696–702. Epub 1998/05/20.
64. Rosbe KW, Jones KR. Usefulness of patient symptoms and nasal endoscopy in the diagnosis of chronic sinusitis. Am J Rhinol. 1998;12(3):167–71. Epub 1998/07/08.
65. Bhattacharyya T, Piccirillo J, Wippold 2nd FJ. Relationship between patient-based descriptions of sinusitis and paranasal sinus computed tomographic findings. Arch Otolaryngol Head Neck Surg. 1997;123(11):1189–92. Epub 1997/11/21.
66. West B, Jones NS. Endoscopy-negative, computed tomography-negative facial pain in a nasal clinic. Laryngoscope. 2001;111(4 Pt 1):581–6. Epub 2001/05/19.
67. Schreiber CP, Hutchinson S, Webster CJ, Ames M, Richardson MS, Powers C. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "sinus" headache. Arch Intern Med. 2004;164(16):1769–72. Epub 2004/09/15.
68. Tarabichi M. Characteristics of sinus-related pain. Otolaryngol Head Neck Surg. 2000;122(6):842–7.
69. Ozturk O, Oz F, Karakullukcu B, Oghan F, Guclu E, Ada M. Hoarseness and laryngopharyngeal reflux: a cause and effect relationship or coincidence? Eur Arch Otorhinolaryngol. 2006;263(10):935–9. Epub 2006/07/04.
70. de Shazo RD, Stringer SP. Atrophic rhinosinusitis: progress toward explanation of an unsolved medical mystery. Curr Opin Allergy Clin Immunol. 2011;11(1):1–7. Epub 2010/12/16.
71. Hildenbrand T, Weber RK, Brehmer D. Rhinitis sicca, dry nose and atrophic rhinitis: a review of the literature. Eur Arch Otorhinolaryngol. 2011;268(1):17–26. Epub 2010/09/30.
72. Stankiewicz JA, Chow JM. Nasal endoscopy and the definition and diagnosis of chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2002;126(6):623–7.
73. Casiano RR. Correlation of clinical examination with computer tomography in paranasal sinus disease. Am J Rhinol. 1997;11(3):193–6. Epub 1997/05/01.
74. Stewart MG, Sicard MW, Piccirillo JF, Diaz-Marchan PJ. Severity staging in chronic sinusitis: are CT scan findings related to patient symptoms? Am J Rhinol. 1999;13(3):161–7. Epub 1999/07/07.
75. Tarp B, Fiirgaard B, Christensen T, Jensen JJ, Black FT. The prevalence and significance of incidental paranasal sinus abnormalities on MRI. Rhinology. 2000;38(1):33–8. Epub 2000/04/26.
76. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. Otolaryngol Head Neck Surg. 2010;143(1):147–51.
77. Rosenfeld RM, Andes D, Bhattacharyya N, Cheung D, Eisenberg S, Ganiats TG, et al. Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg. 2007;137(3 Suppl):S1–31.
78. Stankiewicz JA, Chow JM. A diagnostic dilemma for chronic rhinosinusitis: definition accuracy and validity. Am J Rhinol. 2002;16(4):199–202. Epub 2002/09/12.
79. Hwang PH, Irwin SB, Griest SE, Caro JE, Nesbit GM. Radiologic correlates of symptom-based diagnostic criteria for chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2003;128(4):489–96.
80. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy. 2006;61(11):1280–9. Epub 2006/09/28.
81. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza D. Long-term results of functional endoscopic sinus surgery. Laryngoscope. 1998;108(2):151–7. Epub 1998/02/24.

82. Watelet JB, Annicq B, van Cauwenberge P, Bachert C. Objective outcome after functional endoscopic sinus surgery: prediction factors. Laryngoscope. 2004;114(6):1092–7. Epub 2004/06/05.
83. Deal RT, Kountakis SE. Significance of nasal polyps in chronic rhinosinusitis: symptoms and surgical outcomes. Laryngoscope. 2004;114(11):1932–5. Epub 2004/10/29.
84. Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. Am J Rhinol. 2002;16(6):303–12. Epub 2003/01/07.
85. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: developing guidance for clinical trials. J Allergy Clin Immunol. 2006;118(5 Suppl):S17–61. Epub 2006/11/07.
86. Thomas M, Yawn BP, Price D, Lund V, Mullol J, Fokkens W. EPOS Primary Care Guidelines: European Position Paper on the Primary Care Diagnosis and Management of Rhinosinusitis and Nasal Polyps 2007 – a summary. Prim Care Respir J. 2008;17(2):79–89. Epub 2008/04/29.
87. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1–12. Epub 2012/04/04.
88. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124(1):37–42. Epub 2009/06/30.
89. Reh DD, Wang Y, Ramanathan Jr M, Lane AP. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. Am J Rhinol Allergy. 2010;24(2):105–9. Epub 2010/03/27.
90. Cryer J, Schipor I, Perloff JR, Palmer JN. Evidence of bacterial biofilms in human chronic sinusitis. ORL J Otorhinolaryngol Relat Spec. 2004;66(3):155–8. Epub 2004/08/19.
91. Ferguson BJ, Stolz DB. Demonstration of biofilm in human bacterial chronic rhinosinusitis. Am J Rhinol. 2005;19(5):452–7. Epub 2005/11/08.
92. Sanclement JA, Webster P, Thomas J, Ramadan HH. Bacterial biofilms in surgical specimens of patients with chronic rhinosinusitis. Laryngoscope. 2005;115(4):578–82. Epub 2005/04/05.
93. Singhal D, Psaltis AJ, Foreman A, Wormald PJ. The impact of biofilms on outcomes after endoscopic sinus surgery. Am J Rhinol Allergy. 2010;24(3):169–74. Epub 2010/06/12.
94. Hochstim CJ, Masood R, Rice DH. Biofilm and persistent inflammation in endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2010;143(5):697–8.
95. Shin HW, Cho K, Kim DW, Han DH, Khalmuratova R, Kim SW, et al. Hypoxia-inducible factor 1 mediates nasal polypogenesis by inducing epithelial-to-mesenchymal transition. Am J Respir Crit Care Med. 2012;185(9):944–54. Epub 2012/02/11.
96. Endam LM, Bosse Y, Filali-Mouhim A, Cormier C, Boisvert P, Boulet LP, et al. Polymorphisms in the interleukin-22 receptor alpha-1 gene are associated with severe chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2009;140(5):741–7.
97. Ramanathan Jr M, Lee WK, Dubin MG, Lin S, Spannhake EW, Lane AP. Sinonasal epithelial cell expression of toll-like receptor 9 is decreased in chronic rhinosinusitis with polyps. Am J Rhinol. 2007;21(1):110–6. Epub 2007/02/08.

Chapter 11
Sinusitis, Rhinitis, Asthma, and the Single Airway Hypothesis

Christopher C. Chang

Introduction

Diseases of the sinuses are frequently a result of a dysregulation of immunologic function that may range from infection to allergic or autoimmune diseases. Sinus disease may be a part of multisystem or systemic conditions that frequently also involve the nasal passages, eyes, upper and lower airways, and even the gastrointestinal tract. It has been proposed that parts of the human airway from top to bottom, including the nasal passages, sinuses, pharynx, bronchi, and bronchioles, are all of the same histomorphological makeup. The corollary of this theory is that a common airway will be uniformly susceptible to any insults or disease processes. Diseases of the lower and upper respiratory tract, therefore, are all intricately linked. The truth is, as always, not that simple. The reason for the interrelationships between these diseases may not be simply based on a single airway theory, but on systemic changes in immunologic paradigms of the individual during his or her lifetime. For example, immunologic and autoimmune conditions that affect both the sinuses and the lower airway are well known, as in the case of aspirin-exacerbated respiratory disease and granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis). The immunologic basis that leads to the susceptibility of both sinuses and lower airways in these diseases is a subject of ongoing research.

Epidemiological evidence for a connection between the upper and lower airways is abundant. For example, treatment of diseases of the upper airway often leads to clinical improvement in lower airway symptoms. The impact of upper airway inflammation on lower airway diseases such as asthma has been clearly demonstrated, but the mechanisms of this interaction are not entirely clear. It may not be simply explained by a similar epithelial lining of the two structures [1].

Allergic Rhinitis, Sinusitis, and Asthma

Historical Evidence for a Relationship Between Allergic Rhinitis, Sinusitis, and Asthma

The idea that there are common features in upper and lower inflammatory airway disease was described in some of the earliest recorded histories of medicine. Conditions consistent with asthma had been described in Egyptian recorded medical history over 2,400 years ago. The term "asthma" first appeared in the Greek epic work "The Iliad" by Homer. In the twelfth century, Maimonides, in his "Treatise of Asthma," actually described a patient whose asthma symptoms frequently started as a common cold.

In 1819, J Bostock describes his own affliction in his paper, "A Periodical Affection of the Eyes and Chest," in which he describes a condition that includes "the sneezings" and "a farther sensation of tightness in the chest, and a difficulty of breathing, with a general irritation of the fauces and trachea," thus linking lower and upper airways.

C.C. Chang, MD, PhD, MBA, FAAAAI, FACAAI
Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: cchang@nemours.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_11,

In 1873, Charles Blackley, one of the fathers of allergology, described nasal and bronchial symptoms after exposure to pollen grains [2]. In 1883, it was proposed, but not proven, that aspiration of nasal secretions could lead to asthma exacerbation. This theory has in fact never been proven, and modern studies have revealed that radiolabeled allergen introduced into the nose found its way not to the lower respiratory system, but to the digestive system [3, 4]. This does not, on the other hand, discount the possibility of upper airway pathology influencing lower airway symptoms. Even in the absence of direct contact or direct transmission of the inciting agent, other mechanisms may be in play.

In 1886, F.H. Bosworth published an article entitled, "Hay Fever, Asthma, and Allied Affections," in which he describes the function of the nose in keeping tissues moist and mucous hydrated. He also addresses both "hay fever" and "hay asthma," thereby also forging a link between upper and lower airways.

Epidemiological Evidence of a One Airway Disease

Evidence of a relationship between the upper and lower airways can be deemed from examination of epidemiological studies of three conditions, rhinitis, sinusitis, and asthma. It should be noted that these comparisons do not necessarily reflect a role for atopy by itself, although many studies have specifically addressed the association of "allergic" rhinitis and asthma or sinusitis. In fact, it will be seen that these relationships may also exist when atopy is not involved, as in the case of nonallergic asthma, chronic obstructive pulmonary disease, or chronic rhinitis, to name a few conditions in which atopy may be irrelevant. Thus, the unified airway concept extends beyond the borders of allergy [5].

Rhinitis and Asthma

It has long been known that patients with allergic rhinitis have a higher incidence of asthma, and vice versa [6]. The rates vary from region to region, but a comprehensive review of the literature presented by Cruz et al. in their ARIA report describes coexistence of these two conditions in almost all regions of the world [7]. One of the exceptions was in certain areas in China, where only 6.2 % of asthmatic patients described concurrent nasal rhinitis symptoms. The rates of asthma in rhinitis patients and vice versa are presented in Table 11.1. Much of the available data on the impact of allergic rhinitis on asthma is derived from the International Study of Asthma and Allergies in Childhood (ISAAC). Perennial rhinitis is considered to be a risk factor for nonatopic asthma [20, 21]. In the European Community Respiratory Health Survey, evaluation of 20–44-year-old subjects revealed that asthma is more common in patients with both atopic and nonatopic individuals. Moreover, even in nonasthmatic patients, those with symptoms of rhinitis were more likely to have concurrent bronchial hyperresponsiveness. In a study in Rochester, Minnesota, health-care costs for patients with concurrent asthma and allergic rhinitis were found to be higher than for patients with asthma alone [22].

Further supporting the common airway principle is the fact that there are nonallergic respiratory diseases that demonstrate an association between the lower and upper airways. Disease processes such as bronchiectasis, cystic fibrosis, primary cilia dyskinesia, α1-antitrypsin deficiency, smoking, and Young's syndrome all have concurrent upper and lower airway symptoms [23].

In general, the increase in the rates of asthma in the past 30 years has been accompanied by an increase in the incidence of allergic rhinitis [24–26]. In "modern" Asian countries such as Japan, the prevalence of allergic rhinitis increased from 3.8 % in 1984 to 32 % as reported in an AIRA update in 2008. The prevalence of asthma similarly increased from 4.6 % in 1992 to 9.1 % in 2008 [25]. In "poorer" countries, the rates are still much lower, an example being Tibet, in which the rates of allergic rhinitis, current wheezing, and asthma were 5.2, 0.8, and 1.1 %, respectively [27]. In developing countries within Asia, the rates have already started to rise, mimicking the trend that has already occurred in developed countries. Between 1995 and 2008, the prevalence of asthma in Thailand increased from 12.2 to 14.5 %, while the prevalence of allergic rhinitis increased from 37.9 to 50.6 % [28].

A study of 22 grass allergic patients and 10 controls investigated the existence of bronchial hyperresponsiveness (BHR) and airway inflammation in those with allergic rhinitis. In this study, the authors used bronchoprovocation with histamine and measurements of exhaled nitric oxide and exhaled breath concentrate levels of NO and pH to evaluate the presence of airway inflammation. In allergic patients with BHR, they found that BHR and FeNO levels increased during the pollen season [29]. Further evidence of the link between rhinitis and asthma is presented in a study on 20 grass allergic patients, in whom a number of functional and inflammatory parameters including nasal airflow, FEV1, eosinophils, IL4, and interferon-γ levels were measured. A Th2 cytokine profile correlated with airway flow and was present in both the upper and lower airways [30]. Studies such as these establish a link that supports the unified airway concept.

Table 11.1 Rates of asthma in allergic rhinitis patients

	Place where research was done	Number of subjects in research	Population chosen in research	Asthma in allergic rhinitis patient	Asthma parameters	Allergy rhinitis parameters	Comments
1	Sweden (nested case controlled study) [8]	$N=15{,}813$ Doctor-diagnosed asthma ($n=235$) Controls ($n=2{,}044$)	Random sample from general population aged 21–51 years	Adult-onset doctor-diagnosed asthma was associated with occurrence of noninfectious asthma (OR: 5.4)	Doctor-diagnosed asthma	Comprehensive respiratory questionnaire	Chronic rhinitis is associated with increased risk for adult-onset asthma
2	Arizona, USA (nested case controlled study) [9]	Doctor confirmed asthma ($n=173$) Controls who reported no asthma or shortness of breath with wheezing ($n=2{,}177$)	Random sample from general population	Rhinitis was found to be significant risk factor Crude (OR = 4.13) Adjusted OR = 3.21 (adjusted for years of follow-up, age, sex, atopic status, smoking status, and presence of COPD)	Doctor-diagnosed asthma	Presence of rhinitis by questionnaire	1. Rhinitis increased the risk development of asthma both by about three times among atopic nonatopic patients and by more than 5 times among patients with highest IgE titers 2. Patients with rhinitis with persistent and severe nasal symptoms and a personal history of doctor confirmed sinusitis had an additional increased risk of asthma development
3	Sweden (multivariate logistic regression analysis, cross-sectional study) [10]	$N=1{,}370$	Random sample of adults aged 20–44 years	Onset of asthma was associated with AR (OR = 4.9), sensitization to pets (OR:2.4), and smoking (OR:3.0) Asthma was strongly associated with AR among atopics (OR = 5.7), but asthma and rhinitis also tended to be related among nonatopic (OR = 3.5)	Postal questionnaires were used as follow-up after skin tests	Skin prick tests were conducted. Onset of AR was associated with sensitization to birch (OR:6.5), parietaria (OR:7.4), and pets (OR:3)	Onset of asthma is strongly associated with atopics They tend to be associated in nonasthmatics as well
4	Sao Paulo, Brazil [11]	6–7-year-old ($n=3{,}033$) 13–14-year-old ($n=3{,}487$)	School children living in Sao Paulo			ISAAC questionnaire	Prevalence of severe asthma was higher among children and adolescents with asthma, rhinitis, and eczema combined, and each one had a higher risk individually for asthma

(continued)

Table 1.1 (continued)

	Place where research was done	Number of subjects in research	Population chosen in research	Asthma in allergic rhinitis patient	Asthma parameters	Allergy rhinitis parameters	Comments
5	Pelotas, Brazil (birth cohort study followed up to 90 years, multivariate analysis) [12]	$n=494$	Children born in the year 1993	The prevalence of asthma was found to be 12.8 % (95 % CI:10–15.9 %) In the multivariate analysis, risk factors such as nonwhite skin color were found to be associated with a relative risk (RR) of 1.9 (95 % CI1.1–3.3 %); family history of asthma, RR:2.8 (95 % CI:1.5–5.1); AR, RR:2.6 (95 % CI:1.5–4.4); and maternal smoking during pregnancy, RR:1.7 (95 % CI:1–2.9)	Standardized and validated asthma questionnaire, based on ISAAC, was applied		Rhinitis is demonstrated as a risk factor for asthma
6	Denmark (12-year follow-up study) [13]	$n=281$	Random population sample of individuals aged 7–17 years without asthma	At follow-up, 37.9 % of individuals with BHR to histamine and 30 % of individuals with EIB had developed current asthma, compared with only 5 % of individuals in whom these test results were negative In patients with BHR to histamine, parental asthma, OR:12.6 (95 % CI:1.5–108.5); furred pet ownership, OR:6.0 (95 % CI:1.2–19.6); and dermatitis and/or rhinitis in childhood, OR:2.2 (95 % CI:1.1–5.1), predicted the subsequent development of asthma	BHR to histamine, EIB		Rhinitis is a risk factor for asthma
7	Arizona, USA (large longitudinal cohort study, Tucson Children's Respiratory Study) [14]	Among $n=1,246$ originally enrolled $n=1,024$ children who completed questionnaire were included	Children between the ages of 6 and 18 were included	After adjusting for sex, skin test reactivity, and parental asthma, both rhinitis, OR:2.47 (CI:1.84–3.30), and sinusitis, OR:1.54 (CI:1.11–2.14), were associated with an increased risk of cough and wheezing	Cough or wheezing or both by questionnaire		Rhinitis is significantly associated with cough and wheezing

8	Pisa (cohort study with a follow-up of 5 years) [15]	$N=1,670$	Subjects were greater than or equal to 15 years old and had no positive history of cough apart from the colds at the baseline survey; among them, 299 (18 %) had rhinitis at baseline	16 % of the subjects with rhinitis had developed any cough apart from colds, when compared to only 10 % of the subjects without rhinitis, OR:1.7 (95 % CI:1.2–2.5)	Information on cough rhinitis was obtained by standardized questionnaire		Rhinitis remains significantly associated with an increased risk of cough after adjusting for age, gender, smoking, and occupational exposure
9	Italy (7-year follow-up study) [16]	$n=28$	Homogenous population of nonasthmatic children with AR (6–15 years)	After 7 years, none of the children with negative methacholine test developed asthma, but only 2 out 13 hyperreactive to methacholine reported asthma symptoms			
9	Europe (ECRHS, international cross-sectional study) [17]	$N=90,478$ adults		The risk of asthma increased from 2.0 % in subjects without rhinitis to 6.7 % in subjects with rhinitis only when exposed to pollen, 11.9 % in subjects when exposed to animals, and 18.8 % in subjects with rhinitis when exposed to either pollen or animal	Pulmonary function tests, detailed ECRHS questionnaire	IgE measurements	In all countries, rhinitis was significantly associated with asthma after adjustment for IgE, parental history of asthma
10	Brescia, Italy (follow-up study up to 10 years) [18]	$N=99$ allergic patients 44 suffered from AR alone, 12 from allergic asthma alone, 43 from both AR and asthma		31.8 % of the AR patients developed allergic asthma, and 50 % of the patients with allergic asthma developed allergic rhinitis			
11	Sweden (follow-up study for 7 years) [19]	$N=94$ with atopic dermatitis		43 % developed asthma and 45 % developed AR			

It is important to appreciate that rhinitis, itself, is a risk factor for asthma, whether or not the rhinitis is allergic in nature. In other words, the commonality between the upper and lower airway responsiveness cannot simply be attributed to a state of "atopy" [31]. This is an important consideration in our discussion on the pathogenesis of the one airway, one disease concept below.

Rhinosinusitis and Asthma

The association between rhinosinusitis and asthma has been studied, and results have been varied. In one series of 590 patients, the prevalence of asthma in allergic rhinitis, chronic sinusitis, and nonallergic rhinitis patients was 33, 42, and 8.7 %, respectively [32]. Other sources estimate that between 60 and 90 % of patients with chronic rhinosinusitis may have evidence of asthma [33, 34]. The converse is also true, as up to 80 % of asthma patients may have evidence of chronic rhinosinusitis [34]. Morphological abnormalities of the sinuses have also been reported to occur more frequently in asthmatics [35].

A Swedish study investigated the relationship between symptoms of asthma and chronic rhinosinusitis. The group utilized data extracted from the West Sweden Asthma Study and found that 2.1 % of the general population had "multi-symptom" asthma. They determined that symptoms of chronic rhinosinusitis were associated with a higher risk of having multi-symptom asthma rather than fewer-symptom asthma. Moreover, they found that the incidence of allergic rhinitis was no different between the multi- and fewer-symptom asthma groups but that rhinorrhea and nasal congestion were higher in the multisystem group [36].

A study of 35 subjects with severe steroid-dependent asthma and 34 subjects with mild-to-moderate asthma revealed that 74 % of the former group and 70 % of the latter group also had symptoms of sinonasal disease. It was also noted that 100 % of the severe asthmatics and 88 % of mild-to-moderate asthmatics had abnormal CT scans. The CT scan and clinical scores appeared to be more severe in the severe asthma group [37]. This finding was further confirmed by Brinke et al., who discovered that the frequency of abnormal CT scans in severe asthma patients was 84 %. They also noted that there was a correlation between sinusitis in severe asthma patients and sputum eosinophilia, providing an additional link between the upper and lower airways [38]. A correlation has also been described between markers of airway inflammation such as exhaled nitric oxide (eNO) and sinus CT scores and between eNO levels and nasal polyps [39].

Rhinosinusitis and Rhinitis

It has been estimated that allergic rhinitis may play a role in up to 30 % of cases of acute sinusitis and may be significantly greater in cases of chronic sinusitis [40]. Twenty-six percent of patients with rhinosinusitis have been found to have concomitant allergic rhinitis [41]. Another study of 40 allergic rhinitis patients and 30 controls showed that 67.5 % of perennial allergic rhinitis patients had evidence of sinusitis on CT scan, whereas these findings were present in only 33.4 % of controls [42]. It has also been found that most patients with chronic rhinosinusitis are more likely to be sensitized to perennial allergens over seasonal allergens. On the other hand, in examining the relationship between in vitro IgE sensitization to allergens (atopy) and the degree of severity of rhinosinusitis, there appeared to be no significant correlation [43].

Rhinosinusitis and Upper and Lower Airway Infection

Chronic rhinosinusitis describes a persistent inflammatory state in the sinuses that may or may not be a result of an infectious process. Both bacteria and viruses can infect the sinuses, and common bacteria found in sinusitis among immunocompetent hosts include *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*, and *Staphylococcus aureus*. Viruses frequently involve the sinuses in common upper respiratory tract infections and may play a pivotal role in the overlap between sinusitis and asthma. Although previous studies have failed to detect the presence of viruses in biopsy samples from the sinus mucosa in patients with chronic rhinosinusitis, the possibility still remains that a viral infection may have provided an initial inflammatory stimulus [44].

Pathogenic Pathways That Link the Upper and Lower Airways

The pathogenic links between upper and lower airways have been attributed to various systems, including the nervous, cardiac, and pulmonary systems. The physical proximity and contiguous nature of the upper and lower airways can lead to common disease mechanisms. Similarities in the histomorphology of the two parts of the airway may also contribute to the comorbidity

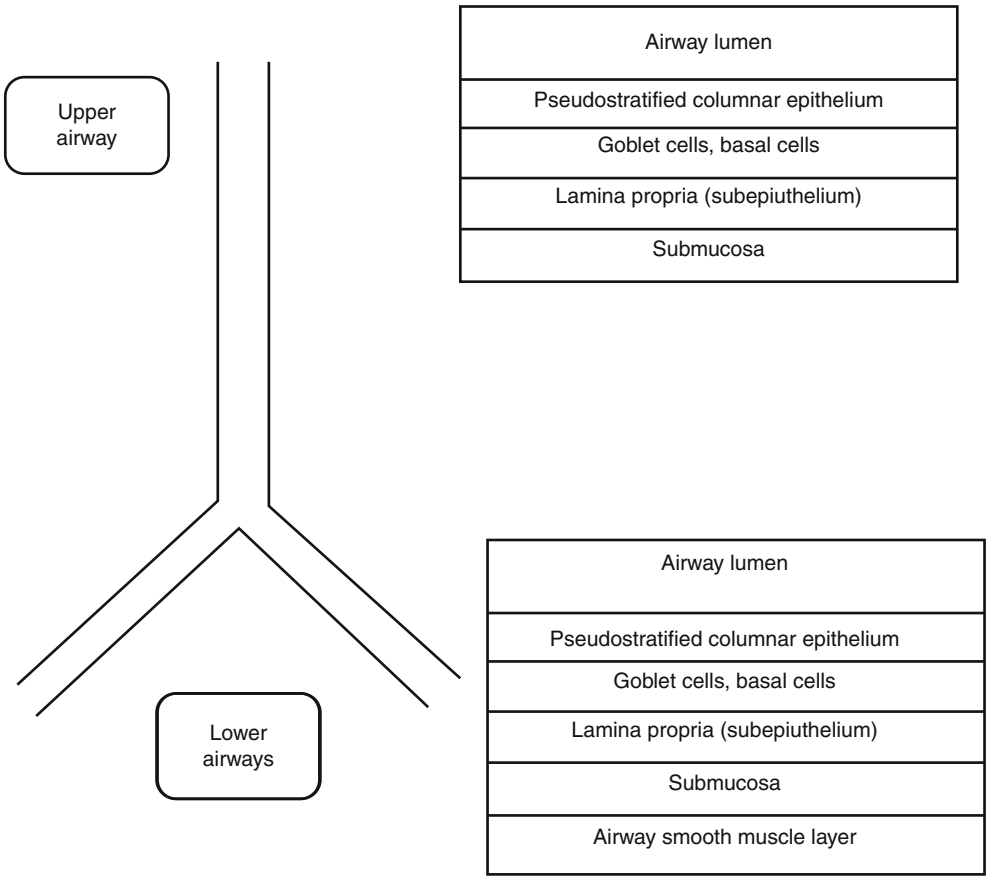


Fig. 11.1 Histopathologic and immunologic parallels between the upper and lower airways: a schematic representation

between sinus disease, upper airway allergies and infections, and lower airway disease such as asthma and bronchiolitis. In addition, immune mechanisms, both local and systemic, may play a role in the unified airway hypothesis (Fig. 11.1).

Functions of the Nose

The nose possesses several normal functions that may explain a relationship between nasal disease and lower airway disease (Table 11.2) [45]. Cilia in the nose are important in filtering out foreign particulate material, including allergens and adjuvants that may potentiate allergenic effects. Moreover, air that passes through the nose and around the nasal turbinates becomes "air-conditioned," so as to reduce its ability to trigger a hypersensitivity reaction [45]. The nose also serves to humidify inhaled air. Slowing down the flow of air through the generation of turbinate air by nasal turbulence helps to keep the mucosa surfaces hydrated for subsequent breaths.

Normal breathing draws air in through the nose. If the nose is not patent, then we become mouth breathers. When we become mouth breathers, all of the normal functions of the nose are not utilized fully. Cold, dry, unfiltered air has the potential to lead to asthma symptoms [46, 47]. Rhinitis sicca, a form of dry nose syndrome or atrophic rhinitis, is an example whereby the normal air-conditioning function is compromised which could exacerbate or serve as a nidus for sinusitis and/or asthma [48]. The nose also provides us with a sense of smell, which can serve as a protective mechanism to avoid areas of potentially harmful inhalants [49].

Anatomical and Histomorphological Comparison of the Upper and Lower Airways

The mucosal surfaces of the lower and upper airways demonstrate significant similarities. Both the lower and upper airway mucosae consist of a pseudostratified columnar ciliated epithelium which covers a reticular basement membrane. Ciliated cells predominate over goblet cells, and triangular basal cells also populate the tracheal and bronchial epithelium [50]. The

Table 11.2 Functions of the nose and upper airway

Warming	Prevents cold-air-induced bronchospasm
Filtering	Limits access of allergens and irritants to the lower airway
Humidification	Prevents dry-air-induced bronchial hyperresponsiveness (especially in EIB)
Smell	Helps us avoid danger signals
Creating turbulence	Turbinates reduce laminar flow for facilitation of other functions listed
Expulsion	Sneezing helps to expel dangerous material from the airways
Moisture recovery	Recover water from exhaled air

EIB exercise-induced bronchospasm

Table 11.3 Similarities and differences in the cellular and histological characteristics in the upper and lower airways

Similarities
Pseudostratified columnar ciliated epithelium over a reticular basement membrane
Goblet cells
Triangular basal cells
Lamina propria
Differences
Lower airway has airway smooth muscle cells in a helical pattern
Upper airway has more subepithelial capillaries and venous cavernous sinusoids
Clara cells are more important in lower airway
Cartilage in upper airway becomes less prominent in the lung

basal cells are small cells which attach to the basement membrane [51, 52]. Under the basal cells lies the subepithelium or lamina propria. Blood vessels populated the submucosa, along with nerves, mucous glands, inflammatory cell infiltrates, and other vascular elements. The bronchioles of the lower airway also possess airway smooth muscle cells arranged in a helical pattern, while the nasal mucosa has more subepithelial capillaries and venous cavernous sinusoids. Clara cells are more unique to the lower airway and predominately exist in the membranous bronchioles. Clara cell-specific protein may have a role in the generation of local inflammatory responses in the airway (Table 11.3) [53]. In the trachea, bronchi and bronchioles are cartilage that starts in the upper airway and gradually becomes less prominent toward the periphery of the lung. The 18–20 C-shaped rings in the trachea become even less complete rings in the bronchi and disappear by a bronchiolar diameter of about 1 mm.

When we review the gross anatomy of the upper and lower airways, specifically when comparing the nose and bronchi, the differences appear more significant than the similarities. The upper airway passages within the nose are surrounded by a rigid framework consisting of bony parts, whereas the lower airway is an elastic, easily pliable tube within a relatively flexible environment. This may explain the effectiveness of β-agonists in the treatment of lower airway conditions such as asthma. This part of the airway, with its smooth airway muscle outside layer, is pliable enough to respond to these bronchodilator drugs, whereas the upper airway is relatively unmovable [54].

Inflammatory Changes in the Upper and Lower Airways

The medical evaluation of the upper and lower airways is generally initiated by rigid or flexible nasal rhinolaryngoscopy of the nose and upper airway and/or bronchoscopy for the lower airway. In general, rhinolaryngoscopy is performed by otolaryngologists or allergists, while pulmonologists usually perform bronchoscopy. Inflammation of the nose can be evaluated by obtaining nasal washings, biopsies, or smears for examination of the cellular infiltrate. Samples obtained during bronchoscopy may include biopsies, bronchial brushings, bronchoalveolar lavage, and culture specimens. Expressed sputum can be generated under varying conditions including hypertonic saline. Tests performed on these samples may include cytology and histology of mucosal surface to identify inflammatory cells such as eosinophils, presence of proinflammatory Th1 and Th2 cytokine profiles, and secreted mediators of inflammation such as eosinophilic cationic protein, leukotrienes, or prostaglandins.

Fiber-optic rhinolaryngoscopy is simple to perform and presents fewer limitations compared to bronchoscopy. Limitations of fiber-optic rhinolaryngoscopy include the inability of the scope to penetrate into the sinuses unless there has been previous sinus surgery and the lack of biopsy sampling during most office procedures. Rigid rhinoscopy however allows the user to biopsy a specific site and directly samples with localized suction any suspicious secretions from the sinus cavities. Limitations of bronchoscopy include the inability of the scope to penetrate into the distal or terminal bronchioles, thus the evaluation being limited to larger lower airways.

An emerging measure of inflammation among more and more medical practitioners is the measurement of fractional exhaled nitric oxide (FeNO). Like peripheral blood eosinophilia and IgE, FeNO measurements are indicative of a systemic eosinophilic inflammatory response. At the present time, fractional exhaled nitric oxide has been utilized as a diagnostic and monitoring tool for lower airway disease such as asthma [55, 56]. Its role in upper airway disease and other eosinophilic disorders is not yet elucidated.

The inflammatory changes that occur in the lower and upper airway as a result of the atopic state were investigated in a study of 19 subjects with allergic asthma and rhinitis, 18 subjects with allergic rhinitis but no asthma, 8 atopic subjects with neither allergic rhinitis nor allergic asthma, and 16 nonatopic controls [57]. The authors found that the number of eosinophils was elevated in patients with rhinitis, whether or not they had asthma, when compared with the atopic non-symptomatic group and the control group. Thickening of the reticular basement membrane in both the upper and lower airways was also detected in the former two groups in a manner similar to the eosinophilia findings. In all groups of atopic individuals, there was significantly increased epithelial desquamation. Airway remodeling, defined as a change in structure of the mucosa and submucosa of the airway, specifically epithelial fragility, thickening of the reticular basement membrane, airway smooth muscle mass increase, and fibrosis [58], was detectable in the lower airway but not in the nasal mucosa. The reverse is also true whereby evidence of inflammatory markers in upper airways has been detected in patients with lower airway disease, including nonallergic asthma and chronic obstructive pulmonary disease (COPD) [5]. Nitric oxide, a marker of inflammation, has been attributed to both lower airway inflammation and nasal polyposis. A study of surgical tissue from 15 patients with nasal polyps demonstrated an increase in all three isoforms of nitric oxide synthetase in leukocytes from nasal polyp tissue which contrasts from normal middle turbinate tissue [59].

The parallels between the upper and lower airway patency were also studied in 221 children aged 6 years in the Copenhagen Prospective Study on Asthma in Childhood. An association was found between decongested nasal airway patency and post-bronchodilator FEV1, after correction for confounding variables, including sex, FVC, body size, and atopic disease. The authors proposed that this association reflected a common physiologic basis for comorbidities of the lower and upper airways [60].

Systemic and Lower Airway Effects of Allergen Exposure in the Nose

One of the mechanisms proposed for the linkage of the upper and lower airways is the systemic effect generated by allergen exposure in the nasal passages. As described above, the nose functions as a regulator of bronchial homeostasis. Besides the physical effects on air characteristics the nose imparts, it also functions as a filtration device. Allergenic particles are one of the primary entities that are filtered by the nose. In doing so, the nose is subject to the inflammatory effects triggered by the exposure to allergen in a hypersensitive host.

Although inflammatory effects are first localized to the nose, additional studies have also revealed evidence of systemic effects. A systemic effect has been shown to occur in mouse models following the induction of a nasal allergic response. The exposure of *Staphylococcus aureus* endotoxin B in the nose has been shown to lead to a systemic release of Th2 cytokines including IL-4, IL-5, and IL-13 in a mouse model. In addition, an increase in bronchial eosinophilia was also detected [61]. Immunologic unity has also been demonstrated in human studies. A correlation between IL-4, interferon-γ, eosinophilia in nasal cytology specimens, nasal airflow, and airway function (FEV1) was detected in a study of 20 patients with seasonal allergic rhinitis and asthma [30]. A nasal allergen provocation study showed that out of season nasal introduction of grass pollen leads to the infiltration of eosinophils into the epithelium and lamina propria of both the nasal and bronchial mucosae 24 h after nasal provocation. In addition, increased levels of ICAM-1 and an increase in the percentage of CD31 vascular endothelial expression of ICAM1, E-selectin, and VCAM1 were detected in the nasal and bronchial mucosae. The authors concluded that out of season nasal provocation in patients with grass allergy leads to inflammatory infiltrates and cytokine and chemokine expression in both the upper and lower airways [62].

Clinical markers of lower airway inflammation following dust mite nasal challenge have been described. In a study of 10 nonallergic children, 16 children with rhinitis alone, and 15 children with rhinitis and asthma, ages 6–10 years, Marcucci et al. studied bronchial symptoms, nasal-specific IgE, nasal and sputum eosinophilic cationic protein (ECP) and tryptase, spirometry, and exhaled nitric oxide (eNO) [63]. The authors conducted the nasal challenge at the beginning of the study in July (considered a low exposure time) and at the end of the study (during the winter which was considered a high exposure season). The results showed that baseline nasal IgE levels were higher in the summertime compared to winter. Also elevated from baseline in allergic or asthmatic subjects compared to controls were sputum ECP and exhaled nitric oxide eNO levels. The response to nasal challenge in asthmatics was mixed, with 3/15 asthmatics experiencing an increase in ECP in summer but 11/15 experiencing the increase in the wintertime. A similar result was seen in the rhinitis patients. Again, a more frequent response in eNO to nasal challenge was seen in the winter compared to the summer. The link between lower airway

and upper airway is perhaps best illustrated in this study from the observed increase in sputum ECP and eNO levels in asthmatic children in winter upon nasal challenge with dust mite allergen. However, in rhinitis patients, only the increase in eNO was detected after challenge in winter.

An increase in sputum ECP has also been detected after nasal allergen challenge with grass or birch pollen in 16 nonasthmatic seasonal allergic rhinitis patients between the ages of 22 and 33 [64].

Other cytokines studied included IL-5, sICAM (soluble intracellular adhesion molecule), and IL-10. The authors noted that in peripheral blood or sputum, there was no change in eosinophils after placebo or allergen challenge, but the plasma levels of IL-5 did increase after challenge. The increase in IL-5 correlated with an increase in sputum ECP and sICAM after nasal allergen challenge. However, sputum IL-10 levels decreased after nasal allergen provocation compared to challenge with placebo.

Bronchoprovocation Effects in the Upper Airway

The united airway theory proposes that the effects between the lower and upper airways should be bidirectional. A study in eight nonasthmatic grass pollen allergic patients and eight healthy controls compared the effects of bronchoprovocation with grass pollen extract [65]. Nasal and bronchial biopsy was performed in all cases at three time points, baseline, 1 h after challenge, and at 24 h after challenge. At 24 h following segmental bronchial provocation (SBP), there was an increase in blood eosinophil levels only in allergic patients compared to controls, suggesting a systemic effect of bronchial allergen challenge in sensitized patients. Bronchial biopsy results revealed that BMK13+ cells, or eosinophils, increased in allergic rhinitis patients in the bronchial segments challenged by allergen or saline, suggesting a local effect. IL-5-positive cells were increased in locally challenged epithelium in allergic rhinitis patients as well. At 24 h post bronchial challenge, nasal biopsies revealed that the number of BMK13+ cells detected in the nasal lamina propria and the number of IL-5-positive cells in the nasal epithelium were both increased in allergic rhinitis patients. Eotaxin-positive cells were also increased in the nasal subepithelium as well as the nasal lamina propria in allergic patients.

Braunstahl studied the effects of bronchoprovocation (SBP) on mast cell and basophil numbers in the nasal and bronchial mucosa of allergic rhinitis patients [66]. In this study, the authors found an increase in basophils in the bronchial mucosa following SBP. In contrast, the numbers of chymase mast cells (MC_C) and chymase/tryptase (MC_{TC}) mast cells were decreased in the nasal mucosa of allergic patients, whereas the numbers of basophils actually increased. The authors also noted an increase in the levels of interleukin-5 in the blood of allergic patients after SBP. Together, these studies support the induction of an inflammatory response in the upper airway in response to provocation with allergen in the lower airway.

The Role of Viral Respiratory Diseases in the Pathogenesis of Rhinitis, Sinusitis, and Asthma

It is well known that one of the main triggers of an asthma exacerbation, especially in children, is a viral respiratory infection. Studies have shown that viruses may be associated with up to 80 % of all asthma exacerbations in children and up to 50 % in adults [67]. It has also been demonstrated that objective measurements of asthma exacerbation, such as a decrease in forced expiratory volume in 1 s (FEV_1), result after infection with rhinovirus in an experimental setting [68]. Changes in other measures of airway hyperresponsiveness and inflammatory cell infiltration have also been described [69].

The most common upper respiratory viral infection is caused by rhinovirus. Other viruses incriminated in upper respiratory tract infections include metapneumonia virus, enterovirus, adenovirus, respiratory syncytial virus (RSV), coronavirus, and picornavirus. Viral infectious diseases that affect the upper airway can lead to lower airway disease by virtue of the resultant interference with normal function of the nose. However, there may be other mechanisms by which upper respiratory infections can affect lower airway function. Whether or not these are direct effects of the virus reaching the lower airways, or systemic inflammatory effects that impact the lower airway, is not clear. Various mechanisms have been proposed. Rhinovirus has, in fact, been isolated in bronchial specimens of individuals infected in the upper airway [70, 71]. Other mechanisms may be related to inflammatory changes mediated by cytokines and chemokines triggered by viral interaction within cellular elements of the upper respiratory tract.

The immunologic mechanisms that link rhinovirus upper respiratory infections with lower respiratory symptoms may involve activation of the nuclear factor κB (NFκB) pathway, a critical mechanism for the activation of multiple proinflammatory genes [72]. It is known that rhinovirus binds to an intracellular adhesion molecule, leading to infection of airway

epithelial cells. Included among the many functions that are mediated by activation of NFκB is the upregulation of an adhesion molecule known as intracellular adhesion molecule (ICAM)-1. Binding of rhinovirus to ICAM-1 allows rhinovirus to enter airway epithelial cells and leads to further activation of other proinflammatory mediators, which subsequently leads to recruitment of other proinflammatory cells such as neutrophils, monocytes, lymphocytes, and eosinophils. This positive feedback loop involving upregulation of the expression of ICAM-1 opens the door for further infection by rhinovirus. What results is the induction of an inflammatory state that is enhanced by the expression of multiple proinflammatory cytokines, including IL-1, IL-6, IL-8, RANTES, and IL-16. Further recruitment of inflammatory cells to the bronchial tree can ultimately lead to lower airway inflammatory symptoms, including cough, wheezing, and dyspnea [70].

Since asthma subjects tend to have a cytokine profile skewed toward a Th2 paradigm, a rhinovirus infection of the upper airway may result in lower production of interferon-γ. A reduction of interferon-γ may accentuate a lower airway involvement in asthma. It has also been shown that granulocyte colony-stimulating factor (G-CSF) levels are increased both locally (in the nose) and systemically (in the circulation) of allergic subjects subjected to experimental rhinovirus-16 infection. Increased G-CSF levels lead to higher neutrophil counts and activity and may play a role in the increased inflammatory state at sites distant from the upper airway. Other cells that may be stimulated and infiltrate to the lower airway include eosinophils, lymphocytes, monocytes, and macrophages [73]. The effects of viral infections extend to selected nonasthmatic subjects with respiratory disease as well [68]. In adults, more than 40 % of exacerbations of COPD can be linked to an upper respiratory infection [74].

Chronic Rhinosinusitis and Asthma

Chronic rhinosinusitis with and without nasal polyps is associated with an inflammatory state that involves increased serum IL-5 and an increased eosinophilia within the bone marrow. Immunologically, this pattern is similar to that seen in asthma. There are also parallels between the cytokine profiles in the sinus tissue of patients with chronic rhinosinusitis and in the bronchial tissue of patients with asthma. Histological findings in chronic rhinosinusitis include epithelial shedding and thickening of the basement membrane, which are hallmarks of asthmatic bronchitis. Eosinophilic degranulation and release of mediators such as eosinophilic cationic protein have been demonstrated to occur in the nose and in the lower airway in patients with sinusitis and asthma.

Interleukin-17 is a cytokine with known effects in asthma. It is a proinflammatory cytokine released by Th17 cells, which is thought to be involved in neutrophilic infiltration of the bronchial tissue in patients with asthma. Saitoh et al. demonstrated that IL-17 is increased in nasal polyps compared to normal sinus tissue and correlated this with an increase in eosinophils and CD4+ T lymphocytes. They were also able to correlate the extent of basement membrane thickening with IL-17 levels [75]. These observations suggest a common role of IL-17 in both the upper and lower airways.

Fungi as a Model for Unifying Lower Airway and Upper Airway Disease

An interesting observation of the ability of fungi to generate an inflammatory airway disease, such as allergic bronchopulmonary aspergillosis in the lungs and allergic fungal sinusitis in the sinuses, further supports the concept of a unified upper and lower respiratory tract. Pakdaman et al. have reviewed the possible role of fungi as superantigens or as adjuncts that enhance the inflammatory response, suggesting that the similarities in the histomorphology of the upper and lower airways present a common target for fungi. In their reviews, they discuss how fungi may be the initial inflammatory insult that leads to chronic airway inflammation [76–78].

Nasal Polyps and Asthma

A Japanese study investigated the cytokine profile of 19 patients with chronic rhinosinusitis with nasal polyps compared to 9 patients without nasal polyps and 14 normal controls [79]. They found elevated levels of eosinophil cationic protein (ECP), *Staphylococcal* enterotoxin-IgE (SAE-IgE), IgE, and IL-5 only in the group with rhinosinusitis with nasal polyps. The polyp group demonstrated a skewing toward a Th2 cytokine profile with relatively lower TGF-β levels, while the group with

rhinosinusitis without nasal polyps demonstrated higher TGF-β levels suggesting a Th1 profile. A very interesting component of this small study was the fact that 31.6 % of the patients with rhinosinusitis with nasal polyps had asthma, while none in the group without polyps had asthma.

A paper comparing the histological and morphological differences between nasal polyps and asthma raised an interesting question concerning the unique infrequency of polyps in the lung compared to the upper airway mucosa and other organ systems with a mucosal surface such as the gastrointestinal and urinary tracts [80]. So what is it about lung mucosa that renders it less prone to the development of polyps? The authors suggest that this observation could be explained by comparing differing mucosal characteristics of the nose and the lung. One factor that stands out is TGF-β which plays an important role in the remodeling process. Epithelial injury results from increased TGF-β, which is upregulated in asthmatics and downregulated in nasal polyposis. On the other hand, the presence of TGF-β in the lung prevents the development of polyps. In the nose, the nasal reticular basement membrane becomes less thickened which is a feature of nasal polyposis. Incidentally, TGF-β also plays a protective role in the development of benign polyps in the large intestine as well, in that a mutation of SMAD4 disrupts TGF-β signaling pathways in juvenile polyposis syndrome.

The Nasobronchial and Nasopharyngeal Reflex

Nasobronchial and nasopharyngeal reflex mechanisms have been mentioned in support of a unified airway in health and disease. Bucca has reported that increased lower airway hyperresponsiveness occurs in patients with sinusitis. In some of these patients, the increased airway hyperresponsiveness also included extrathoracic airway hyperresponsiveness, as measured by MIF_{50}. The authors suggested that the mechanism by which this occurs is through activation of a nasopharyngeal-bronchial reflex. A study of 24 nonasthmatic patients with sinusitis investigated the relationship between pharyngeal mucosal changes and bronchial hyperresponsiveness. The authors used histamine PC_{20} as a threshold for bronchial responsiveness and $PC_{25}MIF_{50}$ as a threshold for extrathoracic airway hyperresponsiveness. In these patients, they found that the epithelial thinning, representing pharyngeal mucosa damage, correlated with extrathoracic airway hyperresponsiveness. Bronchial hyperresponsiveness was also associated with long-standing sinusitis, increased submucosal nerve density, increased eosinophils in the nasal lavage fluid, and a lower $PC_{25}MIF_{50}$. The authors interpreted these results as an indication that pharyngeal damage contributes to airway dysfunction through the stimulation of mucosal nerve endings to activate constrictive reflexes leading to increased extrathoracic airway hyperresponsiveness. They also postulated that it is pharyngeal damage and the failure of normal physiologic filtering functions that grant access of irritants and allergens to submucosal nerve endings [81].

Gravitational Factors and Postnasal Drainage

Whether or not nasal secretions can stimulate lower airway inflammatory response by direct contact is a matter of great debate [82]. Intuitively, it seems to make sense that postnasal drip, facilitated by gravity, will end up in the lower airway. If the mucous contains allergic or inflammatory mediators, then an inflammatory response in the lower airways is expected. However, in two separate studies, nasal application of radioactive-labeled allergen only showed deposition in the digestive tract and not in the lower respiratory tract [3, 4]. In contrast, there have been studies to support the concept that a cough can be associated with postnasal drip [83–85], suggesting an alternative mechanism for the effect of upper airway secretions on lower airway inflammation. It is possible that aspiration of stomach contents may be responsible for a cough in these patients or that the stimulation of pharyngolaryngeal receptors by inflammatory mediators emanating may be the key mechanism for postnasal drip-related cough [86].

A summary of the potential pathogenic mechanisms behind the link between the upper and lower airways is illustrated in Fig. 11.2.

Other Clinical Associations

Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD), also known previously as Samter's triad, describes a perennial condition comprised of three components, namely, aspirin sensitivity, asthma, and chronic rhinosinusitis with nasal polyposis. The rhinitis/nasal polyposis symptoms include rhinorrhea, nasal congestion, sneezing, and anosmia. Both asthma and the chronic rhinosinusitis in AERD are characterized by eosinophilic infiltrates in the mucosa of the corresponding tissues.

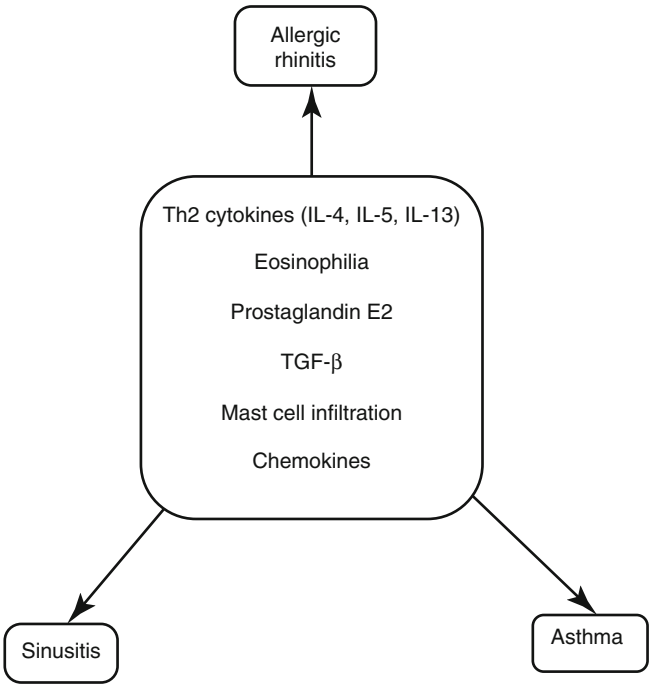


Fig. 11.2 Links between the upper and lower airways: mechanisms of the one airway, one disease hypothesis

Aspirin-induced asthma is a surprisingly common phenomenon [87]. Data has suggested that the prevalence of aspirin-induced asthma is much higher in adults than in children (21 % vs. 5 %). Asthma is usually diagnosed 2–3 years after the onset of upper airway symptoms and is commonly difficult to treat. Nasal polyps are recurrent and frequently require multiple surgeries. The aspirin sensitivity usually occurs in these patients who were previously able to tolerate aspirin. Aspirin is a nonsteroidal anti-inflammatory drug (NSAID), and its mode of action is through inhibition of cyclooxygenase 1. The result of this inhibition is an increase in the substrate arachidonic acid, leading to increased activity of the lipoxygenase pathway and the release of leukotrienes into the circulation and surrounding tissue. Leukotrienes are potent mediators of inflammation. The details of aspirin-exacerbated respiratory disease are discussed in other chapters of this book. This discussion will focus only on why this mechanism predisposes patients to disease of both the upper and lower airways, in the context of a unified airway disease.

In the respiratory tract, mast cells and other secretory cells of the respiratory tract can release leukotrienes upon stimulation. LTC4 synthase is the key enzyme catalyzing the synthesis of leukotriene C4, which binds to the leukotriene receptor, CysLTR1, to trigger inflammatory mediator release. It has been found that CysLTR1 is upregulated in patients with AERD, and CysLTR1-positive cells are reduced after intranasal desensitization with aspirin. The high cysteinyl leukotriene level is accompanied by a low production of prostaglandin E2 [88]. Cyclooxygenase-2 is downregulated in the nasal polyps of aspirin-sensitive patients. Eosinophils from nasal polyps in AERD patients show increased expression of LTC4 synthase [89].

In the airway, excessive production of cysteinyl leukotrienes leads to induction of airway smooth muscle contraction, increased vascular permeability, and airway remodeling. Abnormalities in the arachidonic acid pathway are the mechanism for induction of these effects, as occurs in nasal polyp tissue. Levels of prostaglandin E2 receptor expression are reduced in airway leukocytes in asthmatic patients with aspirin sensitivity [90]. Eosinophils from the bronchial biopsies in patients with asthma also demonstrated increased LTC4 synthase [91]. Together, these observations of common pathologic features in both the mucosa of nasal polyps and asthma support a common susceptibility in distant parts of the airway.

An Autoinflammatory Link Between Sinuses and Lung

Several autoimmune diseases involve the upper and lower airways, specifically the sinuses and the lungs. These include Wegener's granulomatosis and Churg-Strauss syndrome. The types of autoimmune diseases that affect the lung are thought to be related to small-vessel vasculitides. Whether involvement of the lung and sinuses in these conditions is strictly a function of vascular pathology or other mechanisms that would impact both parts of the airway is not known.

Sinuses and the GI Tract

Gastroesophageal reflux has been shown to be a comorbid condition of asthma. As early as the 1,800 s, William Osler had identified a link between the gastrointestinal and respiratory systems, noting that overeating can induce coughing paroxysms in asthmatics [92]. In general, the majority of asthmatic subjects will describe having symptoms of reflux. Similarly, many patients with asthma will complain of respiratory symptoms related to reflux. Even to this day, it is not yet clear if asthma causes reflux or vice versa. A study on upper airway obstruction and gastroesophageal reflux performed in dogs suggested that it is the upper airway obstruction that causes gastroesophageal reflux by generation of a negative inspiratory pressure. Temporally, they showed that it was induction of the airway obstruction that led to gastroesophageal reflux about 1 week after creation of the obstruction [93]. Why abnormal pressures on the esophagus in airway obstruction can predispose patients to reflux can be explained by Bernoulli's principle [94]. Bernoulli's principle states that there is an inverse relationship between the velocity of a fluid through a tube and the pressure exerted perpendicularly by that fluid. On the other hand, it has been suggested that gastroesophageal reflux can trigger asthma through aspiration-induced inflammation resulting in hyperresponsiveness of the airway. In support of this concept, a review of the literature suggests that treatment of symptomatic gastroesophageal reflux improves asthma symptoms [95]. However, this has not been valid in the case of silent or asymptomatic gastroesophageal reflux. The effects of reflux on asthma thus remain unclear. It is probable that putting these two events together produces a vicious cycle, where one disease exacerbates the other. Treatment of either disease will break the cycle and improve symptoms.

A critical review of the literature focused on analyzing three concepts as supporting evidence for a role of GER in sinusitis. Firstly, the authors noted that a higher prevalence of gastroesophageal reflux exists in patients with hard-to-treat sinusitis. Secondly, they reviewed the pathogenic mechanisms for GER and sinusitis and were able to formulate a plausible explanation for a relationship. Part of this evidence included the observation that gastric acid contents can be found in the middle ear of patients with otitis media with effusion [96]. Additionally, Wong et al. showed that a hyperactive reflux can induce autonomic nervous system and lead to sinonasal edema, a compromise in normal drainage, and chronic rhinosinusitis [98]. This was previously described by Pinto et al. [97]. Thirdly, patients who had successful treatment of gastroesophageal reflux experienced a higher degree of resolution of sinus symptoms and global well-being [98, 99]. The authors present an algorithm that involves using acid-lowering drugs like proton pump inhibitors in the treatment of sinusitis [100].

The independent relationships between gastroesophageal reflux and asthma and sinusitis suggest a common susceptibility throughout the entire respiratory tract to contents of the stomach. While the exact mechanism for these effects is unknown, the correlation seems to support a one airway, one disease model.

Upper Airway Disease and Laryngitis

An interesting extension of the one airway, one disease concept is related to the link between rhinitis and laryngitis. A study of 134 allergic rhinitis patients, 54 nonallergic rhinitis patients, and 62 normal controls demonstrated that those patients with either allergic or nonallergic rhinitis had a markedly significant higher rate of dysphonia than patients without rhinitis (32.8, 26.9, and 8.1 %, respectively). The presence of asthma and the use of inhaled corticosteroids were confounding variables that were controlled for in the study. Curiously, however, the use of intranasal corticosteroids, while presumed to be either an exclusion criteria or a variable that would be controlled for, was not specifically mentioned in the paper [101]. Earlier reports have also noted that allergic rhinitis patients who may benefit from immunotherapy were at least three times more likely to have dysphonia than normal controls [102]. Other investigators have also proposed a link between vocal cord problems and allergic rhinitis symptoms that may or may not be simply attributed to postnasal drainage [103, 104]. The relationship between sinusitis and voice abnormalities has also been proposed, and parameters necessary to evaluate vocal characteristics in sinusitis patients were established, although no differences in these parameters were detected in this pilot study of 10 chronic sinusitis and 9 control subjects. The authors proposed that at least 126 patients would be needed to conduct a study that would demonstrate reliable and statistically valid results [105].

Table 11.4 Comparison of the classification systems and treatment of allergic rhinitis and asthma

	Allergic rhinitis		Asthma	
	Controller med	Rescue med	Controller med	Rescue med
Mild intermittent	None	Antihistamines	None	β-agonist
Mild persistent	Intranasal steroid	Antihistamine	Inhaled steroid	β-agonist
Moderate persistent	Intranasal steroid, leukotriene receptor antagonist	Antihistamine	Inhaled steroid, leukotriene receptor antagonist	β-agonist
Severe persistent	Intranasal steroid, leukotriene receptor antagonist, immunotherapy	Antihistamine	Inhaled steroid, leukotriene receptor antagonist	β-agonist, oral or parenteral steroids

How Treatment of One Disease Affects the Other

The Effect of Treatment of Sinusitis on Asthma

Pharmacotherapy of Allergic Rhinitis, Sinusitis, and Asthma

The treatment of allergic rhinitis with medications led to interesting observations regarding the effectiveness of these drugs to also treat asthma [106, 107]. Effective treatment of allergic rhinitis has been associated with a reduced frequency of emergency department visits for asthma and a reduced risk for hospitalization for asthma [108]. Antihistamines used to treat allergic rhinitis may have some benefit in asthma. Glucocorticoids, of course, will treat both areas of the respiratory tract, when applied "topically" to that region. Perhaps more interesting is the effect of immunotherapy on asthma. Because it is believed that immunotherapy works on a systemic basis to modulate the immune system, then one might infer that immunotherapy used to treat allergic rhinitis should help with allergic asthma as well. In fact, numerous studies have supported the role of immunotherapy in asthma [109]. An illustration of the parallel strategies in treatment of allergic rhinitis and asthma is shown in Table 11.4.

Numerous studies in the pediatric population have suggested that treatment of sinusitis in patients with concurrent asthma leads to a more rapid resolution of their exacerbation [110].

A discussion of the role of leukotriene pathway medications is important because of the existence of disease complex known as Samter's triad, which consists of nasal polyposis, aspirin sensitivity, and severe asthma and is now referred to as aspirin-exacerbated respiratory disease (AERD). The role of aspirin in sinusitis is discussed in the chapter on aspirin-induced sinus disease. Leukotriene receptor antagonists such as montelukast have been found to have efficacy in the treatment of both allergic rhinitis and asthma [111, 112]. Leukotriene receptor antagonists have also been found to play a role in the treatment of chronic sinusitis. These conclusions have mostly been established through the study of leukotriene receptor antagonists in the treatment of AERD whereby both asthma (the intended indication) and chronic sinusitis (unintended consequence) have shown improvement [113].

In chronic sinusitis, the eosinophil and the mast cell have been the most commonly implicated cell types. Inhibiting the proinflammatory activity of eosinophils has been shown to reduce IL-4 and IL-5 levels. Anti-IL5 has been found to be effective in the treatment of nasal polyps [114]. Anti-IL4 has been proposed as a therapy for asthma, by virtue of its potential effect on decreasing IL-4 levels. IL-4 has been shown to be able to increase CysLT1 and CysLT2 receptor levels in eosinophils and lymphocytes. Thus, targeting of cytokine pathways may be a means to reduce the effects of leukotrienes. A pilot study of mepolizumab for treatment sinusitis in Churg-Strauss syndrome led to improvement in all seven patients after 4 months of treatment [115]. Withdrawal of the drug led to a reversal of the beneficial effects of mepolizumab.

In addition to targeting cytokines generated by eosinophils and mast cells, imatinib, a tyrosine kinase inhibitor, has also been found to directly inhibit activation and function of these cell lines. A study of eight patients with chronic hypereosinophilic sinusitis showed that imatinib could lead to decreased eosinophils in the blood in most subjects and symptom improvement in about half of the subjects [116].

Immunotherapy in Allergic Rhinitis and Asthma

One of the risk factors for adverse reactions to immunotherapy is asthma. However, immunotherapy has also been associated with improvements in asthma. In fact, this observation may further support the existence of a one airway, one disease paradigm, since the benefit of this mode of therapy extends to both upper and lower airways [72].

Anti-IgE Therapy in Allergic Rhinitis and Asthma

Omalizumab is a recombinant humanized monoclonal antibody (primarily IgG1 class) directed against IgE [117]. Omalizumab was first developed for the treatment of moderate to severe persistent asthma. However, it has also been studied for the treatment of upper airway allergic rhinitis as well. A randomized controlled trial studying the effect of omalizumab on allergic rhinitis symptoms was conducted on 536 patients between the ages of 12 and 75 years [118]. Outcome measures included self-assessment of daily nasal symptom scores, antihistamine use, and quality-of-life assessments. Free IgE levels were also measured. The results indicated that omalizumab was an effective mode of therapy with improvements in all three outcome measures. No increase in adverse side effects was noted in the treatment group compared with the placebo group. Similar results were found in studies on the use of omalizumab in birch pollen- [119] and cedar pollen-induced seasonal allergic rhinitis [120]. In the lower airway, Holgate et al. showed that omalizumab has similar beneficial effects in asthma, and patients were more likely to be able to reduce their inhaled corticosteroid usage with an accompanying reduction in asthma-related hospitalizations and emergency room visits [121]. Quality-of-life improvements were also detected in the INNOVATE study, one of the earlier studies on the effectiveness of omalizumab in allergic asthma [122]. The beneficial effects seen that are common throughout the respiratory tract, in both the upper and lower airways, suggest a common mechanism that can be targeted by a single agent.

Parallel Management of Allergic Rhinitis and Asthma

Classification of asthma into various categories based on risk and control has been an ongoing project since the early 1990s. There have been several iterations of these guidelines with the most recent version focusing on impairment and risk. Controller medications and rescue medications have been relatively clearly delineated, and treatment and management algorithms have been introduced to assist physicians and other caregivers. More recently, a similar set of classification and guidelines have also been introduced for the treatment of allergic rhinitis as well [21, 123]. The most recent version of these guidelines was introduced in 2008 and was put forth by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group and the Allergic Rhinitis and Its Impact on Asthma (ARIA) guideline panel, by review of systemic reviews and best available evidence [124].

The approaches to classifying allergic rhinitis and asthma have been remarkably similar, and probably by design, to reflect the similarities between the two diseases. Both are first categorized into intermittent and persistent, then the persistent form is divided into mild, moderate, and severe groups. The first-line treatment is with topical (either inhaled or intranasal) corticosteroids, reflecting the need to provide anti-inflammatory control that is based on pathologic observations already discussed above. Other maintenance medications include the leukotriene receptor antagonists, montelukast, zafirlukast, and pranlukast, which, as a class effect, may be variably effective in treating symptoms of both the lower and upper respiratory tract. Antihistamines are useful in allergic rhinitis, and their role in allergic asthma is not quite so clear. But the overall parallels in the current recommendations for treatment of upper and lower airway allergic disease are nearly identical, as illustrated in Table 11.3, given more prudence to the one airway, one disease theory.

The Effect of Surgical Treatment of Sinus Disease on Asthma

A prospective study of 68 asthma patients who also had nasal polyposis was conducted to investigate whether or not surgical treatment of the nasal disease led to improvement in asthma [125]. The study lasted 21 weeks, and various asthma-related parameters were evaluated as therapeutic endpoints. Upper airway parameters include both subjective measures such as nasal congestion and rhinorrhea and objective measures such as peak nasal inspiratory flow. Lower airway parameters included symptoms of asthma such as cough and dyspnea along with objective tests including peak expiratory flow rate measurements

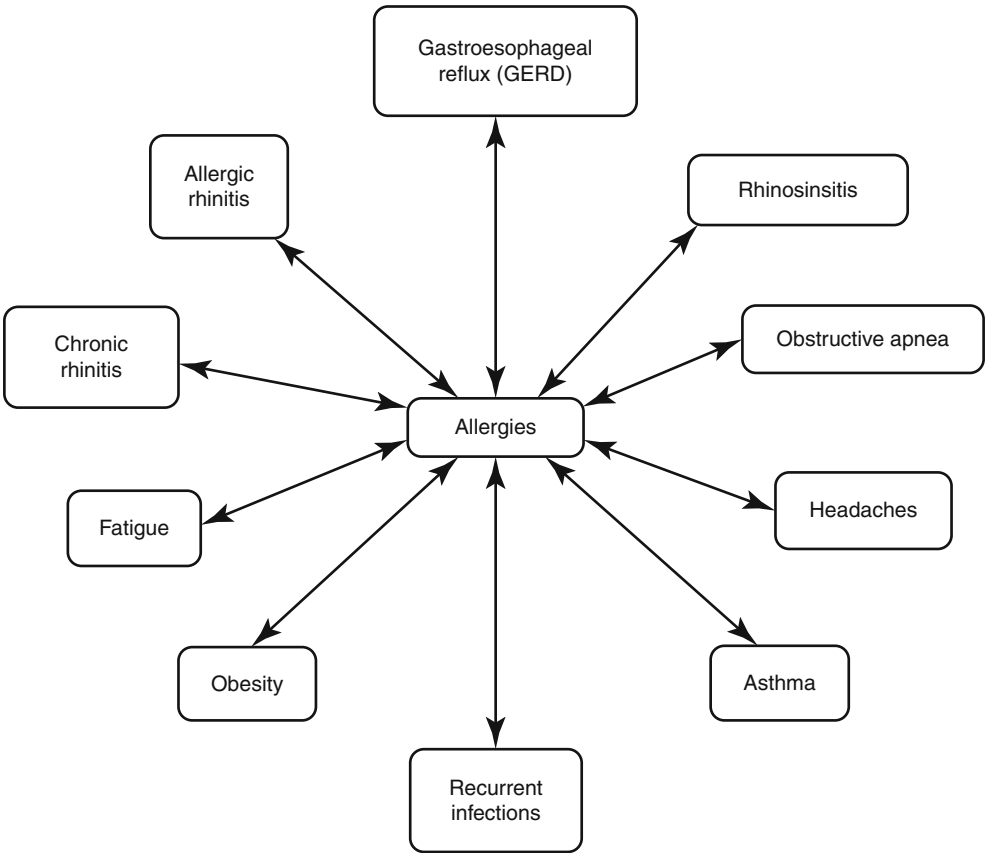


Fig. 11.3 Comorbid conditions associated with asthma

and lung function tests. The study included adult patients and also evaluated the use of fluticasone propionate nasal spray prior to surgery in a double-blind randomized controlled format. The results of the study indicated that functional endoscopic sinus surgery led to a significant improvement in both upper and lower airway symptoms, as well as improvements in objective measurements in both parts of the airway. The inclusion of a double-blind randomized controlled trial of presurgical fluticasone confounds the data somewhat and does not answer the question the investigators had regarding the effectiveness of presurgical use of nasal steroids to improve surgical outcome.

A more recent study evaluated whether or not improvements in asthma were sustained after functional endoscopic sinus surgery. Fifty-one adult patients with both nasal polyposis and asthma underwent functional endoscopic surgery. The improvements in subjective and objective lower and upper airway parameters that occurred immediately after surgery were maintained 1 year post surgery [126]. Another study provided long-term data (average 6.5 years) on 30 patients with asthma who underwent functional endoscopic sinus surgery. Subjective and objective parameters of asthma severity were recorded, including utilization of hospital visits, medication use, and clinical symptoms. A sustained improvement was noted in all parameters [127].

A corollary of these noted benefits of sinus surgery in improving asthma was demonstrated in a study of 510 patients with chronic rhinosinusitis, of whom 68 underwent revision endoscopic sinus surgery. This study showed that biofilm-forming bacteria and asthma were independently associated with a risk for refractory chronic rhinosinusitis requiring revision endoscopic surgery. This would suggest that treatment of asthma may be an important factor in determining the efficacy of surgical treatment of sinus disease, illustrating the bidirectional nature of the association between asthma and sinus disease.

Difficult-to-treat asthma may result from a failure to recognize and treat comorbid conditions associated with asthma. These may include allergic rhinitis, perennial rhinitis, nonallergic rhinitis with eosinophilia, viral bronchitis, pneumonia, atelectasis, chronic postnasal drip, gastroesophageal reflux, obstructive sleep apnea, and rhinosinusitis. These relationships are illustrated in Fig. 11.3. An algorithm depicting an approach to the treatment of difficult asthma is shown in Fig. 11.4.

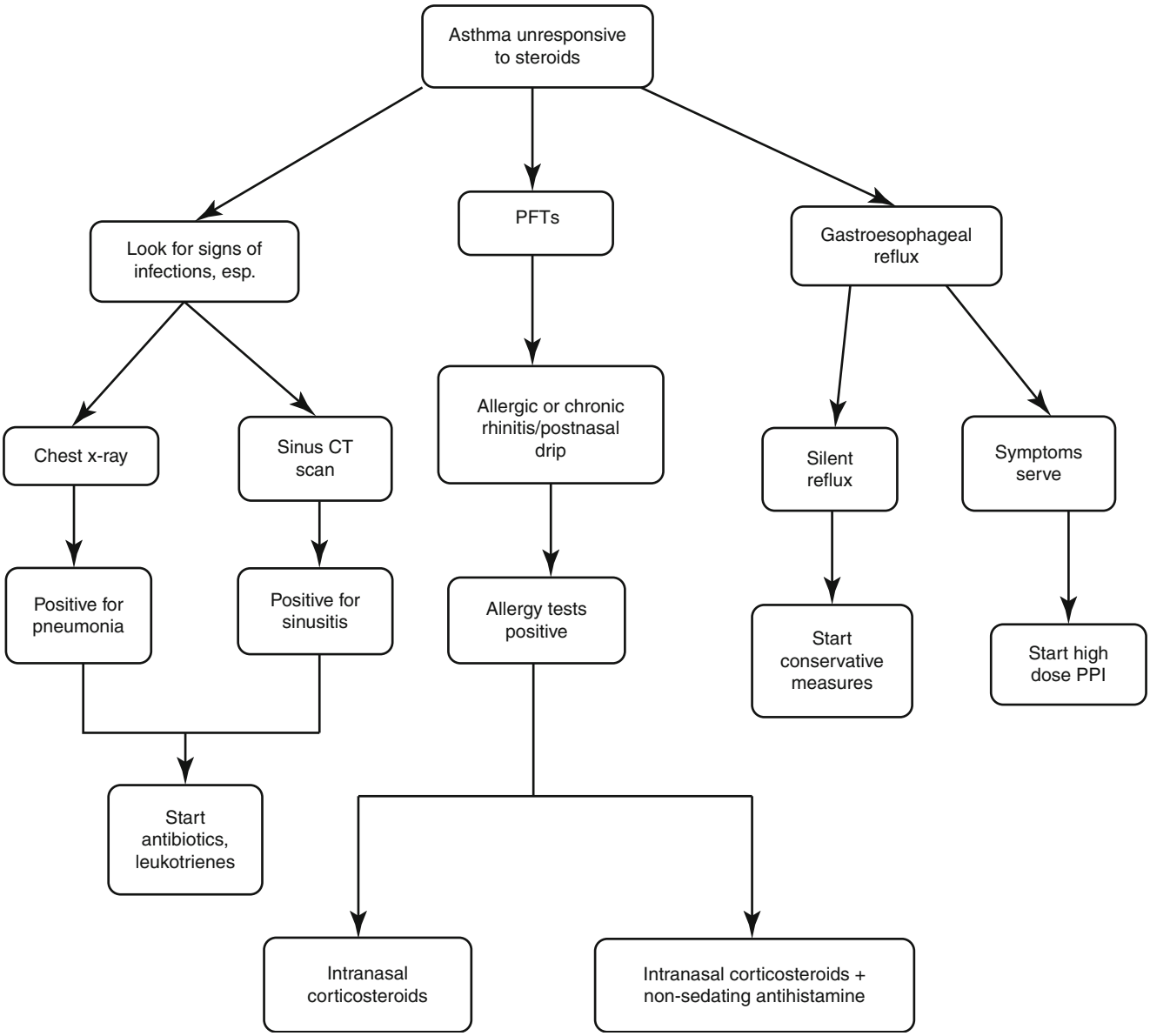


Fig. 11.4 Difficult-to-treat asthma: an algorithm

Conclusions

From ancient times, physicians have appreciated the connection between the upper airway and lower airway. Throughout history, the link has been consolidated, and our understanding of the pathogenic mechanisms behind this link has been cultivated, and now it is no longer simply an intuitive or presumed relationship. Several mechanisms are in play, and these involve neural, vascular, immunologic, and physical pathways. It is now known that there are anatomical and histomorphological similarities between the upper and lower airways that would lead one to believe that effects on one part of the airway should be duplicated in other parts. However, there are also differences between the upper and lower airways. The relationship between the upper and lower airways may in fact be mediated by a multitude of factors. Nasobronchial reflexes may trigger vascular changes between the two parts of the airway. Allergen challenge to one part of the airway may trigger local changes that can lead to similar changes in other parts of the airway but may also mediate inflammatory effects by a systemic inflammatory response, leading to infiltration of inflammatory cells and generation of inflammatory cytokines in distant sites. It has been shown that this may involve the action of Th2 cytokines such as IL-4, IL-5, and IL-13, and that Th1 cytokines

such as TGF-β may actually provide a protective effect. There are similar cytological changes in nasal polyp tissue and lower airway tissue, but polyps themselves are not often seen in the lower airway. Further research on the pathologic mechanisms of upper and lower airway inflammation will bring about a better understanding of the similarities and differences of inflammation in these two areas of a contiguous organ and hopefully lead to better and safer therapeutic modalities.

Acknowledgments The author thanks Rama Krishna Reddy Patel for help with the tables.

References

1. Hellings PW, Prokopakis EP. Global airway disease beyond allergy. Curr Allergy Asthma Rep. 2010;10:143–9.
2. Blackley C. Experimental researches of the causes and nature of catarrhus aestivus. London: Oxford Historical Books; 1873.
3. Bardin PG, Van Heerden BB, Joubert JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. J Allergy Clin Immunol. 1990;86:82–8.
4. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. J Allergy Clin Immunol. 1992;89:611–8.
5. Hens G, Vanaudenaerde BM, Bullens DM, et al. Sinonasal pathology in nonallergic asthma and COPD: 'united airway disease' beyond the scope of allergy. Allergy. 2008;63:261–7.
6. Grossman J. One airway, one disease. Chest. 1997;111:11S–6.
7. Cruz AA, Popov T, Pawankar R, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. Allergy. 2007;62 Suppl 84:1–41.
8. Toren K, Olin AC, Hellgren J, Hermansson BA. Rhinitis increase the risk for adult-onset asthma–a Swedish population-based case-control study (MAP-study). Respir Med. 2002;96:635–41.
9. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol. 2002;109:419–25.
10. Plaschke PP, Janson C, Norrman E, Bjornsson E, Ellbjar S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med. 2000;162:920–4.
11. Sole D, Camelo-Nunes IC, Wandalsen GF, Melo KC, Naspitz CK. Is rhinitis alone or associated with atopic eczema a risk factor for severe asthma in children? Pediatr Allergy Immunol. 2005;16:121–5.
12. Chatkin MN, Menezes AM. Prevalence and risk factors for asthma in schoolchildren in southern Brazil. J Pediatr (Rio J). 2005;81:411–6.
13. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen SC, Backer V. Outcome in adulthood of asymptomatic airway hyperresponsiveness to histamine and exercise-induced bronchospasm in childhood. Ann Allergy Asthma Immunol. 2005;95:137–42.
14. Sherrill DL, Guerra S, Minervini MC, Wright AL, Martinez FD. The relation of rhinitis to recurrent cough and wheezing: a longitudinal study. Respir Med. 2005;99:1377–85.
15. Guerra S, Sherrill DL, Baldacci S, et al. Rhinitis is an independent risk factor for developing cough apart from colds among adults. Allergy. 2005;60:343–9.
16. Cibella F, Cuttitta G, La Grutta S, et al. Bronchial hyperresponsiveness in children with atopic rhinitis: a 7-year follow-up. Allergy. 2004;59:1074–9.
17. Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004;113:86–93.
18. Lombardi C, Passalacqua G, Gargioni S, et al. The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years. Respir Med. 2001;95:9–12.
19. Gustafsson D, Sjoberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis–a prospective follow-up to 7 years of age. Allergy. 2000;55:240–5.
20. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol. 1999;104:301–4.
21. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8–160.
22. Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. J Allergy Clin Immunol. 1999;103:54–9.
23. Guilemany JM, Mullol J, Picado C. Relation between rhinosinusitis and bronchiectasis. Arch Bronconeumol. 2006;42:135–40.
24. Mullol J, Valero A, Alobid I, et al. Allergic Rhinitis and its Impact on Asthma update (ARIA 2008). The perspective from Spain. J Investig Allergol Clin Immunol. 2008;18:327–34.
25. Pawankar R, Bunnag C, Chen Y, et al. Allergic rhinitis and its impact on asthma update (ARIA 2008)–western and Asian-Pacific perspective. Asian Pac J Allergy Immunol. 2009;27:237–43.
26. Ozdoganoglu T, Songu M. The burden of allergic rhinitis and asthma. Ther Adv Respir Dis. 2012;6:11–23.
27. Droma Y, Kunii O, Yangzom Y, Shan M, Pingzo L, Song P. Prevalence and severity of asthma and allergies in schoolchildren in Lhasa, Tibet. Clin Exp Allergy. 2007;37:1326–33.
28. Trakultivakorn M, Sangsupawanich P, Vichyanond P. Time trends of the prevalence of asthma, rhinitis and eczema in Thai children-ISAAC (International Study of Asthma and Allergies in Childhood) Phase Three. J Asthma. 2007;44:609–11.
29. Skiepko R, Zietkowski Z, Tomasiak-Lozowska MM, Tomasiak M, Bodzenta-Lukaszyk A. Bronchial hyperresponsiveness and airway inflammation in patients with seasonal allergic rhinitis. J Investig Allergol Clin Immunol. 2011;21:532–9.

30. Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Airway function and nasal inflammation in seasonal allergic rhinitis and asthma. Clin Exp Allergy. 2004;34:891–6.
31. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol. 2000;106:S201–5.
32. Rolla G, Guida G, Heffler E, et al. Diagnostic classification of persistent rhinitis and its relationship to exhaled nitric oxide and asthma: a clinical study of a consecutive series of patients. Chest. 2007;131:1345–52.
33. Ponikau JU, Sherris DA, Kephart GM, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? J Allergy Clin Immunol. 2003;112:877–82.
34. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2007;2007:1–136.
35. Matsuno O, Ono E, Takenaka R, et al. Asthma and sinusitis: association and implication. Int Arch Allergy Immunol. 2008;147:52–8.
36. Lotvall J, Ekerljung L, Lundback B. Multi-symptom asthma is closely related to nasal blockage, rhinorrhea and symptoms of chronic rhinosinusitis-evidence from the West Sweden Asthma Study. Respir Res. 2010;11:163.
37. Bresciani M, Paradis L, Des Roches A, et al. Rhinosinusitis in severe asthma. J Allergy Clin Immunol. 2001;107:73–80.
38. ten Brinke A, Grootendorst DC, Schmidt JT, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. J Allergy Clin Immunol. 2002;109:621–6.
39. Guida G, Rolla G, Badiu I, et al. Determinants of exhaled nitric oxide in chronic rhinosinusitis. Chest. 2010;137:658–64.
40. Spector SL. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol. 1997;99:S773–80.
41. Slavin RG. Complications of allergic rhinitis: implications for sinusitis and asthma. J Allergy Clin Immunol. 1998;101:S357–60.
42. Berrettini S, Carabelli A, Sellari-Franceschini S, et al. Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors. Allergy. 1999;54:242–8.
43. Robinson S, Douglas R, Wormald PJ. The relationship between atopy and chronic rhinosinusitis. Am J Rhinol. 2006;20:625–8.
44. Wood AJ, Antoszewska H, Fraser J, Douglas RG. Is chronic rhinosinusitis caused by persistent respiratory virus infection? Int Forum Allergy Rhinol. 2011;1:95–100.
45. Hens G, Hellings PW. The nose: gatekeeper and trigger of bronchial disease. Rhinology. 2006;44:179–87.
46. Strauss RH, McFadden Jr ER, Ingram Jr RH, Jaeger JJ. Enhancement of exercise-induced asthma by cold air. N Engl J Med. 1977;297:743–7.
47. Assanasen P, Baroody FM, Naureckas E, Solway J, Naclerio RM. The nasal passage of subjects with asthma has a decreased ability to warm and humidify inspired air. Am J Respir Crit Care Med. 2001;164:1640–6.
48. Hildenbrand T, Weber RK, Brehmer D. Rhinitis sicca, dry nose and atrophic rhinitis: a review of the literature. Eur Arch Otorhinolaryngol. 2011;268:17–26.
49. Serrano C, Valero A, Picado C. Rhinitis and asthma: one airway, one disease. Arch Bronconeumol. 2005;41:569–78.
50. Rhodin JA. The ciliated cell. Ultrastructure and function of the human tracheal mucosa. Am Rev Respir Dis. 1966;93(Suppl):1–15.
51. Tamai S. Basal cells of the human bronchiole. Acta Pathol Jpn. 1983;33:123–40.
52. Boers JE, Ambergen AW, Thunnissen FB. Number and proliferation of basal and parabasal cells in normal human airway epithelium. Am J Respir Crit Care Med. 1998;157:2000–6.
53. Jorens PG, Sibille Y, Goulding NJ, et al. Potential role of Clara cell protein, an endogenous phospholipase A2 inhibitor, in acute lung injury. Eur Respir J. 1995;8:1647–53.
54. Passalacqua G, Canonica GW. Impact of rhinitis on airway inflammation: biological and therapeutic implications. Respir Res. 2001;2:320–3.
55. Scadding G. Nitric oxide in the airways. Curr Opin Otolaryngol Head Neck Surg. 2007;15:258–63.
56. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184:602–15.
57. Braunstahl GJ, Fokkens WJ, Overbeek SE, KleinJan A, Hoogsteden HC, Prins JB. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. Clin Exp Allergy. 2003;33:579–87.
58. Jeffery PK. Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2004;1:176–83.
59. Yoshimura T, Moon TC, St Laurent CD, et al. Expression of nitric oxide synthases in leukocytes in nasal polyps. Ann Allergy Asthma Immunol. 2012;108:172–7.e2.
60. Chawes BL, Kreiner-Moller E, Bisgaard H. Upper and lower airway patency are associated in young children. Chest. 2010;137:1332–7.
61. Hellings PW, Hens G, Meyts I, et al. Aggravation of bronchial eosinophilia in mice by nasal and bronchial exposure to Staphylococcus aureus enterotoxin B. Clin Exp Allergy. 2006;36:1063–71.
62. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol. 2001;107:469–76.
63. Marcucci F, Passalacqua G, Canonica GW, et al. Lower airway inflammation before and after house dust mite nasal challenge: an age and allergen exposure-related phenomenon. Respir Med. 2007;101:1600–8.
64. Beeh KM, Beier J, Kornmann O, Meier C, Taeumer T, Buhl R. A single nasal allergen challenge increases induced sputum inflammatory markers in non-asthmatic subjects with seasonal allergic rhinitis: correlation with plasma interleukin-5. Clin Exp Allergy. 2003;33:475–82.
65. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. Am J Respir Crit Care Med. 2000;161:2051–7.
66. Braunstahl GJ, Overbeek SE, Fokkens WJ, et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. Am J Respir Crit Care Med. 2001;164:858–65.
67. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ. 1995;310:1225–9.
68. Lemanske Jr RF, Dick EC, Swenson CA, Vrtis RF, Busse WW. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest. 1989;83:1–10.

69. Grunberg K, Timmers MC, de Klerk EP, Dick EC, Sterk PJ. Experimental rhinovirus 16 infection causes variable airway obstruction in subjects with atopic asthma. Am J Respir Crit Care Med. 1999;160:1375–80.
70. Papadopoulos NG, Bates PJ, Bardin PG, et al. Rhinoviruses infect the lower airways. J Infect Dis. 2000;181:1875–84.
71. Mosser AG, Vrtis R, Burchell L, et al. Quantitative and qualitative analysis of rhinovirus infection in bronchial tissues. Am J Respir Crit Care Med. 2005;171:645–51.
72. Hellings PW, Hens G. Rhinosinusitis and the lower airways. Immunol Allergy Clin North Am. 2009;29:733–40.
73. Gern JE. Rhinovirus respiratory infections and asthma. Am J Med. 2002;112(Suppl 6A):19S–27.
74. Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164:1618–23.
75. Saitoh T, Kusunoki T, Yao T, et al. Role of interleukin-17A in the eosinophil accumulation and mucosal remodeling in chronic rhinosinusitis with nasal polyps associated with asthma. Int Arch Allergy Immunol. 2010;151:8–16.
76. Pakdaman MN, Corry DB, Luong A. Fungi linking the pathophysiology of chronic rhinosinusitis with nasal polyps and allergic asthma. Immunol Invest. 2011;40:767–85.
77. Pakdaman MN, Luong A. The links between chronic rhinosinusitis and asthma. Curr Opin Otolaryngol Head Neck Surg. 2011;19:218–23.
78. Ragab A, Clement P. The role of fungi in the airway of chronic rhinosinusitis patients. Curr Opin Allergy Clin Immunol. 2007;7:17–24.
79. Sejima T, Holtappels G, Kikuchi H, Imayoshi S, Ichimura K, Bachert C. Cytokine profiles in Japanese patients with chronic rhinosinusitis. Allergol Int. 2012;61:115–22.
80. Pezato R, Voegels RL. Why do we not find polyps in the lungs? Bronchial mucosa as a model in the treatment of polyposis. Med Hypotheses. 2012;78:468–70.
81. Rolla G, Colagrande P, Scappaticci E, et al. Damage of the pharyngeal mucosa and hyperresponsiveness of airway in sinusitis. J Allergy Clin Immunol. 1997;100:52–7.
82. Braunstahl GJ. The unified immune system: respiratory tract-nasobronchial interaction mechanisms in allergic airway disease. J Allergy Clin Immunol. 2005;115:142–8.
83. Bucca C, Rolla G, Brussino L, De Rose V, Bugiani M. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? Lancet. 1995;346:791–5.
84. Bucca C, Rolla G, Scappaticci E, et al. Extrathoracic and intrathoracic airway responsiveness in sinusitis. J Allergy Clin Immunol. 1995;95:52–9.
85. Boulet LP, Turcotte H, Laprise C, et al. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. Clin Exp Allergy. 1997;27:52–9.
86. Undem BJ, McAlexander M, Hunter DD. Neurobiology of the upper and lower airways. Allergy. 1999;54 Suppl 57:81–93.
87. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ. 2004;328:434.
88. Perez-Novo CA, Watelet JB, Claeys C, Van Cauwenberge P, Bachert C. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. J Allergy Clin Immunol. 2005;115:1189–96.
89. Adamjee J, Suh YJ, Park HS, et al. Expression of 5-lipoxygenase and cyclooxygenase pathway enzymes in nasal polyps of patients with aspirin-intolerant asthma. J Pathol. 2006;209:392–9.
90. Corrigan CJ, Napoli RL, Meng Q, et al. Reduced expression of the prostaglandin E(2) receptor E-prostanoid 2 on bronchial mucosal leukocytes in patients with aspirin-sensitive asthma. J Allergy Clin Immunol. 2012;129(6):1636–46.
91. Calabrese C, Triggiani M, Marone G, Mazzarella G. Arachidonic acid metabolism in inflammatory cells of patients with bronchial asthma. Allergy. 2000;55 Suppl 61:27–30.
92. Osler W. The principles and practice of medicine: designed for the use of practitioners and students of medicine. New York: D. Appleton and Company; 1892.
93. Boesch RP, Shah P, Vaynblat M, et al. Relationship between upper airway obstruction and gastroesophageal reflux in a dog model. J Invest Surg. 2005;18:241–5.
94. Turbyville JC. Applying principles of physics to the airway to help explain the relationship between asthma and gastroesophageal reflux. Med Hypotheses. 2010;74:1075–80.
95. McCallister JW, Parsons JP, Mastronarde JG. The relationship between gastroesophageal reflux and asthma: an update. Ther Adv Respir Dis. 2011;5:143–50.
96. Tasker A, Dettmar PW, Panetti M, Koufman JA, P Birchall J, Pearson JP. Is gastric reflux a cause of otitis media with effusion in children? Laryngoscope. 2002;112:1930–4.
97. Pinto JM, Baroody FM. Chronic sinusitis and allergic rhinitis: at the nexus of sinonasal inflammatory disease. J Otolaryngol. 2002;31 Suppl 1:S10–7.
98. Wong IW, Rees G, Greiff L, Kyers JC, Jamieson GG, Wormald PJ. Gastroesophageal reflux disease and chronic sinusitis: in search of an esophageal-nasal reflex. Am J Rhinol Allergy 2010;24:255–9.
99. DiBaise JK, Olusola BF, Huerter JV, Quigley EM. Role of GERD in chronic resistant sinusitis: a prospective, open label, pilot trial. Am J Gastroenterol. 2002;97:843–50.
100. Dibaise JK, Sharma VK. Does gastroesophageal reflux contribute to the development of chronic sinusitis? A review of the evidence. Dis Esophagus. 2006;19:419–24.
101. Turley R, Cohen SM, Becker A, Ebert Jr CS. Role of rhinitis in laryngitis: another dimension of the unified airway. Ann Otol Rhinol Laryngol. 2011;120:505–10.
102. Simberg S, Sala E, Tuomainen J, Ronnemaa AM. Vocal symptoms and allergy–a pilot study. J Voice. 2009;23:136–9.
103. Roy N, Merrill RM, Gray SD, Smith EM. Voice disorders in the general population: prevalence, risk factors, and occupational impact. Laryngoscope. 2005;115:1988–95.
104. Cohen SM. Self-reported impact of dysphonia in a primary care population: an epidemiological study. Laryngoscope. 2010;120:2022–32.
105. Cecil M, Tindall L, Haydon R. The relationship between dysphonia and sinusitis: a pilot study. J Voice. 2001;15:270–7.

106. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108:S147–334.
107. Jeffery PK, Haahtela T. Allergic rhinitis and asthma: inflammation in a one-airway condition. BMC Pulm Med. 2006;6 Suppl 1:S5.
108. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. J Allergy Clin Immunol. 2002;109:57–62.
109. Zuberbier T, Bachert C, Bousquet PJ, et al. GA(2) LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy. 2010;65:1525–30.
110. Lai L, Hopp RJ, Lusk RP. Pediatric chronic sinusitis and asthma: a review. J Asthma. 2006;43:719–25.
111. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. Allergy. 2006;61:737–42.
112. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. Curr Med Res Opin. 2004;20:1549–58.
113. Steinke JW, Kennedy JL. Leukotriene inhibitors in sinusitis. Curr Infect Dis Rep. 2012;14:147–54.
114. Gevaert P, Lang-Loidolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol. 2006;118:1133–41.
115. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. J Allergy Clin Immunol. 2010;125:1336–43.
116. Amrol D, Murray JJ. Alternative medical treatment strategies for chronic hyperplastic eosinophilic sinusitis. Curr Opin Otolaryngol Head Neck Surg. 2005;13:55–9.
117. Vichyanond P. Omalizumab in allergic diseases, a recent review. Asian Pac J Allergy Immunol. 2011;29:209–19.
118. Casale TB, Condemi J, LaForce C, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA. 2001;286:2956–67.
119. Adelroth E, Rak S, Haahtela T, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol. 2000;106:253–9.
120. Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. Allergol Int. 2006;55:379–86.
121. Holgate ST, Djukanovic R, Casale T, Bousquet J. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clin Exp Allergy. 2005;35:408–16.
122. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005;60:309–16.
123. Bousquet J, Reid J, van Weel C, et al. Allergic rhinitis management pocket reference 2008. Allergy. 2008;63:990–6.
124. Brozek JL, Baena-Cagnani CE, Bonini S, et al. Methodology for development of the Allergic Rhinitis and its Impact on Asthma guideline 2008 update. Allergy. 2008;63:38–46.
125. Ehnhage A, Olsson P, Kolbeck KG, et al. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. Allergy. 2009;64:762–9.
126. Ehnhage A, Olsson P, Kolbeck KG, Skedinger M, Stjarne P. One year after endoscopic sinus surgery in polyposis: asthma, olfaction, and quality-of-life outcomes. Otolaryngol Head Neck Surg. 2012;146(5):834–41.
127. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza DC. Long-term impact of functional endoscopic sinus surgery on asthma. Otolaryngol Head Neck Surg. 1999;121:66–8.

Chapter 12
Nonsteroidal Anti-inflammatory Drug Hypersensitivity and Sinus Disease

Jinny E. Chang, Andrew A. White, and Ronald A. Simon

Introduction

Some chronic rhinosinusitis patients have concurrent nasal polyposis, asthma, and aspirin sensitivity. These patients have aspirin-exacerbated respiratory disease (AERD). AERD is a condition consisting of both upper and lower airway inflammation with respiratory reactions to cyclooxygenase-1 (COX-1) inhibitors including aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs). First described by Widal in 1922 [1], it has been referred to as Samter's triad after Samter and Beers revisited the disease in 1968 [2]. The disease has also been referred to as aspirin-sensitive asthma and aspirin-intolerant asthma but is most aptly described by aspirin-exacerbated respiratory disease. AERD is characterized by the tetrad of adult onset of asthma, chronic rhinosinusitis with nasal polyposis, and ASA/NSAID sensitivity.

Initial Clinical Presentation

Many patients with AERD report that they can pinpoint the start of their disease with a viral upper respiratory infection in their late teens to middle age. The mean age of presentation however is approximately 34 years old [3]. The initial symptoms mimic a viral illness but seem persistent beyond the window of a typical infection and include chronic nasal congestion, rhinorrhea, and postnasal drip. This symptomatology evolves further into chronic rhinosinusitis with development of nasal polyposis, asthma, and anosmia within 1–5 years [4]. Interestingly, the sensitivity to ASA/NSAID can develop at any time in the course of the patient's disease. The reaction to aspirin can involve both upper and lower airway reactions including naso-ocular reactions (tearing, rhinorrhea, nasal congestion) and shortness of breath from laryngospasm and/or bronchospasm.

There is usually no pattern of familial inheritance or ethnic predilection in AERD. AERD is marginally more prevalent among females (57 % vs. 43 % males) [5].

There are many differences between CRS in AERD and CRS alone. CRS in AERD includes the other components of the tetrad in AERD of nasal polyposis, asthma, and aspirin sensitivity. Furthermore, the disease course, severity, and characteristics of AERD-associated CRS more profoundly affect quality of life. These will be discussed in greater detail later in this chapter. It is unclear at this time if the differences are due to the comorbidities affecting both upper and/or lower airways or possibly due to differences in the inherent pathophysiology of the disease.

J.E. Chang, MD (✉)
Department of Allergy, Asthma and Immunology, Sansum Clinic, 215 Pesetas Lane, Santa Barbara 93110, CA, USA
e-mail: jinny.chang@gmail.com

A.A. White, MD • R.A. Simon, MD
Division of Allergy, Asthma and Immunology, Scripps Clinic, 3811 Valley Centre Drive, S99, San Diego 92130, CA, USA
e-mail: simon.ronald@scrippshealth.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_12,

Asthma and AERD

Approximately 34 million Americans and most patients with AERD have been diagnosed with asthma by a healthcare provider [6]. Asthma in AERD, like all forms of chronic asthma, is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing [7]. These episodes are associated with airflow obstruction that often reverses spontaneously or with treatment. The generally accepted degree of reversibility in forced expiratory volume in 1 s (FEV1) that indicates a diagnosis of asthma is 12 % and 200 mL from the pre-bronchodilator value [7]. Immunohistopathologic features of asthma include inflammatory cell infiltration with neutrophils, eosinophils, lymphocytes, mast cell activation, and epithelial injury presenting as bronchoconstriction, airway edema, airway hyperresponsiveness, and airway remodeling. The clinical spectrum of asthma is highly variable in degree of presentation and clinical progression. The treatment goal of asthma is defined as using appropriate treatment which results in only occasional flare-ups with rare severe exacerbations. The mainstay medications for the treatment of AERD-associated asthma is consistent with standard asthma treatment guidelines and include short-acting beta agonists, long-acting beta agonists, leukotriene modifiers, inhaled corticosteroids, and systemic corticosteroids in cases of exacerbations. A stepwise approach to asthma therapy has been published as a national guideline and global strategy [7, 8] and should be referenced when determining which medications to start patients on.

The incidence and prevalence of asthma are rising in both adults and children [6]. While asthma is commonly thought of as a disease starting in childhood, onset can occur in adulthood. In AERD, patients generally experience adult-onset asthma. AERD comprises a relatively small proportion of asthmatics (up to 5 %) [9], but given the high prevalence of asthma, there are noteworthy number of patients with AERD.

Asthma in AERD patients behave differently than asthma in the general population. *The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens* study observed severe or difficult-to-treat asthma patients [10]. When comparing AERD patients ($n=459$) with non-aspirin-sensitive asthma ($n=2{,}848$), AERD patients had markers of more severe disease. AERD patients had objective markers of lung impairment with lower mean post-bronchodilator percent predicted FEV1 (75.3 % vs. 79.9 % ($p<0.001$) as well as higher intubation rates of 20 % vs. 11 % ($p<.001$). Among patients who required intubation, 8 % of asthma exacerbations were actually triggered by an NSAID. AERD patients also had more severe asthma by physician assessment (66 % vs. 49 % $p<.001$) and increased rates of high-dose inhaled corticosteroid use 34 % vs. 26 % ($p<.001$). In a study at Scripps Clinic, 230 of 300 (77 %) AERD patients had taken systemic corticosteroids in the previous year [5]. Daily prednisone was used in 51 of 230 (22 %) AERD patients, with an average of 7.5 mg/day, and 39 of 230 (17 %) were taking prednisone every other day. Short courses of prednisone for treatment of sinusitis or respiratory inflammation were taken in the past by 140 of 230 (61 %) of subjects during the year before undergoing a positive challenge to aspirin confirming AERD. Koga et al. studied a Japanese population of asthmatics, and AERD patients were much more likely (34.4 % vs. 5.4 %) to have multiple asthma exacerbations during the previous year and used higher inhaled corticosteroid maintenance dose including oral steroids [11]. This data suggests that AERD patients most commonly exhibit characteristics of severe asthma.

In general, severe asthma is more common in patients with CRS when compared to those without CRS [12]. The association becomes even stronger for asthmatic patients with chronic rhinosinusitis and nasal polyposis (CRSwNP) [13, 14]. It comes as no surprise that in AERD where both the upper and lower airways are involved with chronic inflammation, evidence of CRS would indicate worse disease. The diffuse airway involvement characteristic of AERD suggests that the treatment of asthma in these patients requires careful monitoring, medication use and compliance, and control of both the upper and lower airways concurrently.

Aspirin/NSAID Sensitivity in AERD

NSAIDs are used for their analgesic, antipyretic, and anti-inflammatory properties and are one of the most commonly administered medications. NSAIDs are a mainstay therapy for patients with arthritides to achieve pain relief and an acceptable quality of life. Aspirin is also used for primary and secondary prevention of cardiovascular events and strokes [15, 16]. Patients with AERD develop ASA/NSAID sensitivity anytime along their disease course as previously described. Until the sentinel event, these patients have a history of tolerating ASA/NSAID without respiratory reactions. Remarkably, symptoms of rhinorrhea, nasal congestion, laryngospasm, and bronchospasm following ASA/NSAID exposure are specific to ASA and COX-1 inhibitors. Specialized COX-2 inhibitors have not proven to be involved, and AERD patients appear able to tolerate COX-2 inhibitors [17, 18] (Table 12.1).

Table 12.1 Examples of inhibitors

Examples of COX-1 inhibitors
Aspirin
Ibuprofen
Ketorolac
Indomethacin
Diclofenac
Naproxen
Nabumetone
Etodolac
Sulindac
Ketoprofen
Examples of COX-2 inhibitors
Celecoxib
Rofecoxib[a]
Valdecoxib[a]

[a]Taken off the US market

Chronic Rhinosinusitis in AERD

CRS is the second most prevalent chronic medical condition and affects approximately 1 in 7 adults [19]. CRSwNP comprises 20–33 % of CRS disease [20]. AERD patients suffering from CRSwNP comprise of up to 15 % of total patients with CRSwNP. The histopathology of AERD-related CRSwNP demonstrates eosinophil-dominant inflammation and is characterized as hyperplastic sinusitis. In fact, chronic hyperplastic eosinophilic sinusitis has been used as a predictor of AERD by a study done by Mascia et al. [21].

CRSwNP is one of the most common indications for sinus surgery [22]. In 1994 alone, approximately 200,000 sinus surgeries for CRSwNP were performed in the United States. AERD patients have a more aggressive form of nasal/sinus polyposis based on symptom scores, objective CT and endoscopies, and frequency of repeat surgical procedures [23]. In general, the presence of polyps is associated with higher preoperative CT scores and higher preoperative and postoperative symptom scores [24]. However, aspirin-sensitive patients have significantly worse preoperative CT and endoscopy scores when compared to aspirin-tolerant patients with CRS [25].

It has been suggested that the AERD patients are predisposed to secondary infections and biofilm formation as the polypoid tissue is abnormal and lacks a ciliary mucosal blanket [26]. The implied decreased ciliary clearance and biofilm formation superimposed on the already swollen AERD sinus membranes may lead to manifestations of more aggressive disease. While a similar proportion of aspirin-sensitive and aspirin-tolerant CRS patients improve following functional endoscopic sinus surgery (FESS) using quality of life (QOL) instruments [25], Kim et al. found that patients with AERD had 10 times as many previous FESS procedures than those without AERD. Furthermore, these authors found that AERD patients had higher rates of symptom recurrence (nasal obstruction, facial pain, postnasal drip, and anosmia) at 6-month follow-up [27]. AERD patients appear to have higher rates of symptom recurrence, are much less likely to retain long-term benefits from FESS, and are more likely to require repeated future sinus procedures [28–30].

It has been suggested that this more aggressive form of polyp disease is secondary to a greater degree of inflammation and mucosal hyperplasia in AERD, as evidenced by CT imaging scores of the sinuses when compared to aspirin-tolerant asthmatics [21]. In a study over a 12-month period, CRS patients received an average of 2.7 antibiotic courses and used nasal steroids and prescription antihistamines 18.3 and 16.3 weeks, respectively [31]. In contrast, patients with AERD suffer an average of 5.5 sinus infections per year [5].

Anosmia/Hyposmia in AERD

Anosmia or hyposmia is a frequent complaint of AERD patients. Decreased or loss of ability to smell can impair QOL. Problems associated with anosmia include taste disturbance, anorexia, and health risks such as not being able to smell smoke in an emergency. Olfactory function correlates best with mucosal inflammation in contrast to nasal patency in chronic rhinosinusitis [32]. Therefore, one would expect that FESS would not commonly resolve anosmia in AERD. In fact, recovery of

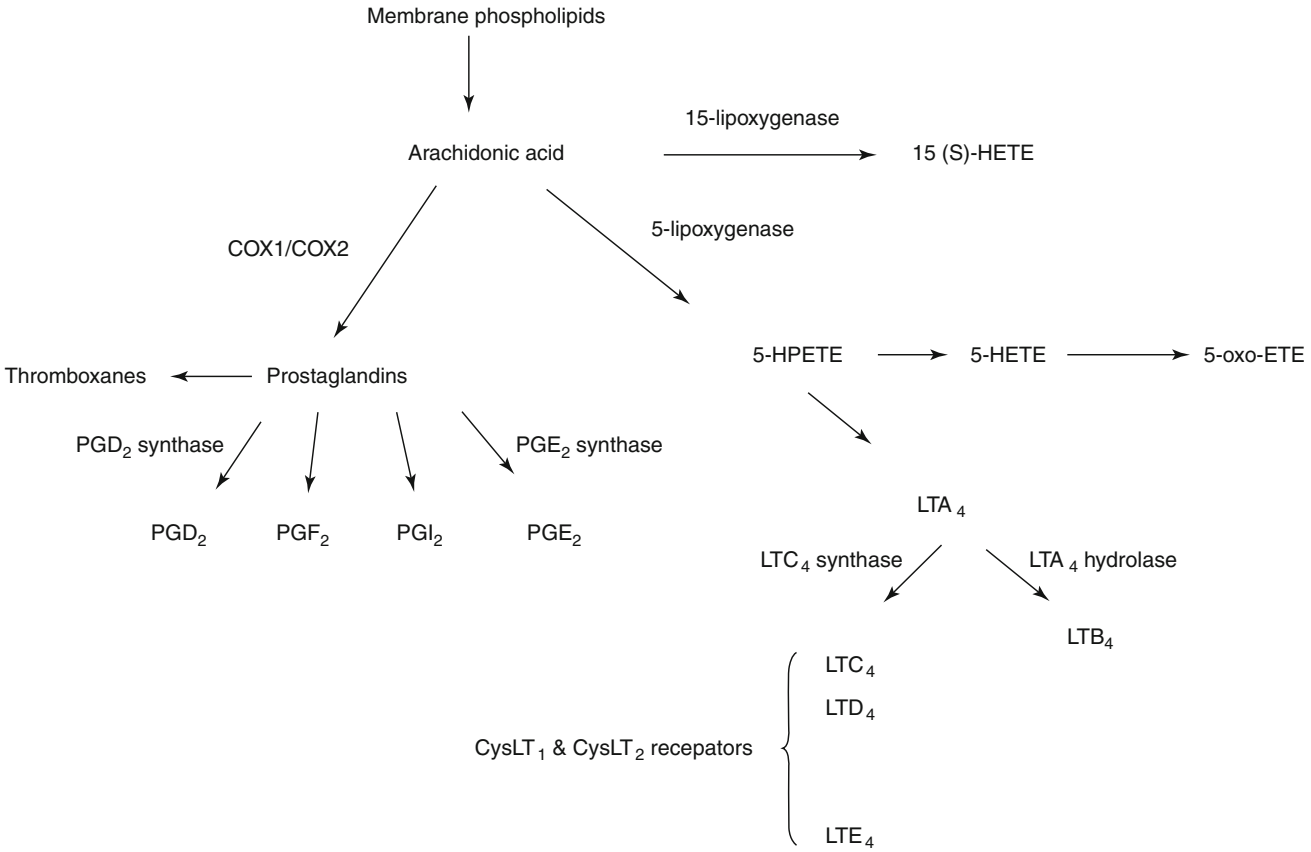


Fig. 12.1 Arachidonic acid metabolism toward the 5-lipoxygenase pathway and the synthesis of prostaglandins

a normal sense of smell remained limited in post-FESS AERD patients in a study of olfactory outcome using Sniffin' Sticks 6 months following FESS [33].

Pathogenesis of AERD

The pathogenesis of AERD is not yet clear. Aspirin and NSAIDs are nonselective COX-1 inhibitors that promote a shunt of arachidonic acid (AA) metabolism toward the 5-lipoxygenase pathway and alter the synthesis of prostaglandins (PG). The resultant AA metabolic shift increases the release of inflammatory mediators such as cysteinyl leukotrienes (LTs) LTC4, LTD4, and LTE4 which are potent bronchoconstrictors [34]. The altered metabolic pathway also leads to a decrease in PGE2, a well-known suppressor of inflammation [6, 9]. The interplay of proinflammatory metabolites and a decrease in inflammatory suppressors may play a role in AERD development (Fig. 12.1).

Like many other diseases, environmental factors and their effects on epigenetics may play a role in AERD development. To date, environmental tobacco smoke including prenatal exposure to tobacco has been linked to asthma [35]. However, epidemiologic research on environmental tobacco smoke and CRS has not been conclusive [36]. A recent case-control study has linked 5 years of environmental tobacco smoke during adulthood with CRS [37]. However, AERD may be different. In a recent study examining the association between AERD development and exposure to environmental tobacco smoke during childhood and adulthood, the exposure during both childhood and adulthood demonstrated an odds ratio (OR) of 5.09 (95 %CI, 2.75–9.43) [38]. Active tobacco smoke also proved to be associated with AERD development (OR, 1.54; 95 % confidence interval [CI], 1.04–2.28). In the same study, no statistically significant risk was found in patients who experienced adulthood environmental tobacco smoke alone, perhaps highlighting the importance of childhood exposure in development of AERD.

Given the clinical history of viral infection as a possible trigger for AERD patients and accumulated studies on the role of upper respiratory viral infections as triggers for asthma development and subsequent exacerbations, viral infection may be the potential "hit" in a multifactorial cascade that leads to AERD. In fact, one hypothesis suggests that the onset and

perpetuation of AERD begins with a rhinovirus infection. Due to defects in immune regulators found in AERD, there is perpetuation of viral infection/susceptibility. In a study using reverse transcription polymerase chain reaction, the results of bronchial biopsies of 7 of 7 AERD patients were positive for rhinovirus RNA [39]. While this finding was not limited to asthmatic patients with AERD, this may be a clue that AERD patients lack important antiviral protective responses. In fact, since viral respiratory infections are one of the most common provoking factors of acute asthma exacerbations in both children and adults with all varieties of asthma [40], it is plausible that all asthmatic patients may lack important antiviral protective responses in airway epithelium such as innate immune responses (interferon secretion, macrophage, and TH1 cell dysfunction) and poorly functioning mucociliary clearance. Such an altered immune response to rhinovirus infection could be enhanced through epithelial cells exposed to cigarette smoke and possibly closing the link between the asthmatic patient and an increased risk for AERD [41].

While genetic studies in AERD patients have suggested a variability of genes that might promote susceptibility [42], polymorphisms identifying definitive molecular candidates for the pathogenesis or biomarkers of AERD have not been found. Examples of polymorphisms identified for AERD include LTC4 synthase (LTC4S), cysteinyl-LT receptors, and prostaglandin E receptor [43]. However, genetic data demonstrating an association with AERD have been conflicting. In a Polish study of AERD patients, an LTC4S SNP with increased transcription of the enzyme LTC4S has been previously described [44]. Neither phenotype nor enzyme functionality has been replicated in a US population [45]. In fact, the same LTC4S polymorphism was associated with chronic hyperplastic eosinophilic sinusitis and was independent of aspirin sensitivity [46].

In another study, cysteinyl-LT receptor 1 promoter SNP in AERD patients was shown to be a useful marker for predicting montelukast requirements to control asthma symptoms [42]. In the same study, SNPs in various genes, including *LTC4S*, *COX-2,* and *TBXA2R* (thromboxane A2 receptor), were studied without revealing the same clinical relevance.

Non-Mendelian inheritance is highlighted in aspirin sensitivity as only 5.1 % of patients have a familial occurrence [47]. Given the likely multifactorial nature of AERD, further genetic evaluation may uncover numerous SNPs. Perhaps a specific pattern will emerge in the future that will point to the key culprit in the pathogenesis of AERD. Currently, it is unclear what clinical implication genetic evaluation may have on diagnostic or therapeutic approaches to AERD. Although genetic polymorphisms may serve as biomarkers for AERD research, establishing AERD in the individual patient remains a clinical diagnosis.

Burden of Disease in AERD

Burden of disease can be divided into direct and indirect costs. Direct costs include money spent on physician visits, medications, operations, or procedural costs such as surgery. Indirect costs include missed work/school days as well as loss of productivity. AERD is a unique syndrome with a tetrad of disorders; therefore, the burden of disease is an aggregate for the overlapping components of CRSwNP, asthma, and aspirin sensitivity. The burden additionally includes the effects of common comorbid condition such as allergic rhinitis. Due to the overlays in direct and indirect costs from each disease component, data for each condition cannot be simply added together. However, we can infer that there is a high degree of strain on AERD patients. As this is a disease without a cure, the burden of disease would also be cumulative.

Asthma

The healthcare costs for all asthmatics in the United States were $50.1 billion in 2007 [48]. Analyzing productivity, the United States lost about $3,300 per person with asthma each year from 2002 to 2007 in medical expenses, missed school and work days, and early deaths. As asthma in AERD is unveiled in adulthood, adult data should be highlighted. In 2007, adults with asthma had 7.2 million visits to private physician offices, 1.11 million emergency department visits, and 600,000 hospital outpatient department visits [49]. In 2008, adult patients with asthma missed 14.2 million workdays due to their asthma, and nearly 34 % missed at least 1 work day due to asthma in the previous year [49]. While these numbers should be adjusted to the proportion of AERD patients (up to 5 % of asthmatics), the cost-related load remains high.

The Impact of Asthma Control

Severe and difficult-to-control asthma is a common phenotype in AERD. Healthcare expenditure (office visits and drug costs) for asthmatic patients whose symptoms were well controlled was $6,352 vs. $14,212 for uncontrolled disease [50].

Uncontrolled asthma also leads to a rise in indirect costs. In 1,199 patients with moderate to severe asthma who completed the Asthma Therapy Assessment Questionnaire (ATAQ) scores ranging from 0 to 4 (0 indicating no asthma control problems), decreasing levels of asthma control were associated with greater prevalence of sleep problems, depression, functional impairment, and effect on work and regular activities [51].

Aspirin Sensitivity

For those with aspirin sensitivity, alternative approaches in cardiac care, such as clopidogrel, make aspirin therapy a more cost-effective choice by tenfold for quality-adjusted life year (QALY) gained [52]. When anti-inflammatory or analgesic medications are required, selective COX-2 inhibitors [17, 18] are well tolerated in AERD patients. However, the direct cost of these medications is considerably higher when compared to over-the-counter NSAIDs [53]. Even AERD patients who know they must avoid COX-1 inhibitors sometimes inadvertently take aspirin or other NSAIDs, leading to a costly flare of symptoms. Following aspirin desensitization, however, patients with AERD are able to tolerate aspirin and other NSAIDs again and experience disease improvement leading to a cost-saving benefit.

Allergic Rhinitis

Allergic rhinitis is not a defined element of AERD; however, 66 % of patients have positive skin testing and clinically demonstrate a range of allergic severity [47]. In some patients, symptoms are mild and do not add morbidity to AERD. In others, atopic disease is severe and leads to additional symptoms that confound the AERD picture. As a disease, the mean annual expenditure for those with an out-of-pocket expense related to allergic rhinitis was $520 per person in 2005 [54]. Allergic rhinitis was the fifth most costly disease in a study evaluating ten different diseases in 375,000 employees [55]. Productivity is an indirect cost and Blaiss et al. showed that patients rated their productivity at work when symptomatic vs. asymptomatic was 95 % vs. 72 % [56]. Allergic rhinitis patients also have sleep deprivation and sexual impairment [57]. For AERD patients, many of the direct and indirect costs of CRS and asthma are amplified by any coexisting allergically triggered airway dysfunction.

Treatment in AERD

AERD is a unique inflammatory condition of the respiratory tract. Although several treatments options are similar in effectiveness to therapy used in other inflammatory sinus diseases, it is the option of aspirin desensitization that sets AERD apart in terms of treatment from all other diseases of the sinuses.

AERD and Desensitization

Desensitization to ASA in AERD becomes an integral pillar of treatment for many patients. In this setting, desensitization refers to the regular administration of ASA in order to maintain a desensitized state. The actual “desensitization procedure” takes place under the supervision of an allergist and generally requires 2 days to accomplish, but as a therapy, desensitization is the long-term administration of aspirin to maintain a desensitized state. The benefits from ASA desensitization occur only in the setting of regular daily administration of ASA and are lost approximately 48 h after the last dose is taken. For most patients, desensitization is undertaken in an effort to better control underlying airway inflammation. Patients with a compelling need for ASA therapy such as for cardiovascular disease [58] or those with rheumatologic conditions requiring regular NSAIDs gain both the respiratory disease benefits as well as the benefits from ASA or NSAIDs on the other coexistent diseases.

Numerous studies quantify the benefit from ASA therapy in AERD [47, 59–62]. In the upper airways, a decrease in sinus surgery requirements, a decrease in sinus infections, and an improvement in sense of smell have all been shown. Similarly,

the lower airways benefit with effects that include decreased need for systemic corticosteroids, less emergency room visits and hospitalizations for asthma, and improvement in asthma symptoms. Another obvious benefit of ASA desensitization is the ability to use this medication daily for cardiovascular indications [58]. Therefore, ASA desensitization should be considered for the individual with a need for unacceptably high doses of systemic corticosteroids and recalcitrant sinus disease requiring repeated surgical interventions or those with persistent ongoing symptoms that have not responded to other conventional therapies [63]. While the process of aspirin desensitization itself is a direct cost to the AERD patient, the procedure can decrease both direct and indirect costs. In an economic analysis of aspirin desensitization of AERD, a study showed that ambulatory desensitization for AERD cost $6,768 per QALY saved ($18.54 per additional symptom-free day). Aspirin desensitization for AERD remained cost-effective (<$50,000 per QALY saved) across a wide range of assumptions. While this is not a direct study of patients with AERD vs. patients without the disease, it shows a significant difference in those with AERD and those with better-controlled AERD as a result of aspirin desensitization [64].

Dose of Aspirin for Desensitization

The bulk of evidence shows that the dose of ASA necessary to treat the airway disease is in the range of 650 to 1,300 mg of ASA per day (dose 325 mg, 1 tablet twice daily to 2 tablets twice daily). In one smaller study, 100 mg of daily ASA was ineffective while 300 mg was effective at controlling sinus disease [65]. Therefore, 300–325 mg of daily ASA therapy represents the lower limits of effectiveness of chronic ASA therapy in AERD. Doses of 325 mg per day are less likely to give clinical benefit when compared with higher doses [66]. A recent report identified the difficulty in predicting the dose of ASA that patients will have an optimum response to. In this study patients were randomly assigned to 650 or 1,300 mg cumulative daily ASA dose. While both doses were effective, about half of the patients in the high-dose arm were able to decrease to a 650 mg daily dose, while half of the group initially randomized to the 650 mg daily dose found it necessary to increase to the high dose (1,300 mg daily dose) due to inadequate symptom control [61]. This suggests the presence of a dose effect of ASA therapy in AERD. While some patients may have a benefit from ASA doses in the 300 mg daily range, many of these would likely enjoy a greater benefit to their respiratory tree by increasing the ASA dose.

Side Effects

Chronic ASA therapy is not without risk. Dyspepsia ranks as the most common reason that patients discontinue or reduce the dose of ASA [61]. Bleeding or ecchymosis and urticaria/angioedema were also some of the more common reasons for ASA cessation. Another less common but more severe adverse effect is gastric bleeding (2/172) [47]. At the end of 1 year, between 14 and 16 % of patients will discontinue ASA due to adverse effects [47, 61]. Another adverse effect of ASA or NSAID therapy is acute kidney injury. Many patients are on angiotensin converting enzyme inhibitors or angiotensin receptor blockers at the time of ASA desensitization. Co-therapy with either of these antihypertensives and ASA can increase the risk of acute kidney injury and should be taken into consideration if long-term treatment with ASA is planned [67]. Although the benefits of aspirin desensitization will outweigh the risks for most patients, an informed discussion of the risks of lifetime treatment with aspirin is warranted.

ASA Desensitization Specifics

Over the last two decades, great improvements to the protocol for aspirin desensitization have been made. What once used to be carried out as an inpatient over the course of a week can now be performed over the course of 2 days as an outpatient for most individuals. Improvements in the use of prophylactic agents taken during the time of desensitization and alternative techniques such as local nasal ketorolac application have made aspirin desensitization accessible to many local allergists/immunologists.

The desensitization should take place after a properly selected patient is identified. Patients should have stable airway disease and an FEV1 > 70 %. Stable airways can be identified by performing two FEV1 maneuvers in the weeks before desensitization. Patients with unstable airways should be given systemic steroids to optimize pulmonary function during

Table 12.2 Sample outpatient aspirin desensitization protocol

Prior to desensitization
1. Document airway stability with FEV1 >60–70 % predicted (>1.5 L absolute)
2. FEV1 every hour × 3 h with <10 % variability
3. Start montelukast 10 mg daily for 7 days prior
4. Adequately control underlying airway disease with ICS/LABA
5. If evidence of low FEV1 or instability, start systemic corticosteroids
6. No antihistamines 48 h prior to challenge
Protocol
1. Start intravenous line with heparin lock
2. First dose 20.25–40.5 mg[a]
3. Subsequent doses: 60, 81, 101, 162.5 (1/2 of 325 mg), and 325 mg
4. Doses are administered every 3 h with clinical assessment and FEV1 each hour[b]
5. Reactions generally occur between 20 and 100 mg (see Table 12.1 for treatment)
6. After the patient has stabilized, readminister the "provoking dose"
7. If time limits the readministration of the provoking dose, it can be given at the beginning of day 2
8. The desensitization can be stopped when 325 mg of aspirin is administered without reaction
9. Discharge patient on 650 mg of aspirin twice daily

Reprinted from Lee et al. [61]. With permission from Elsevier
[a]Some protocols recommend dosing every 90 min
[b]Doses can be made using a pill cutter to an 81 mg aspirin

desensitization. Also, the addition of a long-acting beta agonist during the desensitization likely prevents instability of the airways during the desensitization and limits the chances of falsely identifying a drop in pulmonary function from airway instability during the challenge as a positive aspirin challenge. While not all patients necessarily need to have an intravenous line started before the desensitization, it should be considered in patients where a more aggressive reaction is anticipated. Finally, all desensitization centers should have resuscitation equipment available and experienced nursing staff to assist in the treatment and monitoring of reactions when they occur. While most ASA desensitizations can be performed in an outpatient setting, some physicians still choose to perform desensitization as an inpatient due to nursing requirements or inability to adequately manage asthmatic reactions in the clinic.

Aspirin Desensitization Protocol

Doses are administered starting at approximately 30 mg ASA. The dose which causes the reaction is termed the "provoking dose." The reaction is treated and then the same dose is then repeated. In most cases the reaction to the second dose is attenuated if not absent altogether. Initial protocols used doses of 30, 45, 60, 100, and 150 mg of aspirin. These doses need to be created in a compounding pharmacy and may not be practical for many clinics. Table 12.2 shows an alternative dosing strategy based on splitting 81 mg aspirin with a pill cutter. This is another acceptable strategy to create the necessary doses for desensitization. The desensitization is completed when the patient has received 325 mg of ASA without reaction. Older protocols continued desensitization until 650 mg of aspirin was successfully given, but in a large series of patients, no patient reacted after the 650 mg dose, so giving this dose is no longer necessary to complete desensitization. Without continued dosing, the desensitized state lasts approximately 48 h. After this time, if no more ASA is administered, desensitization will be lost completely by 96 h. It is incumbent on the patient to understand that ASA desensitization is an ongoing treatment.

Nasal Ketorolac

In the United States, the only accessible form of ASA has been in an oral formulation. The use of an aqueous form of aspirin (lysine-aspirin) is well documented in many other countries around the world to be useful in nasal challenges, intravenous challenges, or bronchial inhalation challenges. In fact, previous desensitization and ongoing treatment with nasal L-ASA has been reported [68]. Although the United States does not have an FDA-approved aqueous preparation of ASA, ketorolac (a potent COX-1 inhibitor) is available for intravenous or intramuscular administration for pain. In a simple dilution with saline, this can then be administered nasally either for a diagnostic challenge or to enhance the aspirin challenge [69, 70].

An initial pilot study demonstrated that the sensitivity and specificity of nasal ketorolac compared favorably with L-ASA in various European studies. Interestingly, in this pilot study, several patients clearly reacted to the nasal challenge, but subsequent dosing with oral aspirin led to no further reaction, suggesting that desensitization was completed during the nasal ketorolac nasal application.

A subsequent study demonstrated that when used during the initial phases of aspirin desensitization by decreasing the severity of gastrointestinal or laryngeal symptoms and also by improving the time it takes to completely desensitize the patient from 3 to 2 days. The ease of use of nasal ketorolac and the favorable improvement in symptoms during desensitization make this a useful addition for clinical use.

Leukotriene-Modifying Drugs (LTMDs) in AERD and During Desensitization

Given the dramatic outpouring of leukotriene mediators in the AERD reaction, the use of pharmacologic therapy targeting this particular pathway would seem to offer promise in treatment of the underlying disease and attenuation of the acute reaction to ASA in AERD. In the United States, the leukotriene receptor antagonists montelukast and zafirlukast are available, as is the 5-lipoxygenase inhibitor zileuton. In treatment of the underlying inflammatory airway disease in AERD, both zileuton and montelukast have been evaluated. Zileuton was associated with improvement in pulmonary function, need for less rescue inhaler use, and improvement in sense of smell [71]. In a similar double-blinded, placebo-controlled trial of 80 patients, montelukast was shown to improve several measures of asthma including FEV1 [72]. Similarly, an improvement in nasal symptoms and function was observed after a 4-week trial of montelukast when compared with placebo [73]. What is unexpected is that AERD patients do not have an enhanced response to leukotriene modifier drugs. The response to treatment appears to be roughly similar to the non-AERD asthmatic population [74, 75].

However, during the reaction from ASA, LTMDs, particularly montelukast, have an important modulatory role. Montelukast has been studied the most, likely due to its ready availability in the United States. It is clear that the use of montelukast during ASA challenges changes the nature of the reaction. Reactions shift from involving both the upper and lower airways to primarily upper airway reactions [76, 77]. This has been shown to decrease the magnitude drop in FEV1, thereby enhancing the safety of these reactions [78]. In these studies, the negative challenge rate remained unchanged from historical rates prior to the introduction of LTMDs to the market or to the negative challenge rate in those patients not taking an LTMD. Thus, there does not appear to be a significant risk that the entire ASA reaction could be completely masked by the use of montelukast. One study challenged 10 patients with ASA before and then while using montelukast. In one of these ten patients, the reaction appeared to be blocked completely by montelukast [79]. So, while likely very rare, there may be patients who undergo a "silent" challenge or desensitization to ASA while taking an LTMD.

In other studies, pranlukast use during ASA challenge led to diminished respiratory reactions yet failed to decrease aspirin-induced leukotriene production [80]. In studies evaluating the nasal response, montelukast pretreatment protected against local effects from nasal ASA-lysine challenge with no difference observed between a 10 and 40 mg montelukast dose [81]. In a 4-week placebo-controlled trial, montelukast significantly improved nasal flow and symptoms to nasal ASA-lysine challenge [74]. Discordant results evaluating zileuton in protection of the ASA-induced reaction exist. Israel and colleagues found zileuton to completely protect the upper and lower airways from ASA challenge at a predetermined provoking dose [82]. Increasing doses of ASA were not investigated. Pauls et al. found that zileuton did not offer complete protection to any of six patients undergoing ASA challenge and desensitization [83]. The authors conclude that zileuton may offer a degree of benefit by shifting the response to a higher dose of ASA, but that complete blockade of the ASA-induced reaction by zileuton likely does not occur.

These studies demonstrate that LTMD therapy can be considered as part of the maintenance therapy for the AERD patient, recognizing that benefit to the airways would not be any different than in aspirin-tolerant asthma. But, during the acute desensitization process, LTMD therapy, specifically montelukast, should be strongly considered as a means of increasing the safety of the oral challenge.

Local Nasal Desensitization

Several studies have evaluated a role of ASA-lysine in desensitization, primarily to treat nasal polyposis [68, 84–86]. Of these, two have demonstrated an improvement in outcomes with intranasal chronic ASA-lysine administration, yet the only

double-blinded controlled trial failed to show significant clinical benefit [86]. Further studies in this regard are recommended to address this important issue.

Desensitization Events

The mechanism behind ASA desensitization remains unclear. It certainly represents a uniquely different desensitization process when compared with traditional allergen immunotherapy which effects a long-term immunological change or standard antibiotic desensitization which allows continued use of the drug on a regular basis but leads to no long-term immunological effect. In ASA desensitization, the continued use of ASA exerts a disease-modifying effect, yet permanent effects are not seen in that the ability to safely take ASA is lost after 48–96 h have elapsed from the last dose [87]. The beneficial effects of ASA desensitization are thought to rapidly wane after that time.

Several concepts have shaped the degree to which the mechanism of ASA desensitization is understood. Leukotriene B4, one of the products of AA metabolism, is reduced after ASA desensitization to levels seen in normal controls [88]. In AERD patients after acute and chronic desensitization, a rise in urinary LTE_4 still occurred with administration of ASA, but this rise was less intense than during the ASA-provoked reaction. Despite the increase in urinary LTE_4, there was no concomitant decrease in FEV1 [89]. Airway responsiveness to inhaled LTE_4 decreases markedly on the day following ASA desensitization [90, 91]. Cys-LT1 receptors are elevated at baseline in AERD patients, yet decrease to levels seen in ASA-tolerant asthmatics after chronic desensitization [92]. These findings support a conclusion that in the desensitized individual, although leukotrienes are still produced, they are no longer able to effect the pronounced inflammatory changes.

A recent paper by Katial et al. demonstrated a decrease in sputum IL-4 6 months following aspirin desensitization [62]. This important observation corroborates observations by in vitro studies showing that aspirin, at therapeutic levels, can decrease IL-4 through a STAT6 mechanism. It is likely that it is through off-target, non-COX-1-mediated pathways that ASA exerts an anti-inflammatory benefit. CysLT receptor production, as well as several other inflammatory pathways in AERD, is dependent on IL-4. It is certainly possible that the beneficial effects of aspirin desensitization may be mediated by blocking IL-4 activity. This concept is worthy of further extensive study.

It is unclear why this possible anti-IL4 effect of aspirin in AERD is not effective in the approach to patients with nasal polyps or asthma that do not have AERD. It is still unknown why aspirin therapy is only effective in AERD, as well as why AERD only occurs in a minority of patients with a similar phenotype of chronic sinusitis, nasal polyposis, and asthma.

Concomitant Allergic Diseases of the Sinuses

Aspirin desensitization in AERD can be achieved in nearly every patient, but approximately 10–15 % of patients will not receive benefit from ongoing aspirin therapy. It is unknown why not all patients obtain benefit from aspirin therapy, particularly since there is such a consistent phenotype to this inflammatory disease of the sinuses. It is likely though that in addition to AERD, many of these patients may have severe allergic rhinitis and some also may develop allergic fungal sinusitis. Some patients also may be found to have a humeral immunodeficiency. Therefore, clinicians must be persistent in evaluating and treating these conditions when they coexist with AERD.

Additional Therapies for Asthma

AERD is a condition that involves the entire respiratory tract. While ASA is a proven therapy for AERD, it is not a cure, and when patients have symptoms of asthma, it is critical that asthma symptoms be treated. Generally, most AERD patients will likely require an inhaled corticosteroid for control of lower airway inflammation with systemic corticosteroid use in cases of severe exacerbations. A stepwise approach to asthma therapy has been published as a national guideline, and an updated version should be referenced when determining starting medication as well as maintaining asthma control. Close monitoring of symptoms and treatment from a trained physician along with objective measurements such as FEV1 is recommended. In the case of AERD, asthma maintenance requires great care given the morbidity and possible mortality issues that arise given the severity of the asthma.

Conclusion

AERD is defined by concurrent condition of chronic rhinosinusitis with nasal polyposis, asthma, and aspirin/NSAID sensitivity. The sensitivity to aspirin and other NSAIDs presents as upper and/or lower airway reactions including naso-ocular reactions and shortness of breath from laryngospasm and/or bronchospasm. Patients with presumed AERD should avoid aspirin and other NSAIDs. Patients who have AERD can be diagnosed clinically; however, only aspirin challenge can confirm the diagnosis. Aspirin desensitization can both allow patients with AERD to tolerate aspirin and other NSAIDs as well as aid in the treatment of AERD. The management of AERD requires vigilant treatment of all the components of AERD with multiple controller agents as exacerbation of each condition can overlap and affect the overall disease state of AERD.

References

1. Widal MF, Abrami P, Lenmoyez J. Anaphylaxie et idiosyncrasie. Presse Med. 1922;30:189–92.
2. Samter M, Beers Jr RF. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. Ann Intern Med. 1968;68:975–83.
3. Szczeklik A. Aspirin-induced asthma as a viral disease. Clin Allergy. 1998;18(1):15–20.
4. Szczeklik A, Nizankowska E, Duplaga M, On behalf of the AIANE Investigators. Natural history of aspirin-induced asthma. Eur Respir J. 2000;16:432–6.
5. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2002;89:474.
6. American Lung Association. Epidemiology & Statistics Unit, Research and Program Services. Trends in asthma morbidity and mortality. 2011.
7. From the Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA). 2011. Available from: http://www.ginasthma.org/.
8. Expert panel report 3: guidelines for the diagnosis and management of asthma. Update on selected topics 2007. NIH Publication No. 08-4051. Bethesda: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program; 2007.
9. Kasper L, Sladek K, Duplaga M, Bochenek G, Liebhart J, Gladysz U, et al. Prevalence of asthma with aspirin hypersensitivity in the adult population of Poland. Allergy. 2003;58:1064–6.
10. Lee JH, Haselkorn T, Borish L, et al. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: insights from the TENOR study. Chest. 2007;132(6):1882–9.
11. Koga T, Oshita Y, Kamimura T, et al. Characterization of patients with frequent exacerbation of asthma. Respir Med. 2006;100:273–8.
12. Liou A, Grubb JR, Schechtman KB, et al. Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care. Chest. 2003;124:1781–8.
13. Bachert C, Claeys SE, Tomassen P, et al. Rhinosinusitis and asthma: a link for asthma severity. Curr Allergy Asthma Rep. 2010;10:194–201.
14. Pearlman AN, Chandra RK, Chang D, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. Am J Rhinol Allergy. 2009;23:145–8.
15. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;150(6):405–10.
16. Antithrombotic Trialists' Collaboration, Biagent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. Lancet. 2009;373(9678):1849–60.
17. Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. J Allergy Clin Immunol. 2001;108:47–51.
18. Woessner KM, Simon RA, Stevenson DD. The safety of celecoxib in aspirin exacerbated respiratory disease. Arthritis Rheum. 2002;46:2201–6.
19. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. Vital Health Stat. 2009;10(242):1–157.
20. Dykewicz MS, Hamilos DL. Rhinitis and sinusitis. J Allergy Clin Immunol. 2010;125(suppl):S103–15.
21. Mascia K, Borish L, Patrie J, et al. Chronic hyperplastic eosinophilic sinusitis as a predictor of aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2005;94:652–7.
22. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. J Allergy Clin Immunol. 2011;128(4):693–707.
23. Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside. Current findings, future directions. J Allergy Clin Immunol. 1997;99(suppl):S829–48.
24. Kountakis SE, Arango P, Bradley D, et al. Molecular and cellular staging for the severity of chronic rhinosinusitis. Laryngoscope. 2004;114(11):1895–905.
25. Robinson JL, Griest S, James K, et al. Impact of aspirin intolerance on outcomes of sinus surgery. Laryngoscope. 2007;117(5):825–30.
26. Lenz H. The surface of nasal polyps in the scanning electron microscope. Laryngol Rhinol Otol. 1975;54(12):950–64.
27. Kim J, Kountakis SE. The prevalence of Samter's triad in patients undergoing functional endoscopic sinus surgery. Ear Nose Throat J. 2007;86(7):396–9.
28. Garrel R, Gardiner Q, Khudjadze M, et al. Endoscopic surgical treatment of sinonasal polyposis-medium term outcomes (mean follow-up of 5 years). Rhinology. 2003;41:91–6.

29. Young J, Frenkiel S, Tewfik MA, et al. Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis. Am J Rhinol. 2007;21:743–7.
30. Veno SI, Ertama LO, Hytonen ML, et al. Nasal polyposis: clinical course during 20 years. Ann Allergy Asthma Immunol. 2000;85:209–14.
31. Bhattacharyya N. The economic burden and symptom manifestations of chronic rhinosinusitis. Am J Rhinol. 2003;17(1):27–32.
32. Litvack JR, Mace JC, Smith TL. Olfactory function and disease severity in chronic rhinosinusitis. Am J Rhinol Allergy. 2009;23(2):139–44.
33. Katotomichelakis M, Riga M, Davis S, et al. Allergic rhinitis and aspirin-exacerbated respiratory disease as predictors of the olfactory outcome after endoscopic sinus surgery. Am J Rhinol Allergy. 2009;23(3):348–53.
34. Holgate ST, Peters-Golden M, Panettieri RA, Henderson WR. Roles of cysteinyl leukotrienes in airway inflammation, smooth muscle function, and remodeling. J Allergy Clin Immunol. 2003;111(1 Suppl):S18–34; discussion S34–6.
35. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. Pediatrics. 2004;113(S3):1007–15.
36. Scientific Committee on Tobacco and Health. Report of the Scientific Committee on Tobacco and Health. London: HMSO; 1998.
37. Lieu JE, Feinstein AR. Confirmations and surprises in the association of tobacco use with sinusitis. Arch Otolaryngol Head Neck Surg. 2000;126:940–6.
38. Chang JE, Ding D, Martin-Lazaro J, White A, Stevenson DD. Smoking, environmental tobacco smoke, and aspirin exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2012;108:14–9.
39. Wos M, Sanak M, Soja J, Olechnowicz H, Busse WW, Szczeklik A. The presence of rhinovirus in lower airways of patients with bronchial asthma. Am J Respir Crit Care Med. 2008;177:1082–9.
40. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. J Allergy Clin Immunol. 2010;125:1178–87.
41. Eddleston J, Lee RU, Doerner AM, Herschbach J, Zuraw BL. Cigarette smoke decreases innate responses of epithelial cells to rhinovirus infection. Am J Respir Cell Mol Biol. 2011;44:118–26.
42. Kim SH, Ye YM, Hur GY, et al. CysLTR1 promoter polymorphism and requirement for leukotriene receptor antagonist in aspirin-intolerant asthma patients. Pharmacogenomics. 2007;8:1143–50.
43. Palikhe NS, Kim JH, Park HS. Update on recent advances in the management of aspirin exacerbated respiratory disease. Yonsei Med J. 2009;50:744–50.
44. Szczeklik A, Sanak M. Genetic mechanisms in aspirin-induced asthma. Am J Respir Crit Care Med. 2000;161:S142–6.
45. Van Sambeek R, Stevenson DD, Baldasaro M, et al. 5 = flanking region polymorphism of the gene encoding leukotriene C4 synthase does not correlate with the aspirin-intolerant asthma phenotype in the United States. J Allergy Clin Immunol. 2001;107:561–2.
46. De Alarcon AM, Steinke JW, Cughey R, et al. Expression of leukotriene C4 synthase and plasminogen activator inhibitor 1 gene promoter polymorphisms in sinusitis. Am J Rhinol. 2006;20:545–9.
47. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2003;111:180–6.
48. Asthma in the US: growing every year. Centers for Disease Control and Prevention, Vital Signs. 2011. Available from: http://www.cdc.gov/vitalsigns/asthma/
49. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. National health statistics reports; no 32. National Center for Health Statistics: Hyattsville; 2011.
50. Sullivan SD. The burden of uncontrolled asthma on the U.S. health care system. Manag Care. 2006;14(suppl):4–7; discussion 25–7.
51. Wertz DA, Pollack M, Rodgers K, et al. Impact of asthma control on sleep, attendance at work, normal activities, and disease burden. Ann Allergy Asthma Immunol. 2010;105:118–23.
52. Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel or both for secondary prevention of coronary heart disease. N Engl J Med. 2002;346:1800–6.
53. Chen YF, Jobanputra P, Barton P, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2008;12(11):1–278.
54. Blaiss MS. Allergic rhinitis: direct and indirect costs. Allergy Asthma Proc. 2010;31(5):375–80.
55. Goetzel RZ, Long SR, Ozminkowski RJ, et al. Health, absence, disability, and presenteeism costs estimates of certain physical and mental health conditions affecting U.S. employers. J Occup Environ Med. 2004;46:398–412.
56. Blaiss MS, Meltzer EO, Derebery MJ, et al. Patient and healthcare-provider perspectives on the burden of allergic rhinitis. Allergy Asthma Proc. 2007;28(suppl):S4–10.
57. Benninger M, Benninger R. The impact of allergic rhinitis on sexual activity, sleep and fatigue. Allergy Asthma Proc. 2009;30(4):358–65.
58. Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. JAMA. 2004;292:3017–23.
59. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long term outcomes. J Allergy Clin Immunol. 1996;98:751–8.
60. Berges Gimeno MP, Simon RA, Stevenson DD. Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2003;90:338–41.
61. Lee JY, Simon RA, Stevenson DD. Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2007;119:157–64.
62. Katial RK, Strand M, Prasertsuntarasai T, Leung R, Zheng W, Alam R. The effect of aspirin desensitization on novel biomarkers in aspirin-exacerbated respiratory diseases. J Allergy Clin Immunol. 2010;126(4):738–44.
63. Stevenson DD, Simon RA. Selection of patients for aspirin desensitization treatment. J Allergy Clin Immunol. 2006;118:801–4.
64. Shaker M, Lobb A, Jenkins P, et al. An economic analysis of aspirin desensitization in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2008;121(1):81–7.
65. Rozsasi A, Polzehl D, Deutschle T, et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300mg aspirin daily. Allergy. 2008;63:1228–34.

66. Stevenson DD, Pleskow WW, Simon RA, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind cross-over study of treatment with aspirin. J Allergy Clin Immunol. 1984;73:500–7.
67. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999;106:13S–24.
68. Nucera E, Schiavino D, Milani A, Del Ninno M, Misuraca C, Buonomo A, et al. Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. Thorax. 2000;55(S2):S75–8.
69. White A, Bigby T, Stevenson D. Intranasal ketorolac challenge for the diagnosis of aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2006;97:190–5.
70. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2010;105(2):130–5.
71. Dahlen B, Nizankowska E, Szczeklik A, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-sensitive asthmatics. Am J Respir Crit Care Med. 1998;157:1187–94.
72. Dahlen S, Malstrom K, Nizankowska E, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double blind, placebo controlled trial. Am J Respir Crit Care Med. 2002;165:9–14.
73. Micheletto C, Tognella S, Visconti M. Montelukast 10 mg improves nasal function and nasal response in ASA-sensitive asthmatics: a controlled study vs. placebo. Allergy. 2004;59:284–94.
74. Israel E, Cohn J, Dube L, Drazen J. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. JAMA. 1996;275:931–6.
75. Joos S, Miksch A, Szecsenyi J, et al. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. Thorax. 2008;63:453–62.
76. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. Clin Exp Allergy. 2002;32:1491–6.
77. White AA, Stevenson DD, Simon RA. The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2005;95:330–5.
78. White A, Ludington E, Mehra P, Stevenson DD, Simon RA. Effect of leukotriene modifier drugs on the safety of oral aspirin challenges. Ann Allergy Asthma Immunol. 2006;97:688–93.
79. Stevenson DD, Simon RA, Mathison DA, Christiansen SC. Montelukast is only partially effective in inhibiting aspirin responses in aspirin-sensitive asthmatics. Ann Allergy Asthma Immunol. 2000;85:477–82.
80. Obase Y, Shimoda T, Tomari S, et al. Effects of pranlukast on aspirin-induced bronchoconstriction: differences in chemical mediators between aspirin-intolerant and tolerant asthmatic patients. Ann Allergy Asthma Immunol. 2001;87:74–9.
81. Lee DKC, Haggart K, Robb FM, Lipworth BJ. Montelukast protects against nasal lysine-aspirin challenge in patients with aspirin-induced asthma. Eur Respir J. 2004;24:226–30.
82. Israel E, Fischer AR, Rosenberg MA, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. Am Rev Respir Dis. 1993;148:1447–51.
83. Pauls JD, Simon RA, Daffern PJ, Stevenson DD. Lack of effect of the 5-lipoxygenase inhibitor zileuton in blocking oral aspirin challenges in aspirin-sensitive asthmatics. Ann Allergy Asthma Immunol. 2000;85:40–5.
84. Ogata N, Darby Y, Scadding G. Intranasal lysine-aspirin administration decreases polyp volume in patients with aspirin-intolerant asthma. J Laryngol Otol. 2007;121:1156–60.
85. Patriarca G, Bellioni P, Nucera E, et al. Intranasal treatment with lysine acetylsalicylate in patients with nasal polyposis. Ann Allergy. 1991;67:588–92.
86. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. Laryngoscope. 2005;115:1385–90.
87. Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. J Allergy Clin Immunol. 1982;69:11–9.
88. Juergens UR, Christiansen SC, Stevenson DD, Zuraw BL. Inhibition of monocyte leukotriene B4 production following aspirin desensitization. J Allergy Clin Immunol. 1995;96:148–56.
89. Nasser SM, Patel M, Bell GS, Lee TH. The effect of aspirin desensitization on urinary leukotriene E4 concentrations in aspirin-sensitive asthma. Am J Respir Crit Care Med. 1995;15:1326–30.
90. Arm JP, Austen KF. Leukotriene receptors and aspirin sensitivity. N Engl J Med. 2002;347:1524–6.
91. Arm JP, O'Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E(4) in subjects with aspirin-induced asthma. Am Rev Respir Dis. 1989;140:148–53.
92. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med. 2002;347:1493–9.

Chapter 13
Headache and Sinonasal Disease

Michael J. Marmura and Stephen D. Silberstein

Introduction

Headache disorders are extremely common in clinical practice and frequently cause frontal or sinus pain and pressure. Many patients attribute their symptoms to sinus pathology, which may bring them to the attention of an otolaryngologist and allergist. Primary headache disorders, such as migraine and cluster headache, which commonly produce associated autonomic symptoms, such as tearing, ptosis, rhinorrhea, conjunctival injection, or facial flushing, may cause patients or clinicians to wrongly diagnose "sinus headache" [1].

Clinicians who treat sinus disease should be familiar with common headache disorders, such as migraine and tension-type headache, and trigeminal autonomic cephalalgias, such as cluster headache, that present with frontal pain. Sinusitis, more accurately rhinosinusitis, does not usually cause severe headache and is usually diagnosed on the basis of clinical symptoms and imaging studies. Sphenoid sinusitis, however, may present with intractable headache without typical sinusitis symptoms. The anatomy of the nasal cavity may contribute to headache presentation or location and may cause chronic pain. This chapter focuses on the common headaches that might present with frontal headache, reviews common secondary headaches, and outlines the diagnosis and treatment of headache associated with sinusitis.

Headache Disorders and the Sinus

Headache and rhinosinusitis are both extremely common. In most cases diagnosing either is relatively straightforward. Many patients will not seek medical attention for mild cases of either disorder. Acute rhinosinusitis usually involves nasal airway inflammation and infection of one or more paranasal sinuses. Viral infections are the most common cause of upper airway inflammation and up to 2 % of patients develop bacterial infections [2]. Common symptoms include nasal discharge, tooth pain, anosmia or hyposmia, pain when bending forward, fever, malaise, and facial pain or headache. The sinus areas affected predict the pain's location, but severe headache is relatively uncommon. In fact, the sinuses are not particularly pain sensitive [3].

Recurrent frontal headache in a patient without signs of sinusitis is more typically caused by a primary headache disorder. Migraine and other headaches commonly produce frontal or facial pain during attacks. Nasal congestion is a common migraine prodrome [4]. Parasympathetic fibers of the sphenopalatine ganglion and their surrounding blood vessels in the pterygopalatine fossa commonly produce autonomic symptoms that may be mistaken for sinus disease in association with headache attacks [5]. These autonomic symptoms, common in migraine and obligatory in cluster headache (CH), include nasal congestion or rhinorrhea, conjunctival injection or lacrimation, and eyelid edema.

M.J. Marmura, MD (✉) • S.D. Silberstein, MD
Department of Neurology, Jefferson Medical College, Thomas Jefferson University, 900 Walnut Street, Suite 200, Philadelphia, PA 19107, USA
e-mail: michael.marmura@jefferson.edu; stephen.silberstein@jefferson.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_13,

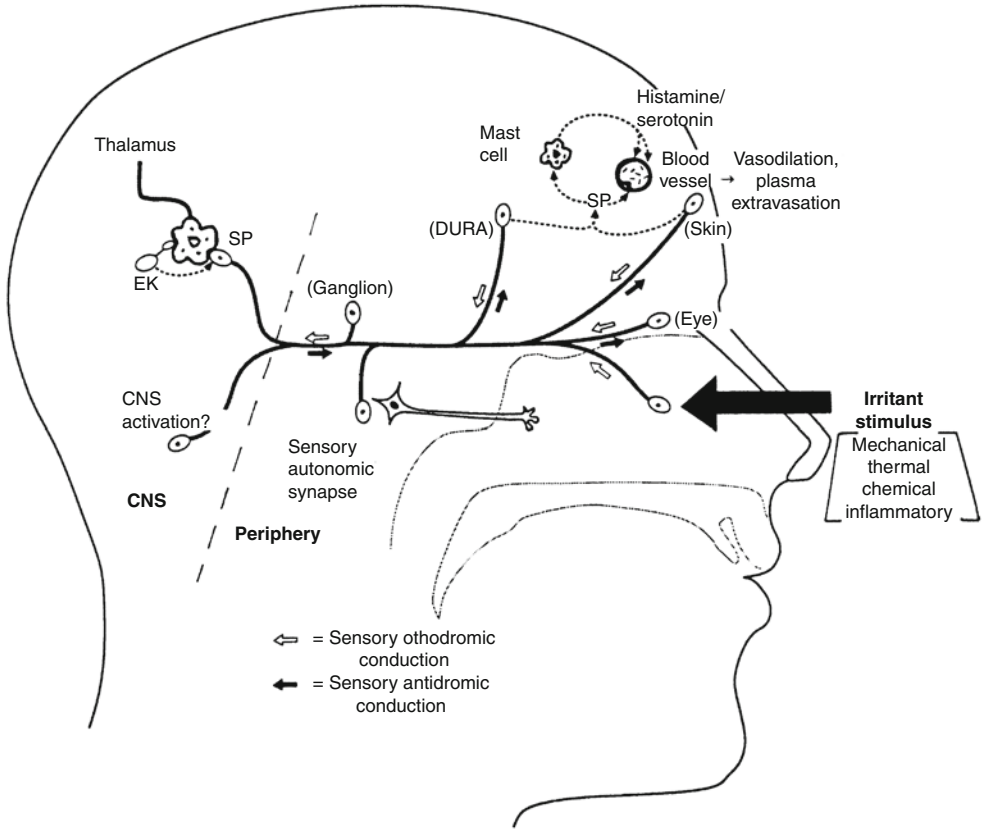


Fig. 13.1 Diagram depicting how an intranasal irritant stimulus (mechanical, thermal, chemical, or inflammatory) can induce referred reflex pain in other areas in the distribution of the trigeminal nervous system, as well as autonomic phenomena. The intranasal stimulus initiates an orthodromic sensory impulse back to the CNS. However, the signal may also get rerouted along other branches of the stimulated nerve (antidromic conduction). These branches innervate pain-sensitive structures such as the dura, eye, and skin of the scalp. The release of substance P (*SP*) as a result of antidromic conduction at these other peripheral terminals leads to inflammatory events pictured. Since SP-immunoreactive nerves have been found in high concentration around the sphenopalatine ganglion, reflex parasympathetic stimulation may also ensue. The CNS probably modulates incoming impulses through a variety of mechanisms, including the influence of enkephalins (*EK*) (Reprinted from Clerico [6]. With permission from John Wiley & Sons, Inc.)

Referred Pain and Wolff's Experiments

The phenomenon of referred pain is well known to health-care providers with examples such as shoulder pain being triggered from gall bladder or cardiac dysfunction. Although the exact mechanisms remain obscure, the concept of axonal reflex initiated through the nasal mucosa and the release of neuropeptides has long been discussed [6] (Fig. 13.1). Harold Wolff, in his classic experiments in the 1940s, defined patterns of referred pain from stimulating the various points in the nasal cavity [7] (Table 13.1). Wolff evaluated the pain distribution and intensity referred from stimulating the nasal and sinus mucosa of human volunteers with a blunt probe, faradic electric current, and epinephrine-soaked cotton pledgets. His study group was composed of five normal subjects, ten subjects who were post-complete excision of a left acoustic neuroma with facial nerve resection, five with CRS, four with acute rhinosinusitis, and one subject with an oroantral fistula. Wolff came to three basic conclusions:

1. The mucosa covering the sinus ostia are the most pain-sensitive areas in the sinonasal cavity, followed by the turbinates, and then the septum and mucosa within the sinuses.
2. Stimulation within the sinonasal cavity produced referred pain rather than pain at the site of stimulation.
3. If a headache was not associated with inflammation and engorgement of the turbinates, it was in all probability not referred from nasal and sinus structures [8].

Subsequent studies have suggested that the middle turbinate is more sensitive than the inferior turbinate using a pressure probe and gives credence to the nasal contact point theory as a possible headache source (see below) [9].

Table 13.1 Summary of Wolff's intranasal stimulation studies on human volunteers

Site stimulated	Pain intensity	Pain quality	Pain distribution
Nasopharynx	1+ to 2+	Aching	Throat
Septum	1+ to 2+	–	Local
Middle			Zygoma, preauricular
Ethmoid			Outer, inner canthus
Inferior turbinate	4+ to 6+	Dull, aching	
Anterior			Upper teeth
Middle			Under eye, zygoma, ear
Posterior			Same as above
Middle turbinate	4+ to 6+	–	Zygoma, ear, temple
Superior turbinate		–	Medial canthus, forehead, lateral nose
Natural maxillary os	6+ to 9+	Sharp, burning	Local, nasopharynx, molars, zygoma, temple
Nasofrontal duct	5+ to 7+	–	Medial canthus, under eye, zygoma, temple
Frontal sinus	1/2+	–	Forehead
Ethmoid sinus	5+ to 6+	–	
Anterior			Over eye, medial canthus, upper jaw, deep in eye
Posterior		Aching	Upper teeth, lateral canthus, lateral nose
Sphenoid sinus			
Anterior wall	5+ to 6+	–	"Deep in head," over eye, upper teeth
Interior	1+ to 2+		Vertex of skull
Maxillary sinus	Mild	–	
Roof			Eye
Lower lateral wall			Jaw, molars

Based on data from Ref. [7]

The chemosensory innervation of the nasal respiratory epithelium has been more recently investigated, and the information sheds some light on why certain individual patients complain of headache from nasal stimuli and sinus infection while others do not. The nasal mucosa is the first tissue of the body to have contact with potentially toxic agents within the inhaled airstream. Consequently, a number of protective neurovascular mechanisms are associated with the nasal mucosa. The nasal respiratory epithelium is densely innervated by the first and second branches of the trigeminal nerve. This intranasal sensory system provides feedback to protective neuromechanisms about our airborne environment. Thus, humidity, temperature, and irritation of inhaled air are all directly analyzed. Many agents, such as dust, smoke, or irritative gases such as some perfumes, activate trigeminal nerve fibers that innervate the epithelium, triggering local axon reflexes. These have been shown to generate, for example, calcitonin gene-related peptide and substance P liberation and nasopulmonary reflexes such as sneezing and coughing to prevent noxious substances from entering the respiratory system [10]. Innervation of the nasal/sinus epithelium depends on two major trigeminal fiber systems: the unmyelinated C-fibers and the myelinated Ad-fibers [11]. C-fibers stimulation induces a burning pain sensation and Ad-fibers mediate a sharp, stinging sensation [12].

A number of studies have established that intranasal trigeminal fibers act as a detection system for noxious chemicals and trigger a protective respiratory response [13–16].

The nerve endings of trigeminal fibers in the nasal mucosa are not covered by squamous epithelium which provides most chemicals and inflammatory mediators ready access to receptors that innervate the nasal mucosa and increases their sensitivity to painful stimuli [17]. In a study by Meusel et al., the authors found that trigeminal sensitivity of the human nasal mucosa varies in relation to the site of stimulation and to the type of chemical irritants with the posterior region of the nasal cavity, namely, the posterior septum and the lateral side wall of the posterior nasal cavity, being the most sensitive to noxious stimuli [18]. Several authors have shown specific distribution patterns of sensory immune reactivity and sensitivity within the nasal mucosa. For example, Scheibe et al. showed repeatedly that the anterior nasal septum is more sensitive to stimulation by CO2, ethyl acetate, and acetic acid compared with other locations within the nasal cavity [19]. Frasnelli et al. reported that the anterior region is more sensitive to chemical irritation, while the opposite is true for mechanical stimulation [20]. Taken together, these observations indicate that irritants entering the nasal cavity trigger a defense mechanism in the human airway. The posterior region of the nose appears to be specifically responsive to pungent and cooling agents, and the middle turbinate and septal wall to pressure and some noxious stimuli.

In summary, these studies suggest that the chemosensory system within the respiratory mucosa of the nasal cavity is not homogeneous but rather heterogeneous with various specific functions. It is not unreasonable to consider that some patients, through the irritant effect of noxious stimuli (such as perfume, smoke, gases) or a neurovascular response to a milieu of inflammatory mediators, can experience pain and a headache through trigeminal nerve receptor stimulation from inspired air or from a mucosal impaction site.

Primary Headache Disorders

Migraine

Migraine is a very common, highly disabling primary headache disorder. Attacks consist of moderate to severe pain that is often unilateral, with a throbbing or pulsating quality that is aggravated by movement. Associated symptoms, such as nausea or vomiting and autonomic dysfunction, are common and physical activity usually worsens symptoms. During migraine, most sufferers are sensitive to light (photophobia), noise (phonophobia), and odors (osmophobia). Multiple triggers, including stress, foods, weather changes, menstrual changes, or sleep changes, can lead to attacks. About 20 % of patients experience an aura involving neurologic symptoms. Visual auras are the most common [21]. Migraine has a 1-year prevalence of approximately 18 % in women and 8 % in men and is most common between the ages of 25 and 55 [22]. If the headaches occur fewer than 15 days per month, it is classified as episodic migraine; if headache occur 15 or more days per month (of which at least 8 are migraine), it is classified as chronic migraine [1]. Individuals with migraine cannot work the equivalent of 1 day per month on average, although the most disabled patients account for the majority of those on disability [23]. Patients who have a recurrent headache accompanied by nausea, light sensitivity, or any disability overwhelmingly have migraine [24].

The current accepted criteria for migraine without aura are as follows [1]:

Diagnostic criteria:

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not attributed to another disorder

Migraine is now recognized as a neurologic disorder that is generally inherited. It is estimated that about 70–80 % of migraine sufferers have a relative with migraine [25]. Migraine and severe headaches are often underreported in first-degree relatives in family history interviews, meaning a negative family history may underestimate the true prevalence [26].

Although rhinosinusitis is common, moderate or severe headache is more likely to indicate migraine. Because migraine and other primary headaches often present with frontal, ocular, or facial pain, patients or clinicians may falsely attribute their symptoms to sinus disease. Making an accurate diagnosis reassures the patient, prevents unnecessary diagnostic testing, and allows better treatment with migraine-specific medications [27].

The ICHD-II does not recognize chronic rhinosinusitis as a cause of headache. Many patients or clinicians incorrectly diagnose primary headache disorders as “sinus headache” due to the location of their pain or the parasympathetic symptoms that accompany attacks. Eross and colleagues evaluated 100 consecutive patients with self-diagnosed sinus headache. The actual diagnoses were migraine (52 %), probable migraine (23 %), chronic migraine (11 %), other unclassifiable headaches (9 %), cluster headaches (1 %), and hemicrania continua (1 %). Only 3 % of patients could be accurately diagnosed as headache attributable to rhinosinusitis [28]. Nasal congestion was present in 73 % of patients and postnasal drip in 56 %. Most reported pain is triggered by changes in weather or season, and many noted changes with allergies or altitude, which are also common migraine triggers [29].

Orbital or retro-orbital pain, rhinorrhea, nasal congestion, miosis, lacrimation, and facial sweating are common in both primary headache disorders and rhinosinusitis. The proximity of the parasympathetic nerves to the trigeminal nerves may explain this overlap.

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Trigeminal autonomic cephalalgias (TAC) are a group of primary headache disorders characterized by unilateral headache and autonomic features. Cluster headache is the most common, with a prevalence of up to 3 per 1,000 persons [30].

Table 13.2 Migraine and cluster headache: clinical features

Clinical features	Migraine	Cluster
Severe attacks	>4 h	2 h or less
Side	Often bilateral	Strictly unilateral
Location	Frontal, occipital, ocular, temporal, neck	Usually ocular
Character of pain	Usually throbbing/pulsating	Often boring, stabbing
Onset and cessation	Usually gradual	Rapid
Movement/activity	Worsens symptoms	May improve symptoms
Autonomic features	Occasionally	Always
More common in	Women	Men
Attacks triggered by alcohol	Common, but headache hours later	Almost always, often severe within minutes
Response to subcutaneous sumatriptan	Usually	Almost always
Response to high-flow oxygen	Unknown	Usually
Seasonal attacks	Occasionally	Common
Circadian periodicity	Uncommon	Very common

The current accepted criteria for cluster headache are as follows [1]:

A. At least five attacks fulfilling criteria B–E
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 min if untreated
C. Headache is accompanied by at least one of the following:

- Ipsilateral conjunctival injection and/or lacrimation
- Ipsilateral nasal congestion and/or rhinorrhea
- Ipsilateral eyelid edema
- Ipsilateral forehead and facial sweating
- Ipsilateral miosis and/or ptosis
- A sense of restless or agitation

D. Attacks occur from one every other day to eight per day
E. Not attributed to another disorder

Unlike migraine, cluster headache is more common in men. Recent case series report the male to female ratio to be between 2.5:1 and 3.5:1. Cluster headache can begin at any age, but most commonly begins in the second to fourth decade of life. The majority of cluster headache sufferers are smokers and may be more likely to consume excessive coffee. About 4 % of patients have a family history of cluster headaches. Cluster headache is 5–18 times more common in first-degree relatives, suggesting a genetic link for the disease [31].

Cluster headache is one of the most painful conditions we see in clinical practice. The pain typically becomes maximally intense within 10 min. Attacks often occur with circadian patterns, often nocturnally starting about 1–2 h after sleep onset. This suggests a correlation with the rapid eye movement sleep stage and may be related to oxygen desaturation and obstructive sleep apnea in some patients [32]. Light and sound sensitivity are unusual, but alcohol is a common trigger for attacks. Common pain descriptors include burning, boring, or screwing. Some patients report a feeling of a "hot poker in the eye." A minority of patients experience throbbing or pulsating pain [33]. Some patients experience fluctuations of pain during an attack, and a few experience milder head pain between attacks [34]. Cluster headache pain is typically located over the retro-orbital, supraorbital, or temporal area, but may occur in the jaw, cheek, teeth, ear, nose, or neck.

Many patients report seasonal attacks, with cycles of attacks lasting weeks to months, with periods of remission. The majority of cluster headache patients experience cycles of attacks about twice a year to every 2 years, although some patients go many years between cycles. A typical cycle lasts 1–3 months, often with a seasonal pattern, with the cycle always beginning around the same month of the year. Cluster headache attacks tend to be milder at the beginning and near the end of a cycle.

Treatment of acute cluster headaches includes sumatriptan injection and inhaled oxygen. Oxygen may work by blocking the release of inflammatory neuropeptides, including calcitonin gene-related peptide [35]. Given the frequent nature of cluster headaches, preventive treatment is usually indicated, and corticosteroids are often effective for short-term use in CH cycles.

Differentiating between migraine and cluster headache is usually straightforward, but occasionally the disorders overlap [36]. The following table reviews the distinguishing features of these two distinct diseases (Table 13.2).

Paroxysmal hemicrania is a trigeminal autonomic cephalalgia with shorter-lasting (usually 5–30 min), unilateral attacks that occur 5 or more times per day, accompanied by autonomic symptoms. The disorder resolves completely with therapeutic doses of indomethacin. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) are very short lasting (5 s to 4 min), with orbital or frontal pain. Autonomic symptoms are usually dramatic, and

Table 13.3 Mimics of trigeminal autonomic cephalalgias

Condition	Distinguishing features
Ophthalmic disorders	
Acute angle-closure glaucoma	Severe conjunctival injection, pupil poorly reactive, mid-dilated, cloudy cornea, elevated intraocular pressure
Corneal erosion	Sharp pain, moderately injected, dull cornea, vision loss
Optic neuritis	Vision loss, afferent papillary defect
Vascular disorders	
Carotid/vertebral dissection	Thunderclap onset (both), facial pain, Horner's syndrome (carotid), neck pain, cerebellar symptoms (vertebral)
Giant cell arteritis	Jaw claudication, polymyalgia rheumatica, amaurosis fugax, increased sedimentation rate and/or c-reactive protein
Pituitary tumors	Visual field loss, endocrine abnormalities (elevated prolactin)
Herpes zoster (V1)	Rash, severe allodynia, cranial nerve palsies
Multiple sclerosis	Acute SUNCT during an exacerbation has been reported

patients may experience dozens or even hundreds of attacks per day. Hemicrania continua is a strictly unilateral, constant headache with milder autonomic features. Technically, hemicrania continua is not a trigeminal autonomic cephalgia, but it does have an absolute response to indomethacin [1].

Multiple case reports of secondary trigeminal autonomic cephalgias exist in the literature, and neuroimaging should be performed if any unusual features are present (Table 13.3).

A recent area of interest is the use of sphenopalatine ganglion blockade or stimulation to treat cluster headaches and other disorders characterized by headache and autonomic symptoms. Blocking the sphenopalatine ganglion after endoscopic surgery appears to improve postoperative analgesia [37]. Intranasal lidocaine has been proposed as a possible treatment of cluster headaches [38]. Stimulating the sphenopalatine ganglion may be effective in both the acute and chronic treatment of migraine and particularly cluster attacks [38–40].

Facial Pain and Trigeminal Neuralgia

Trigeminal neuralgia is a short-lasting, sharp, and distinct pain in the face, usually lasting only seconds. This shock-like pain may be precipitated by touching the affected area or by seemingly trivial stimuli, such as wind or talking. Trigeminal neuralgia is most common in elderly patients (ICHD 2004) and felt to be related to compression of the trigeminal nerve by a vascular loop in most cases [1, 41]. Secondary causes, such as multiple sclerosis and posterior fossa tumors, have been described, but sinus disease does not usually cause TN [42]. Most individuals have pain-free periods between attacks, but others have constant pain, and these patients have a worse prognosis [43]. The attacks are typically located in multiple areas with V2 and combinations such as V2 and V3 being the most common distribution.

Secondary Headaches

Headache Attributed to Sinusitis

Rhinosinusitis is a common illness characterized by nasal discharge (sometimes purulent), nasal congestion, hyposmia or anosmia, facial pain or headache worse with bending forward, fever, malaise, maxillary tooth pain, halitosis, and pain with mastication. Rhinosinusitis is divided into four categories based on the time frame and symptoms of the disease as follows:

- *Acute rhinosinusitis*: One day to 4 weeks, usually viral if less than 7 days, often bacterial if >1 week, with complete resolution of symptoms
- *Recurrent rhinosinusitis*: Four or more episodes of at least 7 days in a year
- *Subacute rhinosinusitis:* Four to 12 *weeks*
- *Chronic rhinosinusitis:* Signs or symptoms last more than 12 weeks

The International Classification of Headache Disorders, 2nd edition defines headache attributed to rhinosinusitis as follows [1]:

A. Frontal headache accompanied by pain in one or more regions of the face, ears, or teeth, fulfilling criteria C and D.
B. Clinical, nasal endoscopic, CT and/or MRI imaging, and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis.

Table 13.4 Predictors of rhinosinusitis

Major	Minor
Maxillary toothache	Cough
Abnormal transillumination	Ear pain/fullness
Purulent or colored nasal discharge	Halitosis
Poor response to decongestants	Headache
Fever (acute only)	Fatigue
Anosmia/hyposmia	Fever (chronic)
Facial pain/pressure[a]	

[a]Facial pain/pressure must be accompanied by other major nasal symptom or sign for the diagnosis of rhinosinusitis

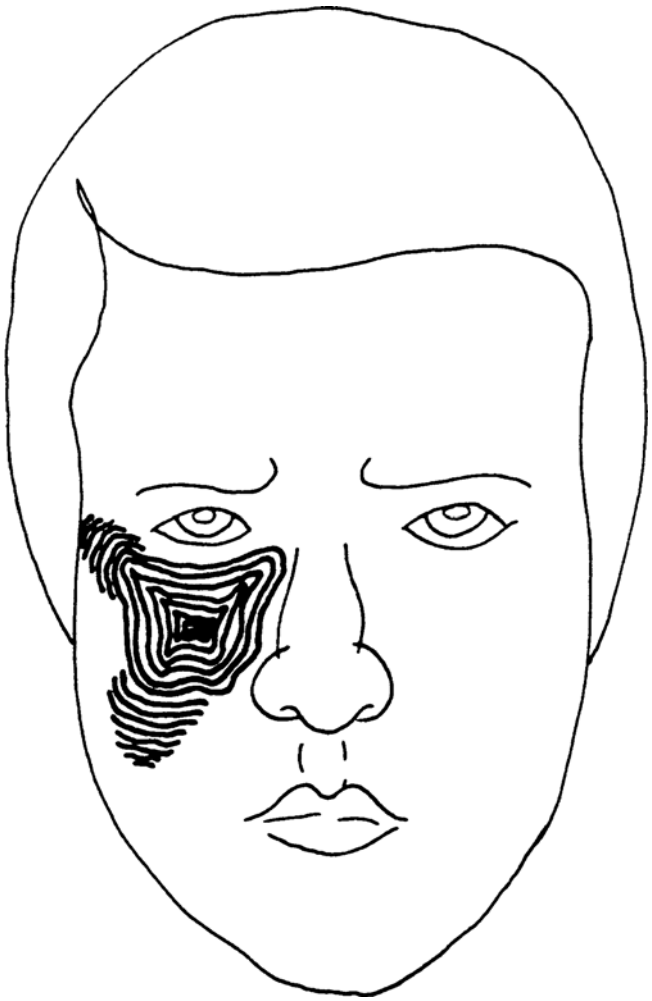


Fig. 13.2 Area of pain in acute maxillary sinusitis (Courtesy of David W. Kennedy, MD, FACS, FRCSI)

C. Headache and facial pain develop simultaneously with onset or acute exacerbation of rhinosinusitis.
D. Headache and/or facial pain resolves within 7 days after remission or successful treatment of acute or acute-on-chronic rhinosinusitis.

Headache location and severity, however, does *not* predict the presence of infection [44]. Other symptoms such as maxillary toothache are more predictive of sinusitis but less common. Hyposmia and purulent nasal discharge are strong predictors of sinus infection [45, 46].

The clinical predictors of rhinosinusitis are shown in Table 13.4.

The four major pairs of sinuses and their association with pain are as follows:

- *Maxillary sinuses:* The largest sinuses, the maxillary sinuses, are present at birth and located anteriorly within the maxilla. Acute inflammation can cause pain in the cheeks, upper teeth (particularly molar), and jaw (Fig. 13.2).

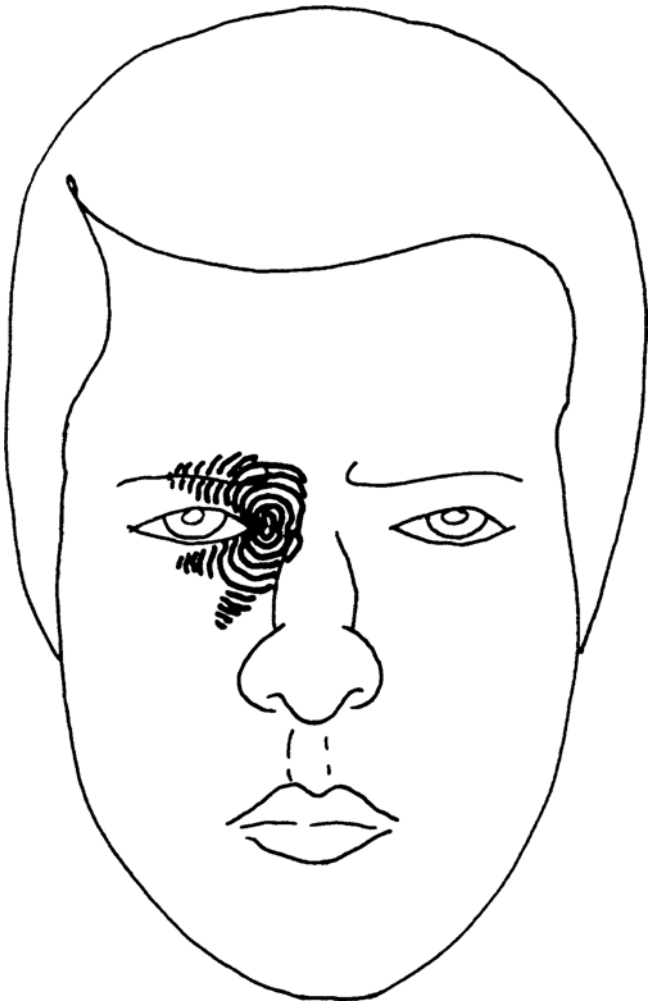


Fig. 13.3 Area of referred pain in acute ethmoid sinusitis (Courtesy of David W. Kennedy, MD, FACS, FRCSI)

- *Ethmoid sinuses*: Located between the eyes, behind the bridge of the nose, the ethmoid sinuses are present and filled with fluid at birth but become pneumatized in the first year of life. Inflammation tends to cause pain behind the eyes and nose (Fig. 13.3).
- *Frontal sinuses*: Located above the eyes, these sinuses variably develop by about 6 years of age and can be unilateral. Inflammation may cause pain in the forehead (Fig. 13.4).
- *Sphenoid sinuses:* Located behind the eyes and nasal structures, the sphenoid sinuses are present at birth, but pneumatization does not begin until around age three. Inflammation may produce earache, deep aching at the vertex, and neck pain (Fig. 13.5). *Neurologic symptoms can also be generated from the* cavernous sinuses, which are lateral to the sphenoid sinus and contain the third, fourth, fifth, and sixth cranial nerves and the internal carotid arteries. Symptoms of cavernous sinus syndrome include ophthalmoplegia, proptosis, Horner syndrome, and trigeminal sensory loss. Potential causes of neurologic symptoms associated with the sphenoid sinus and cavernous sinus include infection, inflammatory disorders such as Tolosa-Hunt syndrome, vascular problems such as internal carotid artery aneurysm, trauma, and neoplasm.

Sphenoid Sinusitis and Its Unique Association with Headache and Other Neurologic Symptoms

Maxillary, frontal, and ethmoid sinusitis are usually associated with nasal discharge and may be diagnosed with direct examination, endoscopy, or CT scanning. Clinicians are usually able to identify most cases of acute, subacute, and

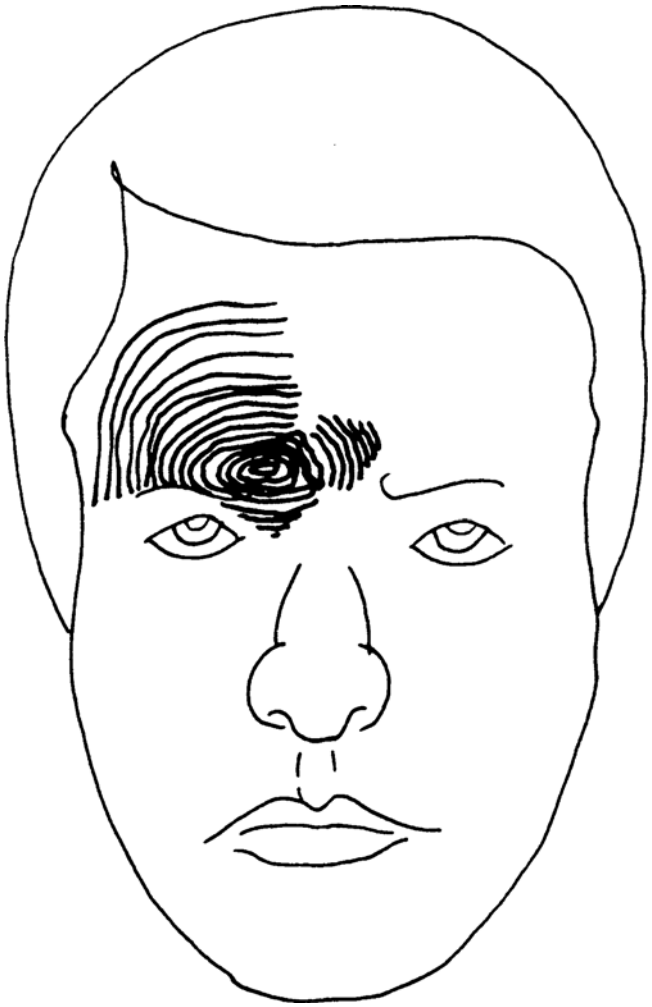


Fig. 13.4 Areas of referred pain seen in acute frontal sinusitis (Courtesy of David W. Kennedy, MD, FACS, FRCSI)

chronic sinusitis. However, about 3 % of those with sinusitis have sphenoid sinusitis, which, due to its location, is difficult to diagnose clinically without radiographic or endoscopic confirmation. Symptoms such as postnasal drip or discharge are less common in sphenoid sinusitis and headache becomes more common. In a case series of 30 patients, headache was the most prominent symptom [47]. The headache of sphenoid sinusitis is often severe, with either frontal, retro-orbital, or temporal pain. Pain may radiate to the occipital or trigeminal (V1–V3) regions. Usually sphenoid sinusitis occurs with pansinusitis, but it may occur alone, causing acute or subacute headache. Mucocele and neoplasm are potential noninfectious causes of sphenoid sinus disease and should be considered in the differential diagnosis [48] (Table 13.5).

Sinus infections, especially sphenoid sinusitis, may produce serious complications when the diagnosis is missed or treatment is ineffective, leading to head pain and a variety of neurologic abnormalities depending on the location of the complication. Those serious medical conditions are summarized as follows:

1. Orbital diseases (cellulitis, edema, abscess)
2. Epidural or cerebral abscess
3. Meningitis
4. Superior sagittal sinus thrombosis
5. Cavernous sinus thrombosis, ophthalmoplegia
6. Pituitary insufficiency
7. Mucocele (retention cyst)

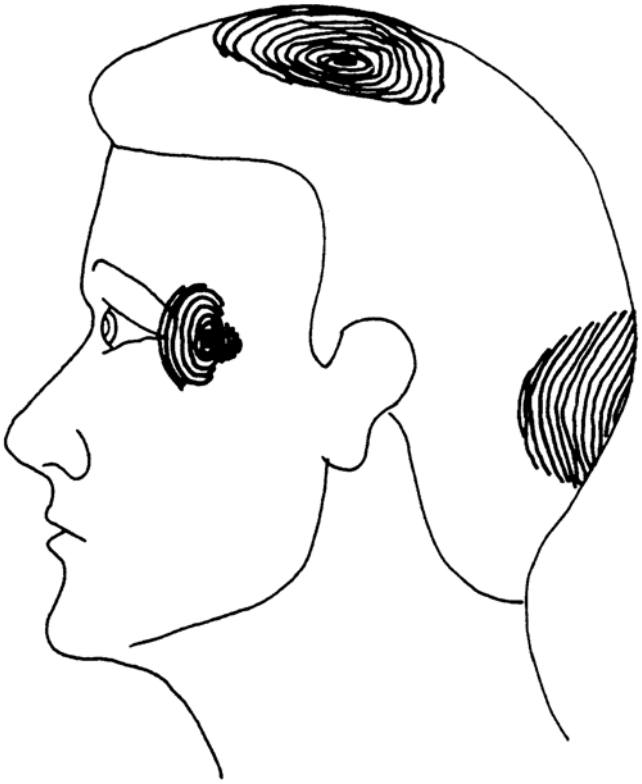


Fig. 13.5 Patterns of referred pain in acute sphenoid sinusitis (Courtesy of David W. Kennedy, MD, FACS, FRCSI)

Table 13.5 Common clinical features of sphenoid sinusitis

Interferes with sleep	Progressive symptoms
Facial paresthesias	Fever
Visual loss/cranial nerve palsies	Not relieved with analgesics
Occipital, periorbital, or temporal (less often vertex) headache	Aggravated by standing, walking, bending, or coughing
Nausea and vomiting	Eyelid ptosis

Nasal or Contact Point Headache

Physicians for years have pondered on whether or not the existence of chronic headache can be due to nasal contact points on sensitive structures (Fig. 13.6). Septal deformations with a contact point on the lateral nasal wall may produce episodic or transient headache. McAuliffe et al. reported that the nasal turbinates and sinus ostia were more sensitive than the general nasal lining of the septum and sinuses [49]. These abnormalities may be ignored by radiologists and should be considered in cases of headache refractory to standard therapy. ENT evaluation may be useful, and intranasal blockade with an anesthetic such as lidocaine may confirm the diagnosis. If diagnosed correctly, removal of the contact point may improve headaches.

Given that these radiologic abnormalities are common in patients without headache, it is unclear if contact point headache can occur without a central disorder, such as a genetic predisposition to migraine or headache. Schønsted-Madsen et al. noted that successful surgical intervention that relieved sinus obstruction was most effective in relieving sinusitis-associated headache [50]. A lack of controlled trials makes the relationship between contract points and headache difficult to determine [51] (Figs. 13.7 and 13.8).

Low-Pressure Headache

Low-pressure headache is characterized by orthostatic head pain. The most common cause is a leak of cerebrospinal fluid (CSF), usually in the cervical spine. MRI of the brain with gadolinium is usually abnormal and suggests a CNS origin to the

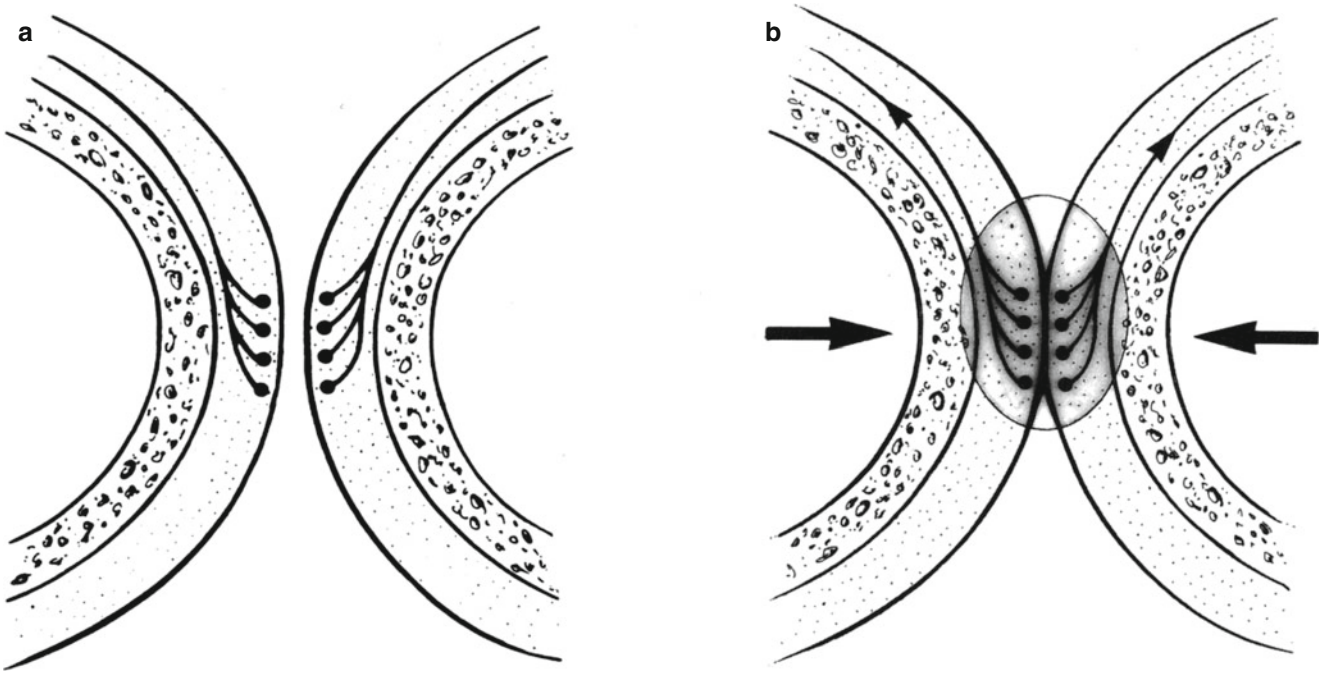


Fig. 13.6 Schematic demonstrating the phenomenon of mucosal contact causing a pain reflex with hyperalgesia. (**a**) Depicts two mucosa-covered structures with intact sensory supply in close approximation but not contacting each other. (**b**) Demonstrates that with mucosal contact, such as by the continued pneumatization of a concha bullosa or the continued growth of a septal spur (*arrows*), sensory stimulation results in the transmission of an electrical signal back to the CNS (*arrow heads*), as well as the release of neuropeptides (such as SP) at the site of stimulation and the surrounding mucosa (*shaded area*). This local release of SP excites other free nerve endings and induces inflammatory changes in the mucosa

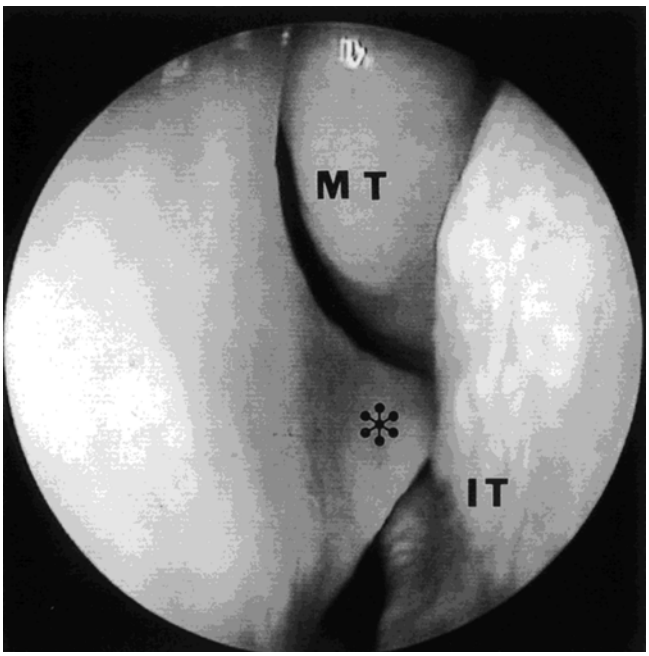


Fig. 13.7 Left-sided septal spur (*asterisk*) impacting the inferior turbinate (*IT*) as seen with a 0° nasal telescope. Injection of the spur with local anesthesia abolished the patient's pain, suggesting that the septum, rather than the inferior turbinate, was the cause of pain. *MT* middle turbinate

head pain. Other common abnormalities seen in this setting include pachymeningeal enhancement, low-lying cerebellar tonsils, subdural fluid collections, engorged pituitary and venous sinuses, and small ventricles [52, 53]. Multiple cases of CSF rhinorrhea due to nasal trauma, pituitary tumor, or iatrogenic complications of sinus surgery have been described, often with headache as a prominent symptom [54]. However, it is unclear if CSF rhinorrhea always causes orthostatic headache when present.

The primary goal of endoscopic surgery to repair CSF leaks is to prevent ascending meningitis [55]. Neuroimaging is indicated whenever CSF leak is suspected. Cisternography with nasal pledgets is useful in confirming the diagnosis. CSF

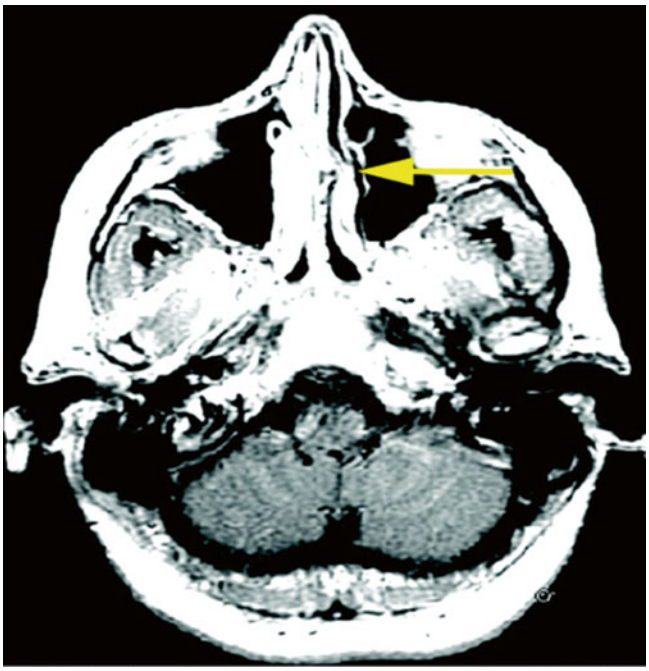


Fig. 13.8 Left nasal contact point (*arrow*) in a patient with chronic migraine (Reprinted from Rozen [51]. With permission from Wolter Kluwers Health)

leaks from the skull base producing orthostatic headache are exceedingly rare. Scheivink et al. report no cases of CSF leaks at the skull base in 273 consecutive cases at a large tertiary center [56].

Allergy and Headache

Although sinus congestion and tearing are common in migraine due to parasympathetic activation, headache in this setting is rarely related to sinus disease. In contrast, there appears to be an increased prevalence of migraine in persons with allergic rhinitis or atopy who, in turn, experience a higher frequency of sinus disease [57, 58]. Allergic rhinitis, like migraine, is an extremely common disorder that typically presents in early adulthood. Martin et al. evaluated 536 consecutive patients presenting at an allergy clinic, 174 of whom met criteria for migraine. In this group, the treatment of allergies with immunotherapy was significantly associated with less migraine frequency and disabling discomfort. This study supports some causative or influencing connection between atopic disorders and migraine headaches [59].

Conclusion

Many patients conclude that facial pain, with or without congestion, is a sinus-related event. Scientific evidence points to the exact opposite conclusion. This is particularly true for the head pain sufferer who has no direct evidence of airway inflammation and normal sinus CT imaging where the majority of such patients are found to be experiencing migraine headaches. It is important for the primary care provider to look closely for definitive signs and symptoms of sinus infection before prescribing antibiotics for a patient whose primary complaint is headache. The otolaryngologist must be cautious in associating variations in nasal structural and/or abnormal sinus CT findings of mucosal thickening as a source of an individual patient's head pain. Though a higher proportion of atopic patients experience migraine headaches as compared to the general population, the allergist must be cautious in identifying atopic triggers as a source of head pain or suggesting that the treatment of atopic disease will resolve a head pain problem. The triggers and sources of a headache problem are potentially as heterogeneous as the neuroreceptor responses of the nasal mucosa.

References

1. Headache Classification Committee. The international classification of headache disorders, 2nd edition. Cephalalgia. 2004;24 Suppl 1:1–160.
2. Piccirillo JF. Acute bacterial sinus infections are frequently overdiagnosed. N Engl J Med. 2004;351:902–10.
3. Wolff HG. Wolff's headache and other head pain. 1st ed. New York: Oxford University Press; 1948.
4. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. Headache. 2004;44(9):865–72.
5. Hardebo JE, Elner A. Nerves and vessels in the pterygopalatine fossa and symptoms of cluster headache. Headache. 1987;27(10):528–32.
6. Clerico DM. Sinus headaches reconsidered: referred cephalgia of rhinologic origin masquerading as refractory primary headaches. Headache. 1995;35:185–92.
7. Dalessio DJ, Silberstein SD, editors. Wolff's headache and other head pain. 6th ed. New York: Oxford University Press; 1993. p. 297–305.
8. Gershwin ME, Incaudo GA, editors. Diseases of the sinuses, a comprehensive textbook of diagnosis and treatment. 1st ed. Ottawa: Humana Press; 1996. p. 409.
9. Fairley JW, Yardley MPJ, Durham LH. Pressure applied to the middle turbinate causes pain at the lower threshold than the inferior turbinate or nasal septum (Abstract). Abstract book-14th Congress European Rhinologic Society, Rome; 6–10 Oct, 1992. p. 96.
10. Eccles R, Lancashire B, Tolley NS. Experimental studies on nasal sensation of airflow. Acta Otolaryngol. 1987;103:303–6.
11. Sekizawa S, Tsubone H, Kuwahara M, Sugano S. Nasal receptors responding to cold and l-menthol airflow in the guinea pig. Respir Physiol. 1996;103:211–9.
12. Torebjork HE, Hallin RG. Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. Exp Brain Res. 1973;16:321–32.
13. Doty RL. Intranasal trigeminal detection of chemical vapors by humans. Physiol Behav. 1975;14:855–9.
14. Doty RL, Brugger WE, Jurs PC, Orndorff MA, Snyder PJ, Lowry LD. Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. Physiol Behav. 1978;20:175–85.
15. Silver WL, Moulton DG. Chemosensitivity of rat nasal trigeminal receptors. Physiol Behav. 1982;28:927–31.
16. Stevens JC, Cain WS. Aging and the perception of nasal irritation. Physiol Behav. 1986;37:323–8.
17. Handwerker H, Kobal G. Psychophysiology of experimentally induced pain. Physiol Rev. 1993;73:639–71.
18. Meusel T, Negoias S, Scheibe M, Hummel T. Topographical differences in distribution and responsiveness of trigeminal sensitivity within the human nasal mucosa. Pain. 2010;151(2):516–21.
19. Scheibe M, van Thriel C, Hummel T. Responses to trigeminal irritants at different locations of the human nasal mucosa. Laryngoscope. 2008;118:152–5.
20. Frasnelli J, Heilmann S, Hummel T. Responsiveness of human nasal mucosa to trigeminal stimuli depends on the site of stimulation. Neurosci Lett. 2004;362:65–9.
21. Silberstein SD. Migraine symptoms: results of a survey of self-reported migraineurs. Headache. 1995;35:387–96.
22. Lipton RB, Bigal M, Diamond M. Migraine prevalence, disease burden and the need for preventive therapy. Neurology. 2007;68:343–9.
23. VonKorff M, Stewart WF, Simon DS, Lipton RB. Migraine and reduced work performance: a population-based diary study. Neurology. 1998;50:1741–5.
24. Lipton RB, Kolodner K, Dodick D et al. A self-administered screener for migraine in primary care: the ID migraine validation study. Headache 2003;43 (abstract).
25. Russell MB. Genetic epidemiology of migraine and cluster headache. Cephalalgia. 1997;17:683–701.
26. Ottman R, Hong S, Lipton RB. Validity of family history data on severe headache and migraine. Neurology. 1993;43:154–96.
27. Silberstein SD, Lipton RB. Overview of diagnosis and treatment of migraine. Neurology. 1994;44 suppl 7:6–16.
28. Eross E, Dodick D, Eross M. The Sinus, Allergy and Migraine Study (SAMS). Headache. 2007;47(2):213–24.
29. Chabriat H, Danchot J, Michel P, Joire JE, Henry P. Precipitating factors of headache. A prospective study in a national control-matched survey in migraineurs and nonmigraineurs. Headache. 1999;39(5):335–8.
30. Sjaastad O, Bakketeig LS. Cluster headache prevalence. Vaga study of headache epidemiology. Cephalalgia. 2003;23(7):528–33.
31. Russell MB. Epidemiology and genetics of cluster headache. Lancet Neurol. 2004;3(5):279–83.
32. Kudrow L, McGinty DJ, Phillips ER, Stevenson M. Sleep apnea in cluster headache. Cephalalgia. 1984;4:33–8.
33. Donnet A, Lanteri-Minet M, Guegan-Massardier E, et al. Chronic cluster headache: a French clinical descriptive study. J Neurol Neurosurg Psychiatry. 2007;78(12):1354–8.
34. Marmura MJ, Silberstein SD. Current understanding and treatment of headache disorders: five new things. Neurology. 2011;76(7 Suppl 2):S31–6.
35. Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Brain. 1994;117:427–34.
36. Peatfield R. Migrainous features in cluster headache. Curr Pain Headache Rep. 2001;5(1):67–70.
37. DeMaria Jr S, Govindaraj S, Chinosorvatana N, Kang S, Levine AI. Bilateral sphenopalatine ganglion blockade improves postoperative analgesia after endoscopic sinus surgery. Am J Rhinol Allergy. 2012;26(1):e23–7.
38. Bakbak B, Gedik S, Koktekir BE, Okka M. Cluster headache with ptosis responsive to intranasal lidocaine application: a case report. J Med Case Rep. 2012;6:64.
39. Ansarinia M, Rezai A, Tepper SJ, et al. Electrical stimulation of sphenopalatine ganglion for acute treatment of cluster headaches. Headache. 2010;50(7):1164–74.
40. Oomen KP, van Wijck AJ, Hordijk GJ, de Ru JA. Effects of radiofrequency thermocoagulation of the sphenopalatine ganglion on headache and facial pain: correlation with diagnosis. J Orofac Pain. 2012;26(1):59–64.
41. Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. Brain. 2001;124(Pt 12):2347–60.
42. Zakrzewska JM. Diagnosis and differential diagnosis of trigeminal neuralgia. Clin J Pain. 2002;18(1):14–21.

43. Szapiro Jr J, Sindou M, Szapiro J. Prognostic factors in microvascular decompression for trigeminal neuralgia. Neurosurgery. 1985;17(6):920–9.
44. Gupta M, Silberstein SD. Therapeutic options in the management of headache attributed to rhinosinusitis. Expert Opin Pharmacother. 2005;6(5):715–22.
45. Cady RK, Dodick DW, Levine HL, et al. Sinus headache: a neurology, otolaryngology, allergy, and primary care consensus on diagnosis and treatment. Mayo Clin Proc. 2005;80(7):908–16.
46. Houser SM, Levine HL. Chronic daily headache: when to suspect sinus disease. Curr Pain Headache Rep. 2008;12(1):45–9.
47. Lew D, Southwick FS, Montgomery WW, Weber AL, Baker AS. Sphenoid sinusitis: a review of 30 cases. N Engl J Med. 1983;19:1149–54.
48. Levine HL, Setzen M, Cady RK, et al. An otolaryngology, neurology, allergy, and primary care consensus on diagnosis and treatment of sinus headache. Otolaryngol Head Neck Surg. 2006;134(3):516–23.
49. McAuliffe GW, Goodell H, Wolff HG. Experimental studies on headache: pain from the nasal and paranasal structures. Res Publ Assoc Res Nerv Ment Dis. 1943;23:185–206.
50. Schonsted-Madsen U, Stoksted P, Christensen PH, Koch-Henriksen N. Chronic headache related to nasal obstruction. J Laryngol Otol. 1986;100:165–70.
51. Rozen TD. Intranasal contact point headache: missing the "point" on brain MRI. Neurology. 2009;72(12):1107.
52. Spelle L, Boulin A, Tainturier C, Visot A, Graveleau P, Pierot L. Neuroimaging features of spontaneous intracranial hypotension. Neuroradiology. 2001;43(8):622–7.
53. Mokri B, Bahram MD. Spontaneous cerebrospinal fluid leaks: from intracranial hypotension to cerebrospinal fluid hypovolemia–evolution of a concept. Mayo Clin Proc. 1999;74(11):1113–23.
54. Makin V, Hatipoglu B, Hamrahian AH, et al. Spontaneous cerebrospinal fluid rhinorrhea as the initial presentation of growth hormone-secreting pituitary adenoma. Am J Otolaryngol. 2011;32(5):433–7.
55. Daele JJ, Goffart Y, Machiels S. Traumatic, iatrogenic, and spontaneous cerebrospinal fluid (CSF) leak: endoscopic repair. B-ENT. 2011;7 Suppl 17:47–60.
56. Schievink WI, Schwartz MS, Maya MM, Moser FG, Rozen TD. Lack of causal association between spontaneous intracranial hypotension and cranial cerebrospinal fluid leaks. J Neurosurg. 2012;116(4):749–54.
57. Ku M, Silverman B, Prifti N, Ying W, Persaud Y, Schneider A. Prevalence of migraine headaches in patients with allergic rhinitis. Ann Allergy Asthma Immunol. 2006;97(2):226–30.
58. Mortimer MJ, Kay J, Gawkrodger DJ, Jaron A, Barker DC. The prevalence of headache and migraine in atopic children: an epidemiological study in general practice. Headache. 1993;33(8):427–31.
59. Martin VT, Taylor F, Gebhardt B, et al. Allergy and immunotherapy: are they related to migraine headache? Headache. 2011;51(1):8–20.

Chapter 14
Immunodeficiency and Sinus Disease

Stephen J. McGeady and Gary A. Incaudo

Introduction

The hallmark of immune deficiency is recurrent, unusual, or persistent infection. Primary immune deficiency diseases (PID) refer to a genetically heterogenous group of disorders in which different components of the host defense system are intrinsically impaired. There are more than 120 genes that have been implicated in PID which account for more than 180 primary immunodeficiency diseases described and the number keeps expanding [1]. Primary immunodeficiency diseases are commonly recognized due to recurrent or difficult to treat sinopulmonary or gastrointestinal tract infections, organ abscesses, autoimmunity, or systemic signs, such as prolonged fever or failure to thrive. Although the clinical characteristics of PIDs are widespread, they commonly present with chronic or recurrent airway infections such as recurrent sinopulmonary infections and chronic otitis media. Their infrequency suggests that screening for immunodeficiency is *NOT* necessary with isolated episodes of acute bacterial rhinosinusitis. The probabilities of a positive screening study for PID increase in patients with chronic rhinosinusitis refractory to medical therapy and requiring surgical management. This is particularly true of primary antibody deficiency (PAD) disorders. Although there are limited studies defining the frequency of PID in CRS, some specific antibody deficiencies have been reported in nearly 12 % of recalcitrant CRS surgical patients [2]. Medical care providers seeing patients with recurrent or chronic CS must keep PID, particularly PAD on their radar screen.

Immune deficiency can also present secondary to another medical problem. Primary and secondary immunodeficiencies have many clinical similarities in that their clinical presentation results from an immune dysfunction. Secondary immunodeficiencies may occur after immunosuppression to prevent graft rejection after transplantation, during treatment of systemic autoimmune disease or cancer with immune-modulating drugs, or during certain viral infections such as human immunodeficiency virus (HIV). HIV can result in a sudden onset of immunodeficiency and lead to recurrent or fatal infection with opportunistic organisms. Additionally, secondary immunodeficiencies can be seen in B-lymphoproliferative disorders such as chronic lymphatic leukemia, myeloma, and Waldenstrom's macroglobulinemia [3]. Because of the diversity of immune defects, range of ages at clinical presentation, and different clinical manifestations, distinguishing patients with primary or secondary immune deficiencies in clinical practice can be challenging.

The incidence and prevalence of PID have been estimated in a patient survey and population-based analysis. The Immune Deficiency Foundation (IDF) provided the first population-based estimate of the prevalence of PID in the United States in 2005 [4]. They conducted a national telephone survey of about 10,000 randomly selected households and found that about 1 in 1,200 individuals in the United States (or 250,000 people) has been diagnosed with PID. The first population-based analysis of the incidence of PID was conducted in Olmsted County, Minnesota (2,000 US census population of 124,277) [5]. This historical cohort study conducted from January 1, 1976, to December 31, 2006, showed that the overall incidence of PID for the 31-year period was 4.6 per 100,000 person-years. The rate of PID, as measured in incidence per 100,000 person-years, increased from 2.4 from 1976 to 1980, to 5.5 from 1996 to 2000, and to 10.3 from 2001 to 2006. These figures suggest that

S.J. McGeady, MD (✉)
Department of Pediatrics, Thomas Jefferson University, 833 Chestnut St. E., Philadelphia, PA 19107, USA
e-mail: smcgeady@nemours.org

G.A. Incaudo, MD, FAAAAI, FACAAI
Division of Rheumatology, Allergy and Clinical Immunology, University of California School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA
e-mail: gincaudo@norcalallergy.com

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_14,

Table 14.1 Primary antibody deficiency disorders

1. X-linked (Bruton's or XLA) and autosomal recessive (ARH) hypo-/agammaglobulinemia
2. B cell intrinsic immunoglobulin class switch recombination (Ig-CSR) deficiencies (formerly hyper-IgM syndromes)
3. Common variable immunodeficiency (CVID)
4. IgG subclass deficiency
5. IgA deficiency

earlier studies likely underestimated the true incidence of PID. The higher incidence figures in more recent studies suggest better diagnostic techniques and broader health-care provider awareness of PID. In general, with the exception of IgA deficiency, all forms of PID are rare and have an overall prevalence of approximately 1:10,000 live births.

A broad classification of PIDs can be primarily based on the chief component(s) of the immune system affected resulting in at least four broad categories:

1. Defects in adaptive immune responses including primary antibody production (B cell), cellular function (T cell), or combined T and B cell defects
2. Defects in innate immunity, primarily phagocyte-associated defects
3. Toll-like receptor-mediated signaling defects
4. Complement deficiencies

These categories are by no means exclusive, and there can be considerable clinical and immunologic overlap between them. There are other approaches to classification that can include immunophenotyping for specific PIDs which is beyond the scope of this text [6]. Of the more than 180 phenotypes of PID, the five most commonly associated most with sinus disease are PADs; common variable immunodeficiency (CVID), IgA deficiency, Bruton's XLA, B cell intrinsic immunoglobulin class switch recombination (Ig-CSR) deficiencies (formerly hyper-IgM syndromes), and IgG subclass deficiency (Table 14.1). The reason for an increased likelihood of PAD in CRS is thought to be due to antibodies being the principal host immune defense of mucosal surfaces. The presence of secreted antibody in the mucus secretions that bathe the mucosal lining of the sinuses and nasal passages is thought to be essential to resist infection, and some immunodeficiencies may fail to provide such antibody. The number of potentially pathogenic microbes in inspired air to which these mucosal surfaces are exposed is enormous, and the presence of secreted antibody together with innate immune mechanisms is thought to be the bulwark of host defense.

A comprehensive review of all PID disorders is beyond the scope of this text. Rather, this chapter will present practical information on sinusitis-associated immune deficiency disorders and present some differentiating features of several important diseases as they relate to age and clinical presentation. We will then review an approach that uses the most basic tests and clues in patients with CRS to begin an assessment of immunity in patients who are suspected of having underlying immune deficiency. A review of some of the more specific and sophisticated methods of diagnosis is included. Finally, a brief overview of treatment will be described to familiarize a medical care provider with concepts of antibody deficiency treatment. In the end, any patient found to have an immune deficiency should be referred to a specialist in immunology for a consultation and management plan. The most important message in this chapter for primary care, ENT, and allergy specialists is to maintain a high index of suspicion and never hesitate to look for immune deficiency in patients who are not responding to care as expected, have a family history of PID, have unusual infectious complications from sinusitis or otitis, or present with additional sites of recurrent infection beyond the paranasal sinuses and middle ear space.

A Primer on the Immune System, B Cell, and Antibody Production

The human immune system is a conglomeration of cells and molecules that cooperate to protect the host from infectious agents. This immune system also provides a surveillance ability to monitor the integrity of host tissues. Although the immune system is incredibly intricate and elaborate, its function can be distilled into two basic roles: recognition of a foreign substance that is not the host and removal of such agents through a diverse repertoire of cells and proteins that act in concert to initiate and complete the removal process.

The human body has three levels of immune defense. The first is the *physical barrier* to infection that is provided, in the nose and sinuses, by the *mucosal surface*. The nose is the body's air filter. Therefore, the mucosal surface is exposed to a wide array of infectious agents and toxic materials. Any infectious agent attempting to gain entry to the body must first breach the mucosal barrier. The mucosal barrier system of the nose and paranasal sinuses is reviewed in detail in Chap. 3. The second level of defense is the *innate immune system*. This is a broad-acting defensive layer that primarily attempts to kill infectious agents from the moment they enter the body. The innate immune system recognizes pattern recognition molecules that are foreign to those present

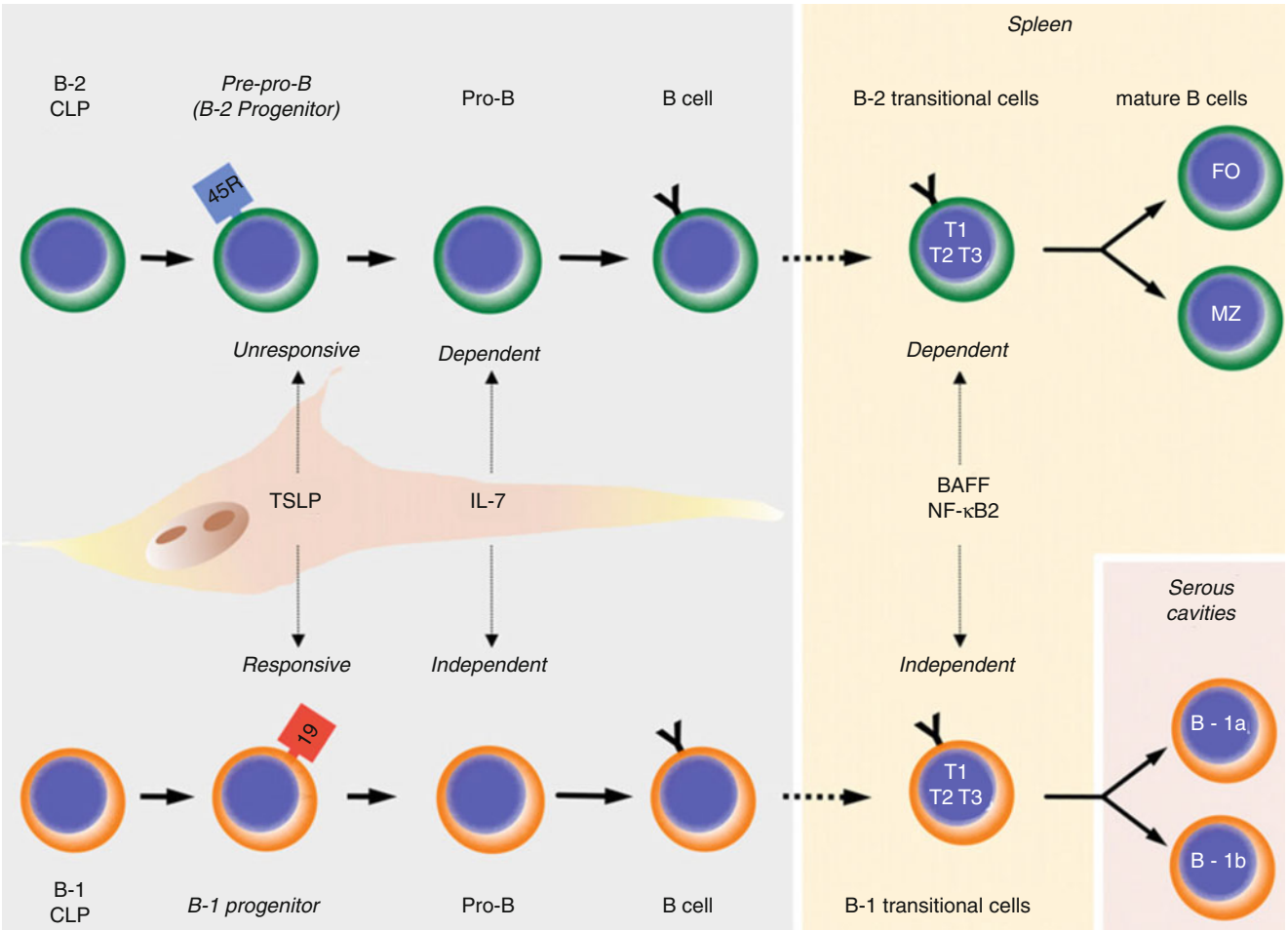


Fig. 14.1 B-1 and B-2 development. B-2 cells (*top*) are produced in the bone marrow after birth. Common lymphoid progenitors (*CLPs*) mature sequentially through B cell intermediates into immature sIgM+B cells (shown as "B cell" in figure). Immature sIgM+cells migrate to the spleen where they mature through B-2 cell transitional 1 (*T1*) and transitional 2 and 3 (*T2* and *T3*) stages into follicular (*FO*) or marginal zone (*MZ*) B cells. Mature B-1 cells are generated from B-1 cell-specified common lymphoid progenitors that sequentially differentiate to immature sIgM+B-1 cell stages. These cells then mature in the spleen through the transitional cell stages shown. Mature B-1 cells that migrate to serous cavities acquire the B-1a and B-1b cell phenotype. The figure also shows that B-1, but not B-2, cell progenitors are TSLP responsive; that B-2, but not B-1, cell development is dependent on IL-7; and that B-1 transitional cell survival and maturation is BAFF and NF-κB2 independent (Modified from Montecino-Rodriguez and Dorshkind [7]. With permission from Elsevier)

in the body. The key players in the innate immune system include macrophages, neutrophils, and soluble proteins such as complement and lysozymes. The innate immune system is also responsible for alerting the cells that operate the third level of defense, the *adaptive or acquired immune system*. The adaptive immune responses take longer to achieve functional significance, perhaps 4–5 days after the innate immune response has been triggered but is specifically designed to react definitively with the infectious agent. Importantly, the adaptive immune response is capable of improving upon each encounter with a particular infectious agent, a process termed immunologic memory responsiveness. This memory adaptive function is carried forward in the body through memory lymphocytes without the need for continuous antigen stimulation.

The *adaptive immune response* is mediated primarily by two sets of lymphocytes: *T lymphocytes* and *B lymphocytes*. These cells display specific receptors on their surface membranes that can be structured to recognize an almost limitless array of foreign structures called antigens. One of the primary and most important products of T and B cell activation are *immunoglobulins*. Immunoglobulins are produced by plasma cells which represent the final stage of B lymphocyte differentiation. B cells are divided into two types, referred to as B-1 and B-2 (Fig. 14.1). B-1 cells are part of the innate (nonspecific first line of defense) immune system and produce immunoglobulins (Ig) distinguished by their recognition of self-antigens [8, 9]. B-2 cells are present in secondary lymphoid organs and are generally considered to be mediators of adaptive (acquired) immunity [10, 11]. They include a predominant population of follicular (FO) and a minor population of marginal zone (MZ) B cells within the lymph nodes and spleen, both of which can undergo immunoglobulin class switching and differentiate into memory cells.

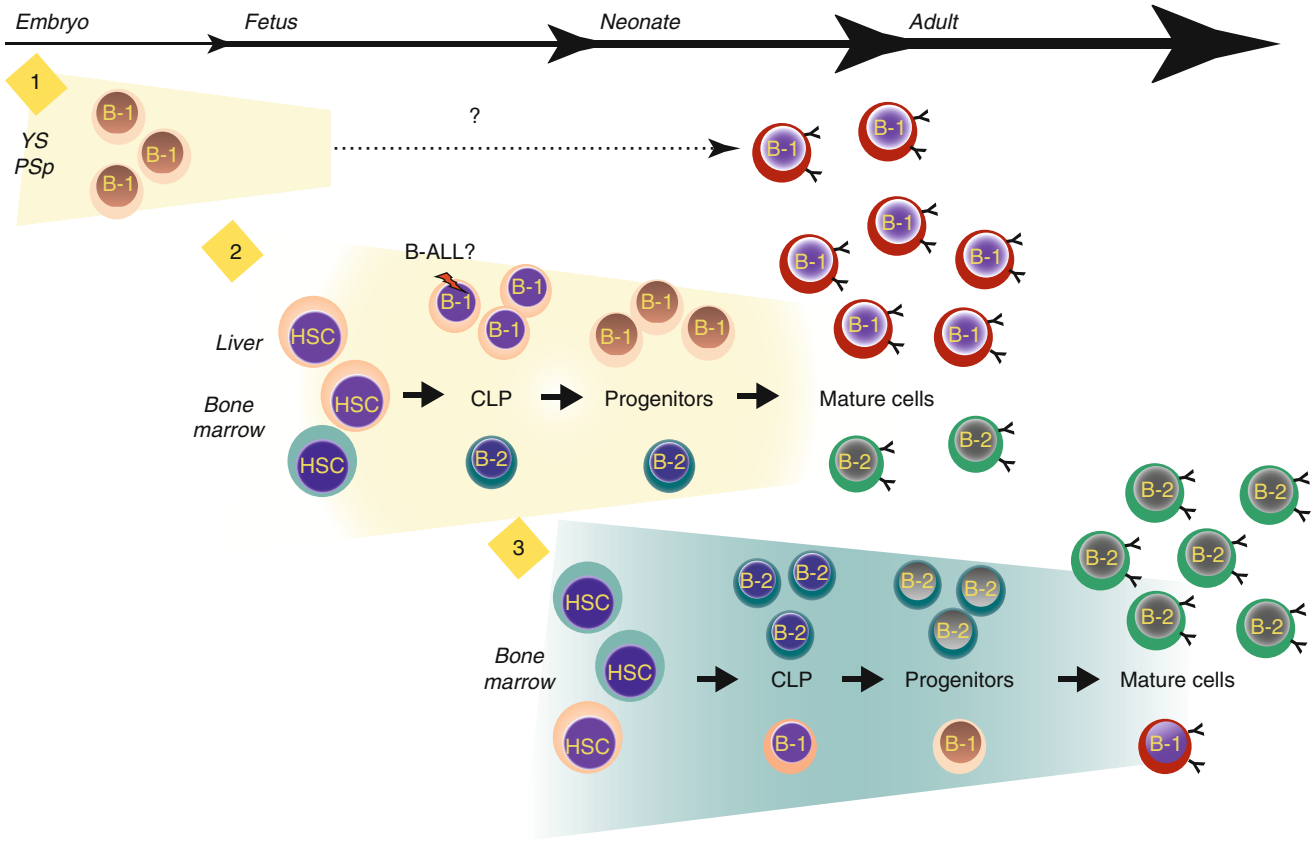


Fig. 14.2 B-1 and B-2 development occur in distinct, overlapping waves. Three waves of B-1 cell development are proposed. The first wave ("1") initiates in the yolk sac (*YS*) and para-aortic splanchnopleura (*PSp*) region before the emergence of definitive hematopoietic stem cells (*HSCs*). It is not clear, as indicated by the *dashed line*, whether B-1 cell progenitors produced during this initial phase mature into B-1 cells that become part of the adult B-1 pool. If so, they may do so in YS and PSp or migrate to the fetal liver and bone marrow and complete maturation in those tissues. During the second wave ("2"), which initiates in the fetal liver and fetal bone marrow, hematopoietic stem cells generate B-1 cell progenitors from which mature B-1 cells are derived. Although B-2 cell development initiates during this second phase, B-1 cell production predominates. Whether or not B-1 and B-2 cell common lymphoid progenitors are produced from a single type of human stem cell or multiple B-1 and B-2 cell-specified stem cells exist, as indicated by the different colored HSCs, is not known. B-1 cell production peaks during late embryogenesis and then begins to decline just before birth. The third wave ("3") of B cell development takes place in the bone marrow and results primarily in the production of B-2 B cells. B-1 B cells can be produced during this third wave, but the efficiency with which this occurs in comparison to wave two is substantially reduced (Modified from Montecino-Rodriguez and Dorshkind [7]. With permission from Elsevier)

B-1 and B-2 cells develop in distinct "waves" during human development. B cells originate from hematopoietic stem cells and undergo maturation in the fetal bone marrow and fetal liver. Following birth, the predominant B cell is the B-2 cell which undergoes maturation and proliferation in the bone marrow (Fig. 14.2) [7]. In the bone marrow, a rearrangement of the B cell receptor genes occurs. Successful expression of the first μ heavy chain followed by either the kappa or lambda light chain on the cell surface allows the B cell to differentiate to a mature, antigen-naïve B cell. The mature B cell, with IgM and IgD on the surface, then leaves the bone marrow and circulates though the body looking for trouble and understands self from non-self. Defects in B cell development lead to a variety of antibody deficiency states which vary according to the stage in maturity in which the block occurs (Fig. 14.3). Primary antibody deficiency disorders (PAD) comprise virtually all the PIDs that might present to the primary care provider, pediatrician, otolaryngologist, internist, or allergist for evaluation of chronic or recurrent rhinosinusitis and will be discussed next (Table 14.1).

Clinical Patterns in Primary Antibody Deficiency (PAD) Disorders

The heterogeneity of antibody deficiency disorders produces different clinical presentations although the hallmark of PID, recurrent infection, remains a common theme. Patients with PAD can present either in early childhood or in adulthood depending on the severity of the disorder. This pattern usually coincides with how early in the B cell development pathway

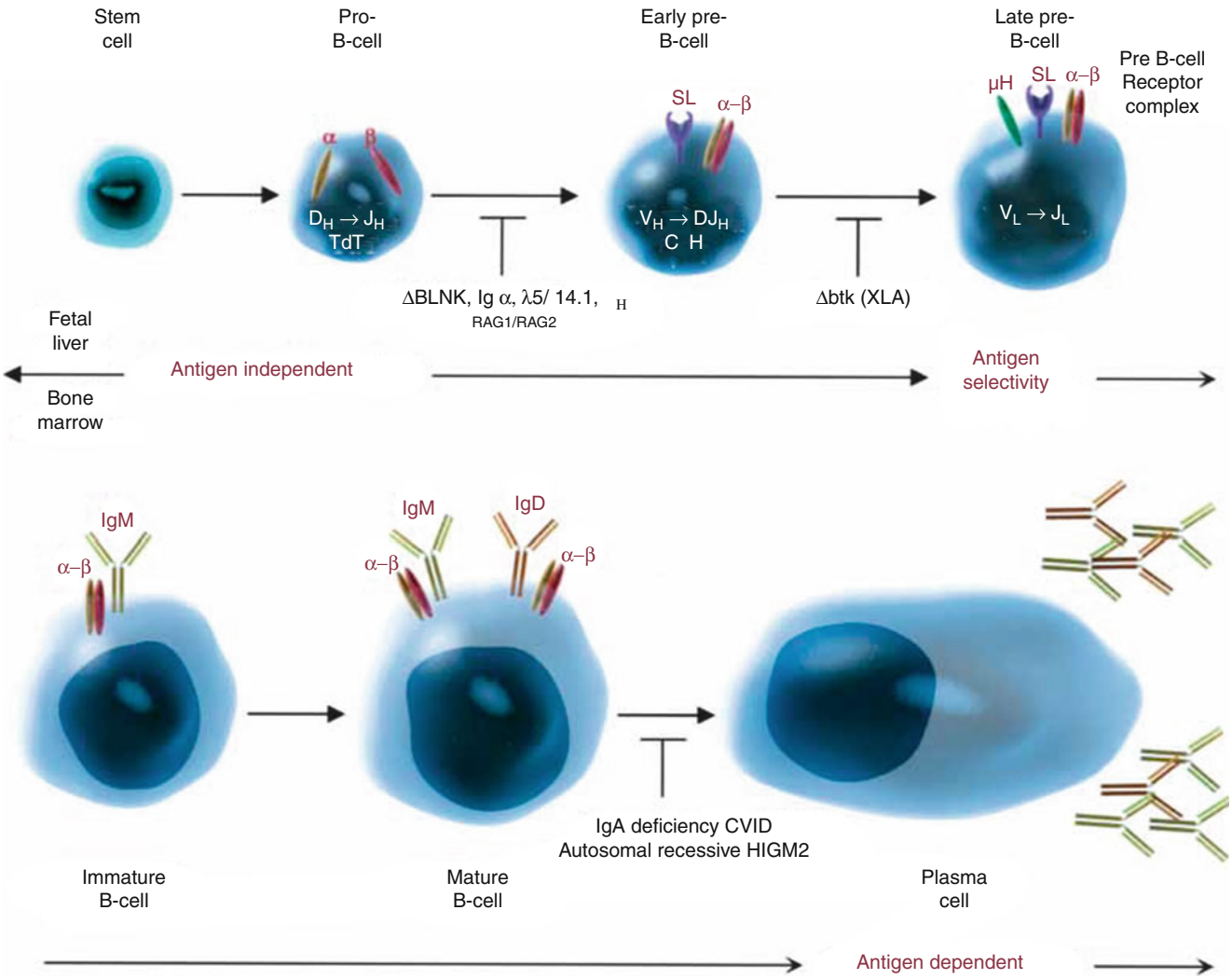


Fig. 14.3 Normal B cell development and mutations that lead to antibody deficiencies. Mature B cells undergo class switching and somatic hypermutation of the variable region genes to increase receptor affinity and differentiation into memory B cells or plasma cells. Abnormalities in these latter processes of B cell differentiation lead to IgA deficiency and CVID, although the molecular basis for these antibody deficiencies is largely unknown. Earlier in B cell development, deletions or mutation in the μ heavy chain (*μH*), the surrogate light chain (*SL*), or Igα (α−β) leads to a block in B cell development and severe agammaglobulinemia. Similarly, defects in the B cell signaling pathways mediated by Btk and the adaptor protein BLNK lead to an arrest at the pro-B cell stage of development and suggest that a functional pre-B cell receptor is critical for the progression of the pre-B cell to an immature B cell (Reprinted from Ballow [12]. With Permission from Elsevier)

the defect occurs; the earlier the defect, the more clinically severe the disorder. This variability is also not simply based upon the degree of antibody deficiency, but also varies with epigenetic factors such as modifying genetic alterations, age of the patient at the time of diagnosis, and environmental exposures [13, 14]. All forms of primary immunodeficiencies are characterized by increased susceptibility to recurrent infection, severe infections, or both. In addition, given the complexity of the human immune system and the wide diversity of immune disorders possible, it is no wonder that PIDs can also present with involvement in virtually every organ system in the body. Therefore, we see a broad pattern of clinical disease that can extend beyond infection in patients with PADs (Table 14.2).

Typically, PAD patients present a mixed clinical history of recurrent upper and lower respiratory tract infections such as sinusitis, otitis media, and pneumonia. Infections can also be seen in other areas such as skin abscesses and urinary tract infections. The most common infectious agents are *Streptococcus pneumoniae* and *Haemophilus influenzae*, but infections with *Staphylococcus* and *Giardia lamblia* are also found frequently. Patients with agammaglobulinemia are unusually susceptible to enteroviral infections [15]. More serious complications involve clinical entities beyond infection such as granulomatous disease of the lung, liver, and spleen and idiopathic diffuse lymphadenopathy with monoclonal or oligoclonal populations of lymphocytes often complicated by splenomegaly. Caring for these comorbidities can be challenging and can

Table 14.2 Organ-specific complications of PAD

Upper airway/ear space
Recurrent and/or chronic rhinosinusitis
Recurrent and/or chronic otitis media
Mastoiditis
Lower airway
Pneumonia
Lung abscesses
Bronchiectasis
Bronchial wall thickening, bronchitis symptoms
Gastrointestinal
Atrophic gastritis/pernicious anemia
Villous atrophy
Inflammatory bowel disease
Celiac disease
Chronic diarrhea
Infectious diarrhea
Nodular lymphoid hyperplasia
Hepatic
Primary biliary cirrhosis
Sclerosing cholangitis
Granulomatous liver disease
Hepatomegaly
Infectious hepatitis (rare)
Splenic
Splenomegaly with or without generalized lymphadenopathy
Thrombocytopenia
Hematologic
Idiopathic thrombocytopenic purpura
Autoimmune hemolytic anemia
Neutropenia
Neurologic
Bacterial infections
Idiopathic neurodegenerative disease
Rheumatologic
SLE particularly juvenile
Nonspecific arthritis
Juvenile rheumatoid arthritis
Endocrine
Graves disease
Type 1 diabetes mellitus
Cutaneous
Infection/abscess
Granuloma formation
Erythroderma
Malignancy
Lymphomas, especially non-Hodgkin's
Epithelial malignancy, especially gastric carcinoma

sometimes result in thrombocytopenia requiring a splenectomy. Furthermore, autoimmunity such as autoimmune hemolytic anemia, lymphoproliferative malignancy such as non-Hodgkin's lymphoma, and gastric cancer are observed more commonly in PAD patients compared to the general population [16, 17] (Table 14.1).

As always, a good history is the best starting point. Table 14.2 outlines the array of potential problems seen in patients with PAD and Table 14.3 the typical presenting symptoms in cohorts with PAD. In any patient with CRS, a single severe infection or coexisting lymphoid or granulomatous disease may be the first inference of a primary or secondary underlying immune disorder. In general, the first and foremost complaint will be recurrent bacterial infection of the upper and lower airway space. Inquiring about the family history is important to be alert to possible genetic disorders although mutations in PAD may be new and many PIDs present without a positive family history [24]. In evaluating any patient with recurrent or

Table 14.3 Presenting location of infection in cohorts of patients with PAD

Site of infection						
Respiratory/chest including pneumonia (%)	66	77	58	37	69	90
Recurrent sinus infections (%)	60	98[a]	38	19	80	66
Gastrointestinal infections (%)	17	6	12	7	19	38
Cutaneous infections (%)	5	1	19		13	
CNS/meningitis (%)	6	2	6	2	9	4
Septic arthritis/osteomyelitis (%)	1	2	7	2	1	
Ophthalmic infections (%)	10		2			
References	[18]	[19]	[20]	[21]	[22]	[23]

[a]Data includes sinusitis, bronchitis, and otitis media

chronic rhinosinusitis, a search for comorbid conditions, particularly pulmonary, autoimmune, and gastrointestinal disorders, will help identify those patients who need a more expansive differential diagnosis as to causes.

Clinical Features of Specific Antibody Deficiency Disorders

Early B Cell Developmental Defects

Bruton's and Autosomal Recessive Hypo-/Agammaglobulinemia

As shown in Fig. 14.3, defects in the B cell signaling pathways mediated by Bruton's tyrosine kinase (Btk) and the adaptor B cell linker (BLNK) lead to an arrest at the pro-B cell stage of development. In all cases, there is a block at the pro-B and pre-B cell stage of differentiation in the bone marrow resulting in a virtual absence of circulating B lymphocytes seen on flow cytometry. In contrast to the Btk mutation which is X-linked, mutations in the μ heavy chain (μH), light chain lambda 5 (λ5), and BLNK cause an autosomal recessive form of agammaglobulinemia [25–28]. As the pre-B cell receptor complex has been dissected, two additional defects in pre-B cell function has been more recently identified. Gene mutations in the pre-B cell receptor anchoring molecules, CD79a and CD79b, have also been described as generators of agammaglobulinemia [29, 30].

Mutation in the gene encoding Btk in an early stage of B cell development produces X-linked agammaglobulinemia (Bruton's disease) [31]. Defects in Btk (Bruton's tyrosine kinase) are the most common form (85 %) of early-onset hypo-/agammaglobulinemia. The autosomal recessive mutations in μ heavy chain account for 5 % of early-onset hypo-/agammaglobulinemia, and defects in several others comprise the remainder [16]. Although the autosomal recessive forms and Btk defects share a similar phenotype, the Btk mutation tends to be clinically more severe resulting in significant recurrent infections of the ear, sinus, and lung starting in early childhood. In addition to bacterial infections, patients with agammaglobulinemia are uniquely susceptible to enteroviral infections which sometimes lead to meningoencephalitis or severe dermatomyositis and mycoplasma infections underscoring the complex interdependency of the human immune system. In essence, genetic defects identified in agammaglobulinemia patient all affect pre-B cell receptor expression or downstream signaling which results in a block in precursor B cell differentiation, a lack of circulating mature B cells, and a profound reduction in antibody formation (Fig. 14.3). It should be noted that the Btk defect can be incomplete in less severely affected patients with Bruton's disease resulting in some B cells and immunoglobulin appearing in the peripheral blood.

B Cell Defects Following B Cell Maturation

B Cell Intrinsic Immunoglobulin Class Switch Recombination (Ig-CSR) Deficiencies

Further development of a mature B cell into a plasma cell capable of producing a repertoire of antibodies requires two key processes: class switch recombination and somatic hypermutation. Mature B cells have, on their surface, IgM. Defects early in the process whereby a mature B cell becomes a plasma cell have been termed, in the past, "hyper-IgM syndromes" due to the commonly abundant IgM in these patients with little IgA, IgG, and IgE. The newer terminology prefers to identify these disorders as "B cell intrinsic immunoglobulin class switch recombination (Ig-CSR) deficiencies" which better describes the

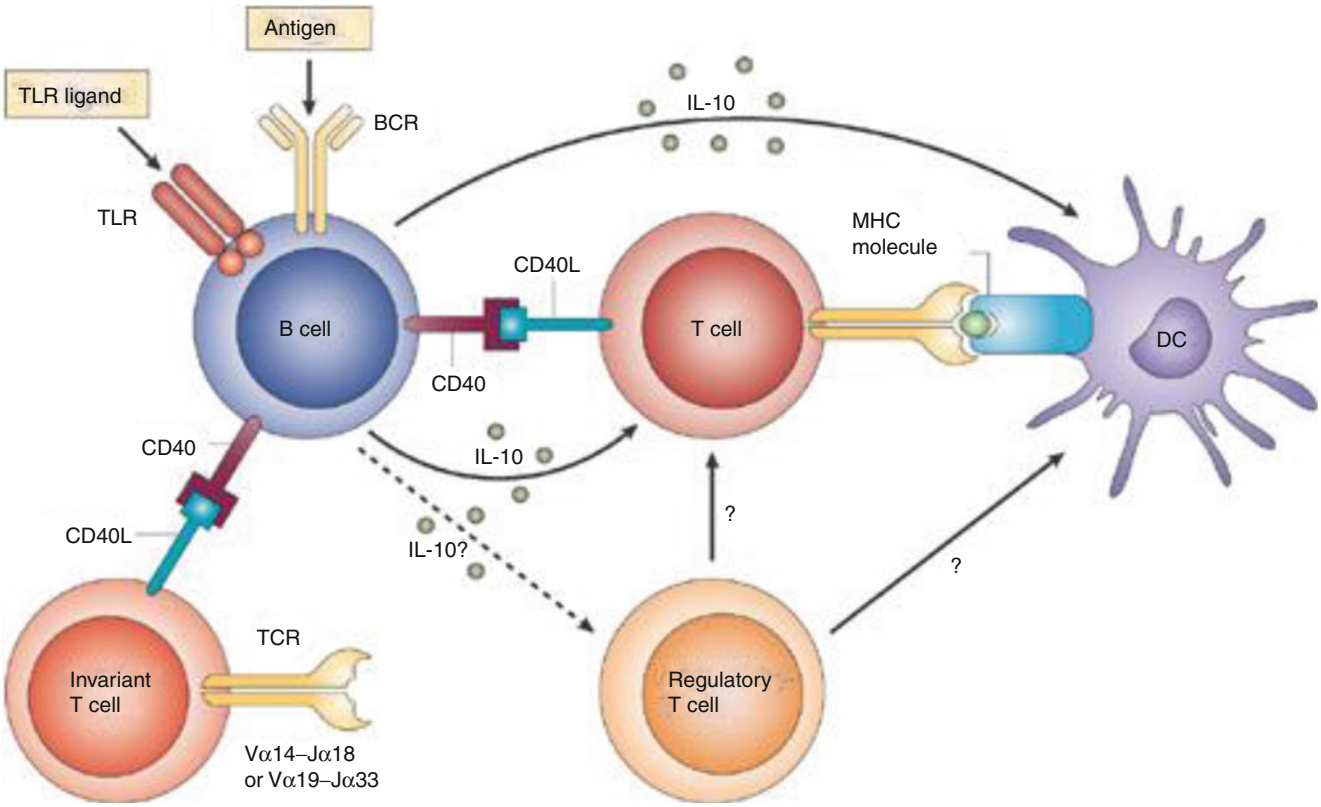


Fig. 14.4 Communication between the T cell and B cell requires CD40 and CD40L. CD40L is predominantly expressed by activated CD4+ T lymphocytes and interacts with CD40, which is expressed by B lymphocytes, monocytes, dendritic cells, and other cell types (Reprinted from Fillatreau et al. [34]. With permission from Nature Publishing Group)

general abnormality. Considerable progress has been made in defining the genetic mutations responsible for Ig-CSR deficiencies. In spite of such progress, approximately 15 % of class-switching defects remain genetically undefined [32, 33]. A detailed overview of each of the known defects is beyond the scope of this text. Furthermore, the clinical phenotype is similar among all of these disorders making such descriptions laborious to the practicing clinician, and there are no additional therapeutic applications currently available as a result of identifying different subsets.

The only exception to the common clinical presentation among the various subgroups of Ig-CSR deficiencies is CD40 ligand deficiency. In general, B cells require two signals to become productively activated and for class switching between antibodies. This most likely represents a safeguard to limit the production of autoantibodies. One is the B cell co-receptor complex mentioned earlier which is capable of interacting with opsonized or coated antigenic material such as complement generated through the innate immune system. The other form of co-stimulation required by B cells is provided by T lymphocytes through their membrane-associated CD40 ligand (CD40L) (Fig. 14.4) [34]. This ligand or receptor engages the surface CD40 on the mature B cell and provides a vital stimulus for class switching and somatic hypermutation. A significant number of patients with Ig-CSR deficiencies have an X-linked form of a disease involving point mutations and deletions in the T cell CD40L. These mutations largely map to the part of the molecule involved in the interaction with the B cell CD40 rendering the T cell incapable of transmitting the necessary signals for immunoglobulin class switching. In this circumstance, the result is a more severe combined immunodeficiency often with infections by opportunistic organisms such as *Pneumocystis jirovecii*, *Toxoplasma*, and *Cryptosporidium*. Neutropenia is also seen on the CBC in 65 % of patients with CD40L deficiency. An autosomal recessive form of CD40L defect exists that results in a clinical phenotype similar to other Ig-CSR deficiency states [35].

Common Variable Immunodeficiency (CVID) or Idiopathic Hypogammaglobulinemia

Common variable immune deficiency (CVID) is the most common form of clinically significant primary immunodeficiency with an incidence of between 1:30,000 and 1:50,000. In contrast to the gene mutations mentioned earlier which clinically present in childhood, CVID most commonly presents in adulthood. Although the diagnosis is typically made around 30 years

Table 14.4 Key immunologic/genetic features of major primary antibody deficiency disorders

Disease	B cells	Immunoglobulins	Inheritance	Gene mutations
Pre-B cell	Absent/low	IgA, IgG, IgM ↓↓	AR	BLNK, IGHM, CD79A, CD79B
Receptor defect chain				μ5 surrogate light
XLA	Absent/low	IgA, IgG, IgM ↓↓	X-linked	Btk
Ig-CSR defects	Normal	Normal/elevated IgM	X-linked	CD40L
		Low IgG and IgA	AR	CD40
			AR	AID
			AR	UNG
			AR	PMS2
CVID	≥1 %	One or more Ig↓	None	Heterozygous defects
	Most normal	Impaired response to		(e.g., TNFRSF13B → TACI)
	Some low	Vaccination/infection		Homozygous defects (e.g., ICOS)
				CD19
				>95 % no gene identified
IgA deficiency	Normal	IgA ≤ 0.07 g/L	None	Unknown
		Some IgG subclass ↓		
		Especially IgG2		
IgG subclass	Normal	Normal IgG, IgA, IgM	None	Unknown deficiency

Blnk B cell linker, *Btk* Bruton's tyrosine kinase, *IGHM* Igμ heavy chain, *AID* activation-induced cytidine deaminase, *UNG* uracil N-glycosidase, *PMS2* post-meiotic segregation, *TNFRSF13B* tumor necrosis factor receptor superfamily member 13B, *ICOS* inducible co-stimulator, *TACI* transmembrane activator

of age, about 28 % of patients are less than 21 years of age at diagnosis, and many others give a history of clinical events suggestive of an immune disorder well before the age of diagnosis [19, 36]. Generally, health-care providers are reluctant to diagnose CVID in young children (under age 4) because physiologic immaturity can mimic CVID in the early years. In addition, the possibility of immune defects in children under the age of 4 years opens a greater array of PID disorders to be considered. In general, most CVID patients experience a delay in the diagnosis of approximately 6–7 years from disease onset [37]. Even then, some patients with CVID are surprisingly free of infections at presentation and see a provider for another problem initially such as selected autoimmune or inflammatory problems common in CVID (Table 14.2). CVID is then innocently uncovered during the investigation of these comorbidities.

CVID is characterized by reduced serum levels of IgG and usually either IgA and/or IgM by at least two standard deviations below the age-adjusted mean. The definition of CVID also includes demonstrating a functional deficiency in antibody quality with reduced or absent isohemagglutinins (antibodies to non-self surface antigens – both IgG and IgM) and/or a poor response to vaccines (an IgG function) in a patient of more than 2 years of age in whom other causes of immune deficiency have been ruled out [38]. Most patients have variable numbers of circulating B cells but always in excess of 1 % of lymphocytes (Table 14.4).

CVID is the most common PAD and the least understood. In contrast to the other PAD noted above, genetic mutations in CVID have been identified in <5 % of patients suggesting this syndrome might well be polygenic. In fact, CVID is a diagnosis of exclusion in >95 % of cases making this truly a heterogenous group of disorders with a wide range of clinical phenotypes and a broad array of clinical complications that can go far beyond recurrent respiratory infections [39]. About 20 % of patients with CVID have signs of autoimmunity and/or lymphoproliferation [40]. In general, nearly a third of CVID patients will have infections only without complications, 28 % will have chronic lung disease or autoimmunity, 15 % gastrointestinal disease, nearly 10 % granulomatous or liver disease, 8 % lymphomas and other lymphoid malignancies, and 7 % other cancers [37, 41].

CVID patients can usually be classified into two main groups by disease phenotype that generally remains consistent over time. One group contains subjects who present primarily with a history of recurrent infections and a second group who may have infections, but in addition, present with a variety of inflammatory and/or autoimmune conditions. For the second group of patients, these comorbid conditions typically emerged as the most difficult to deal with in that they often require forms of immune suppression for control which may aggravate the infectious predisposition. Furthermore, in contrast to the infectious predisposition, the inflammatory/autoimmune comorbidities typically do not respond to IVIG therapeutics. The two group categorization became evident when studying large collections of patients. In the largest European study, 334 subjects from the European Society for Immune Deficiency (ESID) were followed for an average of 25.5 years; 71 % had one or more inflammatory/autoimmune complications and the reminder had infections only [36]. In the US group, of 476 patients studied from one medical center, 68 % had one or more inflammatory/autoimmune manifestations of their CVID and the rest had infections only [37].

The most common autoimmune diseases in CVID in all studies were immune thrombocytopenia followed by autoimmune hemolytic anemia. Other autoimmune conditions reported from the US study included (alphabetically listed) anticardiolipin antibody, antiphospholipid syndrome, autoimmune thyroid disease, diabetes mellitus, inflammatory bowel disease, juvenile rheumatoid arthritis, multiple sclerosis, neutropenia, pernicious anemia, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, uveitis, vasculitis, and vitiligo [37].

The gene defects that have been described in CVID to date are shown in Table 14.4 and Fig. 14.5. The first genetic defect identified as being associated with CVID was the ICOS (inducible co-stimulator) gene. ICOS is expressed on activated T cells and interacts with its ligand, ICOSL, B cells, and dendritic cells. ICOS-ICOSL interaction is important for T/B cell co-activation, CD40-mediated class switching for plasma cells to change antibody production, the secretion of proinflammatory cytokines, and the development of the Th2 immune response [42] (Fig. 14.6). Mutations in inducible T cell co-stimulator (ICOS) or the B cell co-receptor CD19 are occasionally found in patients with CVID. However, ICOS and CD19 defects are not as frequent as mutations in transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), which has been found to affect 8 % of patients with CVID [44] (Fig. 14.7).

TACI, which is expressed by B cells, has been shown to induce immunoglobulin class switching after binding either of its ligands: transmembrane B cell-activating factor (BAFF) receptor (BAFF-R) and a proliferation-inducing ligand (APRIL) (Fig. 14.7). Accordingly, individuals with mutations that interfere with binding of APRIL appear to have impaired B cell proliferation and defective class switching in response to interleukin-10 and APRIL or BAFF. As a result, these individuals experience humoral immunodeficiency characterized by low serum IgM level and impaired IgG and IgA production, making them susceptible to recurrent bacterial infections. Lymphoproliferation and signs of autoimmunity are also evident in TACI-deficient individuals suggesting a role for TACI and BAFF-R in the induction of autoimmunity. TACI and BAFF-R belong to the TNF receptor superfamily and are crucial for the development and maintenance of the antibody-producing immune response [37, 42]. Mutation of both TACI alleles is always associated with insufficient antibody production and, frequently, with CVID. It is generally thought that heterozygous TACI mutations predispose to CVID instead of actually causing the disease and underscores the complexity of this group of disorders [44]. Data supporting this concept are: (1) 2 % of the control population carry a mutant TACI allele, (2) CVID develops most of the time in the absence of TACI mutations, (3) a heterozygous TACI mutation did not segregate with disease in one familial case of CVID, and (4) in the case of two brothers with a homozygous TACI mutation, one was affected with CVID but the other had hypogammaglobulinemia with no clinical

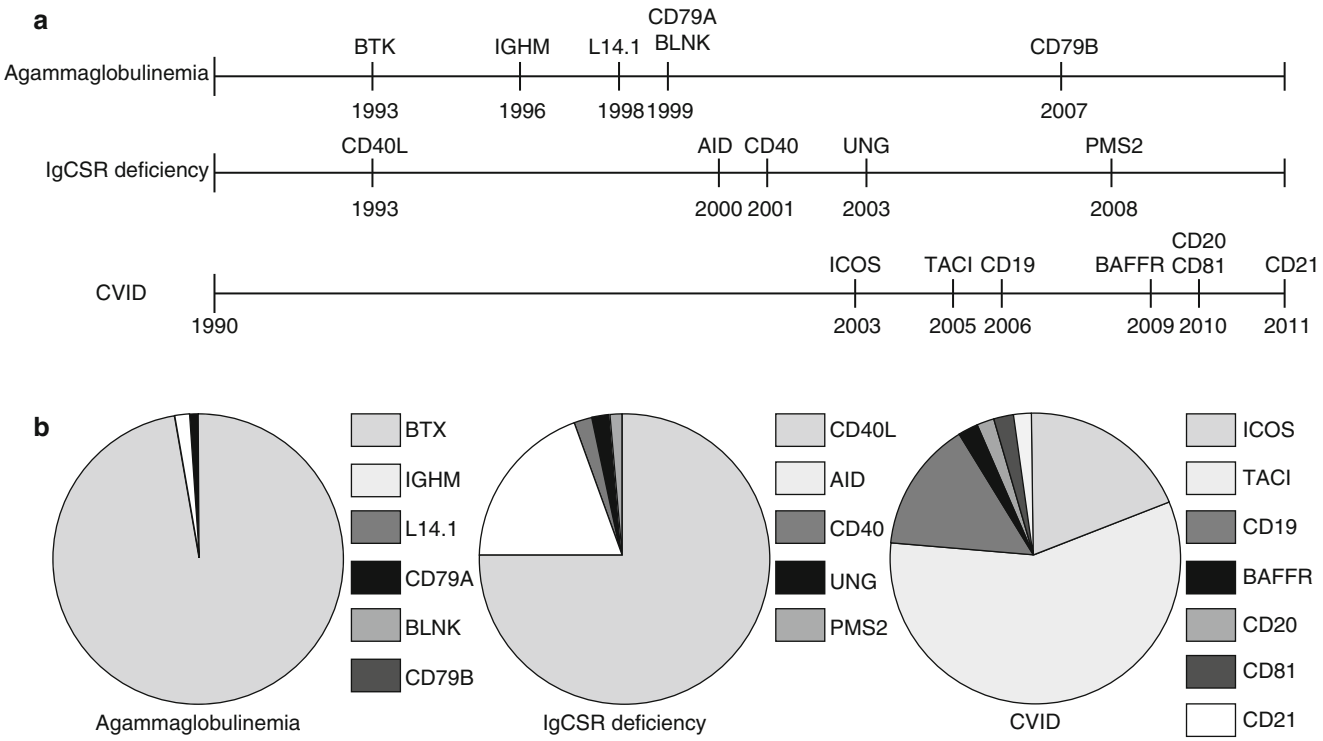


Fig. 14.5 Historical overview and frequencies of genetic defects in PAD. (**a**) Identification of genetic defects in agammaglobulinemia, Ig-CSR deficiencies, and CVID from 1990 to 2010. (**b**) Frequencies of PAD gene defects in agammaglobulinemia, Ig-CSR deficiencies, and CVID (Reprinted from Van der Burg et al. [39]. With permission from Springer Science + Business Media)

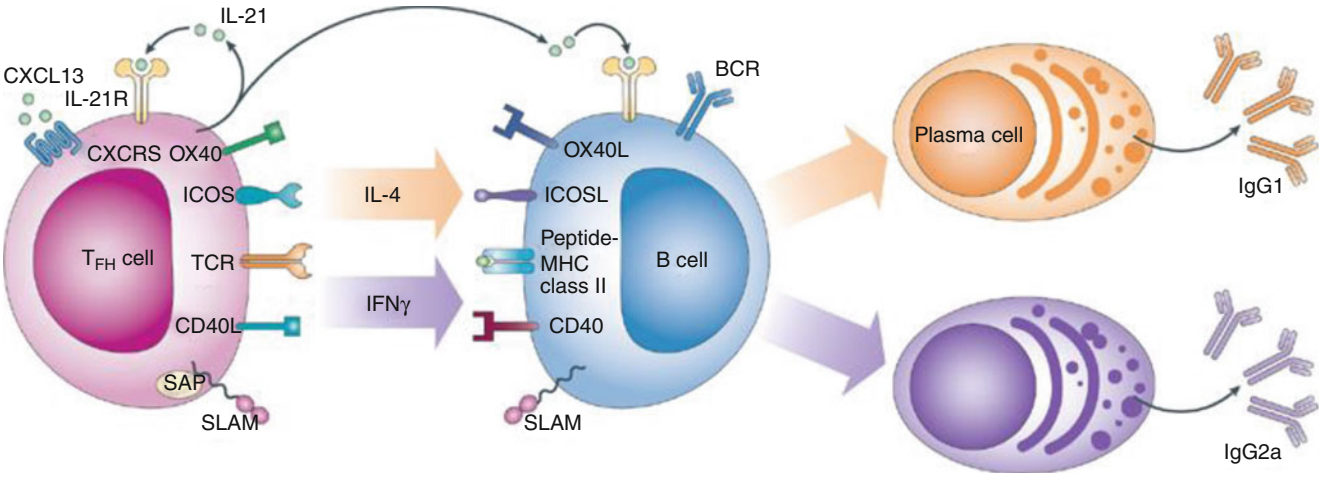


Fig. 14.6 ICOS and antibody class switching – many players are involved. A range of cytokines produced by T follicular helper (TFH) cells can direct antibody class switching. The acquisition of T cell cytokine competency begins in the T cell zone and precursor TFH cells have the capacity to induce class switching during their interaction with B cells at the border of the T cell zone and B cell follicle. Interleukin-4 (*IL-4*) induces the switch to IgG1 production (and then IgE production, not shown), and interferon-γ (*IFNγ*) induces the switch to IgG2 production. *BCT* B cell receptor, *CXCL13* CXC, chemokine ligand 13, *CXCR5* CXC-chemokine receptor 5, *ICOS* inducible T cell co-stimulator, *IL-21R* IL-21 receptor, *L* ligand, *SAP* SLAM-associated protein, *SLAM* signaling lymphocytic activation molecule, *TCR* T cell receptor (Reprinted from King [43]. With permission from Nature Publishing Group]

signs of immunodeficiency. These observations suggest that in the case of TACI mutations, other genetic or environmental factors are likely required to produce clinically active CVID [41, 45].

The common genetic basis of CVID and IgA deficiency has long been suspected, as these disorders have been shown to coexist within families [46]. The gene location for this CVID/IgA deficiency association appears to reside in the TACI/BAFF complex. Patients with CVID and IgA deficiency have been described with mutations in TACI in several studies [44–46]. Furthermore, a patient with CVID lacking BAFF-R with accompanying severe B cell lymphopenia has been reported [47]. If it can be confirmed that a mutation in BAFF-R can cause the B cell lymphopenic/CVID phenotype, it will suggest that human B cells strongly rely on BAFF signals for their survival (Fig. 14.7).

Another antibody deficiency syndrome that falls within the CVID group of deficiencies is due to mutations in the CD19 complex. The CD19 complex consists of CD19, CD21, CD81, and CD225. It is responsible for reducing the threshold for antigen-dependent stimulation of the B cell receptor. Defects in the CD19 gene complex have been described as a source of antibody deficiencies in several studies [48–51].

In summary, CVID commonly presents as an individual who has had normal immune parameters for the early part of their life but then undergoes a waning of immunoglobulin levels. Eventually, these individuals typically develop recurrent sinopulmonary infections as immunoglobulin levels decline, and the ability to produce adequate antibody responses is lost. Such a decline suggests the possibility of a gene-environment interaction playing a role in the pathogenesis of CVID. The identified genetic defects in CVID to date are few compared to the number and variety of affected individuals. Furthermore, the few identified genetic defects in CVID affect different steps or processes in B cell differentiation suggesting that the overall underlying immunopathological mechanisms and genetic defects are, in fact, heterogenous and diverse. In the end, as the specific genetic defects underlying individual patients with CVID are identified, most researchers suggest that CVID be defined by the gene mutation rather than lumped into a broad classification as is currently the practice. Despite a complexity of definitions, CVID remains identifiable and mostly treatable. While the prevalence of CVID in the general population suggests that it is an uncommon condition, it is much more prevalent in cohorts of patients with recurrent CRS infection. The diagnosis should especially be considered in individuals who develop complex, persistent, or recurrent CRS infections, particularly if the clinical history also contains one or more of the other PAD-associated comorbid conditions mentioned in Table 14.2.

IgG Subclass Deficiency

Although controversial, there is some data to suggest that patients with IgG subclass deficiency experience a high frequency of respiratory tract infections (Table 14.5). However, a deficiency in an individual IgG subclass can occur in as many as 2 %

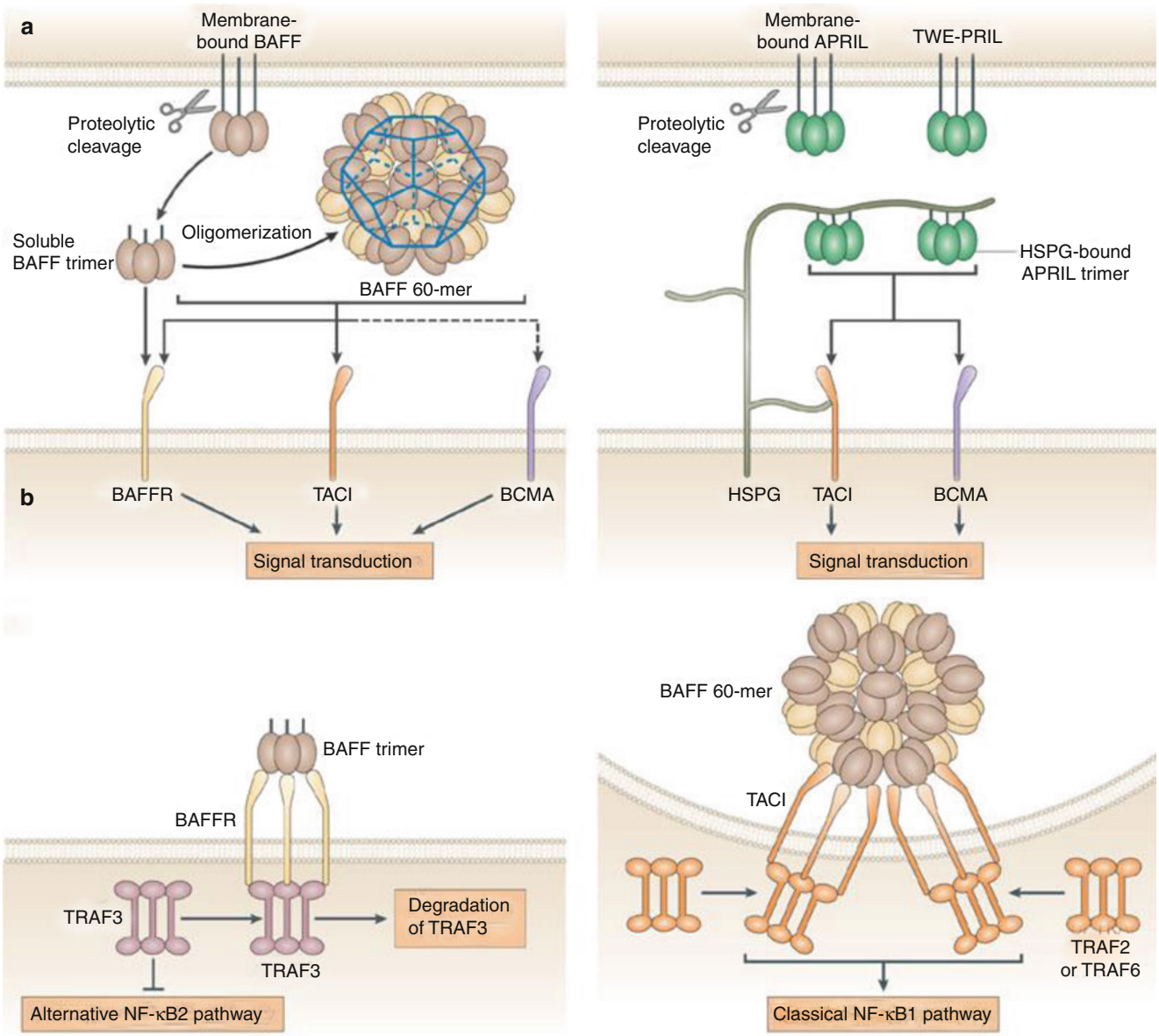


Fig. 14.7 The importance of TACI, BAFF, and APRIL in B cell proliferation and survival. (**a**) Schematic of various forms of B cell-activating factor (*BAFF*) and APRIL (a proliferation-inducing ligand) and their binding to BAFF receptor (*BAFFR*), transmembrane activator, and calcium modulator and cyclophilin ligand interactor (*TACI*) and B cell maturation antigen (*BCMA*). BAFF and APRIL are synthesized as membrane-bound proteins that can be released as soluble cytokines by proteolytic cleavage. The *arrows* indicate interactions that can induce signaling, although BAFF trimer can also bind to TACI and BCMA. The *dashed arrow* indicates weak affinity of BAFF 60-mer for BCMA. (**b**) Model of signaling induced by BAFF trimer and higher order oligomers. TNF receptor-associated factors (*TRAFs*) are trimeric intracellular signaling molecules that are recruited to three receptors held in the correct geometry by a trimeric ligand (Reprinted from Mackay and Schneider [42]. With permission from Nature Publishing Group)

of the healthy population suggesting that a careful immunologic investigation is required in these subjects before a diagnosis of PAD can be made [52]. As an isolated problem, IgG subclass deficiency may eventually be dropped as a primary antibody deficiency disorder and given clinical relevance only when bundled with other immune disorders such as IgA deficiency. The age at which each of the IgG subclasses reaches adult levels varies, and every age group in childhood has its own normal levels [53, 54].

Human IgG can be subdivided into four subclasses: IgG1, IgG2, IgG3, and IgG4. IgG1 makes up most of the total IgG (66 %), followed by IgG2 (24 %), IgG3 (7 %), and IgG4 (3 %) [55, 56]. IgG1 and IgG3 appear early in ontogeny, are efficient activators of the classical complement pathway [57], and are directed mainly against protein antigens. Deficiency of IgG1 usually results in low levels of total IgG and is often associated with susceptibility to bacterial infections. IgG2 appears much

Table 14.5 The most common PIDs associated with CRS: clinical characteristics and laboratory findings

PAD	Clinical presentation	Laboratory values
CVID	Recurrent sinopulmonary infection with encapsulated or unusual organisms	IgG < 2 SD from age-related normals Low IgA, low or normal IgM
IgA deficiency	Normal of recurrent sino pulmonary infections	IgA ≤ 0.07 g/L, IgG and IgM normal Some with IgG subclass deficiency, esp. IgG2
IgG subclass deficiency	Normal or recurrent sino pulmonary infections	IgG subclass <2 SD from age-related normals Normal IgM low or normal IgA
XLA	Early-onset recurrent sino pulmonary infections	Profoundly low IgG, IgA, and IgM Flow cytometry absent or low B cells

Table 14.6 Serum IgG subclass levels (mg/mL): expected values for each year of age up to 18 and median values in adults; 3rd and 97th percentile values are indicated between parentheses

Age	No of subjects	IgG1	IgG2	IgG3
6–11 months	3	4.5 (2.5–8.5)	0.72 (0.29–1.71)	0.21 (0.07–0.55)
1 year	10	4.7 (2.6–8.9)	0.78 (0.31–1.85)	0.22 (0.07–0.58)
2 years	18	5.2 (2.9–9.7)	0.90 (0.36–2.14)	0.24 (0.08–0.63)
3 years	43	5.6 (3.1–10.5)	1.03 (0.41–2.45)	0.26 (0.09–0.69)
4 years	24	6.1 (3.4–11.4)	1.18 (0.47–2.79)	0.29 (0.10–0.76)
5 years	36	6.5 (3.6–12.3)	1.32 (0.53–3.13)	0.32 (0.11–0.84)
6 years	30	6.9 (3.8–13.0)	1.43 (0.57–3.39)	0.36 (0.12–0.93)
7 years	37	7.1 (3.9–13.4)	1.50 (0.66–3.57)	0.39 (0.14–1/02)
8 years	24	7.3 (4.0–13.7)	1.60 (0.64–3.80)	0.42 (0.15–1.10)
9 years	38	7.4 (4.1–13.8)	1.71 (0.69–4.07)	0.44 (0.16–1.16)
10 years	48	7.4 (4.1–14.0)	1.85 (0.47–4.40)	0.48 (.17–1.25)
11 years	62	7.4 (4.1–14.0)	2.06 (0.83–4.90)	0.51 (0.18–1.34)
12 years	37	7.1 (3.9–13.4)	2.28 (0.91–5.42)	0.50 (0.18–1.32)
13 years	11	6.8 (3.8–12.9)	2.37 (0.95–5.63)	0.47 (0.17–1.22)
14 years	10	6.8 (3.8–12.9)	2.46 (0.98–5.84)	0.43 (0.15–1.12)
15 years	10	6.8 (3.8–12.9)	2.59 (1.04–6.15)	0.40 (0.14–1.04)
16–18 years	7	6.8 (3.8–12.9)	2.75 (1.10–6.54)	0.36 (0.12–0.94)
>18 years	141	5.6 (3.8–9.4)	3.40 (1.46–7.20)	0.36 (0.12–0.94)

Adapted from Plebani et al. [60]. With permission from Springer Science + Business Media

later in development, and adult levels of this subclass are not reached until 5–10 years of age. IgG2 antibodies are mainly directed against polysaccharide antigens, whereas IgG3 are mostly constituted antibodies directed to viral antigens [58]. Isolated undetectable IgG4 subclass levels are occasionally seen but affected individuals tend to be clinically free of infectious predisposition. Other than some isolated reports of IgG4 deficiency and recurrent sinopulmonary infections, the clinical relevance of isolated low or absent IgG4 remains questionable [58]. IgA when combined with IgG subclass deficiencies, particularly IgG2 subclass, are commonly associated with clinical morbidity whose phenotype is typically one of recurrent bacterial infections [59].

Despite the lack of concrete clinical evidence that IgG subclass deficiency in isolation has any clinical relevance, it remains prudent to measure this parameter and match it against age-related normal values as part of the routine screening for PAD [60] (Table 14.6). Clinical relevance should be given to decreased levels of IgG1–3 only. When encountered in the presence of low IgA and/or a poor or borderline immunologic response to mucopolysaccharide vaccine challenge (see laboratory procedures below), more in-depth immunologic studies are in order.

IgA Deficiency (SIgAd)

Immunoglobulin (Ig) A deficiency is defined as decreased or absent level of serum IgA in the presence of normal serum levels of IgG and IgM in a patient older than 4 years of age, in whom other causes of hypogammaglobulinemia have been excluded [35, 61]. In general, serum IgA level of less than 7 mg/dL (0.07 g/L) is defined as selective IgA deficiency since

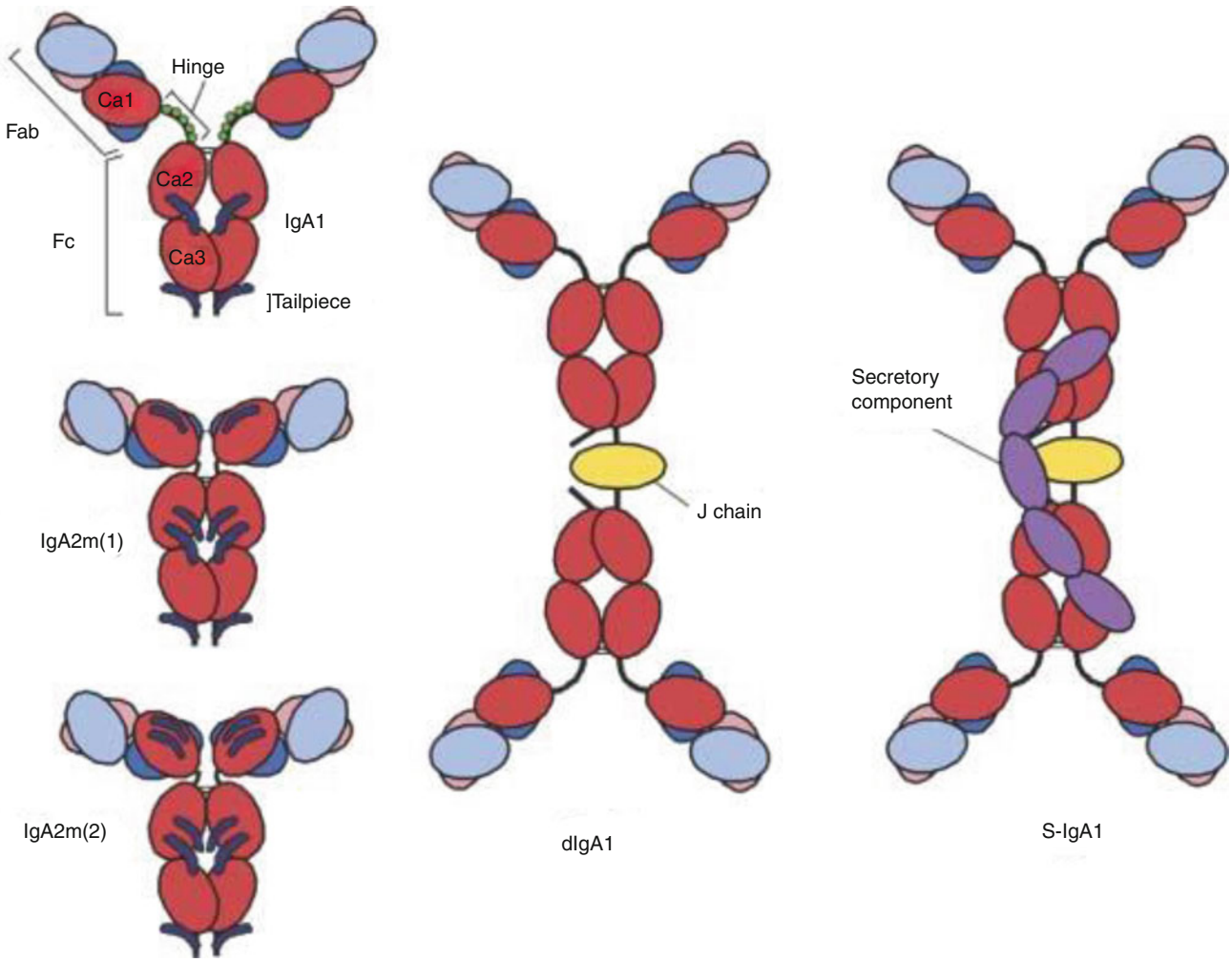


Fig. 14.8 Schematic representation of the monomeric forms of human IgA1, IgA2m(1), and IgA2m(2) and the dimeric (*dIgA1*) and secretory (*S-IgA1*) forms of IgA1. Constant regions of the heavy chain are shown in red and the variable domains of the heavy chain in pink. For the light chains, constant regions are shown in mid-blue and variable regions in pale blue. J chain is shown in *yellow* and secretory component in *purple*. On the monomeric forms of IgA, *O*-linked sugars (on the IgA1 hinge) are shown as *green circles*, while *N*-linked oligosaccharides are shown in *dark blue*. For clarity, the oligosaccharide moieties of dIgA and S-IgA1 are not included (Reprinted from Woof and Kerr [63]. With permission John Wiley & Sons, Inc.)

this concentration is the lowest detectable limit established by most laboratories. When the serum IgA level is higher than 7 mg/dL but two standard deviations below normal for age, the condition may be referred to as partial IgA deficiency. Partial IgA deficiency is quite common and it remains unclear if this finding has any clinical relevance. The threshold of 4 years of age is used to avoid premature diagnosis of IgA deficiency since IgA development may be transient in younger children due to an innocent delayed ontogeny of IgA production after birth.

Selective IgA deficiency (SIgAd) is the most common primary immunodeficiency in humans and may occur in up to 1/220–1/1,000 people in the general population. The majority of people (85–90 %) with SIgAd are unaware that they have this disorder and enjoy good health. In a subset of IgA-deficient patients, however, a phenotype emerges of recurrent sinopulmonary and middle ear infections. Many of these patients have concomitant IgG subclass deficiency which may favor infection in some IgA-deficient patients [62]. These infections are thought to occur as a result of secretory IgA antibody being deficient or absent at the mucosal level resulting in diminished host defense. Since secretory IgA is the principal immunoglobulin class providing mucosal protection, its absence is thought to provide an advantage to organisms responsible for acute and chronic CRS, particularly encapsulated bacteria.

IgA is the most abundant antibody produced in the body. It is the second dominant antibody in the blood circulation following IgG. It can be found in both monomeric and polymeric forms. Circulating IgA is in monomeric form, whereas secretory IgA is dimeric and resides in the mucosal secretions of respiratory, intestinal, and genitourinary systems. In humans, there are two subclasses of IgA: IgA1 and IgA2 [63] (Fig. 14.8). It is thought that the main reason for the structural difference

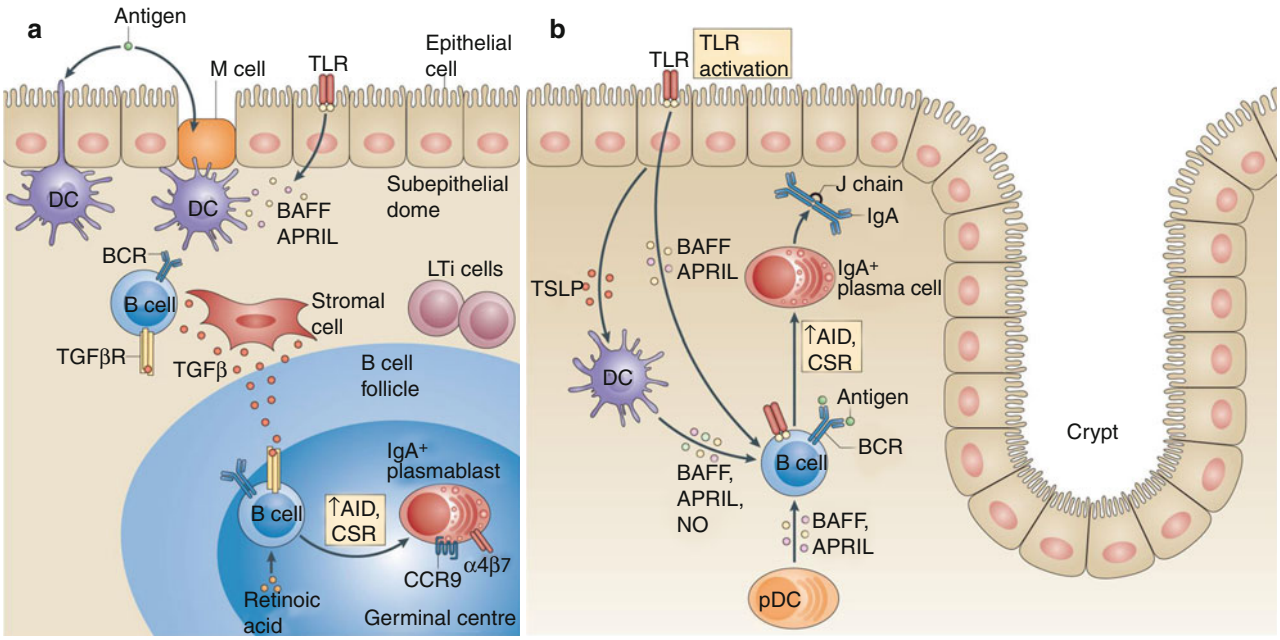


Fig. 14.9 The production of IgA in the gut lumen. Dendritic cells (*DCs*) and Toll-like receptor (*TLR*) signals play a crucial role in activating B cells and cooperate with B cell-activating factor (*BAFF*) and a proliferation-inducing ligand (*APRIL*) to induce activation-induced cytidine deaminase (*AID*) and class switch recombination (*CSR*) to IgA. (**a**) T cell-independent IgA induction in isolated lymphoid follicles. (**b**) T cell-independent IgA induction in the lamina propria (Reprinted from Pabst [65]. With permission from Nature Publishing Group)

between IgA1 and IgA2 is that IgA2 has a shorter hinge region which may render it more resistant to bacterial proteases in the lumen of gastrointestinal or respiratory systems [64]. In Fig. 14.9, the production of IgA in the gut lumen is schematically demonstrated. Dendritic cells (DCs) and Toll-like receptor (TLR) signals play a crucial role in activating B cells and cooperate with B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) to induce activation-induced cytidine deaminase (AID) and class switch recombination (CSR) to produce IgA. A distinct type of stromal cell secretes transforming growth factor-β (TGFβ) which also promotes class switching of plasma cells to IgA production. The schematic also shows lymphoid tissue inducer (LTi) cells which play an important role in orchestrating the structural formation of the lymphoid follicle. This structure provides cytokines that further facilitate IgA induction. IgM-expressing B cells can switch to IgA expression within the lymphoid follicle and further promote IgA1-expressing B cells to switch to IgA2 production for transport to the secretory surfaces such as the nose and sinuses [65].

It remains unclear exactly where the defect in SIgAd lies within the immune system. In a recent study, two different subgroups of class-switched memory B cells were identified in SIgAd patients. The low-switched memory B cell subgroup of patients exhibited more severe clinical features including CRS, pneumonia, autoimmune diseases, and bronchiectasis suggesting that this classification could aid physicians in determining the clinical prognosis for such patients. The early identification of at-risk patients for significant comorbidities would provide the basis for more cautious surveillance of this at-risk subgroup [66]. Other researchers have investigated the major lymphocyte subpopulations and B lymphocyte subsets in patients with SIgAd looking for defects. These studies seem to demonstrate a reduction in terminally differentiated B lymphocyte subsets, similar to what has previously been found in patients with CVID, although less pronounced [67]. The defect in SIgAd appears to involve the stem cells since IgA deficiency can be transferred by bone marrow transplantation [68]. In SIgAd, B cells appear to be able to express IgA. However, these B cells are an immature phenotype with the co-expression of IgM and IgD. Ultimately, they seem unable to fully develop into IgA-secreting plasma cells [69]. Despite these reports, a whole host of abnormalities are still being discussed in relation to SIgAd with no clear coherent immunologic source as yet defined. The defect clearly appears to reside within the regulatory network of IgA production in that the phenotype can be reversed in vitro [69]. Furthermore, there does not appear to be a coherent Mendelian genetic pattern in SIgAd despite suggestions of some clustering within families [70]. As with CVID, IgA deficiency may not a single disease and perhaps represents a heterogenous group of immune disorders with a deficiency of IgA as a common feature.

Although the majority of SIgAd are symptomatic, there remains a subgroup that is not readily identifiable who demonstrates a tendency toward recurrent sinopulmonary infections, gastrointestinal infections and disorders, allergies, autoimmune conditions, and malignancies. The overrepresentation of recurrent sinopulmonary infections and autoimmune diseases

Table 14.7 Overrepresentation of autoimmunity in SIgAd

Idiopathic thrombocytopenic purpura
Hemolytic anemia
Graves disease
SLE
Type I diabetes
Celiac disease
Juvenile rheumatoid arthritis
Autoantibodies such as sulfatide, Jo-1, cardiolipin, phosphatidylserine, and collagen

Table 14.8 Common causes of secondary immunodeficiency

Malnutrition
HIV
Malignancy
Immunosuppressive drugs
Immunomodulatory agents
Rituximab (affecting B cells)
Infliximab, etanercept, adalimumab, anakinra (affecting cellular immunity)
Drug-induced hypogammaglobulinemia
Certain antiepileptics (e.g., diphenylhydantoin, carbamazepine, valproate)
Protein loss (especially if presenting with low IgG but normal IgA and IgM)
Nephrotic syndrome, protein-losing enteropathy, severe burns
Metabolic disease
Diabetes, severe liver disease, uremia

Reprinted from Azar and Ballas [76]. With permission with Elsevier

among this subgroup stands most prominently. One hint readily available to the clinician is the measurement of IgG subclasses in any patient with SIgAd. SIgAd patients with IgG subclass 2 and 4 deficiencies commonly suffer recurrent sinopulmonary infections and deserve both careful follow-up and evaluation of the quality of their immune response to antigens (see below) [71, 72]. Furthermore, a variety of autoimmune diseases (Table 14.7) should be kept in mind and added to the clinical/laboratory surveillance whenever caring for a patient with SIgAd [73–75].

Secondary Immunodeficiency

Conditions leading to secondary immune dysfunction are far more common in adults than PIDs. Secondary sources of immunodeficiency should always be ruled out first in a patient with CRS who presents with a clinical condition that suggests the possibility of concomitant PID. A detailed review of this topic is beyond the goals of this text. The common conditions that are associated with secondary immunodeficiency are listed in Table 14.8 [76]. Generally, a higher level of suspicion that a condition listed in Table 14.9 may be inducing secondary immune deficiency becomes clear from a thorough history and physical exam. The pattern of recurrent rhinosinusitis also can be a distinguishing feature differentiating immune deficiency from other more common etiologies. For example, recurring RS at the same anatomic site is usually structural in nature and represents a fixed ostial obstruction that results from recurrent/chronic infection, ipsilateral severe septal deviation with compression of the middle meatus, or perhaps an odontogenic source in the case of recurrent localized maxillary disease. In contrast, PID or secondary immunodeficiency will typically be accompanied by a pattern of diffuse sinus infections that do not have a specific anatomic predilection. Furthermore, both primary and secondary immune deficiencies are commonly accompanied by a history of infection beyond the confines of the paranasal sinuses such as otitis media, mastoiditis, meningitis, and/or pneumonia/bronchiectasis.

The Evaluation of CRS Patients with Suspected Immune Deficiency

The Primary Immunodeficiency Resource Center (Jeffrey Modell Foundation) lists ten warning signs to help identify patients with PID (Table 14.10) [78]. The presence of two or more warning signs or a history of prolonged antibiotic treatment should prompt assessment for PID. Over the years, others have modified this approach for greater accuracy but there is no

Table 14.9 Ten warning signs of PID

1. ≥8 new ear infections within 1 year
2. ≥2 serious sinus infections within 1 year
3. ≥2 months on antibiotics with little effect
4. ≥2 episodes of pneumonia within 1 year
5. Failure of an infant to gain weight or grow normally
6. Recurrent deep skin or organ abscesses
7. Persistent thrush in mouth or on skin after age 1 year
8. Need IV antibiotics to clear infections
9. ≥2 deep-seated infections
10. Family history of PID

Adapted from Modell et al. [77]. With permission with Springer Science + Business Media

Table 14.10 Clues suggesting the presence of an immunodeficiency

Aspects of infections
Unusual frequency
Unusual severity
Unusual duration
Unusual complications
Unusual organisms
Noninfectious clues
Premature loss of dentition
Poor wound healing
Unexplained bronchiectasis
Chronic diarrhea or malabsorption
Autoimmunity, especially if more than one (e.g., hypothyroidism and alopecia or vitiligo)
Hematologic disorders (hemolytic anemia, neutropenia, thrombocytopenia)
"Failure to thrive"

Reprinted from Azar and Ballas [76]. With permission with Elsevier

Table 14.11 Advance laboratory tests for PAD

Lymphocyte subset quantitation (flow cytometry) for T, B, and NK cells
Immunofixation of concentrated urine (adults)
Pre- and postvaccination (4–6 weeks) IgG to tetanus toxoid, 12+ isotypes of *S. pneumoniae* and possibly *H. influenzae* type B
HIV screening

universally accepted checklist of conditions that is highly sensitive and specific [79]. Comorbid conditions, particularly autoimmune endocrine disorders, rheumatic conditions, autoimmune hemolytic anemia, thrombocytopenia, and gastrointestinal disorders, are particularly common in primary antibody deficiencies. The coexistence of CRS and Crohn's disease, ulcerative colitis, or celiac disease should alert the medical care provider of possible coexisting IgA deficiency or CVID. Such coexisting diagnosis should be vigorously sought. A more comprehensive list of clinical clues that might trigger an immune evaluation is listed in Table 14.11 [76]. In fact, any patient presenting with difficult to control or recurrent CRS, particularly if they have failed both medical and surgical intervention, should be screened for PAD. It would be rare for other forms of PID to present to the primary care/ENT/allergist when the chief complaint is CRS.

After a thorough history and physical examination has been performed, laboratory studies are required to rule in or out PAD (Table 14.11). The core laboratory evaluation for PAD begins with a complete blood count with differential, quantitative serum immunoglobulin levels, serum IgG subclasses, and, in the adult, serum protein electrophoresis. The next level of evaluation in suspected cases of PAD would be specific antibody response to protein and polysaccharide antigens and the measurement of lymphocyte subsets through flow cytometry (Table 14.12). In either case, adding more general laboratory studies such as a comprehensive chemistry panel, UA, and HIV screen is always a good idea depending on when these studies were last done, if at all. Depending on the degree of clinical suspicion and what is found on initial screening, additional tests may be ordered when considering the comorbidities specific for PAD disorders. For example, if IgA deficiency is found, pertinent laboratory testing for the associated conditions, such as autoimmune disease (CRP, sedimentation rate, ANA, RF, TSH, antithyroid antibodies including thyrotrophic-receptor autoantibodies if available) and especially celiac disease (IgG

Table 14.12 Screening laboratory tests for PAD

Complete blood count (CBC) with differential
Comprehensive chemistry panel
Complete urinalysis
Immunoglobulin quantitation (IgG, IgA, IgM, IgE)
IgG subclass quantitation
Serum protein electrophoresis (adults)

and IgA anti-transglutaminase and antigliadin peptides antibodies), should be performed. In SIgAd, most celiac disease screening should include only IgG isotypic antibodies against gliadin and tissue transglutaminase since IgA isotype antibodies may not be detectable. However, more sensitive immunoassays are being developed that are capable of detecting very small amounts of IgA antibodies [80].

Determination of serum levels of IgG subclasses has limited value but is still commonly used as a screening assay. IgG subclass measurements are especially indicated if the IgG levels are low, IgA deficiency is present, or there is a documented history of recurrent pneumonia or bronchiectasis. Therefore, many health-care providers now restrict this assay to a secondary level depending on the presence or absence of the factors just cited.

More important information is provided by the assessment of IgG antibody titers induced by available vaccine administration. In particular, antibodies to tetanus toxoid and diphtheria toxoid represent robust assays that measure the antibody response to protein (T-dependent) antigens. Vaccines containing *S. pneumoniae* represent robust assays measuring antibody response to capsular mucopolysaccharide structures (T cell independent). The measurement of anti-tetanus and antipneumococcal antibodies followed by the administration of tetanus toxoid and pneumococcal vaccine and re-measuring the IgG antibody levels 4–6 weeks later is a key laboratory parameter in identifying individuals with PAD.

In the United States, a heptavalent pneumococcal conjugate vaccine (PCV 7) (e.g., Prevnar[Rx]) is recommended for all children aged 2–23 months and for at-risk children aged 24–59 months. The normal 4-dose series is given at 2, 4, 6, and 12–14 months of age [52]. In 2010, a pneumococcal conjugate vaccine which protects against an additional six serotypes was introduced (PCV 13/brand name: Prevnar 13) and can be given instead of the original Prevnar[Rx] [81]. Conjugated vaccines were developed since children under 2 years of age tend to have a poor antibody response to non-conjugated vaccines, and pneumococcal disease prevention was particularly important in this age group. It is important to remember that use of conjugated vaccines to pneumococcus, *H. influenzae*, or meningococcus elicits T cell-dependent responses, even if the antibodies are ultimately directed against polysaccharide antigens. Therefore, since we are most interested in B cell function, conjugated vaccines are not typically used in evaluating PAD. Rather, pneumococcal polysaccharide vaccine (e.g., Pneumovax) is used to test the antibody response to polysaccharide (T-independent, B cell generated) antigens. Pneumococcal polysaccharide vaccine (Pneumovax Rx) gives at least 85 % protection in those under 55 years of age for 5 years or longer [82]. The standard 23-valent vaccines are less effective for children 1–2 years old and ineffective under the age of one year. A protective antibody response is defined as a serotypic antibody concentration of 1.3 μg/mL or higher or 200–300 ng of antibody nitrogen per milliliter (conversion factor is 160 ng of antibody N/mL to 1 μg/mL) [52].

The interpretation of anti-tetanus antibody concentrations is based on vaccination-induced antibody increases over the pre-immunization level and enumerating those that exceed what is considered the protective level of response. The minimum protective threshold of 0.15 IU/mL is considered to be the minimum value pre or post immunization that determine vaccine response normalcy. If the minimum protective threshold is present with the first blood draw, immunization and post-immunization assessment are not necessary. Approximately 80 % of the total anti-tetanus toxoid activity is represented by IgG1 [82]. Since it represents a T cell-dependent event, nearly all cases of PAD demonstrate an intact IgG antibody response to tetanus toxoid vaccine.

In contrast, poor vaccination response to *S. pneumoniae* is a key feature of PAD in most circumstances. Impaired polysaccharide responsiveness is observed commonly with CVID and young patients with IgG2 deficiency [83]. Impaired antibody production may not be seen in adults with IgG3 subclass deficiency [84]. The interpretation of antipneumococcal antibody concentration results is based on antibody increases over pre-immunization concentrations (immune response) and on final concentrations following immunization. A good response post vaccination to individual *S. pneumoniae* serotypes is an IgG concentration ≥1.3 μg/mL and demonstrating a four-fold serotype-specific IgG increase compared to pre-immunization antibody levels. However, high pre-immunization antibody concentrations (>1.3 μg/mL) to a specific serotype are less likely to rise significantly (four-fold) after immunization. Most patients with a pre-vaccine titer ≥1.3 mg/mL can mount at least a two-fold increase in titer post immunization. Only a minority of patients with high initial titers will be capable of mounting a four-fold increase in antibody titers after vaccination. The probability of a four-fold antibody response approaches zero if

the pre-immunization titer is between 4.4 and 10.3 μg/mL, depending on the pneumococcal serotype [82]. In patients previously immunized with heptavalent pneumococcal conjugate vaccine, it is important to measure antibody responses against at least the six serotypes present only in the polysaccharide vaccine.

Age also plays a significant role in the interpretation of responses to polysaccharide immunization. Well-validated age-adjusted criteria that define normal responsiveness to pure polysaccharides are yet to be developed. In general, responses to pure polysaccharide antigens are unreliable and should be avoided in patients younger than 2 years. Licciardi et al. studied the immunologic response to pneumococcal polysaccharide vaccine in 12-month-old infants and found that 30 % were capable of generating a high avidity serotype-specific antibody response but not to the majority of serotypes responsible for the majority of disease in their developing country population [85]. Children between the ages of 2 and 5 years should respond to approximately half (50 %) or more of the pneumococcal type-specific polysaccharides. Although controversy exists regarding the actual number of pneumococcal serotypes needed to determine a normal response, most groups recommend that for patients older than 5 years (including adults), at least 70 % of pneumococcal serotypes should appropriately respond to vaccine administration [52].

In summary, we recommend measuring IgG antibody level against serotypes 1, 3, 4, 6B, 7F, 9V, 11, 12F, 14, 15, 18C, 19F, 23F, and 33 by a standardized enzyme-linked immunosorbent assay (ELISA). If less than 70 % basal antibody titers appear nonprotective, a boosting immunization should be performed with Pneumovax, followed by repeat measurement of specific antibodies 4 weeks later. For children 24 months through 5 years of age, a normal response to PPV is defined as "protective" antibodies (>1.3 μg/mL) to 50 % or more of the serotypes tested, with at least a two-fold increase in the titers. For subjects aged 6–65 years, a normal response has been defined as protective antibodies to 70 % of the serotypes tested, with at least a two-fold increase and preferably a four-fold increase compared to pre-vaccination antibody levels [86–90]. Remember that very high levels pre-vaccination may not boost even twofold but still represent a positive B cell functional activity in that they are well above the protective antibody level.

Isohemagglutinins are antibodies directed against the polysaccharide moieties of AB0 blood group antigens and represent "natural" anti-polysaccharide antibodies. They represent both IgG and IgM antibodies. However, isohemagglutinin titers are difficult to obtain in many laboratories. Furthermore, they do not add anything significant to the PAD evaluation other than a reflection of an IgM response. On this basis, we no longer order this study.

Diagnosis of HIV infection is established by ELISA of which serum demonstrates the presence of antibody to viral antigens of the HIV. The positive test is then confirmed by Western blot testing which demonstrates viral proteins to be present. The serologic tests become positive 4–24 weeks following HIV infection, and PCR testing for proviral DNA or viral RNA has been used for earlier detection. High-risk groups of individuals with CRS should always be screening for HIV infection.

Ultimately, if the initial screening tests are abnormal and suggest PID, it is prudent for the primary care provider and ENT specialist to refer the patient to a physician skilled in immunology to continue the evaluation. Many allergists have the training to continue the evaluation to and beyond the advanced laboratory stage. Even then, if a PID diagnosis is made, referral to a tertiary center that specializes in immune deficiency is always prudent. The purpose of early referral would be to confirm a presumed PID diagnosis and establish a connection where more advanced forms of diagnosis and therapy can be readily available to patients in this rapidly changing field of medicine.

Treatment

The standard of care in CVID and specific IgG antibody deficiencies that do not respond to intermittent or prophylactic antibiotic therapy is replacement immunoglobulin given monthly for life. Gamma globulin is not used for replacement of IgA. Gamma globulin can be given either intravenously every 3–4 weeks or subcutaneously once weekly. Both methods of administration are equally effective. The doses range from 300–600 mg/kg a month or more depending on clinical response and IgG trough levels or a calculated weekly subcutaneous delivery based upon the optimal monthly dosing. Less frequent dosing or lower doses is not substantiated by clinical data. We generally like to keep the IgG trough level above 500 mg/dL and balance the level against the desired clinical response. Which route of administration to choose is best dictated by patient choice and convenience. Generally, some patients prefer the intravenous route (IVIG) since it can be done in their home or a medical center over several hours once monthly. Others like the convenience of subcutaneous weekly self-administration that does not require IV placement and avoids the many hours an IVIG infusion requires. It is important to remember that IVIG is not a generic drug and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to insure patient safety. A change of IVIG product should occur only with the active participation of the prescribing physician.

Although immunoglobulin therapy greatly reduces the number of bacterial infections and enhances survival, it does not appear to address the characteristic inflammatory complications sometimes seen such as progressive lung disease, gastrointestinal disorders, granulomatous disease, autoimmunity, lymphoid hyperplasia, and cancers such as lymphoma. With the advent of gamma globulin therapy, these complications now appear to be the major cause of morbidity and death in CVID [36, 37, 91].

IgA-deficient patients demand special counseling. SIgAd patients who are diagnosed coincidentally and are asymptomatic do not need treatment. However, awareness and education are of prime importance, particularly to prevent a potential anaphylactic reaction secondary to blood transfusion. If an IgA-deficient patient is given blood with IgA, anti-IgA antibodies will be produced. Any subsequent transfusion will result in a potential serious transfusion reaction. In this regard, we recommend that patients with selective IgA deficiency wear a medical alert bracelet. In case of a blood transfusion is required, an SIgAd patient should be screened for anti-IgA antibodies and any blood product prepared from an IgA-deficient individual or, as an alternative, use saline-washed red blood cells. All blood products should be given with caution in patients with SIgAd, and the supervising medical provider should be prepared to treat a potential anaphylactic reaction. In IgA deficiency, other than the issues surrounding blood product administration, the mainstay of treatment is related to any associated diseases. If the patient experiences recurrent infections, daily or intermittent prophylactic antibiotics may be beneficial. In case of associated specific antibody deficiency such as IgG2 and recurrent sinopulmonary infections, immunoglobulin administration choosing a product with minimal IgA (see individual product information) may be given.

Conclusion

Nearly all patients with CRS who are diagnosed with a primary immunodeficiency have a primary antibody deficiency. Although over 21 genes (Fig. 14.10) have been identified to be affected in PAD, there remain many unanswered questions in the vast majority of patients, particularly those with CVID. Phenotyping patients with PAD based on a molecular diagnosis whenever possible is vital to both the patient and the family in terms of defining inheritance patterns and forming the basis for treatment and prognosis. The most important clue to defining a PID is to consider this in the differential diagnosis of any patient with recurrent or difficult to treat respiratory infection, particularly if the history includes an infectious predisposition in other anatomic sites, autoimmune disease, inflammatory bowel disease, bronchiectasis, or infections with unusual

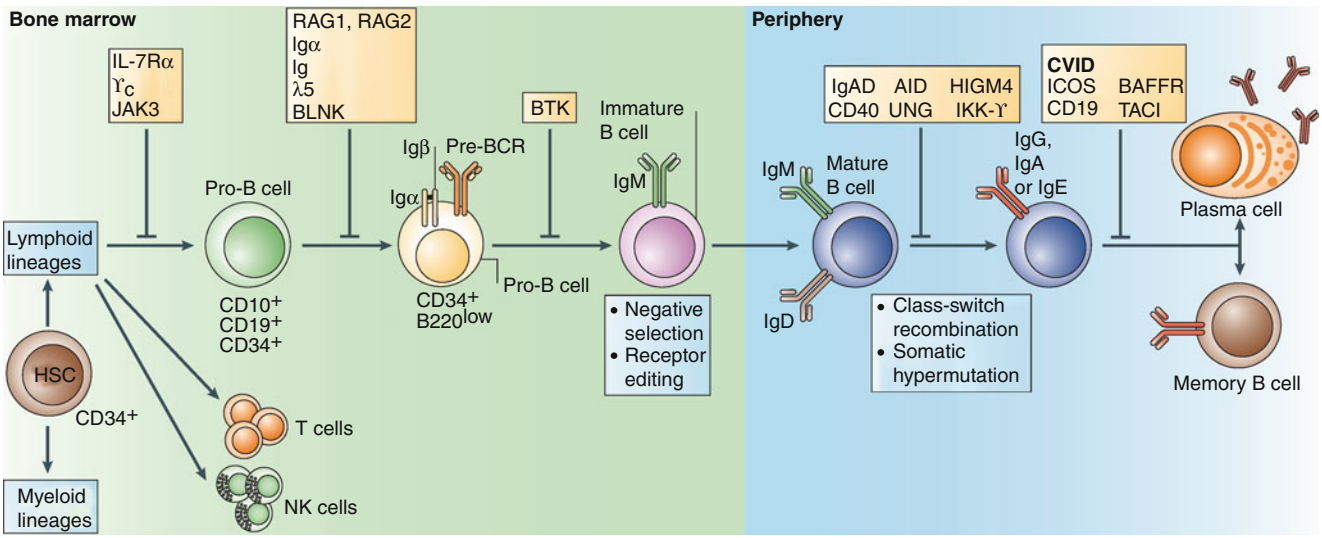


Fig. 14.10 Identified gene mutations in B cell differentiation that give rise to PAD developmental blocks throughout B cell maturation, and differentiation occurs as a result of defects in genes encoding the molecules listed in the *yellow boxes*. Blocks in the function of mature B cells can also occur. Primary immunodeficiency syndromes that cause these blocks are also listed. *AID* activation-induced cytidine deaminase, *BAFFR* B cell-activating factor receptor, *BCR* B cell receptor, *BLNK* B cell linker, *Btk* Bruton's tyrosine kinase, *γc* common cytokine-receptor γ-chain, *CVID* common variable immunodeficiency, *HIGM4* hyper-IgM syndrome 4, *ICOS* inducible T cell co-stimulator, *IgAD* selective IgA deficiency, *Igμ* immunoglobulin heavy chain, *IKK-γ* inhibitor-of-nuclear-factor-κB kinase-γ, *IL-7α* interleukin-7 receptor-α chain, *JAK3* Janus kinase 3, *NK cell* natural killer cell, *RAG* recombination-activating gene, *TACI* transmembrane activator and calcium-modulating cyclophilin ligand interactor, *UNG* uracil-DNA glycosylase (Reprinted from Cunningham-Rundles and Ponda [92]. With permission from Nature Publishing Group)

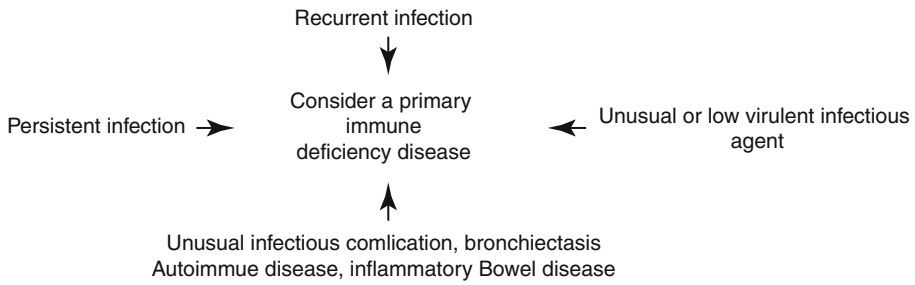


Fig. 14.11 Clinical clues that suggest PID

organisms (Fig. 14.11). Early laboratory identification of reduced immunoglobulin levels is a critical component in the clinical evaluation. Even if antibody levels are normal, a high level of suspicion based on the history should still prompt further investigation such as assessment of vaccine responsiveness.

Ultimately, the routine consideration of PID in any patient with CRS will lead to a more timely diagnosis, early intervention, and improved prognosis. Early referral to a physician or tertiary medical center skilled in managing PID is the best management philosophy.

References

1. Buckley R, editor. Diagnostic and clinical care guidelines for primary immunodeficiency diseases. Towson: Immune Deficiency Foundation; 2009.
2. Carr TF, Koterba AP, Chandra R, et al. Characterization of specific antibody deficiency in adults with medically refractory chronic rhinosinusitis. Am J Rhinol Allergy. 2011;25:241–4.
3. Karlsson J, Andreasson B, Kondori N, Erman E, Riesbeck K, Hogevik H, Wenneras C. Comparative study of immune status to infectious agents in elderly patients with multiple myeloma, Waldenstrom's macroglobulinemia and monoclonal gammopathy of undetermined significance. Clin Vaccine Immunol. 2011;18:969–77.
4. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27:497–502.
5. Joshi AY, Iyer VK, Hagan JB, et al. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clin Proc. 2009;84:16–22.
6. Samarghitean C, Vihinen M. Bioinformatics services related to diagnosis of primary immunodeficiencies. Curr Opin Allergy Clin Immunol. 2009;9:531–6.
7. Montecino-Rodriguez E, Dorshkind K. B-1 B cell development in the fetus and adult. Immunity. 2012;36(1):13–21.
8. Baumgarth N. The double life of a B-1 cell: self-reactivity selects for protective effector functions. Nat Rev Immunol. 2011;11:34–46.
9. Hardy RR, Hayakawa K. Development of B cells producing natural autoantibodies to thymocytes and senescent erythrocytes. Springer Semin Immunopathol. 2005;26:363–75.
10. Allman D, Pillai S. Peripheral B cell subsets. Curr Opin Immunol. 2008;20:149–57.
11. Monroe JG, Dorshkind K. Fate decisions regulating bone marrow and peripheral. B lymphocyte development. Adv Immunol. 2007;95:1–50.
12. Ballow M. Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol. 2002;109(4):581–91.
13. Conley ME, Dobbs AK, Farmer DM, Kilie S, Paris K, Grigoriadou S, Doustan-Smith E, Howard V, Campana D. Primary B cell immunodeficiencies: comparisons and contrasts. Annu Rev Immunol. 2009;27:199–227.
14. Sriram G, Martinex JA, McCabe ER, Liao JC, Dipple KM. Single gene disorders: what role could moonlighting enzymes play? Am J Hum Genet. 2005;76:911–24.
15. Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, Viallard JF, Gardembas M, Galicier L, Schleinitz N, Suarez F, Soulas-Sprauel P, Hachulla E, Jaccard A, Gardeur A, Theodorou I, Rabian C, Debre P. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46:1547–54.
16. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010;125:S182–94.
17. Wood P. Primary antibody deficiency syndromes. Ann Clin Biochem. 2009;46(Pt 2):99–108.
18. Kainulainen L, Nikoskelainen J, Ruuskanen O. Diagnostic findings in 95 Finnish patients with common variable immunodeficiency. J Clin Immunol. 2001;21:145–9.
19. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34–48.
20. Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. Q J Med. 1993;86:31–42.
21. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol. 2005;58:546–7.
22. Eley BS, Hughes J, Cooper M, Pienaar S, Beatty DW. Primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital. S Afr Med J. 1997;87:1684–8.
23. Hermans PE, Diaz-Buxo JA, Stobo JD. Idiopathic late-onset immunoglobulin deficiency. Clinical observations in 50 patients. Am J Med. 1976;61:221–37.

24. Stiehm ER, Ochs HD, Winkelstein JA. Immunodeficiency disorders: general considerations. In: Stiehm ER, Ochs HD, Winkelstein JA, editors. Immunologic disorders in infants and children. 5th ed. Philadelphia: WB Saunders; 2004. p. 289–355.
25. Yel L, Minegishi Y, Coustan-Smith E, Buckley RH, Tru¨bel H, Pachman LM, Kitchingman GR, Campana D, Rohrer J, Conley ME. Mutations in the mu heavy-chain gene in patients with agammaglobulinemia. N Engl J Med. 1966;335:1486–93.
26. van Zelm MC, Geertsema C, Nieuwenhuis N, de Ridder D, Conley ME, Schiff C, Tezcan I, Bernatowska E, Hartwig NG, Sanders EA, Litzman J, Kondratenko I, van Dongen JJ, van der Burg M. Gross deletions involving IGHM, BTK, or Artemis: a model for genomic lesions mediated by transposable elements. Am J Hum Genet. 2008;82:320–32.
27. Minegishi Y, Coustan-Smith E, Wang Y-H, Cooper MD, Campana D, Conley ME. Mutations in the human k5/14.1 gene result in B cell deficiency and agammaglobulinemia. J Exp Med. 1998;187:71–7.
28. Minegishi Y, Rohrer J, Coustan-Smith E, Lederman HM, Pappu R, Campana D, Chan AC, Conley ME. An essential role for BLNK in human B cell development. Science. 1999;286:1954–7.
29. Minegishi Y, Coustan-Smith E, Rapalus L, Ersoy F, Campana D, Conley ME. Mutations in Igalpha (CD79a) result in a complete block in B-cell development. J Clin Invest. 1999;104:1115–21.
30. Dobbs AK, Yang T, Farmer D, Kager L, Parolini O, Conley ME. Cutting edge: a hypomorphic mutation in Igbeta (CD79b) in a patient with immunodeficiency and a leaky defect in B cell development. J Immunol. 2007;179:2055–9.
31. Bruton OC. Agammaglobulinemia. Pediatrics. 1953;9:722–8.
32. Warnatz K, Bossaller L, Salzer U, Skrabl-Baumgartner A, Schwinger W, van der Burg M, van Dongen JJ, Orlowska-Volk M, Knoth R, Durandy A, Draeger R, Schlesier M, Peter HH, Grimbacher B. Human ICOS deficiency abrogates the germinal center reaction and provides a monogenic model for common variable immunodeficiency. Blood. 2006;107:3045–52.
33. Durandy A, Taubenheim N, Peron S, Fischer A. Pathophysiology of B-cell intrinsic immunoglobulin class switch recombination deficiencies. Adv Immunol. 2007;94:275–306.
34. Fillatreau S, Gray D, Anderton SM. Not always the bad guys: B cells as regulators of autoimmune pathology. Nat Rev Immunol. 2008;5:391–7.
35. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol. 1999;93:190–7.
36. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, Fieschi C, Thon V, Abedi MR, Hammarstrom L. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112:277–86.
37. Resnick ES, Moshier EL, Godbold JH, et al. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119:1650–7.
38. Resnick ES, Cunningham-Rundles D. The many faces of the clinical picture of common variable immunodeficiency. Curr Opin Allergy Clin Immunol. 2012;12:595–601.
39. Van der Burg M, van Zelm MC, Driessen GJA, van Dongen JJM. New frontiers of primary antibody deficiencies. Cell Mol Life Sci. 2012;69:59–93.
40. Salzer U, et al. Relevance of biallelic versus monoallelic *TNFRSF13B* mutations in distinguishing disease-causing from risk-increasing *TNFRSF13B* variants in antibody deficiency syndromes. Blood. 2008;113:1967–76.
41. Cunningham-Rundles C. The many faces of common variable immunodeficiency. Hematology. 2012;2012:301–5.
42. Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol. 2009;9:491–502.
43. King C. New insights into the differentiation and function of T follicular helper cells. Nat Rev Immunol. 2009;9:757–96.
44. Garibyan L, et al. Dominant-negative effect of the heterozygous C104R TACI mutation in common variable immunodeficiency (CVID). J Clin Invest. 2007;117:1550–7.
45. Salzer U, et al. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet. 2005;37:820–8.
46. Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet. 2005;37:829–34.
47. Rizzi M, et al. BAFF receptor expression in CVID patients. Clin Immunol. 2007;123:S15.
48. van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL. An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med. 2006;354:1901–12.
49. Kanegane H, Agematsu K, Futatani T, Sira MM, Suga K, Sekiguchi T, van Zelm MC, Miyawaki T. Novel mutations in a Japanese patient with CD19 deficiency. Genes Immun. 2007;8:663–70.
50. Smet J, Van Zelm MC, Van der Burg M, Ferster A, Le PQ, Schandene L, Van Dongen JJM, Mascart F. Antibody due to a missense mutation in CD19 demonstrates the importance of the conserved tryptophan 41 in immunoglobulin superfamily domain formation. Hum Mol Genet. 2011;20:1854–63.
51. van Zelm MC, Smet J, Adams B, Mascart F, Schandene L, Janssen F, Ferster A, Kuo CC, Levy S, van Dongen JJ, van der Burg M. CD81 gene defect in humans disrupts CD19 complex formation and leads to antibody deficiency. J Clin Invest. 2010;120:1265–74.
52. Bonilla FA, Bernstein IL, Khan DA, et al.; American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005;94(Suppl 1):S1–63.
53. Schur P, Rosen F, Norman M. Immunoglobulin subclasses in normal children. Pediatr Res. 1979;13:181–3.
54. Aksu G, Kutukculer N, Ferah G, Koturoglu G, Kurugol Z. Serum immunoglobulin (IgG, A, M) and IgG subclass concentrations in healthy children: a study using nephelometric technique. Turk J Pediatr. 2006;48:19–24.
55. Alexander R. IgG subclass deficiency and the day-care generation. Pediatr Infect Dis J. 1999;18:462–6.
56. Pan Q, Hammarstrom L. Molecular basis of IgG subclass deficiency. Immunol Rev. 2000;178:99–110.
57. Morell A, Skvaril F, Hitzig WH, Barandun S. IgG subclasses: development of the serum concentrations in normal infants and children. J Pediatr. 1972;80:960–4.
58. Herrod HG. Clinical significance of IgG subclasses. Curr Opin Pediatr. 1993;5:696–9.

59. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics. 1991;87:311–6.
60. Plebani A, Uazio AG, Avanzini MA, Massimi P, Zonta L, Monafo V, Burgio GR. Serum IgG subclass concentrations in healthy subjects at different age: age normal percentile charts. Eur J Pediatr. 1989;149:164–7.
61. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol. 2007;120:776–94.
62. Latiff AH, Kerr MA. The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem. 2007;44:131–9.
63. Woof JM, Kerr MA. The function of immunoglobulin A in immunity. J Pathol. 2006;208:270–82.
64. Corthésy B. Roundtrip ticket for secretory IgA: role in mucosal homeostasis? J Immunol. 2007;178:27–32.
65. Pabst O. New concepts in the generation and functions of IgA. Nat Rev Immunol. 2012;12:821–32.
66. Aghamohammadi A, Abolhassani H, Biglari M, et al. Analysis of switched memory B cells in patients with IgA deficiency. Int Arch Allergy Immunol. 2011;156:462–8.
67. Nechvatalova J, Pikulova Z, Stikarovska D, et al. B-lymphocyte subpopulations in patients with selective IgA deficiency. J Clin Immunol. 2012;32:441–8.
68. Hammarström L, Lönnqvist B, Ringdén O, Smith CI, Wiebe T. Transfer of IgA deficiency to a bone-marrow-grafted patient with aplastic anaemia. Lancet. 1985;1:778–81.
69. Lawton AR, Royal SA, Self KS, Cooper MD. IgA determinants on B-lymphocytes in patients with deficiency of circulating IgA. J Lab Clin Med. 1972;80:26–33.
70. Yel L. Selective IgA deficiency. J Clin Immunol. 2010;30:10–6.
71. Chipps BE, Talamo RC, Winkelstein JA. IgA deficiency, recurrent pneumonias, and bronchiectasis. Chest. 1978;73:519–26.
72. Edwards E, Razvi S, Cunningham-Rundles C. IgA deficiency: clinical correlates and responses to pneumococcal vaccine. Clin Immunol. 2004;111:93–7.
73. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol. 2009;29:130–6.
74. Barka N, Shen GQ, Shoenfeld Y, Alosachie IJ, Gershwin ME, Reyes H, et al. Multireactive pattern of serum autoantibodies in asymptomatic individuals with immunoglobulin A deficiency. Clin Diagn Lab Immunol. 1995;2:469–72.
75. Jorgensen GH, Thorsteinsdottir I, Gudmundsson S, Hammarstrom L, Ludviksson BR. Familial aggregation of IgAD and autoimmunity. Clin Immunol. 2009;131:233–9.
76. Azar AE, Ballas ZK. Evaluation of the adult with suspected immunodeficiency. Am J Med. 2007;120:764–8.
77. Modell F, Puente D, Modell V. From genotype to phenotype. Further studies measuring the impact of a Physician Education and Public Awareness Campaign on early diagnosis and management of primary immunodeficiencies. Immunol Res. 2009;44(1-3):132–49.
78. Jeffrey Modell Foundation. 10 Warning signs of primary immunodeficiency for adults. 2009. http://www.info4pi.org/aboutPI/pdf/Adult10WarningSigns-FINAL.pdf. Accessed 25 Mar 2012.
79. O'Sullivan MD, Cant AJ. The 10 warning signs: a time for a change? Curr Opin Allergy Clin Immunol. 2012;12:588–94.
80. Conrad K, Roggenbuck D, Ittenson A, et al. A new dot immunoassay for simultaneous detection of celiac specific antibodies and IgA deficiency. Clin Chem Lab Med. 2012;50:337–43.
81. CDC. Licensure of a 13-valent pneumococcal conjugate vaccine (PCVB13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep. 2010;59(9):258–61.
82. Orange JS, Ballow M, Stiehm R, Ballas Z, Chinen J, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2012;130:S1–24.
83. Umetsu DT, Ambrosino DM, Quinti I, et al. Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG subclass deficiency. N Engl J Med. 1985;313:1247–51.
84. Barlan IB, Geha RS, Schneider LC. Therapy for patients with recurrent infections and low serum IgG3 levels. J Allergy Clin Immunol. 1993;92:353–5.
85. Licciardi PV, Balloch A, Russell RM, Burton RL, Lin J, Nahm MH, Mulholland EK, Tang MLK. Pneumococcal polysaccharide vaccine at 12 months of age produces functional immune responses. J Allergy Clin Immunol. 2012;129:794–800.
86. Boyle R, Le C, Balloch A. The clinical syndrome of specific antibody deficiency in children. Clin Exp Immunol. 2006;146:486–92.
87. Kamchaisatian W, Wanwatsuntikul W, Sleasman JW, Tangsinmankong N. Validation of current joint American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma and Immunology guidelines for antibody response to the 23-valent pneumococcal vaccine using a population of HIV infected children. J Allergy Clin Immunol. 2006;118:1336–41.
88. Rose M, Schubert R, Strand N. Priming of immunological memory by pneumococcal conjugate vaccine in children unresponsive to 23-valent polysaccharide pneumococcal vaccine. Clin Diagn Lab Immunol. 2005;12:1216–22.
89. Sorensen R, Leiva L, Giansgrosso P. Response to a heptavalent conjugate of Streptococcus pneumoniae vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. Pediatr Infect Dis J. 1998;17:685–91.
90. Sorensen R, Leiva L, Javier III F. Influence of age on the response to Streptococcus pneumoniae vaccine in patients with recurrent infections and normal immunoglobulin concentrations. J Allergy Clin Immunol. 1998;102:215–21.
91. Wood P, Stanworth S, Burton J, et al.; UK Primary Immunodeficiency Network. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. Clin Exp Immunol. 2007;149:410–23.
92. Cunningham-Rundles C, Ponda PP. Molecular defects in T- and B-cell primary immunodeficiency diseases. Nat Rev Immunol. 2005;5:880–92.

Chapter 15
Autoimmunity and Sinus Disease

Stanley M. Naguwa, Christopher C. Chang, and Gary A. Incaudo

Introduction

Sinusitis is a common feature of a variety of autoimmune diseases. The most well-known association is with granulomatosis with polyangiitis, which was formerly known as Wegener's granulomatosis. Other autoimmune diseases in which sinusitis has been reported include allergic granulomatosis (AG or Churg–Strauss syndrome) and microscopic polyangiitis (MPA). These diseases have in common the presence of antineutrophil cytoplasmic antibodies (ANCA). Sinusitis has also been rarely associated with non-antineutrophil cytoplasmic antibody autoimmune diseases, such as systemic lupus erythematosus (SLE), Sjögren's syndrome, and others. As part of a thorough evaluation of any patient with recurrent or chronic rhinosinusitis, it is important to inquire if the patient also suffers from concomitant autoimmune disease. Otherwise, a sinusitis patient who has an associated autoimmune disease may experience less than optimal or negative outcomes from conventional sinusitis therapy, particularly surgery.

Basic Immunology of Autoimmunity

The concept of autoimmunity arose from the discovery of autoantibodies in conditions such as rheumatoid arthritis, systemic lupus erythematosus, and hemolytic anemia [1]. With increased understanding of the immune system, ideas about mechanisms of autoimmunity broadened to include roles for T cells, B cells, and the innate, primary, or secondary immune responses. Many categories of autoaggressive disorders have ultimately been defined with the number growing annually.

Many of these conditions are now known to be associated with genetic variations in molecules that regulate the activation of immune cells, ranging from MHC molecules, complement components, cytokines, Toll-like receptors (TLRs), NOD (nucleotide-binding oligomerization domain) proteins, and inflammasomes (components responsible for activation of inflammatory processes) [2, 3]. Understanding the ways in which each genetic variation facilitates the engagement of a particular autoimmune process remains a major challenge. The pathways involved are clearly diverse and continue to be discovered as we publish this chapter. The following are some general concepts to help understand the origins of autoimmune disorders and the scope of current and future therapeutic strategies such as T- and B-cell targeting.

S.M. Naguwa, MD
Division of Rheumatology, Allergy and Clinical Immunology, University of California, Davis, School of Medicine, GBSF, Rm 6510, 451 Health Sciences Dr., Davis, CA 95616, USA
e-mail: smnaguwa@ucdavis.edu

C.C. Chang, MD, PhD, MBA, FAAAAI, FACAAI
Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: cchang@nemours.org

G.A. Incaudo, MD, FAAAAI, FACAAI (✉)
Division of Rheumatology, Allergy and Clinical Immunology, University of California School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA
e-mail: gincaudo@norcalallergy.com

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_15,

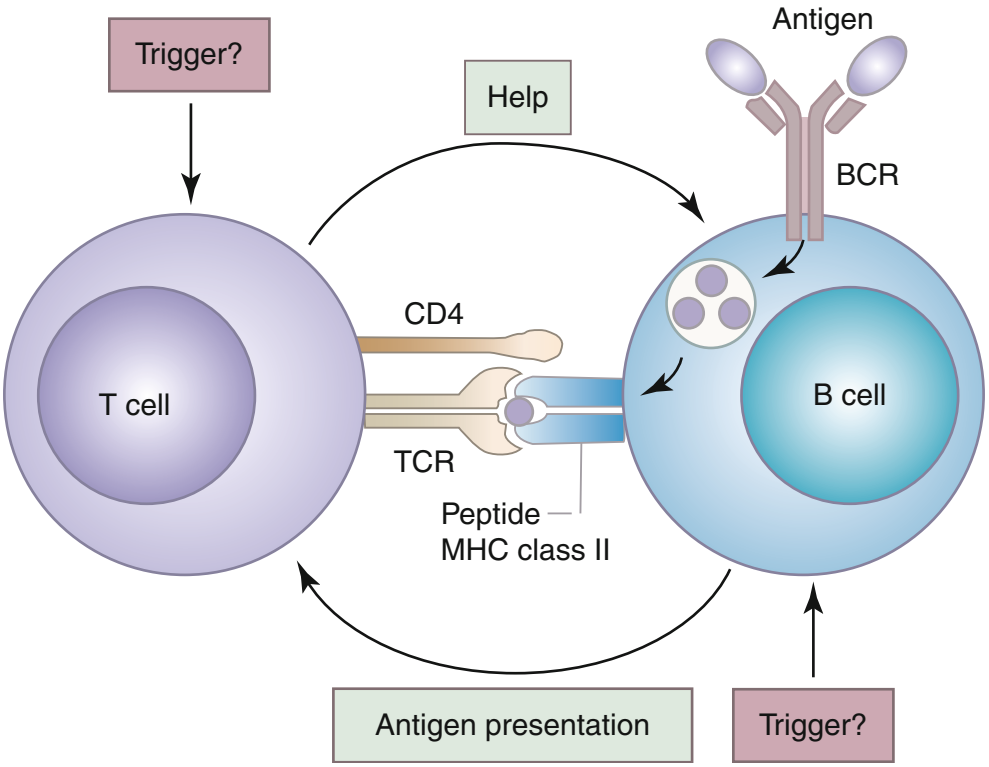


Fig. 15.1 The two-way interaction between B cells and T cells provides the basis for the concept that in certain autoimmune diseases, an amplification cycle might allow persistent immunopathology to arise from a minor "trigger" factor. Such a trigger might initiate the cycle through events in either the B-cell or the T-cell compartment, including the stochastic generation of both B-cell receptors (*BCRs*) and T-cell receptors (*TCRs*) (Reprinted from Edwards and Cambridge [6]. With permission from Nature Publishing Group)

Most of the disorders discussed below have a wide variety of autoantibodies associated with them although commonly one or two autoantibodies are more characteristic of a specific disease description. If and when a susceptible individual develops a disease depends, in many cases, on additional acquired "trigger" factors such as ill-defined environmental exposures and hormonal changes [4]. These have proved remarkably hard to identify. However, a concept that might prove useful in understanding the autoantibody-associated disorders, in particular, is that a minor event such as an environmental exposure triggers a positive-feedback cycle, which leads to persistent immunopathology [5]. Of particular interest to researchers seeking cures is the in-depth understanding of the two-way interaction between B cells and T cells. B cells provide signals to T cells through antigen presentation, and T cells provide "help" to B cells through the delivery of cytokines and cell-surface ligands. At times, the control mechanisms become faulty and clonal expansion of autoreactive cells can develop (Fig. 15.1). These interactions create the potential for a positive-feedback loop resulting from a clonal expansion of an autoreactive T or B cell that infiltrates tissue and promotes disease expression [6] (Fig. 15.2). It remains unclear which cell makes the crucial mistake to trigger an autoimmune disease, and indeed, it likely varies from disease to disease.

Ultimately, the goal for immunologists is to provide clinicians with a set of tools to precisely retune the immune system for each type and variation of immune dysregulation. The best tools will accomplish this task by preserving sufficient basic immune function to ensure a healthy defense against pathogens while preferentially limiting certain autoreactive components. For example, the discovery of the B-cell-activating factor of the tumor necrosis factor family (BAFF) system has provided immunologists with a new insight into the mechanisms that control B-cell survival during maturation in the periphery and a target for future therapy. BAFF enhances B-cell survival and has a role in enhancing immune responses. Although BAFF is a beneficial factor that promotes B-cell maturation and enhances immune responses, excessive BAFF production seems to be able to disrupt B-cell survival. Moreover, the overexpression of BAFF in mice results in severe autoimmune disorders. In humans, elevated serum levels of BAFF have been seen in some patients with autoimmune diseases such as Sjögren's syndrome and rheumatoid arthritis (Fig. 15.3).

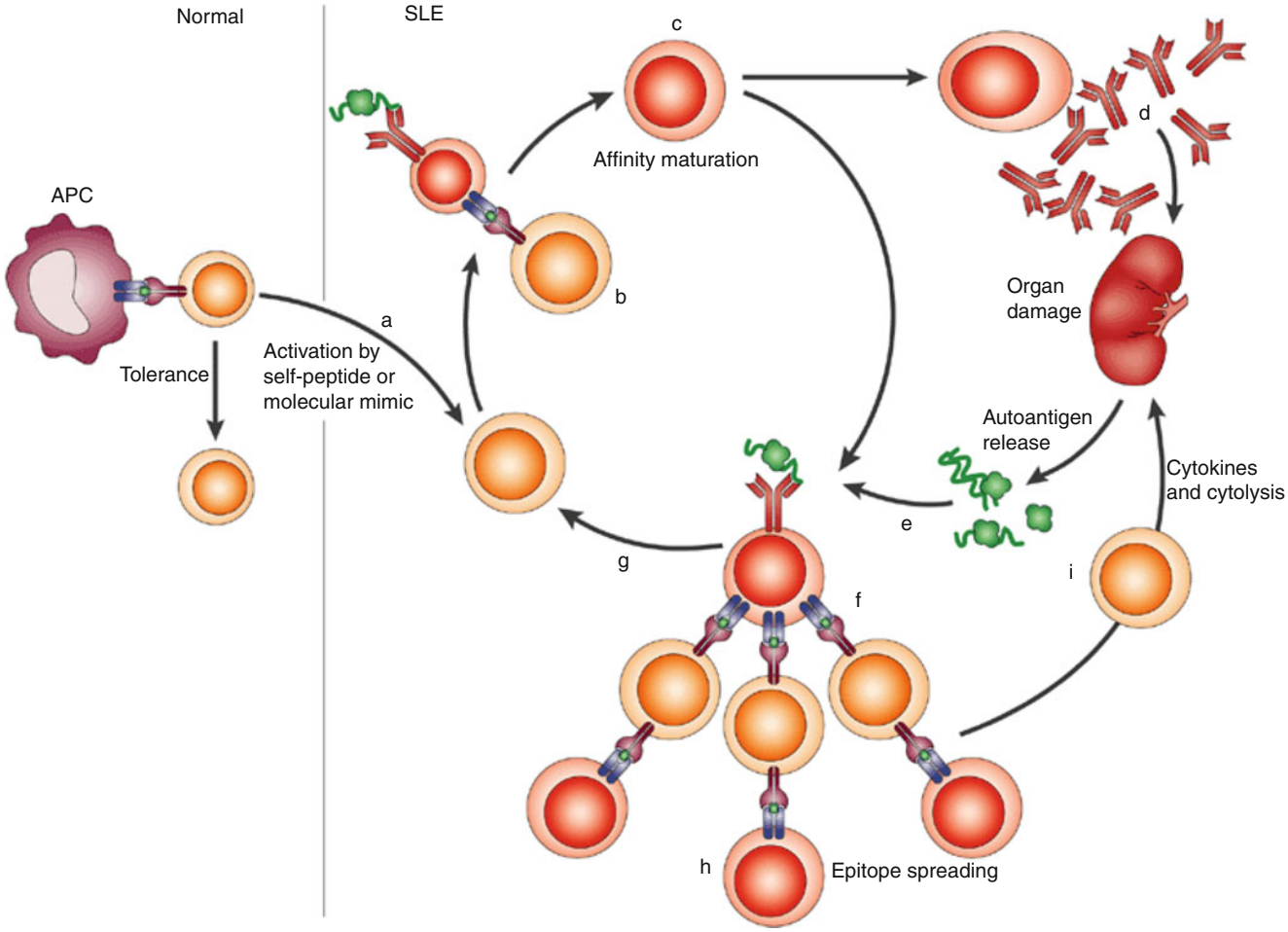


Fig. 15.2 (*a*) Although normal T cells exposed to self-antigen in the periphery become tolerized, lupus-prone T cells are sensitive to lower thresholds of activation by agonist or weak-agonist peptides. (*b*) Once activated, T cells can provide primary stimulation to genetically hyperresponsive B cells. (*c*) These autoantigen-stimulated B cells undergo somatic hypermutation and affinity maturation. (*d*) On the synthesis of pathogenic autoantibodies, tissue damage results in the release of self-antigen, (*e*, *f*) which is also taken up and presented by specific antigen-presenting B cells in a second round of T-cell activation, (*g*) therefore leading to a positive-feedback cycle. (*h*) Autoimmune T- and B-cell responses are diversified, which results in epitope spreading. This continuing and cyclic process of B-cell–T-cell cognate interaction serves to amplify the ensuing autoimmune processes. (*i*) Activated T cells can also directly cause tissue pathology by migrating to the target organ and releasing cytokines and by mediating direct cytotoxicity. *APC* antigen-presenting cell. T cells are shown *orange*; B cells are *red* (Reprinted from Shlochik et al. [3]. With permission from Nature Publishing Group)

Autoreactive T-regulatory cells have also been named as sources of autoimmune disease. Autoreactive CD4 and CD8(+) regulatory T cells (Tregs) play important roles as modulators of immune responses against self. Numerical and functional defects in CD4 and CD8(+) Tregs have been linked to autoimmunity (Fig. 15.1).

Definitions

The change in the nomenclature is an effort by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) to move away from eponyms and for ethical reasons [8, 9]. The most common autoimmune diseases that involve the airway are categorized as granulomatous diseases. These diseases share ANCA positivity and vasculitis of the small and medium vessels at some point in the clinical course. Granulomatosis with polyangiitis and allergic

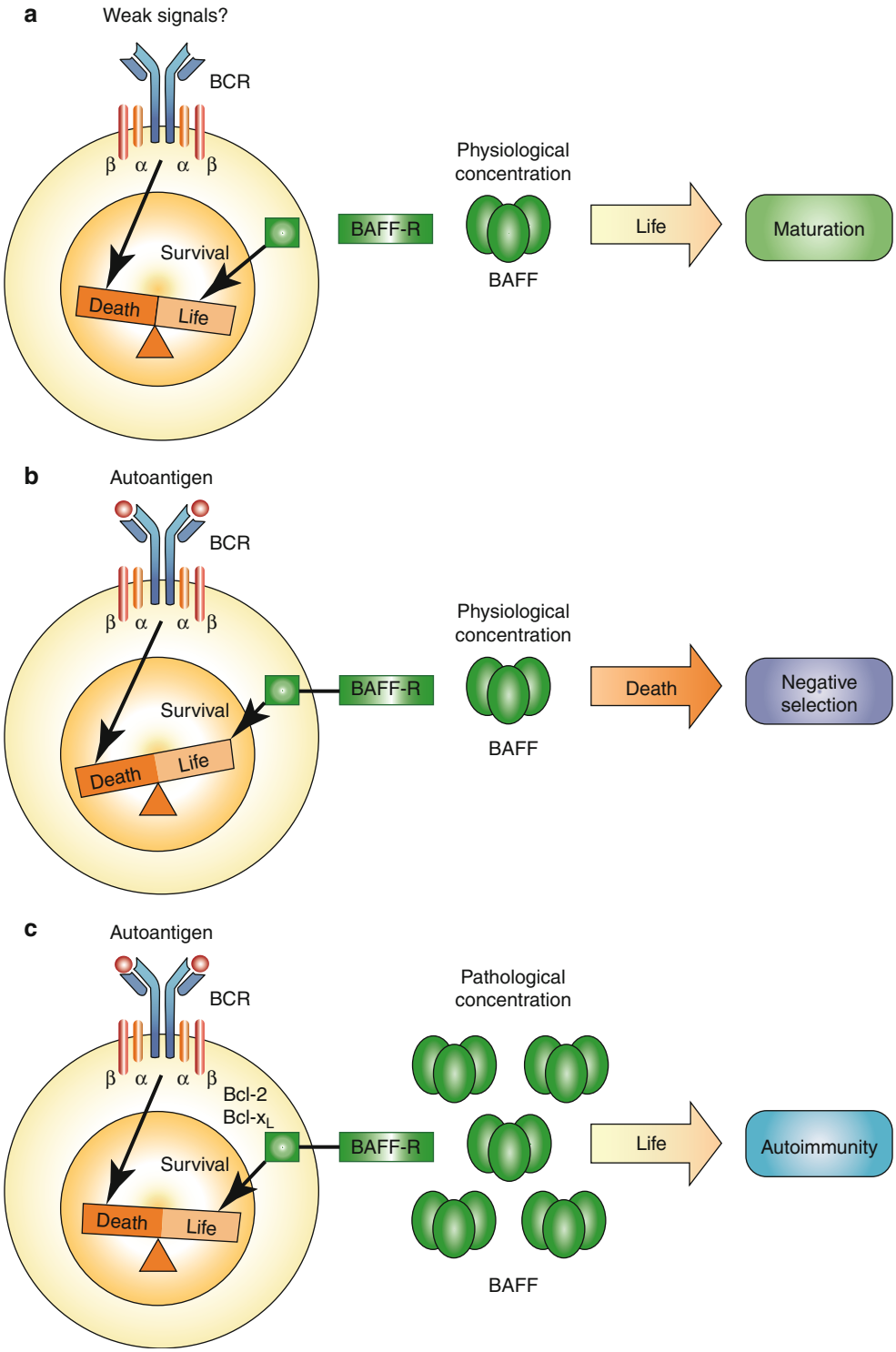


Fig. 15.3 (**a**) Increased BAFF production leads to excess B-cell survival and the escape of autoreactive B cells from negative selection, some of which might localize in the spleen. (**b**) After activation by autoantigen and potential BAFF costimulation, activated B cells might leave the spleen and migrate to lymph nodes and/or target tissues. (**c**) Similarly, the low-level activation of peritoneal B cells by autoantigen might be amplified by BAFF-induced costimulation, leading to the recruitment of activated B cells in target tissues. Activated B cells differentiate into plasma cells, which produce potentially pathogenic autoantibodies, as well as inflammatory cytokines and chemokines. *BAFF* B-cell-activating factor of the tumor necrosis factor family, *BCR* B-cell receptor (Reprinted from Mackay and Browning [7]. With permission from Nature Publishing Group)

Table 15.1 Clinical features of the primary antineutrophil cytoplasmic antibody-associated vasculitides

Feature	Wegener's granulomatosis	Microscopic polyangiitis	Churg–Strauss syndrome
ANCA positivity	80–90 %	70 %	50 %
ANCA antigen specificity	PR3 > MPO	MPO > PR3	MPO > PR3
Fundamental histology	Leukocytoclastic vasculitis; necrotizing, granulomatous inflammation (rarely seen in renal biopsy specimens)	Leukocytoclastic vasculitis; no granulomatous inflammation	Eosinophilic tissue infiltrates and vasculitis; granulomas have eosinophilic necrosis
Ear/nose/throat	Nasal septal perforation, saddlenose deformity, conductive or sensorineural hearing loss, subglottic stenosis	Absent or mild	Nasal polyps, allergic rhinitis, conductive hearing loss
Eye	Orbital pseudotumor, scleritis (risk of scleromalacia perforans), episcleritis, uveitis	Occasional eye disease: scleritis, episcleritis, uveitis	Occasional eye disease: scleritis, episcleritis, uveitis
Lung	Nodules, infiltrates, or cavitary lesions; alveolar hemorrhage	Alveolar hemorrhage	Asthma, fleeting infiltrates, alveolar hemorrhage
Kidney	Segmental necrotizing glomerulonephritis, rare granulomatous features	Segmental necrotizing glomerulonephritis	Segmental necrotizing glomerulonephritis
Heart	Occasional valvular lesions	Rare	Heart failure
Peripheral nerve	Vasculitis neuropathy (10 %)	Vasculitis neuropathy (58 %)	Vasculitis neuropathy (78 %)
Eosinophilia	Mild eosinophilia occasionally	None	All

Reprinted from Stone [10]. With permission from Springer, 2013
Abbreviations: *ANCA* antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *PR3* proteinase 3

granulomatosis share upper and lower airway involvement, while granulomatosis with polyangiitis and microscopic polyangiitis have renal involvement (Table 15.1). As with many systemic rheumatic diseases, there are classification criteria which, with increasing understanding of the diseases, will be undergoing modification in the near future. Currently, classification criteria arise from the 1994 Chapel Hill Consensus Conference on Vasculitis [11].

Sinus Involvement in Autoimmune Diseases

ANCA-Associated Vasculitis

ANCA-associated vasculitides are rare diseases with a prevalence that varies by geographic location and changes with time. The prevalence of granulomatosis with polyangiitis in Sweden has been reported to be 160 per million population in 2003 [12]. In the United States, the prevalence is even lower, at 32 per million in the 1980s [13]. In the United States, men and women are equally affected, Caucasians were predominantly affected, and the average age was 48 [14, 15]. The incidence of granulomatosis with polyangiitis is lower in Japan, but there is a higher incidence of microscopic polyangiitis [15]. The worldwide prevalence of allergic granulomatosis is 11–45 per million.

The precise role of ANCAs in disease pathogenesis remains unclear. There is emerging evidence to suggest that they might directly initiate an inflammatory response in patients with small-vessel vasculitis. If ANCA proves to be a distinguishing feature of vascular inflammation, then the syndromes of Wegener's granulomatosis (now termed granulomatosis with polyangiitis [GPA]), microscopic polyangiitis (MPA), and renal-limited vasculitis will rightfully be defined as ANCA-associated diseases.

Granulomatosis with Polyangiitis (GPA)

General Description

Granulomatosis with polyangiitis, first described in 1931, has its primary manifestations in the respiratory tract. The pathogenesis is a vasculitis that affects the sinonasal passages, lung, kidneys, and skin. The upper respiratory tract is the most

commonly affected region. Upper respiratory symptoms are ultimately present in 90 % of cases. In that GPA also involves small- to medium-sized vessels, 10 % of patients eventually developed generalized symptoms within about 6 years.

Clinical Overview

A multitude of lung lesions may be seen in GPA. Nodules can be noted on chest x-ray without symptoms initially. The patient may develop multiple nodules occasionally with cavitation, and interstitial lung disease. However, it is a vasculitis of the lung causing hemoptysis or diffuse pulmonary hemorrhage in GPA and MPA that is most concerning in that there is a 60 % mortality rate in patients with diffuse pulmonary hemorrhage [16]. In addition to asthma, transient pulmonary infiltrates with eosinophilia on bronchoalveolar lavage and non-cavitating nodules may occur in AG, but hemorrhage is rare [17]. In MPA, approximately 25 % of the patients have lung involvement including pulmonary infiltrates and diffuse pulmonary hemorrhage. Large airways may be involved with secondary stenosis causing hoarseness, cough, wheeze, and stridor, particularly in GPA [16].

Involvement of the kidneys presents with a focal segmental necrotizing glomerulonephritis that may progress to a rapidly progressive glomerulonephritis with crescents. The latter kidney involvement may affect survival [16]. Similar lesions occur in MPA; however, the course is less aggressive [18]. While renal disease may occur in Churg–Strauss, it is less severe.

Peripheral nervous system involvement is most common in Churg–Strauss with about 70 % afflicted [19], with MPA 58 % [18], and less commonly in GPA [16]. Vasculitic neuropathies with mononeuritis multiplex may occur particularly in Churg–Strauss and microscopic polyangiitis, in addition to cranial and sensory neuropathies. The skin is commonly involved in the ANCA-associated vasculitides presenting typically as palpable purpura. Nodules may also be seen in GPA and MPA, and urticaria sometimes appears in Churg–Strauss and MPA [16–18]. The heart is less frequently clinically involved in the ANCA-associated vasculitides (~20 %), though on postmortem 50 % of hearts from patients with ANCA-associated vasculitides have lesions that may contribute to the significant morbidity and mortality seen in these disorders. Approximately 1/3 of Churg–Strauss patients have gastrointestinal symptoms due to eosinophilic gastroenteritis and mesenteric vasculitis. Gastrointestinal problems are rarely seen in GPA. While gastrointestinal symptoms are reported in MPA, any association with ANCA-associated vasculitis is not clear [16–18].

Sinus Disease in GPA

Clinically, chronic rhinosinusitis (CRS) is seen in nearly all patients with GPA. Symptoms include nasal crusting, obstruction, and bloody discharge/epistaxis, and with late/aggressive disease, septal perforation and saddlenose deformity are seen [16, 20]. Even though CRS is the most common presenting symptom in GPA, GPA, is not commonly considered due to its rarity [21]. The development of multisystem symptoms months to years subsequently should prompt the consideration of GPA in the difficult-to-treat CRS patient. The clues that would suggest the diagnosis of an ANCA-associated vasculitides in a patient with severe/recurrent CRS would be concurrent disease of the lung, kidney, joints, and skin, not otherwise explained, or a preexisting diagnosis of autoimmune disease [16]. Epiphora may be a concomitant symptom. Bloody or purulent/necrotic nasal discharge with an ulcer, septal perforation, and saddlenose deformity are common findings seen by ENT after a referral by primary care physicians [20]. Children may present with coincident upper and lower airways involvement with subglottic stenosis and vague constitutional symptoms [22]. Chronic rhinosinusitis (CRS) may develop in GPA requiring functional sinus surgery; however, the outcome is commonly poor [20].

Pathogenesis

ANCA was first reported in the mid-1980s as cytoplasmic immunofluorescence in alcohol-fixed neutrophils appearing in two patterns. One pattern showed diffuse cytoplasmic staining labeled c-ANCA and a second peripheral nuclear pattern labeled p-ANCA. Though ANCAs were frequently but not exclusively seen in GPA and AG, they significantly enhanced the detection and evaluation of ANCA-associated vasculitides. The antigen causing c-ANCA is serine proteinase 3 (PR 3) and that causing p-ANCA was primarily myeloperoxidase (MPO) with other antigens also identified. The detection of c-ANCA is primarily seen in GPA in 80–90 % of the patients, with p-ANCA seen less commonly. P-ANCA is more commonly seen in AG (50 %) and MPA (70 %) [10]. The level of antibody titers does not necessarily correlate with disease severity, and changes in antibody titers do not necessarily predict flare of disease or sustained remission.

Current research shows that ANCAs react with neutrophils and endothelial cells causing endothelial injury, inflammation, and necrotizing vasculitis. Degranulation of neutrophils results in the release of cytokines and chemokines that perpetuates the inflammation [23] (Fig. 15.3). The origin of ANCAs is not known. Compelling data on the role of ANCAs in the disease process have been obtained from the development of animal models of MPO-ANCA-associated vasculitis. These models suggest that Th17 cells, alternative complement pathway, and infection–Toll-like receptor interactions play significant roles in the inflammation [24]. A model of anti-PR 3 AAV is being developed.

Treatment

The management of ANCA-associated vasculitides depends on the organ system involvement. With major life- or organ-threatening system involvement, the treatment is cyclophosphamide (CTX) 1–2 mg/kg daily orally adjusted for eGFR with corticosteroids 1 mg/kg or, alternatively, the newly approved anti-CD20 antibody rituximab (RIT) for GPA. Intravenous cyclophosphamide may also be used. Cyclophosphamide treatment has improved the 5-year survival rate from 18 % to 76 %. For non-life-threatening/organ-threatening disease, methotrexate, azathioprine, leflunomide, and mycophenolate may be used. The need for concomitant use of steroids is not clear. A small percentage (~5 %) of patients may be resistant to CTX. An alternative for the refractory patients is RIT. If there is resistance to RIT, various other biologic agents have been used in small number of patients [25]. With major organ involvement, survival of patients with these diseases was measured in months until the advent of cyclophosphamide treatment in the early 1980s. Since then, sustained remission is the goal of therapy as more varied and newer treatments are being developed [25, 26].

Allergic Granulomatosis or Eosinophilic Granulomatosis with Polyangiitis (EGPA)

General Description

Allergic granulomatosis (AG), eosinophilic granulomatosis with polyangiitis (EGPA), or Churg–Strauss syndrome (CSS) is a rare small-vessel vasculitis principally arising in patients with a history of asthma, atopic disease, or both and often involves nasal polyposis and sinus dysfunction [27]. The history of this disorder dates back to 1951 when doctors Churg and Strauss first described a syndrome characterized by asthma associated with "fever and eosinophilia, and symptoms of cardiac failure, renal damage and peripheral neuropathy resulting from vascular embarrassment in various systems of organs" [28, 29]. Histology of the cases described by Churg and Strauss were all characterized by tissue eosinophilia, necrotizing and granulomatous vascular lesions, and extravascular granulomas in most of the organs studied. There was a particular predisposition for eosinophilic involvement of the airway. Churg–Strauss syndrome was found to be associated with antineutrophil cytoplasmic antibodies (ANCA) in a large proportion of patients since the 1980s [30].

Churg–Strauss syndrome is currently included in the spectrum of ANCA-associated vasculitis. The syndrome continued to be named Churg–Strauss until 2012 when it was revised during a general change in nomenclature for vasculitides as eosinophilic granulomatosis with polyangiitis (Churg–Strauss, EGPA) [31]. To date, there are no commonly accepted diagnostic criteria for EGPA (Table 15.2). In 1984, Lanham et al. proposed that patients with EGPA should present clinically with asthma, eosinophilia, and vasculitic involvement of two or more organs [32]. In 1990, the American College of Rheumatology (ACR) identified six criteria for EGPA:

1. Asthma
2. Eosinophilia >10 %
3. Neuropathy
4. Non-fixed lung infiltrates
5. Paranasal sinus abnormalities
6. Extravascular eosinophils on biopsy

When four or more of these criteria are met, vasculitis can be classified as EGPA with a sensitivity of 85 % and a specificity of 99.7 % [33]. In using the ACR criteria, it is critical that a diagnosis of vasculitis first be made and then the criteria can be used to define the type of vasculitis such as EGPA. Conclusions and proposals made at the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis in 1993 defined Churg–Strauss as an eosinophil-rich granulomatous inflammation involving the respiratory tract with necrotizing vasculitis affecting small- to medium-sized vessels associated with asthma and eosinophilia. Along with Wegener's granulomatosis (GPA) and microscopic polyangiitis, Churg–Strauss was distinguished by being highly associated with the presence of ANCA [35].

Table 15.2 Classification criteria and definitions commonly used for eosinophilic granulomatosis with polyangiitis (Churg–Strauss, EGPA): Lanham's criteria, ACR classification criteria, and Chapel Hill definition

Lanham et al. [32]
Asthma
Eosinophilia >1.5×10^9/l
Clinical or pathological evidence of vasculitis involving at least two organs
ACR 1990[a] [33]
Asthma
Eosinophilia >10 %
Neuropathy (mono- or polyneuropathy)
Non-fixed pulmonary infiltrates
Paranasal sinus abnormalities
Extravascular eosinophil infiltration on biopsy
Chapel Hill Consensus Conference 1994 [8]
Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and eosinophilia

Reprinted from Vaglio et al. [34]. © 2013 John Wiley & Sons A/S. Published by Blackwell Publishing, Ltd.
ACR American College of Rheumatology
[a]At least four of the six ACR criteria are required to classify vasculitis as EGPA

Clinical Overview

Allergic rhinitis or rhinosinusitis and asthma are the initial features prior to the development of the EGPA. While nearly 100 % of patients have asthma, about 70 % have rhinosinusitis. Features which would suggest EGPA are multisystem disease with lung infiltrates (less common non-necrotizing nodules), neuropathy, skin lesions, and cardiac or gastrointestinal involvement in a patient with late-onset asthma with eosinophilia that poorly responds to treatment [17, 19]. Of interest is that the development of leukotriene inhibitors (LTRi) for the management of asthma corresponded to a temporal evolution of EGPA in some patients. This may have been due to the success of this class of drugs in facilitating a tapering of systemic corticosteroids. A definite casual association between EGPA and leukotriene inhibitors has not been established.

Adding EGPA to the differential diagnosis of CRS adds a complexity to the medical fields of otolaryngology and allergy in that EGPA commonly evolves slowly over years. As such, a patient with EGPA may first present with any one or more of the common atopic manifestations such as allergic rhinitis, nasal polyposis, sinusitis, and asthma. There may be years separating the onset of these clinical conditions and the eventual development of classic manifestations of EGPA such as significant peripheral eosinophilia, eosinophilic pulmonary infiltrates, and other organ involvement (e.g., peripheral neuropathy). EGPA is proposed to commonly present as a 3-stage process beginning with atopic disease with asthma, rhinosinusitis, and nasal polyposis; followed by eosinophilia and eosinophilic organ disease (e.g., lung, heart, GI tract); and subsequently vasculitis of the small and medium vessels [17]. The EGPA-associated rhinosinusitis usually lacks the bloody/purulent discharge and septal perforation of GPA. With such a slow progression of the disease, the differentiation between allergic CRS with/without secondary infection and EGPA CRS is sometimes difficult.

Sinonasal Disease in EGPA

In 1980, Olsen et al. reviewed the nasal manifestations of EGPA in a series of 32 patients [36]. The authors found that 69 % (22/32 patients) had nasal disease, 50 % had nasal polyposis, and 36 % had nasal crusting. Importantly, in 32 %, the appearance of polyps preceded the development of asthma or vasculitis. Pansinusitis was found in 80 % of 15 patients who underwent sinus imaging studies. Another study of Churg–Strauss patients in 2001 revealed a prevalence of allergic rhinitis in 62.5 %, rhinosinusitis in 37.5 %, and nasal polyposis in 25 % [37]. In 2006, Bacciu et al. reported on cases of EGPA encountered in an otolaryngology practice [38]. Of their patients with a diagnosis of EGPA, 75 % had involvement of the upper airway or otologic disease. The most common upper airway problems encountered were allergic rhinitis (43 %) and rhinosinusitis with nasal polyposis (76 %). Three (14.2 %) patients developed chronic rhinosinusitis without polyps and three (14.2 %) had nasal crusting. Other otolaryngological manifestations of EGPA encountered were serous otitis media (4.7 %), purulent otitis media (4.7 %), progressive sensorineural hearing loss (9.5 %), and unilateral facial palsy (4.7 %).

Pathogenesis

The exact pathogenesis of eosinophilic granulomatosis with polyangiitis remains elusive. There have been vague genetic associations defined although the data is inconclusive and suggests rather a genetic predisposition requiring another trigger

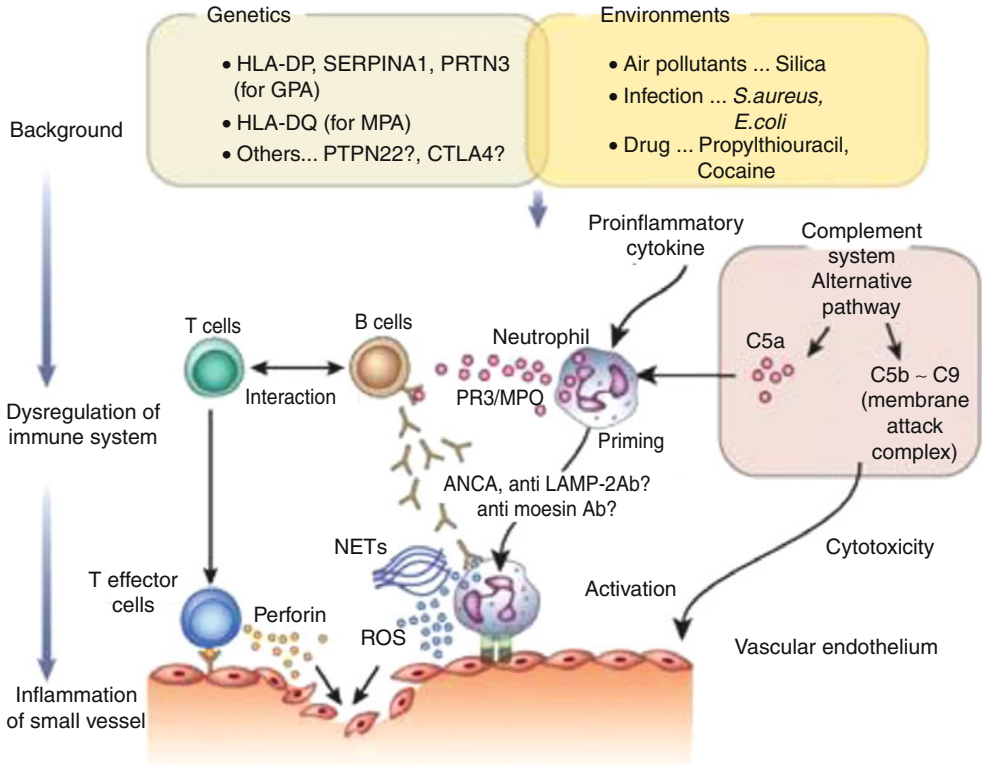


Fig. 15.4 Mechanism of the onset of antineutrophil cytoplasmic antibody (*ANCA*)-associated vasculitis. *LAMP-2* lysosome-associated membrane protein-2, *MPO* myeloperoxidase, *NETs* neutrophil extracellular traps, *PR3* proteinase 3, *ROS* reactive oxygen species (Reprinted from Furuta and Jayne [43]. With permission from Nature Publishing Group)

[39, 40]. Better immunologic data suggests that EGPA is an antigen-driven disease. There has been considerable literature suggesting EGPA is associated with exogenous factors such as environmental agents, infections, vaccinations, and drugs, particularly leukotriene antagonists [41, 42]. The concept of a combination of genetic predisposition and exogenous exposures defining the ANCA-associated vasculitides is depicted in detail in Fig. 15.4.

The key distinguishing features of this group of disorders have been investigated in detail. The major autoantigens (an antigen that despite being a normal tissue constituent is the target of a humoral- or cell-mediated immune response) of ANCA are MPO and PR3. When ordering a laboratory test for ANCA, a screening test is first done. If ANCA positivity is found, further studies defining the two major components of ANCA should be pursued. A perinuclear immunofluorescence pattern (p-ANCA) corresponds with anti-MPO (myeloperoxidase) and is found in 74–90 % of ANCA-positive EGPA cases. The remaining EGPA patients have cytoplasmic ANCA (c-ANCA) that corresponds to anti-proteinase-3 (PR3) antibodies or rarely mixed (C + P) patterns [44]. MPO-ANCA is the predominant serotype in MPA patients, whereas PR3-ANCA is usually found in GPA (Wegener's). True dual ANCA positivity is rare and raises suspicion of a drug-induced vasculitis.

As previously mentioned, in addition to being a diagnostic marker, a pathogenic role for ANCA is supported by experimental data and associations of ANCA with disease activity. However, how distinctive a feature ANCA might be remains unclear. ANCA-associated vasculitides can occur without ANCA, and ANCA levels do not clearly correlate well with disease activity. Ultimately, differences in the functional effects of ANCA epitopes and other autoantibodies associated with vasculitis may explain differing clinical associations, but these remain a research tool.

Recent evidence suggests that a predominant Th2 response is uniquely active in EGPA (Fig. 15.5). A strong association is found between EGPA and elevated IgE levels and peripheral eosinophilia. There is also a dramatic increase in serum IgG4 in active EGPA [34]. Th2 cytokines (i.e., IL-4, IL-13) boost the humoral immune response and IgE and especially IgG4 production although the pathogenic importance of IgG4 is unclear. The current concepts of the main immune mechanisms inducing EGPA are schematically summarized in Fig. 15.5.

Treatment Overview

In approaching a patient with EGPA, it is important to include a comprehensive evaluation of multiple organ systems and involve a variety of medical specialists accordingly. Furthermore, the prognosis in the disease is highly variable. The degree

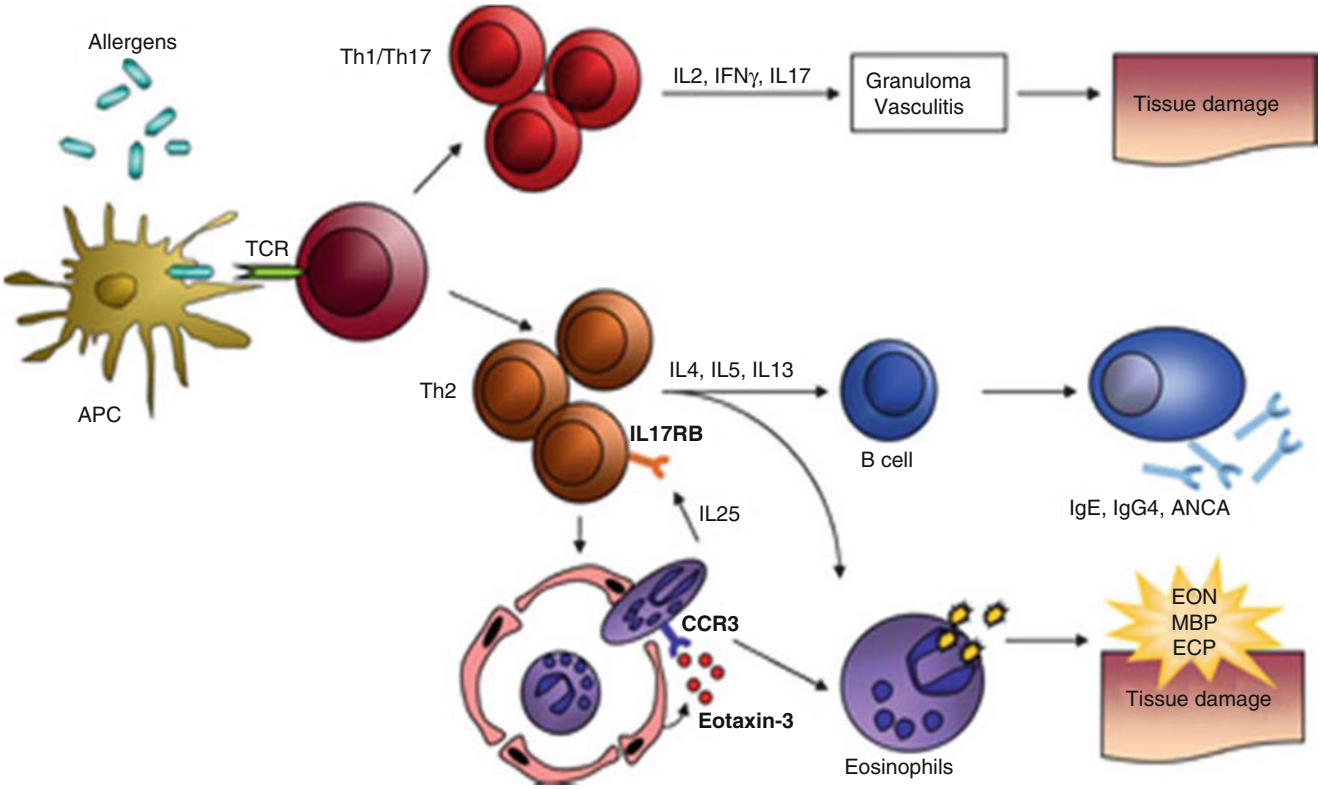


Fig. 15.5 Simplified scheme of pathophysiological events in eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss). Hitherto unidentified allergens elicit an adaptive immune response in EGPA patients. T cells secrete Th1- (IFN-c), Th17- (IL-17), and Th2- (IL-4, IL-13, IL-5) associated cytokines and activate eosinophils. The strong Th2 immune response precipitates a B-cell response resulting in IgG4, IgE, and antineutrophil cytoplasmic antibody (ANCA) production. Increased expression and secretion of eotaxin-3 guide eosinophils to the endothelium and tissues. Eosinophils in turn maintain a vicious circle of T-cell activation by secreting IL-25. Local degranulation of activated eosinophils finally causes damage, necrosis, and fibrosis to tissues and vessels. *APC* antigen-presenting cell, *TCR* T-cell receptor, *ANCA* antineutrophil cytoplasmic antibody, *EDN* eosinophil-derived neurotoxin, *MBP* major basic protein, *ECP* eosinophilic cationic protein (Reprinted from Vaglio et al. [34]. © 2013 John Wiley & Sons A/S. Published by Blackwell Publishing, Ltd.)

of ancillary organ involvement and the presence or absence of ANCA have some predictive value. A negative ANCA result is associated with an increased proportion of cardiac and gastrointestinal involvement, pulmonary infiltrates, and fevers/night sweats and a decreased proportion of peripheral neuropathy when compared with those who have a positive ANCA (anti-MPO) in a study by Healy et al. in 2013 [45]. There was also a strong association in this study between the composite of life-threatening events and deaths and ANCA negativity, suggesting that the absence of anti-MPO might carry a worse prognosis.

Monitoring the course of therapy is also important in that the disease tends to wax and wane over time. Active EGPA is characterized by marked peripheral eosinophilia (usually >1,500 cells/μl or >10 %). Eosinophilia correlates with disease activity, and relapses are often heralded by an increase in the absolute eosinophil count [46]. C-reactive protein and erythrocyte sedimentation rates are also high in the active phase of EGPA.

There is no consensus regarding the use of a staged, remission-induction and remission-maintenance approach in EGPA. Initial therapy is generally determined by a prognostic profile called the Five-Factor Score [47]. The Five-Factor Score (FFS) includes the presence or absence of heart, gastrointestinal, and central nervous system involvement, proteinuria >1 g/24 h, and creatinine >140 lM/l. Patients with an FFS > 1 have a worse prognosis so they are usually treated with a combination of glucocorticoids and immunosuppressants (e.g., cyclophosphamide, azathioprine, cyclosporine, and methotrexate). Glucocorticoids alone are recommended in those with FFS = 0 [48]. The Five-Factor approach, however, has been challenged by researchers who feel that the use of combination of immunosuppressants and glucocorticoids should also be the first-line therapy for patients with peripheral neuropathy and eosinophilic alveolitis or alveolar hemorrhage [49].

Other therapies for EGPA described in the literature include high-dose intravenous immunoglobulins used in combination with plasma exchange, cyclophosphamide and glucocorticoids [50], and interferon-α [51, 52]. More controversial options are treatment with the anti-IgE antibody omalizumab [53–55], mycophenolate [56], and the anti-interleukin 5 antibody mepolizumab [57]. A detailed review of these various treatment modalities and their outcomes is beyond the scope of this text. The reader is referred to references in this chapter for more details (Table 15.3). It should be noted that corticosteroids

Table 15.3 Induction of remission, maintenance, and novel treatments in Churg–Strauss syndrome

	Treatment of Churg–Strauss syndrome
Induction of remission	*Without poor prognosis*
	Oral prednisone 1 mg/kg daily for 3 weeks, tapering 5 mg every 10 days to 0.5 mg/kg. Then, taper 2.5 mg every 10 days to the minimal effective dosage or until definitive withdrawal or 1 intravenous methylprednisolone pulse (15 mg/kg) followed by oral prednisone (as above)
	In case of relapse in the first year or treatment failure, add oral azathioprine 2 mg/kg daily for at least 6 months or 6 CYC pulses (600 mg/m^2) every 2 weeks for 1 month and then every 4 weeks thereafter
	With poor prognosis
	Three consecutive methylprednisolone pulses (15 mg/kg) on days 1–3 plus oral prednisone (see above) plus either 12 cyclophosphamide (CYC) pulses (600 mg/m^2) every 2 weeks for 1 month, then every 4 weeks thereafter, or short course of CYC (oral 2 mg/kg for 3 months or 6 CYC pulses [600 mg/m^2] every 2 weeks for 1 month and then every 4 weeks thereafter), followed by azathioprine 2 mg/kg for 1 year or more
Maintenance of remission	MTX (10–25 mg/week)
	Cyclosporin A (1.5–2.5 mg/kg/day)
	Azathioprine (2 mg/kg/day)
Refractory disease[a]	Plasma exchange
	IVIG (0.4 g/kg/day for 5 days)
	Interferon-alpha (three million IU 3 times/week subcutaneously)
	TNF inhibitors: infliximab, etanercept, adalimumab
	Rituximab (325 mg/m^2 for four consecutive weeks)

Reprinted from Baldini et al. [17]. With permission from Elsevier

[a]The following drugs may be considered but have not been proved efficacious in CSS: mepolizumab (anti-IL-5) (5 monthly infusions of 750 mg each) and omalizumab (anti-IgE) (0.016 mg/kg per IU of IgE every 4 weeks, administered subcutaneously at 4-weeks or 2-weeks intervals)

remain the mainstay of therapy for EGPA. Furthermore, despite achieving remission, the disease may relapse in as many as 50 % of patients.

Microscopic Polyangiitis

In MPA, the sinuses are rarely involved. Management of sinusitis in MPA is similar to GPA [58]. As mentioned above, sinus involvement is minimal in MPA and serves as one of the distinguishing features between the two diseases.

Non-ANCA-Associated Vasculitis

Sjögren's Syndrome

General Description

Sjögren's syndrome is a systemic autoimmune exocrinopathy which results in decrease of secretions from glands, most notably salivary and lacrimal glands. All glands may be affected including that of the nasopharyngeal mucosa. Sjögren's syndrome (SS) is associated with B-cell hyperactivity and the appearance of specific serum autoantibodies. Since Sjögren's syndrome can overlap with other autoimmune disorders, it is considered primary if there are no other associated systemic rheumatic diseases such as rheumatoid arthritis (30–50 %) and SLE. It may affect up to 2 % of the population, particularly older females. As with other autoimmune diseases, there is an immunogenic dysregulation resulting in a polyclonal gammopathy and the production of autoantibodies of many types. Antimuscarinic antibodies appear along with T lymphocyte infiltration which results in the glandular dysfunction characteristic of this disease. The resultant xerostomia causes dysphagia and increased dental caries. The xerophthalmia may cause an irritation sensation, and if chronic and severe, it may result in keratoconjunctivitis sicca [59].

Clinical Overview

A multitude of organ systems are involved in Sjögren's syndrome including cutaneous vasculitis, arthritis, myopathy, neuropathy, and nephropathy. There may be a transition from a polyclonal gammopathy with lymphadenopathy to

pseudolymphoma and rarely B-cell lymphoma. The diagnosis of Sjögren's syndrome has been facilitated by the American College of Rheumatology Sjögren's classification criteria of 2012 [60]. The simplified classification criteria require two of three objective measures including (1) positive ANA and positive SS-A or positive SS-B or positive rheumatoid factor and positive ANA greater than 1:320, (2) labial salivary gland biopsy with a focus score greater than one, and (3) keratoconjunctivitis sicca with staining score greater than or equal to 3. There are exclusionary conditions such as hepatitis C, sarcoidosis, and a history of head or neck irradiation.

Sinus Disease

The upper or lower airways are typically involved with nasal dryness and occasional sinusitis due to decrease in mucus clearance and production [61]. The lower airways involvement includes interstitial pneumonitis, bronchitis, bronchiectasis, BOOP, and COPD. As a systemic process, patients may exhibit a persistent low-grade fever which makes it difficult to diagnose a pyogenic infection of the airways, including the sinuses, as opposed to a primary disease manifestation.

Pathogenesis

Sjögren's syndrome (SS) is a chronic autoimmune disorder associated with B-cell hyperactivity and serum autoantibodies. Sjögren's syndrome is most commonly associated with lymphocyte infiltration of the lacrimal and salivary glands, resulting in dry eyes and a dry mouth; however, lymphocyte infiltration might extend to the skin, lungs, heart, kidneys, and nervous system. Sjögren's syndrome is associated with antibodies that react with the RNA-binding proteins Ro (also known as SS-A) and La (also known as SS-B).

As with all autoimmune diseases, the origin of Sjögren's syndrome appears to be multifactorial. Genetic predisposition and epigenetic phenomenon and hormonal and environmental factors are all cited as sources. Tissue destruction is associated with the infiltration by primarily activated T and B inflammatory cells. The epithelial cells, which are the targets of autoimmune responses in SS, seem to be key regulators of the local inflammatory procedures. Thus, the epithelial cells of the affected organs display an "activated" phenotype and appear equipped to participate in the initiation and perpetuation of the local autoimmune inflammatory responses. The etiologic source of this T- and B-cell activation remains a mystery. The mystery of SS is moreover increased by the fact that SS may occur alone, as a primary condition, or in association with other connective tissue diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc), as secondary SS variants (sSS) [62].

Curiously then, SS can be seen as a clinical entity characterized by a chronic exocrinopathy in which the glandular involvement is associated with different phenotypes of systemic autoimmunity [63]. This complexity has made it difficult, over the years, to identify a homogeneous group of patients with a common etiopathogenesis or prognosis and ultimately to elaborate classification and diagnostic criteria for the disease.

In patients with SLE, rheumatoid arthritis, and Sjögren's syndrome—disorders that primarily affect the kidneys, joints, and salivary/lacrimal glands, respectively—an association has been found between elevated levels of BAFF in the blood and the severity of disease. This is particularly true for SS [64]. In view of the effect of BAFF on B-cell activation and antibody secretion, this observation is consistent with a possible role for BAFF in the pathogenesis of several autoimmune disorders, particularly SS. More severe B-cell disorders, and higher levels of autoantibodies and serum BAFF, are observed in patients that have Sjögren's syndrome compared with other autoimmune disorders [65]. BAFF is also highly expressed in the salivary glands of Sjögren's syndrome patients [66]. These observations indicate that the dysregulation of BAFF might be linked to disease pathogenesis of SS and can overlap with other autoimmune disorders in humans (Fig. 15.6).

Treatment Overview

Management of Sjögren's syndrome is tailored to the clinical manifestations in the individual patient. Commonly, topical therapy for sicca symptoms is employed with addition of oral pilocarpine or cevimeline if symptoms persist or start inducing gum disease. Extraglandular symptoms may require anti-inflammatory or immunosuppressant therapy, with the latter increasing the risk of complicating infection. Promising biologic agents being investigated are the B-cell response modifiers such as rituximab and belimumab.

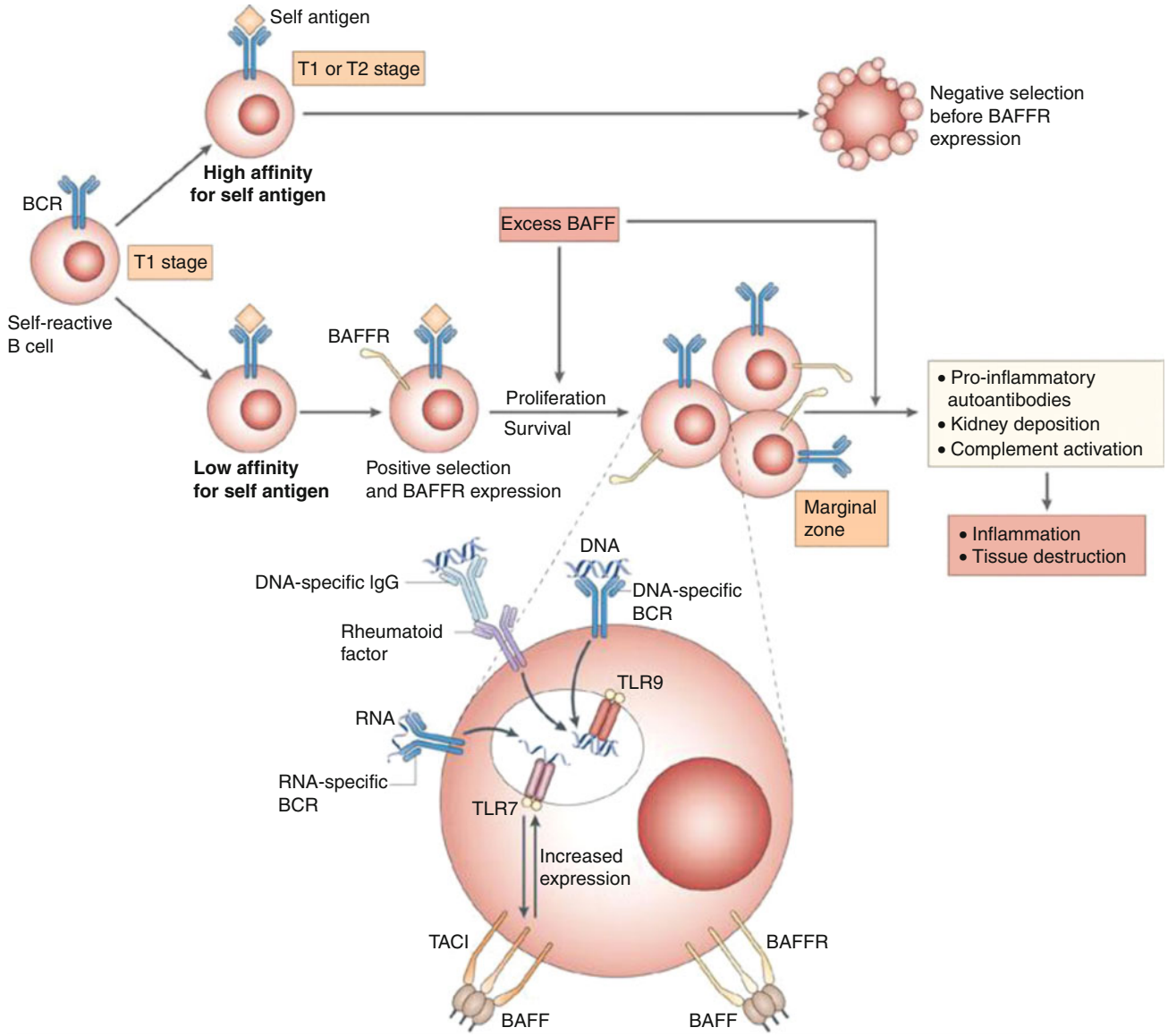


Fig. 15.6 Strongly self-reactive immature transitional type 1 (*T1*) B cells are killed after binding to self-antigen before expressing sufficient B-cell-activating factor receptor (*BAFFR*) on their cell surface and therefore cannot be rescued from deletion by BAFF. By contrast, self-reactive B cells with low affinity for self-antigen are positively selected, acquire expression of BAFFR on their cell surface, proliferate in response to increased levels of BAFF, and mostly accumulate in the marginal zone compartment of the spleen. Low-affinity self-reactive B cells expressing a DNA-specific or RNA-specific B-cell receptor (*BCR*), in particular marginal zone B cells, are highly responsive to Toll-like receptor (*TLR*)-mediated activation. B cells expressing rheumatoid factor can also bind DNA indirectly. After internalization of the antibody–DNA complex, DNA can activate TLR9. DNA-specific and RNA-specific self-reactive B cells could therefore be activated directly through TLR9 and TLR7, respectively. Transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI; also known as TNFRSF13B) activation upregulates TLR expression, and TLR activation increases TACI expression. After TLR activation, and in the presence of high levels of BAFF, self-reactive B cells produce proinflammatory autoantibodies (in particular, IgG2b and IgG2c), which deposit in the kidney and promote complement activation and tissue destruction (Reprinted from Mackay and Schneider [66]. With permission from Nature Publishing Group)

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a destructive inflammatory arthritis associated with autoantibodies rheumatoid factor and anti-cyclic citrullinated peptide. To control the symptoms and prevent destruction of the joints, potent anti-inflammatory immune modulators termed disease-modifying antirheumatic drugs (DMARD), such as methotrexate, leflunomide, and biologic response modifiers, are used. The current approach to disease management is to make an early diagnosis utilizing the 2010

Table 15.4 Major and minor diagnostic criteria for Behcet's syndrome

Major criteria
1. Recurrent oral ulcerations
Minor criteria (two of four criteria)
1. Recurrent genital ulcerations
2. Ophthalmic lesions
3. Dermatologic lesions
4. Pathergy

ACR/EULAR classification criteria for rheumatoid arthritis and initiating DMARD treatment as soon as the diagnosis is confirmed.

Despite the use of DMARDs, whether there is an increased incidence of rhinosinusitis is unclear. A US database suggests that there is no more sinus disease in RA patients than in patients with osteoarthritis or fibromyalgia [67]. However, a 1999 Dutch study showed sinusitis was more prevalent than in controls [68]. While immune modulation with antitumor necrosis factor biologics has brought the goal of remission into management, of concern is the report of six cases of sinus aspergilloma in 550 patients in a 2009 French study [69].

Behcet's Disease

General Description

Behcet's disease was first reported in 1937 by the Turkish physician Hulusi Behcet. But the clinical disease has been described in ancient medical texts. Behcet's disease has a higher incidence in the Mediterranean basin, between the latitudes of 30° and 45° north. The disease predominantly affects males, and the mean age at onset is between 20 and 50 years of life. It is uncommon in children. There is a higher incidence among family members although no consistent pattern of inheritance has been identified.

Clinical Overview

Behcet's syndrome is characterized by recurrent orogenital mucocutaneous ulcerations complicated by eye symptoms, skin lesions, arthritis, neurological disease, gastrointestinal disease, and vascular lesions. It is often associated with pathergy (minor trauma such as a bump or bruise leads to the development of skin lesions or ulcers that may be resistant to healing), especially in the Middle Eastern population [70]. There are geographic differences in the prevalence (highest in the Eastern Mediterranean) and organ system involvement [71]. Because it appears to be more common in the Middle East and central Asia, it became known also as Silk Road disease. Other synonyms include Morbus Behcet disease, Adamantiades syndrome, and Adamantiades–Behcet's syndrome. A necrotizing rhinosinusitis has been rarely reported [72].

The criteria used for the diagnosis of Behcet's syndrome include recurrent oral ulcerations with three or more physician-documented occurrences of minor aphthous, major aphthous, or herpetiform ulcerations in a 12-month period. Minor criteria for diagnosis are shown in Table 15.4 [73].

The presence of an autoantibody has been elusive, although there have been reports of anticardiolipin antibody and anti-endothelial antibodies. Other autoantibodies described in Behcet's disease include antibodies to heat shock proteins and *Saccharomyces cerevisiae*. The presence of these antibodies does not indicate pathogenesis. Moreover, because the presence of a specific autoantibody is far from pathognomonic for this disease, the diagnosis is based primarily on history and physical examination, as indicated by the criteria in Table 15.4. Histological findings consistent with a vasculitis may be seen on biopsy, but again there is no pathognomonic histological finding. The eyes and joints are frequently involved, but the disease usually takes a rather insidious course, whereby the earliest indication is the presence of recurrent oral ulcers. Oral ulcers then progress to eye and skin involvement and eventually the patient experiences genital ulcers as well. Because of the insidious nature, the delay in diagnosis can be as long as a mean time of 6 years. Vasculitis and nervous system signs are usually late manifestations. The gastrointestinal tract can be involved as well, with intestinal ulcers mainly targeting the terminal ileum and colon.

Genetic Associations

An association with HLA-B*51 has been reported in patients of Turkish or Asian origin [74, 75]. This is less strong in the Caucasian populations. The most common alleles that are associated with Behcet's appear to be HLA-B*5101 and HLA-B*5108 [76]. A recent association with HLA-B*57 has been reported in Caucasian populations [77]. Whether or not these alleles are directly related to an increased susceptibility to disease is unknown. Other genetic polymorphisms have been described, including a susceptibility locus on chromosome 6.

Sinus Disease

Sinus disease has been reported to occur in Behcet's disease. However, it is rare in Behcet's. One report attributed sinusitis to Behcet's in a patient in whom granulomatosis with polyangiitis was excluded [72].

Pathogenesis

The pathogenesis of Behcet's disease is unknown. It is characterized as a small-vessel vasculitis. It is believed that the vasculitis is the underlying pathology leading to the ocular, oral, and genital manifestations. Other visceral manifestations such as gastrointestinal, pulmonary, cardiovascular, musculoskeletal, and neurological may also be attributed to a vasculitis. The ulcerative lesions of Behcet's are characterized by a lymphocytic and mononuclear infiltration, with surrounding necrosis. Fibrin deposition in the vessel walls is a variable feature. Neutrophilic infiltration can also be seen early on in the disease.

Diagnosis

The diagnosis is based on the criteria of the International Behcet's Study Group (Table 15.4). Monitoring of the disease is based on clinical severity and recurrences. There is no known biomarker that correlates with disease severity. The differential diagnosis includes viral infections (especially herpes simplex infections), periodic fever syndromes, drug reactions, and other non-IgE-mediated immunologic reactions.

The workup for Behcet's disease should be initiated promptly upon suspicion of the disease because optic nerve involvement may lead to blindness which is a major morbidity of the disease. The workup should include referral to an ophthalmologist for a complete ophthalmologic examination to assess the presence of uveitis. MRI may be helpful in defining optic nerve inflammation. Evaluation of the cerebrospinal fluid may indicate increased protein and variable cellular infiltrate. Angiography may be helpful in evaluating CNS involvement. Laboratory studies should include the evaluation of inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein.

Prognosis and Treatment

There is no cure for Behcet's disease. The treatment of Behcet's disease includes the use of corticosteroids and other immunosuppressive agents, nonsteroidal anti-inflammatory agents, and colchicine. Corticosteroid eye drops can be used to treat acute anterior uveitis. Posterior uveitis requires the use of corticosteroid injections. Newer biologic modulators have also been used to treat Behcet's. A list of medications that have been used in Behcet's is shown in Table 15.5.

Systemic Lupus Erythematosus

General Description

Systemic lupus erythematosus (SLE) is an autoimmune disease associated with antibodies to nuclear factors, most notably DNA. SLE may affect every organ system and may be life-threatening. An increased risk for infection has been long known and documented in a study of 200 SLE patients in 2001, wherein 32 % had infections during a duration of 22 months of follow-up. Two patients had bacterial upper respiratory tract infections (not further specified) with active disease and renal

Table 15.5 Potential medications used in the treatment of Behcet's disease

Medication	Class	Mechanism of action in Behcet's disease	Comments and role in Behcet's
Acyclovir	Antiviral	Unknown	No evidence of efficacy in Behcet's
Anti-CD52	Monoclonal antibody, CAMPATH-1 against CD52	CD52 may be an anti-adhesion molecule	Has history of use in autoimmune diseases and malignancies
Azathioprine	Purine analogue	Immunosuppressive	2.5 mg/kg/day improves prognosis and effective treatment for ocular symptoms [78, 79]
Chlorambucil	Nitrogen mustard alkylating agent	Immunosuppressive	Previously widely used in Behcet's, but significant toxicity
Colchicine	Inhibitor of mitosis	Inhibits microtubule polymerization, inhibits neutrophil migration	1–2 mg/day improves some features of Behcet's [80–82]
Corticosteroids	Steroid hormone	Immunosuppressive, inhibitor of protein synthesis, DNA-altering activity	Mainstay of therapy at current time
Cyclophosphamide	Nitrogen mustard alkylating agent	Immunosuppressive agent	May be useful in uveitis, but significant side effects exist [83]
Cyclosporine	Calcineurin inhibitor	Immunosuppressive	Mainstay of therapy; beneficial effect on mucocutaneous features of disease; be careful with patients who have neurological features as it may worsen these [84–89]
Dapsone	Antibacterial, antimycobacterial	Modifies neutrophil chemotaxis and inhibits myeloperoxidase activity, also acts as an antioxidant	100 mg daily is associated with improvement in orogenital ulcers, but may have side effects including methemoglobinemia, agranulocytosis and hemolysis [90, 91]
Etanercept	Anti-TNF fusion drug	Inhibits TNFα, immunosuppressive	Few case studies have shown efficacy in Behcet's
Infliximab	Monoclonal antibody to TNF	Inhibits TNFα, immunosuppressive	In many autoimmune diseases, response may be better than etanercept. Not clear if this is the case in Behcet's [92–94]
Interferon-α	Cytokine	Immunoregulatory agent	One randomized controlled trial showed reduction in severity of ulcers, articular disease, and ocular disease [95–99]
Methotrexate	Antimetabolite, antifolate	Immunosuppressant	For neurological manifestations [100, 101]
Mycophenolate mofetil	Reversible inhibitor of inosine monophosphate dehydrogenase	T- and B-cell suppression	Steroid-sparing agent, used in Behcet's controversial [102, 103]
NSAID	Nonsteroidal anti-inflammatory agents	Anti-inflammatory	No evidence of efficacy in treating arthritis associated with Behcet's
Penicillin	Beta-lactam antibiotic	Treats potential bacterial involvement in Behcet's	Anecdotal use [104, 105]
Pentoxifylline	Xanthine derivative	Anti-TNF activity Inhibits free radical synthesis, inhibits perforin, suppresses CD8+ lymphocyte proliferation, inhibition of pro-inflammatory cytokines	Used for orogenital ulcerations in Behcet's disease [106–108]
Sulfasalazine	Sulfa drug	Anti-inflammatory or antibacterial	Used in treatment of gastrointestinal symptoms
Tacrolimus	Calcineurin inhibitor	Immunosuppressive	Used to treat refractory posterior uveitis. Different side effect profile from cyclosporine may affect choice of drugs from this class [109]
Thalidomide	Antinausea and sedative drug	Intercalating agent, downregulates TNF synthesis	Significant teratogenic side effects, limited use in Behcet's [110–112]
Warfarin	Anticoagulant	Prevents thrombosis and embolic events associated with Behcet's	No standardized protocol for use

involvement prominent risk factors for all infections [113]. An older study reporting results of imaging (MRI/CT) studies done on 21 patients with a variety of neurological symptoms showed evidence of sinusitis in two patients, both who complained of headaches. The added risk of immunosuppressive therapy is not fully clear [114]. Additional information on the sinus manifestations of other autoimmune diseases can be found in Chap. 9.

Sarcoidosis

General Description

Sarcoidosis is a multisystem noncaseating granulomatous disease of unknown etiology (Fig. 15.7). Sarcoidosis is characterized by a compartmentalization of CD4+ T helper 1 (Th1) lymphocytes and activated monocyte/macrophages within involved organs, including the airway, lymph nodes, and skin [115]. Most cases involve the airway but the disease process may be diffuse [116]. In approximately 60 % of patients, the disease spontaneously resolves without serious sequelae [117]. However, in some subjects, the persistence of the antigenic stimulus favors a chronic inflammatory state resulting in granuloma formation in various organs (including the respiratory tract) and an evolution towards fibrosis.

Pathogenesis

At its most basic level, a granuloma is a compact, organized aggregate of mature macrophages that arises in response to a persistent stimulus [118]. Mature macrophages are characterized by their increased cytoplasmic size and larger numbers of organelles, and by their ruffled cell membranes, which are thought to render them more phagocytic and microbicidal [119]. Granuloma macrophages can undergo additional changes such as fusing into multinucleated giant cells or differentiating into foam cells, which are characterized by lipid accumulation. The consequences of these changes are not well understood [120, 121]. Many other cell types can populate the granuloma, such as neutrophils, dendritic cells, B and T cells, natural killer cells, fibroblasts, and cells that secrete extracellular matrix components [122].

Although the triggering stimulus remains unknown, the pathogenesis of sarcoidosis is orchestrated by a complex symphony of cytokines and chemokines. In the earliest phase, there is a local overproduction of Th1 cytokines, such as interleukin 2 (IL-2) and interferon-γ, associated with the high expression of macrophage-derived molecules such as IL-15, CXCL10, CXCL16, CCL57, and CCL20 [123–126]. Th17, a CD4+ effector T cell, has also been described as a key component of sarcoidosis [127]. Th17 cells release an array of cytokines, including proinflammatory cytokines, and have been incriminated in autoimmunity and Th1 chronic inflammatory diseases, such as psoriasis and inflammatory bowel diseases and lung fibrosis [128–130].

Clinical Overview

Sinonasal involvement in sarcoidosis is unusual. In general, sarcoidosis of the upper respiratory tract occurs in up to 18 % of patients with sarcoidosis and is more common in the nose than in the sinuses [131–133]. Estimates of the prevalence of granulomatous rhinosinusitis in patients with sarcoidosis and coexisting lupus pernio are greater than 50 %. Lupus pernio (LP) is the most characteristic cutaneous lesion in sarcoidosis. LP refers to the blue-violet-colored skin lesions seen on the nose, perioral area, mandible, ears, elbows, hands, fingers, and on the eyelids. Spiteri et al. diagnosed upper respiratory tract disease in 54 % of their LP patients. In 34 % of their patients whose nasal bone and sinus radiographs were available, some abnormality compatible with sarcoidosis was found [134]. In another report, definite or probable sinus involvement was seen in over half of the LP patients [135].

The published experience with sinonasal sarcoidosis consists of case reports supported by histopathologic studies of nasal mucosa and sinus tissue. The diagnosis of sinonasal sarcoidosis can be problematic because nasal granulomas may occur in a variety of conditions other than sarcoidosis, and the sarcoidosis-associated nasal obstruction may produce nongranulomatous bacterial sinusitis [136, 137]. Furthermore, nasal and sinus involvement in sarcoidosis have been reported to occur independently without pulmonary involvement adding to the diagnostic uncertainty with this disorder [133]. A failure to include isolated sarcoid sinonasal disease in the differential diagnosis of chronic rhinosinusitis can result in a delay in diagnosis which can lead to intractable symptoms from atrophic rhinosinusitis and other therapeutic misadventures.

In 1999, DeShazo et al. proposed three diagnostic criteria for sarcoid rhinosinusitis [138]. These criteria included both histopathologic and clinical features (Table 15.6). The proposed criteria were:

- Radiologic evidence of sinusitis—such as mucoperiosteal thickening or opacification of a sinus as detected by plain film, computed tomography scan, or magnetic resonance imaging
- Histopathologic confirmation of noncaseating granuloma in the sinus tissue supported by negative stains for fungus and acid-fast bacilli
- Negative serologic test results for syphilis and antineutrophil cytoplasmic antibodies
- No clinical evidence of other disease processes associated with granulomatous nasal and sinus inflammation

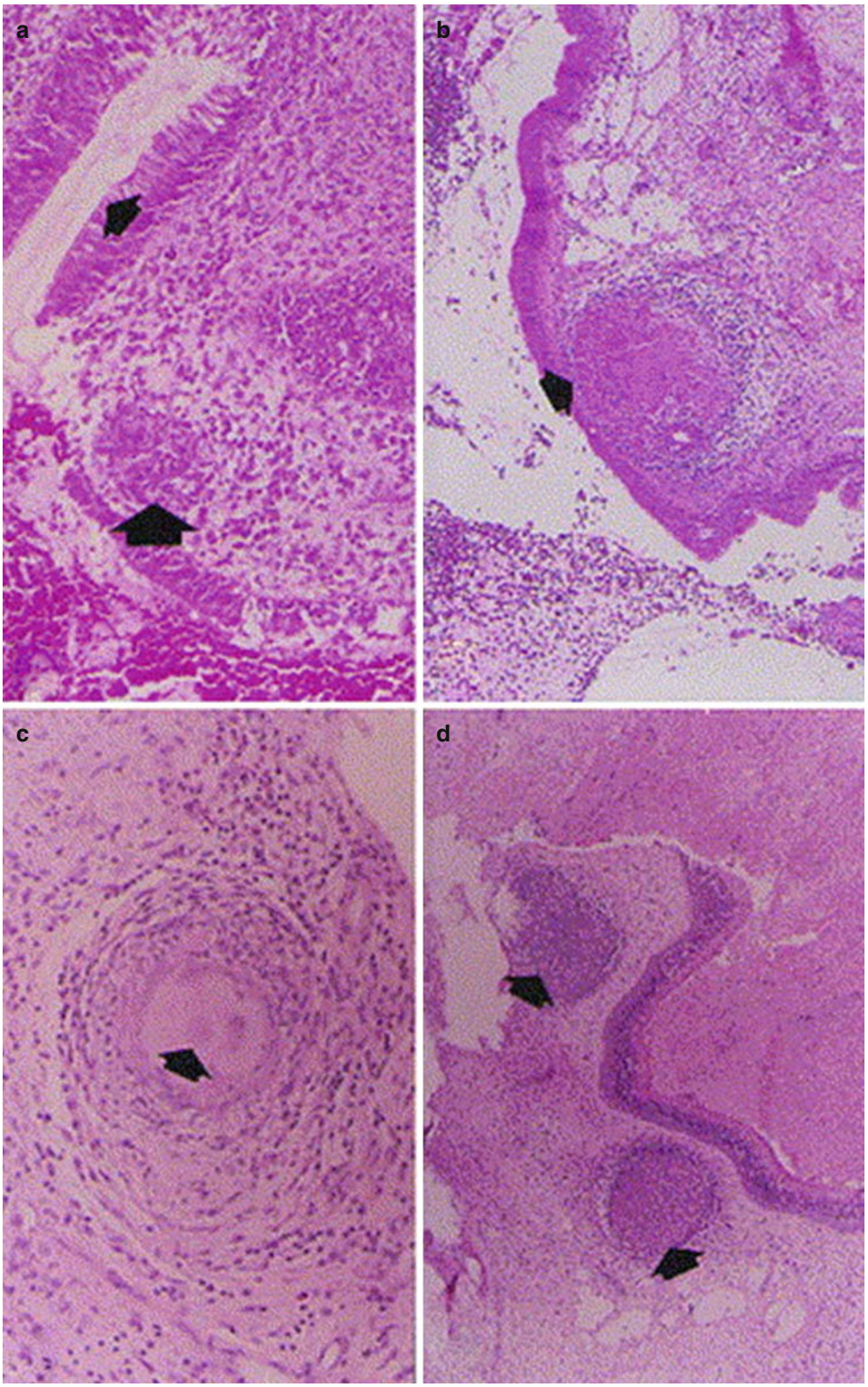


Fig. 15.7 (**a**–**c**) Endoscopic biopsy of left ethmoid sinus in patient 1 (**a**, **b**). The low-power panel (**b**) shows a fairly large granuloma with a Langhans-type giant cell (*arrow*) immediately abutting the respiratory epithelium of the sinus tissue. The higher-power panel (**a**) shows two discrete granulomas, one subepithelial (*large arrow*) and one slightly deeper, with a focally dense background of chronic inflammatory cells, predominantly plasma cells. Note cilia on the respiratory surface (*small arrow*). Endoscopic biopsy of left ethmoid sinus in patient 4 (low-power panel, **d**). Compared with the findings in patient 1, the granulomas (*arrows*) are more uniform and slightly deeper in the mucosa but equally discrete. The inflammatory infiltrate is also less dense. The Langhans-type giant cell (high-power panel, **c**) contains amorphous material (*arrow*) that did not change under polarized light (Reprinted with permission from DeShazo et al. [138])

Table 15.6 Summary of diagnostic criteria for sarcoid rhinosinusitis

1. Mucoperiosteal thickening or opacification of a sinus as detected by plain film, computed tomography scan, or magnetic resonance imaging
2. Histopathologic demonstration of noncaseating granuloma in material taken from the upper respiratory tract. Special stains for fungus and mycobacteria must have been negative, and no evidence of vasculitis or cholesterol crystals may be present
3. Data were required to exclude other disease processes associated with granulomatous inflammation, including tuberculosis, granulomatosis with polyangiitis, and fungal infection

Reprinted from Reed et al. [139]. With permission from Elsevier

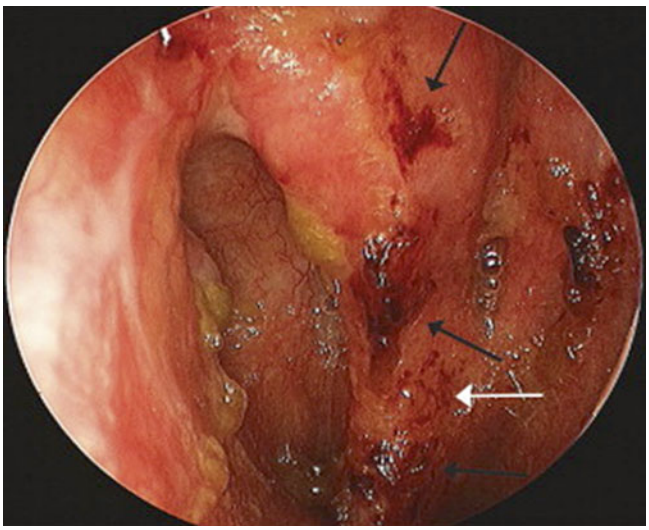


Fig. 15.8 Rhinoscopic findings in a patient in this study with long-standing sarcoidosis and secondary atrophic rhinosinusitis. Pertinent findings inlcude areas of bloody crusts surrounding areas of hemorrhage (*black arrows*) surrounded by hypertrophic mucosa (*white arrow*) (Reprinted with permission from Reed et al. [139])

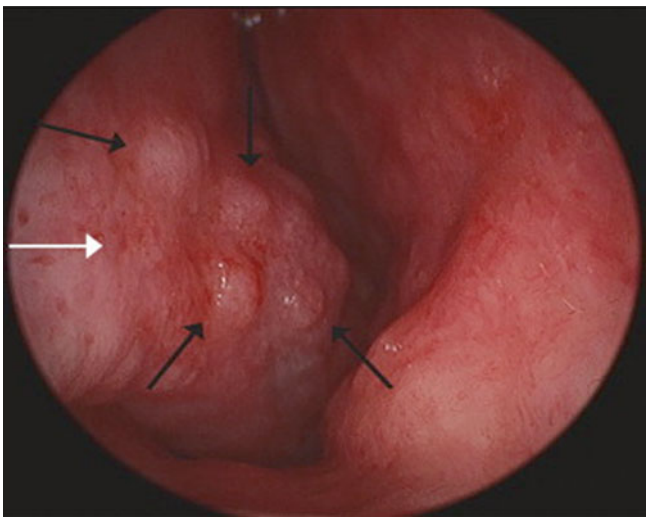


Fig. 15.9 Rhinoscopy findings in a patient with sarcoid rhinosinusitis in this study. Discrete nodules on the inferior turbinate (*black arrows*) are present on a granular mucosa (*white arrow*) that is a lighter shade of red than normal mucosa (Reprinted with permission from Reed et al. [139])

These authors found a close association between sinonasal sarcoidosis and nasal crusting, anosmia, and epistaxis. A false-positive diagnosis of sarcoid rhinosinusitis was not made (sensitivity 19 %, specificity 100 %) if a patient with chronic rhinosinusitis had two (2) signs/symptoms of nasal crusting, anosmia, or epistaxis. With chronic rhinosinusitis and one (1) sign/symptom of nasal crusting, anosmia, or epistaxis, sensitivity was 56 % and specificity was 90 %.

Rhinoscopic examination of patients with sinonasal sarcoidosis and crusting and/or epistaxis reveals changes seen in any form of atrophic rhinitis (Fig. 15.8). Rhinoscopic evaluation of patients without crusting or epistaxis often reveals discrete nodules on the inferior turbinates (Figs. 15.9 and 15.10). Biopsy of a nodule will reveal noncaseating granulomas consistent with the diagnosis of sarcoidosis (Fig. 15.11). CT scan substantiates the diagnosis of chronic rhinosinusitis (Fig. 15.12). At times, changes on CT can raise the suspicion of sarcoidosis if nodular lesions are observed (Fig. 15.13).

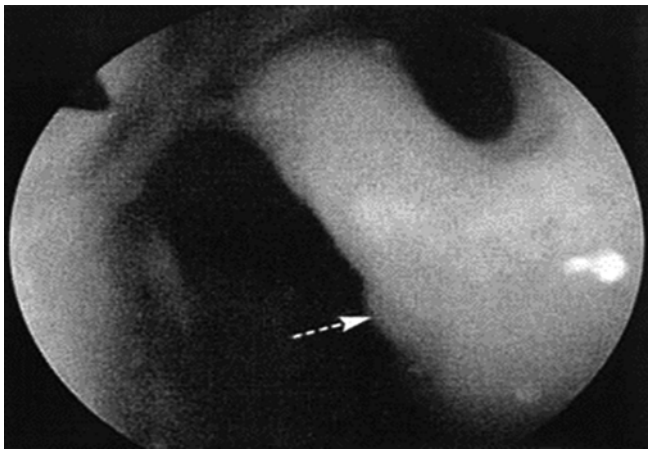


Fig. 15.10 Sarcoid nodule on inferior turbinate (Reprinted from Braun et al. [140]. With permission from Wiley & Sons)

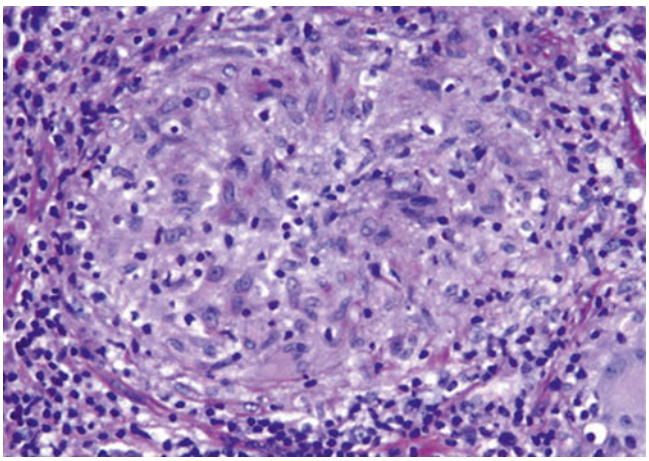


Fig. 15.11 Patients had areas of acute and chronic mononuclear cell mucosal inflammation. This photomicrograph shows a noncaseating granuloma consisting of an aggregate of epithelioid histiocytes surrounded (Reprinted with permission from Reed et al. [139])

Treatment

There have been no studies on the effectiveness of pharmacologic treatment in large series of patients with sarcoidosis of the upper airway. While many patients with sarcoidosis do not require therapy, there are a significant number who require long-term treatment. For most patients, corticosteroids represent the best initial treatment, either systemic or intralesional when critical organs are involved or when symptoms are severe. However, steroid-sparing agents have been increasingly useful for the long-term management of these patients despite the lack of standardized measures to assess such therapy in large randomized double-blind placebo-controlled trials. In chronic patients, immunosuppressive and cytotoxic drugs, such as methotrexate, azathioprine, and cyclophosphamide, have been used with variable success [115, 141, 142]. In patients with chronic refractory sarcoidosis, anti-cytokine agents that block TNF have been proposed. These therapies include pentoxifylline, thalidomide, and more recently infliximab, etanercept, and adalimumab [143–145]. Use of thalidomide is limited by its toxicity and more clinical control trials are necessary to confirm its efficacy [145]. Infliximab is a chimeric antibody, which specifically inhibits TNF alpha. Infliximab and other TNF-blocking agents have been successfully used in patients with persistent symptomatic sarcoidosis [144, 146, 147]. Sharma reported the effectiveness of antimalarial agents (such as chloroquine and hydroxychloroquine) in treating selected patients with sarcoidosis [148]. Surgery is useful for intranasal management of complications such as chronic rhinosinusitis and airway obstruction. However, septoplasty may be complicated by septal perforation.

Despite the lack of FDA-approved therapy for sarcoidosis, the introduction of powerful biologic agents which block cytokines, such as tumor necrosis factor, has expanded the options available for refractory cases. Newer biologic agents are being studied for this disease. As these drugs become more widely available and outcome measures for various disease phenotypes developed, we can expect better quality of life and treatment outcomes.

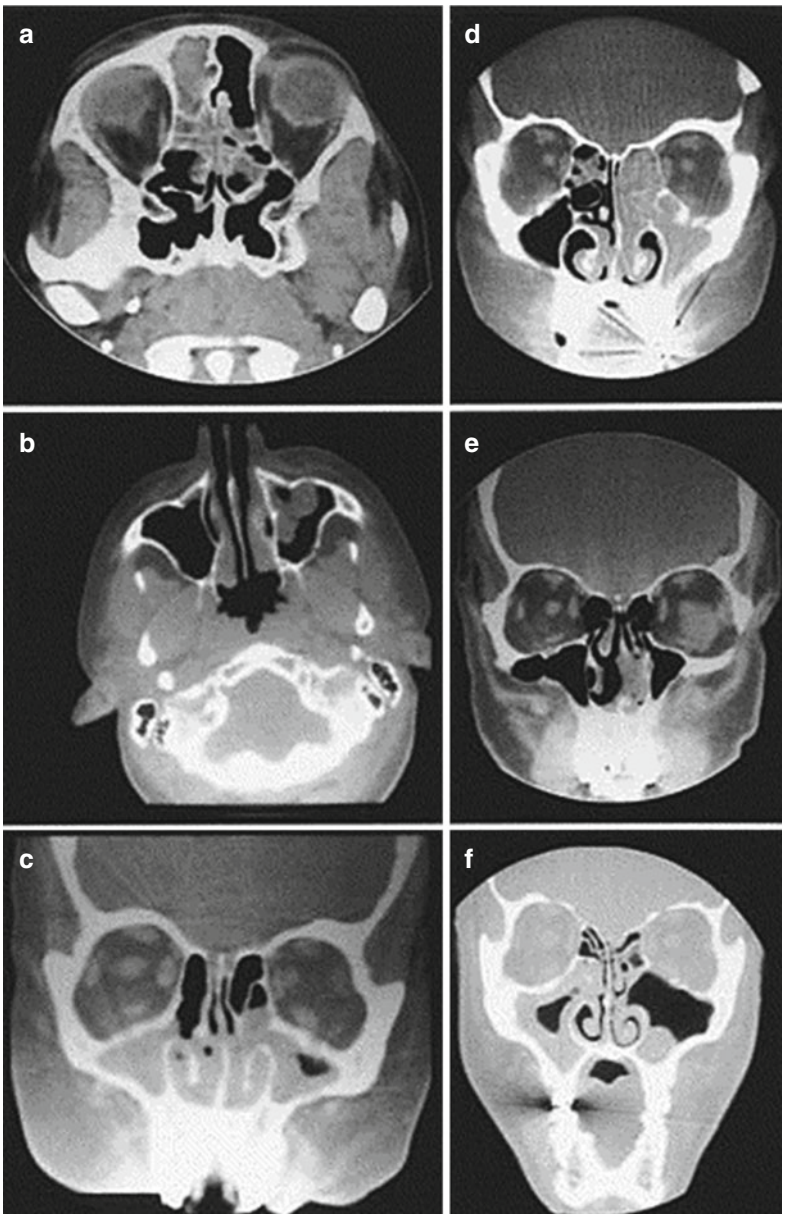


Fig. 15.12 Representative CT findings for our patients with sarcoidosis. (**a**) Axial view of patient 1 shows partial opacification of the right and left ethmoid air cells and mucosal thickening within both maxillary sinuses. (**b**) Axial view of patient 2 shows soft tissue mass in left maxillary sinus with bilateral thickening of the nasal turbinates. (**c**) Coronal view of patient 3 shows recurrence of disease after bilateral functional endoscopic sinus surgery, complete left and subtotal right maxillary sinus opacification with recurrent obstruction of both osteomeatal units, recurrent disease in residual right ethmoid air cells, and bilateral nasal obstruction from mucosal involvement. (**d**) Coronal view of patient 4 shows complete opacification of the left maxillary and ethmoid sinuses with subtotal opacification of the right ethmoid air cells and bilateral hypertrophy of the nasal turbinates. (**e**) Coronal view of patient 5 shows ongoing nasal disease after bilateral functional endoscopic sinus surgery and occlusion of left nasal passage resulting from nasal septal deviation and mucosal thickening of left middle and inferior turbinates. (**f**) Coronal view of patient 6 shows mucosal thickening in both maxillary sinuses with obstruction of the osteomeatal complexes bilaterally and bilateral opacification of ethmoid air cells (Reprinted from DeShazo et al. [138]. With permission from Mosby, Inc.)

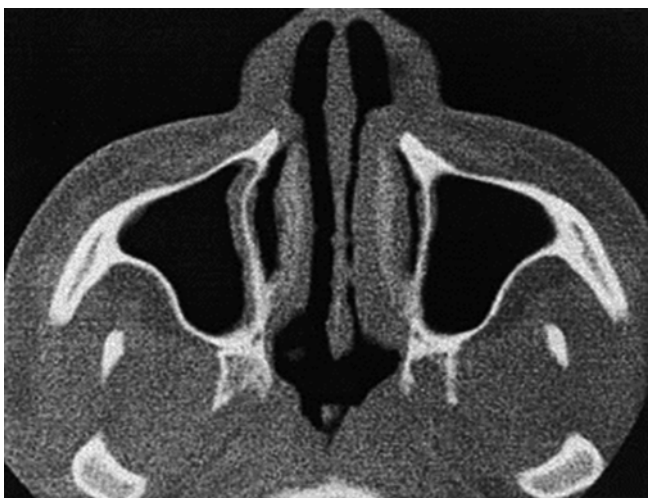


Fig. 15.13 Nasal sarcoidosis, axial computed tomography scan. Sarcoid granulomas on the nasal septum and inferior turbinates (Reprinted from Braun et al. [140]. With permission from Wiley & Sons)

Table 15.7 Differential diagnosis of antineutrophil cytoplasmic antibody-associated vasculitis

Another form of ANCA-associated vasculitis
Granulomatosis with polyangiitis, Churg–Strauss syndrome, microscopic polyangiitis, drug-induced ANCA-associated vasculitis, or renal-limited vasculitis
Another form of vasculitis. Typical vasculitic mimickers:
Polyarteritis nodosa, Henoch–Schönlein purpura, cryoglobulinemia, antiglomerular basement membrane disease
Systemic inflammatory disorders associated with autoimmunity
Systemic lupus erythematosus, sarcoidosis, inflammatory bowel disease, relapsing polychondritis
Infection
Endocarditis, sepsis, deep fungal infections, mycobacteria (Mycobacterium tuberculosis and Mycobacterium avium-intracellulare), actinomycosis, syphilis
Malignancy
Lymphomatoid granulomatosis, lymphoma, Castleman's disease, lung tumors
Hypereosinophilic disorders
Allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, eosinophilic gastroenteritis, eosinophilic fasciitis, hypereosinophilic syndrome, eosinophilic leukemia
Miscellaneous
Idiopathic pulmonary alveolar hemorrhage, illicit drug use (intranasal cocaine, smoking of crack)

Reprinted from Stone [10]. With permission from Springer, 2013
Abbreviation: *ANCA* antineutrophil cytoplasmic antibody

Idiopathic Midline Destructive Disease (IMDD)

Idiopathic midline destructive disease is a rare disease. It is characterized by a progressive course starting with pansinusitis and then extending to destruction of the midline structures of the upper respiratory tract including the nasal septum and the hard and soft palate. There is no systemic involvement. The lesions in both the nasal passages and the oropharyngeal and laryngotracheal areas are characterized by ulcerative, nonhealing lesions that progress to the development of holes in these structures. The erosion of the bony structures can lead to complications including extension into the bony orbit or Eustachian tube damage.

Pathology

The pathological features of IMDD include chronic inflammation with infiltrate of inflammatory cells including neutrophils, lymphocytes, monocytes, plasma cells, and histiocytes. Eosinophils are not usually seen. There is necrosis of the tissue with involvement of arterioles, but a granulomatous vasculitis is not part of this syndrome. Because secondary infection is common, cultures should be done when evaluating these patients.

Prognosis and Treatment

This is a frustrating disease because oftentimes the treatment used to arrest the progression of destruction of the paranasal sinuses and related structures is worse than the disease itself. The main forms of treatment include steroids, cytotoxic agents, and low-dose radiation therapy. Complications of radiation therapy include damage to the brainstem and the development of iatrogenic neoplastic diseases.

Differential Diagnosis of Sinusitis in Autoimmune Diseases

In most autoimmune diseases, sinus manifestations are not the only organ system involvement. Most autoimmune diseases are multisystem, though there are exceptions (e.g., IMDD). Given the multiorgan involvement, the differential diagnosis is broad especially if there is the possibility that each organ system involvement is due to a separate etiology. The differential diagnosis of autoimmune-related sinus disease is noted on Table 15.7.

The European Vasculitis Study (EUVAS) group has established a staging system for ANCA-associated vasculitis. They classify the disease into five stages: localized, early systemic, generalized, severe, and refractory. A description of each stage is shown in Table 15.8.

As discussed above, biopsies play a significant role in the evaluation of ANCA-associated vasculitides. The sensitivity of the biopsy depends on the tissue sampled. In autoimmune vasculitis, the various sites of involvement may be biopsied.

Table 15.8 European Vasculitis Study (EUVAS) disease categorization of anti-neutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis

Category	Definition	Serum creatinine
Localized	Upper and lower respiratory tract disease without any other systemic involvement or constitutional symptoms	
Early systemic	Any, without organ-threatening or life threatening disease	
Generalized	Renal or other organ threatening disease	<500 μmol/l (5.8 mg/dl)
Severe	Renal or other vital organ failure	>500 μmol/l (5.8 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide	

Adapted from Mukhytar et al. [26], with permission from BMJ Publishing Group, Ltd

Table 15.9 Tissue diagnostic yield in ANCA-associated vasculitis

Site of biopsy	Diagnostic yield (%)
Sinus	30
Nerve	55
Nerve and muscle	80
Lung	87
Renal	96

Reprinted from Miloslavsky [149]. With permission from John Wiley & Sons, Inc.

The sites are commonly the upper and lower airway (sinus and lungs), the kidney, the nervous system, and the skin. The yield of the biopsy as a function of site is illustrated in Table 15.9.

What are the clues that there is an autoimmune etiology in a patient with sinus disease? Many autoimmune diseases are systemic. If a patient presents with sinus disease but also gives a history of other organ system disease, then it is important to think about an autoimmune link. The tests with the highest yield in support of a suspicion of concurrent autoimmune-mediated sinus disease are the sedimentation rate and/or CRP and the measurement of ANCA (anti-proteinase 3 or anti-myeloperoxidase antibodies).

Summary and Conclusions

Sinus disease is a relative uncommon component of autoimmune diseases. The mechanisms that lead to the development of sinus disease as a manifestation of autoimmune disorders are not known. The factors that lead sinus disease in patients with autoimmune disease may include host immunologic factors, an environmental factor, or epigenetic factors that influence the expression of certain immune-related genes. Perhaps the most well-known association of sinus disease in autoimmunity occurs in the ANCA-positive vasculitides, granulomatosis with polyangiitis, Churg–Strauss syndrome, and microscopic polyangiitis. The role of autoantibodies in the pathogenesis is not entirely clear, but ANCA (specifically anti-proteinase 3) seems to be a relatively consistent feature of autoimmune sinusitis. But other non-ANCA-associated autoimmune diseases can also manifest with sinus pathology, and therefore, the approach to sinus disease should always include consideration of an autoimmune etiology. It is common that the diagnosis of autoimmune diseases such as GPA or AG is not made during the time when sinus disease presents alone, as there is no pathognomonic laboratory test that will identify these diseases. Other systemic involvement in these diseases affects the skin, lungs, and kidneys. Therefore, the diagnosis of autoimmune-related sinus disease is based on history with supportive objective testing, including markers of inflammation (erythrocyte sedimentation rate or C-reactive protein), detection of autoantibodies (ANCA, in particular), and the presence of urinary tract pathology (such as the presence of RBC casts reflecting glomerular pathology). Additional information can be gained by biopsy of the sinus and nasal structures. Granulomas or giant cells may support the diagnosis of autoimmune disease, but the absence of granulomas does not rule out the disease. Biopsies of other sites, as mentioned above, may be helpful as well.

References

1. Mackay IR. Travels and travails of autoimmunity: a historical journey from discovery to rediscovery. Autoimmun Rev. 2010;9:A251–8.
2. Edwards JC, Cambridge G, Abrahams VM. Do self-perpetuating B lymphocytes drive human autoimmune disease? Immunology. 1999;97:188–96.

3. Shlomchik MJ, Craft JE, Mamula MJ. From T to B and back again: positive feedback in systemic autoimmune disease. Nat Rev Immunol. 2001;1:147–53.
4. Tzioufas AG, Kapsogeorgou EK, Moutsopoulos HM. Pathogenesis of Sjogren's syndrome: what we know and what we should learn. J Autoimmun. 2012;39:4–8.
5. Martin F, Chan AC. Pathogenic roles of B cells in human autoimmunity; insights from the clinic. Immunity. 2004;20:517–27.
6. Edwards JC, Cambridge G. B-cell targeting in rheumatoid arthritis and other autoimmune diseases. Nat Rev Immunol. 2006;6:394–403.
7. Mackay F, Browning JL. BAFF: a fundamental survival factor for B cells nature reviews. Immunology. 2002;2(7):465–75.
8. Jennette JC. Nomenclature and classification of vasculitis: lessons learned from granulomatosis with polyangiitis (Wegener's granulomatosis). Clin Exp Immunol. 2011;164 Suppl 1:7–10.
9. Luqmani RA, Suppiah R, Grayson PC, Merkel PA, Watts R. Nomenclature and classification of vasculitis – update on the ACR/EULAR diagnosis and classification of vasculitis study (DCVAS). Clin Exp Immunol. 2011;164 Suppl 1:11–3.
10. Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides: Wegener's granulomatosis, microscopic polyangiitis and the Churg-Strauss syndrome. In: John H. Klippel, editor. Primer on the rheumatic diseases. 13th ed. New York: Springer; 2008.
11. Sorensen SF, Slot O, Tvede N, Petersen J. A prospective study of vasculitis patients collected in a five year period: evaluation of the Chapel Hill nomenclature. Ann Rheum Dis. 2000;59:478–82.
12. Mohammad AJ, Jacobsson LT, Mahr AD, Sturfelt G, Segelmark M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford). 2007;46:1329–37.
13. Ntatsaki E, Watts RA, Scott DG. Epidemiology of ANCA-associated vasculitis. Rheum Dis Clin North Am. 2010;36:447–61.
14. Hoffman GS, Drucker Y, Cotch MF, Locker GA, Easley K, Kwoh K. Wegener's granulomatosis: patient-reported effects of disease on health, function, and income. Arthritis Rheum. 1998;41:2257–62.
15. Fujimoto S, Watts RA, Kobayashi S, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. Rheumatology (Oxford). 2011;50:1916–20.
16. Holle JU, Laudien M, Gross WL. Clinical manifestations and treatment of Wegener's granulomatosis. Rheum Dis Clin North Am. 2010;36:507–26.
17. Baldini C, Talarico R, Della Rossa A, Bombardieri S. Clinical manifestations and treatment of Churg-Strauss syndrome. Rheum Dis Clin North Am. 2010;36:527–43.
18. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 1999;42:421–30.
19. Sinico RA, Bottero P. Churg-Strauss angiitis. Best Pract Res Clin Rheumatol. 2009;23:355–66.
20. Cannady SB, Batra PS, Koening C, et al. Sinonasal Wegener granulomatosis: a single-institution experience with 120 cases. Laryngoscope. 2009;119:757–61.
21. Takwoingi YM, Dempster JH. Wegener's granulomatosis: an analysis of 33 patients seen over a 10-year period. Clin Otolaryngol Allied Sci. 2003;28:187–94.
22. Akikusa JD, Schneider R, Harvey EA, et al. Clinical features and outcome of pediatric Wegener's granulomatosis. Arthritis Rheum. 2007;57:837–44.
23. Kallenberg CG. Pathogenesis of ANCA-associated vasculitides. Ann Rheum Dis. 2011;70 Suppl 1:i59–63.
24. van Timmeren MM, Heeringa P. Pathogenesis of ANCA-associated vasculitis: recent insights from animal models. Curr Opin Rheumatol. 2012;24:8–14.
25. Rutgers A, Kallenberg CG. Refractory disease in antineutrophil cytoplasmic antibodies associated vasculitis. Curr Opin Rheumatol. 2012;24:245–51.
26. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310–7.
27. Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. Lancet. 2003;361:587–94.
28. Strauss L, Churg J, Zak FG. Cutaneous lesions of allergic granulomatosis; a histopathologic study. J Invest Dermatol. 1951;17:349–59.
29. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol. 1951;27:277–301.
30. Davies DJ, Moran JE, Niall JF, Ryan GB. Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? Br Med J (Clin Res Ed). 1982;285:606.
31. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11.
32. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore). 1984;63:65–81.
33. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33:1094–100.
34. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. Allergy. 2013;68:261–73.
35. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37:187–92.
36. Olsen KD, Neel 3rd HB, Deremee RA, Weiland LH. Nasal manifestations of allergic granulomatosis and angiitis (Churg-Strauss syndrome). Otolaryngol Head Neck Surg (1979). 1980;88:85–9.
37. Solans R, Bosch JA, Perez-Bocanegra C, et al. Churg-Strauss syndrome: outcome and long-term follow-up of 32 patients. Rheumatology (Oxford). 2001;40:763–71.
38. Bacciu A, Bacciu S, Mercante G, et al. Ear, nose and throat manifestations of Churg-Strauss syndrome. Acta Otolaryngol. 2006;126:503–9.
39. Vaglio A, Martorana D, Maggiore U, et al. HLA-DRB4 as a genetic risk factor for Churg-Strauss syndrome. Arthritis Rheum. 2007;56:3159–66.
40. Wieczorek S, Hellmich B, Gross WL, Epplen JT. Associations of Churg-Strauss syndrome with the HLA-DRB1 locus, and relationship to the genetics of antineutrophil cytoplasmic antibody-associated vasculitides: comment on the article by Vaglio et al. Arthritis Rheum. 2008;58:329–30.

41. Lane SE, Watts RA, Bentham G, Innes NJ, Scott DG. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum. 2003;48:814–23.
42. Lilly CM, Churg A, Lazarovich M, et al. Asthma therapies and Churg-Strauss syndrome. J Allergy Clin Immunol. 2002;109:S1–19.
43. Furuta S, Jayne DR. Antineutrophil cytoplasm antibody-associated vasculitis: recent developments. Kidney Int. 2013;84(2):244–9. doi:10.1038/ki.2013.24.
44. Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum. 2005;52:2926–35.
45. Healy B, Bibby S, Steele R, Weatherall M, Nelson H, Beasley R. Antineutrophil cytoplasmic autoantibodies and myeloperoxidase autoantibodies in clinical expression of Churg-Strauss syndrome. J Allergy Clin Immunol. 2013;131:571–6.e6.
46. Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. Curr Opin Rheumatol. 2007;19:25–32.
47. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore). 2011;90:19–27.
48. Ribi C, Cohen P, Pagnoux C, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis Rheum. 2008;58:586–94.
49. Moosig F, Bremer JP, Hellmich B, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. Ann Rheum Dis. 2013;72(6):1011–7.
50. Danieli MG, Cappelli M, Malcangi G, Logullo F, Salvi A, Danieli G. Long term effectiveness of intravenous immunoglobulin in Churg-Strauss syndrome. Ann Rheum Dis. 2004;63:1649–54.
51. Tatsis E, Schnabel A, Gross WL. Interferon-alpha treatment of four patients with the Churg-Strauss syndrome. Ann Intern Med. 1998;129:370–4.
52. Metzler C, Csernok E, Gross WL, Hellmich B. Interferon-alpha for maintenance of remission in Churg-Strauss syndrome: a long-term observational study. Clin Exp Rheumatol. 2010;28:24–30.
53. Puéchal X, Rivereau P, Vinchon F. Churg Strauss syndrome associated with omalizumab. Eur J Intern Med. 2008;19:364–6.
54. Giavina Bianchi P, Giavina Bianchi M, Agondi R, Kalil J. Omalizumab and Churg Strauss syndrome. J Allergy Clin Immunol. 2008;122:217.
55. Spina MF, Miadonna A. Role of omalizumab and steroids in Churg-Strauss syndrome. J Allergy Clin Immunol. 2009;124(3):600–1.
56. Lau EM, Cooper W, Bye PT, Yan K. Difficult asthma and Churg-Strauss-like syndrome: a cautionary tale. Respirology. 2011;16(1):180–1.
57. Corren J. Anti-interleukin-5 antibody therapy in asthma and allergies. Curr Opin Allergy Clin Immunol. 2011;11:565–70.
58. Chung SA, Seo P. Microscopic polyangiitis. Rheum Dis Clin North Am. 2010;36:545–58.
59. Naguwa SM, Gershwin ME. Sjogren's syndrome. In: Goldman L, Ausiello D, editors. Cecil medicine. 23rd ed. Philadelphia: Saunders; 2007.
60. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken). 2012;64:475–87.
61. Takeuchi K, Sakakura Y, Murai S, Majima Y. Nasal mucociliary clearance in Sjogren's syndrome. Dissociation in flow between sol and gel layers. Acta Otolaryngol. 1989;108:126–9.
62. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjogren's Syndrome. Arthritis Rheum. 1999;42:1765–72.
63. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjogren's syndrome. J Autoimmun. 2010;34:400–7.
64. Mackay F, Schneider P, Rennert P, Browning J. BAFF AND APRIL: a tutorial on B cell survival. Annu Rev Immunol. 2003;21:231–64.
65. Mackay F, Sierro F, Grey ST, Gordon TP. The BAFF/APRIL system: an important player in systemic rheumatic diseases. Curr Dir Autoimmun. 2005;8:243–65.
66. Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol. 2009;9:491–502.
67. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol. 2006;33:2412–5.
68. Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos G. Comorbidity in patients with rheumatoid arthritis: effect on health-related quality of life. J Rheumatol. 2004;31:58–65.
69. Leboime A, Berthelot JM, Allanore Y, et al. Sinus aspergilloma in rheumatoid arthritis before or during tumor necrosis factor-alpha antagonist therapy. Arthritis Res Ther. 2009;11:R164.
70. Yazici H, Tuzun Y, Pazarli H, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behcet's syndrome. Ann Rheum Dis. 1984;43:783–9.
71. Yurdakul S, Yazici H. Behcet's syndrome. Best Pract Res Clin Rheumatol. 2008;22:793–809.
72. Martins HM, Santos S, Lourenco JF, Araujo JA. Destructive sinusopathy and middle ear involvement in Behcet's syndrome. A case report. Adv Exp Med Biol. 2003;528:473–5.
73. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990;335:1078–80.
74. Ohno S, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Aizawa M. Close association of HLA-Bw51 with Behcet's disease. Arch Ophthalmol. 1982;100:1455–8.
75. Verity DH, Marr JE, Ohno S, Wallace GR, Stanford MR. Behcet's disease, the Silk Road and HLA-B51: historical and geographical perspectives. Tissue Antigens. 1999;54:213–20.
76. Kotter I, Gunaydin I, Stubiger N, et al. Comparative analysis of the association of HLA-B*51 suballeles with Behcet's disease in patients of German and Turkish origin. Tissue Antigens. 2001;58:166–70.
77. Ahmad T, Wallace GR, James T, et al. Mapping the HLA association in Behcet's disease: a role for tumor necrosis factor polymorphisms? Arthritis Rheum. 2003;48:807–13.
78. Yazici H, Pazarli H, Barnes CG, et al. A controlled trial of azathioprine in Behcet's syndrome. N Engl J Med. 1990;322:281–5.
79. Hamuryudan V, Ozyazgan Y, Hizli N, et al. Azathioprine in Behcet's syndrome: effects on long-term prognosis. Arthritis Rheum. 1997;40:769–74.
80. Greenwood AJ, Stanford MR, Graham EM. The role of azathioprine in the management of retinal vasculitis. Eye (Lond). 1998;12(Pt 5):783–8.
81. Aktulga E, Altac M, Muftuoglu A, et al. A double blind study of colchicine in Behcet's disease. Haematologica. 1980;65:399–402.

82. Yurdakul S, Mat C, Tuzun Y, et al. A double-blind trial of colchicine in Behcet's syndrome. Arthritis Rheum. 2001;44:2686–92.
83. Matsumura N, Mizushima Y. Leucocyte movement and colchicine treatment in Behcet's disease. Lancet. 1975;2:813.
84. Ozyazgan Y, Yurdakul S, Yazici H, et al. Low dose cyclosporin A versus pulsed cyclophosphamide in Behcet's syndrome: a single masked trial. Br J Ophthalmol. 1992;76:241–3.
85. Whitcup SM, Salvo Jr EC, Nussenblatt RB. Combined cyclosporine and corticosteroid therapy for sight-threatening uveitis in Behcet's disease. Am J Ophthalmol. 1994;118:39–45.
86. Binder AI, Graham EM, Sanders MD, Dinning W, James DG, Denman AM. Cyclosporin A in the treatment of severe Behcet's uveitis. Br J Rheumatol. 1987;26:285–91.
87. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behcet's disease. Lancet. 1989;1:1093–6.
88. Fujino Y, Joko S, Masuda K, et al. Cyclosporine microemulsion preconcentrate treatment of patients with Behcet's disease. Jpn J Ophthalmol. 1999;43:318–26.
89. Kotake S, Higashi K, Yoshikawa K, Sasamoto Y, Okamoto T, Matsuda H. Central nervous system symptoms in patients with Behcet disease receiving cyclosporine therapy. Ophthalmology. 1999;106:586–9.
90. Wolf R, Tuzun B, Tuzun Y. Dapsone: unapproved uses or indications. Clin Dermatol. 2000;18:37–53.
91. Sharquie KE, Najim RA, Abu-Raghif AR. Dapsone in Behcet's disease: a double-blind, placebo-controlled, cross-over study. J Dermatol. 2002;29:267–79.
92. Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behcet's disease. Lancet. 2001;358:295–6.
93. Estrach C, Mpofu S, Moots RJ. Behcet's syndrome: response to infliximab after failure of etanercept. Rheumatology (Oxford). 2002;41:1213–4.
94. Sfikakis PP. Behcet's disease: a new target for anti-tumour necrosis factor treatment. Ann Rheum Dis. 2002;61 Suppl 2:ii51–3.
95. Azizlerli G, Sarica R, Kose A, et al. Interferon alfa-2a in the treatment of Behcet's disease. Dermatology. 1996;192:239–41.
96. O'Duffy JD, Calamia K, Cohen S, et al. Interferon-alpha treatment of Behcet's disease. J Rheumatol. 1998;25:1938–44.
97. Georgiou S, Monastirli A, Pasmatzi E, Gartaganis S, Goerz G, Tsambaos D. Efficacy and safety of systemic recombinant interferon-alpha in Behcet's disease. J Intern Med. 1998;243:367–72.
98. Demiroglu H. Behcet's disease and interferon: flaws in research integrity of randomized trial. Lancet. 2000;356:1351–2.
99. Demiroglu H, Ozcebe OI, Barista I, Dundar S, Eldem B. Interferon alfa-2b, colchicine, and benzathine penicillin versus colchicine and benzathine penicillin in Behcet's disease: a randomised trial. Lancet. 2000;355:605–9.
100. Hirohata S, Suda H, Hashimoto T. Low-dose weekly methotrexate for progressive neuropsychiatric manifestations in Behcet's disease. J Neurol Sci. 1998;159:181–5.
101. Jorizzo JL, White WL, Wise CM, Zanolli MD, Sherertz EF. Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behcet's disease. J Am Acad Dermatol. 1991;24:973–8.
102. Adler YD, Mansmann U, Zouboulis CC. Mycophenolate mofetil is ineffective in the treatment of mucocutaneous Adamantiades-Behcet's disease. Dermatology. 2001;203:322–4.
103. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med. 2000;343:1156–62.
104. Calguneri M, Kiraz S, Ertenli I, Benekli M, Karaarslan Y, Celik I. The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behcet's disease. A randomized clinical trial. Arthritis Rheum. 1996;39:2062–5.
105. Calguneri M, Ertenli I, Kiraz S, Erman M, Celik I. Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behcet's disease. Dermatology. 1996;192:125–8.
106. Windmeier C, Gressner AM. Pharmacological aspects of pentoxifylline with emphasis on its inhibitory actions on hepatic fibrogenesis. Gen Pharmacol. 1997;29:181–96.
107. Gan XH, Robin JP, Huerta JM, Braquet P, Bonavida B. Inhibition of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1 beta) secretion but not IL-6 from activated human peripheral blood monocytes by a new synthetic demethylpodophyllotoxin derivative. J Clin Immunol. 1994;14:280–8.
108. Lazarczyk M, Grzela T, Korczak-Kowalska G, et al. Pentoxifylline inhibits perforin-dependent natural cytotoxicity in vitro. Oncol Rep. 2002;9:423–6.
109. Kilmartin DJ, Forrester JV, Dick AD. Tacrolimus (FK506) in failed cyclosporin A therapy in endogenous posterior uveitis. Ocul Immunol Inflamm. 1998;6:101–9.
110. Revuz J, Guillaume JC, Janier M, et al. Crossover study of thalidomide vs placebo in severe recurrent aphthous stomatitis. Arch Dermatol. 1990;126:923–7.
111. Hamuryudan V, Mat C, Saip S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behcet syndrome. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998;128:443–50.
112. Powell RJ. New roles for thalidomide. BMJ. 1996;313:377–8.
113. Zonana-Nacach A, Camargo-Coronel A, Yanez P, Sanchez L, Jimenez-Balderas FJ, Fraga A. Infections in outpatients with systemic lupus erythematosus: a prospective study. Lupus. 2001;10:505–10.
114. Sibbitt Jr WL, Sibbitt RR, Griffey RH, Eckel C, Bankhurst AD. Magnetic resonance and computed tomographic imaging in the evaluation of acute neuropsychiatric disease in systemic lupus erythematosus. Ann Rheum Dis. 1989;48:1014–22.
115. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet. 2003;361:1111–8.
116. Rybicki BA, Iannuzzi MC, Frederick MM, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). Am J Respir Crit Care Med. 2001;164:2085–91.
117. Semenzato G, Adami F, Maschio N, Agostini C. Immune mechanisms in interstitial lung diseases. Allergy. 2000;55:1103–20.
118. Williams GT, Williams WJ. Granulomatous inflammation–a review. J Clin Pathol. 1983;36:723–33.

119. Bouley DM, Ghori N, Mercer KL, Falkow S, Ramakrishnan L. Dynamic nature of host-pathogen interactions in Mycobacterium marinum granulomas. Infect Immun. 2001;69:7820–31.
120. Russell DG, Cardona PJ, Kim MJ, Allain S, Altare F. Foamy macrophages and the progression of the human tuberculosis granuloma. Nat Immunol. 2009;10:943–8.
121. Helming L, Gordon S. The molecular basis of macrophage fusion. Immunobiology. 2007;212:785–93.
122. Hunter RL. On the pathogenesis of post primary tuberculosis: the role of bronchial obstruction in the pathogenesis of cavities. Tuberculosis (Edinb). 2011;91 Suppl 1:S6–10.
123. Agostini C, Trentin L, Perin A, et al. Regulation of alveolar macrophage-T cell interactions during Th1-type sarcoid inflammatory process. Am J Physiol. 1999;277:L240–50.
124. Agostini C, Cabrelle A, Calabrese F, et al. Role for CXCR6 and its ligand CXCL16 in the pathogenesis of T-cell alveolitis in sarcoidosis. Am J Respir Crit Care Med. 2005;172:1290–8.
125. Vasakova M, Sterclova M, Kolesar L, et al. Bronchoalveolar lavage fluid cellular characteristics, functional parameters and cytokine and chemokine levels in interstitial lung diseases. Scand J Immunol. 2009;69:268–74.
126. Facco M, Baesso I, Miorin M, et al. Expression and role of CCR6/CCL20 chemokine axis in pulmonary sarcoidosis. J Leukoc Biol. 2007;82:946–55.
127. Facco M, Cabrelle A, Teramo A, et al. Sarcoidosis is a Th1/Th17 multisystem disorder. Thorax. 2011;66:144–50.
128. Romagnani S, Maggi E, Liotta F, Cosmi L, Annunziato F. Properties and origin of human Th17 cells. Mol Immunol. 2009;47:3–7.
129. Kleinschek MA, Boniface K, Sadekova S, et al. Circulating and gut-resident human Th17 cells express CD161 and promote intestinal inflammation. J Exp Med. 2009;206:525–34.
130. Tesmer LA, Lundy SK, Sarkar S, Fox DA. Th17 cells in human disease. Immunol Rev. 2008;223:87–113.
131. Lindsay JR, Perlman HB. Sarcoidosis of the upper respiratory tract. Ann Otol Rhinol Laryngol. 1951;60:549–66.
132. James DG. A comparison of Blau's syndrome and sarcoidosis. Sarcoidosis. 1994;11:100–1.
133. James DG. Upper respiratory tract. In: James DG, editor. Sarcoidosis and other granulomatous disorders. New York: Marcel Dekker, Inc; 1994. p. 417–21.
134. Spiteri MA, Matthey F, Gordon T, Carstairs LS, James DG. Lupus pernio: a clinico-radiological study of thirty-five cases. Br J Dermatol. 1985;112:315–22.
135. Baughman RP, Judson MA, Teirstein AS, Moller DR, Lower EE. Thalidomide for chronic sarcoidosis. Chest. 2002;122:227–32.
136. Coup AJ, Hopper IP. Granulomatous lesions in nasal biopsies. Histopathology. 1980;4:293–308.
137. Krespi YP, Kuriloff DB, Aner M. Sarcoidosis of the sinonasal tract: a new staging system. Otolaryngol Head Neck Surg. 1995;112:221–7.
138. DeShazo RD, O'Brien MM, Justice WK, Pitcock J. Diagnostic criteria for sarcoidosis of the sinuses. J Allergy Clin Immunol. 1999;103:789–95.
139. Reed J, deShazo RD, Houle TT, Stringer S, Wright L, Moak 3rd JS. Clinical features of sarcoid rhinosinusitis. Am J Med. 2010;123(9):856–62.
140. Braun JJ, Gentine A, Pauli G. Sinonasal sarcoidosis: review and report of fifteen cases. Laryngoscope. 2004;114:1960–3.
141. Sharma OP. Sarcoidosis of the upper respiratory tract. Selected cases emphasizing diagnostic and therapeutic difficulties. Sarcoidosis Vasc Diffuse Lung Dis. 2002;19:227–33.
142. Fazzi P. Pharmacotherapeutic management of pulmonary sarcoidosis. Am J Respir Med. 2003;2:311–20.
143. Zabel P, Entzian P, Dalhoff K, Schlaak M. Pentoxifylline in treatment of sarcoidosis. Am J Respir Crit Care Med. 1997;155:1665–9.
144. Milman N, Graudal N, Loft A, Mortensen J, Larsen J, Baslund B. Effect of the TNF-alpha inhibitor adalimumab in patients with recalcitrant sarcoidosis: a prospective observational study using FDG-PET. Clin Respir J. 2012;6:238–47.
145. Judson MA, Silvestri J, Hartung C, Byars T, Cox CE. The effect of thalidomide on corticosteroid-dependent pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2006;23:51–7.
146. Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respir Med. 2006;100:2053–9.
147. Belkhou A, Younsi R, El Bouchti I, El Hassani S. Rituximab as a treatment alternative in sarcoidosis. Joint Bone Spine. 2008;75:511–2.
148. Sharma OP. Effectiveness of chloroquine and hydroxychloroquine in treating selected patients with sarcoidosis with neurological involvement. Arch Neurol. 1998;55:1248–54.
149. Miloslavsky E. 66-year-old man with visual loss, headache, hematuria, chronic sinusitis. Rheumatologist. 2012.

Part IV
Diagnostic Modalities

Chapter 16
Anterior Rhinoscopy and Nasal Endoscopy in the Diagnosis of Sinonasal Disease

Douglas R. Johnston and Marc R. Rosen

Introduction

Complaints of nasal and sinus disease can often be somewhat vague and overlapping. Clinicians rely heavily on a detailed history and physical examination to support the diagnosis. We emphasize that the sinonasal examination be performed within the context of a complete head and neck examination. With the latest consensus statements on the diagnosis of rhinosinusitis emphasizing characteristic physical examination findings, historical findings are no longer enough to make a diagnosis. For most practitioners (the majority of rhinosinusitis is treated by primary care physicians), the physical examination consists largely of the ability to visualize the anterior to mid-nasal cavities on anterior rhinoscopy. This technique is performed either with an otoscope or with a nasal speculum and external light source. A more comprehensive examination allows the specially trained practitioner to also visualize the posterior nasal cavity and nasopharynx with a rigid or flexible endoscope. The flexible nasopharyngolaryngoscope (NPL) permits the further examination of the posterior oropharynx, hypopharynx, and larynx. Because the NPL is flexible, it is superior than the rigid scope for diagnostic purposes. The rigid scope has advantages of better image quality and a rigid structure that permits the practitioner to operate it with one hand, freeing the other hand for other tasks.

The techniques of sinus percussion and transillumination have largely been abandoned, although palpating the areas over the frontal and maxillary sinuses is thought to be valuable. This chapter aims to outline the indications for anterior rhinoscopy and nasal endoscopy. Additionally, we describe the anatomic landmarks and appearance of the disease that aid in the diagnosis of common nasal and sinus pathologies. The anatomy reviewed herein is not meant to be a comprehensive review, but instead serves to highlight the anatomic features that can be observed on anterior rhinoscopy and nasal endoscopy. A comprehensive anatomic description is found elsewhere in this text. Lastly, examination techniques are described to provide the best opportunity to diagnose nasal and sinus pathology.

Indications for Anterior Rhinoscopy

Anterior rhinoscopy should be a part of the routine head and neck examination, especially if there are complaints of unilateral or bilateral nasal obstruction, epistaxis, rhinorrhea, facial pain, or anosmia. With the use of an otoscope speculum or nasal speculum with a headlight, the practitioner can evaluate from the nasal vestibule anteriorly potentially to the level of the middle turbinate posteriorly. A detailed view of the middle turbinate, middle meatus, and mid-septum can be difficult to obtain, however, due to the limitation of lighting and optics and to anatomic variations, such as septal deviation, significant nasal mucosal edema, or rhinorrhea. The main purpose of anterior rhinoscopy is to evaluate the character and appearance of the nasal mucosa of the septum and inferior turbinates. Mucosal edema from infection and allergic rhinitis, septal deviation, inferior turbinate enlargement, nasal masses, and, occasionally, nasal polyps are the common pathologies usually visible by anterior rhinoscopy.

D.R. Johnston, MD (✉)
Department of Otolaryngology, A.I. duPont Hospital for Children, Jefferson Hospital, 1600 Rockland Rd., Wilmington, DE 19803, USA
e-mail: djohnsto@nemours.org; douglas.johnston@nemours.org

M.R. Rosen, MD
Department of Otolaryngology Head and Neck Surgery, Thomas Jefferson University, 925 Chestnut Street, Philadelphia, PA 19107, USA
e-mail: marc.rosen@jefferson.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_16,

Table 16.1 Indications for nasal endoscopy

Unilateral/bilateral nasal obstruction
Epistaxis
Rhinorrhea
Facial pain/headache
Anosmia
Rhinosinusitis
Sinonasal neoplasms
Eustachian tube or middle ear dysfunction (i.e., otitis media)
Selected cranial nerve deficits
Cervical adenopathy of unknown origin
Obstructive causes of sleep disordered breathing
Assess treatment response
Evaluate pre- and postsurgical patients
Other upper respiratory signs/symptoms not answered by anterior rhinoscopy

Indications for Flexible or Rigid Nasal Endoscopy

Using a flexible fiberoptic nasopharyngolaryngoscope (NPL) affords visualization of the anterior nasal cavity, as in routine anterior rhinoscopy, and further to the posterior nasal cavity, nasopharynx, oropharynx, hypopharynx, and larynx. Many allergists and otolaryngologists employ this instrumentation for routine head and neck examinations. More commonly, the NPL is used by specialists for the same reasons that anterior rhinoscopy is indicated and, additionally, to evaluate rhinosinusitis, potential polyposis, sinonasal neoplasms, unilateral and bilateral Eustachian tube or middle ear dysfunction (i.e., otitis media), certain cranial nerve deficits, headaches, cervical adenopathy, and obstructive causes of sleep disordered breathing. In willing pediatric patients, NPL exam can obviate the need for radiation exposure from a lateral neck x-ray in the diagnosis of adenoid hypertrophy causing upper airway obstruction. Of course, nasal endoscopy can, also, be used to evaluate pre- and postsurgical patients, assess treatment responses, and, in general, answer any clinical question that cannot alone be answered by anterior rhinoscopy (Table 16.1).

Commonly Visualized Sinonasal Anatomy [1, 2]

Nasal Vestibule, Pyriform Aperture, and Anterior Nasal Valve

The inside of the nares, within the hair-bearing portion of the nasal cavity and anterior to the maxillary process (anterior bony nasal floor), is defined as the nasal vestibule. Its roof is the nasal ala. The vestibule ends at the mucocutaneous junction. The nasal pyriform aperture is the bony opening of the nasal cavity and is mentioned herein as it can be congenitally narrowed and cause nasal obstruction. It consists of the anterior cartilaginous nasal septum medially, the nasal bones superiorly, the lateral wall of the maxillary processes laterally, and the bony nasal floor inferiorly. The anterior nasal valve is mentioned, similarly, because its narrowing can cause difficulty with nasal breathing. The anterior nasal valve is defined medially by the septum, superolaterally by the upper lateral cartilage, laterally by the inferior turbinate, and inferiorly by the nasal floor. Whether performing anterior rhinoscopy with an otoscope speculum or a traditional nasal speculum, these areas must be traversed with the instrumentation to visualize the remainder of the anterior and mid-nasal cavities.

Nasal Septum

The nasal septum divides the nasal cavities and is composed, roughly, of cartilage in its anterior half (the quadrangular cartilage) and bone in its posterior half (perpendicular plate of the ethmoid superiorly, vomer inferiorly) until its termination before the nasopharynx at the nasal choanae. The bone of the perpendicular ethmoid plate is thin and attaches superiorly to

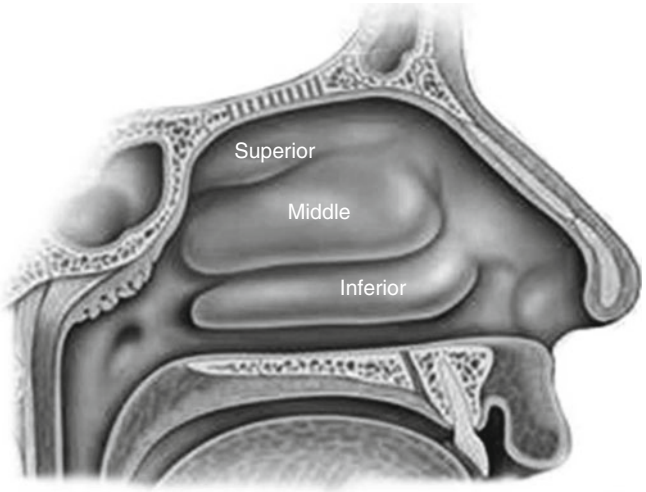


Fig. 16.1 Lateral nasal wall showing the position of the superior, middle, and inferior turbinates

the skull base at the cribriform plate. Thicker bone is found posteriorly in the vomer, which attaches inferiorly to the maxillary crest anteriorly and the palatine bone posteriorly. The tissue overlying the septum consists superficially of mucosa overlying the perichondrium or periosteum.

Inferior Turbinate

The turbinates exist as outgrowths from the lateral nasal wall and have a role in causing airflow turbulence, resulting in humidifying and heating inhaled air (Fig. 16.1). The turbinates are also known as "conchas" because of their thin bone is in the shape of a scroll. They are housed in the normal nasal mucosa and periosteum. The inferior turbinate attaches laterally to the superior projection of the palatine bone as the lateral nasal wall forms the medial border of the maxillary sinus. This turbinate parallels the floor of the nasal cavity. Lateral to the inferior turbinate, approximately 1 cm posterior to its anterior edge, drains the nasolacrimal duct.

Middle Turbinate

Like the inferior turbinate, the middle turbinate emanates from the lateral nasal wall, but its anterior portion differs in that it attaches to the fovea ethmoidalis (ethmoid roof). In its posterior portion behind the ethmoid bulla, the middle turbinate attaches laterally to the medial wall of the orbit (lamina papyracea). This posterior attachment point is called the basal or ground lamella, and it separates the anterior and posterior ethmoid sinuses. An ethmoid cell within the confines of the middle turbinate is known as a concha bullosa.

The middle turbinate defines additional important anatomic boundaries. The space above the inferior turbinate, lateral to the middle turbinate, and medial to the lateral nasal wall is known as the middle meatus. The middle meatus is the drainage point into the nasal cavity of the anterior ethmoid, maxillary, and frontal sinuses.

Uncinate Process

The uncinate process is a vertically oriented bone in its superior half and a horizontally oriented bone in its posterior half, forming a reverse "L" shape. It can sometimes be visualized medial to the middle turbinate as it arises from the lateral nasal wall. Its superior projection normally attaches to the lateral nasal wall at the lamina papyracea but can attach to the middle turbinate or the ethmoid roof. Its vertical segment is anterior to the natural os of the maxillary sinus and its horizontal segment is inferior to it.

Ethmoid Bulla

The ethmoid bulla is the largest of the anterior ethmoid air cells and sits posterosuperior to the natural os of the maxillary sinus. If the middle turbinate is well medialized, this structure can sometimes be visualized posterior to the uncinate process. It may extend superiorly to the roof of the ethmoid labyrinth or form the posterior wall of the nasofrontal recess if a more anterior ethmoid air cell (agger nasi) is absent. Drainage of the ethmoid bulla occurs in the suprabullar, or retrobullar, recess. This space is bounded superiorly by the fovea ethmoidalis, inferiorly by the superior surface of the ethmoid bulla, medially by the middle turbinate, laterally by the lamina papyracea, and posteriorly by the basal lamella.

Superior Turbinate

This turbinate is usually the most superior and posterior of the turbinates, although a supreme turbinate may exist medial to the superior turbinate. The superior turbinate may have a role in olfaction, unlike the middle and inferior turbinates. The superior turbinate has a more oblique orientation posteriorly and superiorly to the middle turbinate. The natural os of the sphenoid can be found posteromedially to the superior turbinate.

Nasopharynx

The nasopharynx is the area within the nasal cavity posterior to the termination of the septum and the choanae. It contains the adenoid tissue superiorly, the ventral surface of the soft palate inferiorly, and the Eustachian tube orifice (torus tubarius) and fossa of Rosenmüller laterally.

Oropharynx, Hypopharynx, and Larynx

The oropharynx, hypopharynx, and larynx are not covered in any detail in this chapter, but are mentioned to be complete with reference to the anatomy that can be visualized by the NPL. The oropharynx is the space that exists inferior to the soft palate, superior to the tip of the epiglottis, and posterior to the circumvallate papilla of the tongue (posterior 1/3 of tongue). It contains the tongue base, palatine tonsils, lingual tonsils, uvula, and lateral and posterior pharyngeal walls. The hypopharynx is comprised of the tissue inferior to the oropharynx that does not belong to the larynx. This includes the pyriform sinus and posterior and lateral pharyngeal walls.

The larynx has an integral function in respiration, phonation, and protection of the airway during deglutition. Its components include the mucosa-covered epiglottic cartilage superiorly and anteriorly, which abuts the base of the tongue and has the potential space called the vallecula in between. The paired false vocal cords are superior to the paired true vocal cords. Posteriorly the arytenoid cartilages are mucosal covered and have an articulation to the true vocal cords posteriorly. The remaining cartilaginous framework of the larynx consists of the thyroid cartilage superiorly and the cricoid cartilage inferiorly. The thyroid cartilage is not circumferential, unlike the cricoid cartilage, which is the only complete cartilage ring of the airway.

Other Anatomic Spaces and Clefts

Osteomeatal Complex (OMC)

This three-dimensional space is the drainage pathway of the frontal sinus, maxillary sinus, and anterior ethmoid sinuses into the nasal cavity. Its boundaries are not precise, but generally is defined by the lateral nasal wall laterally, the middle turbinate medially, and the ethmoid bulla posteriorly.

Ethmoid Infundibulum

A subdivision of the OMC, it is the three-dimensional space that contains the actual sinus ostia of the nasofrontal recess, the maxillary sinus, and the anterior ethmoid cells. It sits lateral to the uncinate process.

Semilunar Hiatus

The two-dimensional space between the uncinate process anteriorly and the ethmoid bulla posteriorly.

Sphenoethmoidal Recess

This recess is hard to access and lies posterior, superior, and medial to the superior turbinate. Within it are the ostia of the posterior ethmoid and sphenoid sinuses.

Fossa of Rosenmüller

Vertical cleft lying posterior to the torus tubarius and anterior to the adenoid pad. It is a common site for nasopharyngeal malignancies.

The Paranasal Sinuses

Frontal Sinus

The frontal sinus lies anterior to the frontal lobe of the brain and is variably pneumatized within the frontal bone of the forehead. The nasofrontal recess is its drainage pathway and exists anterior and superior to the agger nasi cells and lateral to the anterior portion of the middle turbinate, eventually draining into the OMC.

Maxillary Sinus

This aerated chamber is positioned inferior to the orbit and posterior to the maxillary face. Its floor can contain the tooth roots of the maxillary molars. Within the maxillary sinus, a natural flow of mucus directed by the cilia of the respiratory epithelium leads to the natural os on the posterosuperior medial wall. Accessory ostia are not uncommon at a 10 % occurrence rate and may be larger than the natural opening. The maxillary sinus drainage then exits into the OMC via the infundibulum.

Anterior Ethmoid Sinuses

The anterior half of the ethmoid sinuses is anterior to the basal lamella. This group of ethmoid cells consists of the ethmoid bulla and the infundibular cells, which are comprised of the suprainfundibular cell, the terminal cell, and the agger nasi cell. Lateral to the anterior and posterior ethmoids is the orbit and superior is the brain protected by the skull base. The anterior ethmoids contain the suprabullar and retrobullar recesses, or clefts, which are the drainage for the ethmoid bulla. The other anterior ethmoids drain directly into the infundibulum and through the semilunar hiatus into the OMC. Agger nasi cells can

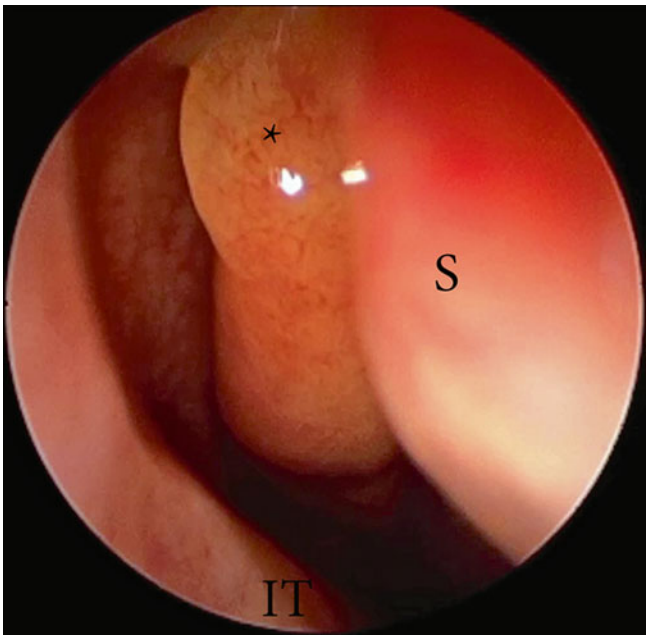


Fig. 16.2 Rigid endoscopic picture of the middle meatus. * watery edema of the middle turbinate, *S* nasal septum, *IT* inferior turbinate

interfere with the nasofrontal outflow depending on their size and position. Supraorbital ethmoid cells can extend laterally over the orbit, and infraorbital ethmoid cells within the maxillary sinus are known as Haller cells.

Posterior Ethmoid Sinuses

The posterior half of the ethmoid sinuses is posterior to the basal lamella and consists of between one and five cells that are generally larger than the anterior cells, except for the ethmoid bulla. Pneumatization of the posterior ethmoid cells may extend into, or laterally and superiorly to, the sphenoid sinus. These extensions are known as Onodi cells and may house an unprotected optic chiasm or petrous carotid artery. Posterior ethmoids usually drain into the superior, or sphenoethmoidal, recess.

Sphenoid Sinus

This is the most posterior paranasal sinus with close relationship to the brain superiorly and posteriorly and to the carotids and cavernous sinuses posterolaterally. The inter-sinus septum between the paired sphenoid sinuses is frequently asymmetric and often inserts over the carotid artery. The natural os is located within the superior extent of the anterior sinus wall.

Common Pathologies Identified on Nasal Endoscopy

Nasal Mucosa

The pseudostratified columnar respiratory epithelium of the upper respiratory tract should have a moist surface and healthy pink color with no edema. Commonly, the appearance of the mucosa alerts the clinician to an inflammatory condition, such as the boggy look or blue hue in the inflammation of allergic rhinitis (Fig. 16.2), the hyperemic appearance of acute or chronic rhinosinusitis, or the very pale or necrotic brown/black appearance of invasive fungal disease. In the case of allergic rhinitis, the persistence of mucosal edema can lead to impaired ciliary function and stasis of secretions, which can play a heavy hand in the etiology of chronic rhinosinusitis. Dry mucosa can be present in sicca syndrome, low humidity environments, or chronic inflammation. The return of a more normal mucosal appearance signifies a return to normal function after disease resolution or therapeutic response.

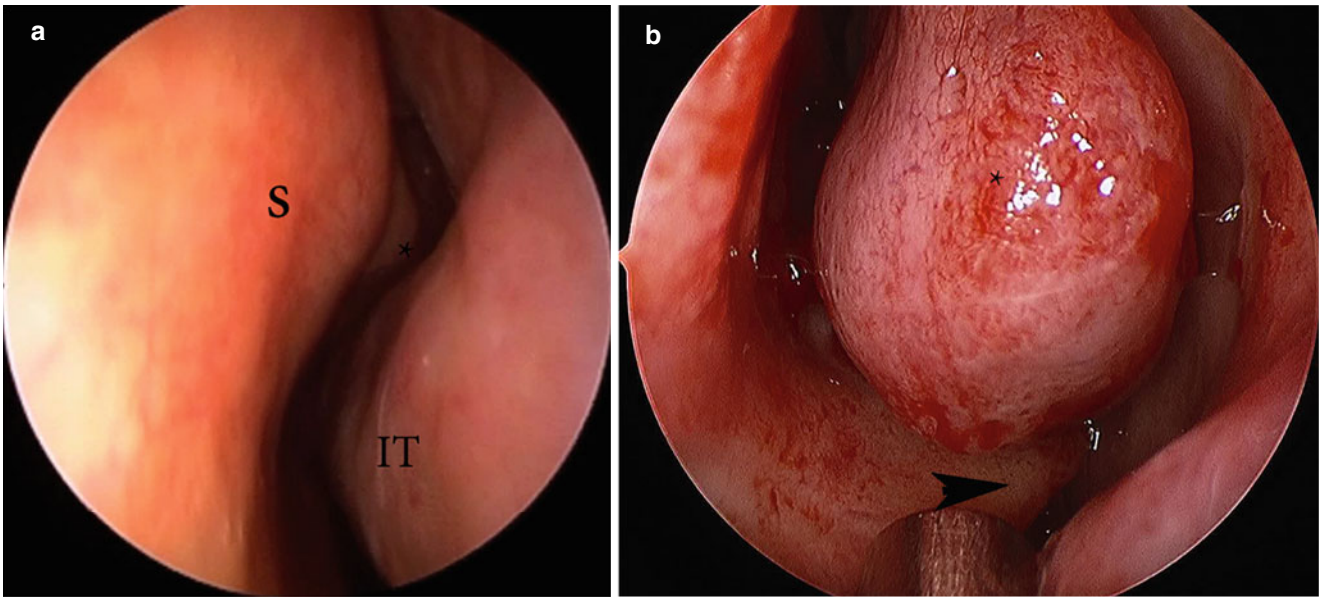


Fig. 16.3 (**a**) Rigid endoscopic picture of anterior broad septal deflection on the left side with underdevelopment of the middle turbinate. *S* nasal septum, * middle turbinate, *IT* inferior turbinate. (**b**) Rigid endoscopic picture of a large bony septal spur (*arrowhead*) extending underneath a middle turbinate that has a concha bullosa (*)

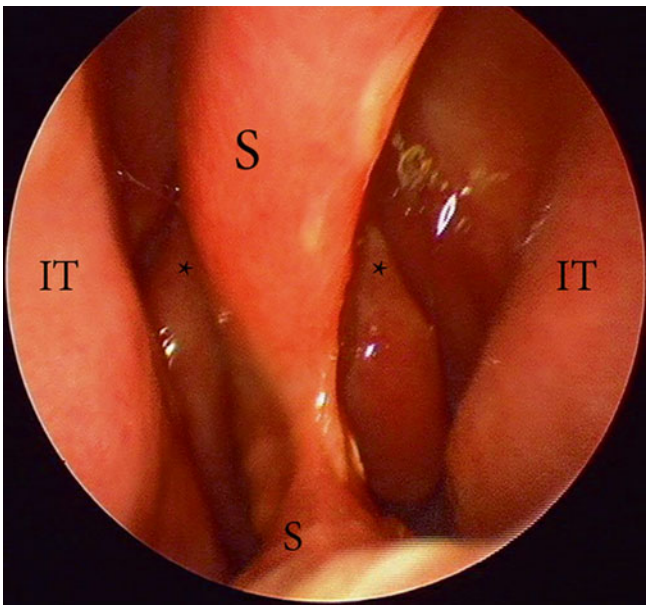


Fig. 16.4 Large septal perforation. The inferior turbinates (*IT*) and middle turbinates (*) are seen bilaterally through the septum (*S*)

Nasal Septum

The most common septal pathology is septal deviation, which exists in most patients to a variable degree. Rarely will the degree of deviation prohibit the practitioner from performing ipsilateral nasal endoscopy, especially if properly anesthetized. A significant anterior septal deflection can measurably limit unilateral nasal airflow, whereas a severe mid-septal deflection can obstruct the osteomeatal complex and result in ipsilateral middle turbinate underdevelopment (Fig. 16.3a, b). Septal deviation can result from deflection of the cartilaginous septum, bony septum, or both. Another nasal septal pathology is perforation, which results from autoimmune processes like granulomatosis with polyangiitis (GPA), cocaine or oxymetazoline abuse, and postsurgical complications (Fig. 16.4). Epistaxis originates most commonly from the anterior septum in the area of Kiesselbach's plexus, which is a confluence of vessels from the internal and external carotid systems (Fig. 16.5).

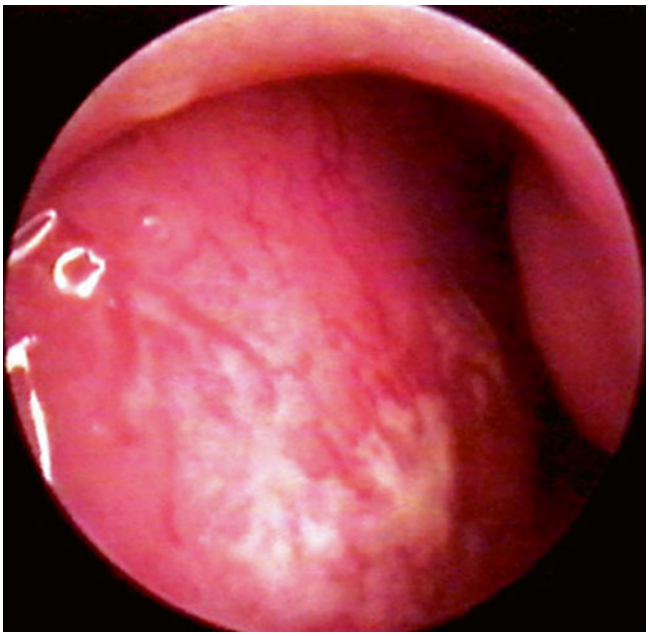


Fig. 16.5 Flexible endoscopic picture of the left anterior septum with prominent vasculature of Kiesselbach's plexus with mild mucosal excoriation

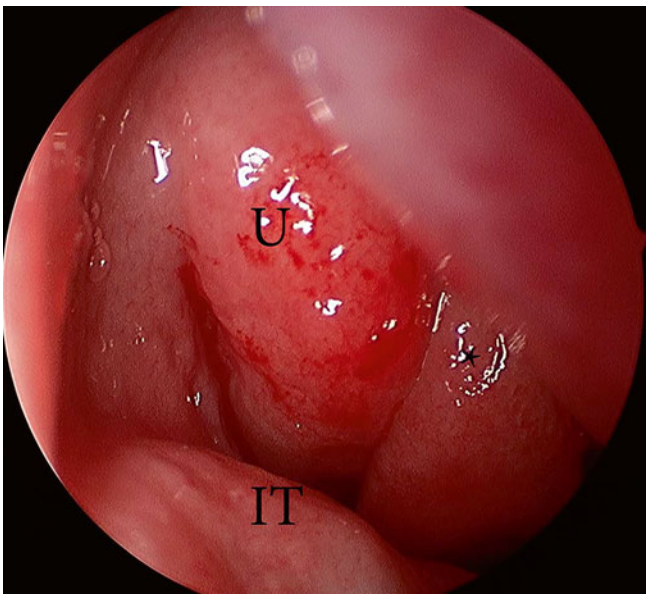


Fig. 16.6 Rigid endoscopic picture of osteomeatal complex obstruction secondary to a pneumatized uncinate process abutting a concha bullosa of the middle turbinate. *U* uncinate process, * concha bullosa of the middle turbinate, *IT* inferior turbinate

Turbinates

Inferior Turbinate: Enlargement of the inferior turbinate can be directly from the underlying bony structure or from chronic inflammation secondary to allergic rhinitis and chemical irritation.
Middle Turbinate: As the middle turbinate is a part of the middle meatus, it is commonly involved in sinonasal pathologic disease. To begin, any source of mucosal inflammation, be it allergic rhinitis or standard viral upper respiratory infection, can result in mucosal congestion and a tendency to obstruct the outflow of the osteomeatal complex. Pneumatization of the middle turbinate with an aberrant ethmoid air cell is known as a concha bullosa, which can obstruct nasal airflow or the common outflow of the frontal, maxillary, and anterior ethmoid sinuses (Fig. 16.6). Those patients prone to nasal polyposis often have polypoid change to the middle turbinate, as well.

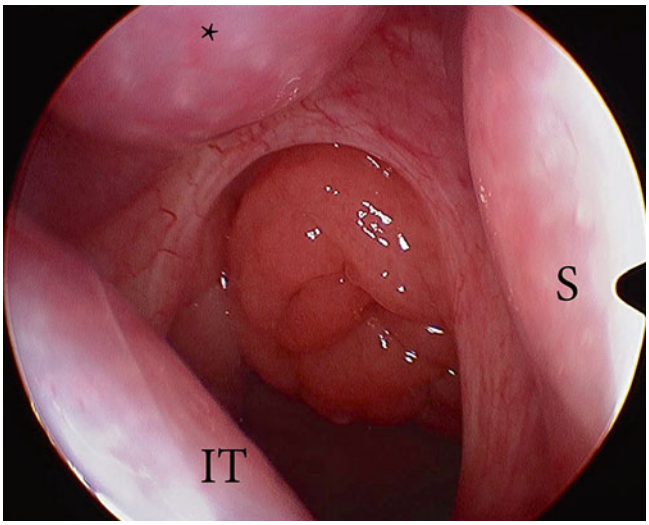


Fig. 16.7 Rigid endoscopic picture of mildly enlarged adenoids seen through the right choana. *S* nasal septum, * middle turbinate, *IT* inferior turbinate

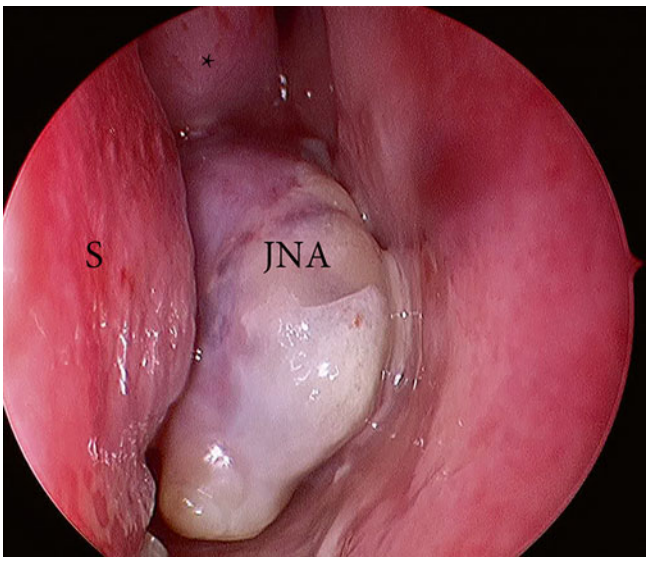


Fig. 16.8 Rigid endoscopic picture of left nasal juvenile nasopharyngeal angiofibroma that originated in the posterior nasal cavity and grew anteriorly. * middle turbinate, *S* nasal septum, *JNA* juvenile nasopharyngeal angiofibroma

Nasopharynx

Nasopharyngeal pathology can cause upper airway obstruction and Eustachian tube dysfunction with resulting middle ear disease and, even, epistaxis in the case of nasopharyngeal neoplasms. Adenoid hypertrophy or chronic adenoiditis are the most common conditions affecting the nasopharynx, producing airflow obstruction, stasis of secretions, and postnasal drip (Fig. 16.7). Children are often diagnosed as having refractory nasal allergies when, in fact, they have adenoid hypertrophy, which can completely obliterate the nasopharyngeal airway and result in sleep disturbance. Adenoidectomy would be the recommended treatment. In the case of persistent unilateral or bilateral Eustachian tube dysfunction, NPL exam is *mandatory* to rule out the presence of nasopharyngeal neoplasms, such as nasopharyngeal carcinoma, usually accompanied by cervical adenopathy, lymphoma of the fossa of Rosenmüller, or a juvenile nasopharyngeal angiofibroma (JNA) in pubertal males, to name a few (Fig. 16.8). Lastly, choanal atresia or stenosis can be ruled out as sources of unilateral or bilateral nasal obstruction in the pediatric age group.

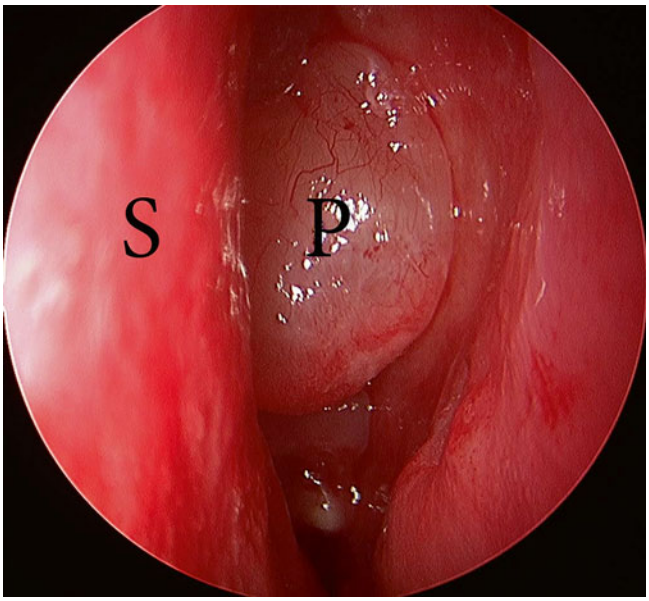


Fig. 16.9 Rigid endoscopic picture of a lobulated, somewhat translucent nasal polyp emanating from the middle meatus. *S* nasal septum, *P* nasal polyp

Sinonasal Polyposis

Nasal polyps, when prominent, can be visualized on anterior rhinoscopy. This condition should be investigated more thoroughly with nasal endoscopy, however. Most commonly, polyps arise from the ethmoid sinuses and prolapse into the nasal cavity, with anterior ethmoid and maxillary polyps visible in the middle meatus (Fig. 16.9). With a sometimes translucent, clear to yellow and gelatinous appearance, polyps can amorphously fill the sinuses and outflow tracts of the sinuses and cause chronic sinusitis. In overwhelming polyposis, these middle meatus polyps can prolapse into and completely obstruct the nasal cavity. Posterior ethmoid and sphenoid sinus polyps extend into the sphenoethmoidal recess and can be seen sometimes medial to the middle turbinate. Samter's triad is the condition of nasal polyposis, asthma, and aspirin allergy that can be difficult to eradicate, requiring surgery, anti-inflammatory modulators, and aspirin desensitization. There exists a strong correlation between the presence of nasal polyposis on endoscopy and CT scan findings positive for sinusitis [3].

Rhinosinusitis

Anterior rhinoscopy is limited in its ability to diagnose rhinosinusitis when compared to both flexible and rigid endoscopy because it can be difficult to see the middle meatus. However, according to the American Academy of Otolaryngic Allergy Working Group on Chronic Rhinosinusitis (CRS), anterior rhinoscopy can support the diagnosis of rhinosinusitis, realizing that the majority of practitioners making this diagnosis are general practitioners [4]. Anterior rhinoscopy *in the decongested state* is the first objective physical exam component in diagnosing acute or chronic rhinosinusitis and represents the minimum degree of the physical exam needed, as flexible and rigid endoscopies are more specific. The Sinus and Health Allergy Partnership published the *objective* requirements for the diagnosis of CRS in 2003 because the subjective historical evidence alone is not accurate, which is an update from the position of the 1997 Task Force on Rhinosinusitis [3, 5, 6]. The most diagnostic findings on anterior rhinoscopy or endoscopy are discolored nasal drainage or nasal polyps. Additional supporting evidence is edema, erythema, or granulation tissue of the middle meatus or ethmoid bulla [7].

Further objective support in diagnosing CRS is through CT scans of the sinuses that reveal mucosal thickening, air-fluid levels, and bony changes of the sinuses. CT scanning is not recommended for diagnosing acute sinusitis, unless there are concerns for facial abscess, orbital complications, or intracranial extension of infection.

Original inquiries into the correlation between endoscopic evidence of sinus disease and CT evidence of sinusitis in those who met the criteria for chronic rhinosinusitis showed a sensitivity of 75 % and specificity of 84 % [8]. Subsequent publications, however, have shown a much less robust correlation in terms of sensitivity and specificity [3, 6]. On the other hand, it appears that the positive predictive value and negative predictive value are useful, according to another study [1]. In other words, when strong endoscopic findings like purulence, polyps, or polypoid congested mucosa were present on endoscopy, the patient was likely to have a positive CT. Likewise, a negative endoscopic exam was predictive of a negative CT in 78 % of patients.

Table 16.2 Subjective criteria for diagnosis of rhinosinusitis

Major criteria	Minor criteria
Facial pain or pressure	Headache
Purulent nasal discharge	Fever
Hyposmia or anosmia	Halitosis
Nasal obstruction	Fatigue
Facial congestion or fullness	Dental pain
	Ear pain, pressure, or fullness
	Cough

The subjective criteria for the diagnosis of chronic rhinosinusitis, which by definition must be of at least 12 weeks' duration, are that published in 1997 by the Task Force on Rhinosinusitis (Table 16.2) [9]. To fulfill the subjective component of diagnosis, two major or one major and two minor criteria must be met.

Sinonasal Neoplasms

Although uncommon, neoplastic masses in the nasal cavity and nasopharynx prompt a thorough work-up and timely referral to an otolaryngologist. Common signs and symptoms include unilateral nasal obstruction, epistaxis, and rhinorrhea. Many common upper airway diagnoses can present similarly, such as rhinosinusitis, but routine diagnoses that are refractory to medical management should be investigated with imaging or referred to an otolaryngologist without delay.

Pathology of the Oropharynx, Hypopharynx, and Larynx

The pathologies of the oropharynx, hypopharynx, and larynx are numerous and most will not be covered in this chapter. Neoplasms of the oral cavity and oropharynx can extend to the nasal cavity, the nasopharynx, or erode through the hard and soft palate where they can be visualized. Extra-esophageal acid reflux, such as seen in laryngopharyngeal reflux, can cause inflammation of the entire upper airway, especially in the neonate and infant who spend more time in the reclined position. Therefore, signs of inflammation and erythema of the larynx can sometimes be linked to nasal and nasopharyngeal inflammation, and this etiology of sinonasal disorders should be considered when clinically appropriate. Cobble stoning of the posterior pharyngeal wall is a sign of inflammatory response of the oropharyngeal mucosa and can signify significant acid reflux. However, it should be mentioned that a chronic postnasal drip can illicit the same mucosal response and result in laryngeal inflammation and voice changes.

Examination Technique

Decongestion and/or Anesthesia

The application of a topical decongestant, such as oxymetazoline, phenylephrine, or ephedrine, is recommended for both anterior rhinoscopy and nasal endoscopy in the diagnosis of rhinosinusitis. Other decongestants are available, some of which also contain anesthetic properties, such as 4 % cocaine solution. Regardless of the type of decongestant, it aids in reducing mucosal edema that can blur anatomic variants. An active rhinosinusitis will not be void of its associated edema or erythema after decongestion, but some practitioners prefer to first perform anterior rhinoscopy or nasal endoscopy in the decongested state to visualize the native appearance of the nasal mucosa. The addition of an anesthetic agent to topicalize the nasal mucosa prior to endoscopy allows for a more pain-free experience for the patient and permits a full endoscopic evaluation. Four percent lidocaine is a popular choice. With proper anesthesia, the endoscopic exam should be associated with minimal pain, but the sensation of pressure is not uncommon. If the delivery device atomizes the liquid, the medications usually reach the desired nasal mucosa, but if a thin spray or stream is used, at least one spray should be directed at a

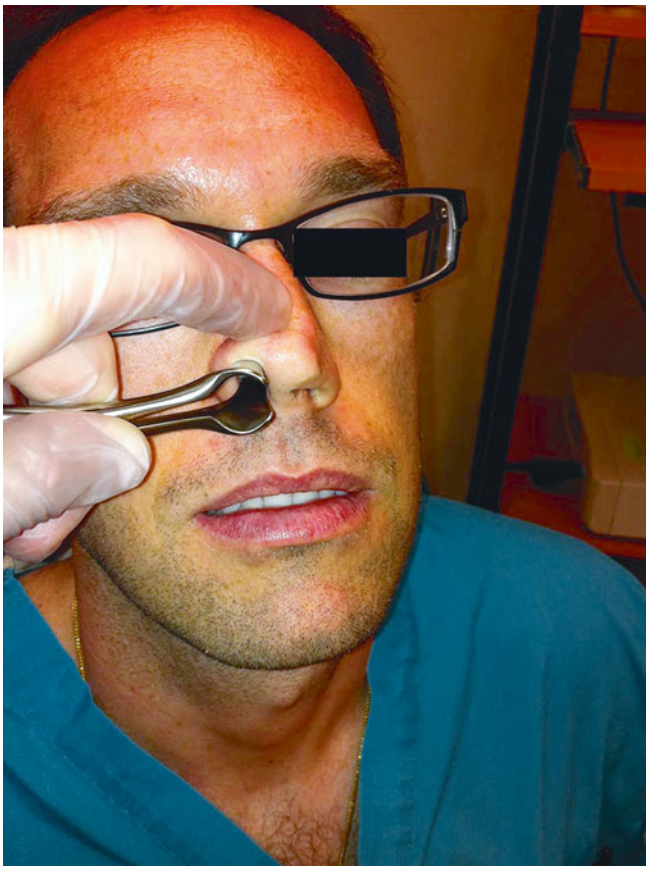


Fig. 16.10 Demonstration of the nasal speculum in the left nasal vestibule with slight opening of prongs and forefinger on the nasal dorsum for point of control

45° angle superiorly to assure adequate effect on the mid and superior sinonasal structures. Alternatively, some practitioners prefer applying viscous medications or cotton tip applicators and cotton swabs soaked with decongestants and/or anesthetics.

Anterior Rhinoscopy

Anterior rhinoscopy is accomplished with either an otoscope with its attached otic speculum or with a nasal speculum and external light source. Either way, the purpose is to obtain a wide view of the anterior nasal cavity. Standing on the patient's right side with the patient's head straight ahead or toward the practitioner and the instrument in the left hand is the proper position. The patient's head position is best when rested on a headrest or wall, if available. The right hand can be used to push the nasal tip superiorly and/or hold the left face for stability and comfort. The practitioner must be reminded to attempt to visualize to the level of the middle turbinate posteriorly, which can be a challenge given the limited focal length of the otoscope of approximately 2.5 cm. The wide view is best accomplished with the otic speculum by placing it against the inferior edge of the lower lateral cartilage (nasal ala) and gently displacing this tissue superiorly. Because the optic properties of the otic speculum are telescopic (they cone down onto the target), instead of endoscopic, the otoscope must be rotated in all directions to gain the most comprehensive picture of the anterior nasal cavity. It is all too common to be satisfied with a limited telescopic view and not attempt to "compile the most evidence" by looking around circumferentially and focusing on the more posterior anatomy. Anterior rhinoscopy can be accomplished without touching the nasal septum, which may cause discomfort and bleeding.

Using the nasal speculum with an external light source is more challenging but affords a more global view than does the otoscope without the limited focal length. This wider view improves recognition of anatomic landmarks. A standard nasal speculum for anterior rhinoscopy need not be large like those used surgically for nasal operations. The metal of a speculum can be cold, so warning the patient can avoid a startled movement. By placing the speculum handles in one's palm, the practitioner can open the speculum. The speculum tip is placed against the inferior edge of the lower lateral cartilage and gently displaced superiorly while the index finger maintains a point of contact with the ipsilateral nasal bone to achieve maximal control in the event of patient movement (Fig. 16.10). The speculum is then opened in a superior-inferior direction with the

handles in the horizontal plane. Otolaryngologists commonly use a head mirror with an external lamp located posterior to the patient or a head lamp because this allows a free right hand to hold another instrument or gently hold the patient's left face. However, it is also acceptable to have an external light source in the right hand for illumination.

Nasal Endoscopy

The comments in this section generally apply to both the rigid and flexible endoscopes; however, it should be emphasized that they each have distinct indications. As it has superior maneuverability, the flexible NPL is the preferred comprehensive diagnostic tool over the rigid scope in that it can more easily image the sinonasal ostia and recesses. In comparison, the rigid scope's rodlike structure offers improved image resolution and the ability to have a second hand free to hold other instruments. Various manufacturers exist for both types of sinonasal endoscopes. The use of endoscopes designed for other anatomic regions should generally be avoided. Rigid endoscopes have superior illumination and optics compared to the traditional flexible scopes because the flexible scopes rely on flexible fiberoptic glass channels that result in an inherent degree of image degradation due to loss of light and image fragmentation. The exception to this rule is the newer "distal chip" scopes in which the image capture device at the distal scope end relays the image digitally to its processor, preventing the usual loss of quality.

The standard diameter of the rigid scope is 4.0 mm, but a 2.7 mm size may be needed in pediatric patients, or those in whom significant anatomic obstruction exists. A zero degree rigid endoscope is the most common type, but 30, 45, and 70° scopes employ special prisms at the tip to allow for superior angled views as dictated by the clinical situation. Likewise, variations in diameter of flexible NPLs result in different quality of optics, and the smaller ones may enhance the practitioner's ability to perform endoscopy on children or through stenotic areas. Some larger endoscopes even have working side channels for the purpose of administering medication, taking biopsies, or performing other procedures. The care and proper cleaning of scopes will not be reviewed here, but it deserves mention that scope condoms, or sheaths, are commonplace these days to protect the instrument, and some sheaths include working side channels.

Depending on the anxiety level of the patient, informing the patient about some details of the examination can provide some assurance. Patients should be encouraged to keep their eyes open and breathe through their nose, making sure to inform the practitioner of any discomfort so that sensitive anatomic sites can be avoided altogether or at least until the termination of the exam. As a general rule, easy to examine areas should be visualized first to engender confidence and avoid any early discomfort. For example, visualizing the maxillary or sphenoid ostia has the greatest likelihood of causing some discomfort because of the angulation required and difficulty of anesthetizing these areas.

Proper patient positioning is important to keep the head still. The patient's head should be in the horizontal plane or slightly flexed, looking straight ahead or slightly toward the examiner, and rested on a headrest of an otolaryngology exam chair or a wall. Otolaryngology exam chairs allow patient height to be adjusted, as well. Once again, the examiner should be on the right side of the patient. If the endoscope is transmitting images to a video screen via a camera, the screen should be opposite the examiner over or behind the patient's left shoulder.

Rigid endoscopes are held in the left hand and the fingers of the right hand either stabilize the scope shaft or gently hold the patient's face (this hand can also hold a second instrument). The rigid scope is rested on the inferior edge of the nasal ala, pushing it gently superiorly as a point of stability to avoid the sensitive nasal septum. For the flexible NPL, the distal end of the scope is held between the thumb and forefinger of the left hand, while the third through fifth fingers rest against the nasal dorsum or forehead and provide a point of contact to stabilize the scope. This patient contact is beneficial if the patient moves unexpectedly or if the practitioner can detect grimacing or wincing secondary to discomfort. Advancing the scope is done cautiously in the anterior-posterior direction, while steering is accomplished with the right hand. The thumb of the right hand controls the lever on the handle of the scope allowing for directing the flexible tip superiorly and inferiorly, and wrist rotation permits rotating the scope to direct the tip medially and laterally.

The examination sequence should be systematic and proceed from the easiest to most difficult areas to examine. Being consistent with the examination sequence prevents forgetting steps and serves as a framework for gathering information. Normally, the anterior nasal cavity and nasopharynx are easiest to examine first, followed by the oropharynx, hypopharynx, and larynx, if indicated during flexible endoscopy, and finish with the sphenoethmoidal recess osteomeatal complex. Occasionally, asking the patient to blow his or her nose or irrigate with saline affords a view without excessive mucus or crusting. At any point when the view is not clear, it is best to slowly withdraw the scope until familiar landmarks are identified.

To begin, defog the tip of the scope with soapy water or a commercial antifog agent and insert the scope into the vestibule. Advance the scope in the anterior-posterior direction approximately 1 cm to gain a global view of the inferior turbinate, nasal floor, septum, and middle turbinate (Fig. 16.11a, b). From this position, flexion of the tip superiorly 60° shows

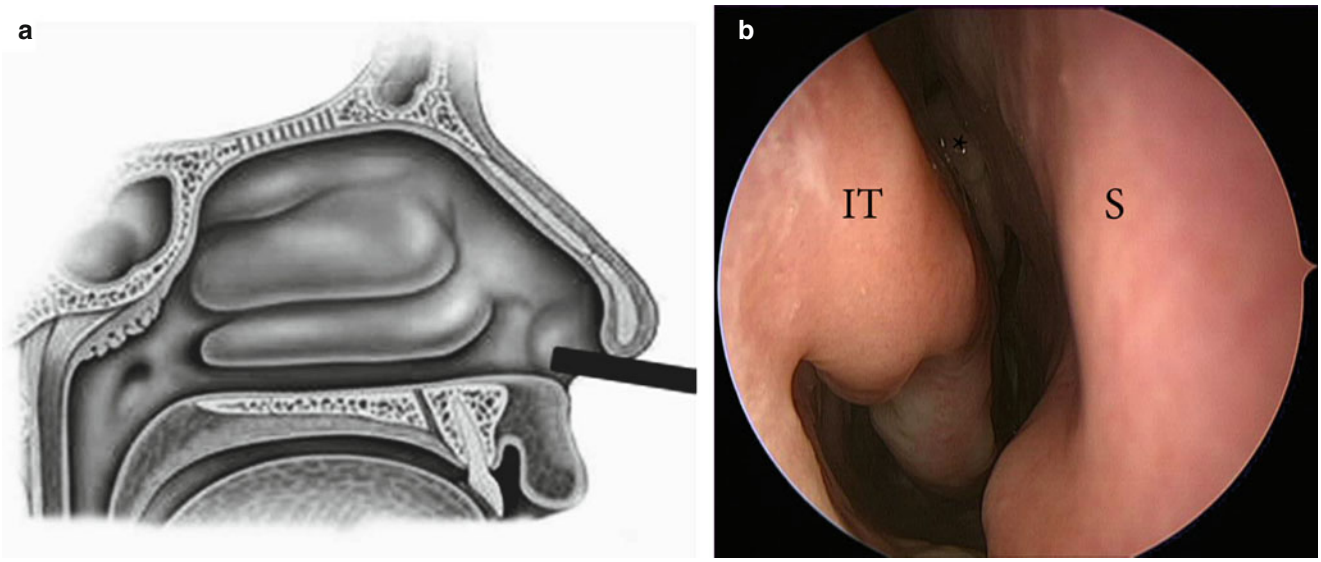


Fig. 16.11 (**a**) Approximate scope position allowing for global nasal view. (**b**) Rigid endoscopic picture from anterior vantage point giving global view. *S* nasal septum, * middle turbinate, *IT* inferior turbinate

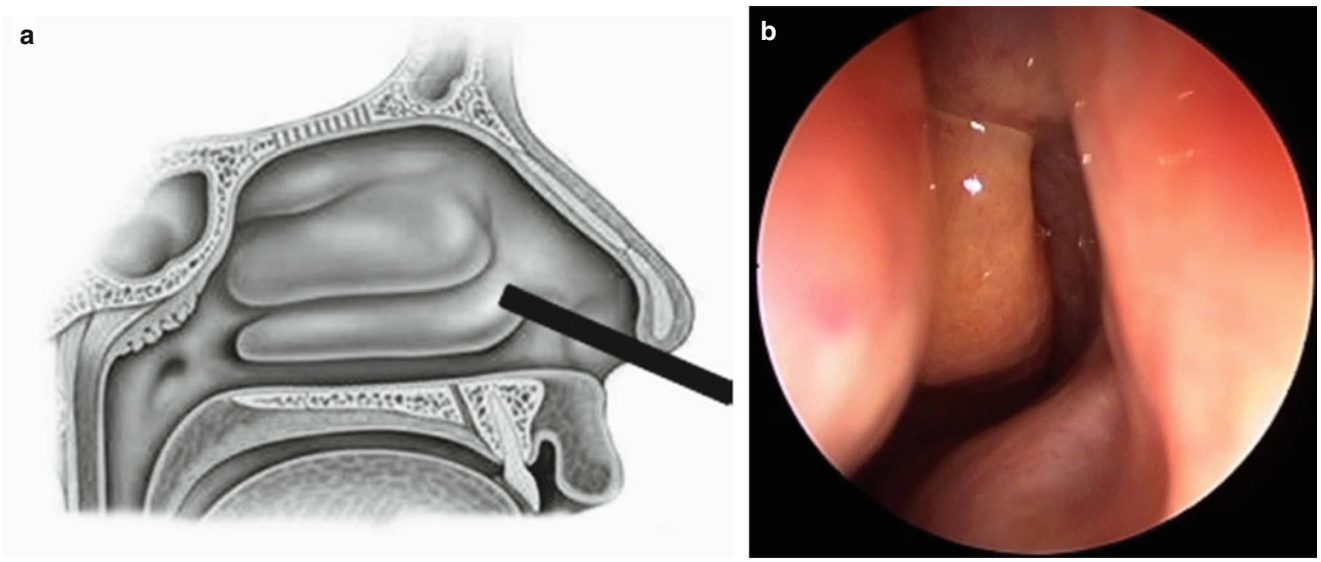


Fig. 16.12 (**a**) Approximate scope position allowing for middle meatus view. (**b**) Rigid endoscopic picture of left middle turbinate with mild allergic edema

the anterior face of the agger nasi cell. The scope can be advanced on the nasal floor between the inferior turbinate and the septum. In the case of turbinate enlargement, the scope can be passed instead superiorly to the inferior turbinate, which also gives a view of the tip of the middle turbinate (Fig. 16.12a, b). Next, advance the scope inferomedial to the middle turbinate on the way to the middle then posterior nasal cavities. At this point, flexing the scope 90° superiorly shows the roof of the nasal cavity. In the posterior nasal cavity, approximately 4–5 cm deep, the nasopharynx can be visualized, taking note of the adenoid size and appearance, the opening of the Eustachian tube (torus tubarius), and the fossa of Rosenmüller (Fig. 16.13).

Examining the torus tubarius and Eustachian tube orifice for signs of patency or obstruction is accomplished by flexing the scope tip superiorly when behind the vomer then rotating the scope approximately 90° in the counterclockwise direction. The contralateral Eustachian tube orifice is visualized by advancing further into the nasopharynx, flexing the tip superiorly, and rotating 90° in the clockwise direction. These maneuvers also allow examination of the fossa of Rosenmüller bilaterally as long as the adenoids are not too hypertrophied.

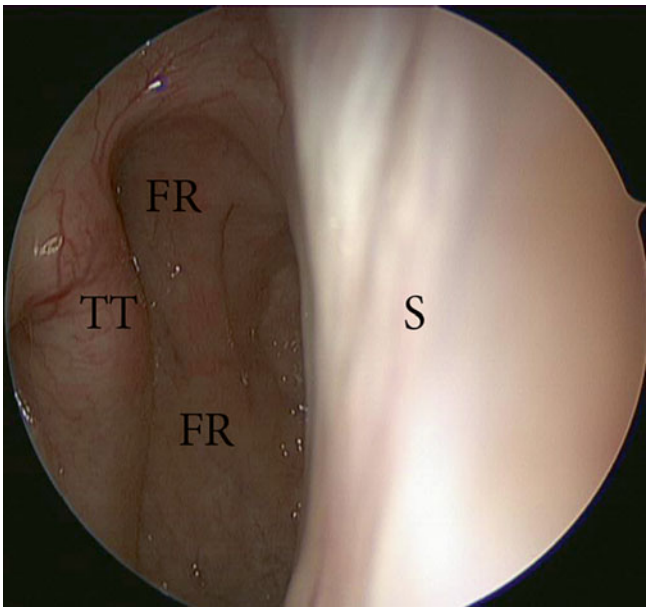


Fig. 16.13 Rigid endoscopic view of the posterior edge of torus tubarius, just posterior to the Eustachian tube orifice and the fossa of Rosenmüller. *TT* torus tubarius, *FR* fossa of Rosenmüller

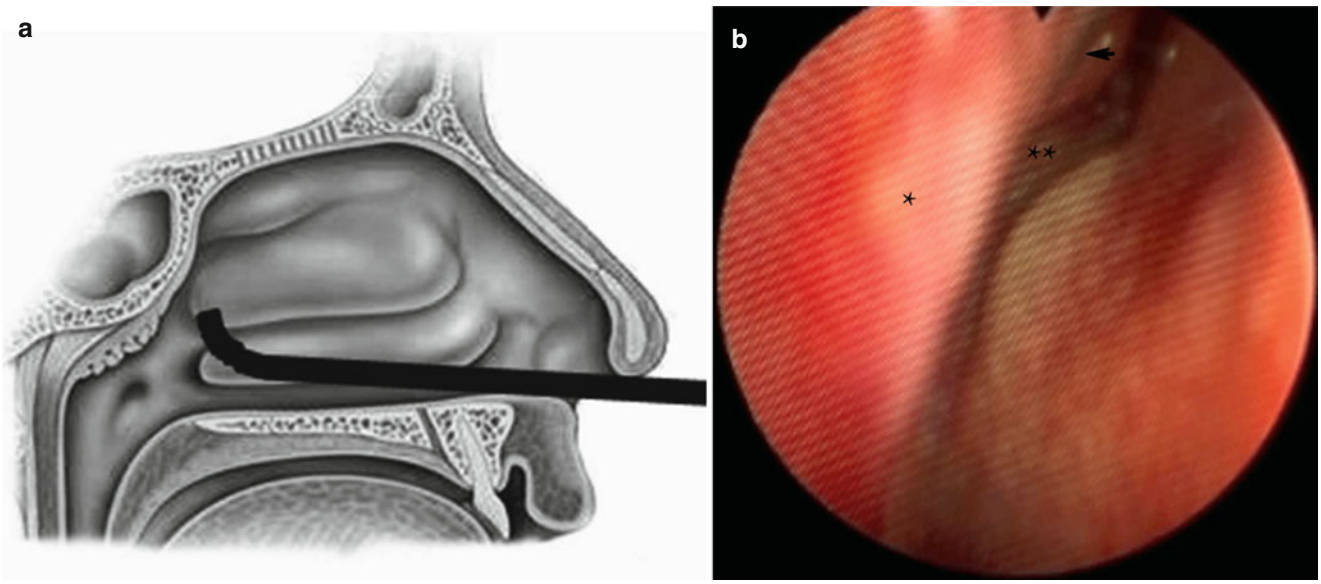


Fig. 16.14 (**a**) Approximate scope position allowing for view of the sphenoethmoidal recess. (**b**) Flexible endoscopic picture of the sphenoethmoidal recess between the superior turbinate and nasal septum above the level of the middle turbinate. * middle turbinate, ** sphenoethmoidal recess, *Arrowhead* superior turbinate

Advancing the scope beyond the soft palate in an inferior direction permits visualization of the oropharyngeal structures. Further advancement along the posterior pharyngeal wall allows the examiner to see the larynx where airway patency, voice function, and protective laryngeal reflexes can be assessed. The details of this portion of the examination are beyond the scope of this chapter.

As the scope is returned to the nasopharynx upon withdrawal, the sphenoethmoidal recess is visualized (Fig. 16.14a, b). This is accomplished more easily with the flexible scope with superior flexion when the tip is a few centimeters from the choana. Traversing the space between the posterior middle turbinate and the septum with the rigid scope can cause discomfort. As the scope is further withdrawn and the inferior edge of the middle turbinate comes into view, superior flexion and counterclockwise rotation may permit a view of the natural maxillary sinus os lateral to the middle turbinate within the infundibulum. Similarly, accessory ostia may be seen. This view is commonly not possible because the turbinate is positioned too laterally to permit visualization. Likewise, the nasofrontal outflow cannot be seen under normal circumstances

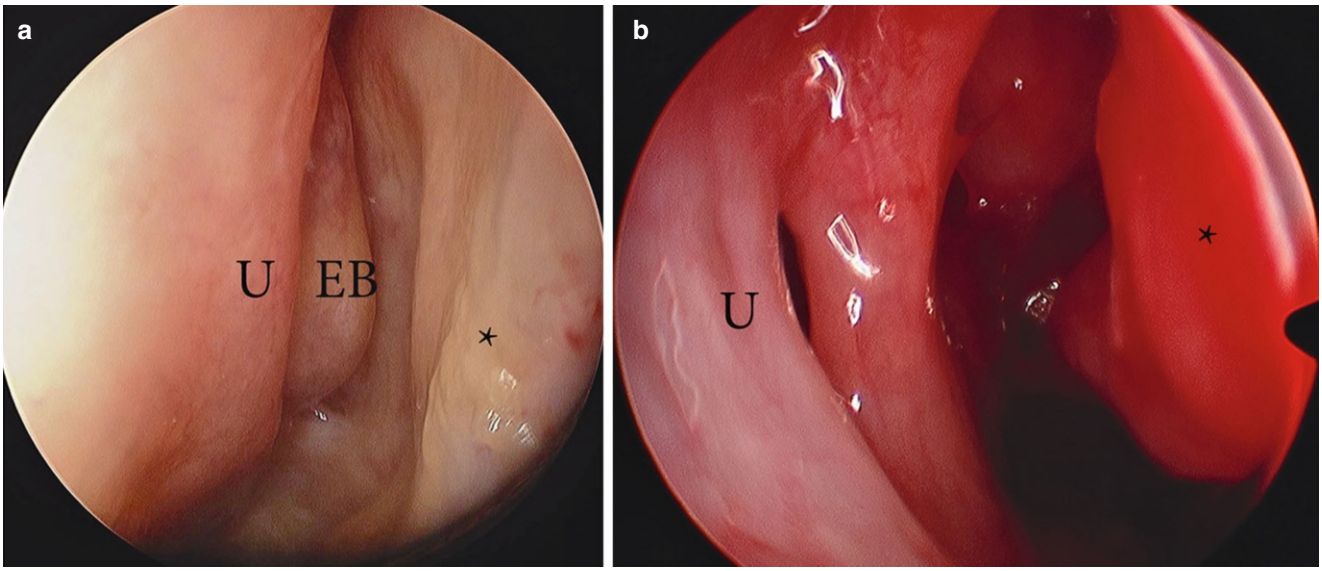


Fig. 16.15 (**a**) Rigid endoscopic picture of the osteomeatal complex. *U* uncinate process, *EB* ethmoid bulla, * middle turbinate. (**b**) Rigid endoscopic picture of the natural maxillary sinus os lateral to the middle turbinate after gentle middle turbinate medialization. *U* uncinate process, * middle turbinate

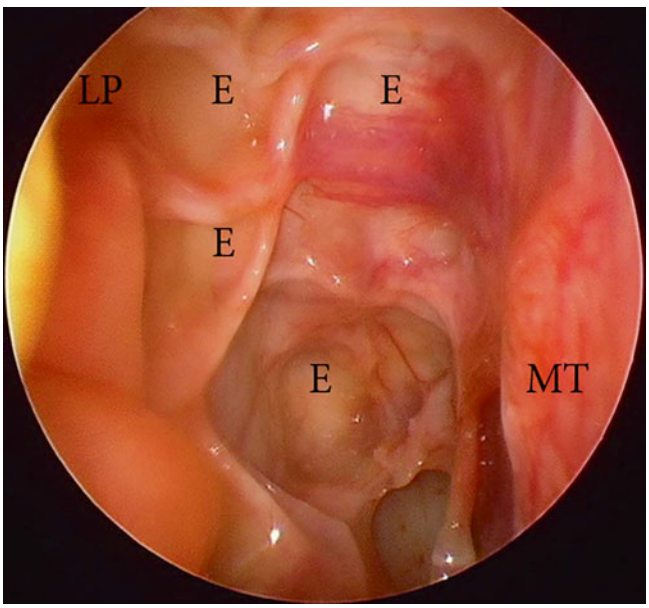


Fig. 16.16 Rigid endoscopic picture of the ethmoid sinuses after ear tube surgery. The lamina papyracea (*LP*) is lateral and the ethmoid sinuses (*E*) now widely opened with the skull base visible superiorly and the middle turbinate medially (*)

either. A view of the osteomeatal complex with a rigid scope is mostly comprised of the anterior tip of the middle turbinate and a view of the uncinate process. Rarely can one see the ethmoid bulla or maxillary sinus os with a rigid scope unless the middle turbinate can be gently medialized, which requires excellent anesthesia (Fig. 16.15a, b).

Following endoscopic sinus surgery, it is possible to see much more in the region of the osteomeatal complex owing to the fact that the middle turbinate has been medialized and the natural os of the maxillary sinus has usually been enlarged. The nasofrontal recess can be seen in many patients, as can some of the anterior and posterior ethmoid cells that otherwise would not have been available for view (Fig. 16.16). The postoperative patient should be examined with the same criteria for evaluating disease, such as the presence of mucosal edema and erythema and the existence of purulence or polypoid change. These patients, however, usually allow the practitioner to more easily discriminate whether acute and chronic sinusitis exists.

Special Considerations in Pediatric Patients

Performing nasal endoscopy on children of ages approximately 2–6 years can be challenging, if not nearly impossible, due to patient fear. Under the age of two, the guardian can hold the patient with the patient's back against the seated guardian's chest. The patient's legs are constrained between the guardian's legs, the patient's arms held by one arm of the guardian, and the patient's head held by the guardian's other arm. Alternatively, an assistant can hold the child's head while the guardian uses both arms to hold the patient's arms. By approximately 6 years of age, a child can potentially understand the purpose of endoscopy and may allow it. Endoscopy in children can more readily be performed if the novelty and technology are played up so that the focus is not on the expectations of the exam. The use of topical medications in the wary child can scare the patient and preclude endoscopy if the medication administration is perceived to be uncomfortable in any way. Thus, it is wise sometimes to minimize the preparation and anticipation in pediatric patients. It goes without saying that it is imperative to build a strong rapport with the child so he or she trusts the practitioner. Although it can generally be stated that for adult patients the easy parts of the endoscopic exam should be performed first, this is not always the case with children because the child may only allow a small window of time before he or she refuses further cooperation. Therefore, it is sometimes recommended to visualize the anatomic region of most interest first.

Conclusions

Anterior rhinoscopy is a routine part of the head and neck examination and can be enhanced by performing it with a nasal speculum because of superior optics compared to an otoscope. Visualizing the middle meatus and nasal mucosa is encouraged for diagnosing sinusitis clinically. The ability to diagnose chronic rhinosinusitis and other sinonasal pathologies, as well as examine the structures distal to the mid-nasal cavity, is predicated upon endoscopy equipment and skills. Familiarity with basic anatomy and commonly encountered pathology is required for all endoscopy practitioners. Likewise, the examination sequence and technique for both children and adults are specific and allow for best diagnostic conditions.

References

1. Lal D, Stankiewicz JA. Primary sinus surgery. In: Flint PW, Haughey BH, Lund VJ, et al., editors. Cummings otolaryngology head and neck surgery. 5th ed. Philadelphia: Elsevier; 2010. p. 597–623.
2. Walsh WE, Kern RC. Sinonasal anatomy, function, and evaluation. In: Bailey BJ, Johnson JT, Newlands SD, editors. Head and neck surgery – otolaryngology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 307–18.
3. Stankiewicz JA, Chow JM. Nasal endoscopy and the definition and diagnosis of chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2002;126:623–7.
4. Marple BF, Stankiewicz JA, Baroody FM, et al. Diagnosis and management of chronic rhinosinusitis in adults. Postgrad Med. 2009;121(6):121–39.
5. Benninger M, Hadley J, Osguthorpe J. Diagnosing acute bacterial rhinosinusitis. Arch Intern Med. 2004;164:568–70.
6. Tahamiler R, Canakcioglu S, Ogreden S, et al. The accuracy of symptom-based definition of chronic rhinosinusitis. Allergy. 2007;62:1029–32.
7. Melroy CT, Dubin MC, Senior BA. The role of nasal endoscopy in the diagnosis and medical management of chronic rhinosinusitis. Clin Allergy Immunol. 2007;20:227–40.
8. Casiano RR. Correlation of clinical examination with computer tomography in paranasal sinus disease. Am J Rhinol. 1997;11(3):193–6.
9. Lanza D, Kennedy D. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg. 1997;117(3 Pt 2):S1–7.

Chapter 17
Imaging of the Paranasal Sinuses: Plain-Film Radiography, Computed Tomography, and Magnetic Resonance Imaging

Mahmood F. Mafee, Nikdokht Farid, and Wei Yen Lim

Introduction

The paranasal sinuses develop as outgrowths of the fetal nasal cavities [1–3]. Maxillary and ethmoid sinuses develop during fetal life. Frontal and sphenoid sinuses are not present at birth but develop during the early years of life [1–3]. By 4–5 months after birth, the maxillary sinuses can be readily identified particularly on computed tomography (CT) scans. At birth, the size of the anterior ethmoid group is approximately 5 mm high, 2 mm long, and 2 mm wide, and the posterior group is 5 mm high, 4 mm long, and 2 mm wide [3]. After birth or a few months later, the maxillary sinuses and in particular ethmoid air cells can be potentially infected and cause orbital sinogenic infection.

Overview of Radiologic Imaging

Conventional plain-film radiography may be used as a screening method for various pathological conditions of the sinonasal cavities [1, 4–7]. This will provide orientation and direction to further indicated examinations, such as computed tomography (CT) and magnetic resonance imaging (MRI) [1, 5, 6]. Detailed bony structures of the paranasal sinuses and base of the skull are best evaluated on CT scans [1, 2, 8–15]. MRI, on the other hand, provides more information concerning soft tissue structures of the sinonasal cavities, face, and base of the skull. The intracranial complications of rhinosinusitis and intracranial extension of sinonasal neoplasms are best evaluated using MRI [1, 2, 5, 16].

The appearance of the lesions of paranasal sinuses, nasal cavity, and the face on CT or MRI scans does not always provide sufficient evidence for a specific histological diagnosis; however, cysts and cartilaginous, fibro-osseous, and osseous tumors are an exception. These lesions often can be accurately diagnosed on CT scans. The combination of CT scan and MRI provides maximum information for orbital and intracranial complications of sinonasal inflammatory conditions, as well as sinonasal tumors [1, 2, 16].

Although a plain-film sinus series can be of value in acute rhinosinusitis and for the initial evaluation of chronic rhinosinusitis and other sinonasal diseases, significant discrepancies are often noted between a sinus series and a CT scan [1, 2, 6]. CT scanning remains the study of choice for the imaging evaluation of acute and chronic inflammatory disease of sinonasal cavities. MRI is superior to CT in differentiating inflammatory conditions from neoplastic processes [1, 2, 10, 16]. Most inflammatory lesions are quite hyperintense (bright) on T2-weighted (T2W) MRI scans, as opposed to most malignant

M.F. Mafee, MD, FACR (✉) • N. Farid, MD
Division of Neuroradiology, Division of Head and Neck Radiology, Department of Radiology, University of California San Diego, 200 West Arbor Dr., San Diego, CA 92103-8756, USA
e-mail: mmafee@ucsd.edu; nfarid@ucsd.edu

W.Y. Lim, MBBS, Master of Radiology
Department of Radiology, ANOC Neuroscience and Orthopaedic Center, Lot 2.02, East Wing, Second Floor, Menara BRDB, Kuala Lumpur 59000, Malaysia
e-mail: limwyen@gmail.com

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_17,

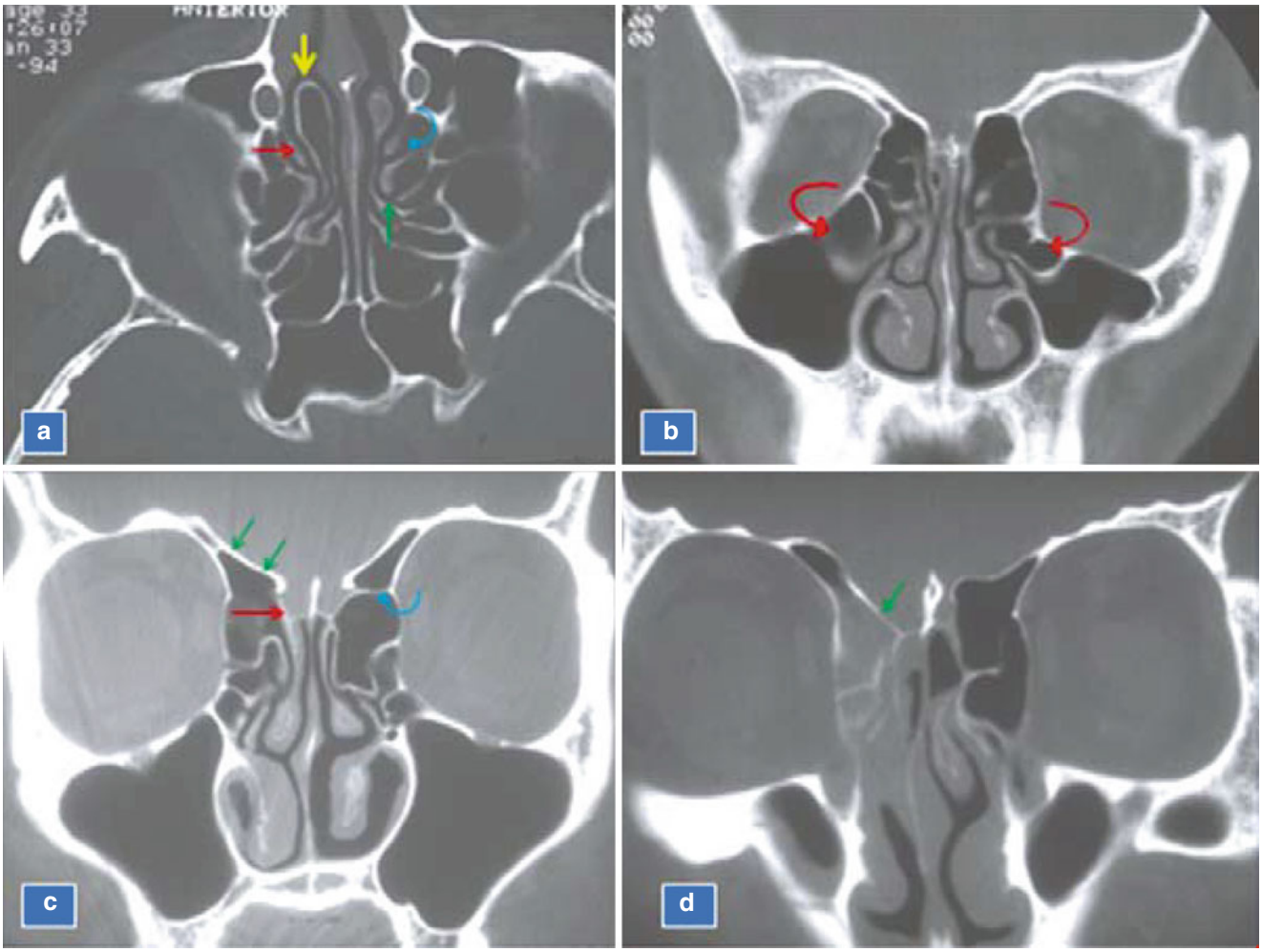


Fig. 17.1 Normal and anatomic variations. (**a**) Axial CT scan showing uncinate process (*red arrow*), concha bullosa (*yellow arrow*), and infundibulum (*blue arrow*). Note hiatus semilunaris (*small green arrow*) where the infundibulum opens into the middle meatus. (**b**) Coronal CT scan showing bilateral Haller cells (*curved red arrows*). (**c**) Coronal CT scan showing fovea ethmoidalis (*green arrows*), lateral lamella of the cribriform plate (*red arrow*), and ethmoid artery canal (*curved blue arrow*). (**d**) Coronal CT scan showing low lying fovea ethmoidalis (*green arrow*)

tumors, lymphoreticular proliferative, myeloproliferative, and chronic granulomatous disorders [1, 16]. Most tumors of the sinonasal cavities are not as hyperintense as the surrounding inflammation and retained secretions; therefore, MRI plays an important role in the mapping and staging of these tumors. Sinogenic intracranial and orbital complications are best evaluated using MRI [1].

CT scanning has afforded the best preoperative evaluation for endoscopic sinus surgery [1, 8–15]. The complex anatomy of the ethmoid bone and the ostiomeatal unit (OMU) can be visualized on CT scans with exquisite detail (Fig. 17.1) [1, 11]. The advent of minimally invasive surgical techniques using powered instruments with real-time suction has further enhanced the knowledge base of the surgical anatomy of the paranasal sinuses. The special relevance of ostiomeatal complex (OMC) (ostiomeatal unit OMU) to functional endoscopic endonasal sinus surgery has given the radiologist an important role in the assessment of patients scheduled for functional endoscopic sinus surgery (FESS). The combination of coronal and axial CT scans allows the surgeon to assess more easily the three-dimensional aspects of the OMC, as well as certain anatomic variations (Fig. 17.1). The reader is referred to Stammberger and Kennedy [17] and others for information about these structures [1].

Risk of Radiation from Sinus Imaging

The biological side effects of ionizing radiation have always been a matter of concern [18, 19]. In general, absorbed doses from most diagnostic studies are quite low [20]. There are no exposure limits for medical radiation as long as the study is clinically indicated [18]. On the average, diagnostic radiology is second to background radiation as a source of exposure for

the population in industrialized countries [17–19, 21, 22]. Natural background radiation may vary by three orders of magnitude throughout the world [19]. It has been postulated that only 1–2 % of all genetically determined diseases are attributable to the natural background radiation [19]. The dose required to double the human mutation rates lie between 2 and 2.5 sievert (Sv) [22]. The incidence of radiation-induced cataracts depends on the dose time and age [19]. The cornea demonstrates few effects until fractionated doses are in the range of 50 GY (5,000 rads). The radiation dose was initially measured in radiation-absorbed dose (or rad) and later in gray (Gy) or milligray (m Gy). One Gy equals 100 rad; 1 rad equals 10 m Gy or 0.01 Gy. The relative biological effectiveness of a given type of radiation is measured by the sievert (Sv) [23]. The earlier terminology of roentgen equivalent man (Rem) was replaced by Sv.

The risk of radiation from the sinus series or screening sinus CT is small [18]. Approximately 0.3 cG is given for each film view obtained during a plain X-ray sinus series [7, 18]. The organs most likely to be affected by a cumulative radiation dose are the lens, thyroid gland, and gonads. The dose to the lens of the eye is small if Waters and Caldwell views are obtained posterior-inferior, as they should be [18]. With the combination of high-speed film and a posterior-inferior projection, the dose to the eye in a sinus series should be on the order of 0.0001 Gy (0.01 cGy) to 0.005 Gy (0.5 cGy) [7, 18]. The radiation dose to the lens of the eye from a CT examination of the head may range from 3 to 6 cGy. The radiation from a CT scan of the sinuses to the lens, cornea, and other organs included in the CT sections can be significantly reduced by decreasing mAs (100–140 mAs) without significantly sacrificing details [23]. The imaging plane also can be chosen to avoid scanning directly through the lens of the eye. Ionizing radiation is an established carcinogen [23]. The patterns and trends in diagnostic imaging procedures have significantly changed, resulting in increased exposures to general population. The estimated per capita dose from medical radiation in the United States has increased approximately 600 % from about .53 mSv in the early 1980s to about 3.0 mSv in 2006 (1.5 mSv per capita from CT scans, .8 mSv from nuclear medicine procedures, 0.4 mSv from interventional procedures, and 0.3 mSv from plain-film radiographic procedures) [23]. The average effective dose for axial and helical scans for a CT of the head is 2 mSv equivalent to 150 chest X-rays [23]. The effective dose for skull AP or PA is 0.015 mSv. To reduce biological risks from diagnostic procedures, Linet et al. [23] advocate the use of evidence-based appropriateness criteria by professionals and professional organizations for decisions about imaging procedures. Unnecessary imaging studies (duplicate studies and those that are not medically necessary) should not be performed. For sinonasal imaging, using helical scans reconstructed (reformatted) coronal and sagittal views should be performed to avoid direct coronal scans.

CT Technique

CT scan is an excellent imaging modality to evaluate the sinonasal cavities. It provides an accurate assessment of the paranasal sinuses, OMU, craniofacial bones, as well as the extent of pneumatization of the paranasal sinuses (Fig. 17.1). In our institution we use the high-resolution multidetector row CT scanner (64-channel detectors, General Electric; Milwaukee, Wisconsin) and incorporate various scanning modes and parameter settings. Using a tube voltage of 120 KVp and a tube current time of 100–120 mAs per section, helical scanning with 0.625 mm detector collimation is performed in the axial plane (standard algorithm), and axial, coronal, and sagittal images are reformatted with 3 mm section thickness and 3 mm section intervals. The landmark study for image-guided endoscopic surgery will include 0.625 mm section thickness and 0.625 mm section interval reconstructed scans.

We prefer CT images to be viewed or filmed for soft tissues as well as with extended window width and level (W/L) bone technique (4,000/700–800 W/L). In case the study is interpreted on hardcopy films, we recommend that the technicians provide a set using soft tissue technique which allows for better evaluation of fluid, inspissated mucosal debris, and microcalcifications.

Contrast-enhanced CT should be performed whenever orbital and intracranial complications of sinonasal infections or tumors are suspected. Routine contrast-enhanced CT should not be part of preoperative CT for endoscopic sinus surgery [1, 2].

MRI Technique

An opinion one frequently hears with regard to sinonasal imaging is that MRI is often not very helpful compared with CT scanning. This may be true for a few specific entities, such as fibro-osseous lesions; however, for benign and malignant tumors, MRI is superior to CT scans to differentiate a tumor from surrounding associated inflammatory disease and retained secretions. The marked hyperintensity on T2W MRI images of the inflammatory mucosal disease, as well as marked enhancement of inflammatory mucosal thickening on enhanced T1-weighted (T1W) MRI images, often allows the radiologist to differentiate tumors from surrounding inflammatory disease. Intracranial tumor extension and intracranial complications of

sinonasal infections are better evaluated by MRI than CT scanning [1, 2, 16]. In general, the combination of MR and CT imaging, in most cases, will allow for better evaluation of the disease and at times for making a more specific diagnosis. The radiologist should always be consulted in determining the most appropriate imaging study or studies for each individual case. In the evaluation of suspected sinonasal disease processes, a typical MRI protocol consists of short time of repetition (TR)/time of echo (TE) sagittal localization, unenhanced short TR/short TE (T1W), and long TR/long TE (T2W) axial sequences, followed by a contrast-enhanced short TR/short TE (T1W) axial, coronal, and sagittal pulse sequences. The addition of fat saturation post-contrast T1W and diffusion-weighted pulse sequences imaging (DWI) can help to differentiate sinogenic abscesses from other simulating processes.

Inflammatory Disease of Sinonasal Cavities

Acute Sinusitis

The diagnosis of rhinosinusitis is not only, or necessarily, an imaging diagnosis. The radiologist should always require some information, positive or negative, about symptoms or signs that might suggest sinusitis, such as nasal discharge or congestion, fever, sinus pain and tenderness, and prior history of sinus draining, irrigation, or surgical procedures. Mucosal thickening, the most common finding on imaging studies, usually indicates the presence of chronic sinusitis, but may be also seen in patients with acute sinusitis. Postoperative scarring and periosteal reaction after a sinus surgery, such as Caldwell-Luc operation, may result in loss of normal aeration of the sinuses. These changes may be permanent, even in the absence of any sinus disease [20]. Although the lack of sclerosis and periosteal reaction speaks against chronic sinusitis, it does not at all rule out a chronic infection. Bilaterality and absence of erosion weigh in favor of an inflammatory rather than neoplastic process.

Diffuse thickening of the mucosa and submucosal lining of the paranasal sinuses is a common finding on plain films, CT, and MRI scans [1, 2]. Indeed, 20–40 % of patients undergoing MRI of the head are found to have edematous tissue of the paranasal sinuses as an incidental finding. An acutely infected sinus that is producing symptoms may show thickening of the mucosa, an air-fluid level, or both. Isolated infections of the maxillary sinus may be caused by dental caries in about 20 % of cases. More severe types of sinusitis occur in patients with diabetes and in patients who are immunosuppressed by various drugs, toxins, or systemic disease. These patients are more prone to aggressive types of fungal infections such as mucormycosis and aspergillosis, which tend to invade the local blood vessels, causing extensive tissue destruction, osteomyelitis, and even cerebral infarction [1, 2, 23]. These types of infection need to be diagnosed as early as possible and treated aggressively and appropriately. Biopsy and special cultures may be required to establish the diagnosis of fungal infection.

Radiological Diagnosis

It should be noted that an air-fluid level does not necessarily indicate the presence of acute sinusitis. Knowledge of the history and physical findings are necessary to differentiate other causes of an air-fluid level, such as a previous antral lavage, recent trauma, recent surgical procedure, barotrauma, or hemorrhage caused by a coagulopathy, such as a platelet disorder or von Willebrand disease. Acute sinusitis is usually evident on clinical examination, confirmed by plain-film studies and followed by CT study as needed. Conventional radiography is adequate for the diagnosis of clinically uncomplicated acute sinusitis [1, 2]. In patients with viral rhinosinusitis, sinus CT scans may reveal mucosal thickening of nasal passages, along with mucosal thickening and an air-fluid level in the paranasal sinuses. There may be air bubbles scattered within the fluid (transudates or exudates) in the sinuses. After the resolution of the common colds, sinus CT scans will demonstrate complete resolution of mucosal changes as well as clearing of the fluid in the sinuses. Subperiosteal edema and bony changes (osteolysis, demineralization) are not seen unless there are associated superimposed bacterial or fungal infections [1, 24].

Sinus Infections and Their Complications

Conventional radiography may be adequate for the diagnosis of acute sinusitis. Even though antibiotics have cut down on the incidence of complicated sinusitis with orbital involvement, it still occurs and may even be the first sign of a sinus infection in children [1, 2]. Infection may spread from the sinuses to the orbit by direct extension. It may also spread by way of numerous valveless communicating veins between the sinuses and the orbit. The orbital involvement from sinusitis includes inflammatory edema, orbital periostitis, subperiosteal induration (phlegmon), subperiosteal abscess (Fig. 17.2), orbital and facial cellulitis (Fig. 17.3), orbital abscess (Fig. 17.4), and ophthalmic vein thrombosis (Fig. 17.5).

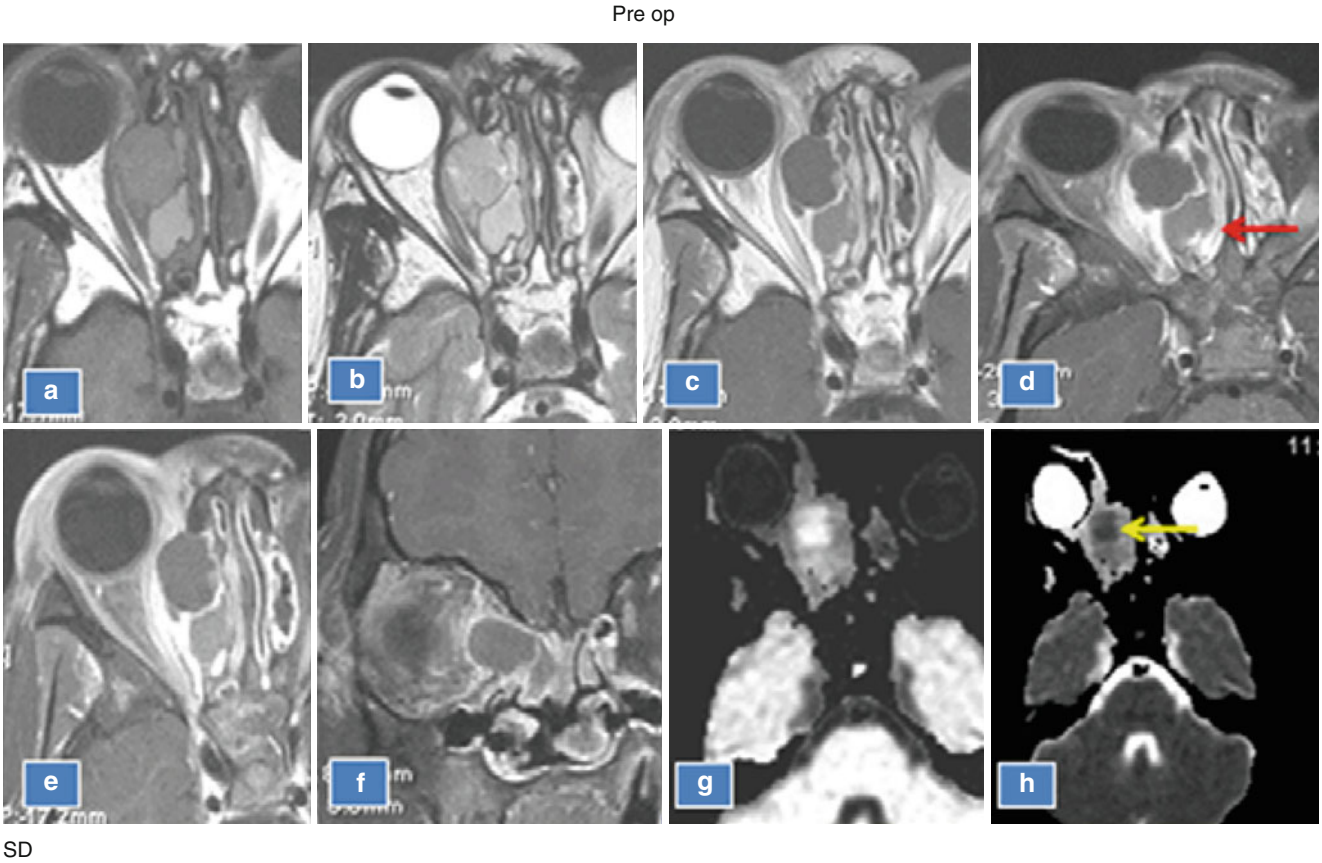


Fig. 17.2 Sinogenic orbital subperiosteal abscess in a 12-year-old boy. Axial unenhanced T1W (**a**), T2W (**b**), enhanced T1W (**c**), enhanced fat saturated T1W (**d**), enhanced fat saturated T1W (**e**), coronal enhanced fat saturated T1W (**f**), axial DWI (**g**), and ADC map (**h**) showing an orbital subperiosteal abscess (*yellow arrow*). Note inflammation of the right ethmoid air cells (*red arrow*)

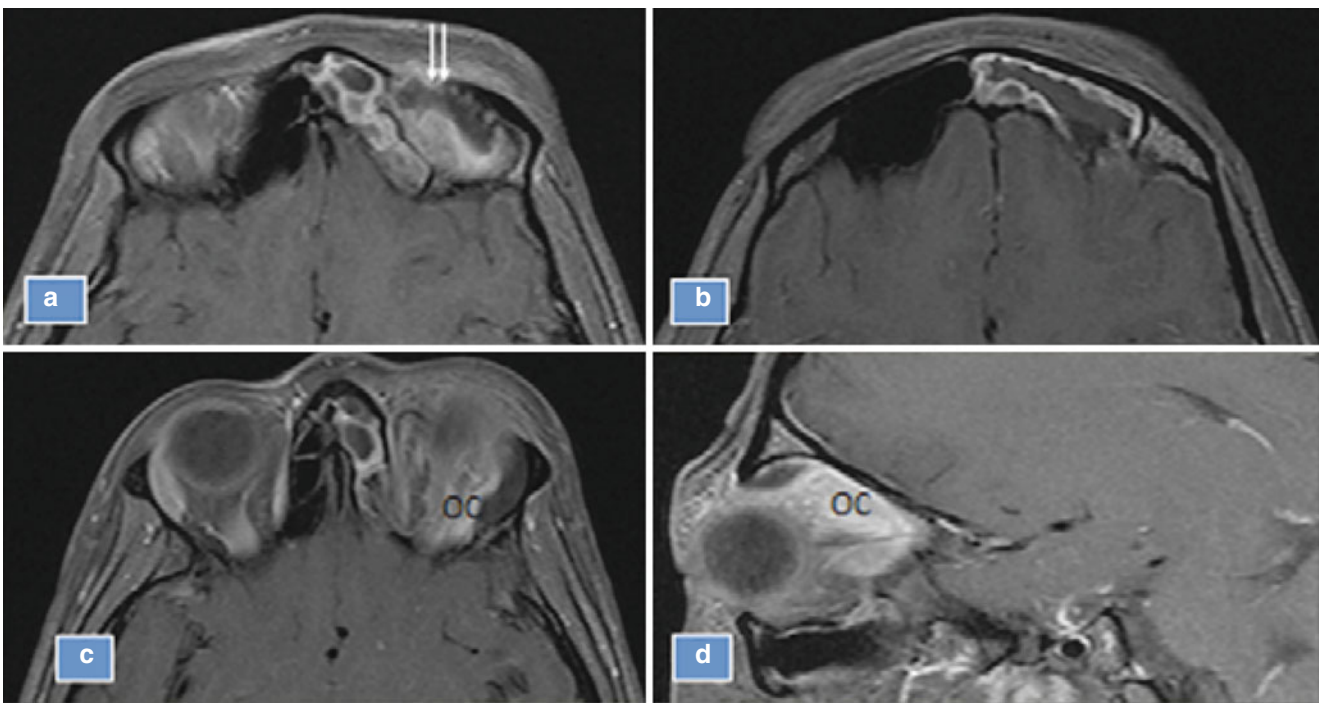


Fig. 17.3 Acute left frontal sinusitis with orbital subperiosteal abscess and orbital cellulitis. Axial enhanced fat saturation (**a**–**c**) and sagittal enhanced T1W (**d**) MR images showing subperiosteal abscess (*double white arrows*), and marked orbital cellulitis (*OC*)

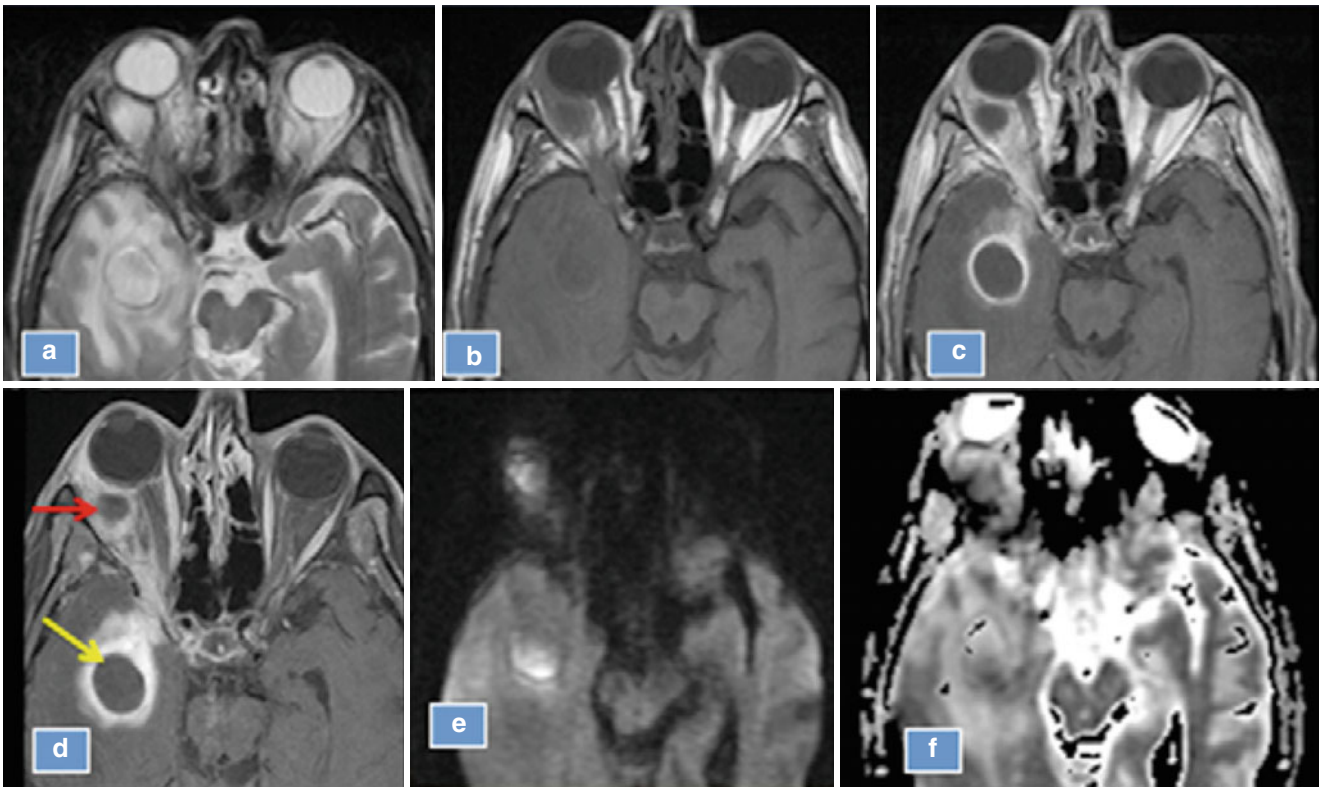


Fig. 17.4 Orbital and brain abscesses. Axial T2W (**a**), unenhanced axial TW (**b**), enhanced T1W (**c**), enhanced fat saturation T1W (**d**), DWI (**e**), and ADC map (**f**) showing an orbital (*red arrow*) and brain abscess (*yellow arrow*) related to a tree branch penetrating the orbit and temporal lobe

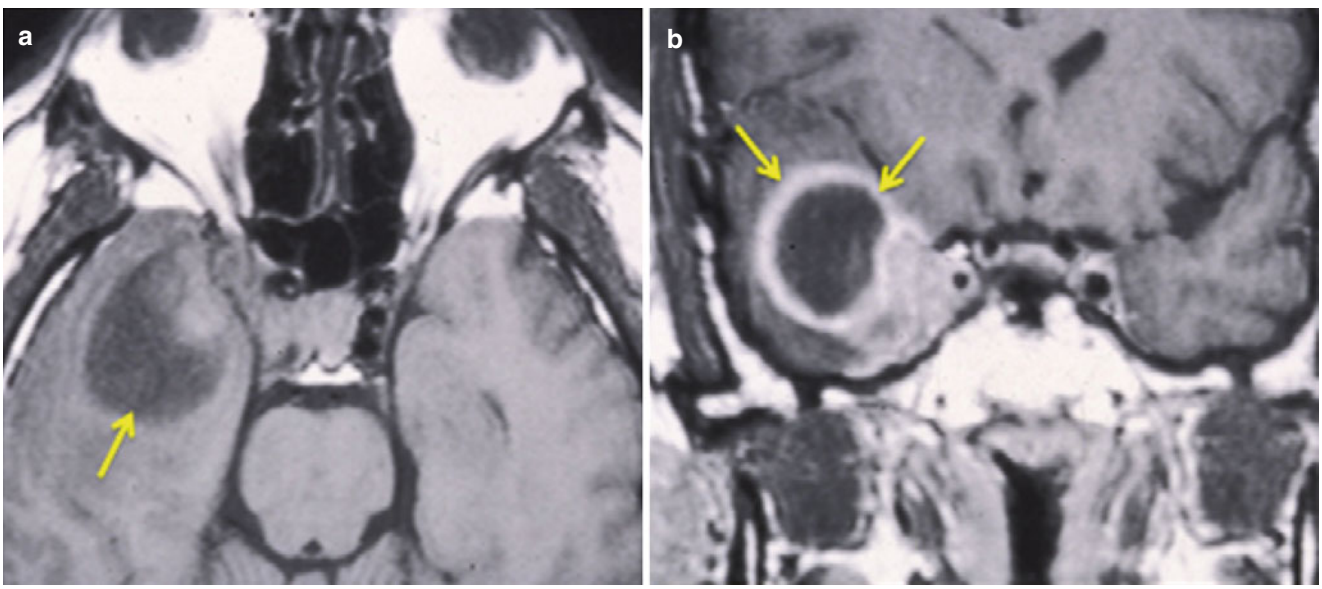


Fig. 17.5 Sinogenic septic thrombosis of cavernous sinus. Axial unenhanced T1W (**a**) and coronal enhanced T1W (**b**) MR images demonstrate right cavernous sinus abscess (*yellow arrows*)

Should the infection spread from the sinuses into the cranial cavity, one or more of the following complications may ensue: cavernous sinus thrombosis, meningitis, epidural and subdural abscess (Fig. 17.6), and brain abscesses (Fig. 17.7). Periostitis and osteomyelitis of the frontal sinus severe enough to involve the orbit may also extend through the posterior plate of the frontal sinus to involve the anterior cranial fossa (Fig. 17.7). Osteomyelitis of the frontal bone may be accompanied by doughy edema overlapping the affected sinus and/or a subgaleal abscess, causing a mass effect termed a "Pott's puffy tumor."

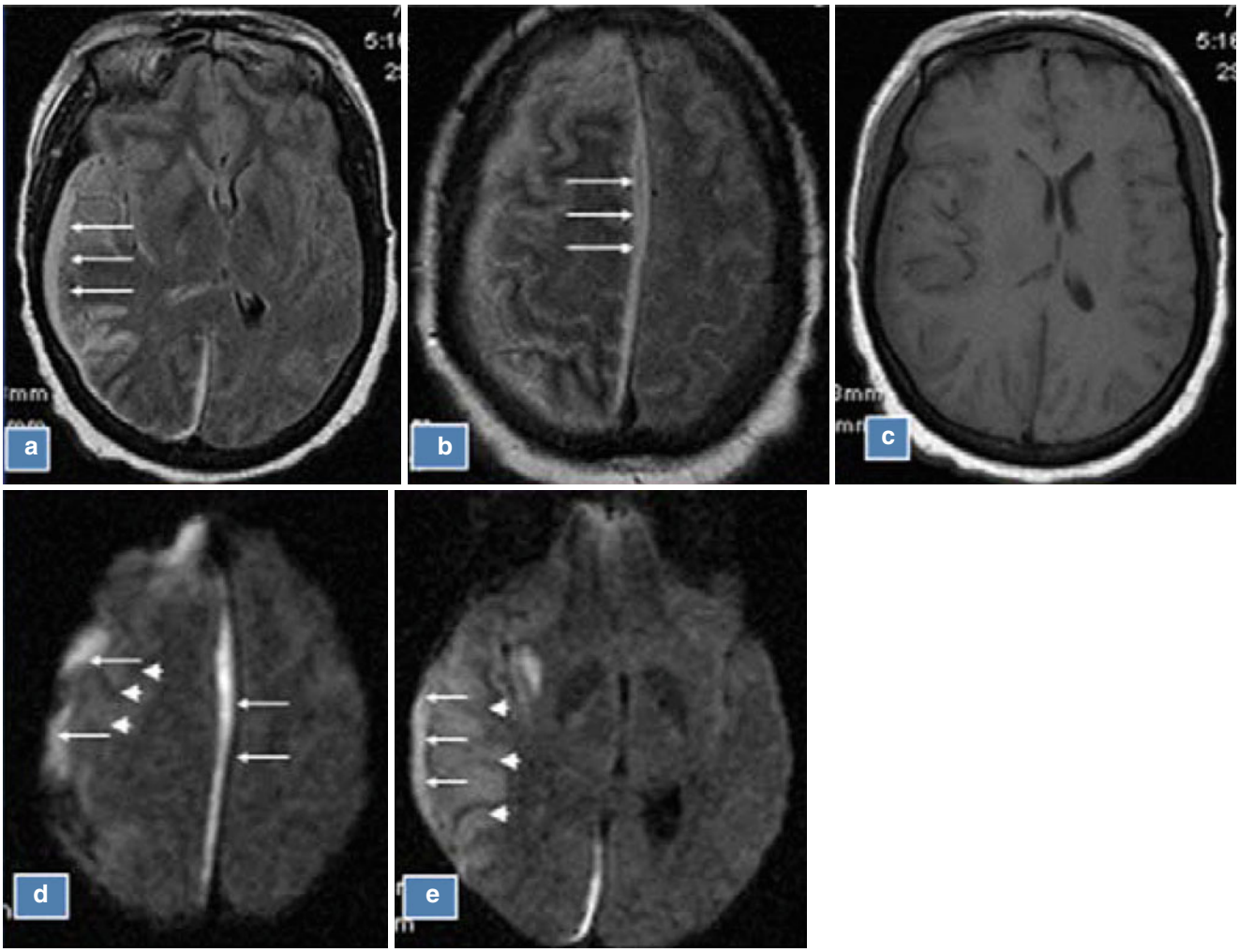


Fig. 17.6 Sinogenic subdural empyema. Axial flair (**a**, **b**), axial unenhanced T1W (**c**), and DWI (**d**, **e**) MR images showing opacification of the frontal sinuses. Note subdural fluid collection (*white arrows* in **a**) extending along the interhemispheric fissure (*white arrows* in **b**) and marked diffusion restriction (*white arrows* in **d**, **e**) indicating subdural empyema. Note acute cerebritis with restricted diffusion (*white arrowheads* in **d**, **e**)

Acute, subacute, or chronic sinusitis that has not responded to appropriate antibiotic and other medical treatments should be biopsied to rule out the presence of any underlying tumor, particularly if infection is limited to a single sinus. In the case of maxillary sinusitis, an underlying dental cause has to be excluded. For example, a persistent air-fluid level following dental extraction may indicate an oral-antral fistula. Orbital and intracranial complications resulting from acute and chronic sinusitis are best evaluated with combination of CT and MRI imaging (Figs. 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, and 17.7).

Complications of Rhinosinusitis in Children

The most common complications of rhinosinusitis in children occur in the orbit. These complications include the following, in order of increasing severity: orbital edema, orbital cellulitis, subperiosteal orbital abscess (Fig. 17.2), true orbital cellulitis (Fig. 17.3), intraorbital abscess (Fig. 17.4), and thrombosis of superior ophthalmic vein and cavernous sinuses (Fig. 17.5). Inflammatory orbital edema owing to sinusitis results in edema of the eyelid, which is often misdiagnosed as orbital or periorbital cellulitis. The infection in this early stage is actually still confined to the sinus [1, 2]. A CT or MRI scan at this stage will demonstrate the edema of the eyelids and conjunctivae and inflammatory changes of the infected sinus or sinuses. As the reaction of the orbital periosteum begins and gradually advances, the edema of the eyelids and conjunctivae becomes more generalized, and the eye begins to protrude. Inflammatory tissue collects beneath the periosteum to form subperiosteal edema or phlegmon; subsequently, pus may form indicative of a subperiosteal abscess (Fig. 17.2).

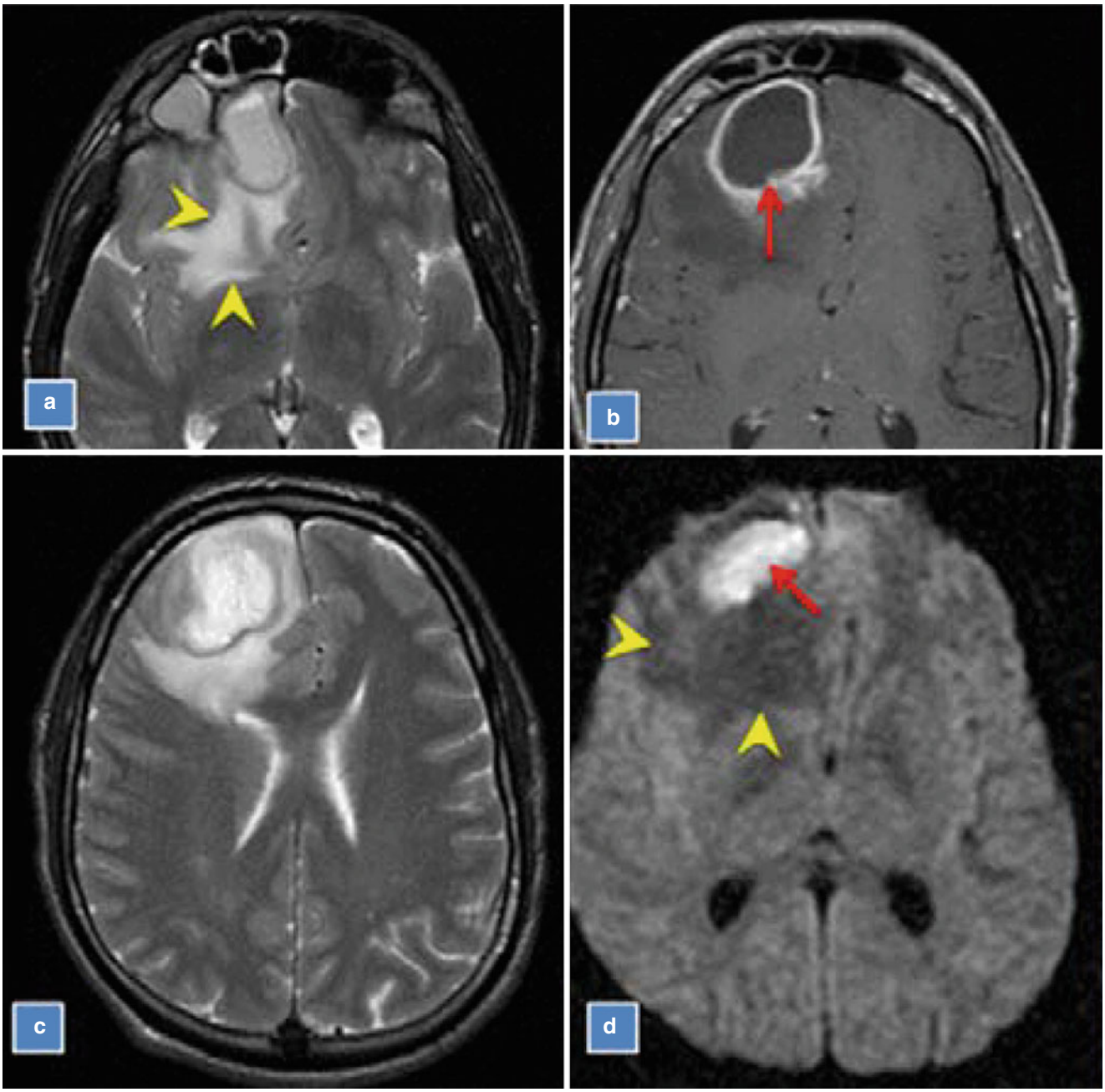


Fig. 17.7 Frontal sinusitis and sinogenic brain abscess. Axial T2W (**a**), axial enhanced T1W (**b**), axial T2W (**c**), and DWI (**d**) showing a brain abscess (*red arrows*) and associated vasogenic edema of the right frontal lobe (*yellow arrowheads*)

As the disease progresses, bacteria may infiltrate the periorbital and retro-orbital fat, giving rise to true orbital cellulitis and abscess (Fig. 17.4). These two conditions frequently coexist. At this stage, extraocular mobility is progressively impaired. With severe involvement, visual disturbances can result from optic neuritis, ischemia (compression), or both. Abscess formation in the orbit may result from extension of a subperiosteal abscess through the periosteum or from localization of orbital and facial cellulitis. Usually ethmoid sinus infection is frequently responsible for orbital swelling, as well as subperiosteal and orbital abscesses through the lamina papyracea. CT is an excellent radiologic method for evaluating an acute ethmoiditis. The information obtained from the CT scan and MRI, together with clinical findings (proptosis, limitation of extraocular muscle movement, and decreased visual acuity), may be the best guide for clinical management and the mode of treatment.

Intracranial Complications of Sinusitis

Although intracranial complications of sinusitis are relatively rare, prompt recognition of these disease states is important to prevent permanent neurological deficit or mortality. Intracranial complications of sinus infection derive from either indirect extension via retrograde thrombophlebitis of valveless emissary veins, or directly, through bony contiguity associated with septic erosion, trauma, or structural abnormality. These complications include osteomyelitis, epidural empyema, subdural empyema (SDE), meningitis, cerebritis, brain abscess, sinodural thrombosis [1, 2] infarct, and tension pneumocephalus related to ruptured intracranial abscess into the ventricles while in continuity with sinonasal cavities. SDE is thought to be the most common complication of the sinus infection [24, 25]. With timely intervention, mortality rates associated with SDE range from 10 to 20 %, but may be as high as 70 % under certain circumstances [24]. SDE is the most common intracranial complication of sinusitis, and the most common cause of SDE is sinusitis [26]. SDE is a neurosurgical emergency that requires drainage to avert a rapidly evolving and fulminant clinical course. Inoculation of the subdural space most often occurs indirectly via thrombophlebitis of valveless emissary veins [24]. The triad of fever, sinusitis, and the neurological deficits is suggestive of intracranial spread of infection. In SDE, the infection lies adjacent to the leptomeninges; therefore, patients with SDE may present with meningeal signs, hemiparesis, seizure, or mental status changes. CT with contrast is usually sufficiently sensitive to detect an SDE, which is appreciated on the scan as a low-density extra-axial fluid collection in the setting of marked cortical swelling [1, 2]. There may be increased vascular enhancement related to generalized increased permeability of the vasculature caused by the inflammatory response. Small interhemispheric subdural collections may be difficult to detect by CT scan. MRI is superior to CT scanning for detection of subdural collection and pyogenic lesions (Fig. 17.6). SDE is a very serious sequel of sinusitis that is seen in young men and is frequently associated with *Streptococcus anginosus* [24]. MRI is the imaging study of choice for the diagnosis of SDE, as well as other sinogenic intracranial complications [1, 2]. Early recognition and treatment are essential to reduce any subsequent morbidity or mortality [25]. In addition to CT scanning, it is prudent to obtain MRI of the sinuses, orbits, and brain whenever extensive or multiple complications of sinusitis are suspected [1, 2].

Acute Mycotic Rhinosinusitis (Rhino-Sinu-Orbito-Cerebral Fungus Infection)

Mycotic infection of the nasal and paranasal sinuses and craniofacial structures is a serious disease that requires prompt surgery and medical therapy to reduce its high morbidity rate [14, 27]. This infection is usually seen in immunocompromised individuals, such as patients with AIDS or patients who have undergone therapy with immunosuppressive drugs and antimetabolites [20, 28–30]. Rhino-orbito-cerebral mucormycosis is also seen in debilitated patients and patients with diabetic ketoacidosis. Leukemia and dialysis have also been reported to predispose patients to this infection [1, 2]. Recently, cases of rhino-sinu-orbito-cerebral mucormycosis have been described in patients with iron overload. The fungi responsible for mucormycosis are ubiquitous and normally saprophytic in humans; they rarely produce severe disease, except in those with predisposing conditions, as noted above [1, 2, 27]. The infection usually begins in the nose and spreads to the paranasal sinuses; then it extends into the orbit and cavernous sinuses. The inflammatory process soon extends along the intracranial and infraorbital fissure and into the infratemporal fossa (Fig. 17.8).

The radiographic findings of mucormycosis of the sinuses were first described by Green et al. [31] who noted three signs: nodular mucosal thickening, absence of fluid levels, and spotty destruction of bony walls. None of these signs can be considered typical for the diagnosis of fungal sinusitis; however, a CT scan or MRI study may be very helpful and sometimes characteristic for the diagnosis of mucormycosis [1, 2, 27]. The main contribution of CT or MRI scanning to the diagnosis of mucormycosis is its clear demonstration of the relationship between nasal, sinus, and orbital disease along with tissue loss (necrosis), a relationship so typical of mucormycosis that this diagnosis should be considered whenever this combination of features exists. Invasion of the medial orbit by the infecting organism results in phlegmon of the periorbital area and, therefore, elevation of the medial rectus, which later on becomes involved via direct invasion by hyphae. Effacement and edema of the facial planes outside the involved sinus, bone destruction of the sinus walls, and, in particular, periosteal irregularity and cortical bony rarefaction indicative of periostitis and osteitis are common. At times, the CT and MRI appearance of rhino-orbital mucormycosis may stimulate a sinonasal malignancy (Fig. 17.8). In an appropriate clinical setting, CT and MRI scans usually help to differentiate the overall picture from that of a sinonasal malignant process.

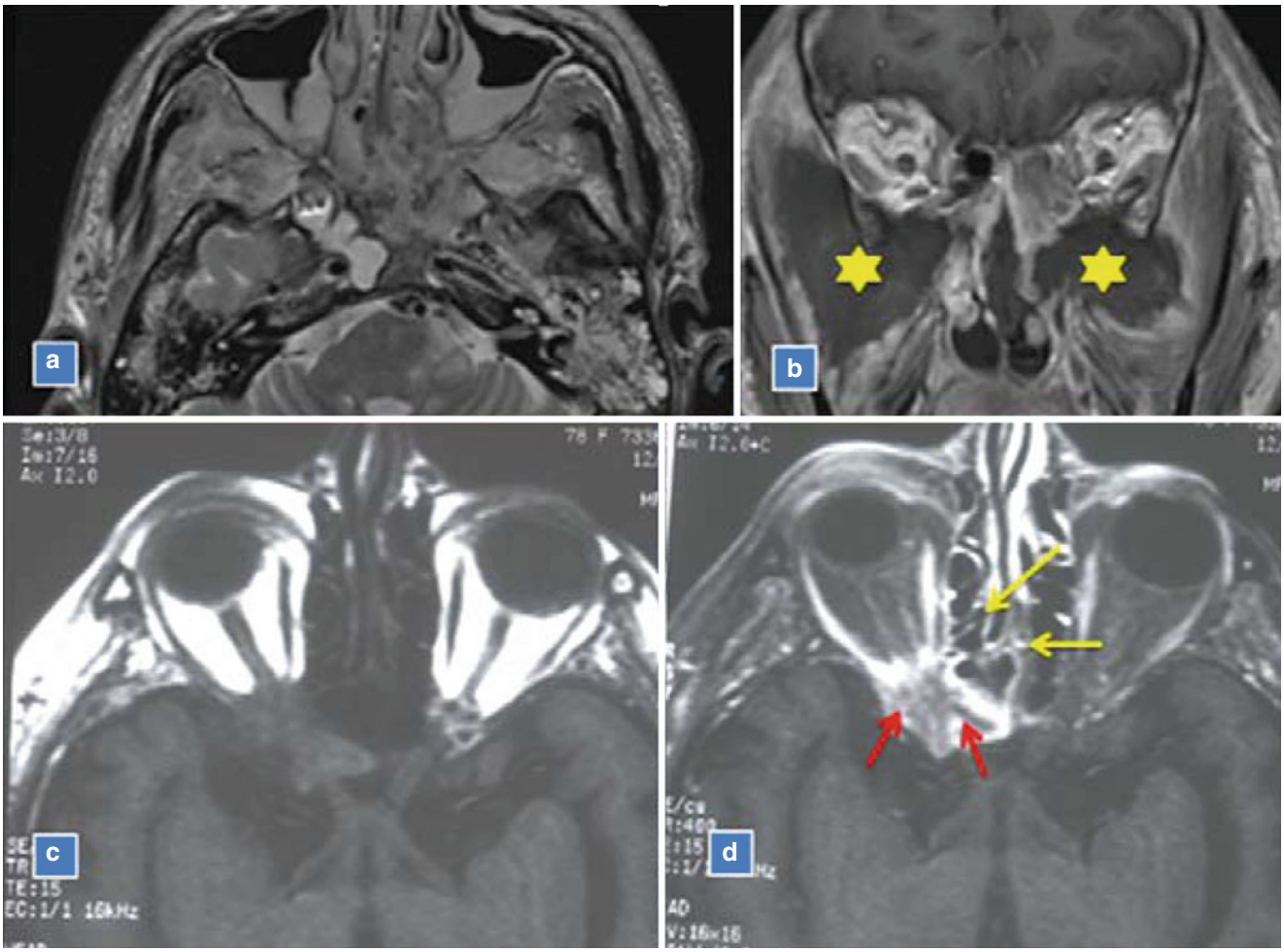


Fig. 17.8 Mucormyocosis. Axial T2W (**a**) and coronal enhanced fat saturation T1W (**b**) showing sinonasal mucormyocosis in a diabetic patient. Note extension into the infratemporal fossa (★). At surgery, necrosis of tissue was found. Axial unenhanced T1W (**c**) and enhanced fat saturation T1W (**d**) in a 98-year-old female showing aspergillosis of the posterior ethmoid air cells (*yellow arrows*) with extension into the orbital apex (*red arrows*)

Aspergillosis

Aspergillosis is a ubiquitous mold found primarily in agricultural dust. It may produce rhinocerebral infection and orbital involvement similar to mucormycosis, although hematogenous spread from the lungs to the brain is more common [27, 31]. This fungus also has a well-known propensity for invading blood vessels, including the internal carotid artery. The combination of orbital sinus involvement on CT or MRI is not pathognomonic of rhinocerebral mucormycosis or aspergillosis; however, awareness of its possibility, particularly when any of the predisposing factors are present, would help in making an early diagnosis and treatment of this aggressive and fatal disease. In our practice, CT and MR scanning have been the most effective imaging modalities for making the correct diagnosis. It is important to include the nasal cavity, nasopharynx, base of the skull, and the brain when performing CT or MRI in a patient with a potential or tentative diagnosis of mucormycosis, aspergillosis, or other opportunistic infections of the sinonasal tracts.

Chronic Rhinosinusitis and Allergic Fungal Rhinosinusitis

Chronic rhinosinusitis (CRS) is an extremely common disease that affects more than 31 million people in the United States alone each year [32]. CRS is defined as an inflammatory condition that involves the paranasal sinuses as well as the lining of the nasal cavities [33, 34]. The diagnosis of CRS with or without polyposis requires that symptoms must be present for

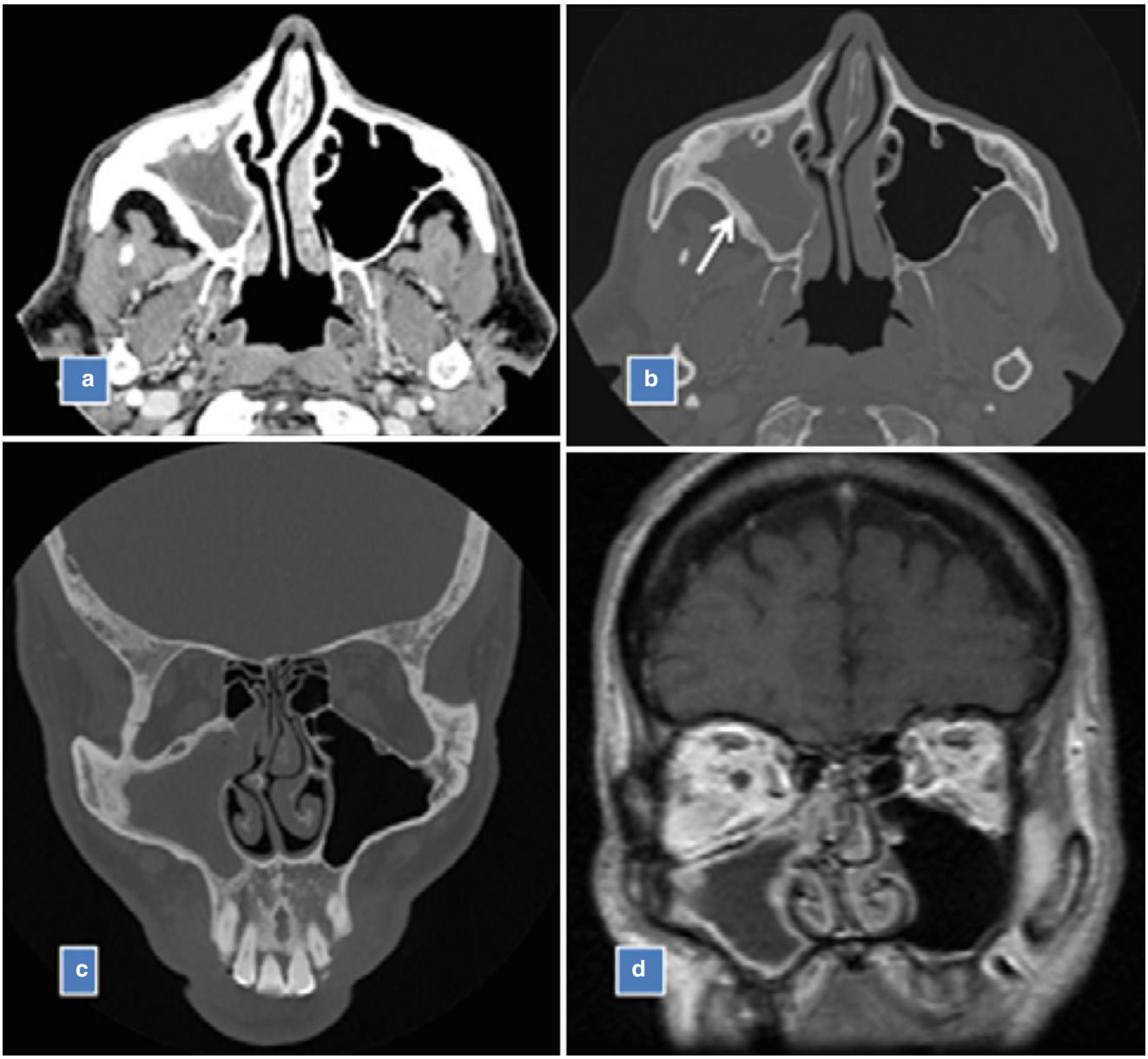


Fig. 17.9 Chronic sinusitis and superimposed presumed suppurative infection. Axial enhanced CT scan (**a**), axial bone window setting CT (**b**), coronal bone window setting CT (**c**), and enhanced coronal T1W MR (**d**) images showing sclerosis of the right maxillary sinus (*white arrow* in **b**). Note enhancement of the thickened mucosa in the fluid filled right maxillary sinus

12 weeks or longer despite appropriate medical therapy [33]. CRS is a complex, multifactorial disease that has genetic, infectious, immune, anatomic, allergic, and inflammatory components [33]. CRS is a clinical diagnosis, confirmed and staged with the CT scan of sinonasal cavities [28, 33–38]. Often, the CT scan is used to plan the extent of surgery for disease that fails to respond to medical management.

CRS is often associated with mucosal thickening and sclerosis of the wall of the sinus and bony septae (Fig. 17.9). Acute infections cause demineralization (rarefaction) of the wall of the sinus (Fig. 17.1) and subsequently, when the process becomes chronic, results in reactive sclerosis of the sinus walls (Figs. 17.9 and 17.10). These sclerotic changes in the wall of the sinus often indicate the presence of osteitis, which requires a prolonged course of antibiotics [2–25, 27, 31–33]. Sclerotic bone (osteosclerosis) may be just a reactive process rather than osteitis. This reactive sclerosis may remain forever and at times may result in a contracted sinus (Fig. 17.11). The contracted sclerotic maxillary sinus is also a common finding following a Caldwell-Luc operation. Complete opacification of one or more anterior ethmoid air cells is commonly seen and may represent the underlying focus of persistent symptoms. Less commonly, other sinus cavities or posterior ethmoid air cells may be

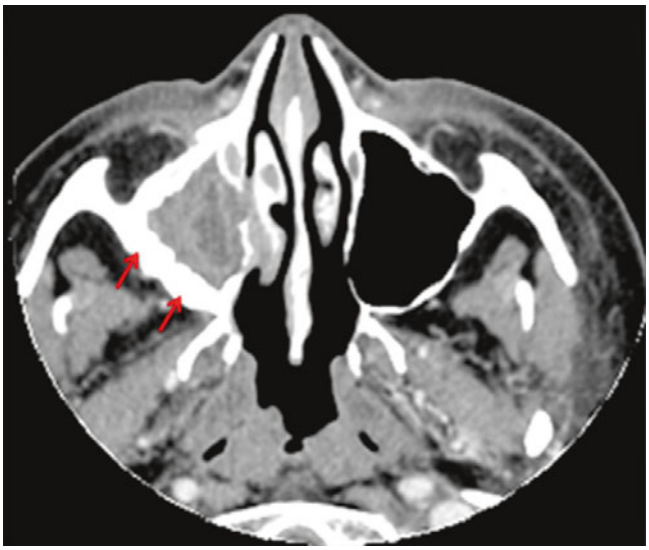


Fig. 17.10 Chronic sinusitis with periosteal bone formation. Axial CT scan shows opacification of the right maxillary sinus. Note the thickened bony wall (*red arrow*) resulting in contracted sinus

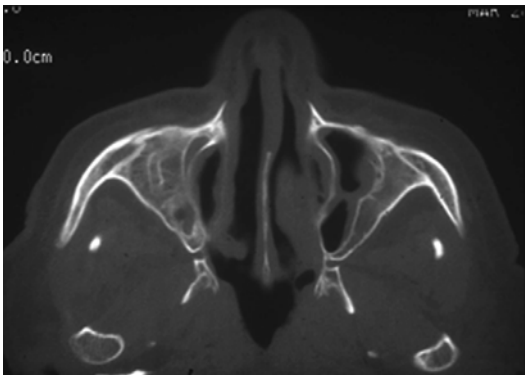


Fig. 17.11 Chronic bilateral maxillary sinusitis resulting in contraction of both sinuses related to reactive periosteal bone thickening

completely opacified. Variable degrees of sinus ostial obstruction are also common in CRS. Obstruction of the OMC has been given special significance (individual "weighting") in some CRS staging systems, such as the Lund and Mackay system based on the presumption that obstruction of this clinical-anatomic pathway is more likely to cause persistent sinus disease.

Mucosal thickening and/or sinus opacification are typically more pronounced in CRS with nasal polyps (NP) than CRS without NP. Polyps are seen on CT scans as mucosal protrusions into the nasal passage (Figs. 17.12 and 17.13). The CT density of polyps cannot be differentiated from nonpolypoid mucosal thickening. The combination of CT and MRI including enhanced CT and MRI provides an imaging appearance that highly favors the presence of polyps. A solitary polyp may not be differentiated from a retention cyst on unenhanced CT and MRI. Unlike cysts, polyps demonstrate moderate to marked contrast enhancement. In aggressive long-standing polyposis, there may be significant expansion of the nasal cavities and the MRI characteristics of sinuses as well as bone erosion. Polyps have various signal intensities on MR pulse sequences. The MRI characteristics of polyps reflect the various stages of the polyps (edematous, glandular, cystic, and fibrous) as well as various stages of desiccation of the entrapped mucosal secretions within the crevices of the polyps and on the surfaces of the polyps [1, 2].

Chronic Fungal (Mycotic) Rhinosinusitis and Chronic Allergic Fungal Rhinosinusitis

Fungal sinus disease is often diagnosed because an apparently routine infection fails to respond to a commonly used antibiotic regimen [27]. In immunocompetent patients, fungal sinus disease may first be recognized as a slowly progressing extramucosal fungus ball and represents noninvasive disease [39]. Chronic extramucosal fungal sinusitis develops as a saprophytic growth in retained secretions in a sinus cavity. This disorder is usually benign and is rarely associated with mucosal invasion. The constellation of allergic mucin, sinonasal polyposis, and the presence of extramucosal fungi have been referred

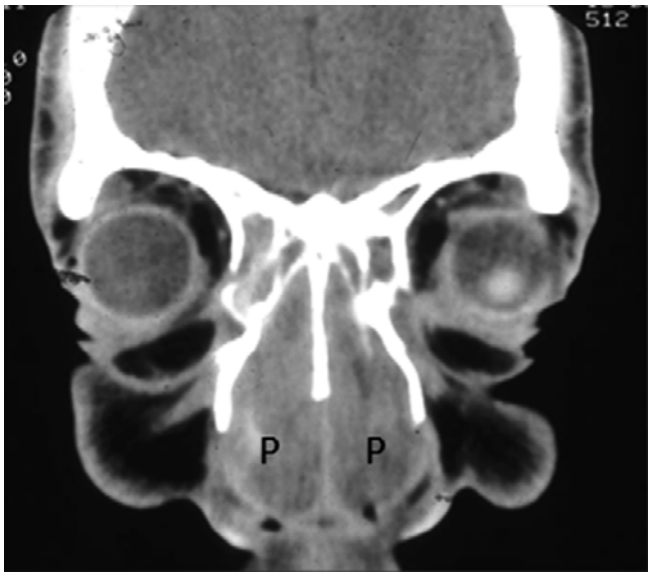


Fig. 17.12 Chronic rhinosinusitis with polyposis (*P*)

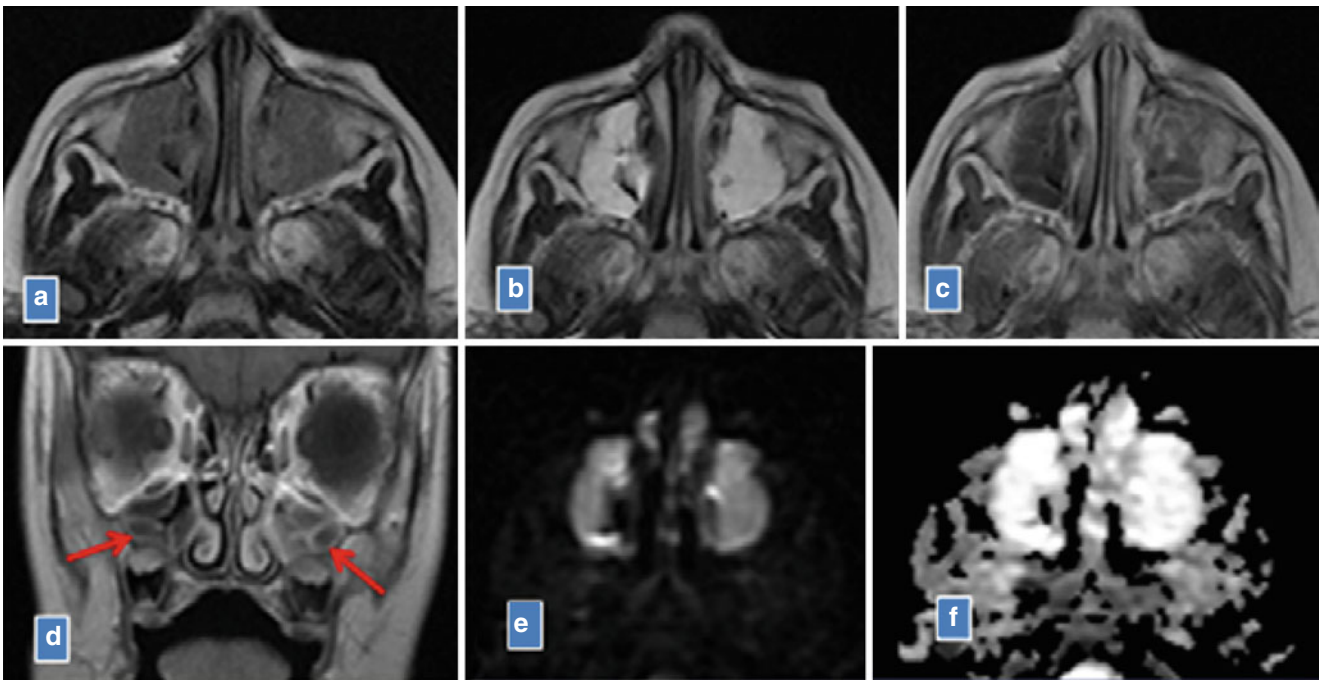


Fig. 17.13 Polypoid mucosal thickening of the maxillary sinuses. Axial unenhanced T1W (**a**), T2W (**b**), enhanced T1W (**c**), enhanced coronal T1W (**d**), DWI (**e**), and ADC map (**f**) showing polyps (*red arrows* in **d**) inside the maxillary sinuses. Note no diffusion restriction (**e**, **f**)

to as "allergic fungal rhinosinusitis," because of its similarity to allergic bronchopulmonary aspergillosis [30]. The highly proteinaceous central mucin creates areas of high attenuation on CT images (Fig. 17.14) and corresponding to low signal on both T1W and T2W MRI images [40].

Imaging of Chronic Allergic Fungal Rhinosinusitis

"Allergic fungal rhinosinusitis" (AFRS) comprises 5–10 % of all cases of CRS requiring surgery [28]. Patients with AFRS commonly present with chronic unilateral or bilateral CRS with nasal polyps [28]. They are usually young, immunocompetent patients with a history of inhalant allergy. To satisfy the criteria for AFRS, the patient must have CRS and demonstrate

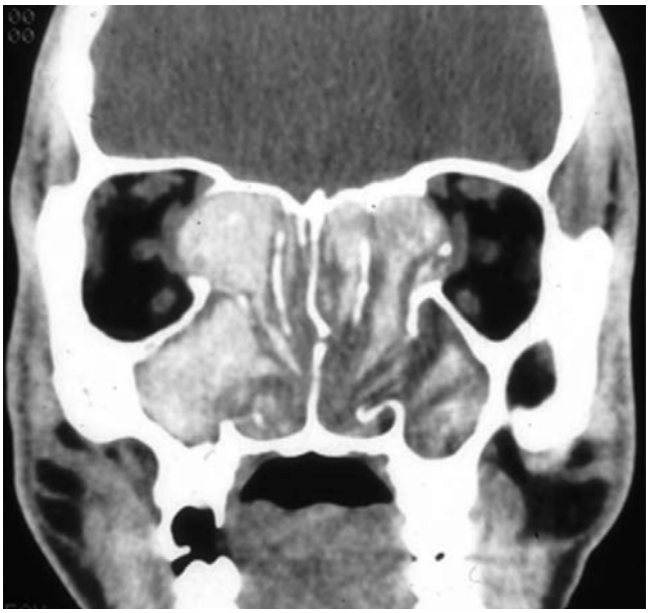


Fig. 17.14 Allergic fungal rhinosinusitis. Coronal CT scan showing marked soft tissue obliteration of the nasal cavities and bilateral maxillary and ethmoid sinuses. Note characteristic increased density related to inspissated mucosal secretion. Note expansion of ethmoid sinuses related to mucocele formation

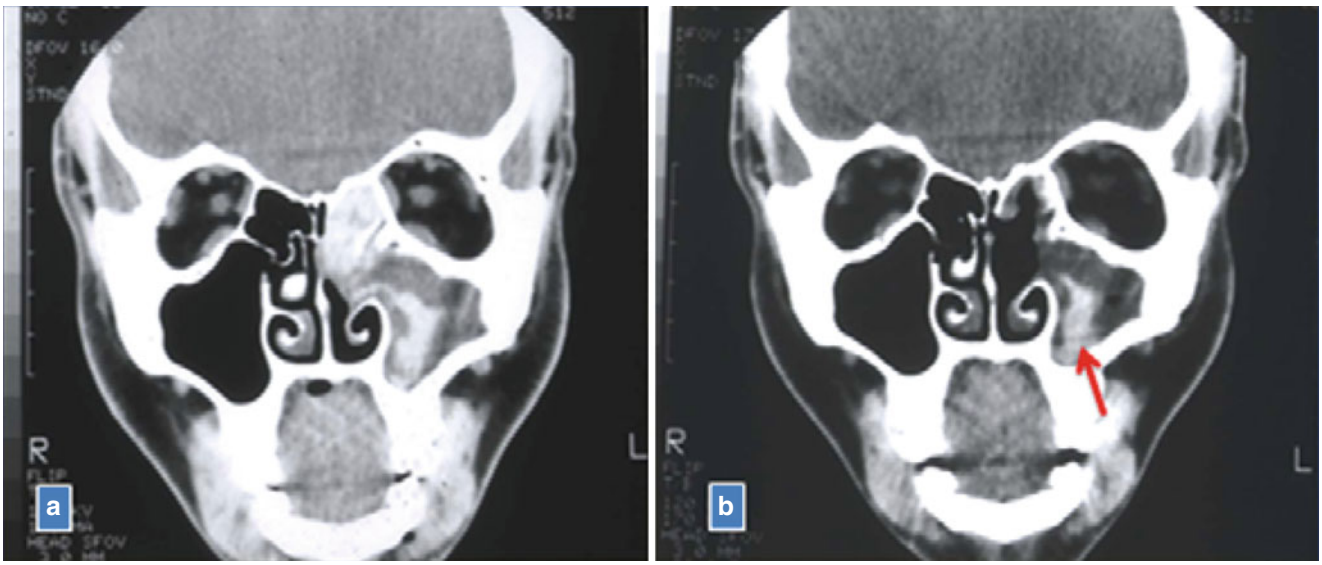


Fig. 17.15 Chronic sinusitis with presumed fungal ball in the left maxillary sinus. Coronal CT scan (**a**) shows characteristic changes of chronic allergic sinusitis in the left maxillary and left ethmoid sinuses. Postoperative coronal CT scan (**b**) shows persistent disease with a central increased density in left maxillary sinus (*red arrow*), presumed to be a fungal ball

evidence of sinus opacification with "allergic mucin" (inspissated mucus with degranulating eosinophils), the presence of fungal hyphae in the sinus cavity, and evidence of fungal-specific IgE. The imaging manifestations of chronic mycotic rhinosinusitis may be nonspecific or highly suggestive of the presence of fungal infection. AFRS most often involves the maxillary, ethmoid, and sphenoid sinuses.

The findings on plain radiography may vary from nonspecific mucosal disease without any bone involvement to an opacified sinus with a polypoid mass with a central peripheral hyperdense (calcified) mass representative of a fungal ball or mycetoma [1, 2, 27, 29, 30]. The fungal balls or mycetomas may appear as either a homogeneous soft tissue mass or a well-defined high-density mass similar to that seen with calcium or bone (Fig. 17.15). The increased density within the polypoid sinus mass in chronic mycotic rhinosinusitis is believed to be caused by calcium phosphate and calcium sulfate deposits within necrotic areas of the mycelium [26, 29, 35].

CT is superior to plain radiography in detecting fungal concretions. The presence of highly proteinaceous inspissated mucus in AFRS creates areas of very high attenuation on CT images [36]. Allergic mucin has areas of high protein content

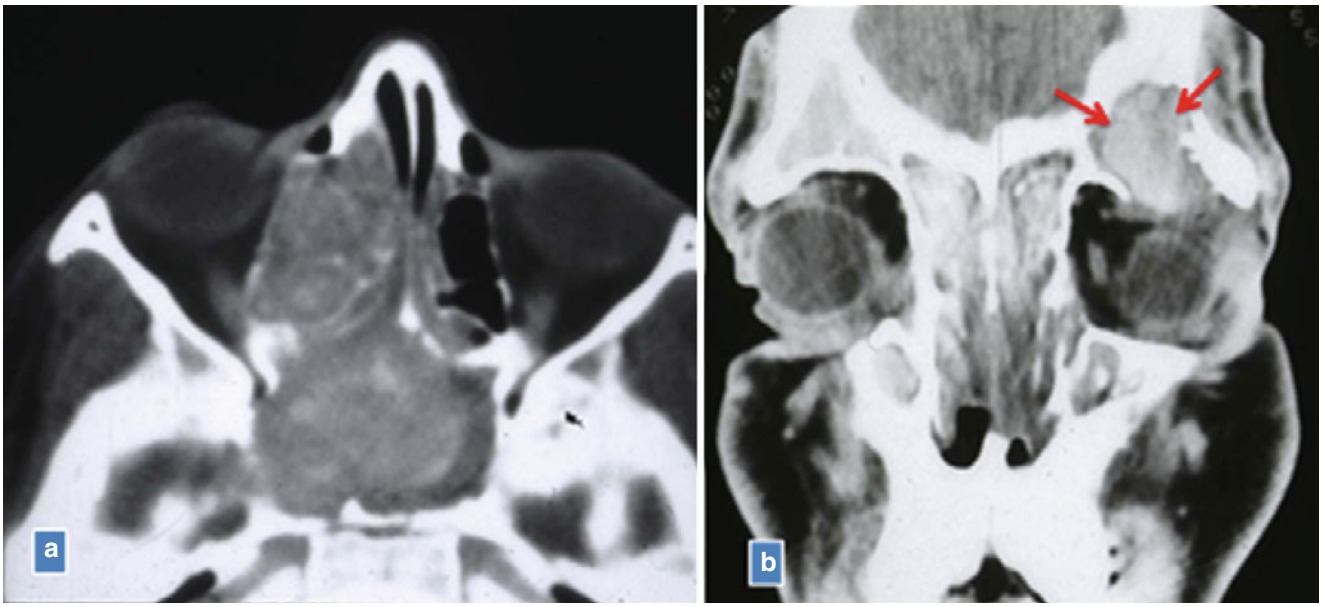


Fig. 17.16 Allergic fungal rhinosinusitis with extension into the left superior orbit. Axial (**a**) and coronal (**b**) CT scans showing pansinusitis. Note extension of a frontal mucocele into the left orbit (*red arrows* in **b**)

and low water concentration that give rise to characteristic imaging appearance of CT and MRI scans. The presence of diffusely increased attenuation within the paranasal sinuses and nasal cavity should be considered as indicative of AFRS or chronic hyperplastic sinusitis and polyposis associated with desiccated, retained mucosal secretions (concretions; Fig. 17.14). Zinreich et al. [29] reported 25 patients with chronic fungal sinusitis. Of these, 22 had foci of increased attenuation on CT scans. Areas of focal hyperattenuation varied in size. The smallest area measured 4 mm in diameter; the largest nearly formed a cast of the maxillary sinus. The presence of areas of increased CT densities in the paranasal sinuses did correlate well with fungal sinusitis [29]. However, because pus, desiccated mucosal secretions, dystrophic calcifications (concretions, antrolith), and acute hemorrhage are also dense on CT scans, CT findings alone are not conclusive of chronic fungal sinusitis in a partially or totally opacified sinus. Therefore, increased CT densities should suggest as a high index of suspicion that chronic noninvasive or chronic indolent fungal sinusitis, especially aspergillosis, exists.

IN AFRS, the walls of the ethmoid air cells become thickened owing to chronic reactive sclerosis. In acute mycotic rhinosinusitis and malignant tumors of the ethmoid, there will ultimately be destruction of these walls. As these materials accumulate within the sinuses, bony demineralization of the sinus walls ensues secondary to the release of inflammatory mediators. Increasing pressure results in expansion of the sinus and mucocele formation [36].

In summary, the sinuses most often involved in AFRS are the maxillary, ethmoid, and sphenoid sinuses. CT scan is the study of choice for evaluating possible AFRS. The CT findings suggesting AFRS include foci of increased density (hyperattenuation) within the opacified sinuses and nasal polyps that represent inspissated allergic mucin. The areas of hyperattenuation vary in size. At times they may form a cast of increased density within the sinus. The process may involve one sinus or several sinuses (Fig. 17.14). Extrasinus extension of AFRS into the orbit and into the cranium may be present (Fig. 17.16). As inspissated allergic mucin accumulates in the sinuses, demineralization of the sinus walls ensues secondary to the release of inflammatory mediators end pressure, resulting in expansion of the sinus and mucocele formation (Fig. 17.16). True bone erosion is less common. However, in hypopneumatized sphenoid sinuses, AFRS may cause erosion of the roots of the lesser wing and lead to significant unilateral or bilateral compressive optic neuropathy.

The MRI characteristics of fungal sinusitis depend on the stage of the disease [41]. In acute invasive fungal sinusitis, regardless of the offending organism, there will be significant inflammatory edema and cellular infiltrate, resulting in marked hyperintensity in proton-weighted (PW) and particularly on T2W MRI images. The process appears relatively hypointense on T1W MR scans. In AFRS, the presence of concretions and desiccated mucosal secretions results in low signal on T1W and marked hypointensity on T2W MR images. The reactive granulations and associated subacute or acute sinusitis will demonstrate hyperintense signal on T2W MR images (Fig. 17.17). There will be enhancement only of the mucosal rim on enhanced MR images. All of the fungal concretions in the study of Zinreich et al. [29] stained positively

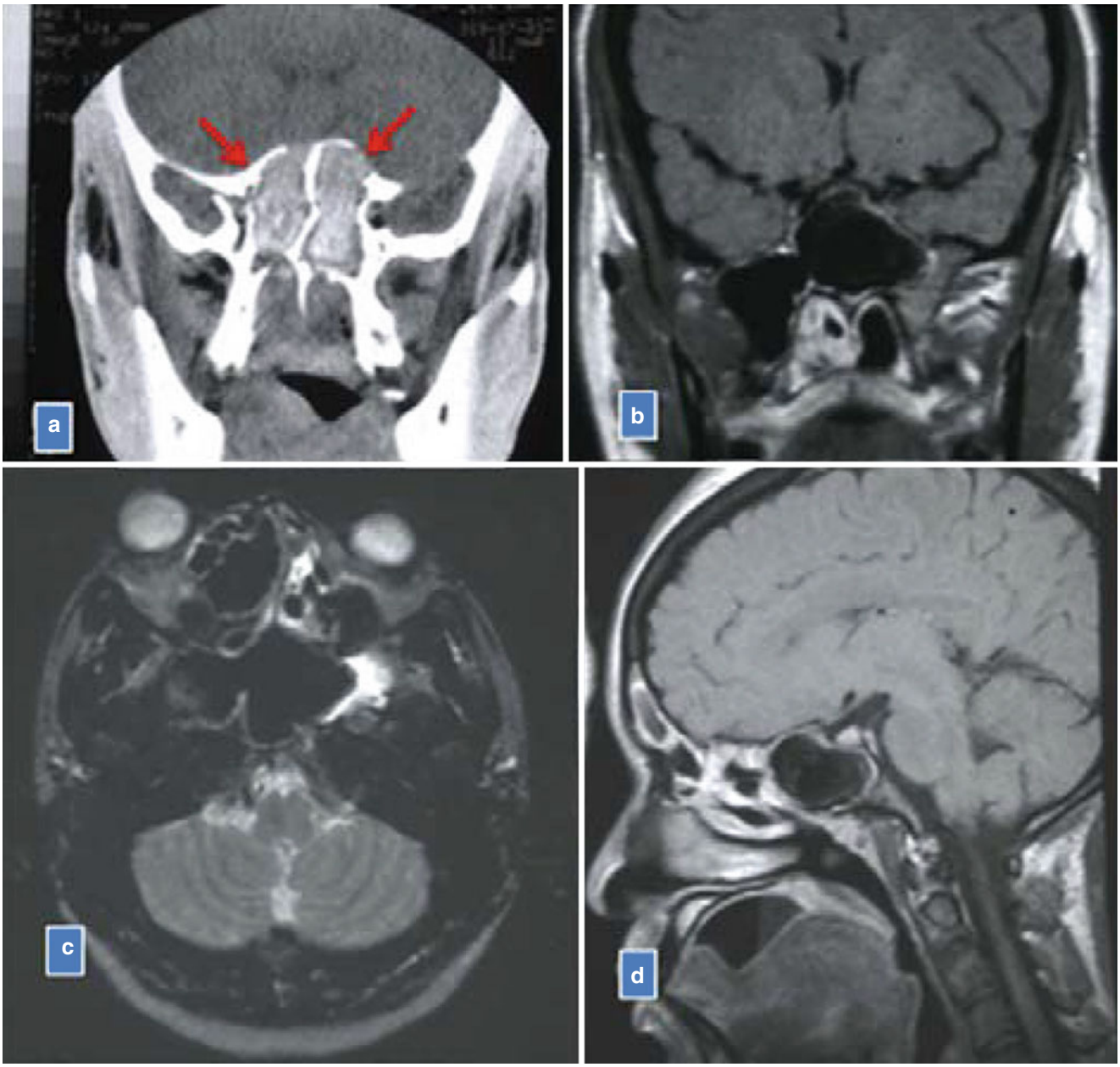


Fig. 17.17 Allergic fungal sinusitis. Coronal CT (**a**), coronal T1W (**b**), axial T2W (**c**), and sagittal enhanced T1W (**d**) MR images showing characteristic high-density material in sphenoid sinuses (*red arrows* in **a**). The sinuses on MR appear hypointense (**b–d**). Note enhancement of the posterior ethmoid air cells as well as mucosal outline of sphenoid sinus

for calcium. Decreased signal intensity on T1W and very decreased signal intensity on T2W MR images were thought by Zinreich et al. [29] to be the result of calcium, as well as iron, magnesium, and manganese, which are known to be essential in fungal amino acid metabolisms [37].

Zinreich et al. [29] examined specimens of fungal concretions from two patients with AFRS with specimens obtained from four patients with bacterial sinusitis and compared them for the presence of iron, magnesium, and manganese. They found that in two patients with proven aspergillus sinusitis, iron and manganese, both electromagnetic elements, were present in larger quantities than in the four patients with bacterial sinusitis. They concluded that increased concentrations of iron and manganese, as well as the presence of calcium in the fungal concretions, may explain the hypointensity on T2W MRI images. However, recent studies suggest that the presence of inspissated mucosal secretions within the sinus cavity or along the crevices of polyps commonly results in a markedly hypointense T2W signal [1, 2, 36]. In fact, the majority of sinus cases with hypointense T2W signal are now felt to be related to desiccated retained mucosal secretion with or without the presence of fungus organism. For example, chronic noninvasive aspergillus sinusitis and AFRS may have the same MR appearance as chronic hyperplastic sinonasal polyposis with inspissation of the retained mucosal secretion. In general, acute and subacute

bacterial or allergic sinonasal mucosal inflammation will demonstrate high-signal intensity on T2W MR images. In contrast, neoplasms tend to have a lower signal intensity compared with acute or subacute sinonasal mucosal inflammation. There will also be more enhancements on post-gadolinium T1W MR images within polyps and the mucosa of acute and subacute sinusitis as opposed to tumors and inspissated mucus.

Chronic Sinonasal Inflammation Secondary to Nasal Cocaine Abuse

Intranasal cocaine abuse can cause a variety of otolaryngological complications secondary to its potent vasoconstrictive effects and direct irritation of the nasal mucosa [2, 38]. Repeated intranasal "snorting" or "sniffing" of cocaine can lead to ischemia and necrosis of the nasal septum resulting in septal perforation, synechia, and chronic sinusitis [38]. Other upper airway complications of cocaine abuse include osteolytic sinusitis and nasolacriminal duct obstruction [38].

Silent Sinus Syndrome

Silent sinus syndrome (SSS) has been described as spontaneous enophthalmos resulting from chronic maxillary rhinosinusitis and maxillary sinus atelectasis. Nasal endoscopy will commonly show retraction of the uncinate process and obliteration of the infundibulum. Imaging findings include obstruction of the MOC at the maxillary infundibulum, atelectatic uncinate process, contracted maxillary component of antrum, opacification of maxillary sinus, inferior bowing antral roof, lateral bowing of the medial wall, and anterior bowing of the posterior maxillary sinus (Fig. 17.18).

Rhinolith

Foreign bodies within the nasal cavity and paranasal sinuses tend to become encrusted and calcified when retained for a long period of time and are thus known as rhinoliths and sinoliths, respectively. These calcareous bodies may be endogenous or exogenous in origin. Teeth, sequestra, and dried blood clots are considered endogenous. Exogenous material includes fruit seeds, beads, buttons, pieces of dirt and pebbles, and the remains of gauze tampon. A calcified nasal mass on CT scan is characteristic of rhinolith. The calcification appears as a cast surrounded by soft tissue related to the inflammatory reaction associated with rhinolithiasis. A sinolith has a similar appearance and is most commonly seen in the maxillary antrum.

Granulomatous Rhinosinusitis

Granulomatous rhinosinusitis (GRS) has an extensive differential diagnosis, including sarcoidosis, fungal infections, tuberculosis, syphilis, leprosy, rhinoscleroma, Wegener's granulomatosis, allergic granulomatous and angiitis (Churg-Straus syndrome), lymphoplasmatoid granuloma, IgG4-related sclerosing disease (pseudotumor), cholesterol granulomas, foreign body granulomas such as lipogranulomas due to oil drops, injected corticosteroids and paraffin, and unknown causes. There are no distinguishing sinus imaging features of these disorders with the diagnosis typically made histologically and through other laboratory studies.

Mucoceles

The etiology of mucoceles (collections of mucus) is debatable. Most otorhinolaryngologists believe that mucoceles are secondary to obstruction of the main ostium of the sinus [42]. This obstruction may be the result of inflammation, trauma, osteoma, fibrous dysplasia, or repeated surgery in and around the nasal cavity [1, 2, 38]. Approximately two-thirds of all mucoceles involve the frontal sinuses; the majority of the remainder involves the ethmoidal labyrinth. Maxillary and sphenoid mucoceles are rare. Bilateral mucoceles are rare. The degree of inflammatory changes that either initiate or accompany the mucocele determines the amount of chronic inflammatory reaction in the covering wall of the mucous membrane.

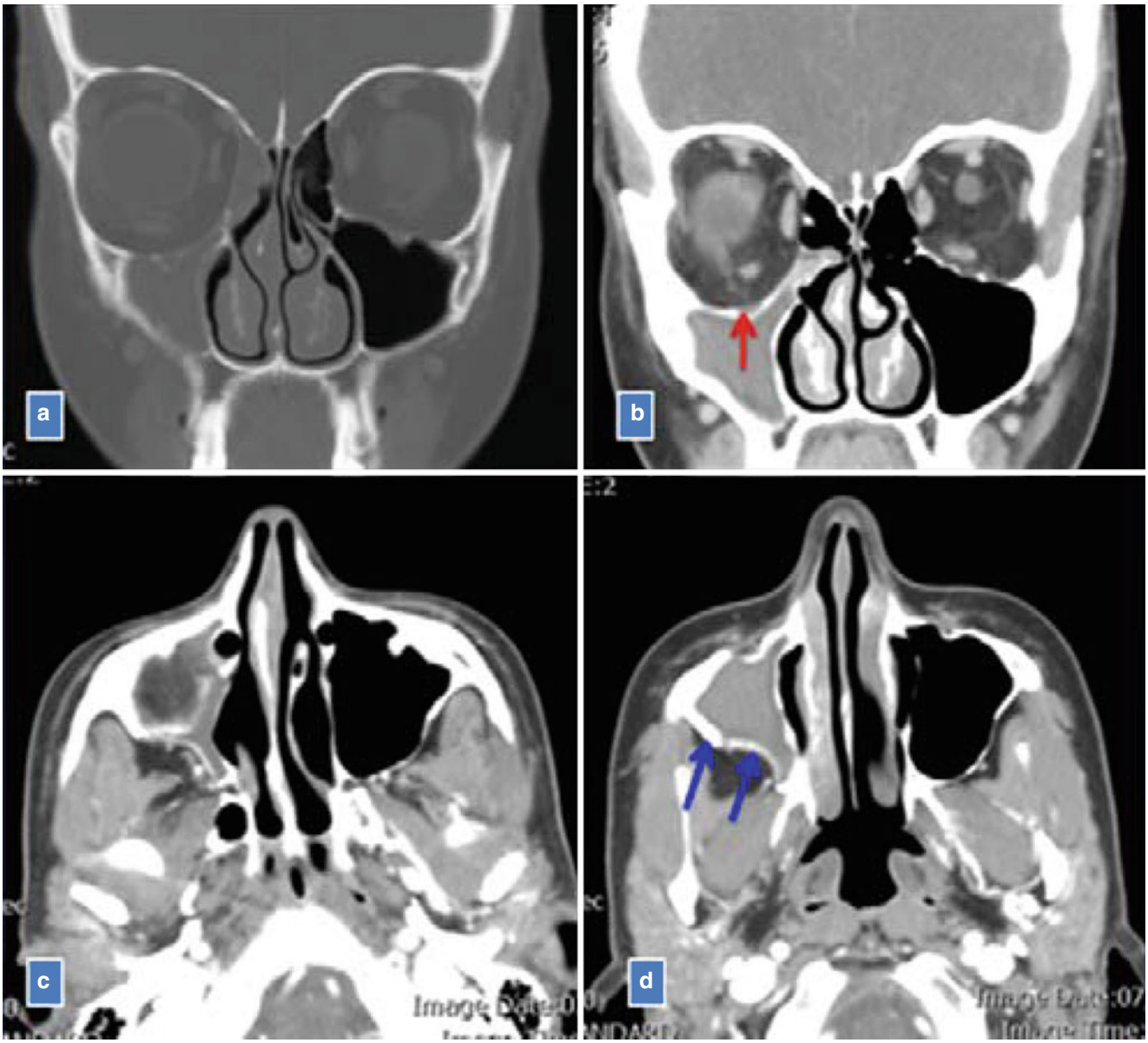


Fig. 17.18 Silent sinus disease. Coronal bone window (**a**), coronal soft tissue window (**b**), and axial soft tissue window (**c**, **d**) CT scans showing contracted right maxillary sinus. Atelectasis of the uncinate process, downward displacement of the floor of the right orbit (*red arrow* in **b**), and anterior bowing of the right posterior maxillary sinus (*blue arrows* in **d**)

Their secretion is usually clear, thick (mucoid), and tenacious unless the mucocele has been converted to a pyocele by the invasion of bacteria. Mucoceles are frequently discussed from the standpoint of sinus of origin. The sinus of origin, of course, is the most important for treatment planning.

Imaging in the Diagnosis of Mucoceles

CT and MRI should be considered the imaging methods of choice for the diagnosis and management of mucoceles [1, 2]. The radiographic characteristics of mucoceles have been well described [1, 27, 28, 33, 38]. A large mucocele produces a classic roentgenographic appearance of an enlarged (expanded) distorted sinus with a large bony defect representing a breakthrough into the adjacent structures (Fig. 17.19). Not all mucoceles are so classic, and there are many with subtle bone erosion. The gradual pressure atrophy and erosion of the bone by the retained mucosal secretion/debris and enlarging soft tissue mass of mucoceles produce the expansible appearance on CT or MRI scanning, with no enhancement after contrast infusion (except around the inflamed capsule and peripheral induration), and occasional peripheral calcification. Mucoceles are typically seen on MRI as hypointense or less frequently as hyperintense images on T1W and hyperintense on T2W MRI scans (Fig. 17.20).

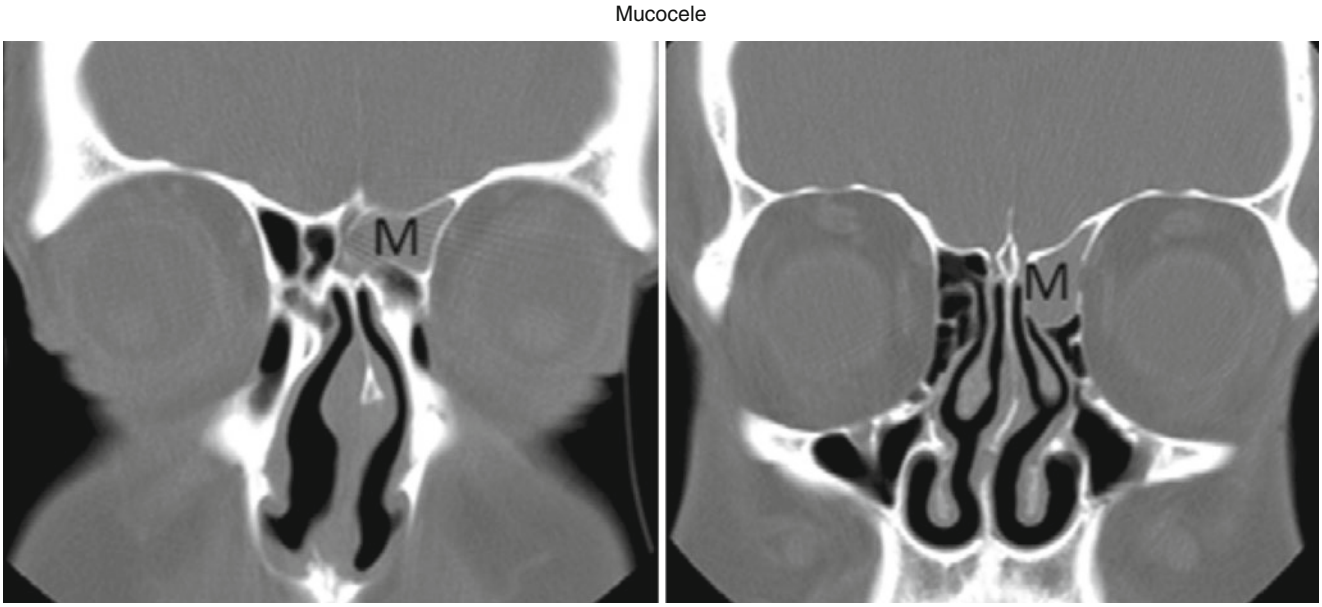


Fig. 17.19 Mucocele. Coronal CT scans showing mucocele of frontoethmoid recess (*M*)

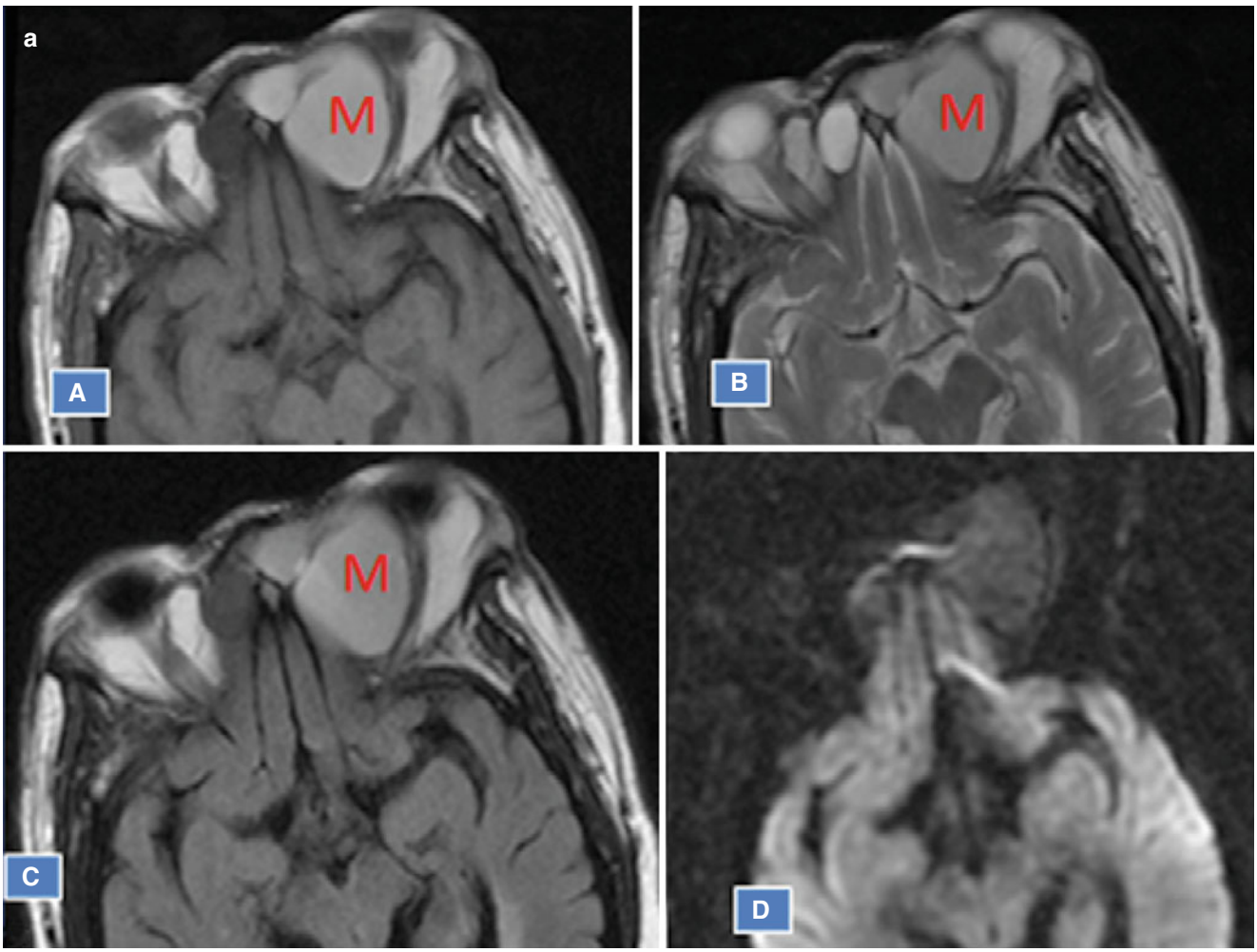


Fig. 17.20 (**a**) Mucocele of the left frontal sinus. Axial T1W (*A*), axial T2W (*B*), axial FLAIR (*C*), and axial DWI (*D*) MR images showing expansion of the left frontal sinus by a mucocele (*M*). Note that there is no diffusion restriction on DWI (*D*). The hyperintensity of the mucocele on T1W image indicates high proteinaceous fluid. (**b**) Sagittal T1W (*E*, *F*), coronal T2W (*G*), and coronal enhanced T1W (*H*) MR image showing the large frontal mucocele extending into the left orbit (*white arrows*). *FE* denotes trapped fluid in the right frontoethmoid recess

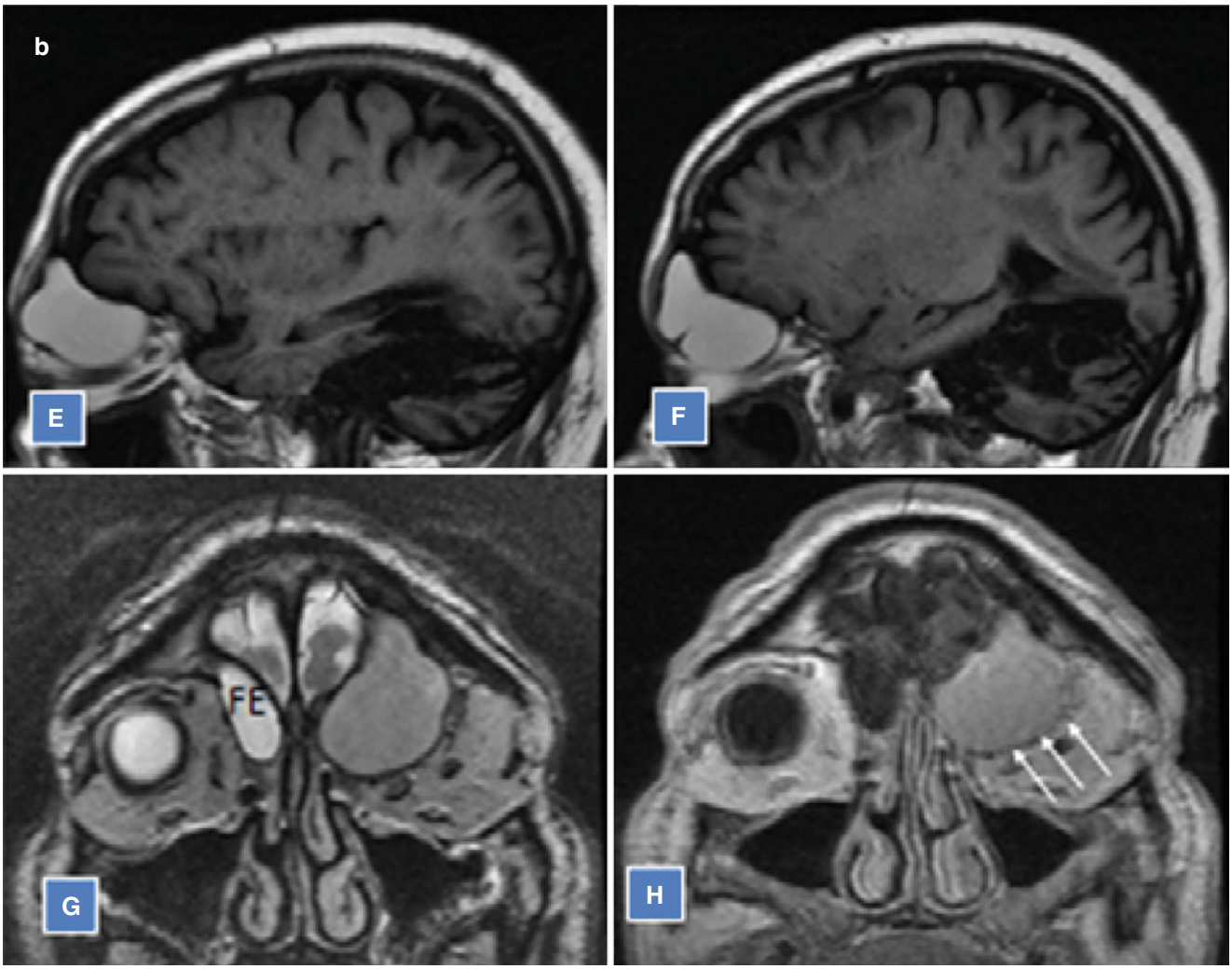


Fig. 17.20 (continued)

Because of variable protein content within long-standing mucoceles, signal intensity can be highly variable on both T1W and T2W sequences. Some mucoceles contain thick mucus and inspissated mucosal-retained secretions that may be hypointense on T2W MRI scans. The increased signal intensity of mucoceles on T1W MRI images is related to the proteinaceous content of mucosal secretion. Therefore, depending on the protein content, a mucocele may be slightly or markedly hyperintense on T1W MR images. On MRI, chronic fungal rhinosinusitis (both fungal balls and allergic fungal rhinosinusitis) and fungal mucoceles demonstrate a low or intermediate signal on both T1W and T2W MRI images [39], with expansion of affected sinuses, as well as peripheral rim enhancement on enhanced MRI images. MRI may also demonstrate neoplastic or inflammatory disease obstruction of the sinus ostium, the cause of mucocele formation. The traditional teaching has emphasized the need for complete removal of the mucocele lining to achieve a cure [43]. However, simple drainage and marsupialization of mucoceles have been performed with good long-term results [43]. With the introduction of endoscopic techniques, there has been a trend toward transnasal endoscopic management of paranasal mucoceles [43].

Nasal Polyps

Nasal polyps (NPs) are the most common mass lesion in the nose [44]. They are benign mucosal protrusions into the nasal cavity of multifactorial origin and characterized by chronic mucosal inflammation [44]. Chronic sinus inflammation most commonly results from repeated episodes of acute or subacute diseases of the sinonasal cavities. The sinus mucosa reflects these pathological alterations as a combination of areas of hypertrophic, polypoid, atrophic, and fibrotic changes intermixed

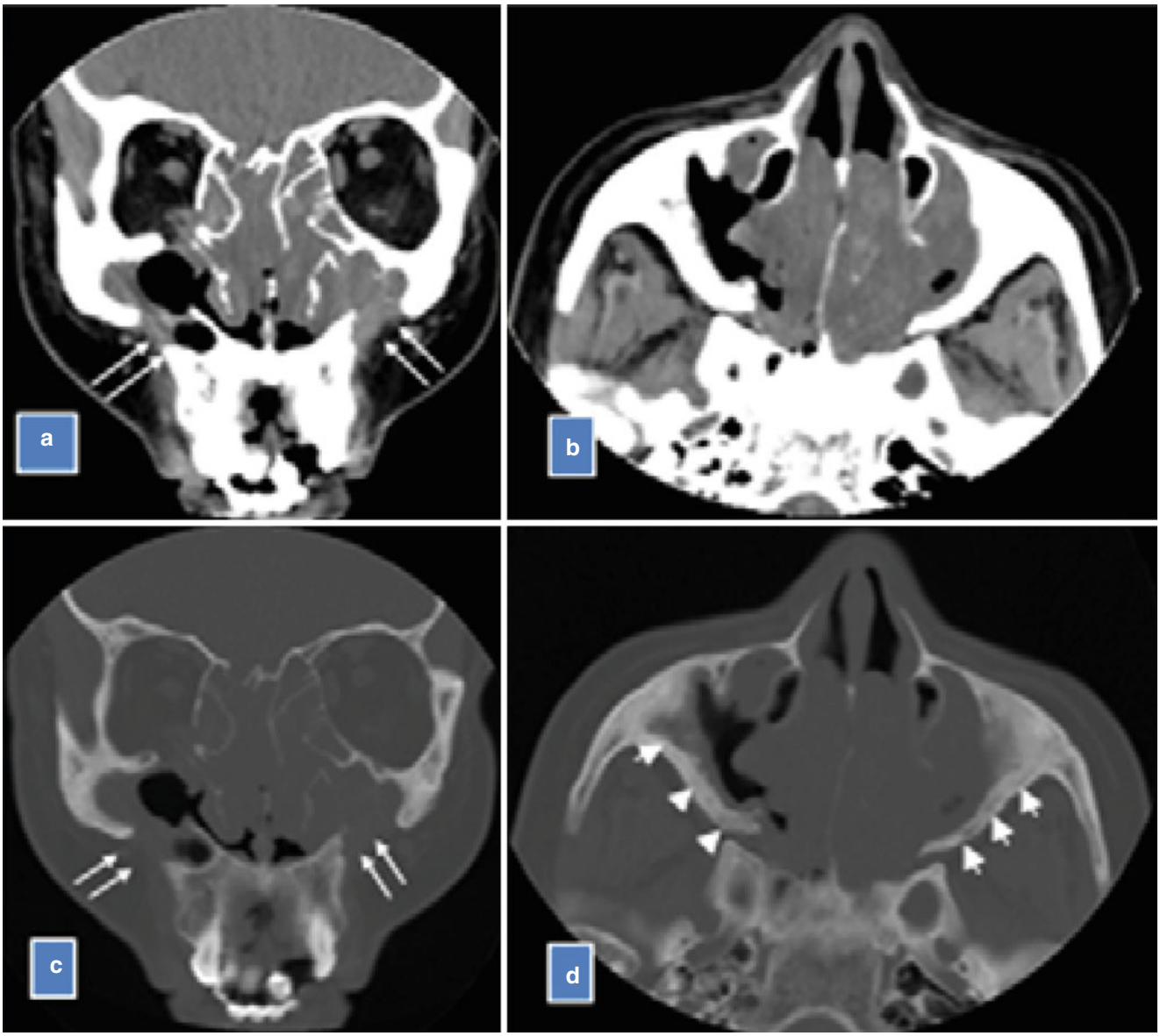


Fig. 17.21 Nasal polyposis in a patient with aspirin sensitivity. Coronal (**a**) and axial (**b**) soft tissue setting CT and coronal (**c**) and axial (**d**) bone window setting CT scans showing bilateral nasal polyps. Note bone defect (*arrows*) related to prior Caldwell-Luc operation. Note marked sclerosis of the maxillary sinus walls (*arrowheads*)

with regions of acute or chronic inflammations that are of either an infectious or an allergic origin. Chronic infections and allergies have both been regarded as probable causes in the formation of NPs although their exact origin remains a mystery.

Imaging Study of Polyps

A solitary polyp may not be distinguishable from a retention cyst on an unenhanced CT and MRI. Unlike cysts, polyps demonstrate marked contrast enhancement. When multiple polyps are present, sinus secretions become entrapped within the crevices between the polyps, as well as on the surfaces of the polyps. On CT scans, they show soft tissue attenuation. However, depending on the concentration of the entrapped mucosal secretions, the CT attenuation rises, and the chronic sinonasal polyposis may show mixed CT attenuation with areas of increased density simulating focal or diffuse dystrophic calcifications (Fig. 17.13). One important feature of NPs sometimes seen on CT or MRI is a smooth expansion of nasal fossae (Fig. 17.21) and pressure atrophy of the adjacent bony wall of the sinonasal cavities. Bone erosion is not common

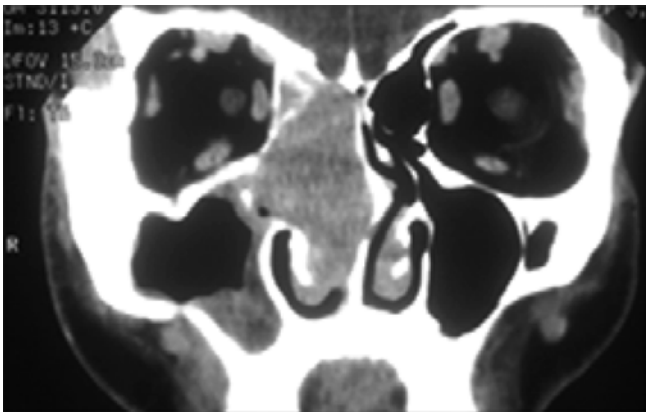


Fig. 17.22 Inverted papilloma vs. carcinoma. Coronal CT scan showing a right nasal cavity mass extending into the ethmoid sinus. This was a pathologically proven carcinoma

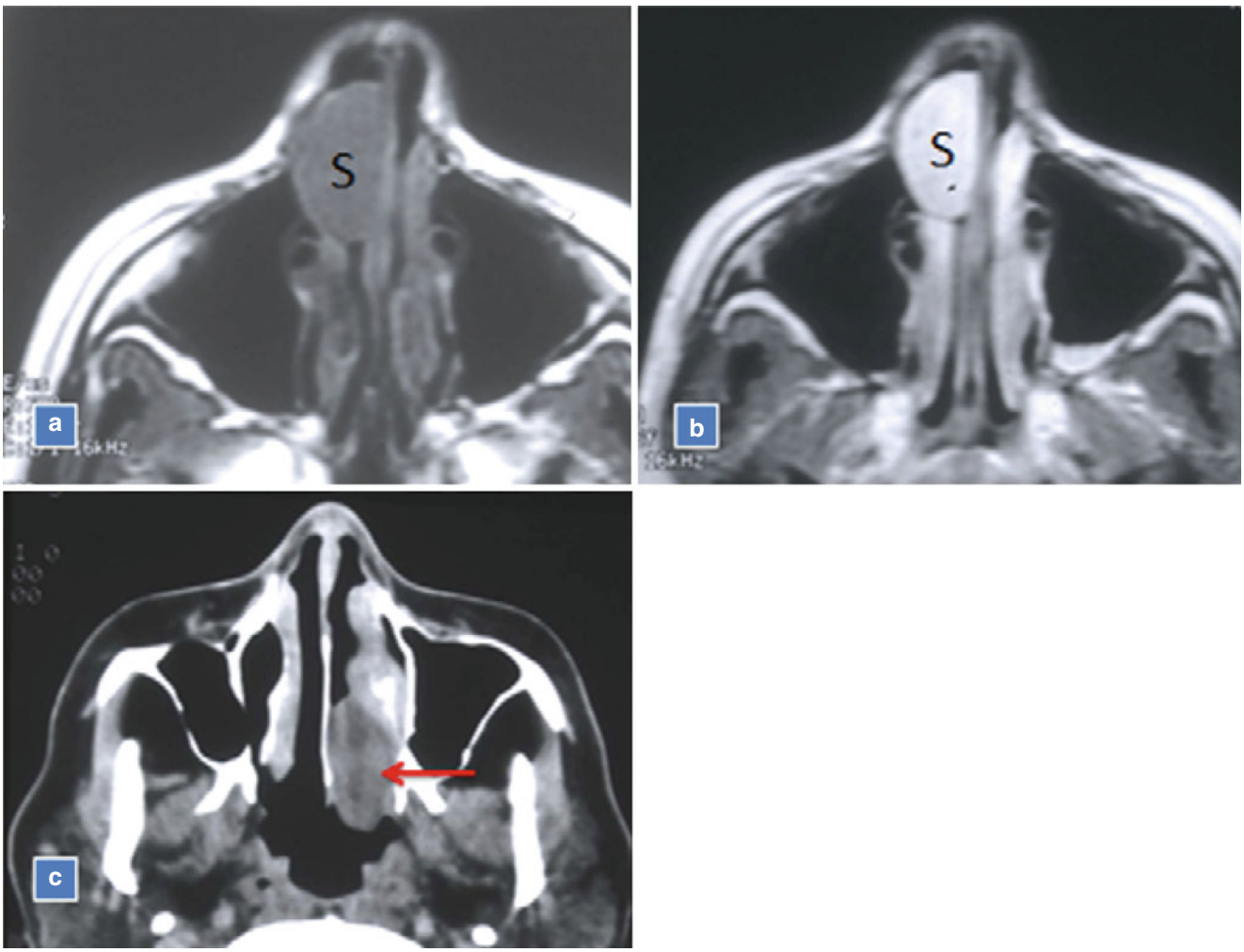


Fig. 17.23 Nasal schwannoma. Unenhanced axial T1W (**a**) and T2W (**b**) showing schwannoma in the anterior right nasal cavity (*S*). Axial enhanced CT scan (**c**) in another patient showing a posterior nasal schwannoma (*red arrow*)

with polyps. However, in aggressive, long-standing polyposis, there may be significant expansion of the sinuses, as well as bone erosion. Polyps tend to have various signal intensities on MRI pulse sequences. The MRI characteristics of polyps reflect the various stages of polyps (edematous, glandular, cystic, and fibrous), as well as various stages of desiccation of the entrapped mucosal secretions within the crevices between the polyps (Fig. 17.21). This appearance distinguishes them from tumors that do not have variable signal intensity in each MRI sequence. Polyps may coexist with mucoceles. At times, it may be impossible to distinguish between mucoceles and multiple polyps through imaging techniques. An inverted papilloma (Fig. 17.22), schwannoma (Fig. 17.23), hemangioma (Fig. 17.24), and malignant tumors of the sinonasal cavity may simulate a sinonasal polyp on CT and MRI.

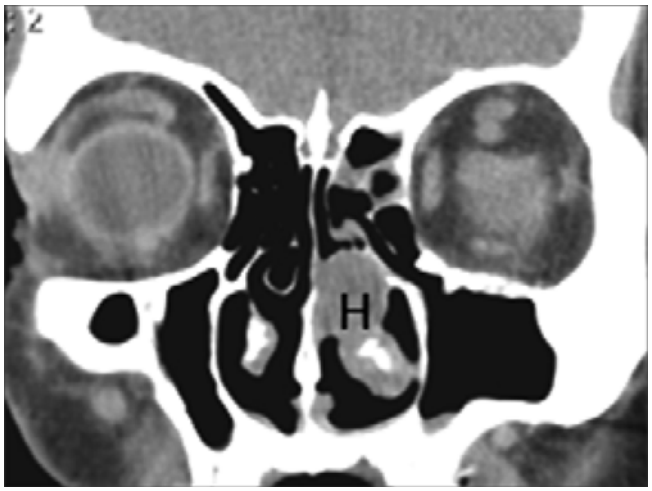


Fig. 17.24 Nasal hemangioma. Coronal CT scan showing a left nasal hemangioma (*H*)

Retention Cysts

Intramural maxillary sinus cysts, defined by Lindsay as nonsecreting cysts [40], are a common incidental finding in sinus plain roentgenograms, CT, and MRI of the sinuses. They are estimated to be present in about 10 % of the healthy adult populations [45]. These cysts result from the obstruction of the ducts of mucosal serous and/or mucinous glands, and the cysts are usually small. Rarely, however, they can enlarge sufficiently to fill a sinus cavity. The maxillary sinuses, being the largest of the paranasal sinuses, most commonly harbor intramural retention cysts [1, 2]. The sphenoid sinuses are the second most common sinus to harbor retention cysts. These cysts are seen as a smoothly marginated, convex configuration (dome-shaped) of water or soft tissue density on CT scans [46]. Most commonly, they are seen along the floor of maxillary sinuses and sphenoid sinuses.

The MRI appearance of retention cyst reflects an image with long T1 and long T2 characteristics. These are seen, therefore, as low-signal intensity on T1W and high-signal intensity on T2W MR images. Mucous retention types, as opposed to serous types, may show slightly higher signal intensity on T1W MRI images, related to their increased protein content. Retention cysts do not show contrast enhancement on enhanced CT and MRI scans.

Choanal Polyps

The choanal polyp develops from an expanding intramural cyst that protrudes through the maxillary antrum ostium and into the nasal cavity [47]. The close relationship between choanal polyps and the maxillary sinus was first described by Killian in 1906 [48], when he traced the polyps from the nasopharynx to the region of the ostium of maxillary sinus, but not into the maxillary sinus cavity. Other authors found choanal polyps to be attached to the lateral wall of the maxillary sinus by a fibrous or polypoid pedicle [49, 50]. Mills [42] suggested that the antrochoanal polyps arise from blocked and ruptured mucous glands during the healing process of bacterial sinusitis. Berg et al. [47] were also able to show that a choanal polyp develops from the expanding intramural cyst protruding through the maxillary ostium and into the nasal cavity. On CT and MR imaging, a choanal polyp has the same characteristics of other sinonasal polyps. The mass is seen from the ostium of the maxillary sinus to the choana and beyond, protruding into the nasopharynx (Fig. 17.25).

Tumors of the Paranasal Sinuses and Nasal Cavity

Tumors and tumorlike lesions of the sinonasal tract may be classified as benign or malignant and according to the tissue of origin (epithelial, bone, lymphoid, mesenchymal, etc.). The World Health Organization prefers to classify the tumors according to the tissue of origin and subdivide them into benign and malignant. Benign tumors of the sinonasal cavities are rare in comparison with malignant tumors. In decreasing order of frequency, the benign tumors are osteoma, hemangioma, papilloma, angiofibroma, benign mixed tumor, schwannoma, and other less-common tumors [1, 2, 4]. “Nasal gliomas” are

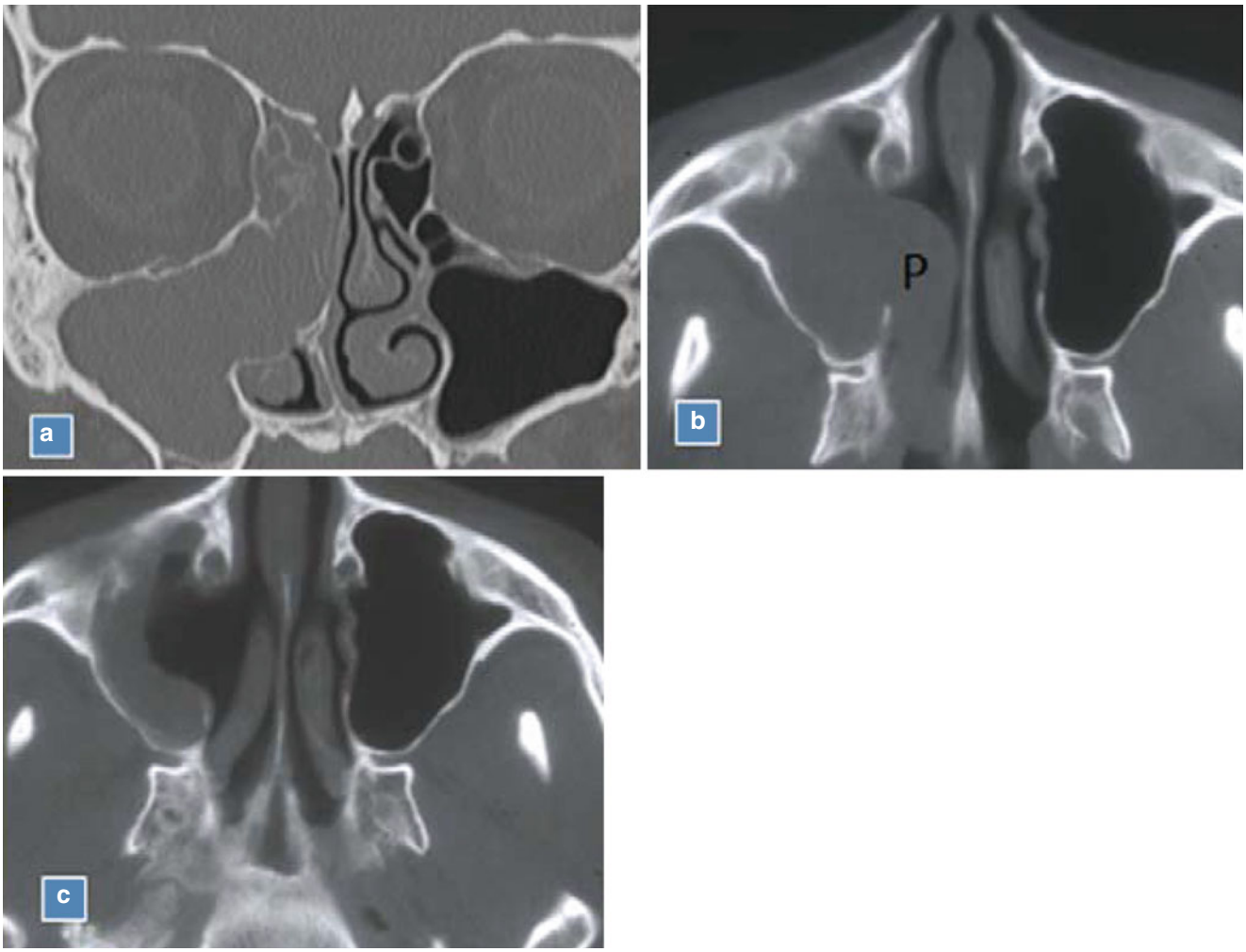


Fig. 17.25 Antrochoanal polyp. Preoperative coronal (**a**) and axial (**b**) bone window setting CT and postoperative axial CT (**c**) showing antrochoanal polyp (*P*)

attributed to glial cell rests and can simulate polyps on imaging. Extension of meningiomas and pituitary adenomas into the sinonasal cavities may occur as an inverting papilloma and even as a carcinoma, also simulating a polyp. Intrasinus meningiomas may be completely calcified simulating an osteoma or fibrous dysplasia. Many odontogenic cysts and tumors arise in the maxilla and mandible. These include dentigenous cysts, which are epithelialized sacs that develop from the enamel organ of unerupted tooth. Dentigenous cysts tend to be expansile and well circumscribed on CT and MR scans (Fig. 17.26). Odontogenic keratocyst (OKC) is an important odontogenic cyst that is notorious for its destructive, aggressive behavior and propensity for reoccurrence. Multiple odontogenic cysts, especially the keratocyst, tend to occur in the first and second decades of life as part of the basal cell nevus syndrome (Gorlin-Goltz syndrome) which is inherited as an autosomal dominant disorder [1, 2].

Malignant epithelial tumors of the sinonasal cavities account for a small percentage of cancer cases in the United States. Malignant epithelial tumors carry an incidence estimated to be less than 0.4 % of all new cancers [1]. Most sinonasal malignancies, however, are epithelial tumors. The differential diagnosis of cancer in the sinonasal cavities includes squamous cell carcinomas, adenocarcinomas, undifferentiated carcinomas, anaplastic carcinomas, mucosal melanomas, lymphomas, adenoid cystic carcinomas, and rarely mucoepidermoid carcinomas. Sarcomas include osteogenic and chondrogenic sarcomas, rhabdomyosarcomas, and other rare tumors.

Imaging of Sinonasal Tumors

Conventional plain films, although infrequently used, may still be used as the screening study in various pathological conditions of the sinonasal cavities to give orientation and direction to the preferred imaging examination, a sinus CT and MRI. Benign tumors tend to expand the area of origin by virtue of their slow growth or mass effect (Fig. 17.26). Malignant tumors on the other hand usually destroy bone and invade the adjacent hard-and-soft tissue structures (Fig. 17.27). Extension into the orbit, pterygopalatine fossa, infratemporal fossa, and cranial cavity can be demonstrated by contrast CT scans and in particular by MR scans (Fig. 17.28). Although it is possible to distinguish tumor from associated inflammatory disease on CT, the differentiation may be difficult. MRI is superior to CT for tumor mapping, as inflammatory reactions and retained secretions can be easily differentiated on MRI scans.

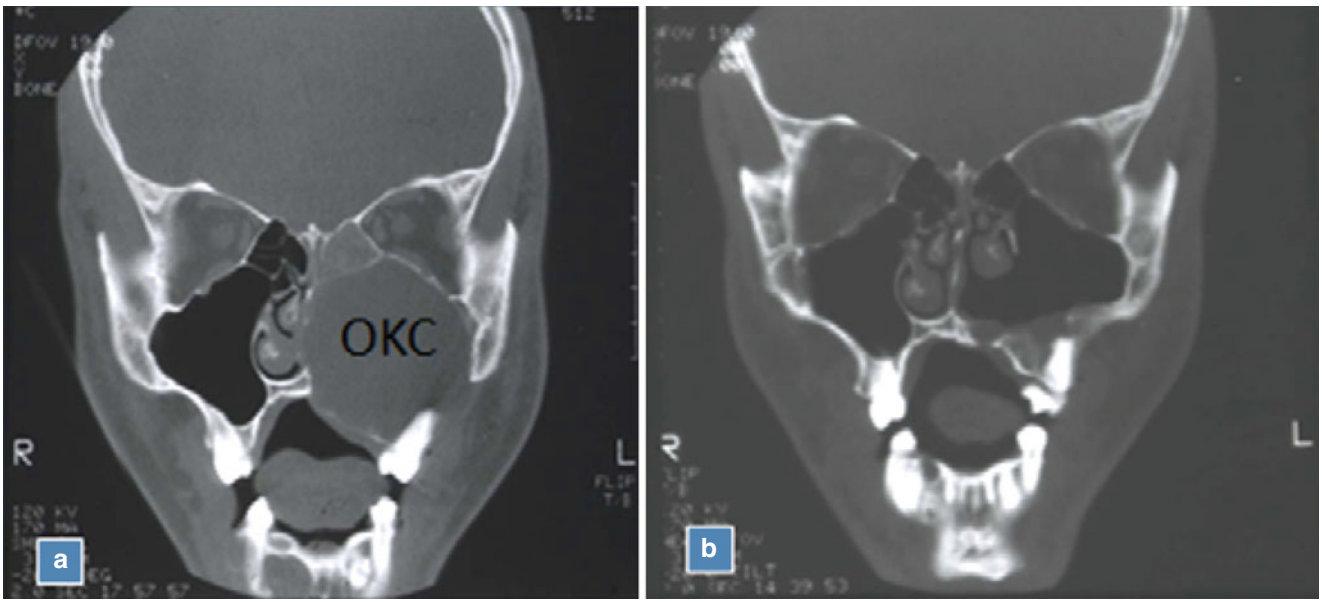


Fig. 17.26 Odontogenic keratocyst (*OKC*). Coronal bone window setting CT (**a**) demonstrates a large expansile mass in the left maxillary sinus, displacing a molar tooth, compatible with an odontogenic keratocyst. Postoperative coronal bone window setting CT (**b**) demonstrates near complete removal of the mass

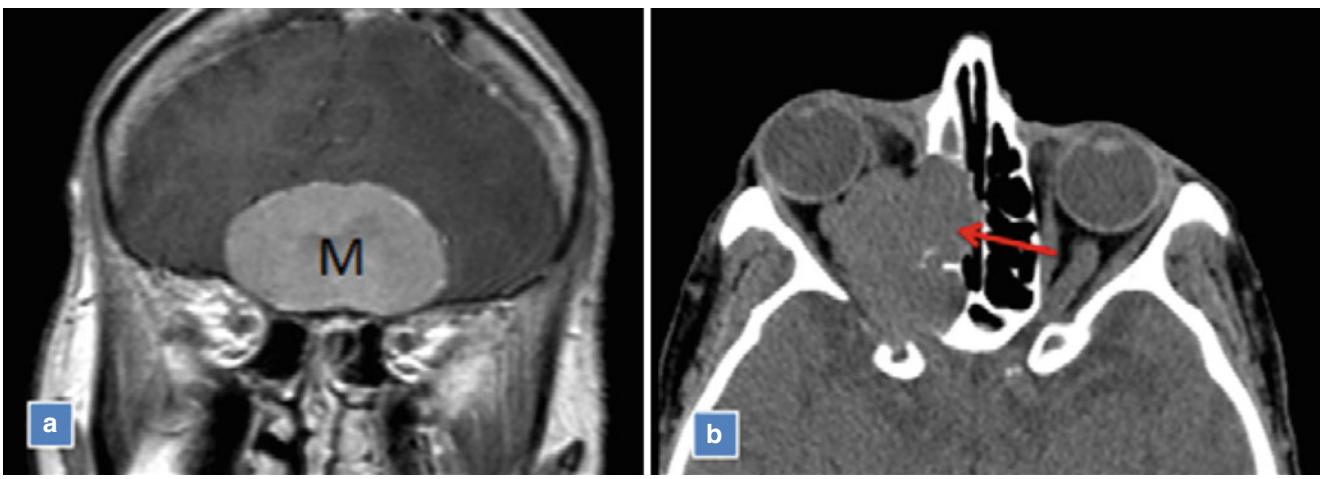


Fig. 17.27 Olfactory meningioma with extension into the nasal cavity. Coronal enhanced T1W MR (**a**), axial CT scans (**b–d**) showing a large meningioma (*M*), extending into the right ethmoid, and nasal cavity (*red arrow* in **b**)

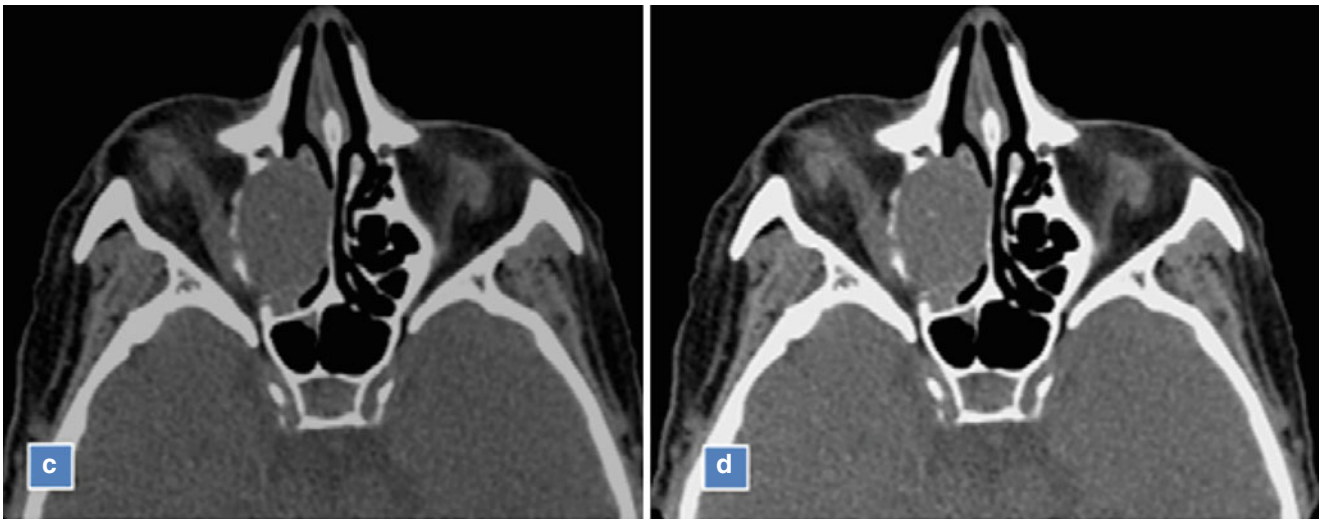


Fig. 17.27 (continued)

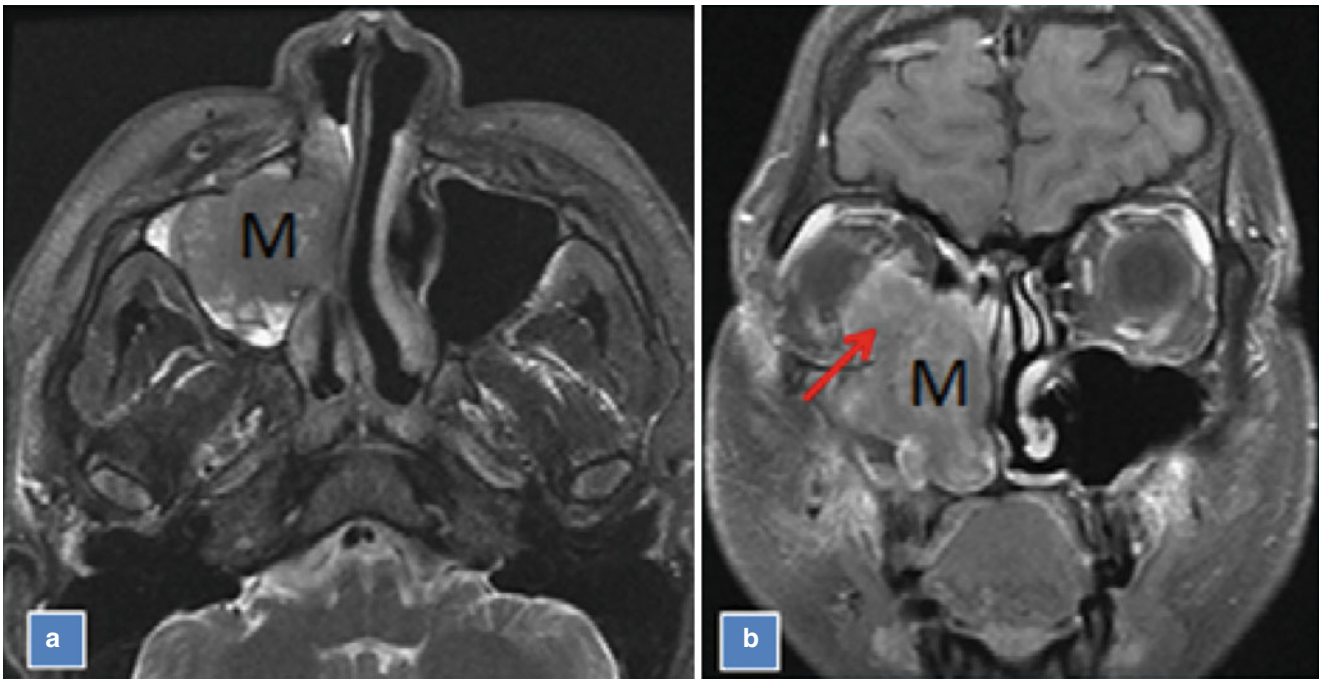


Fig. 17.28 Undifferentiated squamous cell carcinoma. Axial T2W (**a**) and coronal enhanced fat saturated T1W (**b**) showing a large mass (*M*) in the right nasal cavity and maxillary sinus with involvement of the right orbit (*red arrow*)

The high water content of inflammatory conditions results in markedly increased signal on T2W MR images. In contrast, the overwhelming majority of sinonasal tumors are highly cellular and therefore have an intermediate signal intensity on T2W MR images (Fig. 17.28). It is important to realize, however, that the more benign tumors and glandular-type tumors such as polyps, papillomas, hemangiomas, benign minor salivary gland tumors, and schwannomas usually have sufficient water content to produce hyperintensity on T2W MR images. Lymphomas are cellular and have an intermediate signal intensity on T2W MR images. Unlike many other malignant tumors, lymphomas are restricted on diffusion-weighted MR images (DWI); therefore, they appear hyperintense (bright) on DWI scans (Fig. 17.29). Some of the malignant epithelial tumors may also show restriction on DWI. On contrast-enhanced CT and MRI, tumors can be differentiated from inflammatory fluid retention, cysts, hemorrhage, and associated inflammatory changes. In this regard MRI is superior to CT scanning. Intracranial and orbital extension is best evaluated by MRI including enhanced MR scans (Figs. 17.27 and 17.28).

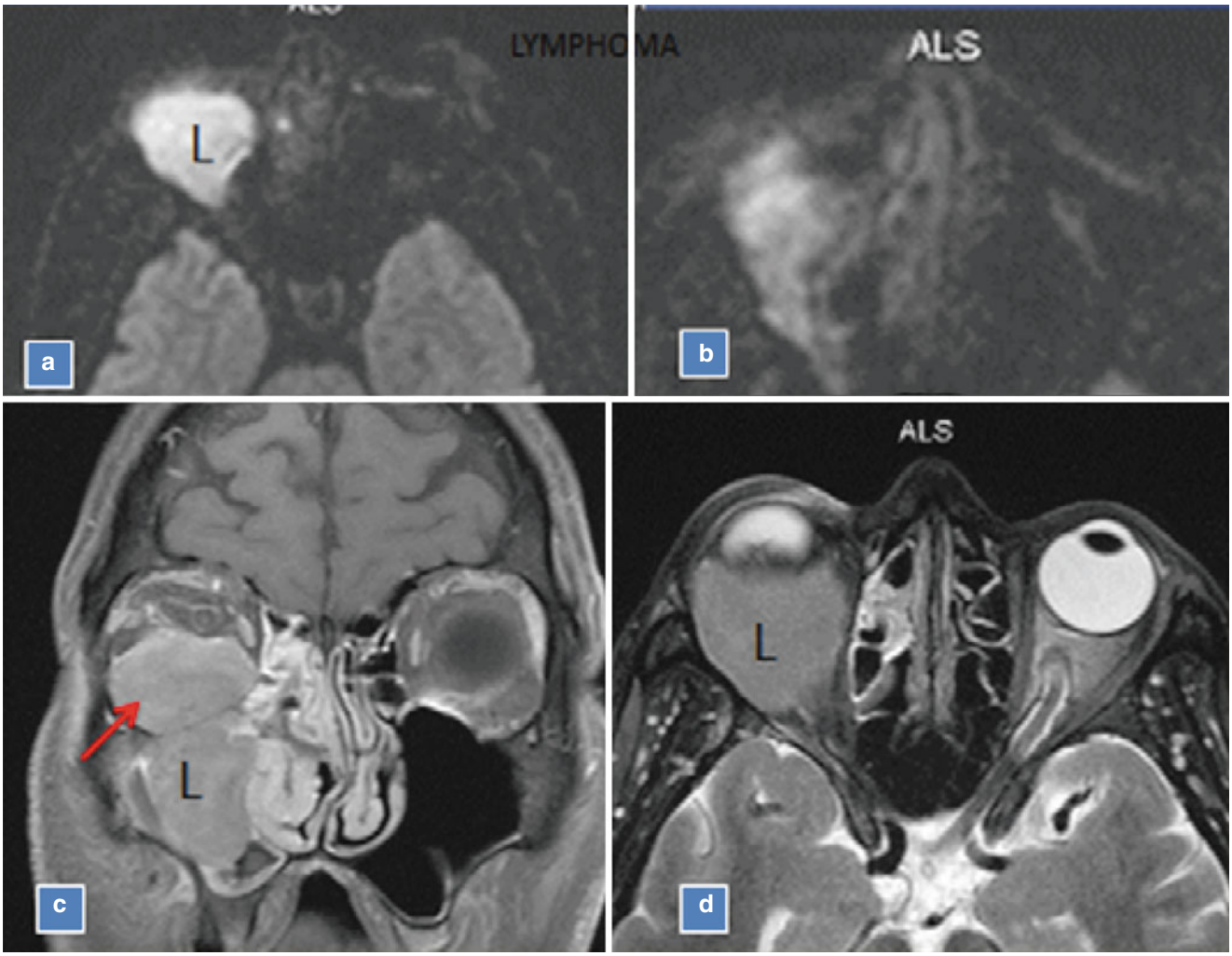


Fig. 17.29 Lymphoma. Axial DWI (**a**, **b**), coronal enhanced T1W (**c**), and axial T2W (**d**) showing a right maxillary lymphoma (*L* in **a**, **c**, and **d**), extending into the right orbit (*red arrow*). The mass demonstrates characteristic restricted diffusion on DWI images

Acknowledgement The authors wish to acknowledge the contribution of Mrs. Mary Kale and Ms. Brenda Guzman for the preparation of the manuscript.

References

1. Mafee MF. Imaging of the nasal cavity and paranasal sinuses. In: Mafee MF, Valvassori GE, Becker M, editors. Imaging of the head and neck. 2nd ed. Stuttgart: Thieme; 2005. p. 353–474.
2. Mafee MF. Imaging of paranasal sinuses and rhinosinusitis. In: Hamilos DL, Baroody FM, editors. Chronic rhinosinusitis: pathogenesis and medical management (clinical allergy and immunology). 1st ed. New York: CRC Press; 2007. p. 185–226.
3. Graney DO, Rice DH. Paranasal sinuses- anatomy. In: Cummings CW, Fredrickson JM, Harker LA, Krause CJ, Schuller DE, editors. Otolaryngology head and neck surgery. St. Louis: Mosby, Year Book; 1993. p. 901–6.
4. Mafee MF. Imaging of the nasal cavities, paranasal sinuses, nasopharynx, orbits, infratemporal fossa, pterygomaxillary, fissure, parapharyngeal space, and base of the skull. In: Ballenger JJ, Show JB, editors. Ballenger's Otorhinolaryngology head and neck surgery: head and neck surgery. 16th ed. Hamilton: B.C. Decker; 2003. p. 654–707.
5. Mafee MF. Imaging of paranasal sinuses and nasal cavity. In: English GM, editor. Diseases of the nose and sinuses, vol. 2. Philadelphia: Lippincott-Raven; 1995. p. 1–42.
6. Mafee MF. Modern imaging of paranasal sinuses and the role of limited sinus computerized tomography; considerations of time, cost, and radiation. Ear Nose Throat J. 1994;73(8):532–4, 536–8, 540–2 passim.
7. Mafee MF. Imaging methods for sinusitis. JAMA. 1993;269:2808.

8. Chow JM, Mafee MF. Radiologic assessment preoperative to endoscopic sinus surgery. Otolaryngol Clin North Am. 1989;22:691–701.
9. Mafee MF, Chow JM, Meyers R. Functional endoscopic sinus surgery: anatomy, CT screening, indications, and complications. AJR Am J Roentgenol. 1993;160:735–44.
10. Mafee MF. Nonepithelial tumors of the paranasal sinuses and nasal cavity. Role of CT and MR imaging. Radiol Clin North Am. 1993;31:75–90.
11. Zinreich SJ, Kennedy DW, Rosenbaum AE, et al. Paranasal sinuses: CT imaging requirements for endoscopic survey. Radiology. 1987;31:709–75.
12. Kennedy DW, Zinrich J, Rosenbaum AE, et al. Functional endoscopic sinus surgery: theory and diagnostic evaluation. Arch Otolaryngol. 1985;111:576–82.
13. Mafee ME. Endoscopic sinus surgery: role of the radiologist. AJNR Am J Neuroradiol. 1991;12:855–60.
14. Mafee ME. Preoperative imaging anatomy of nasal-ethmoid complex for functional endoscopic sinus surgery. Radiol Clin North Am. 1993;31:1–20.
15. Rice DH. Basic surgical techniques and variations of endoscopic sinus surgery. Otolaryngol Clin North Am. 1989;22:713–26.
16. Som PE, Brandwein-Genster M, Kassel EE, Genden EM. Tumors and tumor-like conditions of the sinonasal cavities. In: Som PE, Curtin HD, editors. Head and neck imaging. 5th ed. St. Louis: Mosby; 2011. p. 253–410.
17. Stammberger HR, Kennedy DW, The Anatomic Terminology Group. Paranasal sinuses: anatomic terminology and nomenclature. Ann Otol Rhinol Laryngol Suppl. 1995;167:7–16.
18. Poznanski AK. Do sinus roentgenograms in children pose a radiation risk? JAMA. 1989;262(21):3058.
19. Mettler FA, Moseley RD. Medical effects of ionizing radiation. Orlando: Grune and Stratton; 1985.
20. Wagner LK. Absorbed dose in imaging why measure it? Radiology. 1991;178:622–3.
21. Upton AC. The biological effects of low-level ionizing radiation. Sci Am. 1982;246(2):41–9.
22. National Council on Radiation Protection and Measurement. Exposure of the U.S. population from diagnostic medical radiation: recommendations of the National Council on Radiation Protection and Measurements (NCRP report). Bethesda: Natl Council on Radiation; 1989.
23. Linet MS, Slovis TL, Miller DL, et al. Cancer risks associated with external radiation from diagnostic imaging procedures. CA Cancer J Clin. 2012;62:75–100.
24. Hutchin ME, Shores CG, Bauer MS, Yarbrough WG. Sinogenic subdural empyema and streptococcus anginosus. Arch Otolaryngol Head Neck Surg. 1999;125:1262–6.
25. Jones NS, Walker JL, Bassi S, et al. The intracranial complications of rhinosinusitis: can they be prevented? Laryngoscope. 2002;112:59–63.
26. Stammberger H. Endoscopic surgery for mycotic and chronic recurrent sinusitis. Ann Otol Rhinol Laryngol Suppl. 1985;119:1–11.
27. Mafee MF. Orbital and intraocular lesions. In: Edelman RR, Hesselink JR, Zlatkin MC, editors. Clinical magnetic resonance imaging. Philadelphia: W.B. Sanders; 1995. p. 985–1020.
28. Schubert MS. Allergic fungal sinusitis. In: Hamilos DL, Baroody FM, editors. Chronic rhinosinusitis. New York: Informa Health Care; 2007. p. 263–71.
29. Zinreich SJ, Kennedy DW, Malat J, et al. Fungal sinusitis: diagnosis with CT and MR imaging. Radiology. 1988;169:439–44.
30. Saferstein B. Allergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. Chest. 1976;70:788–90.
31. Green WH, Goldberg HI, Wohl GT. Mucormycosis infection of the cranio-facial structures. Am J Roentgenol Radium Ther Nucl Med. 1967;101:802–6.
32. Berger G, Kattan A, Bernheim J, Ophir D. Polypoid mucosa with eosinophilia and glandular hyperplasia in chronic sinusitis: a histopathological and immunohistochemical study. Laryngoscope. 2002;112:738–45.
33. Hamilos DL. Chronic rhinosinusitis patterns of illness. In: Hamilos DL, Baroody FM, editors. Chronic rhinosinusitis. New York: Informa Health Care; 2007. p. 1–13.
34. Stammberger H, Jakse R, Beaufort E. Aspergillosis of the paranasal sinuses. X-ray diagnosis, histopathology, and clinical aspects. Ann Otol Rhinol Laryngol. 1984;93:251–6.
35. Kopp W, Fotter R, Steiner H, et al. Aspergillosis of the paranasal sinuses. Radiology. 1985;156:715–6.
36. Mukherji SK, Figueroa RE, Ginsberg LE, et al. Allergic fungal sinusitis: CT findings. Radiology. 1998;207:417–22.
37. Ma H, Kubicek CP, Röhr M. Metabolic effects of manganese deficiency in Aspergillus niger: evidence for increased protein degradation. Arch Microbiol. 1985;141(3):266–8.
38. Mafee MF. Eye and orbit. In: Som PM, Curtin HD, editors. Head and neck imaging. St. Louis: Mosby; 1996. p. 1009.
39. Lee JT, Bhuta S, Lufkin R, Calcaterra TC. Fungal mucoceles of the sphenoid sinus. Laryngoscope. 2002;112:779–83.
40. Lindsay JR. Nonsecreting cysts of the maxillary sinus mucosa. Laryngoscope. 1942;52:84–100.
41. Lund VJ, Kennedy DW. Staging for rhinosinusitis. Otolaryngol Head Neck Surg. 1997;117(Suppl):35–40.
42. Mills CP. Secretory cysts of the maxillary antrum and their relation to the development of antrochoanal polypi. J Laryngol Otol. 1959;73:324–34.
43. Har-El G. Endoscopic management of 108 sinus mucoceles. Laryngoscope. 2001;111:2131–4.
44. Liu CM, Hong CY, Shun CT, Hsiao TY, Wang CC, Wang JS, Hsiao M, Lin SK. Inducible cyclooxygenase and interleukin 6 gene expressions in nasal polyp fibroblasts. Arch Otolaryngol Head Neck Surg. 2002;128:945–51.
45. Hanna HH. Asymptomatic sinus disease in aircrew members. Aerosp Med. 1974;45:77–81.
46. Mafee MF. Computed tomography, magnetic resonance imaging. In: Ballenger JJ, Snow JB, editors. Otorhinolaryngology head and neck surgery. 15th ed. Baltimore: Williams and Wilkins; 1996. p. 699.
47. Berg O, Carenfelt C, Silfversward C, Sobin A. Origin of the choanal polyp. Arch Otolaryngol Head Neck Surg. 1988;114:1270–1.
48. Killian G. The origin of choanal polypi. Lancet. 1906;2:81–2.
49. Van Alyea OE. Management of non-malignant growths in the maxillary sinus. Ann Otolaryngol. 1956;65:714–22.
50. Mafee MF. Nasal cavity and paranasal sinuses. In: Mafee MF, Valvassori GE, Becker M, editors. Valvassori's Imaging of the head and neck. Stuttgart: Thieme; 2005. p. 353–474.

Chapter 18
Direct or Objective Evaluation of Nasal Function: Nasal Mucosal Microscopy, Mucociliary Transport, Flow Rhinometry, Acoustic Rhinometry and Olfactory Assessment

Anton R. Dotson and Gary A. Incaudo

Introduction

In-office laboratory studies are performed to confirm or exclude the presence or absence of suspected nasal/sinus disorders or to obtain additional information about that disorder such as response to treatment or potential treatments. Anterior rhinoscopy, nasal endoscopy, skin prick and intradermal tests, nasal cytology, specific IgE analysis, rhinomanometry, acoustic rhinometry, olfactory screening, mucociliary transport, and imaging studies comprise the tools used by the allergist and otolaryngologist to clarify or confirm a diagnosis in patients with rhinitis and/or rhinosinusitis symptoms. This section critically reviews in-office methods used to study nasal mucosal cytology, nasal patency, olfaction, and mucociliary transport (Table 18.1).

Nasal Cytology

An accurate evaluation of nasal mucosal cytology provides a great deal of information to the healthcare practitioner (Table 18.2). Nasal cytology functions to help differentiate allergic, nonallergic, and infectious rhinitis, viral and bacterial infections, and inflammatory and noninflammatory forms of rhinitis. The information obtained provides the practitioner with an objective measure to help clarify a clinical picture by describing the type and degree of cellular infiltrate present within the nasal mucosa. Serial measurements provide a means by which the examiner can follow the course of a nasal disorder and evaluate the response to treatment.

The components within the nasal cavity available for cytologic examination include nasal mucous and the structures that make up the superficial nasal mucosa (Fig. 18.1, Table 18.3). The in-office method for obtaining a sample of primarily nasal secretions is nose blowing or lavage. Nasal mucous, mucosa, and submucosa can be obtained for examination by swabbing, brushing, or scrapping the nasal surface or through a biopsy (Table 18.4).

The examiner can obtain a sample of mucous for cytologic examination through nose blowing on to a nonabsorbable surface such as wax paper or lavaging the nasal cavity with a known quantity of saline into a receptacle. Lavaging and nose blowing obtain only nasal secretions for examination. Such an examination provides limited information but is generally simple to perform. The cytologic data obtained is limited to staining for the presence of eosinophils, but bacteria, neutrophils, and active phagocytosis as seen in acute infections can sometimes be demonstrated with the Wright-Giemsa stain if there are sufficient cells present for examination.

A.R. Dotson, MD (✉)
Allergy Associates, 145 Mission Ranch blvd, Suite 110, Chico, CA 95926, USA
e-mail: adotson@norcalallergy.com

G.A. Incaudo, MD, FAAAAI, FACAAI
Division of Rheumatology, Allergy and Clinical Immunology, University of California School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA
e-mail: Gincaudo@norcalallergy.com

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_18,

Table 18.1 Objective in-office measurements of nasal function

Cytology
Mucociliary transport
Olfaction
Patency

Table 18.2 Usefulness of nasal cytologic examination

Differentiate between allergic, nonallergic, and infectious rhinitis
Differentiate between viral and bacterial infections
Differentiate inflammatory from noninflammatory nasal diseases
Classify the immune response: (a) eosinophilic, (b) basophilic, (c) goblet cells, and (d) neutrophilic
Follow the course of the disease and evaluate the response to treatment

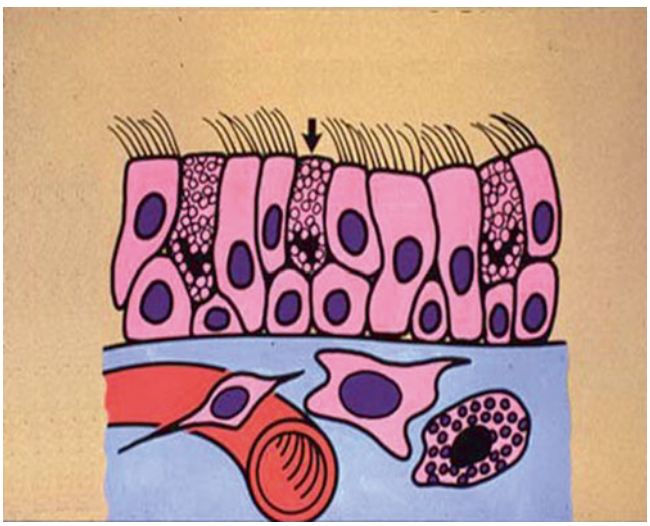


Fig. 18.1 Schematic view of the nasal mucosa and submucosa. → Indicates goblet cell in between ciliated columnar epithelium; basal cells line the basement membrane. Submucosal with two macrophages, blood vessel, and mast cell

In contrast, scraping the mucosal lining along the middle third of the inferior and middle turbinates allows harvesting samples of secretions, mucosa, and sometimes submucosa. Sampling of tissue and secretions in this manner provides the optimum specimen for in-office diagnostics that does not require special surgical precautions.

Effective scrapping of the mucosa requires direct visualization of the nasal cavity at a minimum before and preferably during the sampling procedure. Figure 18.2 is a photograph of the nasal cavity beyond the liminal valve as it would appear to the examiner using a nasal specula and head lamp/mirror. The nasal septum appears on the right and inferior and middle turbinates on the left in this example.

The general equipment necessary to examine the cytologic components of the nasal cavity are listed in Table 18.5. Unless the examiner is exclusively looking for eosinophils, the Wright-Giemsa stain can be used for viewing all the necessary mucosal cellular components under light microscopy (Table 18.6).

The following are a description of the methods, value, and limitations of each of the procedure for examining nasal secretions and mucosa.

Nose Blowing

Method: The nose blowing procedure onto a nonabsorbable surface is easy to perform (Table 18.7). Nose blowing causes no discomfort and only requires cooperation of the patient and adequate mucous to expel.

Value and Limitations: Despite its simplicity, this sampling technique has significant limitations. Some patients find it offensive and "messy" to blow their nose publicly. Furthermore, infants or very small children cannot or commonly will not blow their nose on demand. Staining material obtained by nose blowing is of limited value in that the specimen is contaminated by the contents of the vestibule, and only cells within the mucous are available for study. Hansel staining can be used

Table 18.3 The types of nasal cytologic specimens include

Secretions
Superficial epithelium
Mucosa and submucosal

Table 18.4 Techniques to acquire a nasal cytologic specimen

Nose blowing
Lavaging
Swabbing
Brushing
Scraping
Biopsy

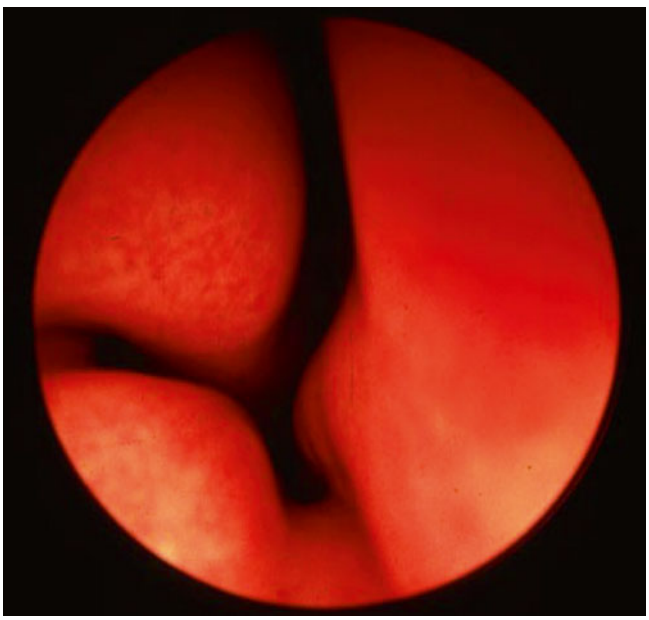


Fig. 18.2 View of nasal passage beyond vestibule. Nasal septum on right, inferior, and middle turbinates and middle meatus on left (Courtesy of Alfredo A. Jalowayski, PhD)

for a rapid and accurate demonstration of eosinophils, but no other cellular structures or bacteria can be visualized. Other problems include staining difficulties when there is abundant mucous. Excessive mucous produces a dilutional factor that can interfere with the interpretation of the number of cells visualized. Furthermore, nose blowing specimens are commonly contaminated with bacteria and many necrotic cells from the vestibule obscuring any conclusions about infection when the Wright-Giemsa stain is used. As the specimen is mucous only, mucosal and ciliary structure and function cannot be evaluated by this method.

Swabbing

Method: In swabbing the nasal cavity to collect a specimen for cytologic analysis, the patient is first asked to blow excess secretions. The objective here is to collect as many cells lining the mucosal surface as possible, and not just the cells found in the secretions. A cotton-tipped applicator or preferably a calcium alginate (Calgiswab) swab can be used (Fig. 18.3). The swab is introduced into the nasal cavity and vigorously moved in the area of the inferior and middle turbinates to sample the nasal mucosa. The applicator is removed, and the specimen is smeared on to a microscopic slide. The smeared specimen is fixed, stained, and examined microscopically.

Value and Limitations: The swabbing procedure yields a more complete specimen compared to blowing. However, the process of procuring an adequate specimen of mucosa by swabbing is irritating and commonly causes considerable discomfort to the patient. Furthermore, many cells are lost when they adhere to the cotton fibers, and others are distorted and

Table 18.5 Equipment and supplies

Microscope slides: The preferred slides are fluorescent, with a single frosted end. Optionally can add two etched 10 mm circles
Fixative: 95 % ethyl alcohol (ETOH) in 2 oz. round bottles
Histological stain: Wright-Giemsa stain; buffer and rinse or Hansel stain for eosinophils
Specula of different sizes
Head lamp, head mirror, or Welch Allyn nasal illuminator
Microscope: binocular, panchromatic lenses, 100× oil immersion and 10× lenses
Immersion oil: Zeiss
Curettes: Rhinoprobe, calcium alginate swab

Table 18.6 Examining nasal cytograms

1. Place drop of oil immersion on specimen site
2. Scan whole specimen at low power (100×)
3. Determine adequacy of the specimen. An adequate specimen is one that contains several fields of non-squamous epithelial cells, with very few to no squamous epithelial cells, and scant secretions
4. Grade nasal cytogram at high power (1,000×)
5. Examine mucous secretions if present

Table 18.7 Nose blowing

Expelled secretions are collected on to a piece of waxed paper, Saran Wrap, or plastic bag
Secretions are mixed with a wooden or plastic stick and a portion of the specimen is transferred on to a clean microscopic slide
The specimen is usually allowed to air-dry
Stained with Hansel stain for the presence of eosinophils or Wright-Giemsa for white blood cells

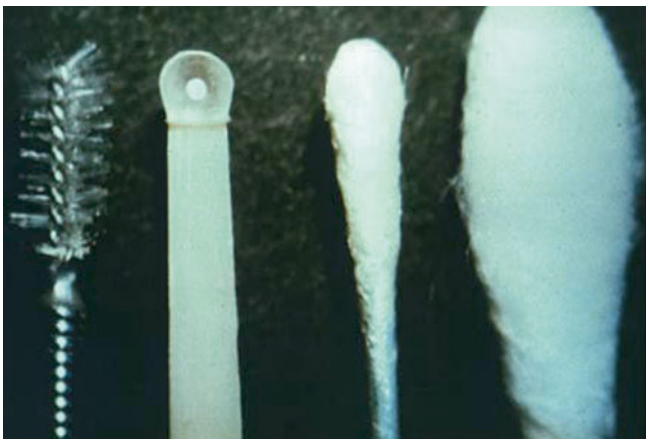


Fig. 18.3 Sampling tools listed left to right: Brush, Rhinoprobe ®, Caligswab, cotton swab (Courtesy of Alfredo A. Jalowayski, PhD)

degranulate when the specimen is smeared on the slide. Like nose blowing, cilia function and structure cannot be adequately evaluated by this method.

Brushing

Method: Like swabbing, prior to sampling the nasal cavity with a brush, the patient is asked to blow excess secretions. In infants, the secretions are removed with an aspirating bulb or by suction. The biopsy brush is introduced into the nasal cavity and rotated with some vigor in the area of the inferior and middle turbinates to sample the nasal mucosa (Fig. 18.3). The device is withdrawn and the specimen collected applied to the surface of a microscopic slide.

Unlike swabbing, cilia function and structure can be studied by this technique. In such a circumstance, the specimen is placed into a test tube containing appropriate media or fixative. The brush is twirled while immersed in the solution, until the specimen is dislodged for later staining and examination.

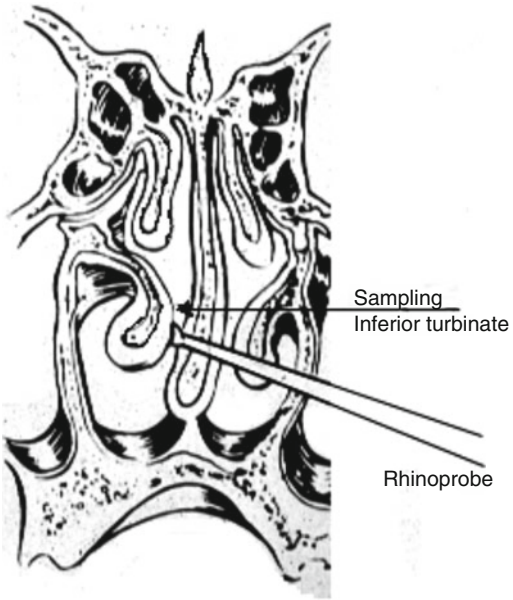


Fig. 18.4 Schematic of the Rhinoprobe sampling from the inferior turbinate

Value and limitations: This procedure is better than swabbing in that there is less cell distortion and cilia function and structure can be added to the evaluation if needed. Furthermore, more mucosal cells will be harvested with a more abrasive instrument. However, the brush method has several drawbacks. The brush applicator is expensive compared to swabs. Like swabbing, it is uncomfortable and quite irritating to the patient during sampling, and the cells are not easily dislodged from the brush fibers. Finally, cell distortion and disruption can occur with this technique during the transfer of the specimen to a slide if the examiner is not careful.

Scraping

Method: Platinum wire loops or flexible plastic curettes ("Rhinoprobe¨) can be used to scrape the superficial epithelium lining the nasal turbinates (Figs. 18.4 and 18.5). In our office, we exclusively use the Rhinoprobe (Table 18.8) which will be discussed. The patient first blows excess secretions. In infants, secretions are removed using a bulb syringe or some other suctioning device. Patients are informed that they will perceive a slight irritation for 3–4 s and that sometimes the ipsilateral eye will reflexively tear. The nasal cavity is examined with the aid of a speculum and a headlight to determine any obstacles to the probe placement. Enlarged turbinates, deviated septum, and the presence of polyps can interfere with procuring a sample with minimal discomfort. Therefore, it is very important to perform this procedure only after visual inspection of the nasal cavity has been completed. We commonly spray lidocaine and a topical decongestant prior to sampling which provides a maximum visual field to ensure accurate sampling location and minimizes patient discomfort during the brief procedure.

The tip of the "Rhinoprobe" can be bent slightly while still in the plastic envelope. This will facilitate going around the head of the inferior turbinate. The curette is removed from the envelope and introduced into the nasal cavity. Avoid touching the vestibule and the septum to minimize contaminating the sample and causing any additional discomfort to the patient. We generally sample the mid-inferior or posterior inferior portion of the inferior turbinate, but the middle turbinate can also be sampled effectively. Start by gently pressing the tip of the probe on the mucosal surface and moving the probe outward 2–3 mm. Remove the pressure on the mucosal surface and move the probe inward 2–3 mm. Repeat this scraping motion 1–2 more times. Before removing the Rhinoprobe¨ completely, position the cupped tip upward and then withdraw the curette carefully to avoid contamination from the vestibule during withdrawal.

Transfer the specimen to a clean slide by gently spreading contents of the cupped tip in a circular manner to a glass slide marked with the date and patient identification number (Figs. 18.6 and 18.7). Fix the specimen quickly in a slide jar containing 95 % ethyl alcohol for a minimum of 30–60 s or longer as necessary. We commonly accumulate the slides and stain them at the end of the day. For the study of cilia function and rapid viral diagnosis, the specimen is transferred to a small test tube containing Hanks' Balanced Salt Solution. The Rhinoprobe handle is twirled vigorously while the tip of the probe is immersed in the solution. Transfer a specimen to a test tube containing glutaraldehyde fixative for the study of cilia ultrastructure by electron microscopy (Fig. 18.8).

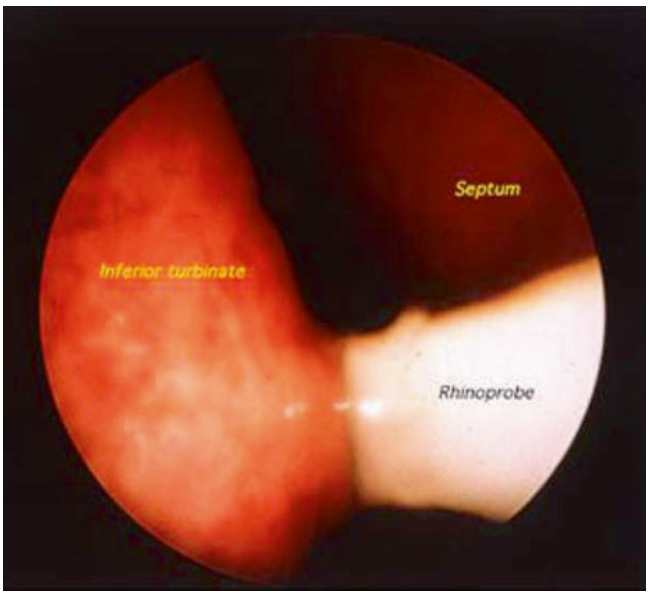


Fig. 18.5 Rhinoprobe sampling of inferior turbinate (Courtesy of Alfredo A. Jalowayski, PhD)

Table 18.8 Collecting specimens with the Rhinoprobe

1. Instruct patient to blow his/her nose. In infants, use a rubber bulb to aspirate excess mucus
2. Use headlight and specula to examine the nasal cavities
3. Carefully maneuver the Rhinoprobe between the septum and inferior turbinate. Avoid touching the anterior bulb area
4. Gently press cupped tip of probe on the mucosal surface and move outward 2–3 mm. Repeat motion twice. Withdraw probe, using caution to not touch the nasal vestibule, as contamination would result
5. Spread the specimen gently over a small area of a microscope slide and fix quickly in a jar containing 95 % ethyl alcohol (ETOH) for 1 min or until stained

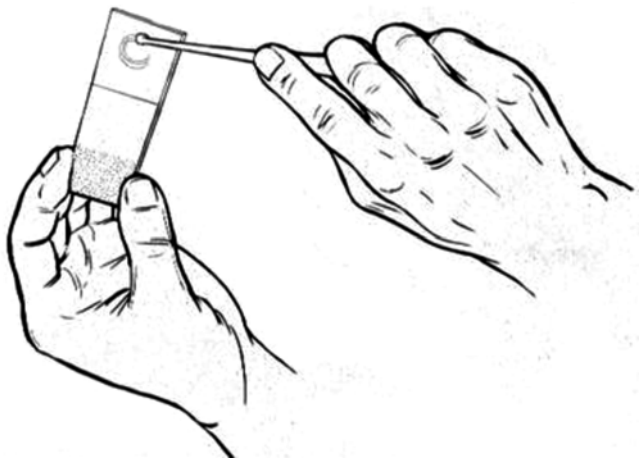


Fig. 18.6 Apply specimen to slide in a circular manner

Value and limitations: With the scraping technique using a small plastic cup (Rhinoprobe), there is no loss of tissue due to adherence, very little distortion of cells, and typically only a few degranulation artifacts seen. There is usually brief, minimal discomfort to the patient in obtaining the specimen even without the use of local anesthesia. The scraping technique is an excellent method for evaluating respiratory cilia structure and function, for rapid viral diagnosis, and can be used for the measurement of chemical mediators should such methods become available to the office practitioner in the future. The specimen is not full thickness and only mucosal cellular activity is typically defined.

Biopsy

A biopsy sample of the nasal mucosa is useful to determine changes taking place near the surface and below the basement membrane (Fig. 18.9). Taking a full thickness biopsy specimen of the superficial nasal mucosa and submucosa requires local

Fig. 18.7 Transferring of specimen to a test tube with glutaraldehyde fixative for EM

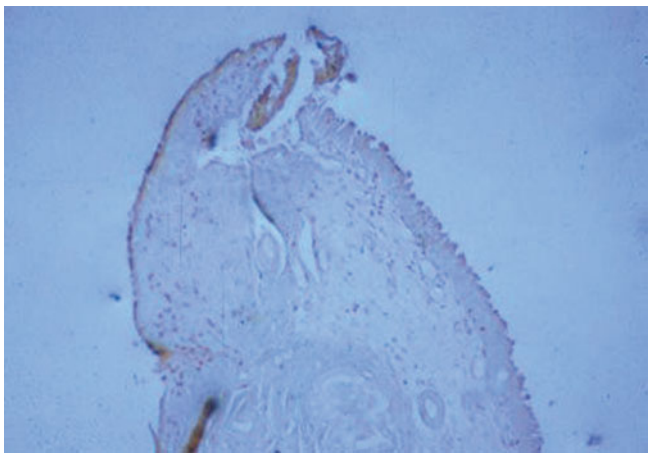


Fig. 18.8 Full thickness nasal turbinate mucosal biopsy (Courtesy of Alfredo A. Jalowayski, PhD)

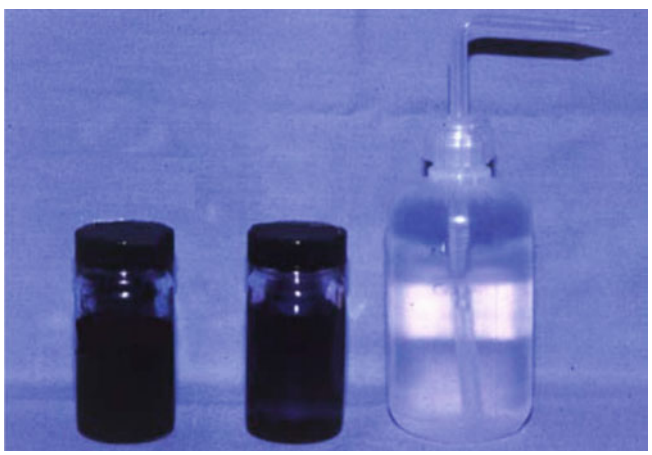


Fig. 18.9 Staining supplies

anesthesia and care to avoid excessive bleeding from the highly vascular turbinate. This procedure is generally performed by the head and neck surgeon. A biopsy is recommended to examine isolated growths within the nasal cavity especially for suspected malignancy. For the study of cilia structure and function, a biopsy sample is preferred, but not necessary unless

Table 18.9 Staining specimens

I.	Dip method (rapid)
1.	Place approximately 50 ml Wright-Giemsa stain in a Coplin jar
2.	Fill another Coplin jar with water or phosphate buffer
3.	Place thoroughly dried slide, feather edge DOWN, in Wright-Giemsa Stain for approximately 20–30 s. NOTE: Rapid dipping for 5–10 s may reduce water artifacts on films that are not thoroughly dried
4.	Remove slide from stain and place in deionized water or phosphate buffer, pH 6.8–7.2, feather edge DOWN, for approximately 1–10 min. DO NOT AGITATE SLIDE WHILE IT IS IN DEIONIZED WATER
5.	Rinse briefly in running deionized water, wipe back of slide with paper towel, and air-dry thoroughly before evaluation
II.	Horizontal staining method
1.	Place thoroughly dried blood film on an appropriate staining rack
2.	Flood slide with 1–2 ml Wright-Giemsa stain
3.	After 1 min, add an equal volume of deionized water or phosphate buffer, pH 6.8–7.2, and mix thoroughly by gently blowing on slide
4.	After 1–3 min, thoroughly rinse with deionized water and air-dry

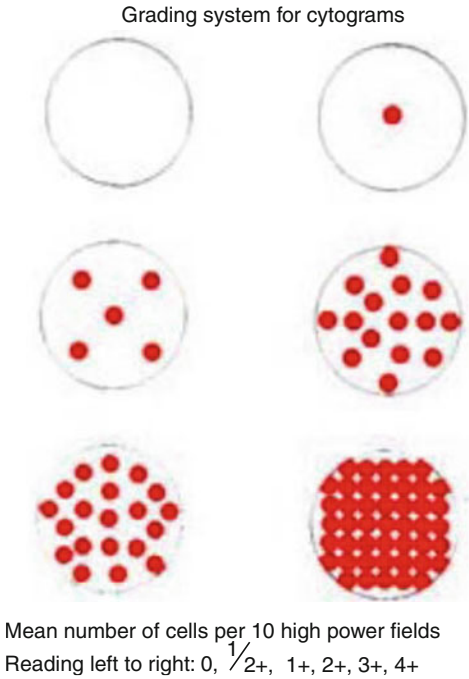


Fig. 18.10 Grading system for cytograms

real-time visualization of living mucosal function is desired. Electron microscopy for ciliary morphology can be used with a specimen obtained with the Rhinoprobe or biopsy after it is placed in glutaraldehyde fixative.

In-Office Staining, Viewing, and Describing the Nasal Cytologic Specimen

After the slide has been in fixative for up to several hours, it is removed and allowed to air-dry. Wright-Giemsa is an easy and accurate staining method for these specimens (Fig. 18.9). The staining method is described in Table 18.9.

A thin layer of oil is applied to the slide prior to light microscopy examination. The specimen is examined under low magnification to identify adequate tissue and to locate secretions to examine more carefully. Those chosen areas are then examined under high magnification. At least 10 high-powered fields should be examined. It is important to evaluate the adequacy of the specimen before recording the results. An adequate specimen is one that contains several fields of non-squamous epithelial cells, few to no squamous epithelial cells, and scant secretions. Once the adequacy of the specimen has been established, the results are recorded or graded as defined in (Fig. 18.10 and Tables 18.10, 18.11). The grading system is reasonably quick and simple and provides adequate accuracy for the in-office diagnosis of common nasal disorders.

The following section will serve as a tutorial for identifying the different cellular structures obtained through the scraping technique where both mucous and mucosal structures are examined using the Wright-Giemsa staining technique.

Table 18.10 Grading nasal cytograms

1. Quantitative analysis: To perform, count the number of cells in each of ten high power fields and then calculate the mean
2. Qualitative analysis: The grading is done on a scale of 0–4+, where 0 is none and 4+ is large number f cells, as shown in Fig. 18.11 and described in more detail for each cell type in

Table 18.11 Quantitative/qualitative analysis

Eosinophils/neutrophils/monocytes	**Basophils**	**Grading**
0/None	0/None	0
0.1–1.0/Occasional cells ½+	0.1–0.3/Occasional cells	½+
1.1–5.0/Few scattered 1+	0.4–1.0/Few scattered	1+
5.1–15.0/Moderate # of cells 2+	1.1–3.0/Moderate # of cells	2+
15.1–20.0/Large clumps of cells 3+	3.1–6.0/Many easily seen	3+
>20.0/Large clumps over entire slide 4+	>6.0/Large number per HPF	4+
Goblet cells	**Grading**	
<1/None	0	
1–24/Occasional to few	1+	
25–49/Moderate number	2+	
50–74/Many easily seen	3+	
≥75/Large # may cover HPF	4+	
Epithelial cells	**Grade**	
Normal morphology	N	
Abnormal morphology	A	
Ciliocytophthoria	CCP[a]	
Bacteria	**Grade**	
None seen	0	
Occasional clump	1+	
A moderate number	2+	
Many easily seen	3+	
Large number, may cover entire field	4+	

Count the number of cells in each of ten high power fields and calculate the mean

[a]Ciliocytophthoria: Evidence of viral infection

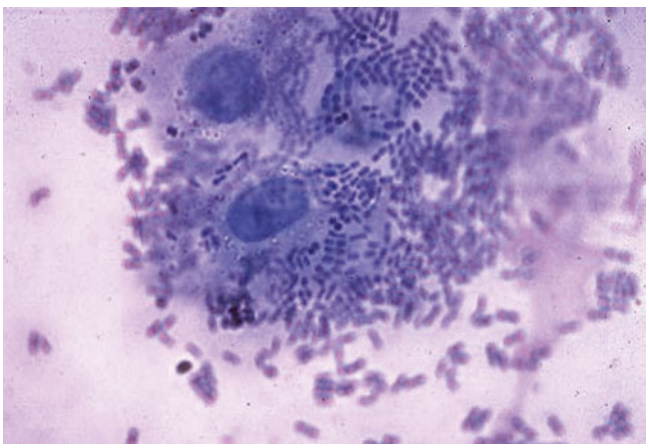


Fig. 18.11 Photomicrograph of squamous epithelial cells and bacteria. Typical of a sample taken from the nasal vestibule (Courtesy of Alfredo A. Jalowayski, PhD)

The Morphology of Cell Structures Seen on Nasal Mucosal Sampling

Squamous Epithelial Cells

Squamous epithelial cells are relatively large compared to other cells seen on a sample slide and shaped as irregular polygons. They have an oval nucleus located in the center of the cell. These cells line the nasal vestibule and the anterior bulb of the inferior turbinate. When squamous epithelial cells are present in nasal scrapings, it suggests that the sample was taken from the nasal vestibule and not a good representation of mucosal immune activity (Fig. 18.11). Infrequently, in chronic conditions such as chronic sinusitis and allergic rhinitis, non-squamous epithelial cells undergoing metaplastic changes can be found on the turbinates and mistaken for squamous epithelia.

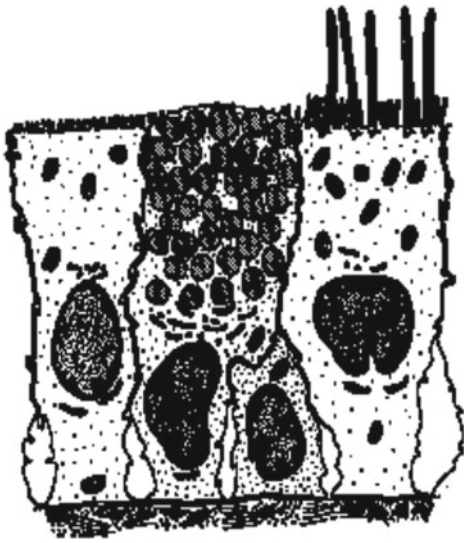


Fig. 18.12 Schematic of non-squamous epithelial cells

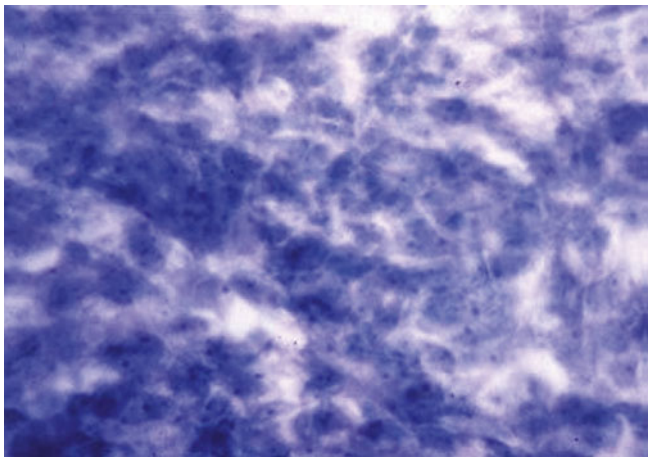


Fig. 18.13 Photomicrograph of non-squamous epithelial cells (Courtesy of Alfredo A. Jalowayski, PhD)

Non-squamous Epithelial Cells and Goblet Cells

Non-squamous epithelial cells are located on the nasal turbinates above the basement membrane and form the superficial mucosal layer where the majority of nasal function occurs (Figs. 18.12 and 18.13). Columnar cells can be either non-ciliated (covered by microvilli) or ciliated. A ciliated columnar epithelial cell can often be seen on a mucosal specimen obtained by scraping if found isolated on a slide. More frequently, non-squamous epithelium appears as shown in Fig. 18.13. Basal cells schematically represented in Fig. 18.12 are difficult to differentiate by the scrapping methodology. Scanning through the epithelial cells, goblet cells can be readily seen in selected areas as depicted in Fig. 18.14. Goblet cells are clearly demarcated by their vacuolated appearance in contrast to epithelial cells. The normal columnar to goblet cell ratio is approximately 5:1. Greater numbers (e.g., goblet cell hyperplasia) can be seen as a long-standing nasal irritation and/or inflammation.

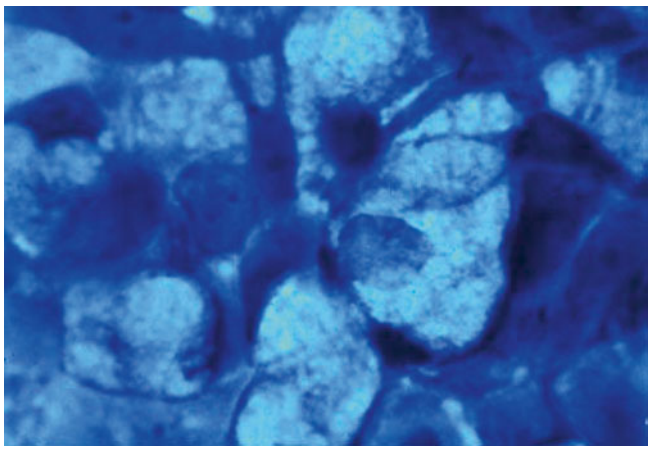


Fig. 18.14 Photomicrograph of goblet cells among non-squamous epithelial cells (Courtesy of Alfredo A. Jalowayski, PhD)

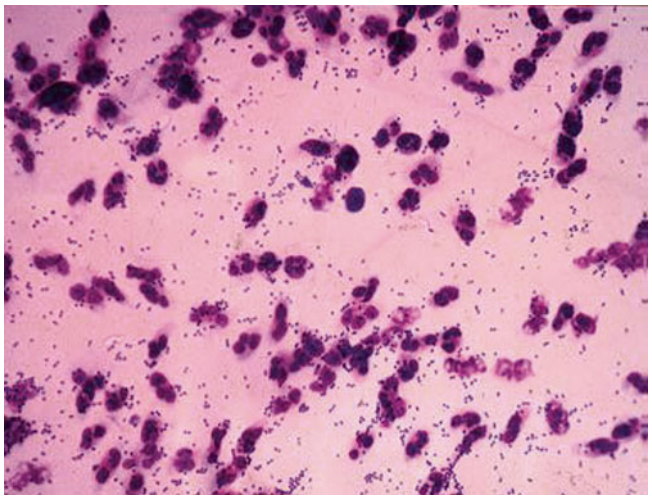


Fig. 18.15 Photomicrograph of bacteria and neutrophils engaged in active phagocytosis (Courtesy of Alfredo A. Jalowayski, PhD)

Neutrophils

Neutrophils in the nasal epithelium are normally absent or seen only occasionally. Their appearance is similar to those in blood smears when using the Wright-Giemsa stain. Neutrophils have multilobed, blue-purplish nuclei with lightly stained and finely granulated cytoplasm. When present in large numbers, neutrophils commonly appear with bacteria as shown in Fig. 18.15. Bacteria will stain a dark purple/blue with Wright-Giemsa staining and appear as cocci or rods. In Fig. 18.15, many bacteria are seen within the cytoplasm of the neutrophil demonstrating active phagocytosis. This finding is pathognomonic of an acute bacterial infection such as acute bacterial sinusitis.

When bacteria are present without significant neutrophilia, the sample was likely taken from the nasal vestibule and should be discarded. Another hint of poor sampling technique is the fact that a nasal vestibule specimen would contain mostly squamous epithelial cells.

Eosinophils

Eosinophils are not commonly found in nasal epithelium or secretions under normal conditions. These cells are about the size of neutrophils or slightly larger and demonstrate a two-lobed nucleus pushed toward the periphery of the cell. Like neutrophils, the nucleus is not obscured by the cytoplasmic structures. In contrast to neutrophils, the cytoplasm of eosinophils is filled with distinct large granules, which stain orange/red with Wright-Giemsa stain. Sometimes it is difficult to differentiate

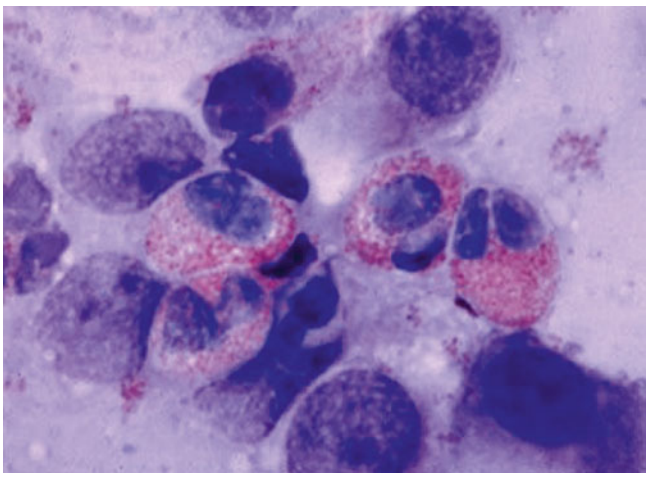


Fig. 18.16 Photomicrograph of eosinophils and epithelial cells (Courtesy of Alfredo A. Jalowayski, PhD)

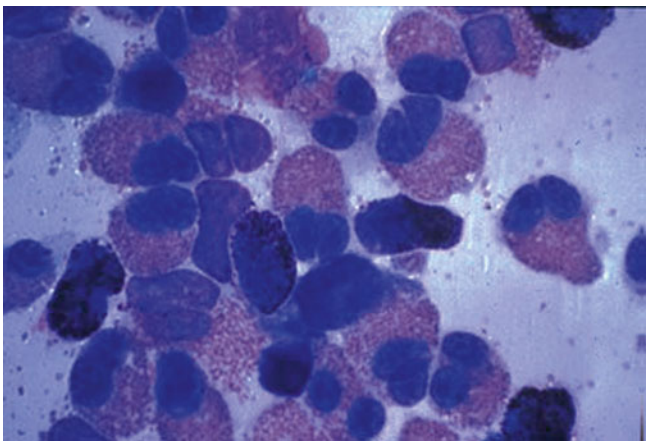


Fig. 18.17 Photomicrograph of basophils (*dark*) and eosinophils (*red*) (Courtesy of Alfredo A. Jalowayski, PhD)

the granules of neutrophils from eosinophils if the specimen is lightly stained or when the neutrophil granules are unusually large and the stain is heavy. In this circumstance, the granules can be somewhat orange/red and confusing. With good staining technique, however, this problem is not commonly encountered. Key points distinguishing eosinophils from neutrophils are the bilobed nucleus and red-staining large cytoplasmic granules which have distinct uniformity and shape (Fig. 18.16). Eosinophilic granules will also appear larger than their neutrophilic counterpart; something appreciated most commonly if the cells appear side by side.

Basophils

Basophil leukocytes are smaller than eosinophils and neutrophils. They are distinct in that their granules are varying in size and stain a very dark purple or red obscuring some or the entire nucleus. The darkly stained colored and obscured nucleus is a distinct contrast to the eosinophil staining and morphology. When seen, the nucleus is segmented into two or three lobes. Basophils are not normally found in the nasal epithelium and, when present, are few in number. These cells most commonly migrate to the superficial nasal epithelium and into the secretions in response to an allergic reaction, hence are usually found in the presence of eosinophils (Figs. 18.17, 18.18 and 18.19). Distinguishing basophils from mast cells is nearly impossible without special staining techniques or perhaps when visible in the same field. Basophils are usually smaller than mast cells but otherwise stain similarly with Wright-Giemsa.

Mast Cells

Mucosal mast cells (Fig. 18.20) may take many shapes and normally can be seen only in the submucosa, below the lamina propria. In nasal disease, such as chronic allergic rhinitis, mast cells can be found in large numbers in the superficial epithelium but are difficult to distinguish from basophils. When visible, the nucleus of a mast cell is large and oval in shape.

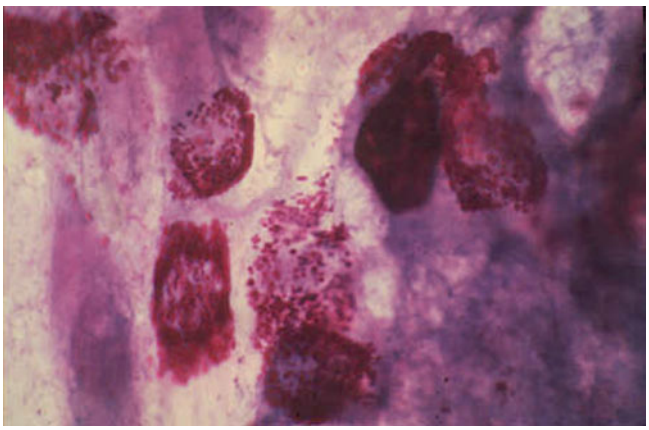


Fig. 18.18 Basophilic cells within non-squamous epithelial cells (Courtesy of Alfredo A. Jalowayski, PhD)

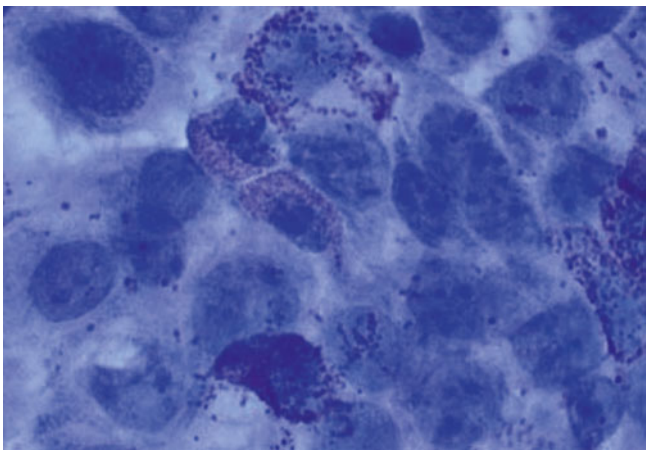


Fig. 18.19 Eosinophils (red granules, visible nucleus) and basophils (dark granules obscuring nucleus) among non-squamous epithelial cells as seen in chronic allergic rhinitis (Courtesy of Alfredo A. Jalowayski, PhD)

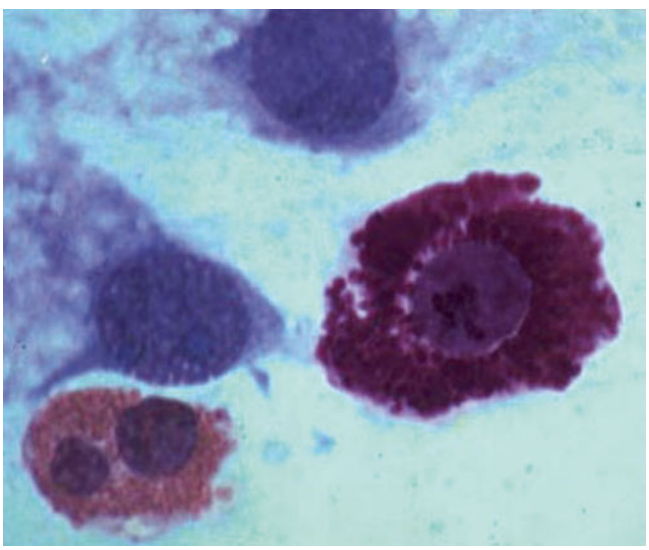


Fig. 18.20 Photomicrograph of a mast cell (*right*), an eosinophil (*left*) and two non-squamous epithelial cells (Courtesy of Alfredo A. Jalowayski, PhD)

However, like the basophil, the nucleus is commonly obscured by secretory granules which are large, round, and stain purplish red with Wright-Giemsa.

Mononuclear Cells

Lymphocytes and monocytes in the nasal mucosa appear morphologically similar to those seen in blood smears. Lymphocytes have a round, oval or slightly indented nucleus. The cytoplasm is basophilic with few to no granules evident with

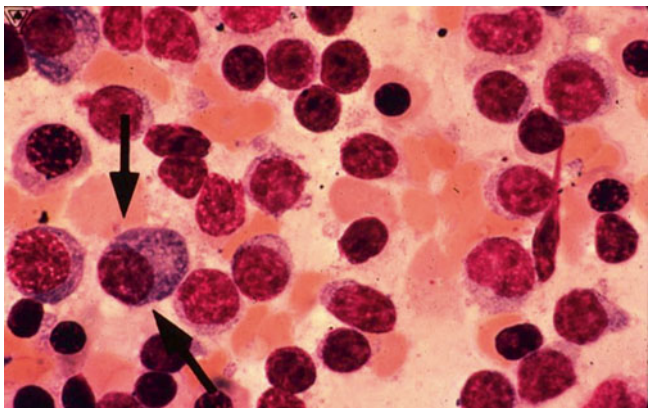


Fig. 18.21 Photomicrograph of lymphocytes (Courtesy of Alfredo A. Jalowayski, PhD)

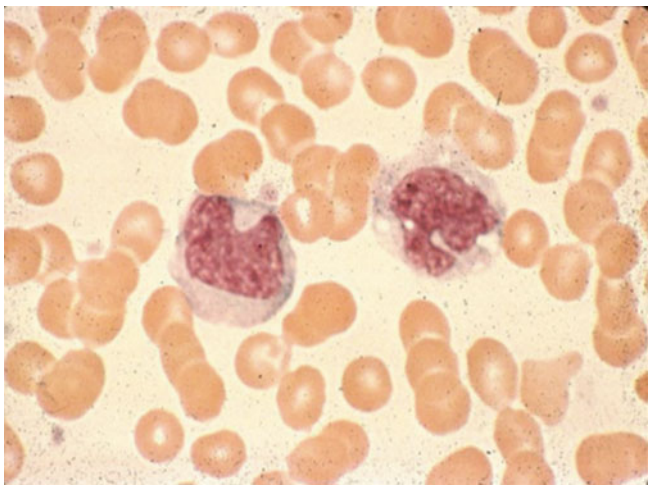


Fig. 18.22 Photomicrograph example of monocytes morphology (Courtesy of Alfredo A. Jalowayski, PhD)

Wright-Giemsa staining. A key point distinguishing the lymphocyte from the monocyte is the fact that within the lymphocyte, the nucleus appears more round and typically very large in relation to the cytoplasm (arrow Fig. 18.21). Monocytes, in contrast to lymphocytes, have a larger amount of cytoplasm in relation to the nucleus and more distinctively shaped nucleus. Figure 18.22 demonstrates the typically kidney-shaped nucleus seen in the monocyte which contrasts with the slightly indented or round lymphocyte nucleus. The granules within the cytoplasm of a monocyte, when seen, are fine and evenly distributed.

Viral Infection, Ciliocytophthoria

Although far too small to be seen using light microscopy, the harmful effects of a virus infection on respiratory epithelial cells can sometimes be indirectly appreciated; a process called ciliocytophthoria (CCP). In CCP, a viral infection induces a clumping of the fine chromatin material within the nuclear membrane. This is followed by margination of the clumped chromatin and ultimately more clumping into larger units until a single pyknotic nucleus is formed (Fig. 18.23). The nucleus of a virally infected respiratory epithelial cell is eventually surrounded by a clear area which appears as a halo. Ultimately, the cell undergoing CCP changes splits into two portions and dies.

Mucociliary Transport

Normal nasal airway mucus lines the epithelial surface and provides an important innate immune function in the human body. Moisture and warmth is provided for inspired air to the sensitive lower airway. Trapped noxious chemicals, particulates, and pathogens are removed from the airway before they can invade the mucosa by a mechanism termed mucociliary clearance, mucociliary transport, or the mucociliary escalator.

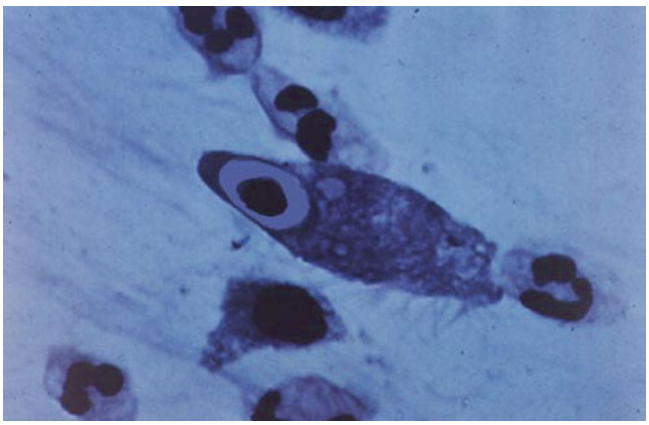


Fig. 18.23 Photomicrograph of an epithelial cell with a pyknotic nucleus and halo from a viral infection (Courtesy of Alfredo A. Jalowayski, PhD)

Nasal mucous primarily is derived from goblet cells. Throughout the respiratory tract, mucous is composed of 1 % sodium chloride, 0.5–1 % free protein, 0.5–1 % mucins, 1 % lipids and phospholipids, and approximately 95 % water [1]. It possesses different rheological properties, such as viscosity, elasticity, humidification, and adhesiveness. The viscoelastic property is an important determining factor for mucus transport capacity. An intermediate viscoelasticity is required for optimal mucociliary transport [2, 3].

Nasal mucous appears in two layers on the mucosal surface; the periciliary "sol" phase and the viscous surface "gel" phase. The propulsion of mucus is accomplished through the beating of cilia, located at the tip of non-squamous epithelial cells. There are approximately 50–200 cilia per epithelial cell [4]. In the forward-powered stroke, the cilia are erect with the tips touching the viscous or gel mucus layer. As the cilia recover from this beat, they become flaccid and bend as they return to their starting position, traveling in the sol phase of the mucus. The cilia of a particular nasal/sinus mucosal cell and the cilia from adjacent cells beat in a coordinated fashion at 10–12 beats per second to propel mucus and any trapped pathogens or particulates toward the oropharynx in a "waveform" where it is swallowed and transported to the stomach for digestion and eventual elimination [5].

Two processes contribute to mucociliary clearance: mucus volume/content and mucus transport. In order to transport nasal mucous effectively, there has to be a general balance between volume and composition of the mucous, adequate periciliary liquid volume for ciliary movement, adequate cilial beat frequency, and ciliary beat coordination. Different biochemical constituents contribute to the gel properties of respiratory mucus, such as proteins, lipids, proteoglycans, glycoproteins, and the degree of hydration [6]. Nasal mucous which experiences altered macromolecular composition and biophysical properties of either the gel or sol phase can hinder mucous clearance if ciliary movement is blunted. For example, loss of water, absence of glycoproteins, and an increase in macromolecule components will increase mucous viscosity and typically result in impaired mucociliary transport [7].

Mucous transport is also regulated by the cilia. Mechanical or chemical stimulation from the environment, thermal conditions, humidity, aging, thyroid disease, sinonasal surgery, lacrimal duct obstruction, infection, structural variations in the nose (septal deviation, hypertrophied turbinates), nasal polyps, and allergy can separately or in combination alter ciliary beat frequency resulting in impaired nasal mucous transport [8–12]. The unifying consequence of altered mucous and/or ciliary function in the nasal/sinus cavity is impairment of mucociliary clearance resulting in nasal/sinus congestion and mucosal inflammation. The paranasal sinuses are particularly vulnerable in this circumstance in the maintenance of a bacteria-free environment is dependent upon adequate mucociliary clearance. Otherwise, bacteria from the nose that favor a low-oxygen environment will have an opportunity to migrate and proliferate in the sinus cavities [13, 14].

Abnormalities in mucociliary clearance can also result from dysmorphology of the ciliary structure. Such variations are commonly referred to as ciliary dyskinesias. Primary ciliary dyskinesia or ciliary immotility syndrome is a rare, usually inherited, autosomal disease with a recessive pattern. It affects between 1:20,000 and 1:60,000 individuals [15]. Ciliary dyskinesias are a group of entities that are characterized by abnormal motility of respiratory cilia and distinguished morphologically by the structure of their cilia. Specific morphologic abnormalities may be expressed as ciliary immotility, dysmotility, or a combination of both. The coexistence of primary ciliary dyskinesias and situs inversus is called Kartagener's syndrome. Kartagener's syndrome has a frequency between 40 and 50 % among patients with primary ciliary dyskinesia [16]. The ciliary dyskinesias are characterized clinically by chronic infections of the upper and lower respiratory tracts, including the middle ear, starting from early infancy. Therefore, the diagnosis should be considered in any individual who presents with a lifelong history of airway-directed recurrent infections. Despite the fact that these disorders have a highly variable clinical presentation from patient to patient, it behooves the medical examiner to consider these disorders earlier rather than later in the disease course. Longitudinal studies have revealed irreversible lung damage in prepubertal children with these disorders. Early diagnosis allows the early initiation of a number of respiratory measures that can minimize and slow the airway damage that invariably evolves over time [17].

Table 18.12 Functional assays of nasociliary transport

Saccharin granule test
Charcoal tablet test
Rhinoscintigraphy

Methods used to define abnormalities of mucociliary transport include general functional assessment of mucous movement and measurements of beat frequency and individual ciliary morphology. In-office assessment of mucociliary function is confined to the gross measurement of mucous transport which best serves as a screening method for transport abnormalities before more in-depth studies are ordered. Having an adequate number of cilia, the correct beat frequency, appropriate waveform, and intercellular coordination are all necessary to achieve efficient and effective mucociliary clearance, and each holds an area that can be investigated. However, in-office procedures are limited to evaluating the cumulative outcome of this effort. Functional screening assays clinically available to the healthcare provider are listed in Table 18.12.

A comparison between mucociliary transport speed and various study methods with soluble and insoluble substances is difficult. Papers report either velocity figures, total mucociliary transport time, or both. The reported values also show a high range of variability (i.e., from 4.6 to 12.3 mm/min for the saccharine test; from 3.4 to 7.8 mm/min for the carbon powder test, and around 10–11 mm/min for various radiopharmaceuticals (colloidal solutions, resin particles, and albumin microspheres) [17]. Generally, the normal nasopharynx should clear a substance from the nose in 10–15 min when free of ancillary nasal/sinus disease (such as acute infection, nasal polyps, or allergic rhinitis) or major structural anomalies. The upper limits of normal, no matter what the method of study is being used, are 20 min, and most investigators suggest that >30 min transport time is distinctly abnormal and deserves further study.

Saccharin Granule Test

A saccharin granule approximately 1 mm in diameter (5 mg) is introduced into the upper portion of the inferior turbinate approximately 1.5 cm from the nasal opening (or 1 cm behind the mucocutaneous junction) under direct visualization. Time is measured from the introduction of the granule until the patient reports a sweet taste. The lapsed time is the saccharine transit time. The upper limit of the waiting time is generally 30 min, but longer than 20 min should be viewed with suspicion especially if the clinical presentation is highly suspicious of ciliary dyskinesias. Most normal adults will taste the sweetness around 10–15 min after application [18]. Some investigations dissolve the saccharin particle with methylene blue or charcoal. Thus, when the patient reports the taste sensation, the presence of blue dye or black charcoal in the oropharynx can be used as visual confirmation of the patient's report. If, after 30 min, there is no sweetness noted by the patient, a saccharin tablet is placed on the tongue to ensure the patient's sense of taste is intact.

Charcoal Carbon Test

As in the saccharin granule test, a small piece of a charcoal tablet is placed just posterior to the anterior tip of the inferior turbinate and the posterior oropharynx visually examined every 5 min up to 15 min then every minute or two thereafter until 40 min have passed. When the black carbon appears, the lapsed time is recorded as the carbon transit time. Generally, movement of the black carbon is slower than saccharine and therefore visual detection is somewhat delayed. The upper limits of normal for the carbon test are approximately 25 min, and 35 min is considered distinctly abnormal.

Rhinoscintigraphy

A more objective approach to assess nasal mucociliary clearance utilizes scintigraphy with various radiopharmaceuticals (colloidal solutions, resin particles, and albumin microspheres) labeled with ^{51}Cr, Tc-99m, or I-131. Tc-99m is preferred by most authors [18–20]. With this technique, a droplet of a suspension of colloid particles labeled with technetium-99 (usually 50 mCi diluted in 0.05 ml of saline) is placed one centimeter behind the mucocutaneous junction of the nasal cavity just posterior to the tip of the inferior turbinate. Some authors have preferred spraying the colloid into the nostril while the patient holds their breath thereby allowing more widespread distribution and mimicking natural exposure. Movement of the radioactivity is recorded with a gamma camera with images obtained every 30 s during the first 10-min period. The camera is positioned laterally, ipsilateral to the nares in which the isotope is placed. Crying, sneezing, and coughing have not been

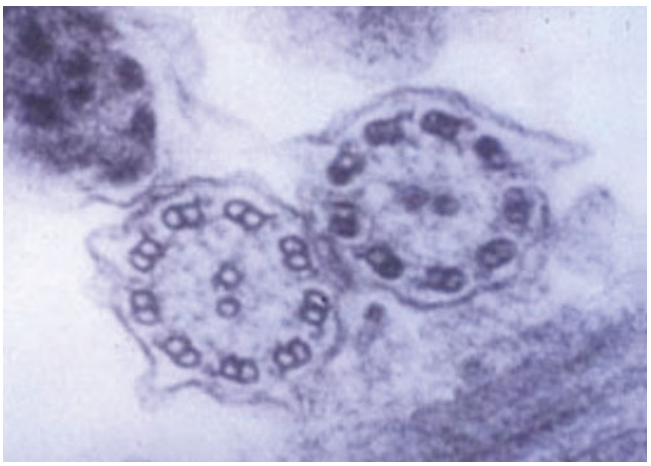


Fig. 18.24 Cilia ultrastructure at low magnification

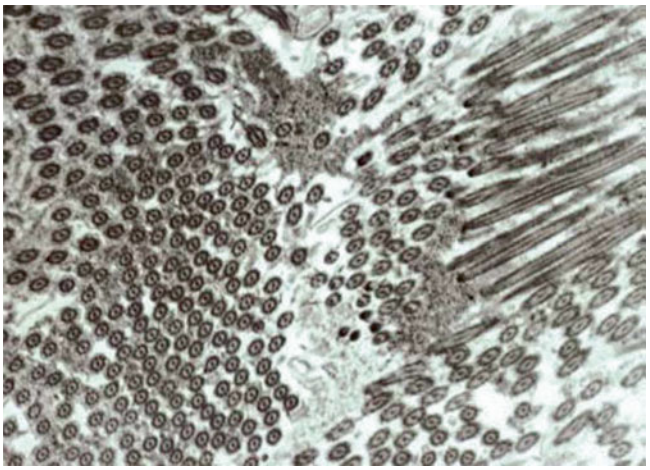


Fig. 18.25 EM X-section of normal cilia morphology Normal cilium cross section demonstrating the presence of all axonemal components including 9 + 2 microtubular arrangement, inner and outer dynein arms, and radial spokes (Courtesy of Alfredo A. Jalowayski, PhD)

reported to influence the test. When mucociliary transport is normal, the droplet travels at least halfway toward the posterior reference point within 10 min. When used as a screening test, the test is considered abnormal when no motion toward the posterior reference source is detected or when the droplet travels less than half the desired distance. Most studies report an average velocity of 10.9 mm/min for control populations or transport time of 10–16 min [21]. These data compare favorably with the saccharine test (4.6–12.3 mm/min) and the carbon test (3.4–7.8 mm/min) reported in the literature.

Evaluation of Nasal Cilia Ultrastructure

If the patient fails one or more of the screening tests noted above, more detailed analysis of ciliary structure and function is required. The study of mucociliary transport by different methods, such as saccharin, carbon, or isotopic agents, does not distinguish between a deficit in transport due to alterations in mucus and/or nasal structure and a defect in ciliary movement due to a structural abnormality (e.g., primary ciliary dyskinesia). The studies noted above do not differentiate between primary ciliary dyskinesia (PCD) and secondary ciliary dysfunction as might occur with noxious air exposure, thermal conditions, low humidity, aging, thyroid disease, sinonasal surgery, lacrimal duct obstruction, chronic naso-sinus infection, structural variations in the nose (septal deviation, hypertrophied turbinates), nasal polyps, and chronic allergy.

An example of low- and high-magnification electron microscopy of mucosal cilia is shown in Figs. 18.24 and 18.25. An abnormal screening study should be followed by an investigation of the ultrastructure of individual cilia (Fig. 18.26). Although PCD has a rather uniform clinical presentation, electron microscopy of patients with this disorder reveals a variety of structural abnormalities to account for the movement deficit (Fig. 18.26). Dynein arm defects affect 70–80 % of patients suffering from this disorder and represent the most severe phenotype of this group of ciliary defects [22]. However, the

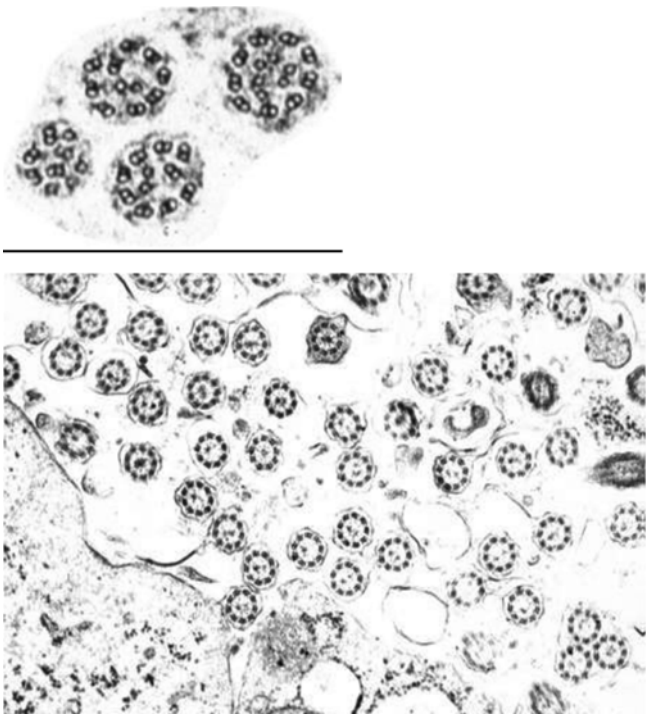


Fig. 18.26 EM examples of abnormal nasal mucosal cilia in PCD-disarray of microtubules (*upper figure*) and sporadically missing central microtubules (*lower figure*) (Courtesy of Alfredo A. Jalowayski, PhD)

presence of normal ultrastructure, in the absence of abnormal ciliary function studies, does not exclude PCD if the clinical setting remains suspicious. Disease-causing mutations in the DNAH11 gene have been identified in individuals with a compatible clinical phenotype. In this mutation, affected individuals have a normal ultrastructure but an abnormal ciliary function [23]. A recently described model using high-speed and precision digital video imaging makes it possible to study the pattern and frequency of ciliary beat, which may be useful in the diagnosis of PCD [24]. At the time of this writing, there are no genetic tests available that have been validated for the majority of PCD cases.

Obtaining Nasal Cilia for Ultrastructure Analysis

Ciliated epithelial cells can be obtained by biopsy or by gently scraping the inferior turbinate, as described earlier. The specimen is placed in glutaraldehyde fixative for EM analysis. It is sometimes difficult to obtain a suitable and adequate specimen for EM study of ciliary structure. In general, a biopsy at an experienced center ensures the examiner of an adequate specimen for study.

Evaluation of Nasal Patency

Office-Based Use of Acoustic Rhinometry and Rhinomanometry

"The nose is the preferred organ of respiration." [25]

In addition to olfaction, the nose serves as the body's "preferred" portal of respiration. The nasal mucosa has enhanced surface area by way of the turbinates whose mucosal lining is "designed" to prepare incoming air for delivery to the lungs under optimized conditions. The nose adjusts air temperature and humidity, filters out particulates, and acts as an immune-processing center that prevents delivery of infectious agents to the lower airway.

Any process that adversely affects nasal airway patency can affect the usually easy delivery of air to lower structures. This can diminish resistance to infection; enhance the pathology and discomfort associated with allergy; predispose to upper respiratory tract infections and sinusitis; and exacerbate other forms of rhinitis.

Even mentation and dentition can be affected by diminished nasal airway patency. Nasal obstruction that forces a change from predominant nasal breathing to mouth breathing alters normal mouth flora and favors disadvantageous microbe predominance, predisposing to more easily induced dental carries. It also adversely affects sleep quality and nocturnal oxygenation [26]. This can be of particular concern in children. Jefferson et al. in General Dentistry (*The Journal of the Academy of*

General Dentistry) January/February 2010 summarized, "Over time, children whose mouth breathing goes untreated may suffer from abnormal facial and dental development, such as long, narrow faces and mouths, gummy smiles, gingivitis and crooked teeth. The poor sleeping habits that result from mouth breathing can adversely affect growth and academic performance" [27].

Patients with chronic nasal obstruction often habituate to their circumstances and may not accurately report the degree of nasal obstruction that it presents. For some patients, subjective reporting regarding airway patency is not an accurate means of evaluating nasal airway status and can lead to both under- and overutilization of methods of remediation. Paradoxically, patients who have undergone previous turbinectomy or turbinate reduction sometimes report sensation of nasal obstruction that is actually due to diminished sensation of velocity of airflow despite *hyper-patent* nasal airways [28].

Rationale for Objective Measures of Nasal Airway Patency

Objective measures of nasal airway patency can be useful in assisting the clinician on two important fronts:

Assessing airway patency at baseline. Rhinometry is done pre- and postnasal decongestion.

Lack of response to decongestant is associated with lower likelihood of response to other medical intervention and can serve as an indicator for referral for further anatomic evaluation and potential procedural remediation [29].

Response to decongestant is an indication that improvement with other medical intervention may be fruitful – such as trials of antiallergy medications, oral decongestants, etc. [30].

Assessing airway patency in serial fashion over time offers the opportunity to track a patient's response to therapy and to monitor for early signs of disease recrudescence. Examples would include tracking response to medical therapy or as follow-up after procedures such as turbinate reduction, adenoidectomy, or polypectomy [29, 31–33].

Rhinometry allows objectification of nasal airway status and can help determine which route of intervention would offer the best opportunity for improvement.

Rhinometric Methods

For measuring nasal airway patency, there are two commonly used rhinometric methods:

Rhinomanometry describes airway patency based on nasal airflow and airway resistance measurements. Rhinomanometry is accomplished by tracking inspiratory and expiratory airflow vs. pressure. This type of device was the first to become available commercially, appearing in the marketplace in the late 1970s (Fig. 18.27).

Acoustic rhinometry estimates patency based on the measurement of the reflected sound waves (echo) that emerge from various portions of the nasal cavity. A sound pulse is created which is then propagated through the nasal cavity. The reflected signals are then used to calculate nasal cross-sectional airway patency. The first acoustic rhinometers became available in the late 1980s.

Both forms of rhinometry are accurate, painless, and readily accomplished in the office setting, using an easily placed mask or nasal appliance. Minimal patient cooperation is required, making testing relatively easy to perform on small children

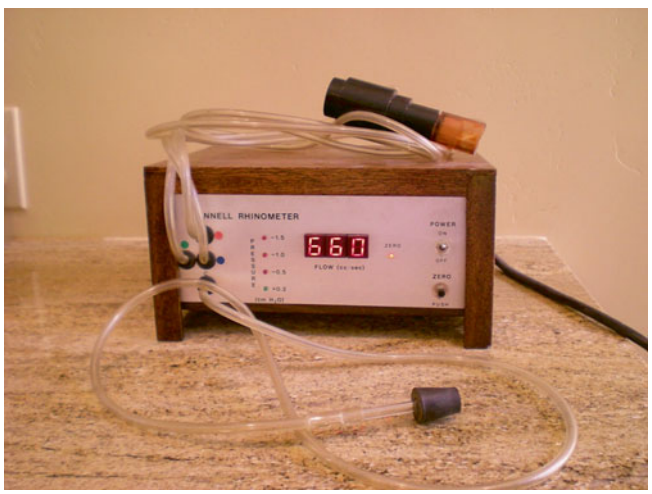


Fig. 18.27 Example of a circa 1980 Connell rhinomanometer that provided basic data regarding airflow vs. airway pressure

or infants, as well. Rhinomanometry offers a dynamic measure of actual airway flow and resistance, while acoustic rhinometry offers a more precise, but static, depiction of airway anatomy.

Results between methods are consistent and acoustic rhinometry has been shown to correlate well with CT imaging [34, 35], with greater convenience and reduced cost. Rhinomanometry and acoustic rhinometry results are regarded as complementary, with neither study claiming definitive superiority [36].

Testing is typically performed both before and after the administration of a topical decongestant. Changes in barometric pressure, humidity, and temperature can alter pre-decongestant readings. As mentioned, post-decongestant values are regarded as being the most definitive regarding underlying nasal anatomy.

Rhinomanometry

Rhinomanometry is obtained by placing a soft occlusive mask over the nose and mouth and occluding one nostril while the patient respires through the other nostril (Figs. 18.28 and 18.29).

A prototypical normal rhinomanometry (Fig. 18.30 and 18.31) reveals symmetric airflow and airway pressure. It is important to note that left and right airway results are "crossed," with expiration values appearing on the left-hand side of the graph and inspiratory values on the right. In this normal representation, the two curves mirror each other and there is no associated mismatch in airflow/pressure.

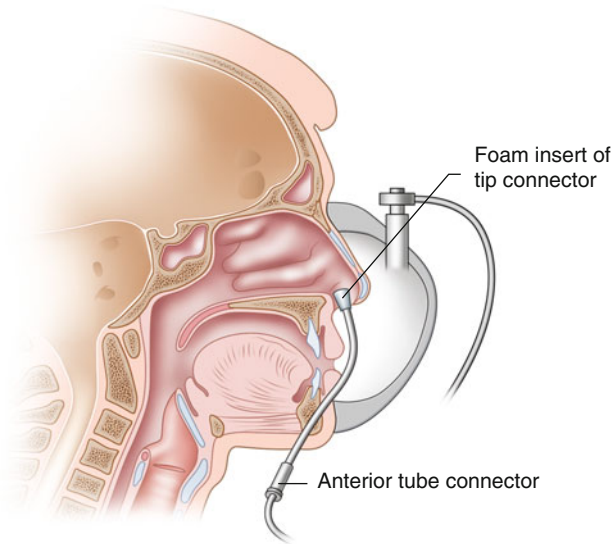


Fig. 18.28 Anterior rhinomanometry: the subject tested in a sitting position. The pressure-flow relationship during quiet breathing is measured independently for both nasal cavities. An airtight mask is fitted over the nose and connected to a pneumotachograph to measure flow through the side to be tested. A tube is sealed to the nostril of the opposite side to measure the pressure gradient between the nostril and the nasopharynx of the tested side

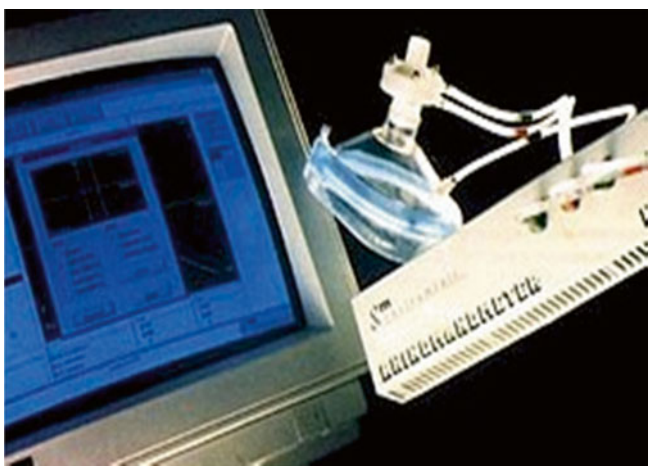


Fig. 18.29 Modern rhinomanometers have a computer interface and generate preprogrammed standardized results

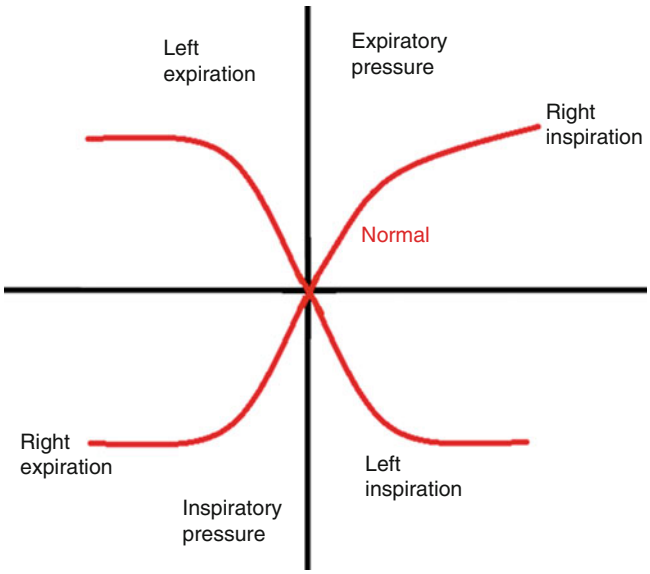


Fig. 18.30 Schematic normal rhinomanometry curves

In Fig. 18.32, taken from an actual test report, the teal curve represents baseline airway resistance to airflow. At any given time, inspiratory (negative) or expiratory (positive) pressure is tracked vs. airflow. The coral curve represents airflow after administration of topical decongestant. The coral curve demonstrates that for any given air pressure, the airflow is greater (and occurs at lower pressures) after decongestion. In a study demonstrating no response to decongestion, the curves would be identical.

Clinical Example 1: Septal Deviation to the Left

In the resulting printout (Fig. 18.33) and in the representative diagram (Fig. 18.34), we see that the airway resistance pattern is normal on the right. However, the left nostril demonstrates increased airway resistance in both inspiration and expiration, typical of airway narrowing and consistent with a septal deviation to the left. As can be noted, there is a "straightening" of the left-sided inspiratory and expiratory pressure curves, and the left nostril reveals increased expiratory and inspiratory airway pressures that would be associated with a narrowed nasal airway.

Nostrils are evaluating one at a time. A nosepiece is placed at the opening of the desired nostril (Figs. 18.35 and 18.36). The patient is instructed to hold his/her mouth slightly open during the study.

Rhinomanometry dynamically identifies "nasal minimum cross-sectional area," corresponding to the closest approximation of the inferior turbinate and nasal valve area (described as the area bordered below by the nasal floor and medially by the septum). Minimum cross-sectional airway patency correlates well with a patient's perceived nasal patency. It can be thought of as the patient's "rate limiting" factor with regard to total airway patency [28].

Acoustic Rhinometry

Acoustic rhinometry can present information regarding nasal anatomy beyond "nasal minimum cross-sectional area" of the nasal cavity, providing anatomic information all the way to the choana. Although a "static" test, acoustic rhinometry can identify where in the nasal cavity an obstruction may be present.

This test is also readily performed and requires only slight patient assistance.

Interpretation of acoustic rhinometry results include the following parameters:

1. Nosepiece, steady-state flow
2. Internal orifice, inferior turbinate
3. Nasal cavity, moving from the anterior inferior and middle turbinate to posterior portion of the same turbinates
4. Nasopharynx
5. Minimum cross-sectional area, which corresponds to the head of the inferior turbinate and nasal valve area
6. Before topical decongestant
7. After topical decongestant

In Fig. 18.37, the corresponding anatomic sites are marked on the rhinomanometry curve and noted in the description. The solid lines represent pre-decongestants values, and the scored lines represent the post-decongestant results. In this example,

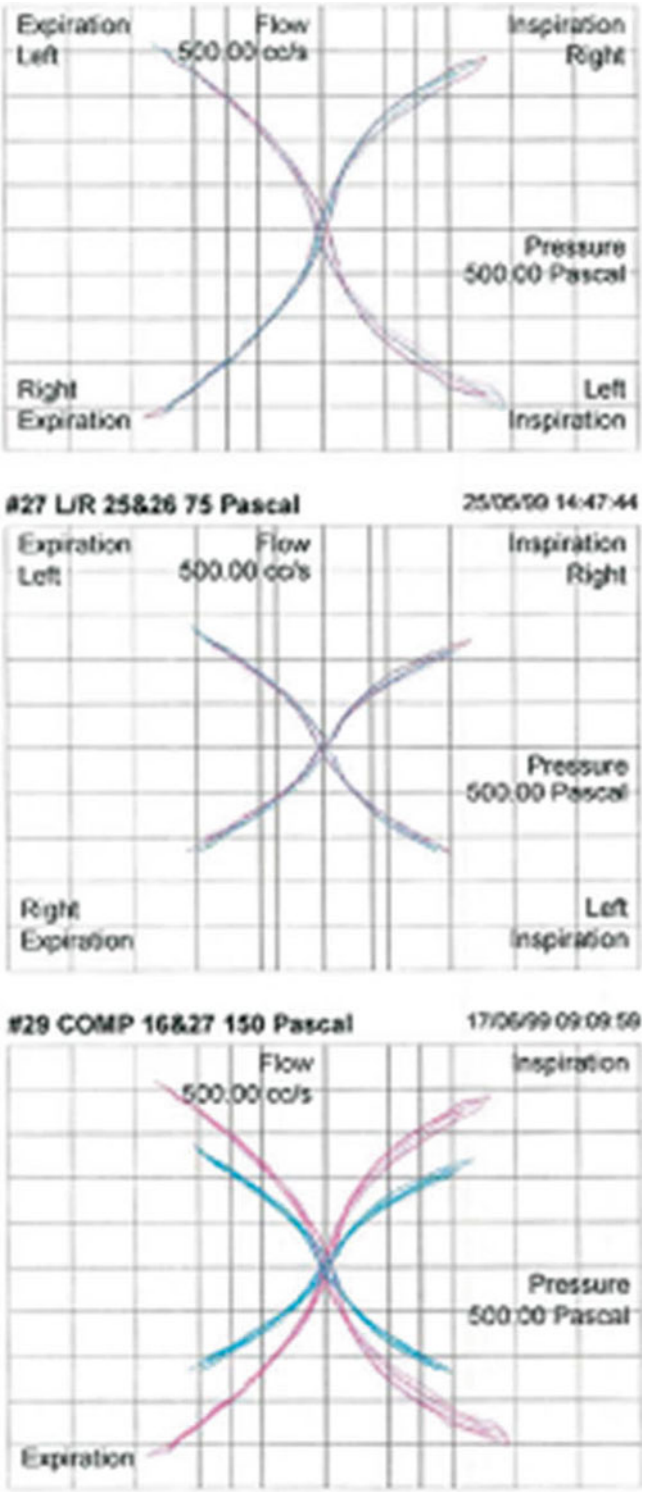


Fig. 18.31 Normal rhinomanometry

there is a demonstrated post-decongestant response. If there had been no response, the solid and dotted lines would have overlapped.

Clinical Example 2: In Fig. 18.38, acoustic rhinometry is performed for a patient with rightward septal deviation. There is narrowing of the airway associated with septal deviation, and there is a greatly diminished response to nasal decongestant, consistent with a fixed nasal airway obstruction (Figs. 18.39 and 18.40).

Clinical Example 3: Acoustic rhinometry curves can assist with evaluation of nasal polyps on the nasal airway and delineate which parts of the nasal airway are affected. In Fig. 18.41, we see a patent lower airway and some retained response to

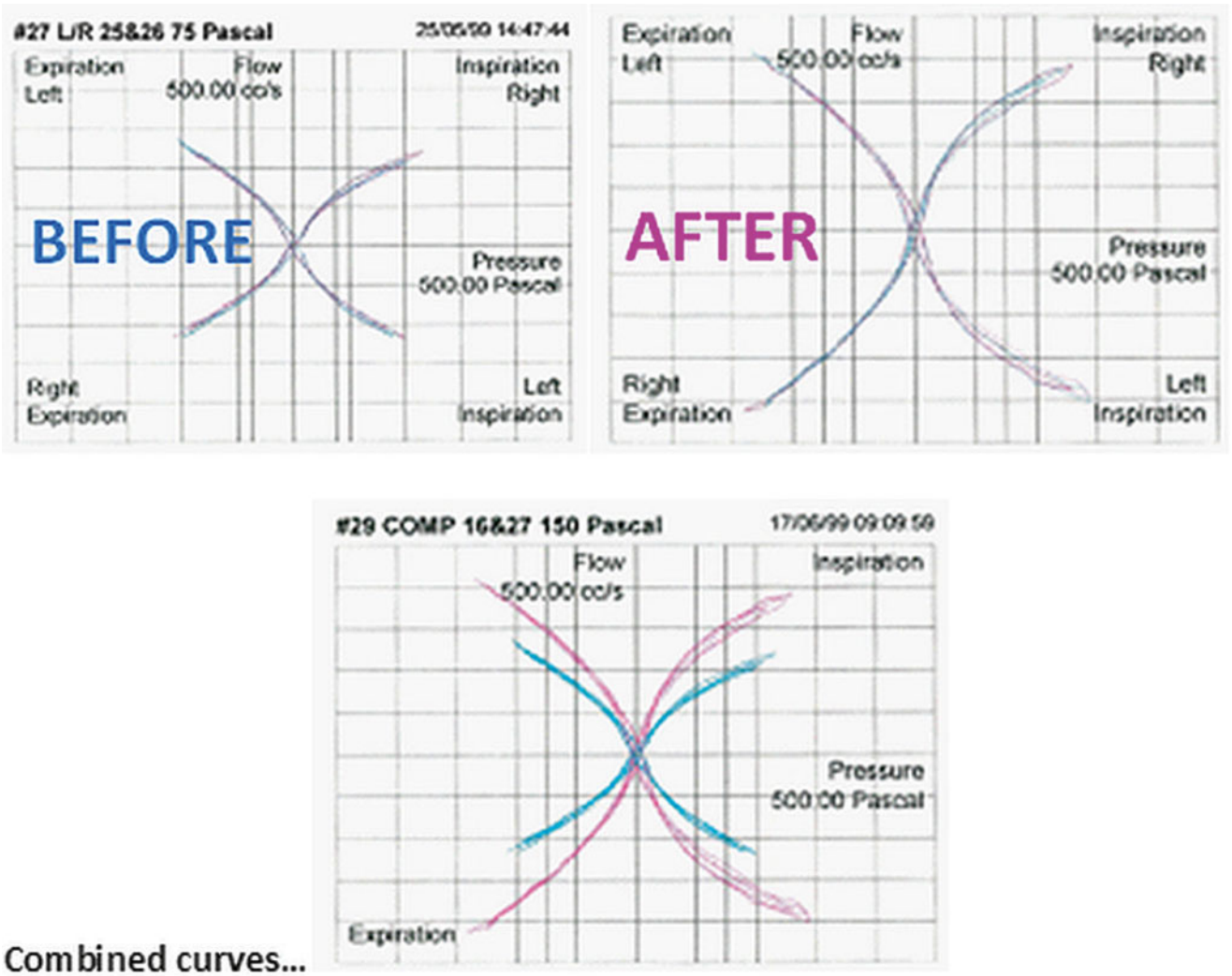


Fig. 18.32 Rhinomanometry curves pre- and post-decongesting

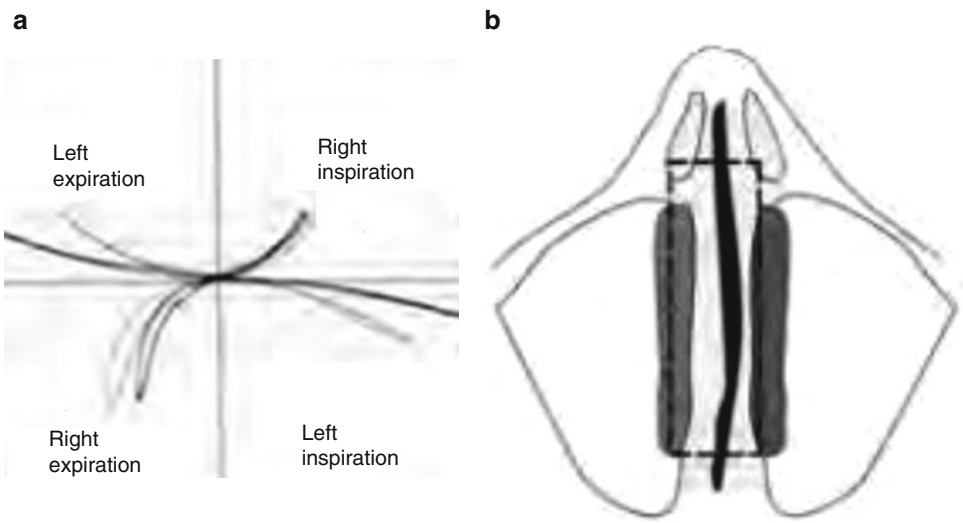


Fig. 18.33 (**a**) Rinomanometry in Left septal deviation. (**b**) Corresponding anatomy (Reprinted from Passali et al. [12]. With permission from Springer Science & Business Media)

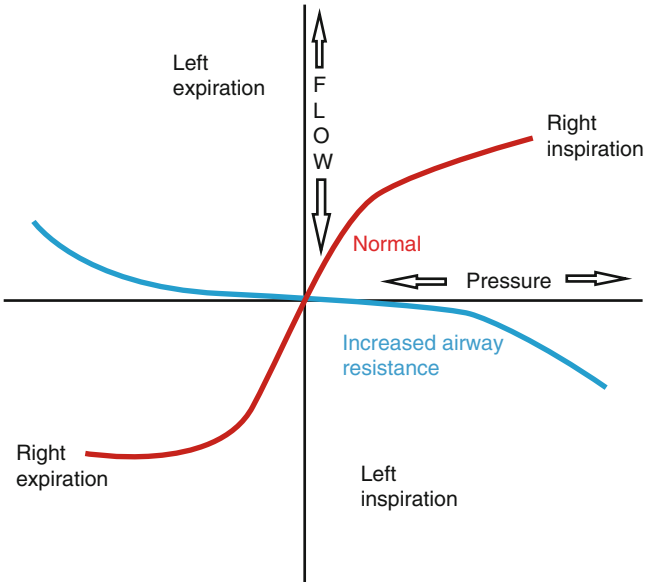


Fig. 18.34 Schematic rhinomanometry in aerodynamically significant left septal deviation

Fig. 18.35 Acoustic rhinomanometry technique

Fig. 18.36 Success!

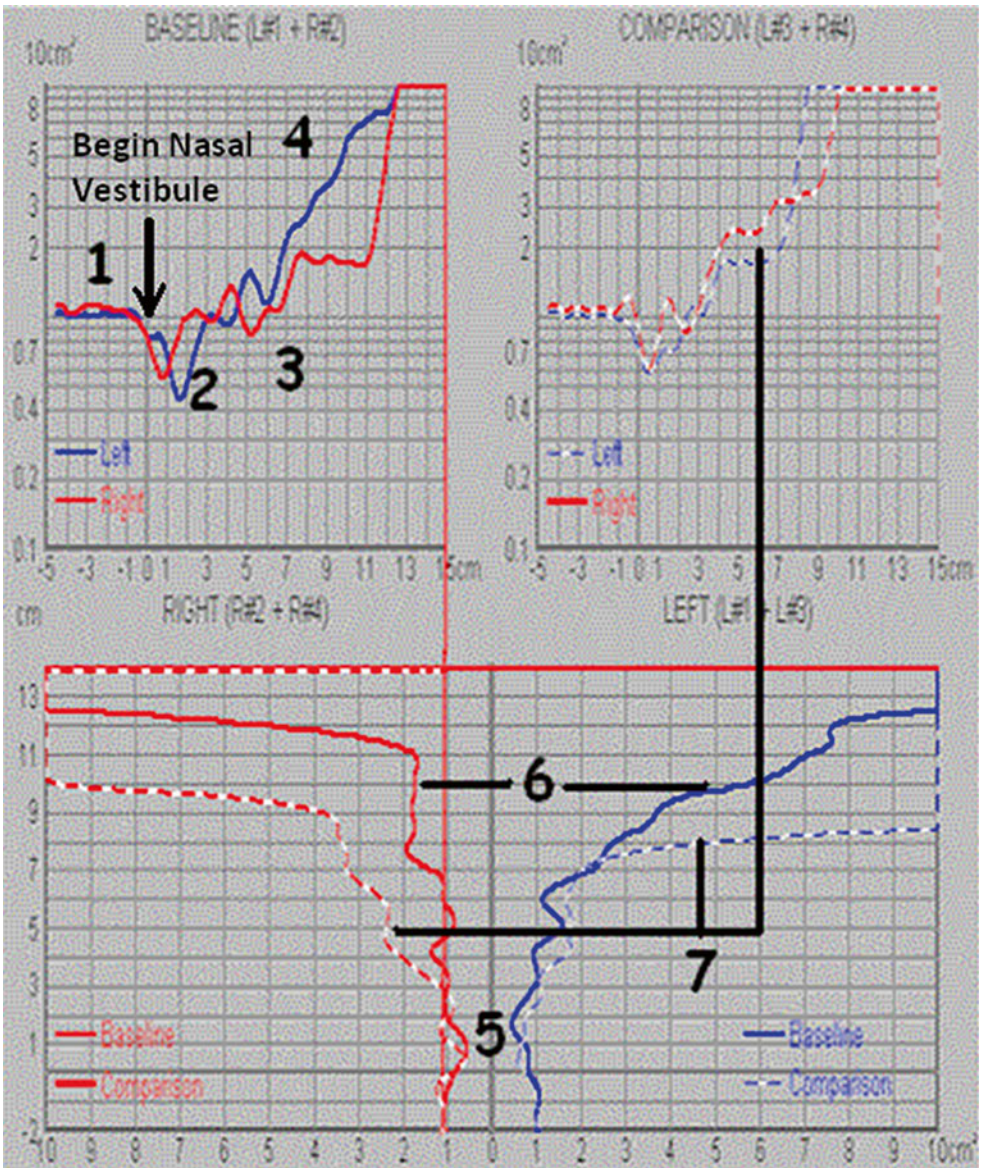


Fig. 18.37 Example of an acoustic rhinomanometry tracing

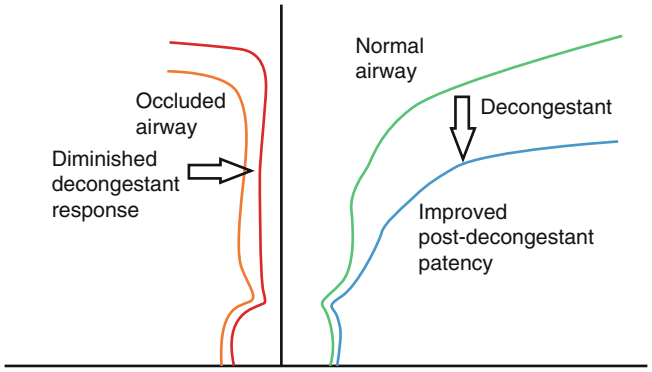


Fig. 18.38 Prototype for results seen with septal deviation

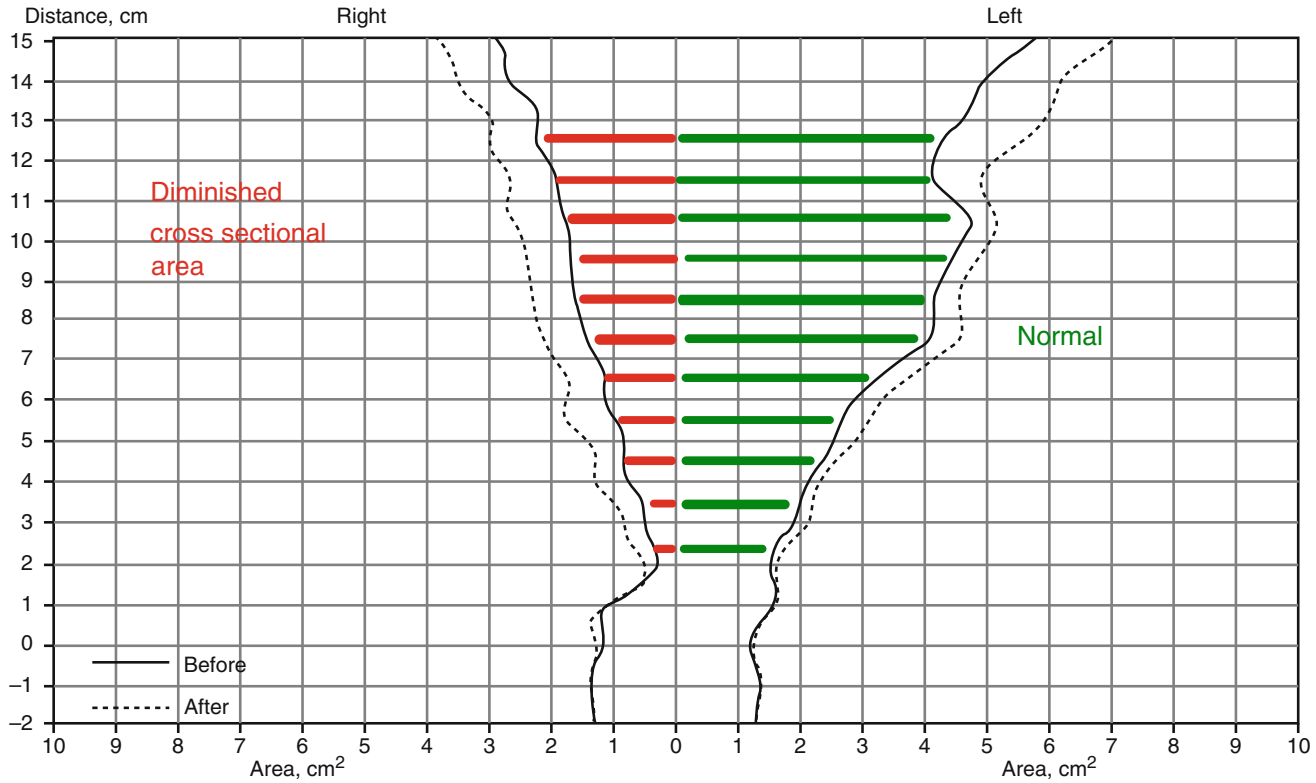


Fig. 18.39 Printout revealing diminished cross-sectional area of the right nasal airway and minimal change after topical decongestant suggesting a fixed airway obstruction

decongestion. However, further superior and posterior, we see a site of airway obstruction with no response to decongestant illustrative of an airway compromised by nasal polyps.

Rhinometry in Medical Decision Making

In patients where there is a question of etiology for nasal congestion, or when trying to delineate which patient may be a candidate for a surgical intervention, rhinometry can provide additional data that confirms the presence of a localized obstruction. The pre- and post-decongesting information can also assist in the determination of whether or not procedures such as in-office high-frequency ablation of the inferior turbinate would be of benefit. The data also helps determining whether a septal deviation seen on exam is a source of objectifiable airway obstruction.

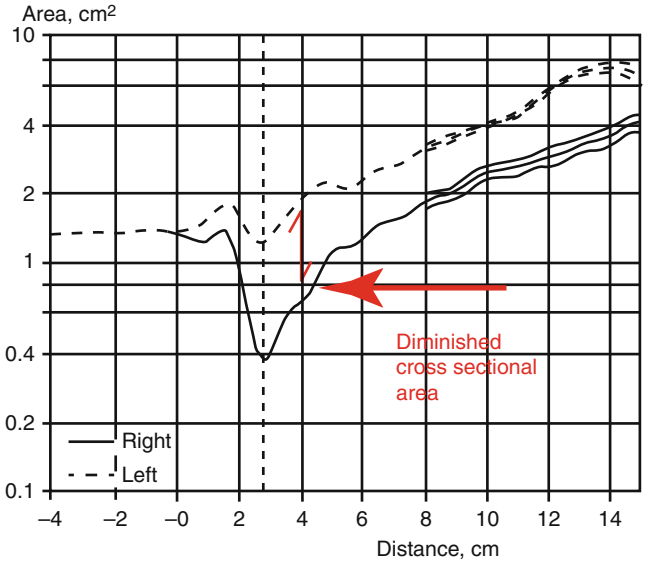


Fig. 18.40 Printout shows diminished cross-sectional area

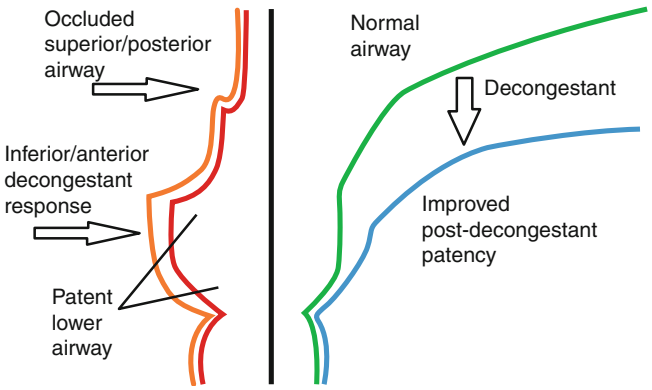


Fig. 18.41 Fixed nasal airway obstruction as seen with polyps

Summary

The nasal airway is the passageway of optimum respiration. Nasal airway obstruction is associated with multiple causes: mucosal edema, nasal polyps, and anatomic derangement of the inferior turbinate and nasal septum being the primary sources. In addition to patient discomfort, there are relatively far-reaching sequelae that can include alteration in anatomy during growth, sleep disruption, and detrimental dental changes that may accompany nasal obstruction. Rhinometry can assist in decision making regarding choosing medical vs. surgical management of the underlying problem and also provides longitudinal information regarding response to therapy and recrudescence of disease [37].

In-Office Assessment of Olfaction

Introduction

Don't it always seem to go that you don't know what you've got 'til it's gone…. Joni Mitchell lyric [38]

Derangement of sense of smell is associated with myriad nasal/sinus/and other pathologies, and its loss can greatly diminish patient quality of life. Often regarded as an "afterthought sense," olfaction plays a large part in a patient's interaction with his/her environment. It is an integral part of recollection of complex events and situations, and olfactory memory triggers are

associated with greater retention and recall of past events and their emotional context. Olfactory sense memory shows a high degree of persistence and resistance to interference, as well [39]. Decline in olfaction has even been described as a risk factor for general cognitive decline [40, 45–47].

Olfaction plays a role in food identification, assessing food quality, sexual behaviors, and is important in the home and work environment as an "early warning system" for changes in the environment (gas leaks, the earliest possible detection of smoke, airborne chemicals, etc.). The association between intact olfaction and sense of taste is well known [41], and patients typically report a decline in olfactory sensitivity within the context of perceived decline in both sense of taste and smell.

Simple, office-based assessment of olfactory acuity is available and can play a vital role in patient care and maintaining quality-of-life parameters. A complete examination of disorders that may affect olfaction and their corresponding pathologies is beyond the scope of this text. The following pages will focus on olfaction and office-based measurement modalities as they present in the context of nasal and sinus disease.

Overview of Olfactory Physiology

Odor molecules bind an "odor-presenting intermediary," and this complex activates olfactory neurons, with signal propagation to olfactory bulb, then on to the cerebrum, and ultimately the conscious "experience" of olfaction.

The olfactory chain of events is as follows: Olfactory sensory neurons have dendritic components interlaced within the olfactory epithelium in the mid-uppermost portion of the nasal vault. (Interestingly, each neuron is specific for only one type of odor molecule.) As odor molecules come into contact with the mucosa of this area, they interact with a variety of enzymes, mucopolysaccharides, ionic salts, or odorant-binding proteins; all of which "prepare" the odor molecule for recognition by the olfactory receptor neuron and then diffuse into the membrane in order to come into contact with the olfactory receptor. Upon activation, the receptor propagates signal along axonal projections through the cribriform plate to the olfactory bulb, and then onward to brainstem structures and cortical destinations [42].

Medications Associated with Decline in Olfaction

In addition to assessing for "endogenous" causes of loss of sense of smell, a survey of possible exogenous causes should be done. Drug-induced anosmia/hyposmia bears mentioning.

A screening list of the medications/substances that have been associated with a decline in olfaction is a useful starting point [43, 44]. There are many drugs that can exert a negative effect on a patient's olfaction. These effects may be generated via alteration in the olfactory mucosa, via changes in the cells lining the olfactory mucosa or changes in the character of the mucous overlying this epithelium. There may also be alteration of receptor expression or changes in circulation to the area or alteration of signal propagation which would interfere with olfaction sensitivity.

A list of drugs that have been associated with a reduction in olfaction is listed in Table 18.13. For example, cytotoxic drugs such as chemotherapeutic (cisplatin, vincristine, doxorubicin) or anti-inflammatory/antiproliferative drugs (methotrexate) and antirheumatologic drugs (such as allopurinol) may alter intracellular metabolism and signaling. Early generation antihistamines and antihypertensive drugs may alter the character of the mucous of the olfactory lining and inhibit transport of odorant molecules to their receptors via an alteration in the transition of odorant molecules from air phase to mucosal phase.

Antidepressant medications such as doxepin, imipramine, and amitriptyline act upon the olfactory mucosa in similar fashion to early generation antihistamines, and both classes of drug may also exhibit anticholinergic affects that may lead to derangement in olfaction, as well. Antiepileptic drugs and psychopharmacologic medications may alter nerve cell propagation. Antibiotics (most notably aminoglycosides) may exert neurotoxic effects that manifest if decreased olfaction. Interestingly, the ototoxic effect of aminoglycosides is frequently mentioned, but their potential negative effect on olfaction is overlooked. Topical zinc administration (earlier forms of Zicam (Rx) were notorious) can also be associated with neurotoxic (direct neuronal toxicity) effects.

Many drugs have idiopathic mechanisms of inducing anosmia/hyposmia. For example, some drugs alter perception of odor (opiates and anesthetics), but there is also a paradoxical residual hyposmic/anosmic effect that may occur that cannot be explained by the standard pharmacologic effects of these drugs.

Products change over time, so a history of both past and present medication and supplement use is imperative in any patient with demonstrable decline or loss of olfaction.

Table 18.13 Medications suspected of causing a decline in olfaction

Alcohol use in excess
Amebicides and anthelmintics: metronidazole; niridazole
Analgesic-antipyretic: D-penicillamine; phenylbutazone
Antibiotics: aminoglycosides, macrolides, fluoroquinolones, tetracyclines, and beta lactam drugs
Anticholesteremics: clofibrate
Anticoagulants: phenindione
Antidepressants (primarily tricyclics): doxepin, nortriptyline, amitriptyline, imipramine
Antiepileptic drugs: phenytoin; psilocybin; trifluoperazine
Antifungal agents: amphotericin B, griseofulvin
Antihistamine overuse-1st Generation: chlorpheniramine predominates
Antihypertensives: ACE inhibitors, HCTZ, beta-blockers, calcium channel blockers
Antirheumatic: allopurinol; colchicine; gold; levamisole
Antithyroid agents: carbimazole; methizole; methylthiouracil; propylthiouracil; thiouracil
Antitubercular medications: ethambutol hydrochloride
Decongestants
Dental hygiene: sodium lauryl sulfate (toothpaste)
Diuretics and ACE inhibitors (primarily captopril); diazoxide; ethacrynic acid
Hypoglycemic drugs glipizide; phenformin and derivatives
Immunosuppressants and cancer specific drugs: azathioprine, methotrexate, glucocorticoids, vincristine, anthracyclines, and cisplatin
Local anesthetics: e.g., benzocaine, cocaine hydrochloride; and tetracaine
Muscle relaxants: baclofen; chlormezanone
Nicotine and other smoked recreational substances
Opiates codeine; hydromorphone hydrochloride; morphine
Parkinson's disease medications: primarily levodopa combinations
Psychopharmacologic: carbamazepine; lithium carbonate
Sympathomimetic drugs: amphetamines
Misc: some insecticides germine monoacetate; idoxuridine; iron sorbitex; acetazolamide

Olfaction and Nasal/Sinus Pathology

Any process that interferes with the normal physiologic milieu of the nasal mucosa can be associated with inhibited olfaction. Table 18.14 outlines the basic types of nasal pathology that can interfere with olfaction.

The location of the olfactory cleft in the human body creates an environment where any variety of changes in a previously normal nasal environment can alter olfaction. Office testing for olfactory acuity has proven to be very useful. If asked, many patients will complain of a smell disorder that ultimately proves to be absent or slightly altered upon testing. When present, testing then establishes a baseline status and can be used in surveying a response to therapy and as part of clinical surveillance for recrudescence of a problem after medical or surgical intervention [57–60].

Methods of Assessing Olfaction

Assessing a patient's sense of smell requires some reliance on subjective data, in that we are required to use the patient's report in order to try to objectify our evaluation. Short of using evoked potentials and EEG or functional MRI, it remains quite appropriate to use the patient as the gauge upon which we rely for our information.

Olfaction is assessed by having patients "smell" (or not) various known quantities and then tracking their ability to identify the presence of odor in any amount or potentially tracking the threshold at which a patient begins to note a scent.

"Scratch and sniff" style screening tests are readily available and have been standardized for ethnicity [48], age [49, 55], and gender [50].

Tests can be performed quickly in the office and include easily understood "yes/no"-type testing in which the patient reports on whether or not a scent is noted/identified.

For screening purposes, assessing for the ability to detect odors is the first step in diagnosing hyposmia/anosmia or possible derangement in the sense of smell (as can be seen with chronic inflammatory conditions). The Pocket Smell Test is an excellent and easy to use screening method (Figs. 18.42 and 18.43). With this type of screen, a misidentified scent or failure

Table 18.14 Basic ways nasal pathology can affect olfaction

I. Alteration of the character of nasal secretions
   A. Changes in secretions/mucosa
      1. Increased viscosity inhibiting molecule diffusion
      2. Inflammatory disorders – accompanying sinusitis, sarcoidosis, Wegener's granulomatosis, Sjogren's syndrome, etc. [51, 52]
      3. Decreased viscosity inhibiting ability of molecule to remain on mucosa
      4. Amount of mucous produced
         (a) Excess mucous production inhibiting molecular response on mucosa
         (b) Decrease in mucous production causing change in hydration status of mucosa
      5. Alteration in the typical array of olfactory-facilitating molecules
      6. Other physiologic changes associated with atopy [54]
II. Alteration of nasal anatomy [55]
   A. Mucosal edema creating greater distance between the environment and the olfactory neurons [53]
   B. Other anatomic alterations that diminish air delivery to the mucosa [56]
      1. Nasal polyps inhibiting contact between odor molecules and receptors
      2. Nasal anatomy that does not allow proper airflow to olfactory mucosa
         (a) eptal deviation
         (b) Hypertrophy of turbinates
         (c) Mass lesions/neoplasm
         (d) Leptorrhine nasal anatomy
      3. Paradoxical: Prior surgery with residual hyper-patency of airway that diminishes airflow

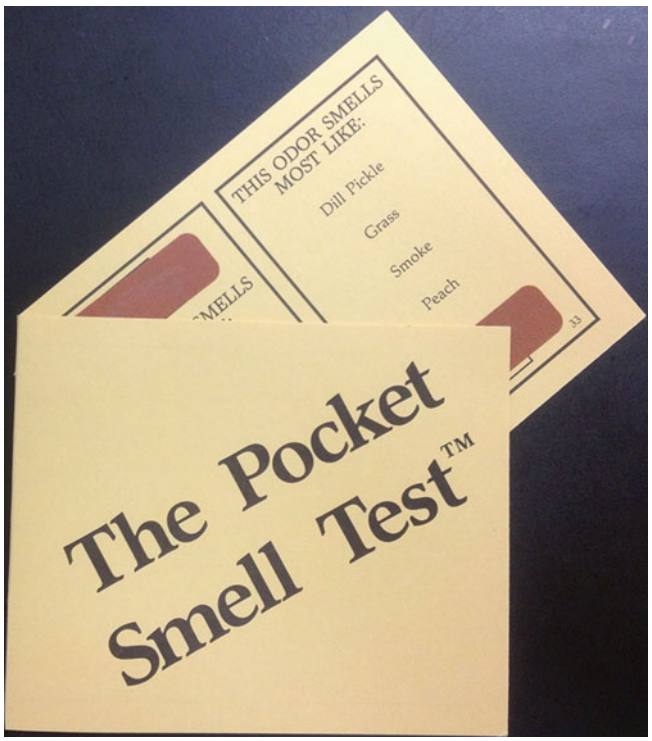


Fig. 18.42 The Pocket Smell Test. A scratch and sniff methodology for quick and easy office screening for smell disorders

to detect a scent can be used as a tool to decide whether or not to undertake further diagnostic testing. Similar testing designed for pediatric use has been made available (Fig. 18.44). It is designed to be engaging for younger patients and offers a game-like test procedure.

The University of Pennsylvania Smell Identification Test (UPSIT) (Fig. 18.45) offers more elaborate testing in the same format and can be used to screen for odor thresholds – results offer a broad range of scent challenges and can be compared over time to qualitatively track a patient's clinical status, response to therapy, and maintenance of response. This test requires approximately 15 min to complete. Patients can perform this test before an office visit and results can be discussed afterward. An abbreviated form of the UPSIT is available as the "Brief Smell Identification Test." This test features 12 odors that are

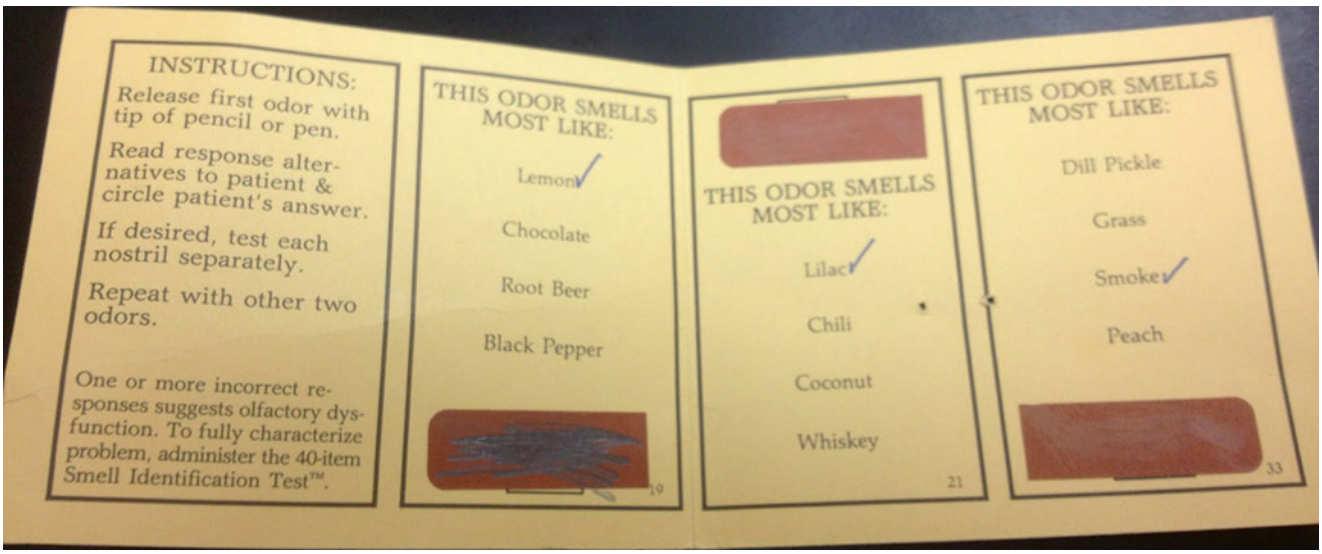


Fig. 18.43 The Pocket Smell Test expanded to show the three-item screening test for smell disorders

Fig. 18.44 Pediatric smell test: the Pediatric Smell Wheel is a game-like test for evaluating olfaction in young children. A rotating cardboard disk exposes 1 of 11 odors at a time for sampling. Multiple-choice alternatives use both words and pictures. When the disk is completely rotated, the child's answers appear as dark dots in a series of holes in the jacket. The number of marks signifies the test score

well known in most cultures: banana, chocolate, cinnamon, gasoline, lemon, onion, paint thinner, pineapple, rose, soap, smoke, and turpentine. Tests that include potential hazard-related odors are also available. With a larger palate of tests, cross-cultural differences/experiences are more readily accommodated.

A Note About "Derangement" of Sense of Smell

Sometimes, a smell screening test can produce an answer that is not "yes" or "no." The answer can be "wrong" but the patient, nevertheless, is still smelling something. In addition to a general decrease in olfaction, disorders such as chronic sinusitis or inflammatory rhinitis can present with "deranged" sense of smell – a metallic, putrid, or ineffably unpleasant smell may permeate the patient's olfactory experience when these disorders are present. This phenomenon can alter or cloud a patient's ability to properly experience other olfactory stimuli, and sensory testing may yield incorrect responses to smell testing, even though odors can be detected – the patient's smell sense is "corrupted" by accompanying pathology, in this case. Tracking

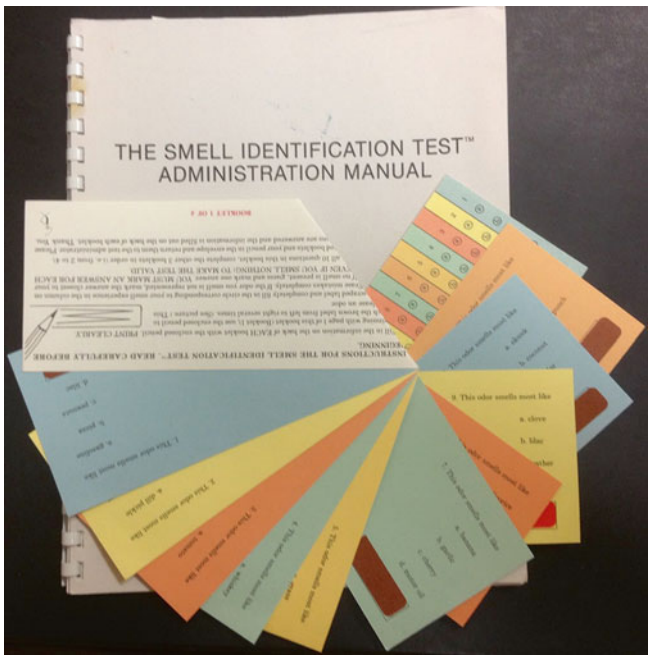


Fig. 18.45 The University of Pennsylvania Smell Identification Test: a comprehensive 40-item test for greater accuracy

with screening tests over time can also assist the patient and practitioner by identifying deviations from expected answers on smell testing and offers another avenue of clinical surveillance using olfaction as indicator or underlying disease.

Summary

Olfaction can be a clinically underappreciated member of the "sense family." Its loss can impact quality of life and have safety ramifications, potentially limiting a patient's ability to properly survey his/her environment. Derangement in sense of smell can be seen with a variety of upper airway pathologies, and olfactory status can be used as a gauge of potential underlying pathology and, after therapy, can be used to monitor response to therapy and monitor for return of disease.

There are easily utilized tests that are noninvasive and offer easy and efficient patient evaluation and outcome analysis.

References

1. Thornton DJ, Rousseau K, McGuckin MA. Structure and function of the polymeric mucins in airways mucus. Annu Rev Physiol. 2008;70:459–86.
2. Rose MC, Voynow JA. Respiratory tract mucin genes and mucin glycoproteins in health and disease. Physiol Rev. 2006;86:245–78.
3. Houtmeyers E, Gosselink R, Gayan RG, Decramer M. Regulation of mucociliary clearance in health and disease. Eur Respir J. 1999;13:1177–88.
4. Voynow JA, Rubin BK. Mucins, mucus, and sputum. Chest. 2009;135(2):505–12.
5. Wanner A, Salathe M, O'Riordan TG. Mucociliary clearance in the airways. Am J Respir Crit Care Med. 1996;154:1868–902.
6. Satir P, Sleigh MA. The physiology of cilia and mucociliary interactions. Annu Rev Physiol. 1990;52:137–55.
7. Cohen NA. Sinonasal mucociliary clearance in health and disease. Ann Otol Rhinol Laryngol Suppl. 2006;196:20–6.
8. Naiboglu B, Deveci I, Kalaycik C, Daylan A, Habesoglu TE, Toros SZ, Deveci SE, Egeli E. Effect of nasolacrimal duct obstruction on nasal mucociliary transport. J Laryngol Otol. 2010;124:166–70.
9. Clary-Meinesz CF, Cosson J, Huitorel P, Blaive B. Temperature effect on the ciliary beat frequency of human nasal and tracheal ciliated cells. Biol Cell. 1992;76:335–8.
10. Kirtsreesakul V, Somjareonwattana P, Ruttanaphol S. Impact of IgE-mediated hypersensitivity on nasal mucociliary clearance. Arch Otolaryngol Head Neck Surg. 2010;136:801–6.
11. Atsuta S, Majima Y. Nasal mucociliary clearance of chronic sinusitis in relation to rheological properties of nasal mucus. Ann Otol Rhinol Laryngol. 1998;107:47–51.

12. Passali D, Feri R, Becchini G, Passali GC, Bellussi L. Alterations of nasal mucociliary transport in patients with hypertrophy of the inferior turbinates, deviations of the nasal septum and chronic sinusitis. Eur Arch Otorhinolaryngol. 1999;256:335–7.
13. Majima Y, Sakakura Y, Matsabura T, Miyoshi Y. Possible mechanisms of reduction of nasal mucociliary clearance in chronic sinusitis. Clin Otolaryngol Allied Sci. 1986;11:55–60.
14. Antunes MB, Cohen NA. Mucociliary clearance–a critical upper airway host defense mechanism and methods of assessment. Curr Opin Allergy Clin Immunol. 2007;7(1):5–10.
15. Stillwell PC, Wartchow EP, Sagel SD. Primary ciliary dyskinesia in children: a review for pediatricians, allergists, and pediatric pulmonologists. Pediatr Allergy Immunol Pulmonol. 2011;24:192–6.
16. Kartagener M, Stucki P. Bronchiectasis with situs inversus. Arch Pediatr. 1962;79:193–207.
17. Marthin JK, Petersen N, Skovgaard LT, Nielsen KG. Lung function in patients with primary ciliary dyskinesia: a cross sectional and 3-decade longitudinal study. Am J Respir Crit Care Med. 2010;181:1262–8.
18. Asai K, Haruna S, Otori N, Yanagi K, Fukami M, Moriyama H. Saccharin test of maxillary sinus mucociliary function after endoscopic sinus surgery. Laryngoscope. 2000;110:117–22.
19. Brondeel L, Sonstabo R, Clement P, et al. Value of Tc-99m particle test and the saccharine test in mucociliary examinations. Rhinology. 1983;21:135.
20. Sun SS, Hsieh JF, Tsai SC, Ho YJ, Kao CH. The role of rhinoscintigraphy in the evaluation of nasal mucociliary clearance function in patients with sinusitis. Nucl Med Commun. 2000;21:1029–32.
21. De Boeck K, Proesmans M, Mortelmans L, et al. Mucociliary transport using 99mtc-albumin colloid: a reliable screening test for primary ciliary dyskinesia. Thorax. 2005;60:414–7.
22. Afzelius BA. Cilia-related diseases. J Pathol. 2004;204:470–7.
23. Schwabe GC, Hoffmann K, Loges NT, Birker D, Rossier C, de Santi MM, Olbrich H, Fliegauf M, Failly M, Liebers U, Collura M, Gaedicke G, Mundlos S, Wahn U, Blouin JL, Niggemann B, Omran H, Antonarakis SE, Bartoloni L. Primary ciliary dyskinesia associated with normal axoneme ultrastructure is caused by DNAH11 mutations. Hum Mutat. 2008;29:289–98.
24. Armengot M, Bonet M, Carda C, Gómez MJ, et al. Development and validation of a method of cilia motility analysis for the early diagnosis of primary ciliary dyskinesia. Acta Otorrinolaringol Esp. 2012;63:1–8.
25. Public domain, unattributable.
26. Lenders H, Schaefer J, Pirsig W. Turbinate hypertrophy in habitual snorers and patients with obstructive sleep apnea: findings of acoustic rhinometry. Laryngoscope. 1991;101(6 Pt 1):614–8.
27. Jefferson Y. Mouth breathing: adverse effects on facial growth, health, academics, and behavior. Gen Dent. 2010;58(1):18–25.
28. Laine MT, Warren DW. Perceptual and respiratory responses to added nasal airway resistance loads in older adults. Laryngoscope. 1995;105(4 Pt 1):425–8.
29. Kase Y, Itimura K, Iinuma T. An evaluation of nasal patency with acoustic rhinometry, preoperative and postoperative comparisons. Nipon Jibiinkoka Gakkai Kaiho. 1993;96(2):197–202.
30. Fouke J, Jackson A. Acoustic rhinometry: effects of decongestants and posture on nasal patency. J Lab Clin Med. 1992;119(4):371–6.
31. Hilberg O, Grymer LF, Pedersen OF, Elbrønd O. Turbinate hypertrophy. Evaluation of the nasal cavity by acoustic rhinometry. Arch Otolaryngol Head Neck Surg. 1990;116(3):283–9.
32. Elbrønd O, Hilberg O, Felding JU, Blegvad Andersen O. Acoustic rhinometry used as a method to demonstrate changes in the volume of the nasopharynx after adenoidectomy. Clin Otolaryngol. 1991;16(1):84–6.
33. Lildholdt T. Surgical versus medical treatment of nasal polyps. Rhinol Suppl. 1989;8:31–3.
34. Lenders H, Pirsig W. Diagnostic value of acoustic rhinometry: patients with allergic and vasomotor rhinitis compared with normal controls. Rhinology. 1990;28(1):5–16.
35. Lam DJ, James KT, Weaver EM. Comparison of anatomic, physiological, and subjective measures of the nasal airway. Am J Rhinol. 2006;20(5):463–70.
36. Numminen J, Ahtinen M, Huhtala H, Rautiainen M. Comparison of rhinometric methods to intranasal pathology. Rhinology. 2003;41(2):65–8.
37. Vogt K, Zhang L. Airway assessment by four-phase rhinomanometry in septal surgery. Curr Opin Otolaryngol Head Neck Surg. 2012;20:33–9.
38. Mitchell J. Big yellow taxi. Ladies of the canyon. Warner Brothers, July 1970.
39. McLaughlin N. Odor identification deficits in frontotemporal dementia: a preliminary study. Arch Clin Neuropsychol. 2008;23(1):119–23.
40. Alvin V, Silverstein R. Smell, the subtle sense. New York: William Morrow & Company; 1992.
41. Margot C. A noseful of objects. Nat Neurosci. 2009;12(7):813–4.
42. FDA advisory. Zicam cold remedy nasal products (Cold remedy nasal gel, cold remedy nasal swabs, and cold remedy swabs, kids size), June 2009.
43. Ackerman BH. Disturbances of taste and smell induced by drugs. Pharmacotherapy. 1997;17(3):482–96.
44. Tuccori M. Drug-induced taste and smell alterations: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. Drug Saf. 2011;34(10):849–59.
45. Westervelt HJ, Bruce JM, Coon WG, Tremont G. Odor identification in mild cognitive impairment subtypes. J Clin Exp Neuropsychol. 2008;30(2):151–6. (BSIT).
46. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. Ann Neurol. 2008;63(2):159–66.
47. Jones RE, Bown CC, Ship JA. Odor identification in young and elderly African-Americans and Caucasians. Spec Care Dentist. 1995;15(4):138–43.
48. Yousem DM, Maldjian JA, Hummel T, Alsop DC, Geckle RJ, Kraut MA, Doty RL. The effect of age on odor-stimulated functional MR imaging. AJNR Am J Neuroradiol. 1999;20(4):600–8.
49. Frye RE, Doty RL, Shaman P. Bilateral and unilateral olfactory sensitivity: relationship to handedness and gender. In: Doty RL, Müller-Schwartze D, editors. Chemical signals in vertebrates VI. New York: Plenum Press; 1992. p. 559–64.

50. Tomita H, Ikeda M. Clinical use of electrogustometry: strengths and limitations. Acta Otolaryngol Suppl. 2002;546:27–38.
51. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. Laryngoscope. 2000;110(7):1071–7.
52. Litvack JR, Mace JC, Smith TL. Olfactory function and disease severity in chronic rhinosinusitis. Am J Rhinol Allergy. 2009;23(2):139–44.
53. Guss J, Doghramji L, Reger C, Chiu AG. Olfactory dysfunction in allergic rhinitis. ORL J Otorhinolaryngol Relat Spec. 2009;71(5):268–72. Epub 2009 Sept 30.
54. Ghorbanian SN, Paradise JL, Doty RL. Odor perception in children in relation to nasal obstruction. Pediatrics. 1983;72(4):510–6.
55. Doty RL, Frye R. Influence of nasal obstruction on smell function. Otolaryngol Clin N Am. 1989;22(2):397–411.
56. Eichel BS. Improvement of olfaction following pansinus surgery. Ear Nose Throat Journal. 1994;73(4):248–50, 253.
57. Jiang RS, Lu FJ, Liang KL, Shiao JY, Su MC, Hsin CH, Chen WK. Olfactory function in patients with chronic rhinosinusitis before and after functional endoscopic sinus surgery. Am J Rhinol. 2008;22(4):445–8.
58. Soler ZM, Hwang PH, Mace J, Smith TL. Outcomes after middle turbinate resection: revisiting a controversial topic. Laryngoscope. 2010;120(4):832–7.
59. Sugiyama K, Matsuda T, Kondo H, Mitsuya S, Hashiba M, Murakami S, Baba S. Postoperative olfaction in chronic sinusitis: smokers versus nonsmokers. Ann Otol Rhinol Laryngol. 2002;111(11):1054–8.
60. Doty RL, Mishra A. Olfaction and its alteration by nasal obstruction, rhinitis, and rhinosinusitis. Laryngoscope. 2001;111(3):409–23.

Part V
Medical and Surgical Management

Chapter 19
Medical Management of Acute Rhinosinusitis in Children and Adults

Nathan Richards, Shannon Doyle Tiedeken, and Christopher C. Chang

Introduction

Rhinosinusitis is one of the most commonly seen health problems worldwide and is responsible for the use of vast healthcare resources. According to the US National Health Interview Survey, rhinosinusitis affects approximately 1 in 7 adults yearly [1]. In children, upper respiratory infections are contracted on an average of 6–8 per year with 0.5–5 % of these subsequently developing acute rhinosinusitis [2]. Twenty million doctor visits annually in the United States contribute to the high healthcare utilization of people with rhinosinusitis [3]. Nearly 3 billion dollars per year in the United States are used for the treatment of rhinosinusitis, with the costs derived from medications, testing, procedures, and outpatient and emergency room visits [4, 5].

Rhinosinusitis is the fifth most common diagnosis for which antibiotics are prescribed [4, 5]. Primary care physicians tend to make the diagnosis of acute bacterial rhinosinusitis clinically with little supportive objective criteria, and it is common to prescribe antibiotics as a first-line therapy in most cases. It has been estimated that antibiotics are initiated in up to 85–98 % of presumed rhinosinusitis cases [6, 7]. This contrasts with the fact that the majority of rhinosinusitis episodes are of viral origin and unrelated to a bacterial infection acutely. Nearly all cases of viral rhinosinusitis in an otherwise normal host will commonly resolve without antibiotic treatment provided the sinuses adequately drain once the virally induced inflammation resolves. If the disease has a nonbacterial inflammatory mechanism as the source of symptoms rather than a bacterial one, the addition of antibiotics will not be of benefit. In fact, the overuse of antibiotics will promote further bacterial resistance as well as increase the risk of the patient of the consequences of any adverse drug reaction. A major issue for healthcare providers in treating acute rhinosinusitis is when the initiation of antibiotic treatment will provide cost-effective clinical benefit.

Clinical Presentation

The clinical presentation of acute rhinosinusitis can differ between adults and children. In children, the ethmoid and the maxillary sinuses form in utero [8], and the sphenoid sinuses are generally pneumatized by 5 years of age [8]. On the other hand, the frontal sinuses frequently do not appear till about 7–8 years of age and typically do not completely develop until late adolescence [8] (see Chap. 2 for a more detailed discussion of the ontogeny of the sinuses). Pediatric guidelines describe acute bacterial rhinosinusitis as an infection of the paranasal sinuses lasting less than 30 days that presents with either persistent or severe symptoms of nasal or postnasal drainage, daytime cough, headache, facial pain, or some combination of

N. Richards, MD
Department of Allergy and Immunology, Thomas Jefferson University, 1600 Rockland Rd, Wilmington, DE 19803, USA
e-mail: nbrichards11@gmail.com

S.D. Tiedeken, MD
Department of Pediatrics, Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: shannon.tiedeken@gmail.com

C.C. Chang, MD, PhD, MBA, FAAAAI, FACAAI (✉)
Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: cchang@nemours.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_19, © Springer Science+Business Media New York 2014

Table 19.1 Comparison of diagnostic criteria for acute bacterial rhinosinusitis

Guideline	Persistent symptoms	Severe symptoms	Worsening symptoms	Max duration symptoms	Radiographic studies
IDSA [9]	Yes, >10 days	Yes	Yes	None	Not required
RI [10]	Yes, >10 days	Yes	Yes	<28 days	Not required
EPOS [11]	Yes, >10 days	No	Yes	<12 weeks	Not required
CPG:AS [4]	Yes, >10 days	No	Yes	<4 weeks	Not required
BSACI [12]	Yes	No	No	<12 weeks	Required
JTFPP [13]	Yes, >10–14 days	Yes	No	<12 weeks	No required
Pediatrics [8]	Yes, >10–14 days	Yes	No	<30 days	Not required

these [8]. Persistent symptoms are those lasting longer than 10–14 days but less than 30 days [8]. Severe symptoms include a temperature of at least 39 °C and purulent nasal discharge which present concurrently for at least 3–4 consecutive days in an ill-appearing child [8].

For adults, multiple treatment guidelines have been set up to aid in differentiating bacterial from viral acute rhinosinusitis. These have been developed and presented by:

1. Infectious Diseases Society of America (IDSA) [9]
2. Rhinosinusitis Initiative (RI) [10]
3. Europeans Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EP^{3}OS) [11]
4. Clinical Practice Guideline: Adult Sinusitis (CPG:AS) [4]
5. British Society for Allergy and Clinical Immunology (BASCI) [12]
6. Joint Task Force on Practice Parameters (JTFPP) [13]

Table 19.1 provides a comparison of the guidelines, with regard to severity and duration of symptoms, as well as radiographic findings. A more detailed description of each individual guideline is outlined below.

Definitions of Acute Rhinosinusitis

In the IDSA guideline, three clinical presentations are identified for which antimicrobial therapy should be initiated. The first clinical presentation is persistent symptoms or signs compatible with acute rhinosinusitis, lasting greater than or equal to 10 days without evidence of clinical improvement [9]. The second presentation is severe symptoms or signs of high fever (>39 °C) and purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the beginning of illness [9]. The final presentation is worsening symptoms or signs characterized by the onset of fever, headache, or an increase in nasal discharge following a typical viral upper respiratory infection that lasted 5–6 days which was initially improving [9]. These guidelines advise that anyone with one of these presentations should be started on empiric antimicrobial therapy [9].

The RI guidelines use a similar pattern of presentation of persistent, severe, or worsening symptoms. The criteria for diagnosis include pattern of symptoms, duration of symptoms with a minimum of 10 days and maximum of 28 days, presence of purulent nasal discharge for 3–4 days accompanied with fever or worsening disease, and symptoms that initially regress but proceed to worsen within 10 days of onset [10]. The criteria also include the following symptoms mandatory for diagnosis: anterior and/or posterior mucopurulent drainage in addition to nasal obstruction, facial pain, pressure, or fullness [10]. Finally, objective documentation of nasal airway examination for mucopurulent drainage beyond the vestibule by either anterior rhinoscopy or endoscopy for posterior pharyngeal drainage or radiographic evidence of acute rhinosinusitis is required [10].

The EPOS defines rhinosinusitis as inflammation of the nose and the paranasal sinuses characterized by 2 or more symptoms, including either nasal blockage, obstruction or congestion, or nasal discharge (anterior or posterior nasal drip) [11]. Facial pain or pressure and reduction of smell are also included as symptoms in rhinosinusitis [11]. Presumed bacterial rhinosinusitis is defined by an increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration [11].

The CPG:AS criteria state that acute rhinosinusitis is diagnosed by up to 4 weeks of cardinal rhinosinusitis symptoms [4]. The cardinal symptoms include purulent nasal drainage accompanied by nasal obstruction, facial pain, pressure, or fullness [4]. The guidelines differentiate bacterial versus viral infection based upon duration and presentation of symptoms. Bacterial rhinosinusitis is presumed when symptoms or signs of acute rhinosinusitis are present 10 or more days beyond the onset of upper respiratory symptoms or symptoms worsen within 10 days after initial improvement [4].

BSACI guidelines define acute rhinosinusitis as symptoms lasting less than 12 weeks in duration [12]. The patient must have one of the following major symptoms: nasal congestion, nasal obstruction, posterior or anterior nasal discharge with or without facial pain, pressure, or olfactory disturbance [12]. The patient must also have either endoscopic signs of polyps, mucopurulent discharge from the middle meatus, edema or obstruction at the middle meatus, or CT signs of sinus disease [12]. The authors of the BSACI guidelines do not provide criteria for starting antimicrobial therapy.

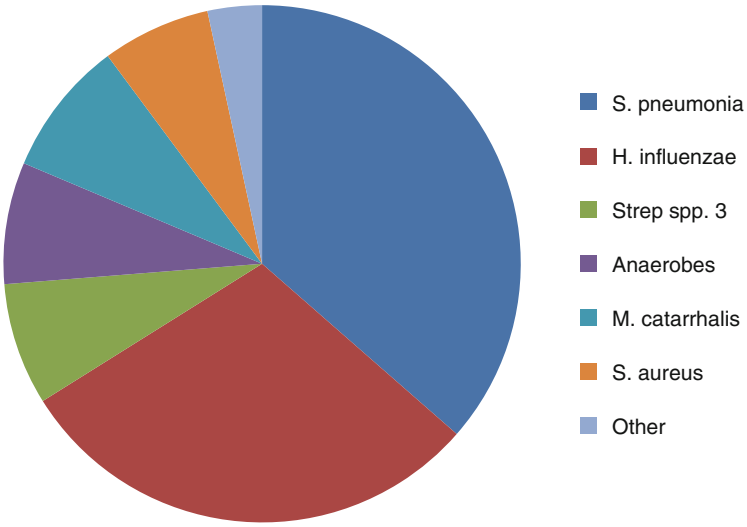


Fig. 19.1 Bacterial pathogens in adult acute rhinosinusitis (Adapted from Sinus and Allergy Health Partnership [14]. With permission from Sage Publications)

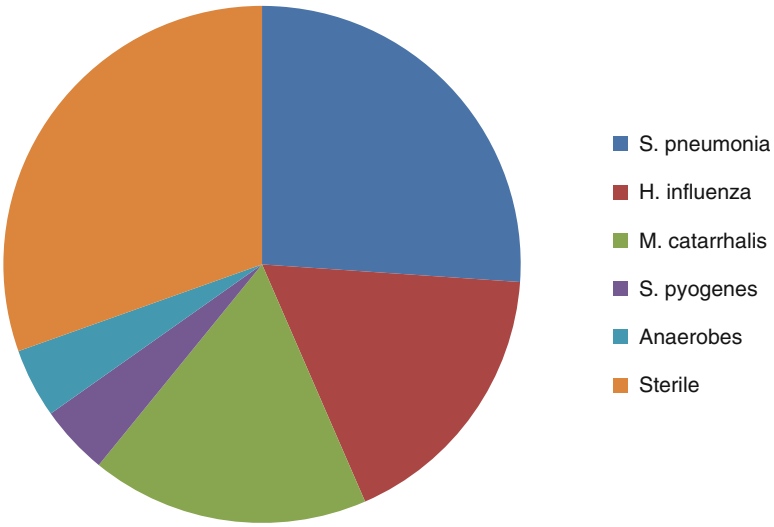


Fig. 19.2 Bacterial pathogens in childhood acute rhinosinusitis (Adapted from Sinus and Allergy Health Partnership [14]. With permission from Sage Publications)

The JTFPP state that the signs and symptoms of rhinosinusitis are nasal congestion, purulent rhinorrhea, facial or dental pain, postnasal drainage, headache, cough, sinus tenderness to palpation, and dark circles under the eyes [13]. The guidelines state that if symptoms last >10–14 days and are unusually severe or if there is a history of fever with purulent nasal discharge, facial pain or tenderness, or periorbital swelling, it should be considered a bacterial etiology [13].

Pathogens

Although there is some disagreement regarding what exactly constitutes bacterial rhinosinusitis, overall, the guidelines are fairly consistent among the recommended criteria from different agencies. In truth, only culture of the sinuses can ever definitively diagnose a role of a bacterial pathogen in a case of rhinosinusitis. This is a difficult hurdle in that nasal swabs do not commonly represent the predominant bacteria within an infected sinus. Moreover, inflammation is often confused with infection. Nevertheless, from the perspective of a practicing physician, any of these diagnostic guidelines can be used to establish the probable diagnosis of acute bacterial rhinosinusitis. Once the diagnosis is made, the appropriate antibiotic can be prescribed.

In order to initiate empiric therapy, it is important to know the typical bacterial causes of rhinosinusitis. Between adults and children, the pathogenic bacteria in acute rhinosinusitis are similar but not identical. The main difference is a higher prevalence of *Moraxella catarrhalis* infections in children than in adults. Figures 19.1 and 19.2 depict pie charts representing a breakdown of the typical bacterial pathogens in acute rhinosinusitis infections [14]. In children and adults, *Streptococcus*

pneumoniae is the main bacteria causing up to 1/3 of the cases of acute bacterial rhinosinusitis followed closely by *Haemophilus influenzae* and *Moraxella catarrhalis*. In children, one third of the cases of presumed bacterial rhinosinusitis have no causal agent with bacterial cultures being sterile.

Most cases of acute rhinosinusitis are caused by viral infections associated with the common cold [15]. The most commonly implicated virus is rhinovirus (30–80 %) [16]. Other viral entities implicated in causing acute rhinosinusitis are coronavirus (10–15 %), influenza virus (5–15 %), human parainfluenza virus, human respiratory syncytial virus (RSV), adenoviruses, enteroviruses, and metapneumovirus [16–18]. Frequently, more than one virus is present [19]. In total, over 200 different viral species are associated with colds [18].

Fungi are rarely implicated in acute rhinosinusitis and only seen in a secondary immune-compromised host. In contrast, fungi, when involved, can induce three variations of allergic inflammation: eosinophilic fungal rhinosinusitis, eosinophilic mucin rhinosinusitis, and allergic fungal rhinosinusitis. None of these represent acute infections. All refer to a rhinosinusitis state that is chronic (>12 weeks' duration) and accompanied by sinus opacification with allergic mucin [20] (see Chap. 8 for a detailed discussion of fungal rhinosinusitis). Allergic rhinitis flares can be complicated by a superimposed acute fungal rhinosinusitis. However, none of these involve fungal invasion below the mucosal surface. Rather, they are symptomatic rhinosinusitis events that result from various atopic sensitizations. Despite more than 100,000 molds recognized in the environment, few genera are associated with allergic disease [20]. *Aspergillus* species and the dematiaceous molds that include *Alternaria* and *Cladosporium* species are those most frequently implicated, although *Bipolaris* and *Curvularia* species have also been reported [20].

Defining the bacterial pathogens, if any, in cases of chronic rhinosinusitis is difficult and discussed in more detail in Chaps. 5 and 6. It should be remembered that chronic rhinosinusitis (CRS) is a group of inflammatory diseases of the nasal cavities that may or may not include polyp formation with no unifying theory based on scientific evidence that will explain the pathophysiology of chronic airway disease in all cases. In contrast, the etiology appears to be multifactorial. Research has focused on alterations involving inflammatory cell and T-cell stimulation, the role of TGF-β on remodeling, generation of inflammatory mediators such as leukotrienes and prostaglandins, the role of IgE and microorganisms, and also the role of the epithelium as an immunologic barrier to infection or insult. While much of the more recent literature appears to focus primarily on CRS as an inflammatory disease, that is not to say that bacteria and microorganisms are not involved in some cases and that antibiotics will not be helpful in alleviating some symptoms [21]. Bacteria have been shown to play a role in some patients with CRS either directly by infection or by stimulation of infection [22]. The main bacteria implicated in causing infection or triggering inflammation in patients with CRS, especially those with nasal polyps and asthma, is *Staphylococcus aureus* (*S. aureus*) [22]. In a recent study, swabs from the middle meatus of controls and patients with CRS were taken during endoscopic surgery and analyzed by quantitative polymerase chain reaction (PCR). There was no statistically significant difference in the total bacteria seen between CRS patients and the controls, but the abundance of *S. aureus* was increased in CRS patients with allergic rhinitis, nasal polyps, and asthma [22]. Nevertheless, the antibiotic approach to a CRS patient experiencing an acute flare of rhinosinusitis should include a drug choice directed against the same organisms defined above. Although there is no consensus on when or how long to treat flares of acute disease in CRS patients, the majority of medical providers would tend to use antibiotics earlier and sometimes longer than traditional guidelines suggest.

Medical Management

Antibiotics

The role of antibiotics in acute rhinosinusitis is controversial. As stated earlier, in a majority of cases, sinusitis is triggered by a viral upper respiratory infection and not responsive to antibiotic therapy. In general, only 1–2 of every 100 otherwise healthy patients with sinus symptoms have a concomitant bacterial infection [23]. It is often difficult to distinguish between those who will recover spontaneously and those who will require antibiotic therapy. In many cases, there is no evidence of any infectious etiology (viral, bacterial, or fungal), and indeed the disease may be a manifestation of an inflammatory process rather than infection. Antibiotics would only have minimal to no benefit to these patients. It is therefore imperative to at least attempt to determine which patients will benefit from antibiotic therapy, so as to avoid unnecessary antibiotic use and potentiating the development of bacterial resistance.

With growing concerns about antibiotic resistance among community-acquired pathogens, choosing the appropriate empiric antibiotic can be challenging. In adults, the empiric therapy should cover *Streptococcus pneumoniae* and *Haemophilus influenzae*. In children, the antibiotic of choice should also cover *Moraxella catarrhalis*. In the latest Cochrane Review, the studies that compared different classes of antibiotics demonstrated a similar efficacy among them [23]. However, the risk of clinical failure on amoxicillin-clavulanate compared to that for cephalosporins at 7–15 days was statistically significant, but the risk of failure disappeared at longer follow-up [23]. Based on their review, it was concluded that none of the antibiotic preparations in this study were significantly inferior in terms of efficacy [23].

Another randomized, open-labeled, double-blind study of acute rhinosinusitis patients was performed comparing the efficacy and safety of amoxicillin-clavulanate and a third-generation cephalosporin. A group of 50 patients received 2 weeks of treatment with either amoxicillin-clavulanate or a third-generation cephalosporin and afterward received paranasal sinus X-rays and nasal endoscopies to evaluate their progress and symptom relief. After 2 weeks, the improvement rate was 95–96 % for both groups. The only noted benefit of the third-generation cephalosporin over amoxicillin-clavulanate was that there were fewer adverse effects, primarily less gastrointestinal complications [24].

While beta-lactamase-resistant antibiotics are the current first-line recommendation for treatment of acute bacterial rhinosinusitis, cefdinir, a third-generation cephalosporin, also offers a convenient treatment option in patients with mild disease and no other recent antibiotic use. Cefdinir is an oral third-generation cephalosporin which has rapid oral absorption and efficient respiratory tissue penetration. It can be prescribed daily and has bactericidal activity against the most common bacterial pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Cefdinir is well tolerated and does not significantly suppress the normal gut flora causing less gastrointestinal adverse effects. Children have also been seen to favor cefdinir due to its taste and smell [25].

A recent study evaluated the treatment of acute rhinosinusitis with amoxicillin. The study included 166 adults with RI diagnostic criteria for acute bacterial rhinosinusitis. It was found that after 3 days of treatment with amoxicillin versus placebo, there was no difference in symptoms between the two groups [26]. While amoxicillin is a typical starting point for the treatment of acute rhinosinusitis, this study demonstrated the ineffectiveness of amoxicillin on either antibiotic-resistant pathogens or nonbacterial causes of acute rhinosinusitis.

Most traditional courses of antibiotic treatment for acute bacterial rhinosinusitis are 10 days in duration. Newer studies have looked at an abbreviated course of treatment with azithromycin [27]. A 3–5-day course of treatment with azithromycin has proven equally effective, and the shorter course increases the likelihood of patient compliance. Other advantages include lower rates of bacterial resistance and fewer adverse effects to the medication [27]. The efficacy of azithromycin was evaluated for its clinical efficacy and tolerability in treating children with acute respiratory infections. A study of 135 children treated with a single 10 mg/kg dose of azithromycin for 3 consecutive days showed 100 % resolution of symptoms in those with acute rhinosinusitis after 10 days and no recurrences were observed. Benefits of treating with the shorter course again included increased tolerance and improved compliance to the medication [28].

Due to the increasing resistance of causal bacteria to beta lactams and macrolides, new treatment guidelines have been instituted to aide physicians in choosing an appropriate antibiotic. Fluoroquinolones including moxifloxacin, gatifloxacin, and levofloxacin are often recommended as second-line therapy, or even first line for patients who have recently received other antibiotic therapy [29]. The Respiratory Surveillance Program (RESP) sampled 16,213 nasal swabs taken by primary care physicians in an outpatient setting on patients believed to have bacterial rhinosinusitis over a 10-month period. Pathogens were isolated from 34 % of samples with four accountable for most cases: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. High rates of resistance were seen against penicillins and macrolides. The four major causal bacteria had a 95–100 % susceptibility rate to fluoroquinolones. This study provided physicians with information about susceptibilities of pathogens within different communities and aided them in choosing appropriate antibiotic therapy. It also supported the use of fluoroquinolones in treating patients with previous antibiotic exposure [30].

One of the main adverse effects of fluoroquinolones in children is arthropathy. A systemic literature search was done to investigate the safety of using ciprofloxacin in pediatric populations. The search identified 105 articles that met inclusion criteria. Of the 16,184 pediatric patients included across all studies, 1,065 reported adverse reactions with the most common being musculoskeletal. Of all the musculoskeletal adverse effects, arthralgia accounted for 50 %. The age of occurrence ranged from 7 months to 17 years with the mean age of 10 years old. However, all cases of arthropathy resolved with appropriate management. From this study, it was estimated that the risk of a pediatric patient developing arthropathy from a fluoroquinolone is 1.57 %. Arthropathy is an adverse effect but can be reversed with appropriate treatment. At the present time, fluoroquinolones will require further controlled studies before they can be routinely recommended for treatment in children [31].

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated in some cases of acute and chronic rhinosinusitis. A literature search was performed to study cases of acute or chronic rhinosinusitis that were culture positive for MRSA and treated for MRSA. Twelve different studies discussed patients with acute and chronic rhinosinusitis with positive cultures for MRSA. Subjects received different treatment regimens. It was found that no one therapy was superior to the others [32]. *Staphylococcus aureus* can also cause sinusitis in children. In a recent study by Texas Children's Hospital, 56 patients were identified to have *S. aureus* sinus infections based on positive cultures from sinus surgery. Twelve of the 56 patients had MRSA. None of the MRSA cases were susceptible to macrolides and co-pathogens. The most commonly seen co-pathogen was *Haemophilus influenzae*, which was isolated in 77 % of the cases. Children with MRSA had higher recurrence of disease but were not found to be at greater risk than children with MSSA sinusitis to develop complications including cellulitis, abscess, meningitis, subdural empyema, or orbital cellulitis [33].

Table 19.2 Oral antibiotics used in the treatment of acute bacterial rhinosinusitis

Antibiotic	Dosage/frequency	Calculated clinical efficacy (%)	Cost (in 2004)
Amoxicillin-clavulanate Potassium salt (Augmentin)	500 mg q8 h; 875 mg q12 h	91	$83.96–112.08
High-dose Augmentin XR	2 g q12 h	–	$112.08
Amoxicillin (Amoxil)	500 mg q8 h; 875 mg q12 h	88	$7.35–8.77
High-dose amoxicillin	1 g q8 h	–	$14.70–17.54
Cefpodoxime (Vantin)	200 mg q12 h	87	$118.48
Cefuroxime (Ceftin)	250 mg or 500 mg q12 h	85	$108.53–197.75
Cefdinir (Omnicef)	300 mg q24 h	83	$44.66
Ceftriaxone (Rocephin)	1 g IM q24 h	91	$255.80
TMP-SMX DS (Bactrim DS)	160–800 mg q12 h	83	$6.64–27.76
Doxycycline (Vibramycin)	100 mg q12 h	81	$5.00–27.36
Azithromycin (Zithromax)	500 mg day 1 and 250 mg day 2–5	77	$47.44
Clarithromycin (Biaxin)	250 mg or 500 mg q12 h	77	$90.22
Gatifloxacin (Tequin)	400 mg q24 h	92	$95.68
Levofloxacin (Levaquin)	500 mg q24 h	92	$101.47
Moxifloxacin (Avelox)	400 mg q24 h	92	$101.92

Based on data from Ref. [34]

Table 19.3 Susceptibilities of most common isolates to antibiotics commonly prescribed for sinusitis

	S. pneumoniae % S/I/R (*N*=618)	*H. influenzae* % S/I/R (*N*=1,189)	*M. catarrhalis* % S/I/R (*N*=1,588)	*S. aureus* % S/I/R (*N*=983)
Penicillin	64/20/16 (2)	Not done	8.5/0/91.5 (1)	10.8/0/89.2 (6)
Gatifloxacin	99.8/0.2/0 (2)	100/0/0 (3)	100/0/0 (7)	97/1.1/2.0 (6)
Erythromycin	68/0.3/32 (2)	Not done	85/13/2 (7)	39/32/29 (7)
Azithromycin	64.7/0.6/34.7 (264)	99.4/0/0.6 (3)	100/0/0 (324)	31.2/18.7/50.1 (448)
Clarithromycin	65/0/35 (264)	64/31/5 (3)	100/0/0 (324)	68.8/2.1/29.2 (448)
Levofloxacin	99.8/0/0.2 (2)	100/0/0 (3)	100/0/0 (7)	95.1/1.6/3.3 (6)

Reprinted from Poole and Portugal [35]. With permission Elsevier
Values in parentheses indicate number not tested
S susceptible, *I* intermediate, *R* resistant

When choosing which antibiotic should be the drug of choice used to treat a patient with either acute rhinosinusitis or an acute flare of chronic rhinosinusitis, each individual case should be evaluated on its own merit. Many antibiotics have similar efficacy, so the primary factors to take into consideration include the differences in the adverse effects, costs of medication, history of drug sensitivity, and risk of promoting bacterial resistance [23]. Table 19.2 reviews antibiotics dosage, calculated clinical efficacy, and cost [34]. In general, the most effective antibiotic choice will be one that is beta lactamase resistant. Table 19.3 reviews susceptibilities of common community-acquired pathogens to frequently prescribed antibiotics [35]. In more severe and complicated cases, intravenous antibiotics may be warranted but that discussion is beyond the scope of this chapter [36].

Adjunctive Therapies

Mild symptoms, including minimal pain, low-grade temperature elevation, and non-purulent rhinorrhea, lasting less than 10 days may be managed by supportive care only [4]. Supportive therapies that have been investigated for treatment of acute rhinosinusitis include antihistamines, intranasal corticosteroids, oral corticosteroids, analgesics, decongestants, mucolytics, antileukotrienes, saline nasal irrigation, and herbal preparations. Table 19.4 lists all adjunctive therapies for treatment of acute rhinosinusitis.

Table 19.4 Adjunctive therapies for treatment of acute rhinosinusitis

Analgesics
Antihistamines
Antileukotrienes
Decongestants
Herbal preparations
Mucolytics
Nasal corticosteroids
Nasal irrigation
Oral corticosteroids

Antihistamines

The association of acute rhinosinusitis and allergy and atopy has not been clearly defined [37]. (See Chap. 11 for more details on this subject.) However, first-generation antihistamines have been used in acute rhinosinusitis to combat nasal drainage. This is primarily due to the anticholinergic effect of these drugs, an activity that is mostly absent in second-generation drugs (loratadine, fexofenadine, cetirizine) that are also now available over the counter. First-generation antihistamines may cause overdrying of the nasal mucosa and thus lead to further discomfort limiting their usefulness [15]. On the other hand, antihistamines can be effective in atopic patients due to their antihistamine activity. Antihistamines block the H1 histamine receptor and have been demonstrated to be effective in patients with documented aeroallergen allergies. Basophils and mast cells are stimulated to release histamine by the binding of cell-bound IgE antibodies to the offending aeroallergen protein. Therefore, antihistamines only help the acute sinusitis patient when rhinorrhea, sneezing, nasal congestion, and nasal pruritus are associated with basophil and mast cell release of histamine. A recent Cochrane Review noted that there is no evidence supporting the routine use of antihistamines in the treatment of acute rhinosinusitis in children. For most patients, antihistamines will not significantly alleviate nasal congestion, rhinorrhea, or sneezing in patients with an upper respiratory infection [38]. Therefore, antihistamines should not be used in acute rhinosinusitis unless the patient has documented allergies to aeroallergens that are present during the time of the infection. Further research needs to be conducted [39].

Though commonly utilized, the evidence above suggests that antihistamines should not be used as first-line treatment of acute rhinosinusitis. Not only has no study showed efficacy, but there are also potential side effects. First-generation H1 antihistamines cross the blood-brain barrier and are known to cause sedation. Other side effects of antihistamines include dizziness, dry mouth, a feeling of nervousness, excitability, irritability, blurry vision, and decreased appetite. Table 19.5 provides information on the different generations of antihistamines and some of their common adverse effects. Antihistamines, in general, are not an effective adjunctive therapy for acute rhinosinusitis unless the patient is experiencing concomitant allergy disease. In this circumstance, second-generation (e.g., loratadine, fexofenadine, cetirizine, levocetirizine) or topical antihistamines (e.g., azelastine, olopatadine) should be first considered.

Intranasal Corticosteroids

Intranasal corticosteroids are anti-inflammatory agents that reduce inflammation and edema. They have been shown to reduce inflammation of the nasal mucosa, nasal turbinates, and sinus ostia. Intranasal corticosteroids generally do not affect symptoms until after 2–4 days of usage. A recent study demonstrated the effectiveness of mometasone furoate nasal spray in the treatment of acute rhinosinusitis [40]. In this study, the authors evaluated minimal symptom days (defined by less than 4 days with symptom including rhinorrhea, postnasal drip, congestion, and sinus tenderness) while taking mometasone furoate nasal spray 200 μg once daily, versus twice daily, versus treatment with amoxicillin 500 mg three times a day, versus placebo [40]. The study concluded that mometasone furoate nasal spray twice daily significantly decreased symptom days as compared to amoxicillin or placebo in patients with acute rhinosinusitis and can improve outcomes with decreased unnecessary antibiotic use [40]. A previous study found that antibiotics and intranasal corticosteroids, either alone or in combination, were ineffective [41]. However, other studies have suggested that intranasal corticosteroids provide additional benefit in symptoms when used with antibiotics [42–48].

Table 19.5 Antihistamines by generation

Generic name	Trade name	Half-life (±5 h)	Skin test suppression mean (max) days	Adverse effects
First generation (H1)				*Cross the blood-brain barrier*
Brompheniramine	Dimetapp	24.9	>2 (4)	*More common:* sedation, dizziness, tinnitus, blurred vision, euphoria, uncoordination, anxiety, increased appetite leading to weight gain, insomnia, tremor, nausea and vomiting, constipation, diarrhea, dry mouth, and dry cough *Infrequent:* urinary retention, palpitations, hypotension, headache, hallucination, and psychosis
Chlorpheniramine	Chlor-Trimeton	27.9	3 (6)	
Clemastine	Tavist	21.3	5 (10)	
Cyproheptadine	Periactin	16	9 (11)	
Diphenhydramine	Benadryl	9.2	2 (5)	
Hydroxyzine	Atarax	20	5 (8)	
Promethazine	Phenergan	9–16	3 (5)	
Triprolidine	Actifed	3.2	3 (7)	
Second/third generation				*More selective for peripheral histamine receptors*
Acrivastine	Semprex-D	1.4	3	*Most common:* drowsiness, fatigue, headache, nausea, and dry mouth
Azelastine HCl	Astelin Nasal	22	2	
Cetirizine	Zyrtec	7	3	
Desloratadine	Clarinex	7.8	7	
Fexofenadine	Allegra	14.4	2	
Levocetirizine	Xyzal	7	Unknown	
Loratadine	Claritin	7.8	7	
Olopatadine HCl	Patanase Nasal	12	Unknown	

Table 19.6 Intranasal corticosteroids

Generic name	Trade name	Effects	Mechanism of action	Dose	Common adverse effects
Beclomethasone	Beconase AQ	First-line therapy to treat symptoms including nasal congestion	Decreases inflammation associated with allergies	1–2 sprays per nostril 1–2 times per day depending on agent use	Epistaxis
Budesonide	Rhinocort				Altered taste
Ciclesonide	Omnaris				Altered smell
Flunisolide	Nasarel, Nasalide				Nasal burning/stinging
Fluticasone	Flonase				Headache
Mometasone	Nasonex				Nasal septum perforation
Triamcinolone	Nasacort AQ				

A Cochrane Review published in 2009 evaluated four randomized controlled trials that included 1,943 patients in total [44–46, 48]. The review concluded that although the current evidence is limited, it does support the use of intranasal corticosteroids as monotherapy or as adjunctive therapy to antibiotics in acute rhinosinusitis [49]. Although the data for the use of intranasal corticosteroids is somewhat controversial, guidelines still recommended this class of drug as an option in treating acute rhinosinusitis [4, 8, 9, 11, 13]. Intranasal corticosteroids are effective for controlling symptoms including nasal congestion, nasal discharge, pruritus, sneezing, and postnasal drip. There are several intranasal corticosteroids that are available by prescription only (Table 19.6). In comparing oral antihistamines and nasal corticosteroids, the intranasal corticosteroids have shown to provide better overall relief [50].

Adverse effects associated with intranasal corticosteroids include nasal burning, epistaxis, nasal pruritus, headache, and pharyngitis. Rare and questionable systemic adverse effects include insomnia, nervousness, increased appetite, indigestion, headache, hyperglycemia, and diaphoresis. Systemic adverse effects are only seen if the nasal steroids are used off label in high doses for prolonged periods of time [51]. Another adverse effect of intranasal corticosteroids is nasal septum perforation. Patients should be advised to point away from the septum and laterally toward the inner canthus of the eye when administering intranasal steroids. Intranasal corticosteroids are a relatively safe medication and should be considered as an option alone or adjunctive medication for treatment of acute rhinosinusitis. Table 19.6 lists common intranasal corticosteroids and their adverse effects.

When beginning the discussion of starting a child on an inhaled corticosteroid, one of the parents' main concerns is how the inhaled corticosteroid will affect their child's growth and development. The word "steroid" poses fear in the hearts of parents used to hearing the serious effects this class of drug has on athletes that abuse them. In a recent controlled prospective study, growth and pulmonary function in children was evaluated during long-term treatment with orally inhaled budesonide. The results were compared to children who were not treated with inhaled corticosteroids. The study showed that there were

Table 19.7 Systemic corticosteroids

Corticosteroid	Relative glucocorticoid potency	Plasma half-life (min)	Estimated biological half-life (h)
Hydrocortisone	1	90	8–12
Cortisone acetate	0.8	30	8–12
Dexamethasone	25	200	36–54
Fludrocortisone	10	Unknown	18–36
Prednisone	3.5	60	18–36
Prednisolone	4	200	18–36
Methylprednisolone	5	180	12–36

no statistically significant changes in growth velocity, weight gain, or lung development in those treated with inhaled budesonide as compared to those who were not [52]. One study on intranasal steroids showed that there is no growth suppression with 100 mg intranasal mometasone furoate once daily in children. Overall, there is much less data regarding the effects of intranasal corticosteroids on growth. However, since there is less systemic exposure with intranasal corticosteroids than orally inhaled corticosteroids used for asthma due to lower total dosing, the risk should be even smaller.

Oral Corticosteroids

Some guidelines recommend oral corticosteroids as an option in treating acute rhinosinusitis [12]. Oral corticosteroids are used either alone, or in addition to intranasal corticosteroids for severe nasal obstruction and for short-term rescue treatment for uncontrolled respiratory symptoms despite conventional pharmacotherapy [12]. The recommended daily dosing of oral corticosteroids is 0.5 mg/kg orally for 5–10 days [12]. In a double-blind, randomized controlled study, patients over the age of 18 years with acute rhinosinusitis were treated with either antibiotic therapy in addition to a 3-day course of oral corticosteroids or antibiotic therapy alone [53]. The results showed that after the first 3 days of treatment, patients who received oral corticosteroids had fewer symptoms including pain and nasal obstruction. However, at the end of treatment protocol, both the antibiotic alone and the antibiotic plus steroid treatment groups were symptom free [53]. This study showed the positive impact oral corticosteroids have in the initial recovery phase while not significantly affected the ultimate outcome.

There is a continued debate between allergist/immunologists and otolaryngologists regarding the use of oral corticosteroids for the treatment of acute rhinosinusitis. Otolaryngologists tend to favor the use of oral corticosteroids to treat the severe nasal congestion and inflammation that is commonly associated with acute rhinosinusitis. Allergist/immunologists generally defer the use of oral corticosteroids to only the most severe circumstances because of potential side effects. They point out that side effects from even a short course can include aseptic necrosis of the hip, glaucoma, lower extremity edema, hypertension, mood swings, and weight gain. When oral steroids are used more chronically, the list expands to include cataracts, hyperglycemia, osteoporosis, adrenal suppression, thinning of the skin, an increased risk of infection, and, in children, reduction in growth velocity. Further clinical trials are needed to assess the risks/benefit relationship of treating acute rhinosinusitis with oral corticosteroids before this debate can be settled. In general, considering the side effect profile, the oral method of steroid administration should not be considered a first-line treatment of acute rhinosinusitis. Table 19.7 outlines the different classes of oral corticosteroids [54].

When looking at growth velocity in children taking oral as compared to inhaled corticosteroids, there is a notable difference and deserves special mention. A meta-analysis of the effect of oral and inhaled corticosteroids on growth was performed which compared attained heights with expected heights in children treated with either oral or inhaled corticosteroids [55]. The study revealed that there was a weak association with growth impairment in children being treated with prednisone and other oral corticosteroids. In comparison, treatment with inhaled corticosteroids was associated with attaining normal stature. It is important to review these adverse effects with parents when considering treating children with oral corticosteroids under all circumstances.

Analgesics

Over-the-counter analgesics are typically used for mild to moderate pain associated with acute rhinosinusitis, including facial tenderness or sinus headaches. Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used analgesics. Symptomatically treating pain may allow the patient to carry on with daily activities more easily while sick. No studies have been done to evaluate if analgesics alone or in combination with antibiotics quicken resolution of acute

rhinosinusitis symptoms. There is no clear role for any stronger analgesics such as narcotics in the symptomatic relief of acute rhinosinusitis. Some patients with acute rhinosinusitis may develop migraine headaches. These are most commonly treated with oral NSAIDs along with triptans if this class of drug has already been established as effective for the individual patient in question. When presenting to a primary care physician, approximately 56 % of patients are recommended to take analgesics to help improve their symptoms and decrease inflammation [56]. This suggestion seems reasonable except in the case of a CRS patient with nasal polyps who demonstrate a high incidence of NSAID hypersensitivity (see Chap. 12). In general, more studies are needed to evaluate different classes of analgesics and their role in providing sinus symptom relief.

Decongestants

Intranasal decongestants, i.e., ephedrine, an α_1-agonist, and xylometazoline, an α_2-agonist, are sympathomimetics that increase nasal vasoconstriction. When combined with an intranasal corticosteroid, it has been demonstrated to have short-term benefits in acute exacerbations of chronic rhinosinusitis with nasal blockage [57]. In a Cochrane Review, seven studies were evaluated, and topical nasal decongestants were found to be modestly effective for short-term relief of congestion in adults with the common cold [38]. Oral decongestants such as pseudoephedrine are commonly suggested but there is little data to support their efficacy or an improvement in long-term outcome [58].

The abbreviated use of topical decongestants for less than 4 days is advised in order to avoid a rebound effect that sometimes occur from this class of medication (rhinitis medicamentosa) [12]. Rhinitis medicamentosa is a type of non-allergic rhinitis. Very little information is known about this phenomenon and there is no literature devoted solely to it. While there are no current treatment recommendations for rhinitis medicamentosa other than avoiding the inciting agent, an intranasal corticosteroid can be used to alleviate symptoms. If the intranasal corticosteroid alone is not providing sufficient relief in rhinitis medicamentosa, an intranasal antihistamine can also be added [59]. Ultimately, this problem generally self resolves once the topical decongestant has been discontinued.

Mucolytics

Mucolytics are not routinely recommended in the guidelines for treatment of rhinosinusitis. In a randomized placebo-controlled study, mucolytics as an adjunctive therapy were studied in the treatment of children with acute rhinosinusitis. Erdosteine, a mucolytic, was administered to 49 children while 43 received placebo [60]. Both groups also received an antibiotic throughout the course of treatment. After 2 weeks of treatment with either antibiotic and mucolytic or antibiotic alone, there was no significant difference between the two groups [60]. This study concluded that the use of erdosteine as a mucolytic agent in children with acute rhinosinusitis does not improve or hasten resolution of symptoms. Mucolytics are not routinely given for treatment of acute rhinosinusitis. To date, there is little evidence supporting them as a beneficial adjunctive therapy.

Antileukotrienes

While antileukotrienes have been proven to be modestly effective in treating allergic rhinitis, there are no randomized, controlled trials on the use of antileukotrienes in the treatment of acute rhinosinusitis. Antileukotrienes have also demonstrated efficacy in the treatment of nasal polyposis [61]. The exact anti-inflammatory role of montelukast on inflammatory cells in the nasal passages and sinuses has not been firmly defined. In 2012, a pilot study was initiated to evaluate the role of montelukast in preventing early and late inflammatory cells response to specific allergens causing persistent rhinitis. Patients were randomized into montelukast versus placebo groups for 4 weeks after both received a 4 week nasal wash out. There were fewer inflammatory cells noted, specifically macrophages and neutrophils, in the treatment group after receiving montelukast as compared to the control group, but the results were not statistically significant [62].

In general, there is no place for antileukotrienes as adjuvant therapy for acute rhinosinusitis unless the drug is being used regularly for concurrent allergic rhinitis, asthma, and/or nasal polyposis.

Saline Nasal Irrigation

Saline nasal irrigation or nasal douching is a safe, inexpensive treatment for acute rhinosinusitis. It is commonly used in continental Europe. It may be used to soften viscous secretions and improve mucociliary clearance. Evidence exists that saline nasal irrigation reduces the symptoms of chronic rhinosinusitis [63–67]. No clinical trials exist for the treatment of

acute rhinosinusitis, but irrigation with nasal saline appears safe. Minor adverse effects can be avoided with modification of administration technique and adjustment of the saline concentration, and there have been no reports of serious adverse events. Nasal saline irrigation can be recommended as a supportive mode of treatment in acute rhinosinusitis.

Herbal Preparations

Nasodren (Sinuforte) is a nasal spray obtained from the juice and natural aqueous extract of fresh tubers of the plant *Cyclamen europaeum*. In two studies from Russia, Nasodren has been reported to be effective in the treatment of acute rhinosinusitis [68, 69]. The first study evaluated 50 patients with acute suppurative bacterial rhinosinusitis [68]. Half were treated with Nasodren, amoxicillin, and xylometazoline with the other half treated with only amoxicillin and xylometazoline for 8 days [68]. A higher proportion of patients receiving the Nasodren described their overall treatment as excellent. The treatment group also had a statistically significant increase in mucociliary transport time [68]. Another study evaluated 30 patients with acute rhinosinusitis treated with Nasodren alone [69]. All 30 patients received Nasodren monotherapy [69]. The study showed that for these patients with moderately severe acute rhinosinusitis, Nasodren alone ensured recovery in 73 % of cases by day 7 [69]. Based on these studies, Nasodren proved to be beneficial in relieving symptoms due to acute rhinosinusitis both as an adjunctive therapy and on its own. Sinupret ® is an herbal medicinal product made from gentian root, primula flower, elder flower, sorrel herb, and verbena herb. It is frequently used as a complementary and alternative medicine (CAM) in the treatment of acute and chronic rhinosinusitis and URIs. Sinupret ® was shown to have significant antiviral activity against many viruses including adenovirus C subtype 5, human rhinovirus B subtype 14, and RSV [70].

More people are using herbal preparations for treatment of a multitude of diseases. In fact, it has been shown that many individuals will seek out complementary and alternative medications to help them find a more natural approach to the treatment of their diseases. Many people are also wary of the side effects of the various commercially prepared "Western" medications, and with the rising costs of these medications, the herbal preparations appear to many patients to be a more attractive therapeutic option.

One should be careful in using complementary and alternative medicines. Most of these have not been adequately studied and may contain components that are harmful to health. Some even contain corticosteroids, and the chronic ingestion of these products may lead to severe long-term sequelae. Many of these products are under investigation using modern laboratory methods, but as of the present time, they are not under the regulation of a federal agency, in the same manner that drugs are regulated by the FDA.

Immunotherapy

The role of subcutaneous immunotherapy (SCIT) in the treatment of rhinosinusitis is unclear. If the rhinosinusitis is related to an underlying allergic disease, then immunotherapy may be of benefit. Immunotherapy has been effective in the treatment of allergic fungal rhinosinusitis. This is discussed in more detail in Chap. 8. The use of sublingual immunotherapy (SLIT) has not been adequately studied in the treatment of rhinosinusitis.

Conclusion

The diagnosis and medical treatment of acute rhinosinusitis remains controversial, but general guidelines to therapy have been defined. A majority of cases of rhinosinusitis are caused by viral infections. The difficulty is defining when a case of acute rhinosinusitis is complicated by bacterial infection. Many guidelines have been developed to aid in the diagnosis of acute bacterial rhinosinusitis and to differentiate it from other nonbacterial causes. Most of the guidelines state severe persistent symptoms as the main reason to treat a patient with oral antibiotics. However, recent evidence has shown that even if a bacterial cause for the acute rhinosinusitis is suspected, antibiotic treatment may not promote a more rapid clearance of the bacteria from the sinuses or resolution of symptoms. When choosing to use antibiotics, the best choice in the ambulatory care setting is a drug that is beta lactamase resistant such as amoxicillin-clavulanate or a second-generation cephalosporin. Nasal rinsing with isotonic or hypertonic tepid saline is commonly beneficial and has been shown to hasten recovery. There is some data to support the use of topical nasal steroids and even short-course systemic corticosteroids for symptom relief although the side effect profile of this format of therapy clearly favors the topical application. Other adjunctive therapies such as antihistamines, decongestants, and mucolytics may be beneficial for symptomatic relief in selected cases, but few studies clearly show additional efficacy when used alone or in conjunction with antibiotics.

References

1. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U. S. adults: National Health Interview Survey, 2008. National Center for Health Statistics. Vital Health Stat. 2009;10(242):1–157.
2. Ramadan HH. Pediatric sinusitis: update. J Otolaryngol. 2005;34 Suppl 1:S14–7.
3. Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, Liira H, Williams Jr JW, Makela M. Antibiotics for acute maxillary sinusitis (Review). Cochrane Rev. 2011;(Issue 3):1.
4. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg. 2007;137(3 Suppl):S1–31.
5. Anon JB, Jacobs MR, Poole MD, et al., Sinus and Allergy Health Partnership (SAHP). Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 2004;130(1 Suppl):S1–45.
6. Gonzales R, Steiner JF, Lum A, Barret PH. Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. JAMA. 1999;273:214–9.
7. Dosh SA, Hickner JM, Mainous AG, Ebell MH. Predictors of antibiotic prescribing for non-specific upper respiratory infections, acute bronchitis, and acute sinusitis. An UPRNet study. Upper Peninsula Research Network. J Fam Pract. 2000;49:407–14.
8. Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108:798–808.
9. Chow AW, Benninger MS, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):1041–5.
10. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis initiative. Rhinosinusitis: developing guidance for clinical trials. J Allergy Clin Immunol. 2004;118(5 Suppl):S17–61.
11. Thomas M, Yawn B, et al. EPOS primary care guidelines: European position paper on the primary care diagnosis and management of rhinosinusitis and nasal polyps 2007 – a summary. Prim Care Respir J. 2008;17(2):79–89.
12. Scadding GK, Durham SR, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. Clin Exp Allergy. 2007;38:260–75.
13. Slavin RG, Spector SL, Bernstein IL, et al., AAAAI, the ACAAI, and the JCAAI. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6 Suppl):S13–47.
14. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 2004;130(1 Suppl):1–45.
15. Aring AM, Chan MM. Acute rhinosinusitis in adults. Am Fam Physician. 2011;83(9):1057–63.
16. Palmenberg AC, Spiro D, Kuzmickas R, Wang S, Djikeng A, Rathe JA, Fraser-Liggett CM, Liggett SB. Sequencing and analyses of all known human rhinovirus genomes reveals structure and evolution. Science. 2009;324(5923):55–9.
17. Eccles R. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis. 2005;5(11):718–25.
18. Common Cold. National Institute of Allergy and Infectious Diseases. 2011. http://www.niaid.nih.gov/topics/commoncold/Pages/default.aspx. Retrieved 30 June 2012.
19. Stefanska I, Romanowska M, et al. Co-infections with influenza and other respiratory viruses. Adv Exp Med Biol. 2012;756:291–301.
20. Thompson GR, Patterson TF. Fungal disease of the nose and paranasal sinuses. J Allergy Clin Immunol. 2012;129:321–6.
21. Van Crmbruggen K, Zhang N, Gavaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. J Allergy Clin Immunol. 2011;128(4):728–32.
22. Ramakrishnan VR, Feazel LM, Abrass LJ, Frank DN. Prevalence and abundance of Staphylococcus aureus in the middle meatus of patients with chronic rhinosinusitis, nasal polyps, and asthma. Int Forum Allergy Rhinol. 2013;3(4):267–71.
23. Ahovuo-Saloranta A, Rautakorpi UM, et al. Antibiotics for acute maxillary sinusitis: Cochrane Review. Cochrane Collaboration. 2011;3:1–145.
24. Lee JE, Han DH, Won TB, Rhee CS. A randomized, double-blinded, open label study of the efficacy and safety of cefcapene pivoxil and amoxicillin•clavulanate in acute presumed bacterial rhinosinusitis. Clin Exp Otorhinolaryngol. 2011;4(2):83–7.
25. Hadley JA. The efficacy of cefdinir in acute bacterial rhinosinusitis. Expert Opin Pharmacother. 2006;7(8):1075–83.
26. Garbutt JM, Banister C, Spitznagel E, Piccirillo JF. Amoxicillin for acute rhinosinusitis: a randomized controlled trial. JAMA. 2012;307(7):685–92.
27. Hadley JA. Value of short-course antimicrobial therapy in acute bacterial rhinosinusitis. Int J Antimicrob Agents. 2005;26:S164–9.
28. Bottaro G, Rotolo N, Bonforte S, De Luca P, Ficarra G, Gulino A, Melillo P, Nicosia A, Prestifilippo F. Evaluation of the clinical efficacy of azithromycin in acute respiratory infections in children. Clin Ter. 1994;145(7):35–9.
29. Anon JB. Current management of acute bacterial rhinosinusitis and the role of moxifloxacin. Clin Infect Dis. 2005;41 Suppl 2:S167–76.
30. Sokol W. Epidemiology of sinusitis in the primary care setting: results from the 1999-2000 respiratory surveillance program. Am J Med. 2001;111(9):19–24.
31. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child. 2011;96(9):874–80.
32. McCoul ED, Jourdy DN, Schaberg MR, Anand VK. Methicillin-resistant Staphylococcus aureus sinusitis in nonhospitalized patients: a systematic review of prevalence and treatment outcomes. Laryngoscope. 2012;122:2125–31.
33. Whitby CR, Kaplan SL, Mason Jr EO, Carrillo-Marquez M, Lamberth LB, Hammerman WA, Hultén KG. Staphylococcus aureus sinus infections in children. Int J Pediatr Otorhinolaryngol. 2011;75(1):118–21.
34. Scheid DC, Hamm RM. Acute bacterial rhinosinusitis in adults: part II. Treatment. Am Fam Physician. 2004;70(9):1697–704, 1711–12.
35. Poole MD, Portugal LG. Treatment of rhinosinusitis in the outpatient setting. Am J Med. 2005;118(7A):45S–5050.
36. Schaberg MR, Anand VK, Singh A. Hyperostotic chronic sinusitis as an indication for outpatient intravenous antibiotics. Laryngoscope. 2010;120 Suppl 4:S245.

37. Karlsson G, Homberg K. Does allergic rhinitis predispose to sinusitis? Acta Otolaryngol Suppl. 1994;515:26–8.
38. De Sutter AI, Lemiengre M, Campbell H. Antihistamines for the common cold. Cochrane Database Syst Rev. 2003;(3):CD001267.
39. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. Cochrane Database Syst Rev. 2012;(9):CD007909.
40. Meltzer EO, Gates D, Bachert C. Mometasone furoate nasal spray increases the number of minimal-symptom days in patients with acute rhinosinusitis. Ann Allergy Asthma Immunol. 2012;108(4):275–9.
41. Williamson IG, Rumsby K, Benge S, et al. Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. JAMA. 2007;298(21):2487–96.
42. Meltzer EO, Orgel HA, Backhaus JW, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. J Allergy Clin Immunol. 1993;92(6):812–23.
43. Meltzer EO, Charous BL, Busse WW, et al. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. J Allergy Clin Immunol. 2000;106(4):630–7.
44. Dolor RJ, Witsell DL, Hellkamp AS, et al., Ceftin and Flonase for Sinusitis Investigators. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFF trial: a randomized controlled trial. JAMA. 2001;286(24):3097–105. Published correction appears in JAMA. 2004;292(14):1686.
45. Nayak AS, Settipane GA, Pedinoff A, et al., Nasonex Sinusitis Group. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. Ann Allergy Asthma Immunol. 2002;89(3):271–78.
46. Barlan IB, Erkan E, Bakir M, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Ann Allergy Asthma Immunol. 1997;78(6):598–601.
47. Yilmaz G, Varan B, Yilmaz T, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Eur Arch Otorhinolaryngol. 2000;257(5):256–9.
48. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. J Allergy Clin Immunol. 2005;116(6):1289–95.
49. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. Cochrane Database Syst Rev. 2009;(4):CD005149.
50. Allergy statistics. American Academy of Allergy, Asthma & Immunology. www.aaaai.org/media/resources/media_kit/allergy_statistics.stm. Accessed 11 Mar 2008.
51. DeShazo RD, Kemp SF. Management of allergic rhinitis. UpToDate. www.uptodateonline.com.proxy.uwlib.uwyo.edu. Accessed 7 Mar 2008.
52. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med. 1994;88(5):373–81.
53. Klossek JM, Desmonts-Gohler C, Deslandes B, Coriat F, Bordure P, Dubreuil C, Gehanno P, Gilain L, Jankowski R, Serrano E, Stoll D. Treatment of functional signs of acute rhinosinusitis in adults. Efficacy and tolerance of administration of oral prednisone for 3 days. Presse Med. 2004;33(5):303–9.
54. About pharmacology: approximate relative potency and half-lives of oral corticosteroids (Table 5.34). About pharmacology. N.p., 2 Nov 2011. Web. 16 Jan 2013.
55. Allen D, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. J Allergy Clin Immunol. 1994;93(6):967–76.
56. Klossek JM, Mesbah K. Presentation and treatment of acute maxillary sinusitis in general practice: a french observational study. Rhinology. 2011;49(1):84–9.
57. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomized, controlled trial. Laryngoscope. 2004;114:923–30.
58. Sharp HJ, Denman D, Puumala S, Leopold DA. Treatment of acute and chronic rhinosinusitis in the United States, 1999–2002. Arch Otolaryngol Head Neck Surg. 2007;133(3):260–5.
59. Varghese M, Glaum MC, Lockey RF. Drug-induced rhinitis. Clin Exp Allergy. 2010;40(3):381–4.
60. Unuvar E, Tamay Z, Yildiz I, Toprak S, Kilic A, Guler N, Oguz F, Sidal M. Effectiveness of erdosteine, a second generation mucolytic agent, in children with acute rhinosinusitis: a randomized, placebo controlled. Double-blinded Clinical Study. Acta Pediatr. 2010;99(4):585–9.
61. Ragab S, Parikh A, Darby YC, Scadding GK. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clin Exp Allergy. 2001;31:1385–91.
62. Braido F, Riccio AM, Rogkakou A, Massacane P, Guerra L, Fumagalli F, Stagi E, Balestracci S, Porcu A, Canonica GW. Montelukast effects on inflammation in allergic rhinitis: a double blind placebo controlled pilot study. Eur Ann Allergy Clin Immunol. 2012;44(2):48–53.
63. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. Laryngoscope. 2000;110:1189–93.
64. Taccariello M, Parikh A, Darby Y, et al. Nasal douching as a valuable adjunct in the management of chronic rhinosinusitis. Rhinology. 1999;37:29–32.
65. Rabago D, Pasic T, Zgierska A, et al. The efficacy of hypertonic saline nasal irrigation for chronic sinonasal symptoms. Otolaryngol Head Neck Surg. 2005;133:3–8.
66. Heatley DG, McConnell KE, Kille TL, Leverson GE. Nasal irrigation for the alleviation of sinonasal symptoms. Otolaryngol Head Neck Surg. 2001;125:44–8.
67. Shoseyov D, Bibi H, Shai P, et al. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. J Allergy Clin Immunol. 1998;101:602–5.
68. Ovchinnikov A, Dzhenzhera GE, Lopatin AS. Efficiency of sinuforte in combined therapy of acute suppurative rhinosinusitis. Vestn Otorinolaringol. 2009;5:59–62.
69. Semenov VF, Banashek-Meshcheriakova TV. The efficacy of sinuforte in the starting monotherapy of the patients presenting with acute rhinosinusitis. Vestn Otorinolaringol. 2011;3:68–70.
70. Glatthaar-Saalmuller B, Rauchhaus U, Rode S, et al. Antiviral activity in vitro of two preparations of the herbal medicinal product Sinupret ® against viruses causing respiratory infections. Phytomedicine. 2011;19:1–7.

Chapter 20
Medical Management of Chronic Rhinosinusitis in Children and Adults

Samuel L. Friedlander

Introduction

Chronic rhinosinusitis (CRS) is defined as an inflammatory condition affecting the nasal passageways and sinuses lasting over 12 weeks. Defined by survey criteria from the National Health Interview Study, CRS affects 12.5 % of Americans [1, 2]. Worldwide, 10.9 % of the population around 19 European centers had CRS based on EP [3] OS criteria [3, 4] and it was present in 7 % in South Korea [5]. CRS is subdivided into two groups depending on whether nasal polyps are present or not. The differential diagnosis of CRS is presented in Fig. 20.1. Chronic rhinosinusitis with polyps (CRSwNP) occurs in approximately 20–33 % of cases, and chronic rhinosinusitis without polyps (CRSsNP) is present in 60–65 % [6]. The diagnosis is supported by nasal endoscopy and/or sinus CT scans. However, depending on the research or clinical need, sinus CT scan is supported by some guidelines [7] and not routinely recommended by other societies [8].

Multiple medical therapies are recommended for the treatment of CRS [9]. Some of the therapies vary by specific phenotypes of the disease while other recommendations are universal (Table 20.1) [9]. Several publications have definitively highlighted the treatment of CRS as based on evidence-based research and consensus guidelines [1, 4, 10, 11]. This chapter will focus on the medical management of CRS in adults and children by reviewing the evidence, preferably high-level, for the many available treatment modalities. Included in this review are the usage of nasal corticosteroids, systemic corticosteroids, oral antibiotics, the role of biofilms as related to treatment of CRS, nasal saline irrigation, topical antibiotics, and a combination of medical therapies.

What Is the Evidence for Using Nasal Corticosteroids in CRS?

Nasal corticosteroids are the primary modality for the medical management of chronic rhinosinusitis [1]. They have been shown to improve symptom scores and objective measures in CRS. Guidelines on rhinosinusitis support their usage for both CRSwNP and CRSsNP. The European Position Paper on Rhinosinusitis and Nasal Polyposis 2012 recommends nasal steroids for mild, moderate, and severe CRS with and without nasal polyps [10]. Also, the Joint Task Force on Practice Parameters (JTFPP) and the British Society for Allergy and Clinical Immunology (BSACI) advise using nasal corticosteroids for CRS [8, 11].

However, no corticosteroids are FDA approved for use in CRSsNP and neither are any antihistamines, alpha-adrenergic decongestants, or mucolytics [12].

In 2004, mometasone furoate 200 mcg BID became FDA approved for CRS with nasal polyposis in adults. The approved dosage is double that approved for allergic rhinitis. Beclomethasone (Beconase ®) also is approved for prevention of polyp recurrence after surgical removal [13]. However, this product is not currently available in the USA but is sold worldwide. A newer formulation of beclomethasone nasal does not currently have the CRSwNP indication.

S.L. Friedlander, MD
Department of Allergy/Immunology and Sleep Medicine, University Hospitals of Cleveland, 34055 Solon Road #104A, Solon, OH 44139, USA
e-mail: Samuel.Friedlander@uhhospitals.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_20,

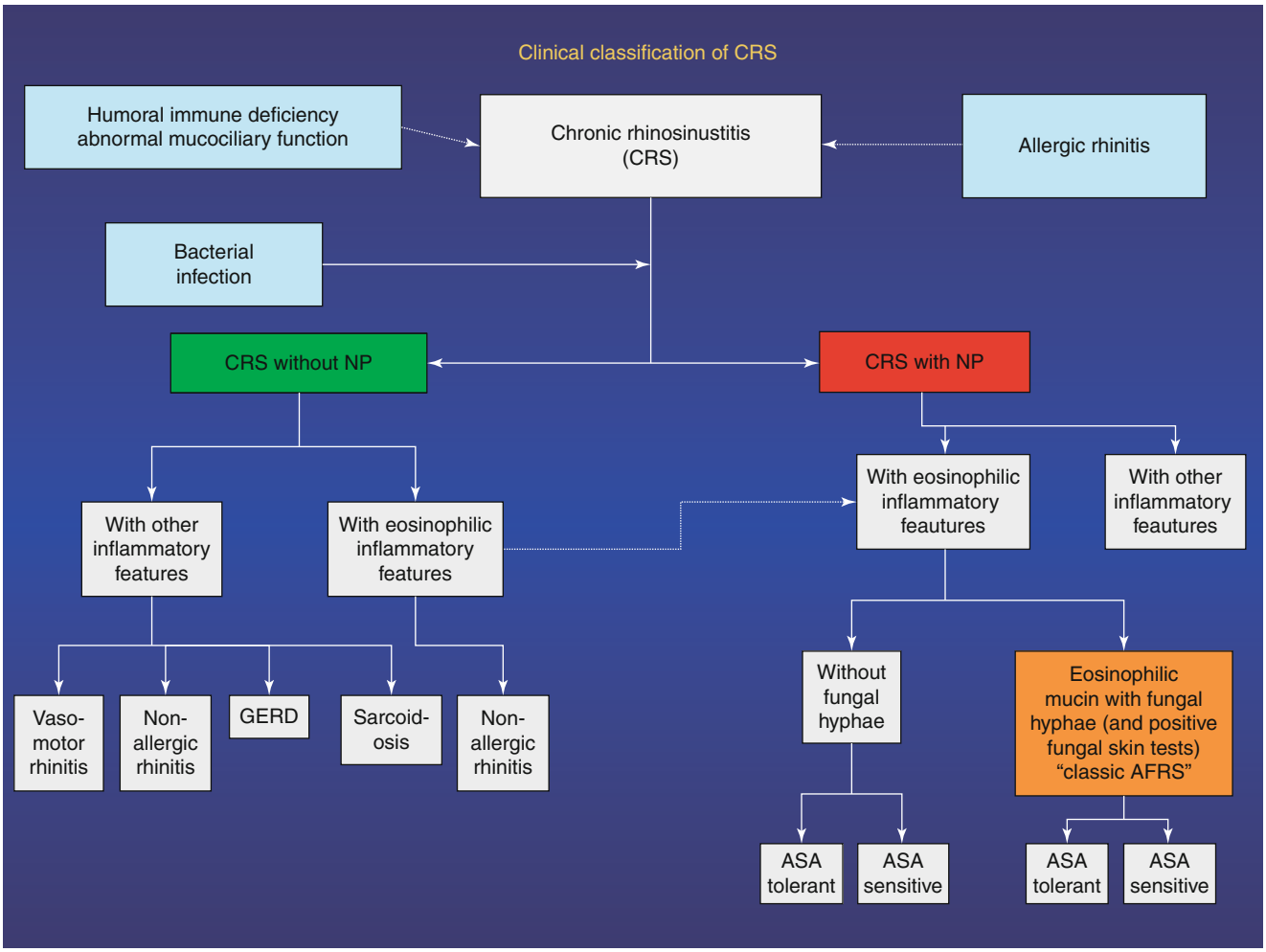


Fig. 20.1 Proposed subclassification of chronic rhinosinusitis. *AFRS* allergic fungal rhinosinusitis, *ASA* aspirin, *GERD* gastroesophageal reflux disease, *NP* nasal polyposis (Reprinted from Meltzer et al. [35]. With permission from Elsevier)

Mechanism of Action and Pharmacologic Properties

The mechanism of action of intranasal steroids is thought to be related to their anti-inflammatory action on inflammatory cells, altering properties of nasal constitutive cells, and inducing T regulatory cells [14, 15]. The corticosteroid binds the intracellular glucocorticoid receptor. This forms a complex that translocates into the nucleus. The anti-inflammatory effects occur through transactivation and transrepression pathways. Transactivation indicates that glucocorticosteroid binding activates promoter regions encoding anti-inflammatory genes [16]. Conversely, transrepression pathways deactivate pro-inflammatory genes [17]. On a cellular level, corticosteroids inhibit the maturation and function of mast cells and basophils, induce apoptosis of eosinophils, and decrease eosinophilic inflammation and chemotactic cytokines [18–22]. Antigen-presenting cell recruitment is limited and T helper type 2 cells and production of their related cytokines, IL-4, IL-5, and IL-13, are reduced [23–25]. Further effects include various adhesion molecules and chemokines are downregulated. Cytokines of fibroblasts, epithelial, and endothelial cells are decreased and goblet cells produce less mucin [14].

Nasal corticosteroids are classified by potency, lipophilicity, and systemic bioavailability (Table 20.2) [26–28]. Potency can be measured by receptor binding affinity and relative cutaneous vasoconstriction [29]. The newer steroid molecules tend to be the most potent. There are some differences in the literature as to whether fluticasone or mometasone is the most potent molecule among the available intranasal steroids. However, clinical studies also do not necessarily correlate potency with clinical efficacy [30]. It is possible that there is a ceiling at which more potent molecules would not be any more efficacious. Lipophilicity increases absorption and retention in the nasal mucosa and is thus beneficial [31]. However, this property can also allow undesired accumulation of steroid in other tissue compartments. Systemic absorption from swallowing drug

Table 20.1 Summary of evidence-based recommendations for the treatment of CRS

Organization		
JTFPP [11]	Antibiotics: role is controversial; may be useful for acute exacerbation of chronic disease Intranasal corticosteroids: may be modestly beneficial as adjunctive therapy Antihistamines: possible role in CRS if underlying risk factor is allergic rhinitis Topical and oral decongestants: prospective studies evaluating use are lacking Antifungal agents: role has not yet been established	
EPOS [4]	*Chronic rhinosinusitis w/o polyps*	*Chronic rhinosinusitis with polyps*
	Mild Topical corticosteroids Nasal lavage If failure by 3 months, treat as mod/sev Moderate/severe Topical corticosteroids Long-term macrolide therapy Culture Cases that improve Follow-up with nasal lavage, topical corticosteroids, consider long-term macrolide therapy	Mild Topical corticosteroids for 3 months If beneficial, continue and review every 6 months If no benefit, add short course of oral steroids If still no improvement, continue CT; assess surgical options If improved after 1 month, switch to topical steroid drops; Review after 3 months Moderate Topical corticosteroid drops for 3 months If beneficial, continue and review every 6 months If no improvement after 3 months, add short course of oral corticosteroids, consider CT, and evaluate surgical candidate. If improved after 1 month, switch to topical steroid drops Severe Short course of oral corticosteroids plus topical steroid for 1 month If beneficial, topical corticosteroid drops only Review after 3 months, if no improvement, perform CT and evaluate for surgical intervention
CPG:AS [7]	Take preventive measures to minimize symptoms and exacerbations of CRS: Saline nasal irrigation daily Concomitant treatment of any underlying conditions (e.g., GERD) Good hand hygiene to prevent viral rhinosinusitis Assess patient for factors that could modify therapy such as allergic rhinitis, immune deficiency, cystic fibrosis, ciliary dyskinesis, structural factors	

JTFPP Joint Task Force on Practice Parameters, *EPOS* European Position Paper on Rhinosinusitis and Nasal Polyps, *CPG:AS* Clinical Practice Guideline: Adult Sinusitis

Table 20.2 Corticosteroids

	Relative receptor affinity[a]	Lipophilicity[b]	Bioavailability (%)	FDA-approved conditions
Beclomethasone[c]	1,345	Moderate	44.0	AR (p, s), NAR, NP, asthma
Budesonide[d]	855	Moderate	31.0	AR, asthma; also NAR in adults
des-Ciclesonide	1,212	High	0.1	AR (p, s), asthma
Flunisolide	177	Low	50.0	AR (p, s), asthma
Fluticasone furoate[e]	2,989	High	0.5	AR (p, s)
Fluticasone propionate[e]	1,775	High	0.5	AR, NAR, asthma
Mometasone furoate[f]	2,244	High	0.1	AR (p, s), asthma; also NP in adults
Triamcinolone[g]	233	Low	44.0	AR (p, s), asthma

Refs. Valotis and Hogger [29], Mullol et al. [27], Micromedex Thomson Reuters [28]
Pharmacokinetic properties and rhinitis and respiratory-related indications of nasal corticosteroids that are used in the treatment of CRS
Note that these medications are not FDA approved for CRS except as stated
Ped pediatric, *AR* allergic rhinitis, *NAR*nonallergic rhinitis, *NP* nasal polyp, *p* perennial, *s* seasonal
[a]Relative receptor affinity versus dexamethasone that has a receptor affinity of 100
[b]Lipophilicity based on ranked order of the above molecules
[c]Beconase, no longer marketed in the USA, was indicated for AR and NAR for 6 years and older; it also had indication for prevention of recurrence of NP following surgical removal in adults. It is indicated for asthma ≥5 years old and rhinitis for ≥6 years old. Currently, Qnasl is indicated for AR in 12 years and older
[d]Budesonide suspension is indicated for asthma at age 1–8 years and for AR at 6 years old
[e]Fluticasone furoate is approved at age 2 years old for AR and fluticasone propionate is approved at age 4 years old for AR and asthma
[f]Mometasone is approved at age 2 years old for AR and at age 4 years old for asthma
[g]Triamcinolone is approved at age 2 years old for AR. Azmacort, used for asthma, has been discontinued

through the gastrointestinal tract also influences what may adversely enter other sites. The newer agents have low bioavailability profiles so very little enters the systemic circulation via hepatic first-pass mechanisms [32]. Drug that is absorbed directly through the nasal and sinus passages bypasses hepatic first-pass pathways and is thus systemically bioavailable [26].

Nasal Corticosteroids in CRSsNP

A Cochrane review of topical steroids in CRSsNP found them to be beneficial [33]. The meta-analysis included 10 studies with 590 patients aged 15–79 using low-pressure delivery devices including sprays, intrasinus and intranasal tubes, and aerosols. Both symptom scores and proportion of patients responding to treatment favored the topical steroid group, with greater effects using sinus delivery methods compared to nasal delivery methods. The EPOS 2012 evidence-based guidelines came to similar conclusions [10].

Lund et al. performed a randomized, double-blind, placebo-controlled multicenter and multinational trial to evaluate the efficacy of budesonide 128 mcg twice a day in CRS over 20 weeks [34]. Over a 3-year period, 244 subjects were enrolled, 167 were eligible for randomization, and 134 completed treatment. This was the largest trial evaluated in the above Cochrane meta-analysis. At the end of the study, the mean improvement in combined symptom scores was 1.85 with budesonide compared to 1.02 taking placebo ($p=0.005$). Improvements were seen in facial congestion/nasal blockage/obstruction, nasal discharge, and impairment in sense of smell. No significant improvement was observed in the facial pain/pressure/headache score. In subjects treated with budesonide, 43.1 % reported substantial or total control of symptoms compared with 25.9 % in the placebo group. There was also a significant improvement in peak nasal inspiratory flow (49.1 l/min in treatment group compared to 10.4 l/min in placebo group, $p<0.001$). Subgroup analysis found budesonide improved combined symptoms scores in allergic but not nonallergic subjects. Peak nasal inspiratory flow was improved in both the allergic, 40 % of the total, and nonallergic groups. Nasal steroids lead to decongestion and it has been difficult to objectively distinguish their effect in CRS from the improvement in nasal congestion alone [35]. Further studies are required to define optimal treatment and delivery methods and which subgroups are most likely to respond to treatment.

Nasal Corticosteroids in CRSwNP

Randomized trials have demonstrated the clinical effectiveness and prevention of polyp regrowth after sinus surgery. A meta-analysis of intranasal corticosteroids in CRSwNP evaluated data on polyp size and recurrence and nasal airflow [10]. There were 3,532 subjects in 38 studies given fluticasone, beclomethasone, betamethasone, mometasone, flunisolide, or budesonide. The dosages in many of the studies were higher than FDA-approved dosages for allergic rhinitis, such as using fluticasone 400 mcg BID or mometasone 200 mcg BID.

In their meta-analysis, the EPOS 2012 reported that symptom scores, the proportion of responders to the medicines, polyp score, and change in polyp score significantly improved with intranasal corticosteroids. Also, the report found improvement using nasal steroids on measures of peak nasal inspiratory flow and improvement in nasal airflow. Subgroup analyses were performed based on surgical status, topical delivery method, and modern versus first-generation nasal steroids. Compared to sprays, nasal aerosols and turbuhaler improved symptom scores better although there was no difference in terms of polyp size reduction or nasal airway scores. Turbuhaler has a similar design as the asthma medication, Pulmicort Flexhaler ®, using a nasal adaptor, but is not available in the USA. There did not appear to be any difference between modern and first-generation corticosteroids on symptom scores. Those with prior surgery responded greater in polyp size reduction, but symptom scores and nasal airflow were not different than those without sinus surgery. Improvement in sense of smell has not been consistent between studies.

These subgroup analyses are limited by smaller sample sizes and the inability to pool all studies for analysis. Reasons for the inability to include all studies are in part due to many publications of trials not containing numeric data of the outcomes, standard deviations, standard error, 95 % confidence intervals, range, or interquartile ranges that are needed to perform a meta-analysis. This reduces the confidence of meta-analyses in general.

In one representative 12-week study, subjects with severe polyposis were treated with fluticasone 200 mcg or beclomethasone 200 mcg both twice a day versus placebo [36]. There was a significant improvement in polyp score, nasal cavity volume using acoustic rhinometry, peak nasal inspiratory flow rate, and nasal blockage in those treated with fluticasone compared to placebo. Beclomethasone also showed improvement in nasal cavity volume and nasal blockage. Loss of sense of smell and numbers of patients requiring polypectomy were no different between the nasal steroids and placebo.

The following ingredients are required:

1. Pickling or canning salt. It should not contain iodine, anti-caking agents, or preservatives
2. Baking soda
3. 8 ounces of lukewarm distilled water

Mix 3 teaspoons of iodide-free salt with 1 teaspoon of baking soda and store in a small airtight container. To make isotonic saline (0.9 %), add 1/2 teaspoon of the mixture to 8 ounces (1 cup) of lukewarm distilled or boiled water. Use 1–1½ % teaspoons for hypertonic saline (2–3 %). Commercially available buffered saline packets are also readily available.

Important points

1. For children, use a quarter-teaspoon in 4 ounces of water for isotonic saline.
2. Adjust head position so the solution does not go down the back of the throat and one can breathe normally through the mouth.
3. Neti-pot devices using gravity require a horizontal head position. The head should be slightly forward and tilted for positive pressure devices.
4. After usage, blow solution out of nose very gently and do not cover the nostrils. Otherwise the solution may enter the Eustachian tube and cause ear discomfort. Some individuals require bending the head forward and lightly blowing out remaining solution. Otherwise the saline can be retained in the sinuses.
5. Use less buffered salt solution if nasal irritation or burning occurs.
6. Clean and disinfect the saline rinse device as per manufacturer instructions so it does not become microbiologically contaminated.

Fig. 20.2 Saline rinse recipe and instructions

A 12-week, double-blind, placebo-controlled study demonstrated the benefit of using topical corticosteroid nasal drops for the treatment of established nasal polyps [37]. The study recruited 28 male patients from the Netherlands with severe nasal polyps or CRS indicated for functional endoscopic sinus surgery (FESS). Subjects were instructed to lie on their back with their head hanging down in an inverted vertical position over the edge of the bed. Fluticasone propionate drops were administrated 200 mcg per nostril once daily. Subjects stayed in the inverted vertical position for 2 min to allow deposition of the medicine. The primary efficacy endpoint was based on a scoring method that took into consideration patients' symptoms, sinus computed tomography (CT) score, and the physician's clinical impression of the patient's need for sinus surgery. Fluticasone nasal drops reduced the need for sinus surgery, improved hyposmia, and decreased nasal polyp volume. Of note, fluticasone nasal drops are not available in the USA.

Aqueous budesonide (Pulmicort Respules ®) or other steroids can be used "off-label" similar to the fluticasone nasal drops [38, 39]. There are several different delivery methods including one similar to the above Aukema study as well as adding the corticosteroid to nasal irrigation or nebulization devices. Some are highlighted in the below section on "safety of intranasal corticosteroids." It is important to deliver the topical steroid to the polypoid tissue, sinus ostia, and the sinus cavities. One recommendation is to mix 0.5-mg budesonide with 5 ml of saline and instill it in the right nostril once daily either in the head down forward or head hanging down in an inverted vertical position over the edge of the bed. Then, the patient moves to the right lateral decubitus position and finally in the supine position, each for 1–2 min (Fig. 20.2) [40]. One should blow out the remaining nasal solution and repeat the procedure for the left nostril [40].

Are Intranasal Corticosteroids Safe?

The long-term safety profile of intranasal corticosteroids has been studied given that systemic corticosteroids are associated with decreased bone density [41], glaucoma, cataract [42], and growth suppression [43, 44]. The majority of trials evaluating topical steroids have been performed in the context of allergic rhinitis. A 1-year trial of the older beclomethasone dipropionate aqueous nasal spray Vancenase ® 168 micrograms twice a day was associated with 0.9 cm lower mean change in height in 6–9-year-olds [44]. Also, a relatively high dose of budesonide 200 mcg twice a day for 6 weeks was associated with short-term lower leg growth velocity over 6 weeks [45]. Fortunately, the majority of studies have not shown any adverse effect on growth or the HPA axis with fluticasone, mometasone, ciclesonide, and other studies with budesonide [46, 47]. In general,

the newer intranasal corticosteroids have decreased bioavailability and subsequent improved safety profiles [48, 49]. A 1-year study of mometasone 100 mcg daily in 3–9-year-olds had no adverse effect on growth velocity, change in height from baseline, or defects in cosyntropin stimulation testing [50].

Side effects of intranasal corticosteroids are generally mild and include the following reported conditions: nasal irritation, epistaxis, nausea, changes in taste, headache, and respiratory infection [26, 51, 52]. No adverse change in nasal mucosal biopsies, plasma cortisol levels, and nasal examination, including septal perforation, blood chemistry, or hematology, after 1 year of nasal steroid treatment was found [53]. After 36 months, no atrophic rhinitis, squamous metaplasia, or changes in the type of surface epithelium occurred [54].

Regarding using budesonide respules for topical use to the sinuses, some recent evidence is available. Budesonide 0.25 mg/per nostril daily using head forward, lateral decubitus, and supine positioning for 30 days was studied in nine adults with chronic sinusitis [55]. In this open label, non-randomized, non-controlled study, this dosage did not suppress the HPA axis using cosyntropin stimulation testing. Also, quality of life improved as measured by the Sino-Nasal Outcome Test-20 (SNOT-20) standardized instrument. Side effects occurred in 3 subjects including 2 people with epistaxis, 1 with headache, and 1 with diarrhea, dyspepsia, and irritability.

Also, patients using budesonide nasal irrigations 0.5 mg mixed with 240 ml of saline for 6 weeks were evaluated. There was no decrease in serum cortisol or 24-h urinary cortisol. However, the sample size was 10 patients and this was also not a randomized or controlled study [56]. Therefore, adverse effects on the HPA axis with long-term use cannot be excluded so side effects should be monitored. Some authors recommend yearly ocular pressure checks with off-label budesonide 0.5 mg usage [40].

Also, one must always be mindful of safety issues not only with the treatment of a disease but from the lack of treatment of the disease. Failing to adequately treat CRS potentially can lead to complications as well. Although rare, there are reports of sphenoid sinusitis causing acute ischemic stroke and optic neuritis [57, 58].

Systemic Oral Steroids

Systemic oral steroids have not been studied as extensively as topical steroids although reports have found an improvement in symptom scores and reduction in polyp size. A Cochrane review found benefit for using oral corticosteroids in CRSwNP based on three randomized controlled studies [59].

In the first study, Van Zele found a 20-day tapering course of steroids benefited symptom and polyp scores up to 8 weeks. However, this effect did not persist later after discontinuation as no differences were seen at 12 weeks. In this study, oral doxycycline also decreased nasal polyp size and both reduced systemic markers of inflammation [60]. A second study found improved symptom scores and a reduction in the magnetic resonance imaging score in the treatment group [61].

The third study evaluated patients with nasal polyposis that were given oral prednisone for 2 weeks followed by intranasal budesonide for 48 weeks in a prospective trial [62]. The dosage used was 30 mg per day for 4 days with a 5 mg reduction every 2 days compared to a randomized control group not receiving prednisone. At the end of the 2 weeks, the oral prednisone group had a significant improvement in quality of life, nasal obstruction, sense of smell, and polyp size. Intranasal budesonide 400 mcg/day was continued for 48 weeks and in this trial maintained the treatment effect. At 48 weeks there was only a minimal worsening of clinical symptoms. However, no control group was compared for this longer arm of the study for ethical reasons. In 17 % of patients, surgery was required for failure of medical therapy.

Another study was published after the Cochrane review. Vaidyanathan evaluated 60 subjects with nasal polyposis receiving a 2-week regimen of oral prednisolone 25 mg plus 6 months of intranasal steroids versus intranasal steroids alone [63]. The topical steroid dosage was fluticasone propionate nasal drops 400 mcg twice a day for 8 weeks, then fluticasone propionate nasal spray 200 mcg twice a day for 18 weeks. They found a significant improvement in polyp grade and hyposmia score up to 10 weeks, but no statistical differences at 6 months. At the end of the oral prednisolone course, the mean decreases in polyp grade and hyposmia score were 2.1 units and 31.1 mm, respectively, in the steroid group compared to 0.1 unit and 1.4 mm in the placebo group. Despite the high doses of fluticasone, there was no adrenal suppression at 10 and 28 weeks compared to baseline. This was measured by overnight urinary cortisol levels corrected for creatinine and adrenocorticotropic hormone-stimulated serum cortisol. At 2 weeks on prednisone, both measures were suppressed as expected.

A recent review evaluated oral steroids in CRSsNP and found low-level evidence from retrospective and prospective trials to support this management strategy [64]. Improved subjective and objective data were found using oral corticosteroids. However, the trials were not randomized or controlled, and they also used oral antibiotics and nasal corticosteroids making it difficult to attribute improvement solely to the steroids.

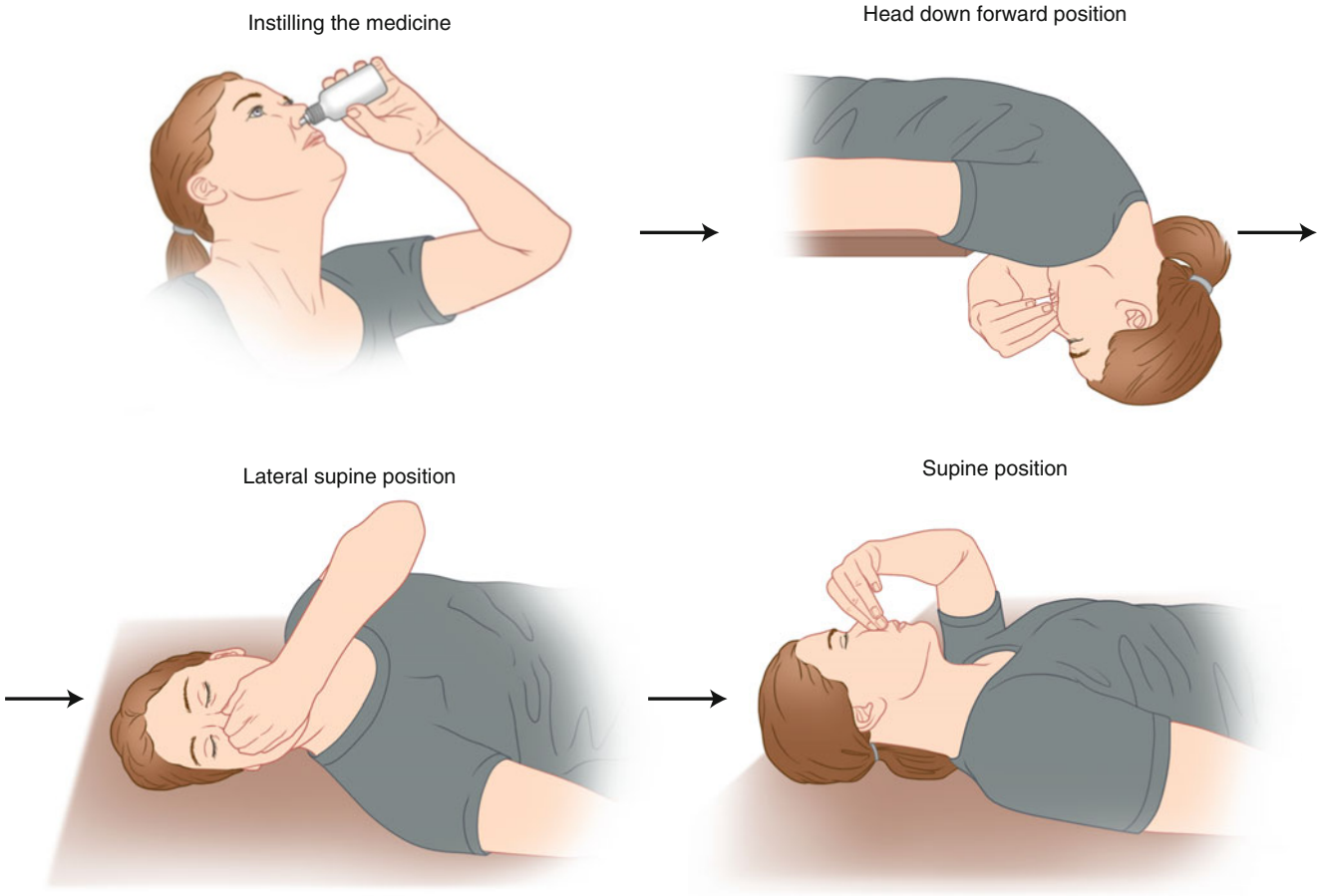


Fig. 20.3 Intranasal instillation of aqueous corticosteroid mixture. A 0.5 mg budesonide respule is mixed with 1 teaspoon of saline, and this mixture is instilled in the right nostril. The nose is pinched closed and the head is rotated, first in the head down forward, then right lateral supine position, and finally in the supine position each for up to 1–2 min, following which the residual nasal solution is expelled from the nose. The procedure is then repeated in the left nostril changing to the left lateral supine position. A controlled clinical trial of this treatment has not been performed, and the long-term safety of this procedure has not been established. The head-down-forward position can also be accomplished by kneeling and having the top of the head touch the floor

Nasal Saline

There are a variety of proprietary devices and dry salt powders on the market. The "original" Neti-pot-type irrigation devices require the patient to tilt their head to the side and saline is instilled using gravity. Newer devices include "squeeze bottles," nebulizers, and electricity-driven units that may be used to deliver saline or medications topically. Bulb syringes may be used as well. It is very important to instruct patients properly in the use of nasal saline [65]. Warm distilled water is instilled using proper head position depending on which device is used. The technique should be gentle with caution not to blow the nose too forcefully as this may cause ear discomfort (Fig. 20.3).

A randomized controlled trial of 76 subjects using 2 % buffered saline led to an improvement in the Rhinosinusitis Disability Index. Fewer sinus symptoms and less antibiotics were used in the treatment group. Levels of satisfaction and whether subjects would recommend this treatment to others were high, and adverse effects were uncommon and mild [66]. A Cochrane review found a modest improvement with saline in the treatment of CRS in their evaluation of 8 trials meeting evidence-based criteria [67].

There are conflicting reports regarding mucociliary clearance and ciliary beat frequency after use of hypertonic saline versus isotonic saline [67]. More recent studies show improvement with hypertonic compared to isotonic saline. Ciliary beat frequency increased with hypertonic solution at 5 min but no differences were found at 60 min. The improvement was hypothesized to be the result of increased osmolarity increasing fluid into the mucous layer [68]. Compared to isotonic saline, 2.3 % saline improved saccharine clearance time and nasal airway patency in postoperative septoplasty patients [69]. However, with increasing salinity, temporary nasal irritation has been reported.

As with all medical treatments, patients should be advised regarding side effects of this over-the-counter treatment. Adverse effects of using nasal saline are generally minor and include nasal irritation, burning, tearing, epistaxis, headache, and nasal drainage [66]. If one forcefully blows their nose afterward or instills the solution too rapidly, fluid can enter the Eustachian tube with resultant ear pain. Recently, there has been concern for bacterial contamination so sterilization of the bottles or changing them is recommended [70–73].

Do Topical Sinus Irrigation and Nebulization Penetrate into the Sinuses?

Saline rinses are able to penetrate the sinus cavities but their efficacy depends on which technique is used and their ability to enter the sinus ostia. Turbinate lateralization and obstruction of ostia from polyps and synechiae limit the ability of saline to enter the sinuses. Nasal irrigation can reach the anterior and posterior nasal cavity, ethmoid, and maxillary sinuses but are less able to penetrate the frontal and sphenoid sinuses. Also, large-particle nebulization was less effective in reaching the sinuses than nasal douching. Surgical enlargement of the ostia allows saline to better reach the sinuses [74–76].

Positive-pressure sinus rinses were able to penetrate into the sinuses depending on the size of ostia. Blue dye in 200 ml of buffered saline from a squeeze bottle was endoscopically studied to detect ostial penetration in 17 subjects. A minimum ostial size of 3.95 mm allowed delivery of the irrigation solution in 95 % of cases. Surgically enlarged ostia were more likely to allow irrigant penetration. In patients with history of sinus surgery, ostia in 24 out of 28 were penetrated compared to nonsurgically operated sinuses with 8 out of 21 penetrated. Massive polyps, large synechiae, and severe turbinate lateralization causing obstruction did not allow saline to enter the sinuses [75].

In another study, sinus douching performed better in entering the sinus cavities than large-particle saline nebulization or sprays [76]. Patients had CRSsNP and were without gross deviated nasal septal deviations. They were over 40 years old and 9 were status post-functional endoscopic sinus surgery (FESS) and 3 were control patients. Saline was administered in the (1) head down position (5 ml), (2) 4 puffs of metered spray (1.5 ml), and (3) 2 ml saline nebulized with a large-particle nebulizer. Nuclear imaging was performed at 8 sites: nasal anterior cavity, posterior cavity, maxillary sinus, sphenoid sinus, frontal recess, frontal sinus, oropharynx-larynx-esophagus, and face. The anterior and posterior nasal cavity was well irrigated by all three techniques. Nasal saline rinses had significantly better delivery to the maxillary sinus. Using nasal spray, none entered the maxillary sinuses. Only 3 out of 9 patients entered maxillary sinuses by nebulizer. The frontal recess was penetrated in 6 out of 9 with nasal douching, 1 with nebulizers, and none with spray. The frontal sinus was only penetrated by 2 out of 9 using nebulization and none with other methods. The sphenoid sinuses were not entered by any means. In the control patients with no history of FESS, the anterior and posterior cavities were well irrigated with all techniques. Nasal irrigation reached the maxillary sinus in 2 out of 3, frontal recess and sinus in 1 out of 3, and sphenoid sinus in 1 out of 3. Nasal spray and nebulizers did not reach the sinuses. In another investigation, positive- and negative-pressure irrigation performed better for the ethmoid and maxillary sinuses than a nebulizer using 20–30 μm particles [74]. Frontal and sphenoid sinuses were poorly irrigated by all methods in this trial.

What Is the Role of Biofilms in the Management of CRS?

Biofilms have been discovered in 40–80 % of patients with chronic rhinosinusitis and appear to play a role in the disease process [77]. One possible mechanism involves ciliary and epithelial layer damage in biofilm-positive individuals leading to mucociliary stasis and subsequent pathogenicity [78]. Treatment strategies against biofilms include antibiotics to target the bacterial organism, dissociating bacteria from the biofilm, or physically removing the biofilm itself. Multiple antibiotics have been proposed including mupirocin, Manuka Honey, tobramycin, and moxifloxacin although the majority of the studies utilize in vitro designs. In a pilot study, 16 post-FESS patients with recalcitrant CRS and *Staphylococcus aureus* were treated with 0.05 % mupirocin nasal lavages for 3 weeks. The majority noted symptom improvement and 15/16 had improved endoscopic findings and cultures reverted to negative. However, a larger retrospective trial found a high rate of microbiological failure several months after rinses were discontinued [79]. Further study is required.

Chemical surfactants have been suggested as a possible means to remove biofilm. An open label study was conducted in 18 patients with CRS using 1 % baby shampoo solution in normal saline [80]. This readily available and inexpensive formulation was found to inhibit Pseudomonas biofilm formation in vitro. However, baby shampoo had no effect on the eradication of preformed Pseudomonas biofilms. An overall improvement in subjective symptoms was experienced in 46.6 % of patients,

and 60 % of patients noted improvement in symptoms of thickened mucus and postnasal drainage. Review of safety found 2 patients discontinued use because of minor nasal and skin irritation.

Additional research has evaluated xylitol nasal irrigation in a 15 person randomized, double-blinded controlled crossover study. Subjects had a small but statistically significant improvement in Sino-Nasal Outcome Test 20 (SNOT-20) scores with 5 % xylitol compared to 0.9 % saline. The majority tolerated the treatment well. The authors propose that xylitol leads to an improvement in antibacterial properties of the airway surface liquid [81]. High concentrations of chloride are reduced allowing innate antimicrobial agents of the airway surface to operate. Also, xylitol may actively damage biofilms [82].

With concern for *Staphylococcus aureus* colonization and enterotoxins causing an inflammatory response in CRS, sodium hypochlorite nasal lavage solution has been studied for its antiseptic properties [83]. In 20 post-functional endoscopic surgical patients with persistent *Staphylococcus aureus* carriage, 0.05 % NaOCl plus 0.9 % saline twice a day for 3 months improved nasal symptoms, endoscopy scores, and nasal airway resistance. But there was no difference in nasal nitric oxide or reduction in S. aureus by middle meatus endoscopically guided cultures [84]. Since no placebo or control group was used and patients were also using mometasone 400 mcg/day, it is difficult to make definitive conclusions regarding efficacy but the therapy was well tolerated and deserves further study.

Oral Antibiotics

The role of bacteria and treatment with antibiotics in CRS is controversial as bacterial colonization is found and not necessarily pathological. The evidence for using short-term antibiotics in CRSsNP is scant and no placebo-controlled trials are available. Despite this lack of high-level data showing efficacy, antibiotics are widely used by practitioners for treating CRS [85]. Acute exacerbations are treated with antibiotics similar to those for acute rhinosinusitis [86, 87]. Also, the choice should be based on local bacterial resistance patterns, cost, and side effects individualized to the patient. As discussed below, a multifaceted treatment approach that includes antibiotics may be helpful.

There may also be a role for long-term antibiotic treatment. In CRSsNP, long-term macrolides are recommended by EPOS 2012 based on evidence for anti-inflammatory action and symptom improvement. Macrolides can block interleukin-8 (IL-8), eosinophilic cationic protein, and tumor necrosis factor-alpha (TNF-α), mitigate neutrophil migration and adhesion, and reduce the synthesis and secretion of mucus [88–90]. Cervin et al. evaluated the effects of a macrolide on nasal lavage-fluid markers of inflammation in subjects with prior sinus surgery and persistent CRS symptoms [89]. In an open study design, clarithromycin 250 mg was given daily for 12 weeks. Treatment was associated with reduced levels of IL-8, a pro-inflammatory neutrophilic cytokine, and eosinophilic cationic protein (ECP), granulocytic products of eosinophils. Exudative mucosal responsiveness to histamine, an important measure of airway inflammation as measured by α2-macroglobulin, was reduced. Also histamine-induced mucinous secretion, measured by fucose which is found in goblet cells and airway glands, was significantly reduced. These results indicate that clarithromycin induces an anti-inflammatory effect in CRS.

Two 12-week placebo-controlled studies with approximately 60 subjects per trial are available to address the role of macrolides in CRS. A course of roxithromycin 150 mg daily improved quality of life, as assessed by the SNOT-20 measure, nasal endoscopy scores, and mucociliary transit time in CRSsNP [91]. The mean symptom response score was significantly improved at the end of treatment. At 3 months after treatment, the change in SNOT-20 was not clinically significant as it was at the end of treatment. Subgroup analysis found those with lower IgE levels (<200 mcg/l) seemed to respond in particular.

Conversely, Videler et al. found no significant improvement with azithromycin in patients with and without nasal polyps [92]. Adults were recruited from tertiary ENT clinics with severe CRS failing nasal saline irrigation, intranasal corticosteroids, oral antibiotics and, in 92 %, endoscopic sinus surgery. They were given 500 mg for 3 days in the first week, then 500 mg per week for the 12 week treatment period. Compared to placebo, there was no significant difference in nasal endoscopy, peak nasal inspiratory flow, sense of smell, and microbiology.

In a Cochrane review, out of 38 controlled clinical trials, only the Wallwork study met inclusion criteria for analysis. The Videler study was published later and not available for review. Using the sole included trial, they indicate the evidence for using antibiotics in CRSsNP is limited. It was not clear if the numerically significant effects translated to a clinically significant effect. As a result, the Cochrane review did not recommend the use of any antibiotics pending further data [93]. A larger randomized and controlled trial is indicated to better answer whether macrolides or other antibiotics may be indicated to treat CRS. The writers of the EPOS 2012 document do endorse macrolides in CRSsNP as a grade A recommendation and propose checking nasal swabs with culture every 3 months to survey for bacterial resistance [10]. They discuss safety and bacterial resistance concerns but rate long-term antibiotic therapy as relatively safe. Comparisons with using long-term doxycycline for acne, trimethoprim-sulfamethoxazole for patients with immune deficiency, and macrolides in cystic fibrosis are cited.

Topical Antibiotics

There are 3 placebo-controlled randomized trials evaluating topical antibiotics in CRSsNP that all had negative results. However, these trials are limited by small sample sizes, short treatment periods, and possible differences in nebulization particle size and type of antibiotics than are currently available.

Other topical antibiotic studies have been prospective observational studies only, not double-blind or placebo-controlled. The study population has included postoperative patients only. The treatments involved a nebulized antibiotic for 3–6 weeks. Scheinberg and Otsuji studied 41 patients with CRS with history of at least one functional endoscopic sinus surgery (FESS). Excellent to good improvement was reported in 82 % of cases in this non-randomized, non-controlled chart review [94]. Endoscopic improvement and an increase in infection-free interval after treatment were reported in another trial [95]. The antibiotic was chosen based on culture results and they reported a 76 % success rate with clearing the organism. Both studies reported a low rate of side effects that included sore throat, skin irritation, tinnitus in a patient on gentamicin, joint pain in a patient on levofloxacin, and cough.

If a topical antibiotic solution is used, it should be based on antimicrobial culture and susceptibility reports. Theoretically, it is best that the sinuses should be surgically patent to allow penetration of the antibiotic rinse. The antibiotic can be administered as a rinse or with the use of a nebulizer [40]. If a sinus rinse system is used, the supine position should not be used with aminoglycosides. There is concern for ototoxicity if medicine reaches the sphenoethmoidal region in this position. The expected delivery of antibiotic to the various sinuses has been reviewed above.

Topical and oral antifungals in CRS are highly controversial and not supported by randomized controlled trials or by evidence-based guidelines [10]. Further discussion of antifungal therapy has been reviewed in the literature [96–98]. (

Medical Therapy, Multiple Treatments

Retrospective evidence is available in patients with CRS that were treated with multiple medical therapeutic interventions. Lal performed a retrospective study finding medical therapy was successful in 51 % of 145 patients. Treatment included oral steroids and antibiotics, topical nasal steroids and intermittent nasal decongestants, and saline rinsing. Treatment lasted 4 weeks and response to therapy was measured at 2-month follow-up. “Failure” was defined as relapse or persistence of symptoms and was associated with facial pressure or pain, higher endoscopic scores, and severe mucosal inflammation. Some of the “failures” had partial improvement and 69 % of the total group did not require surgical intervention [99].

A retrospective review of 40 patients with CRS with and without nasal polyps found 36 to have both symptomatic and radiographic improvement in chronic sinusitis. They were treated with 1 month of antibiotics, nasal saline irrigations, intranasal steroids, and prednisone taper. The majority also did not relapse defined as requiring additional antibiotics or oral steroids over a 2-month time period [100].

Ancillary Treatments

No high-level evidence supports the use of decongestants or mucolytic treatment in CRS. Mucolytics were studied in a double-blind, placebo-controlled study in 23 HIV patients with rhinosinusitis given guaifenesin 2,400 mg per day. They reported significantly less nasal congestion and thinner postnasal drainage [101]. Decongestants can decrease nasal resistance but are limited by their side-effect profile that includes increases in blood pressure, central nervous system stimulation, insomnia, urinary retention, and mydriasis [11]. Leukotriene antagonists are not supported by large, randomized controlled trials. There is limited evidence they may improve CRS with nasal polyps. Antihistamines may have a drying effect and play a role in allergic rhinitis patients with sinusitis. Allergy immunotherapy has not been well studied in CRS but may be considered if concurrent allergic rhinitis is present [11]. There is also evidence that patients with aspirin-exacerbated respiratory disease (AERD) and CRSwNP can benefit from oral aspirin desensitization and/or leukotriene inhibitors [102]. However, these trials are limited by the lack of placebo-controlled evidence due to the difficulty of blinding subjects and finding an adequate placebo.

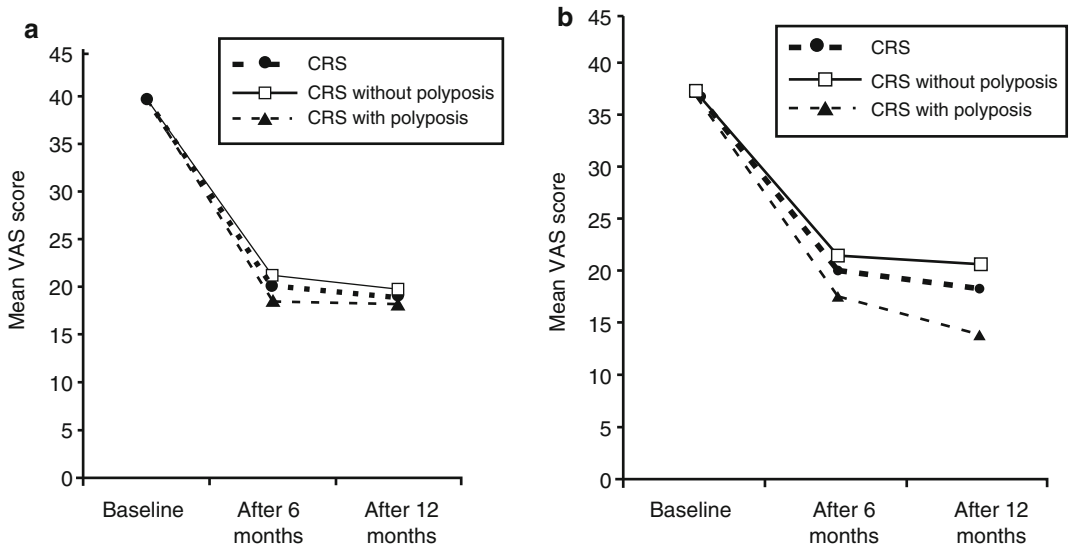


Fig. 20.4 Twelve-week course of low-dose erythromycin, alkaline nasal douche, topical corticosteroids, and short courses of oral corticosteroids in this study was an effective, well-tolerated therapy for CRS. When compared to FESS, all groups tended to show a slightly better improvement by 12 months, but the differences between the 6- and 12-month VAS and individual symptom scores were statistically insignificant for all groups studied ($p > .05$) suggesting that the medical treatment regimen and surgical intervention had equivalent outcomes over 1 year. (**a**) Change in visual analogue scores (VAS) of the surgical group. *CRS* chronic rhinosinusitis. (**b**) Change in visual analogue scores (VAS) of the medical group. *CRS* chronic rhinosinusitis (Reprinted from Ragab et al. [104]. With permission from John Wiley & Sons, Inc)

Medical Therapy Versus Surgical Therapy

The Cochrane group performed an analysis of the results of medical therapy versus surgical therapy. They were only able to identify 3 trials that met strict evidence-based medicine criteria. The meta-analysis did not find any benefit of surgical therapy over medical therapy with or without saline rinses [103]. The safety profile for FESS was good and complications were minimal. In one of the studies, medical therapy consisted of a 3-month course of the macrolide antibiotic erythromycin, nasal rinses, and topical corticosteroids (Figs. 20.4) [104]. Rather than eliminate surgery as a beneficial option, the Cochrane review highlights the limited amount of randomized controlled trials available in this field of medicine. Additional high level of evidence studies are needed. It also does promote an exhaustive trial of medical therapy prior to consideration of surgery.

Management of CRS in the Pediatric Population

There is limited evidence for the medical management of CRS in children with few randomized, placebo-controlled studies [10]. Antibiotics have been used for treatment both for short- and long-term durations as with adults. Comparing antibiotics plus nasal decongestants, maxillary sinus drainage, both, or nasal saline drops as a placebo, there was no significant difference between the 4 groups [105]. This non-randomized, non-blinded study included 3–10-year-old children with CRS lasting at least 3 months with purulent rhinitis on rhinoscopy and abnormalities on plain x-rays. Similarly, in another study, there was no difference in resolution rate at 6 weeks between cefaclor and placebo given for 1 week [106]. Both groups were also treated with sinus lavage. Limitations of these studies include not using longer-term durations of antibiotics and using plain x-rays for diagnosis. As with the above section on antibiotics, acute bacterial exacerbations, although difficult to define, may be treated with similar antibiotics as with acute rhinosinusitis. However, risks and benefits should be weighed considering the lack of good evidence to support this therapy [10].

Unfortunately, there is also a lack of data with intranasal corticosteroids. No randomized, controlled studies in children have been performed. Their use has been translated from beneficial studies in allergic rhinitis that are found in children [107, 108].

Oral methylprednisolone has been studied in a pediatric, randomized, controlled study as add-on therapy to 30-day treatment with amoxicillin/clavulanate. A 15-day tapering course of oral steroids was significantly superior to placebo in improving CT scores, total rhinosinusitis symptoms, and individual symptoms including cough, nasal obstruction, and postnasal discharge [109]. Based on the study design, the role of antibiotics alone cannot be ascertained.

Nasal saline irrigations have demonstrated benefit in both children and adults with CRS [67]. A Cochrane meta-analysis concluded saline lavage was beneficial for improving symptoms in CRS. This review contained 3 studies from the pediatric population extending the positive results to children. However, some of these individuals had the diagnosis of allergic rhinitis rather than true CRS. Due to low sample sizes or lack of data, they could not make recommendations as to which specific solutions, dosage, or delivery method performed best. Wei et al. performed a prospective, randomized, double-blinded study in children with CRS using daily saline irrigation versus saline/gentamicin for 6 weeks. Both groups demonstrated improved quality of life and sinus CT scores with no differences between the groups [110].

No specific information is available regarding other ancillary treatments such as antihistamines and leukotriene inhibitors on CRS in children. Clearly the research need in this population is great.

Conclusions

Multiple medical therapies are available for the treatment of CRS in adults and children. Among them are nasal and systemic corticosteroids, oral and topical antibiotics, nasal saline irrigation, and a combination of medical therapies. Nasal corticosteroids are recommended for all types of CRS by multiple rhinosinusitis guidelines and evidence-based meta-analyses. However, stronger evidence is available for nasal corticosteroid use in CRSwNP and additional larger studies for CRSsNP would solidify current guidelines. Delivering treatment directly to the sinus cavities is important and has implications in discovering the best treatment strategies for CRS. The role of antibiotics is controversial and continues to be defined. Particularly the use of macrolides in CRSsNP is promising. Nasal saline has also been shown to be beneficial for all types of CRS. Additives such as surfactants may be beneficial as well. Despite the research as highlighted in this chapter, gaps in knowledge base remain. The large amount of patients affected by CRS highlight the urgency for additional research funding. Additional high-level controlled studies with adequate sample sizes as well as experimental bench research are greatly needed.

References

1. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. J Allergy Clin Immunol. 2011;128:693–707; quiz 708–9.
2. Pleis JR, Ward BW, Lucas JW. Summary health statistics for U.S. Adults: National Health Interview Survey, 2009. Vital Health Stat 10. 2010;249:1–207.
3. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe–an underestimated disease. A GA(2)LEN study. Allergy. 2011;66:1216–23.
4. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2007;45 Suppl 20:1–136.
5. Kim YS, Kim NH, Seong SY, Kim KR, Lee GB, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in Korea. Am J Rhinol Allergy. 2011;25:117–21.
6. Hamilos DL. Clinical manifestations, pathophysiology, and diagnosis of chronic rhinosinusitis. 2012. http://www.uptodate.com/contents. Accessed 12 June 2012.
7. Rosenfeld RM. Clinical practice guideline on adult sinusitis. Otolaryngol Head Neck Surg. 2007;137(3 Suppl):S1–31.
8. Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. Clin Exp Allergy. 2008;38:260–75.
9. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc. 2011;86:427–43.
10. Fokkens WJ, Lund V, Mullol J, et al. The European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2012;23:1–299.
11. Slavin RG, Spector SL, Bernstein IL, et al. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116:S13–47.
12. Guidance for industry: Sinusitis: designing clinical development programs of nonantimicrobial drugs for treatment. US Department of Health and Human Services (DHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072037.pdf. Accessed 22 May 2012.
13. GlaxoSmithKline. Beconase AQ (R): prescribing information. Research Triangle Park: GlaxoSmithKline; 2002.
14. Okano M. Mechanisms and clinical implications of glucocorticosteroids in the treatment of allergic rhinitis. Clin Exp Immunol. 2009;158:164–73.

15. Li HB, Cai KM, Liu Z, et al. Foxp3+ T regulatory cells (Tregs) are increased in nasal polyps (NP) after treatment with intranasal steroid. Clin Immunol. 2008;129:394–400.
16. Barnes PJ. Corticosteroid effects on cell signaling. Eur Respir J. 2006;27:413–26.
17. Pascual G, Glass CK. Nuclear receptors versus inflammation: mechanisms of transrepression. Trends Endocrinol Metab. 2006;17:321–7.
18. Smith SJ, Piliponsky AM, Rosenhead F, Elchalal U, Nagler A, Levi-Schaffer F. Dexamethasone inhibits maturation, cytokine production and Fc epsilon RI expression of human cord blood-derived mast cells. Clin Exp Allergy. 2002;32:906–13.
19. Crocker IC, Zhou CY, Bewtra AK, Kreutner W, Townley RG. Glucocorticosteroids inhibit leukotriene production. Ann Allergy Asthma Immunol. 1997;78:497–505.
20. Stellato C, Atsuta J, Bickel CA, Schleimer RP. An in vitro comparison of commonly used topical glucocorticoid preparations. J Allergy Clin Immunol. 1999;104:623–9.
21. Meagher LC, Cousin JM, Seckl JR, Haslett C. Opposing effects of glucocorticoids on the rate of apoptosis in neutrophilic and eosinophilic granulocytes. J Immunol. 1996;156:4422–8.
22. Roca-Ferrer J, Mullol J, Lopez E, et al. Effect of topical anti-inflammatory drugs on epithelial cell-induced eosinophil survival and GM-CSF secretion. Eur Respir J. 1997;10:1489–95.
23. Erin EM, Zacharasiewicz AS, Nicholson GC, et al. Topical corticosteroid inhibits interleukin-4, -5 and -13 in nasal secretions following allergen challenge. Clin Exp Allergy. 2005;35:1608–14.
24. Till SJ, Jacobson MR, O'Brien F, et al. Recruitment of CD1a+ Langerhans cells to the nasal mucosa in seasonal allergic rhinitis and effects of topical corticosteroid therapy. Allergy. 2001;56:126–31.
25. Malmhall C, Bossios A, Pullerits T, Lotvall J. Effects of pollen and nasal glucocorticoid on FOXP3+, GATA-3+ and T-bet+ cells in allergic rhinitis. Allergy. 2007;62:1007–13.
26. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. Allergy. 2008;63:1292–300.
27. Mullol J, Obando A, Pujols L, Alobid I. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. Immunol Allergy Clin North Am. 2009;29:657–68.
28. Micromedex (R) 2.0. Thomson Reuters. http://www.thomsonhc.com/micromedex2/librarian/. Accessed 13 June 2012.
29. Valotis A, Hogger P. Human receptor kinetics and lung tissue retention of the enhanced-affinity glucocorticoid fluticasone furoate. Respir Res. 2007;8:54.
30. Johnson M. Development of fluticasone propionate and comparison with other inhaled corticosteroids. J Allergy Clin Immunol. 1998;101:S434–9.
31. Corren J. Intranasal corticosteroids for allergic rhinitis: how do different agents compare? J Allergy Clin Immunol. 1999;104:S144–9.
32. Crim C, Pierre LN, Daley-Yates PT. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. Clin Ther. 2001;23:1339–54.
33. Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ. Topical steroid for chronic rhinosinusitis without polyps. Cochrane Database Syst Rev. 2011;(8):CD009274.
34. Lund VJ, Black JH, Szabo LZ, Schrewelius C, Akerlund A. Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. Rhinology. 2004;42:57–62.
35. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol. 2004;114(6 Suppl):S155–212.
36. Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg. 1998;124:513–8.
37. Aukema AA, Mulder PG, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. J Allergy Clin Immunol. 2005;115:1017–23.
38. AstraZeneca Pharmaceuticals. Product Information: Pulmicort Respules (R) inhalation solution, budesonide inhalation solution. Wilmington: AstraZeneca Pharmaceuticals; 2009.
39. AstraZeneca Pharmaceuticals. Product Information: RHINOCORT(R) AQUA nasal spray, budesonide nasal spray. Wilmington: AstraZeneca Pharmaceuticals; 2005.
40. Hamilos DL. Approach to the evaluation and medical management of chronic rhinosinusitis. In: Hamilos DL, Baroody FM, editors. Chronic rhinosinusitis: pathogenesis and medical management. New York: Informa Healthcare; 2007. p. 299–320.
41. Eastell R. Management of corticosteroid-induced osteoporosis. UK Consensus Group Meeting on Osteoporosis. J Intern Med. 1995;237:439–47.
42. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med. 1997;337:8–14.
43. Dluhy RG. Clinical relevance of inhaled corticosteroids and HPA axis suppression. J Allergy Clin Immunol. 1998;101:S447–50.
44. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics. 2000;105:E23.
45. Wolthers OD, Pedersen S. Short-term growth in children with allergic rhinitis treated with oral antihistamine, depot and intranasal glucocorticosteroids. Acta Paediatr. 1993;82:635–40.
46. Boner AL. Effects of intranasal corticosteroids on the hypothalamic-pituitary-adrenal axis in children. J Allergy Clin Immunol. 2001;108:S32–9.
47. Skoner DP, Gentile D, Angelini B, Kane R, Birdsall D, Banerji D. The effects of intranasal triamcinolone acetonide and intranasal fluticasone propionate on short-term bone growth and HPA axis in children with allergic rhinitis. Ann Allergy Asthma Immunol. 2003;90:56–62.
48. Bachert C, Lukat KF, Lange B. Effect of intranasal fluticasone propionate and triamcinolone acetonide on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity in healthy volunteers. Clin Exp Allergy. 2004;34:85–90.
49. Skoner DP, Gentile DA, Doyle WJ. Effect on growth of long-term treatment with intranasal triamcinolone acetonide aqueous in children with allergic rhinitis. Ann Allergy Asthma Immunol. 2008;101:431–6.
50. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics. 2000;105:E22.

51. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. Clin Otolaryngol Allied Sci. 1998;23:69–73.
52. Giger R, Pasche P, Cheseaux C, et al. Comparison of once- versus twice-daily use of beclomethasone dipropionate aqueous nasal spray in the treatment of allergic and non-allergic chronic rhinosinusitis. Eur Arch Otorhinolaryngol. 2003;260:135–40.
53. Lindqvist N, Balle VH, Karma P, et al. Long-term safety and efficacy of budesonide nasal aerosol in perennial rhinitis. A 12-month multicentre study. Allergy. 1986;41:179–86.
54. Mygind N, Sorensen H, Pedersen CB. The nasal mucosa during long-term treatment with beclomethasone dipropionate aerosol. A light-and scanning electron microscopic study of nasal polyps. Acta Otolaryngol. 1978;85:437–43.
55. Sachanandani NS, Piccirillo JF, Kramper MA, Thawley SE, Vlahiotis A. The effect of nasally administered budesonide respules on adrenal cortex function in patients with chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2009;135:303–7.
56. Welch KC, Thaler ER, Doghramji LL, Palmer JN, Chiu AG. The effects of serum and urinary cortisol levels of topical intranasal irrigations with budesonide added to saline in patients with recurrent polyposis after endoscopic sinus surgery. Am J Rhinol Allergy. 2010;24:26–8.
57. Righini CA, Bing F, Bessou P, Boubagra K, Reyt E. An acute ischemic stroke secondary to sphenoid sinusitis. Ear Nose Throat J. 2009;88:E23–8.
58. Bashkaran K, Shatriah I, Zunaina E, Bakiah S, Sakinah Z. Pansinusitis causing bilateral optic neuritis in a 9-year-old child. Orbit. 2009;28:377–9.
59. Martinez-Devesa P, Patiar S. Oral steroids for nasal polyps. Cochrane Database Syst Rev. 2011;(7):CD005232.
60. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. J Allergy Clin Immunol. 2010;125:1069.e4–76.
61. Hissaria P, Smith W, Wormald PJ, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. J Allergy Clin Immunol. 2006;118:128–33.
62. Alobid I, Benitez P, Pujols L, et al. Severe nasal polyposis and its impact on quality of life. The effect of a short course of oral steroids followed by long-term intranasal steroid treatment. Rhinology. 2006;44:8–13.
63. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. Ann Intern Med. 2011;154:293–302.
64. Lal D, Hwang PH. Oral corticosteroid therapy in chronic rhinosinusitis without polyposis: a systematic review. Int Forum Allergy Rhinol. 2011;1:136–43.
65. Saline sinus rinse recipe. American Academy of Allergy, Asthma, and Immunology. http://www.aaaai.org/conditions-and-treatments/Treatments/Saline-Sinus-Rinse-Recipe.aspx. Accessed 22 June 2012.
66. Rabago D, Zgierska A, Mundt M, Barrett B, Bobula J, Maberry R. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. J Fam Pract. 2002;51:1049–55.
67. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev. 2007;(3):CD006394.
68. Wabnitz DA, Wormald PJ. A blinded, randomized, controlled study on the effect of buffered 0.9% and 3% sodium chloride intranasal sprays on ciliary beat frequency. Laryngoscope. 2005;115:803–5.
69. Suslu N, Bajin MD, Suslu AE, Ogretmenoglu O. Effects of buffered 2.3 %, buffered 0.9 %, and non-buffered 0.9 % irrigation solutions on nasal mucosa after septoplasty. Eur Arch Otorhinolaryngol. 2009;266:685–9.
70. Lewenza S, Charron-Mazenod L, Cho JJ, Mechor B. Identification of bacterial contaminants in sinus irrigation bottles from chronic rhinosinusitis patients. J Otolaryngol Head Neck Surg. 2010;39:458–63.
71. Lee JM, Nayak JV, Doghramji LL, Welch KC, Chiu AG. Assessing the risk of irrigation bottle and fluid contamination after endoscopic sinus surgery. Am J Rhinol Allergy. 2010;24:197–9.
72. Welch KC, Cohen MB, Doghramji LL, et al. Clinical correlation between irrigation bottle contamination and clinical outcomes in post-functional endoscopic sinus surgery patients. Am J Rhinol Allergy. 2009;23:401–4.
73. Williams GB, Ross LL, Chandra RK. Are bulb syringe irrigators a potential source of bacterial contamination in chronic rhinosinusitis? Am J Rhinol. 2008;22:399–401.
74. Olson DE, Rasgon BM, Hilsinger Jr RL. Radiographic comparison of three methods for nasal saline irrigation. Laryngoscope. 2002;112:1394–8.
75. Grobler A, Weitzel EK, Buele A, et al. Pre- and postoperative sinus penetration of nasal irrigation. Laryngoscope. 2008;118:2078–81.
76. Wormald PJ, Cain T, Oates L, Hawke L, Wong I. A comparative study of three methods of nasal irrigation. Laryngoscope. 2004;114:2224–7.
77. Foreman A, Jervis-Bardy J, Wormald PJ. Do biofilms contribute to the initiation and recalcitrance of chronic rhinosinusitis? Laryngoscope. 2011;121:1085–91.
78. Galli J, Calo L, Ardito F, et al. Damage to ciliated epithelium in chronic rhinosinusitis: what is the role of bacterial biofilms? Ann Otol Rhinol Laryngol. 2008;117:902–8.
79. Jervis-Bardy J, Wormald PJ. Microbiological outcomes following mupirocin nasal washes for symptomatic, Staphylococcus aureus-positive chronic rhinosinusitis following endoscopic sinus surgery. Int Forum Allergy Rhinol. 2012;2:111–5.
80. Chiu AG, Palmer JN, Woodworth BA, et al. Baby shampoo nasal irrigations for the symptomatic post-functional endoscopic sinus surgery patient. Am J Rhinol. 2008;22:34–7.
81. Weissman JD, Fernandez F, Hwang PH. Xylitol nasal irrigation in the management of chronic rhinosinusitis: a pilot study. Laryngoscope. 2011;121:2468–72.
82. Katsuyama M, Kobayashi Y, Ichikawa H, et al. A novel method to control the balance of skin microflora part 2. A study to assess the effect of a cream containing farnesol and xylitol on atopic dry skin. J Dermatol Sci. 2005;38:207–13.
83. Zhang N, Gevaert P, van Zele T, et al. An update on the impact of Staphylococcus aureus enterotoxins in chronic sinusitis with nasal polyposis. Rhinology. 2005;43:162–8.
84. Raza T, Elsherif HS, Zulianello L, Plouin-Gaudon I, Landis BN, Lacroix JS. Nasal lavage with sodium hypochlorite solution in Staphylococcus aureus persistent rhinosinusitis. Rhinology. 2008;46:15–22.

85. Suh JD, Kennedy DW. Treatment options for chronic rhinosinusitis. Proc Am Thorac Soc. 2011;8:132–40.
86. Friedlander S. Acute rhinosinusitis – does quality of life explain continued rates of antibiotic overusage? Prim Care Respir J. 2012;21:130–1.
87. Lindbaek M. Acute sinusitis: guide to selection of antibacterial therapy. Drugs. 2004;64:805–19.
88. Tamaoki J. The effects of macrolides on inflammatory cells. Chest. 2004;125:41S–50; quiz 51S.
89. Cervin A, Wallwork B, Mackay-Sim A, Coman WB, Greiff L. Effects of long-term clarithromycin treatment on lavage-fluid markers of inflammation in chronic rhinosinusitis. Clin Physiol Funct Imaging. 2009;29:136–42.
90. Cervin A, Wallwork B. Macrolide therapy of chronic rhinosinusitis. Rhinology. 2007;45:259–67.
91. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. 2006;116:189–93.
92. Videler WJ, Badia L, Harvey RJ, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. Allergy. 2011;66:1457–68.
93. Piromchai P, Thanaviratananich S, Laopaiboon M. Systemic antibiotics for chronic rhinosinusitis without nasal polyps in adults. Cochrane Database Syst Rev. 2011;(5):CD008233.
94. Scheinberg PA, Otsuji A. Nebulized antibiotics for the treatment of acute exacerbations of chronic rhinosinusitis. Ear Nose Throat J. 2002;81:648–52.
95. Vaughan WC, Carvalho G. Use of nebulized antibiotics for acute infections in chronic sinusitis. Otolaryngol Head Neck Surg. 2002;127:558–68.
96. Weschta M, Rimek D, Formanek M, Polzehl D, Podbielski A, Riechelmann H. Topical antifungal treatment of chronic rhinosinusitis with nasal polyps: a randomized, double-blind clinical trial. J Allergy Clin Immunol. 2004;113:1122–8.
97. Ponikau JU, Sherris DA, Kern EB. Immunologic response to fungus is not universally associated with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2010;143:607–10.
98. Orlandi RR, Marple BF, Georgelas A, Durtschi D, Barr L. Immunologic response to fungus is not universally associated with rhinosinusitis. Otolaryngol Head Neck Surg. 2009;141:750–6.e1–2.
99. Lal D, Scianna JM, Stankiewicz JA. Efficacy of targeted medical therapy in chronic rhinosinusitis, and predictors of failure. Am J Rhinol Allergy. 2009;23:396–400.
100. Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. Am J Rhinol. 2002;16:303–12.
101. Wawrose SF, Tami TA, Amoils CP. The role of guaifenesin in the treatment of sinonasal disease in patients infected with the human immunodeficiency virus (HIV). Laryngoscope. 1992;102:1225–8.
102. Stevenson DD, Simon RA. Selection of patients for aspirin desensitization treatment. J Allergy Clin Immunol. 2006;118:801–4.
103. Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. Cochrane Database Syst Rev. 2006;(3):CD004458.
104. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. Laryngoscope. 2004;114:923–30.
105. Otten FW, Grote JJ. Treatment of chronic maxillary sinusitis in children. Int J Pediatr Otorhinolaryngol. 1988;15:269–78.
106. Otten HW, Antvelink JB, Ruyter de Wildt H, Rietema SJ, Siemelink RJ, Hordijk GJ. Is antibiotic treatment of chronic sinusitis effective in children? Clin Otolaryngol Allied Sci. 1994;19:215–7.
107. Ratner PH, Meltzer EO, Teper A. Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis. Int J Pediatr Otorhinolaryngol. 2009;73:651–7.
108. Maspero JF, Rosenblut A, Finn Jr A, Lim J, Wu W, Philpot E. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. Otolaryngol Head Neck Surg. 2008;138:30–7.
109. Ozturk F, Bakirtas A, Ileri F, Turktas I. Efficacy and tolerability of systemic methylprednisolone in children and adolescents with chronic rhinosinusitis: a double-blind, placebo-controlled randomized trial. J Allergy Clin Immunol. 2011;128:348–52.
110. Wei JL, Sykes KJ, Johnson P, He J, Mayo MS. Safety and efficacy of once-daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. Laryngoscope. 2011;121:1989–2000.

Chapter 21
Sinus Surgical Techniques from Caldwell-Luc to MIST

Peter J. Catalano, Rahul C. Gupta, Meir Warman, and Rohan C. Wijewickrama

Introduction

Many nasal surgical procedures have been depicted in the ancient Egyptian and Hindu medical texts dating back to 700 BC. While paranasal sinus diseases have been known to humanity since ancient times, inferences of infection of the sinuses are in the literature of Hippocrates' era (460–370 BC):

> In a person having a painful spot in the head, with intense headaches, pus or fluid running from the nose removes the disease. [1]

Hippocrates also documented medical afflictions related to nasal polyps and sinusitis. He described a "sponge method" for removal of nasal polyps which was later practiced and published by Voltolini in the 1800s [2].

In 1651, Nathaniel Highmore provided the first descriptions of involvement of the maxillary sinus with infections of dental origin. He reported surgical decompression of maxillary sinus suppuration by introducing a silver bodkin through an empty tooth socket [3]. Many external and intranasal methods of surgical treatment of maxillary sinus infections were later described including:

1. Molar tooth extraction and irrigation—Cowper (1707) and Meibomius (1718)
2. Canine fossa approach—Lamorier (1743) and Desault (1798)

Surgical procedures for drainage of frontal sinus infections also evolved over the past two centuries. These procedures were associated with high morbidity and mortality secondary to intracranial or orbital damage along with high re-stenosis and recurrence risks. These frontal sinus procedures include:

1. Anterior frontal sinus wall trephination—Ogston (1884) and Luc (1896)
2. Anterior and inferior wall sinus collapse—Riedel (1898) and Killian (1903)
3. Intranasal frontal sinus drainage—Halle (1907), Goode (1908), and Ingals (1909)
4. Anterior frontal floor, intersinus septum, and superior nasal septum open resection following ethmoidectomy—Lothrop (1914)
5. Osteoplastic flap procedures with or without obliteration—Montgomery (1950s)

During the following two centuries (preceding the discovery of antibiotics), surgical evacuation and drainage of infection was the mainstay of treatment for infections of the sinuses. Although understanding of the importance of the middle meatus was further advanced by the work of Emil Zuckerkandl in the nineteenth century, concurrent developments took place in surgical management of sinus disease in several areas of the world and help lay the foundation for significant advancement over the following two centuries.

P.J. Catalano, MD, FACS, FARS (✉) • R.C. Gupta, MD • M. Warman, MD • R.C. Wijewickrama MD
Department of Otolaryngology, St. Elizabeth's Medical Center, Tufts University School of Medicine, 736 Cambridge Street, Boston, MA 02135, USA
e-mail: peter.catalano@steward.org; dr.rahulgupta@gmail.com; warman_m@yahoo.com; meirwarma@gmail.com; rohan.wijewickrama@tufts.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_21,

Caldwell-Luc

In 1893 George Caldwell (United States) described his technique aimed at improving the treatment for infection of the maxillary sinus. He wrote:

> Make a large temporary opening in the canine fossa, through which the antrum is thoroughly explored, all deleterious material removed, and the antrum thoroughly cleansed. A large counter opening is then made into the inferior meatus and the primary opening closed. [4]

Similar techniques were later published by Spicer (England) in 1894 and Luc (France) in 1897 [5, 6]. The Caldwell-Luc procedure subsequently gained significant support throughout the world and remained the mainstay of surgical management for nearly a century as depicted by Macbeth:

> Under the heading of conservative measures would be antibiotic and antihistaminic treatment, nasal soaks, suction displacements, and repeated direct lavage. If after all this the symptoms are unimproved or continue to relapse, and if the x-ray films continue to show mucosal thickening, the right thing to do is a Caldwell-Luc operation. [7]

Macbeth's former quotation represents the mainstream thought process of the mid-twentieth century and provided generations of otolaryngologists with dogmatic management strategies for disease processes of the maxillary sinuses. Although previously published indications for the Caldwell-Luc procedure were quite extensive in the pre-endoscopic era [8], the indications for this open approach at the time of this writing are few. The procedure remains in the armamentarium of the rhinologic surgeon primarily for the need for endoscopic-assisted access or instrumentation beyond the scope of that afforded by endonasal exposure (i.e., antrum, orbit, pterygomaxillary space). However, this technique has no role in the management of chronic rhinosinusitis.

Current Indications

1. Endoscopic-assisted access to antrum, orbit, pterygomaxillary space, lateral maxilla
2. Debridement of maxillary osteomyelitis or osteoradionecrosis

Contraindications for Caldwell-Luc

1. Malignancy of the maxillary sinus

Technique

The transbuccal radical antrostomy is performed by incising the mucosa at the gingivolabial fold below the canine fossa and elevating the soft tissue in a subperiosteal plane off the anterior face of the maxilla (Fig. 21.1). Bone overlying the antrum of the maxilla is then removed (using drill, rongeur, or osteotome/chisel) providing access to remove the necessary components of the sinus and/or maxilla (Figs. 21.2 and 21.3). Intranasal inferior antrostomy is performed to provide dependent drainage and access for irrigation (Figs. 21.4, 21.5, 21.6, and 21.7).

Outcomes of Caldwell-Luc Operation

Single-institution experiences with this technique have been published detailing multiple-associated morbidities of the Caldwell-Luc procedure. Several pioneers in sinonasal surgery including Cottle (1966) and Horowitz (1967) reported use of an osteoplastic flap in attempts to help reduce the comorbidities of the procedure [11, 12]. However, similar paresthesias resulted likely from placement of an inferior antrostomy in the maxilla.

The largest collection of single-institutional data on the Caldwell-Luc procedure was reported by Defreitas in 1988 which reported a sinusitis recurrence rate of 17 % and identified the following postoperative comorbidities (in descending order):

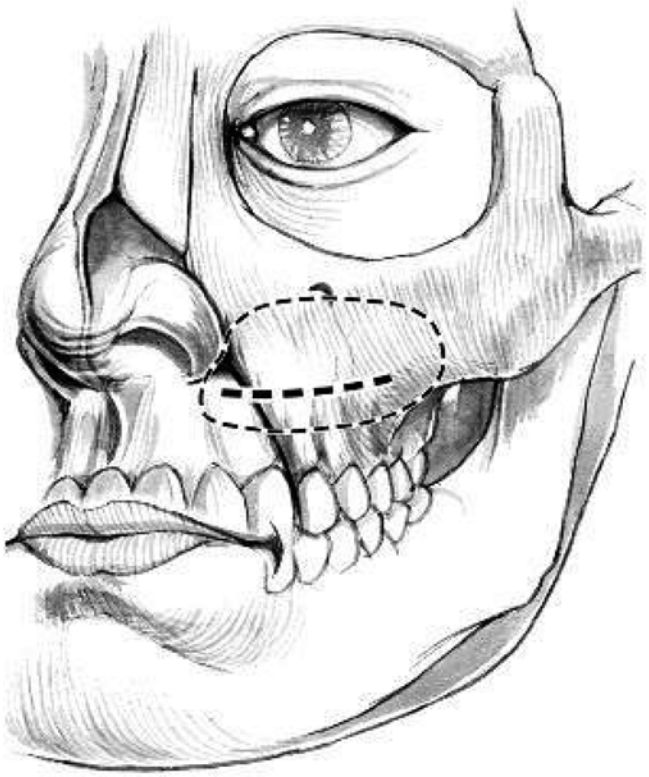


Fig. 21.1 Extent of periosteal elevation; bound by the infraorbital nerve superiorly and the lateral buttress (Reprinted from Kim and Duncavage [9]. With permission from Elsevier)

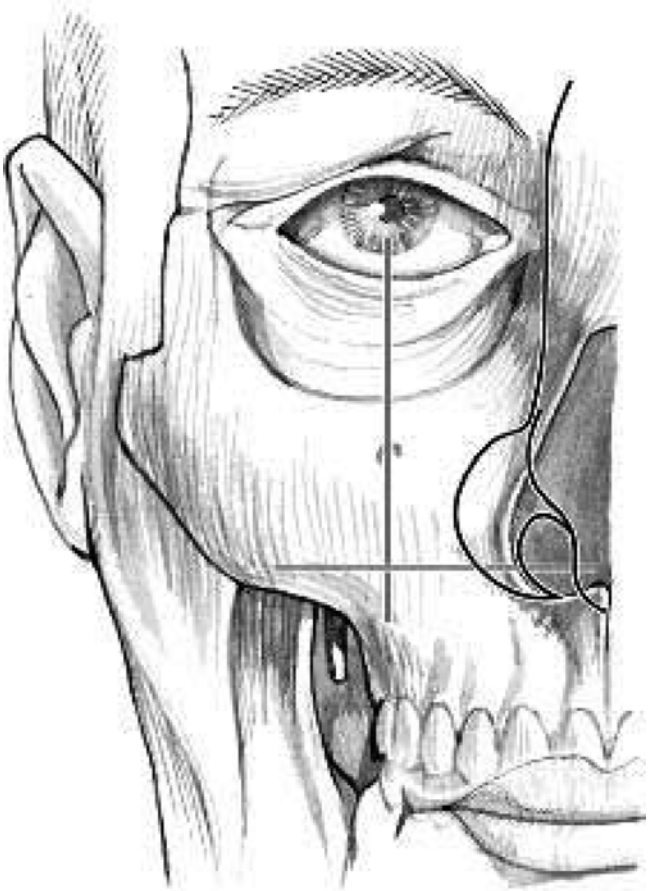


Fig. 21.2 Landmark for the trocar placement; intersection of the midpupillary line with a horizontal line drawn from the alar base (Reprinted from Kim and Duncavage [9]. With permission from Elsevier)

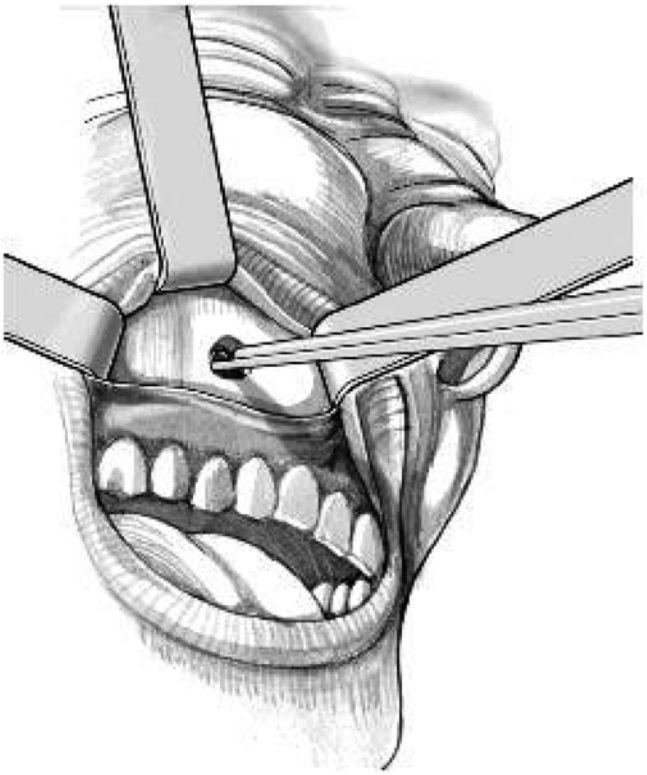


Fig. 21.3 A 3-mm Kerrison rongeur is used to remove bone from the anterior maxilla (Reprinted from Kim and Duncavage [9]. With permission from Elsevier)

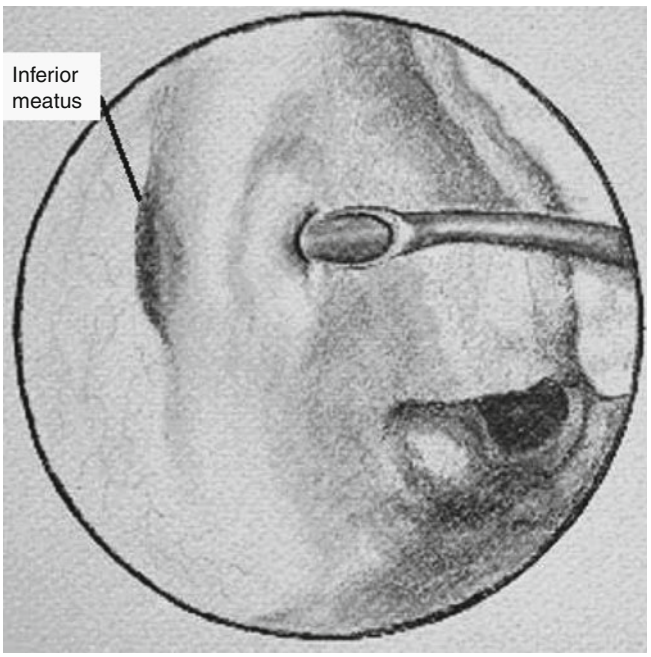


Fig. 21.4 Location of antrostomy (drawing) (Reprinted from Moeller and Stankiewicz [10]. With permission from Elsevier)

immediate postoperative facial edema, cheek discomfort, fever, and epistaxis [13]. Six-year average follow-up demonstrated the most common long-term sequelae as recurrent sinusitis (12 %), facial paresthesia (9 %), recurrent polyps (5 %), and dacryocystitis (2.6 %). Sensation of facial numbness/pain results from injuries to the intricate branches of the infraorbital nerve and/or anterior superior alveolar nerve (Fig. 21.8).

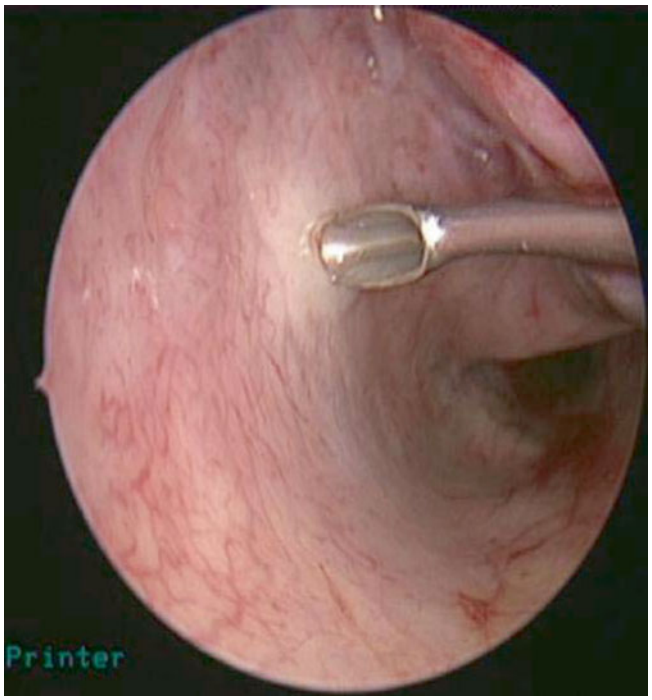


Fig. 21.5 Location of antrostomy (endoscopy) (Reprinted from Moeller and Stankiewicz [10]. With permission from Elsevier)

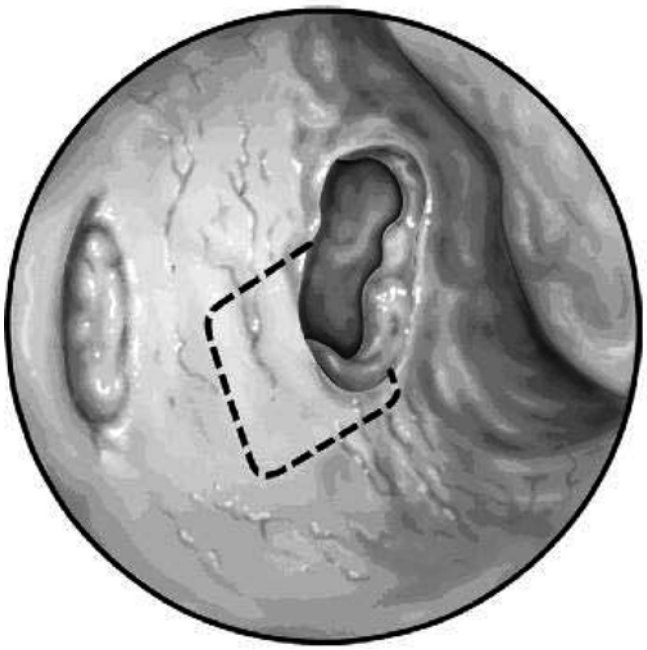


Fig. 21.6 Completed antrostomy Illustration (Reprinted from Moeller and Stankiewicz [10]. With permission from Elsevier)

Modifications to Caldwell-Luc Operation

Several modifications to the Caldwell-Luc procedure were reported with the aim of reducing associated comorbidity. Published techniques have detailed methods of minimizing trauma to the anterior maxilla through "careful entrance" using

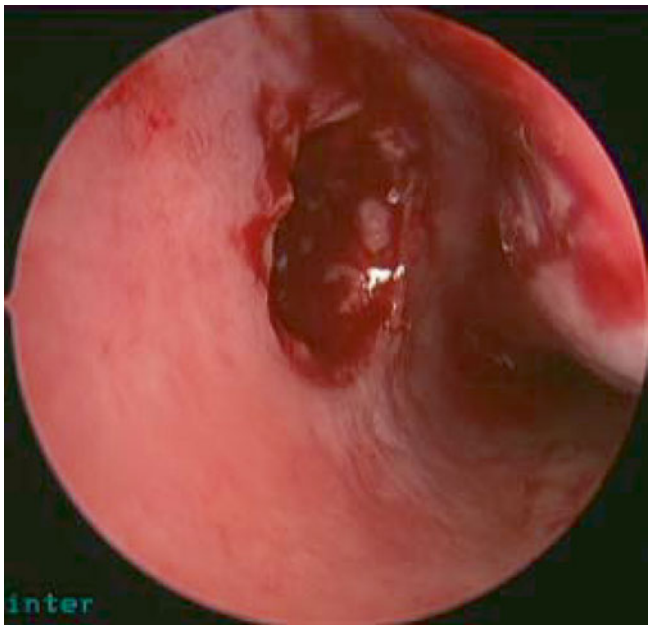
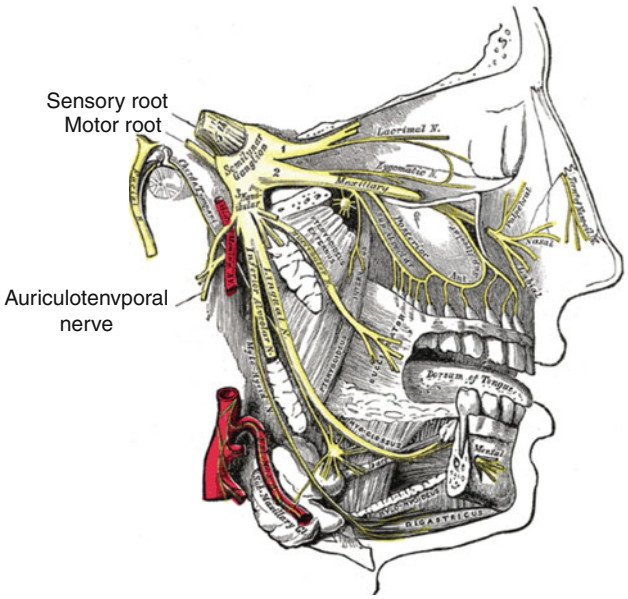


Fig. 21.7 Completed antrostomy (Reprinted from Moeller and Stankiewicz [10]. With permission from Elsevier)

Fig. 21.8 Distribution of the second branch of the trigeminal nerve (V2) (Reprinted from the *Gray's Anatomy* (On-line), 20th edition. With permission from Bartleby.com, Inc.)



a trocar and Kerrison rongeur for open transbuccal access to the maxillary antrum [14]. However, all conclusions reported in this study were based largely on opinion (EBM Level VI data) without controlled evidence. Reports of open access without inferior antrostomy have been suggested along with many studies attempting to identify the "ideal" size and location of inferior antrostomy [15]. An endoscopic Caldwell-Luc procedure was also reported by Masterson et al. claiming to further reduce morbidity [16]. Despite these modifications, advances during the past decade have demonstrated significant improvement in recurrence rates of patients with chronic rhinosinusitis using the endonasal endoscopic approach refuting the need for more radical open surgery of the maxillary sinus with rare exception.

The Caldwell-Luc procedure of more than a century ago served to provide some relief for patients based on the scientific knowledge, means of visualization, and sinus instrumentation of that time. During the 1990s rise of the endoscopic era, the Caldwell-Luc operation with mucosal exenteration was recommended as a salvage treatment for patients who had failed all other medical or surgical options to rid patients of "irreversible mucosal disease" [17]. However, long-term outcome studies of patients who underwent Caldwell-Luc operations demonstrated large numbers of patients requiring revision surgery. In

contrast to the high recurrence rate of the Defreitas study, Albu reviewed 400 patients undergoing endoscopic sinus surgery and identified only 6.8 % recurrence [18]. Further, JK Han et al. eloquently demonstrated that patients who failed the Caldwell-Luc operation did equally as well following endoscopic sinus surgery as with a repeat Caldwell-Luc [19].

The Evolution from Caldwell-Luc to the Endoscopic Era

The Caldwell-Luc procedure was extensively debated during the twentieth century and decreased in popularity with improved understanding of the functional significance of the natural maxillary ostium. Further teachings of E.B. Kern and others helped foster concepts of mucosal preservation due to its key role as "the organ of the nose." Many authors published their "indications" for Caldwell-Luc throughout the twentieth century, which were largely based on individual experience and single-institution cohorts [7, 8]. During the past two decades, however, indications for the Caldwell-Luc procedure have been dramatically reduced with advancements in less morbid endonasal endoscopic techniques. The Caldwell-Luc procedure remains significant in understanding the history and development of rhinologic surgery, however has limited clinical application in the present-day surgical management of sinonasal disease.

Despite popularization of the Caldwell-Luc technique as it became known throughout the early twentieth century, Messerklinger (Austria) continued to explore the observations of Zukerkandl using rigid endoscopic examination allowing identification of the predestined course of mucociliary clearance of the maxillary sinus contents through the natural ostium. Stammberger communicated Messerklinger's findings to the English medical literature at the end of the twentieth century introducing "functional endoscopic sinus surgery" which was associated with a paradigm shift in the surgical management of disease of the sinuses to focus management to the middle meatus [20]. The principles of predetermined mucociliary flow to a respective "natural" ostium serve as the basis for the present-day concepts in management of diseases of the paranasal sinuses.

Hirschmann is stated to be the first to attempt nasal endoscopy in 1901 using a modified Nitze cystoscope [21]. Later, Maltz coined the term sinuscopy and described techniques of maxillary sinus endoscopy through inferior meatus and canine fossa routes [22]. The Hopkins optic telescope rod was a significant development in the mid- twentieth century which brought in the modern era of sinus surgery [23]. More recently, there have been technological advances in endoscopic visualization and instrumentation with comparable pace in development of better diagnostic imaging techniques beyond a simple X-ray.

Advancements in technology including angled endoscopes and handheld and powered instrumentation along with image-guidance navigation resulted in a transition to less invasive techniques including endonasal methods for orbital decompression, epistaxis management, and access to the pterygomaxillary space [24]. This further decreased the need for inpatient hospitalization following surgery, reduced associated morbidity, and opened the door for development of minimally invasive techniques for management of diseases of the paranasal sinuses and beyond.

Functional Endoscopic Sinus Surgery (FESS)

Concept of FESS: Two Important Principles

Anatomic obstruction of the lateral nasal wall within the narrow clefts of the ethmoid hinders the physiologic function of the maxillary and frontal sinuses, thereby predisposing patients to recurrent infections. Secondly, relief of anterior ethmoidal obstruction provides ventilation and drainage for the peripheral sinuses to heal without direct surgical intervention on the latter [17, 25]. These two principles have been well studied over the past three decades demonstrating improved clinical response [26, 27].

Indications

FESS was introduced as a surgical technique for treatment of refractory rhinosinusitis with or without polyposis which fails to improve with antibiotics, nasal steroid sprays, or nasal decongestants. The applications of endoscopic sinus surgery (ESS)

were later extended to cover a wide range of conditions listed below which are treatable via an endonasal approach as detailed in the following chapters.

Inflammatory

- Chronic rhinosinusitis
- Recurrent acute rhinosinusitis
- Complications of rhinosinusitis
- Sinonasal polyposis
- Mucoceles
- Allergic fungal sinusitis and mycetoma invasive/non invasive
- Dacryocystitis

Noninflammatory/Others

- Septal deviation and hypertrophy of turbinates
- Choanal atresia
- Orbital blow out fractures
- Foreign body removal
- CSF leaks and anterior skull base meningoencephaloceles
- Tumors
- Pituitary surgery
- Extended application to skull base and orbit

In both chronic rhinosinusitis and recurrent acute sinusitis, FESS is considered to provide a functional conservative approach to relieve the obstructing anatomy and reverse the altered physiology of the paranasal sinuses. Bone and tissue removal should be dependent on the extent of the disease process and FESS provides a significantly less morbid alternative to prior surgical procedures entailing an open approach.

Contraindications

There are no absolute contraindications for FESS. However, the decision for external, endoscopic, or combined approach lies on the surgeon's preference based on training/experience and patient factors. Combining endoscopy with an external approach was appropriate during the "transition years" from open to endoscopic surgery by helping to minimize trauma by providing better visualization and reducing complications.

Preoperative Evaluation

Assessment of patients undergoing endoscopic sinus surgery include a complete history (including environmental allergies, occupation, prior nasal injury), physical examination (including anterior rhinoscopy, 0° and 30° nasal endoscopy), and computed tomography (CT) imaging (Fig. 21.9). Additional assessments include allergy evaluation (i.e., intradermal skin testing, RAST), immunologic testing to identify subclass deficiency, and possibly smell testing if clinically warranted.

Diagnosis: History and Examination

A detailed clinical history with review of specific symptoms related to CRS is an important first step toward the diagnosis of CRS. Review of prior history including medical therapy and surgeries is imperative to determine the need for surgery.

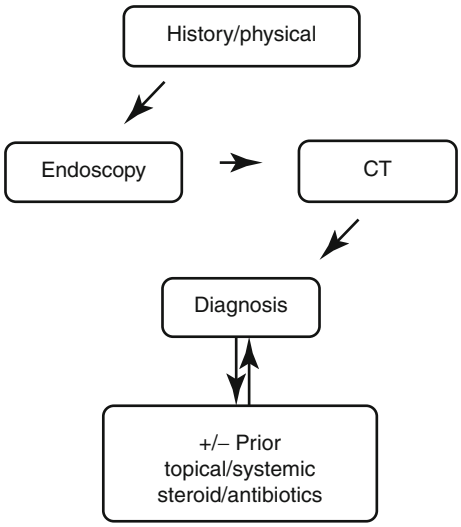


Fig. 21.9 Preoperative evaluation

Table 21.1 RSTF diagnosis of rhinosinusitis

Major	Minor
Facial pain/pressure	Headache
Nasal obstruction/blockage	Fever (nonacute)
Facial congestion/fullness	Halitosis
Nasal discharge/purulence	Dental pain
Altered sense of smell	Cough
Purulence in nasal cavity on examination	Fatigue
Fever (acute rhinosinusitis)	Ear pain/pressure/fullness

A history of other related conditions including aspirin sensitivity, asthma, allergic rhinitis, polyps, rhinitis medicamentosa, cystic fibrosis, and immunocompromised status is obtained. Patients with CRS present to multiple medical providers including primary care, pulmonary medicine, and allergy/immunology. All such patients require a complete head and neck examination by an otolaryngologist including nasal endoscopy to support the appropriate confirmatory imaging to diagnose/define the extent of disease and demonstrate relevant anatomy.

In 1997, the Rhinosinusitis Task Force (RSTF) established definitions and guidelines for the diagnosis of rhinosinusitis [28]. Major and minor criteria were established to better define the key symptoms of rhinosinusitis (Table 21.1). Chronic rhinosinusitis was defined as the presence of two or more major findings or one major and two or more minor findings lasting longer than 12 weeks.

The European Position Paper on Rhinosinusitis and Nasal Polyps proposed the criteria for diagnosis of "chronic rhinosinusitis" in adults as 12 or more weeks of persistent symptoms and signs with no complete resolution [29]. Rhinosinusitis (including nasal polyps) is defined as inflammation of the nose and the sinuses characterized by two or more of the following symptoms:

- Blockage/obstruction/congestion
- Discharge—anterior/posterior (discolored)
- Facial pain/pressure
- Reduction or loss of smell
- Plus either:
- Endoscopic signs of:
  - Polyps
  - Mucopurulent discharge from middle meatus
  - Or edema/mucosal obstruction primarily in middle meatus

And/or:

- Computed tomography (CT) changes—mucosal changes within osteomeatal complex and/or sinuses

Medical Therapy

With the diverse pathophysiology and microbiology involved in CRS, medical treatment can involve multiple options including:

- Allergen and/or irritant avoidance
- Sinonasal saline irrigations
- Antihistamines
- Corticosteroids—oral/topical
- Decongestants—oral/topical
- Antibiotics—oral/topical
- Antifungals—oral/topical
- Antileukotrienes—oral
- Immune therapy—intravenous/sublingual
- Other therapies

Macrolide Therapy

The role of antibiotics is questionable in the absence of purulence. However, macrolides have demonstrated immunomodulatory effects in refractory CRS distinct from their antimicrobial properties. Given in low doses for a minimum of 6 months, they have been found to downregulate the excessive immune and inflammatory responses observed in refractory CRS patients while promoting mucociliary clearance and tissue repair and improving quality of life [30].

Intranasal Corticosteroids

Topical corticosteroids have a proven therapeutic effect on the symptoms of nasal polyposis and may reduce one of the underlying causes of polyps, namely, mucosal inflammation. Most patients respond well to topical corticosteroid treatment of their nasal polyps and consequently can reduce the need for repeat surgery. The efficacy of topical corticosteroids such as betamethasone sodium phosphate nose drops, beclomethasone dipropionate, fluticasone propionate, and budesonide nasal sprays in reducing polyp size and rhinitis symptoms has been demonstrated in several randomized placebo-controlled trials. Beclomethasone dipropionate, flunisolide and budesonide sprays have also been shown to delay the recurrence of polyps after surgery [31]. Incorporating intranasal steroids such as budesonide in the nasal irrigation solutions has demonstrated remarkable efficacy postoperatively in patients with chronic sinusitis with minimal systemic absorption [32, 33].

Anesthesia for FESS

Functional endoscopic sinus surgery has been performed under both local and general anesthesia depending on the patient factors, procedure duration, experience of the surgeon/anesthesiologist, and extent of sinonasal disease. Excellent results can be achieved with both techniques. Communication during the procedure allows the patient to inform the surgeon of increased pain thereby reducing the risk of potential injury or complication. Although many of the early FESS cases were performed under local anesthesia (associated with reduced bleeding), anesthetic improvements have resulted in a transition away from local anesthesia for FESS [34, 35].

Local Versus General Anesthesia

In the early days of FESS, an effective topical and regional anesthetic technique was described using 25 % cocaine paste combined with IV midazolam reporting excellent intraoperative visualization and minimal patient discomfort. Patients recovered rapidly from sedation and were usually fit for discharge on the same day without major anesthetic complications. The major surgical complication rate was 0.5 % [36]. Strategies for optimal topical cocaine application to the nose with

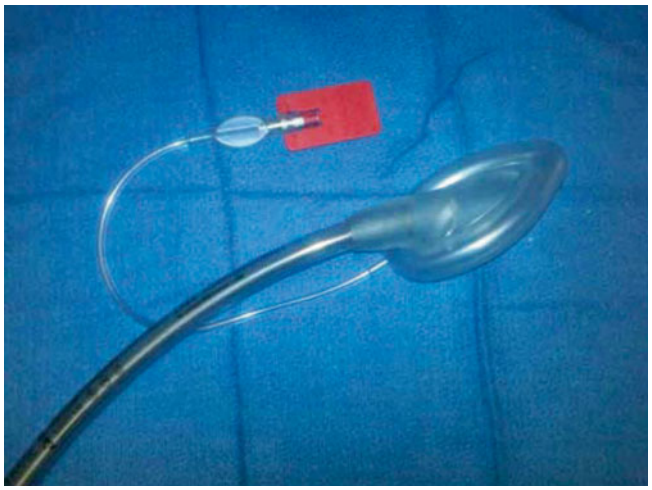


Fig. 21.10 LMA. Delivery of mechanical ventilation

infiltration of anesthetics including lidocaine with vasoconstrictive agents (i.e., epinephrine) have been published, with some reports including the adjunctive use of an intravenous sedative.

Although complex endoscopic procedures have been performed under local anesthesia (including surgery of the frontal sinuses), reports of serious complications including blindness, carotid artery damage, and intracranial violation were published resulting from intraoperative patient movement [37, 38]. The importance of patient comfort and surgeon experience during FESS cannot be overemphasized to ensure an optimal surgical result. The evolution of FESS since the late 1980s has seen advancement in complexity and extent of surgery which sometimes requires increased operative time and can be associated with unexpected bleeding. The latter can be more problematic under local anesthesia due to an unprotected and somewhat anesthetized airway. Given the inherent limitations of local anesthesia coupled with improved safety of general anesthesia techniques, general anesthesia is preferred by both patients and surgeons.

Total Intravenous Anesthesia (TIVA) Versus Inhaled Anesthesia

The role of an experienced anesthesiologist capable in maintaining low mean arterial blood pressure remains paramount in the goal of reducing intraoperative bleeding. Tirelli et al. studied the differences between inhaled anesthesia with isoflurane and fentanyl versus TIVA using propofol and remifentanil. Both techniques were equally effective in achieving hypotension (mean arterial pressure 60–70 mmHg), but only TIVA was effective in reducing bleeding during FESS [39]. Propofol decreases cerebral blood flow while simultaneously decreasing cerebral metabolic rate. This, in effect, reduces arterial blood flow to the autoregulated branches of the internal carotid artery which supply the ethmoid, frontal, and sphenoid sinuses.

Use of inhalational anesthetics including halothane, isoflurane, and sevoflurane in combination with nitrous oxide provide both anesthetic and analgesic effects. However, these agents require deeper levels of anesthesia not necessary for endonasal endoscopic procedures. Additionally, these agents can be associated with significant perioperative side effects including cardiac dysrhythmia, laryngospasm, and malignant hyperthermia.

Multiple regimens have been reported to provide optimal intraoperative visualization by providing intraoperative hypotension. TIVA does not affect the prearteriolar muscle tone or the precapillary sphincter thereby preventing the vasodilatory effects of inhaled agents [40]. The use of propofol and remifentanil further provides moderately controlled hypotension in most patients without the administration of additional antihypertensive agents required with traditional inhaled anesthetics [41–43].

The need to achieve and maintain controlled hypotension resulted in a transition away from inhalational anesthetics, thereby providing surgeons with dramatic improvement in intraoperative visualization. To attain this optimal condition in the same-day surgery patient, techniques were developed for efficient induction, controlled maintenance, and timely emergence with minimal postoperative ailments (i.e., nausea/vomiting). A comparison study of 1,460 patients who underwent endoscopic sinonasal surgery (1987–2001) found TIVA with oxygen-enriched air through a laryngeal mask airway (LMA-Fig. 21.10) to be the ideal anesthetic regimen [44].

Compared to conventional use of endotracheal tube intubation (ETT), the LMA provides distinctive advantages including easier placement and reduced cardiovascular or respiratory response from the lack of direct laryngeal stimulation and is

Table 21.2 Potential complications following ESS

Major	Minor
Intracranial injury or bleeding	Synechia/adhesions
Cerebrospinal fluid leak	Ostial stenosis
Persistent diplopia	Minor hemorrhage
Blindness	Periorbital ecchymosis
Carotid artery injury	Orbital emphysema
Orbital hematoma	Transient diplopia
Severe hemorrhage	Tooth numbness and pain
Meningitis and brain abscess	Nasolacrimal duct injury
Pneumocephalus	Olfactory disturbances
	Headache/facial/dental pain

becoming a new standard of practice to provide better and faster patient recovery after FESS. This is most important in the asthmatic patient which accounts for a significant percentage of all patients undergoing ESS. Atef and Farwaz demonstrated improved intraoperative conditions using flexible LMA compared to ETT during functional endoscopic sinus surgery, reflected by a shorter time to achieve controlled hypotension with propofol-remifentanil TIVA and lower infusion rate/total dose of remifentanil [45]. The improved operative field was measured by both visual scale scores and decreased blood loss. Lower doses of TIVA with LMA allow precise titration of emergence upon completion of surgery and incidence of blood pressure elevation due to coughing after LMA device removal is significantly decreased in comparison to tracheal extubation. LMA further reduces the risk of supraglottic pooling of fluids intraoperatively thereby reducing obstructive complications during anesthetic emergence [46].

Patient Preparation and Positioning

Preparation and positioning of patients undergoing ESS is focused on the prevention of perioperative bleeding. This includes advising patients to refrain from medications containing aspirin, nonsteroidal anti-inflammatory agents (i.e., ibuprofen), or supplements (i.e., fish oil, gingko, etc.) known to affect coagulation. Vasoconstrictive medications including oxymetazoline 0.05 %, phenylephrine (0.25–1 %), epinephrine 1:1,000, and topical cocaine are administered via nasal spray, cotton carriers, or pledgets prior to surgery via a number of published regimens.

Lidocaine with epinephrine infiltration of the anterior insertion of middle turbinate, sphenopalatine orifice, and the sphenoid face below the level of ostium provides additional vasoconstrictive and analgesic effect. Although systemic absorption of locally injected vasoconstrictive agents occurs, adrenaline-related side effects during FESS are rare with appropriate patient monitoring [47].

Optimal patient positioning with 15° head of bed elevation and reverse Trendelenburg position ("beach chair position") improves venous return to minimize intraoperative bleeding. In addition this positioning decreases the likelihood of inadvertent intracranial penetration. In addition to meticulous surgical skills with thorough understanding of each patient's anatomic variations, these methods for reducing intra- and postoperative bleeding help to provide optimal intraoperative visualization for achieving a successful operation.

Steroids decrease capillary endothelial permeability which reduces mucosal edema. Dexamethasone is frequently administered as a single dose intraoperatively due to its anti-inflammatory potency providing a 25 times greater effect than hydrocortisone with a long half-life of 36–72 h. In addition, a single postoperative long-acting steroid can be administered which further reduces mucosal inflammation and tissue edema during the early phases of healing. Caution is required with steroid use in patients with diabetes and the pediatric population.

Surgery: Surgical Techniques and Instrumentation

The basic concepts of functional endoscopic sinus surgery were established when Messerklinger proposed the functional theory of sinus disease. Using endoscopy, provided insights to understand mucociliary clearance pathways within the sinuses and changes in the osteomeatal complex (OMC) with simultaneous CT evaluation of the ethmoid sinuses [25]. He delineated definite routes for the drainage of secretions toward the respective sinus ostia. This reinforced the importance of mucosal preservation and more targeted surgery focusing on the osteomeatal complex with emphasis on mucosal edema and obstructive anatomic variations. While the details of FESS and its potential complications (Table 21.2) are detailed in other chapters,

the development of the procedure provided CRS patients and surgeons with an alternative to the morbidity of the Caldwell-Luc technique.

Minimally Invasive Sinus Technique (MIST)

Preface

Since the advent of FESS, the success rate of treating patients with CRS has been substantially high with decreased morbidity as compared to previous open approaches. However, a significant drawback of FESS is the lack of standardization. There is no description of a stepwise procedure detailing anatomic progression or defined endpoints which has resulted in significant variation in the aggressiveness and extent of surgery and often misleads and confuses both surgeons and patients alike. Moreover in certain endoscopic sinus procedures, functional outcome can be seriously debated when overly aggressive techniques (i.e., middle turbinectomy) are employed or a large maxillary antrostomy is created with or without the presence of a preserved uncinate process.

When questioning such "functional" results of sinus surgery, Messerklinger's basic concepts of sinus physiology and the functional theories of Messerklinger that lead to the establishment of FESS as the initial surgical intervention for the medically refractory sinonasal diseases must be reviewed. Unfortunately, many surgeons consider a transnasal sinus procedure performed with an endoscope as "FESS" when in reality what is done to the nose is anything but functional! Thus, there is a significant distinction between minimal access surgery and minimally invasive surgery, and it is unfortunate that many surgeons and patients are unaware of this difference.

MIST: Embodiment of the "Functional" Concept

One of the first concepts of FESS, suggested by Messerklinger, is the transition space theory [25]. It was shown that the maxillary, frontal, and anterior ethmoid sinuses do not drain directly to the nasal cavity but drain into narrowed mucosal-lined corridors which subsequently empty into the nasal cavity [48]. Messerklinger referred to these channels as "prechambers" and Setliff later renamed them "transition spaces" to reflect the fact that they were conduits of activity. Mucus flows through these transition spaces from the larger sinuses via their respective ostia via mucociliary transport. In disease states, mucosal swelling and contact between opposing mucosal surfaces may disrupt mucociliary clearance causing retention of secretions and consequent sinus inflammation. These transition spaces are named the ethmoidal infundibulum, retroaggar space or frontal recess area, and the hiatus semilunaris superioris (HSS). Obstruction in these bottleneck areas will result in inflammation of the involved maxillary, frontal, or anterior ethmoid sinuses. The etiologies for mucosal inflammation triggering contact points may include viral, bacterial, and fungal infections, allergens, environmental irritants, primary or secondary ciliary dysfunction, and even anatomic abnormalities.

The theory that transition spaces are the key areas for the development of maxillary, frontal, and anterior ethmoid sinusitis is further supported by clinical symptoms, and the majority of mucosal disease seen on CT imaging is limited to the anterior sinuses. It is commonly thought that the posterior ethmoid and sphenoid sinuses do not drain into transition spaces but rather into the nasal cavity. MIST offers a standardized intranasal procedure to address the transition spaces via a stepwise anatomic dissection based on progression of surgery with a defined beginning and end. An anatomic landmark is associated with each transition space and identified first as the transition space is then approached. The primary goal is minimal mucosal disruption without unnecessary manipulation of the natural ostia of the sinuses.

Mucosal Disease in Chronic Rhinosinusitis

The inflammatory mucosa of the paranasal sinuses is reversible. Previously, all diseased sinus mucosa was thought to be irreversible, and therefore the sinus needed to be stripped to bare bone. Studies later showed that FESS can improve mucociliary clearance in CRS patients with impaired mucociliary function, thus proving the ability to reverse the sinonasal mucosal disease [49–51]. Moreover, mechanical damage to the fragile pseudostratified respiratory epithelium causes loss of cilia and decreases mucociliary transport. Therefore, the ideal surgical intervention must avoid destruction of cilia and maintain

physiologic mucociliary clearance making the handheld "grasp and tear" instrumentation commonly used with FESS far from ideal for serving this purpose [52].

Powered Instrumentation

The introduction of powered instrumentation in endoscopic sinus surgery coupled with MIST led to a significant breakthrough in truly minimally invasive sinus surgery. The need to preserve healthy mucosa while removing diseased tissue led to a transition from the traditional hand instruments to powered precision tools preventing stripping of healthy mucosa. The introduction of continuous real-time suctioning ability improved operative visibility, decreased instrument exchange, and reduced mucosal trauma, operative time, and potentially operative morbidity. Setliff et al. showed that the powered microdebrider was associated with accelerated healing and reduced synechia formation [53].

Maxillary Antrostomy

Based on the evidence that the maxillary, ethmoid, and frontal sinuses drain into narrow mucosal-lined clefts (transition spaces), the bottleneck areas serve as conduits that subsequently drain into the nasal cavity. Since these transition spaces serve as the predisposing factor for sinus obstruction without distinct pathology of the natural ostia, endoscopic surgery should avoid manipulation of the ostia prior to relieving obstruction of narrow transition space. A study by Albu et al. found no correlation between the size of the middle meatal antrostomy size and severity of postoperative maxillary sinus symptoms when comparing the results of patients who had 6 mm antrostomy ("small hole") versus 16 mm ("large hole") [54]. On the contrary, an association was found between small-sized antrostomies and better functional results than larger antrostomies.

The finding that neither persistent obstruction, facial pain, nor rhinorrhea correlated with small maxillary sinus ostia was further supported by other studies [55, 68]. Moreover, the observation that if the natural maxillary sinus ostium is left undisturbed in its oblique plane (as opposed to the parasagittal plane of a middle meatal antrostomy), the tilt away from the midline protects it from obstruction secondary to middle turbinate lateralization or synechia formation [55]. Relative indications for a large maxillary antrostomy include biopsy of an antral mass, resection of maxillary sinus fungal ball, or inverted papilloma.

Targeted surgery of the transition space regions of the anterior ethmoid and maxillary sinus are the cornerstone to complete recovery of the maxillary antrum and improved functional results in most chronic rhinosinusitis patients. Therefore, routine enlargement of the maxillary sinus ostium is avoided in MIST.

Nitric Oxide

During the last decade, significant data has been published on the role and function of the nitric oxide molecule. Nitric oxide (NO) is a free radical gas implicated in several key physiologic mechanisms in the nose and paranasal sinuses including mucociliary clearance, neurotransmission, and antimicrobial properties. Nitric oxide is produced by an enzyme called nitric oxide synthase (NOS). One isoform, inducible nitric oxide synthase (iNOS), has an important role in acute and chronic sinus diseases. iNOS is expressed in epithelial cells in response to proinflammatory cytokines or bacterial components. This isoform generates large amounts of NO in high concentrations for an extended period of time [56]. In a rabbit model of chronic maxillary sinusitis, Schlosser found that there is an increase in the level of NO metabolites measured in the infected sinus [57]. Whether the decrease preceded and was therefore etiologic to the infection or the result of it is unknown.

In a study by Kirihene et al., the level of NO was measured in the maxillary sinuses of 29 patients after FESS. Fifty-two maxillary ostia were examined: 22 "large" antrostomies (average 57 mm^2) and 30 "small" natural maxillary ostia (average 9 mm^2). In large antrostomies the level of NO was significantly low both in the maxillary sinus itself and in the nasal cavity, as compared with "small" natural maxillary ostia. Minimal evidence is available to prove that patients with large maxillary antrostomies are more prone to recurrent infections due to lowered bactericidal effect of NO. However, NO is significant for maintaining normal mucociliary transport further providing the sinuses with antibacterial properties [58]. Although not completely elucidated as of the time of this writing, increasing evidence is mounting regarding the role of NO in maintaining healthy mucociliary flow and preventing bacterial overgrowth in the paranasal sinuses.

The importance of NO function within the normal maxillary sinus, combined with the finding of decreased levels of NO when large antrostomies are performed further, questions the necessity for routine maxillary antrostomy. The benefit of performing routine middle meatal antrostomy should be scrutinized and does not exceed the potential risks of increased middle meatal scarring, interruption of mucociliary clearance, and the potential for recirculation from failure to include the natural ostium.

Frontal Sinus Surgery

One of the routine steps in MIST is to remove the superior portion of the uncinate at its anterior articulation with the agger nasi cell. The full thickness of the upper uncinate is removed using powered instrumentation and a 30° endoscope. This is a crucial step in the minimally invasive approach to the frontal sinus. Upon removal of the most superior aspect of the uncinate, the mucous membranes of the floor of the agger nasi cell are opened. The agger nasi cell is the anatomic landmark by which the surgeon may approach its associated transition space—the frontal recess area (retro-aggar space). Adequate exposure of the dome of the agger nasi cell can be further employed by removing the anterior wall of the agger nasi cell in its connection with the root of the middle turbinate, using a Kerrison rongeur and a microdebrider. Powered instruments are then used to resect the posterior and medial edges of the agger nasi cell by applying the cutting side of the instrument in a superior and lateral direction. Medial manipulation toward the upper insertion of the middle turbinate increases the risk of cerebrospinal fluid leak. Although frontal recess anatomy may vary between patients, the most common frontal sinus draining pathway is directed posterior and medial to the agger nasi cell [53]. This region is visualized by dissecting the posterior agger nasi wall forward to reveal the hidden frontal recess. If the frontal sinus is completely opacified by CT imaging and the frontal recess is either completely obstructed or aberrant, the "minitrephine" procedure is indicated and effective.

Turbinate Resection

The turbinates (including their mucosa) serve a critical role in the nasal cavities to regulate temperature, sense airflow, and filter and humidify the inspired air. Despite published outcomes data [59] claiming no difference in quality of life following middle turbinate preservation versus resection, the routine resection of the middle turbinate produces compensatory glandular hypertrophy of the remaining nasal mucosa. Amputation at the root of the middle turbinate results in edema and stenosis of the frontal recess area. These sequelae can be overlooked on review of relatively short postoperative follow-up.

As stated by Setliff, "there is no rationale for implicating the nasal turbinates in the etiology of sinus disease…it appears that the turbinate proximity to the disease has resulted in a verdict of guilt by association with no clear evidence of culpability." He further posed the following question "…is [the] turbinate removed for the convenience of the surgeon or is there an undefined benefit for the patient… might turbinate excision be viewed as a legitimate effort to compensate for the lack of precision in sinus surgery?" [48] Amputation of a turbinate with disregard to its important function is condemned as this is an irreversible step which results in detrimental sequelae for both patients and surgeons faced with revision surgery. An alternative to this need for greater space in the middle meatus is powered shaving of the lateral aspect of the middle turbinate or concha bullosa to both improve middle meatal airflow and provide access without irreversible risks or complications.

MIST Procedure

After anesthesia is administered, a 0° endoscope is used to examine the bilateral nasal cavities and determine whether septoplasty may be required for access to the middle meatus. Three injections of lidocaine 1 % with epinephrine 1:100,000 are delivered to the attachment of the middle turbinate to the lateral wall (anterior to agger nasi), the head and body of the middle turbinate (Fig. 21.11). The middle meatus is approached with a Freer elevator gently medializing the middle turbinate. If the contralateral nasal cavity is to be operated as well, preinjections are avoided as to prevent bleeding from a rebound effect of the epinephrine.

The first anatomic landmark identified is the uncinate process and its associated hiatus semilunaris inferioris. The hiatus semilunaris inferioris is the exit of the ethmoid infundibulum [60]. Using a pediatric backbiter in a retrograde approach, uncinotomy is initiated at the junction of the superior two-thirds and inferior one-third of the uncinate process at the level of

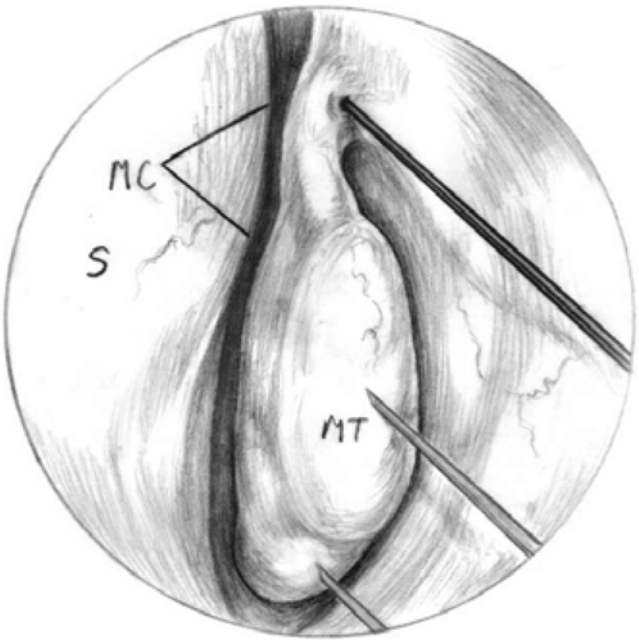


Fig. 21.11 The head and body of the middle turbinate, *MC* medial corridor, *S* septum, *MT* middle turbinate

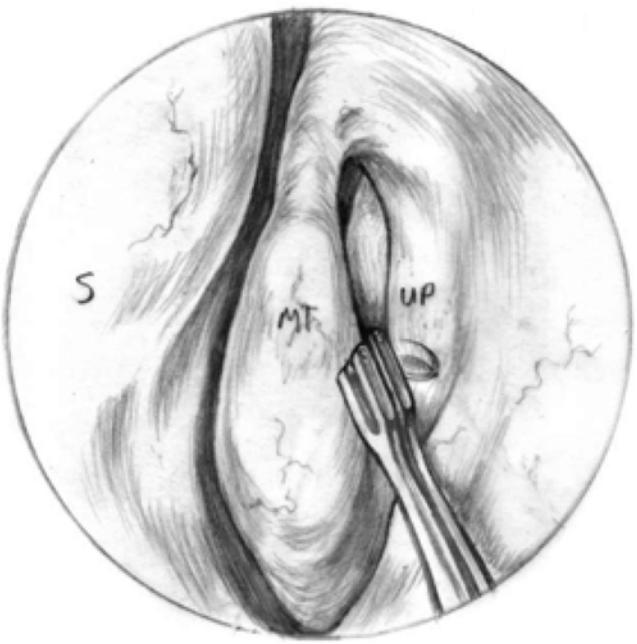


Fig. 21.12 A pediatric backbiter is initiated at the junction of the superior two-thirds and inferior one-third of the uncinate process at the level of the natural maxillary ostium, *S* septum, *MT* middle turbinate, *UP* uncinate process

the natural maxillary ostium (Fig. 21.12) [61]. Resection of all three layers (mucosa, bone, and mucosa) of the uncinate process is imperative and begins from posterior to anterior and from medial edge of the uncinate to its lateral insertion. This provides safety for prevention of injury to both the nasolacrimal duct (the anterior border of the uncinotomy) and the lamina papyracea which can be easily injured with alternative use of a sickle knife for the uncinectomy. Powered instrumentation is then employed to complete the uncinectomy superiorly to the opening of the agger nasi cell and then inferiorly from the exit of the infundibulum to the natural maxillary ostium which is best viewed with a 30° or 45° endoscope (Figs. 21.13 and 21.14). Further manipulation of the maxillary sinus ostium is rarely indicated.

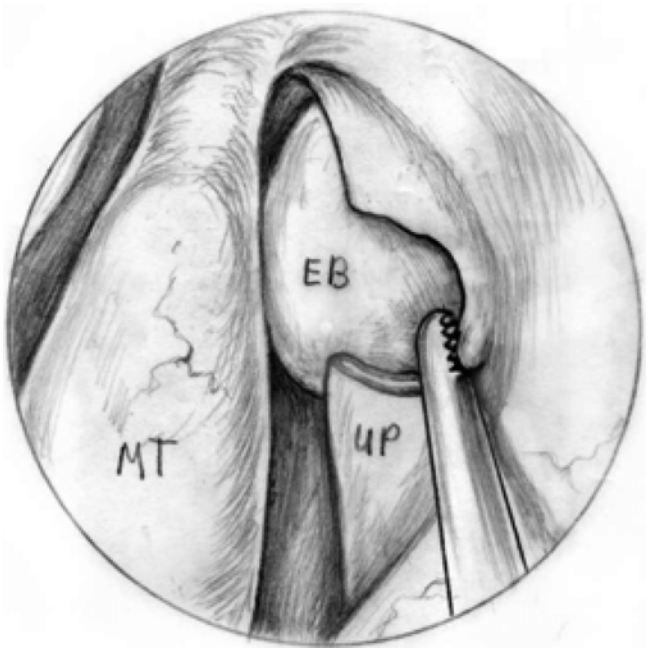


Fig. 21.13 Powered instrumentation to complete the uncinectomy superiorly to the opening of the agger nasi cell and inferiorly from the exit of the infundibulum to the natural maxillary ostium, *MT* middle turbinate, *EB* ethmoid bulla, *UP* uncinate process

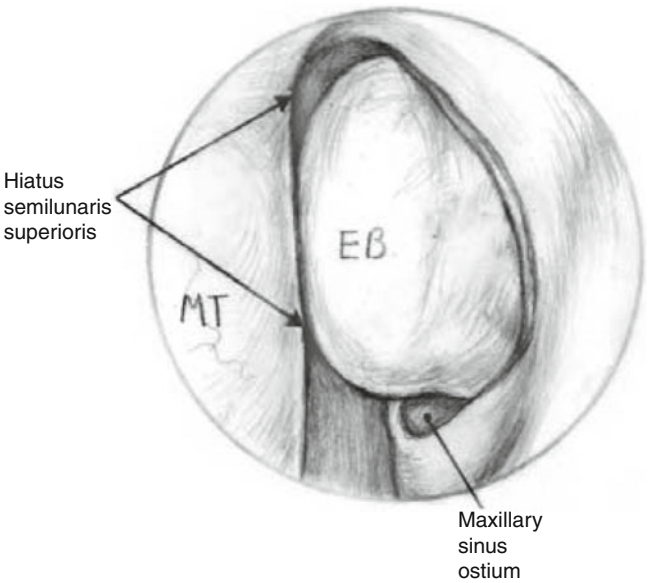


Fig. 21.14 The hiatus semilunaris superioris is a space located between the lateral wall of the middle turbinate and the medial edge of the ethmoid bulla, *MT* middle turbinate, *EB* ethmiod bulla

Uncinectomy of the superior insertion of the uncinate process reveals the agger nasi cell and its posteromedial border which is the second anatomic landmark. This directs the surgeon to the frontal recess (retro-aggar space area) the next transition space to be opened (Figs. 21.15 and 21.16).

The next landmark identified is the ethmoid bulla, and its associated transition space is the hiatus semilunaris superioris (HSS). The HSS is a space located between the lateral wall of the middle turbinate and the medial edge of the ethmoid bulla (Fig. 21.14). Powered instrumentation is used for anterior ethmoidectomy starting in the inferior and medial most portion of the ethmoid bulla. Dissection is carried out from medial to lateral to minimize risk to the lamina papyracea (Fig. 21.16). The basal lamella is the fourth landmark identified and correlates with exposure of the retrobullar space. The standard MIST procedure is completed once the basal lamella is reached. The procedure can be extended to include the posterior ethmoid cells when clinically indicated. At the end of the procedure, a bio-absorbable sponge may be placed in the middle meatus to medialize the middle turbinate (Fig. 21.17). If disease exists in the medial corridor or extends beyond the basal lamella (i.e., posterior ethmoid or sphenoid sinuses), then surgery is extended to those areas as well. Typically, no nasal packing is placed, and the nasal cavity, nasopharynx, and hypopharynx are suctioned of blood/secretions prior to extubation.

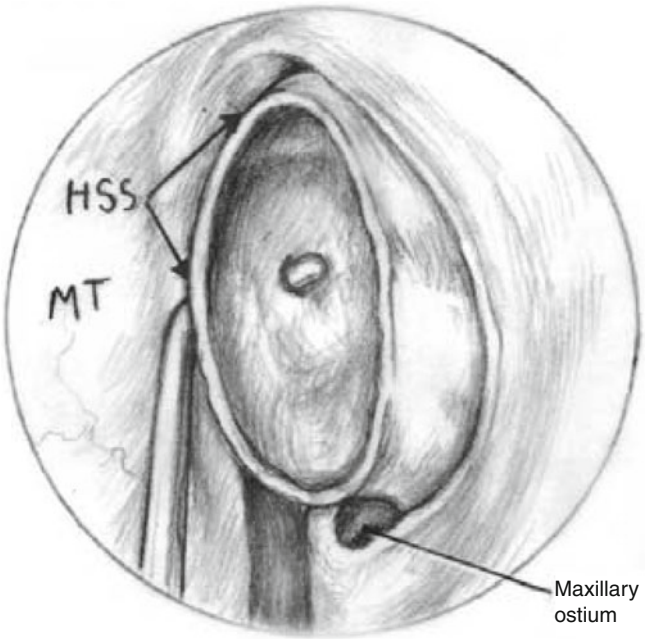
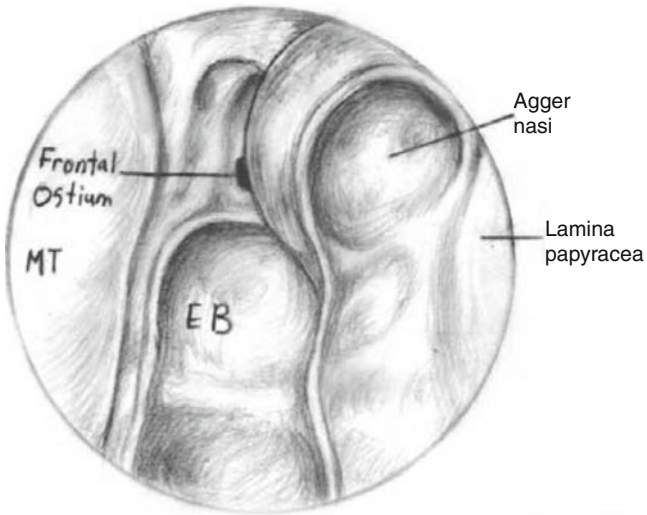


Fig. 21.15 Ethmoid bullae is removed, *MT* middle turbinate, *HSS* hiatus semilunaris superioris

Fig. 21.16 Uncinectomy of the superior insertion of the uncinate process reveals the agger nasi cell and the lamina papyracea, *MT* middle turbinate, *EB* ethmoid bulla



MIST Postoperatively

Patients receive oral antibiotics for 1 week after surgery and one dose of intramuscular steroid injection (methylprednisolone, 20 mg) to decrease postoperative edema. The steroid dose is adjusted or eliminated in pediatric and diabetic patients. Pain is usually minimal and well controlled with acetaminophen. When severe pain is involved, one should consider postoperative complications (i.e., septal hematoma/abscess or sinus infection). Nasal saline irrigations are initiated within 24 h after surgery and are continued twice daily for at least 4 weeks. Most patients return to work 48 h after surgery without significant diet or activity restrictions. Patients are advised to refrain from vigorous nose blowing and avoid continuous positive airway pressure machine (CPAP), nonsteroidal anti-inflammatory drugs (NSAIDS), flying, and water sports for 2 weeks. Middle meatal debridement is rarely necessary, and topical nasal medications for control of atopy are resumed 3 weeks postoperatively.

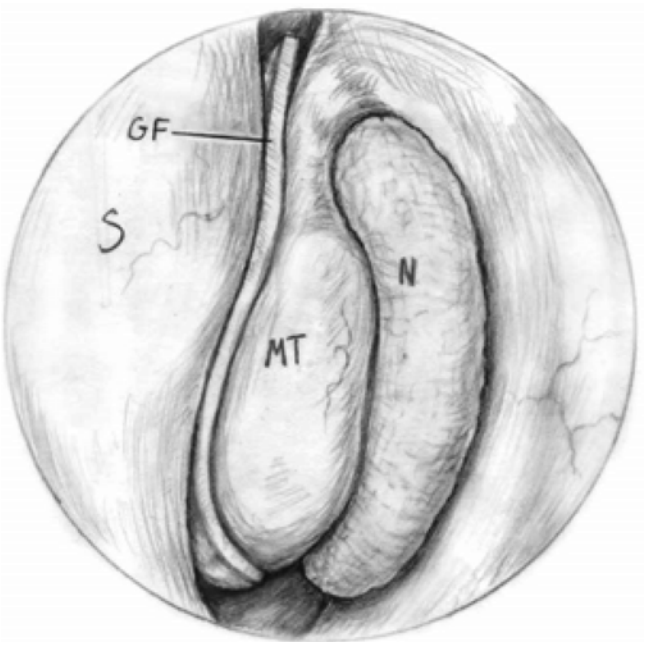


Fig. 21.17 A bio-absorbable sponge in the middle meatus to medialize the middle turbinate, *S* septum, *GF* gelatin film, *MT* middle turbinate, *N* polyurethane sponge

MIST and Traditional FESS

The evolution of FESS has seen deviation from its presumed role in treating patients with CRS. The practice of contemporary "FESS" is not a targeted procedure but rather an overly aggressive technique including partial or total turbinate resection with large (size) middle meatal antrostomy. The functional principle of targeting transition spaces has been lost and stripping of sinonasal mucosa continues unnecessarily. The extent of surgery in any given FESS procedure can only be speculated as consistency and standardization are lacking.

The first outcome study of MIST was published in 2003 which compared MIST and FESS using the Chronic Sinusitis Scale (CSS), a Harvard Medical School validated outcome tool [62]. It showed that MIST patients had equal or better results than FESS patients in CSS medication scores, CSS symptom scores, and CSS total scores when compared to matched controls. The MIST group was followed up twice as long as the FESS group (23 months versus 12 months) and still demonstrated improvement in measured outcome. The surgical revision rate for MIST patients was only 5.9 % in comparison to 10 % in the FESS group. Furthermore these results were consistent across computed tomography severity grades of I to IV, demonstrating the effectiveness of MIST across the spectrum of chronic rhinosinusitis. Salama et al. evaluated 143 patients undergoing MIST using the Glasgow benefit inventory and demonstrated significant reductions in nasal symptoms scores and increased total quality of life scores at 1, 3, 12, and 36 months follow-up [62]. Kuehnemund and colleagues published additional evidence that the minimally invasive approach has comparable results to more aggressive endoscopic sinus procedures in their randomized study of 65 patients who underwent "limited" (infundibulotomy, anterior ethmoidectomy, and maxillary antrostomy) versus "extended" endoscopic sinus surgery (spheno-ethmoidectomy, frontal recess dissection, and partial middle turbinate resection) [63]. Patients were matched for disease severity, symptoms, and saccharin transition time, and study outcome measures were equal in both study groups.

Another study performed in the geriatric population investigated the quality of life of 100 patients aged 65–93 years at least 6 months after MIST [64]. The objectives were to assess patient age with outcomes, surgical morbidity, and complications, including any exacerbation of a preexisting medical condition or onset of a new medical problem. The results showed that 84 % of the patients reported feeling significantly better 6 months after the surgery, 10 % were somewhat better, and 6 % were unchanged. Interestingly, eight patients of the ten reporting "somewhat better" results and two of the six reporting "no change" had previously undergone aggressive FESS. This suggests that in some patients, aggressive sinus surgery may have an irreversible adverse effect on nasal and sinus function. Twelve patients in this study had medical complications occurring during the first 72 h following surgery and included 12 with headaches, 6 with sinusitis, 4 with nausea and vomiting, and 1 with ataxia and hyposmia (self-limited). These results support MIST as an effective surgical treatment for CRS even in the "frail" geriatric population.

One theory for supporting aggressive endoscopic sinus surgery is osteitis of the ethmoid and maxillary bones. It has been proposed that the osteitic bone serves as a nidus for recurrent infection and persistent mucosal inflammation despite medical/surgical treatment; thus, aggressive removal of all osteitic bone may theoretically decrease the risk of recurrence [65]. However, this theory has several flaws. Osteitis is a histopathologic diagnosis made by single photon emission computed tomography (SPECT) bone scanning with technetium and cannot be identified intraoperatively [66]. Secondly, the extent of osteitic bone removal at the time of surgery is unclear given the lack of an intraoperative tool which identifies the existence of such pathology. This theory is further flawed given the potential for osteitis of the fovea ethmoidalis and the lamina papyracea which are routinely retained in such patients. Lastly, the incidence of osteitic changes in the ethmoid bone in the normal population has not been demonstrated; therefore, the clinical relevance of such histopathologic findings must be further delineated.

Arguments against MIST include inability to apply topical medical therapies to the maxillary sinus or effectively manage thick eosinophilic mucin. In patients with fungal sinusitis, small (<10 mm) antrostomies are made for this reason, and access for administration of topical medical therapies is not compromised in clinical practice. Although a minority of patients (5.9 %) undergoing MIST require revision surgery, by no means does it justify an aggressive and irreversible surgery as a primary intervention on the majority of CRS patients [67].

MIST and Combined Techniques: Balloon Catheter Sinusotomy

A decade after the first paper about MIST was published, balloon catheter sinusotomy was presented as a surgical option to treat patients with CRS. The transnasal system of balloon catheter sinusotomy, first introduced by Acclarent, Inc. (Menlo Park, CA, USA), consisted of three components: a sinus guide catheter, guide wire, and a balloon catheter. The guide catheter is the vehicle through which the guide wire is first passed into the appropriate sinus and thereafter the balloon is passed over the guide wire and into the sinus where the balloon is inflated with saline to a pressure of 10 atm to dilate the sinus ostium and its related drainage pathways. The advent of the balloon catheter sinusotomy technique was a welcomed option for both patients and surgeons.

The mechanism of balloon catheter sinusotomy entails preservation of sinus and nasal mucosa by repositioning diseased mucosa instead of resecting this tissue. The “dilation” expression may be misleading as balloon sinusotomy does not result in anything close to a middle meatus antrostomy and is much more consistent with “small hole” maxillary sinusotomy and with proven success. The 5-mm diameter balloon is most commonly used since its diameter correlates well with the average diameter of the natural birth maxillary ostium. The length of the balloon varies between 16 and 20 mm. When the balloon is placed either in the frontal sinus or maxillary sinus, its whole length is used to treat the associated transition space.

Limitations of balloon catheter sinusotomy include its inability to resect polypoid mucosa and concha bullosa or treat the anterior ethmoidal transition space. In MIST, targeted surgery is available for all transition spaces and anterior ethmoidectomy is routinely performed. MIST promotes a standard sinus surgery with consistent clearing of all transition spaces; however, balloon techniques provide a useful adjunct for implementation within MIST.

Balloon catheter sinusotomy has become an integral tool used within the realm of FESS and MIST. This tool has been found to be safe and effective and provides excellent long-term results [68, 69]. Out of the 109 patients who completed the study, SNOT-20 scores showed a significant and durable improvement over baseline both in the balloon-only and the FESS-balloon (hybrid) patients at 24-month follow-up [70].

Conclusions

The transition from Caldwell-Luc to FESS and MIST has transpired over the past three decades and continues to evolve into an even less invasive and more targeted procedure than originally proposed. One must, however, question the true need for an aggressive procedure for all patients when excellent long-term results are achieved by less invasive and less morbid techniques which are targeted while still allowing for more aggressive surgery for the minority of patients who require such a procedure. While many training programs throughout the world teach conventional FESS and now embrace balloon technology, the principles of MIST appear to be returning full circle from its initial conception. Balloon dilation technologies and other minimally invasive surgical options will continue to move us in this direction in the years to come.

> We shall not cease from exploration and the end of all our exploring will be to arrive where we started and know the place for the first time
> T.S. Eliot.

References

1. Hippocrates. The aphorisms of Hippocrates, Section 6, No. 10. In: Marks E, editors. The aphorisms of Hippocrates. New York: Collins & Co.; 1817. p. 125–7.
2. Wright J. The Hippocratic treatises. In: Wright J, editor. A history of laryngology and rhinology. 2nd ed. New York: Lea & Febiger; 1914. p. 55–8.
3. Highmore N. Corporis humani disquisitio anatomica. Hagae Comitis. 1651:225–8.
4. Caldwell GW. Diseases of the accessory sinuses of the nose and an improved method of treatment for suppuration of the maxillary antrum. N Y Med J. 1893;58:526–8.
5. Spicer S. The surgical treatment of chronic empyema of the antrum maxillare. BMJ. 1894;2:1359.
6. Luc H. Une nouvelle methode operatoire pour la cure radicale et rapide de l'empyeme chronique du sinus maxillaire. Arch Int Laryngol Otol Rhinol. 1897;10:273–85.
7. Macbeth R. Caldwell-Luc operation 1952–1966. Arch Otolaryngol. 1968;87(6):630–6.
8. Mabry RL. The case for the Caldwell-Luc procedure. Am J Rhinol. 1994;8(6):311–5.
9. Kim E, Duncavage J. Caldwell-Luc procedure. Oper Tech Otolaryngol. 2010;21(3):163–5.
10. Moeller CW, Stankiewicz JA. Endoscopic inferior meatal antrostomy. Oper Tech Otolaryngol. 2010;21(3):156–9.
11. Cottle MD. Chronic inflammation of the nose and paranasal sinuses. In: Ono J, editor. Proceedings VIIIth international congress of otorhinolaryngology, Tokyo, 23–30 Oct 1965. Int Congr Ser. 1966;113:116–7.
12. Horowitz MS. Functional approach to surgery of the maxillary and ethmoidal sinuses. Rhinology. 1967;5:175–80.
13. Defreitas J, Lucente FE. The Caldwell-Luc procedure: institutional review of 670 cases:1975–1985. Laryngoscope. 1988;98(12):1297–300.
14. Metheny KE, Duncavage JA. Contemporary indications for the Caldwell-Luc procedure. Curr Opin Otolaryngol Head Neck Surg. 2003;11(1):23–6.
15. Lund VJ. Fundamental considerations of the design and function of intranasal antrostomies. Rhinology. 1985;23(3):231–6.
16. Masterson L, Al GW, Bath AP. Endoscopic Caldwell-Luc technique. J Laryngol Otol. 2010;124(6):663–5.
17. Blitzer A, Lawson W. The Caldwell-Luc procedure in 1991. Otolaryngol Head Neck Surg. 1991;105(5):717–22.
18. Albu S, Baciut M. Failures in endoscopic surgery of the maxillary sinus. Otolaryngol Head Neck Surg. 2010;142(2):196–201.
19. Han JK, Smith TL, Loehrl TA, Fong KJ, Hwang PH. Surgical revision of the post-Caldwell-Luc maxillary sinus. Am J Rhinol. 2005;19(5):478–82.
20. Stammberger H. Endoscopic endonasal surgery—concepts in treatment of recurring rhinosinusitis: part I. Anatomic and pathophysiologic considerations and part II. Surgical technique. Otolaryngol Head Neck Surg. 1986;94(2):142–56.
21. Hirschmann A. Uber Endoskopie der Nase und deren Nebenhohlen. Arch Laryngol Rhinol. 1903;14:195–202.
22. Maltz M. New instrument: the sinuscope. Laryngoscope. 1925;35:805–11.
23. Jennings CR. Harold Hopkins. Arch Otolaryngol Head Neck Surg. 1998;124:1042.
24. Kennedy DW, Goodstein ML, Miller NR, Zinreich SJ. Endoscopic transnasal orbital decompression. Arch Otolaryngol Head Neck Surg. 1990;116(3):275–82.
25. Messerklinger W. On the drainage of the human paranasal sinuses under normal and pathological conditions [German]. Monatsschr Ohrenheilkd Laryngorhinol. 1966;100(1–2):56–68.
26. Kennedy D. Prognostic factors, outcomes, and staging in ethmoid sinus surgery. Laryngoscope. 1992;102:1–18.
27. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza D. Long-term results of functional endoscopic sinus surgery. Laryngoscope. 1998;108(2):151–7.
28. Report of the Rhinosinusitis Task Force Committee Meeting. Alexandria, Virginia, August 17, 1996. Otolaryngol Head Neck Surg. 1997;117 (3 Pt 2):S1–68.
29. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2007;20:1–136.
30. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. 2006;116(2):189–93.
31. Badia L, Lund V. Topical corticosteroids in nasal polyposis. Drugs. 2001;61(5):573–8.
32. Lavigne F, Cameron L, Renzi PM, et al. Intrasinus administration of topical budesonide to allergic patients with chronic rhinosinusitis following surgery. Laryngoscope. 2002;112(5):858–64.
33. Steinke JW, Payne SC, Tessier ME, Borish LO, Han JK, Borish LC. Pilot studies of budesonide inhalant suspension irrigations for chronic eosinophilic sinusitis. J Allergy Clin Immunol. 2009;124(6):1352–4.
34. Stammberger H. Functional endoscopic sinus surgery. Philadelphia: BC Decker; 1991.
35. Bhattacharyya N. Ambulatory sinus and nasal surgery in the United States: demographics and perioperative outcomes. Laryngoscope. 2010;120(3):635–8.
36. Lee WC, Kapur TR, Ramsden WN. Local and regional anesthesia for functional endoscopic sinus surgery. Ann Otol Rhinol Laryngol. 1997;106:767–9.
37. Moriyama H. The technique of endoscopic surgery and diagnosis of frontal recess and sinus disease under local anesthesia. J Otolaryngol. 1991;20(6):382–4.
38. Maniglia AJ. Fatal and major complications secondary to nasal and sinus surgery. Laryngoscope. 1989;99:276–83.
39. Tirelli G, Bigarini S, Russolo M, et al. Total intravenous anesthesia in endoscopic sinus-nasal surgery. Acta Otorhinolaryngol Ital. 2004;24:137–44.
40. Laguna D, Lopez-Cortijo C, Millan I, Gonzalez FM, Garcia-Berrocal JR. Blood loss in endoscopic sinus surgery: assessment of variables. J Otolaryngol Head Neck Surg. 2008;37(3):324–30.
41. Hogue Jr CW, Bowdle TA, O'Leary C, et al. A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery. Anesth Analg. 1996;83:279–85.

42. Eberhart LH, Folz BJ, Wulf H, Geldner G. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. Laryngoscope. 2003;113(8):1369–73.
43. Larsen B, Seitz A, Larsen R. Recovery of cognitive function after remifentanil-propofol anesthesia: a comparison with desflurane and sevoflurane anesthesia. Anesth Analg. 2000;90:168–74.
44. Danielsen A, Gravningsbraten R, Olofsson J. Anaesthesia in endoscopic sinus surgery. Eur Arch Otorhinolaryngol. 2003;260:481–6.
45. Atef AM, Farwaz A. Comparison of laryngeal mask with endotracheal tube for anaesthesia in endoscopic sinus surgery. Am J Rhinol. 2008;22:653–7.
46. Kaplan A, Crosby G, Bhattacharyya N. Airway protection and the laryngeal mask airway in sinus and nasal surgery. Laryngoscope. 2004;114:652–5.
47. Anderhuber W, Walch C, Nemeth E, et al. Plasma adrenaline concentrations during functional endoscopic sinus surgery. Laryngoscope. 1999;109(2 Pt 1):204–7.
48. Setliff III RC. Minimally invasive sinus surgery. Otolaryngol Clin North Am. 1996;29(1):115–29.
49. Min YG, Yun YS, Song BH, Cho YS, Lee KS. Recovery of nasal physiology after functional endoscopic sinus surgery: olfaction and mucociliary transport. ORL J Otorhinolaryngol Relat Spec. 1995;57(5):264–8.
50. Katsuhisa I, Takeshi O, Masayuki F, Yukio K, Akira S, Tomonori T, Shin M. Restoration of the mucociliary clearance of the maxillary sinus after endoscopic sinus surgery. J Allerg Clin Immunol. 1997;99(1):48–52.
51. Asai K, Haruna S, Otori N, Yanagi K, Fukami M, Moriyama H. Saccharin test of maxillary sinus mucociliary function after endoscopic sinus surgery. Laryngoscope. 2000;110(1):117–22.
52. Yang TQ, Majima Y, Guo Y, Harada T, Shimizu T, Takeuchi K. Mucociliary transport function and damage of ciliated epithelium. Am J Rhinol. 2002;16(4):215–9.
53. Setliff III RC, Parsons DS. The “Hummer”: new instrumentation for functional endoscopic sinus surgery. Am J Rhinol. 1994;8(6):275–8.
54. Albu S, Tomescu E. Small and large middle meatus antrostomies in the treatment of chronic maxillary sinusitis. Otolaryngol Head Neck Surg. 2004;131(4):542–7.
55. Setliff III RC. The small-hole technique in endoscopic sinus surgery. Otolaryngol Clin North Am. 1997;30(3):341–51.
56. Lundberg JO. Nitric oxide and the paranasal sinuses. Anat Rec (Hoboken). 2008;29(11):1479–84.
57. Bentz BG, Simmons RL, Haines GK, Radosevich JA. The Yin and Yang of nitric oxide: reflections on the physiology and pathophysiology of NO. Head Neck. 2000;22:71–83.
58. Schlosser RJ, Spotnitz WD, Peters EJ, Fang K, Gaston B, Gross CW. Elevated nitric oxide metabolite levels in chronic sinusitis. Otolaryngol Head Neck Surg. 2000;123:357–62.
59. Kirihene RK, Rees G, Wormald PG. The influence of the size of the maxillary sinus ostium on the nasal and sinus nitric oxide levels. Am J Rhinol. 2002;16:261–4.
60. Soler ZM, Hwang PH, Mace J, Smith TL. Outcomes after middle turbinate resection: revisiting a controversial topic. Laryngoscope. 2010;120(4):832.
61. Catalano PJ, Strouch M. The minimally invasive sinus technique: theory and practice. Otolaryngol Clin North Am. 2004;37:401–9.
62. Parsons ES, Phillips SE. Functional endoscopic sinus surgery in children: a retrospective analysis of results. Laryngoscope. 1993;103(8):899–903.
63. Salama N, Oakley RJ, Skilbeck CJ, Choudhury N, Jacob A. Benefit from the minimally invasive sinus technique. J Laryngol Otol. 2009;123:186–90.
64. Kuehnemund M, Lopatin A, Amedee RG, Mann WJ. Endonasal sinus surgery: extended versus limited approach. Am J Rhinol. 2002;16:187–92.
65. Catalano PJ, Setliff RC, Catalano LA. Minimally invasive sinus surgery in the geriatric patient. Oper Tech Otolaryngol Head Neck Surg. 2001;12(2):85–90.
66. Kennedy DW, Senior BA, Gannon FH, Montone KT, Hwang P, Lanza DC. Histology and histomorphometry of ethmoid bone in chronic sinusitis. Am J Rhinol. 1998;108(4):502–7.
67. Catalano PJ, Dolan R, Romanow J, Payne SC, Silverman M. Correlation of bone SPECT scintigraphy with histopathology of the ethmoid bulla: preliminary investigation. Ann Otol Rhinol Laryngol. 2007;116(9):647–52.
68. Catalano PJ, Roffman E. Outcome of patients with chronic sinusitis after the minimally invasive sinus technique. Am J Rhinol. 2003;17(1):17–22.
69. Levine HL, Sertich AP, Hoisington DR, Weiss RL, Pritikin J. Multicenter registry of balloon catheter sinusotomy outcomes for 1036 patients. Ann Otol Rhinol Laryngol. 2008;117(4):263–70.
70. Bolger WE, Brown CL, Church CA, Goldberg AN, Karanfilov B, Khun FA, et al. Safety and outcomes of balloon catheter sinusotomy: a multicenter 24-weeks analysis in 115 patients. Otolaryngol Head Neck Surg. 2007;137:10–20.

Chapter 22
Surgical Management of Rhinosinusitis in Children and Adolescents

Jessica R. Levi and Richard Schmidt

Introduction

The magnitude of pediatric rhinosinusitis cannot be overstated. Acute bacterial rhinosinusitis is the fifth most common disorder in children for which antibiotics are prescribed in an outpatient setting [1]. The health-care expenditure in the United States in 1996 for rhinosinusitis in the pediatric population was estimated to be $1.8 billion [2]. This does not include the economic impact of parental time missed from work while caring for an ill child. Chronic pediatric rhinosinusitis (CRS), defined as 12 weeks or more of signs and symptoms of inflammation of the sinuses, has a large impact on the quality of life. Cunningham et al. [3] looked at 21 children with CRS who had completed the Child Health Questionnaire along with their parents and found that children with CRS were perceived to have more bodily pain and more limitations in physical activities than children with asthma, juvenile rheumatoid arthritis, or other chronic disorders.

Most pediatric otolaryngologists agree that the first-line treatment for pediatric chronic rhinosinusitis is oral antibiotic therapy [4]. The presence of other conditions that are best managed medically, such as allergic rhinitis, immune deficiency, or gastroesophageal reflux disease, must also be investigated and optimally treated as appropriate. However, some cases are refractory to medical therapy and surgery must be considered.

There is much controversy regarding surgical management of chronic sinusitis in children. Some believe that children will "outgrow" these symptoms over time, making surgery unnecessary. Also, there is often difficulty in differentiating chronic sinusitis from allergic rhinitis or adenoiditis in a child. In addition, there has been concern that certain procedures used to treat CRS may disrupt facial growth in children.

Part of the controversy may be because otolaryngologists often try to apply a procedure designed for adults, functional endoscopic sinus surgery (FESS), to manage pediatric CRS even though this disease is most likely a different entity than adult CRS. In adults, CRS is a complex disease often associated with anatomical variations impairing proper sinus drainage leading to microbial colonization. The anatomical variations such as agger nasi cells, septal deviation, Haller cells, concha bullosa, paradoxical middle turbinate, and Onodi cells, known to contribute to CRS in adults, do not appear to be related to the extent of disease in children [5]. Likewise, the mucosal changes in pediatric CRS appear to be different. The inflammatory response in pediatric patients is primarily cellular infiltration of the lamina propria with chronic inflammatory cells. These are mostly lymphocytes, plasma cells, and macrophages with relatively few eosinophils. In contrast the adult sinus mucosa is often characterized by polypoid mucosa with an edematous lamina propria infiltrated with relatively fewer chronic inflammatory cells, but a higher concentration of eosinophils. Patches of complete epithelial shedding are observed in adults, whereas the epithelial layer is generally intact in children [6].

If we agree that medical therapy has failed, the next question is: "What is the appropriate surgical therapy for this child?" Unfortunately, the answer is not always clear. Looking into the effectiveness of FESS compared to medical therapy, Lieu and colleagues [7] conducted a survey of 208 patients 2 years after they were initially seen in an ENT clinic for CRS.

J.R. Levi, MD
Department of Otolaryngology Head and Neck Surgery and the Department of Pediatrics, Boston University/Boston Medical Center, Moakley Building, 830 Harrison Ave, Boston, MA 02118, USA
e-mail: jessica.levi@bmc.org

R. Schmidt, MD (✉)
Department of Surgery, Nemours duPont Hospital for Children, Wilmington, DE 19803, USA
e-mail: rschmidt@nemours.org

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_22, © Springer Science+Business Media New York 2014

Regardless of treatment (maximal medical management vs. maximal medical management and FESS) and regardless of CT findings of sinusitis, patients tended to improve to a "good" outcome 2 years later. They concluded that this is a chronic disease with few "cures," and parental expectations should be managed accordingly. Similarly, Rudnick and Mitchell [8] looked at children diagnosed with CRS undergoing either adenoidectomy or FESS and found no difference in quality of life scores on the SN-5 quality-of-life survey in the two groups. Both procedures increased the quality of life scores post-op (both within 6 months of surgery and between 6 months and 2 years of surgery) from preoperative scores. Conversely, Ramadan [9] noted symptom resolution in 77 % of children who had FESS, compared to 47 % of children who had adenoidectomy for CRS.

In this chapter, we will discuss the role of surgery in chronic sinusitis with particular attention to adenoidectomy and different components of FESS. We will also introduce a few select patient populations that may warrant special consideration. Finally, we will provide specific recommendations for the surgical treatment of chronic sinusitis in the pediatric population.

Adenoidectomy

There has been much research looking at the association between sinusitis and adenoid disease; however, the connection between the two remains uncertain. There are two frequently proposed theories as to how the adenoids contribute to pediatric sinusitis. The first is that the adenoids cause physical obstruction of the posterior nasal cavity leading to stasis of secretions and therefore creating an environment conducive to bacterial growth (adenoid hypertrophy theory). The second is that the adenoids serve as a reservoir for bacteria that can then secondarily infect the sinuses (bacterial reservoir theory).

The adenoid hypertrophy theory, probably the less widely held of the two, has some support nonetheless. Merck [10] noted a positive correlation between the adenoid pad size and incidence of maxillary sinus opacification on plain films. However, other studies have failed to confirm this correlation. In a review of over 400 patients, Shinn et al. [11] found no association between adenoid size and sinusitis symptoms. Likewise, Tuncer et al. [12] found no relationship between adenoid size and maxillary sinus culture positivity in a study of 30 patients.

There is more support for the bacterial reservoir theory. A study by Lee and Rosenfeld [13] found a significant correlation between bacterial load in the adenoids and sinonasal symptom scores in 84 children undergoing adenoidectomy for various reasons. Shin et al. [11] looked at 410 children undergoing adenoidectomy for obstructive symptoms and found that there was an association between increasing sinusitis grades and increased bacterial yield from the adenoid. Other authors have noted that cultures taken from the adenoid as well as the lateral wall of the nose yielded identical bacterial strains 89 % of the time [14].

More recently the identification of adenoid biofilms has added weight to the bacterial reservoir theory. Zuliani and colleagues [15] examined the role of biofilms in pediatric patients in 2006. In a study of 16 patients undergoing adenoidectomy either for OSA or CRS, they found that adenoids removed in patients with CRS had nearly 95 % of their mucosal surface covered with biofilms. This contrasted sharply with the OSA group where only 2 % of the adenoid surface was covered by biofilms. It is likely that biofilms of the adenoid create a repository of bacteria for the development of CRS. Coticchia et al. [16] postulated that these adenoid biofilms, composed of known rhinosinusitis pathogens (*Moraxella catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae*, or *Staphylococcus aureus*), might periodically shed biologically active pathogenic bacteria. If there was inflammation of the osteomeatal complex and altered ciliary function, pathogens could gain entry into the maxillary sinus. A new biofilm could then be established within the sinus. Thus, adenoidectomy is most likely effective by removing this nidus for infection.

Even if the physiologic rationale for the beneficial outcome of adenoidectomy in childhood CRS is not entirely understood, experts believe it to be effective. A 2005 survey of members of the American Society of Pediatric Otolaryngology (ASPO) found that 96 % use adenoidectomy at least sometimes in the management of chronic sinusitis [4]. Evidence of the efficacy of adenoidectomy has been known for some time. In a study by Takahashi et al. [17], 78 patients with otitis media and sinusitis underwent either adenoidectomy or no surgical intervention. In the adenoidectomy group, 56 % had improvement in their sinus symptoms 6 months later while only 24 % in the non-adenoidectomy group had improvement. In a study of 43 patients undergoing adenoidectomy for CRS, Vandenberg and Heatley [18] found 58 % had near or complete resolution of CRS symptoms following adenoidectomy. Twenty-one percent had some improvement while only three patients went on to require FESS. Ramadan [9] found 47 % of children undergoing adenoidectomy had symptom resolution. Rosenfeld [19] found 75 % of children receiving antibiotics and undergoing adenoidectomy had resolution of their symptoms. Ungkanont and Damrongsak [20] noted a decrease in the number of discreet episodes of sinusitis after adenoidectomy. Children undergoing adenoidectomy for sinusitis had an average of 13.7 episodes of sinusitis per year before surgery and 0.76 episodes after

surgery. A recent meta-analysis by Brietzke and Brigger [21] is perhaps most enlightening. They looked at nine articles and found that the overall effectiveness of adenoidectomy ranged from 50 to 100 % at 3- to 9-month follow-up. This led to a summary estimate of 69.7 % efficacy for adenoidectomy.

Antral Lavage

Lavage of the maxillary sinus is used to obtain a culture and to remove trapped, potentially infected secretions from the sinus. However, its principal limitation is that it only addresses one sinus (the maxillary). Furthermore, it generally requires anesthesia in a child and is rarely curative as a stand-alone procedure for CRS. When used, it is therefore often performed in combination with adenoidectomy. It is generally performed through the natural ostium, but can also be performed via the inferior meatus or the canine fossa.

Buchman and colleagues [22] looked at 27 children with CRS unresolved after 1 month of oral antibiotics who then underwent maxillary sinus irrigation (with or without adenoidectomy at the discretion of the surgeon), followed by IV antibiotics. Eighty-nine percent of the patients had resolution of their symptoms, although 60 % had recurrence of their symptoms on follow-up (average 282 days). All of these episodes were responsive to oral antibiotics. In a retrospective review of 23 pediatric patients treated with a protocol consisting of adenoidectomy and antral lavage followed by long-term oral antibiotics, Criddle et al. [23] noted that 96 % of his patients obtained clinical resolution of their symptoms, with 78 % remaining asymptomatic long term. A significant number of those who did not were subsequently discovered to have an immune deficiency. As encouraging as these numbers are, it is difficult to fully assess the relative role the irrigations played in these patients' improvement.

Antral window (inferior meatal window), performed frequently in the past, is currently an uncommon surgical intervention as it does not account for the natural movement of the cilia and clearance of secretions from the maxillary sinus. Moreover, long-term patency is a problem. Lund [24] found 45 % of the windows closed on subsequent evaluation. Windows had to be larger than 1 cm to remain patent. Patency was even less likely in children. At this time it is generally reserved for children with ciliary dysfunction.

Endoscopic Sinus Surgery

The use of FESS to treat pediatric CRS is relatively new. The advent of adult sinus surgery likely began in 1901 with Hirschmann using a modified cystoscope [25]. In 1985, Kennedy brought the procedure to the United States. One of the earliest reports in children was by Gross et al. [26] in 1989 that looked at 57 children undergoing FESS and found no major complications. In a study published in 1990, Lusk and Muntz [27] established the safety of endoscopic ethmoidectomy in 31 children who were medical failures. The only complication reported was scarring in two patients.

Nonetheless, pediatric FESS has historically been approached with a great deal of caution. Major complications of FESS, known to occur in adults, including orbital hematoma, blindness, epiphora, CSF leak, and meningitis are infrequent, but may occur in pediatric patients as well. In addition concerns have been raised about the unintended effects that even successful surgery may have on a child. Specifically, there were concerns about the potential effect that the procedure may have on the long-term facial growth of children. These concerns were based on animal studies that demonstrated altered facial growth after nasal or sinus surgery in a variety of juvenile animals [28].

However, longitudinal analysis of children undergoing FESS has failed to support these concerns. Bothwell et al. [29] compared a group of children who had sinus surgery (46 patients) to a group treated medically (21 patients) at a mean age of 3.1 years. Anthropometric measurements were taken 10 years after treatment. She found no difference between the two groups. Similarly, a volumetric analysis of CT scans obtained an average of 7 years after unilateral FESS in a group of children revealed no difference in facial volume between the operated and non-operated sides [25].

Some issues remain unresolved, however. Is there an age below which sinus surgery might impede facial growth? Are specific surgical procedures (septoplasty, ethmoidectomy, maxillary antrostomy, etc.) more likely to impede growth than others? Continued investigation is needed to answer these questions.

In the opinion of many, FESS has a role in the management of pediatric CRS. However, it is important to note that the Brussels consensus panel in 1996 (Table 22.1) listed pediatric CRS as a relative indication for FESS [30]. The absolute indications included complete nasal obstruction in patients with CF due to polyposis, antrochoanal polyp, intracranial complications of CRS, mucocele, orbital abscess, need for optic decompression, dacryocystitis resistant to antibiotics and, from the

Table 22.1 Indications for endoscopic sinus surgery in children

Absolute indications
Complete nasal obstruction in patients with CF due to polyposis
Antrochoanal polyp
Intracranial complications of CRS
Mucocele
Orbital abscess
Need for optic decompression
Dacryocystitis resistant to antibiotics and from the sinuses
Invasive fungal sinusitis
Some neoplasms
Some meningoencephaloceles
Possible indications
Chronic rhinosinusitis that persists despite optimal medical therapy

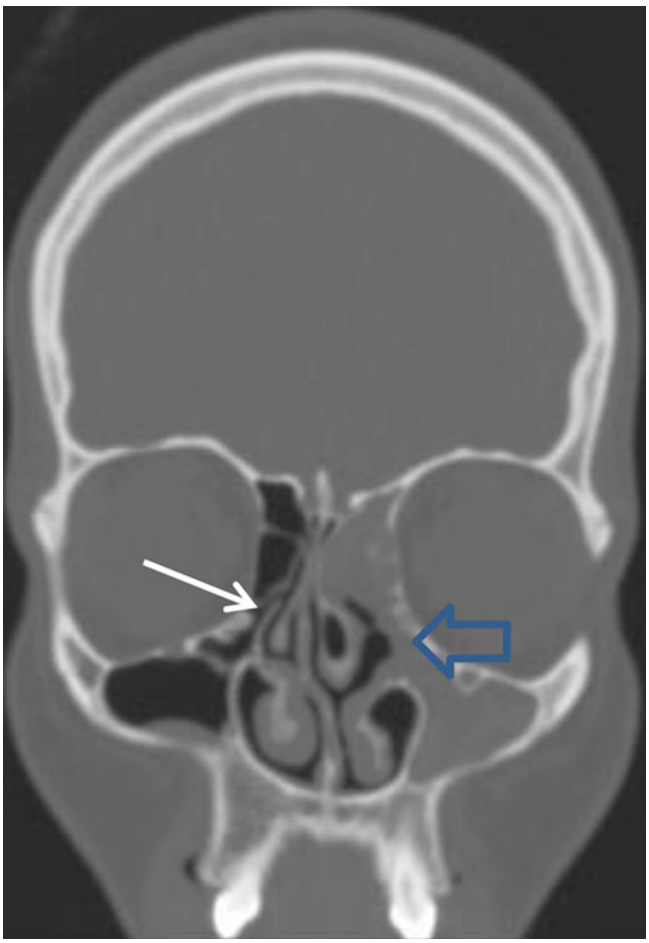


Fig. 22.1 Coronal CT scan demonstrating the osteomeatal complex (OMC), patent on the right (*white arrow*) and occluded by polypoid disease on the left (*blue arrow*)

sinuses, invasive fungal sinusitis, some neoplasms, and some meningoencephaloceles. CRS despite optimal medical management and after exclusion of systemic diseases was listed as a relative indication. Optimal medical management was defined as 2–6 weeks of adequate broad-spectrum antibiotics (either IV or oral) and treatment of any concurrent diseases. The panel further stated that children appropriate for surgery only account for a small percentage of all children with CRS.

When considering FESS to treat pediatric CRS, it is important to consider which sinuses need to be addressed. In their study of 113 children with CRS evaluated by CT scan, Kim and colleagues [5] noted that the maxillary sinus was the most commonly affected. Lusk [31] on the other hand states that the anterior ethmoid is affected more frequently than the maxillary sinus. Most likely it is the osteomeatal complex (OMC) that is the principal location of concern as this region serves as the outflow tract for both the anterior ethmoid and maxillary sinuses (Fig. 22.1). A variety of conditions in children may cause mucosal congestion and, secondarily, obstruction of this narrow region. FESS is effective because it enlarges this

outflow tract. The OMC is the site most pediatric otolaryngologists address during FESS. A survey of ASPO members in 2005 found that 66 % performed a middle meatal antrostomy with an anterior ethmoidectomy when they performed FESS, whereas only 12 % performed a middle meatal antrostomy with total ethmoidectomy and 8 % performed middle meatal antrostomy alone [4]. We recommend that the extent of surgery be directed by the preoperative CT scan. A middle meatal antrostomy and anterior ethmoidectomy should be considered on all children undergoing FESS for CRS.

The literature overwhelmingly supports the efficacy of FESS in the pediatric population. In a prospective study of 202 children, the overall effectiveness of FESS, as measured by parental questionnaires at 12 months after therapy, was 75 % [32]. Chang et al. [33] found that 86 % of parents were satisfied with the improvement in their child's symptoms following limited FESS at 6 months. Siedek et al. [34] looked at 115 patients retrospectively who had undergone FESS and found that the overall effectiveness in relief of symptoms was 76 % and improvement in quality of life was 71 %. Using a meta-analysis of eight articles, Herbert and Bent [35] concluded that FESS for CRS was effective 88.4 % of the time when medical management had failed (among 882 patients). These results have led some proponents of FESS to argue that the effectiveness of FESS over adenoidectomy for CRS outweighs the risk of this more extensive procedure, even as the first line of surgical therapy [9, 32].

However, FESS should not be considered a panacea in the management of pediatric CRS. In 2009, Lee et al. [36] retrospectively examined 53 children who had undergone FESS and found that 21 (39.6 %) had continued mucopurulent discharge for more than 3 months after surgery. Among risk factors for a protracted course were nasal polyposis, history of allergic rhinitis, and male gender. The histological evidence supports such protracted symptoms. In general, mucosa may take 2 months to return to normal, and polypoid antral mucosa may take twice as long [37].

Ramadan [32] noted that, although his overall revision rate was 12 %, children who had FESS prior to 3 years of age required revision 75 % of the time, usually for osteomeatal scarring. Additionally, he reported that children with allergic rhinitis who had not received allergy treatment before surgery did significantly worse after surgery when compared to those who had [38]. In general, adhesions, cicatricial scarring of the maxillary sinus ostia, and recurrent mucosal disease in previously operated sinuses appear to be the most common causes of revision surgery [39]. Similarly, others have noted that children who smoked and had cystic fibrosis, asthma, or allergies had significantly less symptom reduction following FESS than those who were otherwise healthy and nonsmokers [34].

We advocate a stepwise approach from medical therapy, to adenoidectomy, to FESS when treating CRS in most children. Regardless of the therapy used (antibiotics, adenoidectomy, or FESS), Rosenfeld [19] found complete symptom resolution scores of 27 % in all three groups. However, when only "major symptoms" of sinusitis were considered, FESS improved 100 % of those symptoms, adenoidectomy improved 75 %, and additional antibiotics improved 67 %. Children who progressed to FESS more often had comorbidities including asthma and allergic rhinitis, a longer duration of sinusitis symptoms, and a greater number of sinusitis episodes.

In the past, many advocated a "second-look" procedure in children undergoing FESS for CRS, usually 2–4 weeks later. This recommendation was based largely on the presumed benefit of postoperative endoscopic debridement performed in adults after FESS. The rationale for these procedures was that they would speed healing time, lessen the risk of scarring and reduce the need for revision surgery. Of course, endoscopic debridement is performed in the office under topical anesthesia in adults – a process that children are unlikely to tolerate! However, studies have shown that a second-look procedure is usually unnecessary and does not decrease rates for revision surgery [40]. Walner et al. [41] found that the incidence of revision surgery was the same whether or not a second look was performed. The use of mucosal sparing techniques and absorbable packing or stenting materials has decreased scarring and the need for a second-look procedure. Mitchell et al. [42] found that there was no difference in clinical outcome between 50 children who had a second look after FESS and 50 children who did not. At this time, most pediatric otolaryngologists do not perform a second-look procedure [4].

Image Guidance

Image-guided sinus surgery is not new and, like other advances in the field of rhinology, was first utilized on adults. As most readers are aware, the technology allows for the real-time localization of the tip of an instrument in three dimensions using previously obtained CT images (Fig. 22.2). This may allow for more complete disease removal during endoscopic procedures and potentially reduce the risk of injury to adjacent structures including the skull base and orbit. Like many technologies, particularly expensive ones, there were concerns almost from the beginning regarding overutilization. The American Academy of Otolaryngology – Head and Neck Surgery has developed recommended indications for the use of this technology (Table 22.2).

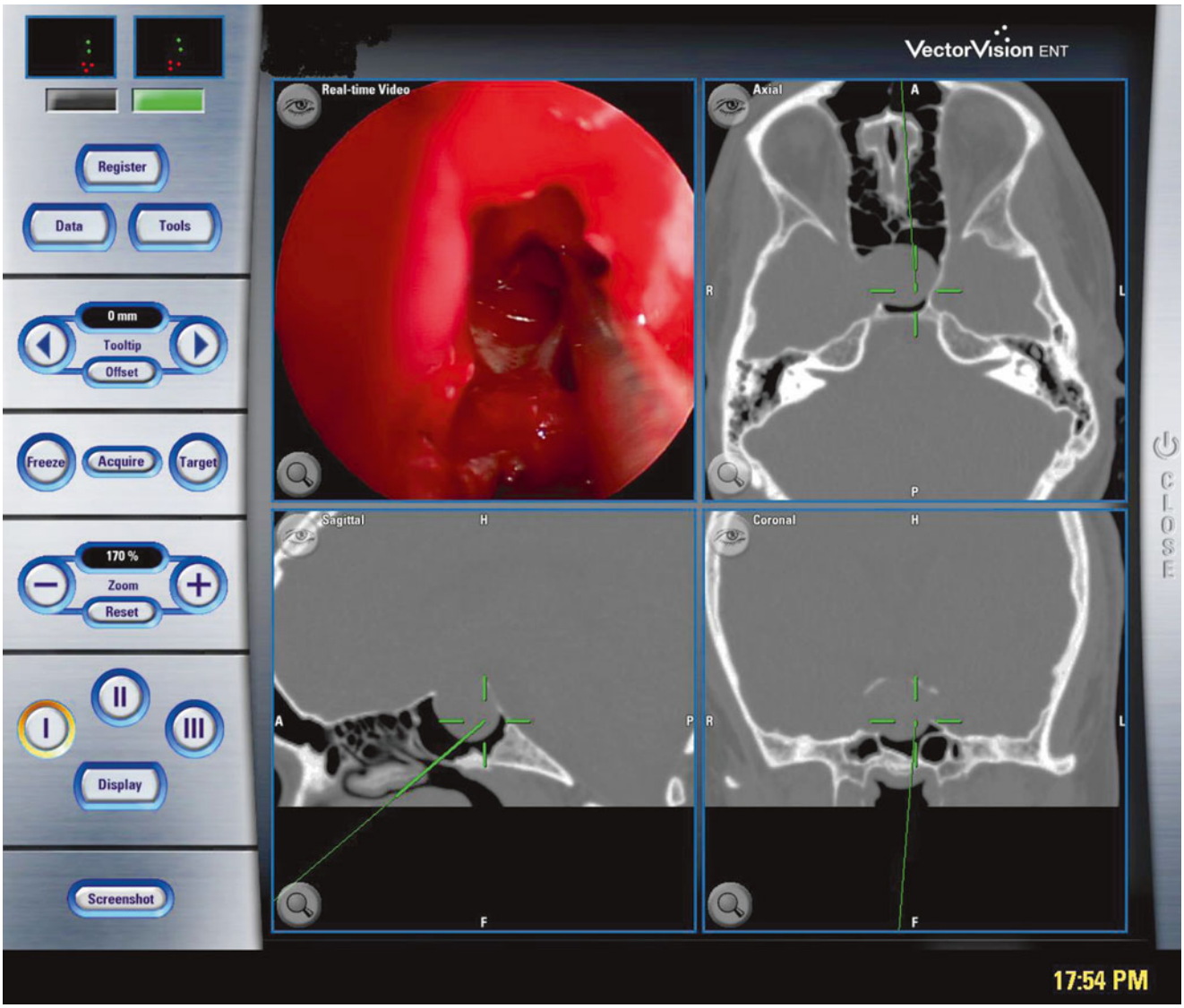


Fig. 22.2 Screen shot of image guidance system being used to confirm the location of an instrument in the sphenoid sinus

Table 22.2 American Academy of Otolaryngology – Head and Neck Surgery indications for computer-assisted endoscopic sinus surgery

1. Revision sinus surgery
2. Distorted sinus anatomy of developmental, postoperative, or traumatic origin
3. Extensive sinonasal polyposis
4. Pathology involving the frontal, posterior ethmoid, and sphenoid sinuses
5. Disease abutting the skull base, orbit, optic nerve, or carotid artery
6. Cerebrospinal fluid rhinorrhea or conditions where there is a skull-base defect
7. Benign and malignant sinonasal neoplasms
8. Choanal atresia

Based on data from American Academy of Otolaryngology-Head and Neck Surgery [88]

The only one of these guidelines specific to the pediatric patient is choanal atresia. Tumors of the nose and sinuses and CSF rhinorrhea are uncommon in children, but do occur. However, these conditions are outside of the scope of this book and will therefore not be further discussed.

Although posterior ethmoid, sphenoid, and frontal sinus diseases are less common in children than adults, they do occur. Image guidance can be helpful in the first case with identification of the ethmoid roof and in the latter cases with

identification of the sphenoid face and nasofrontal duct. As we have previously discussed, children sometimes require revision surgery. Image guidance can be useful in confirming the location of the skull base and lamina papyracea (and avoiding potential CNS or eye injury, respectively) when a patient's anatomy has been distorted by prior surgery. Extensive polyposis present in children with cystic fibrosis or other diseases can have a similar effect on anatomy, and these patients may likewise benefit from the use of image guidance.

The authors find image guidance particularly useful when treating patients with orbital subperiosteal abscesses secondary to sinusitis. These patients universally have significant mucosal inflammation that generally responds poorly to vasoconstriction. Moreover the maxillary and ethmoid sinuses are frequently filled with purulence meaning that seeing "draining pus" is an unreliable indicator of successful abscess drainage. In these cases, image guidance can provide additional confirmation that the abscess has been evacuated.

Overall pediatric otolaryngologists have been relatively slow adopters of image guidance technology. A survey of ASPO members in 2005 found that 34 % of respondents never use image guidance when performing FESS [4]. There are no doubt many reasons for the low adoption rate among this group, including the increased cost and time associated with using this equipment. However, some of the reasons likely have to do with the particulars of applying this technology to the pediatric patient. Obviously young children are much smaller than adults, making reliable attachment of the headset difficult at times. Likewise, the small amount of space in a young child's nose and paranasal sinuses, particularly the ethmoid sinuses, can pose particular problems when using image guidance. A drift or calibration variance of less than 2 mm is generally acceptable in adults; however, Lusk [43] recommends no more than 1.5 mm in children.

Balloon Sinuplasty

Sinus surgery has been characterized by innovation, be it the use of telescopes instead of the headlight or intranasal techniques instead of open procedures. Balloon sinuplasty is one of these advancements. The goals of functional endoscopic sinus surgery are mucosal preservation and restoration of normal sinus function. Because it is more mucosal sparing than traditional FESS, some argue balloon sinuplasty is the newest tool to achieve this goal.

In children the maxillary sinus is most frequently addressed with balloon sinuplasty. The procedure is performed under general anesthesia with the patient in a supine position. After adequate decongestion, the guide catheter is inserted into the nose under endoscopic visualization. A wire is introduced through the catheter and directed toward the maxillary sinus ostium, behind the uncinate. Proper placement can be confirmed with fluoroscopy or alternatively using a wire with a lighted end to transilluminate the anterior maxillary sinus wall. Once the wire is in place, the balloon is advanced over the wire into the maxillary sinus, straddling the ostium. With its location confirmed endoscopically, the balloon is inflated, deflated, and then removed (Fig. 22.3a–c). One may irrigate the sinus or aspirate any contents over the wire if desired.

Balloon sinuplasty has been well studied in adult populations as a way of restoring ventilation and drainage of sinuses with minimal trauma. Published complication rates in adults are as low as 0.01 % [44]. In a meta-analysis the procedure improved symptoms in 95 % of adults [45]. One of the biggest criticisms of balloon sinuplasty in general is the perceived high rate of revisions or secondary procedures. However, Weiss et al. [46] reported that revision surgery was only needed in 9.2 % of adults undergoing the procedure. Levine reported revision rates of 1.3 % with a 40-week follow-up. An additional criticism of the procedure is that it does not address the ethmoid sinuses. As ethmoidectomy is often required as a component of FESS, it can be difficult to determine the relative contributions of balloon sinuplasty and endoscopic ethmoidectomy to the surgical outcome. The surgeon must consider these factors when deciding whether this relatively expensive technology is appropriate for their patient. A criticism of this procedure of particular importance to children is that fluoroscopy, originally used to assess wire placement, exposes a child to added radiation. Illuminated guide wires eliminate this risk and should be considered a better choice in the pediatric population.

Outcomes of balloon sinuplasty have only recently been studied in children. One of the earliest reports is by Ramadan in 2009 [47]. Thirty children who had failed medical therapy were offered balloon sinuplasty. Overall 51 of 56 sinuses could be dilated. In 4 of the 5 unsuccessful cases, the inability to cannulate was due to a hypoplastic sinus. There were no complications. In 2010, the same author compared adenoidectomy to balloon sinuplasty in children who failed medical management of sinusitis. Eighty percent of the children undergoing balloon sinuplasty had improvement in their symptoms at 1 year versus 52.5 % improvement in the adenoidectomy group [48]. While most pediatric otolaryngologists do not obtain routine follow-up CT scans, Nogueira et al. [49] showed that 90 % of patients undergoing balloon sinuplasty had improvement in their symptoms and resolution of sinus disease on follow-up CT scans.

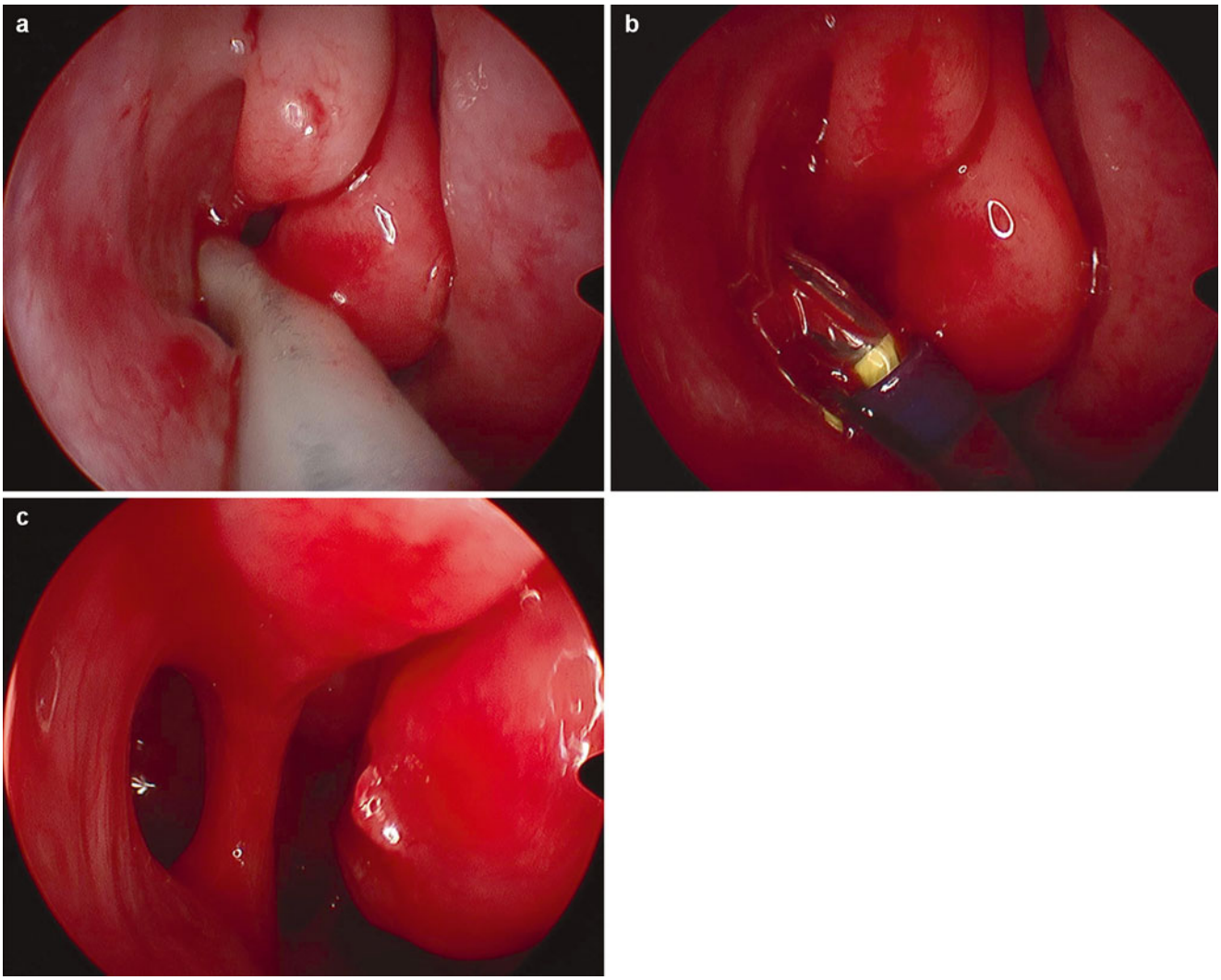


Fig. 22.3 (**a**) Guide catheter in right middle meatus. (**b**) Balloon in maxillary ostium. (**c**) Maxillary ostium after balloon dilatation

Special Patient Populations

Orbital Infections

Patients with orbital abscess or subperiosteal abscess represent a unique patient population in whom surgical management of sinusitis is often necessary. These infections generally come from ipsilateral ethmoiditis, though they also may come from the adjacent frontal sinus [50]. Orbital infections exist on a continuum, and sometimes periorbital (preseptal) cellulitis can be difficult to distinguish from orbital cellulitis, which is more likely to require surgery [51]. When cellulitis progresses to abscess, surgical therapy may be necessary. Medical therapy alone varies from 26 to 93 % in effectivity, while surgical intervention is curative in 95–100 % of cases [52].

Many have attempted to identify clinical indicators on presentation that may predict the need for surgical intervention. A nonmedial abscess location [52] or frontal sinus involvement [53, 54] is more likely to require surgical intervention. The size of the abscess is also a predictor. Ryan et al. [55] found that an abscess larger than 10 mm was more likely to require surgical treatment. Similarly, Todman and Enzer [56] found that an abscess with a volume less than 1,250 mm^3 did not require surgical intervention. Most would agree that surgical intervention is warranted when there is systemic involvement or decreased visual acuity. Surgery is also warranted when a patient does not improve after 48–72 h of antibiotics [52].

The surgical technique involves an uncinectomy and opening up the ethmoid bulla. One can ballot the eye or provide gentle pressure to the lamina with the backside of a freer to determine if there is a dehiscence through which pus can be

evacuated. Such a dehiscence is often present [57]. If a dehiscence is not identified, the lamina papyracea can be gently cracked with a cottle or freer, just posterior to the uncinate process. Care must be taken to not violate the periosteum. At this point or with a small amount of posterior dissection, pus is usually encountered. Evacuation of purulent material can be assisted by gentle external pressure on the orbit. The orbit should become less firm as purulence is drained. Nasal packing is best avoided, if possible. We recommend a maxillary antrostomy and ipsilateral anterior ethmoidectomy be performed at the same time.

Clearly the aim of surgery for this condition is elimination of pus trapped between the lamina papyracea (LP) and the periorbita. However, the extent to which the LP must be opened is not entirely clear. Some recommend a wide resection of the lamina to evacuate all purulence [58]. A wider exposure has greater potential risk of injuring the orbital contents, but this risk must be balanced against the risk of inadequate surgical drainage of the infection [59]. Khalifa [60] compared "limited removal of the lamina" to "wide resection of the lamina" in 13 patients with SPA and decreased visual acuity and ophthalmoplegia and found similar results in the two groups. Overall proptosis, visual acuity, and ophthalmoplegia returned to normal within 24–48 h. Others have reported similar success with limited LP resection [61], and this is our approach as well.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic disease characterized by dysfunction of exocrine glands. The genetic mutation has a negative impact on chloride ion transport. This alteration in chloride ion transport appears to decrease mucociliary clearance throughout the respiratory tract, including the paranasal sinuses. The decrease in mucociliary clearance is likely due to an alteration in the physiochemical properties of the mucus. Mucus stasis then leads to inflammation, which can result in goblet cell dysfunction, further altering the viscosity of the mucus, and squamous metaplasia with resultant loss of cilia [62].

The vast majority of children with CF will have sinonasal involvement, although only a small percentage may be symptomatic [63]. The most common symptoms in these patients are nasal airway obstruction (62 %), rhinorrhea (64 %), and mouth breathing (38 %) [64]. Physical exam findings are variable, though they include polyposis in up to 57 % of patients [65]. Facial changes including hypertelorism, proptosis, or broadening of the nasal bridge may be present as well [66, 67].

Maxillary sinus opacification on CT scan is nearly universally present [65]. The hallmark CT finding in patients with CF, medial displacement of the medial wall of the maxillary sinus, often with demineralization of the bone of the uncinate process [62], is found in up to 75 % of patients [65]. Often the frontal and sphenoid sinuses are underdeveloped in these patients.

Patients with cystic fibrosis who have significant nasal symptoms will often benefit greatly from surgery [68, 69]. However, symptoms will also frequently recur in these patients. Likewise, it is unlikely that sinonasal surgery will have an impact on the child's pulmonary function or lower respiratory symptomatology [70]. It is important for the surgeon to counsel the patient and family regarding these issues preoperatively.

In the past, patients with nasal polyps and CF underwent a polypectomy. With the advent of telescopes and powered instrumentation, managing these patients with endoscopic sinus surgery including ethmoidectomy and wide maxillary antrostomy has led to improved outcomes and decreased (or at least delayed) recurrence rates as well. Cepero et al. [71] noted a 13 % recurrence rate with this approach compared to a 61 % recurrence rate with polypectomy alone. Other studies have reported similar results [72]. This more aggressive approach may facilitate gravitational drainage of the sinuses and improve entrance of any postoperative irrigation into the sinuses.

Not surprisingly, nasal obstructive symptoms are most likely to improve after surgery, whereas headache is less likely to improve [68, 69]. Symptom improvement is of course variable. Fuchsmann et al. [73] reported that of his patients with CF undergoing FESS, 30 % were symptom-free, 40 % had symptoms controlled by medication, and 30 % had another surgery at 3 years follow-up.

While surgery seems to be effective for most symptoms of CF-related sinusitis, it is not without complications. Albritton and colleagues [74] found an overall complication rate of 11.5 % in CF patients undergoing FESS. The most frequent complication encountered was bleeding. They note that many patients have acquired coagulopathies and advanced pulmonary disease making surgical complications more likely.

Sinonasal symptoms frequently recur in these patients, necessitating revision surgery in many. The percentage of patients requiring revision surgery is impossible to accurately ascertain from the literature, as it is dependent on the length of follow-up. However, it is reasonable to conclude that 50 % or more will undergo revision surgery within 4 years of their initial procedure [65]. Not surprisingly, the patient factors that appear to predict the need for repeat surgery are the severity of disease on preoperative CT scan [75] and severity of nasal polyposis prior to the first surgery on clinical examination [76].

Antrochoanal Polyp

Antrochoanal polyps (ACP) are benign masses arising from the maxillary antral mucosa that can grow to fill the nasal passageway and ultimately extend into the choana and nasopharynx. The vast majority of these patients present with nasal obstruction [77]. This tends to be a disease of childhood or early adulthood [78]. The average age at initial presentation varies in the literature from 9 years [79] to 28 years [77]. Antrochoanal polyps account for 4–6 % of all nasal polyps in adults, but 33 % of all polyps in pediatric patients [80].

The etiology of ACP is not clearly understood. Several studies have found a significant association between allergic disease and ACP [77, 81]. On the other hand, histological examination of ACP compared to middle meatal polyps revealed lower numbers of eosinophils and higher numbers of other inflammatory cells in other studies [82, 83].

These lesions can be difficult to remove entirely secondary to variability of their origin within the maxillary sinus and therefore have a high recurrence rate [84]. Ozer et al. [85] found that the attachment site could be identified in only 50 % of patients, with the lateral wall the most common location for attachment (71 %). Other studies have found the posterior wall to be most common [78].

Because of their relatively high recurrence rate, several strategies have been employed in the management of ACP. Endoscopic removal via a wide maxillary antrostomy is the most frequently employed technique [77, 79]. Angled telescopes (45° or 75°) with angled instruments are often employed to insure complete excision of the polyp during endonasal endoscopic surgery [79]. Franche [78] reported a 6.9 % recurrence rate using this approach. Other authors recommend a canine fossa puncture or "mini Caldwell Luc approach" in addition to a transnasal endoscopic approach for removal of ACP (combined approach), citing a much lower recurrence rate. A combined approach yielded no recurrences, whereas an endoscopic transnasal approach alone had a 20–23 % recurrence rate [85–87]. This additional opening in the anterior wall of the maxillary sinus can be used to better access the lateral aspect of the sinus with instrumentation, powered or otherwise, for complete removal of the polyp. These expanded access techniques may potentially lead to dental injury or affect maxillary growth, however. Therefore, the surgeon must carefully weigh the potential benefit of lowered recurrence with these potential increased risks.

Conclusions

Although there remains some controversy in the surgical management of CRS in children, we recommend using a stepwise approach in most children who have failed medical therapy. Adenoidectomy should be performed first. Adenoidectomy is most likely effective as it eliminates a biofilm of pathogenic bacteria from the nasopharynx. If not removed, it has been postulated that these biofilms can seed the paranasal sinuses in certain children. FESS should be considered in those children who have failed adenoidectomy. It has a greater chance of success but carries increased potential risks. To optimize the outcome of FESS, comorbidities, particularly allergic rhinitis, should be managed prior to surgery. Image guidance may increase the safety of pediatric FESS in certain populations. The role of emerging technologies such as balloon sinuplasty in the management of pediatric CRS needs to be further elucidated. Certain diseases, more common in children than adults, such as orbital subperiosteal abscess, sinonasal disease associated with cystic fibrosis, and antrochoanal polyps, are particularly amenable to FESS. These generally require more extensive procedures than pediatric CRS.

References

1. Dugar DR, Lander L, Mahalingam-Dhingra A, Shah RK. Pediatric acute sinusitis: predictors of increased resource utilization. Laryngoscope. 2010;120(11):2313–21.
2. Chan KH, Abzug MJ, Coffinet L, Simoes EAF, Cool C, Liu AH. Chronic rhinosinusitis in young children differs from adults: a histopathology study. J Pediatr. 2004;144:206–12.
3. Cunningham MJ, Chiu EJ, Landgraf JM, Gliklich RE. The health impact of chronic recurrent rhinosinusitis in children. Arch Otolaryngol Head Neck Surg. 2000;126:1363–8.
4. Sobol SE, Samadi DS, Kazahaya K, Tom LW. Trends in the management of pediatric chronic sinusitis: survey of the American Society of Pediatric Otolaryngology. Laryngoscope. 2005;115(1):78–80.
5. Kim HJ, Jung Cho M, Lee JW, Tae Kim Y, Kahng H, Sung Kim H, Hahm KH. The relationship between anatomic variations of paranasal sinuses and chronic sinusitis in children. Acta Otolaryngol. 2006;126(10):1067–72.

6. Berger G, Kogan T, Paker M, Berger-Achituv S, Ebner Y. Pediatric chronic rhinosinusitis histopathology: differences and similarities with the adult form. Otolaryngol Head Neck Surg. 2011;144(1):85–90.
7. Lieu JE, Piccirillo JF, Lusk RP. Prognostic staging system and therapeutic effectiveness for recurrent or chronic sinusitis in children. Otolaryngol Head Neck Surg. 2003;129:222–32.
8. Rudnick EF, Mitchell RB. Long-term improvements in quality-of-life after surgical therapy for pediatric sinonasal disease. Otolaryngol Head Neck Surg. 2007;137(6):873–7.
9. Ramadan HH. Adenoidectomy vs endoscopic sinus surgery for the treatment of pediatric sinusitis. Arch Otolaryngol Head Neck Surg. 1999;125(11):1208–11.
10. Merck W. Pathogenetic relationship between adenoid vegetations and maxillary sinusitis in children. HNO. 1974;22(6):198–9.
11. Shin KS, Cho SH, Kim KR, Tae K, Lee SH, Park CW, Jeong JH. The role of adenoids in pediatric rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2008;72(11):1643–50.
12. Tuncer U, Aydogan B, Soylu L, Simsek M, Akcali C, Kucukcan A. Chronic rhinosinusitis and adenoid hypertrophy in children. Am J Otolaryngol. 2004;25:5–10.
13. Lee D, Rosenfeld RM. Adenoid bacteriology and sinonasal symptoms in children. Otolaryngol Head Neck Surg. 1996;116:301–7.
14. Bernstein JM, Dryja D, Murphy TF. Molecular typing of paired bacterial isolates from the adenoid and lateral wall of the nose in children undergoing adenoidectomy: implications in acute rhinosinusitis. Otolaryngol Head Neck Surg. 2001;125(6):593–7.
15. Zuliani G, Carron M, Gurrola J, et al. Identification of adenoid biofilms in chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2006;70(9):1613–7.
16. Coticchia J, Zuliani G, Coleman C, et al. Biofilm surface area in the pediatric nasopharynx: chronic rhinosinusitis vs obstructive sleep apnea. Arch Otolaryngol Head Neck Surg. 2007;133(2):110–4.
17. Takahashi H, Fujita A, Honjo I. Effect of adenoidectomy on otitis media with effusion, tubal function, and sinusitis. Am J Otolaryngol. 1989;10(3):208–13.
18. Vandenberg SJ, Heatley DG. Efficacy of adenoidectomy in relieving symptoms of chronic sinusitis in children. Arch Otolaryngol Head Neck Surg. 1997;123:675–8.
19. Rosenfeld RM. Pilot study of outcomes in pediatric rhinosinusitis. Arch Otolaryngol Head Neck Surg. 1995;121(7):729–36.
20. Ungkanont K, Damrongsak S. Effect of adenoidectomy in children with complex problems of rhinosinusitis and associated diseases. Int J Pediatr Otorhinolaryngol. 2004;68:447–51.
21. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72(10):1541–5.
22. Buchman CA, Yellon RF, Bluestone CD. Alternative to endoscopic sinus surgery in the management of pediatric chronic rhinosinusitis refractory to oral antimicrobial therapy. Otolaryngol Head Neck Surg. 1999;120:219–24.
23. Criddle MW, Stinson A, Savliwala M, Coticchia J. Pediatric chronic rhinosinusitis: a retrospective review. Am J Otolaryngol. 2008;29(6):372–8.
24. Lund VJ. Fundamental considerations of the design and function of intranasal antrostomies. J R Soc Med. 1986;79(11):646–9.
25. Senior B, Wirtschafter A, Mai C, Becker C, Belenky W. Quantitative impact of pediatric sinus surgery on facial growth. Laryngoscope. 2000;110(11):1866–70.
26. Gross CW, Gurucharri MJ, Lazar RH, Long TE. Functional endonasal sinus surgery (FESS) in the pediatric age group. Laryngoscope. 1989;99(3):272–5.
27. Lusk RP, Muntz HR. Endoscopic sinus surgery in children with chronic sinusitis: a pilot study. Laryngoscope. 1990;100(6):654–8.
28. Verwoerd CD, Urbanus NA, Nijdam DC. The effects of septal surgery on the growth of the nose and maxilla. Rhinology. 1979;17:53–63.
29. Bothwell MR, Piccirillo JF, Lusk RP, Ridenour BD. Long-term outcome of facial growth after functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2002;126(6):628–34.
30. Clement PA, Bluestone CD, Gordts F, Lusk RP, Otten FW, Goossens H, Scadding GK, Takahashi H, van Buchem FL, Van Cauwenberge P, Wald ER. Management of rhinosinusitis in children: consensus meeting, Brussels, Belgium, September 13, 1996. Arch Otolaryngol Head Neck Surg. 1998;124(1):31–4.
31. Lusk RP. Surgical modalities other than ethmoidectomy. J Allergy Clin Immunol. 1992;90(3 Pt 2):538–42.
32. Ramadan HH. Surgical management of chronic sinusitis in children. Laryngoscope. 2004;114(12):2103–9.
33. Chang PH, Lee LA, Huang CC, Lai CH, Lee TJ. Functional endoscopic sinus surgery in children using a limited approach. Arch Otolaryngol Head Neck Surg. 2004;130(9):1033–6.
34. Siedek V, Stelter K, Betz CS, Berghaus A, Leunig A. Functional endoscopic sinus surgery – a retrospective analysis of 115 children and adolescents with chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2009;73(5):741–5.
35. Hebert 2nd RL, Bent 3rd JP. Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. Laryngoscope. 1998;108(6):796–9.
36. Lee TJ, Liang CW, Chang PH, Huang CC. Risk factors for protracted sinusitis in pediatrics after endoscopic sinus surgery. Auris Nasus Larynx. 2009;36(6):655–60.
37. Huang HM, Lee HP, Liu CM, Lin KN. Normalization of maxillary sinus mucosa after functional endoscopic sinus surgery in pediatric chronic sinusitis. Int J Pediatr Otorhinolaryngol. 2005;69:1219–23.
38. Ramadan HH, Hinerman RA. Outcome of endoscopic sinus surgery in children with allergic rhinitis. Am J Rhinol. 2006;20(4):438–40.
39. Ramadan HH. Revision endoscopic sinus surgery in children: surgical causes of failure. Laryngoscope. 2009;119(6):1214–7.
40. Fakhri S, Manoukian JJ, Souaid JP. Functional endoscopic sinus surgery in the paediatric population: outcome of a conservative approach to postoperative care. J Otolaryngol. 2001;30:15–8.
41. Walner DL, Falciglia M, Willging JP, Myer 3rd CM. The role of second-look nasal endoscopy after pediatric functional endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg. 1998;124(4):425–8.
42. Mitchell RB, Pereira KD, Younis RT, Lazar RH. Pediatric functional endoscopic sinus surgery: is a second look necessary? Laryngoscope. 1997;107:1267–9.
43. Lusk R. Computer-assisted functional endoscopic sinus surgery in children. Otolaryngol Clin North Am. 2005;38(3):505–13.
44. Melroy CT. The balloon dilating catheter as an instrument in sinus surgery. Otolaryngol Head Neek Surg. 2008;139:S23–6.

45. Levine HL, Sertich II AP, Hoisington DR, Weiss RL, Pritikin J, PatiENT Registry Study Group. Multicenter registry of balloon catheter sinusotomy outcomes for 1,036 patients. Ann Otol Rhinol Laryngol. 2008;17:263–70.
46. Weiss RL, Church CA, Kuhn FA, et al. Long-term outcome analysis of balloon catheter sinusotomy: two year follow-up. Otolaryngol Head Neck Surg. 2008;139:16–24.
47. Ramadan HH. Safety and feasibility of balloon sinuplasty for treatment of chronic rhinosinusitis in children. Ann Otol Rhinol Laryngol. 2009;118:161–5.
48. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. Ann Otol Rhinol Laryngol. 2010;119(9):578–82.
49. Nogueira Júnior JF, Stamm AC, Pignatari S. Balloon sinuplasty, an initial assessment: 10 cases, results and follow-up. Braz J Otorhinolaryngol. 2010;76(5):588–95.
50. Younis RT, Lazar RH, Bustillo A, Anand VK. Orbital infection as a complication of sinusitis: are diagnostic and treatment trends changing? Ear Nose Throat J. 2002;81(11):771–5.
51. Georgakopoulos CD, Eliopoulou MI, Stasinos S, Exarchou A, Pharmakakis N, Varvarigou A. Periorbital and orbital cellulitis: a 10-year review of hospitalized children. Eur J Ophthalmol. 2010;20(6):1066–72.
52. Coenraad S, Buwalda J. Surgical or medical management of subperiosteal orbital abscess in children: a critical appraisal of the literature. Rhinology. 2009;47(1):18–23.
53. Hawkins DB, Clark RW. Orbital involvement in acute sinusitis. Lessons from 24 childhood patients. Clin Pediatr. 1977;16(5):464–71.
54. Garcia GH, Harris GJ. Criteria for nonsurgical management of subperiosteal abscess of the orbit: analysis of outcomes 1988-1998. Ophthalmology. 2000;107:1454–6.
55. Ryan JT, Preciado DA, Bauman N, et al. Management of pediatric orbital cellulitis in patients with radiographic findings of subperiosteal abscess. Otolaryngol Head Neck Surg. 2009;140:907–11.
56. Todman MS, Enzer YR. Medical management versus surgical intervention of pediatric orbital cellulitis: the importance of subperiosteal abscess volume as a new criterion. Ophthal Plast Reconstr Surg. 2011;27(4):255–9.
57. Deutsch E, Eilon A, Hevron I, Hurvitz H, Blinder G. Functional endoscopic sinus surgery of orbital subperiosteal abscess in children. Int J Pediatr Otorhinolaryngol. 1996;34(1–2):181–90.
58. Eviatar E, Kessler A, Pitaro K. Bidirectional orbital approach enhances orbital abscess drainage. Rhinology. 2009;47:293–6.
59. Mann W, Amedee RG, Maurer J. Orbital complications of pediatric sinusitis: treatment of periorbital abscess. Am J Rhinol. 1997;11:149–53.
60. Khalifa BC. Extent of resection of the lamina papyracea in medial subperiosteal abscess. Otolaryngol Head Neck Surg. 2011;145(1):161–4.
61. Froehlich P, Pransky SM, Fontaine P, Stearns G, Morgon A. Minimal endoscopic approach to subperiosteal orbital abscess. Arch Otolaryngol Head Neck Surg. 1997;123:280–2.
62. Gysin C, Alothman GA, Papsin BC. Sinonasal disease in cystic fibrosis: clinical characteristics, diagnosis, and management. Pediatr Pulmonol. 2000;30(6):481–9.
63. King V. Upper respiratory disease, sinusitis, and polyposis. Clin Rev Allergy. 1991;9:143–57.
64. Stern R, Boat T, Wood R, LeRoy W, Doershuk C. Treatment and prognosis of nasal polyps in cystic fibrosis. Am J Dis Child. 1982;136:1067–70.
65. Yung MW, Gould J, Upton GJ. Nasal polyposis in children with cystic fibrosis: a long-term follow-up study. Ann Otol Rhinol Laryngol. 2002;111(12 Pt1):1081–6.
66. Brihaye P, Clement P, Dab I, Desprechin B. Pathological changes of the lateral nasal wall in patients with cystic fibrosis (mucoviscidosis). Int J Pediatr Otorhinolaryngol. 1994;28:141–7.
67. Hui Y, Gaffney R, Crysdale W. Sinusitis in patients with cystic fibrosis. Eur Arch Otorhinolaryngol. 1995;252:191–6.
68. Keck T, Rozsasi A. Medium-term symptom outcomes after paranasal sinus surgery in children and young adults with cystic fibrosis. Laryngoscope. 2007;117(3):475–9.
69. Nishioka G, Cook P, Davis W, McKinsey J. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. Otolaryngol Head Neck Surg. 1994;110:494–500.
70. Osborn AJ, Leung R, Ratjen F, James AL. Effect of endoscopic sinus surgery on pulmonary function and microbial pathogens in a pediatric population with cystic fibrosis. Arch Otolaryngol Head Neck Surg. 2011;137(6):542–7.
71. Cepero R, Smith R, Catlin F, Bressler K, Furuta G, Shandera K. Cystic fibrosis – an otolaryngologic perspective. Otolaryngol Head Neck Surg. 1987;97:356–60.
72. Crockett D, McGill T, Healy G, Friedman E, Salkeld L. Nasal and paranasal sinus surgery in children with cystic fibrosis. Ann Otol Rhinol Laryngol. 1987;96:367–72.
73. Fuchsmann C, Ayari S, Reix P, Colreavy M, Bellon G, Durieux I, Froehlich P. Contribution of CT-assisted navigation and microdebriders to endoscopic sinus surgery in cystic fibrosis. Int J Pediatr Otorhinolaryngol. 2008;72(3):343–9.
74. Albritton FD, Kingdom TT. Endoscopic sinus surgery in patients with cystic fibrosis: an analysis of complications. Am J Rhinol. 2000;14(6):379–85.
75. Becker SS, de Alarcon A, Bomeli SR, Han JK, Gross CW. Risk factors for recurrent sinus surgery in cystic fibrosis: review of a decade of experience. Am J Rhinol. 2007;21(4):478–82.
76. Scott Rickert S, Banuchi VE, Germana JD, Stewart MG, April MM. Relationship between nasal polyposis and likelihood of revision endoscopic sinus surgery in patients with cystic fibrosis. Arch Otolaryngol Head Neck Surg. 2010;136(10):988–92.
77. Franche GL, Granzotto EH, de Borba AT, Hermes F, Saleh Cde S, de Souza PA. Endoscopic polipectomy with middle meatal antrostomy for antrochoanal polyp treatment. Braz J Otorhinolaryngol. 2007;73(5):689–92.
78. Lee TJ, Huang SF. Endoscopic sinus surgery for antrochoanal polyps in children. Otolaryngol Head Neck Surg. 2006;135(5):688–92.
79. Eladl HM, Elmorsy SM. Endoscopic surgery in pediatric recurrent antrochoanal polyp, rule of wide ostium. Int J Pediatr Otorhinolaryngol. 2011;75(11):1372–5.
80. Başak S, Karaman CZ, Akdilli A, Metin KK. Surgical approaches to antrochoanal polyps in children. Int J Pediatr Otorhinolaryngol. 1998;46(3):197–205.

81. Cook PR, Davis WE, McDonald R, McKinsey JP. Antrochoanal polyposis: a review of 33 cases. Ear Nose Throat J. 1993;72(6):401–2, 404–10.
82. Min YG, Chung JW, Shin JS, Chi JG. Histologic structure of antrochoanal polyps. Acta Otolaryngol. 1995;115(4):543–7.
83. Ozcan C, Zeren H, Talas DU, Küçükoğlu M, Görür K. Antrochoanal polyp: a transmission electron and light microscopic study. Eur Arch Otorhinolaryngol. 2005;262(1):55–60.
84. Woolley AL, Clary RA, Lusk RP. Antrochoanal polyps in children. Am J Otolaryngol. 1996;7(6):368–73.
85. Ozer F, Ozer C, Cagici CA, Canbolat T, Yilmazer C, Akkuzu B. Surgical approaches for antrochoanal polyp: a comparative analysis. B-ENT. 2008;4(2):93–9.
86. Lee JY, Baek BJ, Kim DW, Byun JY, Lee SW, Hong HS. Changes in the maxillary sinus volume and the surgical outcome after the canine fossa puncture approach in pediatric patients with an antrochoanal polyp: results of a minimum 3-year follow-up. Am J Rhinol Allergy. 2009;23(5):531–4.
87. Atighechi S, Baradaranfar MH, Karimi G, Jafari R. Antrochoanal polyp: a comparative study of endoscopic endonasal surgery alone and endoscopic endonasal plus mini-Caldwell technique. Eur Arch Otorhinolaryngol. 2009;266(8):1245–8.
88. American Academy of Otolaryngology-Head and Neck Surgery. Intra-operative use of computer aided surgery. 2013. www.entnet.org/Practice/policyIntraOperativeSurgery.cfm. Last accessed on 7 Aug 2013.

Chapter 23
Surgical Management of Rhinosinusitis with and Without Polyps in Adults

Marcelo B. Antunes and David W. Kennedy

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of multifactorial etiology. It is estimated to affect 5–15 % of the American population, resulting in over 600,000 surgeries in the United States alone with an annual cost that surpasses $8 billion [1–6]. Patients with CRS also have significant decrements in quality of life, having worse scores for physical pain and social functioning than patients suffering from chronic obstructive pulmonary disease, congestive heart failure, back pain, or angina [7].

Despite the incredible impact on the health-care system and on patients' quality of life, its pathogenesis has not been well defined. It appears that CRS is a syndrome with multiple etiologic factors that has inflammation of nasal mucosa and underlying bone as a common end point. The inflammatory process resulting in mucosal edema leads to impairment of mucociliary clearance and ostial obstruction, which, in turn, results in further inflammation or infection. There are many potential causes that could trigger this process such as infection by bacteria, fungi, or viruses, bacterial biofilms, superantigens, osteitis, allergies, and genetic factors [4, 8–12]. A discussion of all the potential pathophysiologic factors and mechanisms that may play a role in CRS has been presented in previous chapters.

CRS has been classically differentiated between CRS with or without nasal polyps (NP). The etiologic factors in both those groups, however, have a significant overlap. Another classification of CRS is based on the histology, and patients are divided into eosinophilic and non-eosinophilic (neutrophilic or mixed). CRS without nasal polyps is rarely eosinophilic while CRS with nasal polyps is eosinophilic in about 80 % of cases. This classification has an important prognostic implication with patients presenting with eosinophilic CRS having a worse long-term outcome. Examples of eosinophilic CRS are patients with allergies, asthma, aspirin-exacerbated respiratory disease, and allergic fungal rhinosinusitis and in CRS induced by superantigens. Examples of non-eosinophilic CRS are patients with cystic fibrosis and antrochoanal polyp and in ciliary dyskinesia syndromes.

Primary Functional Endoscopic Sinus Surgery

General Principles

Several early studies described the importance of the ethmoid area in triggering disease in the maxillary, frontal, and sphenoid sinuses [13–15]. In the 1970s, Messerklinger [16] performed endoscopic studies of mucociliary clearance and

M.B. Antunes, MD • D.W. Kennedy, MD, FACS, FRCSI (✉)
Department of Otorhinolaryngology: Head and Neck Surgery, Perelman School of Medicine of the University of Pennsylvania, University of Pennsylvania Medical Center, 5 Ravdin, Pavilion, 3400 Spruce Street, Philadelphia, PA 19104, USA
e-mail: kennedyd@uphs.upenn.edu; antunes.m@gmail.com

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_23,

established the basis for modern endoscopic sinus surgery. He observed that if two mucosal surfaces are in contact with each other, this would disrupt normal mucociliary clearance and result in mucous stasis. Furthermore, he was able to confirm the area of the ethmoid infundibulum and middle meatus (ostiomeatal unit or ostiomeatal complex) as the primary site of involvement in the process [17]. Ostial obstruction, with blockage of sinus ventilation and mucous drainage, is the final common pathway for the development of rhinosinusitis in most cases. Whether medical or surgical, therapeutic intervention must be aimed, at least in part, at relieving ostial obstruction, reestablishing the sinus ventilation, and restoring mucociliary clearance. With those goals in mind, in the 1980s, the early reports on functional endoscopic sinus surgery (FESS) [18, 19] started to appear in the literature and defined the principles of modern sinus surgery.

Indications

The primary indication for FESS is chronic rhinosinusitis that is refractory to maximal medical therapy, although recurrent acute sinusitis, tumors, and acute sinusitis with threatened complications are less frequent indications. CRS is defined as persistent inflammation of the mucosa and, in some cases, of the underlying bone of the nose and paranasal sinuses that lasts for at least 12 consecutive weeks. Recurrent acute rhinosinusitis is defined as at least four episodes per year with associated persistent CT abnormalities after medical therapy. Although maximal medical therapy has not been formally defined, it may include a combination of prolonged courses of culture-directed or broad-spectrum antibiotics, nasal and oral steroids, antihistamines or decongestants, and other supportive therapies such as nasal irrigations. The duration of the therapy is variable, but it should be remembered that surgery in chronic rhinosinusitis is primarily adjunctive to medical therapy when a patient has continuing symptoms.

The same recommendation applies to sinonasal polyposis, although it frequently requires both medical and surgical treatment to achieve adequate clinical improvement. The goal of FESS in these cases is to remove the polyp mass and reestablish sinus drainage and ventilation. Complete cure of polyposis, particularly when extensive disease is present, is unlikely and should be discussed with the patient. Patients with CRS with NP should be informed that they have an underlying mucosal hyperreactivity and tendency to reform polyps despite efforts to remove them surgically. Although NP tend to recur after sinus surgery, redevelopment of symptomatic disease can often be avoided by careful long-term endoscopic follow-up in the office setting. Local debridement and cleaning, long-term medical management with topical corticosteroids, intermittent courses of antibiotics, and occasional use of oral corticosteroids all play key roles in abating symptomatic disease in most polyp patients. Serial office endoscopy is essential in providing an objective assessment of a patients' response to medical therapy in that persistent postsurgical disease can be frequently asymptomatic. If any residual persistent asymptomatic disease is aggressively treated, and the cavity can be returned to normal such patients do not commonly require revision surgery down the road.

The diagnosis of allergic fungal sinusitis also should be considered in patients who do not respond to conventional medical therapy. These patients usually present with nasal polyps and thick brown nasal secretions (peanut butter consistency). Collaborative findings are the presence of fungal elements on stains or positive identification of organisms on culture, areas of increased signal intensity on computed tomography (CT) (Fig. 23.1) or decreased signal intensity on T_2-weighted magnetic resonance imaging (MRI), and history of hypersensitivity to fungal antigens. Optimal therapy for allergic fungal sinusitis requires endoscopic surgical debridement [20] and careful, long-term endoscopic follow-up, along with oral corticosteroids and in some cases oral antifungal therapy. This topic is discussed in greater detail in another chapter.

Management of the patient's allergies is frequently neglected but extremely important, particularly in cases of CRS complicated with nasal polyposis. An association between CRS with and without NP and allergy has been firmly established, although a causal relationship has not been well defined. Although allergy is an IgE-mediated disorder, eosinophilia is not always related to IgE. Studies have shown that about half of patients with eosinophilic CRS had evidence of inhalant atopy [21]. When comparing CRS with NP versus CRS without NP, skin test for inhalant allergens was positive in 44 % of patient with NP versus 17 % of patients without NP. All patients with CRS should undergo allergy testing to better delineate the patient's allergic profile, to improve environmental control, and to consider allergen-specific immunotherapy.

Other issues that need to be addressed preoperatively are environmental irritants, especially smoking. Tobacco use is a worldwide epidemic that the World Health Organization (WHO) estimates account for 3 % of the world's morbidity and mortality at a cost of tens of billions of dollars annually [22]. Tobacco smoke exposure has been suggested as a risk factor for CRS [23], with studies demonstrating that smokers have a higher prevalence of CRS when compared with nonsmokers [24–26]. Moreover, cigarette smoking has also been implicated in worse outcomes following FESS [27–32]. Although evidence is mounting linking tobacco smoke exposure and CRS, the pathophysiologic mechanisms are yet to be identified. Recently, it was demonstrated that tobacco smoke exposure induces an increase in biofilm mass in respiratory bacteria [33, 34], which may contribute to the refractory nature of many respiratory infections found in smokers. On the other hand,

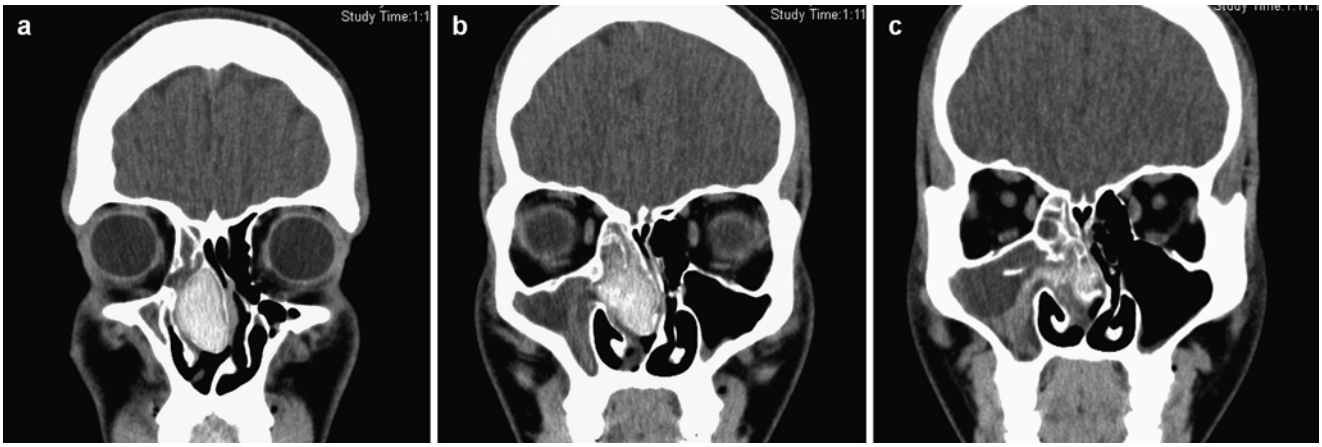


Fig. 23.1 Coronal CT cuts in a patient with right-sided allergic fungal sinusitis. (**a**) An anterior coronal cut demonstrates a concha bullosa on the right side filled with material of increased density (allergic mucin). There is a septal deformity toward the opposite side. (**b**) More posteriorly, some hyperdense material is also seen extending into the maxillary sinus. (**c**) A cut in the region of the anterior ethmoidal neurovascular bundle demonstrates also some bony thickening (osteitis) in the ethmoid bony partitions

recent studies suggest that an active smoking status may not have a negative impact on clinical outcome following FESS, although the degree of any adverse effect may be exposure related [31, 35, 36]. The issue remains controversial. However, based upon the senior author's prior reported outcome experience where the influence of smoking was dramatic, we do not perform elective endoscopic sinus surgery unless the patient has stopped smoking.

There is also an evolving role for surgery in cases of complicated acute rhinosinusitis, such as those with orbital or intracranial extensions or those refractory to medical intervention. Endoscopic surgery in acute rhinosinusitis has been increasingly utilized for acute frontal sinusitis that is refractory to medical management. This has largely replaced external trephination, the traditional approach to severe acute frontal sinusitis, due to its more physiologic and long-lasting effect. Trephination tends to be more invasive and prone to recurrence. In cases of acute rhinosinusitis with orbital complications, FESS can provide access to medial orbital wall. With resection of the lamina papyracea, the surgeon can expose the periorbital fascia, which can be incised to decompress the orbital cellulitis or drain the orbital abscess. In those cases, the acute inflammatory process creates an extremely challenging operative field, which is why such surgery is recommended only for skilled and experienced surgeons. The traditional open approach with external ethmoidectomy may still be used by less experienced endoscopists.

Extended indications for FESS include mucoceles, mucopyoceles, sinus and skull base tumors, intracranial tumors, cerebrospinal fluid leaks, orbital and optic nerve decompression, distal obstruction of the lacrimal system, and other diverse pathologies (Table 23.1). Mucoceles and mucopyoceles are best managed initially with FESS [37]. These lesions tend to erode or remodel the surrounding bone and can extend intracranially or intraorbitally. In these cases, the mucocele membrane is firmly adhered to the underlying dura or periorbita and difficult to detach. Marsupialization though an endoscopic approach is safe and effective, sparing the patient from the morbidity associated with an open approach and craniotomy (Fig. 23.2).

Benign and malignant neoplasms of the sinuses, anterior skull base, or medial orbital wall can be amenable to endoscopic resection (Fig. 23.3). The endoscopic approach may spare the patient a craniotomy and/or more radical extirpative procedures. Perhaps more importantly, office nasal endoscopy permits excellent visualization of the operative site, allowing for earlier detection of recurrent tumor growth in lesions, such as inverting papilloma, which has a known recurrence rate. Cerebrospinal fluid (CSF) rhinorrhea may be idiopathic, iatrogenic, or posttraumatic, and all may be approached endoscopically. If a CSF leak results from prior endoscopic surgery, the most common site of injury is along the vertical lamella of the cribriform plate proximate to the anterior ethmoid artery. The bone is exceptionally thin in this area and the dura tightly adherent. Because of the anatomic orientation of the right-handed surgeon, this complication most commonly occurs on the patient's right side (Fig. 23.4). The dural defect in these cases tends to be limited, and repair of the defect is most easily performed with a free mucosal graft taken from the nose. With more extensive dural defects, such as following a skull base tumor resection, closure may require several layers of support, perhaps with a free bone or cartilage graft along with a local pedicled mucosal flap. The endoscopic management of skull base defects avoids the significant morbidity associated with a craniotomy.

In the surgical treatment of dysthyroid ophthalmopathy, endoscopic orbital decompression compares favorably with traditional techniques [38, 39]. One study reported a 4.7-mm recession with endoscopic decompression alone and a 5.7-mm

Table 23.1 Indications for endoscopic sinus surgery

Inflammatory disease
Chronic rhinosinusitis with or without polyps
Recurrent acute rhinosinusitis
Complicated acute rhinosinusitis
Sinonasal mucoceles or mucopyoceles
Allergic fungal sinusitis
Antrochoanal polyp
Adenoid hypertrophy
Neurorhinologic disorders
Cerebrospinal fluid rhinorrhea and skull base defects
Occasionally rhinopathic headaches refractory to medical therapy
Intractable vasomotor rhinitis (endoscopic Vidian neurectomy)
Neoplastic diseases
Inverting papilloma
Paranasal sinus osteoma
Skull base tumors
Pituitary tumor
Paranasal sinus malignancies
Orbital disorders
Dysthyroid ophthalmopathy
Optic nerve decompression
Nasolacrimal duct obstruction
Other
Epistaxis
Submucous resection of nasal septal deviation
Choanal atresia or stenosis
Intranasal foreign body

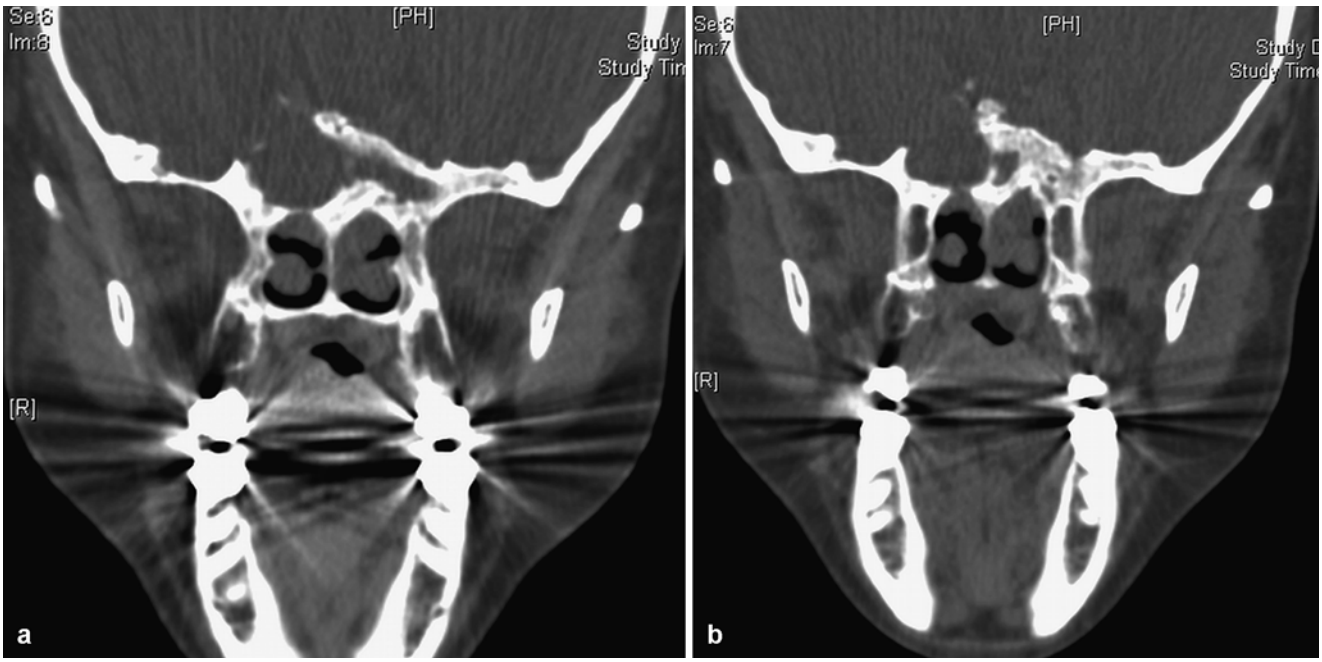


Fig. 23.2 Coronal CT scans (**a, b**) demonstrating a right sphenoid mucocele with erosion of the lateral wall and partial roof of the sphenoid sinus in the region of the carotid artery and optic nerve. Note the osteitic bone on the opposite left side. The patient was satisfactorily managed with an endoscopic procedure and has remained disease-free for 6 years

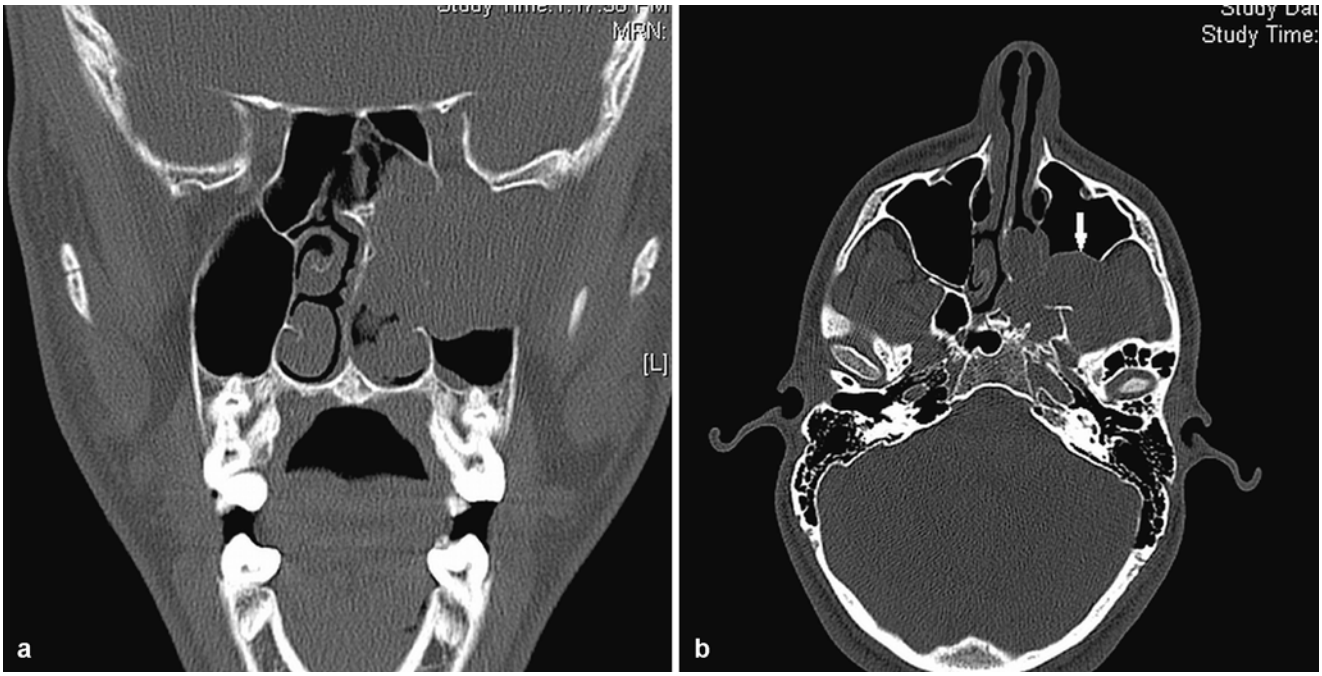


Fig. 23.3 Coronal and axial CT scans in an 18-year-old patient with a left-sided juvenile angiofibroma. (**a**) Coronal CT: a mass is seen within the nasal cavity extending into the pterygopalatine fossa, infraorbital fissure, floor of the sphenoid sinus, and infratemporal fossa. (**b**) Axial CT demonstrates the classical Holman-Miller sign (anterior displacement of the posterior wall of the maxillary sinus) (*arrow*). The tumor was removed endoscopically following embolization

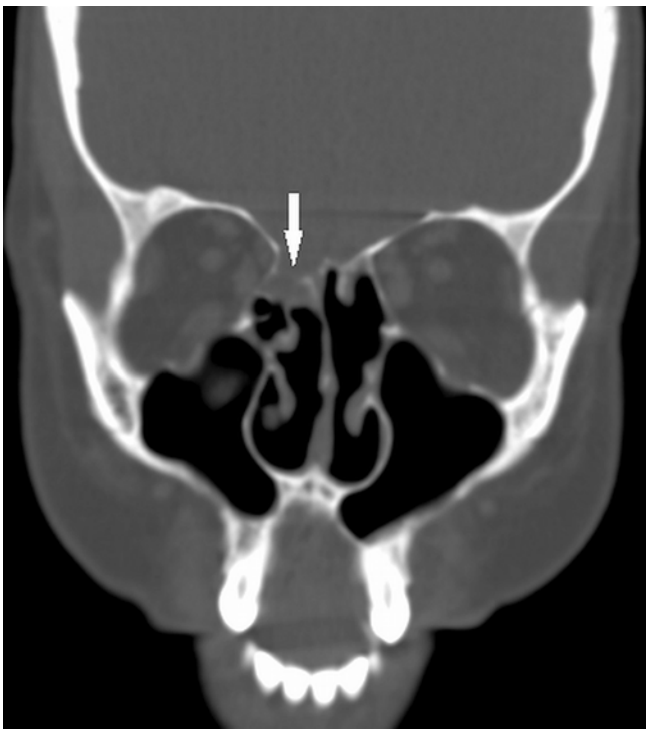


Fig. 23.4 Coronal CT scan demonstrating a right-sided skull base dehiscence with a small meningocele. The patient was referred following prior endoscopic sinus surgery with a history of a cerebrospinal fluid rhinorrhea. The CT scan demonstrates a dehiscence in the right skull base in the region of the attachment of the right middle turbinate (*arrow*). Both inferior turbinates have been partially removed and there is subtotal resection of the left middle turbinate

recession with the endoscopic approach combined with lateral orbitotomy [40]. The nasal telescope permits superior visualization of the orbital apex via the posterior ethmoid sinuses, an area often not fully accessible by the external or transantral routes. This allows for optimal posterior orbit and optic nerve decompression in cases of traumatic optic neuropathy. However, in order to minimize diplopia, a balanced medial and lateral orbital decompression is recommended. Dacryocystitis

and distal lacrimal obstruction requiring surgical intervention can also be managed endoscopically, and encouraging preliminary results have been reported [41].

Endoscopic sinus surgery has been employed in some cases of refractory non-migrainous headache syndromes thought to have a rhinogenic origin through mucosal impaction or presumed pressure changes within a sinus cavity. However, the roles that nasal anatomic abnormalities might play in a headache symptom complex remain very controversial [42–44]. In all cases of headache with absent or limited demonstrable sinus pathology, surgery must be considered the treatment of last resort and the risks of FESS weighed against the possible benefits. This subject is discussed in greater detail in another chapter.

A variety of other conditions can be addressed with the endoscopic approach as described in Table 23.1.

Preoperative Evaluation

Clinical History

On initial patient presentation, a thorough and careful history is obtained investigating in depth all the signs and symptoms associated with the diagnosis of CRS as defined by the 1996 Task Force [45]. The most common symptoms of chronic rhinosinusitis are nasal congestion, obstruction, and postnasal discharge. However, decreased sense of smell, although not specific, is one of the most sensitive symptoms. It is important that the duration, intensity, and localization of facial pain and pressure, nasal obstruction, nasal discharge, postnasal drip, hyposmia, headache, halitosis, dental pain, fatigue, cough, and ear pressure are all determined. Since CRS can masquerade as a variety of other disorders, specific inquiry is made regarding fever, visual disturbances, smell and taste disorder, allergy, immune dysfunction, asthma, bronchitis, and systemic disease. Patients should also be asked about any previous medical and surgical treatments. Multiple sinus-related questionnaires (SNOT-20, CSS, and RSOM-31) are available, but they are used mostly for research purposes. A complete otolaryngologic head and neck exam should precede the endoscopic examination.

Nasal Endoscopy

Perhaps the chief benefit gained from the use of nasal telescopes is the ability to diagnose and follow the course of sinus disease in the office setting. Diagnostic nasal endoscopy is performed with the patient in the upright or semi-sitting position. Each nasal cavity is sprayed with a topical decongestant and anesthetic. A flexible fiber-optic endoscope may be utilized, but it does not facilitate the passage of an endoscopically directed culture or instrumentation, and the optical resolution is suboptimal. The 30°, 4.0-mm rigid scope is most commonly employed in otolaryngologic practice, but occasionally an extremely narrow nasal cavity may necessitate using the 2.7-mm scope. The "three-pass" technique is advocated (Fig. 23.5). The scope is first introduced into the nasal cavity along the floor of the nose, medial to and below the inferior turbinate, and gradually advanced back to the nasopharynx. The examiner should note any inferior turbinate mucosal abnormality, the presence and character of secretions, the adenoids, and Eustachian tube. A second pass of the scope is then made between the middle and inferior turbinates. The middle meatus (anteriorly) and sphenoethmoid recess (posteriorly) can thus be noted. Frequently, the sphenoid ostium can be seen above the posterior nasal choana within the sphenoethmoid recess, and isolated sphenoid or posterior ethmoid disease may be identified in this manner. The third pass of the scope is lateral to the middle turbinate into the middle meatus. This manipulation is frequently more uncomfortable for the patient, so additional anesthesia (4 % cocaine solution on a cotton-tipped applicator) may be required. Within the middle meatus, the components of the OMC (uncinate process, hiatus semilunaris, ethmoid bulla) can usually be visualized, and pathologic changes, such as hypertrophic mucosa, polyps, and purulent secretions, can be noted.

On the basis of clinical history and nasal endoscopic findings, the physician typically prescribes a course of therapy. On return visit, nasal endoscopy is again performed at which time the physician assesses the patient's response to therapy. Nasal endoscopy thus proves diagnostically more sensitive than plain films for accessible changes within the ostiomeatal complex and more cost-effective than repeat CT scanning in the follow-up of chronic rhinosinusitis.

Radiology

Patients are selected for radiographic evaluation based on their response to medical therapy as determined by follow-up endoscopy. Medical responders typically return to the office for periodic endoscopic exams, and the need for CT imaging is avoided.

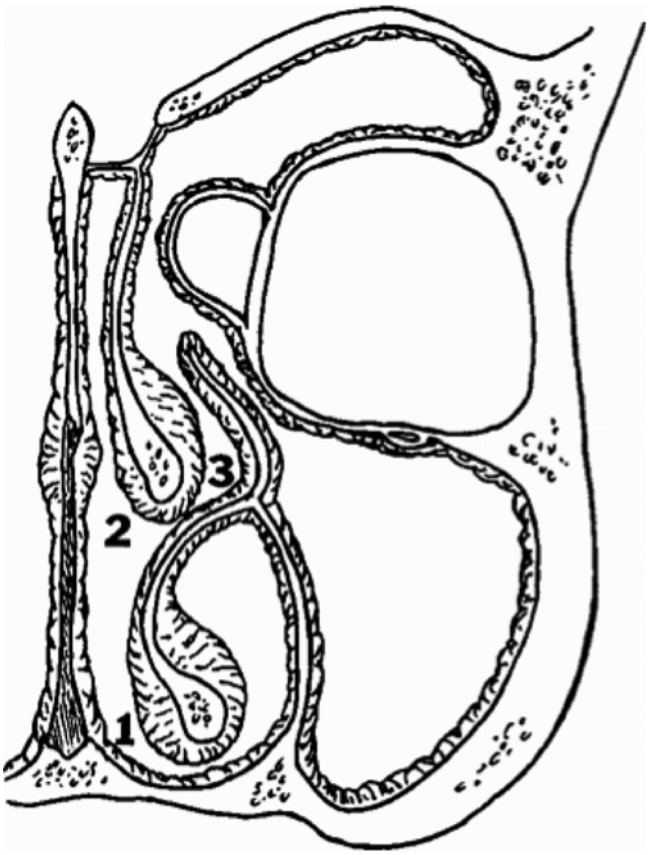


Fig. 23.5 Diagrammatic representation of the 3-pass technique. The *first pass* is along the floor of the nose, the *second pass* is between the middle and inferior turbinate and allows visualization of the sphenoethmoidal recess, and the *third pass* is into the middle meatus. The third pass may require additional anesthesia to the middle turbinate and is not possible in all patients, but frequently can be achieved with some medial displacement of the middle turbinate and a 2.7-mm telescope

Patients whose symptoms recur following cessation of medical therapy, patients with suspected complications, and patients who do not respond to medical therapy are selected for CT evaluation. Patients may have normal endoscopic examinations, but if symptoms are persistent, a sinus CT is indicated. The role of imaging is therefore to define the paranasal sinus anatomy and identify disease, which cannot be identified endoscopically in medical nonresponders. CT evaluation is thus reserved primarily for patients who are considered surgical candidates based on their clinical course and nasal endoscopic findings (Fig. 23.6). Plain films may be of some benefit in evaluating acute sinusitis, but they fail to reveal the anatomic detail in the OMC region and they are therefore not considered useful in the diagnosis of chronic sinusitis. Coronal CT scanning (without contrast) with window width/length ratios to optimize bony detail is the imaging modality of choice [46]. Axial views are occasionally useful in planning revision surgery, especially in the frontal and sphenoid regions. MRI does not define the fine bony architecture of the ethmoid labyrinth well, but is useful in evaluating paranasal sinus neoplasms. MRI should also be performed prior to surgery in all cases where sinus opacification occurs in an area adjacent to a skull base defect. In this situation, this imaging modality is helpful in distinguishing the nature of the soft tissue and helps to exclude the possibility of a meningocele or encephalocele.

With rare exceptions, sinus CT should be obtained only after a prolonged course of medical therapy, so that the abnormal radiographic findings identified have surgical significance. The CT will define areas of mucosal thickening, ostial obstruction, anatomic variations or abnormalities, and air–fluid levels that may indicate persistent or recurrent inflammatory disease (Fig. 23.7). Care must be taken when interpreting sinus CTs, since 24–39 % of the asymptomatic general public will display some mucosal changes on CT and essentially everyone has significant CT changes at some point during a viral upper respiratory tract infection [47]. No patient is considered a surgical candidate on the basis of CT findings alone but rather based on the combined information gathered from careful history, nasal endoscopic examination, response to medical therapy, and CT findings. These guidelines are modified for patients who develop complications of sinusitis while on medical therapy or intolerable side effects of the medications themselves.

A detailed review of the radiographic anatomy of this region is warranted before further discussion of surgical technique. The coronal sinus CT is read in an anterior-to-posterior direction, starting with the frontal sinus. Complete absence of the frontal sinus occurs in 10–15 % of patients and should be considered a variation of normal. The frontal recess is the drainage pathway of secretions that exit the frontal sinus through the frontal ostium and communicates with the ethmoid infundibulum inferiorly. The former term, "frontonasal duct," is no longer an accepted terminology since, in most cases, the anatomy of the

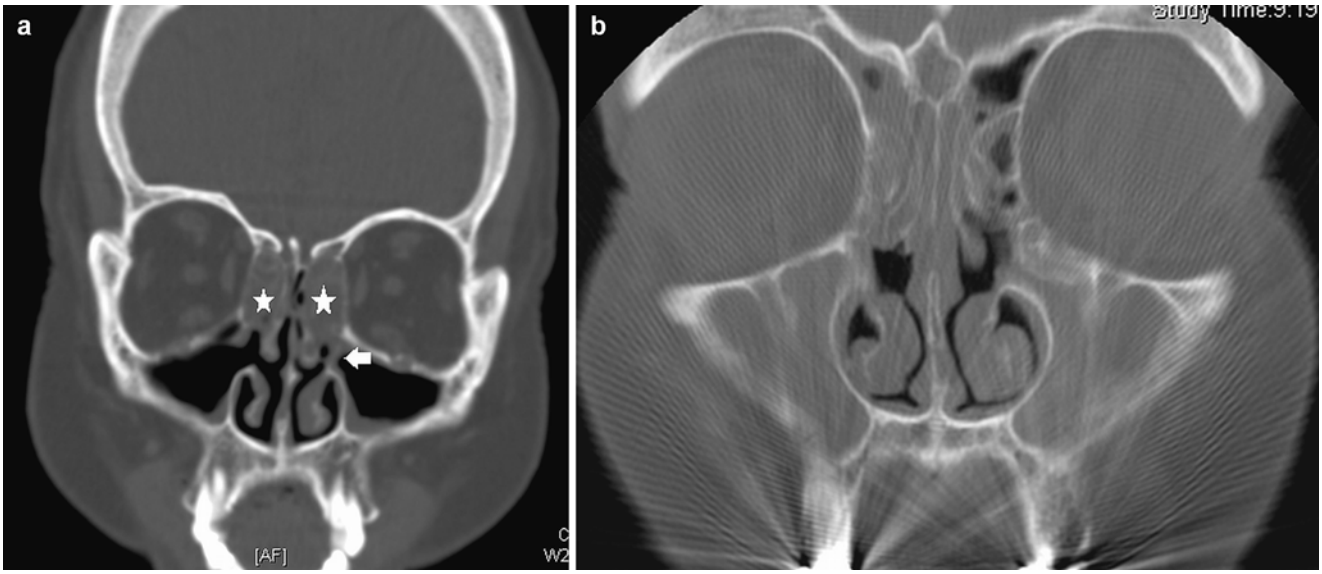


Fig. 23.6 (**a**) Coronal sinus CT scan in the ostiomeatal region demonstrating recurrent or persistent bilateral ethmoid disease (*asterisks*) following prior surgery elsewhere. There are marked residual ethmoid cellular partitions and there is mild bilateral maxillary sinus mucosal thickening. Note there is some residual uncinate process on the left side (*arrow*). (**b**) Coronal CT through the area of the ostiomeatal complex in a patient with bilateral chronic sinusitis. The patient has had some prior surgery and the uncinate processes have been removed bilaterally. There is still bilateral maxillary, ethmoid, and frontal recess disease and the bone in several areas (left infraorbital cell, maxillary sinus, and ethmoid bony partitions) is starting to show thickening (osteitis) as a result of chronic inflammation

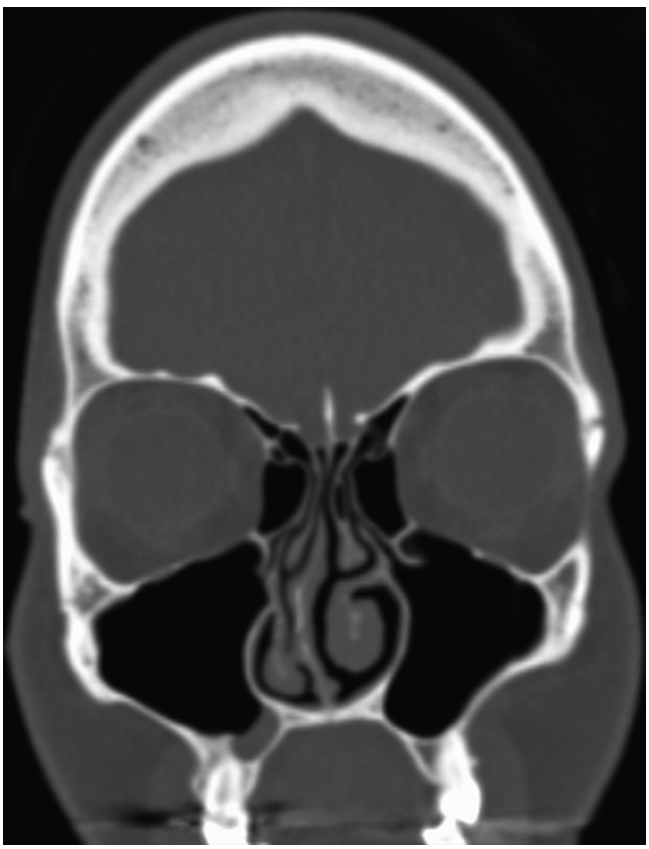


Fig. 23.7 Coronal sinus CT in a patient at the level of the ostiomeatal complex demonstrating a septal deformity and some narrowing of the right ostiomeatal complex and minimal maxillary sinus mucosal thickening on the sinus floor

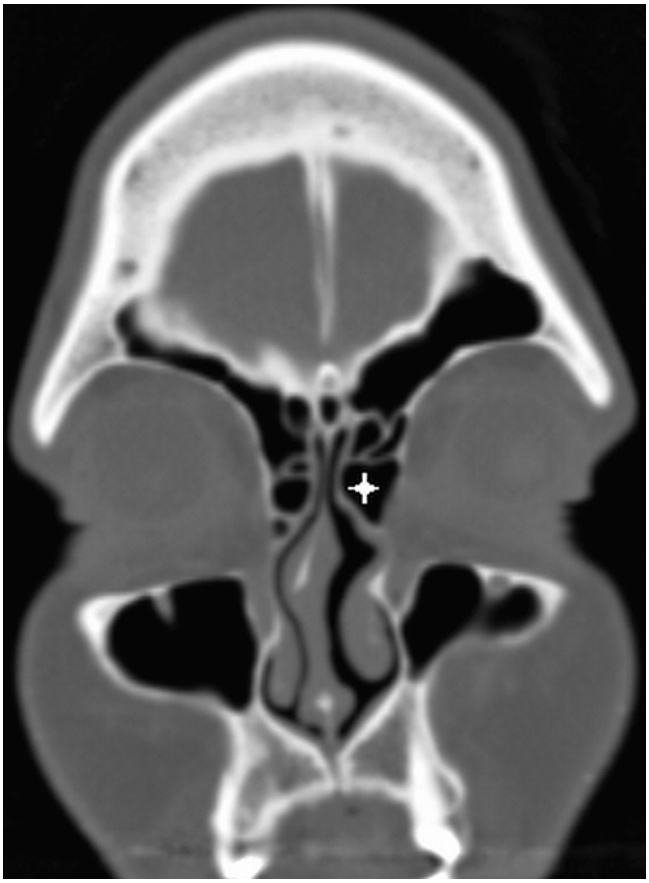


Fig. 23.8 Coronal CT scan through the agger nasi area demonstrates a septal deformity toward the right side and a large left-sided agger nasi cell (*star*). The sinuses are free of mucosal disease

area resembles a recess more than an actual tubular structure. Although the agger nasi and dome of the ethmoid bulla form its anterior and posterior borders, the medial limit of the frontal recess is the superior-most attachment of the middle turbinate. This anatomic arrangement may explain why there is a tendency toward frontal recess stenosis after middle turbinate resection [48]. The frontal ostium has been described as the waist of an hourglass [49], with the dilated chambers of the frontal sinus above and frontal recess below the ostium. Mucociliary transport in the frontal sinus is unique in that the mucus recirculates within the sinus before exiting, and secretions at the frontal recess can even be transported into the sinus [50]. The agger nasi is defined as the eminence on the lateral wall of the nose just anterosuperior to the superior attachment of the middle turbinate. It is usually pneumatized, in which case an agger nasi cell is present. This cell is the most anterior and superior of the anterior ethmoid cells. Its position near the ostium and floor of the frontal sinus gives it considerable significance in frontal sinus disease (Fig. 23.8).

Posterior to the agger nasi, the region of the OMC can be identified. It consists of bony structures (uncinate process, ethmoid bulla, middle turbinate) and air spaces (frontal recess, infundibulum, middle meatus, and the ostia of the anterior ethmoid, maxillary, and frontal sinuses). The uncinate articulates with the lacrimal bone anteriorly and occasionally with the inferior turbinate bone inferiorly. The uncinate usually is confluent with the agger nasi superiorly, often ascending superomedially to form the medial wall of an agger nasi cell. It can also attach laterally into the medial orbital wall (lamina papyracea) or medially into the middle turbinate. The uncinate process then courses posteriorly at its inferior portion, attaching to the membranous tissue of the posterior fontanelle. This fontanelle forms most of the medial wall of the maxillary sinus. The ethmoid bulla is the largest, most consistently found anterior ethmoid cell(s). The bulla lies immediately posterior to the uncinate process, separated only by the three-dimensional, funnel-shaped space known as the ethmoid infundibulum. The two-dimensional distance between the uncinate anteriorly and the ethmoid bulla posteriorly is known as the hiatus semilunaris, which leads into the infundibulum situated more anterolaterally. The bulla is attached to the lamina papyracea and sometimes to the skull base superiorly. The middle turbinate forms the medial border of the ethmoid sinus system. Its

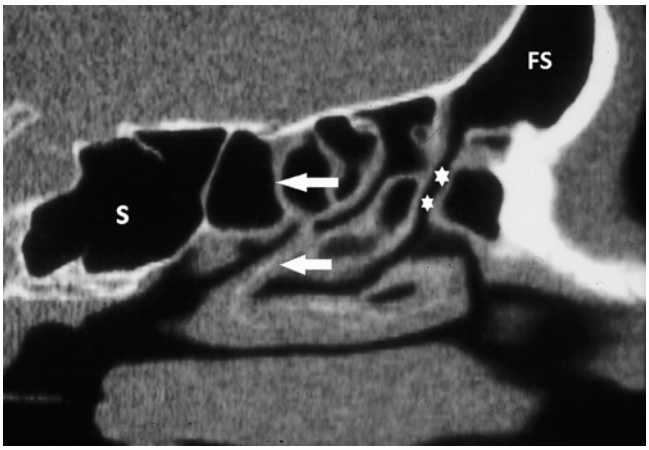


Fig. 23.9 A sagittal CT scan of normal sinus anatomy demonstrates the frontal sinus (*FS*), the hiatus semilunaris (*stars*), basal lamella (*arrows*), and sphenoid sinus (*S*)

superior bony attachment is the lateral edge of the cribriform plate, whereas it has mucosal connections with the lateral nasal wall via the medial aspect of the agger nasi. Various anatomic variations of the middle turbinate have been described, including paradoxical curvature, partial or superior pneumatization (interlamellar cell), complete or inferior pneumatization (concha bullosa), and others. These variations in middle turbinate anatomy potentially have pathologic significance [51].

Posterior to the ethmoid bulla is the basal lamella, the posterolateral attachment of the middle turbinate. This structure is usually a single partition of bone but can occasionally be pneumatized and thus have an anterior and posterior wall. It articulates laterally with the medial orbital wall and with the ascending process of the palatine bone, which forms the posterolateral wall of the maxillary sinus. The lamella has an oblique vertical orientation, so that it lies more anteriorly at its superior aspect and more posteriorly at its inferior aspect. It usually does not articulate fully with the skull base. The basal lamella is the partition separating the anterior from the posterior ethmoid chambers. The posterior ethmoid cells are larger and fewer in number than the anterior ethmoids (Fig. 23.9). They are bounded medially by the superior turbinate, posteriorly by the anterior sphenoid wall, superiorly by the skull base, and laterally by the orbital wall. The superior turbinate may have a lamella by which it attaches to the medial orbital wall. The medial wall of the orbit courses more medially in this posterior region, and occasionally the bony canal housing the optic nerve can be identified in the posterior ethmoid. If a posterior ethmoid cell pneumatizes posteriorly into the sphenoid bone or lateral to the optic nerve, a sphenoethmoidal cell (Onodi) is said to exist. The most posterolateral ethmoid cell typically is a pyramid-shaped sinus, with the wider base anterior and the apex posterior. The anterior face of the sphenoid sinus and sphenoid ostium is usually medial and somewhat inferior to this cell. The anterior wall of the sphenoid typically is convex and bulges forward anteriorly in this area.

The natural ostium of the sphenoid sinus is located medial to the superior turbinate and thus lies outside the ethmoid labyrinth. The floor of the sphenoid sinus lies at a level considerably below the ostium, so that drainage of secretions is not passive or gravity dependent but depends on active mucociliary clearance. Sphenoid sinus pneumatization patterns have been described as presellar (or conchal), sellar, or postsellar [52], depending on the extent of pneumatization and the relationship to the sella turcica. The lateral walls of the sphenoid contain the indentations of the carotid artery and optic nerve.

The natural ostium of the maxillary sinus is located within the ethmoid infundibulum. It cannot be seen without displacing or removing the uncinate process. Accessory ostia, probably indicative of previous sinus disease, typically can be seen endoscopically, and occasionally radiographically, within the fontanelle posterior to the natural ostium. The medial wall of the maxillary sinus is largely devoid of bone, being comprised mostly of membranous tissue known as the posterior fontanelle. The small portion of membranous wall located anterior to the natural ostium is termed the anterior fontanelle. Mucus in the maxillary sinus is propelled by active mucociliary activity out through the natural ostium, which has a superior location along the medial wall of the sinus. If an ethmoid cell is located along the roof of the maxillary sinus within the antrum, an infraorbital (Haller) cell is said to exist.

The anterior ethmoidal neurovascular bundle traverses the skull base in a horizontal direction and is an important landmark during endoscopic surgery. The location of the anterior ethmoidal artery can be determined in coronal cuts immediately posterior to the globe, where the medial rectus muscle and superior oblique muscle cross, described as a “nippling” from the medial orbital wall. The point at which the anterior ethmoid artery enters the cranial cavity through the vertical (or lateral) lamella of the cribriform plate is the thinnest area of the entire skull base [53]. Posterior to this point, the skull base has a horizontal–oblique orientation (when viewed sagittally). Anterior to the anterior ethmoid nerve and artery, the skull base slopes upward in a vertical–oblique course. The bone of the skull base in this area is known as the dome of the

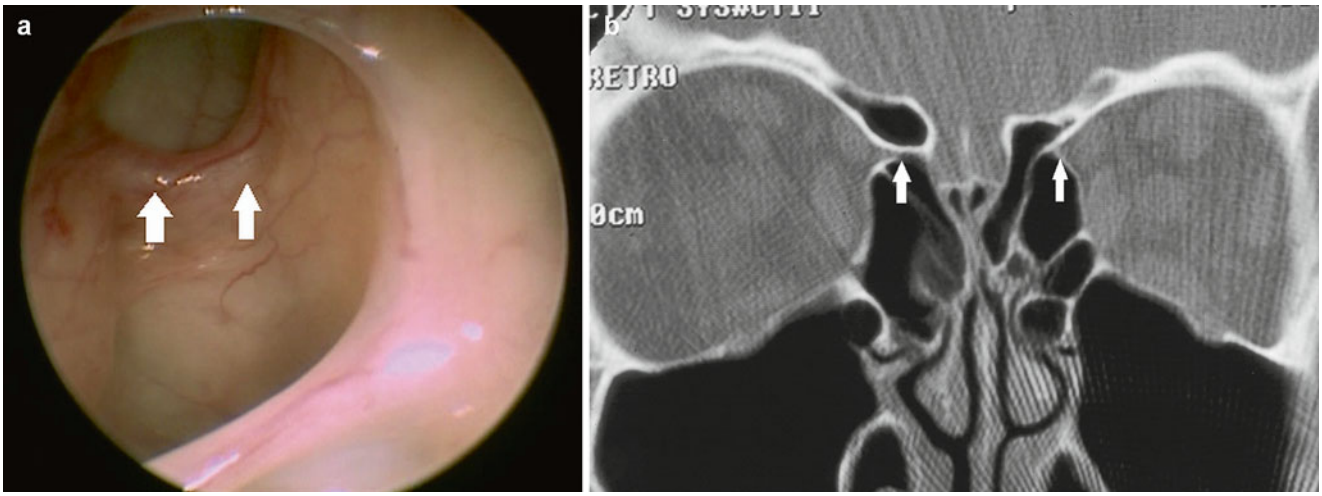


Fig. 23.10 (**a**) Endoscopic view of the anterior ethmoidal arteries (*arrows*) immediately posterior to the opening of the frontal sinus. (**b**) On preoperative coronal CT, the location of the vessels is typically identified by "nipples" on the medial orbital wall posterior to the globe (*arrows*)

ethmoid. The space between the dome of the ethmoid posteriorly and the agger nasi cell anteriorly is the frontal recess (Fig. 23.10).

There are a number of key anatomic features on CT that the endoscopic surgeon must review in each patient undergoing FESS, including:

1. The shape and slope of the skull base, especially the angle that the lateral lamella of the cribriform makes with the horizontal portion of the cribriform Plate.
2. The thickness of the skull base, including the presence of congenital or iatrogenic dehiscences of the skull base and medial orbital wall.
3. The vertical height of the posterior ethmoid labyrinth relative to the roof of the maxillary sinus in its medial portion, and whether an Onodi cell is present. An Onodi cell is a posterior ethmoid cell that has pneumatized into the sphenoid bone and/or sinus, in close relation to the optic nerve.
4. The relationship of the sphenoid intersinus septum to the lateral wall structures of the sphenoid (carotid artery and optic nerve).
5. The presence of atelectasis of the infundibulum or hypoplasia of the maxillary sinus, which would make inadvertent orbital entry more likely.
6. The drainage and ventilation pathway of the frontal sinus, which in most cases is immediately lateral to the attachment of the middle turbinate.
7. The presence of an infraorbital (Haller) cell, the partitions of which may need to be excised to ensure adequate drainage of the maxillary sinus.

It should be emphasized that this is not an exhaustive listing, and the surgeon should thoroughly and carefully examine the patient's CT scan before commencing a sinus surgical procedure. Indeed, it is essential that the surgeon develop a 3-D conceptualization of the sinus anatomy, the cells which will be encountered, and the frontal sinus drainage pathway from the preoperative scans before attempting surgery in this area. This requires reviewing the scans in a variety of planes and can be significantly aided by scrolling dynamically through the CT in multiple directions. The CT scan should also be present in the operating room during the surgery in the event the surgeon needs to refer back to it.

Instrumentation

Endoscopes

The use of endoscopes was introduced in otorhinolaryngology in early 1900s [54–57]. In the 1960s, with the development of the Hopkins endoscopes, the optical quality and light delivery improved dramatically. Further improvements came over

the following decades with the introduction of angle endoscopes of 30°, 45°, 70°, 90°, and 120°, in addition to the 0° endoscope. Moreover, the endoscopes were manufactured in 4 mm and in 2.7 mm. The Hopkins endoscopes employ true optical media with a series of lens rather than fiber optics, thus enhancing the image quality. The introduction of xenon light also contributed to improved overall visualization by increasing the light output with less heat and more energy efficiency.

The senior author primarily utilizes a 30° 2.7-mm endoscope for nasal endoscopy in the office, while using a 0° 4-mm endoscope for as much of the procedure as possible in the operating room, before transitioning to a 45° 4-mm for dissection along the skull base to the frontal sinus and to visualize the maxillary sinus. The 45° endoscopes have a wider angle of view than the 70° scopes facilitating the dissection in the frontal sinus and avoiding multiple changes of endoscopes during the procedure.

Surgical Navigation

Image-guided surgery is a real-time correlation of the surgical field with the preoperative radiologic images. As a result, the location of the tip of the surgical instrument is identified in the radiologic images. Image-guided FESS was introduced in the 1990s [58] following its development for neurosurgical procedures. Its main advantage is to recognize and avoid the violation of boundaries of the paranasal sinuses such as the intracranial cavity and the orbit. The use of image-guided surgery is not considered standard of care in FESS, but the AAO-HNS identifies it as useful in the following circumstances: (a) revision surgery; (b) distorted anatomy; (c) extensive sinonasal polyposis; (d) involvement of frontal, posterior ethmoid, or sphenoid sinuses; (e) disease abutting skull base, orbita, optic nerve, or carotid artery; (f) skull base defect with CSF rhinorrhea or encephalocele; and (g) tumors [59]. Image-guided systems usually require no larger than 2-mm axial cuts on the axial CT scan. MRI can also be used but is usually not required in cases of rhinosinusitis. The process of registration then creates a rigid correlation between the instrument and the imaging. Once registration is complete, the accuracy needs to be determined. This is done using various known fixed landmarks such as the nasal septum, medial and lateral canthus, etc. The accuracy usually has a 1.5- to 2-mm error at best and generally deteriorates as the dissection continues posteriorly [60].

Since the introduction of image-guided surgery, a number of observations have been made. The most important one for the surgeon to recognize is that this technology does not replace a thorough knowledge of the anatomy of the nose and paranasal sinuses. This cannot be overemphasized. A number of studies have looked at whether the technology reduces the incidence of complications [61–66], but such evidence is still lacking. Despite the lack of evidence demonstrating reduced complications, a recent study reported that 73 % of otolaryngologists use image-guided surgery when performing FESS and the majority of surgeons feel that this technology provides a safer operative field [67].

Powered Instrumentation

Over the last three decades, the instrumentation in FESS has evolved significantly with several technological advances. Perhaps the most prominent innovation is the microdebrider. Since its introduction in 1994 [68], the microdebrider has significantly reduced the surgeon's reliance on forceps and curettes and increased the ability of the surgeon to preserve the mucoperiosteal layer and avoid bone exposure. The microdebrider is made of a hollow shaft with an oscillating inner cannula supplied with continuous irrigation and suction. When the inner cannula oscillates, it opens the shaft, leading to suction of the soft tissue. The trapped tissue is then cut with the oscillation of the inner cannula and suctioned. The slower the speed of the oscillation, the larger the tissue bites. Microdebriders are the preferred instruments for many surgeons because of their mucosal-sparing nature, improved precision, and better tissue visualization [69–71]. The minced tissue pieces still preserve their histological architecture and have been shown to be equal to piecemeal resection using forceps when examined by a pathologist [72]. There are a number of blade configurations that have been developed for the microdebriders. To the initially available straight blade were added angled blades to facilitate the reach in areas such as inside the maxillary sinus and the frontal recess and sinus. Newer designs allow the blade's aperture to be rotated on its axis enabling the cutting edge to grasp tissue in a 360° angle. Nevertheless, the biggest advantage of this technology is the ability for continuous suctioning of blood along with the tissue and bone, significantly improving the view of the surgical field. With conventional suction and forceps, the surgeon needs to be constantly alternating the instruments to allow for a safe operation. Despite all the benefits, concerns have been raised regarding the safety of a powered instrument in such close proximity to the orbit and skull base. Nevertheless, there have been relatively few reports of ocular injury and skull base violation [73, 74]. The surgeon needs to be very aware that, although uncommon, complications do occur with the use of a microdebrider. When they do occur, the injury can develop very quickly and be more devastating.

Endoscopic drills are less commonly used than the microdebrider. However, when significant amount of bone needs to be removed, they are often more effective. The drill bits can usually be applied to the same handpiece used for the microdebrider blades. Like the cutting blades, there are several different designs of drill bits and angles. They have a protective sheet that protects the surrounding tissue from the shaft and are equipped with continuous suction and irrigation that helps with removing blood and debris. As with otologic drills, diamond drills are less aggressive than cutting burrs, and the number of flutes on the cutting burr will determine how aggressive it is. In FESS, the most important clinical application for endoscopic drills is surgery of the frontal sinus [75–77]. A 65° curved suction irrigation drill is very effective in removing the bone around the frontal recess and ostium, resecting the nasofrontal break and frontal sinus floor, while minimizing additional trauma. Other uses of this technology include transsphenoidal approaches to the pituitary gland, decompression of the optic nerve and orbit, endoscopic dacryocystorhinostomy, and approaches to the pterygopalatine fossa and lateral recess of the sphenoid sinus.

Other energy sources are also available for FESS, including coblation and laser. These technologies are more commonly used for reduction of inferior turbinates and tumor surgery, but neither of them is routinely used and will not be reviewed here.

Balloon

The concept of balloon dilatation was originally developed in the field of interventional cardiology and subsequently adapted to vascular surgery and urology. In 2005, "Balloon Sinuplasty" ™ was cleared by the FDA [78] and incorporated into rhinology [79, 80] with its use gaining early popularity. The aim of this technology is to restore the sinus drainage through an enlargement of the natural ostium. The equipment consists of a sinus delivery catheter, a guide wire, a sinus balloon, and an inflation device. The delivery catheter is positioned at the entrance of the target sinus (different sinuses have specially designed catheters with appropriate length and angle for that sinus), the guide wire is passed through the catheter into the sinus, and the position is confirmed by transillumination. The balloon is then passed around the guide wire and finally inflated to a high pressure of up to 16 atm [81]. In this manner, rather than excising the inflamed mucosa and underlying bone, the balloon compresses the mucosa and fractures the bone. Most of the literature to date has been limited to accessing the feasibility and safety of the device or are case series without a control group [80, 82–87]. One retrospective chart review [81] evaluated patients that were offered traditional FESS versus balloon dilatation and compared the outcome at the end of 3 months in terms of symptom improvement, patient satisfaction, postoperative narcotic use, and cost. The authors found similar symptom improvement between the two interventions, although a higher overall patient satisfaction was seen with the balloon procedure. To our knowledge, there is only one study that is a prospective randomized controlled trial that compared FESS with traditional frontal sinus dissection (Draf 1 or 2a procedures) with a hybrid procedure of FESS with balloon dilatation of the frontal sinus [88]. This study reported a significant improvement in both groups with no difference in outcomes between the two different interventions using radiologic grading and quality-of-life questionnaires. Nevertheless, a recent Cochrane Review [89] concluded that, to date, there is still a lack of evidence to support the routine use of balloon dilatation.

Although there have been some very enthusiastic proponents for balloon dilatation, other authors expressed concern that the procedure does not address the localized tissue inflammation and therefore the potential for recurrent or persistent disease. As much as 53 % of patients with CRS will have underlying osteitis [90]. Additionally, the inflamed mucosa will also be retained after dilatation, potentially perpetuating the inflammatory cycle [91]. Finally, there is risk of re-pneumatization of the surrounding cells [92] and the still unknown effect of the balloon on the crushed ostium mucosa. Nevertheless, balloon dilatation may yet play a more significant future role, particularly when combined with the use of drug-eluting implants in cases of isolated disease particularly of the sphenoid and frontal sinuses.

Drug-Eluting Implants

The concept of placing stents into the sinuses is not a new idea. This technology has not been successful to date when applied to sinus surgery. However, bioabsorbable stents, which slowly release drugs over time, have been recently developed for the sinuses. A chitosan-based semirigid stent that eludes dexamethasone over 15 days has been shown to reduce postoperative osteoneogenesis and stromal proliferation [93, 94]. An FDA-approved 'polylactide-co-glycolide implant that elutes mometasone has been marketed and has demonstrated reduced mucosal inflammation, less necessity for postoperative interventions, and decreased scarring in double-blind studies [95, 96]. In the longer term, this technology may be utilized for other

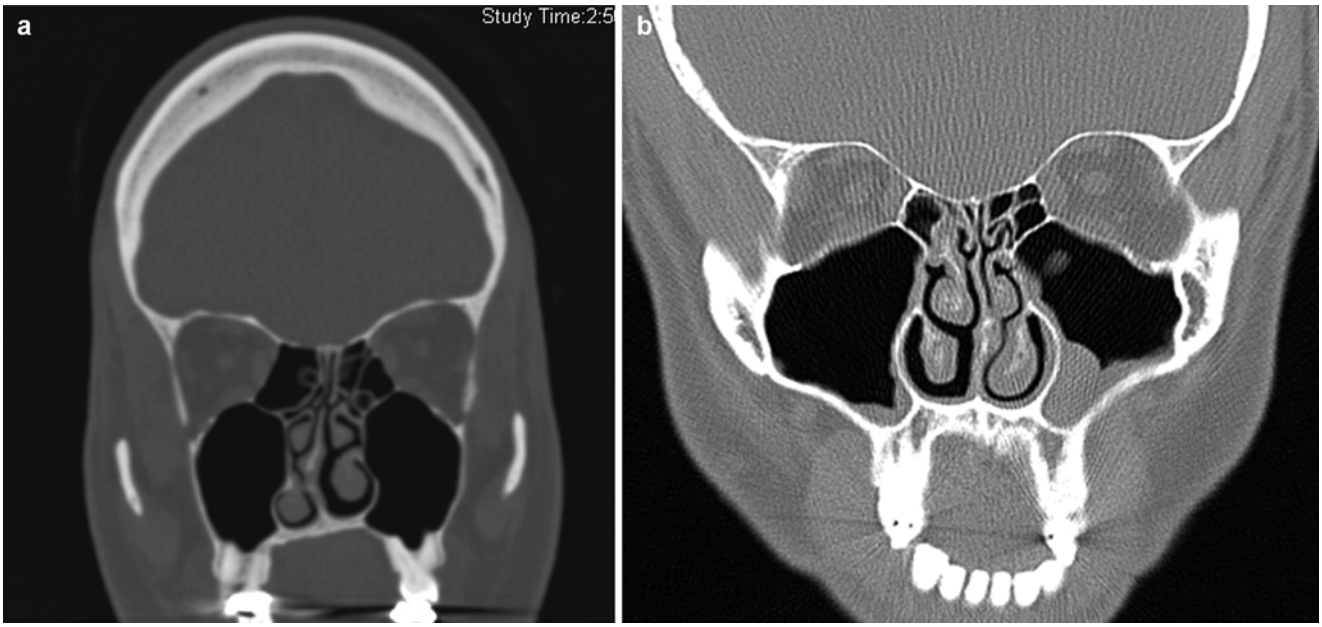


Fig. 23.11 Coronal CT scan demonstrating the height of the skull base at the level of posterior ethmoid sinus in comparison to the vertical height of the maxillary sinuses. (**a**) Normal posterior ethmoid vertical height. (**b**) Low posterior ethmoid roof, which was not recognized by the surgeon preoperatively and resulted in bilateral intracranial injury

anti-inflammatory agents creating new topical therapy options and significantly increasing the benefit of minimal surgical intervention or balloon dilatation. Additionally, it may prove to be an alternative to surgical therapy in the previously operated upon patient.

Surgical Technique

FESS aims to remove the key areas involved in sinus disease while preserving mucosa and restoring normal physiology to the sinonasal tract. The goals include restoration of drainage, removal of polypoid mucosa and osteitic bone, as well as creating a cavity, which can be accessed by topical intranasal therapy. Accordingly, FESS addresses primarily ethmoid disease and secondarily the maxillary, sphenoid, and frontal sinuses. The surgical technique will be discussed below.

As noted previously, the patient's CT scan should be on display in the operating room, and the surgeon should thoroughly review the radiographic findings. The anatomy of the ethmoid labyrinth should be carefully evaluated to the point that the surgeon could create a three-dimensional picture of the anatomy of the cells and its relations to the maxillary, sphenoid, and particularly the frontal sinuses. Anatomic variations, such as concha bullosa, intraorbital (Haller) cells, and sphenoethmoidal (Onodi) cells, must be noted in order to gain access to diseased areas effectively and safely. If the patient has had previous sinus surgery, the integrity of the skull base and orbital wall must be noted to avoid a potential complication. Two additional areas of importance are the lateral lamella of the cribriform plate and the vertical height of the posterior ethmoid sinus. The lateral lamella of the cribriform varies both in its vertical height and the angle at which it meets the horizontal lamella of the cribriform plate. Surgical trauma to this area is more likely if this angle exceeds 90°. Another area where the skull base may be violated and CSF leak may occur is in the posterior ethmoid. This is probably because the skull base slopes slightly downward (inferiorly) in this region. For this reason, the surgeon should carefully note the height of the posterior ethmoid relative to the maxillary sinus before surgery. This is the distance on the CT from the roof of the maxillary sinus at its posterior wall (where the basal lamella inserts) to the roof of the posterior ethmoid sinus (Fig. 23.11).

The nasal cavities are first decongested with a topical oxymetazoline, and then either topical cocaine or 1:1,000 adrenaline is applied under endoscopic visualization. It is important to leave the topical decongestant in place for sufficient time to get maximal decongestion. While topical decongestion is taking effect, a transpalatal sphenopalatine block may be performed trans-orally through the greater palatine foramen. The lateral nasal wall may then be injected with local anesthetic (1 or 2 % lidocaine with epinephrine 1:100,000). Injection sites are placed out of the direct path of the scope, so bleeding onto the scope lens will be minimized. Typical injection sites include the agger nasi (above the anterosuperior attachment of middle

turbinate), the anterior portion of the uncinate process (at the superior attachment of the inferior turbinate), and, if possible depending on the extent of disease, the inferior basal lamella of the middle turbinate where it attaches to the medial orbital wall. In the occasional situation where resection of any portion of the middle turbinate is planned, it is then injected in its anteromedial and inferior region. Waiting 5–10 min at this point will result in improved hemostasis for the rest of the case.

The 0° telescope is used at the outset and for as much of the dissection as possible, since there is less distortion than with angled scopes. Initially, the procedure is performed inferiorly in an anterior-to-posterior direction. In revision cases where normal landmarks are missing, starting posteriorly at the sphenoid ostium region and working forward anteriorly may facilitate safe dissection in some instances. It may be necessary first to medialize the middle turbinate gently with a Freer or Cottle elevator to expose the uncinate process. If a concha bullosa is present, a vertical incision is made down the anterior face of the middle turbinate, and the lateral lamella of the concha is resected. If either purulent secretions or suspicious-looking tissue is seen at any time throughout the operation, appropriate cultures or frozen section biopsies are taken. The key first landmark is identification of the medial orbital wall.

The first, and perhaps the most important, step of the procedure is the uncinectomy. This can be accomplished in a variety of ways. Our preference is to first palpate the infundibulum with the ball-tip sinus seeker, identifying the position of the ostium of the maxillary, and then gently outfracture the uncinate process medially, enlarging the hiatus semilunaris and the infundibulum. Subsequently, a backbiting forceps is introduced into the middle meatus with the blade oriented cranially and then rotated laterally in order to penetrate the infundibulum. Once the blade is engaged in the infundibulum, one or two bites should suffice to reach the insertion of the uncinate. The remaining parts of the uncinate are removed either with the microdebrider or a straight through-cutting forceps. This step can include the posterior fontanelle of the maxillary sinus thus enlarging the ostium or this can be done subsequently. The cranial portion of the uncinate can also be removed with the microdebrider or a 90° upbiting pediatric Blakesley forceps. Alternatively, the uncinectomy can be performed with a sickle knife, starting superiorly in the groove where the uncinate joins the lateral nasal wall. Care should be taken not to make this incision too anterior, since the thicker tissue of the lateral nasal wall in this region will bleed excessively and the bone of the lateral nasal wall will be denuded. There is also some risk of orbital injury with this incision when the uncinate process is lateralized. As the incision is carried inferiorly, the surgeon should attempt to deflect the uncinate bone medially with the knife, bringing it away from the lateral wall so as to avoid abrading the root of the inferior turbinate, as well as making its removal with a straight forceps easier to accomplish. Since the uncinate is a crescent-shaped structure that curves posteriorly in its inferior aspect, the uncinectomy incision must also be carried more posteriorly in this region. The uncinate process is then removed with a Blakesley-Weil forceps. It should be grasped superiorly and the forceps rotated so that the remnant of superior uncinate mucosa will not be pulled away from the lateral nasal wall (clockwise on the left side, counterclockwise on the right). Should the incision be carried too far laterally, orbital fat may be exposed. Should this occur, the surgeon must not traumatize the fat, since this could lead to bleeding within the orbit and possibly orbital hematoma. The surgeon should briefly discontinue the dissection and examine the patient's eye. If no orbital complication is apparent, the surgeon may proceed with further dissection posterior to the herniated orbital fat, taking great care not to induce further trauma to that region. The herniated fat may be bipolar cauterized if it prolapses into the visual field.

The uncinectomy exposes the ethmoid infundibulum and ethmoid bulla. The natural ostium of the maxillary sinus may or may not be visible with a 0° scope at this point, and the middle meatal antrostomy can be deferred until later in the case after the surgeon has changed to a 30° or 45° endoscope. The ethmoid bulla is penetrated with a straight forceps or the short J-curette, and its entire bony wall is removed (Fig. 23.12). Dissection should extend to the medial orbital wall along the lateral aspect of the ethmoid cavity. Other smaller and less consistently found cells may be present, and their partitions are taken down to reveal the basal lamella. The easiest location to identify the basal lamella is by following the inferior margin of the middle turbinate posteriorly. The basal lamella should be penetrated at a sufficiently high level to leave an adequate inferior strut (thus preventing collapse of the middle turbinate against the medial orbital wall) but at a level sufficiently low to avoid traumatizing the skull base (Fig. 23.13). This level roughly corresponds to the roof of the maxillary sinus. Septations and diseased mucosa in the posterior ethmoid are removed. The dissection should be along the medial orbital wall, while leaving the mucosa on the skull base and orbital wall intact. Microdebrider and through-biting or through-cutting instruments can facilitate this in such a way that mucoperiosteal stripping is avoided and bone exposure minimized, so that less healthy mucosa is inadvertently pulled away than what occurs with traditional ethmoid forceps. Care must be exercised when dissecting along the lateral aspect of the posterior ethmoid area, since the bony canal housing the optic nerve is occasionally dehiscent in this area. The last (most posterior) cell of the posterior ethmoid cavity typically has a pyramidal configuration, with the apex pointing posterosuperiorly toward the optic nerve. In contrast to the relative concavity of this posterior ethmoid cell, the anterior wall of the sphenoid sinus typically is convex and bulges somewhat anteriorly.

Once the posterior ethmoid dissection is completed, the position of the superior turbinate is determined. It is located medially within the posterior ethmoid cavity and may have one of three configurations: (1) existing as a free-standing turbinate separate from the true posterior ethmoid cells; (2) pneumatized similar to a concha bullosa; or (3) existing as a single lamella

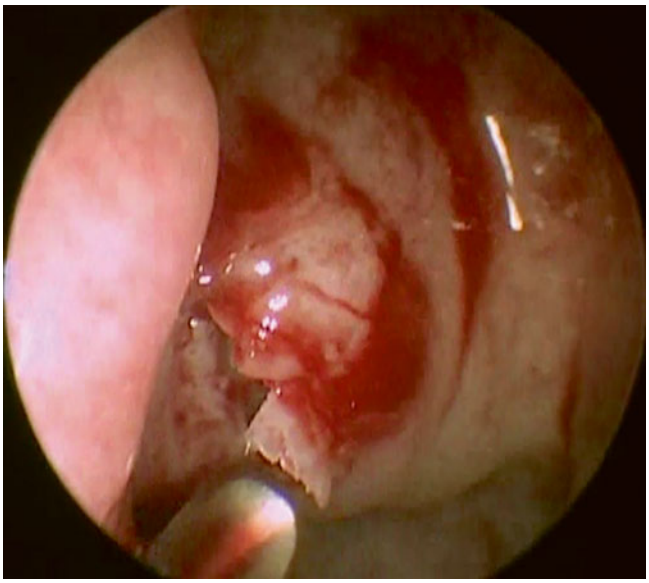


Fig. 23.12 Endoscopic view of using a J-curette to initiate opening of the ethmoidal bulla on the left side of the nose (0° telescope)

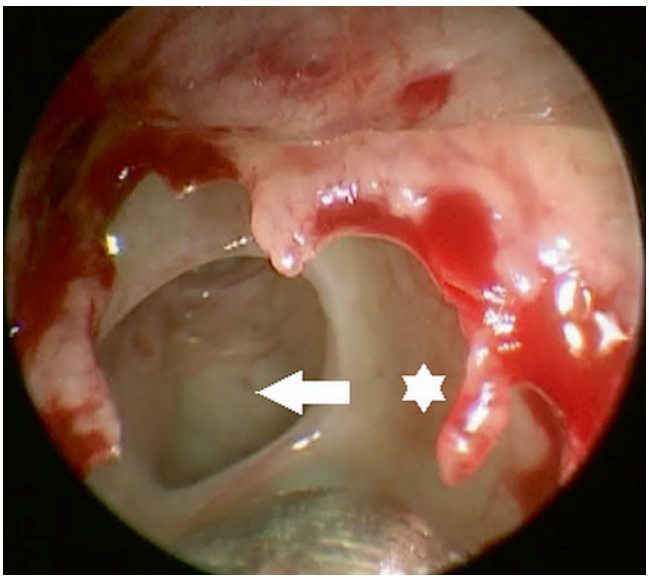


Fig. 23.13 Endoscopic view during ethmoidectomy on the left side of the nose demonstrating the skull base (*arrow*) and the medial orbital wall (*star*)

of bone, but forming the medial wall of a posterior ethmoid cell. In this latter case, the superior turbinate will have a horizontal lamella, situated just posterior to the basal lamella, which articulates with the medial orbital wall. Identifying the anterior face of the superior turbinate is useful at this point and this is best achieved with a ball-tipped seeker, so as to identify the superior meatus from within the ethmoid sinus. The inferior portion of the superior turbinate is then removed if the sphenoid sinus is to be entered, and this leads the surgeon directly to the sphenoid ostium. The natural ostium of the sphenoid is located just medial to the superior turbinate, between the turbinate and the septum. The sphenoid can then be safely entered once the ostium is identified. The anterior sphenoid wall is removed, usually with a rotating sphenoid punch, being careful so that the mucosa on the inner aspect of the wall does not prolapse back into the sinus. The size of the sphenoidotomy depends in part on the presence and extent of disease. The surgeon should keep in mind that even when there is no overt sphenoid disease, blood and secretions will accumulate in the sinus postoperatively. The sphenoidotomy should therefore be large enough for the surgeon to gain access for suctioning and debridement in the postoperative period and should communicate with the sphenoid natural ostium. The lateral wall of the sphenoid sinus should never be manipulated so as to avoid injury to the optic nerve and carotid artery.

After dissection of the sphenoid sinus, the surgeon will then proceed to skeletonize the skull base from posterior to anterior. The easiest area to identify is at its junction with the anterior wall of the sphenoid sinus. From this point, the dissection is

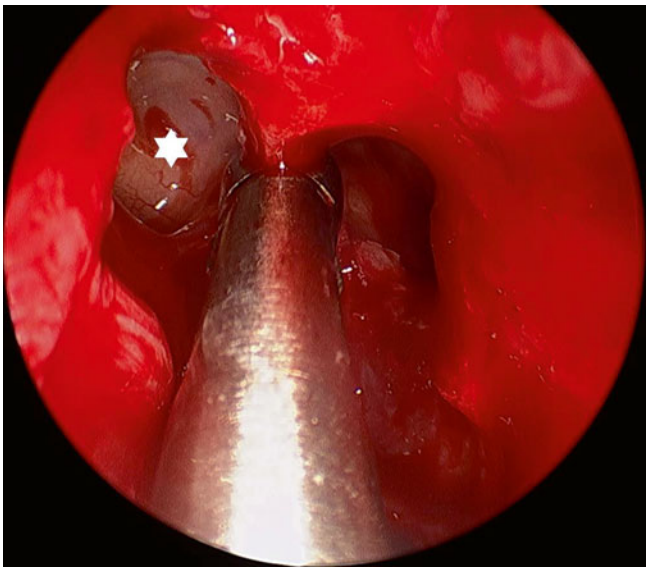


Fig. 23.14 Endoscopic view during left-sided ethmoidectomy and frontal sinusotomy (45° telescope) demonstrating the use of a giraffe side to side forceps to remove any residual intercellular partition. The bone is fractured but not removed by the forceps, so as to avoid mucosal stripping. The fragment is subsequently teased out with a suction or curved probe. The dome of the ethmoid can be visualized (*star*)

carried forward (anteriorly) along the skull base, with either the 30° or 45° scope. Although the posterior ethmoid neurovascular bundle is not reliably seen, the anterior ethmoid artery and nerve can usually be seen in a bony canal coursing across the skull base more anteriorly. Dissection in this superomedial aspect of the ethmoid cavity must be performed with the utmost caution, since the skull base is thinnest and risk of CSF leak greatest in this region. Dissection is performed with the 45° upbiting forceps and through-cutting punches. The forceps are used to palpate behind the bony partitions first, and after confirming that it is indeed a bony partition, the bite is taken. This avoids biting on the skull base and thus markedly reduces the risk of a CSF leak. Polypoid tissue can be removed with caution along the skull base using a straight or curved microdebrider blade. This is done slowly, allowing the tissue to get sucked into the shaft and then the blade rotated. Continuing the dissection forward, just anterior to the anterior ethmoid artery, the skull base turns upward where it is known as the dome of the ethmoid.

Anterior to the dome of the ethmoid are the septations and spaces of the frontal recess. The mucosa in this area should be maximally preserved to prevent frontal recess stenosis. However, some dissection is usually necessary to visualize adequately the true ostium of the frontal sinus. The Kuhn-Bolger frontal recess curette and various through-cutting giraffe-style forceps are used in this area (Fig. 23.14). The location of the frontal ostium will depend on the superior insertion of the uncinate process and should have been identified on the CT scan. It can be confirmed with a malleable probe and is usually medial and anterior in the superior-most reaches of the frontal recess (Fig. 23.15). Openings located more laterally toward the lamina papyracea usually correspond to supraorbital ethmoid cells. Every attempt is made to avoid traumatizing the mucosa around the frontal ostium. Osteitic bony partitions are fractured and meticulously removed with small through-cutting instruments. Loose mucosa may be gently removed with a curved microdebrider; however, grossly diseased mucosa in this area will often normalize once ethmoid disease is eradicated.

A 45° or 70° endoscope is then rotated to look laterally toward the area of the natural ostium of the maxillary sinus (Fig. 23.16). Any residual uncinate process that remains will prevent adequate visualization of the ostium and requires removal, usually with a backbiting forceps. The true ostium of the antrum is located far anteriorly, so that other more easily visualized openings along the medial wall of the sinus most likely represent accessory ostia. The tissue posterior to the natural ostium is the posterior fontanelle, which can be removed when it is necessary to create a large antrostomy with through-biting instruments. The posterior extent of such cuts is variable and can go as far back as the posterior wall of the maxillary sinus, formed by the ascending process of the palatine bone. Ideally, antrostomy should permit passage of a curved suction tip for postoperative care, but the size of the antrostomy is probably secondary in importance to ensuring that it communicates with the natural ostium. Care must be taken not to injure the nasolacrimal duct, situated anterior to the natural ostium of the maxillary sinus. In general, the bone overlying the duct is thicker and less easily traumatized.

The dissection is considered complete after the antrostomy is performed. A last look with the 0° scope to suction blood and a final inspection of the ethmoid cavity are suggested, and any loose bone fragments are removed. Packing is avoided, but a Merocel™ (Medtronic Xomed, Jacksonville, Florida) middle meatal sponge is frequently placed for 24 h to hold open the middle meatal space and tamponade any oozing. When the patient has significant polyposis or mucosal hypertrophy, a steroid-eluting implant is a realistic consideration.

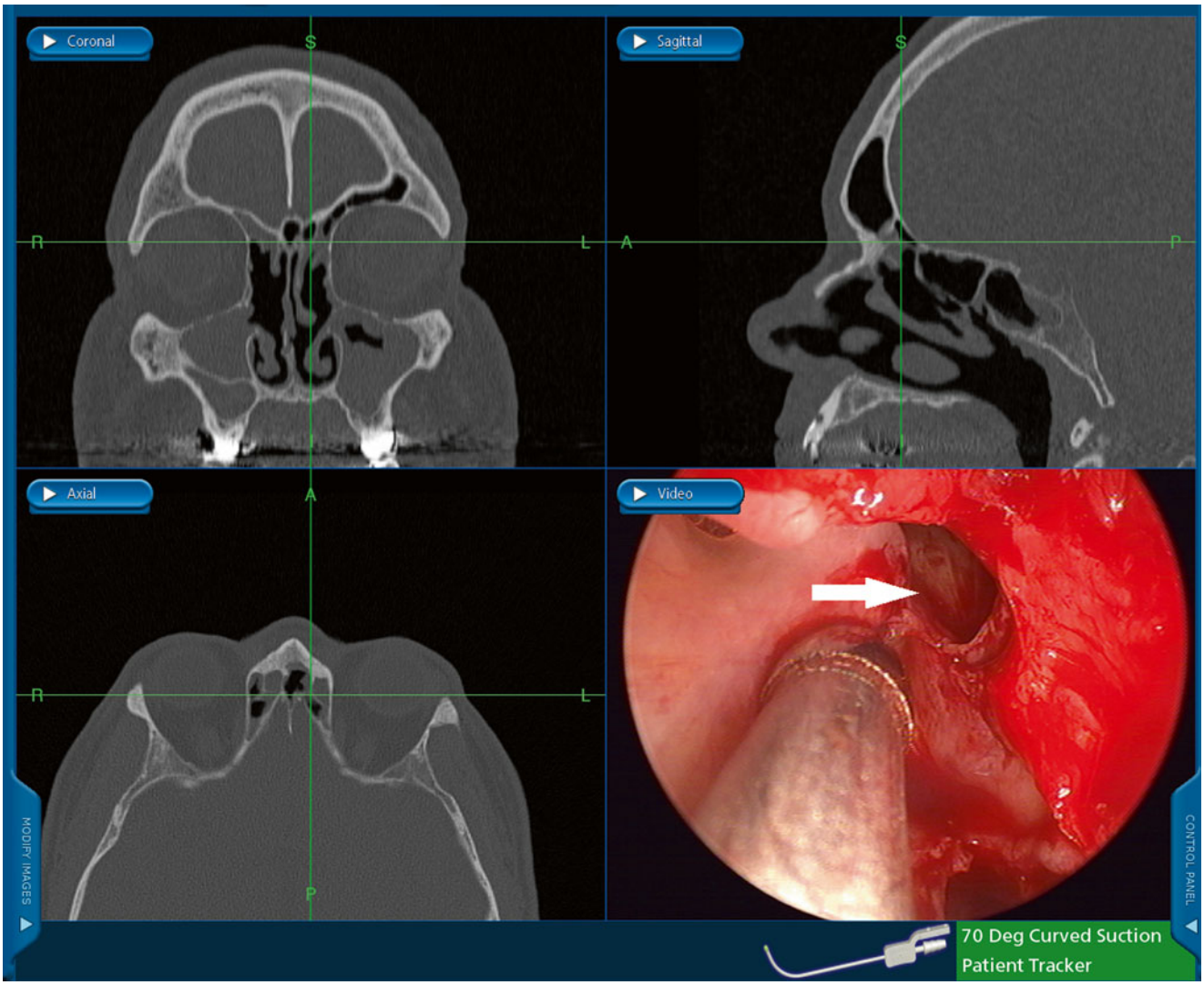


Fig. 23.15 Endoscopic view of probe at the frontal recess and the image-guidance system CT scan confirming the position of the probe. The frontal sinus can now be visualized anterolaterally (*arrow*)

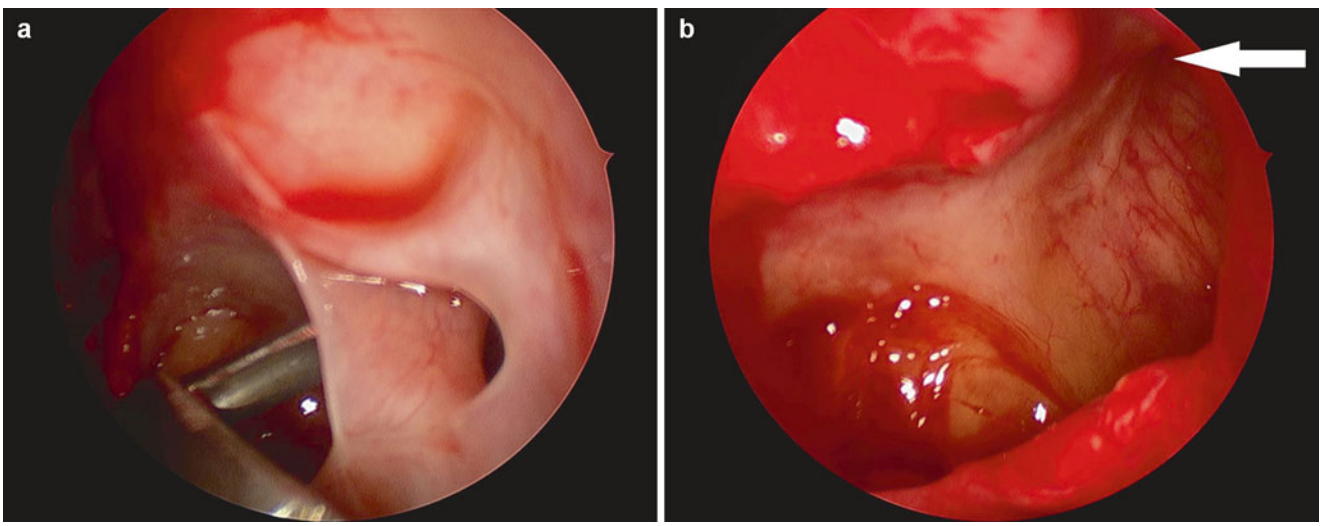


Fig. 23.16 View of the left maxillary sinus with a 45° telescope demonstrating an iatrogenic opening in the posterior fontanelle and the natural ostium of the maxillary sinus anteriorly. (**a**) Backbiting forceps has been introduced to remove the remaining bridge of tissue. (**b**) Endoscopic view of the maxillary sinus after the natural ostium of the maxillary sinus has been included in the antrostomy. Note the sharp angle to the antrostomy anterosuperiorly (*arrow*)

Postoperative Management

Postoperative management is critical for endoscopic sinus surgery for CRS, because persistent inflammation following surgery is the rule, even though it is frequently asymptomatic. The sponges are removed on the first postoperative day and nasal endoscopy is performed. Blood is suctioned and any loose bone fragments are removed. During the early postoperative period (the first 4–6 weeks), the patient returns on a weekly basis for endoscopic examination and, when necessary, debridement. This is performed in the office setting, in most cases only under topical anesthesia. Typically, blood, mucus, clots, and fibrinous material are suctioned from the ethmoid cavity, sphenoid, and maxillary sinuses for the first 2–3 weeks. Occasionally, loose pieces of ethmoid bone become apparent that may have been overlooked during surgery and should be removed with a forceps. This is especially important in the frontal recess, where such bony chips can become osteitic and promote inflammation and stenosis. Eschar, persistently inflamed mucosa, and new scar are removed when present. Any residual osteitic bone is removed. Careful attention to the surgically created sinusotomies is mandated to prevent stenosis and ensure an optimal long-term result. Further along in the postoperative period, the patient returns intermittently for routine examination (Fig. 23.17). Since significant ethmoid disease can be present well before it causes symptoms [29], minor manipulations in the office aimed at removing minimal disease can spare the patient major revision surgery.

The patient typically is kept on medical therapy in the early postoperative period until mucosal healing is complete, granulation tissue resolves, and no blood or mucus can be suctioned from any of the sinuses (Fig. 23.18). This includes a combination of oral steroids, antibiotics, and nasal irrigations. Topical administration of medication has the benefit of minimizing systemic effects while depositing the drug locally and providing sinus lavage at the same time. Studies have demonstrated that nasal sprays and nebulizers deposit drugs mostly in the anterior portion of the nasal cavity with only 2 % of the volume irrigated reaching the sinus mucosa in patients with CRS [97]. FESS has the additional benefit of greatly optimizing topical drug delivery into the sinuses, with a minimum ostium size of 4 mm required to begin seeing the penetration of the irrigation solution [98]. However, large volume irrigation with devices such as the Neti Pot™ (Himalayan Institute, Honesdale, PA) or squeeze bottle appears to have the best penetration, most likely as a result of the larger volume of irrigant and higher pressure [99]. A recent cadaver study demonstrated that larger ostia after surgery results in greater sinus distribution of irrigants and sprays within the sinuses. This result is even greater after medial maxillectomy [100]. Postoperative medication administration becomes an important consideration since it is estimated that 5–37 % of topically delivered drugs will actually be absorbed by the mucosa, with the remaining being removed by mucociliary clearance [101].

The extent of postoperative medical therapy is predicated upon the extent of the disease present. The goal is to return the mucosa within the cavity to normal and to avoid subsequent recurrences. In patients with minor disease, this may require minimal postoperative therapy. On the other hand, in patients with aspirin-exacerbated respiratory disease (AERD) or

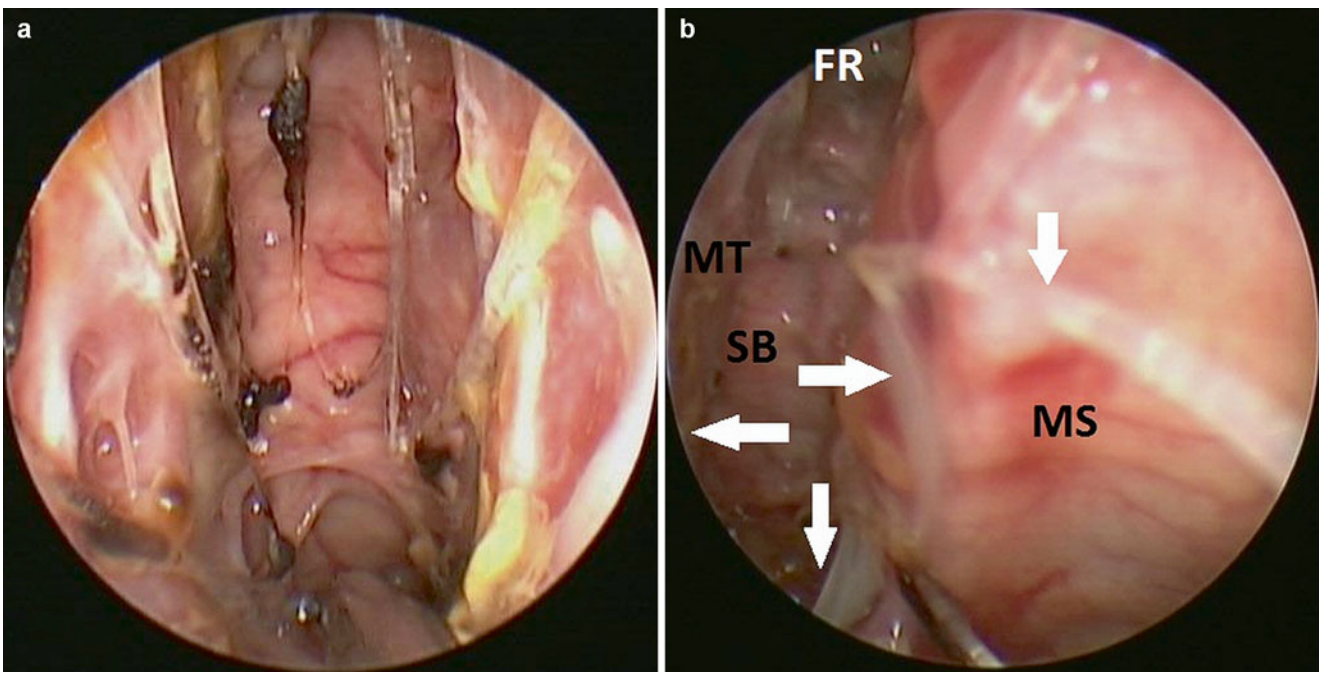


Fig. 23.17 (**a**) Endoscopic view with a 30° telescope of a postoperative ethmoidal cavity 3 weeks postoperatively in a patient who had moderate nasal polyposis preoperatively. (**b**) A Propel ™ mometasone-eluting stent was placed at the end of surgery (*arrows*). The polypoid mucosa has resolved and the cavity appears to have essentially normal mucosa (*MS* maxillary sinus, *MT* middle turbinate, *SB* skull base, *FR* frontal recess)

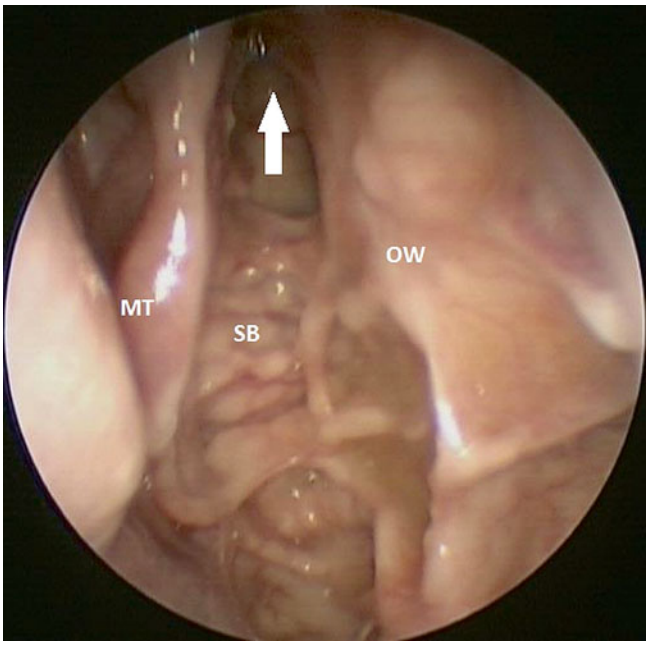


Fig. 23.18 Postoperative endoscopic view of a sphenoethmoidal cavity with complete mucosal healing. The middle turbinate (*MT*) had been largely removed in a prior surgical procedure. The skull base (*SB*) and the frontal sinus (*arrow*) are well visualized. *OW* orbital wall

allergic fungal sinusitis (AFRS), medical therapy is likely to be prolonged or even lifelong. Since persistent inflammation in the early postoperative period is usually asymptomatic, careful endoscopic follow-up is required in all cases and prolonged for extensive disease, AERD, and AFRS. The most sensitive clinical indicator of recurrent or persistent inflammation postoperatively is probably a decrease in olfaction.

Serial endoscopic examinations enable the physician to respond to objective disease and tailor appropriate medical therapy to the patient. The need for long-term endoscopic follow-up cannot be overemphasized. Since FESS removes disease without changing the underlying inciting or precipitating factors, patients suffering from chronic sinus disease are at risk for developing recurrences with exposure to viruses, allergens, pollutants, and so on. Thus, patients may require reintroduction of more potent topical steroid therapy (budesonide 0.5 mg in 200 cc saline irrigation), short courses of oral steroids, or intermittent courses of culture-directed antibiotics in the months to years following surgical intervention. Localized mucosal disease within the ethmoid cavity and dependent sinuses can be identified early and managed in the office under topical anesthesia in the majority of cases. Long-term endoscopic follow-up should therefore prove cost-effective in managing the chronic sinus patient, reducing the need for prescription medications and further surgery, decreasing morbidity from the disease, increasing patient productivity, and improving quality of life. Our experience has demonstrated that, over time, the mucosal inflammation and mucosal reactivity do indeed slowly settle down with a combination of surgery and prolonged medical therapy, although this is less reliably achieved in AERD and AFRS. We have previously demonstrated that at nearly 8 years post surgery, the majority of patients have a marked improvement in their symptoms, both in terms of their nose and in terms of their asthma, and are taking less medication [27].

Outcomes

It has been well documented that the combination of a thorough surgical intervention and aggressive postoperative care can have profound long-term benefits on CRS and asthma with long-term reductions in medical therapy [102–104]. Results indicate an 82–97 % symptomatic improvement rate within 1–2 years following FESS. Our own studies have demonstrated that clinical improvement is maintained for up to 8 years following surgery with appropriate postoperative care [27, 29, 105–107]. Khalid demonstrated that FESS was effective in improving the general health status more than 3 years after surgery, with the scores on the SF-36 quality-of-life questionnaire returning to the levels of general population [108]. Bradley found a significant reduction in the scores using the SNOT-20 questionnaire as early as 3 months postoperatively, an effect that persisted after 1 year. Other studies also demonstrated improvement in olfaction [109], bodily pain [110], asthma [111], and fatigue [112] as a result of FESS intervention.

However, patient symptom improvement does not always correlate well with resolution of mucosal disease. Kennedy found approx 45 % of patients exhibited some evidence of mucosal disease at a mean of 18 months after FESS, despite excellent subjective results [29]. The frontal recess was the most common site of persistent disease. The only significant factor that was found to be predictive of surgical prognosis was the preoperative extent of disease determined by CT scan. These findings highlight the importance of close endoscopic follow-up in the postoperative period. Postsurgical evaluation of results based only on patient symptomatology and anterior rhinoscopy is unreliable and should be abandoned. If late symptomatic recurrence is to be minimized, meticulous postoperative endoscopic evaluation to identify and treat objective disease is mandatory.

Complications of Surgery

The most common complication of endoscopic sinus surgery is disease recurrence. As noted above, persistent inflammation is the post-surgery rule for CRS, and it needs to be managed with appropriate medical therapy. Even so, recurrent symptomatic disease may occur over time in up to 20 % of patients requiring revision surgical intervention. Inflammation, which is poorly managed in the early postoperative period, frequently leads to worsening of disease and possibly even to "nasal cripples." It should be remembered that when endoscopic sinus surgery is performed, it opens up virgin mucosa to the same environmental factors that may have been involved with the initial generation of disease. Endoscopic follow-up and appropriate medical and environmental management are thus essential. Additionally, the combination of inflammation and surgical trauma may lead to scarring, sinus obstruction, and the eventual development of a mucocele.

Infection and bleeding may also occur following surgical intervention. Other more serious complications are much less common. The incidence of CSF leak lies between 0.1 and 0.5 % of surgical interventions and, in most cases, can be closed with a simple mucosal graft at the time of surgical intervention. However, appropriate postoperative measures are required to avoid a renewed leak while the graft is healing in place. The incidence of orbital complications is also said to be in the region of 0.1–0.5 % with the most common being an orbital hematoma. Typically, this occurs as a result of injury to the anterior ethmoidal neurovascular bundle and associated intraorbital bleeding. The rapid rise of intraorbital pressure created from such a bleed requires emergency management if the risk of visual loss is to be minimized. Occasionally, direct trauma may also occur to the medial rectus muscle or even to the optic nerve. However, such injuries are uncommon.

References

1. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. Ann Otol Rhinol Laryngol. 2011;120(7):423–7.
2. Bhattacharyya N. Contemporary assessment of the disease burden of sinusitis. Am J Rhinol Allergy. 2009;23:392–5.
3. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg. 2007;137:S1–31.
4. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg. 2003;129:S1–32.
5. Adams PF, Hendershot GE, Marano MA; Centers for Disease Control and Prevention/National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1996. Vital Health Stat 10. 1999; 200:1–203.
6. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. Vital Health Stat 10. 2002;205:1–109.
7. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg. 1995;113:104–9.
8. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc. 1999;74:877–84.
9. Seiberling KA, Conley DB, Tripathi A, et al. Superantigens and chronic rhinosinusitis: detection of staphylococcal exotoxins in nasal polyps. Laryngoscope. 2005;115:1580–5.
10. Sanclement JA, Webster P, Thomas J, et al. Bacterial biofilms in surgical specimens of patients with chronic rhinosinusitis. Laryngoscope. 2005;115:578–82.
11. Kennedy DW. Pathogenesis of chronic rhinosinusitis. Ann Otol Rhinol Laryngol Suppl. 2004;193:6–9.
12. Kennedy DW, Senior BA, Gannon FH, et al. Histology and histomorphology of ethmoid bone in chronic rhinosinusitis. Laryngoscope. 1998;108:502–7.
13. Hilding AC. Physiologic basis of nasal operations. Calif Med J. 1950;94:147–56.
14. Messerklinger W. On the drainage of the normal frontal sinus of man. Acta Otolaryngol. 1967;643:176–81.
15. Drettner B. The obstructed maxillary ostium. Rhinology. 1967;5:100.
16. Messerklinger W. Endoscopy of the nose. Baltimore: Urban and Schwarzenberg; 1978.

17. Naumann H. Pathologische anatoie der chronischen rhinitis und sinusitis. In: Proceedings VIII international congress of otorhinolaryngology. Amsterdam: Excerpta Medica; 1965. p. 80.
18. Kennedy DW, Zinreich SJ, Rosenbaum AE, Johns ME. Functional endoscopic sinus surgery: theory and diagnostic evaluation. Arch Otolaryngol. 1985;111:576–82.
19. Kennedy DW. Functional endoscopic sinus surgery: technique. Arch Otolaryngol. 1985;111:643–9.
20. Goldstein MF, Dunsky EH, Dvorin DJ, Lesser RW. Allergic fungal sinusitis: a review with four illustrated cases. Am J Rhinol. 1994;8:13–8.
21. Triglia JM, Nicollas R. Nasal and sinus polyposis in children. Laryngoscope. 1997;107(7):963–6.
22. Mackay J, Eriksen M. The tobacco atlas. Geneva: World Health Organization; 2002.
23. US Department of Health. Smoking and Health: report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, DC: US Department of Health, US Public Health Service; 1964.
24. Tammemagi CM, Davis RM, Benninger MS, Holm AL, Krajenta R. Secondhand smoke as a potential cause of chronic rhinosinusitis: a case–control study. Arch Otolaryngol Head Neck Surg. 2010;136(4):327–34.
25. Lieu JE, Feinstein AR. Confirmations and surprises in the association of tobacco use with sinusitis. Arch Otolaryngol Head Neck Surg. 2000;126:940–6.
26. Chen Y, Dales R, Lin M. The epidemiology of chronic rhinosinusitis in Canadians. Laryngoscope. 2003;113:1199–205.
27. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza D. Long-term results of functional endoscopic sinus surgery. Laryngoscope. 1998;108(2):151–7.
28. Krzeski A, Galewicz A, Chmielewski R, Kisiel M. Influence of cigarette smoking on endoscopic sinus surgery long-term outcomes. Rhinology. 2011;49(5):577–82.
29. Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. Laryngoscope. 1992;102 Suppl 57:1–18.
30. Ramadan HH, Hinerman RA. Smoke exposure and outcome of endoscopic sinus surgery in children. Otolaryngol Head Neck Surg. 2002;127:546–8.
31. Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope. 2005;115:2199–205.
32. Briggs RD, Wright ST, Cordes S, Calhoun KH. Smoking in chronic rhinosinusitis: a predictor of poor long-term outcome after endoscopic sinus surgery. Laryngoscope. 2004;114:126–8.
33. Goldstein-Daruech N, Cope EK, Zhao KQ, et al. Tobacco smoke mediated induction of sinonasal microbial biofilms. PLoS One. 2011;6:e15700.
34. Antunes MB, Chi JJ, Liu Z, Goldstein-Daruech N, Palmer JN, Zhu J, Cohen NA. Molecular basis of tobacco-induced bacterial biofilms: an in vitro study. Otolaryngol Head Neck Surg. 2012;147(5):876–84.
35. Rudmik L, Mace JC, Smith TL. Smoking and endoscopic sinus surgery: does smoking volume contribute to clinical outcome. Int Forum Allergy Rhinol. 2011;1(3):145–52.
36. Das S, Khichi SS, Perakis H, et al. Effects of smoking on quality of life following sinus surgery: 4-year follow-up. Laryngoscope. 2009;119:2284–7.
37. Kennedy DW, Josephson JS, Zinreich SJ, Mattox DE, Goldsmith MM. Endoscopic sinus surgery for mucoceles: a viable alternative. Laryngoscope. 1989;99:885–95.
38. Warren JD, Spector JG, Burde R. Long-term follow up and recent observations on 305 cases of orbital decompression for dysthyroid orbitopathy. Laryngoscope. 1989;99:35–40.
39. Desanto LW. The total rehabilitation of Graves' ophthalmopathy. Laryngoscope. 1980;90:1652–78.
40. Kennedy DW, Goodstein ML, Miller NR, Zinreich SJ. Endoscopic transnasal orbital decompression. Arch Otolaryngol Head Neck Surg. 1990;116:275–82.
41. Metson R. The endoscopic approach for revision dacryocystorhinostomy. Laryngoscope. 1990;100:1344–7.
42. Clerico DM, Fieldman R. Referred headache of rhinogenic origin in the absence of sinusitis. Headache. 1994;34:226–9.
43. Clerico DM. "Sinus headaches" reconsidered: referred cephalgia of rhinologic origin masquerading as refractory primary headaches. Headache. 1995;35:185–92.
44. Chow J. Rhinologic headaches. Otolaryngol Head Neck Surg. 1994;111:211–8.
45. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg. 1997;117(3 Pt 2):S1–7.
46. Zinreich SJ, Kennedy DW, Rosenbaum AE, et al. Paranasal sinuses: CT imaging requirements for endoscopic surgery. Radiology. 1987;163:769–75.
47. Havas TE, Motbey JA, Gullane PJ. Prevalence of incidental abnormalities on computerized tomographic scans of the paranasal sinuses. Arch Otolaryngol. 1988;114:856–9.
48. Swanson P. Lanza DC, Kennedy DW, Vining EM. The effect of middle turbinate resection upon the frontal sinus. In: Presented at the American Rhinologic Society. Palm Beach, May 1994.
49. Stammberger H. Functional endoscopic sinus surgery. Philadelphia: B. C. Decker; 1991. p. 35.
50. Stammberger H. Functional endoscopic sinus surgery. Philadelphia: B. C. Decker; 1991. p. 31.
51. Bolger WE, Butzin C, Parsons DS. CT analysis of bony and mucosal abnormalities for endoscopic sinus surgery. Laryngoscope. 1991;101:56–71.
52. Lang J. Clinical anatomy of the nose, nasal cavity and paranasal sinuses. New York: Thieme Medical Publishers; 1989. p. 85.
53. Kainz J, Stammberger H. The roof of the anterior ethmoid—a place of least resistance in the skull base. Am J Rhinol. 1990;4:191–9.
54. Hirschmann A. Über Endoskopie der Nase und deren Nebenhöhlen. Eine neue Untersuchungsmethode. Arch Laryngol Rhinol (Berl). 1903;14:195–7.
55. Reichert M. Über eine neue Unterscuhungsmethode der Oberkieferhöhle mittels des Antroskops. Berl klin Wochenschr. 1902;401:478.
56. Spielberg W. Antroscopy of the maxillary sinus. Laryngoscope. 1922;32:441–4.
57. Maltz M. New instrument: the sinuscope. Laryngoscope. 1925;35:805–11.

58. Anon JB, Lipman SP, Oppenheim D, Halt RA. Computer-assisted endoscopic sinus surgery. Laryngoscope. 1994;104:901–5.
59. American Academy of Otolaryngology-Head and Neck Surgery. Policy on intra-operative use of computer-aided surgery. AAO-HNS Official Website, Policy Statements. 2002. Available at: http://www.entlink.net/practice/rules/image-guiding.cfm. Accessed 29 Aug 2007.
60. Citardi MJ, Batra PS. Intraoperative surgical navigation for endoscopic sinus surgery: rationale and indications. Curr Opin Otolaryngol Head Neck Surg. 2007;15:23–7.
61. Reardon EJ. Navigational risks associated with sinus surgery and the clinical effects of implementing a navigational system for sinus surgery. Laryngoscope. 2002;112(7 Pt 2 Suppl 99):1–19.
62. Fried MP, Moharir VM, Shin J, Taylor-Becker M, Morrison P. Comparison of endoscopic sinus surgery with and without image guidance. Am J Rhinol. 2002;16:193–7.
63. Sindwani R, Metson R. Impact of image guidance on complications during osteoplastic frontal sinus surgery. Otolaryngol Head Neck Surg. 2004;131:150–5.
64. Tabaee A, Hsu AK, Shrime MG, Rickert S, Close LG. Quality of life and complications following image-guided endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2006;135:76–80.
65. Tabaee A, Kassenoff TL, Kacker A, Anand VK. The efficacy of computer assisted surgery in the endoscopic management of cerebrospinal fluid rhinorrhea. Otolaryngol Head Neck Surg. 2005;133:936–43.
66. Metson R, Cosenza M, Gliklich RE, Montgomery WW. The role of image-guidance systems for head and neck surgery. Arch Otolaryngol Head Neck Surg. 1999;125(10):1100–4.
67. Hepworth EJ, Bucknor M, Patel A, Vaughan WC. Nationwide survey on the use of image-guided functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2006;135(1):68–73.
68. Setliff 3rd RC. The hummer: a remedy for apprehension in functional endoscopic sinus surgery. Otolaryngol Clin North Am. 1996;29(1):95–104.
69. Christmas DA, Krouse JH. Powered instrumentation in functional endoscopic sinus surgery I: surgical technique. Ear Nose Throat J. 1996;75:33–40.
70. Goode RL. Power microdebrider for functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 1996;114:676–7.
71. Hamels K, Morre TD, Clement PA. The hummer, shaver or microdebrider. Acta Otorhinolaryngol Belg. 1997;51:89–91.
72. Zweig JL, Schaitkin BM, Fan CY. Histopathology of tissue samples removed using microdebrider technique: implications for endoscopic sinus surgery. Am J Rhinol. 2000;14:27–32.
73. Bhatti MT, Giannoni CM, Raynor E, et al. Ocular motility complications after endoscopic sinus surgery with powered cutting instruments. Otolaryngol Head Neck Surg. 2001;125:501–9.
74. Berenholz L, Kessler A, Sarfaty S, et al. Subarachnoid hemorrhage: a complication of endoscopic sinus surgery using powered instrumentation. Otolaryngol Head Neck Surg. 1999;121:665–7.
75. Draf W. Endonasal micro-endoscopic frontal sinus surgery: the Fulda concept. Oper Tech Otolaryngol Head Neck Surg. 1991;2:234–40.
76. Gross WE, Gross CW, Becker D, et al. Modified transnasal endoscopic Lothrop procedure as an alternative to frontal sinus obliteration. Otolaryngol Head Neck Surg. 1995;113:427–34.
77. Close LG, Lee NK, Leach JL, et al. Endoscopic resection of the intranasal frontal sinus floor. Ann Otol Rhinol Laryngol. 1994;103:952–8.
78. US Food, Drug Administration. Medical Devices. April 2005 Clearances. www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm089999.htm. 2005.
79. Bolger WE, Vaughan WC. Catheter-based dilation of the sinus ostia: initial safety and feasibility analysis in a cadaver model. Am J Rhinol. 2006;20(3):290–4.
80. Brown CL, Bolger WE. Safety and feasibility of balloon catheter dilation of paranasal sinus ostia: a preliminary investigation. Ann Otol Rhinol Laryngol. 2006;115(4):293–9.
81. Friedman M, Schalch P, Lin HC, Mazloom N, Neidich M, Joseph NJ. Functional endoscopic dilatation of the sinuses: patient satisfaction, postoperative pain, and cost. Am J Rhinol. 2008;22(2):204–9.
82. Bolger WE, Brown CL, Church CA, et al. Safety and outcomes of balloon catheter sinusotomy: a multicenter 24-week analysis in 115 patients. Otolaryngol Head Neck Surg. 2007;137(1):10–20.
83. Catalano PJ, Payne SC. Balloon dilation of the frontal recess in patients with chronic frontal sinusitis and advanced sinus disease: an initial report. Ann Otol Rhinol Laryngol. 2009;118(2):107–12.
84. Kuhn FA, Church CA, Goldberg AN, et al. Balloon catheter sinusotomy: one-year follow-up – outcomes and role in functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2008;139(3(Suppl 3)):S27–37.
85. Levine HL, Sertich AP, Hoisington DR, Weiss RL, Pritikin J. Multicenter registry of balloon catheter sinusotomy outcomes for 1,036 patients. Ann Otol Rhinol Laryngol. 2008;117(4):263–70.
86. Luong A, Batra PS, Fakhri S, Citardi MJ. Balloon catheter dilatation for frontal sinus ostium stenosis in the office setting. Am J Rhinol. 2008;22(6):621–4.
87. Weiss RL, Church CA, Kuhn FA, Levine HL, Sillers MJ, Vaughan WC. Long-term outcome analysis of balloon catheter sinusotomy: two-year follow-up. Otolaryngol Head Neck Surg. 2008;139(3(Suppl 3)):S38–46.
88. Plaza G, Eisenberg G, Montojo J, Onrubia T, Urbasos M, O'Connor C. Balloon dilation of the frontal recess: a randomized clinical trial. Ann Otol Rhinol Laryngol. 2011;120(8):511–8.
89. Ahmed J, Pal S, Hopkins C, Jayaraj S. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis. Cochrane Database Syst Rev. 2011;(7):CD008515.
90. Lee JT, Kennedy DW, Palmer JN, Feldman M, Chiu AG. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. Am J Rhinol. 2006;20(3):278–82.
91. Lanza DC, Kennedy DW. Balloon sinuplasty: not ready for prime time. Ann Otol Rhinol Laryngol. 2006;115(10):789–90.
92. Kieff DA, Busaba NY. Reformation of concha bullosa following treatment by crushing surgical technique: implication for balloon sinuplasty. Laryngoscope. 2009;119(12):2454–6.

93. Bleier BS, Paulson DP, O'Malley BW, et al. Chitosan glycerophosphate-based semirigid dexamethasone eluting biodegradable stent. Am J Rhinol. 2009;23(1):76–9.
94. Beule AG, Steinmeier E, Kaftan H, et al. Effects of a dexamethasone-releasing stent on osteoneogenesis in a rabbit model. Am J Rhinol Allergy. 2009;23(4):433–6.
95. Li PF, Downie D, Hwang PH. Controlled steroid delivery via bioabsorbable stent: safety and performance in a rabbit model. Am J Rhinol Allergy. 2009;23(6):591–6.
96. Murr AH, Smith TL, Hwang PH, et al. Safety and efficacy of a novel bioabsorbable, steroid-eluting sinus stent. Int Forum Allergy Rhinol. 2011;1(1):23–32.
97. Snidvongs K, Chaowanapanja P, Aeumjaturapat S, et al. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? Am J Rhinol. 2008;22:483–6.
98. Grobler A, Weitzel EK, Buele A, et al. Pre- and postoperative sinus penetration of nasal irrigation. Laryngoscope. 2008;118:2078–81.
99. Valentine R, Athanasiadis T, Thwin M, et al. A prospective controlled trial of pulsed nasal nebulizer in maximally dissected cadavers. Am J Rhinol. 2008;22:390–4.
100. Harvey RJ, Goddard JC, Wise SK, et al. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. Otolaryngol Head Neck Surg. 2008;139(1):137–42.
101. Benjamin E, Wong DK, Choa D. 'Moffett's' solution: a review of the evidence and scientific basis for the topical preparation of the nose. Clin Otolaryngol Allied Sci. 2004;29:582–7.
102. Cohen NA, Kennedy DW. Endoscopic sinus surgery: where we are—and where we're going. Curr Opin Otolaryngol Head Neck Surg. 2005;13:32–8.
103. Stammberger H, Posawetz W. Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique. Eur Arch Otorhinolaryngol. 1990;247:63.
104. Levine HL. Functional endoscopic sinus surgery: evaluation, surgery, and follow-up of 250 patients. Laryngoscope. 1990;100:79.
105. Hoffmann DF, May M, Mester RTR. Functional endoscopic sinus surgery—experience with the initial 100 patients. Am J Rhinol. 1990;4:129–32.
106. Rice D. Endoscopic sinus surgery results at 2 year follow-up. Otolaryngol Head Neck Surg. 1989;101:476–9.
107. Metson RB, Gliklich RE. Clinical outcomes in patients with chronic sinusitis. Laryngoscope. 2000;110:24.
108. Khalid AN, Quraishi SA, Kennedy DW. Long-term quality of life measures after functional endoscopic sinus surgery. Am J Rhinol. 2004;18:131–6.
109. Litvack JR, Mace J, Smith TL. Does olfactory function improve after endoscopic sinus surgery? Otolaryngol Head Neck Surg. 2009;140:312–9.
110. Chester AC, Sindwani R, Smith TL, Bhattacharyya N. Systemic review of change in bodily pain after sinus surgery. Otolaryngol Head Neck Surg. 2008;139:759–65.
111. Loehrl TA, Ferre RM, Toohill RJ, Smith TL. Long-term asthma outcomes after endoscopic sinus surgery in aspirin triad patients. Am J Otolaryngol. 2006;27:154–60.
112. Sautter NB, Mace J, Chester AC, Smith TL. The effects of endoscopic sinus surgery on level of fatigue in patients with chronic rhinosinusitis. Am J Rhinol. 2008;22:420–6.

Chapter 24
Controversies in the Surgical Management of Chronic Rhinosinusitis

Samuel Jayaraj and Peter James Andrews

Introduction

Chronic rhinosinusitis is common, has a significant impact on quality of life and productivity [1] and may lead to intracranial or orbital complications. The primary treatment strategies involve lifestyle changes and environment modifications followed by medical treatment comprising of numerous classes of pharmaceutical products often used in combination. These pharmaceutical products are developed at great expense. The heavy investment required in their development and meeting compliance with pharmaceutical regulatory authorities around the world necessitates marketing to ensure that knowledge of the product is widely disseminated to patients who may benefit. There is a good scientific basis behind these pharmaceutical products and supportive evidence behind their efficacy and safety when used for patients with appropriate indications. Placebo-controlled, double-blind randomised controlled trials are commonly constructed to determine the best treatment regimen for different clinical problems. Please refer to Chaps. 19 and 20 for a more in-depth discussion of the medical treatment of rhinosinusitis.

Surgical treatments for chronic rhinosinusitis are generally reserved for those patients who have failed to respond to medical intervention [2, 3]. Sometimes, the surgery is directed towards improving access or penetration of medical treatments. Other times, surgery is designed to correct structural issues that may be contributing to the disease process or lack of success of medical treatment. In some circumstances, particularly when there is focal sinus disease present, surgery is easily curative when directed at local inflammatory disease. Sometimes, surgery may be destructive in nature when directed towards the removal or 'debulking' of nasal/sinus polyposis (Chaps. 22 and 23).

Surgery for chronic rhinosinusitis is highly varied in method. It may be through an endonasal approach or external approach; it may involve powered instrumentation, lasers and coblation, or hand instruments; it may require image guidance technology and advanced robotics technology; and it may involve minimally invasive techniques such as balloon technologies and drug-eluting stents (see Chap. 22). Some of these techniques might be considered by some surgeons and patients as being quite exciting, glamorous, groundbreaking and innovative. These are emotive descriptions which are headline grabbing, but are they really suited in the practice of medicine and surgery? As patients' expectations rise, there is a drive towards not only efficacious surgical interventions but also interventions that are safer with less morbidity and less 'downtime' for patients. Key questions that need to be addressed as we develop new innovative techniques are as follows:

- Do these new innovative treatments actually work?
- Do more established surgical techniques that have been widely adopted actually work?
- How do we know?
- What is the current evidence for established surgical intervention in chronic rhinosinusitis?

This chapter is entitled 'Controversies in the Surgical Management of Chronic Rhinosinusitis'. A controversy can be defined as a prolonged public dispute, debate or contention and a disputation concerning a matter of opinion. More emotive definitions include strife or argument. Generally, controversies arise when something has not been conclusively proven. When there is controversy, there is unresolved debate or difference of opinion.

S. Jayaraj, MBBS, FRCS(Eng), FRCS(ORL-HNS) (✉)
Department of ENT Surgery, Barts Health NHS Trust, Whipps Cross University Hospital, Whipps Cross Road, London E11 1NR, UK
e-mail: samuel.jayaraj@bartshealth.nhs.uk

P.J. Andrews, MBBS, BSc (hons) FRCS (ORL-HNS)
Department of ENT Surgery, University College London Hospital, Royal National Throat Nose and Ear Hospital, 330 Grays Inn Road, London wc1x 8da, UK

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_24,

In this chapter, we intend to look at the issues surrounding evidence-based surgical practice, the difficulties that lie in this arena and the controversies amongst surgical treatments and tools used in the surgical management of chronic rhinosinusitis. We will also touch on the role of the regulatory authorities, the adoption of new technologies and their role as a marketing tool. This chapter itself may be considered controversial as the topics covered include the authors' opinions as well as level 5 evidence (Centre for Evidence-Based Medicine, Oxford). In some ways, the choice of topics lacks a critical evidence basis, and they are chosen according to the authors' experience and interpretation of the evidence. However, the authors make no apology for this! We have taken the liberty of choosing those issues we think are controversial in the surgical management of chronic rhinosinusitis. Specifically, we will be critically reviewing FESS, the role of external approach sinus surgery, the role image guidance surgery, middle turbinate resection, balloon sinuplasty and surgery for paediatric chronic rhinosinusitis.

Evidence-Based Surgical Practice

Evidence-based health care is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services [4–7] (Table 24.1). Current best evidence is up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests and the predictive power of prognostic factors. Evidence-based clinical practice is an approach to decision-making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the treatment option that suits that patient best. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

Surgical interventions may be developed after anatomical and pathophysiological research. Safety is then assessed and case studies and case series undertaken followed by case-controlled studies and cohort studies. However, observational data without a control population may be open to prejudice. Observational studies may be tainted by data dredging, confounding and bias, and, therefore, verification is needed through a randomised controlled trial. Surgical interventions based solely on observational data must be carefully and critically scrutinised. Ultimately, the effectiveness of an intervention has to be judged relative to a matching non-intervention control population. The gold standard for any procedure remains the randomised controlled trial (RCT).

Once a number of randomised controlled trials have been concluded, it is possible to perform a meta-analysis. This is a systematic method that uses statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. A meta-analysis produces a stronger conclusion than can be provided by any individual study.

Evidence-Based Surgery

There is generally a perceived deficiency of the evidence base in surgical specialities, especially when compared to medical specialities. There are particular features of surgery as a discipline and the very nature of surgical intervention that pose problems for randomised controlled trials. Many of the conditions treated by surgery are of an anatomical, structural or mechanical nature, and the superiority of the mechanical solution offered by surgery over nontreatment is self-evident. In many surgical scenarios, the benefits are so clear that one would consider a trial unethical or insensible.

Table 24.1 Levels of evidence

Levels	Evidence
1a	Systematic reviews (with homogeneity) of randomised controlled trials
1b	Individual randomised controlled trials (with narrow confidence interval)
1c	All or none randomised controlled trials
2a	Systematic reviews (with homogeneity) of cohort studies
2b	Individual cohort study or low-quality randomised controlled trials (e.g. <80 % follow-up)
2c	'Outcomes' research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'

Surgery is a skilled, multistep process, which makes RCT designs difficult to deliver in surgical studies. There is a learning process in every new operation, even for a fully trained surgeon unfamiliar with the particular procedure. Serious bias can easily be introduced if this is not acknowledged and measured or eliminated, especially for trials of new versus older procedures. There may also be inherent variation in the way in which a surgical procedure is performed by each different, individual surgeon, and this cannot be eliminated. For example, the terminology 'functional endoscopic sinus surgery' (FESS) could be used by some surgeons to indicate surgery confined to the middle meatus or anterior ethmoid sinuses only whereas other surgeons may use the term when they fully clear the entire paranasal sinuses ('full house' FESS). Therefore, it may be appropriate to stratify surgical trials by surgeon. Good surgical quality control means having valid objective measures which can demonstrate that an operation has been carried out according to predefined principles.

The study group in surgical RCTs involves patients who themselves may be a heterogeneous group, and this increases error and bias with regard to their inclusion and outcome assessment measurements. In any study of surgical procedures, researchers are constantly asking 'are we comparing like with like, or apples with pears?' (Fig. 24.1).

For example, in studying surgical interventions in chronic rhinosinusitis, have the patients been carefully stratified by defining those patients with or without allergic disease, those with or without nasal polyposis, those with or without nonsteroidal anti-inflammatory intolerance or those with or without immune deficiency as the primary or an associated aetiology? Much of the cynicism expressed by surgeons about RCTs stems from their concern about this inability of crude designs to acknowledge the critical importance of surgical skill in defining surgical outcome. Large variations in outcome may be observed between surgeons performing similar operations in the same population. The very nature of surgical intervention may make it difficult if not impossible to eliminate bias and lack of blinding of both the patient and the surgeon that is required in effective and accurately performed RCTs.

Despite all these difficulties, we should continue to strive for more RCT evidence. However, it will take years to obtain adequate RCT evidence of surgical procedures in chronic rhinosinusitis if indeed this is ever possible. The gold standard RCT comparing sinus surgery with maximal medical treatment can probably only be achieved through a multicentre multiyear study. Until then, we must make the best efforts we can to analyse the available evidence from available largely nonrandomised published studies. This includes determining the quality of the nonrandomised studies, which tend to be plentiful in surgery, to assess if they are well researched and validated. At the same time, there is an urgent need to develop a system of description that makes estimating the efficacy of a treatment based on the best data, together with an estimate of the relative quality of the evidence.

The lack of an RCT for a particular intervention does not mean it does not work or have a place in the treatment options. In place of the current lack of RCTs, it is necessary to evaluate what evidence we do currently have to guide informed

Fig. 24.1 Comparing apples and pears

decisions, but this allows controversy to enter into the debate. In the absence of RCTs, the justification of a surgical intervention is based on common sense, logical analysis and surgeons' experience and expertise interplaying with published guidelines from learned bodies and institutions. An entertaining spoof on the difficulties physicians, especially surgeons, face with regard to evidence-based practice was published in the British Medical Journal in 2003 by Smith and Pell. These authors looked at the evidence base behind parachutes preventing death during free fall: 'Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials' [8].

The article concludes as follows:

> **Conclusions:** As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Surgical Regulation

Surgical disciplines around the world largely self-regulate themselves with trusted bodies and organisations interplaying with self-interest health-care groups, patient groups, political groups and medical indemnity organisations. Various regulatory bodies around the world are responsible for monitoring and assessing new treatments, drugs and medical devices and for providing treatment guidance documents. In the United States (and Puerto Rico, Guam, the Virgin Islands, American Samoa and other US territories and possessions), the Food and Drug Administration (FDA) [9] is responsible for a number of tasks:

- Protecting the public health by assuring that foods are safe, wholesome, sanitary and properly labelled and that human and veterinary drugs and vaccines and other biological products and medical devices intended for human use are safe and effective
- Protecting the public from electronic product radiation
- Assuring cosmetics and dietary supplements are safe and properly labelled
- Regulating tobacco products
- Advancing the public health by helping to speed product innovations
- Helping the public get the accurate science-based information they need to use medicines, devices and foods to improve their health

FDA monitors reports of adverse events and other problems with medical devices and alerts health professionals and the public when needed to ensure proper use of devices and the health and safety of patients. Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. A physician can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. Guidance documents describe FDA's interpretation of policy on a regulatory issue. These documents usually discuss more specific products or issues that relate to the design, production, labelling, promotion, manufacturing and testing of regulated products. Guidance documents may also relate to the processing, content and evaluation or approval of submissions as well as to inspection and enforcement policies.

In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) [10] is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe. The MHRA is an executive agency of the Department of Health, the UK government department responsible for public health issues. The MHRA is responsible for the regulation of medicines and medical devices and equipment used in health care and the investigation of harmful incidents. The term 'medical devices' includes medical equipment. Medical devices are all products, except medicines, used in health care for the diagnosis, prevention, monitoring or treatment of illness or disability. Examples include X-ray and other imaging equipment, pacemakers, artificial joints, anaesthetic equipment, pregnancy test kits, infusion equipment, beds, wheelchairs, condoms and surgical dressings. The MHRA implements the European Community (EC) Medical Devices Directives into UK law. They place obligations on manufacturers to ensure that their devices are safe and fit for their intended purpose before they are CE marked and placed on the market in any EC member state. Since 1993, CE (Conformité Européenne) marking has been a key indicator of a product's compliance with European Union legislation and enables the free movement of products within the European market. By affixing the CE marking on a product, a manufacturer is declaring, on his sole responsibility, conformity with all of the legal requirements to achieve CE marking and therefore ensuring validity for that product to be sold throughout the European Economic Area (EEA, the 27 Member States of the EU and EFTA countries Iceland, Norway, Liechtenstein), as well as Turkey. This also applies to products made in third countries, which are sold in the EEA and Turkey. CE marking is a declaration by the manufacturer that the product meets all the

Fig. 24.2 NICE

Table 24.2 Adopter categories in innovation and marketing

Innovators	Represent a small percentage of the market that is at the forefront of adopting new products. These people are often viewed as enthusiasts and are eager to try new things, often without regard to price. Whilst a good test ground for new products, marketers find that innovators often do not remain loyal as they continually seek new products
Early adopters	This group contains more members than the innovator category. They share innovators' enthusiasm for new products though they tend to be more practical about their decisions. They also are eager to communicate their experiences with the early majority (next group), and because of their influence, they are important to the future success of the product (i.e. act as opinion leaders)
Early majority	This represents the beginning of entry into the mass market. The early majority account for up to one-third of the overall market. The early majority like new things but tend to wait until they have received positive opinions from others (i.e. early adopters) before purchasing. Adoption by the early majority is key if a new product is to be profitable. On the other hand, many new products die quickly because they are not accepted beyond early trials by innovators and early adopters and never reach mass market status
Late majority	Possibly as large as the early majority, this group takes a wait-and-see approach before trying something new. Marketers are likely to see their highest profits once this group starts to purchase
Laggards	This is the last group to adopt something new and, in fact, may only do so if they have no other choice. Depending on the market, this group can be large though because of their reluctance to accept new products, marketers are not inclined to direct much attention to them

Based on data from Ref. [12]

appropriate provisions of the relevant legislation implementing certain European directives. CE marking gives companies easier access into the European market to sell their products without adaptation or rechecking. It is a declaration by the manufacturer that his product meets the requirements of the applicable European directive(s). According to this, medical devices must not only be safe but also function in a medical and technical way as described in the manufacturer's 'intended purpose'.

The regulatory authorities above are present to ensure devices work and are safe. They do not necessarily confirm that a device may be the best treatment for a condition either from an efficacy or economical aspect. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) [11] produces guidance for the National Health Service (NHS) about preventing, diagnosing and treating different medical conditions. The guidance is written by independent experts, including health-care professionals and people representing patients and carers. They consider how well an interventional procedure works and how safe it is and ask the opinions of expert advisers. Interventional procedure guidance applies to the whole of the NHS in England, Wales, Scotland and Northern Ireland. Health-care workers in the NHS are expected to follow this guidance (Fig. 24.2).

The primary role of each of these regulatory agencies is to determine safety, effectiveness and sometimes value. They do not necessarily determine and critically evaluate the evidence base for a particular treatment device or medication against others. Furthermore, many physicians do not feel they necessarily determine the best treatment for a condition, without prejudice from political interference or economical factors. Political interference (especially with regard to affordability) is thought to play a role in some guidance issued from NICE for example.

Innovation and Marketing

We have already discussed the difficulty obtaining evidence in surgical practice. This difficulty may be compounded by the way new devices or techniques may be publicised or marketed. This may also affect recruitment of participants into RCTs. Furthermore, surgeons' attitude or bias to innovation and new devices may affect their uptake in the marketplace of medicine. There are general principles of marketing and product life cycles that influence this. These general marketing principles may be applied to surgery as well as household products or any other industry and are outlined in Table 24.2 [12].

The adopter categories help explain the shape of the life cycle for new innovations. It is clear that innovators are necessary to push forward medical and surgical advances as a stepwise and rational process. Critics of the early adopters will suggest that the early adopters are using the new innovation as a marketing tool before sufficient validation has occurred. Self-interest can be a powerful motivator in becoming an innovator early adopter. Of course, without early adopters, it will not be possible to get validation. In the end, it is essential that any validation follows the principles of evidence-based medicine, which will encourage the early and late majority to join in.

In some cases, there has been publicity or even direct marketing to the public and patients by the industry behind devices and innovatory products. Patients have then approached doctors or surgeons requesting or demanding a certain treatment that they have seen claims about which may or may not be fully substantiated especially in terms of long-term outcome. The degree of advertising to the public varies from country to country dependent on local practice, regulation and law [13].

Funding structures, health economics, medical establishment structures, subspecialisation and practice workloads vary between continents and nations. The American Academy of Otolaryngology – Head and Neck Surgeons represents 12,000 otolaryngologists though it is thought there are 8,500 practising otolaryngologists in the United States for a population of approximately 313,000,000. This equates to approximately 1 surgeon per 35,000 population in the United States compared to approximately 1 surgeon per 60,000 populace in Europe and 1 per 100,000 in the United Kingdom.

It seems reasonable to assume that attitudes to innovation and marketing innovation also vary between different countries and different health-care markets. If a surgeon is practising in an environment of oversupply of surgeons and competition for patients, then they might be more likely to adopt innovative tools and techniques, which can then be used as marketing tools to attract referrals. Alternatively, a surgeon working in the converse environment with an undersupply of surgeons and too many patients might be more likely to continue with established and proven treatments and await validation of innovative tools and techniques before adopting them. These are controversial statements as we expect all surgical and medical practitioners to always have their patients' best interests at heart and to set aside their own self-interest and promotion. Surgeons may genuinely be doing what they think is the best for their patients, but to corroborate this, we need validation with RCTs rather than just anecdotal evidence.

Whilst we have discussed how surgeons' involvement with innovation may enter the process at different stages and how early adopters may utilise innovation for promotion and marketing purposes, those who work on commission or pay-for-services may take a differing view. Indeed, health-care purchasers and hospital management have embraced EBM as a means of resisting pressure for expenditure which could be detrimental to innovative advances in medicine.

The Cochrane Collaboration

The Cochrane Collaboration [14] was established in 1993 and is an international, non-profit, independent organisation, established to ensure that up-to-date, accurate information about the effects of health-care interventions is readily available worldwide. The Cochrane Collaborative produces and disseminates systematic reviews of health-care interventions and promotes the search for evidence in the form of clinical trials and other studies of the effects of interventions (Fig. 24.3).

It is termed 'collaboration', as it has thousands of contributors worldwide, working collaboratively from within many independent groups of people (referred to as 'Cochrane entities'). The Cochrane Collaboration's principles include fostering good communication, open decision-making and teamwork, reducing barriers to contributing and encouraging diversity. These require people cooperation, setting aside self-interest and working together to provide evidence with which to improve health care.

Cochrane Reviews are updated regularly with the latest scientific evidence. Members of the organisation (mostly volunteers) work together to provide evidence to help people make decisions about health care. Some people read the health-care literature to find reports of randomised controlled trials, others find such reports by searching electronic databases, others prepare and update Cochrane Reviews based on the evidence found in these trials, others work to improve the methods used in Cochrane Reviews, others provide a vitally important consumer perspective and others support the people doing these tasks. The Cochrane Collaboration website provides information on a variety of ways of registering interest or becoming directly involved [15]. As of July 2011, there are more than 28,000 people working within the Cochrane Collaboration in over 100 countries, over 70 % of whom are authors of Cochrane Reviews. In January 2011, the Cochrane Collaboration was accepted as a non-governmental organisation in official relations with the World Health Organization (WHO), the public health arm of the United Nations, establishing formalised communication between the two organisations. The Cochrane Collaboration provides an international benchmark for the independent assessment and assimilation of scientific evidence.

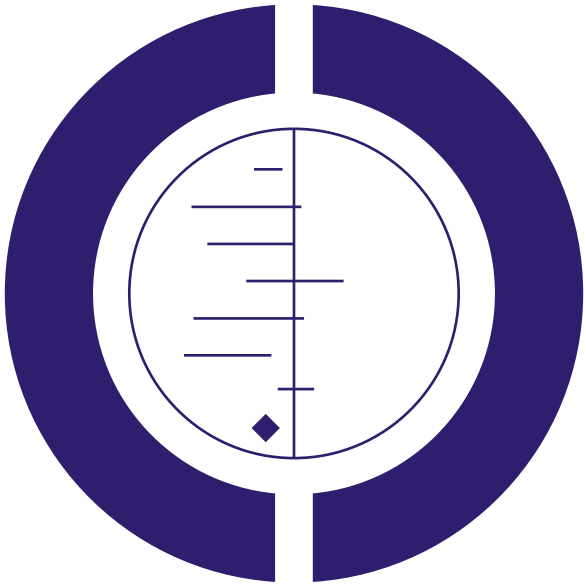


Fig. 24.3 The Cochrane Collaboration logo

What Are Cochrane Reviews?

Cochrane Reviews [16] are systematic assessments of evidence of the effects of health-care interventions, intended to help people to make informed decisions about health care, their own or someone else's. Cochrane Reviews are needed to help ensure that health-care decisions throughout the world can be informed by high-quality and timely research evidence. It should perhaps be noted that many Cochrane Reviews, especially in regard to surgical intervention, surmise that there is insufficient or unconvincing evidence to support a particular surgical intervention. This is usually based on the fact that there are insufficient numbers of RCTs of sufficient similarity and quality to analyse to determine efficacy based on Cochrane criteria.

What Is the Current Evidence for Established Surgical Intervention in Chronic Rhinosinusitis?

Functional Endoscopic Sinus Surgery (FESS)

Current evidence-based medicine (EBM level 1a) does not support surgical intervention as being a more effective treatment when compared with maximal medical treatment for chronic rhinosinusitis (CRS) (see Table 24.3) [17]. Consequently, surgery for CRS remains controversial. This is highlighted in the Cochrane Review, which addressed this issue and based on the three randomised controlled trials that fulfilled their inclusion criteria [18]. Only one of the three RCTs compared surgery with medical treatment [19]; the other two compared different surgical techniques [20, 21].

Although evidence-based medicine strives to quantify evidence and helps guide the best clinical practice, the key is always to scrutinise the data available. Interestingly, the evidence used in this Cochrane Review was flawed because, firstly, CRS was not adequately defined and, secondly, the sample recruited was fundamentally biased towards medical intervention. All three RCTs were flawed in their methodology, not necessarily because of poor planning but the enormity of the design and the scarcity of true surgical patients.

Table 24.3 Cochrane Reviews for the treatment of CRS

1. Functional endoscopic sinus surgery (FESS) for chronic rhinosinusitis
2. Nasal irrigation with saline (salt water) for the symptoms of chronic rhinosinusitis
3. Topical steroid for chronic rhinosinusitis without polyps
4. Antifungal therapy for chronic rhinosinusitis
5. Balloon dilation of sinus openings for chronic rhinosinusitis

A comparison of the results of different trials for FESS in the treatment of CRS is difficult for a number of reasons. The studies lack a single disease staging system (CRS is a multidisease entity, allergic, polypoidal, fungal, etc.); some involve a single sinus, whilst others involve multi-sinus disease; the FESS procedures differ in technique; and the outcome measures are not uniform. The latter difficulty precludes the use of a meta-analysis. For example, only one RCT (Ragab et al. [19]) compared maximal medical treatment with FESS. The authors recruited 90 patients of which 54 % were skin prick test positive (SPT) and 39 % had nasal polyps which biased the recruited population towards a medical cohort. In a single sinus study published by Hartog et al. [20], the authors evaluated and treated a total of 89 patients with chronic maxillary sinusitis. These authors compared medical treatment and sinus irrigation to medical treatment and sinus irrigation followed by FESS. Seventy-seven patients were available for evaluation (41 in the FESS, sinus irrigation and medical treatment group and 36 in the sinus irrigation-only group). The median follow-up was 12 months. The intention-to-treat analysis showed a significant reduction in the symptoms of purulent nasal discharge and hyposmia in the FESS-treated group. However, there was no significant difference between both groups in overall cure rates at the end of 1 year (odds ratio (OR) 1.63; 95 % CI 0.58–4.53, $P=0.35$).

In conclusion, all treatment arms in the three RCTs in the Cochrane Review in 2006 were equally effective, be it maximal medical treatment, endoscopic sinus surgery or a sinus washout. However, the difference in sinus involvement, surgical techniques and disease stratification makes any assessment of the relative value of FESS in CRS impossible. The problem with any data analysis of chronic rhinosinusitis is the fact that CRS is not a single disease entity and can be broadly divided into medical conditions, surgical conditions or both. Patients who are predominately skin prick test positive will require long-term medical treatment, and the role of surgery is debatable. Similarly, many physicians feel that patients with nasal polyps are also a predominately medical entity. To accurately evaluate the value of FESS in CRS, a true surgical CRS population would exclude SPT positivity as well as those with sinus polyps leaving a CRS population who has failed medical treatment or developed comorbid complications as the ideal group of patients to study. When the key question is ‘what is more effective, surgery or maximal medical treatment, in a pure surgical CRS population?’ as described, the answer is self-evident when the indication for surgery is failed medical treatment. Surgery is a necessity when medical treatment fails and when the patient continues to be in discomfort. To prove otherwise would be unethical. This is seen classically in complications of acute/chronic sinusitis such as a peri-orbital abscess and mucocele formation whereby surgery is the only option, treatment of expanding mucin in allergic fungal sinusitis, grade 3 nasal polyposis refractory to steroids and chronic frontal sinusitis refractory to medical treatment [22].

So the real question is whether there is a role of surgery in those subtypes of CRS that are considered ‘medical’, i.e. patients with a significant allergic component or nasal polyps. The current evidence would suggest that maximal medical treatment is just as effective in these circumstances. Assuming medical and surgical treatments are equally effective, other outcome measures need to be assessed including quality of life and financial cost in treating CRS.

Having established that surgery is equally as effective as maximal medical treatment in CRS with a predominately medical component, the next question is ‘when medical treatment fails, which type of sinus surgery is more effective?’ Current level 1b and level 3 evidence would suggest that all types of sinus surgery are equally effective be it a sinus washout or FESS for CRS (without polyps) or a simple polypectomy or FESS polypectomy for nasal polyps [20, 23, 24]. In the National Comparative Audit of Surgery for Nasal Polyposis and CRS, all types of sinus surgery showed improvements in their SNOT 22 scores [23]. The 5-year follow-up study showed very similar revision rates between simple polypectomy and FESS polypectomy although when taking into account multivariate logistic regression to adjust for baseline characteristics, the revision rate was statistically less in the FESS polypectomy arm [25]. The controversy of surgery in CRS remains an ongoing debate with the exception of chronic frontal sinusitis. The endoscopic surgical resolution of frontal CRS is now becoming an accepted practice [22], although the ever-present predilection for stenosis in the frontal ostium calls upon other potential medical treatments [26].

The Role of External Surgical Approaches in Chronic Rhinosinusitis

There is a drive amongst surgical ENT specialists to perform more and more procedures endoscopically. There is concern that the drive to perform all surgery endoscopically is resulting in surgeons and surgical trainees becoming deskilled in the rare but necessary practice of the external approach. The external surgical approach in CRS is more and more uncommon but still a necessity in a small number of scenarios. For example, medical complications of CRS include orbital cellulitis and mucoceles. In both situations, the external approach is recommended if inaccessible by endoscopic surgery. It is recommended that an orbital abscess be drained externally particularly if positioned laterally or superiorly. The controversy in endoscopic decompression of orbital abscesses arises in its efficacy and whether it should be performed by all or by just an experienced rhinologist.

The desire from patients for scar-free surgery and less morbidity drives endoscopic surgery and its increasing use in orbital cellulitis/abscess drainage and treatment of frontal sinus disease [22]. An external approach is used for the ligation of the anterior ethmoidal artery (AEA) as a consequence of haemorrhage secondary to endoscopic sinus surgery for CRS. However, there is an increasing move to clip the AEA endoscopically. The majority of patients who undergo endoscopic sinus surgery are without complication. In the event of a surgical complication, all be it rare, an external approach needs to be discussed as part of the routine consent process. Surgery on the frontal sinus is predominately performed endoscopically using image guidance navigation, as the anatomy is complex with potentially higher morbidity and complications [27]. However, the external approach is always consented as an adjunct particularly in the case of laterally placed lesions whereby the external approach can only be performed.

The Role of Image Guidance in the Surgical Treatment of Chronic Rhinosinusitis

The compulsory role of image guidance technology in every sinus surgery case remains controversial and is perhaps analogous to the use of the facial nerve monitor in middle ear surgery or parotid surgery. Some would argue that it is not a substitute for a surgeons' understanding of the intricate anatomy of the paranasal sinuses or ability to interpret complex multi-planar computed tomography scans. Others will counter that we are potentially negligent if an untoward incident occurred during sinus surgery without the use of navigation. Does the use of navigation give reassurance during surgery?

Image guidance surgery is used in areas where the risk of intracerebral and orbital damage is high. The role of image guidance is to facilitate anatomy definition and reduce complication risk. In frontal sinus surgery, these risks are higher due to the close proximity of the skull base as well as the orbit. Image guidance is also used where access into an area is not visible due to scarring such as frontal sinus surgery or sphenoidal surgery. The Medtronic fusion navigation system is used in our department. This system represents an innovative electromagnetic (EM) image-guided surgery approach. The advantage of an image guidance system is that it allows the surgeon to operate with the maximum amount of information about the unique anatomy of each patient and to 'see' the relative location of the instrument tip in the patient's sinus anatomy during surgery (Fig. 24.4).

Middle Turbinate Surgery

There are two schools of thought with regard to the middle turbinate (MT): resection or preservation [28]. Some surgeons routinely resect the MT without adverse sequelae, whilst others always try to preserve the MT. The middle turbinate is an important landmark, may contain olfactory mucosa to a varying degree, plays a humidifier role and may control or influence airflow through the middle meatus. In conjunction with the uncinate process, this effect on airflow regulation may have a bearing on airflow entering the maxillary sinus and, in turn, may affect varying gaseous concentrations such as nitric oxide levels which play a role in mucociliary function and bacteriostasis. On this basis, many surgeons recommend preserving the middle turbinate as much as possible. Others will counter that a diseased, polypoid middle turbinate should be resected as it will lead to continued congestion and recurrence of polyps. There are others who are concerned that shaving a polypoid MT and leaving MT bone exposed lead to osteitis and prolonged crusting after surgery. The MT can be resected leaving the axillary portion as a landmark should future surgery be required. The data concerning resections versus preservation is conflicting. There is evidence demonstrating a paucity of complications following MT resection. Furthermore, there may be outcome benefits from judicious partial middle turbinate resection in some patients with more severe rhinosinusitis.

Fig. 24.4 An image guidance system

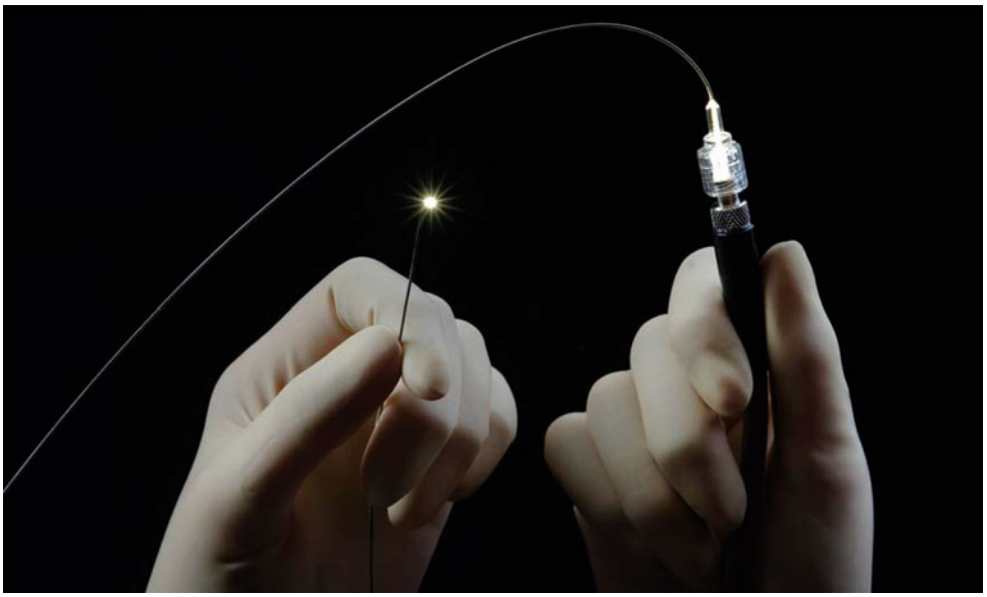


Fig. 24.5 Illuminated Wire used in Balloon Sinuplasty

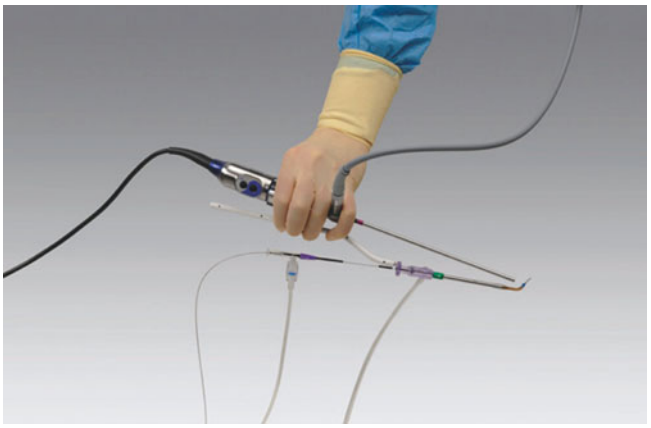


Fig. 24.6 Balloon sinuplasty device system

Other studies looking at quality of life outcomes in patients with bilateral MT preservation versus MT resection have found no difference though patients undergoing MT resection did show greater improvements in endoscopy follow-up examinations and Smell Identification Test scores, which persisted after controlling for confounding factors [29, 30]. This evidence seems contrary to the trend towards more tissue and anatomical preservation surgical approaches such as FESS. The middle ground for most surgeon is preservation but with judicious partial resection in patients with severe polypoid disease. There is yet no answer to the ongoing controversy in MT surgery as to whether we should be decompressing a concha bullosa (pneumatised MT) or resecting paradoxical MT for access and disease control.

Balloon Dilatation/Sinuplasty

Dilation of sinus ostia using a high-pressure balloon has been introduced as a treatment for chronic rhinosinusitis (CRS) refractory to medical treatment. It is commonly referred to as 'balloon sinuplasty' or 'balloon catheter dilatation'. This technique is also described in Chap. 22 (Fig. 24.5). Balloon sinuplasty received FDA clearance in 2005 for marketing (Fig. 24.6).

Balloon sinuplasty is a minimally invasive endoscopic surgical treatment that aims to restore sinus ostia patency with minimal mucosal damage. There are numerous studies demonstrating its safety [31–38], and there are studies confirming short-term effectiveness [33–37, 39–49], but long-term follow-up studies are still not available. Balloon sinuplasty is approved for use in the maxillary and sphenoid sinuses, but it is in the frontal sinuses that most surgeons find this technique most useful. Surgery in the frontal recess can be difficult. But with the illuminated wire used in this procedure, the surgeon can be sure that the frontal sinus has been entered. The balloon is then passed over the wire for dilatation.

There is debate about whether sinus ostia dilation is sufficient in treating chronic sinus disease or whether diseased tissue and bone actually need to be removed to achieve full disease resolution. Does inflammation of the bone contribute to the sinusitis and, if so, will just fracturing the bone outwards with a balloon and widening the ostia be sufficient to relieve the disease process in the long term? The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom published their guidance 'Relieving chronic sinusitis using an inflatable balloon' in September 2008 [50]. NICE said 'this procedure can be offered routinely as a treatment option for people with chronic sinusitis provided that doctors are sure that the patient understands what is involved and agrees to the treatment, and the results of the procedure are monitored'.

Balloon sinuplasty should only be done by doctors who are experienced in complex sinus surgery and who have specific training in this procedure. NICE noted that it can be difficult to decide which patients should be offered balloon sinuplasty and also which sinuses should be treated. NICE noted that the procedure can be carried out at the same time as other procedures (often referred to as hybrid procedure) with balloon sinuplasty and elements of FESS combined. NICE concluded that this procedure is safe enough and works well enough for use in the NHS.

What Does Cochrane Say About Balloon Sinuplasty?

The efficacy of balloon sinuplasty technology was systematically reviewed by the Cochrane Collaboration in 2011 [51]. The review was based on studies published up to 20 December 2010. As of that time, only one study met the review's inclusion criteria (RCT of surgical treatment after failed prolonged course of medical treatment) although it was not as yet a peer-reviewed publication. The study randomised patients with chronic frontal sinusitis who had failed a prolonged course of medical treatment into two groups: balloon dilatation of the frontal recess (plus conventional FESS of other involved sinuses) versus conventional FESS (Draf type 1/2a procedures on the frontal sinuses). The outcome measures were resolution of frontal sinus disease on computed tomography scan and permeability of the frontal recess on endoscopy. At 12-months' follow-up, there was no statistically significant difference in radiological resolution of frontal sinuses between the two groups. The percentages of directly observed patent frontal recesses at 12 months were 75 % in the balloon dilation group versus 63 % in the FESS-only group. The authors state that this was statistically significant, but details of the analysis were not presented. There was bias in the way the study's outcome measures were reported. No major complications were reported. Three patients in the FESS-only group required further revision frontal sinus surgery compared to one in the balloon dilation group, although synechiae were more common in the latter. The summation of the Cochrane Review was that at present, there is no convincing evidence supporting the use of endoscopic balloon sinus ostia dilation compared to conventional surgical modalities in the management of CRS refractory to medical treatment.

With the escalating use of balloon sinuplasty, there is an urgent need for more randomised controlled trials to determine its efficacy over conventional surgical treatment modalities. Despite the numerous publications on balloon sinuplasty [52], RCTs are lacking and an update on the Cochrane Review is expected in 2014. There are abundant data confirming the technique's safety record, and this is no doubt an attractive feature of this tool and technique. Studies have also been completed that demonstrate long-term patency of dilated sinuses (including radiographic evidence of sinus patency) and improved sinus-related quality of life scores for up to 2 years after balloon dilation [40]. However, the published literature consists mainly of noncomparative results on a small number of patients with generally short length of follow-up and no controls. There is a paucity of peer-reviewed, published literature and/or clinical studies regarding balloon sinuplasty as a stand-alone procedure. Often, patients in studies have had hybrid procedures, which are more difficult to compare.

In summary, the long-term efficacy of balloon sinuplasty is unknown. There have been a number of review articles written on the subject. However, more RCTs and longer-term outcome data are needed to determine if symptom improvement, disease resolution and the need for subsequent revision justify its use. In addition, more information is needed to determine which individuals and sinuses are best treated with the balloon technique and which individuals and sinuses require standard approaches.

Controversies in the Surgical Management of Chronic Rhinosinusitis in the Paediatric Population

As with adults, surgery for chronic rhinosinusitis is only considered in children who have failed to respond adequately to medical therapy [53]. The reader is referred to Chap. 22 entitled 'Surgical management of rhinosinusitis in children and adolescents', which covers this subject in detail. Suffice to say, it has long been accepted practice to perform adenoidectomy in paediatric CRS, and a meta-analysis confirms the benefit from this initial approach [54, 55]. There are also studies showing extra benefit from maxillary antral irrigation in addition to adenoidectomy [56, 57]. In 2006, balloon sinuplasty was approved by the FDA, for use in children in the United States. Studies suggest balloon sinuplasty resulted in a greater improvement in symptoms. However, some of these patients underwent maxillary antral irrigation in addition to the balloon sinuplasty, and, therefore, it is unclear as to whether the benefit was from the balloon sinuplasty or from the irrigation or the combined effect of both. The uptake of balloon sinuplasty in Europe has generally been lower compared to the United States and even more so in the paediatric population group. There are extra costs involved in utilising balloon sinuplasty compared to conventional maxillary antral irrigation that requires a more careful cost-effective analysis.

A meta-analysis has shown that symptoms are reduced with functional endoscopic sinus surgery in the paediatric population [58]. Generally, limited FESS has been advocated in children due to concerns over adverse effects of FESS on facial growth. However, a long-term study has shown no impact of FESS on qualitative and quantitative parameters of paediatric facial growth up to 10 years postoperatively [59]. This may help settle a long-standing area of controversy over the safety of FESS in the paediatric group, as fears over the effect on facial growth appear unfounded.

In summary, there is a lack of prospective randomised controlled trials to determine the best surgical management of chronic rhinosinusitis in the paediatric population who have not responded to medical treatment. Generally, it is considered appropriate to initially offer adenoidectomy with maxillary antral irrigation with or without balloon sinuplasty of the maxillary sinus. If this fails, then it appears to be reasonable to consider FESS.

Conclusion

Health-care decision-making throughout the world needs high-quality, research-based evidence. This chapter has been intended to outline the importance of evidence-based practice and to highlight the difficulty in obtaining high-level evidence in surgical specialties including rhinology/otolaryngology.

In general, there is a paucity of peer-reviewed, published literature and clinical studies regarding surgical intervention in chronic rhinosinusitis after adequate medical therapy. This is especially true when one looks at long-term efficacy and outcomes. RCTs and longer-term outcome data are needed to determine symptom improvement, as well as durability of surgical interventions and the need for subsequent revision. In addition, more information is needed to determine which individuals and sinuses might be better treated with one particular technique and which individuals and sinuses may require an alternative approach.

Without sufficient evidence, there will be controversy as to what is the most appropriate or best treatment for a particular patient or anatomical or pathophysiological disease process. We must all strive to do what is best for our patients based on our current understanding of the basic science, the pathophysiology of the disease process and a careful evaluation of contemporaneous data. To achieve this requires cooperation, setting aside self-interest and working together to provide evidence with which to improve health care. Good-quality research needs to be promoted with adequate resources, and contributions to the Cochrane Collaboration should be encouraged. Continued research, in conjunction with postgraduate meetings, seminars and debate, will help to resolve controversies although the very nature of continually advancing surgical science will result in emerging new controversies. For example, there is growing advocacy for the use of robotics in surgery (particularly in urological, neurological and head and neck surgery) though this may not have such a significant role in rhinology because of the current limitation on portal access. With continuing efforts to develop minimally invasive surgery techniques, we are also starting to see drug-eluting stents to deliver medicines to a specific diseased site which may improve drug delivery and clinical efficacy whilst decreasing the need for surgical intervention and associated surgical morbidity. New controversies already!

References

1. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1–12.
2. Guilemany JM, Alobid I, Mullol J. Controversies in the treatment of chronic rhinosinusitis. Expert Rev Respir Med. 2010;4(4):463–77.
3. Baroody FM. Interfacing medical and surgical management for chronic rhinosinusitis with and without nasal polyps. Clin Allergy Immunol. 2007;20:321–36.
4. Gibbon K. Evidence based medicine in otolaryngology. J Laryngol Otol. 1997;111:415–7. Editorial review.
5. Sackett DL, Straus SE, et al. Evidence-based medicine: how to practice and teach EBM. 2nd ed. London: Churchill Livingston; 2000. p. 1–261.
6. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence-based medicine: what it is and what it isn't. BMJ. 1996;312:71–2.
7. Rosenfeld RM, Shiffman RN. Clinical practice guidelines: a manual for developing evidence-based guidelines to facilitate performance measurement and quality improvement. Otolaryngol Head Neck Surg. 2006;135(4 Suppl):S1–28.
8. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ. 2003;327(7429):1459–61.
9. U.S. Food and Drug Administration. 2013. www.fda.gov/.
10. Medicines and Healthcare products Regulatory Agency (MHRA). 2013. www.mhra.gov.uk/.
11. National Institute for Health and Care Excellence (NICE). 2013. www.nice.org.uk/.
12. Rogers EM, editor. Adopter categories: the Rogers curve. Diffusion of innovation. 3rd ed. New York: The Free Press; 1983.
13. Mourdoukoutas P, Siomkos GJ, editors. The seven principles of WOW and buzz marketing: crossing the tipping point. Heidelberg: Springer; 2009.
14. The Cochrane Collaboration. 2013. www.cochrane.org/.
15. The Cochrane Library. 2013. www.thecochranelibrary.com.
16. The Cochrane Collaboration. Cochrane Reviews. 2013. www.cochrane.org/cochrane-reviews.
17. Bellorini J, Dorée C, Chamberlain I, Burton MJ. The Cochrane Ear, Nose and Throat Disorders Group. Otolaryngol Head Neck Surg. 2007;137(4 Suppl):S55–60. Review.
18. Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. Cochrane Database Syst Rev. 2006;(3):CD004458.
19. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. Laryngoscope. 2004;114:923–30.
20. Hartog B, van Benthem PP, Prins LC, Hordijk GJ. Efficacy of sinus irrigation versus sinus irrigation followed by functional endoscopic sinus surgery. Ann Otol Rhinol Laryngol. 1997;106(9):759–66.
21. Fairley JW. Correlation of nasal symptoms with objective findings and surgical outcome measurement [thesis]. London: University of London; 1993.
22. Wormald PJ. The axillary flap approach to the frontal recess. Laryngoscope. 2002;112:494–9.
23. Hopkins C, Browne JP, Slack R, Lund V, Topham J, Reeves B, Copley L, Brown P, van der Meulen J. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Clin Otolaryngol. 2006;31:390–8.
24. Dalziel K, Stein K, Round A, Garside R, Royle P. Systematic review of endoscopic sinus surgery for nasal polyps. Am J Rhinol. 2006;20(5):506–19.
25. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Laryngoscope. 2009;119(12):2459–65.
26. Amonoo-Kuofi K, Lund VJ, Andrews P, Howard DJ. The role of mitomycin C in surgery of the frontonasal recess: a prospective open pilot study. Am J Rhinol. 2006;20(6):591–4.
27. Nouraei SA, Elisay AR, Dimarco A, Abdi R, Majidi H, Madani SA, Andrews PJ. Variations in paranasal sinus anatomy. Indications for the pathophysiology of chronic rhinosinusitis and safety of endoscopic sinus surgery. J Otolaryngol Head Neck Surg. 2009;38(1):32–7.
28. Rudmik L, Soler ZM, Orlandi RR, Stewart MG, Bhattacharyya N, Kennedy DW, Smith TL. Early postoperative care following endoscopic sinus surgery: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2011;1(6):417–30. doi:10.1002/alr.20072. Epub 2011 Oct 29.
29. Havas TE, Lowinger DS. Comparison of functional endonasal sinus surgery with and without partial middle turbinate resection. Ann Otol Rhinol Laryngol. 2000;109(7):634–40.
30. Soler ZM, Hwang PH, Mace J, Smith TL. Outcomes after middle turbinate resection: revisiting a controversial topic. Laryngoscope. 2010;120(4):832–7.
31. Brown C, Bolger W. Safety and feasibility of balloon catheter dilation of paranasal sinus ostia: a preliminary investigation. Ann Otol Rhinol Laryngol. 2006;115(4):293–9.
32. Bolger W, Vaughan V. Catheter based dilation of the sinus ostia: initial safety and feasibility analysis in a cadaver model. Am J Rhinol. 2006;20(3):290–4.
33. Bolger W, Brown C, Church C, Goldberg A, Karanfilov B, Kuhn F, Levine H, Sillers M, Vaughan W, Weiss R. Safety and outcomes of balloon catheter sinusotomy: a multi-center 24 week analysis in 115 patients. Otolaryngol Head Neck Surg. 2007;137:10–20.
34. Leventhal D, Heffelfinger R, Rosen M. Using image guidance tracking during balloon catheter dilation of sinus ostia. Otolaryngol Head Neck Surg. 2007;137:341–2.
35. Levine HL, Sertich AP, Hoisington DR, Weiss RL, Pritikin J. Multicenter registry of balloon catheter sinusotomy outcomes for 1,036 patients. Ann Otol Rhinol Laryngol. 2008;117:263–70.
36. Vaughan WC. Review of balloon sinuplasty. Curr Opin Otolaryngol Head Neck Surg. 2008;16:2–9.
37. Ramadan HH. Safety and feasibility of balloon sinuplasty for treatment of chronic rhinosinusitis in children. Ann Otol Rhinol Laryngol. 2009;118(3):161–5.

38. Friedman M, Wilson M. Illumination guided balloon sinuplasty. Laryngoscope. 2009;119:1399–402.
39. Kuhn FA, Church C, Goldberg A, Levine H, Sillers M, Vaughn W, Weiss R. Balloon catheter sinusotomy: one-year follow-up outcomes and role in functional endoscopic sinus surgery. Otolaryngol HeadNeck Surg. 2008;139(3S3):S27–37.
40. Weiss R, Church C, Kuhn F, Levine H, Sillers M, Vaughan W. Long-term outcome analysis of balloon catheter sinusotomy: two-year follow-up. Otolaryngol Head Neck Surg. 2008;139(3S3):S38–46.
41. Wittkopf ML, Becker SS, Duncavage JA, Russell PT. Balloon sinuplasty for the surgical management of immunocompromised and critically ill patients with acute rhinosinusitis. Otolaryngol Head Neck Surg. 2009;140:596–8.
42. Jurkiewicz D, Szczygielski K, Brzozowski K. Endoscopic sinus balloon catheterisation – evolution or revolution in treatment of rhinosinusitis? Our experience and literature review. Otolaryngol Pol. 2009;63(2):113–7.
43. Welch K, Stankiewicz J. A contemporary review of endoscopic sinus surgery: techniques, tools, and outcomes. Laryngoscope. 2009;119(11):2258–68.
44. Ramadan HH, McLaughlin K, Josephson G, Rimell F, Bent J, Parikh S. Balloon catheter sinuplasty in young children. Am J Rhinol. 2010;24:54–6.
45. Khalid AN, Smith TL, Anderson JC, Mace J, Sautter NB. Fracture of bony lamellae within the frontal recess after balloon dilatation. Am J Rhinol Allergy. 2010;24(1):55–9.
46. Stewart AE, Vaughan WC. Balloon sinuplasty verses surgical management of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2010. doi:10.1007/s/11882-010-0105-3.
47. Wycherley BJ, et al. Balloon dilation in revision sinus surgery. Ann Otol Rhinol Laryngol. 2010;119(7):468–71.
48. Batra PS, et al. Balloon catheter technology in rhinology: reviewing the evidence. Laryngoscope. 2011;121(1):226–32.
49. Bhandarkar ND, Smith TL. Revision frontal sinusotomy using stepwise balloon dilation and powered instrumentation. Laryngoscope. 2010;119(7):468–71.
50. Balloon catheter dilation of paranasal sinus ostia for chronic sinusitis (IPG273). 2008. www.nice.org.uk/IPG273.
51. Ahmed J, Pal S, Hopkins C, Jayaraj S. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis. Cochrane Database Syst Rev. 2011;(7):CD008515.
52. Stewart AE, Vaughan WC. Balloon sinuplasty versus surgical management of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2010;10(3):181–7.
53. Lund VJ, Neijens HJ, Clement PA, Lusk R, Stammberger H. The treatment of chronic sinusitis: a controversial issue. Int J Pediatr Otorhinolaryngol. 1995;32(Suppl):S21–35.
54. Ungkanont K, Damrongsak S. Effect of adenoidectomy in children with complex problems of rhinosinusitis and associated diseases. Int J Pediatr Otorhinolaryngol. 2004;68(4):447–51.
55. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72(10):1541–5. Epub 2008 Aug 23.
56. Ramadan HH, Cost JL. Outcome of adenoidectomy versus adenoidectomy with maxillary sinus wash for chronic rhinosinusitis in children. Laryngoscope. 2008;118(5):871–3.
57. Criddle MW, Stinson A, Savliwala M, Coticchia J. Pediatric chronic rhinosinusitis: a retrospective review. Am J Otolaryngol. 2008;29(6):372–8.
58. Herbert RL, Bent JP. Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. Laryngoscope. 1998;108(6):796–9.
59. Bothwell MR, Piccirillo JF, Lusk RP, Ridenour BD. Long-term outcome of facial growth after functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2002;126(6):628–34.

Chapter 25
Managing Complications of Endoscopic Sinus Surgery in Children and Adults

Brendan C. Hanna and Peter-John Wormald

Introduction

The incidence of major complications in endoscopic sinus surgery appears to have decreased in the past 10 years. A recent retrospective review of a nationwide database of patients who underwent ESS between 2003 and 2007 in the USA identified 62,823 patients in whom the overall major complication rate was 1.0 % (CSF leak 0.17 %, orbital injury 0.07 %, haemorrhage requiring transfusion 0.76 %). This is less than an estimated major complication rate of 1–3 % from early studies with relatively small patient cohorts. This review found a lower rate of CSF leak in the paediatric patient population but a greater chance of orbital complications [1]. In this chapter, major complications are addressed first then the less serious complications of adhesions, trephine injuries, recurrent disease, lacrimal injury and alteration to olfaction.

Major Complications

Haemorrhage

Haemorrhage is the most common major complication of endoscopic sinus surgery in the present era. Two types of bleeding are encountered: arterial squirting that can rapidly fill the surgical field or disseminated ooze that may impede surgery and can accumulate over time to represent significant blood loss.

Sphenopalatine Artery Bleeding

Arterial bleeding occurs most commonly from branches of the sphenopalatine artery (SPA). The posterior nasal artery is easily injured at the inferior margin of the sphenoidotomy and the sphenopalatine artery itself can be injured when the horizontal portion of the ground lamella is disrupted. The SPA or one of its branches can bleed when the inferior posterior ethmoid adjacent to the vertical part of the palatine bone is opened and can also occur when completing the lateral inferior extent of the sphenoidotomy through an ethmoidal corridor. Bleeding from the sphenopalatine artery may not be immediately obvious. The artery may spasm and temporarily thrombose only to bleed later in the procedure or postoperatively as the patient awakes, coughs, strains and dislodges the thrombus. An arterial bleeding point on the anterior sphenoid wall or posterolateral nasal cavity can be cauterised with suction bipolar diathermy. If suction bipolar diathermy is not available, a pterygopalatine fossa block will usually put the vessel in spasm and allow bipolar diathermy without suction. Judicious cautery in these areas at the end of the dissection is a prudent means of averting postoperative bleeds and helps to alleviate the requirement for nasal packing.

B.C. Hanna, MB, BCh, FRCSI, PhD
Department of Surgery-Otolaryngology, Head and Neck Surgery, University of Adelaide, Adelaide, Australia

P.-J. Wormald, MD, FACS, FCS(SA), FRCS(ed), MBChB (✉)
Department of Otolaryngology, Head and Neck Surgery, Queen Elizabeth Hospital, The University of Adelaide, 28 Woodville Road, Woodville South, SA 5011, Australia
e-mail: peterj.wormald@adelaide.edu.au

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_25,

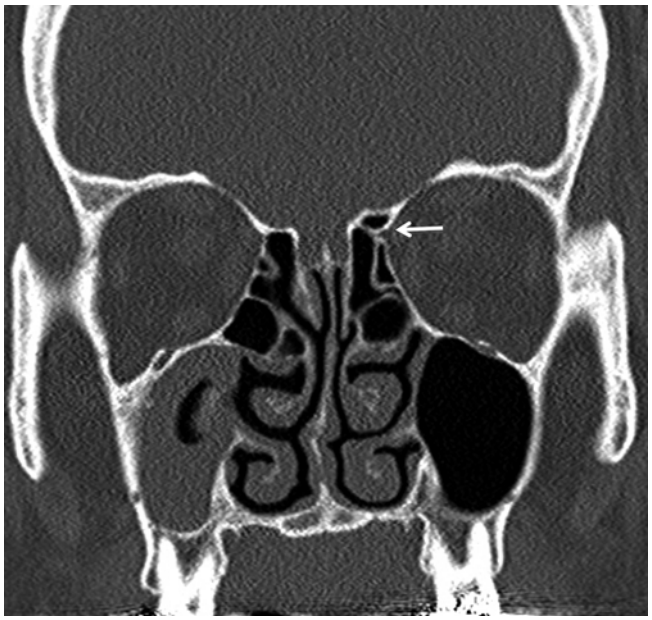


Fig. 25.1 Left anterior ethmoidal artery (*arrow*) is separated from the skull base

Anterior Ethmoid Artery Bleeding

The other major vessel encountered in sinus surgery is the anterior ethmoidal artery. The artery should be identified on the preoperative CT scan by the bony eversion of the lamina papyracea into the ethmoidal labyrinth at the point where it crosses to the orbit. This is between the medial rectus and superior oblique muscles. Careful note should be made of whether the artery is applied to the skull base or if it hangs down from the skull base in a bony mesentery seen in up to 43 % of cases [2]. In this latter position, the artery can be readily injured by an instrument or microdebrider dragged along the skull base from the posterior to the anterior. Figure 25.1 shows a left anterior ethmoidal artery which is vulnerable to such a manoeuvre. In these instances it is preferable to expose the frontal ostium allowing identification of the skull base anterior to the artery and then to move to the sphenoid sinus and identify the skull base in the sphenoid and the posterior ethmoids. The anterior ethmoidal artery is found one cell back from the frontal ostium often in or just behind the lamellae that forms the anterior face of the bulla ethmoidalis. Once the skull base is identified both anteriorly and posteriorly, the intervening bony lamellae in which the anterior ethmoidal artery sits can be gently removed in small pieces with a curette until the dissection is sufficient or the artery is visualised. A microdebrider can be used to clear excess soft tissue in this region and should be used very carefully and should not be dragged along the skull base [3].

If anterior ethmoidal bleeding is encountered, bleeding can be slowed by packing the area with neuropatties soaked in adrenaline and cocaine for several minutes. The artery may be cauterised with bipolar suction diathermy if it is on the skull base or the region of the orbital periosteum and the ethmoid cavity is sufficiently spacious to allow introduction of the bipolar forceps. Monopolar diathermy should not be used as it can arc to exposed dura and cause a CSF leak. Diathermy should not be used at all if bleeding is from the medial region of the frontal recess as the thin bone in this region is easily penetrated with a resultant CSF leak. Instead Surgicel and Gelfoam soaked in thrombin should be placed over the artery and the area firmly packed with ribbon gauze soaked in bismuth iodoform paraffin paste (BIPP) or other suitable packing material. The BIPP gauze can be removed after 48 h. If the surgical field before injury to the anterior ethmoidal artery was already very bloody, consideration should be given to packing early and stopping the procedure as continued attempts to control bleeding in this area without adequate visualisation can lead to complications.

The lateral end of a divided anterior ethmoidal artery may retract into the orbit. Orbital haematoma formation can be immediate or delayed until after arterial spasm has relaxed and any thrombosis of the vessel end is disturbed [4], often in the recovery phase. With attention focused on the field of view of the endoscope, a collecting orbital haematoma may not be immediately appreciated by the surgeon. Frequent ballottement of the globe serves not only to detect breaches in the lamina papyracea but also checks that the globe is not proptosing or becoming difficult to ballot due to rising intraorbital pressure. The intraorbital blood loss causes an expanding haematoma pushing the globe forward. As the globe is held back by the orbital septae and the palpebral ligaments attaching to the orbital rim, pressure in the orbit rises. This increased pressure

reduces retinal blood flow and stretches the optic nerve. This ischaemia may be compounded by pressure on the central retinal artery within the orbit. Animal studies suggest that 90 min of such retinal ischaemia can be tolerated [5] but blindness in humans has been reported after a period of 1 h [6]. If an orbital haematoma is detected during the procedure, the authors recommend an immediate orbital decompression. It has been suggested that gentle digital pressure should be applied to the globe first to tamponade and stop the bleeding. However, there is no evidence to support this manoeuvre. If the globe remains proptosed and firm on ballottement after tamponade, then orbital decompression should be performed.

The decompression can be performed endoscopically if the ethmoidectomy and maxillary antrostomy have been completed. The maxillary antrostomy should be large to reduce blockage of the maxillary sinus if a significant prolapse of fat occurs during the decompression. The lamina papyracea is palpated behind the frontal process of the maxilla and fractured with a Freer's elevator. The bone is flaked off leaving the periosteum intact. Ideally the entire medial orbital wall is removed leaving the upper 1.5 cm of lamina below the frontal recess to prevent blockage of the frontal sinus. The periorbita is then incised from posterior to anterior in a horizontal line (in the direction of the fibres of the medial rectus) with a scalpel or sickle knife. This allows herniation of the orbital fat into the ethmoid cavity and decompression of the orbital contents.

After decompression an ophthalmologist should be consulted if available. The intraocular pressure can be measured by tonometry. Less than 20 mmHg is normal. Up to 30 mmHg the patient can be monitored closely. Above 40 mmHg a poor vision result may ensue and further treatment is necessary. When the pressure is between 30 and 40 mmHg, blood flow to the optic nerve can be assessed by fundoscopy. With normal blood flow digital pressure on the globe raises the ocular pressure above diastolic pressure and the retinal arteries pulsate or "flash". An increase in orbital pressure may cause the arteries to flash spontaneously. Ocular pressures above systolic pressure close the arteries so that no flashing can be produced. Adjunctive medical treatment with intravenous steroids and topical beta blockers can be added. Hyperosmotic agents such as mannitol and anterior chamber paracentesis are not generally useful [7].

So far the setting of anterior ethmoidal bleeding has been limited to the operating room. An orbital haematoma may also form in the recovery period due to delayed anterior ethmoidal bleeding or alternatively slow bleeding from ruptured periorbital veins. Any nasal packs are removed to allow some decompression of a dehiscent orbit or blood to escape nasally rather than tracking intraorbitally. Bruising or mild proptosis with a soft orbit on ballottement can be observed and further checked by ophthalmology. The awake patient can also report pain and be checked for loss of colour vision (red is lost first) and visual acuity. If the globe is proptosed and hard to ballot, canthotomy and cantholysis under local anaesthetic should be performed. However, cases of slowly evolving haematoma postoperatively do not always require decompression. If the vision is normal and the circulation to the optic nerve is not compromised, the patient can be observed with frequent monitoring of vision [8].

Internal Carotid Artery Bleeding

The internal carotid artery is placed at increased risk during skull base procedures but may also be vulnerable during ESS procedures when diseased sphenoid mucosa is removed. Direct trauma may occur to a dehiscent artery or removal of a bony sphenoid septation connected to the carotid canal can damage the artery. The resultant bleeding can be enormous. The anaesthetist should be immediately alerted to obtain large calibre venous access, start resuscitation and call for replacement blood. A second surgeon is immediately called. A large bore nasal suction is placed down the opposite nostril so that the surgical field is sufficiently cleared to allow the primary surgeon to place a ribbon gauze pack in the sphenoid and tamponade the artery. Once haemostasis is achieved, a piece of sternocleidomastoid or lateral thigh muscle approximately 2 cm square and 1 cm thick when spread out is harvested via a neck or thigh incision. This muscle is crushed between two metal kidney dishes and halved giving two pieces of crushed muscle. Both surgeons work together to remove the ribbon gauze and position the muscle graft over the bleeding artery, applying gentle but consistent pressure on the muscle. Haemostasis should occur within 5 min as long as the muscle patch is in contact with the injured vessel wall. A common reason for failure is that the muscle is not on the vessel wall and therefore its haemostatic properties are not able to work. The muscle patch can then be supported with a few pieces of Surgicel (oxidised cellulose) and a pedicled septal flap harvested and swung into the sphenoid to cover the muscle patch. Ribbon gauze or other suitable packing is then placed over the flap to support the repair.

The interventional radiologist and vascular surgeon are called, and immediate angiography is performed to assess the damage to the artery. If there is ongoing bleeding, a stent is placed in the damaged region. If this is not possible and there is still bleeding, occlusion or bypass of the artery may need to be performed. If the angiogram looks normal, the pack should be left for 1 week and removed in theatre. Repacking is performed if there is further bleeding with a view to stenting, occluding or bypassing the vessel later. Otherwise, regular surveillance is performed for pseudoaneurysm formation usually at 6 weeks, then 3 months, 6 months, 1 year and 2 years.

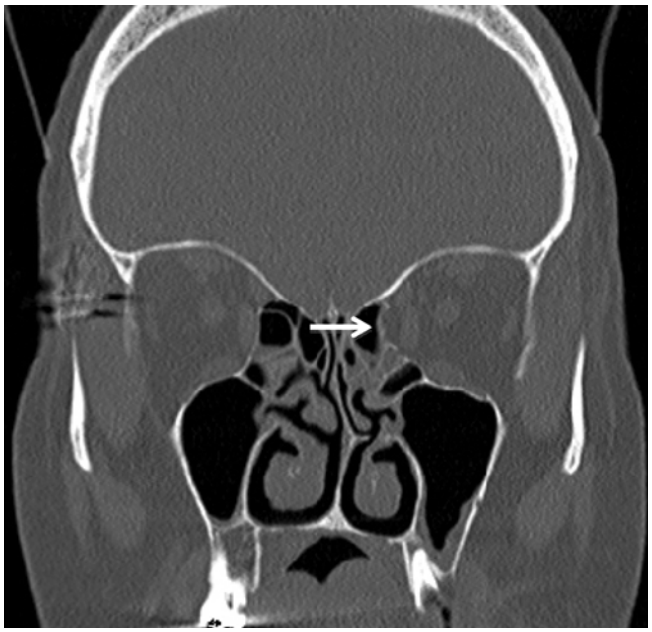


Fig. 25.2 Previous blowout fracture (*arrow*) of left orbit on preoperative scan

Generalised Bleeding from the Surgical Field

In some cases general ooze can become significant bleeding and partly obscure the surgical field. Preoperative preparation with cessation of anticoagulants (both prescribed medications and health supplements such as fish oil) is preferable. There is a suggestion that preoperative treatment of nasal polyposis patients with oral corticosteroids can reduce intraoperative bleeding [9, 10] and that topical corticosteroids can also be beneficial [11]. Intraoperatively tilting the operating table 30–40° head up can reduce bleeding compared to the fully supine position as the arterial pressure in the head is reduced and venous return from the head and neck is facilitated. The type of anaesthesia and the patient's heart rate also affect the surgical field. Vasodilatation is associated with inhalational anaesthetics whereas total intravenous anaesthesia (TIVA) with preparations such as propofol and remifentanil allows hypotension to be achieved without vasodilatation [12]. A mean blood pressure of between 65 and 75 mmHg and a pulse rate of 60 or below (achieved with beta-blockers) should allow a good surgical field [13]. The patient's temperature should be maintained at normal as it can become elevated with warming devices and this will increase bleeding. If bleeding is still troublesome, local anaesthetic infiltration of the pterygopalatine fossa can be performed via the greater palatine canal [14].

Further measures to decrease bleeding include flushes of warm ringer's lactate and gently packing the nasal cavity with neuropatties soaked in 10 % cocaine and 1:1,000 adrenaline. Tranexamic acid given intravenously or sprayed onto the nasal mucosa will also decrease bleeding [15, 16].

Orbital Injury

An intraoperative breach of the lamina papyracea is not uncommon. If it is immediately recognised and the region avoided for the rest of the surgery, then usually little damage is done. There will usually be some bruising in the lower eyelid postoperatively. Significant orbital injury occurs when a breach of the lamina and orbital periosteum is not immediately recognised. If surgery is continued especially with a microdebrider, the suction and sharp revolving blades of the microdebrider can quickly suck in and remove both fat and muscle tissue [8]. The preoperative CT scan should be studied prior to surgery to identify any orbital dehiscences and where these are present the microdebrider should not be used and the surgery conducted solely with handheld instruments. Figure 25.2 shows an example of a previous orbital blowout fracture of the left orbit. Preoperative identification should prevent dissection of the medialised orbital contents.

More posteriorly along the medial orbital wall, the medial rectus is situated very close to the periosteum. The medial rectus is a pale thin band of tissue and not an impressive muscular structure. If the microdebrider is inadvertently used on this tissue, the medial rectus may be divided in a matter of seconds. The medial rectus is the most commonly injured orbital

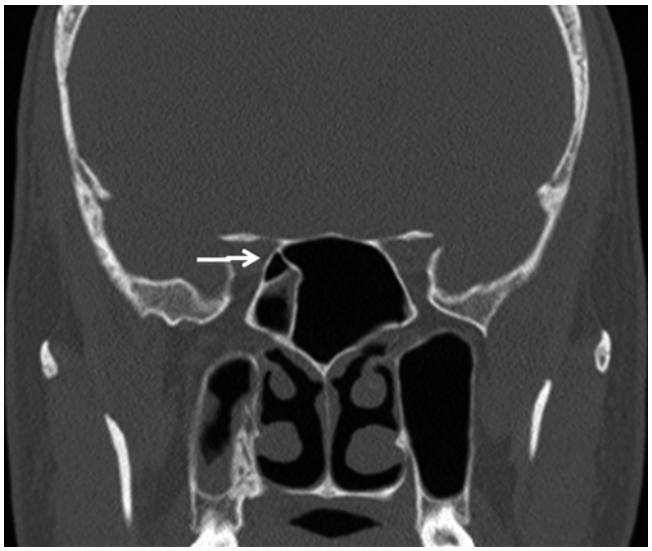


Fig. 25.3 An Onodi cell (*arrow*) above a small right sphenoid sinus

structure with a reported incidence of 1 case in 735 in a large series looking at 30 cases of injury [17]. Medial rectus injury can be devastating. Complete resection of the medial rectus leaves the eye resting in a divergent position from midline; exotropia. Binocular vision is only obtainable by looking to the side on which the injury occurred. The microdebrider has also been used to perform maxillary antrostomies which risks insertion into the orbital floor. The inferior rectus is the second most commonly injured structure. The superior rectus and oblique have been injured with approaches to the frontal sinus [18]. Uncinectomy has been demonstrated to have an impact on orbital injury. A retrograde approach using a backbiter has much less chance of opening the orbital periosteum (with the potential for damage to the intra orbital contents) than incising the mucosal junction of the uncinate with the lateral nasal wall [19].

There are four different patterns of medial rectus muscle injury. Complete or near complete transection resulting in large angle exotropia with an adduction defect is the first. The second pattern is contusion or haematoma within the muscle which produces a moderate to large angle exotropia and a combined abduction/adduction defect. Damage to the oculomotor nerve as it enters the muscle produces a similar result. The fourth injury pattern is entrapment of the medial rectus and is associated with only mild deviation in primary gaze along with a marked abduction defect [17]. Primary repair of a rectus muscle can be performed at the time of injury but it is often not recognised until after the operation. At that time of muscle repair associated injuries should be sought; evidence of orbital haematoma or optic nerve injury. Visual acuity, colour vision and range of eye movement are examined. A CT scan of the orbits will demonstrate the extent of injury, associated haematoma and the presence of bony fragments that may cause additional entrapment of the injured muscle. An MRI scan can give better detail about individual muscle bundles. Unless there is muscle entrapment or a haematoma requiring decompression, there is no other indication for immediate operation. Early referral should be made to an orbital or oculoplastics unit. Studies have shown that treatment should begin within 3–4 weeks to prevent permanent scar contracture and fibrosis [17, 20, 21].

When complete transaction has occurred, orbital exploration and primary anastomosis are recommended when the posterior 20 mm of muscle is present and functional [19]. However, the volume loss from microdebrider injuries and contracture often preclude such anastomosis. Techniques such as interposition muscle grafts and hang back sutures can span the gap but the repaired muscle tends to loosen its strength and ocular movement remains restricted even after repair [22]. The early use of botulinum toxin to the opposing lateral rectus muscle is a useful adjunct to the surgical management. The paralysed lateral rectus is less prone to contracture, facilitates single vision in primary gaze more rapidly and minimises the force generated against the repaired muscle site. Unfortunately though, the prognosis after medial rectus injury is poor with establishment of a binocular single visual field in the direction of primary gaze considered a success in most patients [22].

The other major orbital structure at risk is the optic nerve. The CT scan should also be studied preoperatively for the presence of an Onodi cell. This is a posterior ethmoidal cell that pneumatises over the anterior face of the sphenoid pushing the sphenoid inferiorly. Figure 25.3 shows an Onodi cell above the right sphenoid sinus and adjacent to a dominant left sphenoid sinus. The optic nerve lies in the lateral wall of the Onodi cell and if the surgeon is unaware of which cell they are in may mistake the posterior wall of the Onodi cells for the anterior face of the sphenoid and injure the nerve when trying to enter the sphenoid. The optic nerve has also been injured by continued dissection usually with a microdebrider through the orbit from the ethmoid cavity. Should the optic nerve be transected, the damage is irreparable.

There is little data relating to lesser injuries of the optic nerve. If the nerve has been directly injured, optic nerve decompression is recommended with removal of any bone fragments indenting the canal, intravenous steroids can be administered as indicated for traumatic optic neuropathy and ophthalmology consulted [23]. Optic nerve transaction and on occasions injury will result in blindness in that eye.

CSF Leak

Iatrogenic CSF leak can occur as a consequence of ESS along any part of the skull base but is most commonly seen on the thin lateral wall of the olfactory fossa. Often this will occur if an instrument is turned medially when dissecting along the anterior skull base. A CSF leak will usually be evident at the time of surgery. The authors favour two repair techniques, the fat graft "bath plug" technique and fascial underlay/free mucosa or pedicled mucosa graft. For small defects of up to 10 mm, the bath plug is recommended [24]. Loose bone is removed around the defect and mucosa is removed for 5 mm around the site. Fat is usually harvested from the ear lobule as this contains tightly knitted fat. If this is unavailable, as with multiple piercings, trochanteric fat which is also tightly knit can be used with the more loosely knit abdominal fat as a final preference. The fat graft is prepared to be the same width as the defect (to allow it to be inserted) and about 20 mm long. A Vicryl suture is knotted at one end and inserted into the centre of one end of the graft and passed longitudinally to exit in the centre of the other end. The graft with the inserted suture is gently fed into the defect using a curved sinus seeker probe. If a ball probe is used, the ball tends to stick to the fat and pulls it back out of the defect as the instrument is removed. The instrument should only be inserted a small distance intracranially to prevent damage to intracranial structures. It is also easier to insert small portions of the fat graft at a time. Inserting large portions at once can cause the fat to become larger than the defect and be difficult to insert. When fully inserted, the probe in used to support the graft as the Vicryl suture is gently pulled. The fat slides along the suture and spreads out becoming larger than the defect and solidly sealing the defect. Some prolapse of fat through the defect is expected. The anaesthetist is asked to perform a forced inspiration manoeuvre. No CSF should be seen. Further fat prolapse may be seen as the fat plug is forced further into the defect. A free mucosal graft is slid up the suture and placed against the fat graft and demucosalised surrounding bone. Care is taken to correctly orientate this graft with the mucosal surface facing the nasal cavity. Fibrin glue is applied and then covered with Gelfoam. No other packing is applied.

If the skull base defect is larger than 10 mm, an underlay fascia lata graft is preferred. The graft should overlap the defect by 5 mm so it should be harvested 10–20 mm larger than the diameter of the defect. Especially when repairing meningoencephaloceles, the prolapse brain tissue may need to be held up by a second surgeon while the graft is positioned. Pressure from the brain should then seal the graft in place, and no further CSF leakage should be seen. A free mucosal flap or pedicled septal flap is placed over the repair followed by fibrin glue and Gelfoam. The authors do not position bone or cartilage in the defect. The thickness of these materials pushes the fascia graft away from the edge of the defect and can then prevent the fascia from sealing the leak. Defects larger than 20 mm in diameter are not expected as complications of ESS surgery, and closure with an underlay fascia lata graft and pedicled septal flap is recommended.

Minor Complications

Frontal Sinus Trephines

Frontal sinus trephines can be 5 mm openings in the frontal bone to allow instruments to access the lateral frontal sinus without resorting to an open approach through either a Lynch Howarth incision or osteoplastic flap. Alternatively, they can be small mini trephines to allow the instillation of fluorescein to aid location of the frontal ostium or to allow irrigation of the frontal sinus in the postoperative period. The anterior table of the frontal sinus is thick bone and care needs to be taken to prevent sufficient heating of the bone and overlying skin to cause necrosis. This can result in osteitis with a persistent discharge from the trephination site which may eventually heal with an unsightly scar. The trephining drill should be removed every 2 s and irrigated when performing the trephine. Care should be taken with under pneumatised frontal sinuses so that the trephine is not inserted intracranially. Before instilling fluid into the frontal sinus, the CT scan should be checked for any dehiscence of the walls of the frontal sinus. Figure 25.4 demonstrates a small dehiscence of the right lateral frontal sinus above the orbit. Forced instillation of fluorescein caused mucosal contents of the frontal sinus to prolapse into the preseptal compartment of the upper lid, the resultant mechanical obstruction to eyelid retraction producing a ptosis (Fig. 25.5). Even

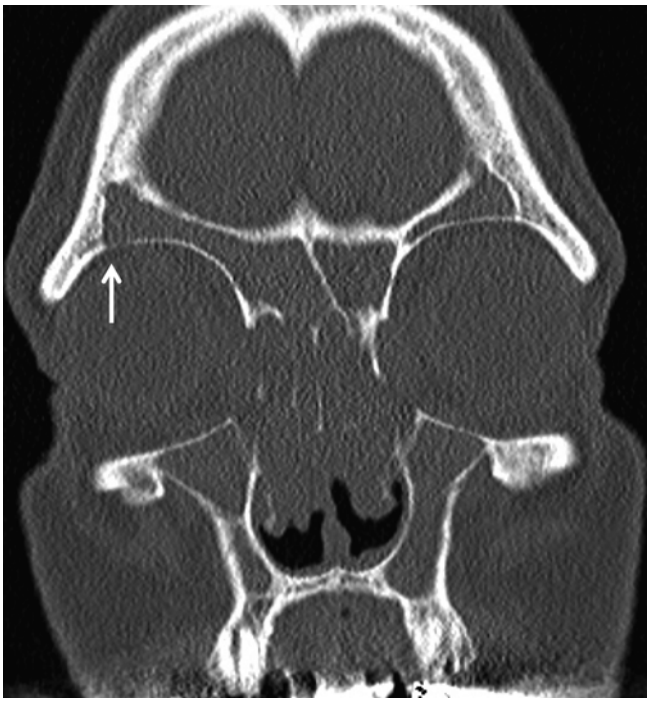


Fig. 25.4 Dehiscence (*arrow*) of floor in the lateral right frontal sinus

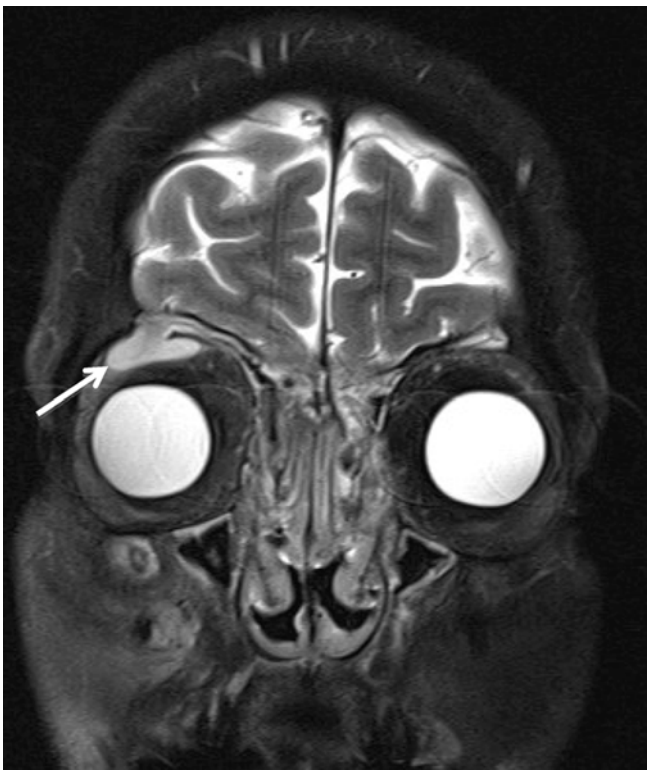


Fig. 25.5 Extravasation of frontal sinus contents (*arrow*) into preseptal compartment of right upper eyelid

if no dehiscence is found, fluid should always be instilled into a frontal trephine with only gentle pressure. This is especially the case with frontal mucoceles which can erode the posterior table or orbital roof [25].

Canine Fossa Trephination of the Maxillary Sinus

Trephination of the canine fossa of the maxillary sinus allows instruments (the microdebrider in particular) to access a much greater volume of the maxillary sinus for disease clearance than a maxillary antrostomy does. The microdebrider should not be activated until the blades can be visualised through the medial maxillary antrostomy if using this approach in case of misplacement of the blade into the orbit. A point of entry in the anterior wall of the maxillary sinus that lies at the intersection of the vertical midpupillary line and the horizontal alar base line has the least chance of injuring branches of the anterior superior alveolar nerve [26]. However, because of the varied anatomy of this nerve, 5 % of patients will still experience dysaesthesia and/or paraesthesia of the upper lip, gums or teeth after this procedure [27]. Although this represents a great improvement compared to the dysaesthesia after the Caldwell Luc approach, these symptoms are difficult to treat and patients should be adequately counselled preoperatively.

Adhesions and Middle Turbinate Lateralisation

Adhesions develop from fibrous replacement of organising blood clots on the surface of traumatised mucosa. They are the most common complication of ESS ranging in incidence from 1 to 36 % [28]. Sometimes adhesions can block the sinus drainage pathway and require revision surgery. Mucosal trauma can be decreased by careful surgical technique. Packing the nasal cavity displaces blood clots, but packs are associated with uncomfortable removal and bleeding with clot formation. There has been considerable investment in recent years in developing dissolvable haemostatic agents and nasal packs that can be positioned not to completely occlude the nasal cavity and which will not require uncomfortable removal. If placed in the middle meatus, they stent the middle turbinate to prevent lateralisation and will allow nasal breathing.

These materials have recently been reviewed and a brief synopsis is presented here [28]. Gelfoam and Gelfilm (Pfizer inc, New York, NY) were the first absorbable packs to be tried. They stented the middle turbinate but caused granulation tissue formation and increased adhesions. Floseal (Baxter Inc., Deerfield, IL) is composed of bovine-derived gelatine matrix and human-derived thrombin. It is an effective intraoperative haemostat and, when used, also decreases postoperative bleeding. It may be associated with increased adhesions. Sepragel (Genzyme Co., Cambridge, MA), a hylan B gel (cross-linked hyaluronic acid molecule), did not affect haemostasis but was associated with decreased adhesions. A separate study has compared carboxymethylcellulose gel to no packing material and found no difference in the rate of adhesions [29]. There is some evidence that postoperative debridement reduces adhesion formation [30]. Detractors have claimed that debridement may cause further bleeding and adhesions.

In addition to stenting the middle meatus with packing material, suturing the middle turbinates to the septum with a soluble suture such as 4/0 viryl rapide can help prevent middle turbinate lateralisation [31]. A middle turbinate which has become flail at the end of an ESS procedure should be excised to prevent lateralisation.

Recurrent Disease

The most common causes of failure of sinus surgery are missed natural os of the maxillary sinus with recirculation, ostial stenosis, polyp formation, complicating contributive diagnosis, such as immune deficiency, and chronic recalcitrant infection. Should the sinus cavities appear healthy on endoscopy, comorbid disease is suspected. This includes gastro-oesophageal reflux which has a reflex action that may produce postnasal drip or mucous [32]. Ongoing topical and systemic therapy may be required and if this fails revision surgery such as the modified Lothrop procedure should be considered.

Lacrimal Injury

Damage to the nasolacrimal duct can occur when backbiting to perform an uncinectomy or enlarging an accessory maxillary antrostomy into the natural os [33]. The initial treatment is expectant with formal evaluation of the lacrimal drainage system

should epiphora occur with a view to endoscopic dacryocystorhinostomy. If trauma occurs during a modified Lothrop procedure or excision of an inverting papilloma, DCR can usually be performed at the same time as the surgery [34].

Olfaction

ESS is most often associated with improved olfaction. It has been proposed that this is because the existing inflammation creates oedema which blocks the airflow to the olfactory receptors and that restoration of normal mucosa by disease control, even if it involves loss of some receptors, improves olfaction [35]. Patients should therefore be counselled that olfaction will usually improve after surgery, but this cannot be predicted for an individual patient and can sometimes remain the same (as in nasal polyposis with NSAID intolerance) or worsen [36].

Paediatric Complications

Children's sinus anatomy differs to that of adults. The sinuses are less developed and the orbits are relatively larger [37]. As stated in the introduction, orbital complications in children are more common than skull base problems. Studies specifically addressing younger children have noted that successful surgery is more difficult in those under 6 and those under 3 required revision surgery in 75 % of cases. Maxillary ostial stenosis was a particular problem [38, 39].

Dealing with a Complication

Surgical complications can be devastating for both the patient and the surgeon. The patient suffers from loss of function, which in turn may affect their employment and livelihood and sometimes be a social handicap. If the complication was unexpected and severe, the surgeon will also suffer remorse, sorrow, loss of confidence and possibly even anxiety. After a complication is recognised, the patient should be informed early and fully of what has happened. It is important that the patient does not develop mistrust of the surgeon because of the way in which the complication is handled postoperatively. The patient should be reviewed regularly to offer any support and medical treatment that is necessary. The surgeon should also confide in colleagues and review the operative planning and procedure. This allows contributory factors to be identified so that the complication will hopefully not recur. The occurrence of such a review should be documented. Neither the patient nor the surgeon should have cause to feel isolated after a complication.

Conclusions

Major complications after endoscopic sinus surgery are uncommon events. Prevention of these events by detailed preoperative assessment of the CT scans and careful surgical dissection will obviously limit the frequency of such occurrences. Risk can never be eliminated though, and it is therefore essential for the surgeon to have an appreciation of possible adverse outcomes and knowledge of how to manage them. It is essential that all ENT surgeons are able to deal with complications such as haemorrhage, orbital injury and CSF leak. Minor complications must be equally well managed for the patient to have the best possible outcome. All complications will have an impact on both the patient and the surgeon, and both parties should have access to adequate support systems.

References

1. Ramakrishan VR, Kingdom TT, Nayak JV, Hwang PH, Orlandi RR. Nationwide incidence of major complications in endoscopic sinus surgery. Int Forum Allergy Rhinol. 2012;2:34–9.
2. Basak S, Karaman C, Akdilli A, Mutlu C, Odabasi O, Erpek G. Evaluation of some anatomical variations and dangerous areas of the paranasal sinuses by CT for safer endonasal surgery. Rhinology. 1998;36:162–7.

3. Tewfik MA, Wormald PJ. Ten pearls for safe endoscopic sinus surgery. Otolarngol Clin North Am. 2010;43:933–44.
4. Stankiewicz JA, Chow JM. Two faces of orbital haematoma in intranasal (endoscopic) sinus surgery. Otolaryngol Head Neck Surg. 1999;120:841–7.
5. Hayreh SS, Kolder HE, Weingeist TA. Central retinal artery occlusion and retinal tolerance time. Ophthalmology. 1980;87:75–8.
6. Ramakrishnan VR, Palmer JN. Prevention and management of orbital haematoma. Otolaryngol Clin North Am. 2010;43:789–800.
7. Kersten RC, Kulwin DR. Anterior chamber paracentesis. Plast Reconstr Surg. 1989;84:701–3.
8. Graham SM, Nerad JA. Orbital complications in endoscopic sinus surgery using powered instrumentation. Laryngoscope. 2003;113:874–8.
9. Wright ED, Agrawal S. Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with the novel Perioperative Sinus Endoscopy (POSE) scoring system. Laryngoscope. 2007;117:1–28.
10. Sieskiewicz A, Olszewska E, Rogowski M, Grycz E. Preoperative corticosteroid oral therapy and intraoperative bleeding during functional endoscopic sinus surgery in patients with severe nasal polyposis: a preliminary investigation. Ann Otol Rhinol Laryngol. 2006;115:490–4.
11. Albu S, Gocea A, Mitre I. Preoperative treatment with topical corticoids and bleeding during primary endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2010;143:573–8.
12. Wormald PJ, van Renen G, Perks J, Jones JA, Langton-Hewer CD. The effect of total intravenous anaesthesia compared with inhalational anaesthesia on the surgical field during endoscopic sinus surgery. Am J Rhinol. 2005;19:514–20.
13. Nair S, Collins M, Hung P, Rees G, Close D, Wormald PJ. The effect of beta-blocker premedication on the surgical field during endoscopic sinus surgery. Laryngoscope. 2004;114:1042–6.
14. Wormald PJ, Athanasiadis T, Rees G, Robinson S. An evaluation of the effect of pterygopalatine fossa injection with local anaesthetic and adrenaline in the control of nasal bleeding during endoscopic sinus surgery. Am J Rhinol. 2005;19:288–92.
15. Alimian M, Mohseni M. The effect of intravenous tranexamic acid on blood loss and surgical field quality during endoscopic sinus surgery: a placebo-controlled clinical trial. J Clin Anesth. 2011;23:611–5.
16. Athanasiadis T, Beule AG, Wormald PJ. Effects of topical antifibrinolytics in endoscopic sinus surgery: a pilot randomized controlled trial. Am J Rhinol. 2007;21(6):737–42.
17. Huang CM, Meyer DR, Patrinely JR, et al. Medial rectus muscle injuries associated with functional endoscopic surgery: characterisation and management. Otolaryngol Head Neck Surg. 2001;125:501–9.
18. Thacker NM, Velez FG, Demer JL, Wang MB, Rosenbaum AL. Extraocular muscle damage associated with endoscopic sinus surgery: an ophthalmology perspective. Am J Rhinol. 2005;19:400–5.
19. Wormald PJ, McDonogh M. The “swing-door” technique for uncinectomy in endoscopic sinus surgery. J Laryngol Otol. 1998;112:547–51.
20. Hong JE, Goldberg AN, Cockerham KP. Botulinum toxin A therapy for medial rectus injury during endoscopic sinus surgery. Am J Rhinol. 2008;2:95–7.
21. Penne RB, Flanagan JC, Stefanyszyn MA, et al. Ocular motility disorders secondary to sinus surgery. Ophthal Plast Reconstr Surg. 1993;9:53–61.
22. Hong JE, Lee HK, Lee JB, Han SH. Recession-resection combined with intraoperative botulinum toxin A chemodenervation for exotropia following subtotal ruptured of medial rectus muscle. Graefes Arch Clin Exp Ophthalmol. 2007;245:167–9.
23. Moeller CW, Welch KC. Prevention and management of complications in sphenoidotomy. Otolaryngol Clin North Am. 2010;43:839–54.
24. Wormald PJ, McDonagh M. The bath-plug closure of anterior skull base cerebrospinal fluid leaks. Am J Rhinol. 2003;17:299–305.
25. Seiberling K, Jardeleza C, Wormald PJ. Minitrephination of the frontal sinus: indications and uses in today’s era of sinus surgery. Am J Rhinol Allergy. 2009;23:229–31.
26. Robinson S, Wormald PJ. Patterns of innervation of the anterior maxilla: a cadaver study with relevance to canine fossa puncture. Laryngoscope. 2005;115:1785–8.
27. Singhal D, Douglas R, Robinson S, Wormald PJ. The incidence of complications using a modified technique of canine fossa puncture. Am J Rhinol. 2007;21:316–31.
28. Weitzel EK, Wormald PJ. A systematic review of middle meatal packing/stents. Am J Rhinol. 2008;22:302–7.
29. Kastl KG, Betz CS, Siedek V, Leunig A. Effect of carboxymethylcellulose nasal packing on wound healing after functional endoscopic sinus surgery. Ear Nose Throat J. 2008;87:E11.
30. Bugten V, Nordgård S, Steinsvåg S. The effects of debridement after endoscopic sinus surgery. Laryngoscope. 2006;116:2037–43.
31. Hewitt KM, Orlandi RR. Suture medialization of the middle turbinates during endoscopic sinus surgery. Clin Otolaryngol. 2008;33:462–5.
32. Hanna BC, Wormald PJ. Gastroesophageal reflux and chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2012;20:15–8.
33. Salam MA, Cable HR. Middle meatal antrostomy: long term patency and results in chronic maxillary sinusitis. A prospective study. Clin Otolaryngol. 1993;18:135–8.
34. Wormald PJ. Salvage frontal sinus surgery: the modified Lothrop procedure. Laryngoscope. 2003;113:276–83.
35. Hosemann W, Goertzen W, Wohlleben R, et al. Olfaction after endoscopic endonasal surgery. Am J Rhinol. 1993;7:11–5.
36. Damm M, Eckle HE, Jungehulsing M, et al. Olfactory changes at threshold and suprathreshold levels following septoplasty with partial inferior turbinectomy. Ann Otol Rhinol Laryngol. 2003;112:91–7.
37. Lazar RH, Younis RT, Long TE. Functional endonasal sinus surgery in adults and children. Laryngoscope. 1993;103(1Pt1):1–5.
38. Chan KH, Winslow CP, Abzug MJ. Persistent rhinosinusitis in children after endoscopic sinus surgery. Otolaryngol Head Neck Surg. 1999;121(5):577–80.
39. Ramadan HH. Relation of age to outcome after endoscopic sinus surgery in children. Arch Otolaryngol Head Neck Surg. 2003;129:175–7.

Chapter 26
Chronic Frontal Sinusitis

Murugappan Ramanathan Jr. and Andrew P. Lane

Introduction

Management of chronic frontal sinusitis is one of the greatest challenges in rhinology. The complicated and restricted anatomy of the frontal sinus makes accessing this area quite difficult especially in the setting of mucosal inflammation. This chapter will provide an overview of the anatomy of the frontal sinus followed by the diagnosis and management of various conditions that can cause frontal sinus inflammation such as mucoceles and benign tumors. A special emphasis will be placed on common external and endoscopic surgical approaches as well as postoperative management of patients. Lastly, this chapter will outline common complications of untreated chronic frontal sinusitis as well as complications of surgery itself.

Anatomy of the Frontal Sinus

The anatomy of the frontal sinus and its drainage pathways is complex and highly variable. Embryologically, the frontal sinus develops and expands from late childhood to early adolescence until the child reaches 18 years of age. Occasionally, frontal sinuses may develop asymmetrically or may be aplastic. Bilateral frontal sinus aplasia has been reported in 3–5 % patients. It is also not uncommon to have one dominant frontal sinus and a contralateral aplastic sinus.

The anatomic boundaries of the frontal recess are the following: (1) posterior wall of the agger nasi region anteriorly, (2) anterior wall of the ethmoid bulla posteriorly, (3) lamina papyracea laterally, (4) anterior vertical portion of the middle turbinate medially, and (5) ethmoid roof superiorly (Fig. 26.1) [1]. It is also important to appreciate that the frontal sinus outflow tract is not a simple circular duct but moreover resembles an hourglass with the inferior aspect configured like an inverted funnel on a sagittal view (Fig. 26.2). Several "frontal" cells can exist within the frontal recess that may complicate the drainage pathways (Table 26.1). For example, the frontal recess can be narrowed anteriorly by a well-pneumatized agger nasi cell. Broadly speaking, the uncinate process dictates the floor and pattern of frontal drainage. If the uncinate process attaches to the skull base or the anterosuperior part of the middle turbinate, the frontal recess drains into ethmoidal infundibulum. In the majority of cases, the uncinate process attaches laterally on the orbit, and the frontal recess opens directly into the middle meatus. Suprabullar and supraorbital ethmoid cells opening variably into the frontal recess are usually located posterior and lateral to the frontal sinus ostium. Highly pneumatized frontal recess cells can extend into or through the internal frontal ostium, may greatly impinge upon frontal sinus drainage, and can be mistaken for the frontal sinus itself during endoscopic surgery.

Successful treatment of chronic frontal sinusitis requires restoration of normal mucociliary clearance patterns. Within the frontal sinus, mucus flows up the interfrontal sinus septum, laterally across the frontal sinus roof, medially along the frontal sinus floor, and finally down the lateral frontal recess (Fig. 26.3). It is critical to preserve mucosa within the frontal sinus outflow tract during surgery, because regenerated lining or scar tissue is unlikely to be as functional as the native membrane.

M. Ramanathan Jr., MD • A.P. Lane, MD (✉)
Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins Medical Institutions, 601 N. Caroline St. JHOC 6th Floor, Baltimore, MD 21287, USA
e-mail: mramana3@jhmi.edu; alane3@jhmi.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_26,

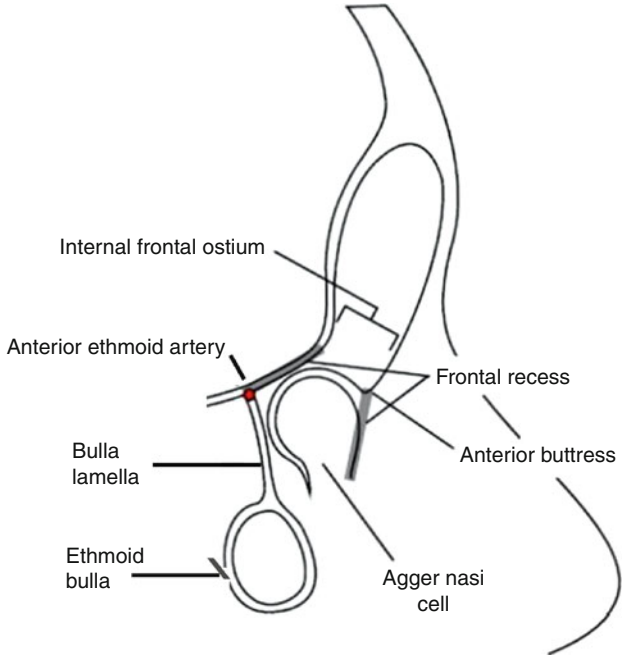


Fig. 26.1 Anatomy of the frontal recess in relation to the internal frontal ostium and surrounding ethmoidal anatomy (Adapted from Kountakis et al. [1]. With permission from Springer, 2013)

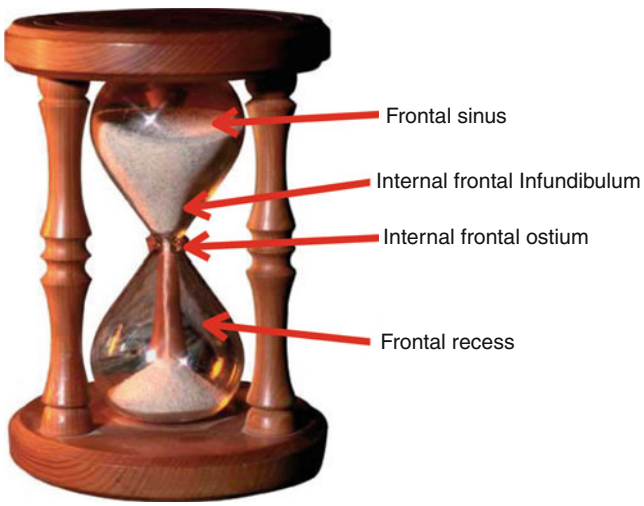


Fig. 26.2 The frontal sinus and frontal recess are similar to an hourglass. The frontal sinus itself is the top part of the hourglass and the inferior narrowing is the internal frontal infundibulum. The narrowest part of the hourglass is the internal frontal ostium. The frontal recess is the bottom part (also referred to as an "inverted" funnel)

Table 26.1 Cells of the frontal recess

Agger nasi cell
Supraorbital ethmoid cell
Frontal bullar cell
Suprabullar cell
Interfrontal sinus septal cell
Recessus terminalis
Type I: single cell above agger nasi cell
Type II: tier of cells
Type III: single massive cell that invades the frontal sinus and attaches to the anterior table
Type IV: cell within a cell; no communication with frontal recess

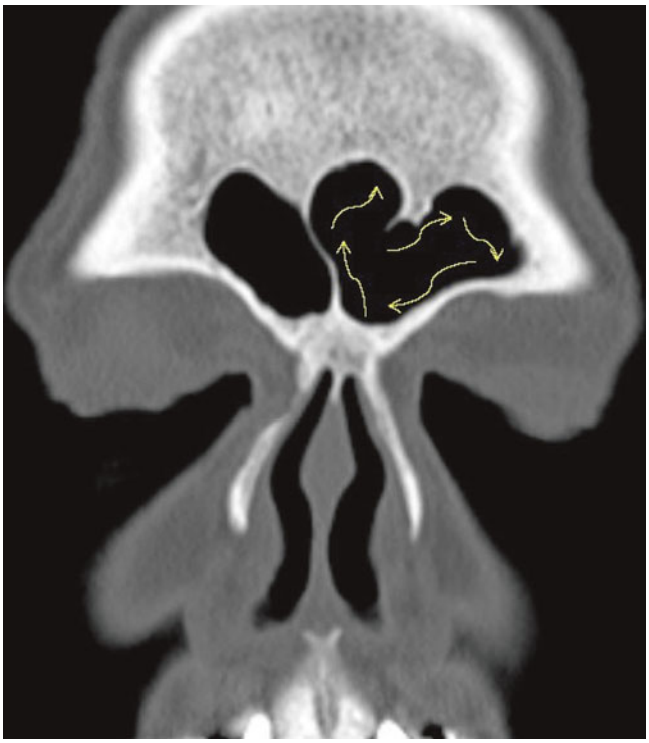


Fig. 26.3 The *yellow arrows* depict frontal sinus mucociliary clearance. Mucus travels up the interfrontal sinus septum laterally and down the floor and through the lateral mucosa of the frontal recess (contiguous with the medial mucosa of the superior aspect of the middle turbinate)

Presentation and Diagnosis of Chronic Frontal Sinusitis

Most often, patients with chronic frontal sinusitis also have disease present in the other paranasal sinuses and lack localizing signs in the frontal region. A recent study found that among 70 patients with nasal polyps of the frontal recess or frontal sinus, only 29 % of patients complained of headaches or frontal pressure [2]. By definition, frontal sinusitis becomes chronic when the duration of symptoms is greater than 3 months. The majority of uncomplicated chronic frontal sinusitis has the potential to be reversed with treatment. However, when chronic frontal sinusitis becomes recalcitrant to repeated courses of medical therapy and multiple surgeries, it is a particularly challenging entity to control. The various management strategies for specific presentations of chronic frontal sinusitis, such as allergic fungal rhinosinusitis, mucoceles, or benign tumors (e.g., inverted papillomas or osteomas), are described in further detail later in the chapter.

A critical element of diagnosis is nasal endoscopy performed with adequate decongestion. The middle turbinate and middle meatus should be carefully examined for edema and secretions, which should be cultured if they appear abnormal. A more thorough endoscopic exam can be performed in patients with previous sinus surgery using angled (30°, 45°, or 70°) endoscopes. Non-contrasted multiplanar CT imaging is the gold standard for diagnosis. Sagittal reconstructions of fine-cut axial images will best demonstrate the anatomy of the frontal sinus outflow tract including the anterior-posterior dimensions in addition to any obstructing frontal recess cells (Fig. 26.4).

Microbiology of Infections

The microorganisms involved in chronic frontal sinusitis are distinct from acute frontal sinusitis. A study by Brook et al. compared cultures from 15 patients with acute frontal sinusitis with 13 patients with chronic frontal sinusitis and found a predominance of Gram-negative bacilli (*H. influenzae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*) and anaerobes (*Prevotella, Peptostreptococcus,* and *Fusobacterium*) in chronic frontal sinusitis patients. Patients with acute frontal sinusitis commonly grew out *H. influenzae, M. catarrhalis,* and *S. pneumoniae*, which are all frequently found in acute maxillary, ethmoid, and sphenoid sinusitis as well [3]. Another study by Schlosser et al. obtained cultures from chronic frontal sinusitis patients via trephination and found that 38 % of patients had no growth of microorganisms, 21 % grew *Staphylococcus aureus*, 21 % grew coagulase-negative *Staphylococcus*, and 9 % grew out *H. influenzae* [4]. These studies emphasize that antibiotic selection in patients with chronic frontal sinusitis should reflect coverage for these organisms.

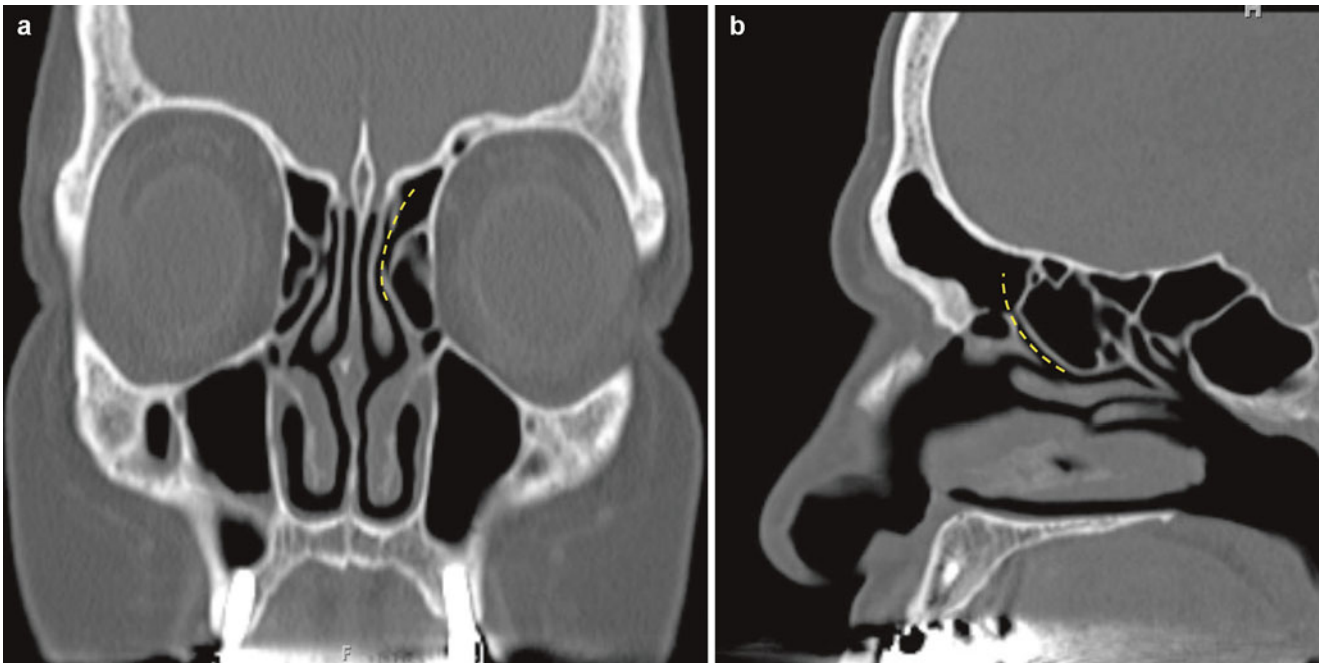


Fig. 26.4 Coronal (**a**) and sagittal (**b**) depictions of the frontal recess (*yellow dots*) in relation to ethmoidal anatomy on high-resolution CT scan

Medical Management of Chronic Frontal Sinusitis

Maximal medical therapy is the first line of treatment for chronic frontal sinusitis prior to surgery similar to chronic maxillary, ethmoid, or sphenoid sinusitis. This includes extended courses of antibiotics, which should be culture-directed whenever possible. Newer evidence also demonstrates that extended courses of macrolide antibiotics may exert an anti-inflammatory effect [5, 6]. Other medications include oral and topical corticosteroids, nasal saline irrigations, mucolytics, and antihistamines if allergic. In addition, allergen immunotherapy is also recommended for atopic patients recalcitrant to antihistamines and leukotriene inhibitors. The side effects and interactions of these medications should be carefully evaluated with regard to patient comorbidities and relative contraindications. There remains a great debate as to what constitutes "maximal" medical therapy. Dubin et al. surveyed 308 members of the American Rhinologic Society and found that >90 % of practitioners used 3–4 weeks of oral antibiotics with nasal steroids [7]. In patients with previous endoscopic sinus surgery and/or frontal sinusotomy, additional topical steroid drops or rinses have shown to have some efficacy in reducing inflammation in the frontal recess [8].

Indications for Frontal Sinus Surgery

The indication for frontal sinus surgery depends on the clinical scenario and patient desires/expectations. Unnecessary instrumentation of the frontal recess itself is often the cause of chronic frontal recess stenosis and debilitating patient symptoms. Therefore, practitioners must be cautious in recommending surgery. Opacification of the frontal sinus itself is not an indication for surgery as this likely represents retained secretions and secondary mucosal edema that may clear with medical therapy. In general, for chronic inflammatory disease, patients must have failed a sufficiently sustained and intensive course of medical therapy and have continued frontal sinus opacification on CT scans with symptoms related to the frontal sinus region. In many patients, depending on the specific frontal sinus anatomy and extent of disease, a partial ethmoidectomy is sufficient for drainage of the frontal sinus. In cases with recalcitrant chronic polypoid inflammation or with AFRS, it is often necessary to open the frontal recess and remove polyps (and possibly fungus) to achieve the best ventilation. Other indications for frontal sinus surgery, either by endoscopic instrumentation of the frontal recess or rarely by open approaches, include mucoceles, tumors, obstructive osteomas, or barotrauma.

Preoperative Considerations

Preoperative planning is essential prior to endoscopic instrumentation of the frontal recess. The often narrow anatomy of the frontal recess in the setting of inflammation can cause bleeding and poor endoscopic visualization of vital structures. It is essential that patients stop antiplatelet drugs, anticoagulants, or other medications that promote bleeding such as nonsteroidal anti-inflammatory medications and supplements for 10–14 days prior to surgery. The authors also advocate the use of oral corticosteroids if tolerated by the patient preoperatively, as they have been shown to decrease intraoperative bleeding [9, 10]. Stereotactic computer-assisted image-guided navigation is frequently helpful in primary or revision endoscopic frontal sinus surgery. Regardless of the use of image guidance, patients should ideally undergo a fine-cut axial CT scan reformatted into coronal and sagittal views allowing for three-dimensional analysis of the frontal recess and its associated cells prior to surgery. This imaging should be directly available to the surgeon in the operating room.

Endoscopic Approaches to the Frontal Sinus

Endoscopic Frontal Sinusotomy

Wolfgang Draf described a series of endoscopic endonasal approaches to draining the frontal sinus (Table 26.1): Type I, Type IIa/b, and Type III. The Type I procedure is a simple drainage procedure performed by an ethmoidectomy without instrumenting the frontal recess. Type IIa/b represents extended drainage procedures achieved after an ethmoidectomy is performed. Type IIa (also known as an endoscopic frontal sinusotomy) involves resecting the frontal sinus floor between the orbit and middle turbinate while Type IIb (extended frontal sinusotomy) extends this resection through the middle turbinate to the nasal septum unilaterally. Lastly the Draf III procedure (also referred to as an endoscopic modified Lothrop) involves extending the Type IIb procedure to the contralateral orbit and resecting the intersinus septum whereby achieving median drainage.

Since the workhorse of surgery for chronic frontal sinusitis is the endoscopic frontal sinusotomy (Draf IIa), emphasis will be placed on the technical details and postoperative management of this procedure. Functional endoscopic sinus surgery of the frontal sinus employs all the basic tenets of surgery in the other sinuses. Surgery is directed at preserving the mucociliary clearance of the frontal sinus, primarily through preservation of the mucosa of the lateral frontal recess.

Proper instrumentation is critical for endoscopic frontal sinus surgery: high-resolution camera/video, 45° and 70° angled nasal endoscopes, and a complete set of frontal sinus instruments including thru-cutting forceps (55° and 90°), seekers, curettes, and curved suctions. Powered instrumentation must be used with extreme caution within the frontal recess, but narrow-angled microdebrider blades can permit precise removal of soft tissue while avoiding mucosal stripping and injury. Lastly, stereotactic computer-assisted image guidance is crucial in chronic frontal surgery when anatomic landmarks are obscured by previous surgery or by profound inflammation and polyps. Optimal registration of the image guidance system is essential to its use in frontal sinus surgery, and surgical judgment is needed to determine an appropriate level of confidence in the navigational information.

General Operative Technique

To perform an endoscopic frontal sinusotomy, a standard uncinectomy and anterior ethmoidectomy is first performed with middle turbinate preservation. The superior attachment of the uncinate process is removed under visualization with an angled endoscope (45° or 70°) and using thru-cutting frontal sinus punch forceps. At this time, the variable bony partitions within the frontal recess are identified and the anatomic relationships corresponded to the preoperative imaging. In most cases, the uncinate will attach laterally on the upper orbital wall, creating a "recessus terminalis" that may be continuous with a pneumatized agger nasi cell system anteriorly. Removal of the remaining uncinate process insertion and "uncapping" of the agger nasi cell will frequently expose the internal frontal ostium. That being said, the variation in frontal recess cell configuration is infinite, so a unique operative strategy must be determined for each frontal sinusotomy. The common technical points include definitive identification of the orbital wall and skull base, avoidance of mucosal stripping, and meticulous removal of bony fragments. At no time should instruments or suctions be forced through the frontal recess as this can lead to mucosal trauma and disruption of normal anatomy, not to mention risk of inadvertent orbital or skull base entry. Once an opening is achieved into the frontal sinus, remaining bony partitions may be further dissected and removed to maximize the dimensions

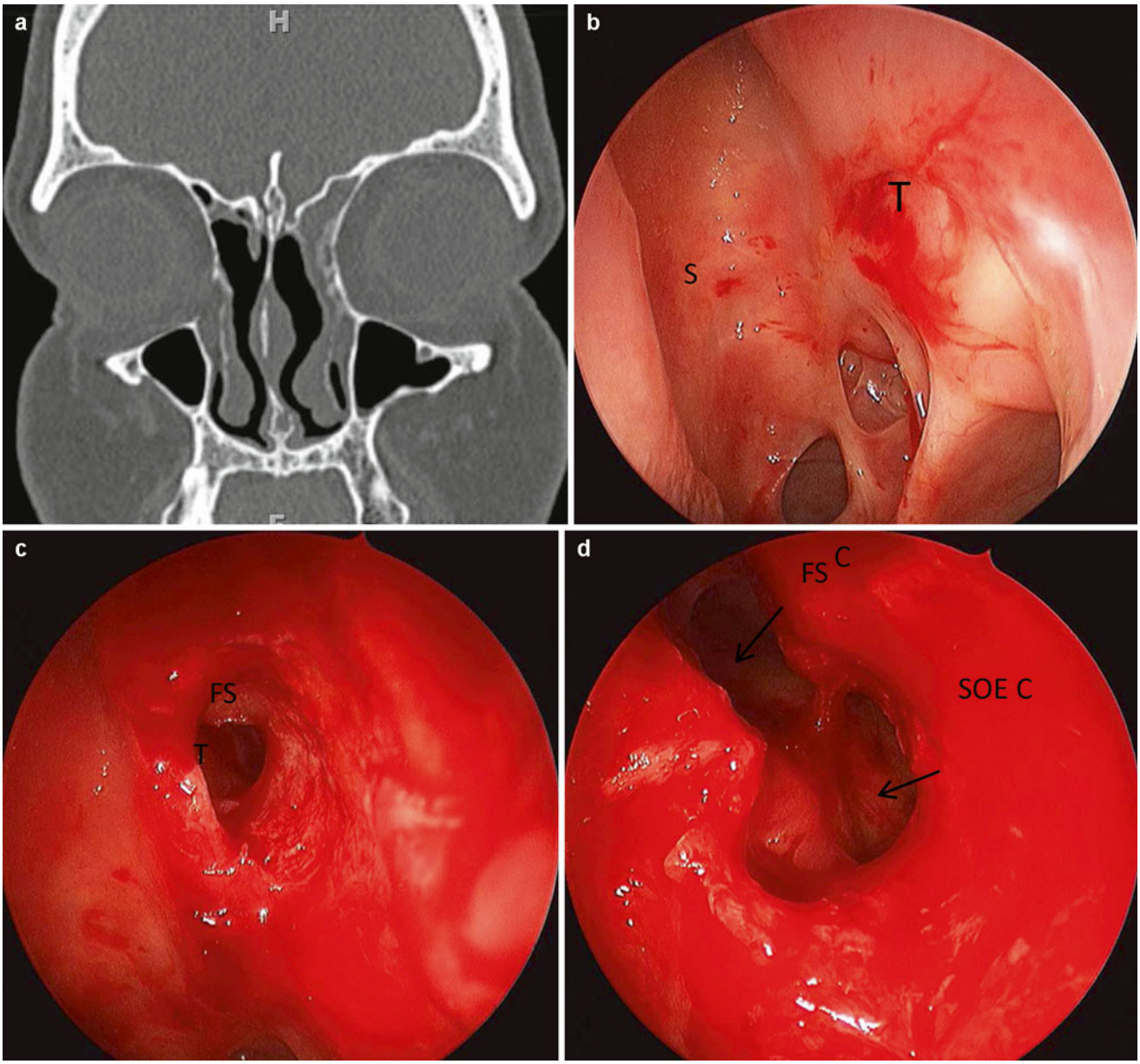


Fig. 26.5 Patient with chronic frontal sinusitis secondary to lateralization of a previously resected middle turbinate stump. (**a**) Coronal and sagittal CT scans with the coronal image depicted the lateralized middle turbinate stump. (**b**) Nasal endoscopy with a zero-degree scope. *S* septum, *C* cribriform plate, *MT* middle turbinate. (**c**) Endoscopy with a 45° scope after the middle turbinate stump has been resected and frontal recess is visible. *FS* frontal sinus. (**d**) Final view demonstrating frontal sinus and supraorbital ethmoid (*SOE*) tract

of the frontal opening. When supraorbital cells are present, they will be found posterior and lateral to the frontal ostium. Large supraorbital ethmoid cells may be mistaken for the frontal sinus itself. Removal of the dividing wall between the frontal sinus and supraorbital cell will help ensure patency of both outflow tracts (Fig. 26.5). Image guidance may be employed to verify the position of the middle turbinate insertion, orbital wall, frontal bone, and skull base, which comprise the margins of the sinusotomy (Fig. 26.6).

An alternative direct approach to opening the frontal sinus can be achieved in select patients with well-aerated agger nasi cells by "punching" out the anterior face and superior part of the agger nasi cell starting at the axilla of the middle turbinate attachment using a Kerrison punch [11]. This allows immediate visualization into the frontal recess using a 0° scope. While this technique has the potential to destabilize the middle turbinate, two published series report no increased incidence of middle turbinate lateralization [11, 12].

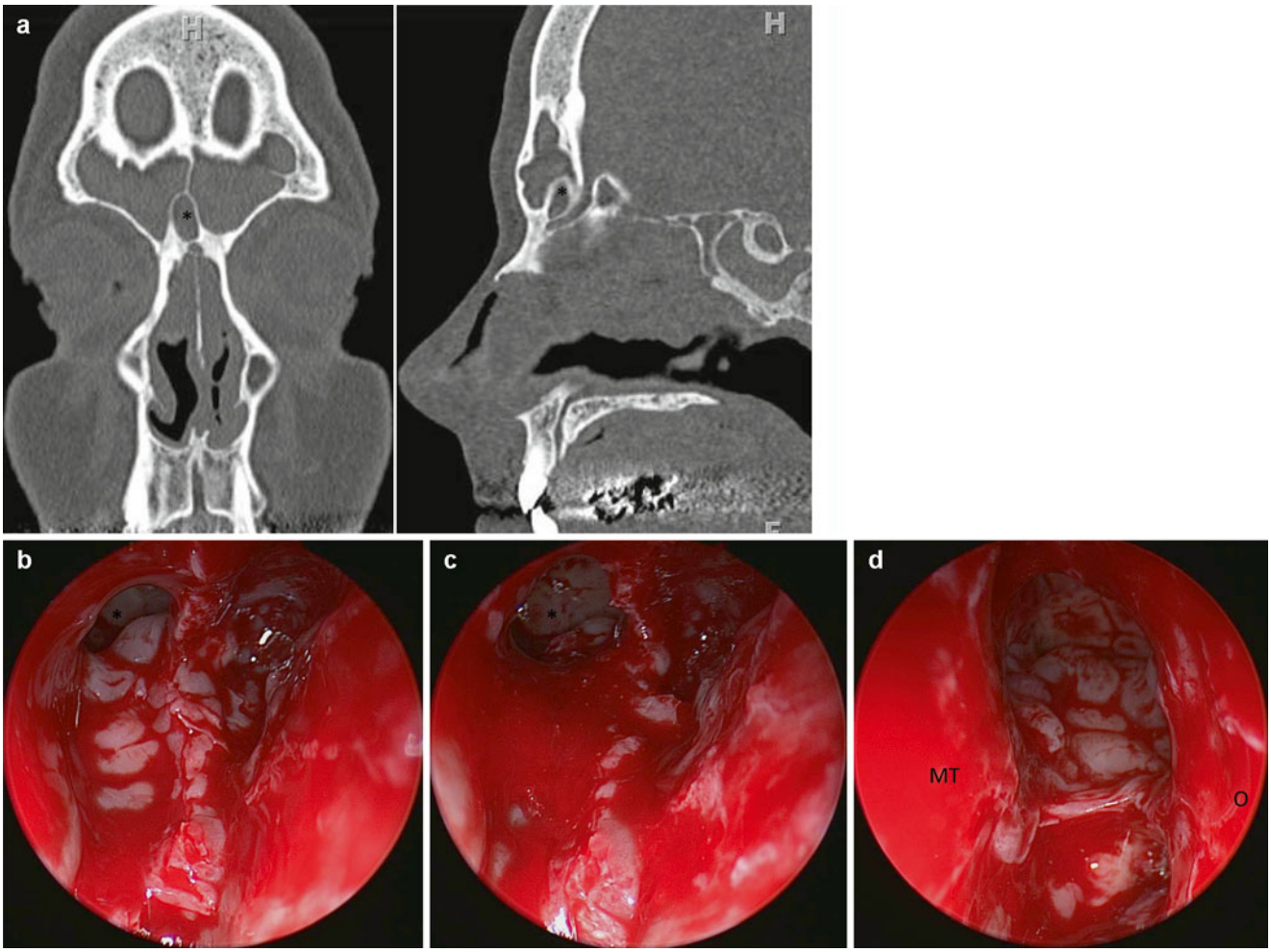


Fig. 26.6 Patient with chronic polypoid rhinosinusitis involving the frontal sinus. Panel **a** shows coronal and axial CT scans which depict a central frontal sinus cell, noted by an *asterisk* (*). (**b**–**d**) Shows an endoscopic view of the frontal recess using a 45° endoscope. (**b**) Frontal recess anatomy including the central frontal cell (*). (**c**) The interfrontal sinus septum is partially removed and the central frontal cell (*) is enlarged. (**d**) Frontal recess after completely removing the interfrontal sinus septum, incorporating the L frontal sinus and central cell into one cavity. Note the inflamed mucosa. *MT* middle turbinate, *O* orbit

Endoscopic Modified Lothrop Procedure (EMLP) or "Frontal Drill Out"

Lothrop's initial frontal sinusotomy consisted of an external ethmoidectomy to enlarge the nasofrontal drainage pathway while removing the floors of the frontal sinuses through a large nasal septectomy and removal of the lacrimal bone and part of the lamina papyracea [13]. Montgomery introduced and later popularized the osteoplastic frontal sinus fat obliteration procedure, whereby the anterior table of the frontal sinus was removed, the mucosa was stripped out, fat was placed into the sinus, and the bone flap was replaced [14].

The introduction of nasal endoscopes and angled instrumentation allowed for better visualization of the frontal recess, and, subsequently, the Lothrop procedure was modified by Draf to be performed endoscopically in patients refractory to standard endoscopic frontal sinusotomy. Gross later went on to develop the modern-day endoscopic modified Lothrop procedure (EMLP) which removes the bilateral frontal sinus floors, upper part of the middle turbinates, and septum/interfrontal sinus septum using a powered endoscopic drill [15] (Fig. 26.7). The success of this procedure depends on the frontal recess anatomy and mucosal pathology. Anatomically, the anterior-posterior dimension at the superior margin of the frontal recess should be at least 1.5 cm, and the anterior-posterior thickness of the nasal beak should not exceed 1 cm. EMLP has an important place in the armamentarium of the endoscopic sinus surgeon as a revision approach when a standard frontal sinus approach has failed due to scarring or recalcitrant disease. The development of extended endoscopic approaches to the

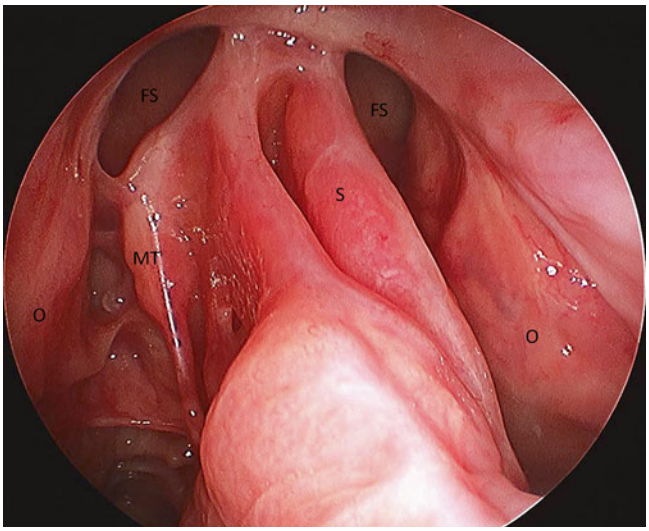


Fig. 26.7 View of an endoscopic modified Lothrop procedure. *O* orbit, *FS* frontal sinus, *MT* middle turbinate

frontal sinus has decreased the need for more invasive open procedures. EMLP has likewise been employed in the management of tumors such as inverting papillomas and osteomas, where the large frontal opening allows sufficient access for resection as well as postoperative surveillance in the clinic.

The outcomes of EMLP have been reported by many groups, with patency rates of 87.5–93 % at 22–24 months and primary complications of postoperative stenosis secondary to mucosal trauma in the frontal recess from drilling [16, 17]. In order to reduce this mucosal trauma, use of thru-cutting punches may be preferable to drilling when feasible [18]. Alternatively, some groups have also reported covering the bare bone in the frontal recess after drilling with mucosal transplants from the nasal septum or inferior turbinate [19, 20].

Balloon Catheter Dilation of the Frontal Sinus

The concept of balloon catheter dilation of sinuses was modeled after catheter-based interventions in cardiology and urology and was first introduced in 2006 through an initial feasibility study in cadavers [21]. The proposed advantage of balloon catheter dilation of the frontal sinus is less trauma to the frontal recess mucosa, thereby preventing long-term scarring. Although various balloon products exist, the general technique is to place a guidewire by endoscopic guidance into the frontal recess (with or without an ethmoidectomy). Although fluoroscopy was initially used to confirm placement, guidewires with a lighted tip are more commonly used to confirm placement into the frontal sinus by transillumination of the frontal sinus. Next a balloon catheter is threaded over the guidewire into the frontal recess and inflated, causing the agger nasi and frontal recess cells to be crushed (Fig. 26.8). Although these procedures were formerly only performed in the operating room, practitioners have started performing balloon dilation of sinuses in the office with topical anesthesia.

The long-term patency of the frontal recess after balloon dilation is not well understood. One study reported an 82 % frontal recess patency rate after 24 weeks following the procedure [22]. Another study reported an 86 % patency rate after a mean of 13-month follow-up [23]. Unfortunately, no other studies report long-term patency rates following balloon dilation.

Although balloon catheter dilation of the frontal sinus appears safe and fairly effective, the indications for balloon catheter dilation of the frontal sinus remain controversial with reports of its use for acute frontal sinusitis, frontal headaches, and recurrent acute rhinosinusitis. At present, many experts believe that the indications to perform a frontal sinusotomy should not change with the introduction of new technology such as the balloon catheter.

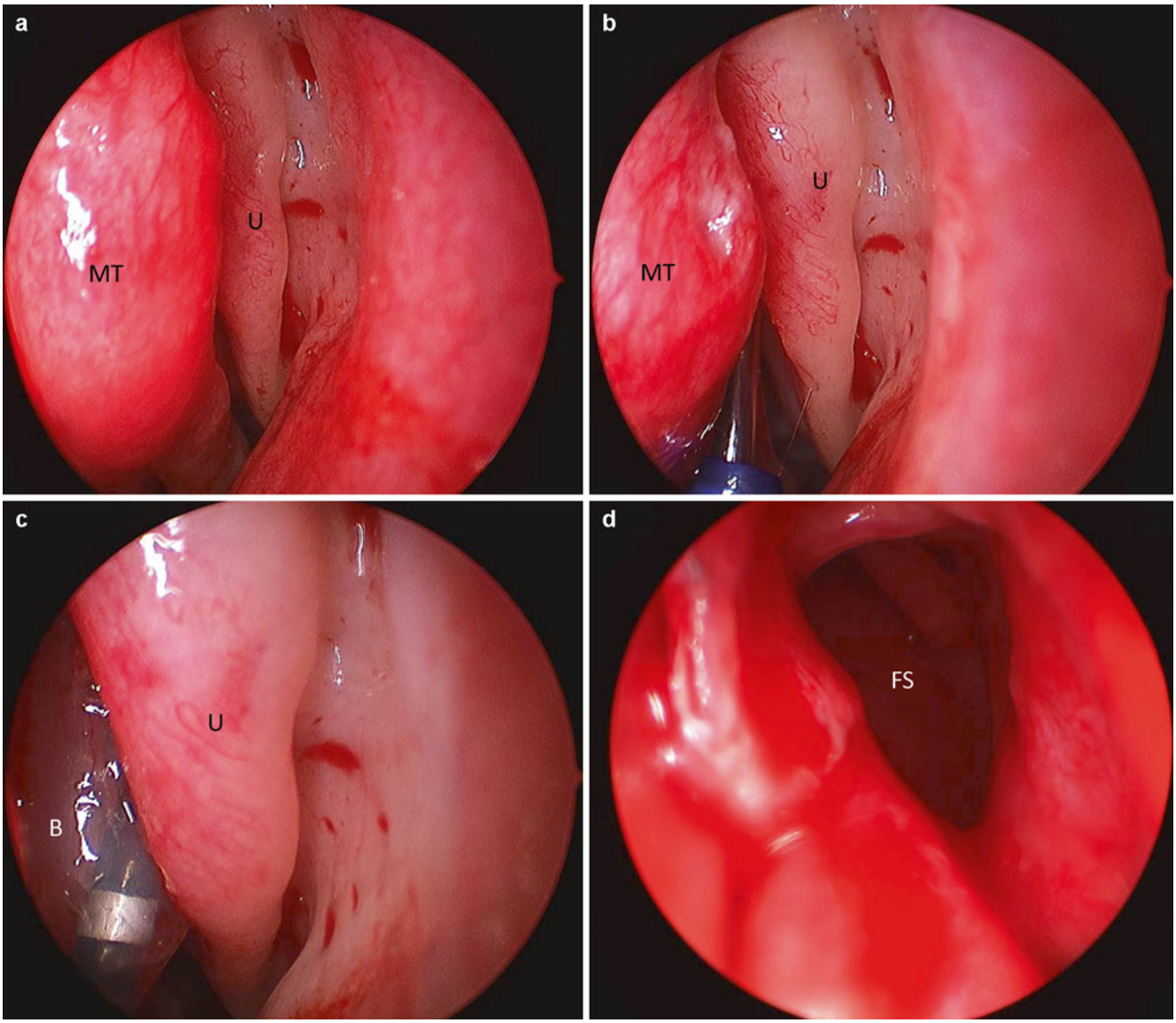


Fig. 26.8 Patient undergoing balloon sinus dilation of the frontal sinus. (**a**) Endoscopic anatomy of the middle meatus. *MT* middle turbinate, *U* uncinate. (**b**) Once the guidewire is inserted into the frontal sinus between the uncinate process (*U*) and ethmoidal bulla (*B*), the balloon catheter (*B*) is threaded over the guidewire through an angled sheath (seen in *blue*). (**c**) The balloon (*B*) is inflated causing the frontal recess cells to be crushed. (**d**) Endoscopic view with a 45° scope depicting the frontal sinus

Postoperative Management

Meticulous postoperative management is crucial following endoscopic frontal sinus surgery to retain patency of the frontal recess. Postoperative outcomes are directly influenced by intraoperative decisions including mucosal preservation and management of the middle turbinate to prevent lateralization. A lateralized or scarred middle turbinate from previous resection can cause chronic frontal sinusitis through closure of the frontal recess (Fig. 26.6). Special maneuvers to retain a patent middle meatus include preventing middle turbinate destabilization by preserving adequate attachments, the use of middle meatal spacers, and controlled synechiae techniques or suture pexy of the middle turbinate to the septum [24]. Further infections and inflammation are limited by the use of postoperative antibiotics and the addition of oral corticosteroids in patients with nasal polyps.

The use of intraoperative frontal recess stenting remains controversial. In theory, with circumferential mucosal preservation, stenting is not required. If there is concern for mucosal integrity or the dimensions of the internal frontal ostium are small, stents can be placed. Kuhn et al. advocated the use of custom-designed 0.01 in. silastic sheeting which is rolled up and

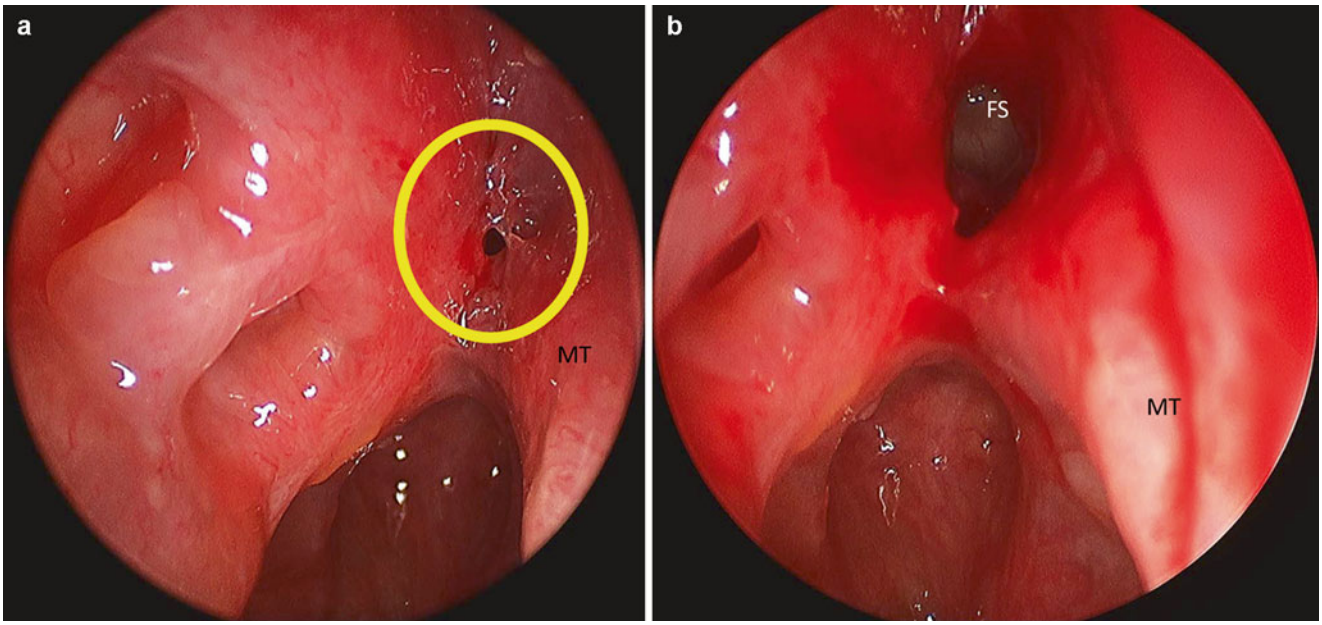


Fig. 26.9 Postoperative endoscopic examination (at 2 months) of a patient who underwent an endoscopic frontal sinusotomy for chronic sinusitis. (**a**) Soft tissue stenosis of the frontal recess (*yellow circle*), *MT* middle turbinate. (**b**) Open frontal recess following dilation using a Farrell cotton applicator in the clinic

placed through the internal frontal ostium [25]. Other commercial frontal sinus stents also exist with the ability to elute corticosteroids. These products have not been well studied, and, again, their long-term efficacy is not known.

After middle meatal spacers are removed (if no spacers are placed, patients start rinsing after 24 h), patients are asked to start low-pressure high-volume saline irrigations twice a day. Practitioners follow different schedules to debride patients, and this is dictated largely by individual patients' healing course. For adequate debridement, the patient must be properly decongested and topically anesthetized, and the surgeon must have instrumentation suitable for frontal sinus manipulation. The frontal recess is examined using either a 45° or 70° endoscope, and blood clots are gently and meticulously suctioned out of the recess under direct visualization. An olive tip suction is not forced into the sinus blindly as this can cause further trauma and bleeding. In subsequent visits, the frontal recess will become less edematous, and bony fragments may become visible that were not initially apparent. These should be removed, and any adhesions or webbing should be divided with thru-cutting forceps to maintain wide sinus ostial patency. After revision frontal sinusotomy in chronically inflamed patients, repeated office dilation of the frontal opening may be needed to achieve a stable patent opening (Fig. 26.9). In the face of ongoing inflammation, topical corticosteroids may be applied as drops placed in the Moffett or "Mecca" positions (maneuvers to place the frontal sinus in a dependent position) or added to nasal saline irrigation solution. Systemic corticosteroids may also be used judiciously if persistent inflammation or polyps obstruct the frontal recess and interfere with complete postoperative healing. A subset of patients will continue to have chronic frontal sinusitis despite adequate frontal sinus openings. In these cases, intrinsic inflammatory mucosal disease is presumed, and ongoing medical therapy may be required to maintain control over symptoms.

In conclusion, successful outcomes in frontal sinus surgery require meticulous intraoperative and postoperative attention to detail. The focus is on mucosal preservation and restoration of mucociliary function. In cases of recalcitrant chronic frontal sinus inflammatory disease, complete frontal sinusotomy followed by conscientious postoperative care optimizes access for long-term topical therapies.

External Surgical Approaches to the Frontal Sinus

Historically, frontal sinus disease was treated using open or external approaches using trans-facial incisions. The first report of a frontal sinus trephination dates back to 1800. Other open approaches were popularized by Lynch with his fronto-ethmoidectomy in the 1920s and by Montgomery using the osteoplastic flap approach with fat obliteration of the frontal sinus, which for years was considered the gold standard for management of frontal disease. Although numerous open approaches exist, the more commonly used techniques are described below.

Trephination

Frontal sinus trephination allows direct access into the frontal sinus and is most commonly employed for drainage of acute frontal sinusitis. However, this technique can also be combined with endoscopic approaches to perform an "above and below" dissection, which can allow access to laterally or superiorly located lesions in the frontal sinus. The procedure itself is performed through a 1–2 cm incision carefully placed in the eyebrow, medial to the supraorbital neurovascular bundle, with beveling parallel to the hair shafts. The inferior limit should be above the medial canthus to avoid injury to the trochlea. Dissection is carried down to the bone, and the incision is retracted superiorly while a 4 mm drill bit is used to make the external trephine into the frontal sinus anterior wall, which can be enlarged using Kerrison punches if needed. The pathology of the frontal sinus can then be addressed using an endoscope and instruments through the trephine. Alternatively, a "mini-trephine" can be used to localize the frontal recess endoscopically through irrigating the trephine with methylene blue-stained saline while visualizing the middle meatus. These uses of trephination to identify the frontal sinus and safely dissect the frontal recess have become less commonplace with the availability of reliable computer-assisted surgical navigation. In cases of unilateral chronic frontal sinusitis with a well-aerated contralateral frontal sinus, a frontal intersinus septum takedown (FISST) procedure can be performed via a trephine or an endoscopic approach to aerate the diseased frontal sinus through the contralateral healthy frontal recess (Fig. 26.10) [26].

Frontal Sinus Osteoplastic Flap

Although the frontal sinus osteoplastic flap procedure with or without obliteration was the salvage procedure traditionally used for inflammatory frontal sinus disease recalcitrant to endonasal approaches, the endoscopic modified Lothrop procedure has largely taken over as the endoscopic salvage procedure of choice. Most osteoplastic flaps are now performed for tumors such as osteomas and inverting papillomas, for laterally located lesions, or for frontal sinus fractures. The osteoplastic flap itself provides wide access to the entire frontal sinus and is generally approached using a bicoronal scalp incision. A subperiosteal dissection is performed to the supraorbital ridge and over the root of the nose. While the position of the frontal sinus was previously identified using a plain X-ray template, image guidance is now often used to outline the borders of the frontal sinus. Osteotomies are made using a combination of the oscillating saw and osteotomes, and titanium plating is used to reattach the bone flap at the conclusion. Once the bony flap is removed, there is wide access to the frontal sinus to address pathology. At that point, there is an option of replacing the osteoplastic flap and leaving the sinus aerated and connected to the nasal cavity or attempting to obliterate the sinus.

Frontal sinus obliteration involves stripping of the lining, drilling the bony walls of the frontal sinus to remove all remaining mucosa, and placing fat or muscle inside the sinus after plugging the frontal recess. This procedure carries a high rate of mucocele formation and carries a high revision rate with time as is it is difficult to completely remove the mucosa in the irregular crevices of the frontal sinus [27, 28]. In addition, obliteration of the frontal sinus with fat after tumor resection does not allow for postoperative radiographic or endoscopic surveillance.

An alternative external approach to the frontal sinus for tumors is a trans-blepharoplasty orbitofrontal mini craniotomy [29]. This procedure is performed entirely through an upper blepharoplasty cosmetic incision and makes a mini orbitofrontal osteotomy only involving the frontal sinus and orbital rim. This approach allows for an opening that can accommodate an endoscope and instruments to be placed for resection of lesions (Fig. 26.11). The trans-blepharoplasty orbitofrontal mini craniotomy is less invasive and has less postoperative morbidity compared to the osteoplastic flap approach.

Cranialization

Cranialization of the frontal sinus is a modification of the osteoplastic flap technique that involves removal of the posterior frontal sinus table. It is reserved for severe comminuted fractures of the frontal sinus or in cases of posterior table destruction due to inflammation or neoplasms. Figure 26.12 depicts a patient who previously underwent a frontal craniotomy with obliteration of the frontal sinus and presented 3 years later with chronic frontal sinusitis. Given the posterior table defects, cranialization was the safest method to manage this patient.

Special Management Considerations for Various Frontal Sinus Pathologies

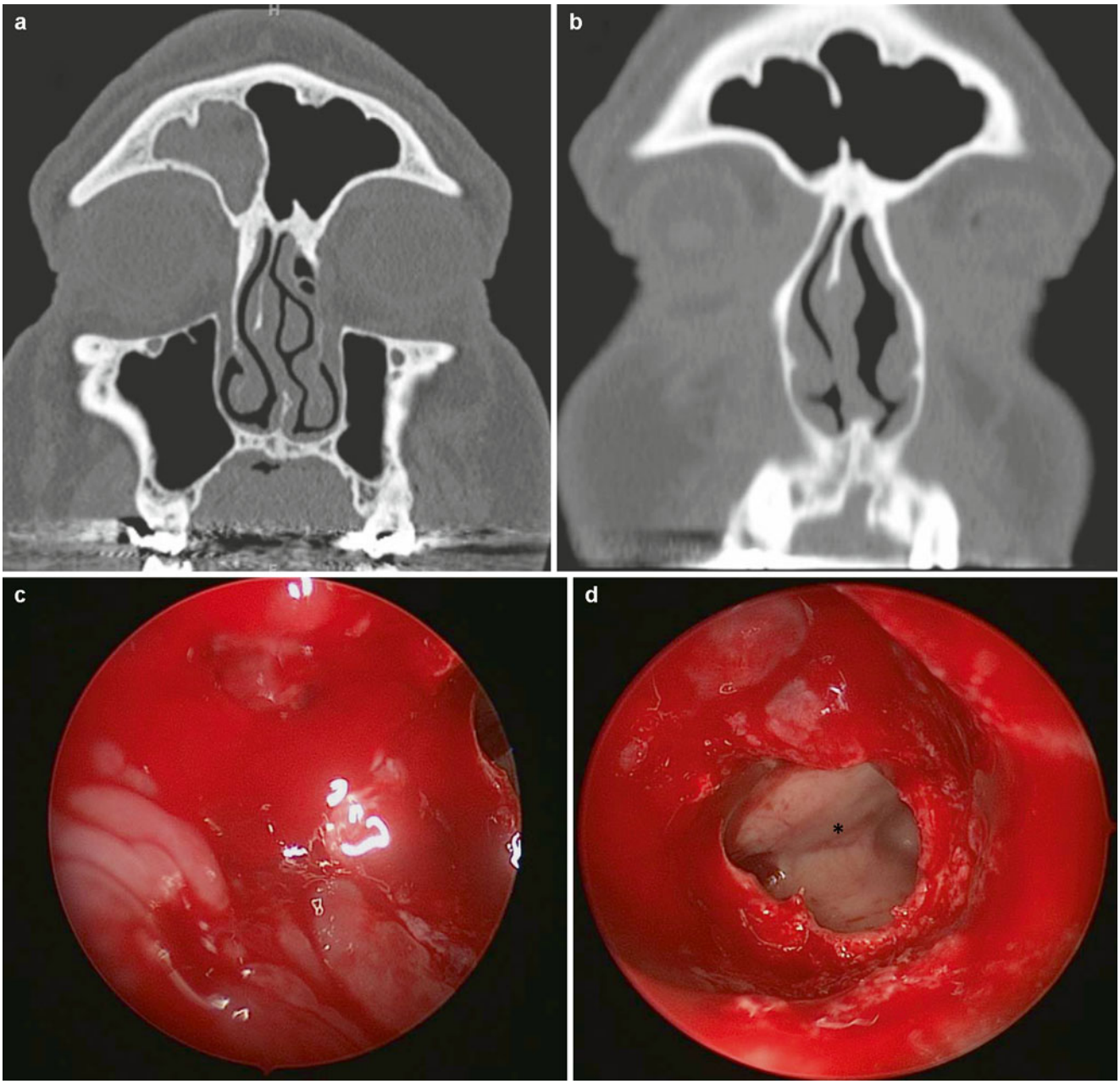


Fig. 26.10 Patient with isolated right frontal sinusitis with a history of a medial orbital wall fracture with fat and medial rectus herniation into the right ethmoid cavity. A right frontal sinus trephine with frontal intersinus septum takedown (FISST) was performed. (**a**) Coronal CT with right frontal opacification but normal left frontal sinus. (**b**) Coronal CT 6 months after FISST shows a well-aerated right frontal sinus. (**c**) Intraoperative endoscopy into the right frontal sinus through a trephine. Shows edematous mucosa filled with mucus. (**d**) Endoscopic view with a 70° scope shows part of the frontal intersinus septum that was removed including a view of the normal left frontal sinus (*)

Frontal Sinus Mucoceles

Mucoceles are slow-growing expansile cysts of mucus secreted by goblet cells. They commonly occur in the frontal sinus causing isolated frontal sinus opacification and/or localized pain and pressure symptoms. Infected mucoceles are called mucopyoceles. Long-standing mucoceles also tend to be locally destructive causing bony resorption and often displacement of the orbit (Fig. 26.13). Delayed mucoceles of the frontal sinus can occur years after a frontal sinus fracture or a consequence of surgical approaches that involve the frontal sinus that did not adequately address the frontal sinus outflow tract such as a frontal craniotomy [30]. In addition, frontal sinus obliterations can frequently result in a mucocele secondary to

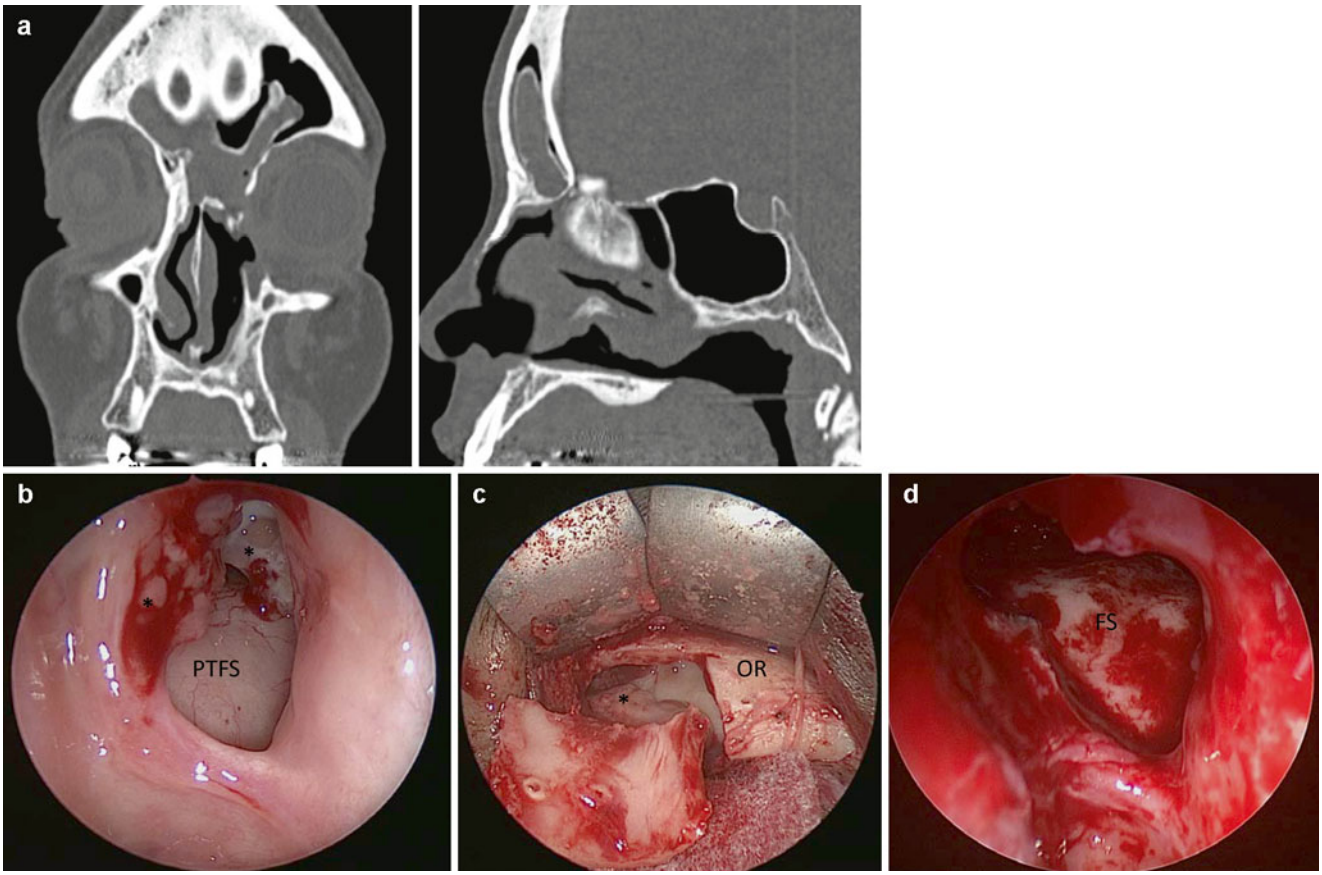


Fig. 26.11 Patient with inverted papilloma of the frontal sinus. Instead of the traditional osteoplastic flap, this patient underwent a trans-blepharoplasty orbitofrontal mini craniotomy to access the frontal sinus using an endoscope. (**a**) Fine-cut coronal and sagittal CT scans depicting bony encasement of the inverted papilloma crossing midline. (**b**) Endoscopic view of a frontal sinusotomy with a 70° scope depicting inverted papilloma (*). *PTFS* posterior table of the frontal sinus. (**c**) Orbitofrontal osteotomies (medial to the supraorbital neurovascular bundle which is visible) to access the frontal sinus via a trans-blepharoplasty incision. Tumor is immediately encountered (*). *OR* orbital rim. (**d**) Endoscopic view at the end of a surgery using a 70° scope shows no residual tumor and a clear view into the frontal sinus (*FS*). Endoscopy through this opening will allow for surveillance of inverted papilloma in the clinic

inadequate removal of the frontal sinus mucosa and fat or muscle placed in the frontal sinus and its recess [31]. Most mucoceles can be marsupialized endoscopically. Since bone may be dehiscent, care must be exercised when using powered instrumentation to prevent a CSF leak or orbital injury. A combined "above and below" approach using a trephine and endoscope can be used for laterally occurring mucoceles.

Chronic Polypoid Frontal Sinusitis

Chronic rhinosinusitis with nasal polyps frequently affects all sinuses including the frontal sinus (Fig. 26.14). Numerous etiologies exist with regard to the pathogenesis of nasal polyps ranging from chronic biofilms, superantigen stimulation of the nasal mucosa, dysregulated host epithelial barrier function, and epithelial innate immune dysfunction [32–34]. While the frontal recess can commonly have nasal polyps, the frontal sinus itself in these patients is usually filled with post-obstructive secretions or inflamed mucosa rather than frank polypoid changes (Fig. 26.5). A study by Larsen et al. shows that most nasal polyps originate from the mucosa of the ostia, clefts, and recesses, three entities that are not found in the frontal sinus [35]. Most patients with this condition complain of thick nasal drainage, anosmia, and nasal obstruction. Many do not complain of specific headache or frontal pressure. Although endoscopic sinus surgery was initially performed to ventilate sinuses, the primarily goal of performing an endoscopic frontal sinusotomy in managing recalcitrant polypoid sinusitis is particularly to provide access for topical therapy. Surgery itself is not a cure for this condition but is an important part of the overall management of chronic polypoid inflammation. Numerous modalities exist to deliver topical medications to the sinuses, spanning

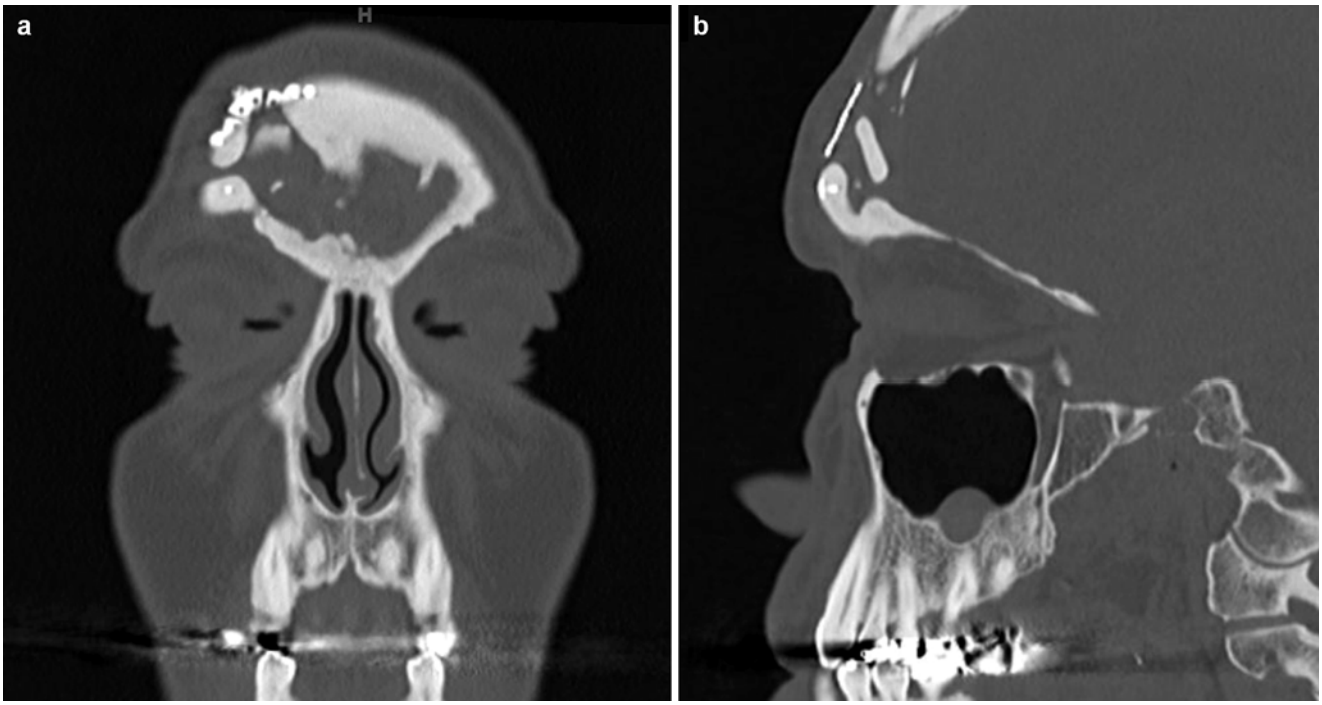
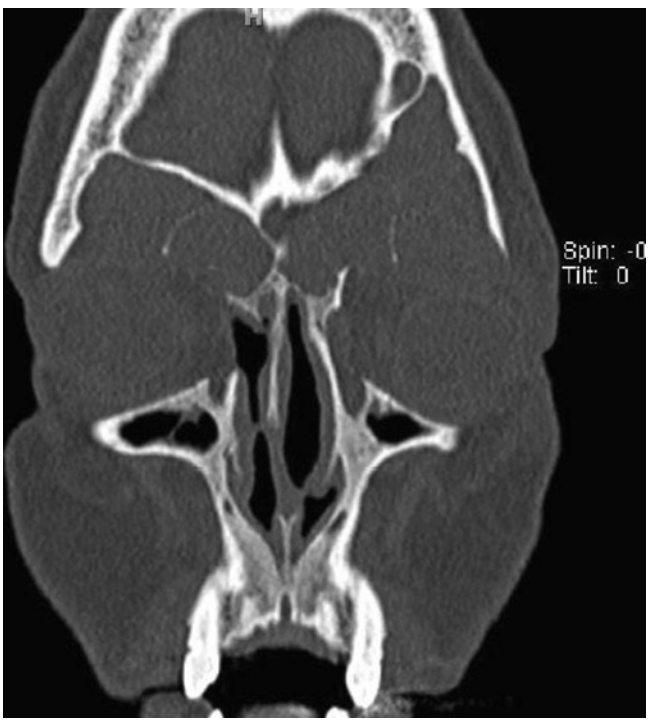


Fig. 26.12 Coronal (**a**) and sagittal (**b**) CT scans from a patient who underwent a frontal craniotomy for a meningioma and had his frontal sinus obliterated with muscle 3 years ago. This patient developed forehead pressure and pain and therefore underwent cranialization due to the extensive posterior table defects

Fig. 26.13 Coronal CT from a patient with bilateral frontal sinus mucoceles causing extensive erosion of the orbital roofs



from medication vials (antibiotics, corticosteroids, or antifungals) that can be added to saline irrigation bottles to medications that can be directly nebulized. In addition, patients with allergies are adjunctively managed with antihistamines, leukotriene inhibitors, or allergen immunotherapy. Lastly, for patients who do not desire surgery or are poor surgical candidates, primary therapy can focus on prolonged courses of oral corticosteroids and medicated irrigations.

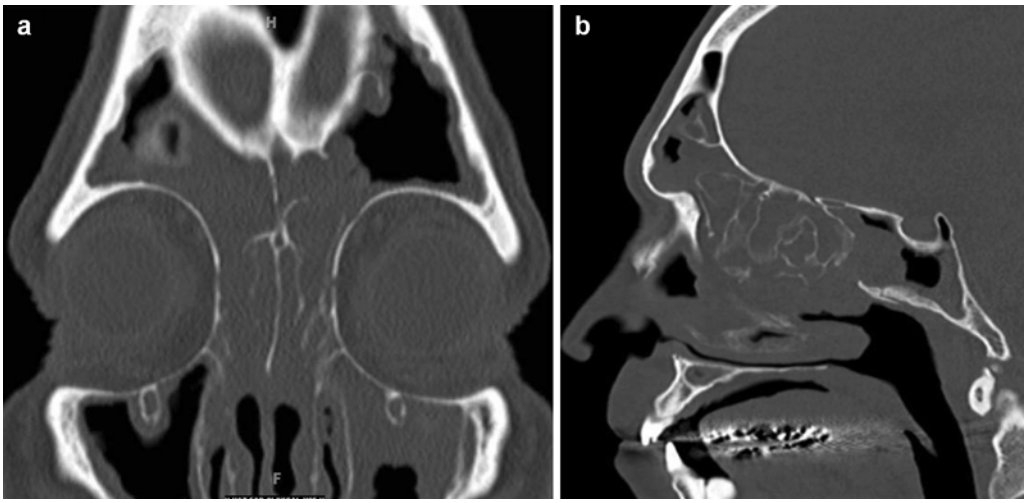


Fig. 26.14 Coronal (**a**) and sagittal (**b**) CT scans from a patient with chronic polypoid sinusitis (involving both frontal recesses) despite multiple surgeries

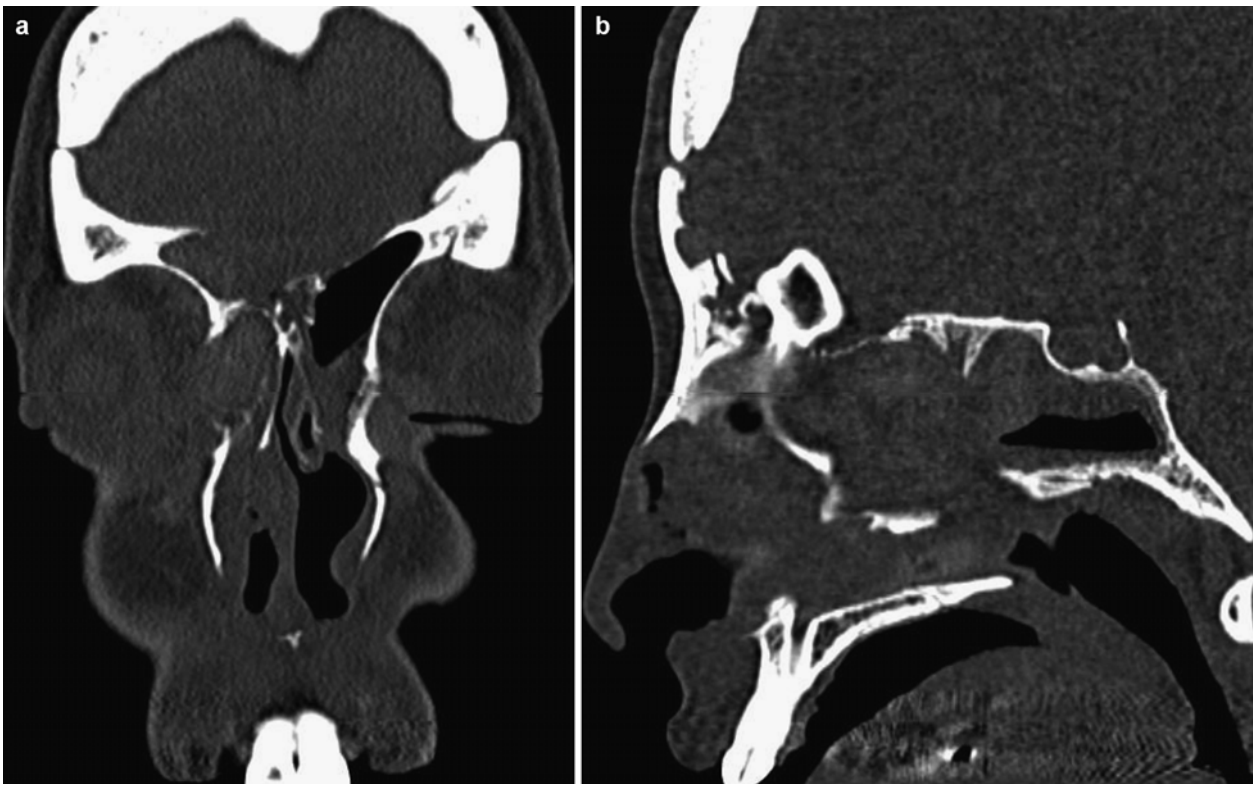


Fig. 26.15 Coronal (**a**) and sagittal (**b**) CT scans from a patient with allergic fungal rhinosinusitis (AFRS) who previously underwent a craniofacial resection (bifrontal craniotomy present) in a foreign country. Note the dehiscence of bone in the right posterior table of the frontal sinus

Allergic Fungal Frontal Sinusitis

Allergic fungal rhinosinusitis (AFRS) is a condition associated with an atopic response to fungi. AFRS is associated with an intense eosinophilic inflammatory response associated with thick allergic mucin. AFRS is considered as the sinonasal correlate of allergic bronchopulmonary aspergillosis (ABPA) and creates a cycle of sinonasal mucostasis, fungal proliferation, and obstruction associated with inflammatory polyps. The disease is thought to be an atopic reaction to dematiaceous fungi in an otherwise immunocompetent host. There is also a clear geographic predilection for AFRS in humid regions such as the southeast and southwest. AFRS can often mimic a tumor by its unilateral presentation and ability to cause bony remodeling, decalcification, and extension into surrounding spaces including the orbit. Mukherji et al. in a radiographic study estimate that the frontal sinus is involved in as high as 71 % of cases [36]. The proximity to the frontal sinus to the anterior cranial fossa and orbit makes it necessary to surgically address AFRS disease in this location. Many patients upon presentation often have dehiscences of the orbit or posterior table of the frontal sinus, making surgery more challenging (Fig. 26.15).

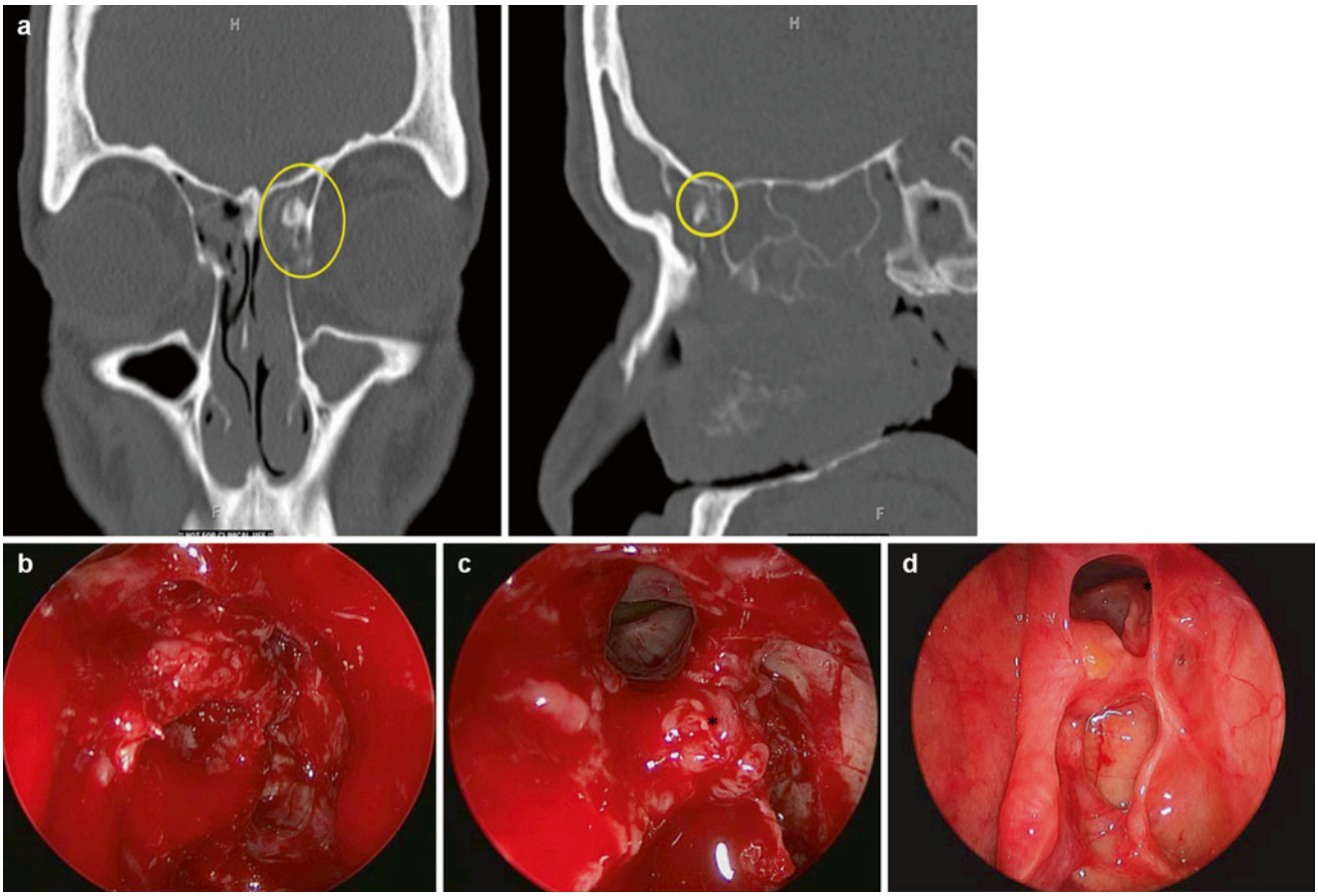


Fig. 26.16 Patient with left frontal recess inverting papilloma initially presenting with exclusive forehead pressure. (**a**) Coronal and sagittal CT scans with left frontal sinus opacification. The *yellow circle* represents the bony attachment of the tumor to the frontal recess. (**b**) Endoscopic view with a 70° scope showing tumor obstructing the fontal recess. (**c**) Further resection of the tumor endoscopically allows ventilation of the frontal sinus and highlights the attachment site of the tumor depicted by a "*". (**d**) Endoscopy at 1-year postoperative visit with a 30° scope in the office shows no evidence of tumor recurrence and a patent frontal sinus

Therapy usually begins with oral corticosteroids to reduce inflammation in preparation for surgery and often continues postoperatively. The surgical goals are to endoscopically evacuate fungal concretions and allergic mucin from the frontal sinus to minimize the atopic response and to allow access for topical therapy. In general, AFRS patients tend to improve rapidly after the fungus has been removed and mucosal inflammation is controlled. Since AFRS does tend to recur, many patients do require long-term medical and surgical therapy with endoscopic monitoring.

Frontal Sinus Inverted Papilloma

Schneiderian inverted papilloma is a benign soft tissue tumor occurring unilaterally that has a propensity to transform into squamous cell carcinoma. Rates of malignant transformation vary but most authors agree on 10 % [37]. Inverted papilloma also has the propensity to recur despite surgical excision with reported recurrence rates between 25 and 50 %. The high rate of recurrence is primarily due to incomplete resection [38]. Traditionally the management of inverting papilloma without involvement of the frontal sinus was through a lateral rhinotomy or midfacial degloving approach. Extension of inverting papilloma into the frontal recess or frontal sinus manifesting as unilateral chronic frontal sinusitis can be challenging to manage. Endoscopic approaches (either frontal sinusotomy or modified endoscopic Lothrop procedure) are gaining popularity in managing inverting papilloma involving the frontal recess. A recent systematic review of frontal sinus inverting papilloma cases reports that over 60 % of cases were exclusively managed endoscopically [39]. Unfortunately, inverted papillomas that extend higher into the frontal sinus may require open approaches such as osteoplastic flaps. Regardless of the papilloma location, the endoscopic approach is commonly used concurrently with an open approach since the ultimate goal is to create a cavity that can be monitored endoscopically for recurrence in the clinic (Fig. 26.16d).

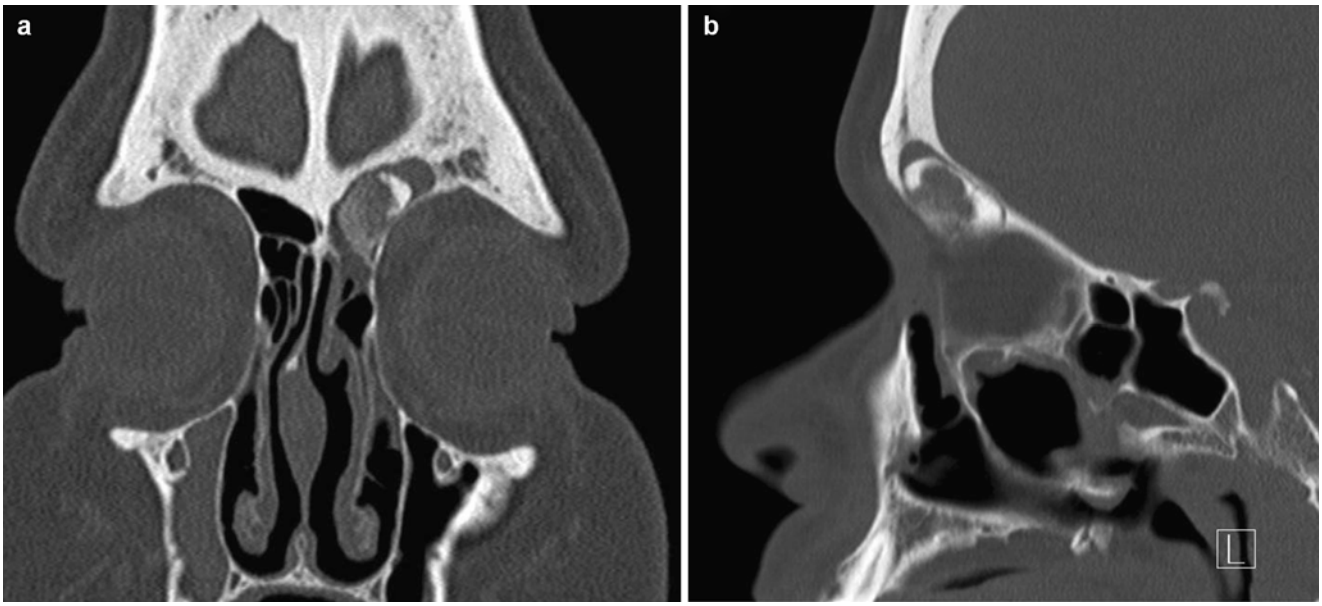


Fig. 26.17 Coronal (**a**) and sagittal (**b**) CT scans from a patient with a large left frontal sinus osteoma with post-obstructive secretions lateral to the osteoma

Fibro-Osseous Frontal Sinus Tumors

Benign fibro-osseous tumors such as osteomas are the most common tumors of the frontal sinus. Osteomas can be present in the general population without symptoms and are often incidental findings on routine imaging. However, with enlargement they can cause obstruction in the frontal recess causing obstructive secretion retention (Fig. 26.17). Resection of osteomas can be very challenging depending on location and proximity to the skull base and the anterior ethmoid artery. Although most osteomas can be approached endoscopically, those that arise laterally or superiorly in the frontal sinus may require an open approach.

Complications

Most of the complications from untreated frontal sinusitis are from acute infections and result from spread of infection to adjacent anatomical structures such as the orbit and brain. Orbital complications are the most common followed by intracranial complications, frontal bone osteomyelitis, and lastly soft tissue abscesses [40]. Orbital infections arising from the frontal sinuses evolve through direct extension of the infection or via retrograde thrombophlebitis. Complicating orbital infections can start with periorbital cellulitis eventually leading to a subperiosteal abscess, orbital abscess, and cavernous sinus thrombosis if left untreated [41]. In general, orbital infections secondary to a frontal sinusitis tend to be aggressive and more often require surgery drainage as well as a medical approach.

Although less common in the antibiotic era, central nervous system complications of frontal sinusitis still occur. The frontal sinus is the most common sinus source of intracranial complications including meningitis, epidural abscess, subdural empyema, intracerebral abscess, and cavernous sinus or superior sagittal sinus thrombosis.

Infection can travel hematogenously from the frontal sinus to the intracranial space via small valveless diploic veins (veins of Breschet) that extend from the posterior table of the frontal sinus to the venous plexi of the periosteum and dura [42]. In most cases, the intracranial process should be addressed simultaneously with the frontal sinus (usually approached via trephination) for optimal care.

CNS complications from functional endoscopic sinus surgery are often increased when the frontal sinus is addressed. Numerous factors such as the narrow and variable anatomy of the frontal recess, poor visualization with inflammation and bleeding, and skill level of the surgeon can lead to violation of the skull base resulting in a cerebrospinal fluid (CSF) leak. In addition, other frontal sinus pathologies such as mucoceles and AFRS can cause dehiscences of the posterior table, making instrumentation of this area more vulnerable to a CSF leak. Lastly, more aggressive surgical techniques such as the modified endoscopic Lothrop procedure can carry an iatrogenic CSF leak as high as 10 % [43].

Conclusion

Chronic inflammation of the frontal sinus remains difficult to manage for numerous reasons. The complicated anatomy and critical location of the frontal sinus make instrumentation particularly difficult especially in an inflammatory state. Numerous conditions can cause chronic frontal sinusitis including polypoid inflammation, AFRS, mucoceles, or tumors, and the management of each of these conditions is unique. With technological advances in angled instrumentation and scopes and stereotactic image guidance, endoscopic approaches are now the mainstay of frontal sinus surgery, reserving external approaches largely for tumors. Meticulous preoperative and intraoperative planning and postoperative debridement are crucial in achieving the best postoperative frontal sinus surgery outcomes.

References

1. Kountakis SE, Senior BA, Draf W. The frontal sinus. Berlin/New York: Springer; 2005.
2. DelGaudio JM, Wise SK, Wise JC. Association of radiological evidence of frontal sinus disease with the presence of frontal pain. Am J Rhinol. 2005;19:167–73.
3. Brook I. Bacteriology of acute and chronic frontal sinusitis. Arch Otolaryngol Head Neck Surg. 2002;128:583–5.
4. Schlosser RJ, London SD, Gwaltney Jr JM, Gross CW. Microbiology of chronic frontal sinusitis. Laryngoscope. 2001;111:1330–2.
5. Harvey RJ, Wallwork BD, Lund VJ. Anti-inflammatory effects of macrolides: applications in chronic rhinosinusitis. Immunol Allergy Clin North Am. 2009;29:689–703.
6. Cervin A, Wallwork B. Macrolide therapy of chronic rhinosinusitis. Rhinology. 2007;45:259–67.
7. Dubin MG, Liu C, Lin SY, Senior BA. American Rhinologic Society member survey on "maximal medical therapy" for chronic rhinosinusitis. Am J Rhinol. 2007;21:483–8.
8. DelGaudio JM, Wise SK. Topical steroid drops for the treatment of sinus ostia stenosis in the postoperative period. Am J Rhinol. 2006;20:563–7.
9. Albu S, Gocea A, Mitre I. Preoperative treatment with topical corticoids and bleeding during primary endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2010;143:573–8.
10. Sieskiewicz A, Olszewska E, Rogowski M, Grycz E. Preoperative corticosteroid oral therapy and intraoperative bleeding during functional endoscopic sinus surgery in patients with severe nasal polyposis: a preliminary investigation. Ann Otol Rhinol Laryngol. 2006;115:490–4.
11. Pletcher SD, Sindwani R, Metson R. The Agger Nasi Punch-Out Procedure (POP): maximizing exposure of the frontal recess. Laryngoscope. 2006;116:1710–2.
12. Wormald PJ. The axillary flap approach to the frontal recess. Laryngoscope. 2002;112:494–9.
13. Lothrop HA. XIV. Frontal sinus suppuration: the establishment of permanent nasal drainage; the closure of external fistulae; epidermization of sinus. Ann Surg. 1914;59:937–57.
14. Hardy JM, Montgomery WW. Osteoplastic frontal sinusotomy: an analysis of 250 operations. Ann Otol Rhinol Laryngol. 1976;85:523–32.
15. Gross WE, Gross CW, Becker D, Moore D, Phillips D. Modified transnasal endoscopic Lothrop procedure as an alternative to frontal sinus obliteration. Otolaryngol Head Neck Surg. 1995;113:427–34.
16. Wormald PJ. Salvage frontal sinus surgery: the endoscopic modified Lothrop procedure. Laryngoscope. 2003;113:276–83.
17. Eloy P, Vlaminck S, Jorissen M, et al. Type III frontal sinusotomy: surgical technique, indications, outcomes, a multi-university retrospective study of 120 cases. B-ENT. 2011;7 Suppl 17:3–13.
18. Dubin MG, Kuhn FA. Endoscopic modified Lothrop (Draf III) with frontal sinus punches. Laryngoscope. 2005;115:1702–3.
19. Hildenbrand T, Wormald PJ, Weber RK. Endoscopic frontal sinus drainage Draf type III with mucosal transplants. Am J Rhinol Allergy. 2012;26:148–51.
20. Conger Jr BT, Riley K, Woodworth BA. The Draf III mucosal grafting technique: a prospective study. Otolaryngol Head Neck Surg. 2012;146:664–8.
21. Brown CL, Bolger WE. Safety and feasibility of balloon catheter dilation of paranasal sinus ostia: a preliminary investigation. Ann Otol Rhinol Laryngol. 2006;115:293–9; discussion 300–1.
22. Bolger WE, Brown CL, Church CA, et al. Safety and outcomes of balloon catheter sinusotomy: a multicenter 24-week analysis in 115 patients. Otolaryngol Head Neck Surg. 2007;137:10–20.
23. Wycherly BJ, Manes RP, Mikula SK. Initial clinical experience with balloon dilation in revision frontal sinus surgery. Ann Otol Rhinol Laryngol. 2010;119:468–71.
24. Hewitt KM, Orlandi RR. Suture medialization of the middle turbinates during endoscopic sinus surgery. Ear Nose Throat J. 2008;87:E11.
25. Kuhn FA, Citardi MJ. Advances in postoperative care following functional endoscopic sinus surgery. Otolaryngol Clin North Am. 1997;30:479–90.
26. Reh DD, Melvin TA, Bolger WE, Lane AP. The frontal intersinus septum takedown procedure: revisiting a technique for surgically refractory unilateral frontal sinus disease. Laryngoscope. 2011;121:1805–9.
27. Hwang PH, Han JK, Bilstrom EJ, Kingdom TT, Fong KJ. Surgical revision of the failed obliterated frontal sinus. Am J Rhinol. 2005;19:425–9.
28. Hahn S, Palmer JN, Purkey MT, Kennedy DW, Chiu AG. Indications for external frontal sinus procedures for inflammatory sinus disease. Am J Rhinol Allergy. 2009;23:342–7.

29. Chu EA, Quinones-Hinojosa A, Boahene KD. Trans-blepharoplasty orbitofrontal craniotomy for repair of lateral and posterior frontal sinus cerebrospinal fluid leak. Otolaryngol Head Neck Surg. 2010;142:906–8.
30. Hwang K, Kim EY. Delayed development of mucocele in the fractured frontal sinus. J Craniofac Surg. 2008;19:1419–22.
31. Rosado P, de Vicente JC, Villalain L, Fernandez S, Pena I. Posttraumatic frontal mucocele. J Craniofac Surg. 2011;22:1537–9.
32. Ramanathan Jr M, Lane AP. Innate immunity of the sinonasal cavity and its role in chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2007;136:348–56.
33. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124:37–42.
34. Kern RC, Conley DB, Walsh W, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. Am J Rhinol. 2008;22:549–59.
35. Larsen PL, Tos M. Origin of nasal polyps: an endoscopic autopsy study. Laryngoscope. 2004;114:710–9.
36. Mukherji SK, Figueroa RE, Ginsberg LE, et al. Allergic fungal sinusitis: CT findings. Radiology. 1998;207:417–22.
37. Senior BA, Lanza DC. Benign lesions of the frontal sinus. Otolaryngol Clin North Am. 2001;34:253–67.
38. Hyams VJ. Papillomas of the nasal cavity and paranasal sinuses. A clinicopathological study of 315 cases. Ann Otol Rhinol Laryngol. 1971;80:192–206.
39. Walgama E, Ahn C, Batra PS. Surgical management of frontal sinus inverted papilloma: a systematic review. Laryngoscope. 2012;122(6):1205–9.
40. Goldberg AN, Oroszlan G, Anderson TD. Complications of frontal sinusitis and their management. Otolaryngol Clin North Am. 2001;34:211–25.
41. Chandler JR, Langenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. Laryngoscope. 1970;80:1414–28.
42. Remmler D, Boles R. Intracranial complications of frontal sinusitis. Laryngoscope. 1980;90:1814–24.
43. Schlosser RJ, Zachmann G, Harrison S, Gross CW. The endoscopic modified Lothrop: long-term follow-up on 44 patients. Am J Rhinol. 2002;16:103–8.

Chapter 27
Orbital and Intracranial Complications of Acute and Chronic Rhinosinusitis

Jan Kastner, Daniel Simmen, David Netuka, Jan Kastner Sr., and Volker Gudziol

Introduction

The Task Force of the American Rhinologic Society has defined rhinosinusitis as a condition manifested by an inflammatory response involving the mucous membranes of the nasal cavity and paranasal sinuses and/or underlying bone. Symptoms associated with rhinosinusitis are varied and include nasal obstruction, congestion, anterior discharge, postnasal drip, facial pressure and pain, cough and sometimes hyposmia/anosmia, headache, fatigue and ear pressure [1]. The European Position Paper on Rhinosinusitis and Nasal Polyposis clinically defines rhinosinusitis as inflammation of the nose and paranasal sinuses characterised by two or more symptoms, one of which should be either nasal obstruction or nasal discharge, facial pressure and/or loss of smell, and supported by positive endoscopic findings and/or sinus CT pathology [2]. Rhinosinusitis is further subdivided by the duration of symptoms. In acute rhinosinusitis (ARS), the symptoms last less than 12 weeks. Chronic rhinosinusitis (CRS) is defined as symptoms lasting more than 12 weeks. Finally, the definition also includes the presence or absence of nasal polyposis.

Clinical ENT examination is preferably performed using rigid or flexible endoscopes (Fig. 27.1) which aid in the scrutiny for otherwise more serious illness (Fig. 27.2). Computerised tomography of the paranasal sinuses is not recommended unless the course of disease is very severe, the patient is immunocompromised or the clinical signs of complications are present.

Complications of acute rhinosinusitis involve extension of disease into surrounding tissues. Complications are, therefore, divided into orbital, intracranial and osseous or soft tissue involvement. Osseous complications (found mostly in chronic rhinosinusitis) include osteitis and osteomyelitis, foremost of the frontal bone. Early recognition of orbital and intracranial complications is particularly important due to their high morbidity and occasional mortality.

J. Kastner, MD (✉)
Department of Otorhinolaryngology and Head and Neck Surgery, Motol Hospital, 1st Medical Faculty of Charles University, V Uvalu 84, Prague 15006, Czech Republic
e-mail: jan@orl-kastner.cz, jkastner@email.cz

D. Simmen, MD, PhD
ORL-Zentrum, Center for Rhinology, Skull Base Surgery and Facial Plastic Surgery, The Hirslanden Clinic, Witellikerstrasse 40, Zurich 8032, Switzerland
e-mail: simmen@orl-zentrum.com

D. Netuka, MD, PhD
Department of Neurosurgery, Central Military Hospital, 1st Medical Faculty of Charles University, U vojenske nemocnice 1200, Prague 16902, Czech Republic
e-mail: david.netuka@uvn.cz

J. Kastner, Sr., MD
Department of Neuroradiology, Medical Faculty in Pilsen, Charles University, Prague, Czech Republic
e-mail: kastner@fnplzen.cz

V. Gudziol, MD, PhD
Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Carl Gustav Carus, Dresden, Germany
e-mail: volker.gudziol@uniklinikum-dresden.de

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_27,

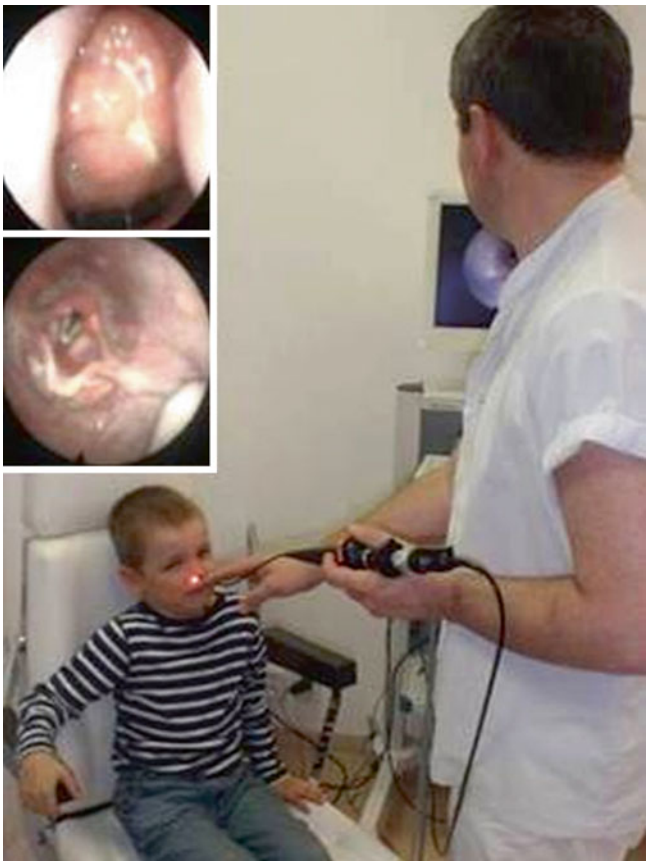


Fig. 27.1 Flexible endoscopy in a paediatric patient. The examination enables visualization of the nasal cavity, adenoids and larynx

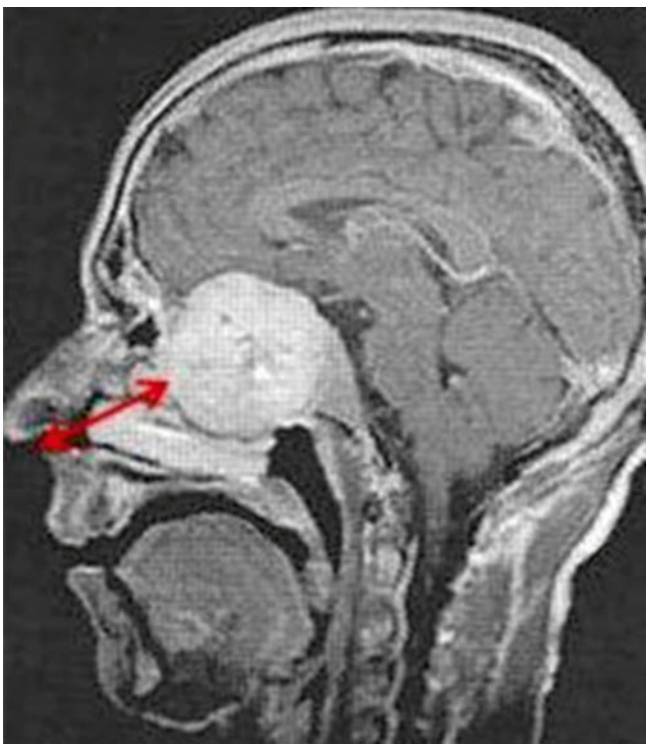


Fig. 27.2 Patient with chondrosarcoma of the nasal cavity/skull base in an MRI sagittal scan. *Red arrow* shows that the process is located approx four centimeters from the nasal vestibule, which is not obvious using anterior rhinoscopy, but only after nasal endoscopy (he was 'treated' with local corticosteroids at allergology dept. for several months as allergic rhinitis was presumed and nasal endoscopy not performed)

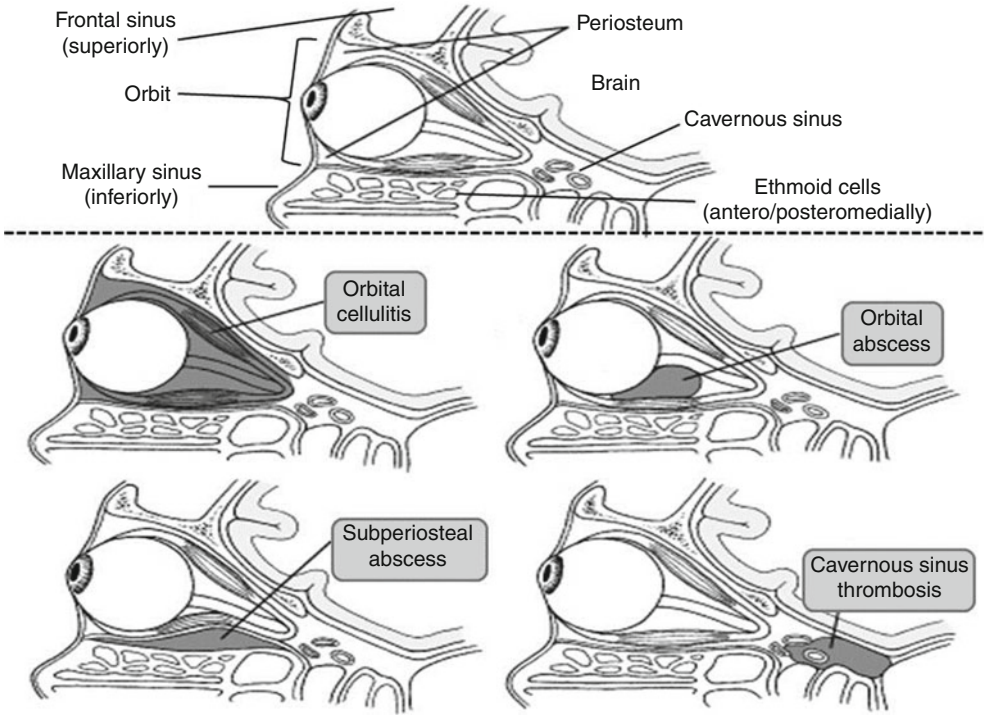


Fig. 27.3 Scheme of various orbital inflammatory processes reflecting anatomical relationships

EP³OS 2012

In 2012, the European Rhinologic Society updated similar evidence-based position papers published in 2005 and 2007 – the European Position Paper on Rhinosinusitis and Nasal Polyps. The document contains chapters on definitions and classification, newly proposed definitions for difficult to treat rhinosinusitis, control of disease and better definitions for rhinosinusitis in children. More emphasis was placed on the diagnosis and treatment of acute rhinosinusitis. Throughout the document, the terms chronic rhinosinusitis without nasal polyps and chronic rhinosinusitis with nasal polyps are used to further point out differences in pathophysiology and treatment of these two entities. There are extensive chapters on epidemiology and predisposing factors, inflammatory mechanisms, differential diagnosis of facial pain, genetics, cystic fibrosis, aspirin-exacerbated respiratory disease, immunodeficiencies, allergic fungal rhinosinusitis and the relationship between upper and lower airways. The chapters on paediatric acute and chronic rhinosinusitis were totally rewritten. All available evidence for management of acute rhinosinusitis and chronic rhinosinusitis with or without nasal polyps in adults and children was analysed and presented, and management schemes based on the evidence were proposed. The complications associated with rhinosinusitis were reviewed and analysed. The full document can be downloaded for free on the website of *Rhinology International Journal*: http://www.rhinologyjournal.com [3].

Classification of Rhinosinusitis Complications

Orbital complications have been defined according to several classifications. They reflect the anatomy of the orbit and the mechanism causing the inflammation (Fig. 27.3) (Tables 27.1 and 27.2). Hubert in 1937 was the first to classify these complications. He studied clinical data from about 114 patients during the preantibiotic era. He based his classification on the anatomy of orbit, perceived progression of infection, responsiveness to treatment and general prognosis [4]. In 1970, Chandler modified this classification system further. He divided his patients into five groups. Chandler used the classification from Hubert (I, eyelid inflammatory oedema; II, orbit subperiosteal abscess; III, diffuse orbital cellulitis; IV, orbital abscess; V, cavernous sinus thrombophlebitis) and removed the term eyelid from category I. He further modified category III as 'diffuse cellulitis' in order to describe inflammatory cells infiltrating orbital fat tissue [5]. The term preseptal was added to Chandler's category I (inflammatory oedema) by Moloney in 1987. This author divided orbital complications into *preseptal and postseptal complications*. Signs indicating postseptal complications were defined as proptosis, gaze restriction, decreased visual acuity, colour vision defects and efferent pupillary defect [6]. The Groote Schuur Hospital classification published by

Table 27.1 Orbital complications of rhinosinusitis – Chandler's classification

	Type I	Type II	Type III	Type IV	Type V
Chandler's classification	Preseptal cellulitis	Orbital cellulitis	Subperiosteal abscess	Orbital abscess	Cavernous sinus thrombosis
Pathology	Inflammatory oedema anterior to orbital septum	Pronounced oedema and inflammation of orbital contents without abscess formation	Abscess develops in the space between the bone and periosteum	Abscess within the orbital contents	Belongs to orbital as well as intracranial complications
Symptoms	Eyelids swelling (restricted venous drainage) No chemosis, no eyeball movement limitation, no vision impairment Mild proptosis	Signs of proptosis and reduced ocular mobility Chemosis Vision should be constantly monitored	Chemosis and proptosis	Severe proptosis, complete ophthalmoplegia, loss of vision	Development of bilateral ocular signs Fever, headache, photophobia, proptosis, ophthalmoplegia, loss of vision, cranial nerve palsies involving III, IV, V1, V2 and VI

Table 27.2 Minor and major orbital and intracranial complications of FESS

Location	Minor complications	Major complications
Orbital	Orbital emphysema	Orbital haematoma
	Ecchymosis of the eyelid	Loss of visual acuity/blindness
		Diplopia
		Enophthalmia
		Nasolacrimal duct damage
Intracranial	CSF leak – uncomplicated	CSF leak
		Pneumocephalus (tension)
		Encephalocoele
		Brain abscess
		Meningitis
		Intracranial (subarachnoid)
		Bleeding
		Direct brain trauma

Mortimore and Wormald insisted on dividing the inflammatory process strictly into preseptal (which is not organ threatening) and postseptal (genuine orbital infections). They further divided postseptal inflammation into subperiosteal and intraconal groups. These authors observed that visual impairment occurred only in the postseptal group. They stressed that radiological differentiation between cellulitis/phlegmon and abscess formation was important in determining whether surgical intervention is appropriate or not [7] (Figs. 27.4, 27.5 and 27.6). The last attempt from 2007 to simplify and adapt the classification of orbital complication to present diagnostic options is the classification by Velasco e Cruz [8]. This author divides intraorbital infections into three groups: (1) orbital cellulitis, (2) subperiosteal abscess and (3) orbital abscess.

Intracranial complications of acute rhinosinusitis include either phlegmonous inflammation (meningitis and/or cerebritis) or abscess formation (Fig. 27.7) (epidural, subdural or intracerebral) and cavernous sinus (or other sinus) thrombophlebitis/thrombosis. All endocranial complications start as a phlegmonous process, but as necrosis and liquefaction of brain tissue progresses, a capsule develops resulting in a brain abscess [9].

According to EP^{3}OS 2012, there are specific *complications in chronic rhinosinusitis* with or without nasal polyposis. These are less dramatic and rarer than those that can occur in acute rhinosinusitis but may be more difficult to manage. Complications of chronic rhinosinusitis are rare and are largely found due to effect on the surrounding bone. They generally result from an imbalance in the normal process of bone resorption, regeneration and remodelling [3].

They include bone erosion and expansion due to mucocoeles or polyps, osteitis (Fig. 27.8) and metaplastic bone formation and occasionally optic neuropathy. Generally, these are far less documented in the literature than those associated with acute infection and inflammation. In some cases, they may be simply considered as a manifestation of the natural history of the condition. There is no evidence that chronic rhinosinusitis is associated with neoplastic change, either benign or malignant. A few case reports suggest that orbital, intracranial and osseous complications typical of acute rhinosinusitis can occur in chronic rhinosinusitis but are almost always secondary to a superimposed acute infective episode [7].

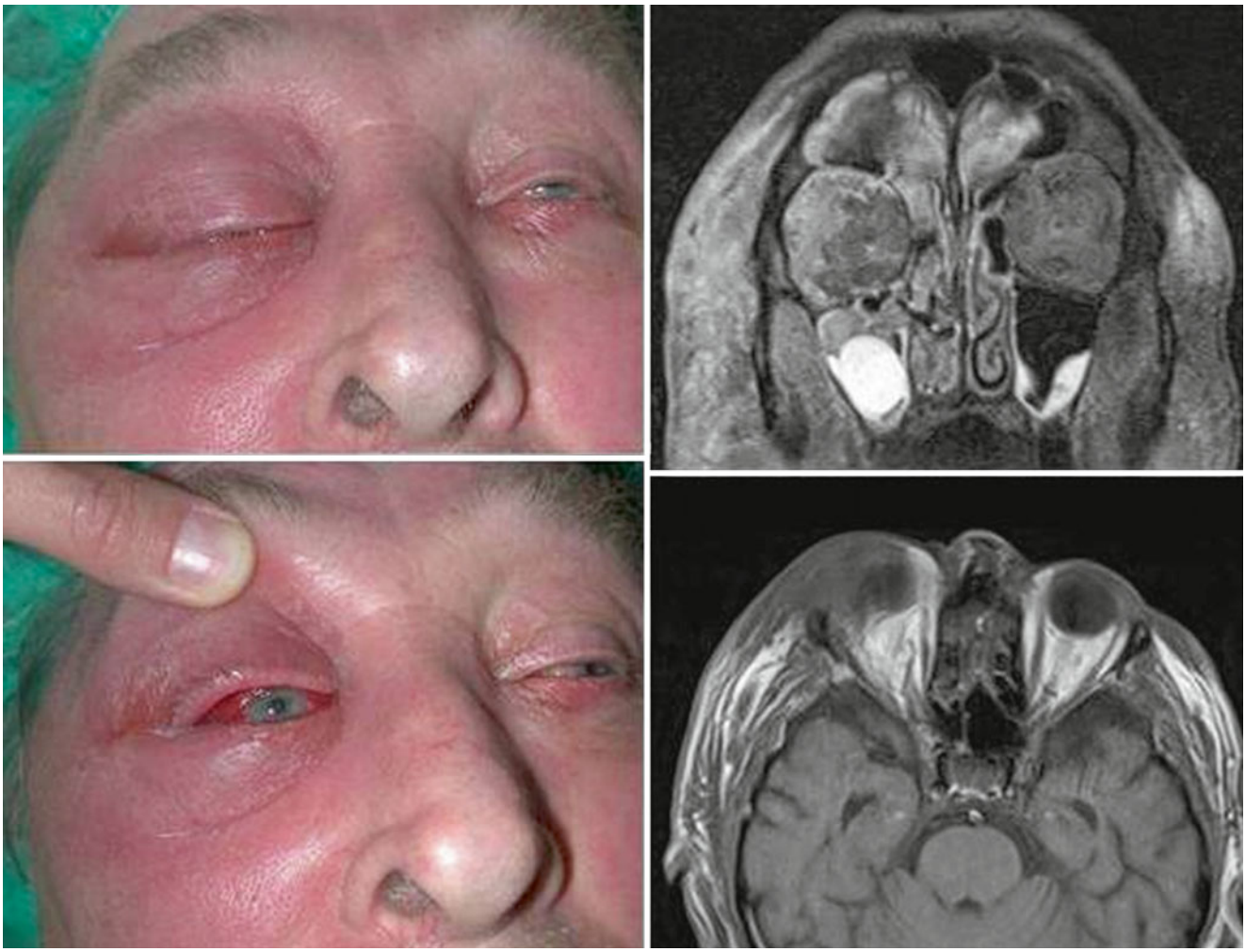


Fig. 27.4 Patient with a fulminant fungal rhinosinusitis involving right orbit (taken preoperatively before an urgent surgical treatment)

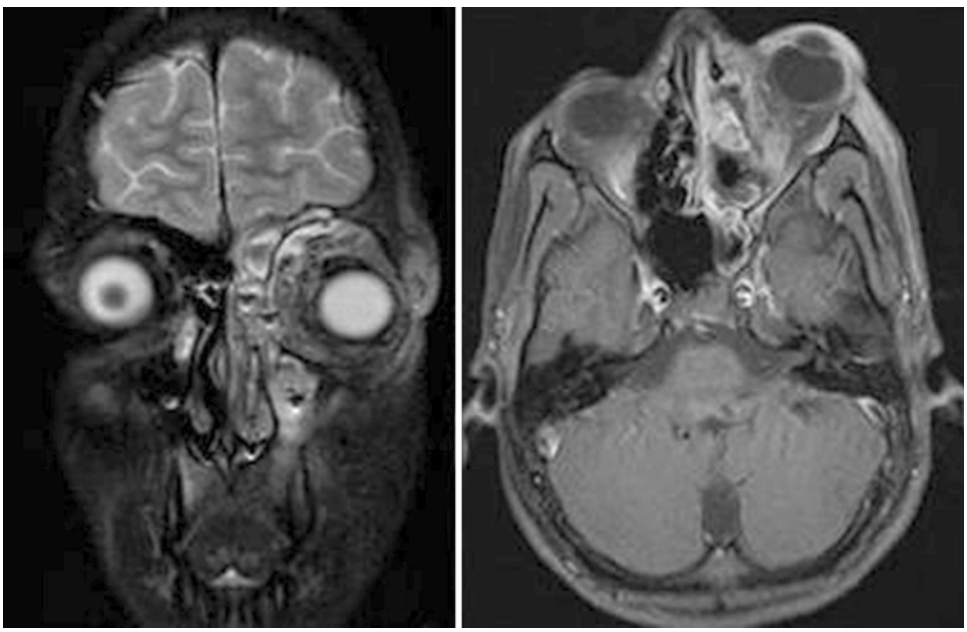


Fig. 27.5 Coronal and axial MRI scans in a patient with orbital complication of acute rhinosinusitis left. Swelling of soft tissue and eye protrusion left – signs of orbital cellulitis. In the medial portion of the orbit is a minor abscess formation

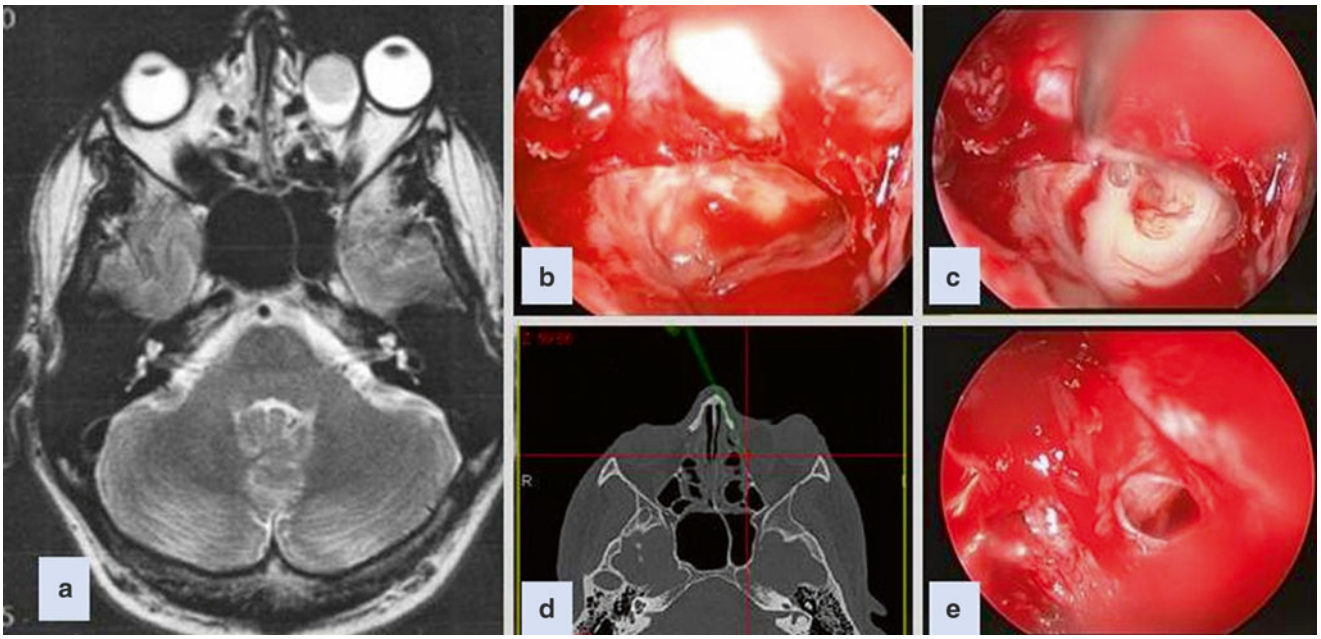


Fig. 27.6 Well-developed periorbital abscess *left side*; (**a**) preoperative MRI with a 'third eyeball' look; (**b**) perioperative lamina papyracea displacement and streaming abscess in the lateral nasal wall; (**c**) endoscopic abscess drainage with a guided instrument inserted in the abscess cavity; (**d**) same procedure upon CT navigation; (**e**) wide opening and empty abscess cavity

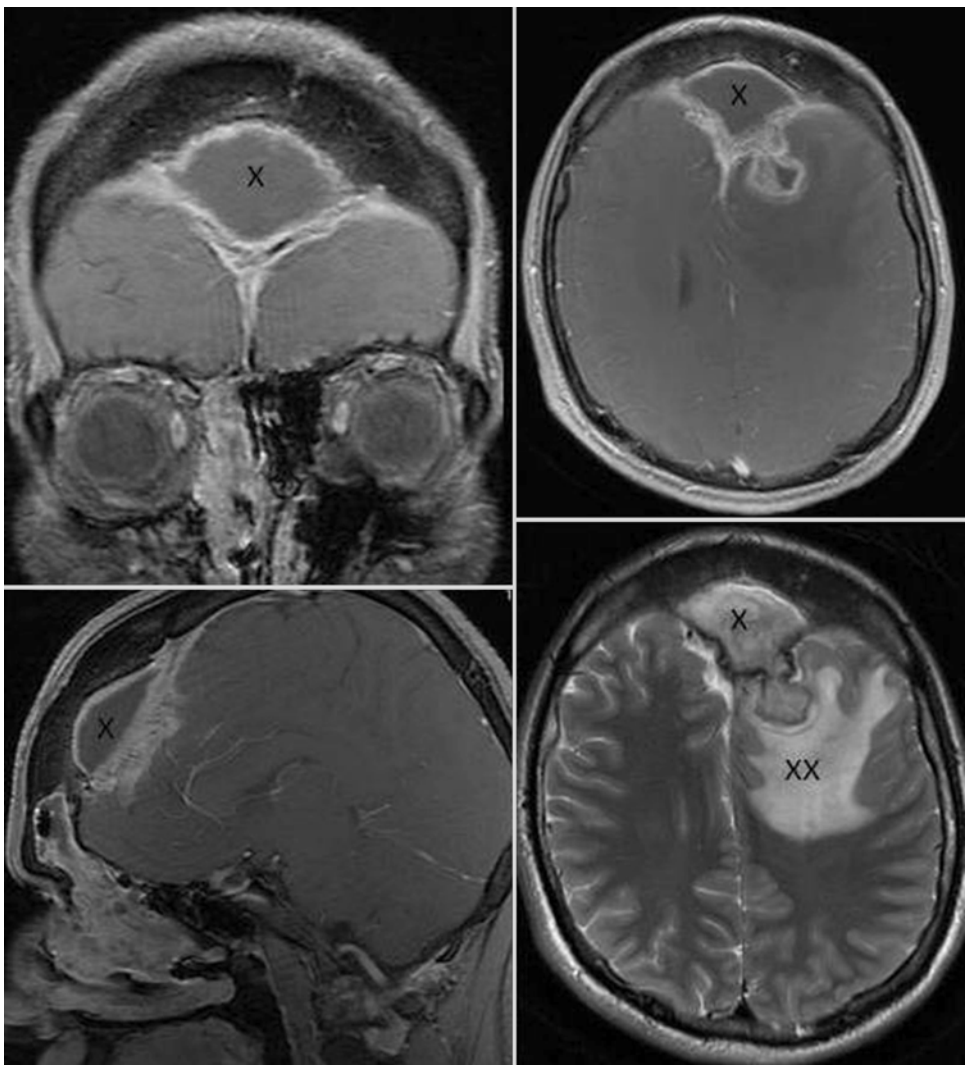


Fig. 27.7 MRI scans of a patient with a rhinosinusitis (frontoethmoidal), epidural empyema (x – marked) and intracranial abscess. Coronal, axial and sagittal T1-weighted (Gd contrast) images; T2-weighted image (*right bottom*) showing significant perifocal oedema (xx – marked) in the left frontal lobe

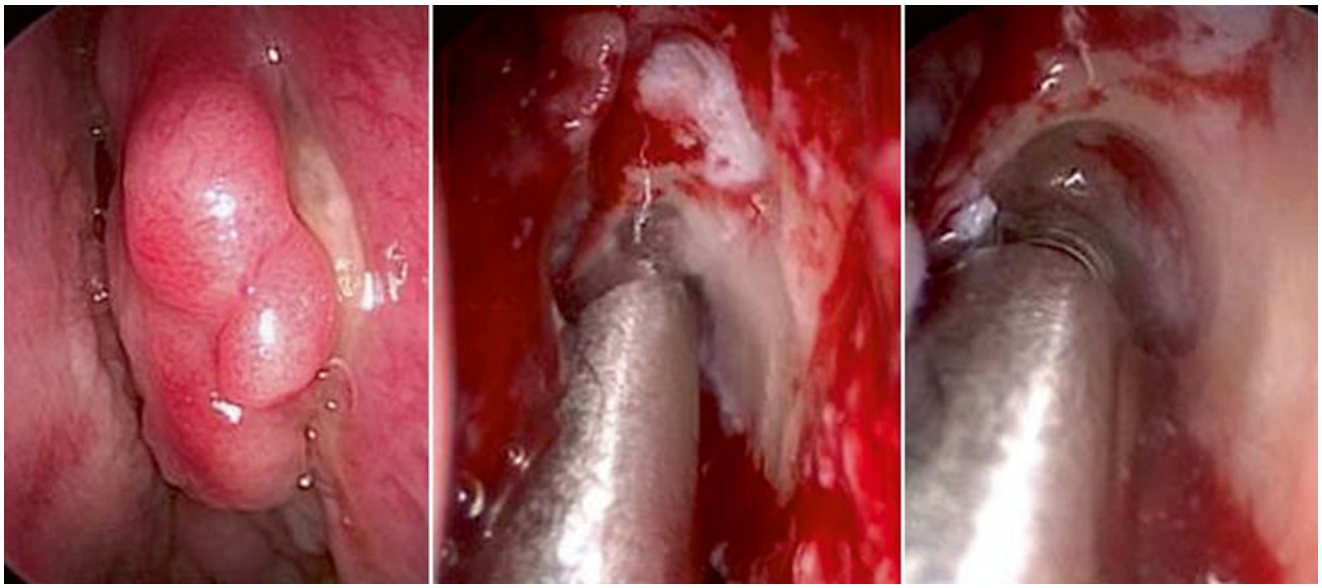


Fig. 27.8 Osteitic bone in chronic rhinosinusitis (polypous formations, viscous pus secretion) and surgical management by drilling out

Epidemiology

Epidemiological data concerning the complications of rhinosinusitis vary widely. There is no consensus on the exact prevalence of the different types of complications listed above. Moreover, the relationship between acute or chronic rhinosinusitis and the various complications is not clearly defined in the literature. This is probably related to the different number and methods of sampling patients in various studies and a lack of consideration for local demographic bias. In general, it appears that about 0.5–3 % of patients with sinusitis will have some form of orbital involvement. These complications are more common in children than in adults. Complicated rhinosinusitis is the most common cause of orbital infection, accounting for 60–84 % of reported cases in the literature [10].

Intracranial complications from acute rhinosinusitis are not infrequent when orbital infection occurs. Clayman suggests that the overall incidence of intracranial complications in patients with complicated rhinosinusitis is about 3.7 % [11]. This incidence has dramatically decreased when compared to the preantiobiotic era. Nevertheless, despite adequate therapy, the incidence of morbidity and mortality is still significant in patients affected by acute bacterial rhinosinusitis with intracranial spread [12].

More recently, data concerning the global prevalence of specific intracranial complications from rhinosinusitis were summarised in EP^{3}OS 2012 and reviewed by Bayonne et al. [13]. These authors found that subdural empyema is the most frequent complication reported (33 % [22–45 %]), followed by brain abscess (27 % [19–35 %]) and meningitis (20 % [15–26 %]). Whereas complete recovery in the literature can be expected in majority of cases (71 % [61–81 %]) with intracranial extension of infection, fatalities still are reported in 6 % (3–9 %) and the mean incidence of adverse sequelae is 23 % [13].

Epidemiological studies describing the incidence of intracranial complications from intraorbital involvement also seem to vary worldwide. Two North American studies by Clayman et al. and Lerner et al. on intracranial complications in rhinosinusitis in a predominantly adult population and some children did not include orbital co-complications [11, 14]. However, 2 out of 24 patients (8.3 %) in Clayman's study suffered from symptoms associated with intracranial complications typical of orbitocellulitis (ophthalmoplegia and decreased visual acuity). Another North American retrospective study that focused on intracranial complications of rhinosinusitis described 3 of 15 patients (20 %) with complicating subperiosteal abscess formation in the orbit [9]. They found that ethmoid sinusitis was the predominant source of intraorbital complications. In a study by Handler, intracranial spread occurred in 6 of 65 (9.3 %) patients with orbital cellulitis [15]. One of the latest North American studies documented only 4 cases of intracranial complications among 74 paediatric patients who were admitted for orbital infection (5.4 %) [16]. Only 1 of 52 patients (1.9 %) with orbital cellulitis/orbital abscess subsequently developed an intracranial complication in a large retrospective study from Australia (meningitis) [17]. In contrast, some studies from Africa and the Middle East have detailed an overall comparatively large number of intraorbital and intracranial complications in rhinosinusitis, probably due to the delayed or reduced availability of antibiotics administered for acute rhinosinusitis. One study from the region of West Africa revealed that orbitocellulitis developed in 47 of 90 (52 %) patients admitted for rhinosinusitis. In 10 of 47 (19 %) suffering from orbitocellulitis, a subsequent intracranial complication developed (cavernous sinus thrombosis, meningitis) [18]. Another study from South Africa subdivided the intraorbital and intracranial complications among 59 patients (children and young adults) presenting with complicating rhinosinusitis. They found intracranial complications

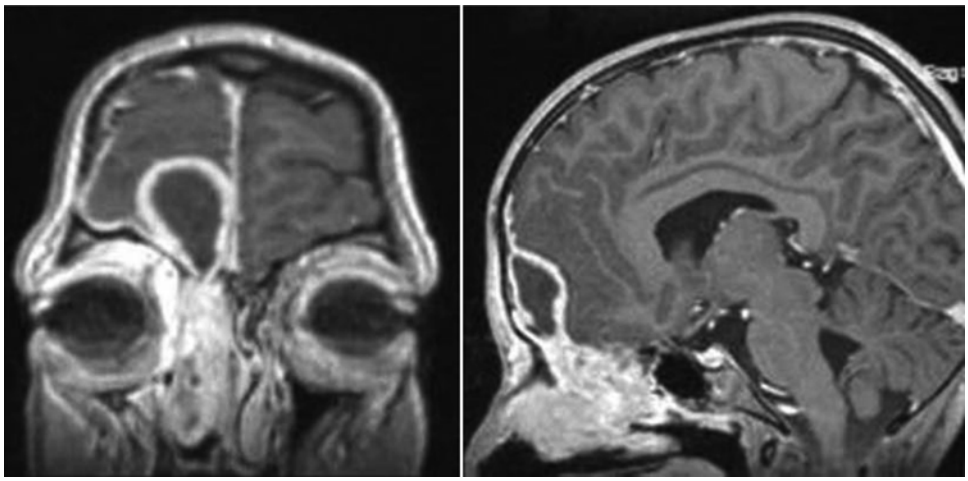


Fig. 27.9 Orbital (orbital cellulitis) and intracranial (epidural empyema) complications of acute frontoethmoidal rhinosinusitis on the right side – coronal and sagittal MRI scans (T1-weighted contrast)

in 36 patients (61 %), intraorbital complications in 13 (22 %), both intracranial and intraorbital complications in 10 patients (17 %) and a mortality of 5 % (3 of 59) [19]. Another large retrospective study looking at rhinogenic intracranial complications in a South African population has shown that despite advances of modern medicine, a relatively high mortality of 16 % (35 from 219 patients) can be seen from intracranial complications; typically highlighted is meningitis followed by brain abscess and subdural empyema [20]. In a study from the Middle East, 9 of 116 patients (8 %) developed an orbital abscess and intracranial complications following rhinosinusitis and trauma [21]. A study from Israel on orbital complications secondary to acute rhinosinusitis in children aged 2 and younger strongly relied on a meticulous multidisciplinary hospital treatment and follow-up. Surgical intervention was avoided in the majority of cases with prompt diagnosis and treatment (only 1 from 52 required surgery) [22]. A German study by Eufinger and Machtens in 2001 described 25 patients with complicated rhinosinusitis who were all treated with early surgical intervention. Of those, 20 (80 %) patients had orbital complications, 3 (12 %) had intracranial complications and 2 (8 %) experienced both orbital and intracranial complications [23].

It appears that no matter what region of the world you are studying, what age group of patients or how you address the numbers, there exists a group of patients with infectious rhinosinusitis who will experience complicating orbital extension of infection. This group of patients with orbital complications of rhinosinusitis provides the predisposing factors for developing intracranial complications [24] (Fig. 27.9).

The precise incidence of any infectious complications from rhinosinusitis in all age groups remains elusive. There are four studies that attempted to collect nationwide or large-scale data on acute rhinosinusitis (ARS) complications. In 2004, Hansen from the Netherlands reported 48 acute rhinosinusitis complications corresponding to an incidence of three per million of population per year or approximately 1 per 12,000 ARS episodes in children and 1 per 36,000 episodes of ARS in adults [25]. Very similar results were reached by a US study which reported an annual incidence of intracranial complications in children between 2.7 and 4.3 per million per year [26]. A French study among 12 million individuals recorded a yearly incidence of 2.5 ARS complications per million of population, excluding paediatric patients [27]. In almost all studies, males are significantly more frequently affected than females [13]. ARS was more often the precipitating factor in children, while CRS with or without NP was more important in adults [7, 28]. In most studies, the most frequent complications were orbital appearing at least twice as often as intracranial complications. Osseous involvement was the least common complication described. While orbital complications tend to occur primarily in small children, intracranial complications can occur in any age, with predilection for the second and third decade of life. The study by Babar-Craig et al. [29] was based on returned questionnaires and had shown that the complications which require surgical treatment are similar in both the prior antibiotic treated group and the no prior antibiotic group, suggesting limited benefit of oral antibiotics in the primary care setting. Prescribing antibiotics for ARS did not appear to prevent the occurrence of infectious complications, merely an early recognition with CT scanning and appropriate hospital management is essential to reduce any subsequent morbidity or mortality. These facts, together with the risk of antibiotic resistance and of masking intracranial complications, argue strongly against the routine use of antibiotics in ARS.

Aetiology

The pathogens causing serious complications are viral, bacterial, fungal and parasitic. In immunocompromised patients, particularly congenital or acquired immunodeficiency and transplant patients, the infection caused by common viruses or fungi may develop into a life-threatening situation. The *viruses* encountered by otolaryngologists and allergists that play a role in neuroinfections are

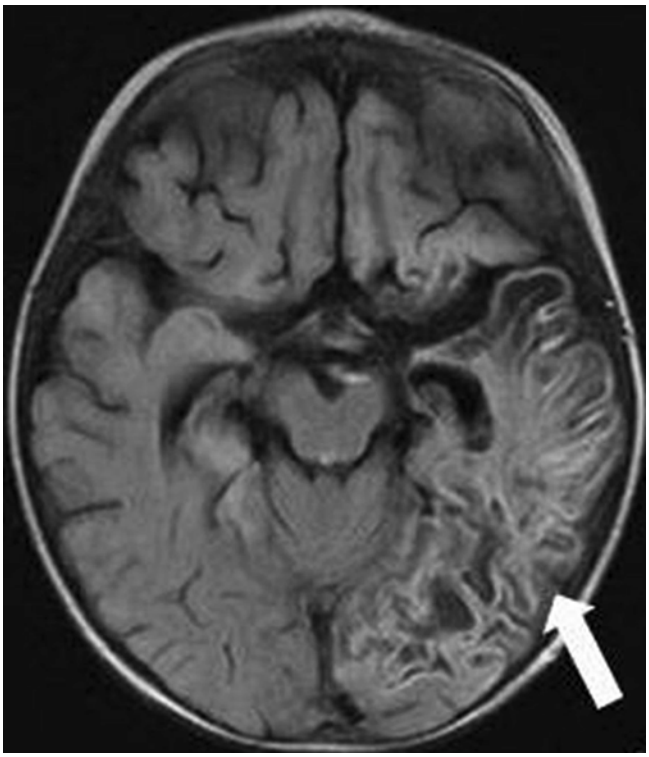


Fig. 27.10 Encephalomalacia (*white arrow*) in a child with intracranial infection caused by herpes simplex virus

herpes simplex virus (HSV 1 and HSV2) [30, 31] and cytomegalovirus (CMV) (Fig. 27.10). Another serious and still incurable viral infection is HIV which weakens the immunity of the affected patient and 'prepares' the host for unusual opportunistic infections such as toxoplasmosis and cryptococcosis and promotes intracranial involvement (AIDS dementia complex) [32]. The most common *bacterial species* isolated from patients with complicated acute rhinosinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, the latter being more common in children. Due to available immunisations since the early 1990s, *H. influenzae* infections are encountered less frequently from a sinusitis-complicated orbital abscess. *Staphylococcus aureus*, diphtheroids and anaerobic bacteria are observed more in situations where chronic rhinosinusitis is the source of intraorbital involvement, particularly if the infection is of odontogenous origin. The association between inappropriate antibiotic consumption and the changing prevalence of antibiotic resistance is widely seen as the source of differing emerging organisms [33].

The role of *anaerobes* is emerging as more cultures in adults now yield these organisms in chronic rhinosinusitis. Generally, adults with chronic rhinosinusitis when cultured surgically grow multiple pathogens including anaerobes in most cases [34]. The complexity of pathogens and responsiveness to antimicrobial therapy appear to be age related [35]. Patients in the first decade of life generally suffer from infections by single aerobic pathogens which are usually responsive to medical therapy alone. As the size of the sinus cavities enlarge, the ostia appear to narrow with increasing age creating optimal conditions for anaerobic bacterial growth. With increasing age, there is a trend towards more complex infections. In mixed infections, aerobes consume oxygen which encourages anaerobic microbial growth [36].

Fungi are normally present in healthy individuals. Fungal rhinosinusitis has been defined as three non-invasive forms (superficial sinonasal mycosis, fungus ball, allergic fungal rhinosinusitis) and two invasive forms (chronic invasive fungal rhinosinusitis, acute/or fulminant/invasive fungal rhinosinusitis) (Fig. 27.11) [37]. Fungal rhinosinusitis is discussed in detail in another chapter in this text. The invasive forms of fungal-induced complications of rhinosinusitis are found particularly in immunocompromised individuals and are the most lethal. Aspergillus is predominantly found as a pathogen of non-invasive and invasive forms too. Mucor is also a fungal pathogen found in the sinuses. Rhinocerebral mucormycosis is a fulminant disease that requires urgent therapeutical management including orbital exenteration and neurosurgical procedures [38].

Pathogenetic Factors

The origin of the orbital extension of infection from the paranasal sinuses occurs most commonly from the ethmoid sinuses followed by the frontal, sphenoid and maxillary sinuses in decreasing order of frequency (Table 27.3). The ethmoid and maxillary sinuses are present at birth and therefore are the exclusive source in younger children. The spread of infection into

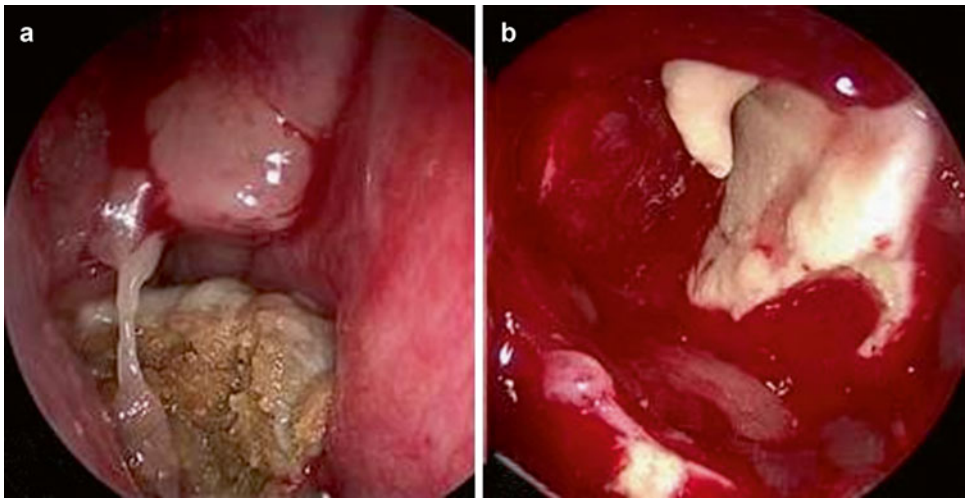


Fig. 27.11 (**a**) Non-invasive fungal rhinosinusitis (fungal ball); (**b**) invasive fungal disease invading orbital floor

Table 27.3 Spread of infection into orbit or intracranially

The proposed mechanism for spread of infectious agents beyond the confines of the paranasal sinuses:
Direct path – natural (e.g. in lamina papyracea) or posttraumatic dehiscences in the bones
Indirect route – via osteitis/osteomyelitis or lacrimal system
Haematogenous spread

the orbit and intracranial space in this age group may follow through venous drainage. The superior ophthalmic vein drains into the cavernous sinus. The inferior ophthalmic vein, however, may drain either into the cavernous sinus through the superior orbital fissure or into the pterygoid plexus through the inferior orbital fissure. Sinus infection can extend via any of these pre-existing routes. Valveless veins interconnect the orbit with sinuses, eyelids and cavernous sinus. Ultimately, fatal complications of intracranial abscess may result from cavernous sinus thrombosis and intracranial rupture of the abscess.

Alternatively, infection from particularly the ethmoid sinuses may spread by eroding the sinus bones. Infection may extend directly through a dehiscence, for example, in the lamina papyracea. Lamina papyracea separates the ethmoidal sinuses from orbital contents. Anterior and posterior ethmoidal foramina serve as additional connections that may allow infection to gain access from ethmoidal air cells to the orbital contents. The periorbita in this area is loosely attached to bone and may be elevated by a purulent collection, resulting in subperiosteal abscess [39].

In orbital cellulitis the irreversible visual loss is accompanied by a vascular pathology most frequently, whereas reversible visual loss in patients responsive to antibiotic therapy and drainage procedures most likely occurs through infiltrative or compressive optic neuropathy. The confinement of the optic nerve in the orbital apex and within the bony canal and its proximity to the posterior ethmoid and sphenoid sinuses underline the importance of the aetiopathogenetic factors in posterior orbital cellulitis [40].

The *mechanism of vision loss* in orbital inflammation involves:

- Inflammatory optic neuropathy – optic neuritis as a reaction to adjacent or nearby infection
- Ischaemic optic neuropathy – ischaemia resulting from thrombophlebitis along the valveless orbital veins
- Compressive optic neuropathy – compressive/pressure ischaemia possibly resulting in central artery occlusion

Acute visual loss may be associated with acute rhinosinusitis either secondary to complicated orbital cellulitis or as a part of the orbital apex syndrome. Slavin and Glaser described three cases of sphenoethmoiditis causing irreversible visual loss associated with minimal signs of orbital inflammation and renamed the entity ‘posterior orbital cellulitis’. They suggested that early severe visual loss may overshadow or precede accompanying inflammatory orbital signs [41]. Acute blindness may also result from an orbital infarction syndrome. Orbital infarction is a disorder that may occur secondary to different mechanisms such as acute perfusion failure (in carotid artery occlusion), systemic vasculitis (giant-cell arteritis) or orbital cellulitis with vasculitis (mucormycosis). The resulting blindness and retinal and optic nerve damage can be permanent [42].

Indirect pathways from which infection can spread from rhinosinusitis into the orbit include the lacrimal duct, sac and gland. Infectious spread to the lacrimal system has been described in acute or chronic rhinosinusitis [43]. Acute dacryocystitis usually induces preseptal infection. In rare instances, the infection that is confined to the lacrimal sac can extend to the orbital contents resulting in orbital cellulitis [44, 45].

As previously noted, *intracranial complications* occur mostly in acute rhinosinusitis and include either phlegmonous inflammation (meningitis, cerebritis), abscess formation (epidural, subdural, intracerebral) and/or cavernous sinus

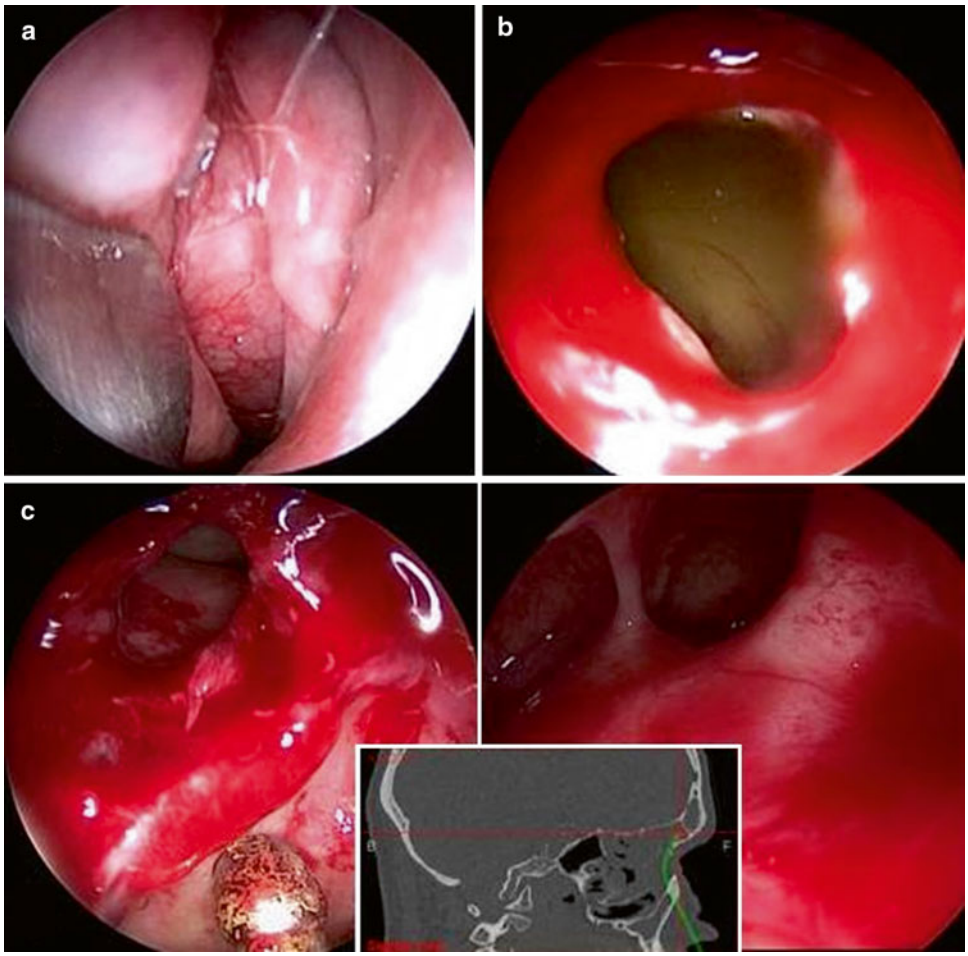


Fig. 27.12 Mucocoele of the frontoethmoidal region on the left side. (**a**) Intact mucocoele formation in the middle nasal passage, (**b**) yellow-green mucous inside the preformed cavity, (**c**) frontal recess (*image left*) and frontal sinus (*image right*) with normal mucosa appearance. *Bottom middle*: CT-guided surgery – suction (*green*) inserted in the frontal recess perioperatively

thrombosis. Frontal posterior ethmoid/sphenoid and maxillary sinuses are the most common sources of intracranial complications of chronic rhinosinusitis [11]. The pathway of infectious spread can be indirect such as in frontal bone osteomyelitis or through the orbit or haematogenous. Overall, the haematoencephalic barrier is generally felt to be less commonly the route of orbital complications in previously healthy individuals. However, the predominance of intracranial complications in patients during the second and third decades of life is thought to be associated with a peak in the vascularity of the bony diploic system, particularly the frontal sinus. The predominant location of complicated rhinosinusitis is the frontoethmoidal region [46]. Understandably, this implies that retrograde septic thrombophlebitis may be the most likely route of infection spreading beyond the sinus confines. Haematogenous spread would imply that some atypical locations of the intracranial abscess might be found but that has not proven to be the case. Overall, most researchers feel that the direct or haematogenous route of infection spreading is less common than direct pathways as the primary route of infectious spread of complicating rhinosinusitis. Rarely, viruses may enter the brain from the nasal cavity primarily via the olfactory bulb [47–49]. Infection can result in rapid, transneuronal spread to connected areas of the brain.

Direct spread of infection intracranially is very rare in rhinosinusitis unless there is:

- Predisposed dehiscence (posttraumatic, CSF leak)
- Immunocompromised patient (congenital, acquired including transplant patients)
- Aggressive infectious agent (e.g. mucormycosis)

Mucocoeles may also play role in spreading infections from the sinuses to the orbit especially in the frontoethmoidal region by eroding through the lamina papyracea (Fig. 27.12). Mucocoeles are mostly sterile but may lead to bone erosion with eye globe deviation or protrusion. The posterior wall of the frontal sinus may become diminished as well. When a mucocoele is infected, a direct pathway for the spread of infection into the orbit or intracranially is created. One of the main sources of mucocoele development is previous frontoethmoidal surgery. This is most commonly associated with external procedures and inappropriate frontal sinus obliteration. Mucocoeles can also result from functional endoscopic sinus surgery (FESS), particularly in the frontal recess, where in anterior ethmoidectomy and frontal recess

management of a blockage of frontal recess is performed instead of an adequate frontal sinusotomy (Fig. 27.12) or drainage (Stammberger's uncapping the egg, Wormald's axillary flap technique, Draf I–III procedures or modified procedures) [50–52].

FESS procedures for recurrent acute or chronic rhinosinusitis can be directly responsible for orbital and intracranial complications as a surgical mishap and are discussed elsewhere in this text. FESS itself produces a significant portion of orbital and intracranial complications by iatrogenic damage of borders between the nasal/paranasal cavities and orbit or brain (Table 27.2) [53–59].

Diagnostics: Symptoms, Clinical Examination and Imaging Methods

Patients suspected or at risk for serious and possibly life-threatening orbital or intracranial complication must be admitted to the hospital. In the initial diagnostic evaluation, a careful medical history should be done. Special attention is given to specific clinical conditions such as congenital or acquired immunodeficiency, upper and lower airway comorbidity (severity of sinus disease – asthma, allergy, unmet needs in severe chronic upper airway disease (SCUAD)), previous surgery or head trauma (dehiscences of natural barriers) and ancillary orbital and intracranial disease history.

Blood tests (blood count, C-reactive protein and other inflammatory markers, serology) are fundamental to assessing the severity of the inflammatory process. In case of normal findings but clinical deterioration, be aware of the risk of viral or fungal disease, and the pathogens might require serology methods. The beta-trace protein test is essential in patients who underwent FESS and present with meningitis [59]. Culture methods help to detect the infectious agents and are recommended if the swab is taken directly from the pus intranasally under direct or endoscopic visualisation but have serious limitations [60]. Unfortunately, microbiologic identification of an infectious origin can take 48 h and, in many cases, can be negative due to antibiotic pretreatment or culture failure. A lumbar puncture, though contraindicated if intracranial pressure is elevated, can also be useful, if meningitis is suspected once an intracranial abscess has been excluded [9]. PCR probes or other immunologic assays are being developed to more quickly identify an infectious pathogen [61, 62].

Symptoms and Clinical Examination

Symptoms of an orbital and/or intracranial complication of rhinosinusitis generally include periorbital oedema or erythema, displaced globe, double vision, ophthalmoplegia, reduced vision acuity, severe unilateral or bilateral frontal headache, frontal swelling, signs of meningitis or other neurological signs [63–66]. Visual acuity testing, pupillary reactivity and ocular motility assessment are helpful in postseptal inflammatory assessment. Since blindness can occur without any fundoscopic abnormalities, it is crucial to monitor visual acuity at frequent intervals. Cavernous sinus thrombosis represents the most severe form of postseptal cellulitis and is suspected clinically by bilateral disease with ophthalmoplegia and loss of vision. Signs of intracranial involvement are soft tissue oedema (especially of the superior lid), high fever, severe headache, meningeal irritation, nausea and vomiting, diplopia, photophobia, papilloedema, coma and focal neurological signs.

The classic neurological presentation of intracranial abscess seen in adults is often subtle and symptoms can be minimal or absent in children. Neurological signs of meningitis associated with intracranial abscess may simply alter mental status. Ocular signs can appear contralaterally. Alternatively, a patient with intracranial abscess may be asymptomatic or present with nausea, vomiting or seizures.

The essential and imperative diagnostic procedure in rhinosinusitis is *nasal endoscopy* using rigid or flexible endoscopes. It is easy to perform with or without (to assess the natural appearance of nasal mucosa and better swab collection) anaesthesia. In experienced hands, the investigation is easy and fast (last less than one minute in most cases). The preferred diagnostic endoscopy in children is a thin flexible endoscope, which enables the operator to assess the whole upper airways including the adenoids and larynx (Fig. 27.1). Technical advancement in diagnostic endoscopy may help not only to define the presence of rhinosinusitis but to determine the different underlying processes better (Fig. 27.13). Mucosal congestion, hyperaemia, nasal polyps or pus may be evident on direct endoscopic examination (Fig. 27.14). Finding a black eschar (typical for Mucor in acute invasive fungal rhinosinusitis) is a pathognomonic endoscopic finding intranasally of a fungal infection (Fig. 27.11).

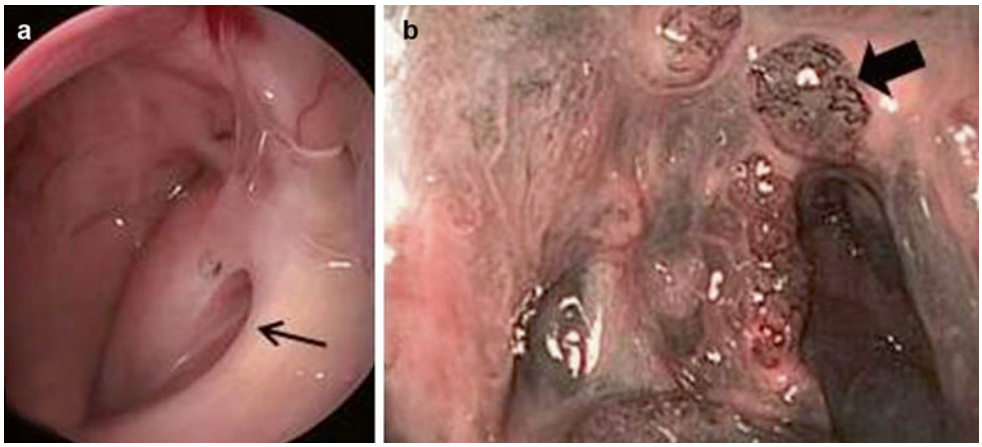


Fig. 27.13 New trends in diagnostic nasal endoscopy: (**a**) HD image of nasopharynx (*left side*) and Eustachian tube opening (*arrow*), (**b**) narrow band imaging (NBI) endoscopy and suspicious tumour recurrence (*thick arrow*) – irregularity of microvascularization

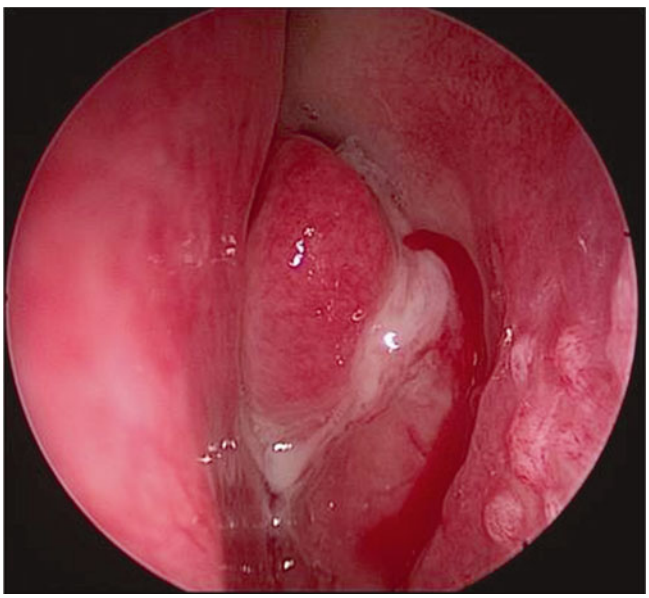


Fig. 27.14 Acute rhinosinusitis – image of the left nasal cavity with oedema, mucosal congestion and pus beneath the middle turbinate

Diagnostic Imaging

The diagnostic value of plain sinus radiographs is limited by poor sensitivity and specificity. The Waters' view may demonstrate fluid accumulation in the maxillary sinus or asymmetrical maxillary opacification. However, this radiographic study is not recommended as a diagnostic aide for either acute or much less in chronic rhinosinusitis. Ultrasound also has limited diagnostic value. However, the results in well-trained hands are comparable to plain X-ray in the diagnostics. Some physicians prefer ultrasound in an effort to avoid X-ray exposure in children (Figs. 27.15 and 27.16).

Computerised tomography scanning is the imaging modality of choice since it is capable both of confirming the extent of pathology and describing the anatomy. Sinus disease and intracranial complications are mostly evident on CT scan [34]. Together with MRI, the CT is the only diagnostic imaging tool indicated if a complication of rhinosinusitis is supposed [2, 3, 56]. CT scans projection/reconstruction in all three axis (coronary, axial, sagittal) is advocated since up to one-third of orbital abscesses might be missed if only one projection (axial or coronary) is performed [67]. Since the development of an orbital abscess does not correlate specifically with visual acuity, proptosis, chemosis or any other sign, a CT scan emerges as the essential screening diagnostic tool. Contrast media can enhance the surrounding wall of an abscess and should be requested if suspected. Furthermore, a CT can differentiate between preseptal and postseptal orbital cellulitis (effusion of the pre- and postseptal orbital soft tissue components).

If there appear to be coexisting orbital and intracranial complications in rhinosinusitis, an MRI is ultimately the best diagnostic imaging method [24, 49, 68]. T1- and T2-weighted sequences of magnetic resonance imaging can be used

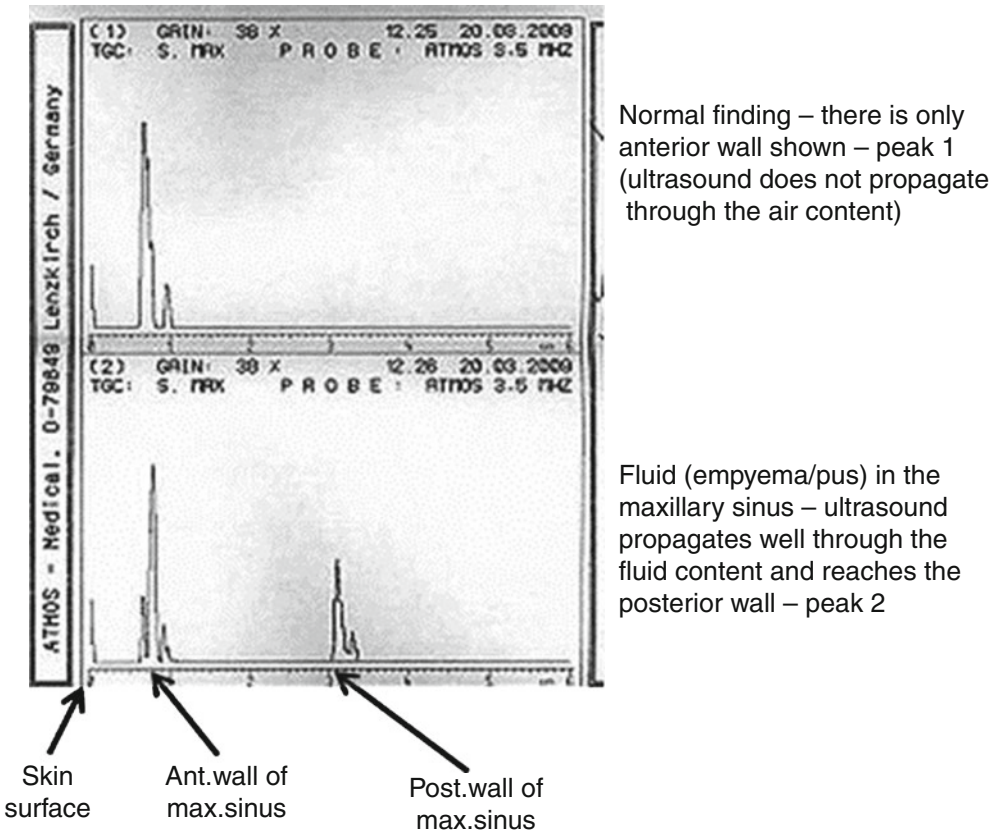


Fig. 27.15 Maxillary sinuses ultrasonography (A mode)

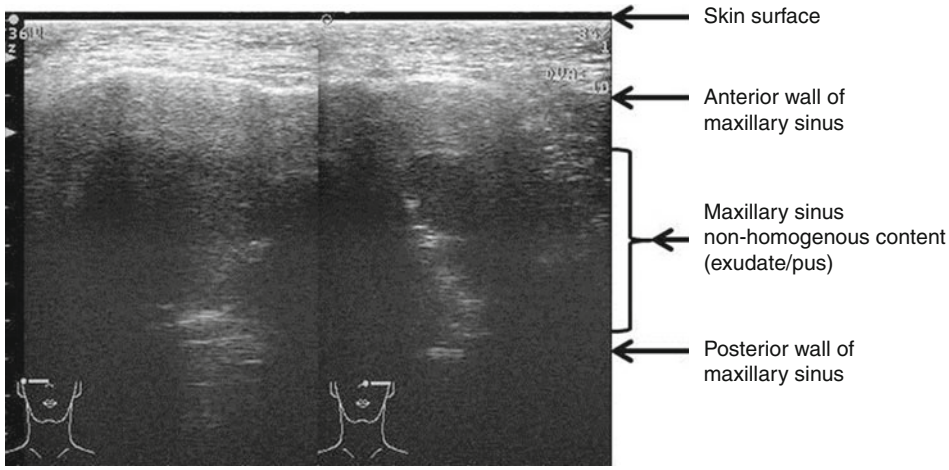


Fig. 27.16 Maxillary sinuses ultrasonography (B mode)

to provide different imaging information. On a T2-weighted scan, water- and fluid-containing tissues are bright and fat-containing tissues are dark. The reverse is true for T1-weighted images. Damaged tissue tends to develop oedema, which makes a T2-weighted sequence very sensitive for tissue pathology. To accentuate signal difference of pathological and normal tissue, the paramagnetic contrast medium (gadolinium) is used. Both the rim of intracranial abscess and subdural empyema almost always enhance after contrast media application. The ependyma of ventricles also enhances after contrast media application in cases of infection within the cerebral ventricles. Diffusion-weighted imaging (DWI) studies are of utmost importance in cases of intracranial infection in that fat suppression (in T-1w) can be used for visualising the intracranial component in suspected cases of meningeal inflammatory lesions [69]. DWI improves diagnostic confidence in nearly all cases of orbital abscess when used in conjunction with contrast-enhanced imaging. DWI also confirms abscess in a majority of cases without contrast-enhanced imaging, which may be of particular use when contrast material is contraindicated. The use of DWI in all cases of orbital abscess is recommended [70].

Despite its utility, only few published studies have stressed the role of MRI in early detection of intracranial complications [16]. Additionally some authors propose performing an additional CT of the brain or MRI in patients admitted with orbital complications of rhinosinusitis despite negative findings on the initial CT of the orbit and paranasal sinuses. Due to the different settings of CT of the orbit and CT of the brain, it is sometimes impossible to detect interhemispheric subdural empyema in an atypical location. At the present time, the vast majority of diagnostic guidelines on orbital and intracranial complications of rhinosinusitis strongly rely on initial CT scanning, while the study by Herrmann and several case reports emphasised adjuvant MRI scanning due to the presence of some false-negative results of CT scans in patients who were subsequently found to have intracranial abscess [16, 49, 63]. MRI is definitely advisable in patients with positive symptomatology or indefinite CT findings. Taking into consideration how fatal the delayed treatment of complicated rhinosinusitis might develop, we feel that performing an additional entrance MRI at the time of admission is the most prudent approach. Carefully performed imaging methods are not only mandatory in making the proper diagnosis of spread of infection beyond the confines of the paranasal sinuses, they are also very helpful in any planning of a surgical procedure and for image-guided surgery [71, 72].

Therapy

Conservative Treatment

Intravenous antibiotics are usually started once the diagnosis of orbital cellulitis is suspected. Broad-spectrum antibiotics that cover most gram-positive and gram-negative bacteria as monotherapy or combined treatment should be selected. The possibility of anaerobic bacteria involvement should be also taken into consideration, especially in older patients. MRSA and other multidrug-resistant bacteria (*E. coli*, *Enterobacter*, *Klebsiella*) are the novel serious problems of modern infectious medicine [73]. If the patient is immunocompromised, parenteral antiviral and antimycotic therapy must be considered early in the treatment course. Standard treatment does not involve corticosteroids. These are administered only if the patient may benefit from reducing intracranial or intraorbital oedema.

Surgery

Surgical procedures are indicated in order to manage predisposing disease and to accomplish orbital or intracranial abscess drainage. Successful surgical management includes a multidisciplinary experienced team comprised of an ENT surgeon (rhinosurgeon), oculoplastics surgeon, neurosurgeon and infectious disease expert. The preferred surgical approach in complicated rhinosinusitis with or without nasal polyposis, which is resistant to conservative therapy, is FESS [2, 3, 50]. FESS is an ideal approach to drain the underlying sinus inflammation in orbital and intracranial complications of rhinosinusitis (Figs. 27.6, 27.8, 27.12, 27.17 and 27.18). Advanced FESS also enables the surgeon to manage complicated processes (esp. in frontal sinus) where osteitis has occurred (Fig. 27.8). Many intraorbital complications from sinus disease can be managed endoscopically through the nose also. Moreover, endoscopic skull base surgery (and transnasal intracranial surgery) is an emerging discipline where the ENT surgeon and neurosurgeon cooperate in surgical management [51, 52, 54, 55]. Most importantly, delayed surgical intervention commonly leads to a higher frequency of further complications, higher adverse sequelae and, most importantly, a higher risk of mortality [3, 9, 34]. Despite the advent of modern diagnostic and therapeutical possibilities, the morbidity and mortality rate of complicated rhinosinusitis still remains relatively high. Early diagnosis together with combined medical and surgical therapy, inclusive of neurosurgical procedures, plays a crucial role (Table 27.4).

Neurosurgical Procedures

In case of *solitary abscess* and no obvious communication between paranasal and intracranial compartments, a frameless *stereotactic puncture and aspiration* is indicated. First, navigation CT or MRI data are acquired. The best puncture trajectory is defined by the shortest one, the one which is not entering the ventricles and not crossing any major arteries or veins or eloquent brain areas. The head of the patient is fixed in head holder under general anaesthesia. Navigation is registered. The burr hole is performed and the abscess is punctured according to the selected trajectory. Increased resistance is usually observed at the level of abscess wall during puncture. Afterwards, the pus is going out of the drain. Material for bacterial testing is taken for both aerobic and anaerobic pathogens. A drain is left in the abscess cavity for further drainage. The drain

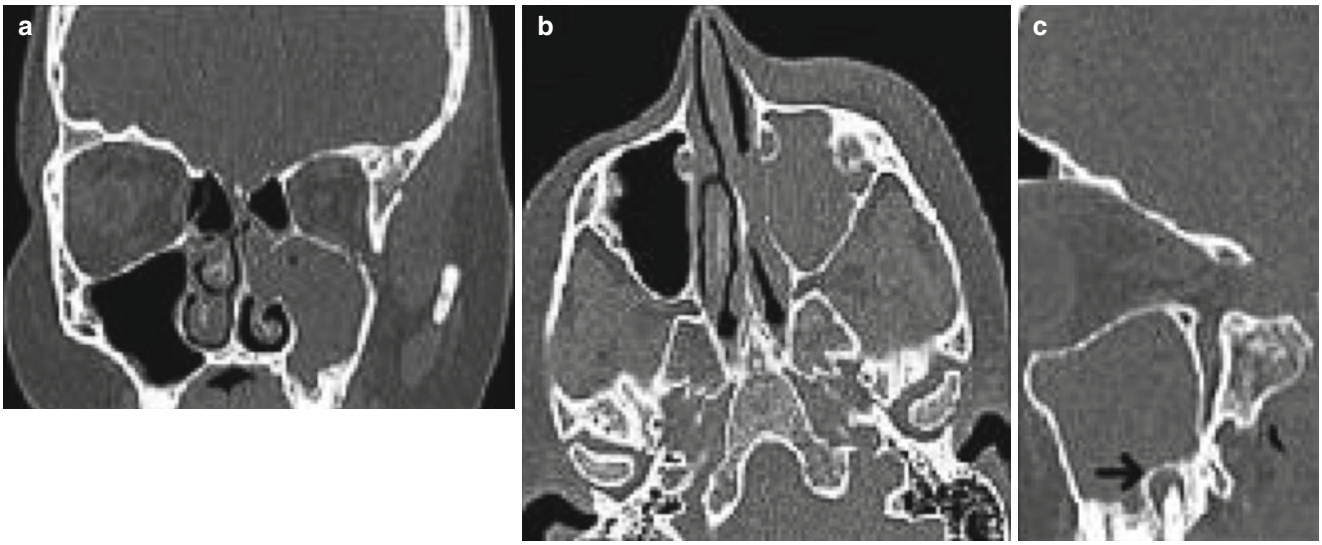


Fig. 27.17 (**a**) Coronal, (**b**) axial and (**c**) sagittal CT scans in a patient with left-sided odontogenous (*black arrow*) complicated acute rhinosinusitis

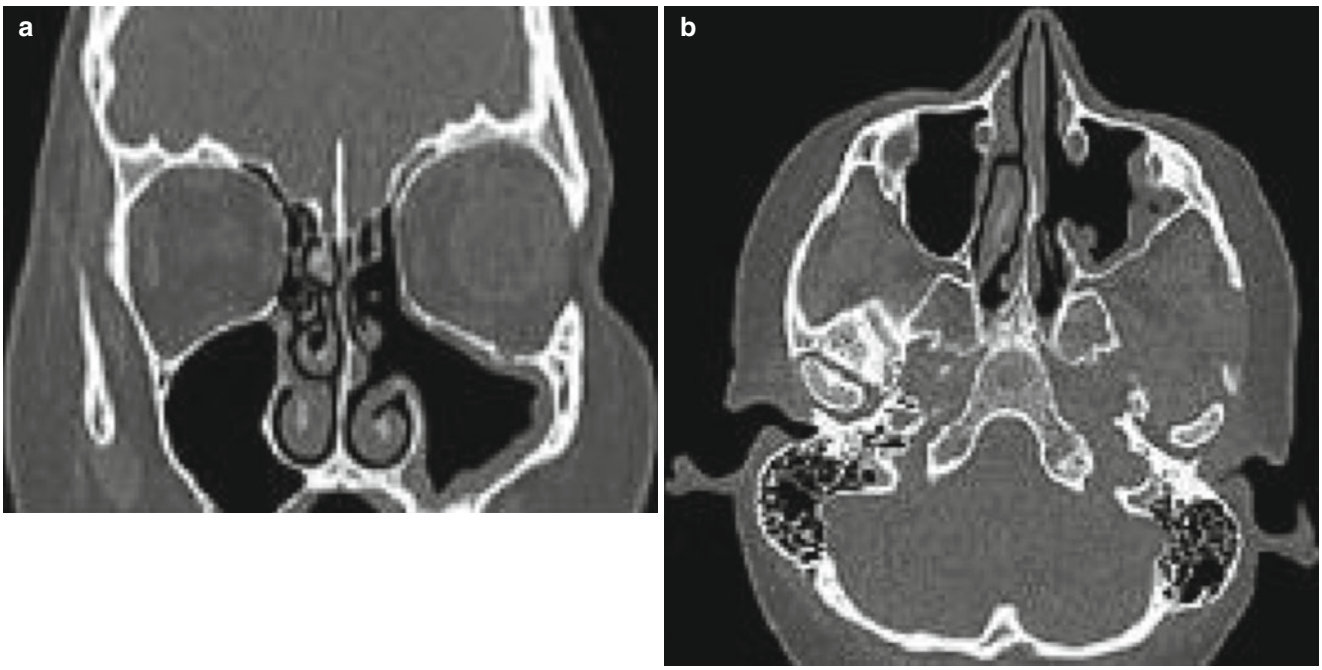


Fig. 27.18 (**a**) Coronal and (**b**) axial CT scans 3 weeks postoperatively documenting the post-endoscopic sinus surgery result – wide maxillary sinus supraturbinal opening and diminished pathology contents

Table 27.4 Surgical intervention in orbital complications

Indications for *surgical intervention in orbital complications* are:
Evidence of subperiosteal or intraorbital abscess in CT or MRI
Reduced visual acuity, reduced colour vision, affected afferent pupillary reflex or inability to assess vision
Progressing or not improving orbital signs (diplopia, ophthalmoplegia, proptosis, swelling, chemosis) after 48 h of parenteral antibiotics
Progressing or not improving general condition (fever, infection parameters) after 48 h of parenteral antibiotics

Based on data from Ref. [3]

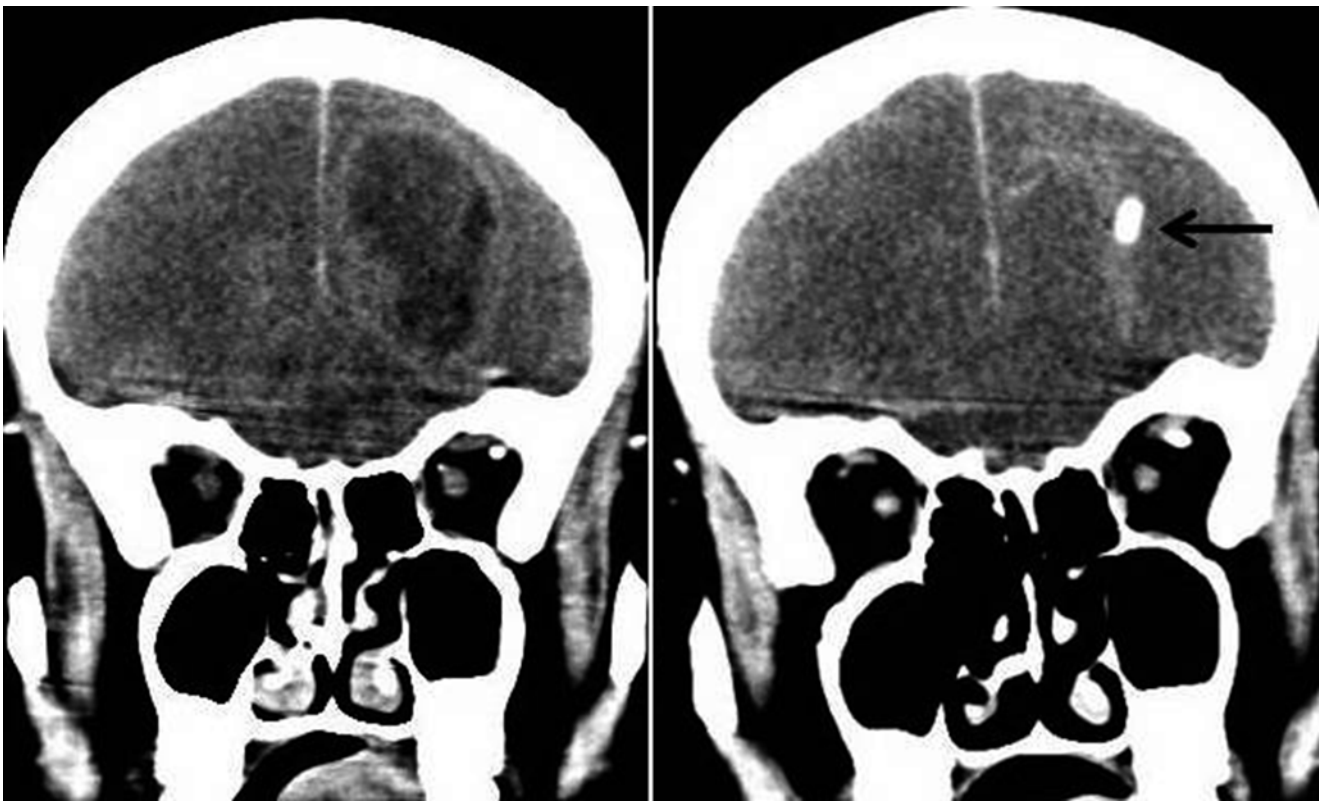


Fig. 27.19 Solitary intracerebral abscess formation before (*image left*) and after stereotactic puncture and aspiration with drain remaining (*black arrow*) and complete resolution

is removed if follow-up MRI or CT shows complete resolution of pus from the abscess cavity (Fig. 27.19). Antibiotics are given according to the bacteriologic outcome from samples taken from abscess.

In the case of a *subdural empyema with or without intracranial abscess* and no obvious communication between paranasal and intracranial compartments, the procedure is the same as mentioned above with the addition of drainage of subdural empyema.

Epidural abscess or subdural empyema with or without intracranial abscess and communication between paranasal and intracranial compartments has a more complex approach. It is important to close the communication between paranasal and intracranial compartment. In such a case, it is recommended performing a *combined procedure* involving both the ENT and neurosurgeon working together. The ENT surgeon performs the endonasal approach for drainage of the infection and sealing of the communication from below. The neurosurgeon typically performs bifrontal craniotomy, evacuates the epidural abscess/subdural empyema and drains the intracranial abscess if present. Frontal sinuses are cranialised. An anterior skull base reconstruction is performed. The use of non-artificial materials (e.g. pericranial flap, own fat tissue, fascia lata, etc.) in cases of an infectious process is preferred to seal the communication from above.

An abscess resection is rarely performed and only in case of recurrent abscess appearance unresponsive to repeated puncture/drainage and antibiotic treatment.

Conclusion

Orbital and intracranial complications of acute or chronic rhinosinusitis are potentially very serious clinical events. Orbital and intracranial complications of acute or chronic rhinosinusitis are more common in the presence of very aggressive infectious agents and/or in immunocompromised patients. In previously healthy patients with acute or chronic rhinosinusitis, orbital and intracranial complications are generally uncommon but must not be excluded.

Orbital complications include preseptal cellulitis, orbital cellulitis, subperiosteal and intraorbital abscess. Intracranial complications of acute or chronic rhinosinusitis include epidural or subdural abscesses, brain abscess, meningitis, encephalitis and superior sagittal and cavernous sinus thrombosis.

EP^{3}OS 2012 stated in the position paper that orbital and intracranial complications of acute or chronic rhinosinusitis may present with nonspecific signs and symptoms, and their diagnosis requires a high index of suspicion [3]. Prompt recognition and management is vital in order to avoid long-term sequelae. Symptomatology of rhinosinusitis complications may vary in the course of disease but should be suspected whenever periorbital oedema, displaced bulb, double or reduced vision, ophthalmoplegia (orbital), severe frontal headache, frontal swelling, signs of meningitis and/or focal neurological signs or systemic signs (intracranial) occur. Whenever any of these signs or symptoms appears, one must be aware of the risk factors and perform urgent investigations and intervention.

Diagnostic endoscopy of the nose and upper airway tract using a flexible endoscope should be an initial diagnostic procedure in suspected complicating cases, particularly in children. This is followed by imaging studies (CT and/or MRI) and should always be performed if a complication is suspected. Plain sinus radiographs or ultrasound are not useful in this clinical circumstance. Furthermore, CT and MRI studies are mandatory in patients when coexisting orbital and intracranial complications from rhinosinusitis are suspected, or when there is a clinical setting that predisposes to the development of intracranial complications. The examining physician must remember that prior treatment measures may mask these predisposing factors. In general, if one of the complications appears, the others must be carefully excluded. Performing an MRI when an orbital complication has occurred following rhinosinusitis despite a negative CT scan of the brain, orbit and paranasal sinuses is suggested (if not contraindicated due to pacemaker).

A multidisciplinary approach is required in orbital or intracranial abscess formation. Management of complications has been well established (Fig. 27.20). These consist of conservative measures (i.e. in-house treatment, parenteral broad-spectrum antibiotics) and surgical drainage of abscesses (or puncture in intracerebral abscess). Endoscopic surgery is preferred over the external approach in surgical drainage of predisposing rhinosinusitis. On the other hand, one must be aware of iatrogenic complications of FESS in rhinosinusitis patients who have had a previous number of

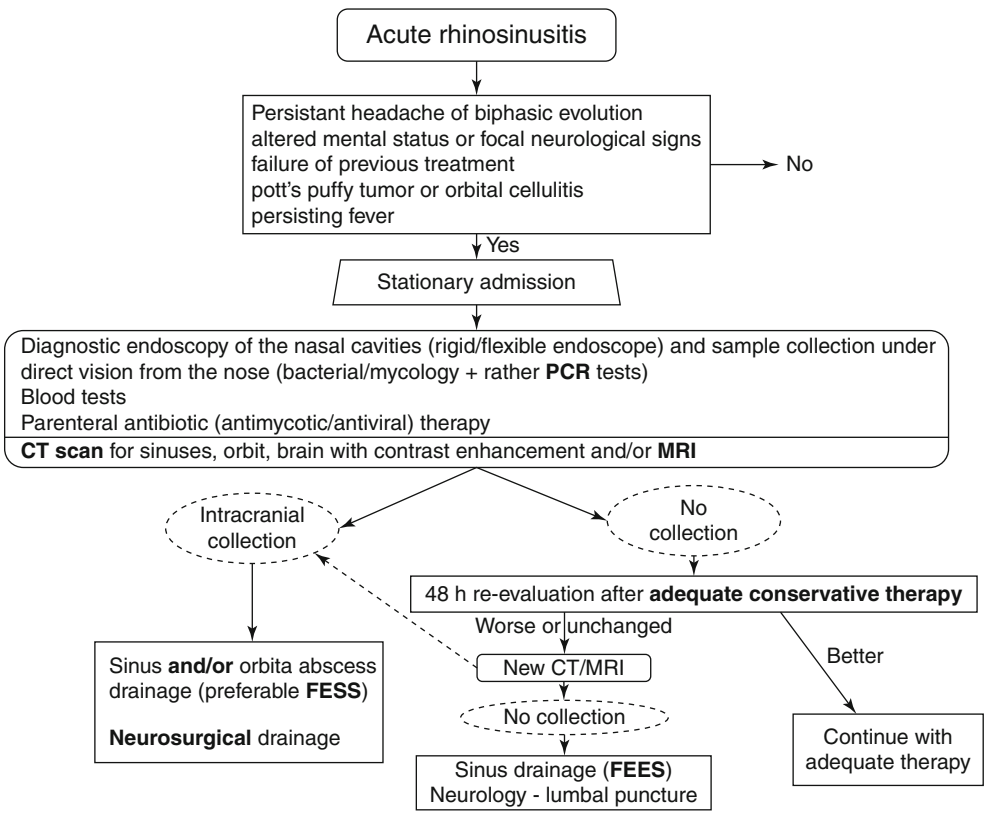


Fig. 27.20 Algorithm of acute rhinosinusitis intracranial complication management according to Bayonne ([13] modified)

FESS procedures for rhinosinusitis or endoscopic transnasal procedures for tumour management of the nose, orbit and skull base.

Complications of rhinosinusitis can give rise to serious morbidity and mortality. Any residual optical and neurological symptoms often result in a significant reduction in the quality of life for a previously healthy individual. Early diagnosis and proper treatment of the underlying inflammatory process as well as aggressive management of complications are crucial.

References

1. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg. 2003;129(3 Suppl):S1–32.
2. Fokkens W, Lund V, Mullol J, European Position Paper on Rhinosinusitis and Nasal Polyps group. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl. 2007;20:1–136.
3. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaerts P, Georgalas C, Goossens H, Harvey R, Hellings P,Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang DY,Wormald PJ. The European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;23:1–298.
4. Hubert L. Orbital infections due to nasal sinusitis. NY State J Med. 1937;37:1559–64.
5. Chandler JC, Lagenbrunner DL, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. Laryngoscope. 1970;80:1414–8.
6. Moloney JR, Badham NJ, McRae A. The acute orbit, preseptal cellulitis, subperiosteal abscess and orbital cellulitis due sinusitis. J Laryngol Otol. 1987;101 Suppl 12:1–18.
7. Mortimore S, Wormald PJ. The Groote Schuur hospital classification of the orbital complications of sinusitis. J Laryngol Otol. 1997;111:719–23.
8. Velasco e Cruz AA, Demarco RC, Valera PC, dos Santos AC, Anselmo-Lima WT, Marquezini RM. Orbital complications of acute rhinosinusitis: a new classification. Rev Bras Otorrinolaringol. 2007;73:684–8.
9. Gallagher RM, Gross CW, Phillips CD. Suppurative intracranial complications of sinusitis. Laryngoscope. 1998;108:1635–42.
10. Osguthorpe J, Hochman M. Inflammatory sinus diseases affecting the orbit. Otolaryngol Clin North Am. 1993;26:657–71.
11. Clayman GL, Adams GL, Paugh DR, Koopmann Jr CF. Intracranial complications of paranasal sinusitis: a combined institutional review. Laryngoscope. 1991;101:234–9.
12. Giannoni CM, Stewart MG, Alford EL. Intracranial complications of sinusitis. Laryngoscope. 1997;7:863–7.
13. Bayonne E, Kania R, Tran P, Huy B, Herman P. Intracranial complications of rhinosinusitis. A review, typical imaging data and algorithm of management. Rhinology. 2009;47:59–65.
14. Lerner DN, Choi SS, Zalzal GH, Johnson DL. Intracranial complications of sinusitis in childhood. Ann Otol Rhinol Laryngol. 1995;104:288–93.
15. Handler LC, Davey IC, Hill JC, Lauryssen C. The acute orbit: differentiation of orbital cellulitis from subperiosteal abscess by computerized tomography. Neuroradiology. 1991;33:15–8.
16. Herrmann BW, Forsen JW. Simultaneous intracranial and orbital complications of acute rhinosinusitis in children. Int J Pediatr Otorhinolaryngol. 2004;68:619–25.
17. Ferguson MP, McNab AA. Current treatment and outcome in orbital cellulitis. Aust N Z J Ophthalmol. 1999;27:375–9.
18. Nwaorgu OGB, Awobem JF, Onakoya PA, Awobem AA. Orbital cellulitis complicating sinusitis: a 15-year review. Niger J Surg Res. 2004;6:14–6.
19. Tshifularo M, Monama GM. Complications of inflammatory sinusitis in children: institutional review. SA Fam Pract. 2006;48:16.
20. Singh B, Van Dellen J, Ramjettan S, Maharaj TJ. Sinogenic intracranial complications. J Laryngol Otol. 1995;109:945–50.
21. Chaudhry IA, Shamsi FA, Elzaridi E, Al-Rashed W, Al-Amri A, Al-Anezi F, Arat YO, Holck DE. Outcome of treated orbital cellulitis in a tertiary eye care center in the middle East. Ophthalmology. 2007;114:345–54.
22. Eviatar E, Gavriel H, Pitaro K, Vaiman M, Goldman M, Kessler A. Conservative treatment in rhinosinusitis orbital complications in children aged 2 years and younger. Rhinology. 2008;46:334–7.
23. Eufinger H, Machtens E. Purulent pansinusitis, orbital cellulitis and rhinogenic intracranial complications. J Craniomaxillofac Surg. 2001;29:111–7.
24. Reynolds DJ, Kodsi SR, Rubin SE, Rodgers IR. Intracranial infection associated with preseptal and orbital cellulitis in the pediatric patient. J AAPOS. 2003;7:413–7.
25. Hansen FS, Hoffmans R, Georgalas C, Fokkens WJ. Complications of acute rhinosinusitis in The Netherlands. Fam Pract. 2011;29:147–53.
26. Piatt Jr JH. Intracranial suppuration complicating sinusitis among children: an epidemiological and clinical study. J Neurosurg Pediatr. 2011;7:567–74.
27. Stoll D, Klossek JM, Barbaza MO. Prospective study of 43 severe complications of acute rhinosinusitis. Rev Laryngol Otol Rhinol (Bord). 2006;127:195–201.
28. Siedek V, Kremer A, Betz CS, Tschiesner U, Berghaus A, Leunig A. Management of orbital complications due to rhinosinusitis. Eur Arch Otorhinolaryngol. 2010;267:1881–6.
29. Babar-Craig H, Gupta Y, Lund VJ. British Rhinological Society audit of the role of antibiotics in complications of acute rhinosinusitis: a national prospective audit. Rhinology. 2010;48:344–7.

30. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. Herpes. 2004;11 Suppl 2:57A–64.
31. Mirakhur B, McKenna M. Recurrent herpes simplex type 2 virus (Mollaret) meningitis. J Am Board Fam Med. 2004;17:303–30.
32. Sacktor N, Lyles RH, Skolasky R, Kleeberger C, Selnes OA, Miller EN, et al. HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990-1998. Neurology. 2001;56:257–60.
33. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet. 2001;357:1851–3.
34. Chaudhry IA, Al-Rashed W, Arat YO. The hot orbit: orbital cellulitis. Middle East Afr J Ophthalmol. 2012;19:34–42.
35. Harris GJ. Subperiosteal abscess of the orbit: age as a factor in the bacteriology and response to treatment. Ophthalmology. 1994;101:585–95.
36. Garcia GJ, Harris GJ. Criteria from nonsurgical management of subperiosteal abscess of the orbit: analysis of outcomes 1988-1998. Ophthalmology. 2000;107:1454–8.
37. Chakrabarti A, Denning DW, Ferguson BJ, Ponikau J, Buzina W, Kita H, Marple B, Panda N, Vlaminck S, Kauffmann-Lacroix C, Das A, Singh P, Taj-Aldeen SJ, Kantarcioglu AS, Handa KK, Gupta A, Thungabathra M, Shivaprakash MR, Bal A, Fothergill A, Radotra BD. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. Laryngoscope. 2009;119:1809–18.
38. Lanza DC, Dhong HJ, Tantilipikorn P, Tanabodee J, Nadel DM, Kennedy DW. Fungal and chronic rhinosinusitis: from bench to clinical understanding. Ann Otol Rhinol Laryngol. 2006;196:27–34.
39. Oliverio PJ, Benson ML, Zinreich SJ. Update on imaging for functional endoscopic sinus surgery. Otolaryngol Clin North Am. 1995;28(3):585–608.
40. Duke-Elder S, MacFaul PA. The ocular adnexa: part 2. Lacrimal orbital and para orbital diseases. In: Duke-Elder S, editor. System of ophthalmology. London: Henry Kimpton; 1974. p. 859–89.
41. Slavin ML, Glaser J. Acute severe irreversible visual loss with sphenoethmoiditis – 'posterior' orbital cellulitis. Arch Ophthalmol. 1987;105:345–8.
42. Borruat FX, Bogousslavasky J, Uffer S, Klainguti G, Schatz NJ. Orbital infarction syndrome. Ophthalmology. 1993;100:562–8.
43. Mirza S, Lobo CJ, Counter P, Farrington WT. Lacrimal gland abscess: an unusual complication of rhinosinusitis. ORL J Otorhinolaryngol Relat Spec. 2001;63:379–81.
44. Martins MC, Ricardo JR, Akaishi PM, Velasco e Cruz AA. Orbital abscess secondary to acute dacryocystitis: case report. Arq Bras Oftalmol. 2008;71:576–8.
45. Kikkawa DO, Heinz GW, Martin RT, Nunery WN, Eiseman AS. Orbital cellulitis and abscess secondary to dacryocystitis. Arch Ophthalmol. 2002;120:1096–9.
46. Lang EE, Curran AJ, Patil N, Walsh RM, Rawluk D, Walsh MA. Intracranial complications of acute frontal sinusitis. Clin Otolaryngol. 2001;26:452–7.
47. Gudziol V, Buschhüter D, Abolmaali N, Gerber J, Rombaux P, Hummel T. Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis – a longitudinal study. Brain. 2009;132:3096–101.
48. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008;82:7264–75.
49. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis. 2004;10:342–4.
50. Stammberger H, Hawke M. Essentials of functional endoscopic sinus surgery. St. Louis: Mosby; 1993.
51. Wormald PJ. Endoscopic sinus surgery. Anatomy, three-dimensional reconstruction and surgical technique. New York: Georg Thieme; 2008.
52. Simmen D, Jones N. Manual of endoscopic sinus surgery and its extended applications. Stuttgart: Georg Thieme; 2005.
53. Rice DH. Endoscopic sinus surgery. Otolaryngol Clin North Am. 1993;26:613–8.
54. Castelnuovo P, Dallan I, Locatelli D, Battaglia P, Farneti P, Tomazic PV, Seccia V, Karligktios A, Pasquini E, Stammberger H. Endoscopic transnasal intraorbital surgery: our experience with 16 cases. Eur Arch Otorhinolaryngol. 2012;269(8):1929–35.
55. Lund VJ, Stammberger H, Nicolai P, Castelnuovo P, Beal T, Beham A, Bernal-Sprekelsen M, Braun H, Cappabianca P, Carrau R, Cavallo L, Clarici G, Draf W, Esposito F, Fernandez-Miranda J, Fokkens W, Gardner P, Gellner V, Hellquist H, Hermann P, Hosemann W, Howard D, Jones N, Jorissen M, Kassam A, Kelly D, Kurschel-Lackner S, Leong S, McLaughlin N, Maroldi R, Minovi A, Mokry M, Onerci M, Ong YK, Prevedello D, Saleh H, Sehti DS, Simmen D, Snyderman C, Solares A, Spittle M, Stamm A, Tomazic P, Trimarchi M, Unger F, Wormald PJ, Zanation A. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinol Suppl. 2010;22:1–143.
56. Kennedy DW, Shaman P, Han W, Selman H, Deems DA, Lanza DC. Complications of ethmoidectomy: a survey of fellows of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg. 1994;111:589–99.
57. Hopkins C, Browne JP, Slack R, Lund VJ, Topham J, Reeves BC, et al. Complications of surgery for nasal polyposis and chronic rhinosinusitis: the results of a national audit in England and Wales. Laryngoscope. 2006;116:1494–9.
58. Kane K. Australian experience with functional endoscopic sinus surgery and its complications. Ann Otol Rhinol Laryngol. 1993;102:613–5.
59. Sampaio MH, de Barros-Mazon S, Sakano E, Chone CT. Beta-trace protein is currently the safe and CSF leak diagnostics. Predictability of quantification of beta-trace protein for diagnosis of cerebrospinal fluid leak: cutoff determination in nasal fluids with two control groups. Am J Rhinol Allergy. 2009;23:585–90.
60. Hsin CH, Tsao CH, Su MC, Chou MC, Liu CM. Comparison of maxillary sinus puncture with endoscopic middle meatal culture in pediatric rhinosinusitis. Am J Rhinol. 2008;22:280–4.
61. Gosepath J, Brieger J, Vlachtsis K, Mann WJ. Fungal DNA is present in tissue specimens of patients with chronic rhinosinusitis. Am J Rhinol. 2004;18:9–13.
62. Sachse F, Becker K, von Eiff C, Metze D, Rudack C. Staphylococcus aureus invades the epithelium in nasal polyposis and induces IL-6 in nasal epithelial cells in vitro. Allergy. 2010;65:1430–7.
63. Kastner J, Taudy M, Lisy J, Grabec P, Betka J. Orbital and intracranial complications after acute rhinosinusitis. Rhinology. 2010;48:457–61.

64. Maniglia AJ, Goodwin WJ, Arnold JE, Ganz E. Intracranial abscesses secondary to nasal, sinus, and orbital infections in adults and children. Arch Otolaryngol Head Neck Surg. 1989;115:1424–9.
65. Masterson L, Leong P. Pott's puffy tumour: a forgotten complication of frontal sinus disease. Oral Maxillofac Surg. 2009;13:115–7.
66. Kombogiorgas D, Solanki GA. The Pott puffy tumor revisited: neurosurgical implications of this unforgotten entity. Case report and review of the literature. J Neurosurg. 2006;105(2 Suppl):143–9.
67. Langham-Brown JJ, Rhys-Williams S. Computed tomography of acute orbital infection: the importance of coronal sections. Clin Radiol. 1989; 40:471–4.
68. Brijlal Meena MK, Sharma P. Epidural empyema secondary to orbital cellulitis: a case report. Eur J Ophthalmol. 2007;17:841–3.
69. Kreuzberg B, Kastner J, Ferda J. The contribution of MRI to the diagnosis of diffuse meningeal lesions. Neuroradiology. 2004;46:198–204.
70. Sepahdari AR, Aakalu VK, Kapur R, Michals EA, Saran N, French A, Mafee MF. MRI of orbital cellulitis and orbital abscess: the role of diffusion-weighted imaging. AJR Am J Roentgenol. 2009;193:244–50.
71. Netuka D, Masopust V, Belsan T, Kramar F, Benes V. One year experience with 3.0 T intraoperative MRI in pituitary surgery. Acta Neurochir Suppl. 2011;109:157–9.
72. Schuknecht B, Simmen D, Briner HR, Holzmann D. Nontraumatic skull base defects with spontaneous CSF rhinorrhea and arachnoid herniation: imaging findings and correlation with endoscopic sinus surgery in 27 patients. AJNR Am J Neuroradiol. 2008;29:542–9.
73. De Angelis G, Restuccia G, Venturiello S, Cauda R, Malhotra-Kumar S, Goossens H, Schrenzel J, Tacconelli E. Nosocomial acquisition of methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum beta-lactamase (ESBL) Enterobacteriaceae in hospitalised patients: a prospective multicenter study. BMC Infect Dis. 2012;12:74.

Chapter 28
Surgical Management of Cysts and Papillomas of the Nose and Sinuses

Jamie L. Funamura, Jonathan Liang, and Craig W. Senders

Introduction

Cysts and papillomas of the nose and sinus include a wide variety of lesions, from the common and benign mucous retention cyst to a rare and aggressive inverted papilloma with the potential for malignant degeneration. An understanding of the origin and natural history of these lesions is key to both diagnosis and appropriate surgical management. Although the topics of this chapter are benign pathologies, many have the potential for recurrence that dictates both the extent of initial surgery and subsequent surveillance. Included in this chapter will be a discussion of the diagnosis and surgical management of congenital and acquired cysts, including nasal dermoid cysts, encephaloceles, gliomas, nasolacrimal duct cysts, mucous retention cysts, and mucoceles, as well as hamartomas and papillomas of the nose and paranasal sinuses.

Congenital Sinonasal Lesions

Nasal dermoid cysts, encephaloceles, and gliomas are the three classically described congenital midline nasal masses. These anomalies typically occur in the nose, although they can also be found in the orbit, oral cavity, nasopharynx, and paranasal sinuses [1]. Although distinct clinical and pathologic entities, they are thought to be embryologically related developmental anomalies of the frontonasal region. While still debated, the most widely accepted theories of development involve the persistence of a dural diverticulum through an anterior cranial defect. Faulty closure of the embryologic structure of origin of the frontonasal region, the anterior neuropore, is thought to be the responsible mechanism [2–4].

In the course of normal development of the frontonasal region, two transient structures exist prior to separation of the intracranial and extracranial spaces: the fonticulus nasofrontalis and the foramen cecum. The fonticulus nasofrontalis forms as a membrane bridging the inferior frontal bone and the nasal bone. At the floor of the anterior skull base, the foramen cecum forms from the nasal processes of the frontal bones to surround a dural diverticulum [5, 6]. This dural projection extends through the prenasal space between the nasal bones and the cartilaginous capsule and connects to the skin [3]. The dural diverticulum normally obliterates, and the fonticulus nasofrontalis and the foramen cecum close, followed by the formation of the cribriform plate [7, 8]. The obliteration of the dural diverticulum with closure of the fonticulus nasofrontalis and foramen cecum establishes the division of the intracranial, intranasal, and external spaces of the nasofrontal region [2]. Persistence of the dural diverticulum may result in the anomalous development of a dermoid sinus or cyst, encephalocele, or glioma [2–5, 7–9] (Fig. 28.1a, b). Defects in the foramen cecum will present as intranasal masses, while extranasal masses result from failed closure of the fonticulus nasofrontalis. Another cause of an intranasal cystic mass is a congenital nasolacrimal duct cyst. The embryology, presentation, and management of these cysts are also discussed below.

J.L. Funamura, MD (✉) • C.W. Senders, MD FACS
Department of Otolaryngology – Head and Neck Surgery, University of California Davis Medical Center, 2521 Stockton Blvd., Suite 7200, Sacramento, CA 95817, USA
e-mail: jamie.funamura@gmail.com; craig.senders@ucdmc.ucdavis.edu

J. Liang, MD
Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins School of Medicine, 601 N. Caroline Street, Baltimore, MD 21287, USA
e-mail: jliang20@jhmi.edu

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_28,

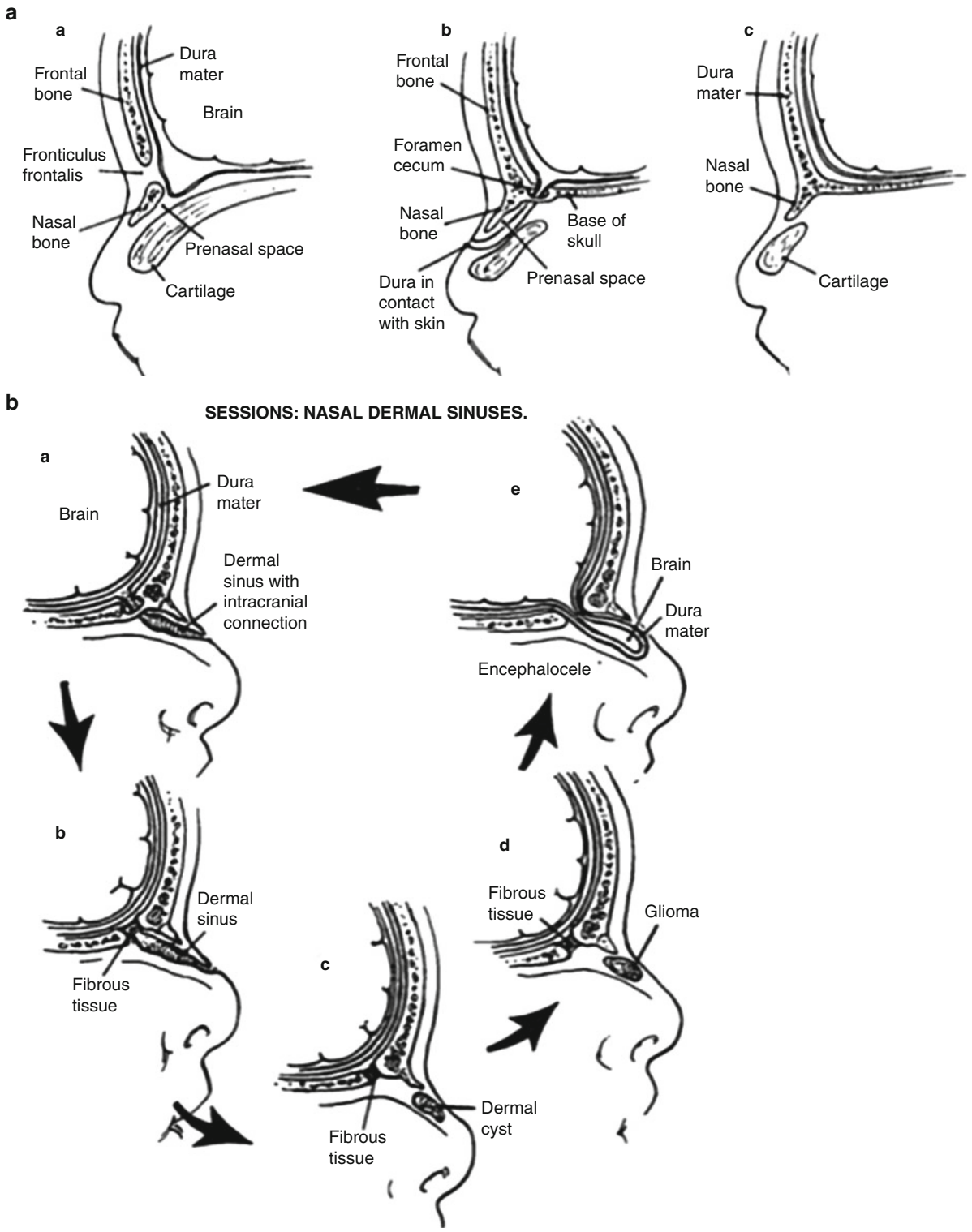


Fig. 28.1 (**a**) Normal development of the frontonasal region. (**b**) Embryologic origin of dermoid cysts, gliomas, and encephaloceles (Reprinted from Sessions [10]. With permission from John Wiley & Sons, Inc)

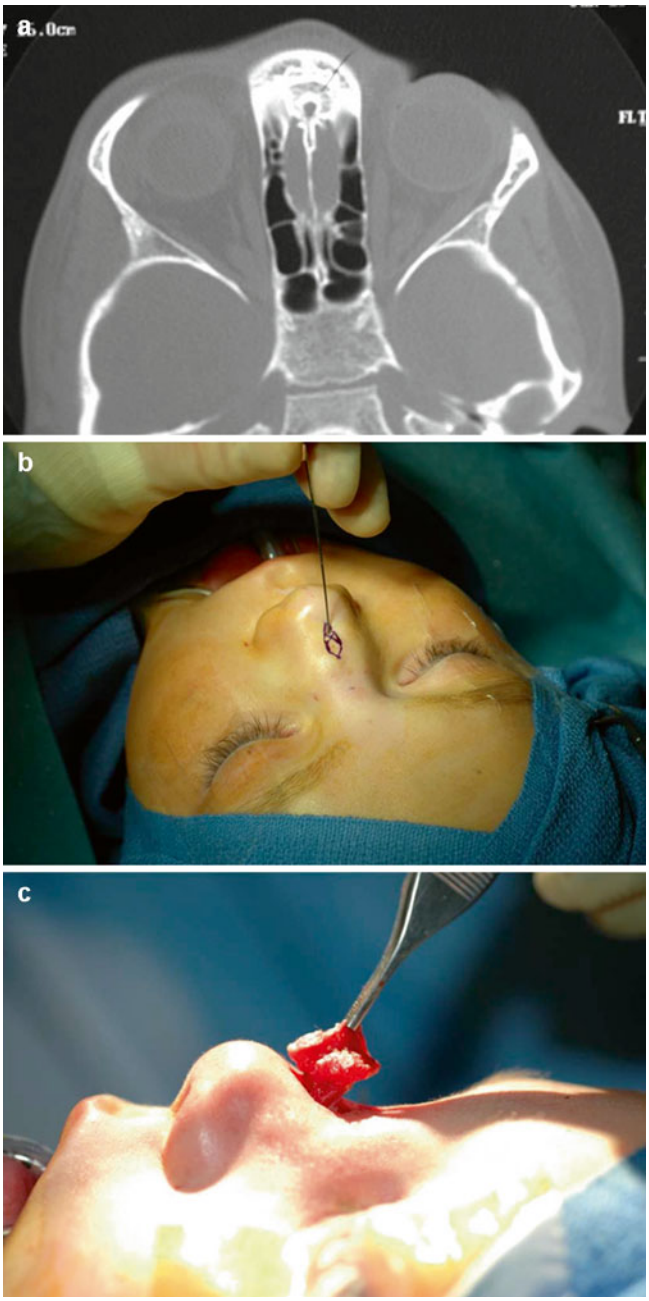


Fig. 28.2 (**a**) Axial CT scan of a 5-year-old boy with a nasal dermoid sinus, demonstrating intranasal sinus tract. (**b**) Same patient with a probe in the nasal dermoid sinus tract. (**c**) Intraoperative photo of same patient after excision via vertical midline nasal dorsal incision with tract intact. (With permission from TT Tollefson)

Nasal Dermoid Sinus and Cysts

Nasal dermoid cysts are the most common of these three anomalies, comprising 60 % of congenital midline nasal lesions. The incidence of nasal dermoid is estimated at 1 in 20,000–40,000 births [2, 7]. Incomplete separation of the dura and skin as the dural diverticulum regresses during development may result in a persistent tract, a closed cyst, or a combination of the two, containing dermal elements [7]. Dermal sinuses and cysts may occur from the glabella to the nasal tip or columella; the most common location is the lower third of the nasal bridge. Clinically, nasal dermoid cysts present as firm, slow-growing masses that are not compressible, nor do they transilluminate. Classically, there is a hair protruding through a pit in the nasal skin near the inferior-most aspect of the mass. These masses do not expand with crying or straining. Histologically, dermoid cysts contain both ectodermal and mesodermal elements, including dermal appendages such as hair follicles and sebaceous glands. CT imaging is an essential part of the workup for a suspected nasal dermoid cyst (Fig. 28.2a). Intracranial extension is reported to occur in 20–45 % of cases but is likely much less in non-referral centers. On CT, characteristics suggestive of intracranial extension include a bifid crista galli and enlargement of the foramen cecum [11]. The ossification of the ethmoid bone and

crista galli is often incomplete at the age of presentation, however, and presence of these characteristics alone have been associated with false positives in some series [12, 13]. It has been proposed that the absence of these signs be used to determine absence of intracranial extension, and their presence be interpreted suggestive (but not diagnostic) of intracranial extension and as indication for subsequent MR imaging [14]. MRI is the imaging study of choice given superior identification of intracranial involvement; the cyst will appear hyperintense on T1-weighted MR images. MR imaging can also be misleading, however, due to the process of normal fat deposition in bone during the maturation of the frontal sinus and nasal bones [15].

If left untreated, dermoid cysts and sinuses may lead to local inflammation or abscess formation. If an intracranial connection is present, these may ultimately lead to CSF leak, meningitis, cavernous sinus thrombosis, and periorbital cellulitis. The dermoid cyst may also cause a cosmetic issue that worsens with time as the expanding cyst deforms the nasal bones and/or cartilages. Early surgical excision of dermoid cysts is recommended in order to prevent complications from cyst infection. Cyst incision and drainage, marsupialization, administration of caustic substances, and partial excision were attempted in the past with poor results [11]. It is now agreed that complete cyst removal is the ideal treatment. In fact, the use of an operative microscope to ensure complete dissection of the dermoid cyst components has been supported by many authors [7, 11, 12]. Numerous types of incisions have been proposed as ideal for the transnasal approach for a nasal dermoid, including midline vertical, transverse, inverted U, open rhinoplasty, and the more extensive lateral rhinotomy and degloving procedures [9, 11]. Midline vertical incisions for cysts of the nasal dorsum have been the mainstay of approaches in the literature (Figs. 28.2b, c) [16], although more recent papers suggest that these can be associated with subsequent scar widening. Pollock suggested that the four criteria for an appropriate surgical approach to the excision of a dermoid cyst and tract be the following: (1) provide access to all midline cysts and permit medial and lateral osteotomies if necessary, (2) favor the rapid repair of cribriform defects and permit control of CSF rhinorrhea if present, (3) allow for reconstruction of nasal dorsum, and (4) offer the probability of acceptable scar formation [11]. Proponents of the open rhinoplasty approach point to the meeting of these criteria as well as a superior cosmetic result [17]. Endoscopic approaches have also been used for primarily intranasal dermoids with limited or no cutaneous involvement [18].

If intracranial extension is present, a combined neurosurgical and transfacial procedure is advised. This may be planned as a staged procedure; however, a single-stage combined intracranial-extracranial approach has been described as a safe and effective procedure [9]. The extracranial portion is typically performed first, with a limited excision of the nasal dorsum involving the dermoid cyst or sinus tract. The tract is then dissected toward the point of origin through the nasal or frontal bones. A coronal incision is then made and the anterior scalp flap elevated in a subperiosteal plane. At the nasofrontal region, dissection is carried out in the supraperiosteal plan to allow for an en bloc resection the cyst/tract. The neurosurgery team will then perform a limited frontal craniotomy to identify and dissect out the intracranial portion [9]. Various approaches have been described for the intracranial aspect of extirpation, including more recent keyhole craniotomies such as transglabellar or supraorbital approaches [19, 20]. It has been proposed that prior to proceeding with a craniotomy routinely for intracranial extension, the dermoid sinus stalk can be biopsied at the skull base; if the stalk is purely fibrous at this location, it is of no clinical consequence, and an unnecessary craniotomy can be prevented [10]. The absence of dermoid elements at the skull base, however, does not guarantee its absence more proximally, and such management may result in an increased incidence of recurrence [9]. The combination of intraoperative findings and preoperative imaging should be used to determine the appropriate extent of surgery.

Nasal Gliomas

Nasal gliomas similarly represent brain tissue that has persisted through an anterior cranial defect; however, unlike encephaloceles, their meningeal connection has been lost. The term glioma implies a true neoplasm and is thus a misnomer; other terms such as encephaloma or nasal cerebral heterotopia have been proposed to more accurately reflect the nature of the lesion. Nasal gliomas are usually firm, non-compressible masses. Sixty percent are extranasal, 30 % are intranasal, and 10 % are both and can be found anywhere from the glabella to the nasal tip [1]. Intranasal gliomas can be misdiagnosed as polyps although they are typically less translucent. As polyps are rare in childhood, visualization of polypoid-type tissue in a young patient should raise suspicion for an intranasal glioma and prompt subsequent imaging. Rarely, a glioma may be diagnosed in an adult; patients in their fifth and sixth decades have been described. [21, 22] A pedicle of glial tissue with a dural connection is found in 15–20 % of cases. However, due to the absence of meninges, gliomas do not have the extracranial continuity of CSF flow that encephaloceles do, thereby clearly delineating the two on MR imaging [3]. Fine needle aspiration or biopsy is not recommended.

Surgical excision is the treatment of choice for nasal gliomas. Delay in treatment may result in distortion of the septum or nasal bones. Infection may also result. A conservative and cosmetic incision is preferred, given that nasal glioma is benign

Table 28.1 Types of encephaloceles

Classification	Site of herniation	Location of mass
Occipital (75 %)		
Sincipital (15 %)		
Nasofrontal	Fonticulus nasofrontalis	Forehead
Nasoethmoidal	Foramen cecum	Nasal dorsum or intranasal
Naso-orbital	Medial orbital wall	Orbit and ethmoid sinuses
Basal (10 %)		
Transethmoidal	Cribriform plate	Intranasal
Sphenoethmoidal	Between ethmoid and sphenoid	Nasopharynx
Trans-sphenoidal	Craniopharyngeal canal	Nasopharynx
Sphenomaxillary	Superior and inferior orbital fissure	Pterygopalatine fossa

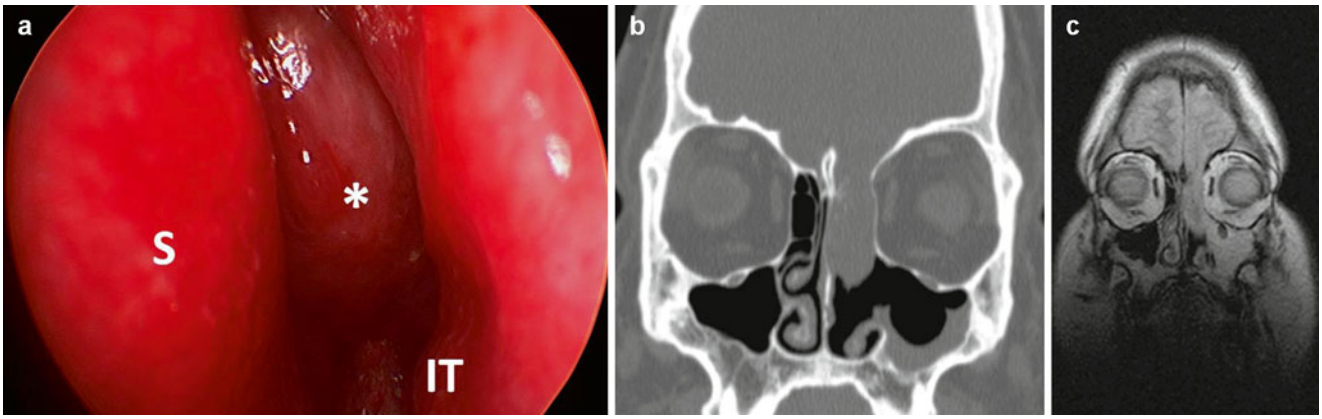


Fig. 28.3 (**a**) Nasal endoscopy of an encephalocele obstructing the left nasal cavity (* mass, *S* septum, *IT* inferior turbinate). (**b**) Coronal CT of an encephalocele extending from left anterior skull base into the nasal cavity. (**c**) Coronal MRI of an encephalocele extending from left anterior skull base into the nasal cavity

with rare cases of recurrence [1, 23]. The intranasal stalk of the glioma should be traced back to its origin in order to determine the presence or absence of intracranial extension. Extranasal gliomas are typically approached via a lateral rhinotomy or external rhinoplasty approach depending on the predominant location of the glioma [1]. These approaches should allow for the best exposure of the posterior and superior elements of the mass so that the connection to the cribriform area can be identified and excised under direct visualization. Intranasal glioma can be approached endoscopically, ideally with an intraoperative guidance system to evaluate for intracranial extension. The surgeon should be prepared for the possibility of a dural defect as a result of glioma excision. Additional tissue, such as a fascial graft, may be required for closure. If intracranial extension is present and cannot by approached safely, neurosurgical involvement with a possible frontal craniotomy is recommended. Other approaches that have been described include sublabial, trans-septal, and transethmoid approaches for select cases depending on the location of the glioma [23].

Nasal Encephaloceles

Congenital nasal encephaloceles represent an extracranial herniation of meninges and brain tissue. Further classification of encephaloceles is determined by the site of herniation (Table 28.1). Reports of the incidence of encephaloceles vary from 1 in 3,000 to 12 in 30,000, with a much higher incidence in Asian populations [4]. The internal skull defect is located in the midline, but the site of presentation of the encephalocele varies depending on the surrounded defect in the facial skeleton [24]. Encephaloceles are soft compressible masses that transilluminate; when encountered intranasally they can be mistaken for polyps (Fig. 28.3a). Patients with encephaloceles have a positive Furstenberg test; the mass enlarges with increased intracranial pressure with crying or straining. On CT, encephalocele appear as a soft tissue density that can be difficult to distinguish from other common nasal lesions such as polyps, but there can be an appreciable skull base bony defect (Fig. 28.3b). On MRI, encephaloceles demonstrate a contiguous CSF space (Fig. 28.3c). If left untreated, encephaloceles carry the risk of CSF leak, meningitis, and intracranial abscess.

Early surgical treatment is also recommended for encephaloceles. Delayed excision may result in infection, progressive herniation, or cosmetic deformity. Emergent surgery, however, is rarely required, allowing for extensive preoperative planning with appropriate imaging and coordination of the subspecialty teams. Indications for emergent surgery include open encephaloceles, hemorrhage, CSF leak, impending ulceration, airway obstruction, or visual impairment [25, 26]. Sincipital encephaloceles generally require a combined intracranial approach via a frontal craniotomy and extracranial-extranasal approach. Historically the intracranial and extracranial portions are performed as a staged procedure, but more often now a two-team single-stage procedure is performed [25–29]. For lesions with wide intracranial communication, typically an encephalocele, a two-stage procedure should be considered. The intracranial portion is performed first. With later resection of the extracranial component, the risk of a CSF leak is diminished. In lesions with suspected communication, general steps include a frontal craniotomy, resection of the intracranial portion of the encephalocele, dural repair, and a second layer such as a pericranial flap for water-tight closure. Calvarial bone grafts may be required to close large defects. The extracranial resection is then completed and may require osteotomies for correction of facial deformities [26–28]. Multiple surgeons have noted that often times an extracranial-extranasal encephalocele can be successfully excised in a single-stage procedure via a bicoronal incision without the need for an additional facial incision [1, 29]. In this case the bicoronal flap is extended inferiorly to the bony-cartilaginous junction of the nasal dorsum without requiring any further incisions. For encephaloceles with a predominantly intranasal extracranial component, an endoscopic approach has been used with success [1]. Use of intraoperative image guidance has been recommended in these cases.

Congenital Nasolacrimal Duct Cysts

A congenital nasolacrimal duct obstruction may also present as a cystic intranasal mass. The nasolacrimal duct arises from ectodermal tissue in the naso-orbital groove. At approximately 3 months' gestation, the ectodermal cord begins to canalize, forming the lacrimal canalicular system. Numerous valves are formed during the canalization process: the most proximal being the valve of Rosenmuller at the junction of the lacrimal canaliculi and lacrimal sac, and the most distal the valve of Hasner at the termination of the duct in the nasal mucosa at the inferior meatus. Obstruction may occur anywhere along the length of the nasolacrimal duct system but is most common at the valve of Hasner [30, 31]. When the nasolacrimal duct fails to canalize completely, typically a thin membrane persists which ruptures during initial neonatal respirations. If the membrane does not rupture, tears and mucoid discharge accumulate in the duct. This accumulation of fluid tends to result in a cystic swelling of either the most proximal or most distal portions of the nasolacrimal duct system due to the bony encasement of the central length of the duct. Congenital nasolacrimal duct cysts have also been referred to as nasolacrimal duct mucoceles and dacryocystoceles [32, 33].

The presentation of a nasolacrimal duct cyst depends on the location of obstruction. If the obstruction is proximal, epiphora, dacryocystitis, and periorbital cellulitis may develop, along with a cystic swelling of the medial canthal area. In the case of distal obstruction, an intranasal cyst may occur. If this cyst is large or bilateral, neonatal respiratory distress may be the initial presenting symptom that can be progressive and life-threatening due to obligatory nasal breathing in infants. Unilateral cysts may be more difficult to diagnose, presenting with feeding difficulties, sleep disturbance, or intermittent acute respiratory distress varying with the physiologic nasal cycle [33].

Direct visualization of the cyst with anterior rhinoscopy and nasal endoscopy in the stable patient is important for characterizing the mass and ruling out other causes of nasal obstruction such as piriform aperture stenosis and choanal atresia. Of note, a nasal endoscope will be able to be passed medially to a nasolacrimal duct cyst but not to an intranasal encephalocele due to its midline origin [34]. Both CT and MRI have been proposed as diagnostic imaging modalities for nasolacrimal duct cysts. CT has the advantage of excellent delineation of bony anatomy and can concurrently evaluate for piriform aperture stenosis, choanal atresia, and other nasal anomalies. On CT, the cyst will appear as a well-defined mass with a low-attenuation center that may enlarge the lacrimal sac and displace the inferior turbinate and nasal septum. With enhanced soft tissue definition, MRI can differentiate the intranasal cyst from surrounding soft tissue structures and evaluate for intracranial extension that may assist in excluding the possibility of a glioma or encephalocele [31, 33, 34].

Nasolacrimal duct cysts presenting without respiratory distress or infection may often be conservatively managed with massage and warm compresses. As many as 86–88 % of infants will be successfully treated with conservative management [35, 36]. For persistent, infected, or obstructing intranasal cysts, surgical intervention is indicated. Three approaches have been described: (1) nasolacrimal duct probing, (2) nasal endoscopy and marsupialization of intranasal cyst, and (3) combined endoscopic marsupialization and nasolacrimal duct probing [31, 33]. Probing allows for proximal disruption of the cyst at the valve of Rosenmuller, while marsupialization decompresses the cyst distally. In cases of nasal obstruction causing respiratory distress, the combined approach of nasal endoscopy with marsupialization of the cyst with probing and irrigation of the nasolacrimal duct is advocated in most published reports. Treatment in subacute and non-emergent cases is more variable. Many authors will treat proximal (medial canthal) cysts with massage or lacrimal probing but advocate that all intranasal cysts undergo marsupialization and probing. Recurrence is rare and tends to occur within 6–12 months of the original surgical intervention [30–34, 37].

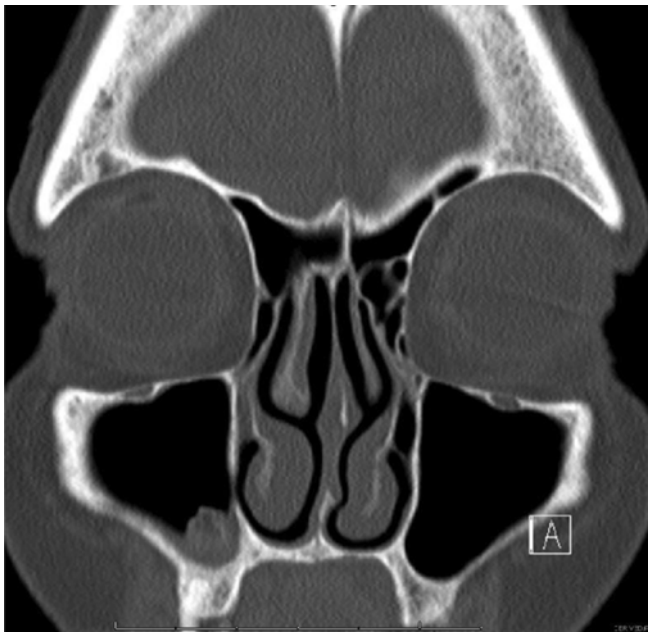


Fig. 28.4 Coronal CT of a left maxillary sinus mucous retention cyst

Acquired Sinonasal Lesions: Non-papillomatous

Mucous Retention Cysts

Retention cysts are the result of obstruction of a seromucinous gland duct of the sinus mucosa. Mucous accumulates causing a cystic dilation that is typically discovered as an incidental finding on CT scans, most commonly of the maxillary sinus (Fig. 28.4). Studies have estimated that incidental maxillary sinus retention cysts are found in 9–22 % of the general population [38–41]. The characteristic radiographic appearance of a mucous retention cyst is a rounded, dome-shaped homogenous mass emanating from a sinus wall or floor. On histopathology, these cysts are lined by an epithelium containing serous or mucous fluid. These cysts tend to be asymptomatic unless they obstruct a sinus ostium. Symptoms, when present, include headache, nasal obstruction, or facial pain. It is generally thought that mucous retention cysts represent a self-limiting and self-resolving pathologic process with spontaneous regression occurring in 18–40 % of cysts [41], with another significant percentage slightly smaller or stable in size with subsequent follow-up imaging. As a result, most therapy consists of medical treatment directed at symptom relief and surgical therapy reserved for unrelenting and severe symptomatic cysts.

Traditional surgical therapy has aimed at puncture and aspiration of symptomatic mucous retention cysts via a natural ostium or a Caldwell-Luc approach. More recently, endoscopic approaches have been advocated. The extent of endoscopic sinus surgery for cyst management, however, is debated. In a comparison of uncinectomy, anterior ethmoidectomy, partial middle turbinate resection, and maxillary antrostomy with and without maxillary sinus cyst extirpation, no significant difference in relief of facial pain, nasal discharge, and nasal obstruction after surgery was found despite similar characteristics between the two groups [42].

Mucoceles

Mucoceles are thought to form from an obstruction of a sinus ostium with continual secretion of mucous leading to an expansion of the mucocele with subsequent bony remodeling and/or erosion. Due to its narrow drainage pathway and propensity for obstruction, the frontal sinus is the most common site for mucocele formation. The presenting symptoms of mucoceles are related to the site of obstruction. Frontal sinus mucoceles often present with frontal headache and in extreme cases, proptosis and vision changes. Sphenoid and ethmoid mucoceles may present with pain and diplopia. Maxillary sinus mucoceles are the rarest and may present with facial pressure or pain, nasal drainage, nasal obstruction, or diplopia. The chronic symptoms associated with mucoceles can present with acute worsening with significant visual and neurologic changes if secondary infection occurs leading to rapid expansion and inflammation. The most common cited causes of mucoceles include chronic

rhinosinusitis, allergic sinonasal disease, trauma, and previous surgery. Oftentimes, however, the origin of a mucocele cannot be identified.

Although suspicion for a mucocele may be raised based on history or physical exam, CT is often required to confirm the diagnosis. A soft tissue mass completely filling the affected sinus typically with bony expansion or rarely erosion is characteristic of a mucocele. MRI may be used to differentiate between a fluid-filled sinus cavity and a solid tumor in cases where the diagnosis may be in question based on presentation. Biopsies are typically not necessary. The treatment of mucoceles is largely surgical; commonly applied surgical approaches to the different types of mucoceles are discussed below.

Sphenoid and Ethmoid Sinus Mucoceles

Due to the close proximity of the sphenoid sinus to a multitude of neurologic and vascular structures, sphenoid sinus mucoceles can present with a variety of different signs and symptoms. Frontal and retro-orbital headaches are common complaints. Ophthalmologic findings include visual loss, diplopia, visual field deficits, and proptosis. Sphenoid sinus mucoceles are rare, representing only 1–2 % of paranasal sinus mucoceles [43]. Commonly identified causes of sphenoid sinus mucoceles include ethmoid sinus disease and nasal polyposis [44]. A number of different approaches have been attempted, including intracranial, antral, trans-septal, transpalatal, external, and extensive intranasal techniques. More recently, endoscopic sphenoid sinusotomy and marsupialization of the mucocele are recommended and may be performed in conjunction with a partial or total ethmoidectomy and turbinate reduction as necessary for exposure [43, 44]. Ethmoid sinus mucoceles may present in similar fashion and are typically managed with a partial or total ethmoidectomy depending on the extent of the disease and pathways of drainage available. Symptomatic isolated sphenoid sinus mucoceles are thought to require earlier surgical intervention due to potential for intracranial complications.

Maxillary Sinus Mucoceles

Mucoceles are rarely found in the maxillary sinus; they are thought to represent approximately 10 % of paranasal sinus mucoceles [45]. Large mucoceles may cause nasal obstruction, nasal drainage, diplopia, facial and dental pain, and rarely a painless bulging of the cheek. Traditionally surgical treatment has consisted of a Caldwell-Luc approach with an inferior nasoantral window and removal of the mucocele lining. More recently, endoscopic evacuation via a wide maxillary antrostomy has been advocated [45–47]. It is noted that extensive mucoceles such as those with erosion of the anterior maxillary sinus wall, extension to the pterygomaxillary fossa or multiloculated/complicated mucoceles as a result of previous trauma or surgery may still benefit from an open approach.

Frontal Sinus Mucoceles

Frontal sinus obliteration procedures have thus largely been favored to address frontal sinus mucoceles in the past. These procedures include cranialization, the Riedel procedure, and osteoplastic flap with obliteration. In patients with short frontal nasal ducts, transnasal endoscopic drainage and marsupialization of frontal sinus mucoceles may have comparable rates of relief and symptom recurrence [46, 48]. It is thought that active mucociliary transport lends itself to development of normal mucosa after marsupialization. Furthermore, in cases of bony erosion of the posterior table or orbit in which the mucosa is attached to dura or periosteum and attempts to remove the mucosa may do more harm than good, marsupialization is the preferred technique.

Hamartomas

Hamartomas are benign malformations or inborn errors of tissue development. Albrect first described the term “hamartoma” in 1904. A hamartoma is composed of disorganized tissue indigenous to a particular site. Hamartomas can occur in any area of the body, with a predilection for the lung, kidney, and intestine [49]. Hamartomas of the head and neck region, in particular the nasal cavity and paranasal sinuses, are very rare [50].

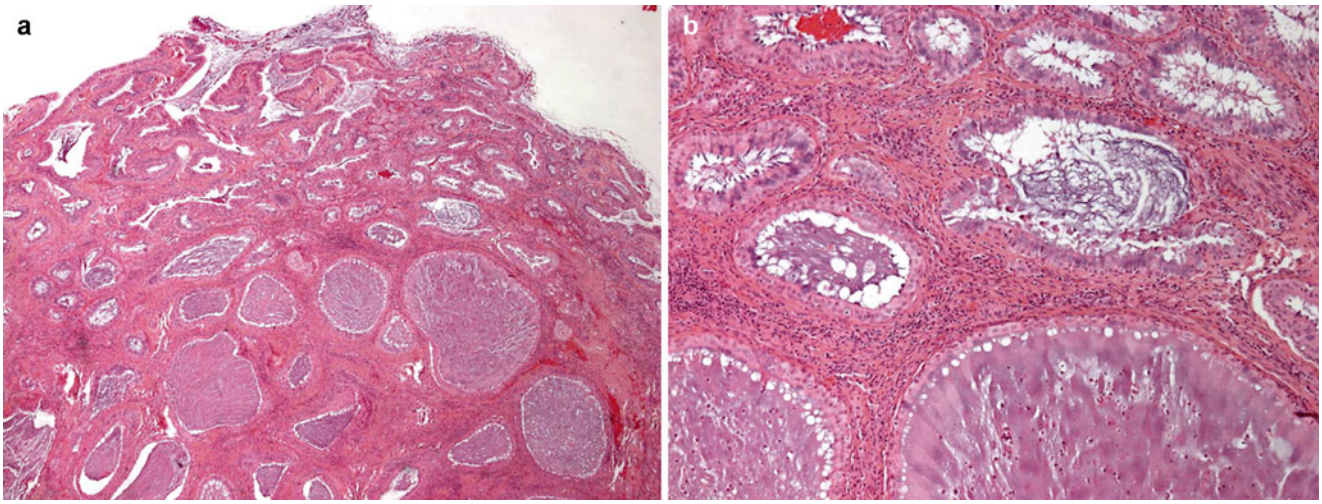


Fig. 28.5 (**a**) Respiratory epithelial adenomatoid hamartoma (H&E, original magnification ×2). (**b**) Respiratory epithelial adenomatoid hamartoma (H&E, original magnification ×10)

Respiratory Adenomatoid Epithelial Hamartoma (REAH)

Respiratory adenomatoid epithelial hamartoma (REAH), although rare, is the most common hamartoma of the sinonasal tract. Wenig and Heffner first described this distinct lesion in 1995 by identifying 31 cases from the files of the Otolaryngic Tumor Registry at the Armed Forces Institute of Pathology [51]. The patients included 27 men and 4 women ranging in age from 27 to 81 years, with a mean age of 58 years. Presenting symptoms included nasal obstruction, nasal stuffiness, deviated septum, epistaxis, and chronic rhinosinusitis, with duration of symptoms ranging from a few months up to 8 years. More recent case reports have also shown that REAH can present with headaches, facial pain, proptosis, and hyposmia. The most common site of occurrence was the nasal septum. It has been estimated that approximately 70 % of REAHs occur in the nasal cavity, most often localized to the posterior nasal septum [51–53]. Other sites of occurrence include the ethmoid sinus, frontal sinus, nasopharynx, and maxillary sinus [52–54]. Radiologically, the most common finding of REAH is an opacification of the affected sinus and some connection to the nasal septum.

The mechanisms inducing a hamartoma are still unknown. REAH often arises in the setting of inflammatory polyps [53–56] suggesting that their development is secondary to the inflammatory process. REAH shares many features with sinonasal inflammatory polyps, including clinical presentation, histopathologic changes, treatment, and behavior. Despite its unknown pathophysiology, hamartomas have no capacity for continuous unimpeded growth, and, thus, its proliferation is self-limiting.

REAH is diagnosed by biopsy. Grossly, they appear as shiny edematous-appearing polypoid masses, and, microscopically, they appear as glandular proliferations with polypoid appearance [52, 53]. The characteristic glandular components consist of respiratory epithelium originating from the surface epithelium with absence of seromucous glands. The polypoid growth results from the respiratory epithelial-lined adenomatoid proliferation [53]. The glands themselves consist of pseudostratified ciliated epithelial cells with no atypia or metaplastic changes (Fig. 28.5a, b).

It is important to differentiate REAH from other pathologic processes in the differential diagnosis, which include inflammatory polyps, inverted papillomas, and adenocarcinomas (Table 28.2). REAH and nasal polyps share common characteristics of fibroblastic and vascular proliferation, stromal edema, mixed inflammatory infiltrate, and seromucous gland proliferation. Adenomatoid proliferation and the absence of a seromucous gland component differentiate REAH from inflammatory polyps [53, 54]. Inverted papillomas originate from the stratified squamous epithelium and are characterized with a markedly thickened proliferative epithelium, whereas REAH shows adenomatoid structures of respiratory epithelium that is often a single layer [53–55]. Inverted papillomas also are characterized by invagination of the surface epithelium in the underlying stroma. Sinonasal adenocarcinomas originate from glandular epithelium and are characterized by a complex glandular growth pattern with a back-to-back or cribriform pattern lacking intervening connective tissue [49, 50, 53, 54]. The intervening stroma between the ciliated glands of REAH is a reliable way to distinguish this entity from low-grade adenocarcinomas, which lack intervening stroma between the glands [57]. Adenocarcinomas may also demonstrate some degree of cellular atypia, pleomorphism, and an increased mitotic index, which are not present in REAH [53]. Furthermore, REAH can also be differentiated from adenocarcinoma through immunohistochemical staining with CD20, CDX-2, and MIB-1 (KI-67) [49, 50, 52].

Table 28.2 Key differentiating features of REAH from nasal polyps, inverted papilloma, and sinonasal adenocarcinoma

	REAH	Nasal polyp	Inverted papilloma	Sinonasal adenocarcinoma
Location of preference	Posterior nasal septum	No predilection for any location	Lateral nasal wall	Any sinus (ethmoid common)
Gross	Induration	Smooth		
Microscopic	Adenomatoid proliferation	Sinus mucosa overlying gelatinous material	Inverted growth of squamous epithelium	Increased mitotic rate
	Stromal hyalinization		Proliferation of epithelium with mucocytes, intraepithelial mucous cysts, and inflammatory cells	Dysplasia
	Single lining epithelium			Nuclear stratification
	Interventing stroma between glands			Cribriform architecture
Immunohistochemistry	CK7 positive		CK7 positive	CK20 positive
	CK20 negative		CK20 negative	CDX-2 positive
	MIB-1 low reactivity			MIB-1 high reactivity
Malignant transformation	No	No	Yes; 5–10 %	

Table 28.3 Pathologic findings of REAH versus glandular hamartoma

	Respiratory epithelial adenomatoid hamartoma (REAH)	Glandular hamartoma
Gross	Polypoid or exophytic mass	Polypoid or exophytic mass
Microscopic	Medium or large glands connected to surface	Epithelial proliferation of small glands, serous acini, and tubules
	Multilayered ciliated respiratory epithelium	Edematous to fibrous stroma
	Thickened basement membrane	Larger glands/cysts lined by ciliated respiratory or flat epithelium
	Mucous metaplasia	Prominent lymphoplasmacytic infiltrate, no eosinophils
	Edematous stroma with variable inflammation	Epithelium flat to cuboidal
Immunohistochemical	Ciliated epithelium positive for CK7	Glands positive for S-100, CK7, and CK19
	Basal cells positive for p63 and HMWK	CK14, p63, and active negative

The treatment of REAH is surgical excision. These lesions are usually limited in size and location, and, thus, endoscopic approaches are usually sufficient. It is important to differentiate REAH from inverted papilloma and sinonasal adenocarcinoma because the latter two are considered true neoplasms that would require more extensive resection.

Glandular (Seromucinous) Hamartoma

Glandular hamartomas were first described by Baillie and Batsakis in 1974 [58]. They can present at any age with a mean age in the fifth decade. Most lesions arise in the posterior nasal septum and rarely in the nasopharynx [59, 60]. Glandular hamartomas are benign polypoid masses that consist of an epithelial proliferation of small glands, serous acini, and tubules. Immunohistochemistry demonstrates glands with positive staining for S-100, CK7, and CK19 and a basal cell layer negative for CK 14, p63, and actin [60]. Some glandular hamartomas have clinical and pathologic features overlapping with those of REAH. Table 28.3 shows the pathologic findings used to differentiate a glandular hamartoma from REAH. Similar to REAH, treatment is surgical excision.

Acquired Sinonasal Lesions: Papillomatous

Sinonasal (Schneiderian) Papillomas

The first documented papilloma of the sinonasal cavity was described by Ward in 1854 [61]. Ringertz, in 1935, noted inversion of the epithelium into the underlying connective tissue and termed the lesion an “inverting” or “inverted” papilloma [62]. There are many synonyms used to describe sinonasal papillomas (Schneiderian papilloma, transitional cell papilloma, and epithelial papilloma). Schneiderian membrane refers to the ectodermally derived ciliated respiratory mucosa that lines

Table 28.4 WHO classification of Schneiderian papillomas

Inverted
Exophytic (i.e., fungiform)
Oncocytic (i.e., columnar or cylindrical)

Table 28.5 Common sites of origin of inverted papilloma (decreasing order or frequency)

Lateral nasal wall
Ethmoid cells
Maxillary sinus
Medial nasal wall/septum
Sphenoid sinus
Frontal sinus

the sinonasal tract, which can give rise to morphologically distinct papilloma [63]. The World Health Organization (WHO) advocates the classification of Schneiderian papillomas into three separate categories (Table 28.4) [64]. However, this terminology has not yet gained wide acceptance. There is a debate as to whether these are three distinct entities or part of a spectrum of papillomatosis. To minimize confusion, we will use the term "sinonasal papilloma" to discuss the various papillomas of the sinonasal tract, recognizing that there is controversy with the classification and terminology.

Sinonasal papillomas are relatively uncommon tumors of the nasal cavity, representing 0.5–4 % of all primary nasal tumors [65]. Sinonasal papillomas are the most common benign sinonasal tumors. They occur with an incidence of 0.2–0.6 % per 100,000. Men are affected more than woman (3:1). Presentation can occur at any age with a peak between the fifth and sixth decades, and it is extremely rare to present in childhood. Caucasians are at increased risk. Most cases are unilateral with no side predilection, but approximately 5 % are bilateral [66].

The etiology of sinonasal papillomas is unknown. Possible cases include allergies, chronic rhinosinusitis, airborne pollutants, and viral infection. Inverted papillomas can occur in the setting of allergies and chronic rhinosinusitis. The theory of chronic inflammation leading to a monoclonal cell proliferation has been proposed [67], but is not well supported, and no significant correlation has been found between these etiologies and inverted papilloma. Similarly, air pollution and carcinogens have been suggested as possible causes [68], but there are no significant studies to support this theory. Most literature investigating the etiology of inverted papilloma has focused on human papilloma virus (HPV). HPV is an epitheliotrophic virus and currently thought to be the leading cofactor in the pathogenesis of sinonasal papillomas. Both low-risk subtypes (HPV 6 and HPV 11) and high-risk subtypes (HPV 16 and HPV 18) have been identified in sinonasal papillomas. HPV 6 and HPV 11 have been found to be associated with both exophytic papillomas and inverted papillomas, but there is no association with oncocytic papillomas [63, 69]. There is some evidence that HPV 16 and HPV 18 may convey a higher risk of carcinogenesis in the setting of inverted papilloma, when compared with HPV 6 and HPV 11 [63, 70]. Sinonasal papillomas likely have a heterogeneous etiology, and further research is needed to elucidate these factors.

Patients most often present with unilateral nasal obstruction. Other symptoms include epistaxis, rhinorrhea, nasal discharge, facial pain, and epiphora. As the lesion expands into the orbit, it can lead to proptosis and diplopia. Physical examination often reveals a unilateral polypoid fleshy nasal mass. These lesions usually appear as an irregular friable lesion that often bleeds when manipulated. They are often reddish gray in color, but can easily be hidden among inflammatory polypoid disease.

Sinonasal papillomas can present in almost any location in the nasal cavity and paranasal sinuses. Anatomic sites for inverted papilloma have been well documented. The most common sites are the nasal listed in Table 28.5 in order of decreasing frequency, with the posterior lateral nasal wall being in the most common [66]. Exophytic papillomas tend to occur on the nasal septum. Oncocytic papillomas occur almost exclusively in the lateral nasal wall or in the maxillary or ethmoid sinuses [63].

Diagnostic Workup

Appropriate diagnostic workup for a sinonasal papilloma includes a comprehensive history and physical examination with nasal endoscopy, radiographic studies, and tissue biopsy. The history should focus on the duration and severity of nasal symptoms and appropriate questions to assess for orbital, perineural, and intracranial involvement. The nasal endoscopy should be performed at the initial consultation to assess the size, origin, and involvement of the lesion (Fig. 28.6a).

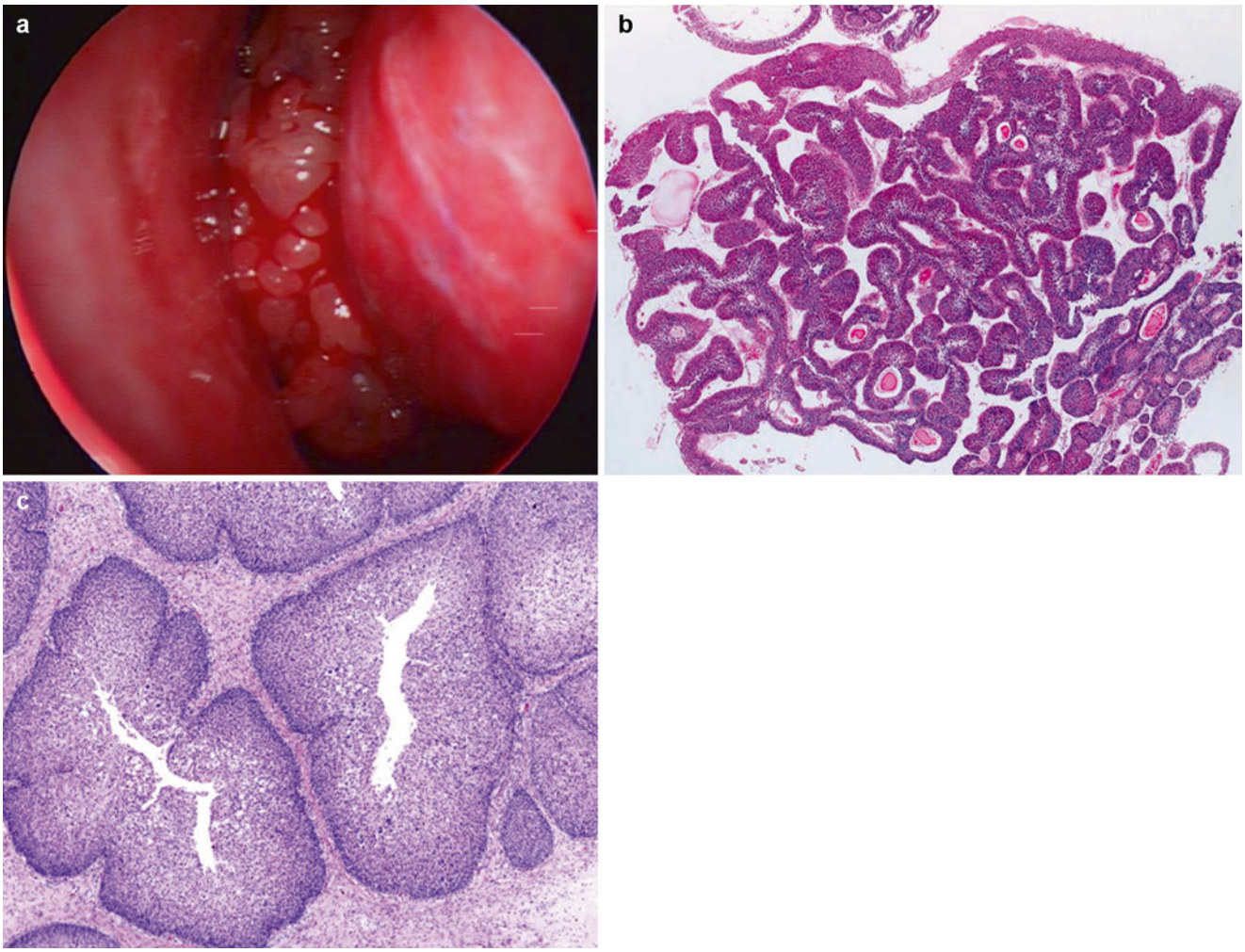


Fig. 28.6 (**a**) Nasal endoscopy of an inverting papilloma obstructing the right nasal cavity. (**b**) Inverted papilloma (H&E, original magnification ×2). (**c**) Inverted papilloma (H&E, original magnification ×10)

Imaging is tantamount in the workup. Computer tomography (CT) is considered the initial study of choice. Up to 75 % of patients with sinonasal papillomas will have evidence of various degrees of bony destruction (thinning, erosion, sclerotic changes). Areas of bone thickening may represent the site of attachment of the tumor [71]. CT alone often overestimates the degree of involvement because it is difficult to differentiate a papillomatous lesion from inspissated mucous, mucoperiosteal thickening, or nasal polyps. CT has a sensitivity of 69 % and a specificity of 10 % in diagnosing sinonasal papillomas [72]. Magnetic resonance imaging (MRI) is superior to CT in distinguishing papilloma from inflammatory disease. Sinonasal papillomas have a heterogeneous appearance on MRI. They appear slightly hyperintense on contrast-enhanced T1-weighted images, whereas secretions and mucus will not enhance but will be rimmed by a bright signal from the inflamed mucosa on contrast-enhanced T1-weighted images. They have an intermediate signal on T2-weighted images, whereas polyps and inspissated mucus appear hyperintense on T2-weighted images. A diagnosis for inverted papilloma can be suggested by a "convoluted cerebriform pattern" on T2-weighted or enhanced T1-weighted MRI [73]. Overall, CT is a very helpful initial imaging modality to assess to bony destruction, and MRI is very useful to define the extent of the lesion.

Biopsy is essential to the diagnosis of sinonasal papillomas. Biopsy should be preceded by appropriate imaging to rule out intracranial lesions that can present as sinonasal masses. Sinonasal papillomas can be divided into three histologic subtypes: inverted, exophytic (fungiform), and oncocytic (cylindrical, columnar). Inverted papillomas, which account for approximately 62 % of all sinonasal papillomas, have an endophytic growth pattern and often originate from the lateral nasal wall. Histology reveals hyperplastic epithelium inverting into the underlying stroma, with a distinct and intact basement membrane (Fig. 28.6a–c) [63, 74]. The epithelium of inverted papilloma is distinct from respiratory mucosa and lacks mucus-secreting cells and eosinophils. Exophytic or fungiform papillomas, which account for approximately 32 % of sinonasal papillomas, have an exophytic growth pattern as suggested by the name. Histology reveals hyperplastic squamous epithelium arranged in papillary fronds with exophytic growth [74]. Oncocytic papillomas are the rarest type, accounting for

Table 28.6 Pathologic findings of Schneiderian papillomas

	Inverted papilloma	Exophytic papilloma	Oncocytic papilloma
Gross	Lateral nasal wall	Nasal septum common	Lateral nasal wall or sinuses
	Large polypoid lesions	Gray-tan cauliflower-like	Small fragments of exophytic tissue
	Deep clefts on surface	Narrow stalk	
	Fibrous appearance		
Microscopic	Endophytic, inverted growth pattern with extension into stroma	Branching, exophytic proliferations	Multilayered columnar or oncocytic epithelium
	Multilayered thick nonkeratinizing squamous epithelium	Stratified squamous epithelium	Intraepithelial mucous cysts
	Intraepithelial mucous cysts	Intraepithelial mucous cysts	Seromucous glands in lamina propria
	No seromucous glands in stroma	Stroma with serous glands	
	Preserved basement membrane		
Immunohistochemical	CK7, CK8, CK19, p63, HMWK	n/a	n/a

Table 28.7 Krouse staging system for inverted papilloma

Stage	Description
I	Tumor limited to the nasal cavity
II	Tumor limited to the ethmoid sinus and/or medial and superior portions of maxillary sinus
III	Tumors involving lateral, inferior, anterior, or posterior walls of the maxillary sinus, sphenoid sinus, or frontal sinus
IV	Tumors extending outside sinonasal cavities (orbital or intracranial extension) or tumors associated with malignancy

Table 28.8 Han et al. staging system for inverted papilloma

Stage	Description
I	Tumor limited to nasal cavity, lateral nasal wall, medial maxillary sinus, ethmoid sinus, or sphenoid sinus
II	Tumor with extension lateral to medial maxillary wall
III	Tumor with extension into frontal sinus
IV	Tumor with extension outside the paranasal sinuses

Table 28.9 Cannady et al. staging system for inverted papilloma

Stage	Description
A	Tumor confined to nasal cavity, ethmoid sinuses, or medial maxillary sinus
B	Tumor with involvement of any maxillary wall (other than medial), frontal sinus, or sphenoid sinus
C	Tumor with extension outside the paranasal sinuses

approximately only 6 % of sinonasal papillomas. Histology reveals a multilayered epithelium with eosinophilic cytoplasm with intraepithelial mucin cysts [74]. The pathologic findings of the sinonasal papillomas are summarized in Table 28.6.

Inverted papillomas have been reported to have a 5–10 % risk of malignant transformation. Of all carcinomas associated with inverted papillomas, approximately two-thirds are synchronous and one-third is metachronous. Oncocytic papillomas have a slightly high risk of malignant transformation at 14–19 % [63, 75]. Squamous cell carcinoma is the most common malignant neoplasm associated with sinonasal papillomas. Exophytic papillomas have not been found to have malignant potential.

Several staging systems have been developed for inverting papilloma to aid in the classification of disease extent. These are summarized in Tables 28.7, 28.8, and 28.9 [76–78]. The most popular one is that proposed by Krouse [76]. He proposed a four-sage system based on the degree of invasion into the paranasal sinuses and the associated malignancy based on endoscopic and imaging findings.

Treatment

The role of medical therapy and radiotherapy is limited for this benign disease. Radiotherapy has been proposed when the tumor was inoperable, or as an adjunct when there is associated malignancy or incomplete removal [79]. Surgical therapy is the mainstay of treatment; however, the type and extent of surgical therapy has been debated. The goals of surgical therapy

Table 28.10 Types of surgery of inverted papilloma

Endoscopic	External
Endoscopic resection	Caldwell-Luc
Endoscopic ethmoidectomy	External ethmoidectomy
Endoscopic medial maxillectomy	Medial maxillectomy via lateral rhinotomy or Weber-Ferguson incision
	Medial maxillectomy via midfacial degloving

Table 28.11 Limitations to endoscopic approaches

Intracranial extension
Orbital extension, lacrimal fossa extension or V2 involvement
Extensive skull base erosion
Extensive frontal involvement
Extensive infratemporal fossa involvement
Extensive scarring and anatomic distortion from prior surgery

are to achieve exposure for complete tumor resection, provide an unobstructed view for postoperative surveillance, and minimize functional and aesthetic disabilities [74].

Current surgical techniques can be divided into endoscopic and external approaches (Table 28.10). Early attempts to treat inverted papillomas with simple and conservative procedures (i.e., non-endoscopic intranasal excision with or without Caldwell-Luc approach) resulted in high recurrence rates [66]. More aggressive treatment with en bloc ethmoidectomy and medial maxillectomy via a lateral rhinotomy approach have resulted in lower recurrence rates [80, 81]. Since the advent of endoscopic sinus surgery, endoscopic approaches, either alone or combined with external approaches, are evolving to be the approach of choice to minimize morbidities associated with external approaches. Endoscopic approaches can have limitations especially with extensive tumor extension (Table 28.11) [82]. However, improved endoscopic techniques are gradually redefining "endoscopic resectability" and have allowed for resection of areas traditionally resected by open external approach. Endoscopic medical maxillectomy has been described and reported to have similar recurrence rates with open medial maxillectomy procedures. Waitz and Wigand were the first to report in a series that endoscopic approaches did not have worse recurrence rates compared with open approaches [83]. A recent meta-analysis and systematic review of literature support endoscopic approach as a favorable option compared with other approaches [84, 85]. The large meta-analysis showed a 12 % rate of recurrence for the endoscopic group (714 patients) versus 20 % rate of recurrence for the non-endoscopic group (346 patients) [84]. However, it is important to recognize that often smaller and less aggressive tumors fall into the endoscopic treatment group. Endoscopic approaches for the resection of inverted papillomas can achieve similar recurrence rates compared to traditional external approaches.

External/Open Medial Maxillectomy

External approaches to the maxilla can be achieved with a lateral rhinotomy, Weber-Ferguson, or midface degloving approach. A lateral rhinotomy involves making a curvilinear incision between the medial canthus and the dorsum of the nose along the nasal facial groove (Fig. 28.7). The incision is made down to through the periosteum, and the periosteum is elevated to expose the medial orbital wall, anterior maxillary wall, and pyriform aperture. The modified Weber-Ferguson incision is a lateral rhinotomy incision combined with superior a horizontal subciliary incision to the lateral orbital rim and an inferior philtral lip-splitting incision (Fig. 28.7). This is often is used to access tumors with orbital and/or alveolus extension. An alternative approach to access the maxilla is the midfacial degloving approach which involves the following incision: bilateral intercartilaginous, septocolumellar transfixion, bilateral sublabial incisions from one maxillary tuberosity to another, and pyriform aperture incisions connecting the septocolumellar transfixion and intercartilaginous incisions. This approach achieves great exposure of the lateral nasal wall and pyriform aperture. These approaches can be combined with craniofacial approaches to treat lesions involving the skull base and anterior cranial fossa.

Whichever approach is chosen, the goal of the external approach is to achieve optimal exposure of the areas of tumor involvement. For tumors limited to the lateral nasal wall, a medial maxillectomy is usually sufficient for complete tumor removal. Circumferential osteotomies are performed to mobilize the medial maxilla. These include osteotomies through the inferior and anterior aspects of the medial maxillary wall, the medial wall of the orbital inferior to the frontoethmoid suture line, and the inferior orbital rim and floor. The specimen is then mobilized from the posterior wall of the maxillary sinus.

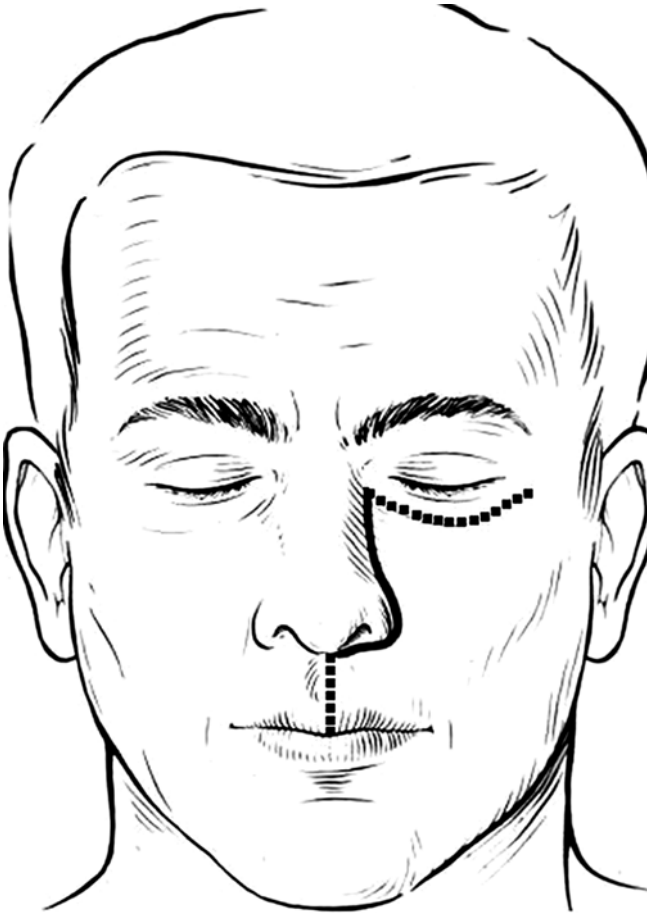


Fig. 28.7 Incisions for open maxillectomy. The lateral rhinotomy incision is shown (*solid line*), along with extensions (*dotted line*) to make a modified Weber-Ferguson incision

Endoscopic Medial Maxillectomy

The first endoscopic approach for sinonasal papilloma was reported by Stammberger in 1981. Whereas open approaches are able to resect the tumor en bloc, endoscopic approaches involve piecemeal resection of the tumor. The degree of endoscopic resection is determined by the extent and origin of the papilloma. Most inverted papillomas involve the lateral nasal wall and extend into the ethmoid and maxillary sinuses. As such, endoscopic resection with a medial maxillectomy, total ethmoidectomy, and partial or complete middle turbinectomy is sufficient.

Endoscopic medial maxillectomy involves resection of the inferior turbinate, medial maxillary wall, nasolacrimal duct, and ethmoid complex. The procedure begins with an uncinectomy and maxillary antrostomy. The maxillary antrostomy is enlarged posteriorly to the posterior wall of the maxillary sinus. The inferior turbinate is medialized and crushed, and then it is resected along the lateral nasal wall. Mucosal cuts are made to the floor of the nose. Bone cuts are then made with an osteotome along the floor of the nose to the posterior wall of the maxillary sinus. The medial maxillary wall is tethered by the nasolacrimal duct anteriorly, and this structure is transected, freeing the entire medial maxilla. A dacryocystorhinostomy can be performed at this point to prevent postoperative scarring and epiphora. Depending on the extent of the papilloma, an ethmoidectomy may be indicated to clear the ethmoid complex and lamina papyracea.

Complications

Complications can occur after both external and endoscopic surgeries for sinonasal papilloma. Blepharitis, diplopia, and dacryocystitis can occur after lateral rhinotomy approaches [82]. Weber-Ferguson approaches can lead to scarring with downward pull of the lower lid leading to ectropion [82]. Vestibular stenosis is a common complication after midfacial gloving. CSF leak can occur with both open and endoscopic procedures. Orbital complications can be serious and include orbital hematoma, diplopia, and blindness. Both approaches can lead to prolonged crusting, epiphora, synechiae/scarring, and epistaxis. It is important to counsel patient preoperatively on the risks associated with each approach.

Surveillance

Close follow-up is of utmost importance after surgery to monitor for disease recurrence. The recurrence rates reported in the literature have ranged from 28 to 74 % [70]. Most recurrences occur within the first 5 years of treatment [86]. Some authors recommend lifelong surveillance [87]. Recurrence can be monitored with in-office nasal endoscopy, and biopsies can be taken or imaging performed if suspicion is high for recurrence. There is no reliable histologic prognostic parameter for inverted papilloma recurrence. However, increased hyperkeratosis, increased mitotic index, and the absence of inflammatory polyps have been showed in some reports to be related to recurrence [88, 89]. One study found that patients with HPV 6 or HPV 11 have lower recurrence rates than those with HPV 16 or HPV 18 [90].

Conclusions

Congenital and acquired sinonasal lesions represent a unique category in the differential of a benign sinonasal mass. Sinonasal cysts are usually found in the pediatric population and originate from developmental anomalies. Sinonasal papillomas are a common nasal lesion, and the inverted and oncocytic types have a small but significant risk for malignant transformation. Recent research interest on HPV is helping to elucidate the underlying pathophysiology of the disease. The surgical management of congenital and acquired lesions centers around total excision and limitation of functional defects and cosmetic deformities. Recent advances in endoscopic sinus surgery have helped developed minimally invasive means to resect these lesions and minimize comorbidities.

References

1. Rahbar R, Resto VA, Robson CD, Perez-Atayde AR, Goumnerova LC, McGill TJ, Healy GB. Nasal glioma and encephalocele: diagnosis and management. Laryngoscope. 2003;113:2069–77.
2. Hughes GB, Sharpino G, Hunt W, Tucker HM. Management of the congenital midline nasal mass: a review. Head Neck Surg. 1980;2:222–33.
3. Hedlund G. Congenital frontonasal masses: developmental anatomy, malformations and MR imaging. Pediatr Radiol. 2006;36:647–62.
4. Elluru RG, Vijaysekaran S. Congenital malformations of the nose and paranasal sinuses. Rhinol Facial Plast Surg. 2009;11:123–38.
5. Szeremeta W, Parikh TD, Widelitz JS. Congenital nasal malformations. Otolaryngol Clin North Am. 2007;40:97–112.
6. Hoshaw TC, Walike JW. Dermoid cysts of the nose. Arch Otolaryngol. 1971;93:487–91.
7. Pratt LW. Midline cysts of nasal dorsum. Laryngoscope. 1965;75:968–80.
8. Rahbar R, Shah P, Mulliken JB, Robson CD, Perez-Atayde AR, Proctor MR, Kenna MA, Scott MR, McGill TJ, Healy GB. The presentation and management of nasal dermoid: a 30 year experience. Arch Otolaryngol Head Neck Surg. 2003;129:464–71.
9. Posnick JC, Bortoluzzi P, Armstrong DC, Drake JM. Intracranial nasal dermoid sinus cysts: computed tomographic scan findings and surgical results. Plast Reconstr Surg. 1994;93:745–54.
10. Sessions RB. Nasal dermoid sinuses – new concepts and explanations. Laryngoscope. 1982;92 Suppl 29:1–28.
11. Pollock RA. Surgical approaches to the nasal dermoid cyst. Ann Plast Surg. 1983;10:498–501.
12. Huisman TA, Schneider JF, Kellenberger CJ, Martin-Fiori E, Willi UV, Holzmann D. Developmental nasal midline masses in children: neuroradiological evaluation. Eur Radiol. 2004;14:243–9.
13. Denoyelle F, Ducroz V, Roger G, Garabedian EN. Nasal dermoid sinus cysts in children. Laryngoscope. 1997;107:795–800.
14. Pensler JM, Bauer BS, Naidich TP. Craniofacial dermoids. Plast Reconstr Surg. 1988;82:953–8.
15. Barkovich AJ, Vandermarck P, Edwards MS, Cogen PH. Congenital nasal masses: CT and MR imaging features in 16 cases. AJNR Am J Neuroradiol. 1991;12:105–16.
16. Kelly JH, Strome M, Hall B. Surgical update on nasal dermoids. Arch Otolaryngol. 1982;108:239–42.
17. Rohrich RJ, Lowe JB, Schwartz MR. The role of open rhinoplasty in the management of nasal dermoid cysts. Plast Reconstr Surg. 1999;104:2163–71.
18. Weiss DD, Robson CD, Mulliken JB. Transnasal endoscopic excision of midline nasal dermoid from the anterior cranial base. Plast Reconstr Surg. 1998;102:2119–23.
19. van Aalst JA, Luerssen TG, Whitehead WE, Havlik RJ. “Keystone” approach for intracranial nasofrontal dermoid sinuses. Plast Reconstr Surg. 2005;116:13–9.
20. Kellman RM, Goyal P, Rodziewicz GS. The transglabellar subcranial approach for nasal dermoids with intracranial extension. Laryngoscope. 2004;114:1368–72.
21. Karma P, Rasanen O, Karja J. Nasal gliomas: a review and report of two cases. Laryngoscope. 1977;87(7):1169–79.
22. Guthrie D, Dott N. The occurrence of brain-tissue within the nose: the so-called nasal glioma. J Laryngol Otol. 1927;2:464–5.
23. Gorenstein A, Kern EB, Facer GW, Laws ER. Nasal gliomas. Arch Otolaryngol. 1980;106:536–40.
24. Hoving EW. Nasal encephaloceles. Childs Nerv Syst. 2000;16:702–6.

25. Holmes AD, Meara JG, Kolker AR, Rosenfeld JV, Klug GL. Frontoethmoidal encephaloceles: reconstruction and refinements. J Craniofac Surg. 2001;12:6–18.
26. Singh AK, Upadhyaya DN. Sincipital encephaloceles. J Craniofac Surg. 2009;20:1851–5.
27. Songur E, Mutluer S, Gurler T, Bilkay U, Gorken C, Guner U, Celik N. Management of frontoethmoidal (sincipital) encephalocele. J Craniofac Surg. 1999;10:135–9.
28. Arshad AR, Selvapragasam T. Frontoethmoidal encephalocele: treatment and outcome. J Craniofac Surg. 2008;19:175–83.
29. Rojvachiranonda N, Mahatumarat C, Taecholarn C. Correction of the frontoethmoidal encephalomeningocele with minimal facial incision: modified Chula technique. J Craniofac Surg. 2006;17:353–7.
30. Donald PJ, Gluckman JL, Rice DH. The sinuses. New York: Raven Press; 1995.
31. Shashy RG, Durairaj V, Holmes JM, Hohberger GG, Thompson DM, Kasperbauer JL. Congenital dacryocystocele associated with intranasal cysts: diagnosis and management. Laryngoscope. 2003;113:37–40.
32. Mazzara CA, Respler DS, Jahn AF. Neonatal respiratory distress: sequela of bilateral nasolacrimal duct obstruction. Int J Pediatr Otorhinolaryngol. 1993;25:209–16.
33. Leonard DS, O'Keefe M, Rowley H, Hughes JP. Neonatal respiratory distress secondary to bilateral intranasal dacryocystocoeles. Int J Pediatr Otorhinolaryngol. 2008;72:1873–7.
34. Roy D, Guevara N, Santini J, Castillo L. Endoscopic marsupialization of congenital nasolacrimal duct cyst with dacryocoele. Clin Otolaryngol. 2002;27:167–70.
35. Peterson RA, Robb RM. The natural course of congenital obstruction of the nasolacrimal duct. J Pediatr Ophthalmol Strabismus. 1978;15:246–50.
36. Nucci P, Capoferri C, Alfarano R, Brancato R. Conservative management of congenital nasolacrimal duct obstruction. J Pediatr Ophthalmol Strabismus. 1989;26:39–43.
37. Hepler KM, Woodson GE, Keams DB. Respiratory distress on the neonate: sequela of a congenital dacryocystocele. Arch Otolaryngol Head Neck Surg. 1995;121:1423–5.
38. Paparella MM. Mucosal cyst of the maxillary sinus: diagnosis and management. Arch Otolaryngol. 1963;77:650–70.
39. Ruprecht A, Batniji S, El-Neweihi E. Mucous retention cyst of the maxillary sinus. Oral Surg Oral Med Oral Pathol. 1986;62:728–31.
40. Halsted CL. Mucosal cysts of the maxillary sinus: report of 75 cases. J Am Dent Assoc. 1973;87:1435–41.
41. Wang JH, Jang YJ, Lee BJ. Natural course of retention cysts of the maxillary sinus: long-term and follow-up results. Laryngoscope. 2007;117:34104.
42. Albu S. Symptomatic maxillary sinus retention cysts: should they be removed? Laryngoscope. 2010;120:1904–9.
43. Soon SR, Lim CM, Singh H, Sethi DS. Sphenoid sinus mucocele: 10 cases and literature review. J Laryngol Otol. 2010;124:44–7.
44. Stankiewicz JA. Sphenoid sinus mucocele. Arch Otolaryngol Head Neck Surg. 1989;115:735–40.
45. Busaba NY, Salman SD. Maxillary sinus mucoceles: clinical presentation and long-term results of endoscopic surgical treatment. Laryngoscope. 1999;109:1446–9.
46. Kennedy DW, Josephson JS, Zinreich J, Mattox DE, Goldsmit MM. Endoscopic sinus surgery for mucoceles: a viable alternative. Laryngoscope. 1989;99:885–95.
47. Har-El G. Endoscopic management of 108 sinus mucoceles. Laryngoscope. 2001;111:2131–4.
48. Har-El G. Transnasal endoscopic management of frontal mucoceles. Otolaryngol Clin North Am. 2001;34:243–51.
49. Athre R, Ducic Y. Frontal sinus hamartomas. Am J Otolaryngol. 2005;26:419–21.
50. Endo R, Matsuda H, Takahasi M, et al. Respiratory epithelial adenomatoid hamartoma in the nasal cavity. Acta Otolaryngol. 2002;122:398–400.
51. Wenig BM, Heffner DK. Respiratory epithelial adenomatoid hamartomas of the sinonasal tract and nasopharynx: a clinicopathologic study of 31 cases. Ann Otol Rhinol Laryngol. 1995;104:639–45.
52. Fitzhugh VA, Mirani N. Respiratory epithelial adenomatoid hamartoma: a review. Head Neck Pathol. 2008;2:203–8.
53. Kessler HP, Unterman B. Respiratory epithelial adenomatoid hamartoma of the maxillary sinus presenting as a periapical radiolucency: a case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;97:607–12.
54. Himi Y, Yoshizaki T, Sato K, et al. Respiratory epithelial adenomatoid hamartoma of the maxillary sinus. J Laryngol Otol. 2002;116: 317–18.
55. Liang J, O'Malley Jr BW, Feldman M, et al. A case of respiratory epithelial adenomatoid hamartoma. Am J Otolaryngol. 2007;28:277–9.
56. Delbrouck C, Fernandez Aguilar S, Choufani G, et al. Respiratory epithelial adenomatoid hamartoma associated with nasal polyposis. Am J Otolaryngol. 2004;25:282–4.
57. Ingram WF, Noone MC, Gillespie MB. Respiratory epithelial adenomatoid hamartoma: a case report. Ear Nose Throat J. 2006;85:190–2.
58. Baillie EE, Batsakis JG. Glandular (seromucinous) hamartoma of the nasopharynx. Oral Surg Oral Med Oral Pathol. 1974;38:760–2.
59. Pineda-Daboin KM. Hamartomas seromucinous nasals. Patologia. 2003;41:103–6.
60. Perez-Ordonez B. Hamartomas, papillomas and adenocarcinomas of the sinonasal tract and nasopharynx. J Clin Pathol. 2009;62:1085–95.
61. Ward N. A mirror of the practice of medicine and surgery in the hospitals of London. Lancet. 1854;2:480–2.
62. Ringertz N. Pathology of malignant tumors arising in the nasal and paranasal cavities and maxilla. Acta Otolaryngol. 1938;27(Suppl):31–42.
63. Barnes L. Schneiderian papillomas and nonsalivary glandular neoplasms of the head and neck. Mod Pathol. 2002;15:279–97.
64. Barnes L, Tse LLY, Hunt JL. Schneiderian papillomas. In: Barnes L, Eveson JW, Reichert P, et al., editors. World Health Organization classification of tumors, pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 28–32.
65. Buchwald C, Nielsen LH, Nielsen PL, et al. Inverted papilloma: a follow-up study including primarily unacknowledged cases. Am J Otolaryngol. 1989;10:272–81.
66. Krouse JH. Endoscopic treatment of inverted papilloma: safety and efficacy. Am J Otolaryngol. 2001;22:87–99.
67. Vrabec DP. The inverted schneiderian papilloma: a 25-year study. Laryngoscope. 1994;104:582–605.
68. Deitmer T, Wiener C. Is there an occupational etiology of inverted papilloma of the nose and sinuses? Acta Otolaryngol. 1996;116:762–5.
69. Kraft M, Simmen D, Casas R, Pfaltz M. Significance of human papillomavirus in sinonasal papillomas. J Laryngol Otol. 2001;115:709–14.
70. Eggers G, Mühling J, Hassfeld S. Inverted papilloma of paranasal sinuses. J Craniomaxillofac Surg. 2007;35:21–9.

71. Lund VJ, Lloyd G. Radiologic changes associated with inverted papilloma of the nose and paranasal sinuses. Br J Radiol. 1984;57:455–61.
72. Sukenik MA, Casiano R. Endoscopic medial maxillectomy for inverted papillomas of the paranasal sinuses: value of the intraoperative endoscopic examination. Laryngoscope. 2000;110:39–42.
73. Ojiri H, Ujita M, Tada S, Fukuda K. Potentially distinctive features of sinonasal inverted papilloma on MR imaging. Am J Roentgenol. 2000;175:465–8.
74. Anari S, Carrie S. Sinonasal inverted papilloma: narrative review. J Laryngol Otol. 2010;124:705–15.
75. Kim K, Kim D, Koo Y, et al. Sinonasal carcinoma associated with inverted papilloma: a report of 16 cases. J Craniomaxillofac Surg. 2012;40:125–9.
76. Krouse JH. Development of a staging system for inverted papilloma. Laryngoscope. 2000;110:965–8.
77. Han JK, Smith TL, Loehrl T, Toohill RJ, Smith MM. An evolution in the management of sinonasal inverting papilloma. Laryngoscope. 2001;111:1395–400.
78. Cannady SB, Batra PS, Sautter NB, Roh HJ, Citardi MJ. New staging system for sinonasal inverted papilloma in the endoscopic era. Laryngoscope. 2007;117:1283–7.
79. Dolgin SR, Zaveri VD, Casiano RR, et al. Different options for treatment of inverting papilloma of the nose and paranasal sinuses: a report of 41 cases. Laryngoscope. 1992;102:231–6.
80. Myers EN, Schramm VL, Barnes EL. Management of inverted papilloma of the nose and paranasal sinuses. Laryngoscope. 1981;91:2071–84.
81. Weissler MC, Montgomery WW, Turner PA, et al. Inverted papilloma. Ann Otol Rhinol Laryngol. 1986;95:215–21.
82. Tomenzoli D, Castelnuovo P, Pagella F, et al. Different endoscopic surgical strategies in the management of inverted papilloma of the sinonasal tract: experience with 47 patients. Laryngoscope. 2004;114:193–200.
83. Waitz G, Wigand ME. Results of endoscopic sinus surgery for the treatment of inverted papillomas. Laryngoscope. 1992;102:917–21.
84. Busquets JM, Hwang PH. Endoscopic resection of sinonasal inverted papilloma: a meta-analysis. Otolaryngol Head Neck Surg. 2006;134(3):476–82.
85. Karkos PD, Fyrmpas G, Carrie SC, Swift AC. Endoscopic versus open surgical interventions for inverted nasal papilloma: a systematic review. Clin Otolaryngol. 2006;31:499–503.
86. Mirza S, Bradley PJ, Acharya A, Stacey M, Jones NS. Sinonasal inverted papillomas: recurrence, and synchronous and metachronous malignancy. J Laryngol Otol. 2007;121:857–64.
87. von Buchwald C, Bradley PJ. Risks of malignancy in inverted papilloma of the nose and paranasal sinuses. Curr Opin Otolaryngol Head Neck Surg. 2007;15:95–8.
88. Batsakis JG, Suarez P. Schneiderian papillomas and carcinomas: a review. Adv Anat Pathol. 2001;8:53–64.
89. Katori H, Nozawa A, Tsukuda M. Histopathological parameters of recurrence and malignant transformation in sinonasal inverted papilloma. Acta Otolaryngol. 2006;126:214–18.
90. Beck JC, McClatchey KD, Lesperance MM, et al. Presence of human papillomavirus predicts recurrence of inverted papilloma. Otolaryngol Head Neck Surg. 1995;113:49–55.

Chapter 29
Tumors of the Nose and Paranasal Sinuses

Aaron D. Robinson, Jonathan Liang, and Quang Luu

Introduction

Nasal and paranasal sinus tumors encompass a wide variety of both benign and malignant pathologies. Challenges lie in the diagnosis and treatment of these tumors as the confined spaces of the nasal vault and paranasal sinuses necessarily force these tumors in close proximity to the orbit, the cavernous sinuses, the base of the skull, the hard palate and dentition, and the soft tissues of the nose and face. The relative rarity of these tumors makes definitive treatment recommendations difficult.

Relevant Anatomy

The borders of the nasal cavity extend from the nose anteriorly to the nasopharynx posteriorly and from the palatine process of the maxillary bone and horizontal plate of the palatine bone inferiorly to the nasal bone, frontal bone, cribriform plate of the ethmoid bone, and sphenoid body superiorly. The septum divides the nasal cavity into right and left halves. Laterally, the nasal cavity ends at the medial wall of the maxillary sinus (Fig. 29.1).

The paranasal sinuses include the paired maxillary sinuses, ethmoid sinuses, sphenoid sinuses, and frontal sinuses. Primary lymphatic drainage for the maxillary antrum includes the parotid, submandibular, retropharyngeal, and jugular nodes [1].

History

Patients with nasal and paranasal sinus tumors present with various symptoms depending on location of the tumor and involvement of adjacent structures. The most common symptoms of nasal cavity tumors include obstruction of airflow through the nose, nasal discharge, pain, and epistaxis (Table 29.1). Sphenoid sinus neoplasms that involve the cavernous sinuses laterally can cause defects of the third, fourth, and sixth cranial nerves. Paranasal sinus tumors manifest insidiously, often hidden within the sinus recesses and mimicking sinusitis or headaches until involvement of adjacent structures such as the eye, nasolacrimal duct, pterygopalatine fossa, palate, and optic chiasm lead to symptoms such as visual changes, epiphora, loss of sensation, loosening of teeth, and double vision. Unfortunately, this insidious presentation explains the often advanced-stage presentation of paranasal sinus tumors.

A.D. Robinson, MD • Q. Luu, MD (✉)
Department of Otolaryngology – Head and Neck Surgery, University of California, Davis Medical Center, 2521 Stockton Blvd, Ste 7200, Sacramento, CA 95817, USA
e-mail: aaron.robinson@ucdmc.ucdavis.edu; quang.luu@ucdmc.ucdavis.edu

J. Liang, MD
Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins School of Medicine, 601 N. Caroline Street, Baltimore, MD 21287, USA

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_29,

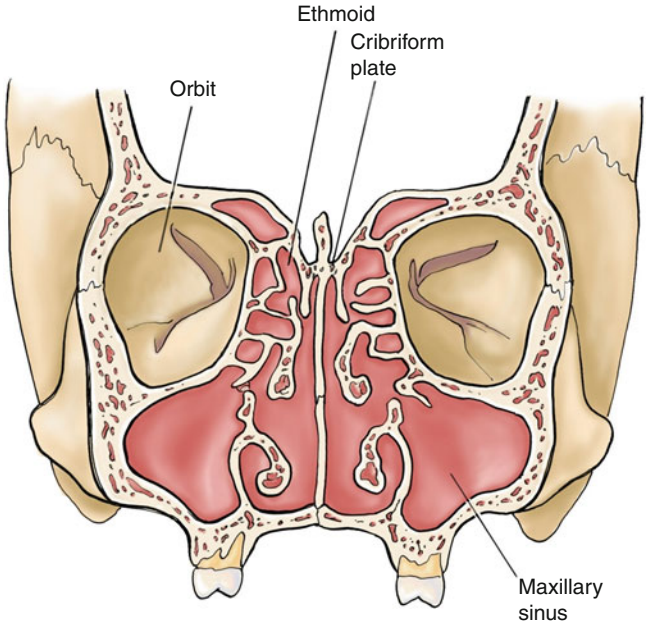


Fig. 29.1 Relationship of paranasal sinuses to the base of skull, orbits, and palate (Reprinted from Donald [102]. With permission from Lippincott Williams and Wilkins)

Table 29.1 Most common presenting symptoms of paranasal sinus tumors

Nasal obstruction	Headache	Nasal discharge	Epistaxis
Anosmia	Diplopia	Cranial nerve palsies	Anesthesia of teeth
Proptosis	Epiphora	Eustachian tube dysfunction	Lymphadenopathy

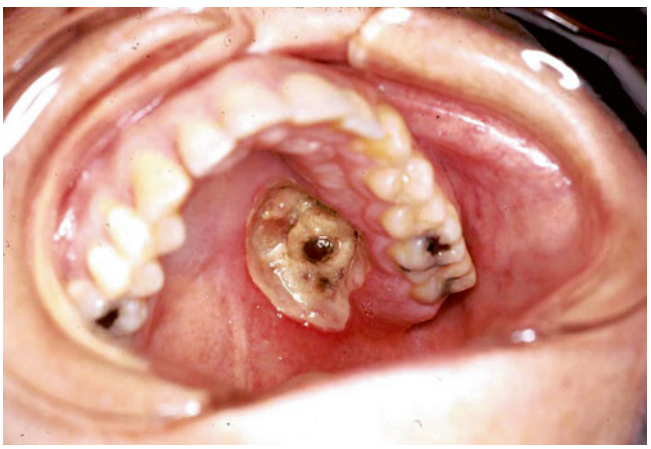


Fig. 29.2 Tumor eroding through hard palate

Physical Examination

Physical examination findings specific to pathology in the nasal and paranasal sinuses are often elicited in a complete head and neck examination. Thorough skin examination can reveal subtle erythema from underlying tumor inflammation. Intraoral examination can reveal erosion of tumor into the soft and hard palate (Fig. 29.2) or loosening of teeth demonstrating submucosal fullness or even frank tumor. Cranial nerve examination can reveal visual changes from optic nerve involvement, numbness in the trigeminal nerve distribution, ocular palsy from abducens and trochlear nerve involvement, and numbness in neurosomes supplied by the nasopalatine nerve and infraorbital nerve. Dry eye suggests possible involvement of the Vidian nerve, while epiphora can suggest involvement of the nasolacrimal duct. Neck palpation, paying particular attention to perifacial, submental, parotid, and upper cervical nodes, helps clinically stage the disease extent.

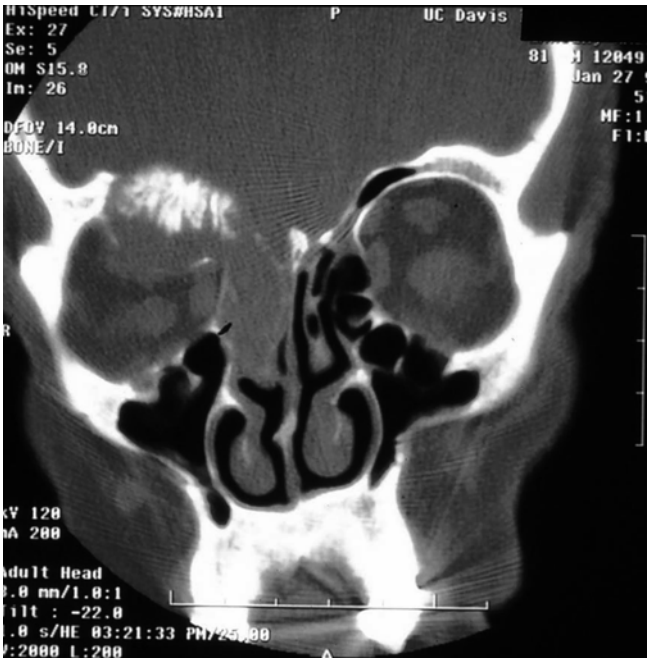


Fig. 29.3 Inverting papilloma eroding into the anterior cranial fossa

Endoscopy is a critical component of sinonasal tumor evaluation. It allows for gross examination of anatomic spread of a lesion and may guide biopsy. It may be limited, however, especially in a clinic setting, in examination of recessed areas such as the anterior cranial vault, orbit, and pterygopalatine fossa.

Imaging

Computed tomography has been a mainstay of paranasal sinus imaging, especially for inflammatory diseases. It provides excellent detail when imaging thin bony walls such as those between sinus cells, the lamina papyracea, and the cribriform plate [2]. Mucosal thickening is appreciated easily. However, magnetic resonance imaging (MRI) is more useful in differentiating benign from malignant tumors. Signal characteristics often allow separation of tumor from normal structures such as the periosteal lining of the periorbita and dura mater. Furthermore, tumor infiltration can be discerned more easily with MRI [3]. Postoperative MRI, however, is somewhat limited for surveillance of recurrent disease as the signal of treated tissues may have changed [4].

Computerized tomography (CT) is superior to MRI for demonstrating fibro-osseous lesions such as an osteoma, an ossifying fibroma, and fibrous dysplasia. MRI is typically superior to CT scan for soft tissue delineation. Benign soft tissue lesions such as inverted papilloma and juvenile nasopharyngeal angiofibromas exhibit characteristic qualities on imaging that may aid in the diagnosis, which will be discussed later in this chapter [5].

Imaging is crucial in mapping tumor extent (Figs. 29.3, 29.4, and 29.5). Most sinonasal malignancies arise from the maxillary sinus, while the next most common site is the nasoethmoidal area. Careful analysis of imaging for nasoethmoidal tumors must include an assessment of the integrity of the orbit, the floor of the anterior cranial fossa, and the sphenoid sinus. If the bone of the lamina papyracea is eroded, an assessment of the periorbita must be made, as patients in whom the periorbita is intact may be spared an orbital exenteration. MRI may demonstrate a thin hypointensity on T2 between the tumor and orbital fat, suggesting integrity of the periorbita [5]. Although the absolute determination will be made intraoperatively, this information is useful for preoperative planning and patient counseling. The radiologic assessment of the skull base naturally includes assessment of the bony interface, and dural changes are better characterized by MRI. Thus, examining the signal changes of the bone/periosteum of the cribriform, of the overlying dura mater, and the subarachnoid space is important.

Because of the complex anatomy and plethora of nerves in the nose and paranasal sinuses, imaging of perineural spread is necessary. Both nerve enhancement and nerve and foraminal enlargement are sensitive predictors of nerve involvement [6]. Disruption of the nerve-blood barrier from tumor infiltration allows seepage of iodinated or

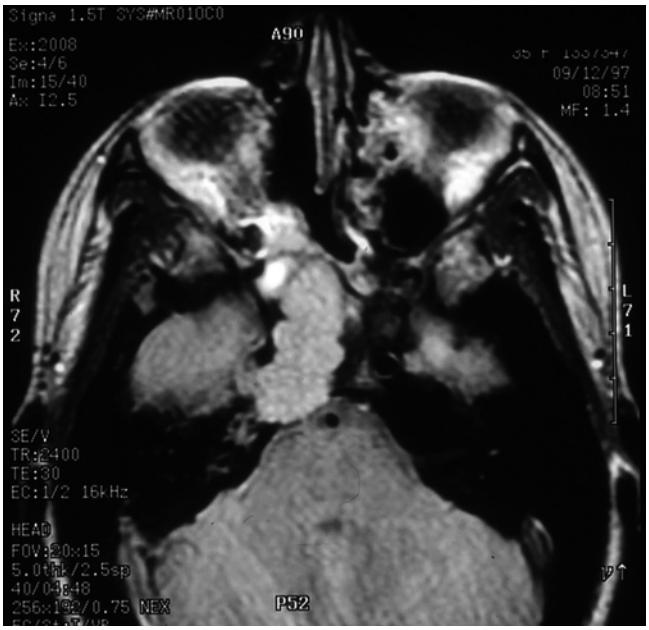


Fig. 29.4 Imaging is important to assess paranasal sinus tumor relation to the orbit. This case demonstrates an inverting papilloma with intracranial invasion and periorbital involvement

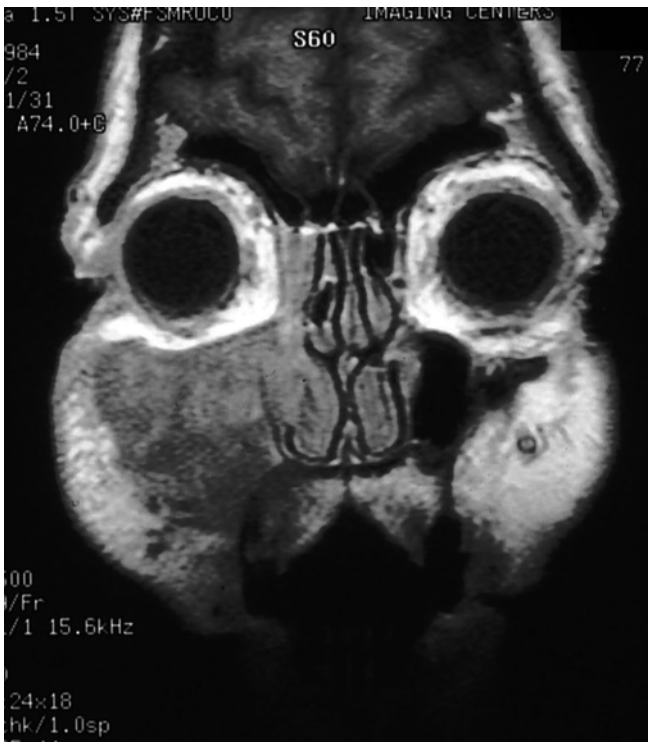


Fig. 29.5 Maxillary sinus carcinoma with invasion into infratemporal fossa and soft tissues of the face

paramagnetic contrast agents, which accounts for segmental nerve enhancement on MRI. Special attention should be directed to Meckel's cave, which is a retrograde central area through which the trigeminal nerve branches reside (Fig. 29.6).

Fused positron emission topography/computed tomography (PET/CT) is increasingly used in staging and management of head and neck cancer. However, the paucity of literature about its role in sinonasal tumor management makes strong recommendations impossible. Several papers suggest that PET/CT may be useful in detection of recurrent disease [5].

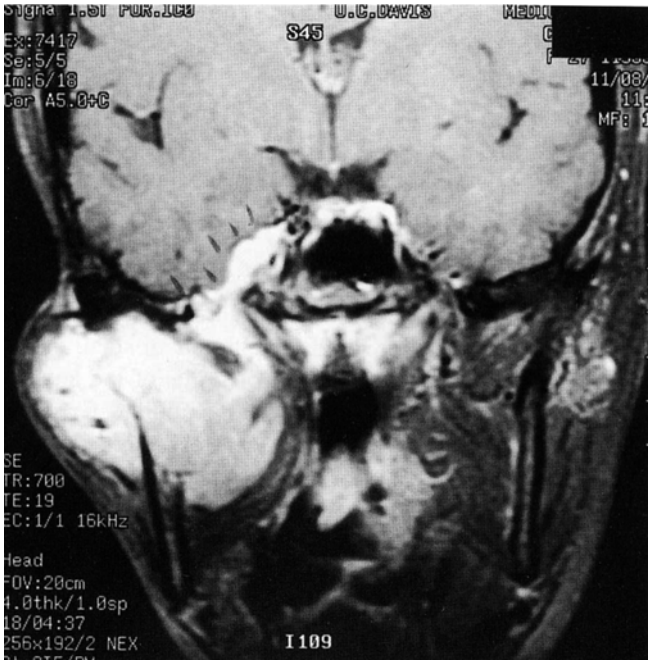


Fig. 29.6 Primary nerve sheath tumor involving trigeminal nerve, with widening of Meckel's cave

Biopsy

Biopsies are important in establishing a tumor diagnosis prior to deciding on definitive treatment. In the clinic setting, excluding coagulopathic patients, it may be reasonable to obtain tissue if the clinician is confident that the tumor arises from the septum, lateral nasal wall, or turbinate, and that generous bleeding can be easily controlled. Furthermore, there should be little suspicion for intracranial pathologies such as encephaloceles or vascular tumors. However, should the origin of the tumor be impossible to ascertain or if a juvenile nasopharyngeal angiofibroma or vascular-appearing tumor is suspected, it may be prudent to obtain imaging to rule out such lesions. Biopsy in the operating room affords a more controlled setting as significant blood loss from biopsy of friable tumors is not uncommon.

Benign Tumors

Juvenile Nasopharyngeal Angiofibroma

Juvenile nasopharyngeal angiofibroma (JNA) was first described by Friedberg in 1940. It is a rare benign vascular lesion and accounts of 0.5 % of all head and neck tumors [7]. It is a lesion most commonly found in adolescent and prepubescent males. Occurrence in females is rare. It often presents with symptoms of nasal obstruction and epistaxis. The etiology is unknown, but theories include hormonal activation and desmoplastic response of the nasopharyngeal periosteum or embryonic fibrocartilage. Patients with the familial adenomatous polyposis gene have a 25-fold risk of having this lesion [8].

On endoscopic examination, patients clearly have a nasal mass. The mass commonly appears sessile, lobulated, rubbery, and red-pink to tan-gray in appearance. Patients can also present with an orbital mass and proptosis. Large extensive tumors may lead to Eustachian tube dysfunction, zygomatic swelling, and trismus. The lesion usually arises near the posterior attachment of the middle turbinate, adjacent to the sphenopalatine artery.

Radiographically, JNA presents as a heterogenous nasal mass in the region of the sphenopalatine foramen. CT helps to define tumor extent, and MRI can help delineate intracranial involvement. JNAs can appear dumbbell shaped with one end in the nasopharynx and the other in the pterygopalatine fossa. Their growth may result in bowing of the posterior wall of the maxillary sinus on CT, termed a Holman-Miller sign, as well as erosion of the pterygoid plates. Angiography classically shows a conglomerate of blood vessels from branches of the external carotid system feeding the area of the mass. The main blood supply of JNA is usually the internal maxillary artery.

Table 29.2 Sessions classification of JNA

Stage I	A: Tumor limited to posterior nares and/or nasopharyngeal vault
	B: Tumor involving posterior nares and/or nasopharyngeal vault with involvement of at least 1 paranasal sinus
Stage II	A: Minimal lateral extension into pterygomaxillary fossa
	B: Full occupation of pterygomaxillary fossa with or without superior erosion of orbital bones
Stage III	A: Erosion of skull base (middle cranial fossa/pterygoid base); minimal intracranial extension
	B: Extensive intracranial extension with or without extension into cavernous sinus

Table 29.3 Fisch classification of JNA

Stage I	Tumors limited to nasal cavity or nasopharynx with no bony destruction
Stage II	Tumors invading pterygomaxillary fossa, paranasal sinuses with bony destruction
Stage III	Tumors invading infratemporal fossa, orbital, and/or parasellar region remaining lateral to cavernous sinus
Stage IV	Tumors invading cavernous sinus, optic chiasmal region, and/or pituitary fossa

JNAs originate from myofibroblasts. Histologically, JNAs demonstrate characteristic thin-walled vessels which lack elastic fibers and have absent or incomplete smooth muscle. Immunohistochemistry is strongly positive for vimentin.

Several staging systems exist. The most commonly used are those formulated by Sessions and Fisch (Tables 29.2 and 29.3).

Treatment for JNA includes medical and surgical therapy. Medical therapy commonly includes hormonal therapy (testosterone receptor blocker flutamide), radiotherapy (external beam, stereotactic, and conformal radiotherapy), and chemotherapy [7]. Studies have demonstrated that local control and recurrence rates with radiation are comparable to surgical results [9]. Surgical therapy includes both open approaches and endoscopic approaches. Various open approaches (transoral, transfacial, and combined craniofacial approaches) are available, and tumor size and extent will dictate the optimal choice. Preoperative embolization is typically recommended to minimize surgical blood loss, but it carries the significant but rare risk of blindness.

Recurrence rates have been reported between 30 and 50 %. Risk factors for recurrence include tumor in the pterygoid fossa, erosion of the clivus, intracranial extension, young age, and arterial feeders from the internal carotid artery. Malignant transformation is exceedingly rare and has only been reported in a handful of cases [10].

Osteoma

Osteomas are benign growths of bone. They are one of the most common benign tumors of the nose and sinuses. It is a common incidental finding in many plain radiographs and CT scans [11]. Osteomas tend to occur in men in the third to fourth decades of life. Common locations include the frontal and ethmoid sinuses and less commonly in the sphenoid and maxillary sinuses. The etiology of osteomas is not well understood. The growth rate is slow, approximately at 1.61 mm per year [12]. Osteomas can be observed in conjunction with Gardner's syndrome. Gardner's syndrome is a genetic disorder characterized by multiple polyps of the colon in association with osteomas of the skull and multiple soft tissue tumors.

Endoscopic examination of an osteoma reveals a smooth protuberance covered by normal-appearing mucosa. Grossly, osteomas appear as hard, white, multi-lobulated masses. Histologically, they usually have dense mature lamellar bone with a variable amount of interosseus space. Subtypes include ivory and mature variants. Ivory osteomas have hard dense bone with few fibrous components and thus require more extensive surgical drilling. Mature osteomas have cancellous bone and interosseous spaces.

Small osteomas can often go untreated. Larger and more extensive osteomas, especially with frontal or orbital involvement, may be symptomatic and warrant surgical excision. Obstructive osteomas can disturb mucosal flow and lead to mucocele formation, which may also warrant surgical excision. Local excision with a margin of normal bone is recommended. This can be performed through a variety of open approaches such as osteoplastic flap or Lynch procedures. Endoscopic approaches are often limited for osteomas unless they are small and easily accessible with endoscopic instrumentation.

Table 29.4 Distinguishing histopathologic features between ossifying fibroma and fibrous dysplasia

	Ossifying fibroma	Fibrous dysplasia
Margins/borders	Well defined	Poorly defined
Histology	Lamellar mature bone	Abortive bony trabeculae and woven bone with hypocellular and collagenized stroma
	Closely packed spindle cells that form whorls	

Ossifying Fibroma and Fibrous Dysplasia

Ossifying fibroma and fibrous dysplasia are benign bony lesions that can occur in the noses and sinuses. Once they were regarded as similar entities, but Reed in 1963 differentiated these lesions [13]. Ossifying fibroma is a true benign neoplasm. In contrast, fibrous dysplasia is a genetically based developmental anomaly that results in replaced normal bony tissue with immature woven bone of variable cellularity. Histologically, fibrous dysplasia lacks a capsule and has immature bone without osteoblastic activity [14]. See Table 29.4 for comparison.

Ossifying fibromas originate from mesenchymal blast cells. They commonly affect the mandible and maxilla, and sinonasal involvement is rare. There is a female predilection. Ossifying fibromas usually present between the second and fourth decades. Radiographically, these lesions appear as well-circumscribed lesions with a characteristic sclerotic band (osteoblastic rimming). These lesions have high signal intensity of T2-weighted MRI and enhance with gadolinium. The natural history of most ossifying fibromas is to regress over time. However, surgical resection is recommended and curative for locally aggressive lesions.

Fibrous dysplasia is not a true neoplasm—it is a noninherited developmental anomaly of bone in which normal bone marrow is replaced by fibro-osseous tissue. This condition was first described by Lichtenstein and Jaffe in 1942 [15]. There are two forms of fibrous dysplasia: monostotic (single bone) and polyostotic (multiple bones). The monostotic type is the most common type and accounts for 70–80 % of cases [16]. This form is usually asymptomatic until the second and third decades of life. The polyostotic form accounts for 20–30 % of cases, and patients typically present in childhood [16]. Craniofacial and skull bone involvement is more common in the polyostotic form [17]. The most severe form of polyostotic fibrous dysplasia is McCune-Albright syndrome (polyostotic lesions, endocrinopathy, precocious puberty, and café au lait spots). Radiographically, these lesions show ground-glass appearance. There is a heterogeneous low to intermediate signal on T1-weighted and T-2 weighted MRI and similar heterogeneous enhancement with gadolinium. Histologically, these lesions demonstrate a fibrocellular matrix of immature collagen containing irregularly shaped trabeculae of immature and inadequately mineralized bone.

Malignant transformation is rare, occurring only in 0.5 % of monostotic and 4 % of polyostotic forms. There is no risk of monostotic form transforming into the polyostotic form. The risk of malignant transformation is increased with radiation doses, and thus the role of radiotherapy is limited. Usually no surgical treatment is required since bone lesions do not progress beyond puberty. Follow-up radiographs every 6 months to evaluate for disease progression have been recommended. Surgical excision or decompression is indicated for correction of disfiguring deformities or symptomatic lesions producing mass effect. Radical surgery is the treatment of choice; however, the proximity of the lesion to critical structures may dictate a subtotal or curettage procedure to minimize functional deficits.

Sinonasal (Schneiderian) Papillomas

This tumor is discussed in depth elsewhere in this text. Briefly, sinonasal papillomas can be divided into three histologic subtypes: inverted, exophytic (fungiform), and oncocytic (cylindrical, columnar). Inverted papillomas, which account for approximately 62 % of all sinonasal papillomas, have an endophytic growth pattern and often originate from the lateral nasal wall. They are associated with a reported 5–10 % malignant transformation risk, most often squamous cell carcinoma. Sinonasal papillomas have been referred to by many synonyms (Schneiderian papilloma, transitional cell papilloma, and epithelial papilloma). Schneiderian membrane refers to the ectodermally derived ciliated respiratory mucosa that lines the sinonasal tract, which can give rise to morphologically distinct papillomas [18].

Sinonasal papillomas are relatively uncommon tumors of the nasal cavity, representing 0.5–4 % of all primary nasal tumors [19], and are the most common benign sinonasal tumor. They occur with an incidence of 0.2–0.6 % per 100,000. Men are affected more than women (3:1). Presentation can occur at any age with a peak between the fifth and sixth decades. It is

Table 29.5 AJCC staging for maxillary, nasal, and ethmoid cancer

TX: The primary tumor cannot be evaluated
T0: No evidence of a tumor is found
Tis: Carcinoma in situ
Primary tumor (*T*) *in the maxillary sinus*
T1: Tumor limited to maxillary sinus and does not erode or invade bone
T2: Tumor erodes or invades bone of the hard palate and/or middle meatus
T3: Tumor invades bone of the posterior maxillary sinus wall, subcutaneous tissue, floor or medial wall of orbit, pterygoid fossa, or ethmoid sinuses
T4a: Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, or sphenoid/frontal sinuses
T4b: Tumor invades orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal, nasopharynx, or clivus
Primary tumor (*T*) *in the nasal cavity and ethmoid sinus*
T1: Tumor limited to any one subsite, without bony invasion
T2: Tumor involves two subsites or extends to involve adjacent region within the nasoethmoidal complex, with or without bony invasion
T3: Tumor invades medial wall or floor of orbit, maxillary sinus, palate, or cribriform plate
T4a: Tumor invades anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, or sphenoid/frontal sinuses
T4b: Tumor invades orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus
Node
NX: The regional lymph nodes cannot be evaluated
N0: No lymph nodes
N1: Metastasis in single ipsilateral lymph node, less than or equal to 3 cm in greatest dimension
N2: Metastasis in single lymph node greater than 3 but less than or equal to 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes less than or equal to 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, less than or equal to 6 cm in greatest dimension
N2a: Metastasis in single lymph node greater than 3 but less than or equal to 6 cm in greatest dimension
N2b: Metastases in multiple ipsilateral lymph nodes less than or equal to 6 cm in greatest dimension
N2c: Metastases in bilateral or contralateral lymph nodes, less than or equal to 6 cm in greatest dimension
N3: Metastasis in a lymph node greater than 6 cm in greatest dimension
Distant metastasis
MX: Distant metastasis cannot be evaluated
M0: No distant metastases
M1: Distant metastases

Adapted from Edge et al. [103]. With permission from Springer, 2013

Table 29.6 Relative frequency of paranasal sinus malignancies

Squamous cell carcinoma	80 %
Adenoid cystic carcinoma	10 %
Melanoma	4 %
Esthesioneuroblastoma	3 %
Other	3 %

extremely rare for sinonasal papillomas to present in childhood. Caucasians are at increased risk statistically. Most cases are unilateral with no side predilection, but approximately 5 % are bilateral [20].

The etiology of sinonasal papillomas is unknown, but human papilloma virus (HPV) is suggested as a frequent cofactor. Possible causes include allergies, chronic rhinosinusitis, airborne pollutants, and viral infection. In addition to physical examination, imaging may reveal erosion, expansion, and thinning of bone. The mainstay of treatment is surgical removal with clear margins.

Malignant Tumors

It is useful to adhere to a common staging system when discussing malignant tumors. For the maxillary sinus, nasal cavity, and ethmoid sinus, the American Joint Commission on Cancer system is often used at our institution (Table 29.5). While reported frequencies of sinonasal malignancies vary in the literature, squamous cell carcinoma is by far the most common (Table 29.6).

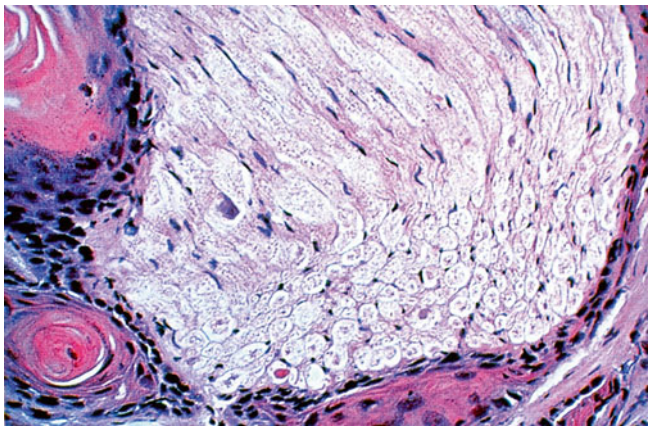


Fig. 29.7 Squamous cell carcinoma with perineural spread in the fifth cranial nerve

Squamous Cell Carcinoma

Squamous cell carcinoma (SCCa) is the most common paranasal sinus cancer, making up 80 % of all malignancies. Histology typically shows varying keratinization, with sheets, ribbons, and round-to-ovoid cells. Treatment is traditionally surgery, with possible adjunctive radiotherapy. Primary sinonasal and paranasal sinus squamous cell carcinoma are rare tumors, but in contradistinction to other head and neck squamous cell malignancies, there is no etiologic link with tobacco or alcohol. Sinonasal SCCa (SNSCCa) tend to present at advanced stages and have a poor outcome (Fig. 29.7). Despite advances in surgery and radiation, 5-year survivals remain approximately 40 % and local recurrence is the main cause of death [21–26]. SNSCCa are associated with exposure to wood, leather, and organic dust. SNSCCa typically present in men with a mean age of presentation from 50 to 60 years and account for 80–90 % of all nasal tumors. The most frequent sites of origin are the nasal cavities and the maxillary sinuses. TP53 mutations and p53 over expression have been found in SNSCCa cases [27]. Lymph node metastases, although rare on presentation, portend a much poorer prognosis. SNSCCa does not seem to have a premalignant precursor analogue such as carcinoma in situ found in the lower aerodigestive tract. However, some consider inverting papilloma to be this analogue [27].

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) arises from minor salivary glands and makes up approximately 10 % of all sinonasal malignancies [28]. Its particular histologic feature is perineural spread. Three forms are described: tubular, cribriform, and solid, in descending order of survival. Late local recurrence and distant metastases are often seen with ACC. Common presenting symptoms again mimic benign conditions such as sinusitis—nasal obstruction, loss of smell, and facial pressure. This benign presentation unfortunately often delays an immediate diagnosis. The maxillary sinus is the most common primary site, with the nasal cavity second in frequency. Involvement of areas proximal to the skull base such as the sphenoid sinus, the cribriform plate, a worse pathologic grade, and a solid histopathologic subtype portends of a poorer prognosis [29–31]. The cribriform subtype is most common and carries a better prognosis. Overall 5-year survival for patients is reported to be anywhere from 50 to 86 %. As with adenoid cystic carcinoma of other sites in the head and neck, late recurrences do occur in spite of aggressive initial surgery and adjunctive radiation therapy (Fig. 29.8).

Adenocarcinoma

Adenocarcinoma of the nose and paranasal sinuses is rare but well characterized. Its risk factors have been extensively reported in the literature. Risk factors include exposure to wood dust, lacquers, and metal dust. In particular, wood dust exposure, as demonstrated by its prevalence in up to 86 % of ethmoidal adenocarcinoma patients in some series, carries a unique risk [32]. Prognosis appears related to staging, especially size, of the lesion as well as lymph nodal involvement and intracranial extension. The criterion standard for treatment has traditionally been surgery with radiation, which has a 5-year

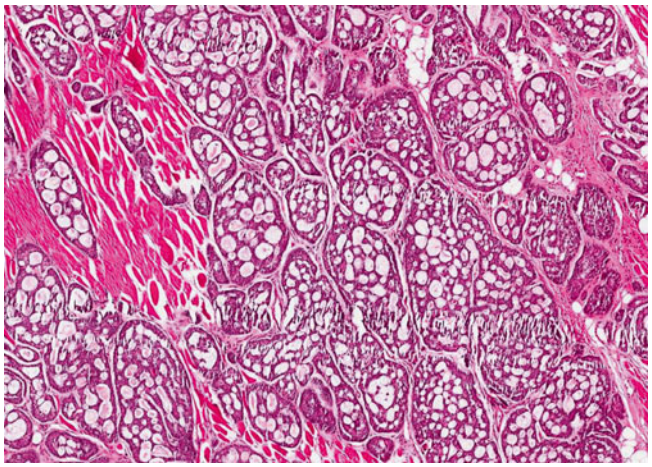


Fig. 29.8 Classic cribriform pattern of cuboidal cells in a dense fibrous stroma

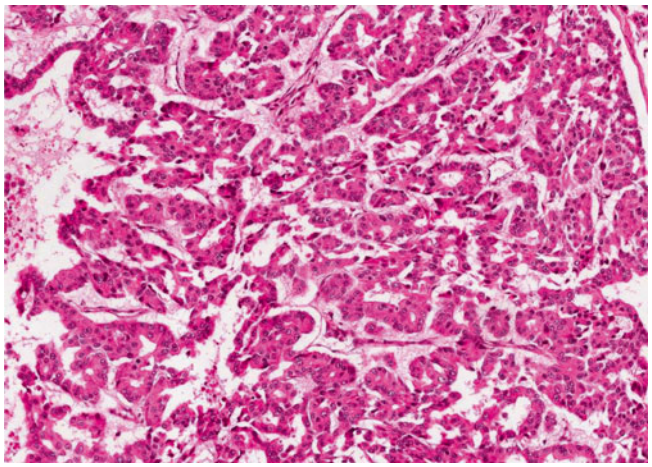


Fig. 29.9 Oncocytic adenocarcinoma: Large glands lined by cells with abundant pink cytoplasm and pleomorphic nuclei

patient survival of 35–70 % [33–39]. Many studies pool different histologies when reporting effectiveness of radiation. It is thus difficult to ascertain from the literature the true effectiveness of postoperative radiation for sinonasal adenocarcinoma. Nevertheless, the combined therapy of surgery and radiation remains standard (Fig. 29.9).

Sinonasal Neuroendocrine Tumors

Unfortunately, confusion in reporting and grouping of different histologies and the rarity of these tumors make interpretation of the literature difficult. Most often, esthesioneuroblastoma (olfactory neuroblastoma), sinonasal undifferentiated carcinoma, small-cell carcinoma, and neuroendocrine carcinoma are the histologies represented by the term "sinonasal neuroendocrine tumors" [33, 40–42]. Neuroendocrine neoplasms are usually classified into well-differentiated, moderately differentiated, or poorly differentiated tumors with poorly differentiated neoplasms characterized by rapid and often fatal outcomes.

Olfactory neuroblastoma arises from the olfactory cells in the cribriform plate. It is the most well studied and well characterized of the sinonasal neuroendocrine tumors. It comprises about 2 % of sinonasal tumors. Various terms have been used previously, including esthesioneuroblastoma, olfactory placode tumor, and esthesioneurocytoma. The lesion is more appropriately referred to as an olfactory neuroblastoma (Fig. 29.10) [41]. These lesions are thought to arise from sensory neuroepithelial olfactory cells in the upper nasal cavity (including upper septum, cribriform plate, and superior nasal concha). Olfactory neuroblastoma may occur at any age but usually displays a bimodal distribution in the second and sixth decades of life. Curiously, anosmia is not a common complaint. The cribriform plate should be considered involved in all tumors to some degree. It has been morphologically described as polypoid, glistening, and red-gray in appearance.

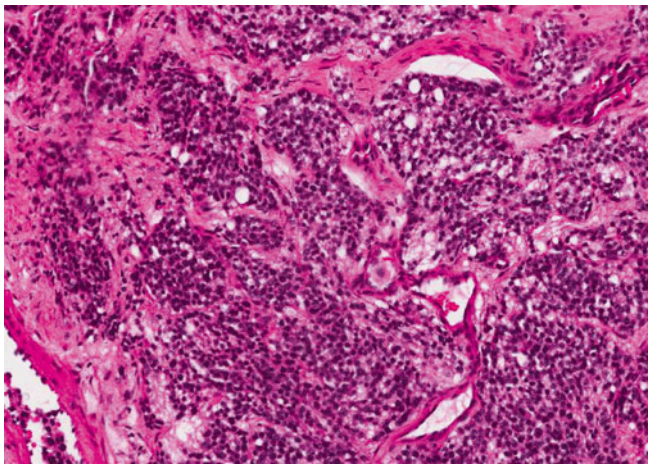


Fig. 29.10 Olfactory neuroblastoma. Clusters of small round cells in a fibrillar matrix

Histologically, the architecture is lobular and comprised of "primitive" neuroblastoma cells. [41, 43] These tumors are often separated into four grades and are based on presence of neural stroma, mitotic figures, necrosis, and degree of differentiation. Staging at our institution most often uses the Kadish system, wherein Stage A is tumor limited to the nasal cavity, stage B involves the nasal cavity and paranasal sinuses, and stage C extends beyond nasal cavity and sinuses [44]. Treatment involves surgical resection with possible postoperative radiotherapy. Survival ranges from 40 to 80 % at 5 years depending on grade and stage [41, 43, 45–51].

Sinonasal undifferentiated carcinoma (SNUC) lacks distinguishing histologic features but are invariably aggressive. SNUC is rarely treated with surgery alone in that local recurrence and a poor prognosis are common. It was first described by Frierson et al. [52]. The tumor likely arises from Schneiderian epithelium of the paranasal sinuses. Survival times are often less than 1 year after diagnosis. SNUC consists of small- to medium-sized polygonal cells which form nests, sheets, and trabeculae. This malignancy often infiltrates and invades blood vessels which can serve as a distinguishing feature [53]. Virtually all SNUCs are positive for cytokeratin, and 50 % stains for neuron-specific enolase. Optimal management is unclear, with varying reports of preoperative chemoradiation following by surgery, versus initial surgery followed by various forms of chemoradiation [54].

Small-cell neuroendocrine carcinoma (SNEC) is another aggressive tumor that carries a poor prognosis. First described by Raychowdhuri in 1965 [55], only a small cohort of cases have been reported since. It usually occurs in the lungs and accounts for about 20 % of primary lung cancer. While carcinoid tumor is considered to be a well-differentiated neuroendocrine carcinoma, SNEC is considered to be a poorly differentiated neuroendocrine carcinoma. Its characteristic behavior encompasses rapid growth, early recurrence, and widespread metastases. The tumor forms sheets and is composed of medium-sized cells with high nuclear/cytoplasmic ratio and demonstrates synaptophysin and CD56 staining. Interestingly, it is more often found in the ethmoid and maxillary sinuses. Smoking has not been strongly correlated with paranasal SNEC, unlike its counterpart in the lung [56]. Rarity of the tumor precludes agreement for management, but various combinations of surgery, chemotherapy, and radiation have been used. Recurrence is reported in up to 70 % of cases, with a 10 % 5-year survival [57].

Although the majority of neuroendocrine carcinomas in the head and neck region occur in the larynx, they are occasional found in the sinonasal region [42, 58–60]. Unfortunately, their rarity and overlapping pathologic features with other sinonasal tumors, combined with an inconsistent classification in the literature, make thorough study difficult [58]. Paranasal neuroendocrine carcinoma (NEC) accounts for about 5 % of malignancies in this anatomical area. Only case series exist in the literature [59]. Most patients present with advanced disease as symptoms such as epistaxis, nasal obstruction, and drainage mimic benign sinus disease and overlap with other conditions delaying the diagnosis. The most common sites of origin are the ethmoid sinuses and nasal cavity. Histologically, these tumors show dense core secretory granules and staining for synaptophysin, keratin, and chromogranin. There is a high rate of locoregional failure and a not insignificant rate of regional failure (up to 25 %) making elective cervical neck treatment a consideration.

Melanoma

Mucosal melanoma is rare and accounts for less than 1 % of all melanomas (Fig. 29.11). Ballantyne's clinical staging system and the American Joint Committee on Cancer (AJCC) system is the most frequently used at our institution. In Ballantyne's system, stage I represents localized lesions, stage II represents cervical lymph node metastasis, and stage III represents distant metastasis

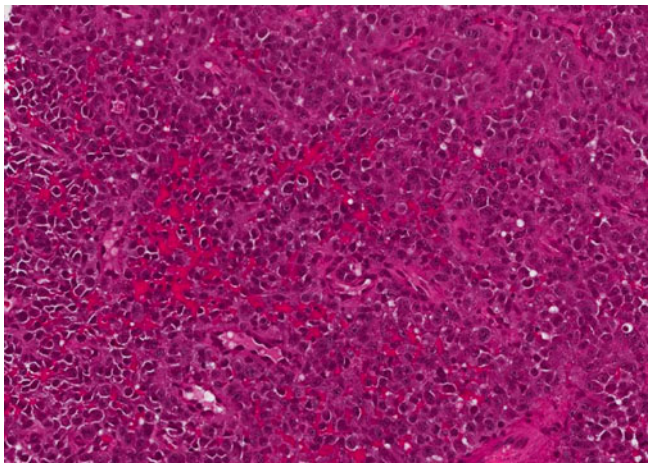


Fig. 29.11 Sinonasal melanoma. Sheets of spindle cells with large nuclei. Pigmentation is typically absent in sinonasal melanoma

[61–64]. The AJCC staging system appears to be an effective predictor of outcome and has been suggested as the staging system of choice [65]. Surgery is the mainstay of treatment for melanoma. Radiation likely increases locoregional control, but has not improved survival. The 5-year survival of mucosal melanoma remains frustratingly low, ranging from 20 to 35 % in the reported literature [63, 64, 66–69]. At presentation, 26 % of nasal mucosal melanomas have local lymphadenopathy.

Sinonasal melanoma tends to present less frequently with locoregional disease than oral melanoma, but prognosis is generally comparable. The most common areas of origination are the septum and lateral nasal wall. Treatment consists of complete tumor excision. Over 50 % of patients who achieve local control with surgery will ultimately develop distant metastases, which is an important point to consider when contemplating radical surgery to clear the primary site [69]. Achievement of negative surgical margins likely increases local control, but overall survival is negatively impacted by the frequency of distant metastases. Adjunctive radiation seems to decrease locoregional recurrence without benefiting overall survival. The MD Anderson group reports improved locoregional control when a total dose of 54 Gy was used in their retrospective series [65].

Nasopharyngeal Carcinoma

Although not a nasal or paranasal tumor in the anatomic sense, nasopharyngeal carcinoma (NPC) presents in similar fashion and must be included in the differential diagnosis of paranasal sinus symptoms. It is common among southern Chinese and is associated with the Epstein-Barr virus [70]. Testing of Epstein-Barr nuclear antigen and antibodies is incorporated into the workup for possible nasopharyngeal cancer and its surveillance in many centers. The World Health Organization classification lists three types of NPC: Type I is keratinizing squamous cell carcinoma, Type IIa is nonkeratinizing squamous cell carcinoma, and Type IIb is undifferentiated carcinoma. NPC is a squamous cell carcinoma arising in the nasopharynx. In addition to common symptoms such as epistaxis and nasal obstruction, the proximity to the Eustachian tubes of the usual primary sites such as the pharyngeal recess and fossae of Rosenmuller can cause serous otitis with hearing loss and even tinnitus. Furthermore, neck metastases are common presenting symptoms. Advanced cases eroding into the skull base can cause cranial neuropathies such as trigeminal, abducens, hypoglossal, or oculomotor nerve palsies [71, 72]. The mainstay of treatment remains primary radiotherapy, although chemotherapy may confer some survival benefit. Recurrent disease of the nasopharynx is treated with re-irradiation, surgery, or palliative measures. Recurrent neck disease is most often salvaged by radical neck dissection. Overall survival varies depending upon the AJCC staging but ranges from less than 10 % with metastatic disease, 40 % for locally advanced disease, and upward of 85–90 % for small-burden tumors confined to the nasopharynx [70, 72, 73]. The AJCC staging system is outlined in Table 29.7.

Sarcoma

Sarcomas make up a very small subset of tumors of the paranasal sinuses. Sarcomas form from aberrant proliferation of the mesenchymal tissues and are classified in accordance with the tissue of origin. Sarcomas overall form a small component of all malignancies,

Table 29.7 AJCC staging for nasopharyngeal cancer

Primary tumor (*T*)
Tx: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor confined to the nasopharynx or extending to oropharynx and/or nasal cavity without parapharyngeal extension
T2: Tumor with parapharyngeal extension
T3: Tumor involves bony structures of skull base and/or paranasal sinuses
T4: Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space
Lymph nodes (*N*)
Nx: Regional lymph cannot be assessed
N0: No regional lymph node metastases
N1: Unilateral metastasis in cervical lymph node(s), less than or equal to 6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, less than or equal to 6 cm in greatest dimension
N2: Bilateral metastasis in cervical lymph node(s), less than or equal to 6 cm in greatest dimension, above the supraclavicular fossa
N3: Metastasis in a lymph node(s) greater than 6 cm and/or to supraclavicular fossa
N3a: >6 cm in greatest dimension
N3b: Extension to the supraclavicular fossa
Metastasis (*M*)
M0: No distant metastasis
M1: Distant metastasis

Adapted from Edge et al. [103]. With permission from Springer, 2013

about 1 %. About 15–20 % of sarcomas are found in the head and neck. Of this portion, only a fraction are found in the paranasal sinuses. The majority of head and neck sarcomas are seen in adults, nearly 80 %, while the remainder are seen in children.

Risk factors for sarcoma in the head and neck do not overlap excessively with the general sarcoma risk. Interestingly, tobacco and alcohol use do not portend an increased risk. Some sarcomas may be related to radiation or other environmental exposure, while others may have a genetic component.

Generally, sarcomas of the paranasal sinuses occur as localized disease and are discovered at a very late stage. A small proportion of these tumors may contain regional metastasis, and distant metastasis is rare in the absence of regional or nodal metastasis. See Table 29.8 for staging of sarcomas of the head and neck.

The evaluation of sarcomas of the paranasal sinuses includes imaging. CT is excellent for identifying bony structure, bony invasion, or calcific changes in sarcomas. For evaluation of soft tissue features, MRI is the modality of choice. MRI is especially useful to evaluate intracranial involvement. The use of both CT and MRI may be necessary to fully elucidate the characteristics of the tumor [74–76].

Treatment consists of complete resection. This often involves extensive craniofacial resections in that the most common reason for treatment failure is local recurrence. Treatment failure or recurrence is often addressed with repeat resection, radiation and/or chemotherapy, or a combination of the three [76, 77].

A few subsets of paranasal sinus sarcomas will be discussed below.

Osteosarcoma

Osteosarcoma is the most common bone sarcoma in the head and neck and comprises nearly 5 % of all head and neck tumors. Within the head and neck, the paranasal sinuses are the third most common location for osteosarcoma after the mandible and the maxilla. Several case series show that nearly one third of sarcomas in the paranasal sinuses are osteosarcomas, one third are chondrosarcomas, and one third are fibrosarcoma or other soft tissue sarcomas [78]. Osteosarcoma occurs most commonly in middle-aged males, and it is postulated to be related to retinoblastoma, history of prior radiation, and Paget's disease and other genetic disorders.

Diagnosis can be made with CT scan. Alkaline phosphatase may be elevated in as many as 50 % of patients with osteosarcoma. Biopsy is the gold standard for diagnosis [79].

As with other soft tissue sarcomas, surgical excision is the treatment of choice. Nodal metastases are rare and usually represent tumor extension rather than true lymphatic spread. In selected cases, adjuvant radiation plus or minus chemotherapy can increase survival in some patients [80].

Table 29.8 Staging of head and neck sarcoma

Primary tumor
Tx – Primary tumor cannot be assessed
T0 – No evidence of primary tumor
T1 – Tumor less than 5 cm in greatest dimension (T1a, superficial; T1b, deep)
T2 – Tumor greater than 5 cm in greatest dimension (T2a, superficial; T2b, deep)
Regional lymph nodes
Nx – Lymph nodes cannot be assessed
N0 – No lymph nodes metastases
N1 – Lymph nodes metastases present
Distant metastases
Mx – Distant metastases cannot be assessed
M0 – No distant metastases
M1 – Distant metastases present
Histopathologic grade
Gx – Grade cannot be assessed
G1 – Well differentiated
G2 – Moderately differentiated
G3 – Poorly differentiated
G4 – Undifferentiated
Combined
IA (G1-2, T1a-b, N0, M0) – Low-grade, small, and superficial or deep tumor
IB (G1-2, T2a, N0, M0) – Low-grade, large, and superficial tumor
IIA (G1-2, T2b, N0, M0) – Low-grade, large, and deep tumor
IIB (G3-4, T1a-b, N0, M0) – High-grade, small, and superficial or deep tumor
IIC (G3-4, T2a, N0, M0) – High-grade, large, and superficial tumor
III (G3-4, T2b, N0, M0) – High-grade, large, and deep tumor
IV (any G, any T, N1, M0) – Any metastasis

Chondrosarcoma

Chondrosarcomas are the second most common tumors of bone after osteosarcoma. Chondrosarcomas of the head and neck are rare. Chondrosarcoma in the paranasal sinuses is extremely uncommon. Risks for chondrosarcoma are similar to those for osteosarcoma and include genetic factors, irradiation, and industrial exposures.

Chondrosarcomas have several distinct characteristics. They commonly contain calcifications, which can assist in the diagnosis with CT imaging. The characteristic pattern on CT is described as sunray spiculation. In general, benign chondromas are less than 3 cm in size, and chondrosarcomas are greater than 3 cm. On microscopic examination chondrosarcoma frequently shows a cellular matrix of hyaline cartilage with irregular nuclei arranged in groups of cells called chondroids [81].

As with other sarcomas, surgical resection is the treatment of choice. Regional and local metastases are uncommon and neck dissection is not indicated due to this low rate of nodal spread. Recurrence is seen in up to 50 % of patients. In the paranasal sinuses, chondrosarcoma is associated with a much poorer prognosis. Radiation or chemotherapy is generally not indicated as chondrosarcomas are considered resistant to such adjuvant therapies [81].

Synovial Sarcoma

Despite the name of this tumor, synovial sarcoma does not arise from synovial tissues but from pluripotent mesenchymal cells. Synovial sarcomas represent less than 10 % of head and neck tumors and an even smaller subset of tumors in the paranasal sinuses. They are most common in young adulthood between the ages of 20 and 40 and are more common in men than women.

Grossly, the lesions are usually firm, white masses but may be cystic or mucoid as well. MRI is a valuable tool to evaluate these tumors, and calcifications may suggest the diagnosis. Histologically, the mesenchymal cells that generate these tumors form two cell components: an epithelioid cell component and a spindle cell component. There are three subsets of synovial sarcoma: biphasic or containing both cellular components, monophasic, and a poorly differentiated type [82]. There has been shown to be a genetic component to these tumors involving a translocation between chromosome 18 and X, t(X;18)(p11.2;q11.2) which can confirm the diagnosis [83].

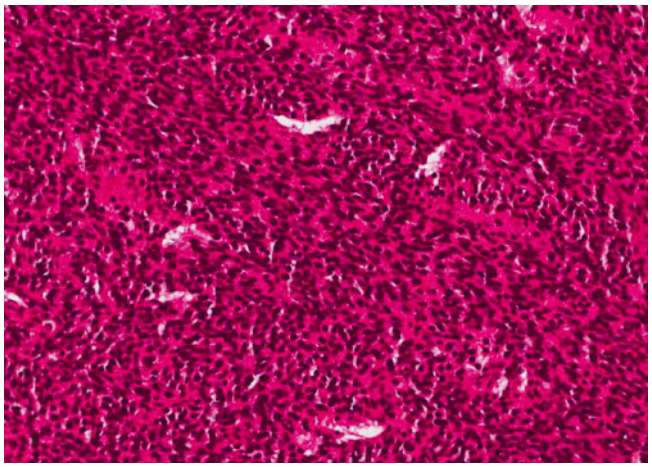


Fig. 29.12 Glomangiopericytoma. Sheets of spindle cells with irregular, stellate vessels

All synovial sarcomas have been classified as high-grade malignancies by the AJCC. Regional metastases are rare, but distant metastases occur in up to 50 % of cases, most commonly to the lungs. Distant metastases signifies poor prognosis.

Without evidence of palpable nodes, neck dissection is not indicated [84]. Surgical excision is the mainstay of treatment with postoperative radiation therapy. Local recurrence rates are significantly decreased with the addition of postoperative radiation therapy.

Glomangiopericytoma

Glomangiopericytoma (hemangiopericytoma) is a rare but interesting vascular tumor that arises from the pericytes of Zimmerman (Fig. 29.12). Pericytes are mesenchymally derived cells whose function is unclear. They exist around capillaries and may function in regulating the capacitance of these vessels. Fifteen to fifty percent of these tumors arise in the head and neck, and the majority of these are found in the sinonasal tract and the paranasal sinuses. Ninety percent of these tumors are found in those aged 50–70 [85].

Physical exam usually shows polypoid growths in the nasal cavity. These are often confused for benign polyps, and only after episodes of bleeding is further workup performed. Microscopic examination shows nests of tightly packed cell surrounding capillaries. Immunohistochemical staining can confirm the diagnosis. Positive staining for vimentin is common [86].

As with other sarcomas, complete surgical excision is the treatment of choice. This is typically accomplished by the endonasal endoscopic approach. Compared with other sarcomas of the paranasal sinuses, there is an improved prognosis. Regional and distant metastases are rare. Radiation and chemotherapy are rarely used postoperatively.

Lymphoreticular Malignancies

Lymphoma

Primary lymphoma of the paranasal sinuses is poorly understood. Non-Hodgkin's lymphoma can be found in the paranasal sinuses and presents nonspecifically with nasal obstruction, rhinorrhea, and epistaxis. Once the diagnosis has been made, standard chemoradiation therapy is the treatment of choice. T-cell/natural killer-cell lymphoma is a much more aggressive tumor that frequently includes destructive bony and soft tissue growth, severe epistaxis, and obstructive symptoms. Several reports in the literature support a link with the Epstein-Barr virus, and similar to nasopharyngeal carcinoma, it is more common in Asia. Treatment is with radiation therapy, plus or minus chemotherapy. Prognosis for these patients, is regrettably, very poor [77, 87].

Plasmacytoma

Plasmacytomas are rare malignant neoplasms derived from plasma cells. Plasmacytoma shows a predilection for the upper respiratory tract, chiefly the paranasal sinuses and the nasal cavity. Although plasmacytoma only makes up 1 % of head and neck tumors, they are particularly problematic. Up to 80–90 % of extramedullary plasmacytomas develop in the mucosa-associated lymphoid tissue of the upper aerodigestive tract with 75 % arising from the plasma cells of nasal and paranasal sinus tissue [88].

There is a male predominance for plasmacytoma, and most are seen during the fifth and sixth decades of life. They present as nasal masses that can masquerade as nasal polyps. Diagnosis requires first a biopsy. In order to confirm extramedullary plasmacytoma, laboratory examination including immunohistochemistry, serum protein electrophoresis, and urinalysis for Bence-Jones proteins must be done to exclude systemic disease such as multiple myeloma.

Radiation therapy is the treatment of choice for plasmacytoma. However, surgical excision is often required for tumors that extend out of the confines of the paranasal sinuses and invade bony structures, intracranial or orbital contents. In cases of metastatic disease, chemotherapy, with or without radiation therapy, has shown some benefit. Five-year survival for this disease ranges from 30 to 80 %, depending on the severity of the disease [89].

Metastases

Metastases to the nose and paranasal sinuses are rare but have been reported to occur in several histologies, including breast cancer, prostate cancer, renal cell carcinoma, and rectal adenocarcinoma [90–94].

Surgery of the Nose and Paranasal Sinuses in Tumor Therapy

It is useful to think of nose and paranasal sinus surgery in terms of external incision, bony cuts, and cranial vault. In this fashion, different external incisions can be used or combined to access the underlying bone. For example, a lateral rhinotomy incision and a midface degloving approach both give comparable access for maxillectomy. The choice relies on the comfort and experience of the surgeon. At our institution, expanded endonasal surgery is not considered a "competing" approach, but rather another method of tumor removal. In fact, it is often an adjunct to our open approaches (or vice versa!), as we often insert an endoscope to magnify and illuminate areas difficult to visualize with purely a headlight and loupes. Recent papers have described comparable tumor control rates when using either endoscopic approaches or open approaches for paranasal sinus tumor surgery [95–99]. The illumination and magnification provided by rigid endoscopy are superior to that afforded by low-power loupe magnification with headlight illumination. In-depth delineation of surgical techniques is beyond the scope of this chapter, but a brief discussion will be undertaken (Fig. 29.13a, b).

Exposure for resection of the maxilla can be achieved via a lateral rhinotomy or midface degloving approach. Tumors extending posteriorly into the infratemporal fossa can be surgically extirpated via an infratemporal fossa approach, which involves various incisions on the lateral aspect of the face, with inferior reflection of the temporalis muscle. Should the tumor extend into the cavernous sinus or middle cranial fossa, a temporal craniotomy can be added to the infratemporal fossa approach to achieve the middle cranial fossa-infratemporal fossa approach. Tumors involving the high nasal vault, and those involving the anterior cranial fossa, are easily accessed with craniofacial incisions, which typically involve a bicoronal incision (Fig. 29.14) combined with midface degloving or lateral rhinotomy.

Endoscopic approaches represent exciting contemporary techniques for minimal incision, with maximal resection, of intranasal and sinus tumors. Previous work has acknowledged that the concept of "piecemeal" resection of paranasal sinus tumors is a valid alternative to the traditional "en bloc" concept of tumor resection [100]. Essentially, expanded endonasal approaches consist of debulking of intranasal tumor down to their skull base, sinus, or septal attachments and then resecting the base of tumor under endoscopic visualization, in effect a "piecemeal" resection. Negative margins are still the ultimate goal which promotes similar oncologic principles when compared with traditional open craniofacial surgery.

Reconstruction of paranasal sinus tumor ablation must balance the need for continued surveillance of the defect with adequate soft tissue and skull base coverage to separate any communication between the intracranial contents and paranasal sinuses. Given the sensitivity of MRI and PET/CT detection of cancer recurrence, our particular institution has favored immediate reconstruction of defects such as radical maxillectomy with free flaps (Fig. 29.15), in contrast to simply skin grafting the orbital defect. Endoscopic resections may create defects of the anterior cranial fossa. Various reconstructive

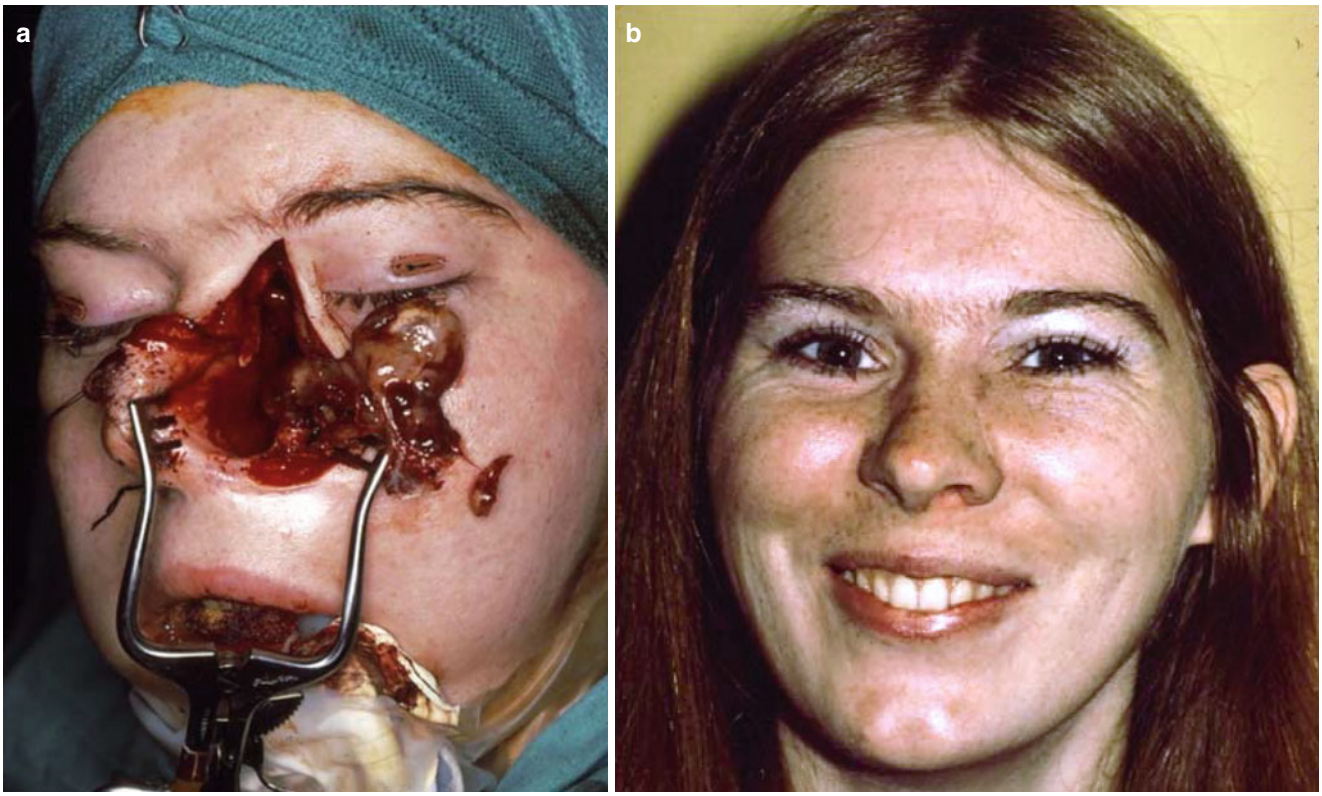


Fig. 29.13 (**a**) Lateral rhinotomy intraoperative photo. (**b**) Lateral rhinotomy, postoperative appearance (Reprinted from Donald [102]. With permission from Lippincott Williams and Wilkins)

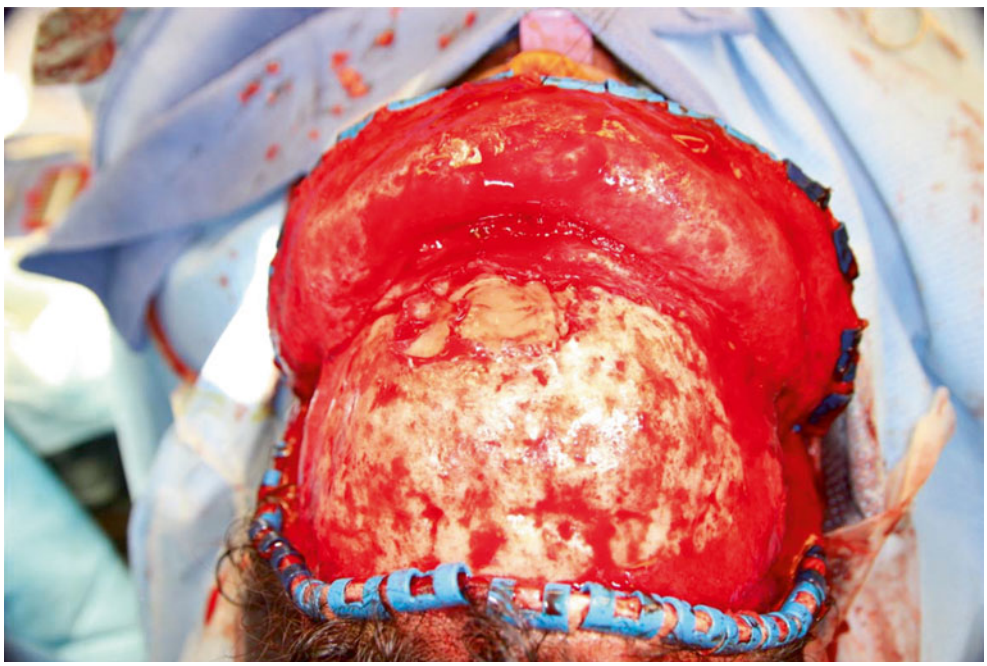


Fig. 29.14 Bicoronal incision allows anterior-inferior reflection of the forehead skin/muscle complex for generous exposure of the anterior cranial vault, with extension into the upper orbit if necessary

techniques have been used, including cadaveric tissue, autogenous fascia, and free mucosal grafts. Our preference has been to use the vascularized nasoseptal flap when possible, as reported rates of cerebrospinal fluid leakage following this type of repair appear lower. However, the undeniable utility of other reconstructive techniques must be recognized [101].

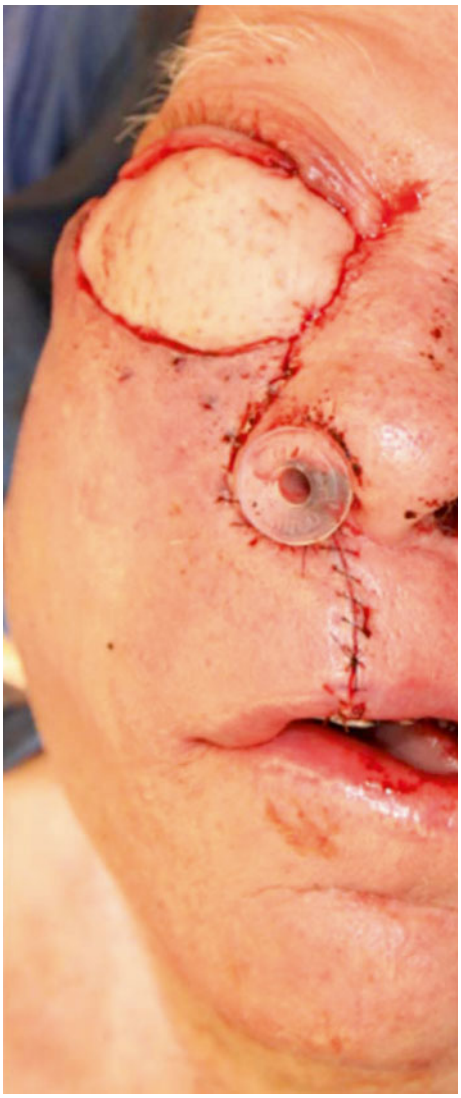


Fig. 29.15 Anterolateral thigh free flap reconstruction of a radical maxillectomy defect. Well-vascularized free tissue tolerates radiation well and allows for better cosmetic outcome compared to skin graft

Conclusion

Thorough evaluation and imaging of a patient with suspected sinonasal neoplasm are important in the workup of prolonged nasal symptoms. Myriad pathologies, both benign and malignant, exist. Unfortunately, the prognosis for many sinonasal malignancies remains frustratingly poor. Nevertheless, improved instrumentation and maintenance of similar oncologic principles have allowed an expansion of indications for endoscopic approaches. These endoscopic approaches should complement, but not necessarily replace, traditional open craniofacial approaches.

Acknowledgments The authors would like to thank Dr. Andrew Cho and Dr. Regina Gandour-Edwards for their histology examples and Dr. E. Bradley Strong and Dr. Paul Donald for generous use of their case examples.

References

1. Mann W. Lymphatic drainage of the maxillary sinus (author's transl). Laryngol Rhinol Otol. 1980;59:782–5.
2. Hahnel S, Ertl-Wagner B, Tasman AJ, Forsting M, Jansen O. Relative value of MR imaging as compared with CT in the diagnosis of inflammatory paranasal sinus disease. Radiology. 1999;210:171–6.
3. Razek AA, Sieza S, Maha B. Assessment of nasal and paranasal sinus masses by diffusion-weighted MR imaging. J Neuroradiol. 2009;36:206–11.

4. Farina D, Borghesi A, Botturi E, Ravanelli M, Maroldi R. Treatment monitoring of paranasal sinus tumors by magnetic resonance imaging. Cancer Imaging. 2010;10:183–93.
5. Maroldi R, Ravanelli M, Borghesi A, Farina D. Paranasal sinus imaging. Eur J Radiol. 2008;66:372–86.
6. Som PM, Costantino PD, Silvers AR. Imaging central skull base neural tumor spread from paranasal sinus malignancies: a critical factor in treatment planning. Skull Base Surg. 1999;9:15–21.
7. Mann WJ, Jecker P, Amedee RG. Juvenile angiofibromas: changing surgical concept over the last 20 years. Laryngoscope. 2004;114:291–3.
8. Guertl B, Beham A, Zechner R, Stammberger H, Hoefler G. Nasopharyngeal angiofibroma: an APC-gene-associated tumor? Hum Pathol. 2000;31:1411–13.
9. Chakraborty S, Ghoshal S, Patil VM, Oinam AS, Sharma SC. Conformal radiotherapy in the treatment of advanced juvenile nasopharyngeal angiofibroma with intracranial extension: an institutional experience. Int J Radiat Oncol Biol Phys. 2011;80:1398–404.
10. Makek MS, Andrews JC, Fisch U. Malignant transformation of a nasopharyngeal angiofibroma. Laryngoscope. 1989;99:1088–92.
11. Earwaker J. Paranasal sinus osteomas: a review of 46 cases. Skeletal Radiol. 1993;22:417–23.
12. Koivunen P, Lopponen H, Fors AP, Jokinen K. The growth rate of osteomas of the paranasal sinuses. Clin Otolaryngol Allied Sci. 1997;22: 111–14.
13. Reed RJ. Fibrous dysplasia of bone. A review of 25 cases. Arch Pathol. 1963;75:480–95.
14. Hyams VJ, Batsakis JG, Michaels L, Armed Forces Institute of Pathology (U.S.). Tumors of the upper respiratory tract and ear. Washington, DC: Armed Forces Institute of Pathology: Supt. of Docs., U.S. G.P.O.; 1988. For sale by the Armed Forces Institute of Pathology.
15. Parekh SG, Donthineni-Rao R, Ricchetti E, Lackman RD. Fibrous dysplasia. J Am Acad Orthop Surg. 2004;12:305–13.
16. Fitzpatrick KA, Taljanovic MS, Speer DP, et al. Imaging findings of fibrous dysplasia with histopathologic and intraoperative correlation. AJR Am J Roentgenol. 2004;182:1389–98.
17. Chong VF, Khoo JB, Fan YF. Fibrous dysplasia involving the base of the skull. AJR Am J Roentgenol. 2002;178:717–20.
18. Barnes L. Schneiderian papillomas and nonsalivary glandular neoplasms of the head and neck. Mod Pathol. 2002;15:279–97.
19. Buchwald C, Nielsen LH, Nielsen PL, Ahlgren P, Tos M. Inverted papilloma: a follow-up study including primarily unacknowledged cases. Am J Otolaryngol. 1989;10:273–81.
20. Krouse JH. Endoscopic treatment of inverted papilloma: safety and efficacy. Am J Otolaryngol. 2001;22:87–99.
21. Bandoh N, Hayashi T, Kishibe K, et al. Prognostic value of p53 mutations, bax, and spontaneous apoptosis in maxillary sinus squamous cell carcinoma. Cancer. 2002;94:1968–80.
22. Ichinose T, Goto T, Motomura H, Terakawa Y, Ohata K. Primary squamous cell carcinoma of the frontal sinus treated with en bloc resection: case report. Neurol Med Chir (Tokyo). 2009;49:481–3.
23. Kondo M, Inuyama Y, Ando Y, et al. Patterns of relapse of squamous cell carcinoma of the maxillary sinus. Cancer. 1984;53:2206–10.
24. Nibu K, Sugasawa M, Asai M, et al. Results of multimodality therapy for squamous cell carcinoma of maxillary sinus. Cancer. 2002;94:1476–82.
25. St-Pierre S, Baker SR. Squamous cell carcinoma of the maxillary sinus: analysis of 66 cases. Head Neck Surg. 1983;5:508–13.
26. Tiwari R, Hardillo JA, Mehta D, et al. Squamous cell carcinoma of maxillary sinus. Head Neck. 2000;22:164–9.
27. Oncel S, Cosgul T, Calli A, Calli C, Pinar E. Evaluation of p53, p63, p21, p27, ki-67 in paranasal sinus squamous cell carcinoma and inverted papilloma. Indian J Otolaryngol Head Neck Surg. 2011;63:172–7.
28. Lupinetti AD, Roberts DB, Williams MD, et al. Sinonasal adenoid cystic carcinoma: the M. D. Anderson Cancer Center experience. Cancer. 2007;110:2726–31.
29. Adachi M, Mitsudo K, Yamamoto N, et al. Chemoradiotherapy for maxillary sinus adenoid cystic carcinoma using superselective intra-arterial infusion via a superficial temporal artery. Head Neck. 2013;35(3):E89–93.
30. Ruo Redda MG, Succo G, Guarneri A, Ragona R. Radiotherapy after surgery for advanced adenoid cystic carcinoma of paranasal sinus. Lancet Oncol. 2005;6:994–6.
31. Wright ED, Raza SN, Heathcote JG. Atypical diagnostic, endoscopic, and pathologic findings in a case of adenoid cystic carcinoma arising from the sphenoid sinus. J Otolaryngol. 2005;34:226–30.
32. Breheret R, Laccourreye L, Jeufroy C, Bizon A. Adenocarcinoma of the ethmoid sinus: retrospective study of 42 cases. Eur Ann Otorhinolaryngol Head Neck Dis. 2011;128:211–17.
33. Babin E, Rouleau V, Vedrine PO, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol. 2006;120:289–97.
34. Bimbi G, Saraceno MS, Riccio S, Gatta G, Licitra L, Cantu G. Adenocarcinoma of ethmoid sinus: an occupational disease. Acta Otorhinolaryngol Ital. 2004;24:199–203.
35. Burns H, Mullaney J. Paranasal sinus adenocarcinoma causing proptosis. Ophthalmologica. 1986;192:57–9.
36. Cantu G, Solero CL, Mariani L, et al. Intestinal type adenocarcinoma of the ethmoid sinus in wood and leather workers: a retrospective study of 153 cases. Head Neck. 2011;33:535–42.
37. Jain R, Gramigna V, Sanchez-Marull R, Perez-Ordonez B. Composite intestinal-type adenocarcinoma and small cell carcinoma of sinonasal tract. J Clin Pathol. 2009;62:634–7.
38. Roth J, Friedlander PL, Palacios E. Primary adenocarcinoma of the maxillary sinus simulating an osteosarcoma. Ear Nose Throat J. 2002;81:14.
39. Singh RK, Sardana DS, Srivastava RN, Kumar S. Adenocarcinoma of the sphenoid sinus. Ear Nose Throat J. 1990;69:770–1.
40. Deviprasad S, Rajeshwari A, Tahir M, Adarsha TV, Gangadhara S. Small-cell neuroendocrine carcinoma originating from the lateral nasopharyngeal wall. Ear Nose Throat J. 2008;87:E1–3.
41. Faragalla H, Weinreb I. Olfactory neuroblastoma: a review and update. Adv Anat Pathol. 2009;16:322–31.
42. Fitzek MM, Thornton AF, Varvares M, et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. Cancer. 2002;94:2623–34.
43. Thompson LD. Olfactory neuroblastoma. Head Neck Pathol. 2009;3:252–9.
44. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer. 1976;37:1571–6.
45. Carta F, Kania R, Sauvaget E, Bresson D, George B, Herman P. Endoscopy skull-base resection for ethmoid adenocarcinoma and olfactory neuroblastoma. Rhinology. 2011;49:74–9.

46. Jiang GY, Li FC, Chen WK, Liu AM, Cai WQ. Therapy and prognosis of intracranial invasive olfactory neuroblastoma. Otolaryngol Head Neck Surg. 2011;145:951–5.
47. Nabili V, Kelly DF, Fatemi N, St John M, Calcaterra TC, Abemayor E. Transnasal, transfacial, anterior skull base resection of olfactory neuroblastoma. Am J Otolaryngol. 2011;32:279–85.
48. Nomoto S, Shioyama Y, Ohga S, Nakamura K, Honda H. Advanced olfactory neuroblastoma treated with combined conventional and hypofractionated stereotactic radiotherapy. J Cancer Res Ther. 2010;6:581–4.
49. Platek ME, Merzianu M, Mashtare TL, et al. Improved survival following surgery and radiation therapy for olfactory neuroblastoma: analysis of the SEER database. Radiat Oncol. 2011;6:41.
50. Smee RI, Broadley K, Williams JR, Meagher NS, Bridger GP. Retained role of surgery for olfactory neuroblastoma. Head Neck. 2011;33:1486–92.
51. Snyderman CH, Gardner PA. "How much is enough?" endonasal surgery for olfactory neuroblastoma. Skull Base. 2010;20:309–10.
52. Frierson Jr HF, Mills SE, Fechner RE, Taxy JB, Levine PA. Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. Am J Surg Pathol. 1986;10:771–9.
53. Wadsworth B, Bumpous JM, Martin AW, Nowacki MR, Jenson AB, Farghaly H. Expression of p16 in sinonasal undifferentiated carcinoma (SNUC) without associated human papillomavirus (HPV). Head Neck Pathol. 2011;5:349–54.
54. Lin EM, Sparano A, Spalding A, et al. Sinonasal undifferentiated carcinoma: a 13-year experience at a single institution. Skull Base. 2010;20:61–7.
55. Raychowdhuri RN. Oat-cell carcinoma and paranasal sinuses. J Laryngol Otol. 1965;79:253–5.
56. Han G, Wang Z, Guo X, Wang M, Wu H, Liu D. Extrapulmonary small cell neuroendocrine carcinoma of the paranasal sinuses: a case report and review of the literature. J Oral Maxillofac Surg. 2012;70(10):2347–51.
57. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer. 1997;79:1729–36.
58. Likhacheva A, Rosenthal DI, Hanna E, Kupferman M, Demonte F, El-Naggar AK. Sinonasal neuroendocrine carcinoma: impact of differentiation status on response and outcome. Head Neck Oncol. 2011;3:32.
59. Mendis D, Malik N. Sinonasal neuroendocrine carcinoma: a case report. Ear Nose Throat J. 2008;87:280–2, 93.
60. Mitchell EH, Diaz A, Yilmaz T, et al. Multimodality treatment for sinonasal neuroendocrine carcinoma. Head Neck. 2012;34(10):1372–6.
61. Ballantyne AJ. Malignant melanoma of the skin of the head and neck. An analysis of 405 cases. Am J Surg. 1970;120:425–31.
62. Brandwein MS, Rothstein A, Lawson W, Bodian C, Urken ML. Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. Arch Otolaryngol Head Neck Surg. 1997;123:290–6.
63. Ferraro RE, Schweinfurth JM, Highfill GR. Mucosal melanoma of the sinonasal tract. Am J Otolaryngol. 2002;23:321–3.
64. Narasimhan K, Kucuk O, Lin HS, et al. Sinonasal mucosal melanoma: a 13-year experience at a single institution. Skull Base. 2009;19:255–62.
65. Moreno MA, Roberts DB, Kupferman ME, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M. D. Anderson Cancer Center. Cancer. 2010;116:2215–23.
66. Koivunen P, Back L, Pukkila M, et al. Accuracy of the current TNM classification in predicting survival in patients with sinonasal mucosal melanoma. Laryngoscope. 2012;122:1734–8.
67. Kumar S, Gupta AK, Yadav BS, Ghoshal S. Primary sinonasal malignant melanoma: a clinicopathologic and prognostic study. Ear Nose Throat J. 2009;88:1269–72.
68. Lund VJ, Chisholm EJ, Howard DJ, Wei WI. Sinonasal malignant melanoma: an analysis of 115 cases assessing outcomes of surgery, postoperative radiotherapy and endoscopic resection. Rhinology. 2012;50:203–10.
69. Roth TN, Gengler C, Huber GF, Holzmann D. Outcome of sinonasal melanoma: clinical experience and review of the literature. Head Neck. 2010;32:1385–92.
70. Wei WI, Kwong DL. Current management strategy of nasopharyngeal carcinoma. Clin Exp Otorhinolaryngol. 2010;3:1–12.
71. Agulnik M, Epstein JB. Nasopharyngeal carcinoma: current management, future directions and dental implications. Oral Oncol. 2008;44:617–27.
72. Faivre S, Janot F, Armand JP. Optimal management of nasopharyngeal carcinoma. Curr Opin Oncol. 2004;16:231–5.
73. Smee RI, Meagher NS, Broadley K, Ho T, Williams JR, Bridger GP. Recurrent nasopharyngeal carcinoma: current management approaches. Am J Clin Oncol. 2010;33:469–73.
74. Wanebo HJ, Koness RJ, MacFarlane JK, et al. Head and neck sarcoma: report of the Head and Neck Sarcoma Registry. Society of Head and Neck Surgeons Committee on Research. Head Neck. 1992;14:1–7.
75. Patel SG, Meyers P, Huvos AG, et al. Improved outcomes in patients with osteogenic sarcoma of the head and neck. Cancer. 2002;95:1495–503.
76. Nappi O, Wick MR. Sarcomatoid neoplasms of the respiratory tract. Semin Diagn Pathol. 1993;10:137–47.
77. Kapadia SB, Barnes L, Deutsch M. Non-Hodgkin's lymphoma of the nose and paranasal sinuses: a study of 17 cases. Head Neck Surg. 1981;3:490–9.
78. Koka V, Vericel R, Lartigau E, Lusinchi A, Schwaab G. Sarcomas of nasal cavity and paranasal sinuses: chondrosarcoma, osteosarcoma and fibrosarcoma. J Laryngol Otol. 1994;108:947–53.
79. Smeele LE, Snow GB, van der Waal I. Osteosarcoma of the head and neck: meta-analysis of the nonrandomized studies. Laryngoscope. 1998;108:946.
80. Oda D, Bavisotto LM, Schmidt RA, et al. Head and neck osteosarcoma at the University of Washington. Head Neck. 1997;19:513–23.
81. Koch BB, Karnell LH, Hoffman HT, et al. National cancer database report on chondrosarcoma of the head and neck. Head Neck. 2000;22:408–25.
82. Carrillo R, el-Naggar AK, Rodriguez-Peralto JL, Batsakis JG. Synovial sarcoma of the tongue: case report and review of the literature. J Oral Maxillofac Surg. 1992;50:904–6.
83. Cihak RA, Lydiatt WM, Lydiatt DD, Bridge JA. Synovial sarcoma of the head and neck: chromosomal translation (X;18) as a diagnostic aid. Head Neck. 1997;19:549–53.

84. Bukachevsky RP, Pincus RL, Shechtman FG, Sarti E, Chodosh P. Synovial sarcoma of the head and neck. Head Neck. 1992;14:44–8.
85. Carew JF, Singh B, Kraus DH. Hemangiopericytoma of the head and neck. Laryngoscope. 1999;109:1409–11.
86. Yokoi H, Arakawa A, Kuribayashi K, Inoshita A, Haruyama T, Ikeda K. An immunohistochemical study of sinonasal hemangiopericytoma. Auris Nasus Larynx. 2011;38:743–6.
87. Momose A, Mizuno H, Kajihara S, et al. EBV-associated nasal-type NK/T-cell lymphoma of the nasal cavity/paranasal sinus in a renal allograft recipient. Nephrol Dial Transplant. 2006;21:1413–16.
88. Megat Shiraz MA, Jong YH, Primuharsa Putra SH. Extramedullary plasmacytoma in the maxillary sinus. Singapore Med J. 2008;49: e310–11.
89. Lomeo PE, McDonald JE, Finneman J. Shoreline. Extramedullary plasmacytoma of the nasal sinus cavities. Am J Otolaryngol. 2007;28: 50–1.
90. Marchioni D, Monzani D, Rossi G, Rivasi F, Presutti L. Breast carcinoma metastases in paranasal sinuses, a rare occurrence mimicking a primary nasal malignancy. Case report. Acta Otorhinolaryngol Ital. 2004;24:87–91.
91. Prescher A, Brors D. Metastases to the paranasal sinuses: case report and review of the literature. Laryngorhinootologie. 2001;80:583–94.
92. Saleh HA, O'Flynn P, Jones NS. Prostatic metastases in the nose and paranasal sinuses. J Laryngol Otol. 1993;107:629–32.
93. Szymanski M, Szymanska A, Morshed K, Siwiec H. Renal cell carcinoma metastases to nose and paranasal sinuses presenting as recurrent epistaxis. Wiad Lek. 2004;57:94–6.
94. Tanaka K. A case of metastases to the paranasal sinus from rectal mucinous adenocarcinoma. Int J Clin Oncol. 2006;11:64–5.
95. Cappabianca P, Kelly DF, Laws Jr ER. Endoscopic transnasal versus open transcranial cranial base surgery: the need for a serene assessment. Neurosurgery. 2008;63:240–1; discussion 1–3.
96. Castelnuovo P, Giovannetti F, Bignami M, Ungari C, Iannetti G. Open surgery versus endoscopic surgery in benign neoplasm involving the frontal sinus. J Craniofac Surg. 2009;20:180–3.
97. de Divitiis O, de Divitiis E. Anterior cranial fossa meningiomas: a new surgical perspective. World Neurosurg. 2012;77(5–6):623–4.
98. Karkos PD, Fyrmpas G, Carrie SC, Swift AC. Endoscopic versus open surgical interventions for inverted nasal papilloma: a systematic review. Clin Otolaryngol. 2006;31:499–503.
99. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal versus open transcranial resection of anterior midline skull base meningiomas: a systematic review of outcomes. World Neurosurg. 2012;77(5–6):713–24.
100. Wellman BJ, Traynelis VC, McCulloch TM, Funk GF, Menezes AH, Hoffman HT. Midline anterior craniofacial approach for malignancy: results of en bloc versus piecemeal resections. Skull Base Surg. 1999;9:41–6.
101. Kassam AB, Thomas A, Carrau RL, et al. Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. Neurosurgery. 2008;63:ONS44–52; discussion ONS52–3.
102. Donald P, editor. Surgery of the skull base. Philadelphia: Lippincott Raven Publishers; 1998.
103. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.

Chapter 30
The Paranasal Sinuses in Facial Trauma

Carmine Taglialatela Scafati and Salvatore Taglialatela Scafati

Introduction

Paranasal sinuses are pneumatic cavities located in the craniofacial skeleton and are often involved in trauma of the superior and middle thirds of the face. Paranasal sinuses can be considered as chambers protecting the brain from direct injury. Trauma-associated forces that are greater than paranasal sinus resistance can still lead to brain injury [1] (Fig. 30.1).

Epidemiology

Distribution of facial trauma varies according to the geographic area. In modern societies motor vehicle accidents and assaults prevail, while in less developed countries, injuries associated with rural activities are more frequent [2–7] (Fig. 30.2). Facial trauma is more common in males. The male to female ratio is variable, ranging from 11:1 in some cases to 2:1 [8–11] (Fig. 30.3). The most common age for facial trauma ranges from 20 to 30 years [6, 7] (Fig. 30.4). In recent times, despite the introduction of systematic speed control, obligatory airbag and helmet use, and more strict alcohol control measures, the incidence of traffic accidents has increased. This can be attributable to the increased number of motor vehicles in various sections of the globe. The decreased mortality due to the improvements in emergency and resuscitation medicine has led to an increased incidence of morbidity related to facial trauma requiring treatment. High-energy injuries leading to complex and multiple traumatic lesions have also increased [12–14] (Fig. 30.5). Alcohol and drug abuse further increase the incidence of traffic-related and assault-related injuries among the young population [15–20].

Anatomy and Pathophysiology

Paranasal sinuses are surrounded by a protective framework of bone buttresses which absorb and transmit traumatic forces directed to the facial skeleton. There are six vertical buttresses and three horizontal [21, 22] (Fig. 30.6). Vertical buttresses are from medial to lateral: nasomaxillary, zygomaticomaxillary, and pterygomaxillary. The nasomaxillary buttress starts from the frontonasal union and goes downward along the medial orbital wall reaching the canine fossa and the piriform aperture where it joins the contralateral buttress. The zygomaticomaxillary buttress starts at the frontozygomatic union, passing along the lateral orbital wall and reaching the maxilla.

C.T. Scafati, MD, FEBOMFS (✉) • S.T. Scafati, MD
Servizio di Chirurgia Maxillo-Facciale, Ospedale Santa Maria delle Grazie, via Domitiana, località La Schiana, Pozzuoli, Naples, Italy
e-mail: carminetaglia@libero.it; salvatoretaglialatela@yahoo.it

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1_30,

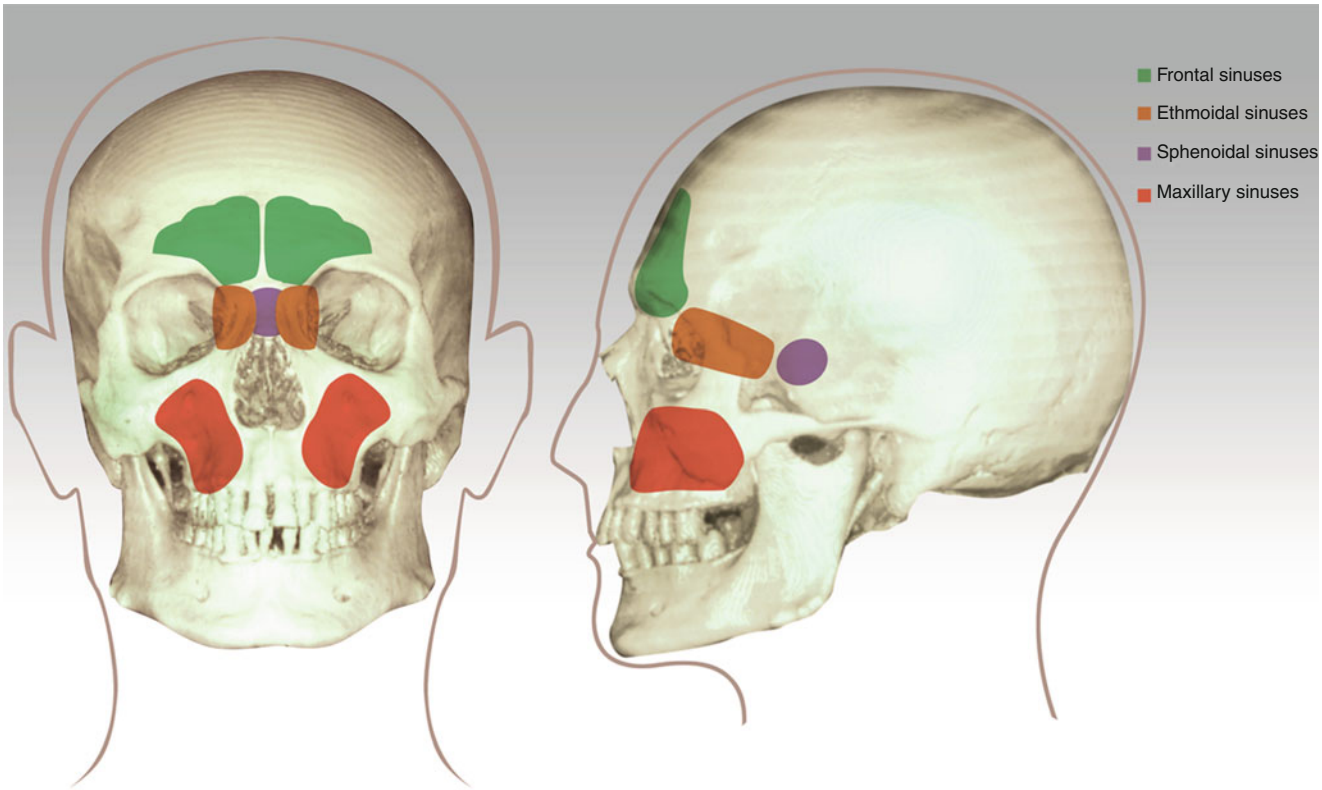
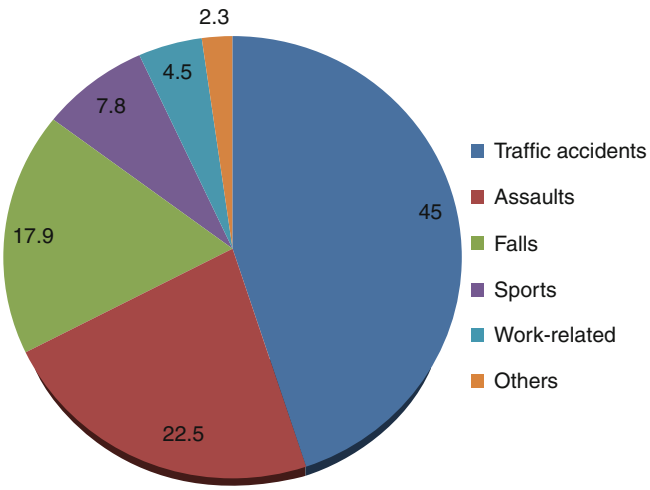


Fig. 30.1 Paranasal sinuses: frontal and lateral view. Frontal (*green*), ethmoid (*brown*), sphenoid (*purple*) and maxillary (*red*) sinuses are shown

Fig. 30.2 Causes most frequent of injuries in patients with maxillofacial fractures



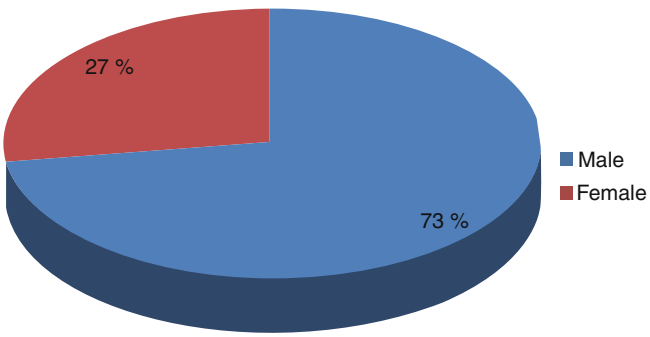


Fig. 30.3 Gender distribution

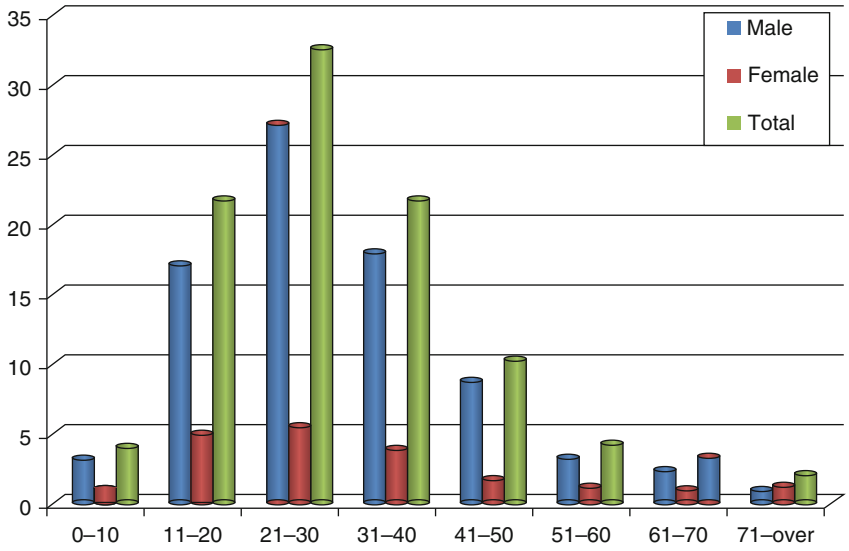


Fig. 30.4 Age distribution of patients with maxillofacial fractures

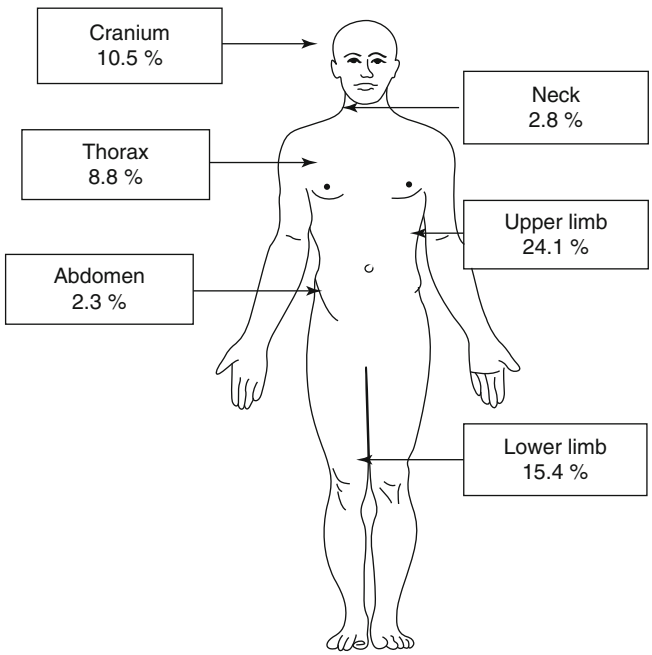


Fig. 30.5 Concomitant corporeal lesion in patients with maxillofacial fractures

Posteriorly, the pterygomaxillary buttress goes from the skull base to the tuber maxillae and pterygoid process. Horizontal buttresses are from superior to inferior and include the frontal bar, infraorbital/nasal bones, and hard palate/maxillary alveolus.

In 1901 Le Fort classified midface fractures analyzing the "lines of weakness" of the facial skeleton. A Le Fort I fracture passes across the inferior margin of the piriform aperture, running below the nasal cavity and going to pterygoid plate. It may be unilateral or bilateral. The fracture leads to a complete detachment of the inferior part of the maxilla from the midface. The detached fragment includes the maxillary alveolar processes, the palate, and part of the pterygoid process. Direct trauma to the nasoalveolar region is usually responsible for this kind of fractures (Fig. 30.7).

A Le Fort II fracture originates at the nasal root and passes the nasal bone, the lacrimal bone, the orbital floor, and across the upper portion of the maxillary sinus and reaches the pterygopalatine fossa. This fracture is usually the result of a direct trauma to the area between the root of the nose and the upper lip (Fig. 30.8).

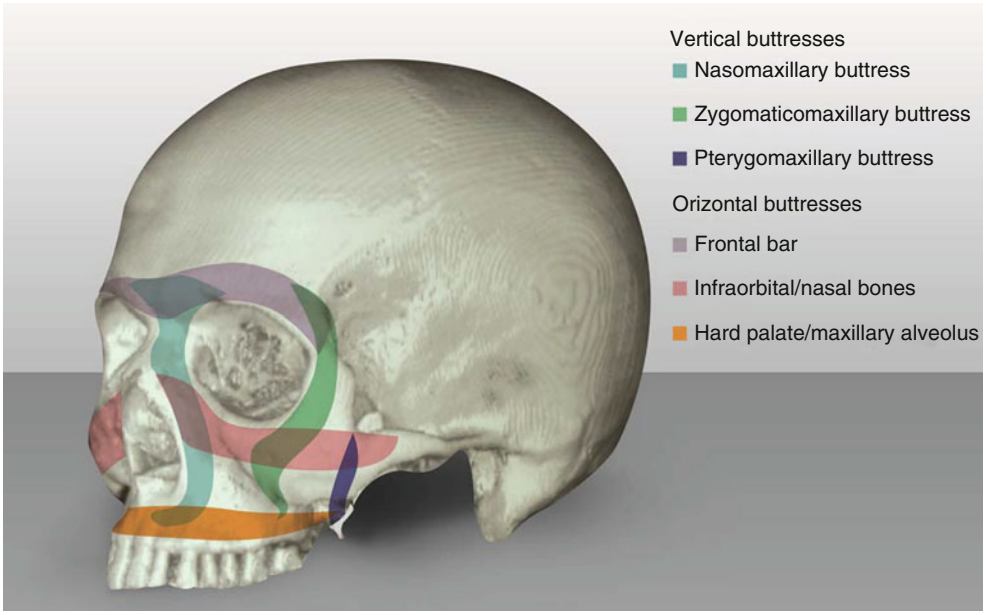


Fig. 30.6 Vertical and horizontal buttresses

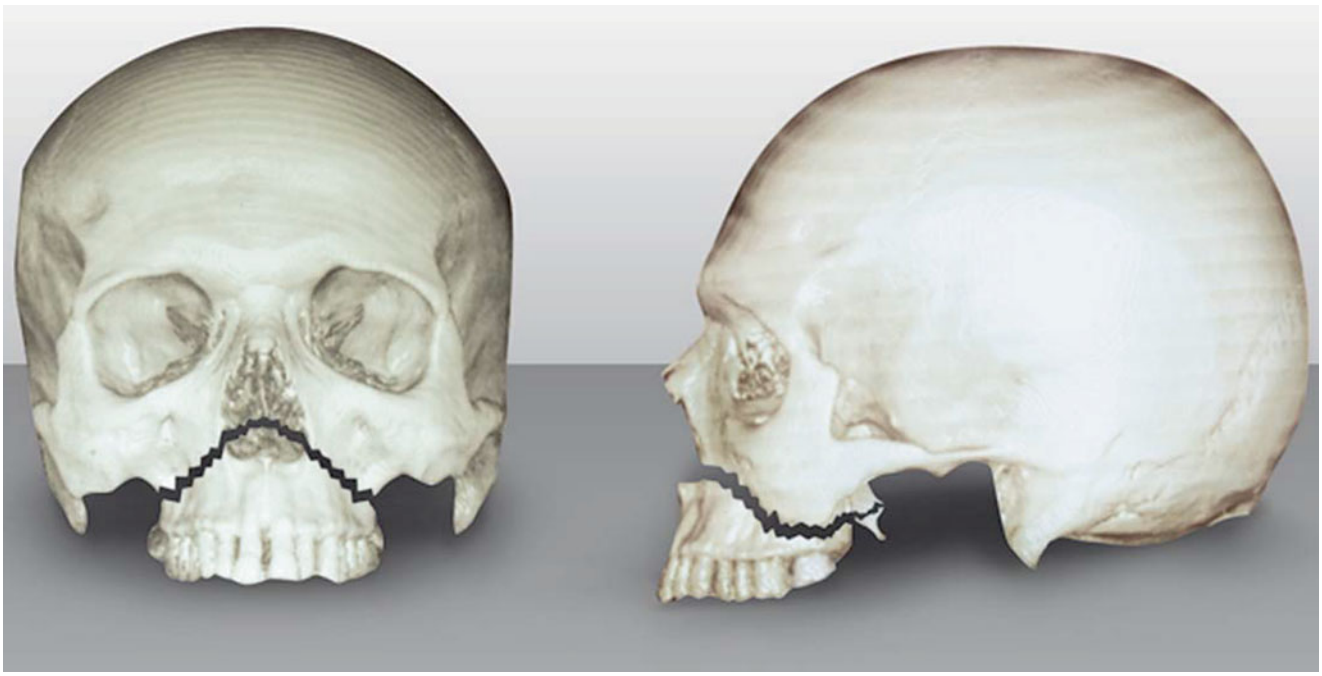


Fig. 30.7 Le Fort I fracture

A Le Fort III fracture starts at the nasal root and extends across the nasofrontal union, passes along the medial orbital wall, the inferior orbital fissure, and the frontozygomatic union to reach the pterygopalatine fossa posteriorly. The fracture involves the zygomatic arch. When it is bilateral, a Le Fort III fracture results in "craniofacial disjunction" with backward dislocation of the middle third of the face (Fig. 30.9).

Other classifications have been described, dividing palatal fractures into sagittal and parasagittal forms [14, 23]. Although Le Fort classification is still the most useful and employed system, high-energy injuries can produce more complex lesions which do not always respect the classic Le Fort fracture lines. For these reasons other criteria for classification have been introduced taking into consideration the subunits composing the midface [15–18, 24, 25]. According to the structures

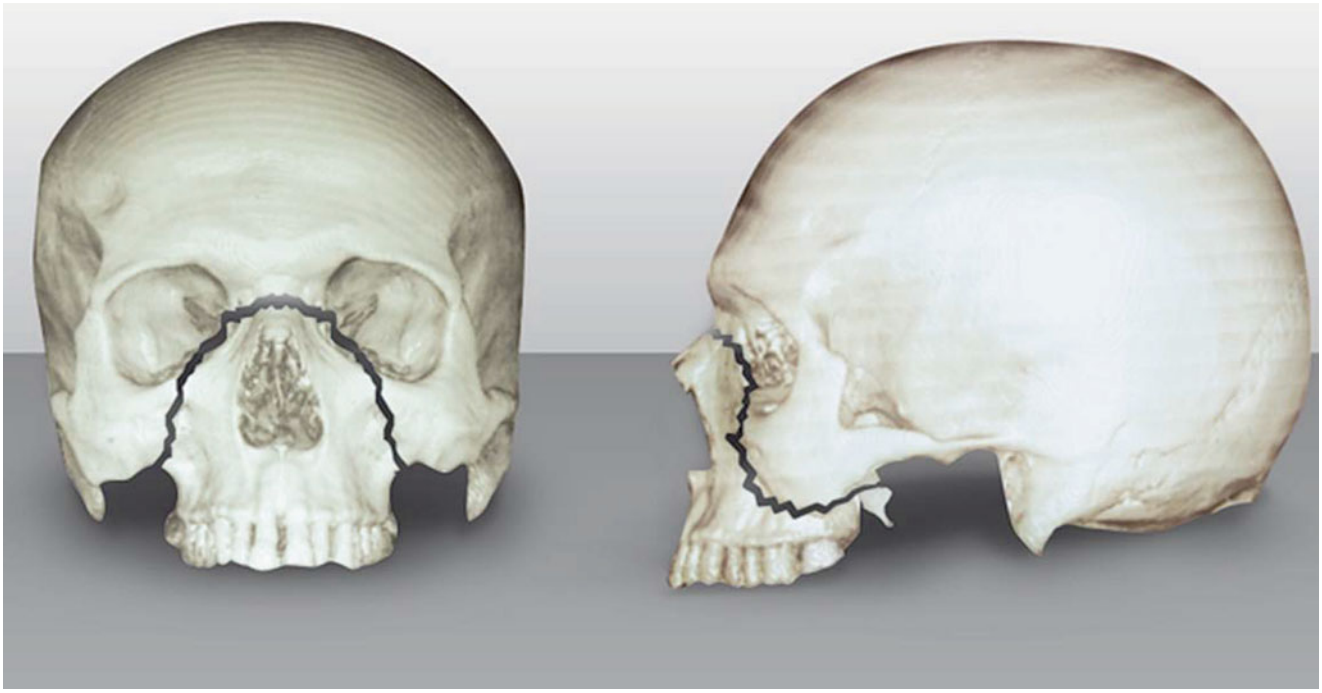


Fig. 30.8 Le Fort II fracture

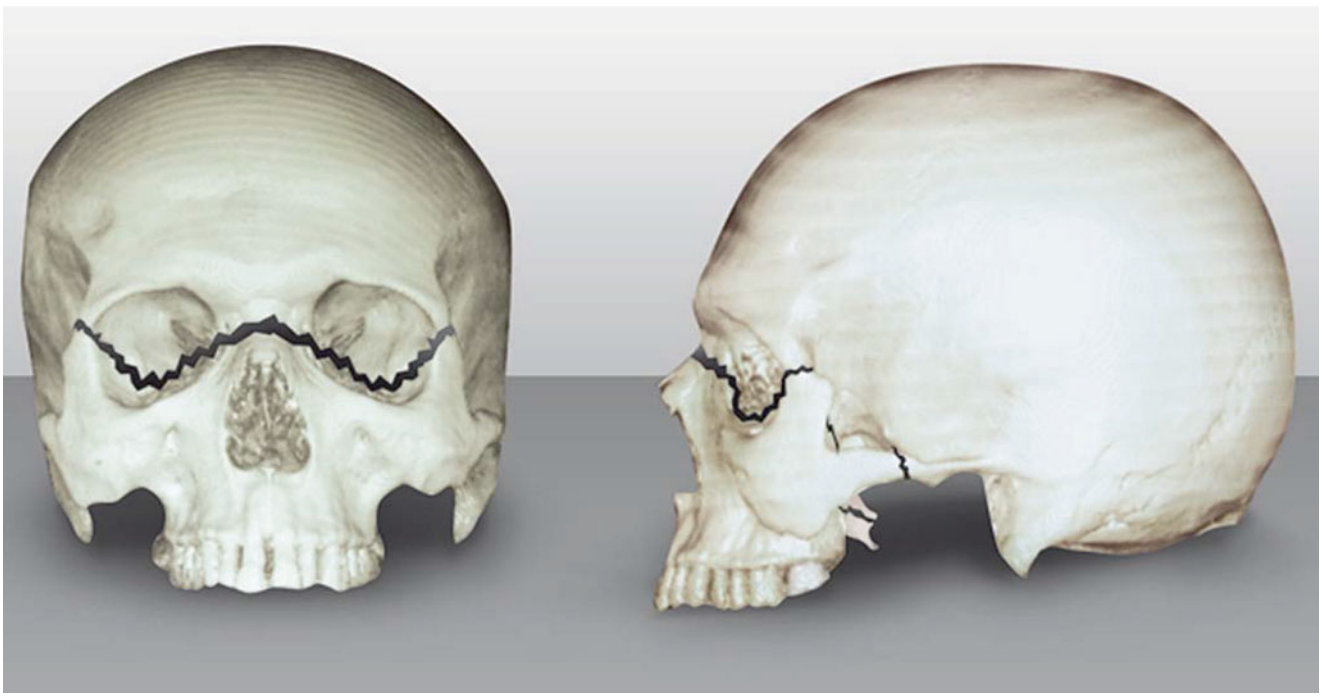


Fig. 30.9 Le Fort III fracture

involved, several subunits can be recognized such as the zygomaticomaxillary complex (ZMC), the nasoorbitoethmoidal complex (NOE), and the dentoalveolar complex (DAC). This classification describes more closely the bone structures involved and can be of great help by improving communication between radiologists and surgeons [18, 26] (Fig. 30.10). Detection of facial fractures is straightforward. CT scan with 3D imaging allows visualization of the most complex facial injuries and helps the surgeon during surgical planning [27] (Fig. 30.11).

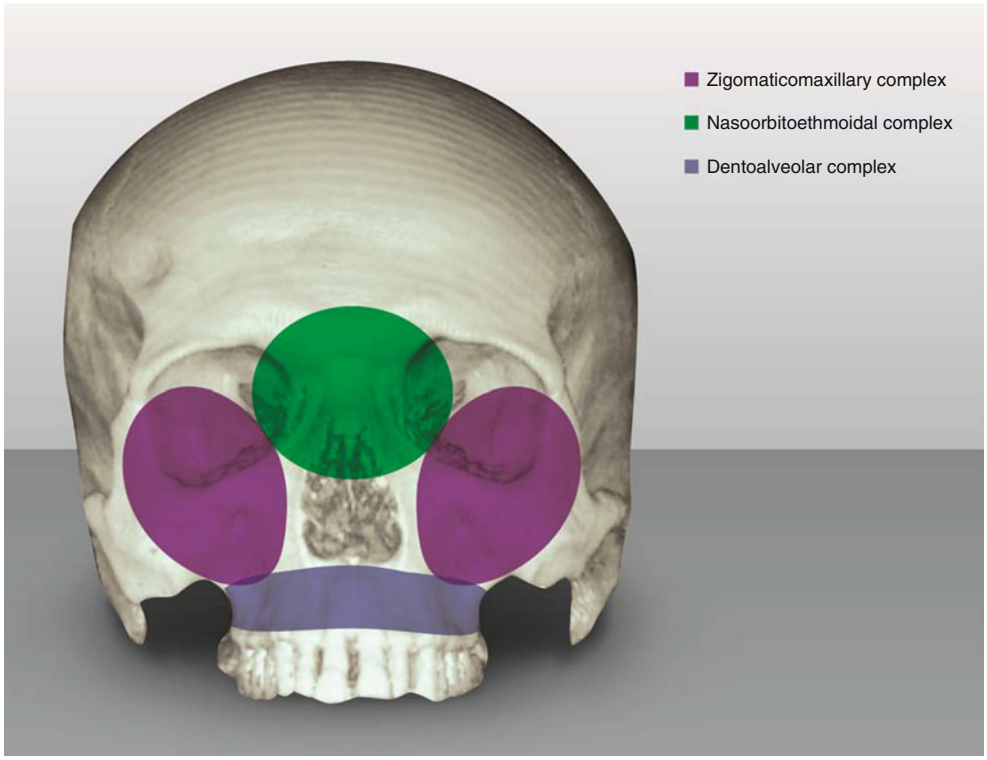


Fig. 30.10 Anatomical subunits of the midface

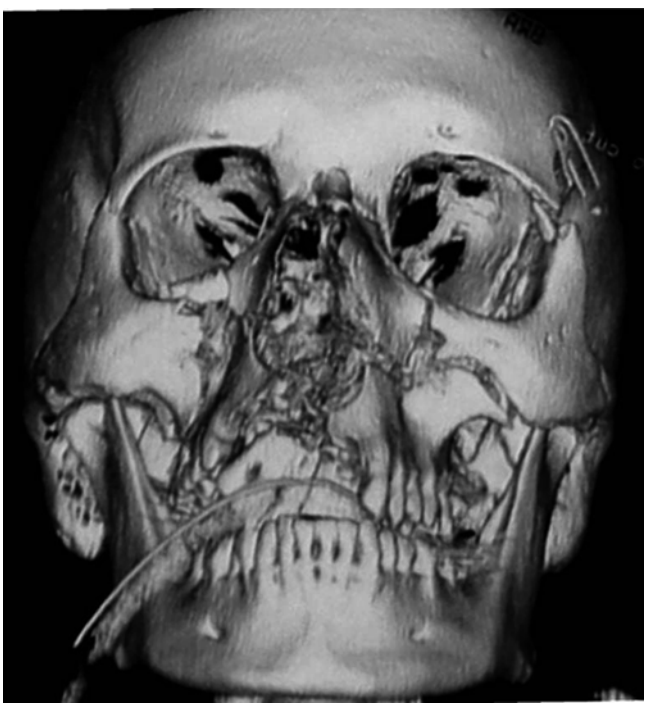


Fig. 30.11 CT scan. Complex midface trauma: dentoalveolar fractures and bilateral Le Fort I and II fractures. *Left side*: monolateral Le Fort III fracture. Involvement of ethmoidal sinus

Injury to the paranasal sinuses can be direct or indirect. Direct lesions are produced when the fracture occurs in the point where traumatic forces act. Indirect injuries occur in a distinct site, often contiguous to the point on which traumatic forces act. An example is the blow-out fracture of the orbital floor related to a high-energy trauma of the eyeball, with a sudden increase of orbital cavity pressure, causing a fracture of the orbital floor into the maxillary sinus (Fig. 30.12).

Fig. 30.12 One of the most common injuries leading to blow-out fracture

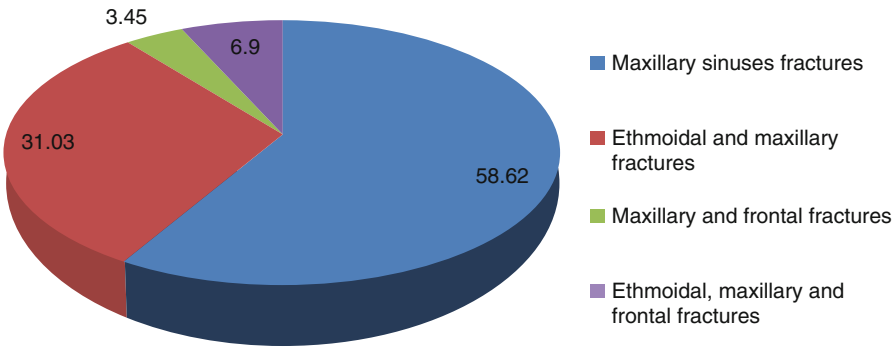


Fig. 30.13 Distribution of midface fractures

Maxillary Sinus Trauma

Among paranasal sinuses, the maxillary sinuses are the most commonly involved in midface trauma [28] (Fig. 30.13). Lesions of maxillary sinuses are associated with Le Fort I and Le Fort II fractures and ZMC fractures and range from simple disruption of the sinus wall to more complex lesions with comminution of bone fragments (Fig. 30.14). An isolated lesion of the maxillary sinuses can be associated with blow-out fractures or with iatrogenic injury, such as seen with an oroantral fistula, displaced dental implants or after endoscopic surgical procedures [29]. Posttraumatic communication with the oral cavity may result in the formation of oroantral fistulae which, when misdiagnosed, can be responsible for maxillary sinus infections (Fig. 30.15).

The blow-out fracture corresponds to a fracture of the superior sinus wall. It is due to direct traumatic forces acting on the eyeball so that the pressure in the orbital cavity leads to fracture of the thin inferior orbital wall. The mechanism may be interpreted as an evolutionary barrier protecting the eye from rupture. Complete dislocation of the eyeball into the maxillary cavity is also possible [30]. Diplopia is a common symptom of blow-out fractures and is due to entrapment of the inferior rectus and/or oblique muscle. Most commonly, it is the periorbital fat in blow-out fractures that herniates (Fig. 30.16) with subsequent enophthalmos.

Frontal Sinus Trauma

Fractures of the frontal sinus are of particular concern because of the close relationships that this structure has with the brain. Injury to the frontal sinus can be complicated by the formation of a dural tear, cerebrospinal fluid (CSF) leakage, and suppurative complications. The frontal sinus, along with the ethmoidal and the sphenoidal sinuses, is found between the brain

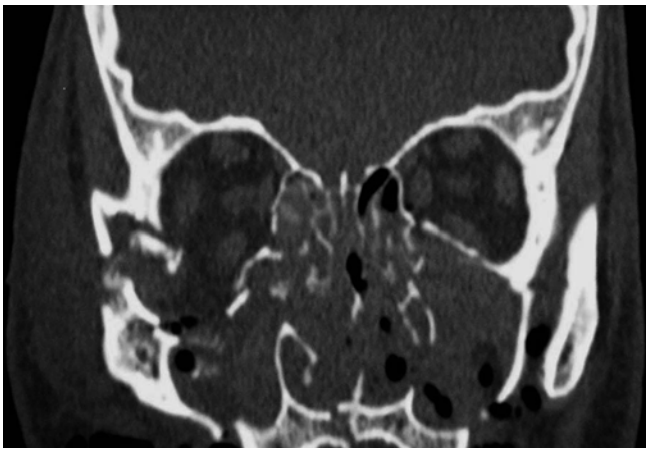


Fig. 30.14 CT scan: comminuted fractures of ethmoidal and frontal sinuses with sinus hematoma

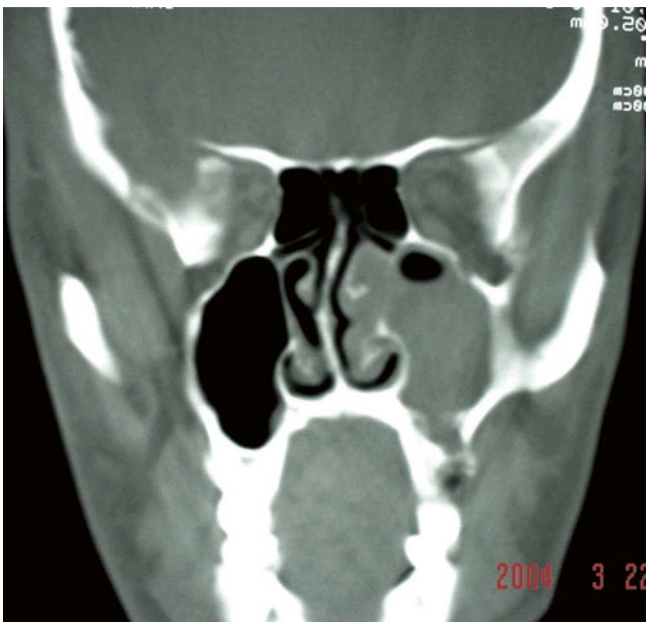


Fig. 30.15 CT scan: maxillary empyema following tooth extraction. Presence of oroantral fistula, with pus going toward the nasal fossa and the orbit

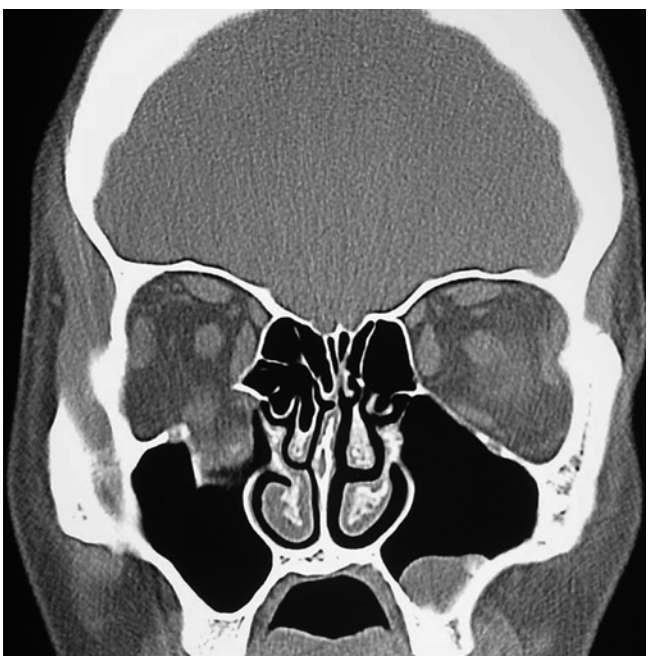


Fig. 30.16 CT scan: blow-out fracture (*right*) with periorbital fat herniation into the maxillary sinus

Table 30.1 Anatomical classification of frontal sinus fractures

Frontal sinus fractures can be anatomically classified as:
Fractures of the anterior wall
Fractures involving the anterior and the posterior walls
Fractures of the orbital roof, with or without involvement of the orbital rim
Fracture with or without involvement of nasofrontal duct

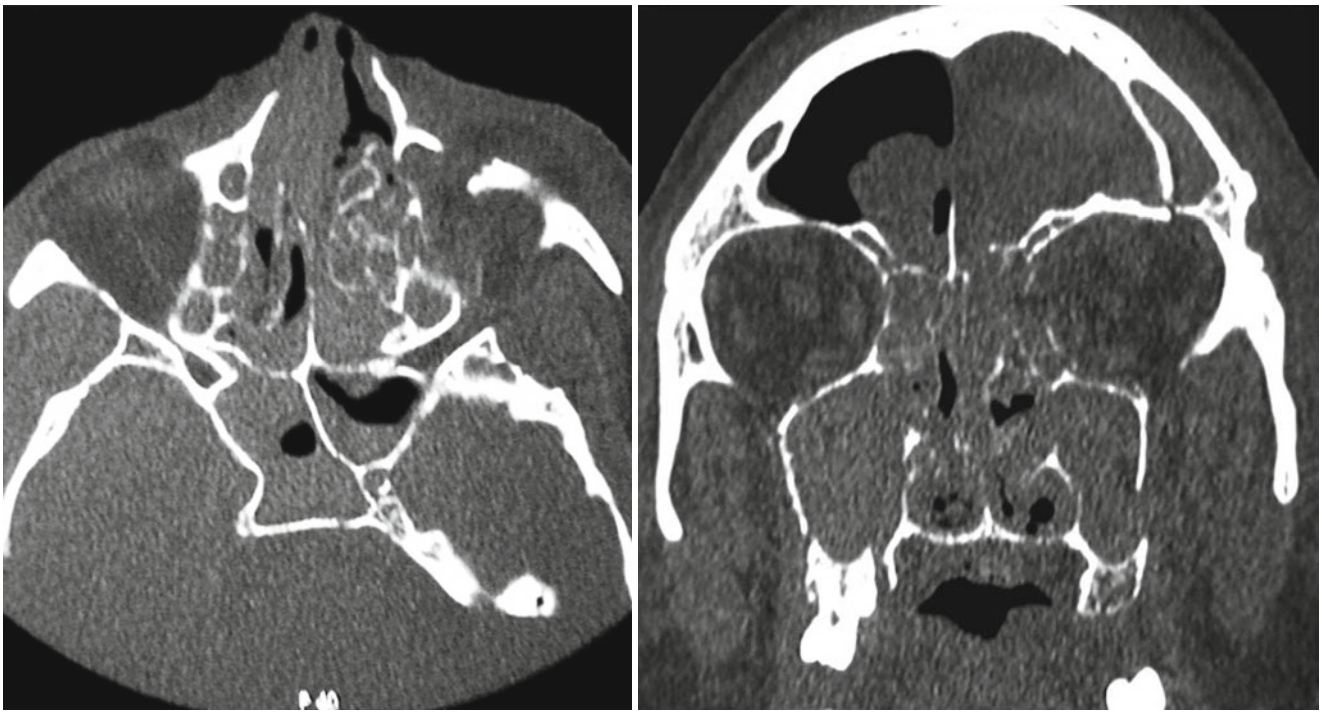


Fig. 30.17 CT scan: frontal sinus fracture with involvement of ethmoidal and sphenoidal sinuses, nasal fossa and maxillary sinuses. Presence of sinus hematoma and pneumocephalus

and the external environment. In the case of injury, trauma to the frontal sinuses can predispose a patient to brain infection with or without abscess formation [31]. The types of frontal sinus fractures are listed in Table 30.1.

Frontal sinus fractures can be comminuted or simple, displaced or nondisplaced. More complex injuries can involve the skull base, the sphenoidal sinus, and the NOE complex, with severe clinical implications [32, 33] (Fig. 30.17).

Posterior wall fractures occur when the strength of the traumatic forces overcomes the resistance of the anterior wall of the frontal sinus. Posterior wall fractures can lead to CSF leakage and suppurative complications (Fig. 30.18). Prognosis can be worsened when the nasofrontal ducts are obstructed, blocking sinus secretion drainage. CSF leakage is typical of posterior wall fractures, due to both the involvement of the dura mater and the cribriform plate of the ethmoid. Late complications include mucocele formation, with subsequent infection which can spread to the orbit or to the brain causing life-threatening conditions including meningoencephalitis [34, 35] (Fig. 30.19).

Ethmoidal Sinus Trauma

Isolated fractures of the ethmoidal sinus are rare, while ethmoidal structures are often affected in injuries to the NOE complex and the frontal sinus. The superior wall of the ethmoid bone is called the cribriform plate. It contains several olfactory nerve filaments passing through small foramina and reaching then the nasal mucosa. The cribriform plate is very thin and susceptible to traumatic injury. Injury to the cribriform plate can expose the dura mater and can lead to suppurative complications. Injuries of the NOE complex can also extend to the middle cranial fossa affecting the sphenoidal sinus. Hyposmia and

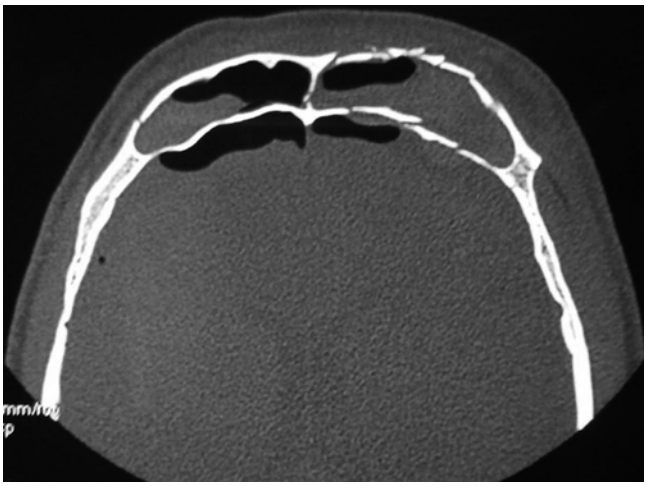


Fig. 30.18 CT scan: maxillary sinus posterior and anterior wall fracture, with sinus hematoma and pneumocephalus

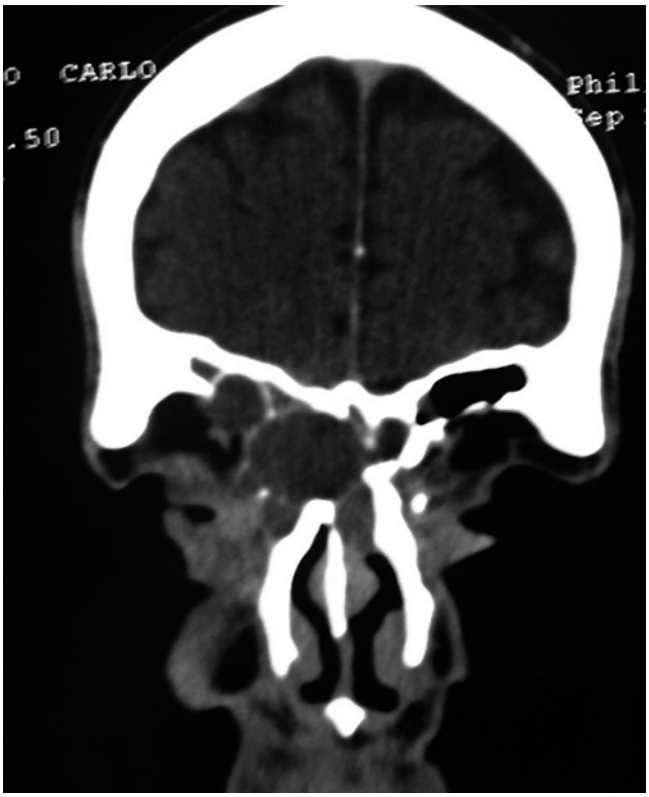


Fig. 30.19 CT scan: posttraumatic mucocele of the frontal sinus invading the ethmoid bone and the orbital cavity

anosmia can occur following NOE complex injury and are attributable to the damage of the olfactory nerve filaments passing through the cribriform plate [36].

The lacrimal system can be also affected in nasoethmoidal fractures because of the close anatomical relationship existing between them. Following injury, the nasolacrimal duct can become obstructed as a result of inflammation of the nasolacrimal sac (dacryocystitis) [37]. Other commonly associated injuries include damage to canthal tendons, the levator palpebrae superioris muscle, as well as orbital wall fractures [38].

Maxillofacial injuries affecting the NOE complex are often a result of high-energy impact at the level of nasoglabellar area, as frequently happens in crush injuries where the driver's head hits the steering wheel or the dashboard (Fig. 30.20). Fracture of the ethmoid bone can also be associated with Le Fort II and Le Fort III fractures, in which the fracture line passes through the root of the nose. Isolated fracture of the lateral wall of the ethmoidal sinus is rare [39], and it is usually secondary

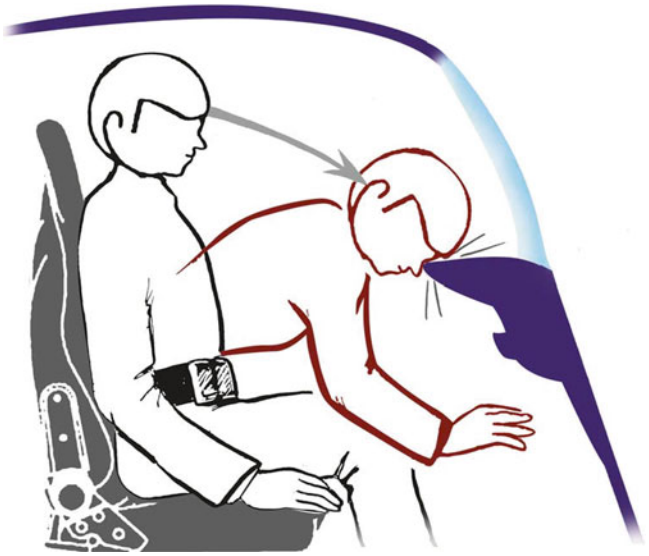


Fig. 30.20 One of the mechanisms leading to NOE injury

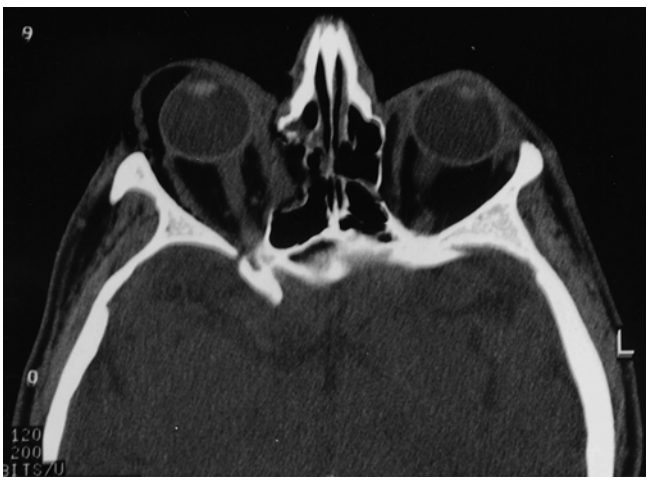


Fig. 30.21 CT scan: medial blow-out fracture (*right*) with medial rectus muscle incarceration

to a blow-out fracture because the lateral wall of the ethmoid is very fragile and is part of the medial orbital wall. Dislocation of the orbital content into ethmoidal cells with muscle incarceration is frequent with these injuries (Fig. 30.21).

Sphenoidal Sinus Trauma

The sphenoidal sinus is well protected from external injuries, being located between the neurocranium and splanchnocranium. Lesions affecting the sphenoidal sinus are normally associated with complex craniofacial injuries. They are challenging due to potential vascular complications resulting from the proximity of the internal carotid arteries and the cavernous sinus. Other complications of sphenoidal injury include frequent CSF leakage due to close proximity to the cerebellomedullary cistern. Concomitant damage to optic and oculomotor nerves passing through the cavernous sinus has been described [40].

Diagnosis

Patients with facial trauma often present to the emergency room exhibiting multiple lesions involving the brain, spine, limbs, chest, and abdomen. Facial injuries present with facial swelling, bruising, and epistaxis. When paranasal sinuses are affected, subcutaneous emphysema is commonly present. Moreover, the eyelids are usually closed due to a conjunctival hematoma.

Fig. 30.22 Panfacial trauma (at 12 h)

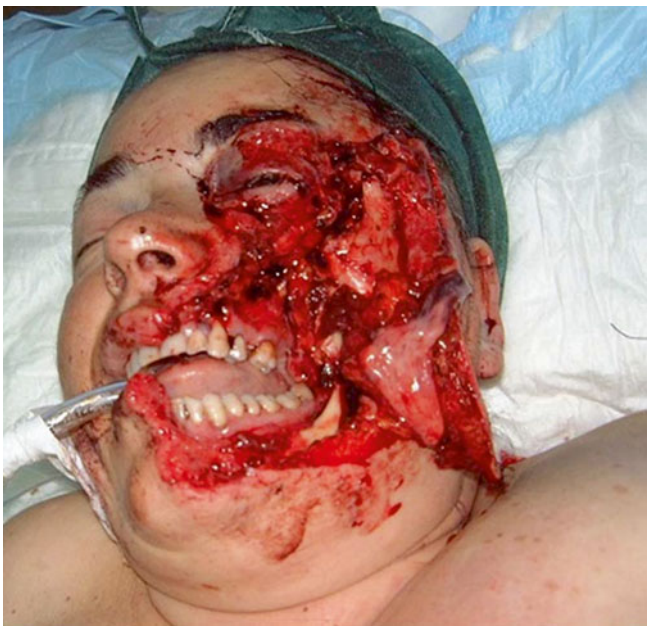


Fig. 30.23 Panfacial trauma with extended soft-tissue defect

All this makes clinical examination difficult (Fig. 30.22). In other circumstances facial fractures are associated with soft-tissue defects (Fig. 30.23). Swelling can be barely visible in some circumstances. A clinical sign that is highly suspicious for upper/lower jaw fracture is malocclusion. When there is involvement of the glabellar area such as in the case of Le Fort II, Le Fort III, and NOE complex fractures, the bruising extends symmetrically on both orbital sides forming the so-called panda eyes (Fig. 30.24).

When the trauma is blunt, swelling can be minimal, as in the case where a patient is elbowed in his cheek bone. Asymmetry of the face can be the only sign of such an injury and usually indicates a zygomatic fracture. In nasoethmoidal fractures, a depression in the glabellar region can be present leading to the "pig snout" deformity attributable to the pushback of the nasoglabellar region toward the ethmoid bone (Fig. 30.25).

Fig. 30.24 Le Fort II fractures with "panda eyes"

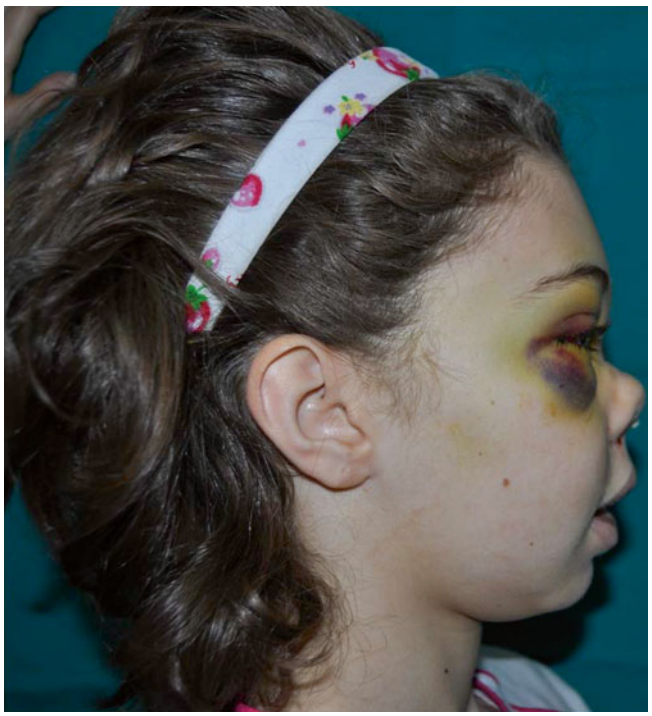


Fig. 30.25 "Pig snout" deformity following trauma of the NOE

CSF leakage is representative of NOE injuries complicated by dural tear formation. CSF leakage of fluid from the nose is often mixed with blood and can be difficult to distinguish. A simple method is to collect the secretion on a gauze pad. In the case of a CSF leakage, a lighter halo surrounding the dark blood stain will be visible (Fig. 30.26); otherwise the sample can be sent to the laboratory for appropriate testing.

In blow-out fractures a downward dislocation of the orbital contents can be observed. This type of injury can be responsible for enophthalmos. The sign is usually visible when early postoperative swelling decreases after a few days [41] (Fig. 30.27). Another characteristic sign of blow-out fractures is diplopia, attributable to muscle entrapment in the orbital floor fracture. The eyeball, being muscle incarcerated, cannot move simultaneously and symmetrically with the contralateral eyeball. The inferior rectus is the most commonly involved muscle defining vertical diplopia (Fig. 30.28).

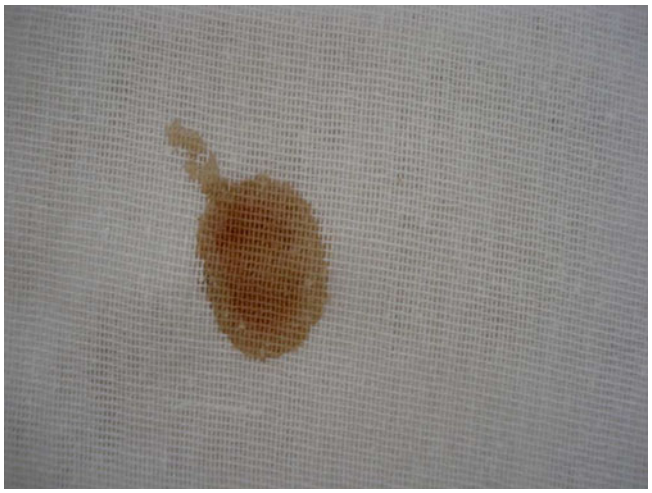


Fig. 30.26 The double halo sign, with CSF surrounding the blood stain

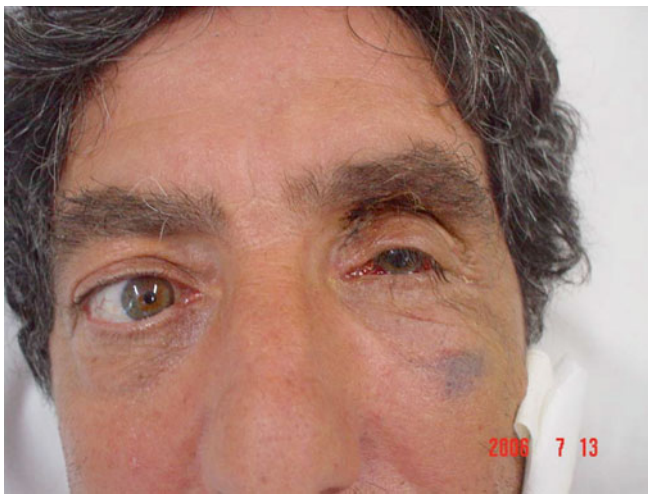


Fig. 30.27 Enophthalmus following blow-out fracture (*left*)

In a medial orbital wall fracture, the medial rectus muscle is incarcerated thus generating horizontal diplopia. Motor deficits of the eyeball can be also generated by facial trauma that involves a central and/or peripheral lesion of the cranial nerves III, IV, and VI.

The forced duction test is useful in determining whether the absence of eye movement is due to a neurological disorder or a mechanical restriction. The inferior conjunctiva is anesthetized with drops, grasped with forceps, and retracted. The patient is asked to move the eye in the direction where the movement is supposed to be restricted. If the restriction is neurological, the eyeball will move according to the traction; if the eyeball does not move according to the traction, the restriction is mechanical as seen in the case of muscle incarceration.

Exploration of the oral cavity is essential to control the occlusion and verify the integrity of the dentoalveolar system (Fig. 30.29). Open-bite deformity is generally present in Le Fort fractures and is due to the dislocation of the maxillary bone that slides backward as a wedge between the skull base and the inferior dental arch. The displacement is responsible for premature posterior occlusal contacts between molars (Fig. 30.30). In maxillary sagittal fracture, a diastema (a gap between two teeth) can be noted along with lacerations of the gingiva (Fig. 30.31).

Subjective symptoms are of great importance in midface trauma. Lesions of the superior and anterior wall of the maxillary sinus are associated with hypoesthesia of the upper lip and dental arch. In blow-out fractures, the infraorbital nerve passing through the sinus can be compressed or irritated. Blood can recollect into the maxillary sinus (hematoma) and pass into the mouth causing discomfort to the patient. Other subjective symptoms include difficulties in chewing and swallowing.

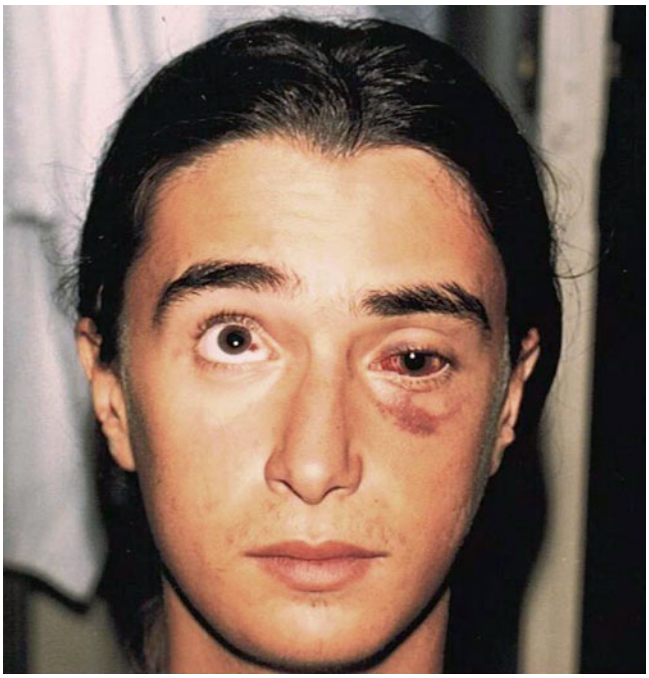


Fig. 30.28 Vertical diplopia (*left*). Left eye does not follow the contralateral eye when gazing upward

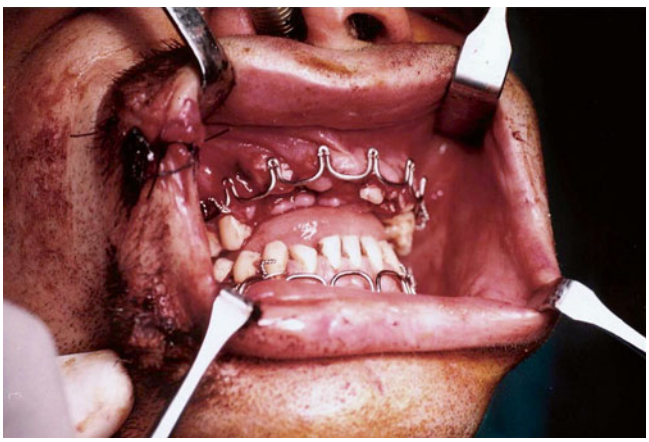


Fig. 30.29 Loss of habitual occlusion along in midface trauma

Extraoral palpation includes examination of facial contour to evaluate the presence of bone irregularities, crackling, and subcutaneous emphysema. Maxillary stability can be evaluated by grasping the premaxilla and the incisive teeth between the first and the second finger. If the maxilla is mobile because of a fracture, bimanual palpation is performed. With one hand, the premaxilla along with the upper dental arch is grasped, while the other hand palpates the zygomaticomaxillary and frontozygomatic sutures on both sides (Fig. 30.32).

Mobility of the zygomaticomaxillary suture is suggestive of Le Fort II fractures, while mobility of the frontozygomatic suture is suggestive of Le Fort II fractures. In the case of Le Fort I fracture, the entire upper dentoalveolar system is mobile. Le Fort classification, however, is not always feasible because the fractures often do not always respect classic Le Fort lines, as in the case of atypical monolateral or bilateral fractures (Fig. 30.33).

Imaging Techniques

Until the introduction of modern imaging techniques, standard x-rays were the gold standard for radiological diagnosis of facial trauma. The Waters and the Caldwell projections were the most employed projections (Fig. 30.34). The former is useful for the evaluation of the maxillary bone and sinus and for the orbit and zygomatic arch. The Caldwell projection allows for the evaluation of the frontal and ethmoidal sinuses, the orbital floor and contour, and the frontozygomatic sutures.

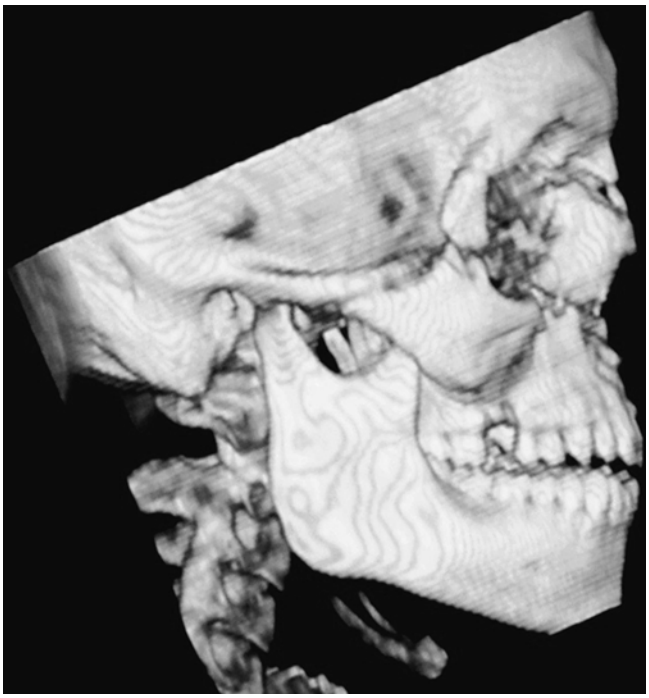


Fig. 30.30 CT scan: open-bite deformity in Le Fort I–II and NOE fractures. Backward dislocation of the maxillary bone responsible for premature occlusal contacts between molars

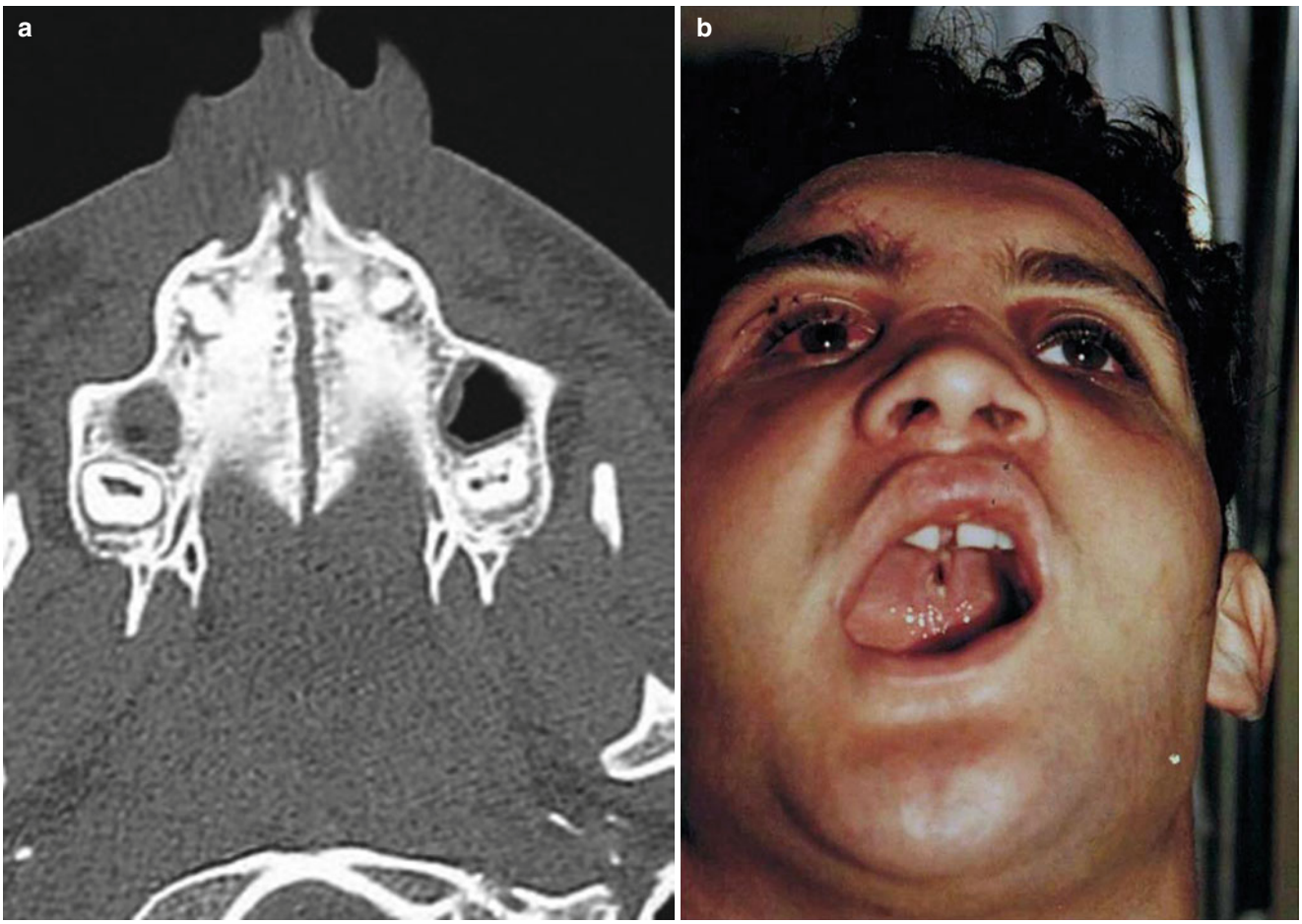


Fig. 30.31 Sagittal palatal fractures with diastema and hard palate fistula

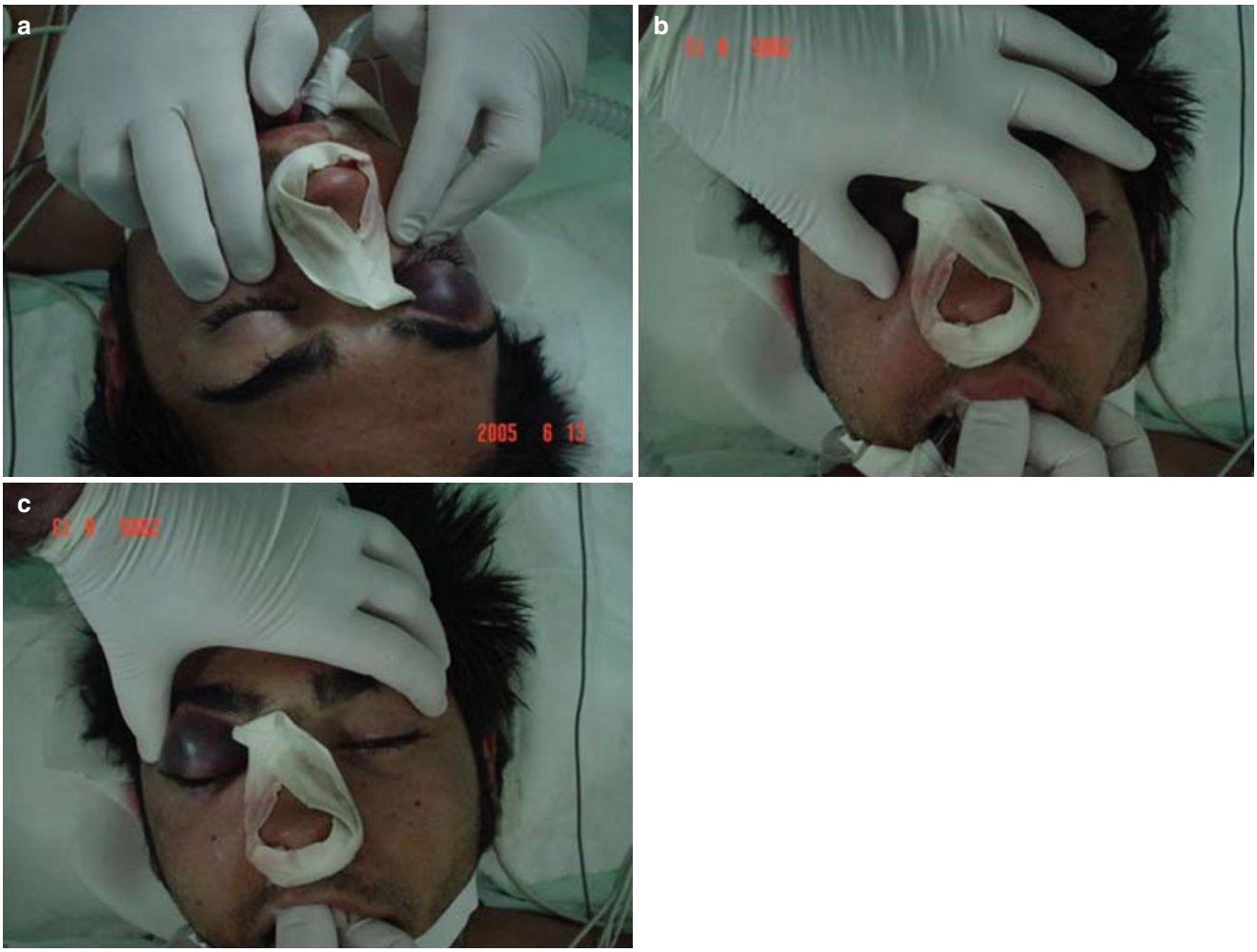


Fig. 30.32 (**a**) Palpation. Evaluation of maxillary mobility at zygomaticomaxillary (**b**) and frontozygomatic (**c**) level

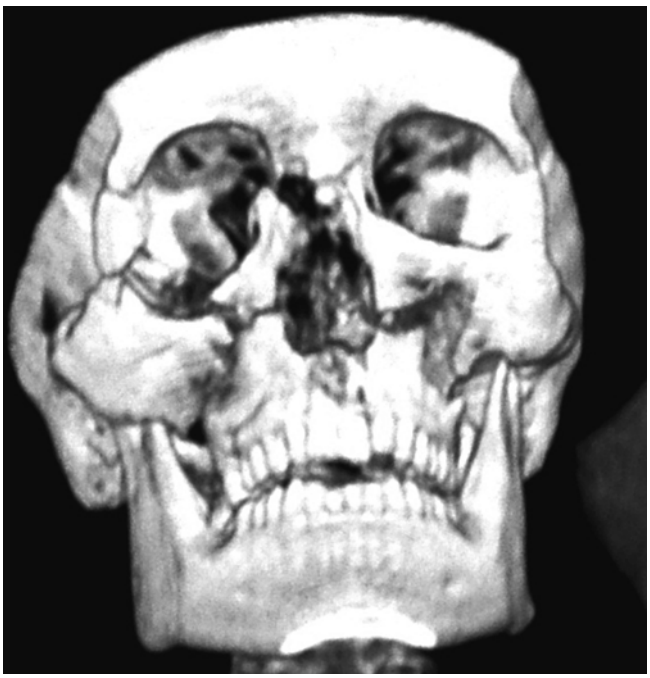


Fig. 30.33 CT scan: midface trauma with bilateral Le Fort I fracture, monolateral Le Fort II and III fractures, NOE fracture, and palatal sagittal fracture

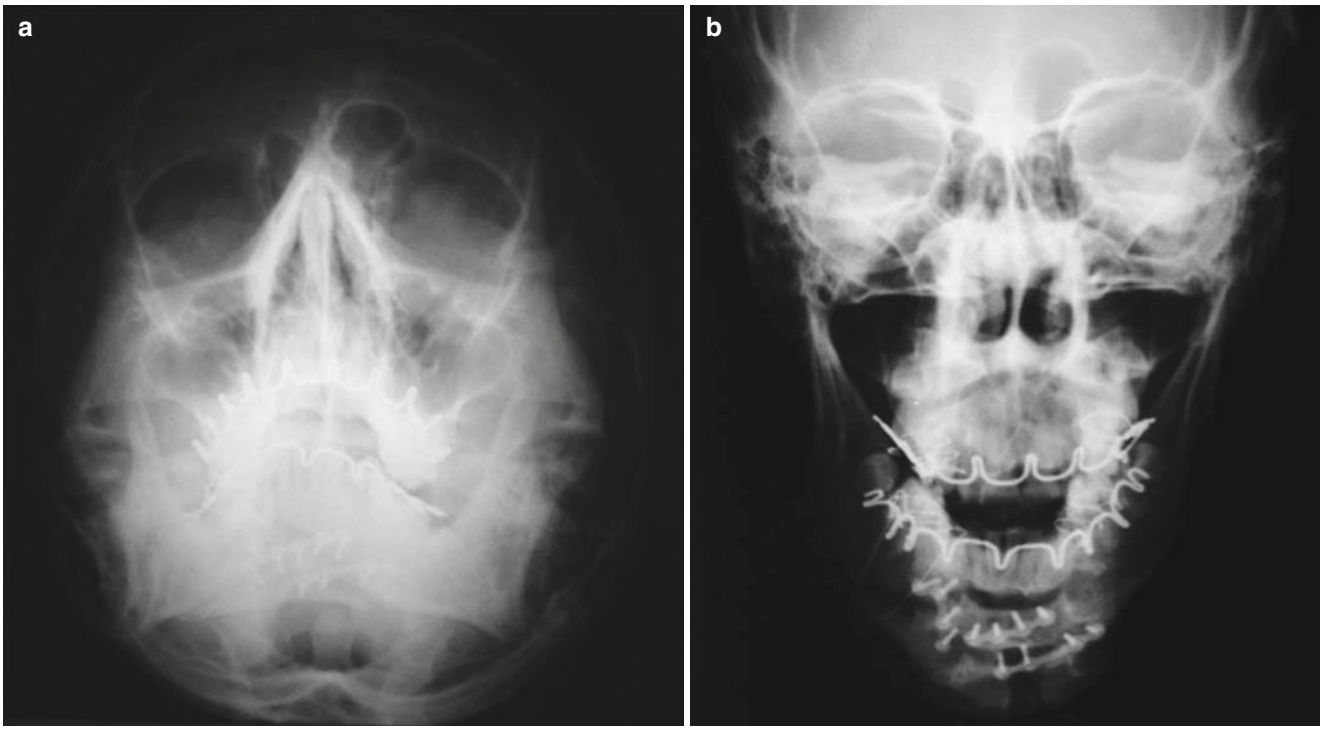


Fig. 30.34 Conventional x-rays: (**a**) Waters projection, (**b**) Caldwell projections

CT scan techniques have radically changed the diagnosis and surgical planning of facial trauma [42, 43] (Fig. 30.35). Multislice helical CT scan provides high-quality images, with three-dimensional reconstruction of facial structures (Fig. 30.36), allowing visualization of the anatomy of the trauma and making surgical planning easier (Fig. 30.37). Multislice helical CT scan is quick and effective providing real-time full-body scanning with the evaluation of the brain and internal organs which are essential in the diagnostic work-up of polytrauma patients [12–14, 44]. Presence of blood in the sinuses is a typical radiologic sign in midface trauma with involvement of paranasal sinuses [45] (Fig. 30.17). Other signs include the presence of dislocated bone fragments and the distribution of air in soft tissues (radiotransparencies). Pneumocephalus is characteristic of head injuries and is attributable to disruption of the ethmoidal and sphenoidal sinus walls with penetration of air into the brain (Fig. 30.17).

Management

Patients suffering from facial trauma are usually treated in emergency settings. Fractures should be reduced within 7–10 days from the trauma, when swelling decreases and fractures are not yet ossified. Vital signs are to be checked first along with inspection for the presence of hemorrhage, respiratory insufficiency, and/or neurological compromise [46]. In Le Fort II and III fractures, the midface can be dislocated backward compromising airway patency. In these cases, maneuvers to mobilize the midface in a posterior to anterior direction are required in order to free the airway.

When upper airway patency is difficult to establish, a tracheotomy or a cricothyrotomy can be performed (Fig. 30.38). Cricothyrotomy is quick and relatively easy to perform, but the risk of laryngeal damage is high [47]. On the other hand, tracheotomy is usually performed in 20 min and is associated with fewer complications. It is routinely performed in complex midface and panfacial trauma surgery, especially when there is brain damage associated.

In the case of hemorrhage, the surgeon can ligate or coagulate the bleeding vessels. Sometimes ligation of external carotid artery is required. In some centers, however, transcatheter selective arterial embolization can be performed [48]. Epistaxis is frequent in facial trauma and requires nasal packing (Fig. 30.39).

Treatment of facial fractures in critically injured patients can be postponed. Reduction and stabilization of fractures can be obtained employing intermaxillary fixation (IMF) with restoration of normal occlusion (Fig. 30.40). Zygomatic

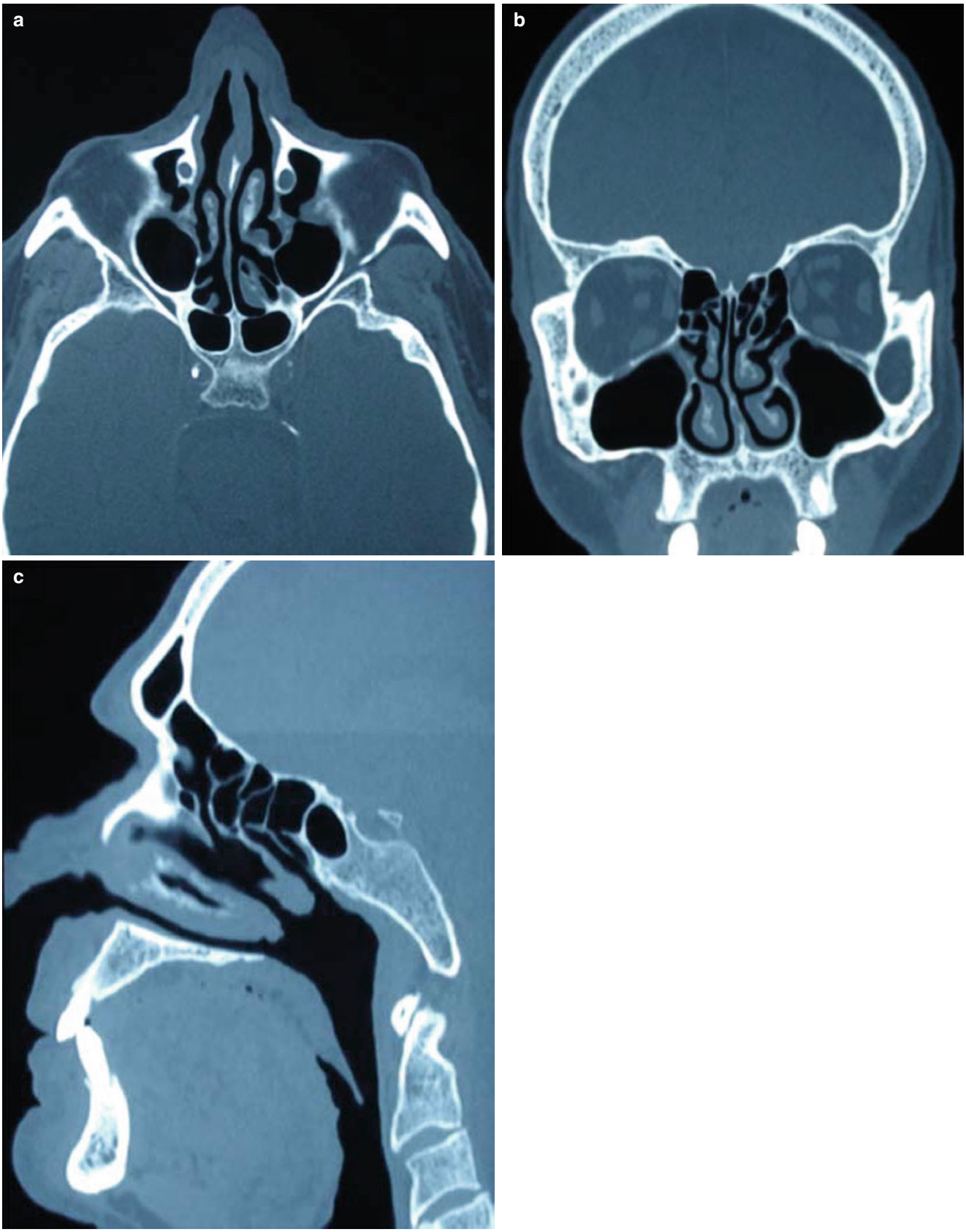


Fig. 30.35 CT scan: normal imaging of paranasal sinuses. (**a**) Axial view, (**b**) coronal view, (**c**) sagittal view

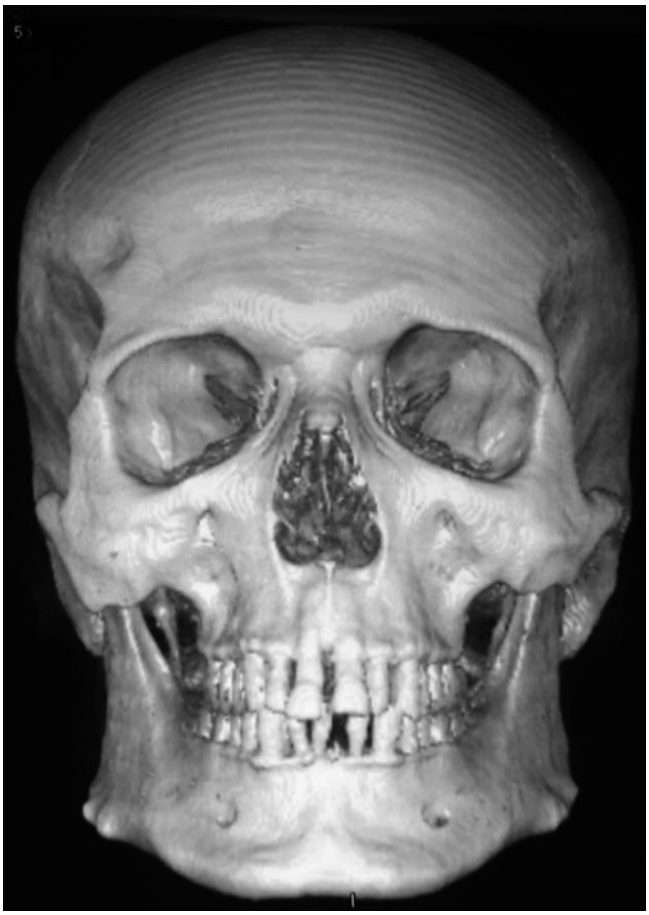


Fig. 30.36 CT scan: normal 3D imaging of facial skeleton

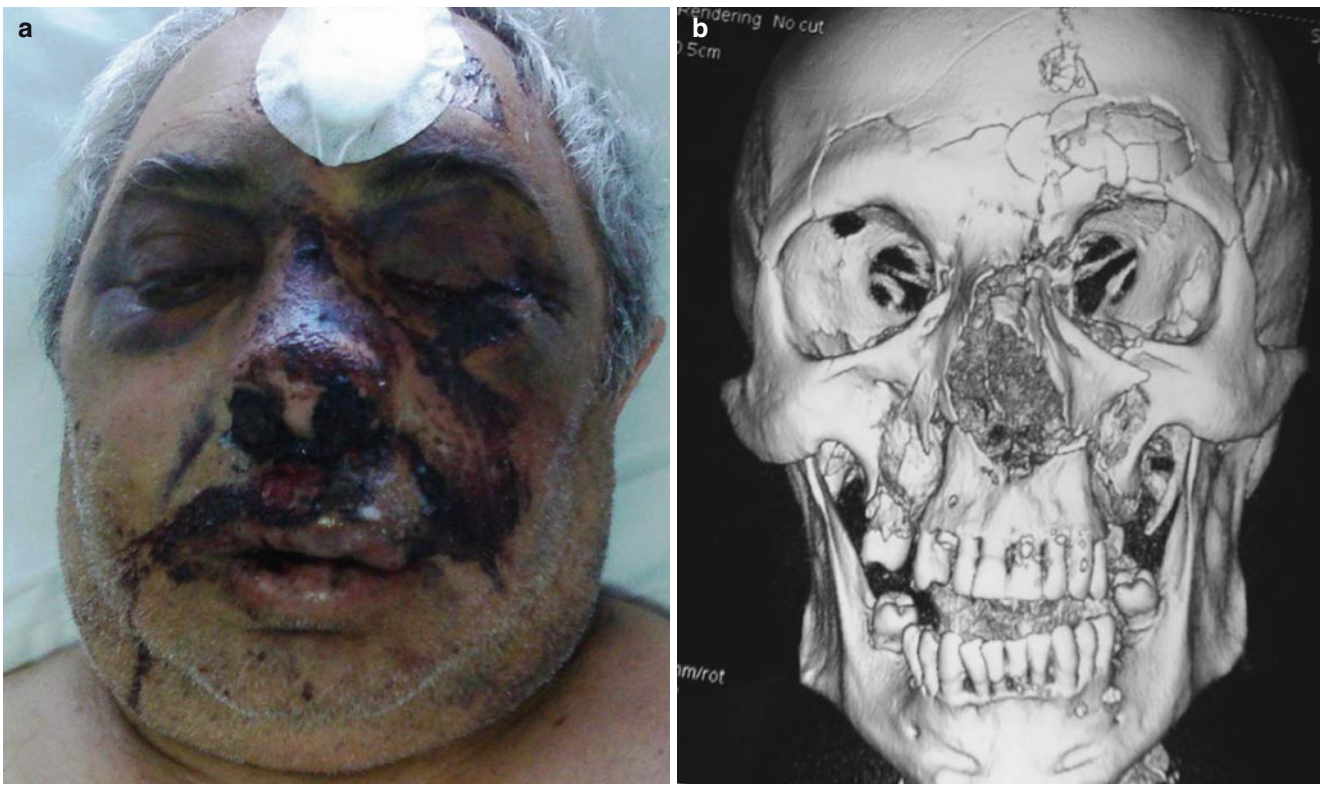


Fig. 30.37 Complex midface trauma (**a**), CT scan shows type, location, and extent of the injury (**b**)

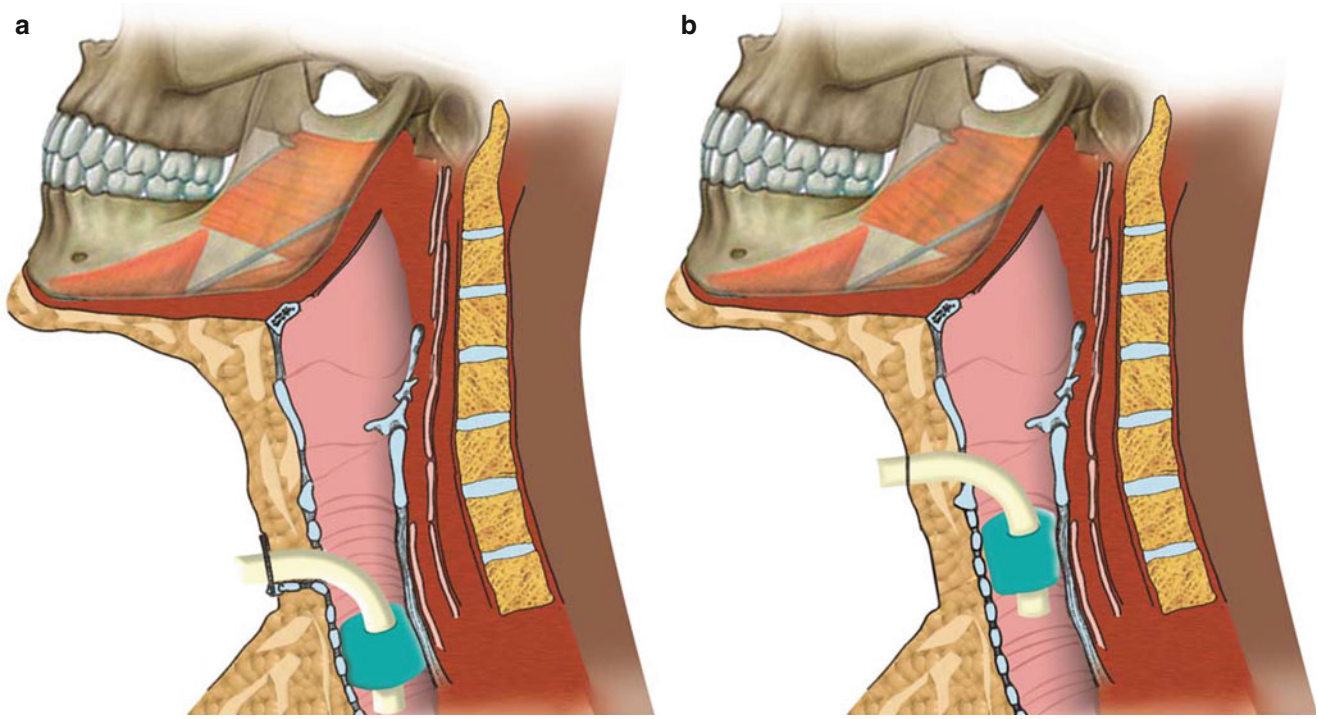


Fig. 30.38 Tracheotomy (**a**), cricothyrotomy (**b**)

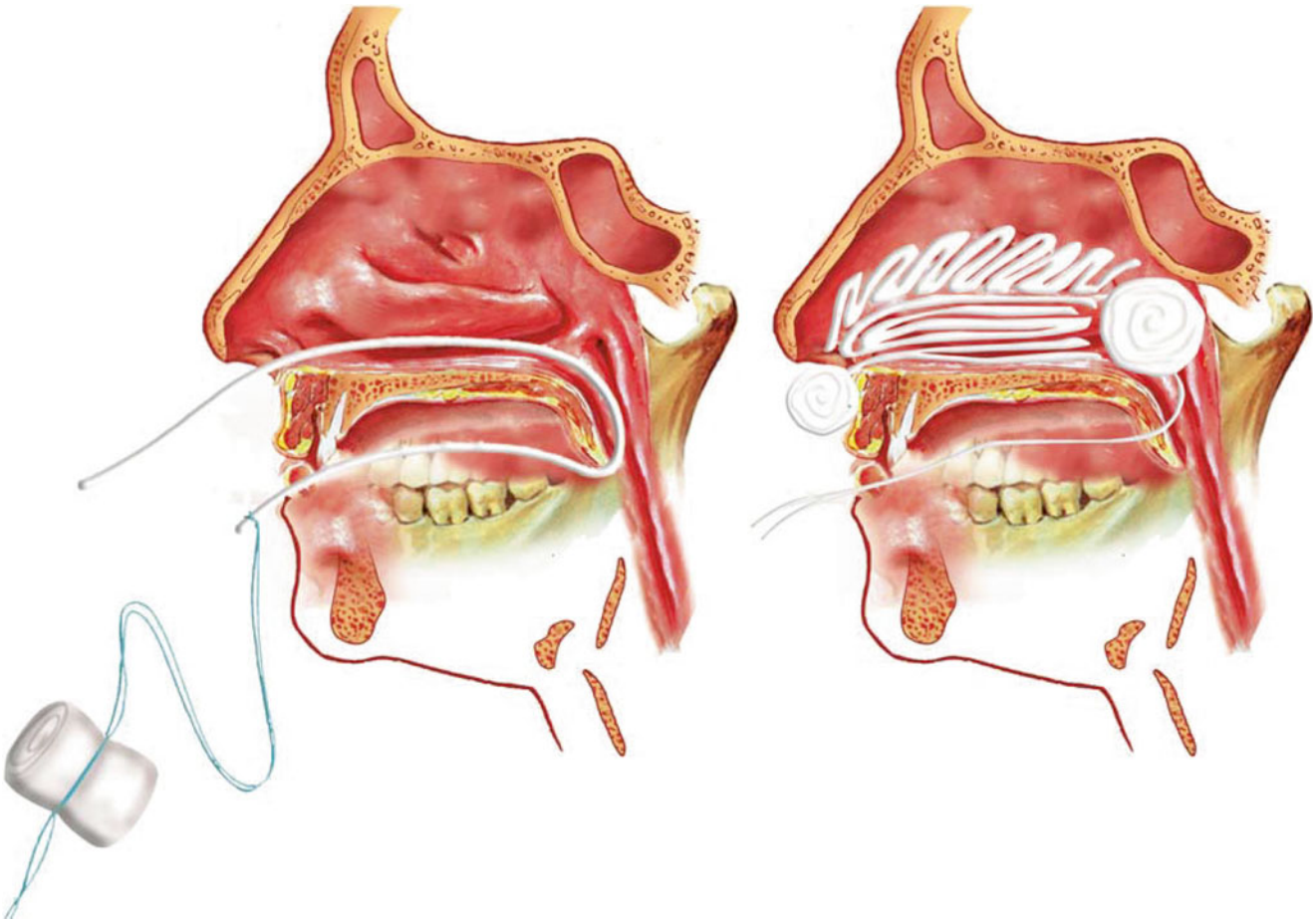


Fig. 30.39 Nasal packing

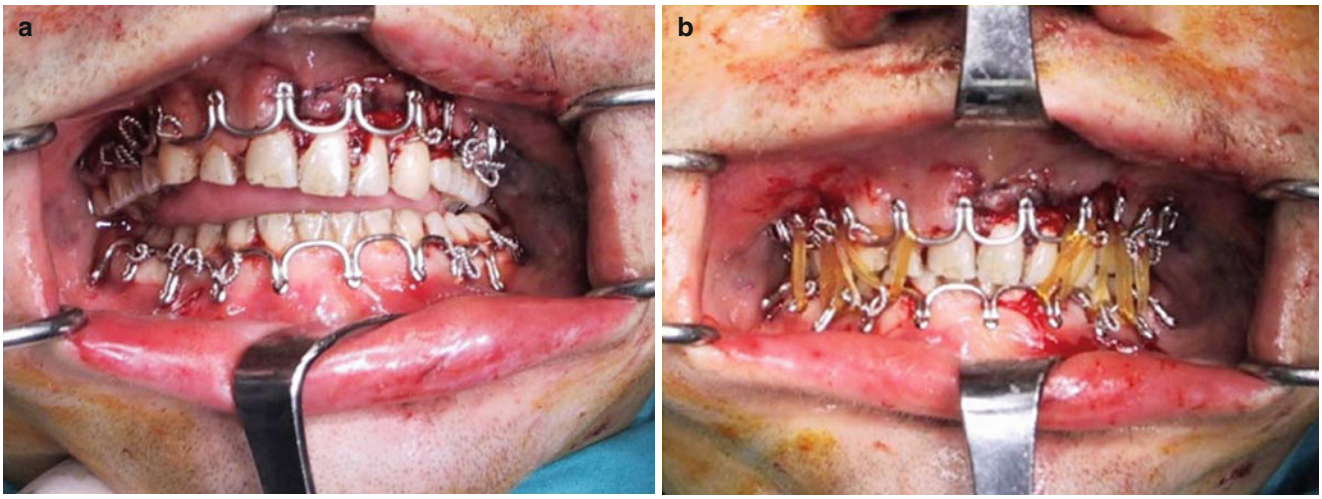


Fig. 30.40 Occlusal splint in place (**a**), IMF can restore habitual occlusion (**b**)

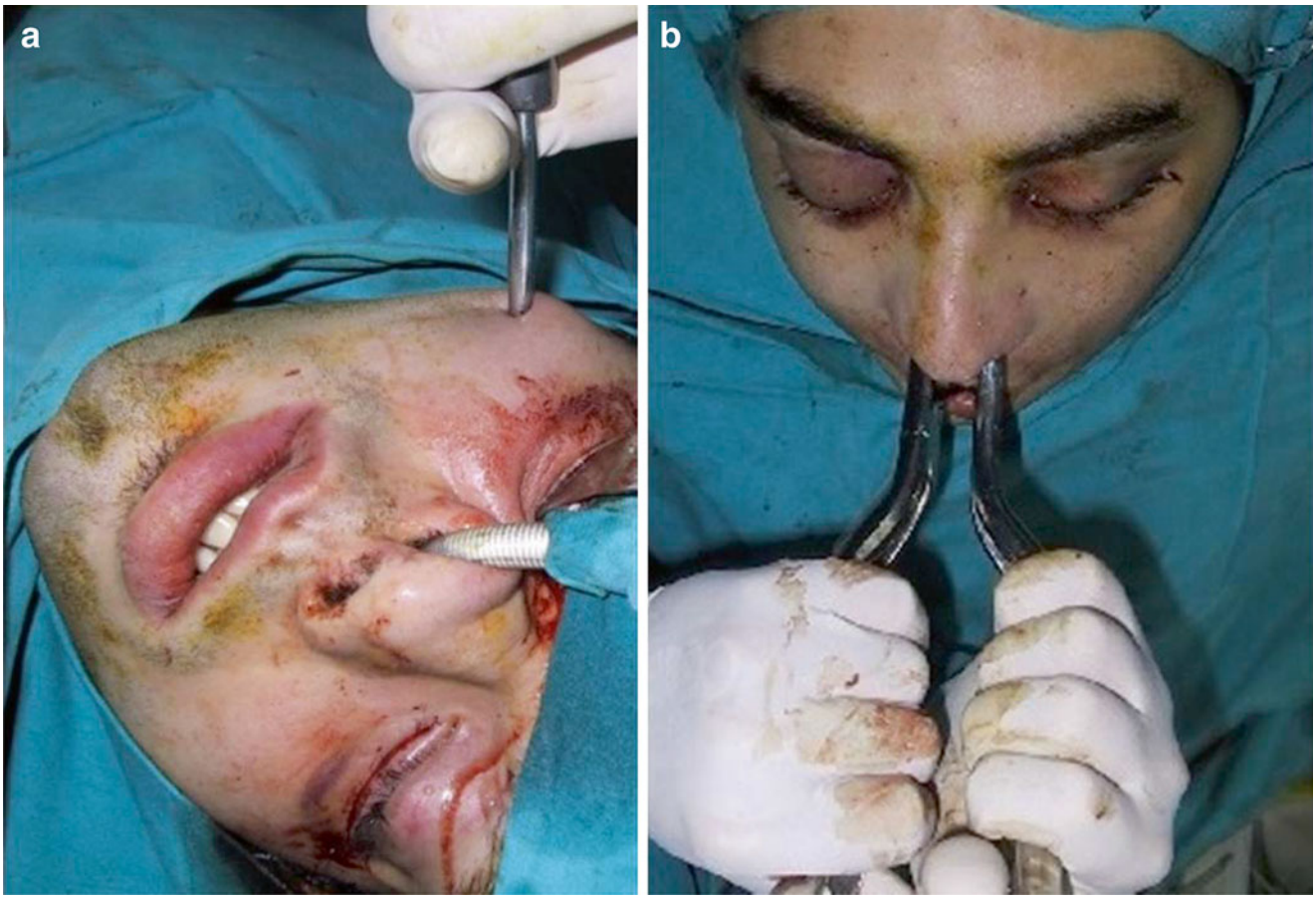


Fig. 30.41 Zygomatic fracture reduction using a bone hook (**a**), reduction of maxillary fracture with Rowe disimpaction forceps (**b**)

fractures can be reduced percutaneously using a bone hook. Midface fractures in which the maxilla is dislocated backward can be mobilized using Rowe disimpaction forceps and IMF restoring normal occlusion (Fig. 30.41). Less invasive procedures performed in critical patients are cost-effective and avoid overtreatment. However, they often do not allow for direct visualization of injured structures. In general, quicker recovery can be achieved by careful and accurate

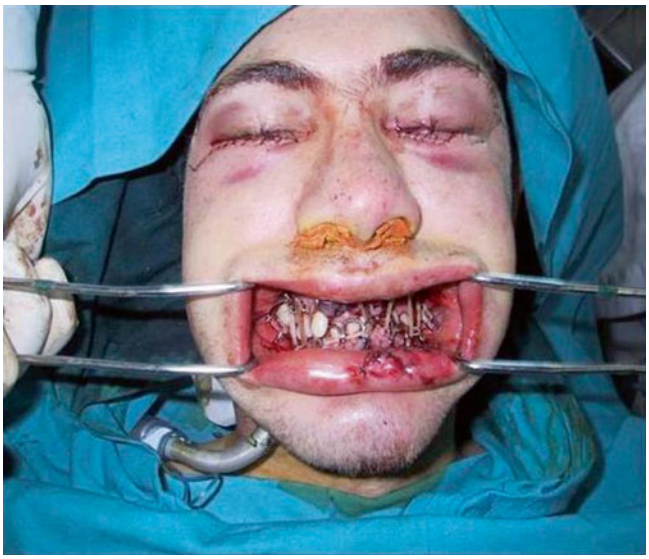


Fig. 30.42 Submental intubation. Note the IMF and the nasal packing

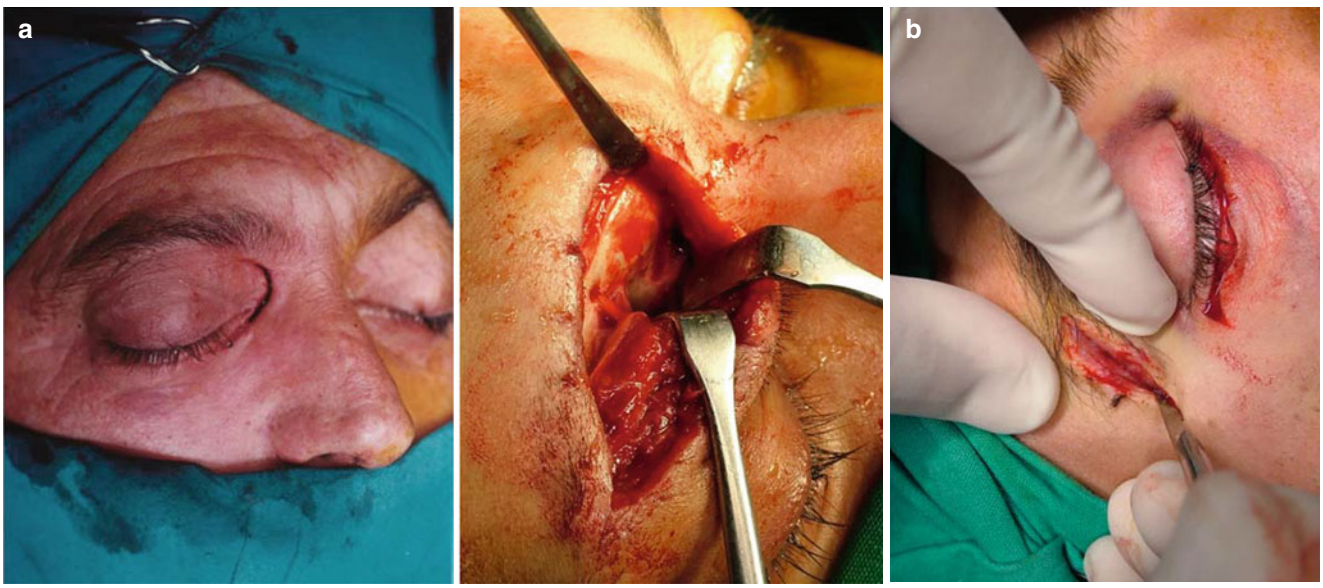


Fig. 30.43 Surgical access to the midface, (**a**) medial orbital wall and (**b**) lateral orbital wall

surgical treatment. IMF is systematically applied in emergency settings providing stabilization of fractures and, in cases of small nondisplaced fractures, definitive treatment. IMF is usually maintained from 2 to 6 weeks.

When undergoing surgery, patients are intubated through the nose or by means of tracheotomy. A simple and effective method is submental intubation which avoids the use of tracheotomy and endotracheal tube exchange [49, 50] (Fig. 30.42). Zygomatic, NOE, and frontal fractures are normally accessed using an open approach, while the orbital floor can be accessed through a subciliary or transconjunctival approach (Fig. 30.43). In case of complex multiple fractures involving the frontal sinus, a bicoronal approach with subgaleal dissection provides wide exposure of the injured area (Fig. 30.44). The intraoral approach is reserved for fractures involving the dentoalveolar system, the maxillary buttress, and the Le Fort II and III fractures (Fig. 30.45).

Bone fragments are reduced and fixed under direct visualization. Rigid internal fixation (RIF) employs titanium plates and screws for fixation [51–55]. This has definitively replaced wire fixation techniques and reduced patient recovery time. The first material used for plates and screws was steel. This has been replaced by titanium which is lighter, more stable, and compatible with magnetic resonance imaging techniques [56, 57]. Biodegradable materials such as poly-L-lactic-polyglycolic

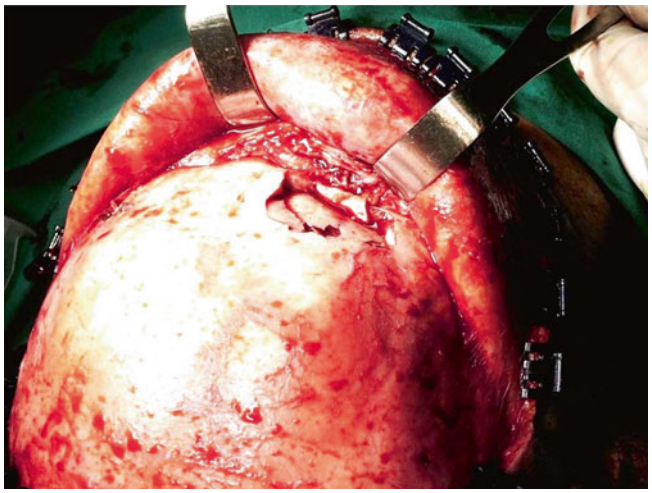


Fig. 30.44 Bicoronal approach

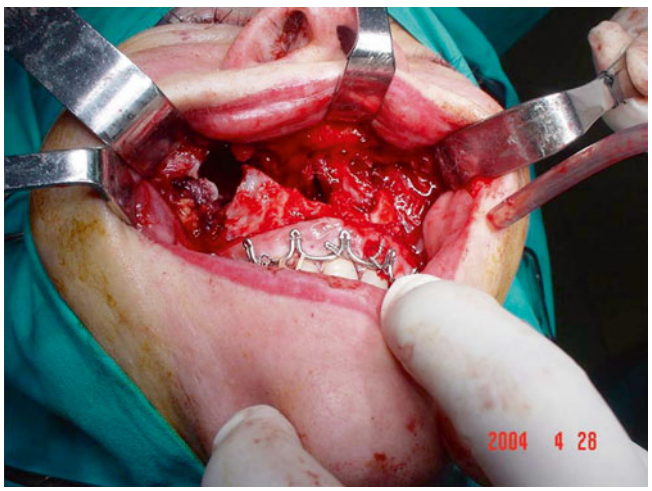


Fig. 30.45 Intraoral approach to Le Fort I fracture

plates are also available and very useful especially in pediatric patients [58, 59]. However, the costs are high and titanium still remains the most employed material (Fig. 30.46). Panfacial trauma with mandibular involvement requires a staged approach. Midface fractures are treated following stabilization, reduction, and fixation of mandibular fractures to obtain normal patient occlusion [60] (Fig. 30.47).

Maxillary Sinus

When affected in facial trauma, maxillary sinuses usually recover spontaneously with resolution of hematomas following reduction and fixation of fractures. Sinus hematoma infection is rare and occurs in patients hospitalized for long periods in which mechanical ventilation bypasses normal paranasal sinus aeration interfering with normal secretion drainage [61, 62] (Fig. 30.48). Isolated anterior, lateral, and posterior wall fractures are treated conservatively. In the presence of greater defects, bone or cartilage graft can be employed [63–65] (Fig. 30.49). Complete Le Fort I fractures are accessed intraorally, and osteosynthesis is achieved with plates and screw fixed on nasomaxillary and zygomaticomaxillary buttresses (Fig. 30.50).

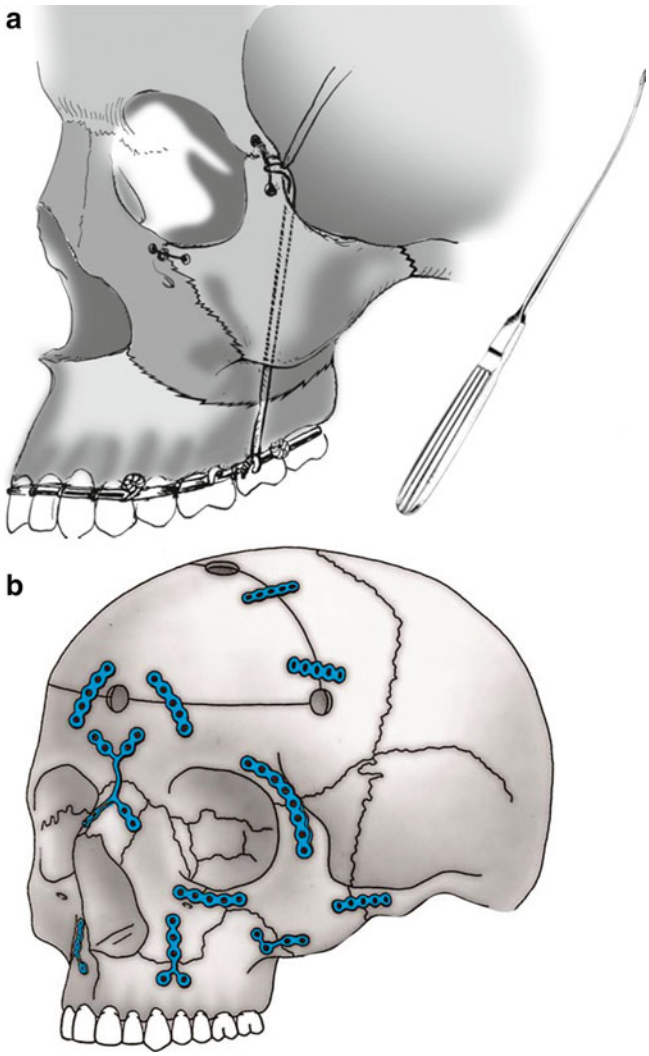


Fig. 30.46 Wire fixation (**a**); rigid internal fixation (RIF) with micro- and miniplates (**b**)

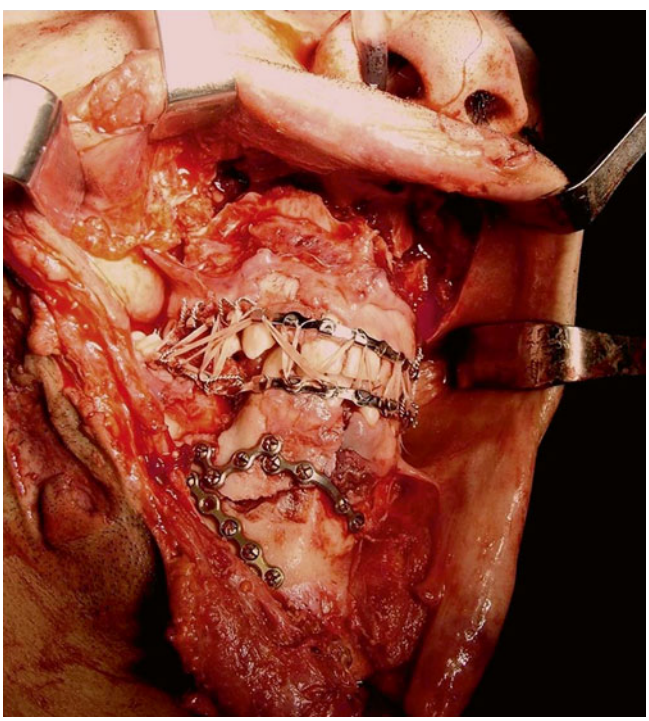


Fig. 30.47 Severe panfacial trauma. Midface fractures are treated following mandibular reduction and fixation

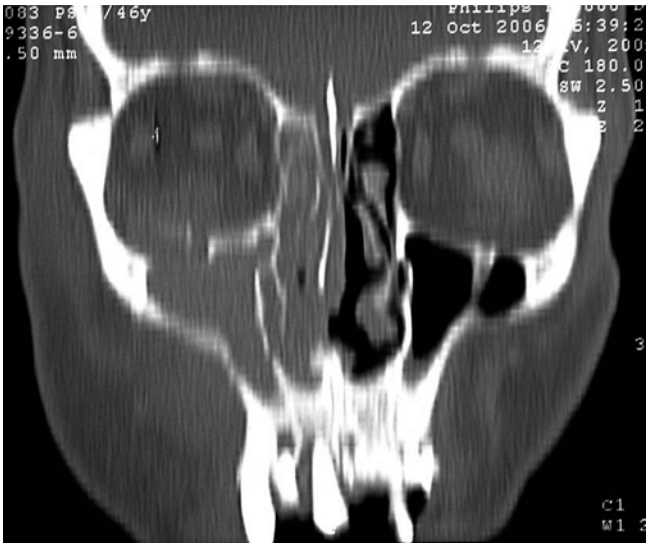


Fig. 30.48 Maxillary sinus and orbital floor fractures (*right*) with nasal, ethmoidal, and maxillary sinus effusion

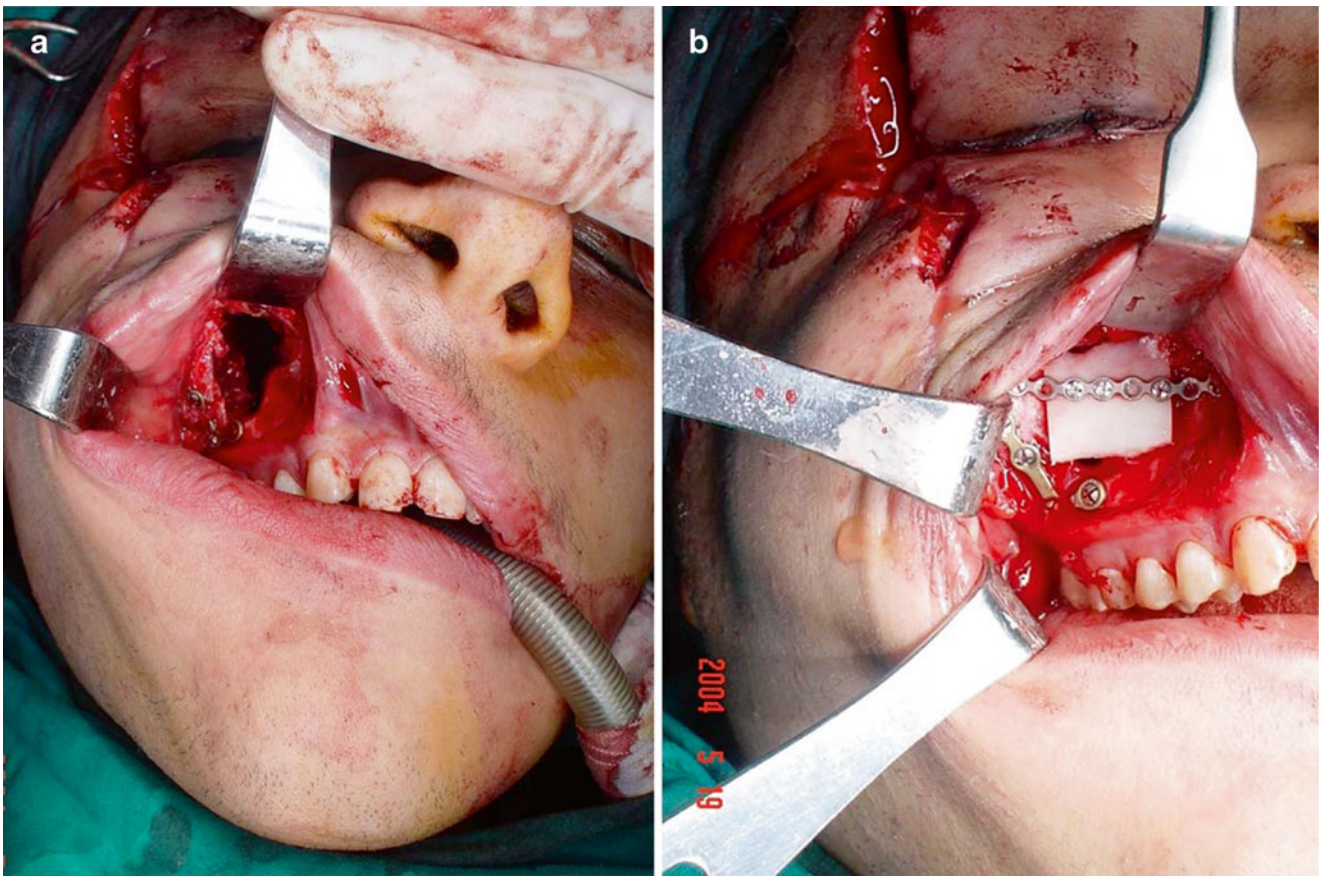


Fig. 30.49 Bone defect (**a**) covered with a free bone graft (**b**) harvested from the mandibular ramus

Le Fort II fractures require a combined approach. The subciliary or transconjunctival route is employed for the orbital region, while the intraoral approach is reserved for maxillary fractures. Reduction of nasal fractures can be performed externally or from the nose. Blow-out fractures require reconstruction of the orbital floor using alloplastic materials

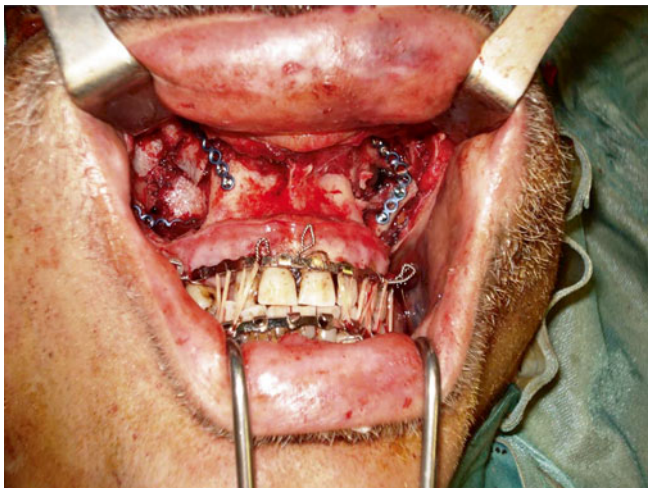


Fig. 30.50 Le fort I fracture: osteosynthesis

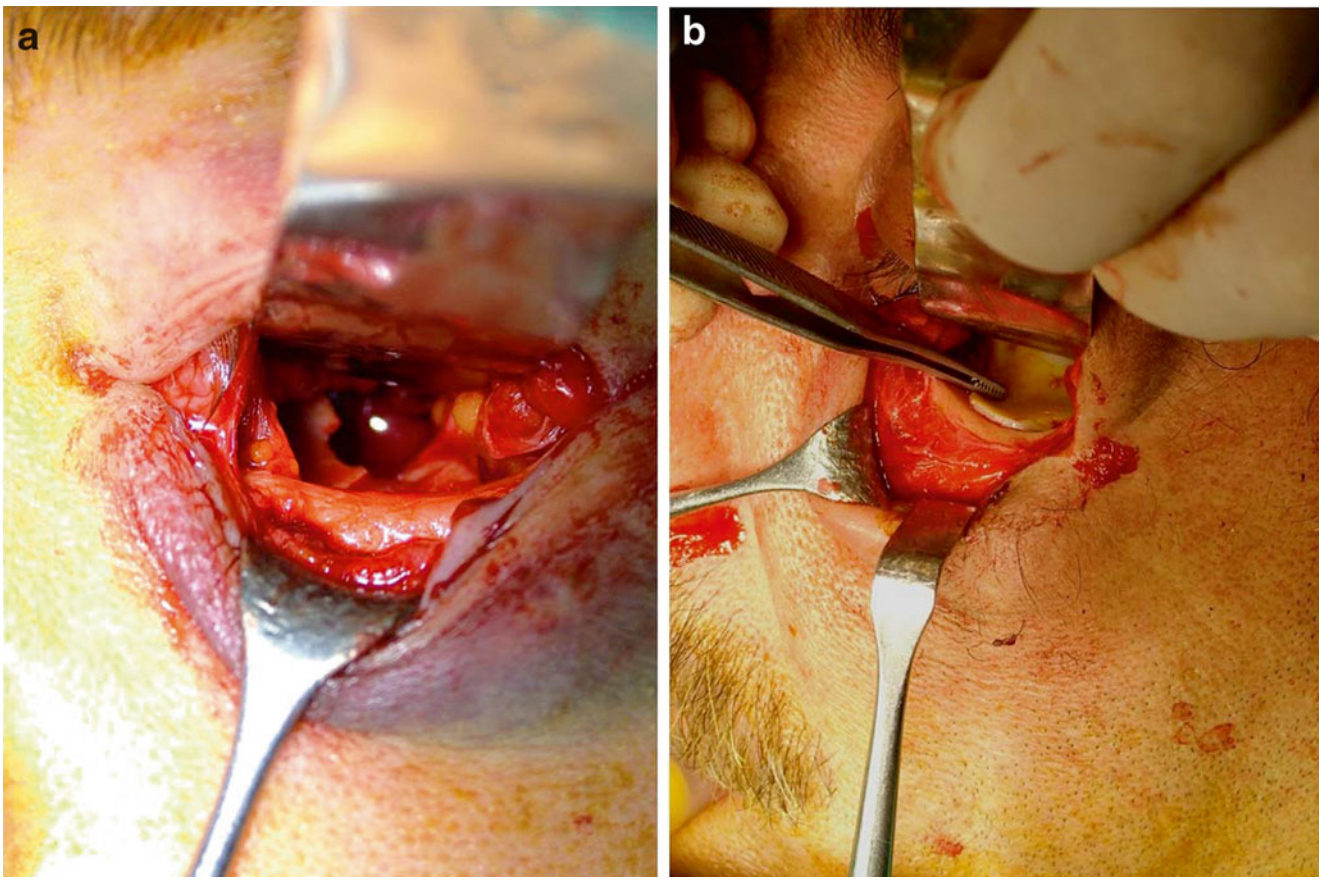


Fig. 30.51 Orbital floor fracture communicating with maxillary sinus (**a**). Reconstruction with a cartilage graft harvested from the nasal septum, transconjunctival approach was used in this case (**b**)

(titanium mesh, polylactic mesh, etc.), heterologous tissue (pericardium, purified cartilage), or autologous tissue (bone or cartilage grafts) [66, 67]. Orbital floor fractures are preferably repaired within 2 weeks from trauma to reduce the risk of sequelae (Fig. 30.51).

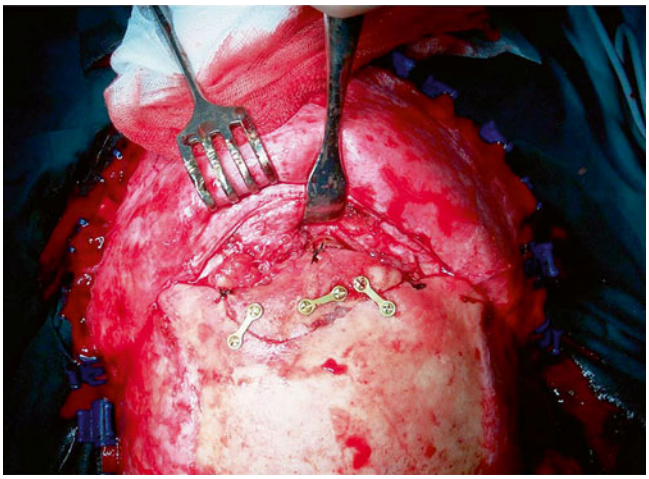


Fig. 30.52 Reduction and internal fixation of fracture fragments of the frontal sinus anterior wall

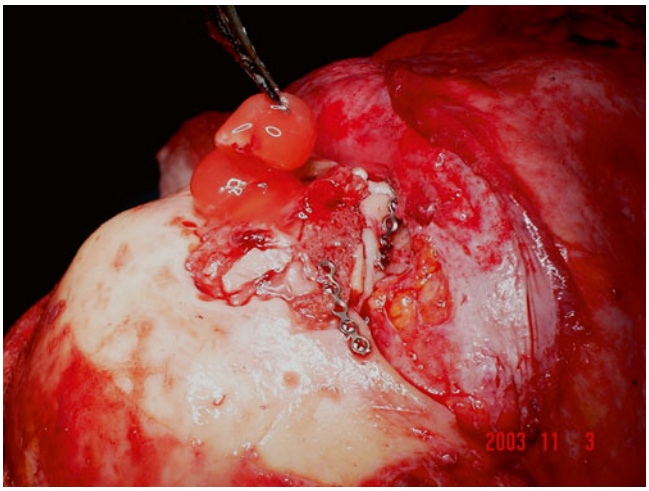


Fig. 30.53 Frontal sinus obliteration and reconstruction of the orbital roof with cancellous bone of the iliac crest, calvarial bone grafts, and platelet-rich plasma

Frontal Sinus

Frontal sinus fractures are challenging, in particular when the posterior wall is fractured being the posterior wall in continuity with brain tissue. Anterior wall fractures without comminution are conservatively managed. If comminution is present, fragments can be reduced and fixed through a bicoronal approach. Care must be taken to not open the sinus (Fig. 30.52). Posterior wall fractures require antibiotic coverage to reduce the risk of infection and sometimes the help of a neurosurgeon with debridement, hematoma drainage, and dura mater repair.

Frontal sinus fractures can be accessed with small incisions in the glabella or the medial orbital wall when the damage is minimal. Otherwise a bicoronal incision provides wide exposure of the area to be repaired [68, 69]. Cranialization of the frontal sinus with mucosectomy and closure of nasofrontal ducts are performed when the posterior wall cannot be repaired. By doing this, the brain expands into the sinus [70, 71]. An alternative is sinus obliteration in which the sinus, after accurate mucosectomy and closure of nasofrontal ducts, is filled using fat graft or bone grafts plus platelet-rich plasma [72, 73] (Fig. 30.53). The sinus mucosa can be preserved when a pedicled galeal flap (Fig. 30.54) is used for sinus obliteration [74] or when the treatment is endoscopic [75].

Ethmoidal Sinus

Treatment of ethmoidal sinus fractures is usually conservative. Fractures of the lateral wall (medial orbital wall fractures) are repaired when muscle incarceration is present [76]. Mobile fragments are removed, and the bone gap can be repaired with a

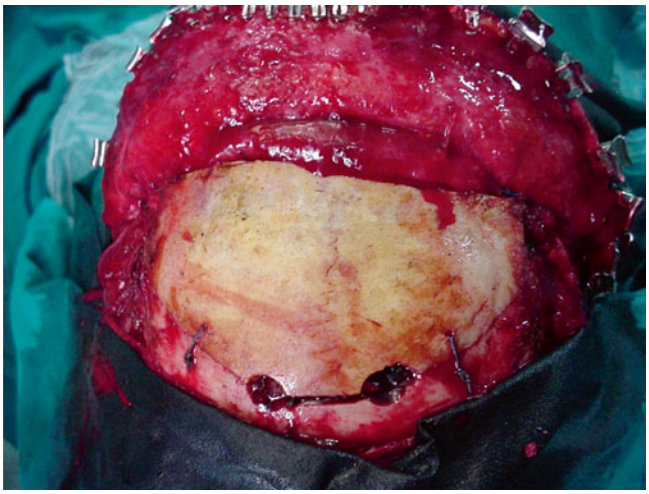


Fig. 30.54 Galeal flap is employed to repair a dural laceration and to obliterate the frontal sinus

cartilage graft or left to heal by secondary intention when the defect is small. Fractures of the NOE are complex and require surgical repair through a bicoronal approach [77, 78]. Endoscopic treatment of dural tears and muscle incarceration has been successfully advocated by some [79, 80]. Patency of the lacrimal system is generally reestablished when NOE fractures are repaired. By contrast if the obstruction persists, a dacryocystorhinostomy is performed [81]. Canthoplasty is performed when the canthal tendon has to be reattached to the medial orbital wall [82].

Sphenoidal Sinus

Lesions of the sphenoidal sinus require neurosurgical treatment. These patients are often unconscious and require resuscitation procedures. Antibiotic prophylaxis is paramount to reduce the risk of suppurative infection considering the proximity of the central nervous system [83]. Neural and vascular structures are encountered in the sphenoidal sinus, and complications can be fatal or extremely severe. In most cases, any persistent CSF leakage can be managed with external drainage [84]. Endoscopic treatment has also been proved to be effective [85].

Conclusions

Due to their anatomical location, the paranasal sinuses are unavoidably involved in injuries of the upper and middle thirds of the face. Le Fort I and II, zygomaticomaxillary, and blow-out fractures are associated with maxillary sinus lesions. Frontal, ethmoidal, and sphenoidal sinuses are often damaged in craniofacial trauma and in isolated NOE, Le Fort II, and Le Fort III fractures. Clinical examination is essential for a prompt diagnosis. Signs of facial swelling, hematoma, epistaxis, and occlusal problems are the most frequent clinical clues of a facial fracture. CT scan with 3D reconstruction of the facial skeleton allows for visualization of the injured areas and facilitates surgical planning.

Management is surgical, using rigid internal fixation for fracture and fragment fixation. Reestablishment of habitual occlusion is the most important surgical goal. Following fracture reduction and fixation, paranasal sinuses recover spontaneously in the majority of cases. Complications include mucocele formation, nasolacrimal injury, meningoencephalitis, CSF leakage, and hyposmia or anosmia. A thorough knowledge of upper and middle third facial fractures is essential for the clinical evaluation and management of paranasal sinus trauma.

Acknowledgments The authors are grateful to *Claudio Schonauer*, neurosurgeon, for his contribution on frontal sinus obliteration with the galeal flap; *Alvaro Antonio Diano*, neuroradiologist, for providing normal 3D CT scans; *Enzo Facciuto*, maxillofacial surgeon, for providing some clinical images; *Giuseppe De Maria*, maxillofacial surgeon, for his precious contribution on literature search; and *Antonio Savanelli*, dentist, for his precious contribution on epidemiology and tables.

References

1. Kazanjian HV, Converse's JM. Surgical treatment of facial injuries, vol. 1. Baltimore: Williams & Wilkins; 1959. p. 231–337 (It. Ed).
2. Batista AM, Marques LS, Batista AE, Falci SG, Ramos-Jorge ML. Urban–rural differences in oral and maxillofacial trauma. Braz Oral Res. 2012;26:132–8.
3. Yoffe T, Shohat I, Shoshani Y, Taicher S. Etiology of maxillofacial trauma–a 10-year survey at the Chaim Sheba Medical Center, Tel-Hashomer. Harefuah. 2008;147:192–6, 280.
4. Motamedi MH. An assessment of maxillofacial fractures: a 5-year study of 237 patients. J Oral Maxillofac Surg. 2003;61(1):61–4.
5. Zhang QB, Zhang B, Zhang ZQ, Chen Q. The epidemiology of cranio-facial injuries caused by animals in southern-central China. J Craniomaxillofac Surg. 2012;40:506–9.
6. Brasileiro BF, Passeri LA. Epidemiological analysis of maxillofacial fractures in Brazil: a 5-year prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;102:28–34.
7. Laski R, Ziccardi VB, Broder HL, Janal M. Facial trauma: a recurrent disease? The potential role of disease prevention. J Oral Maxillofac Surg. 2004;62(6):685–8.
8. Bamjee Y, Lownie JF, Cleaton-Jones PE, Lownie MA. Maxillofacial injuries in a group of South Africans under 18 years of age. Br J Oral Maxillofac Surg. 1996;34:298–302.
9. Iida S, Hassfeld S, Reuther T, Schweigert H, Haag C, Klein J, et al. Maxillofacial fractures resulting from falls. J Craniomaxillofac Surg. 2003;31:278–83.
10. Al Ahmed HE, Jaber MA, Abu Fanas SH, Karas M. The pattern of maxillofacial fractures in Sharjah, United Arab Emirates: a review of 230 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:166–70.
11. Gassner R, Tuli T, Hachl O, Rudisch A, Ulmer H. Cranio-maxillofacial trauma: a 10 year review of 9543 cases with 21067 injuries. J Craniomaxillofac Surg. 2003;31:51–61.
12. Fasola AO, Obiechina AE, Arotiba JT. Concomitant injuries in 531 patients with maxillofacial fractures. Afr J Med Med Sci. 2002;31:101–5.
13. Alvi A, Doherty T, Lewen G. Facial fractures and concomitant injuries in trauma patients. Laryngoscope. 2003;113(1):102–6.
14. Follmar KE, Debruijn M, Baccarani A, Bruno AD, Mukundan S, Erdmann D, Marcus JR. Concomitant injuries in patients with panfacial fractures. J Trauma. 2007;63(4):831–5.
15. Madan AK, Yu K, Beech DJ. Alcohol and drug use in victims of life-threatening trauma. J Trauma. 1999;47(3):568–71.
16. Laverick S, Patel N, Jones DC. Maxillofacial trauma and the role of alcohol. Br J Oral Maxillofac Surg. 2008;46(7):542–6.
17. Ogundare BO, Bonnick A, Bayley N. Pattern of mandibular fractures in an urban major trauma center. J Oral Maxillofac Surg. 2003; 61(6):713–8.
18. Erdmann D, Follmar KE, DeBruijn M, Bruno AD, et al. A retrospective analysis of facial fracture etiologies. Ann Plast Surg. 2008; 60(4):398–403.
19. Shaphiro AJ, Johnson R, Miller SF, McCarthy MC. Facial fractures in a level I trauma centre: the importance of protective devices and alcohol abuse. Injury. 2001;32:353–6.
20. Carvalho TB, Cancian LR, Marques CG, Piatto VB, Maniglia JV, Molina FD. Six years of facial trauma care: an epidemiological analysis of 355 cases. Braz J Otorhinolaryngol. 2010;76(5):565–74.
21. Gruss JS, Mackinnon SE. Complex maxillary fractures: role of buttress reconstruction and immediate bone grafts. Plast Reconstr Surg. 1986;78(1):9–22.
22. Stanley RB. Rigid fixation of fractures of the maxillary complex. Facial Plast Surg. 1990;7(3):176–84.
23. Manson PN, Glassman D, Vanderkolk C, Petty P, Crawley WA. Rigid stabilization of sagittal fractures of the maxilla and palate. Plast Reconstr Surg. 1990;85(5):711–7.
24. Manson PN, Clark N, Robertson B, Slezak S, Wheatly M, Vander Kolk C, Iliff N. Subunit principles in midface fractures: the importance of sagittal buttresses, soft-tissue reductions, and sequencing treatment of segmental fractures. Plast Reconstr Surg. 1999;103(4):1287–307.
25. Marciani RD. Management of midface fractures: fifty years later. Oral Maxillofac Surg. 1993;51:960–8.
26. McMahon JD, Koppel DA, Devlin M, Moos KF. Maxillary and panfacial fractures. In: Booth PW, Eppley BL, Schmelzisen R, editors. Maxillo facial trauma and esthetic facial reconstruction. Edinburgh: Churchill Livingstone; 2003. 14:238.
27. Reuben AD, Watt-Smith SR, Dobson D, Golding SJ. A comparative study of evaluation of radiographs, CT and 3D reformatted CT in facial trauma: what is the role of 3D? Br J Radiol. 2005;78(927):198–201.
28. Brasileiro BF, Cortez AL, Asprino L, Passeri LA, De Moraes M, Mazzonetto R, Moreira RW. Traumatic subcutaneous emphysema of the face associated with paranasal sinus fractures: a prospective study. J Oral Maxillofac Surg. 2005;63(8):1080–7.
29. May M, Levine HL, Mester SJ, Schaitkin B. Complications of endoscopic sinus surgery: analysis patients-incidents and prevention. Laryngoscope. 1994;104:1080–3.
30. Ramstead C, McCabe J, Alkahtani M, Leong-Sit J, Morhart M. Traumatic dislocation of the globe into the maxillary sinus. Can J Ophthalmol. 2008;43:364–6.
31. Larrabee Jr WF, Travis LW, Tabb HG. Frontal sinus fractures–their suppurative complications and surgical management. Laryngoscope. 1980; 90:1810–3.
32. Wallis A, Donald PJ. Frontal sinus fractures: a review of 72 cases. Laryngoscope. 1988;98:593–8.
33. May M, Ogura JH, Schramm V. Nasofrontal duct in frontal sinus fractures. Arch Otolaryngol. 1970;92:534–8.
34. Bordley JE, Bosley WR. Mucoceles of the frontal sinus: causes and treatment. Ann Otol Rhinol Laryngol. 1973;82:696–702.
35. Peral Cagigal B, Barrientos Lezcano J, Floriano Blanco R, García Cantera JM, Sánchez Cuéllar LA, Verrier Hernández A. Frontal sinus mucocele with intracranial and intraorbital extension. Med Oral Patol Oral Cir Bucal. 2006;11:E527–30.
36. Jimenez DF, Sundrani S, Barone CM. Posttraumatic anosmia in craniofacial trauma. J Craniomaxillofac Trauma. 1997;3:8–15.
37. Cruse CW, Blevins PK, Luce EA. Naso-ethmoid-orbital fractures. J Trauma. 1980;20(7):551.
38. Herford AS, Ying T, Brown B. Outcomes of severely comminuted (type III) nasoorbitoethmoid fractures. J Oral Maxillofac Surg. 2005;63: 1266–77.

39. Dodick JM, Galin MA, Littleton JT, Sod LM. Concomitant medial wall fracture and blowout fracture of the orbit. Arch Ophthalmol. 1971;85:273–6.
40. Unger JM, Gentry LR, Grossman JE. Sphenoid fractures: prevalence, sites, and significance. Radiology. 1990;175:175–80.
41. Clauser L, Galiè M, Pagliaro F, Tieghi R. Posttraumatic enophthalmos: etiology, principles of reconstruction, and correction. J Craniofac Surg. 2008;19:351–9.
42. Tanrikulu R, Erol B. Comparison of computed tomography with conventional radiography for midfacial fractures. Dentomaxillofac Radiol. 2001;30(3):141–6.
43. Tello R, Suojanen J, Costello P, McGinnes A. Comparison of spiral CT and conventional CT in 3D visualization of facial trauma: work in progress. Comput Med Imaging Graph. 1994;18(6):423–7.
44. Schuknecht B, Graetz K. Radiologic assessment of maxillofacial, mandibular, and skull base trauma. Eur Radiol. 2005;15(3):560–8. Epub 2005 Jan 21.
45. Lambert DM, Mirvis SE, Shanmuganathan K, Tilghman DL. Computed tomography exclusion of osseous paranasal sinus injury in blunt trauma patients: the "clear sinus" sign. J Oral Maxillofac Surg. 1997;55(11):1207–10; discussion 1210–1.
46. Perry M, Dancey A, Mireskandari K, Oakley P, Davies S, Cameron M. Emergency care in facial trauma a maxillofacial and ophthalmic perspective. Injury. 2005;36:875–96.
47. Givens GC, Shelton SL, Brown EA. Emergency cricothyrotomy in confined space airway emergencies: a comparison. Prehosp Disaster Med. 2011;13:1–3.
48. Bynoe RP, Kerwin AJ, Parker 3rd HH, Nottingham JM, Bell RM, Yost MJ, Close TC, Hudson ER, Sheridan DJ, Wade MD. Maxillofacial injuries and life-threatening hemorrhage: treatment with transcatheter arterial embolization. J Trauma. 2003;55:74–9.
49. Hemández Altemir F. A new technique of endotracheal intubation (submental way). Rev Iberoamer Cirg Oral y Maxillofac. 1984;61:165.
50. Taglialatela Scafati C, Maio G, Aliberti F, Taglialatela Scafati S, Grimaldi PL. Submentosubmandibular intubation: is the subperiosteal passage essential? Experience in 107 consecutive cases. Br J Oral Maxillofac Surg. 2006;44:12–4.
51. Christensen GW. Open operation and tantalum plate insertion for fractures of the mandible. J Oral Surg. 1945;3:194.
52. Luhr HG. On the stable osteosynthesis in mandibular fractures. Dtsch Zahnarztl Z. 1968;23:754.
53. Vuillemin T, Raveh J, Sutter F. Mandibular reconstruction with the titanium hollow screw reconstruction plate (THORP) system: evaluation of 62 cases. Plast Reconstr Surg. 1988;82:804–14.
54. Champy M, Wilk A, Schnebelen JM. Treatment of mandibular fractures by means of osteosynthesis without intermaxillary immobilization according to F.X. Michelet's technic. Zahn Mund Kieferheilkd Zentralbl. 1975;63:339–41.
55. Champy M, Lodde JP, Muster D, Wilk A, Gastelo L. Osteosynthesis using miniaturized screws on plates in facial and cranial surgery. Indications and results in 400 cases. Ann Chir Plast. 1977;22:261–4.
56. Millar BG, Frame JW, Browne RM. A histological study of stainless steel and titanium screws in bone. Br J Oral Maxillofac Surg. 1990;28:92–5.
57. Sullivan PK, Smith JF, Rozzelle AA. Cranio-orbital reconstruction: safety and image quality of metallic implants on CT and MRI scanning. Plast Reconstr Surg. 1994;94(5):589–96.
58. Cheung LK, Chow LK, Chiu WK. A randomized controlled trial of resorbable versus titanium fixation for orthognathic surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:386–97.
59. Eppley BL. Use of resorbable plates and screws in pediatric facial fractures. J Oral Maxillofac Surg. 2005;63:385–91.
60. Helfrick JF. Early assessment and treatment planning in the maxillofacial trauma patient. In: Fonseca RG, Walker RV, Betts NJ, Barber HD, editors. Oral and maxillofacial trauma, vol. 1. 2nd ed. Philadelphia: WB Saunders Company; 1997. p. 364–90.
61. George DL, Falk PS, Umberto Meduri G, Leeper Jr KV, Wunderink RG, Steere EL, Nunnally FK, Beckford N, Mayhall CG. Nosocomial sinusitis in patients in the medical intensive care unit: a prospective epidemiological study.lin. Infect Dis. 1998;27:463–70.
62. Michelson A, Kamp HD, Schuster B. Sinusitis in long-term intubated, intensive care patients: nasal versus oral intubation. Anaesthesist. 1991;40:100–4.
63. Manson PN, Crawley WA, Yaremchuk MJ, Rochman GM, Hoopes JE, French Jr JH. Midface fractures: advantages of immediate extended open reduction and bone grafting. Plast Reconstr Surg. 1985;76:1–12.
64. Singh AK, Mohapatra DP, Kumar V. Spectrum of primary bone grafting in cranio maxillofacial trauma at a tertiary care centre in India. Indian J Plast Surg. 2011;44:29–35.
65. Benzil DL, Robotti E, Dagi TF, Sullivan P, Bevivino JR, Knuckey NW. Early single-stage repair of complex craniofacial trauma. Neurosurgery. 1992;30(166–71):171–2.
66. Burnstine MA. Clinical recommendations for repair of orbital facial fractures. Curr Opin Ophthalmol. 2003;14:236–40.
67. Cavusoglu T, Vargel I, Yazici I, Cavusoglu M, Vural AC. Reconstruction of orbital floor fractures using autologous nasal septal bone graft. Ann Plast Surg. 2010;64:41–6.
68. Metzinger SE, Guerra AB, Garcia RE. Frontal sinus fractures: management guidelines. Facial Plast Surg. 2005;21:199–206.
69. Lee TT, Ratzker PA, Galarza M, Villanueva PA. Early combined management of frontal sinus and orbital and facial fractures. J Trauma. 1998;44:665–9.
70. Donath A, Sindwani R. Frontal sinus cranialization using the pericranial flap: an added layer of protection. Laryngoscope. 2006;116:1585–8.
71. Rohrich RJ, Hollier LH. Management of frontal sinus fractures. Changing concepts. Clin Plast Surg. 1992;19:219–32.
72. Acosta-Feria M, Infante-Cossío P, Hernández-Guisado JM, Torres-Carranza E, García-Perla A, Belmonte-Caro R, Gutiérrez-Pérez JL. Frontal sinus obliteration using tibial bone graft and platelet-rich plasma for the treatment of chronic osteomyelitis. Neurocirugia (Astur). 2006;17:351–6; discussion 356.
73. Taglialatela Scafati C, Taglialatela Scafati S, Aveta A, Cassese M, Vitale C. Chronic frontal sinus disease: combined use of platelet-rich plasma and calvarial bone grafts for sinus obliteration in aggressive and secondary cases. Rev Stomatol Chir Maxillofac. 2010;111:216–20.
74. Bell RB, Dierks EJ, Brar P, Potter JK, Potter BE. A protocol for the management of frontal sinus fractures emphasizing sinus preservation. J Oral Maxillofac Surg. 2007;65:825–39.
75. Carter Jr KB, Poetker DM, Rhee JS. Sinus preservation management for frontal sinus fractures in the endoscopic sinus surgery era: a systematic review. Craniomaxillofac Trauma Reconstr. 2010;3:141–9.

76. Pearl RM, Vistnes LM. Orbital blowout fractures: an approach to management. Ann Plast Surg. 1978;1(3):267–70.
77. Ellis 3rd E. Sequencing treatment for naso-orbito-ethmoid fractures. J Oral Maxillofac Surg. 1993;51:543–58.
78. Papadopoulos H, Salib NK. Management of naso-orbital-ethmoidal fractures. Oral Maxillofac Surg Clin North Am. 2009;21:221–5.
79. Lee MJ, Kang YS, Yang JY, Lee DY, Chung YY, Rohrich RJ. Endoscopic transnasal approach for the treatment of medial orbital blow-out fracture: a technique for controlling the fractured wall with a balloon catheter and Merocel. Plast Reconstr Surg. 2002;110:417–26; discussion 427–8.
80. Landeiro JA, Flores MS, Lázaro BC, Melo MH. Surgical management of cerebrospinal fluid rhinorrhea under endoscopic control. Arq Neuropsiquiatr. 2004;62:827–31. Epub 2004 Oct 5.
81. Gruss JS, Hurwitz JJ, Nik NA, Kassel EE. The pattern and incidence of nasolacrimal injury in naso-orbital-ethmoid fractures: the role of delayed assessment and dacryocystorhinostomy. Br J Plast Surg. 1985;38:116–21.
82. Markowitz BL, Manson PN, Sargent L, Vander Kolk CA, Yaremchuk M, Glassman D, Crawley WA. Management of the medial canthal tendon in nasoethmoid orbital fractures: the importance of the central fragment in classification and treatment. Plast Reconstr Surg. 1991;87: 843–53.
83. Ratilal BO, Costa J, Sampaio C, Pappamikail L. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. Cochrane Database Syst Rev. 2011;(8):CD004884.
84. Yilmazlar S, Arslan E, Kocaeli H, Dogan S, Aksoy K, Korfali E, Doygun M. Cerebrospinal fluid leakage complicating skull base fractures: analysis of 81 cases. Neurosurg Rev. 2006;29:64–71.
85. Hegazy HM, Carrau RL, Snyderman CH, Kassam A, Zweig J. Transnasal endoscopic repair of cerebrospinal fluid rhinorrhea: a meta-analysis. Laryngoscope. 2000;110:1166–72.

Index

C.C. Chang et al. (eds.), *Diseases of the Sinuses*,
DOI 10.1007/978-1-4939-0265-1,