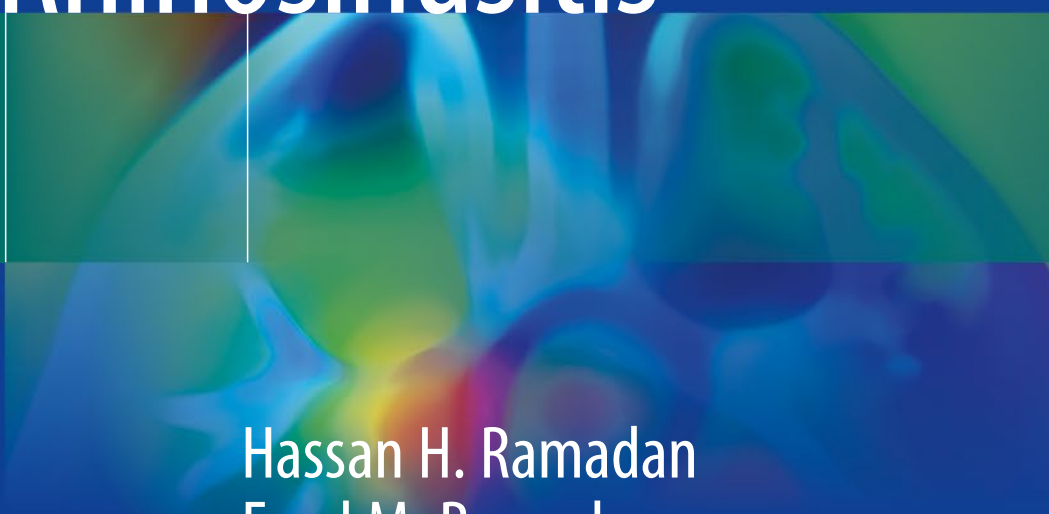
Pediatric Rhinosinusitis



Hassan H. Ramadan
Fuad M. Baroody
Editors

Springer

Pediatric Rhinosinusitis

Hassan H. Ramadan • Fuad M. Baroody
Editors

Pediatric Rhinosinusitis

Springer

Editors
Hassan H. Ramadan
Department of Otolaryngology
West Virginia University
School of Medicine
Morgantown, WV
USA

Fuad M. Baroody
Section of Otolaryngology–Head and Neck Surgery
The University of Chicago Medicine and
The Comer Children's Hospital
Chicago, IL
USA

ISBN 978-3-030-22890-3 ISBN 978-3-030-22891-0 (eBook)
https://doi.org/10.1007/978-3-030-22891-0

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

Contents

Contributors

Sidrah M. Ahmad, MD Department of Surgery, Division of Otolaryngology, Stony Brook University Hospital, Stony Brook University School of Medicine, Stony Brook, NY, USA

Nour Akil, MD Division of Pediatric Pulmonary, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Max April, MD Department of Otolaryngology–Head and Neck Surgery, NYU Langone Medical Center, New York, NY, USA

Randa Barazi, MD Department of Otolaryngology Head and Neck Surgery, American University of Beirut Medical Center, Beirut, Lebanon

Fuad M. Baroody, MD Section of Otolaryngology–Head and Neck Surgery and Department of Pediatrics, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA

John P. Bent, MD Department of Otolaryngology–Head and Neck Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Department of Otolaryngology, Children's Hospital at Montefiore, Bronx, NY, USA

Michele M. Carr, DDS, MD, PhD Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA

Johnathan E. Castaño, MD Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA

Zachariah K. Chandy, MD Department of Head and Neck Surgery, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA

Angela M. Donaldson, MD Department of Otorhinolaryngology Head and Neck Surgery, Mayo Clinic Jacksonville, Jacksonville, FL, USA

Judd H. Fastenberg, MD Department of Otorhinolaryngology–Head and Neck Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Elisabeth H. Ference, MD, MPH Rick and Tina Caruso Department of Otolaryngology–Head and Neck Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

Caitlin E. Fiorillo, MD Department of Pediatric Otolaryngology, Children's National Medical Center, Children's National Health System, Washington, DC, USA

Sara C. Gallant, MD Department of Otolaryngology–Head and Neck Surgery, NYU Langone Medical Center, New York, NY, USA

Mark E. Gerber, MD Otolaryngology, Head and Neck Surgery, Phoenix Children's Hospital, Phoenix, AZ, USA

Lyuba Gitman, MD Division of Otolaryngology, Children's National Medical Center, and the Department of Otolaryngology, George Washington University, Washington, DC, USA

David A. Gudis, MD Department of Otolaryngology - Head and Neck Surgery, Columbia University Irving Medical Center, New York, NY, USA

Osama Hamdi, BS Division of Pediatric Otolaryngology, Children's National Health System, Washington, DC, USA

Aimee A. Kennedy, MD Otolaryngology, Head and Neck Surgery, Children's Hospital Medical Center, Cincinnati, OH, USA

Zeina R. Korban, MD Department of Otolaryngology Head and Neck Surgery, American University of Beirut Medical Center, Beirut, Lebanon

Jivianne T. Lee, MD, FACS Department of Head and Neck Surgery, University of California Los Angeles Medical Center and David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA

Anne S. Lowery, BA Vanderbilt University School of Medicine, Nashville, TN, USA

Surgical Outcomes Center for Kids, Vanderbilt University Medical Center, Nashville, TN, USA

Friederike S. Luetzenberg, BS University of Central Florida College of Medicine, Orlando, FL, USA

Chadi A. Makary, MD Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA

Ahmad Salaheddine Naja, MD Department of Surgery, American University of Beirut Medical Center, Beirut, Lebanon

Douglas M. Nguyen, BS Department of Otolaryngology, University of Miami Miller School of Medicine, Miami, FL, USA

Maria Peña, MD, FACS, FAAP Division of Otolaryngology, Children's National Medical Center, and the Department of Otolaryngology, George Washington University, Washington, DC, USA

Wanda Phipatanakul, MD, MS Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Division of Allergy and Immunology, Boston Children's Hospital, Boston, MA, USA

Diego Preciado, MD, PhD Department of Pediatric Otolaryngology, Children's National Health System, The George Washington University School of Medicine, Washington, DC, USA

Phillip R. Purnell, MD, PhD Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA

Hassan H. Ramadan, MD Department of Otolaryngology, West Virginia University, School of Medicine, Morgantown, WV, USA

Charles Alexander Riley, MD Department of Otolaryngology - Head and Neck Surgery, Columbia University Irving Medical Center, New York, NY, USA

Austin S. Rose, MD, FARS Department of Otolaryngology–Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Jason R. Rudman, MD Department of Otolaryngology–Head and Neck Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Ahmad R. Sedaghat, MD, PhD Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Andrea Shogan, MD Section of Otolaryngology–Head and Neck Surgery, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA

Connor M. Smith, BA Division of Pediatric Otolaryngology, Children's National Health System, Washington, DC, USA

Christian P. Soneru, MD Department of Otolaryngology - Head and Neck Surgery, Columbia University Irving Medical Center, New York, NY, USA

Lauren Sowa, MD Section of Otolaryngology–Head and Neck Surgery, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA

Mikhaylo Szczupak, MD Department of Otolaryngology–Head and Neck Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Abdul Rahman Tarabishy, MD Department of Radiology, Department of Interventional Neuroradiology, West Virginia University School of Medicine, Morgantown, WV, USA

Frank W. Virgin, MD Department of Otolaryngology-Head and Neck Surgery, Vanderbilt University Medical Center, Nashville, TN, USA

Surgical Outcomes Center for Kids, Vanderbilt University Medical Center, Nashville, TN, USA

Julie L. Wei, MD Pediatric Otolaryngology/Audiology, Department of Surgery, Nemours Children's Hospital, Orlando, FL, USA

Otolaryngology-Head Neck Surgery, University of Central Florida College of Medicine, Orlando, FL, USA

Michael S. Weinstock, MD Department of Otolaryngology–Head and Neck Surgery, Montefiore Medical Center, Albert Einstein Medical School, Bronx, NY, USA

Ramzi T. Younis, MD, FACS, FAAP Department of Otolaryngology–Head and Neck Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Habib G. Zalzal, MD Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA

Part I
Definitions and Basics

Chapter 1
Definitions and Clinical Signs and Symptoms

Andrea Shogan and Fuad M. Baroody

Rhinosinusitis (RS) in pediatric patients can be difficult to diagnose due to its similarity with other common conditions such as allergic rhinitis, viral upper respiratory infections, and adenoiditis. It is more broadly defined as inflammation of the nose and paranasal sinuses and has a negative impact on the quality of life of patients and can substantially impair their daily function [1]. The study by Cunningham et al. in 2000 demonstrates that parents of children diagnosed with RS perceived their children to have more bodily pain and to have more limited physical activity than other children with chronic diseases such as asthma or juvenile rheumatoid arthritis [1].

Current guidelines state that a clinical diagnosis of RS can be made in children if they have two or more of the following symptoms, with one of them being either nasal blockage, obstruction, congestion, or nasal discharge and either facial pain or cough [2]. The clinical symptoms have to be accompanied with objective signs that are determined by either nasal endoscopy, with signs of nasal polyps, mucopurulent discharge from the middle meatus, or edema/mucosal obstruction from middle meatus, or computed tomography (CT) of the sinuses demonstrating mucosal changes within the ostiomeatal complex and/or sinuses [2, 3].

RS is further classified, based on the duration of the illness itself. Acute rhinosinusitis (ARS) lasts less than 4 weeks with complete resolution of symptoms, and chronic rhinosinusitis (CRS) is defined as inflammation of the nose and paranasal sinuses with symptoms that last greater than 12 weeks without complete resolution. Recurrent acute rhinosinusitis is defined as four of more episodes of ARS per year with resolution of symptoms between each episode.

A. Shogan · F. M. Baroody (✉)
Section of Otolaryngology-Head and Neck Surgery and Department of Pediatrics, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA
e-mail: fbaroody@surgery.bsd.uchicago.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_1

Acute Rhinosinusitis

Acute rhinosinusitis (ARS) often occurs after a viral upper respiratory illness (URI). Pediatric patients can experience up to seven to ten URIs per year and approximately 5–13% of viral URIs will progress to acute bacterial rhinosinusitis [4]. The peak age of occurrence of bacterial rhinosinusitis is between 3 and 6 years which correlates with the peak incidence of viral upper respiratory infections [5]. A study by Marom et al. also found that girls more frequently developed acute bacterial rhinosinusitis (ABRS) and had more recurrent bouts of ABRS [6]. ARS is defined as the sudden onset of two or more of the following symptoms: nasal blockage/obstruction/congestion, discolored nasal drainage, and/or cough [2].

ARS can be further subdivided into acute viral rhinosinusitis, acute post viral rhinosinusitis, and acute bacterial rhinosinusitis. Patients with acute viral rhinosinusitis have the signs and symptoms of acute rhinosinusitis that commonly last for 5–7 days but less than 10 days, just as do the symptoms of a URI [7–9]. An important point in this context is that the paranasal sinuses are involved even during routine URIs, thus the term, rhinosinusitis, to describe this clinical entity. Kristo and colleagues investigated 60 children (mean age = 5.7 years) who had acute URI symptoms for an average of 6 days before MRI scanning [10]. Approximately 60% of the children had abnormalities in their maxillary and ethmoid sinuses, 35% in the sphenoid sinuses, and 18% in the frontal sinuses. In 26 children with major abnormalities, a follow-up MRI scan taken 2 weeks later showed a significant reduction in the extent of abnormalities irrespective of resolution of clinical symptoms. Similarly, sinus involvement occurs in over 50% of adults evaluated during a URI with spontaneous improvement after symptom resolution [11]. These studies reinforce the notion that every upper respiratory tract infection is essentially a self-limited episode of rhinosinusitis with common involvement of the paranasal sinuses by the viral process. A few of these episodes will evolve into acute bacterial rhinosinusitis as outlined above and those will usually require more than expectant management (Fig. 1.1).

Acute post-viral rhinosinusitis is seen when there is worsening of symptoms after 5 days or persistent symptoms longer than 10 days (Fig. 1.2). ABRS is defined as a persistent illness for more than 10 days, worsening course, double sickening (deterioration after an initial milder phase of illness or a new fever after the sixth or seventh day of illness) [7], or severe onset of fever and purulent nasal discharge for at least 3 consecutive days [8]. The symptoms of ABRS include purulent anterior or posterior nasal discharge, nasal congestion, or and daytime or nighttime cough [9]. ABRS is the fifth most common condition for which an antibiotic is prescribed in the United States [12]. The most common pathogens involved in acute bacterial rhinosinusitis are *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [13].

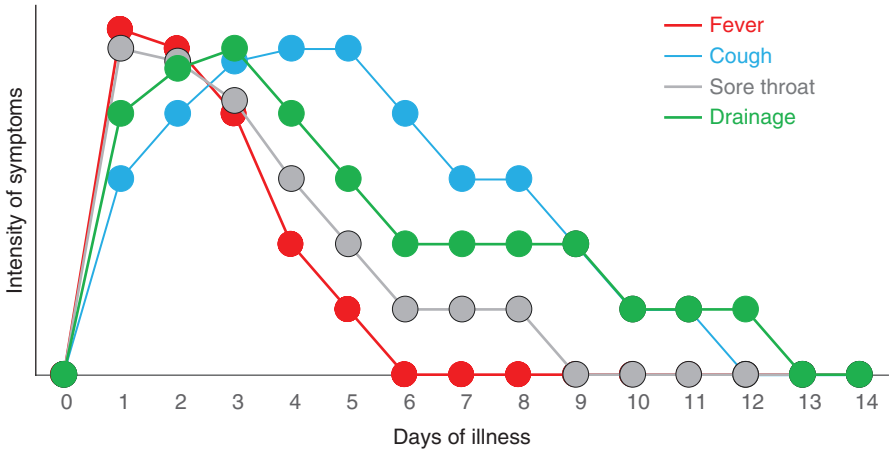


Fig. 1.1 Chronology of symptoms during viral upper respiratory tract infections. Fever and sore throat peak earliest and are the shortest lasting. Cough and nasal drainage peak later in the course of a viral URI and last longer. In uncomplicated URIs, most symptoms resolve within 10–12 days of onset

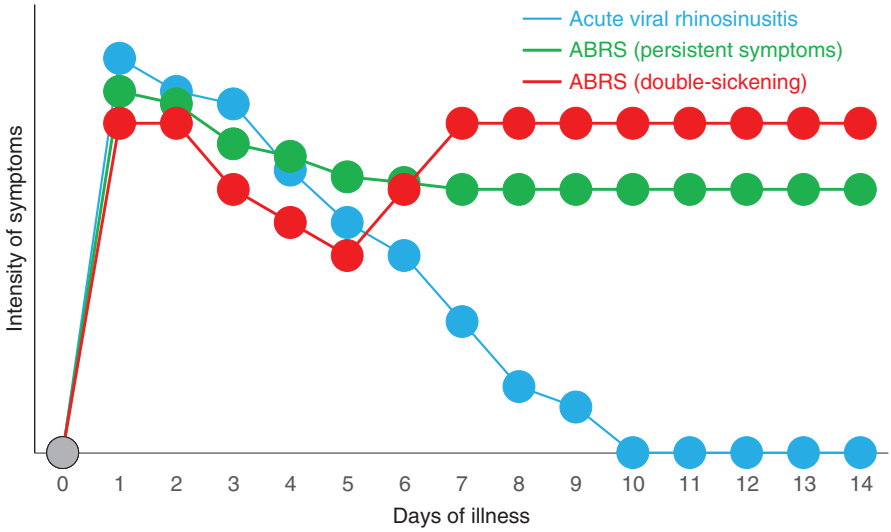


Fig. 1.2 Symptom chronology in viral URI and acute bacterial rhinosinusitis (ABRS). Most of the symptoms of a viral URI resolve within 10 days of illness. Two scenarios justify making the clinical diagnosis of ABRS: symptoms of an URI lasting longer than the typical 10 days and the double-sickening scenario where symptoms of a viral illness start to resolve only to re-exacerbate

Recurrent Acute Rhinosinusitis

Recurrent acute rhinosinusitis (RAR) is defined as multiple episodes of acute sinusitis in which the signs and symptoms of infection resolve completely in between episodes. It is most commonly four or more episodes of ARS per year with episodes separated by at least 10 days. During these periods of at least 10 days, the patient is asymptomatic with no signs and symptoms of ARS. The episodes themselves must meet the definition of ARS [14]. Factors that seem to predispose patients to RAR are older pediatric patients, allergy, atopy, and asthma. These factors are also associated with an increase chance of developing chronic rhinosinusitis [15]. A study by Brooks et al. in 2004 found that the most common pathogens identified in patients with RAR were the same as those isolated in individuals with ARS, *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, yet there was an increase in antimicrobial resistance [16].

Treatment for RAR can be both medical as well as surgical. A literature review by Michalowski and Kacker found that patients with four to six episodes of acute sinusitis that last for 4 weeks or less would benefit from surgical intervention [14]. They recommended that the patients be seen in the office during one of these episodes to confirm the diagnosis and be treated with both intranasal and oral steroids and have a CT scan done prior to proceeding with endoscopic sinus surgery. The extent of the surgery can be limited to bilateral maxillary antrostomies as well as anterior ethmoidectomies and addressing any additional abnormalities identified on the CT scan [14].

Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) in pediatric patients can often be mistaken for other common clinical entities just like ARS. It is defined as at least 90 days of two or more symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough. You must also have either endoscopic signs of mucosal edema, purulent drainage, or nasal polyposis and/or CT scan showing mucosal changes within the ostiomeatal complex and/or sinuses [4]. Patients with immune deficiency, cystic fibrosis, ciliary dyskinesia, and anatomic abnormalities often have chronic rhinosinusitis [17]. After obtaining either endoscopic and/or CT scan findings, CRS can be further subdivided into chronic rhinosinusitis with nasal polyposis or chronic rhinosinusitis without nasal polyposis. Polyps are not a common occurrence in children in the United States and prompt further evaluation to rule out cystic fibrosis or allergic fungal rhinosinusitis. They do sometimes occur in the context of severe asthma. The most common clinical symptoms of pediatric CRS are cough, rhinorrhea, nasal congestion, and postnasal drip.

It is often difficult to distinguish chronic rhinosinusitis from adenoiditis based on symptoms and physical exam findings only. CT scan findings have been shown to

be useful and a Lund Mackay score of 4 or more is considered more consistent with CRS [18]. In a chart review from a tertiary care facility with pediatric patients who presented with symptoms consistent with CRS, Purnell and colleagues identified those with CRS vs those with adenoiditis based on their CT scores as mentioned above [19]. They then analyzed the symptoms to see if any specific symptom complex was likely to differentiate the two entities. Of the 99 pediatric patients included, 22 patients had a diagnosis of adenoiditis and 77 had a diagnosis of CRS. When purulent rhinorrhea was present with facial pain, CRS was statistically more prevalent than chronic adenoiditis. Other symptoms including cough, rhinorrhea, and facial pressure were not predictive of one diagnosis over the other. The authors concluded that purulent rhinorrhea in the presence of facial pain is more indicative of CRS versus chronic adenoiditis.

The age when a patient develops CRS helps to determine contributing factors as well as their management. For example, adenoiditis is a prominent factor in CRS in younger pediatric patients while allergic rhinitis is more important in older children. Unlike ABRS, a study by Brooks et al. identified that CRS is most commonly caused by anaerobic organisms in adult patients. However, aerobic organisms that cause ABRS can appear in some acute exacerbations of CRS [20]. Studies to determine the microbiology of chronic sinusitis have been done in adult patients and have yet to be reproduced in the pediatric population.

The clinical consensus statement on pediatric CRS states that medical treatment consists of 20 days of an appropriate broad-spectrum antibiotic (culture-directed choice is encouraged when possible) in addition to daily intranasal steroids and saline irrigations. For patients who fail medical therapy, adenoidectomy should be considered the first-line surgical treatment in patients up to 12 years of age and then endoscopic sinus surgery should be considered [4]. Clearly individualized care decisions are guided by the treating otolaryngologist within these general guidelines.

Being able to correctly identify and categorize a patient's RS will help the clinician to better treat both the patient and their family. ARS responds well to conservative management and antibiotic treatment once it becomes bacterial. For CRS, culture-directed antibiotic treatment as well as daily intranasal steroids and irrigations are first-line treatment. Identifying any underlying medical problems that are contributing to a patient's RS will help to guide treatment as well.

References

1. Cunningham MJ, Cunningham JM, Chiu EJ, Landgraf JM, Gliklich RE. The health impact of chronic recurrent rhinosinusitis in children. Arch Otolaryngol Head Neck Surg. 2000;126(11):1363–8.
2. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;23(3):1–298.
3. Leo G, Mori F, Incorvaia C, Barni S, Novembre E. Diagnosis and management of acute rhinosinusitis in children. Curr Allergy Asthma Rep. 2009;9(3):232–7.

4. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
5. Conrad DA, Jenson HB. Management of acute bacterial rhinosinusitis. Curr Opin Pediatr. 2002;14(1):86–90.
6. Marom T, Alvarez-Fernandez PE, Jennings K, Patel JA, McCormick DP, Chonmaitree T. Acute bacterial sinusitis complicating viral upper respiratory tract infection in young children. Pediatr Infect Dis J. 2014;33(8):803–8.
7. 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.
8. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262–80.
9. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–112.
10. Kristo A, Uhari M, Luotonen J, Koivunen P, Ilkko E, Tapiainen T, et al. Paranasal sinus findings in children during respiratory infection evaluated with magnetic resonance imaging. Pediatrics. 2003;111(5 Pt 1):e586–9.
11. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med. 1994;330(1):25–30.
12. Venekamp RP, Rovers MM, Verheij TJM, Bonten MJM, Sachs APE. Treatment of acute rhinosinusitis: discrepancy between guideline recommendations and clinical practice. Fam Pract. 2012;29(6):706–12.
13. DeMuri G, Wald ER. Acute bacterial sinusitis in children. Pediatr Rev. 2013;34(10):429–37; quiz 437.
14. Michalowski A, Kacker A. Is sinus surgery indicated for recurrent acute rhinosinusitis? Laryngoscope. 2017;127(6):1255–6.
15. Choi S-H, Han M-Y, Ahn Y-M, Park Y-M, Kim C-K, Kim H-H, et al. Predisposing factors associated with chronic and recurrent rhinosinusitis in childhood. Allergy Asthma Immunol Res. 2012;4(2):80–4.
16. Brook I, Frazier EH. Microbiology of recurrent acute rhinosinusitis. Laryngoscope. 2004;114(1):129–31.
17. Principi N, Esposito S. New insights into pediatric rhinosinusitis. Pediatr Allergy Immunol. 2007;18(Suppl 1):7–9.
18. Bhattacharyya N, Jones DT, Hill M, Shapiro NL. The diagnostic accuracy of computed tomography in pediatric chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2004;130:1029–32.
19. Purnell PR, Ramadan JH, Ramadan HH. Can symptoms differentiate between chronic adenoiditis and chronic rhinosinusitis in pediatric patients. Ear Nose Throat J. 2019:145561319840133. https://doi.org/10.1177/0145561319840133. [Epub ahead of print].
20. Brook I. Bacteriology of chronic sinusitis and acute exacerbation of chronic sinusitis. Arch Otolaryngol Head Neck Surg. 2006;132(10):1099–101.

Chapter 2
Burden and Health Impact of Pediatric Rhinosinusitis

Aimee A. Kennedy and Mark E. Gerber

Prevalence of Pediatric Rhinosinusitis

The exact prevalence of pediatric rhinosinusitis is difficult to estimate. The reason for this difficulty is twofold. First, many episodes of rhinosinusitis will resolve without the patient seeking medical attention, and therefore, these cases will not be captured by reviews of office- or emergency-based visits. Secondly, for the patients who do present for medical care, there is a high potential for misdiagnosis as the signs and symptoms of rhinosinusitis mimic other common pediatric conditions such as allergic rhinitis, adenoiditis, and other upper respiratory tract infections. According to the consensus statement from the American Academy of Otolaryngology, in order to definitively diagnose chronic rhinosinusitis, there must be 90 consecutive days with 2 or more subjective symptoms (nasal congestion, nasal discharge, facial pressure/pain, or cough) and objective evidence of inflammation either on endoscopy or computed tomography (CT) scan [1]. Differentiating between recurrent upper respiratory infections and persistent sinusitis symptoms over 90 days in duration can be difficult in children. In addition, depending on the healthcare setting in which the patient presents, obtaining objective evidence of inflammation may not be possible. In these cases, the diagnosis of rhinosinusitis must be made on symptoms and other exam findings alone.

Most episodes of acute rhinosinusitis (ARS) develop from an upper respiratory tract infection (URI). The average child will experience between 6 and 8 URIs per

A. A. Kennedy
Otolaryngology, Head and Neck Surgery, Children's Hospital Medical Center, Cincinnati, OH, USA

M. E. Gerber (✉)
Otolaryngology, Head and Neck Surgery, Phoenix Children's Hospital, Phoenix, AZ, USA
e-mail: mgerber1@phoenixchildrens.com

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_2

year, of which 5–13% will be complicated by acute sinusitis [2]. Numerous factors increase the likelihood of developing rhinosinusitis either through increased exposure to pathogens or disruption of normal immune functions. One factor consistently linked with increased risk in young children is daycare attendance. Children in daycare have a 2.2 times higher likelihood of being diagnosed with acute sinusitis, which is significant considering that at least 65% of children in the United States attend some form of daycare [3, 4]. Cigarette smoke exposure has also been linked to the development of both ARS and chronic rhinosinusitis (CRS) [5, 6]. Smoke exposure increases local inflammatory mediators, alters the ciliary beat in sinonasal epithelium [3], and aids in the formation of robust biofilms [7]. Many studies have sought to find a link between allergic rhinitis and development of acute and chronic rhinosinusitis; however, no consistent increased risk has been found. Recent cohort studies have concluded that a history of atopy does not predict an increased risk of ARS or CRS development [8, 9]. For CRS, a positive family history can significantly increase a patient's risk for developing the disease. The likelihood of developing CRS is approximately 57.5-fold higher if a sibling has been diagnosed, 5.6-fold higher if a parent has been diagnosed, and ninefold higher if a first cousin has been diagnosed [10]. Several other risk factors have been examined as likely contributors to development of sinusitis and chronic rhinosinusitis, including anatomic abnormalities, gastroesophageal reflux, and systemic medical conditions such as cystic fibrosis, primary ciliary dyskinesia, and immune deficiency [11].

Several large database and cohort-based studies have sought to quantify the prevalence of ARS in the pediatric population. In a prospective cohort study following over 3000 children at a primary care pediatric practice, 9.3% of children over 5 years old and 7.2% of children less than 5 years old were noted to develop ARS [6]. Similarly, a separate cohort study which screened over 1300 patients presenting to a primary care clinic for sinonasal symptoms found that 10% of children between 1 and 5 years of age met clinical criteria for sinusitis, and of the patients presenting specifically with URI symptoms, 17% of those patients had sinusitis [12]. A Swedish cohort survey of 13–14-year-olds found a 12% prevalence of current ARS symptoms [13]. With respect to databases, both the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) have been used. Both are comprised of large surveys administered annually by the National Center for Health Statistics. The NAMCS includes data related to ambulatory care visits to office-based physicians, while the NHAMCS includes data on visits to hospital- and outpatient-based emergency centers. A review of these databases from 2005 to 2012 found an average of 1.6 million visits per year for ARS, which comprised approximately 0.6% of the total visits for all pediatric encounters [14]. For comparison, the visit rate for other common pediatric conditions were 2.6% for allergic rhinitis, 8% for upper respiratory infections, and 6.7% for otitis media [14]. In summary, despite the difficulty with estimating prevalence of ARS, based on the literature, the rate falls somewhere between 7% and 12%, with a lower annual visit burden when compared to other more common pediatric conditions.

For patients with ARS, if the symptoms persist for over 12 weeks, they are considered to have chronic rhinosinusitis (CRS). The prevalence of CRS is well documented in the adult literature, with estimates between 8% and 10% of adults being affected [15, 16]. In the pediatric literature, a prospective cohort study following 3112 Swedish children from birth until 16 years of age, found 1.5% of patients had symptoms of CRS on self-reported survey [17]. At the time of follow-up, only 0.8% had continued symptoms of CRS, and of those patients, endoscopic evidence of CRS was seen in 0.3% [17]. Despite the overall low prevalence of CRS, findings from the NAMCS and NHAMCS database review found between 3.7 and 7.5 million visits per year, which comprised 2.1% of all pediatric ambulatory encounters [14]. Visits for CRS were more common than for ARS across all age groups and became more common than visits for otitis media in the 15–20-year-old age groups. In a study of children with chronic respiratory complains, 63% of them were noted to have sinus disease on CT imaging, with lower age being the most significant predictor of positive CT findings [18]. Similarly, a review of CT scans performed on 196 children with sinonasal symptoms showed that the severity and number of involved sinuses decreased with increasing age [19]. In summary, while CRS is less prevalent than ARS, with less than 1.5% of children meeting criteria, the number of ambulatory visits and healthcare utilization is higher.

Quality of Life Impact

Rhinosinusitis is an inflammatory disease of the nose and paranasal sinuses which may present with purulent nasal discharge, cough, headache, irritability, facial pain, fevers, and/or postnasal drip. In younger patients, the predominant symptoms tend to be purulent rhinorrhea and congestion, whereas in older patients, congestion, postnasal drip, and sore throat related to chronic drainage tend to predominate. Even with adequate treatment of an acute episode, these symptoms can last up to 3 weeks. For patients with CRS, these symptoms can last for years. For patients with rhinosinusitis, particularly CRS, they can have a significantly impaired health-related quality of life. In a study by Cunningham et al. in 2000, the Child Health Questionnaire (CHQ) was given to patients with CRS and their caregivers [20]. These responses were then compared to previously reported healthy controls. The caregivers reported significant reductions in the child's ability to participate in physical activities, perception of overall health, bodily pain, limitations in personal time due to the condition, guardian distress regarding the child's condition, and mental health problems. The children with CRS reported significantly worse body pain scores and limitations in school-related activities and activities with friends. The differences between the CHQ data for the caregivers versus the patients indicates that there is a discrepancy in perception of how significantly CRS is affecting the health-related quality of life. Interestingly, when CRS was compared to other common chronic pediatric conditions such as attention-deficit/hyperactivity disorder (ADHD), psychiatric disorders, juvenile rheumatoid arthritis, epilepsy, and asthma, the CRS children and

their caregivers reported more physical limitations in school- and play-related activities and more bodily pain than what was reported for these other conditions. In the cross-sectional cohort study of 13–14-year-olds in Sweden, 45% of the responders reported severe symptoms in which 35% had sleep disturbances and 54% had limitations in daily activities [13]. Objectively, many patients with CRS have olfactory dysfunction, with mean olfactory thresholds in the hyposmia range, which may also impact quality of life [17].

For those patients who require surgical intervention, adenoidectomy and endoscopic sinus surgery (ESS) are the most commonly performed procedures. Rudnik and Mitchell performed a quality of life assessment for patients undergoing these surgical interventions using the Sinus and Nasal Quality of Life Survey (SN-5) and found that surgical intervention led to improvement in all measured domains, with the greatest improvement in the "emotional distress" category and least improvement in the "allergy symptoms" [21].

Quality of Life Surveys

In adults, there are many different validated tools for assessing quality of life related specifically to sinonasal disease. These surveys include the Sinonasal Outcomes Test (SNOT-22), Chronic Sinusitis Survey (CSS), and the Rhinosinusitis Disability Index (RSDI). Measuring quality of life outcomes in the pediatric population is distinctly different due to the difficulty of extracting subjective data from young children and ensuring that the survey includes the health topics that are important to children, adolescents, and teenagers. These additional topics could address issues such as family relations, self-esteem, and physical/emotional development. Various health-related quality of life surveys have been developed for the pediatric population, such as the Child Health and Illness Profile (ages 11–17 years) and the Child Health Questionnaire (ages 5–18 years). With regard to quality of life specific to pediatric sinonasal disease, currently the only validated symptom questionnaire is the Sinus and Nasal Quality of Life Survey (SN-5) [22]. This tool has been shown to have good test-retest reliability, validity, and responsiveness. It measures symptom severity across five domains of sinus infections, nasal obstruction, allergy symptoms, emotional distress, and activity limitations, as well as an overall quality of life score [22].

Social Disparities

Disparities among access to healthcare, quality of healthcare, diagnosis rates, use of ancillary testing/imaging, and drug prescribing habits have been documented in a variety of pediatric conditions [23, 24]. In a large-scale analysis of primary care pediatricians treating upper respiratory tract infections, Gerber et al. found that

African American children were less likely to be diagnosed with otitis media, sinusitis, or group A streptococcal infection [25]. Additionally, African American children were 25% less likely to receive an antibiotic prescription, even on an individual clinician basis [25]. Using the 2008 National Emergency Department Sample Database, Sedegahat et al. found that emergency rooms in the northeast and south, particularly metropolitan hospitals, were three to six times more likely to use imaging in the workup of acute sinusitis [26]. Additionally, patients with private health insurance and higher socioeconomic status were more likely to have imaging performed in their workup, especially CT scan. These differences in access, workup, and treatment also extend into differences seen among the complications related to sinusitis. Another study by Sedaghat et al. reported a dichotomy between the children with orbital complications versus those with intracranial complications—findings that orbital complications were associated with higher income and private insurance, whereas intracranial complications were associated with Medicaid or no insurance [27]. While the exact cause of these disparities is difficult to pinpoint, it is an area that warrants further investigation in order to better understand and correct these inequities.

Financial and Societal Burden

There are both direct and indirect costs related to the diagnosis and treatment of ARS and CRS. Direct costs include money spent on office visits, emergency room or urgent care visits, imaging, treatments, and medications. In 1996, these costs were estimated at 5.8 billion, with 1.8 billion spent on children under 12 years of age [28]. A more updated figure from 2007 estimated that the direct expenditures were around 8.6 billion [29]. The indirect costs of ARS and CRS are more difficult to quantify but are numerous. In addition to missed school for children and missed work for the caregivers, it is important to also consider things such as risks associated with imaging, side effects related to treatments, and rising resistance of microorganisms related to antibiotic overuse.

CT scan is the gold standard imaging modality for visualizing sinus inflammation/infection. While this is primarily obtained for patients with CRS as opposed to ARS, thoughtful consideration regarding the utility of the study and which patients would benefit from it should be given since CT scans involve radiation exposure. This is especially important in the case of younger children in whom 25–30% of the bone marrow is located in the skull. In order to minimize radiation risk, it is important to be judicious in deciding to proceed with imaging and to use the lowest possible dose of radiation.

Once the determination of ARS and CRS have been made, the majority of patients will then proceed with some form of antibiotic therapy. A variety of different antimicrobials are used including beta-lactams, fluoroquinolones, macrolides/azalides, lincosamides, and sulfonamides/trimethoprim. In addition to the direct monetary cost of these medications, there is great concern regarding overprescrib-

ing. Antibiotic-resistant organisms have been increasing and are a great public health concern. The development of antibiotic resistance is primarily driven by antibiotic use. In order to cut back on inappropriate antibiotic use, both the Centers for Disease Control and the White House have launched campaigns targeted at reducing unnecessary or inappropriate use. In the pediatric population, the top three conditions associated with antibiotic prescriptions are sinusitis, suppurative otitis media, and pharyngitis [30]. While antibiotics for true bacterial infections constitutes appropriate use, up to 50% of the antibiotics prescribed in a primary care pediatric setting for upper respiratory infections are inappropriately prescribed [30]. The high rate of inappropriate prescriptions highlights the importance of accurate diagnosis and antimicrobial stewardship.

Conclusion

ARS and CRS will affect approximately 7–12% and 1–2% of children, respectively. While these conditions are less prevalent than other conditions such as URIs, otitis media, and pharyngitis, they both carry significant quality of life impacts and result in high direct and indirect healthcare expenditures. A better understanding of how quality of life (QOL) is impacted across the various age groups is essential in order to mitigate these negative effects. While many sinonasal specific and validated QOL questionnaires exist for adults, there is currently only one for the pediatric population—the SN-5. Additionally, ARS and CRS are both diseases entities in which improvements can be made in correcting healthcare disparities and decreasing inappropriate antibiotic usage.

References

1. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151:542–53.
2. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. Pediatrics. 1991;87:129–33.
3. Celedon JC, Litonjua AA, Weiss ST, et al. Day care attendance in the first year of life and illnesses of the upper and lower respiratory tract in children with a familial history of atopy. Pediatrics. 1999;104:495–500.
4. West J, Wright D, Hausken EG. Child care and early education program participation of infants, toddlers, and preschoolers. Washington, DC: US Department of Education; Statistics in Brief; 1995.
5. Christensen DN, Franks ZG, McCrary HC, Saleh AA, Chang EH. A systematic review of the association between cigarette smoke exposure and chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2018;158(5):801–16.
6. Kakish KS, Mahafza T, Batieha A, et al. Clinical sinusitis in children attending primary care centers. Pediatr Infect Dis J. 2000;19(11):1071–4.

7. Goldstein-Daruech N, Cope EK, Zhao KQ, et al. Tobacco smoke mediated induction of sinonasal microbial biofilms. PLoS One. 2011;6(1):e15700.
8. Leo G, Incorvaia C, Cazzavillan A, Consonni D, Zuccotti GV. Could seasonal allergy be a risk factor for acute rhinosinusitis in children? J Laryngol Otol. 2018;132(2):150–3.
9. Sedaghat AR, Phipatanakul W, Cunningham MJ. Atopy and the development of chronic rhinosinusitis in children with allergic rhinitis. J Allergy Clin Immunol Pract. 2013;6(1):689–91.
10. Orb Q, Curtin K, Oakley GM, et al. Familial risk of pediatric chronic rhinosinusitis. Laryngoscope. 2016;126(3):739–45.
11. Rose AS, Thorp BD, Zanation AM, et al. Chronic rhinosinusitis in children. Pediatr Clin N Am. 2013;60(4):979–91.
12. Aitken M, Taylor JA. Prevalence of clinical sinusitis in young children followed up by primary care pediatricians. Arch Pediatr Adolesc Med. 1998;152:244–8.
13. Sterner T, Uldahl A, Svensson Å, et al. The Southern Sweden Adolescent Allergy-Cohort: prevalence of allergic diseases and cross-sectional associations with individual and social factors. J Asthma. 2018;5:1–9.
14. Gilani S, Shin JJ. The burden and visit prevalence of pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2017;157(6):1048–52.
15. Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and risk factors of chronic rhinosinusitus, allergic rhinitis, and nasal septal deviation: results of the Korean National Health and Nutrition Survey 2008–2012. JAMA Otolaryngol Head Neck Surg. 2016;142(2):162–7.
16. Chen Y, Dales R, Lin M. The epidemiology of chronic rhinosinusitis in Canadians. Laryngoscope. 2003;113(7):1199–205.
17. Westman M, Stjarne P, Bergstrom A, et al. Chronic rhinosinusitis is rare but bothersome in adolescents from a Swedish population-based color. J Allergy Clin Immunol. 2015;136(2):512–4.
18. Nguyen KL, Corbett ML, Garcia DP, et al. Chronic sinusitis among pediatric patients with chronic respiratory complaints. J Allergy Clin Immunol. 1993;92:824–30.
19. Van der Veken P, Clement PA, Buisseret T, et al. CAT-scan study of the prevalence of sinus disorders and anatomical variation in 196 children. Acta Otorhinolaryngol Belg. 1989;43(1):51–8.
20. Cunningham MJ, Chiu EJ, Landgraf JM, et al. The health impact of chronic recurrent rhinosinusitis in children. Arch Otolaryngol Head Neck Surg. 2000;126:1363–8.
21. 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.
22. Kay DJ, Rosenfeld RM. Quality of life for children with persistent sinonasal symptoms. Otolaryngol Head Neck Surg. 2003;128:17–26.
23. Shay S, Shapiro NL, Bhattacharyya N. Pediatric otolaryngologic conditions: racial and socioeconomic disparities in the United States. Laryngoscope. 2017;127(3):746–52.
24. Flores G. Technical report--racial and ethnic disparities in the health and health care of children. Pediatrics. 2010;125(4):979–1020.
25. Gerber JS, Prasad PA, Localio AR, et al. Racial differences in antibiotic prescribing by primary care pediatricians. Pediatrics. 2013;131(4):677–84.
26. Sedaghat AR, Cunningham MJ, Ishman SL. Regional and socioeconomic disparities in emergency department use of radiographic imaging for acute pediatric sinusitis. Am J Rhinol Allergy. 2014;28(1):23–8.
27. Sedaghat AR, Wilke CO, Cunningham MJ, et al. Socioeconomic disparities in the presentation of acute bacterial sinusitis complications in children. Laryngoscope. 2014;124(7):1700–6.
28. 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(3Pt1):408–14.
29. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. Ann Otol Rhinol Laryngol. 2011;120(7):423–7.
30. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. JAMA. 2016;315(17):1864–73.

Chapter 3
Pathogenesis of Pediatric Rhinosinusitis

Lyuba Gitman and Maria Peña

Rhinosinusitis (RS) is an inflammatory process of the mucosal lining of the paranasal sinuses and the nasal cavities with a complex and multifactorial pathogenesis that is partially impacted by clinical presentation and duration of symptoms [1–5] (Table 3.1). RS presenting for less than 12 weeks is classified as acute RS [1, 2]. The 2012 European Position Paper on Rhinosinusitis and Nasal Polyps further subdivides pediatric acute RS into acute viral RS, acute postviral RS, and acute bacterial RS depending on etiology, in addition to duration of symptoms [1]. Pediatric chronic rhinosinusitis (CRS) is characterized by sinonasal mucosal inflammation for more than 90 consecutive days of sinonasal symptoms. Current consensus is that objective criteria based on nasal endoscopy and/or CT scan should support the diagnosis of CRS [1, 2, 5]. CRS can be further delineated depending on whether patients have NP, which are outgrowths of the sinonasal mucosa. Recurrent acute bacterial RS is defined as four or more episodes per year of acute bacterial RS without signs or symptoms of RS between episodes [1, 2].

Normal Paranasal Sinuses Physiology

Normal sinonasal physiology is dependent on effective mucociliary clearance (MCC). It is the primary physical defense of the respiratory tract, complementing the epithelial layer mechanical barrier, and relies on both mucus production and transport [6, 7].

Each of the paranasal sinuses are each lined with respiratory epithelium composed of pseudostratified columnar ciliated epithelial cells joined by tight junctions

L. Gitman · M. Peña (✉)
Division of Otolaryngology, Children's National Medical Center, and the Department of Otolaryngology, George Washington University, Washington, DC, USA
e-mail: mpena@childrensnational.org

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_3

Table 3.1 Rhinosinusitis definitions

Term	Definition
Acute rhinosinusitis	Sudden onset of two or more of the following symptoms for <12 weeks: mucopurulent drainage (anterior, posterior, or both), nasal obstruction/congestion, facial pain/pressure, or cough
Acute viral rhinosinusitis	Suspected viral etiology; duration of sinonasal symptoms less than 10 days
Acute postviral rhinosinusitis	An increase in sinonasal symptoms after 5 days, or persistent symptoms after 10 days, but lasting less than 12 weeks
Acute bacterial rhinosinusitis	Persistent upper respiratory tract symptoms more than 10 days (cough or nasal discharge or both) OR Recurrence of symptoms (fever, worsening cough, worsening or new purulent rhinorrhea) after initial improvement (double worsening) OR Severe onset of symptoms such as fever or purulent nasal discharge lasting at least 3 consecutive days
Chronic rhinosinusitis	At least 90 continuous days of two or more of the following symptoms: mucopurulent rhinorrhea (anterior, posterior, or both), nasal obstruction/congestion, facial pain/pressure, or cough AND Endoscopic signs of mucosal edema, purulent drainage, or nasal polyps and/or CT scan evidence of mucosal changes in the ostiomeatal complex and/or the paranasal sinuses
Recurrent acute rhinosinusitis	Four or more episodes of acute bacterial rhinosinusitis per year without signs or symptoms of rhinosinusitis between episodes

Adapted from references [1–5]

interspersed with goblet cells [8, 9]. The respiratory epithelium is covered with a film of liquid about 10-μm deep known as the airway surface liquid (ASL) lining made of an upper antimicrobial rich mucus "gel" layer [10] that entraps inhaled particles and pathogens, and rests on top of a less-viscous fluid periciliary layer surrounding the cilia located at the tip of the respiratory epithelial cells. The propulsion of mucus out of the sinonasal cavities is due to coordinated ciliary movements known as the metachronal wave [7, 11]. Each of the paranasal sinuses has a distinct secretion flow pattern (Fig. 3.1) with variations in flow velocities [12]. Effective MCC is critical for adequate drainage of the paranasal sinuses as the sinus ostia are not always located in the most dependent areas of the sinuses.

The normal quality and consistency of the sinonasal secretions and the ASL lining are another integral component of effective MCC. The consistency of ASL layer is regulated by small-molecule neurotransmitter and neuropeptide epithelial receptors that control mucus secretion and viscosity [13]. Sinonasal epithelial cells also contribute to the integrity of the ASL by producing antimicrobial peptides (AMPs) that assist in detecting and eliminating pathogens (Fig. 3.2). These include lysozyme, lactoferrin, antitrypsin, surfactant proteins (SP), defensins, and S100 proteins [14, 15]. Pathogens exhibit conserved microbial-specific structures known as pathogen-associated molecular patterns (PAMPS) [16, 17], which when recognized by PAMP receptors on epithelial cells, induce the release of AMPs. In addition to AMPs, mucin glycoproteins, or mucins, which are the major macromolecular components of mucus [18], bind surface adhesins on microorganisms [19], reducing

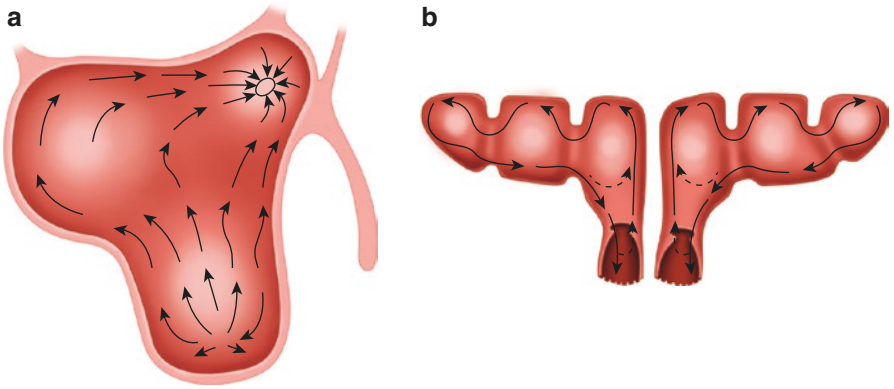


Fig. 3.1 (**a**) Stellate transport routes of mucus in the maxillary sinus which all move toward the natural maxillary ostium. (**b**) Mucus is transported into the frontal sinus along the interfrontal septum and travels laterally along the frontal sinus roof. The mucus then moves medially along the sinus floor and exits the frontal sinus via the lateral aspect of its ostium. A whorl-like formation in the ciliary pattern superior to the frontal sinus ostium results in some of the mucus recirculating through the frontal sinus more than once. Recirculating mucus represented by dotted lines

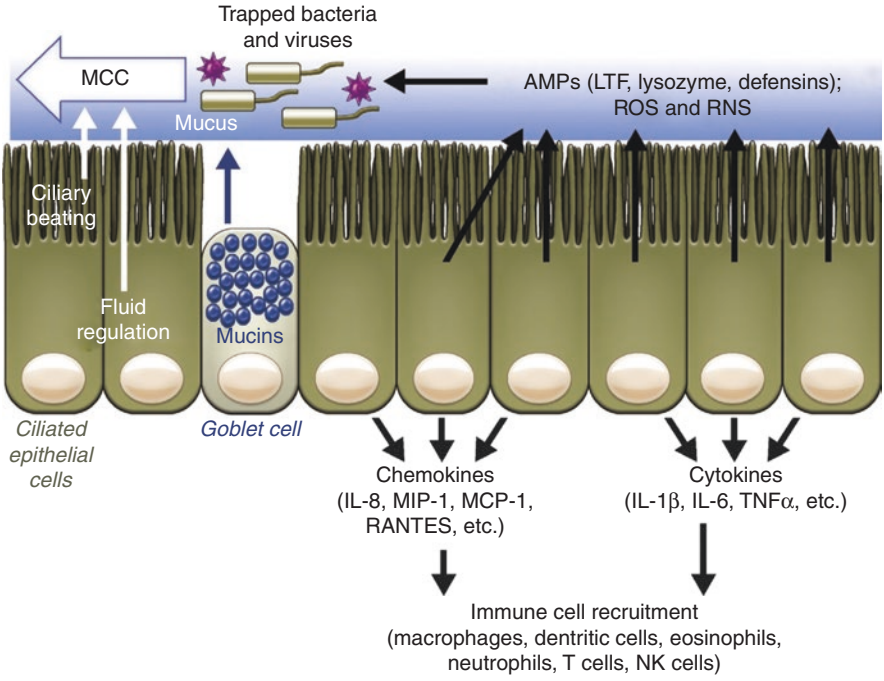


Fig. 3.2 Sinonasal innate immunity is comprised (or composed) of several mechanisms including the protective physical barrier formed by healthy respiratory epithelial cells and the removal of inhaled particles and pathogens by mucociliary clearance (MCC). In addition, sinonasal epithelial cells produce antimicrobial peptides (AMPs), reactive oxygen species (ROS), and reactive nitrogen species (RNS) that assist in detecting and eliminating pathogens. Epithelial cells also secrete cytokines to activate inflammatory pathways and recruit dedicated immune cells with prolonged pathogen exposure. LTF, lactotransferrin; MCP-1, monocyte chemotactic protein 1; MIP-1, macrophage inflammatory protein-1. (Reprinted from Stevens et al. [6]. Used by permission of Elsevier)

their ability to colonize the epithelium [20]. The sinonasal mucosa also generates reactive oxygen species (ROS) that can directly damage bacteria [21], and nitric oxide (NO) thought to be critical for airway innate immunity, due to its antiviral and bacteriostatic properties [22–24] and suspected role in the regulation of epithelial ciliary beat activity [25]. Toll-like receptors (TLRs) are PAMP receptors, which when activated, not only promote airway cells to secrete AMPs, but also induce the secretion of chemokines and cytokines that are important for immune cell recruitment, activation of inflammatory pathways, and ultimately, initiation of communication between the innate and adaptive immune systems [16, 26].

Pathogenesis

In order for the paranasal sinuses to function effectively, the MCC mechanism has to be intact, the sinus secretions normal, and sinus ostia patent. The disruption or alteration of any one of these factors, or combination of these factors, can lead to sinusitis. When sinus ostial obstruction occurs, mucus, which is continuously secreted by the sinus mucosa, accumulates in the sinus cavity and impairs sinus gas exchange reducing sinus ventilation. The entrapped oxygen is absorbed by the mucosa leading to hypoxia, and the sinus secretions stagnate and thicken. This damages the epithelium and cilia, undermining the protective mechanisms of respiratory mucosa. The retained secretions also result in mucosal inflammation, and ultimately, bacteria to adhere and aggregate into biofilms, allowing infections develop (Fig. 3.3) [27, 28]. Even if the infection is cleared, the sinus mucosa may have persistent inflammation and thickening causing continued ostial obstruction perpetuating this cycle [6–9].

The pathogenesis of RS is mediated by many physiologic mechanisms that result in abnormal MCC and sinus ostial obstruction. It is influenced by a number of local and systemic patient comorbidities closely associated with pediatric RS. These con-

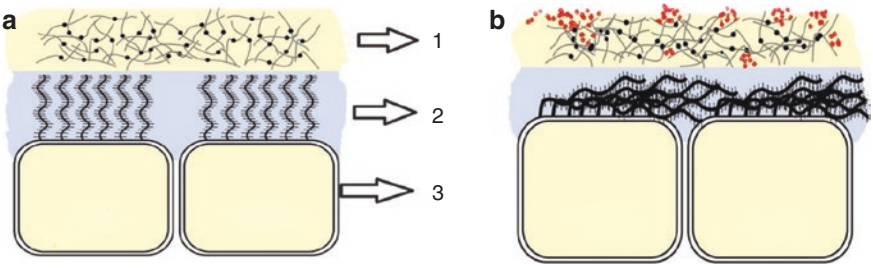


Fig. 3.3 (**a**) The airway surface liquid (ASL) lining is made of a mucus layer (1), periciliary layer (PCL) (2), and ciliated columnar epithelial cells with cilia extending into the PCL (3). (**b**) When the ASL lining becomes thickened, the cilia collapse, so that the viscous mucus cannot be cleared and bacteria can attach and aggregate forming a biofilm (red particles). As the cilia fold over the epithelium, the PCL decreases in height (2) resulting in columnar epithelium with inefficient cilia (3). (From Hendrik and Raubenheimer [27]. Reprinted per open access terms of the Creative Commons Attribution License)

ditions frequently exacerbate and may even precipitate the development of pediatric sinusitis and include asthma, allergy, polyposis, cystic fibrosis, ciliary dyskinesias, and immunodeficiency syndromes, among others. In addition, bacteria, viruses, and environmental agents are thought to play a critical role in initiating and sustaining the altered immune response that results in mucosal inflammation and mucus hypersecretion characteristic of RS.

Systemic Comorbidities Associated with Rhinosinusitis

Allergic Rhinitis

Allergic rhinitis (AR) and RS often occur together, and in children the concordance between these two diseases has been reported to be between 25% and 70% [29]. In a retrospective review of 92 patients (14 adults) with recurrent ARS, those patients with AR sustained 1.09 more sinus infections than nonallergic patients [30]. Children with atopy are more likely to develop ARS than those that are nonatopic [31] and more than 50% of children with AR have abnormal sinus radiographs [32]. Studies in a mouse model showed that an ongoing nasal allergic reaction augmented an acute bacterial sinusitis compared with allergen sensitization without an allergic reaction, suggesting that an ongoing allergic reaction and not sensitization, impacts the expression of acute bacterial RS [33–35]. Yu et al. [36] proposed that local mucosal responses to infection involving Th1 cells is altered by the ongoing local mucosal response to allergens [35, 36].

While there is strong support for a role for allergic inflammation impacting acute bacterial RS [1, 2], the data demonstrating an association between pediatric CRS and AR are variable and have contrasting results. Some studies have reported a positive correlation and a high prevalence of atopy in pediatric CRS patients [37, 38]. Other studies have recorded rates of AR in children with pediatric CRS of between 26.9% [39] and 29.9% [40], which fall within the estimated prevalence rate of 10–40% for AR in the general pediatric population [41, 42]. Sedaghat and colleagues found that those children with AR who developed subsequent CRS did not have more severe subjective AR or more severe objective quantitative atopy measurements [43]. The lack of positive association between atopic conditions and the presence of CRS in the literature makes it difficult to arrive at any conclusions [35, 39, 40, 43]. It is possible that infectious etiologies may play a more significant role rather than just inflammation in the pathogenesis of this disease in the pediatric population [43, 44].

Asthma

Asthma is an inflammatory disease characterized by reversible airway obstruction that frequently coexists in children with RS. Asthmatic children have been demonstrated to have sinonasal abnormalities on radiographic studies [32, 45], and in one

investigation, 61 of 128 pediatric patients with asthma were diagnosed with RS on nasal endoscopy [46]. Several studies have shown that bronchial hyperresponsiveness in asthmatic children with sinusitis dramatically improved with medical therapy for sinusitis [47–50]. Pediatric patients who have undergone sinus surgery are also reported to have an improvement in asthma [51, 52] and sinus [52] symptoms. In 2015, Anfuso and colleagues found that the inflammatory response in the sinus and adenoid mucosa of children with asthma and CRS was similar, but more severe, compared with the pediatric patients that had CRS but no asthma [53], suggesting that children with asthma and CRS have a similar but more severe form of the same inflammatory process [53]. Several paradigms have been proposed to explain the relationship between asthma and sinusitis. They include (a) propagation of inflammation through a contiguous upper and lower respiratory tractor ("united airways" hypothesis), (b) aspiration of mucopurulent secretions or mediators released from activated inflammatory cells in the infected sinonasal tract into the distal airways, (c) systemic absorption of locally produced inflammatory mediators and (d) a neurogenic link based on cholinergic-mediated naso-sino-bronchial reflexes [53–55].

Immunodeficiency

Investigations into immunodeficiency diseases have usually focused on patients with severe recurrent or chronic RS who have failed appropriate medical and/or surgical management. Most of these studies have shown increased rates of immunoglobulin deficiencies and inadequate response to immunization. Shapiro and colleagues [56] prospectively evaluated the immune function of 61 children (2–13 years of age) with refractory CRS by quantitative serum immunoglobulin levels, IgG subclass levels, and response to pneumococcal and *Haemophilus influenzae* vaccines. They found that 17 patients had depressed levels of immunoglobulins, 23 children had an inadequate response to vaccination and 6 patients had both. Decreased IgG3 levels and poor response to pneumococcal antigen 7 were the most common abnormalities seen. Costa Carvalho and associates [57] evaluated 27 children (7–15 years of age) with either recurrent or chronic CRS and found both IgA and IgG subclass deficiencies in these patients. In another retrospective investigation, Javier and associates determined that the most common type of antibody deficiency (23.1%) in a pediatric cohort with an 8-year history of recurrent infections was specific antibody deficiency based on a dysfunctional response to pneumococcal vaccination [58]. Furthermore, it has been shown that pediatric patients who do not produce protective pneumococcal antibodies after pneumococcal vaccination continue to have multiple infections including recurrent sinusitis, otitis media, and pneumonia [59]. Although B-cell or humoral abnormalities are usually associated with pediatric recurrent and chronic sinonasal infections, other components of the immune system may be impaired. Consultation with a clinical immunologist may be beneficial in these cases.

Sinonasal Mucosal Immune Responses

The sinonasal mucosa forms a physical epithelial barrier which functions as part of the innate immune system. Mucins are an important part of this barrier against pathogens and contaminants. They are secreted by surface epithelial goblet cells and submucosal glands and are delineated by MUC genes that encode for the mucin protein backbones [60]. Peña and colleagues demonstrated that the sinus mucosa of children with CRS has a significant increase in the area of submucosal glands compared to children without this disease (Fig. 3.4), and that the glandular mucins MUC5B and MUC7 were expressed in the submucosal glands and goblet cells of children with and without CRS [61]. Moreover, Saieg and co-investigators showed an increased abundance of MUC 5B in the sinus secretions of children with CRS [62]. Taken together, this suggests that glandular mucins are responsible in part for the mucus overproduction characteristic of pediatric CRS. MUC5B and MUC7 may have bacteriostatic properties which also contribute to their role in creating and maintaining the sinus mucosal physical and physiologic barrier to pathogens and cytotoxins [61].

Immunohistopathologic studies have been conducted on the mucosal biopsies of children with CRS to determine the nature of the inflammatory response in pediatric CRS and if it changes with age. Chan and colleagues examined maxillary sinus biopsies of children with CRS ages 1–8 years. They found increased numbers of neutrophils and lymphocytes and less eosinophils and major basic protein positive cells compared with adult maxillary sinus specimens [63]. In addition, they also found less epithelial disruption and thickening of the basement membrane in the pediatric CRS tissues children [63]. In a simi-

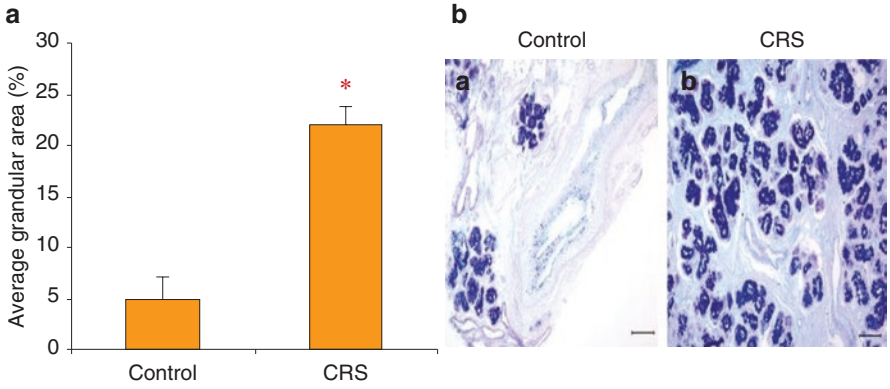


Fig. 3.4 (**a**) Quantification of submucosal glands in the sinus mucosa of children with and without CRS demonstrated a statistically significant increase in the glandular area in pediatric CRS mucosa compared to normal sinus mucosa. (**b**) Alcian blue-periodic acid Schiff staining of (A) normal sinus mucosa and (B) pediatric CRS mucosa. Glandular hyperplasia is present in children with CRS. Bars-100 μm; original 100×. (Table and photos from Peña et al. [61]. Used by permission of Sage Publications)

lar study, Coffinet et al. found more CD8+ (cytotoxic T cells), myeloperoxidase (MPO+) (neutrophils), CD68+ (monocytes/macrophages) cells, and a trend toward more T cells in the epithelium of pediatric CRS maxillary sinus mucosa [64]. Even though the patients were older (mean 11.6 versus 3.9 years), the pediatric tissues had less epithelial damage and eosinophils when compared with adult sinus mucosal biopsies [64]. The higher numbers of monocytes/macrophages, neutrophils, and natural killer cells in the sinus mucosa of children with CRS compared with adults may reflect an elevated activation of the innate immune system, which Coffinet and colleagues hypothesized may be due to a dysregulation of the innate immune system in pediatric CRS [64]. Although children with pediatric CRS had less evidence of epithelial damage than adults, they may have enough disruption of their epithelial barrier to allow for prolonged exposure of pathogens and/or allergens resulting in further aberrations in the innate immune response and subsequent recruitment of the adaptive immune system [8, 65] leading to the immunopathologic changes seen with CRS.

Microarray analyses, which have enabled the identification of differentially expressed genes in sinus mucosa of children with CRS, have demonstrated increased messenger RNA expression of the chemokines CXCL5 and CXCL13 involved in the adaptive immune response and of the innate immune mediators, beta defensin 1 (DEFB1), serum amyloid A2, and serpin B4 [66]. Immunohistochemical analysis localized all five of these mediators to ciliated and basal bells in the pseudostratified epithelium and to glandular cells [67]. CXCL13, a potent B cell chemoattractant [68, 69], was also seen in macrophages and T and B lymphocytes [67] in the pediatric sinus mucosa. This suggests that CXCL13 may be contribute to the recruitment of these immune cells to sustain the mucosal inflammation seen in pediatric CRS. CXCL5, which is involved in chemotaxis of neutrophils [70], was also present in T cells [67]. It may play a role in the recruitment of neutrophils and/or T cells in this disease. Further studies will be needed to help elucidate the role of CXCL13 and CXCL5 in the pediatric RS.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal-recessive disease causing exocrine gland dysfunction that presents with pulmonary obstruction, CRS, and pancreatic insufficiency. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene on the long arm of chromosome 7 (7q31). The CFTR gene encodes for a protein called the CF transmembrane conductance regulator which functions as a chloride channel regulated by cyclic adenosine monophosphate (cAMP). In CF, CFTR gene mutations result in abnormal or nonfunctional c-AMP-regulated chloride channels causing a decrease in chloride permeability across apical

membranes of epithelial cells [71, 72]. The latter leads to an influx of sodium and water into cells, making the extracellular matrix of exocrine secretions much more viscous. The abnormal chloride conductance and sodium exchange destroys the delicate balance of the ASL lining making it more difficult to clear the thickened secretions from the sinonasal passages, even though ciliary beat frequency does not change [73].

MCC in CF is further impaired by bacterial compounds produced by pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa* which are known to colonize the airways of CF patients [74]. These pathogens, in addition to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Aspergillus fumigatus*, all produce compounds that impair ciliary motion, coordination, or both [75–78]. In addition, bacterial infections themselves exacerbate the chronic inflammation seen in CF causing goblet cell hyperplasia, squamous cell metaplasia, and the loss of ciliated epithelial cells [79] further disrupting the epithelial cell barrier. The thickened secretions and chronic inflammatory state present in CF result in chronic sinonasal mucostasis resulting in mucosal hypoxia [80]. Hypoxia, which has been shown to affect epithelial CFTR transcription and function in patients with normal CFTR [81], may lead to acquired defects in chloride transport [81] if persistent.

Approximately 6.75–48% of children with CF have nasal polyps [82, 83]. The pressure exerted by nasal polyps and/or thick inspissated secretions on the lateral nasal wall often lead to medial displacement of the lateral nasal wall and the formation of a "pseudomucocele" (Fig. 3.5). Children with these findings should

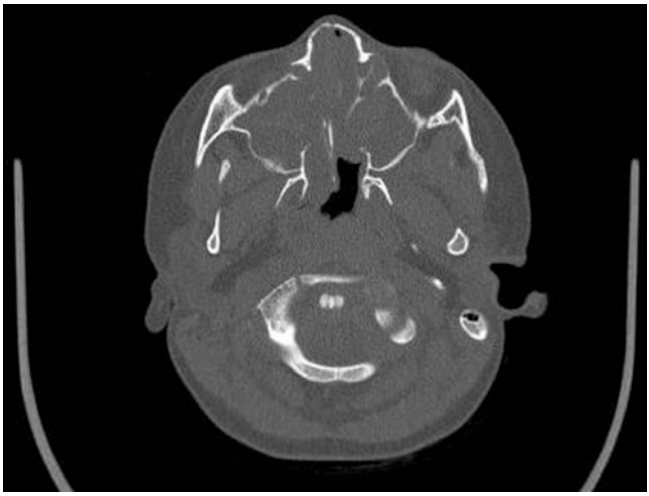


Fig. 3.5 Computed tomography scan of a patient with cystic fibrosis and medial displacement of the medial maxillary sinus wall due to pressure exerted by nasal polyps and/or thick inspissated secretions or a "pseudomucocele"

be evaluated for CF [84, 85]. Although the exact etiology of nasal polyps is not clear, nasal polyps seen in CF are associated with neutrophilic Th1-mediated inflammation [86] and the Th1 inflammatory mediators IL-8 and myeloperoxidase [87]. Claeys and colleagues have also showed that mRNA for the AMP human β defensin 2 and pattern recognition receptor Toll-like receptor 2 were significantly increased in CF nasal polyps [79]. Other AMPs that are upregulated in CF include SP-A, SP-B, and SP-D [88–91]. The upregulation of these and other AMPs may be triggered by the recognition of PAMPs on pathogens colonizing or infecting CF upper airways by Toll-like receptors [92–94]. Hypoxia created by means of anatomic obstructions like nasal polys can also affect MCC by promoting polypogenesis [95].

Nasal Polyps

Nasal polyps are unusual in young children [96]. Most studies suggest that it is uncommon for nasal polyps to present before the age of 10 years [97]. When they occur, pediatric nasal polyps are associated with CRS and systemic disease like CF or primary ciliary dyskinesia (PCD) or, very rarely, aspirin-exacerbated respiratory disease [98]. Unilateral nasal polyps presenting in a child should be evaluated further for congenital abnormalities like meningoencephaloceles and intranasal gliomas, malignancies, or antral choanal polyps [96, 97]. Triglia and colleagues evaluated 46 children with nasal polyps and found 5/46 (10%) with asthma and 27/46 (58.6%) with CF [99]. Other studies found the incidence of NP in CF to be between 6.75% and 48% [82, 83]. Nasal polyps also occur in children with severe CRS. Almost half of children undergoing endoscopic sinus surgery for severe recurrent chronic CRS have nasal polyps [100, 101].

Allergic fungal rhinosinusitis (AFRS), another systemic disorder associated with pediatric nasal polyposis, is the most common form of fungal CRS in children [102]. It is a noninvasive form of fungal CRS caused by a hypersensitive reaction to the inhaled fungi. In 2003, Kuhn and Swain [103] described five major and six minor criteria for diagnosis of AFRS. The former were (1) type I IgE-mediated hypersensitivity, (2) nasal polyposis, (3) characteristic CT findings, (4) allergic mucin, and (5) positive fungal smear and/or culture. The latter criteria included (1) asthma, (2) unilateral predominance, (3) radiographic bone erosion on CT, (4) positive fungal culture, (5) Charcot-Leyden crystals, and (6) serum eosinophilia (Fig. 3.6). The fungi responsible for AFRS in children are similar to those found in the adult population and include Aspergillus, Curvularia, Alternaria, and Bipolaris species [104–107]. Children with AFRS most commonly present with unilateral [104, 106] nasal obstruction. Asymmetrical facial disorders/anomalies are diagnosed more often in children than adults [104, 106–108].

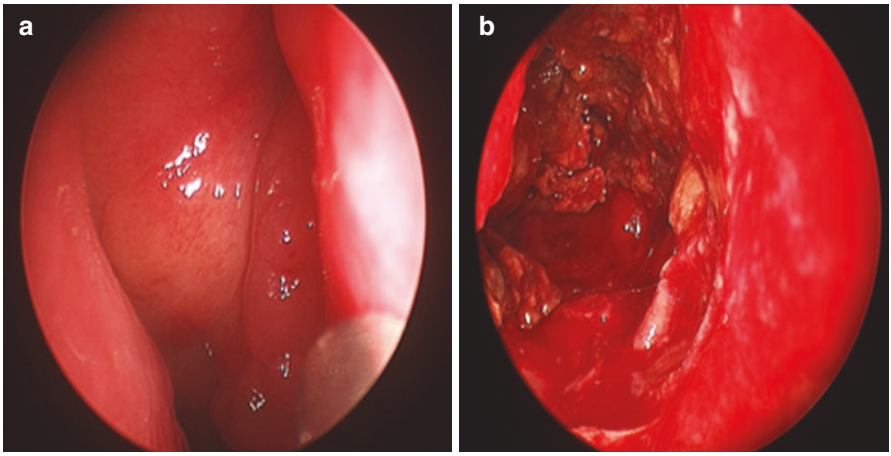


Fig. 3.6 Nasal endoscopic view of polyps (**a**) and allergic mucin (**b**) in a patient with allergic fungal sinusitis

Mucociliary Dysfunction

Primary ciliary dyskinesia (PCD) is a heterogeneous genetic disorder characterized by ciliary dysfunction resulting in impaired MCC that prevents the clearance of mucous from the lungs, paranasal sinuses, and ears. The impaired MCC leads to chronic airway inflammation and infection including CRS. Over 30 mutations in cilia structural genes [109, 110] have been identified in patients with PCD, but the most common cilia abnormalities reported are the lack of outer dynein arms or a lack of both inner and outer dynein arms [111, 112]. The estimated incidence of this disease is between 1 in 15,000 and 1 in 30,000 births [113]. Nasal polyps have been reported to occur in 18–33% of patients with PCD and usually present during adolescence [113–115]. About 50% of patients with PCD have solid organ transposition (situs inversus), bronchiectasis, and CRS, which is known as Kartagener's syndrome [116]. Low intranasal NO production and saccharin transit tests [117, 118] have been used as screening tests to diagnose PCD but have been associated with a high rate of false-negative results in children [2]. Combined approaches using ultrastructural analysis of respiratory epithelial biopsies and ciliary beat frequency assessment have yielded more consistent results [119–121].

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) has been implicated in the pathogenesis of pediatric CRS. Acid-induced injury of the sinonasal mucosa has been proposed to initiate and sustain an inflammatory response leading to paranasal sinus ostial

edema and impaired mucociliary clearance [122]. Although some studies have demonstrated nasopharyngeal reflux in children with symptoms of CRS [122–125] that improved with medical treatment of GERD [123–126], the association between GERD and pediatric CRS remains unclear. In the 2014 Clinical Consensus Statement on pediatric CRS, consensus could not be obtaining regarding the contribution of GERD on pediatric CRS or the routine treatment of GERD in the management of these patients [5].

Regional Anatomical Factors Associated with RS

Sinonasal Anatomic Factors

Structural abnormalities of the nasal cavities or the paranasal cavities are unusual causes of pediatric RS. The most common anatomical abnormalities found in children with CRS are a concha bullosa [127] and agger nasi cell [128, 129]. Other anatomical abnormalities identified include pneumatization of the superior concha, Haller's cell, nasal septal deviation, paradoxical middle turbinate, and obstructive adenoid hypertrophy [1, 127–130]. Nasal septal deformities tended to be less common in children than adults [2, 127]. Although there was no control group in any of these investigations to determine whether sinonasal anatomical abnormalities occurred at a higher incidence in children with CRS compared to children without RS [127–129], Al-Qudah found no radiographic correlation between the severity of pediatric CRS and anatomical abnormalities in the CT scans of children with persistent symptoms of CRS after maximal medical management [128]. Willner and colleagues also failed to demonstrate an association between sinonasal anatomic abnormalities and the presence or extent of CRS in children [131].

Role of the Adenoids

The adenoids may predispose a certain proportion of children to develop RS by causing mechanical obstruction and subsequent stasis of sinonasal secretions [132] or by acting as a reservoir for pathogenic bacteria [133]. The results of most investigations suggest that the function of adenoid as a bacterial reservoir in the pathogenesis of pediatric CRS is more important than the size of the adenoid. Bercin and associates reviewed the paranasal CT scans of children who underwent adenoidectomy for symptoms of RS and showed no correlation between the size of the adenoid and the severity of sinusitis on imaging [134]. Bacterial isolation rates from pediatric adenoids were significantly increased according to the degree of severity of sinusitis seen on radiographs especially for *Haemophilus influenzae* and *Streptococcus pneumoniae*, but not according to adenoid size [135]. Elwany and colleagues demonstrated a significant similarity between bacteria isolated from

adenoid core and middle meatal cultures in pediatric CRS patients which included coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and group A streptococci [136]. The adenoid core cultures in this study had a negative predictive value of 84.3% and a positive predictive value of 91.5% for the middle meatal culture results [136]. Coticchia et al. showed that the adenoid samples of children with CRS had a dense biofilm covering the majority of the adenoid mucosal surface area compared to those from children with obstructive sleep apnea implying that biofilms in the nasopharynx of children with CRS may act as a chronic reservoir for bacterial pathogens [137].

Adenoids may also function as an immunologic organ in the pathogenesis of pediatric CRS. Eun and associates found a significantly decreased expression of IgA in the adenoids of children with CRS compared to those with adenoid hypertrophy [138] indicating that the adenoids in pediatric CRS patients may not be able to generate a strong local immune response. The latter may reflect a primary deficiency or a secondary response to inflammation/infection related to CRS [63]. Shin and colleagues evaluated adenoid tissues from children with and without CRS, and found higher levels of the inflammatory cell activation marker soluble interleukin (IL)-2 receptor (sIL-2R), and cytokines associated with tissue remodeling including transforming growth factor (TGF)-β1, matrix metalloproteinase (MMP) 2 and 9, and tissue inhibitor of metalloproteinase (TIMP)-1, in the adenoids of the pediatric CRS patients [139]. In addition, the investigators found that the levels of sIL-2R, TGF-β1, MMP-2, MMP-9, and TIMP correlated with severity of radiographic RS [139]. These data suggest that the adenoid tissue of children with CRS have more severe inflammation, and that this degree of inflammation may lead to elevated tissue remodeling, similar to what is seen in pediatric CRS sinus mucosa [139].

A confounding factor in studies investigating the role of the adenoids in the pathogenesis of pediatric RS is adenoiditis. Adenoiditis has a similar clinical presentation as RS including anterior and posterior nasal purulent drainage and cough. In an effort to distinguish between adenoiditis and ARS, Marseglia et al. performed nasal endoscopy on 287 children with suspected ARS and found that 89.2% of the children had ARS. ARS was combined with adenoiditis in 19.2% patients and adenoiditis was seen in 7% of the study population. These findings are not surprising as sinus drainage would be expected to involve the adenoids as it moves posteriorly in the nasal cavity [140]. However, distinguishing between adenoiditis and ARS is not straightforward, even with nasal endoscopy. Chronic adenoiditis cannot be differentiated from CRS without a CT scan [141].

Aquired Mucociliary Clearance Dysfunction

Mucociliary dysfunction can be caused by bacterial and viral infections of the paranasal sinuses. The latter have been reported to lead to a direct temporary cytotoxic effect on the cilia [142], the loss of cilia and ciliated cells, and the impairment of

normal mucociliary flow [143]. The transient dyskinesia, sometimes seen with ciliary microtubular abnormalities, usually resolves with time and appropriate management [143–145]. Bacterial and viral infections of the paranasal sinuses have also been associated with abnormal ciliary function with normal ciliary ultrastructure that may represent a metabolic abnormality within the cilia [146, 147]. More often, acquired ciliary dysfunction occurs through exposure to environmental irritants or microbial toxins which impede ciliary beat frequency and/or coordination [75–78, 148, 149]. Mucociliary impairment in AR has also been implicated in predisposing some patients to acute RS [150].

Mucociliary dysfunction may also result from the disruption of the normal mucus ciliary patten of the maxillary sinus due to the existence of an accessory maxillary ostium (AMO). When present, mucus exiting the natural maxillary ostium moves along the lateral nasal wall posteriorly, but instead of moving into the pharynx, it reenters the maxillary sinus via the AMO [35]. The mucus then travels along the medial maxillary sinus wall into the natural maxillary sinus, recirculating the sinonasal mucus including any allergens, bacteria, or inflammatory mediators contained in the mucus. As the volume of mucus in the maxillary sinus accumulates, its viscosity increases, leading to elevated concentrations of inflammatory agents and pathogens within the mucus, sinus mucosal inflammation, and, ultimately, infection [151]. It is not clear if AMOs are due to a congenital defect in the fontanelles which are located in the medial maxillary sinus wall anterior and posterior to the inferior bony attachments of the uncinate process [152] or if they develop after recurrent infections perforate the fontanelle membranes [153, 154].

Environmental Agents Associated with RS

Microorganisms

Viral upper respiratory tract are among the most common risk factors for pediatric acute bacterial RS [155]. In fact, about to 5–10% of viral upper respiratory tract infections in children progress to acute bacterial RS [156]. Viral agents increased the susceptibility of infected sinonasal epithelial cells to bacterial infections by activating inflammatory mechanisms that disrupt mucociliary clearance. Viral infections are also associated with epithelial disruption, reduced numbers of ciliated cells, and increased numbers of goblet cells [157, 158] that increase the risk for secondary bacterial infection. Furthermore, they may predispose the sinonansal mucosa to secondary bacterial infections because of an increase in the adhesion of bacteria to the infected epithelial cells. Wang and colleagues reported an increased adhesion of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* on rhinovirus-infected nasal epithelial cells [159] in vitro. They hypothesized that the rhinovirus-infected nasal epithelial cells had an increased expression of host cell adhesion molecules, making these cells more susceptible to acute bacterial RS [159]. Infection with rhinovirus and colonization with *Moraxella*

catarrhalis were shown to have an increased risk for acute bacterial RS in a recent prospective study of young children with upper respiratory tract infections [160].

The most frequently isolated bacteria from maxillary sinus taps obtained over 35 years ago on children with radiographic maxillary sinus opacification were *Streptococcus pneumoniae* (30%), *Haemophilus influenzae* (20%), and *Moraxella catarrhalis* (20%). Another 25–30% of the maxillary sinus aspirates were sterile [161, 162]. Recent data on the bacteriology of acute RS is limited although several studies performed since then confirmed that *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, and anaerobes are the most common pathogens seen in pediatric acute RS [1, 163]. Estimates of acute pediatric RS microbiology have also been extrapolated from those of acute otitis media [3]. Using this data, and assuming 25% of the maxillary sinus aspirates to be sterile, the current bacteriology of acute pediatric RS would compromise of *Streptococcus pneumoniae* (30%), *Haemophilus influenzae* (20%), and *Moraxella catarrhalis* (10%) [3].

One limitation of using the acute otitis media data to extrapolate estimates of acute pediatric RS is that with the introduction of the heptavalent pneumococcal conjugate vaccine (PCV7), the acute otitis media visit rate has decreased compared to that of the acute RS visit rate. The latter has remained stable at 11–14 visits per 1000 children between 1998 and 2007 [164]. Although the rate of visit for acute RS has remained constant, the widespread use of PCV7 has resulted in changes in the pathogens causing acute maxillary sinusitis. The incidence *Streptococcus pneumonia* has decreased by 18% and the proportion of *Haemophilus influenzae* has increased by 8% in the 5 years after the introduction of PCV7 compared to the 5 previous years [165]. The incidence of *Moraxella catarrhalis* has remained unchanged (13–14%) [165].

Except for a rise in *Staphylococcus aureus* and anaerobic bacteria [2], the bacteriology of CRS has remained consistent over the past 2–3 decades. In 1991, Muntz and Lusk found the most common bacteria isolated from intraoperative pediatric ethmoid bullae specimens were alpha hemolytic *Streptococcus* and *Staphylococcus aureus*, followed by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis.* Anaerobes were present in 6% of the patients [166]. Hsin and colleagues isolated alpha hemolytic Streptococcus followed by *Haemophilus influenzae*, *Streptococcus pneumonia*, and *Staphylococcus aureus* in intraoperative specimens. In this study, anaerobes were found in 8% of the surgical specimens [167]. Between 1991 and 2010, several other studies have also been conducted that have not shown much change in the bacteriology of CRS [2].

Infection and Biofilm Formation

Bacterial biofilms are dynamic multimicrobial communities living within a protective complex self-produced extracellular matrix that become irreversibly attached to either inorganic or organic surfaces [168, 169]. Planktonic bacteria shed from the

biofilm intermittently and migrate to colonize other surfaces [170, 171]. Biofilm-associated bacteria have lower metabolic rates, have been linked to antibiotic resistance [172–174], and have been implicated in recurring infections [175, 176]. In children with pediatric CRS, adenoid samples collected at surgery had an average of 95% of the mucosal surface area covered with biofilm compared to 2% of adenoid surface from children with obstructive sleep apnea [137, 177]. It remains unclear, however, if the biofilms are directly involved with the disease process, or if they serve as a reservoir for infection that can be elicited by changes in the host environment [175, 176].

Tobacco Smoke Exposure

Environmental toxins, especially tobacco smoke, have been implicated in predisposing children to RS. Based on analyses from the 1970 National Health Interview Survey data, Bonham and Wilson [178] reported that children from families with active smokers have more episodes of acute respiratory illness including acute RS, than did children from families with nonsmoking adults. Similar results were found when comparing families in which 45 cigarettes or more were consumed daily to families with nonsmoking adults. In another of study of 76 children with acute RS (ages 4–18 years), 39 (51.3%) were exposed to secondhand smoke, and 2 of the patients (2.6%) were active smokers [130]. The findings from these two studies support the observation that exposure to active or passive tobacco smoke exposure predispose children to acute RS [130, 178]. Tobacco smoke exposure may result in acute RS, in part, due to changes in the normal nasopharyngeal bacterial flora after exposure to primary or second hand smoke exposure, resulting in increased colonization of potential pathogens [179]. Once the cigarette smoke exposure is eliminated, the nasopharyngeal bacterial flora reverts back to that found in nonsmokers [180].

The significance of tobacco smoke exposure in CRS is not entirely clear. Cigarette smoke has been reported to cause aberrations in airway secretions and ciliary beat frequency [181] and the induction of bacterial biofilms [182] associated with CRS. In addition, tobacco smoke produces ROS and reactive nitrogen species (RNS) that have been shown to induce pro-inflammatory cytokine secretion [182], epithelial apoptosis [183, 184], and impaired airway epithelial barrier function [185] in respiratory mucosa. The data from these investigations suggest that cigarette smoke is able to contribute to the damage in the respiratory epithelium and exacerbate inflammation in patients with CRS. However, it is uncertain if tobacco smoke exposure has a role in initiating CRS [1].

The pathogenesis of pediatric RS is complex and multifaceted, involving many physiological and pathophysiological mechanisms influenced by environmental agents, which makes this disease challenging to diagnose and manage. Future investigations will be needed to mitigate these challenges.

References

1. Fokkens WJ, Lund VJ, Mulliol J, Backert C, Alobid I, Baroody F, Cohen N. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2012;23:1–298.
2. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(S1):S22–209.
3. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, American Academy of Pediatrics. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):262–80.
4. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA. Infectious Diseases Society of America clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–112.
5. Brietzke SE, Shin JJ, Choi S, Lee JT, Peña M, Prager JD. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
6. Stevens WW, Lee RJ, Schleimer RP, Cohen NA. Chronic rhinosinusitis pathogenesis. J Allergy Clin Immunol. 2015;136:1442–53.
7. Cohen NA. Sinonasal mucociliary clearance in health and disease. Ann Otol Rhinol Laryngol Suppl. 2006;196:20–6.
8. Hertler MA, Mitchell RB, Lazar RH. Pathophysiology and etiology of pediatric rhinosinusitis. In: Younis RT, editor. Pediatric sinusitis and sinus surgery. New York: Taylor & Francis; 2006. p. 15–28.
9. Kern RC, Conley DB, Walsh W, Chandra R, Kato A, Tripathi-Peters A. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. Am J Rhinol. 2008;22(6): 549–59.
10. Groneberg DA, Peiser C, Dinh QT, Matthias J, Eynott PR, Heppt W, et al. Distribution of respiratory mucin proteins in human nasal mucosa. Laryngoscope. 2003;113:520–4.
11. Sanderson MJ, Sleigh MA. Ciliary activity of cultured rabbit tracheal epithelium: beat pattern and metachrony. J Cell Sci. 1981;47:331–47.
12. Stamberger H. Secretion and transportation. In: Hawke M, editor. Functional endoscopic sinus surgery. Philadelphia: Decker; 1991. p. 17–47.
13. Lee RJ, Foskett JK. Ca(2)(+) signaling and fluid secretion by secretory cells of the airway epithelium. Cell Calcium. 2014;55:325–36.
14. Ooi EH, Wormald PJ, Tan LW. Innate immunity in the paranasal sinuses: a review of nasal host defenses. Am J Rhinol. 2008;22:13–9.
15. Ramanathan M Jr, Lane AP. Innate immunity of the sinonasal cavity and its role in chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2007;136:348–56.
16. Parker D, Prince A. Innate immunity in the respiratory epithelium. Am J Respir Cell Mol Biol. 2011;45:189–201.
17. Sabroe I, Read RC, Whyte MK, Dockrell DH, Vogel SN, Dower SK. Toll-like receptors in health and disease: complex questions remain. J Immunol. 2003;171(4):1630–5.
18. Rose MC. Mucins: structure, function, and role in pulmonary diseases. Am J Phys. 1992;263:L413–29.
19. Lamblin G, Lhermitte M, Klein A, Houdret N, Scharfman A, Ramphal R. The carbohydrate diversity of human respiratory mucins: a protection of the underlying mucosa? Am Rev Respir Dis. 1991;144:S19–24.
20. Badr DT, Gaffin JM, Phipatanakul W. Pediatric rhinosinusitis. Curr Treat Options Allergy. 2016;3(3):268–81.
21. Wijkstrom-Frei C, El-Chemaly S, Ali-Rachedi R, Gerson C, Cobas MA, Forteza R, et al. Lactoperoxidase and human airway host defense. Am J Respir Cell Mol Biol. 2003;29:206–12.
22. Vareille M, Kieninger E, Edwards MR, Regamey N. The airway epithelium: soldier in the fight against respiratory viruses. Clin Microbiol Rev. 2011;24:210–29.

23. Yoon SS, Coakley R, Lau GW, Lymar SV, Gaston B, Karabulut AC, et al. Anaerobic killing of mucoid *Pseumonas aerginosa* by acified nitirite derivatives under cystic fibrosis airway conditions. J Clin Invest. 2006;116:436–46.
24. Major TA, Panmanee W, Mortensen JE, Gray LD, Hoglen N, Hassett DJ. Sodium nitrite-mediated killing of the major cystic fibrosis pathogens *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Burkholderia cepacia* under anaerobic planktonic and biofilm conditions. Antimicrob Agents Chemother. 2010;54:4671–7.
25. Jain B, Rubenstein I, Robbins RA, Leishe KL, Sisson JH. Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. Biochem Biophys Res Commun. 1993;191:83–8.
26. Akira S, Takedo K, Kaiho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immonol. 2001;2(8):675–80.
27. Hendrik HD, Raubenheimer EJ. The role of airway surface liquid in the primary management of rhinosinusitis. J Interdiscipl Med Dent Sci. 2013;1:1–3.
28. Buele AG. Physiology and pathophysiology of respiratory mucosa of the nasal and paranasal sinuses. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2010;9:1–24.
29. Furukawa CT. The role of allergy in sinusitis in children. J Allergy Clin Immunol. 1992;90(2 Pt 2):515–7.
30. Furukawa CT, Sharpe M, Bierman CW, et al. Allergic patients have more frequent sinus infections than non-allergic patients [Abstract]. J Allergy Clin Immunol. 1992;89:332.
31. Lin SW, Wang YH, Lee MY, Ku MS, Sun HL, Lu KH, et al. Clinical spectrum of acute rhinosinusitis among atopic and nonatopic children in Taiwan. Int J Pediatr Otorhinolaryngol. 2012;76(1):70–5.
32. Rachelefsky GS, Goldberg M, Katz RM. Sinus disease in children with respiratory allergy. J Clin Immunol. 1978;61:310.
33. Naclerio R, Blair C, Yu X, Won YS, Gabr U, Baroody FM. Allergic rhinitis augments the response to a bacterial sinus infection in mice: a review of an animal model. Am J Rhinol. 2006;20(5):525–33.
34. Blair C, Nelson M, Thompson K, Boonlayangoor S, Haney L, Gabr U, et al. Allergic inflammation enhances bacterial sinusitis in mice. J Allergy Clin Immunol. 2001;108(3):424–9.
35. Naclerio RM, Baroody FM. Other phenotypes and treatment of chronic rhinosinusitis. J Allergy Clin Immunol Pract. 2016;4(4):613–20.
36. Yu X, Sperling A, Blair C, Thompson K, Naclerio R. Antigen stimulation of TH2 cells augments acute bacterial sinusitis in mice. J Allergy Clin Immunol. 2004;114:328–34.
37. Tantimongkolsuk C, Pornrattanarungsee S, Chiewvit P, Visitsunthorn N, Ungkanont K, Vichyanond P. Pediatric sinusitis: symptom profiles with associated atopic conditions. J Med Assoc Thail. 2005;88(Suppl. 8):S149–55.
38. Poachanukoon O, Nanthapisal S, Chaumrattanatul U. Pediatric acute and chronic rhinosinusitis: comparison of clinical characteristics and out-come of treatment. Asian Pac J Allergy Immunol. 2012;30:134–51.
39. Sedaghar AR, Phipatanakul W, Cunningham MJ. Prevalence of and associations with allergic rhinitis in children with chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2014;78:343–7.
40. Leo G, Piacentini E, Incorvaia C, Consonni D, Frati F. Chronic rhinosinusitis and allergy. Pediatr Allergy Immunol. 2007;18(Suppl 18):19–21.
41. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the pediatric allergies in America survey. J Allergy Clin Immunol. 2009;124.(3 Suppl:S43–70.
42. Wright AL, Holberg CJ, Martinez FD, et al. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics. 1994;94(6Pt1):895–901.
43. Sedaghar AR, Phipatanakul W, Cunningham MJ. Atopy and the development of chronic rhinosinusitis in children with allergic rhinitis. J Allergy Clin Immunol Pract. 2013;1(6):689–91.
44. Mahdavinia M, Grammer LC. Chronic rhinosinusitis and age: is the pathogenesis different? Expert Rev Anti-Infect Ther. 2013;11(10):1029–40.
45. Goldenhersh MJ, Rachelefsky GS, Dudley J. The microbiology of chronic sinus disease in children is respiratory allergy. J Allery Clin Immunol. 1990;85:1030.

46. Tosca MA, Riccio AM, Marseglia GI, Caligo G, Pallestrini E, Ameli F. Nasal endoscopy in asthmatic children: assessment of rhinosinusitis and adenoiditis incidence, correlations with cytology and microbiology. Clin Exp Allergy. 2001;31:609–15.
47. Businco L, Fiore L, Frediani T, Artuso A, Di Fazio A, Bellioni P. Clinical and therapeutic aspects of sinusitis in children with bronchial asthma. Int J Pediatr Otorhinolaryngol. 1981;3:287–94.
48. Oliveira C, Sole D. Improvement of bronchial hyperresponsiveness in asthmatic children treated for concomitant sinusitis. Ann Allergy Asthma Immunol. 1997;79:70–4.
49. Tosca MA, Cosentino C, Pallestrini E, Caligo G, Milanese M, Ciprandi G. Improvement of clinical and immunopathologic parameters in asthmatic children treated for concomitant chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2003;91:71–8.
50. Rachelefsky G, Katz R, Siegel SC. Chronic sinus disease with associated reactive airway disease in children. Pediatrics. 1984;73:526–9.
51. Parsons D, Phillips S. Functional endoscopic surgery in children. Laryngoscope. 1993;103:899–903.
52. Manning SC, Wasserman RL, Silver R, Phillips DL. Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma. Arch Otolaryngol Head Neck Surg. 1994;120(10):1142–5.
53. Anfuso A, Ramadan H, Terrel A, Demirdag Y, Walton C, Skoner DP. Sinus and adenoid inflammation in children with chronic rhinosinusitis and asthma. Ann Allergy Asthma Immunol. 2015;114:103–10.
54. Marney SR. Pathophysiology of reactive airway disease and sinusitis. Ann Otol Rhinol Laryngol. 1996;105:98–100.
55. Campanella SG, Asher MI. Current controversies: sinus disease and the lower airways. Pediatr Pulmonol. 2001;31:165–72.
56. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics. 1991;87(3):311–6.
57. Costa Carvalho BT, Nagao AT, Arslanian C, et al. Immunological evaluation of allergic respiratory children with recurrent sinusitis. Pediatr Allergy Immunol. 2005;16:534–8.
58. Javier FC III, Moore CM, Sorensen RU. Distribution of primary immunodeficiency diseases diagnosed in a pediatric tertiary hospital. Ann Allergy Asthma Immunol. 2000;84:25–30.
59. Hidalgo H, Moore C, Leiva LE, Sorensen RU. Preimmunization and postimmunization antibody titers pneumococcal in children with recurrent infections. Ann Allergy Asthma Immunol. 1996;76:431–6.
60. Rose MC, Voynow JA. Respiratory tract mucin genes and mucin glycoproteins in health and disease. Physiol Rev. 2006;86:245–78.
61. Peña MT, Aujla PK, Zudaire E, Watson A, Przygodski R, Zalzal G, Rose MC. Localization and expression of MUC 5B and MUC7 mucins in pediatric sinus mucosa. Ann Otol Rhinol Laryngol. 2007;116(5):389–97.
62. Saieg A, Brown KJ, Peña MT, Rose MC, Preciado D. Proteomic analysis of pdiatric sinonasal secretions shows increased MUC 5B mucins in CRS. Pediatr Res. 2015;77(2):356–62.
63. 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.
64. 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.
65. Schleimer RP, Kato A, Peters A. Epithelium, inflammation, and immunity in the upper airways of humans: studies in chronic rhinosinusitis. Proc Am Thorac Soc. 2009;6(3):288–94.
66. Wu X, Ghimbovschi S, Ajula P, Rose MC, Peña MT. Expressing array profiling of inflammatory mediators in pediatric sinus mucosa. Arch Otolaryngol Head Neck Surg. 2009;135(1):65–72.
67. Wu X, Mimms R, Lima R, Peters-Hall J, Rose MC, Peña MT. Localization of inflammatory mediators in pediatric sinus mucosa. Arch Otolaryngol Head Neck Surg. 2012;138(4):389–97.
68. Ansel KM, Harris RB, Cyster JG. CXCL13 is required for B1 homing, natural antibody production, and body cavity immunity. Immunity. 2002;16(1):67–76.

69. Patadia M, Dixon J, Conley D, et al. Evaluation of the presence of B cell attractant chemokines in chronic rhinosinusitis. Am J Rhinol Allergy. 2010;24(1):11–6.
70. Sache F, von Eiff C, Stoll W, Becker K, Rudack C. Induction of CXC chemokines in A549 airway epithelial cells by trypsin and staphylococcal proteases: a possible route for neutrophilic inflammation in chronic rhinosinusitis. Clin Exp Immunol. 2006;144(3):534–42.
71. Wilschanski M, Ziclenski J, Markiewicz D. Correlation of sweat chloride concentration with classes of the cystic fibrosis transmembrane conductance regulator gene mutations. J Pediatr. 1995;I(27):705–10.
72. Rowe-Jones J, MacKay IS. Endoscopic sinus surgery in the treatment of cystic fibrosis with nasal polyposis. Laryngoscope. 1996;106:1540–4.
73. Rutland J, Cole P. Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. Thorax. 1981;36:654–8.
74. Bonestroo HJ, de Winter-de Groot KM, van der Ent CK, Arets HG. Upper and lower airway cultures in with children cystic fibrosis: do not neglect the upper airways. J Cyst Fibros. 2010;9(2):130–4.
75. Wilson R, Pitt T, Taylor G, Watson D, MacDermot J, Sykes D, et al. Pyocyanin and 1-hydroxyphenazine produced by *Pseudomonas aeruginosa* inhibit the beating of human respiratory cilia in vitro. J Clin Invest. 1987;79:221–9.
76. Zhao KQ, Goldstein N, Yang H, Cowan AT, Chen B, Zheng C, et al. Inherent differences in nasal and tracheal ciliary function in response to Pseudomonas aeruginosa challenge. Am J Rhinol Allergy. 2011;25:209–13.
77. Shen JC, Cope E, Chen B, Leid JG, Cohen NA. Regulation of murine sinonasal cilia function by microbial secreted factors. Int Forum Allergy Rhinol. 2012;2:104–10.
78. Amitani R, Taylor G, Elezis EN, Llewellyn-Jones C, Mitchell J, Kuze F, et al. Purification and characterization of factors produced by Aspergillus fumigatus which affect human ciliated respiratory epithelium. Infect Immun. 1995;63:3266–71.
79. Gysin C, Alothman GA, Papsin BC. Sinonasal disease in cystic fibrosis: clinical characteristics, diagnosis and management. Pediatr Pulmonol. 2000;30:481–9.
80. Tandon R, Derkay C. Contemporary management of rhinosinusitis and cystic fibrosis. Curr Opin Otolaryngol Head Neck Surg. 2003;11(1):41–4.
81. Blount A, Zhang S, Chestnut M, Hixon B, Skinner D, Sorscher EJ, et al. Transepithelial ion transport is suppressed in hypoxic sinonasal epithelium. Laryngoscope. 2011;121:1929–34.
82. Babinski D, Trawinske-Bartnicka M. Rhinosinusitis in cystic fibrosis: not a simple story. Int J Pediatr Otorhinolaryngol. 2008;72(5):619–24.
83. Drake-Lee AB, Morgan DW. Nasal polyps and sinusitis in children with cystic fibrosis. J Laryngol Otol. 1998;103(8):753–5.
84. Woodsworth BA, Ahn C, Flume PA, Sclosser RJ. The delta F508 mutation in cystic fibrosis and impact on sinus development. Am J Rhinol. 2007;21(1):122–7.
85. April MM, Tunkel DE, DeCelie-Germana J, Zeitlin PL, Zinreich SJ. Computed tomography (CT) scan findings of the paranasal sinuses in cystic fibrosis. Am J Rhinol. 1995;9(5):277–80.
86. Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus disease by measurement of inflammatory mediators. Allergy. 2006;61:1280–9.
87. Claeys S, Van Hoecke H, Holtappels G, et al. Nasal polyps in patients with and without cystic fibrosis: a differentiation by innate markers and inflammatory mediators. Clin Exp Allergy. 2005;35:467–77.
88. Woodsworth BA, Lathers D, Neal JG, et al. Immunolocalization of surfactant protein A and D in sinonasal mucosa. Am J Rhinol. 2006;20:461–5.
89. Woodsworth BA, Neal JG, Newton D, et al. Surfactant protein A and D in human sinus mucosa: a preliminary report. ORL J Otorhinolaryngol Relat Spec. 2007;69:57–60.
90. Woodsworth BA, Wood R, Baatz JE, Schlosser RJ. Sinonasal surfactant A1, A2, and D gene expression in CF: a preliminary report. Otolaryngol Head Neck Surg. 2007;137:34–8.
91. Woodsworth BA, Wood R, Bhargave G, et al. Surfactant protein B detection and gene expression in chronic rhinosinusitis. Laryngoscope. 2007;117:1296–301.

92. Rampey AM, Lathers DM, Woodworth BA, Schlosser RJ. Immunolocalization of dendritic cells and pattern recognition receptors in chronic rhinosinusitis. Am J Rhinol. 2007;21:117–21.
93. Raoust E, Balloy V, Garcia-Verdugo I, et al. Pseudomonas aeruginosa LPS or flagellin are sufficient to activate TLR-dependent signaling in murine alveolar macrophages and airway epithelial cells. PLoS One. 2009;4:e7259.
94. Laube DM, Yim S, Ryan LK, et al. Antimicrobial peptides in the airway. Curr Top Microbiol Immunol. 2006;306:153–82.
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;185:944–54.
96. Settipane GA. Epidemiology of nasal polyps. Allergy Asthma Proc. 1996;17(5):231–6.
97. Chmielik M, Wasiutnyski A, Maldyk J, Wachulski B, Bartoszek D. Histological analysis of nasal polyps in children. Int J Pediatr Otorhinolaryngol. 2001;60(2):131–3.
98. Ameratunga R, Randall N, Dalziel S, Anderson BJ. Samter's triad in childhood: a warning for those prescribing NSAIDs. Paediatr Anaesth. 2013;23(8):757–9.
99. Triglia JM, Nicollas R. Nasal and sinus polyposis in children. Laryngoscope. 1997;107(7):963–6.
100. Wolf G, Greistorfer K, Jebeles JA. The endoscopic endonasal surgical technique in the treatment of chronic recurring sinusitis in children. Rhinology. 1995;33(2):97–103.
101. Hu KH, Lee FP, Cheng YJ, Huang HM. Vascular endothelial growth factor and children featuring nasal polyps. Int J Pediatr Otorhinolaryngol. 2007;71(1):23–8.
102. Dykewicz MS, Hamilos DL. Rhinitis and sinusitis. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S103–15.
103. Kuhn FA, Swain RE. Allergic fungal sinusitis: diagnosis and treatment. Curr Opin Otolaryngol Head Neck Surg. 2003;11:1–5.
104. McClay JE, Marple B, Kapadia L, Biavati MJ, Nussenbaum B, et al. Clinical presentation of allergic fungal sinusitis in children. Laryngoscope. 2002;112:565–9.
105. Al-Swiahb JN, Al-Ammar A, Al-Dousary SH. Allergic fungal sinusitis in children in Saudi Arabia. Saudi Med J. 2007;28:1711–4.
106. Campbell JM, Graham JM, Gray HC, Bower C, Blaiss MS, et al. Allergic fungal sinusitis in children. Ann Allergy Asthma Immunol. 2006;96:286–90.
107. Gupta AK, Bansal S, Gupta A, Mathur N. Is fungal infestation of paranasal sinuses more aggressive in pediatric population? Int J Pediatr Otorhinolaryngol. 2006;70:603–8.
108. Gupta AK, Ghosh AK, et al. Sinonasal aspergillosis in immunocompetent Indian children: an eight-year experience. Mycoses. 2003;46:455–61.
109. Sui W, Hou X, Che W, et al. CCDC40 mutation as a cause of primary ciliary dyskinesia: a case report and review of literature. Clin Respir J. 2016;10(5):614–21.
110. Kurkowiak M, Zietkiewicz E, Witt M. Recent advances in primary ciliary dyskinesia genetics. J Med Genet. 2015;52:1–9.
111. Bush A, Chodhari R, Collins N, et al. Primary ciliary dyskinesia: current state of the art. Arch Dis Child. 2007;92:1136–40.
112. Josephson GD, Patel S, Duckworth L, Goldstein J. High yield technique to diagnose immotile cilia syndrome: a suggested algorithm. Laryngoscope. 2010;120(Suppl4): S240.
113. Rollin M, Seymour K, Hariri M, Harcourt J. Rhinosinusitis, symptomatology and absence of polyposis in children with primary ciliary dyskinesia. Rhinology. 2009;47:75–8.
114. Holzmann D, Ott PM, Felix H. Diagnostic approach to primary ciliary dyskinesia: a review. Eur J Pediatr. 2000;159(1–2):95–8.
115. Mener DJ, Lin SY, Ishman SL, Boss EF. Treatment and outcomes of chronic rhinosinusitis in children with primary ciliary dyskinesia: where is the evidence? A qualitative systematic review. Int Forum Allergy Rhinol. 2013;3:986–91.
116. Sleigh MA. Primary ciliary dyskinesia. Lancet. 1981;2:476.

117. Knowles MR, Daniels LA, Davis SD, et al. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. Am J Respir Crit Care Med. 2013;188:913–22.
118. Werner C, Onnebrink JG, Omran H. Diagnosis and management of primary ciliary dyskinesia. Cilia. 2015;4:2.
119. Barbato A, Frischer T, Kuehni CE, et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. Eur Respir J. 2009;34:1264–76.
120. Lucas JS, Leigh MW. Diagnosis of primary ciliary dyskinesia: searching for a gold standard. Eur Respir J. 2014;44:1418–22.
121. Hosie PH, Fitzgerald DA, Jaffe A, Birman CS, Rutland J, Morgan LC. Presentation of primary ciliary dyskinesia in children: 30 years' experience. J Paediatr Child Health. 2015;51: 722–6.
122. Gilger MA. Pediatric otolaryngologic manifestations of gastroesophageal reflux disease. Curr Gastroenterol Rep. 2003;5(3):247–52.
123. Contencin P, Maurage C, Ployet MJ, Seid AB, Sinaasappel M. Gastroesophageal reflux and ENT disorders in childhood. Int J Pediatr Otorhinolaryngol. 1995;32.(Suppl:S135–44.
124. Phipps CD, Wood WE, Gibson WS, Cochran WJ. Gastroesophageal reflux contributing to chronic sinus disease in children: a prospective analysis. Arch Otolaryngol Head Neck Surg. 2000;126(7):831–6.
125. El-Serag HB, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. Gastroenterology. 2001;121(6):1294–9.
126. Bothwell MR, Parsons DS, Talbot A, Barbero GJ, Wilder B. Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngol Head Neck Surg. 1999;121(3):255–62.
127. Sivasli E, Sirikci A, Bayazyt YA, Gumusburun E, Erbagci H, Bayram M, et al. Anatomic variations of the paranasal sinus area in pediatric patients with chronic sinusitis. Surg Radiol Anat. 2003;24(6):400–5.
128. 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.
129. 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.
130. Eyigor H, Basak S. Evaluation of predisposing factors and bacteriologic agents in pediatric rhinosinusitis. Kulak Burun Bogaz Ihtis Derg. 2005;15(3–4):49–55.
131. Willner A, Choi SS, Vezina LG, Lazar RH. Intanasal anatomic variations in pediatric simusitis. Am J Rhinol. 1997;11:355–60.
132. 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.
133. Lee D, Rosenfeld RM. Adenoid bacteriology and sinonasal symptoms in children. Otolaryngol Head Neck Surg. 1997;116:301–7.
134. Bercin AS, Ural A, Kurluhan A, Yurtas V. Relationship between sinusitis and adenoid size in pediatric age group. Ann Otol Rhinol Laryngol. 2007;116:550–3.
135. Shin KS, Cho SH, Kim KR, et al. The role of adenoids in pediatric rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2008;72:1643–50.
136. 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.
137. 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;133:110–4.
138. Eun YG, Park DC, Kim SG, Kim MG, Yeo SG. Immunoglobulins and transcription factors in adenoids of children with otitis media with effusion and chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2009;73:1412–6.

139. Shin SY, Choi GS, Park HS, Lee KH, Kim SW, Cho JS. Immunological investigation in the adenoid tissues from children with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2009;141(1):91–106.
140. Marseglia GI, Pagella F, Klersey C, et al. The 10 day mark is a good way to diagnose not only acute rhinosinusitis but also adenoiditis, as confirmed by endoscopy. Int J Pediatr Otorhinolaryngol. 2007;71:581–3.
141. Bhattacharyya N, Jones DT, Hill M, Shapiro NL. The diagnostic accuracy of computed tomography in pediatric age group. Ann Otol Rhinol Laryngol. 2004;130:1029–32.
142. Wald ER. Epidemiology, pathophysiology, and etiology of sinusitis. Pediatr Infect Dis J. 1985;4(suppl 6):551–4.
143. Wang DY, Wardani RS, Singh K, Thanaviratananich S, Vicente G, Xu G, et al. A survey on the management of acute rhinosinusitis among Asian physicians. Rhinology. 2011;49(3): 264–71.
144. Wilson R, Sykes DA, Currie D, Cole PJ. Beat frequency of cilia from sites of purulent infections. Thorax. 1986;41:453–8.
145. Rutland J, Cox T, Dewar A, Cole P, Warner JO. Transitory ultrastructural abnormalities of cilia. Br J Dis Chest. 1982;76:185–8.
146. Carson JL, Collier AM, S-CS H. Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. N Engl J Med. 1985;312:463–8.
147. Greenstone M, Cole PJ. Ciliary function in health and disease. Br J Dis Chest. 1985;79:9–26.
148. Greenstone MA, Dewar A, Cole PJ. Ciliary dyskinesia with normal ultrastructure. Thorax. 1983;38:875–6.
149. Gudis D, Zhao KQ, Cohen NA. Acquired cilia dysfunction in chronic rhinosinusitis. Am J Rhinol Allergy. 2012;26:1–6.
150. Vlastos I, Athanasopoulos I, Mastronikolis NS, Panogeorgou T, Margaritis V, Naxakis S, et al. Impaired mucociliary clearance in allergic rhinitis patients is related to a predisposition to rhinosinusitis. Ear Nose Throat J. 2009;88(4):E17–9.
151. Matthews BL, Burke AJ. Recirculation of mucus via accessory ostia causing chronic maxillary sinus disease. Otolaryngol Head Neck Surg. 1997;117:422–3.
152. Kuma RH, Choudhr YR, Kaka RS. Accessory maxillary ostia: topography and clinical application. J Anat Soc India. 2001;50:3–5.
153. Chung SK, Dhong HJ, Na DG. Mucus circulation between accessory ostium and natural ostium of maxillary sinus. J Laryngol Otol. 1999;113:865–7.
154. Genc S, Ozcan M, Titiz A, Unal A. Development of maxillary accessory ostium following sinusitis in rabbits. Rhinology. 2008;46:121–4.
155. Wald ER. Diagnosis and management of acute sinusitis. Pediatr Ann. 1988;17:269–638.
156. Wald ER. Sinusitis in children. N Engl J Med. 1992;326:319–23.
157. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 2004;130(1 Suppl):1–45.
158. Lund VJ. Therapeutic targets in rhinosinusitis: infection or inflammation? Medscape J Med. 2008;10(4):105.
159. Wang JH, Kwon HJ, Jang YJ. Rhinovirus enhances various bacterial adhesions to nasal epithelial cells simultaneously. Laryngoscope. 2009;119(7):1406–11.
160. Marom T, Alvarez-Fernandez PE, Jennings K, Patel JA, McCormick DP, Chonmaitree T. Acute bacterial sinusitis complicating viral upper respiratory tract infection in young children. Pediatr Infect Dis J. 2014;33(8):803–8.
161. Wald ER, Milmoe GJ, Bowen A, et al. Acute maxillary sinusitis in children. N Engl J Med. 1981;304:749–54.
162. 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.
163. Wang DY, Wardani RS, Singh K, Thanaviratananich S, Vincente G, Xu G, et al. A survery on the management of acute rhinosinusitis among Asian physicians. Rhinology. 2011;49(3):264–71.

164. Shapiro DJ, Gonzalez R, Cabana MD, Hersh AI. National trends in visit rates and antibiotic prescribing for children with acute sinusitis. Pediatrics. 2011;127:28–34.
165. Brook I, Gober AE. Frequency of recovery of pathogens from the nasopharynx of children with acute maxillary sinusitis before and after the introduction of vaccination with the 7-valent pneumococcal vaccine. Int J Pediatr Otorhinolaryngol. 2007;71(4):575–9.
166. Muntz HR, Lusk RP. Bacteriology of the ethmoid bullae in children with chronic sinusitis. Arch Otolaryngol Head Neck Surg. 1991;117:179–81.
167. Hsin CH, Su MC, Tsao CH, et al. Bacteriology and antimicrobial susceptibility of pediatric chronic rhinosinusitis: a 6-year result of maxillary sinus punctures. Am J Otolaryngol. 2010;31:145–9.
168. Nazzari E, Torretta S, Pignataro L, Marchisio P, Esposito S. Role of biofilms in children with upper respiratory tract infections. Eur J Clin Microbiol Infect Dis. 2015;34:421–9.
169. Madeo J, Frieri M. Bacterial biofilms and chronic rhinosinusitis. Allergy Asthma Proc. 2013;34(4):335–41.
170. Zulandi G, Carlisle M, Duberstein A, Haupert M, Syamal M, Berk R, et al. Biofilm density in the nasopharynx: recurrent otitis media versus obstructive sleep apnea. Ann Otol Rhinol Laryngol. 2009;118(7):519–24.
171. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284:1318–22.
172. Davies D. Understanding biofilm resistance to antimicrobial agents. Nat Rev Drug Discov. 2003;2:114–22.
173. Vlastarakos PV, Nikolopoulos TP, Maragoudakis P, Tzagaroulakis A, Ferekidis E. Biofilms in ear, nose, and throat infections: how important are they? Laryngoscope. 2007;117:668–73.
174. Pettigrew MM, Gent JF, Revai K, Patel JA, Chonmaitree T. Microbial interactions during upper respiratory tract infections. Emerg Infect Dis. 2008;14:1584–91.
175. Sanchez CJ, Kumar N, Lizcano A, Shivshankar P, Dunning Hotopp JC, Jorgensen JH, Tettelin H, Orihuela CJ. *Streptococcus pneumonia* in biofilms are unable to cause invasive disease due to altered virulence determinant production. PLoS One. 2011;16:e28738.
176. Weimer KE, Armbruster CE, Juneau RA, Hong W, Pang B, Swords WE. Coinfection with *Haemophilus influenza* promotes pneumococcal biofilm formation during experimental otitis media and impedes the progression of pneumococcal disease. J Infect Dis. 2010;202:1068–75.
177. Zuliani G, Carron M, Gurrola J, Colean C, Haupert M, Berk R, Coticchia J. Identification of adenoid biofilms in chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2006;70:1613–7.
178. Bonham GS, Wilson RW. Children's health in families with cigarette smokers. Am J Public Health. 1981;71(3):290–3.
179. Brook I. Effects of smoking on the microbial flora of children and their parents. Int J Pediatr Otorhinolaryngol. 2010;74(5):447–50.
180. Brook I, Grober AE. Effect of smoking cessation on the microbial flora. Arch Otolaryngol Head Neck Surg. 2007;133(2):135–8.
181. Cohen NA, Zhang S, Sharp DB, Tamashiro E, Chen B, Sorscher EJ, Woodworth BA. Cigarette smoke condensate inhibits transepithelial chloride transport and ciliary beat frequency. Laryngoscope. 2009;119(11):2269–74.
182. Goldstein-Daruech N, Cope EK, Zhao KQ, Vukovic K, Kofonow JM, Doghrahji L, et al. Tobacco smoke mediated induction of sinonasal microbial biofilms. PLoS One. 2011;6(1):e15700.
183. Misso NL, Thompson PJ. Oxidative stress and antioxidant deficiencies in asthma: potential modifications by diet. Redox Rep. 2005;10(5):247–55.
184. Comhair SA, Bhathena PR, Farver C, Thunnissen FB, Erzurum SC. Extracellular glutathione peroxidase induction in asthmatic lungs evidence for redox regulation of expression in human airway epithelial cells. FASEB J. 2001;15(1):70–8.
185. Xiao C, Puddicombe SM, Field S, Haywood J, Broughton-Head V, Puxeddu I, et al. Defective epithelial barrier function in asthma. J Allergy Clin Immunol. 2011;128(3):549–56.

Chapter 4
Imaging in Pediatric Rhinosinusitis

Phillip R. Purnell, Abdul Rahman Tarabishy, and Johnathan E. Castaño

Introduction

The American Academy of Pediatrics (AAP) defines acute rhinosinusitis (ARS) as symptoms of rhinorrhea, obstruction, cough, and facial pressure lasting less than 30 days. The term "rhinosinusitis" is preferred to "sinusitis," since sinus inflammation is almost universally associated with nasal inflammation; however, the two terms are often used interchangeably. Chronic rhinosinusitis (CRS) lasts >90 days and is defined by persistent residual respiratory symptoms of cough, rhinorrhea, or nasal obstruction. In patients with recurrent or chronic rhinosinusitis, one must consider comorbidities and potential underlying causes such as asthma, allergic rhinitis, gastroesophageal reflux, immune deficiencies, or cystic fibrosis. Imaging has been an important tool in the clinical diagnosis of pediatric rhinosinusitis. Although guidelines regarding imaging are clear with complicated disease, the role for imaging in subacute and chronic rhinosinusitis are less clear.

Responsible Use of Radiation

With the continued increase in availability and application of different imaging modalities, utilization of imaging has increased in pediatric patients. This has resulted in significant ionizing radiation exposure [1]. This risk is mostly raised by

P. R. Purnell · J. E. Castaño (✉)
Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA
e-mail: jecastano@hsc.wvu.edu

A. R. Tarabishy
Department of Radiology, Department of Interventional Neuroradiology, West Virginia University School of Medicine, Morgantown, WV, USA

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_4

Table 4.1 Indications for imaging in pediatric sinusitis and relative radiation exposure for children with persistent sinusitis (worsening course or severe presentation, or not responding to treatment), or recurrent sinusitis, or chronic sinusitis, or define paranasal sinus anatomy before functional endoscopic sinus surgery. Initial imaging

Procedure	Appropriateness category	Relative radiation level
CT paranasal sinuses without IV contrast	Usually appropriate	☢☢☢
CT paranasal sinuses with IV contrast	Usually not appropriate	☢☢☢
CT paranasal sinuses without and with IV contrast	Usually not appropriate	☢☢☢☢
MRI paranasal sinuses without and with IV contrast	Usually not appropriate	O
MRI paranasal sinuses without IV contrast	Usually not appropriate	O
X-ray paranasal sinuses	Usually not appropriate	☢

overutilization of CT, especially in pediatric patients, where the radiation exposure may be as high as ten times of the per weight dose received. Thus, adherence to the principle of "as low as reasonably achievable" (ALARA) represents a practice mandate that minimizes ionizing radiation exposure while optimizing imaging results[1]. Multiple medical societies have developed practice guidelines and recommendations to guide clinicians in management and ordering of the appropriate imaging [2, 3]. The American Academy of Pediatrics (AAP) has developed a clinical practice guideline regarding the diagnosis and management of acute bacterial rhinosinusitis in children and adolescents [3]. This group suggests "clinicians should not obtain imaging studies (plain films, contrast-enhanced computed tomography [CT], MRI, or ultrasonography) to distinguish acute bacterial sinusitis from viral URI" (Evidence Quality: B; Strong Recommendation) [3]. The American College of Radiology (ACR) has issued appropriateness criteria for each imaging modality ordered to guide clinicians to the best imaging test for a certain clinical scenario [2]. It also references the relative radiation level exposures for these imaging procedures. Adopted from the ACR is Table 4.1 for which a CT sinus without contrast is the only listed appropriate exam for persistent or recurrent rhinosinusitis in pediatric patients. Both of these guidelines emphasize that imaging abnormalities alone are not sufficient for the diagnosis of acute rhinosinusitis as opacification of the paranasal sinuses is often present in healthy children or in children having a computed tomography (CT) scan for other reasons.

Sinus Development and Anatomical Abnormalities

Both the ethmoid and maxillary sinuses are present at birth with continued development with age. A normal appearing pediatric CT is shown and labeled in Fig. 4.1 with axial, coronal, and sagittal views. The ethmoid sinuses are present at birth and

grow into puberty. There are several important anatomical variants which result from development of air cells into adjacent sinuses and surrounding structures [4]. The concha bullosa is an extension ethmoid aeration to the middle turbinate (Fig. 4.2). This structure can be obstructing when large and can also have disease of the internal mucosa [5]. Extension of the ethmoid aeration anteriorly results in the agger nasi cell which can impede on the frontal sinus outflow tract. When ethmoid aeration occurs laterally and infraorbitally, development of Haller cells will occur (Fig. 4.3). The maxillary sinus reaches adult size at about age 12 [6]. Pneumatization of the sinuses and their growth mirrors development of the maxilla. Aplasia and hypoplasia of the maxillary sinus is rare but can be misdiagnosed as sinus opacification [7]. The sphenoid sinus is not pneumatized at birth and continues to grow into

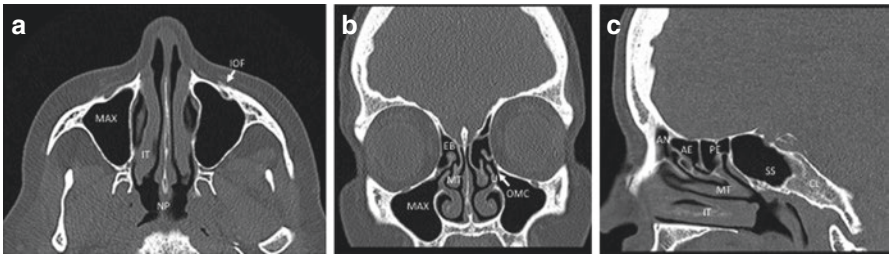


Fig. 4.1 Normal pediatric sinus CT. (**a**) Axial (MAX, maxillary sinus; IT, inferior turbinate; NP, nasopharynx; IOF, infraorbital foramen). (**b**) Coronal (MAX, maxillary sinus; MT, middle turbinate; EB, ethmoid bulla; U, uncinate; OMC, osteomeatal complex). (**c**) Sagittal (AN, agger nasi cell; AE, anterior ethmoid cells; PE, posterior ethmoid cells; SS, sphenoid sinus; CL, clivus; MT, middle turbinate; IT, inferior turbinate)

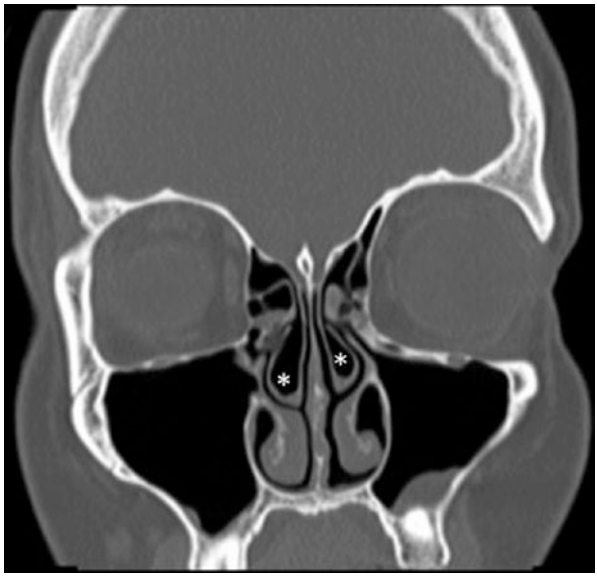


Fig. 4.2 Coronal CT with bone windowing demonstrating air-filled middle turbinates typical of concha bullosa (asterisks)

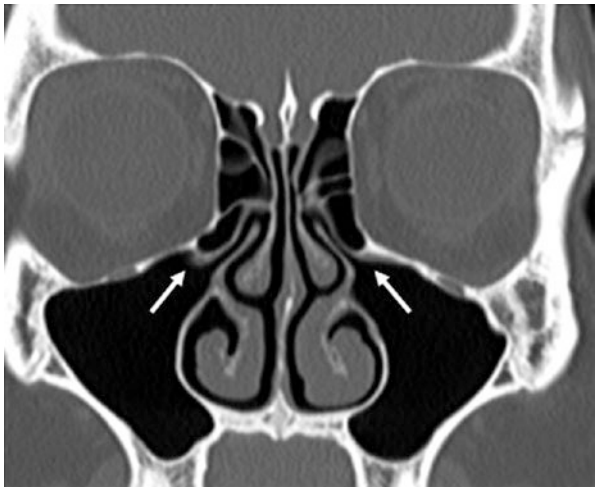


Fig. 4.3 Coronal CT image demonstrates nonopacified Haller air cell (arrows) with bilateral narrowing of the osteomeatal units

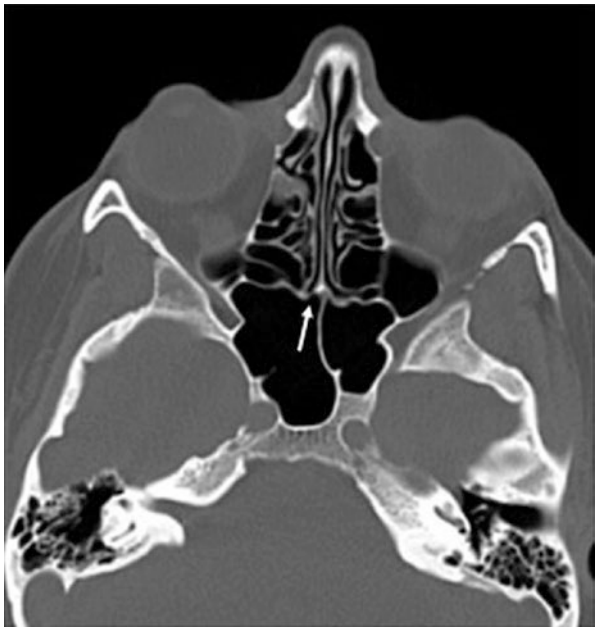


Fig. 4.4 Axial CT image demonstrating the right sphenoid sinus ostium area (arrow)

adolescence. The natural drainage ostium at the anterior face of the sphenoid usually drains medially to the posterior end of the superior turbinate (Fig. 4.4) [8]. The Onodi cell is the extension of the ethmoid sinuses superiorly and laterally to the sphenoid sinus in close approximation to the optic nerve (Fig. 4.5). The frontal sinus develops from pneumatization of the frontal bone and is the last sinus to develop. An aplastic frontal sinus is not uncommon. The frontal sinus resembles a funnel in the sagittal plane with the narrowest point at the natural ostium, also known as the

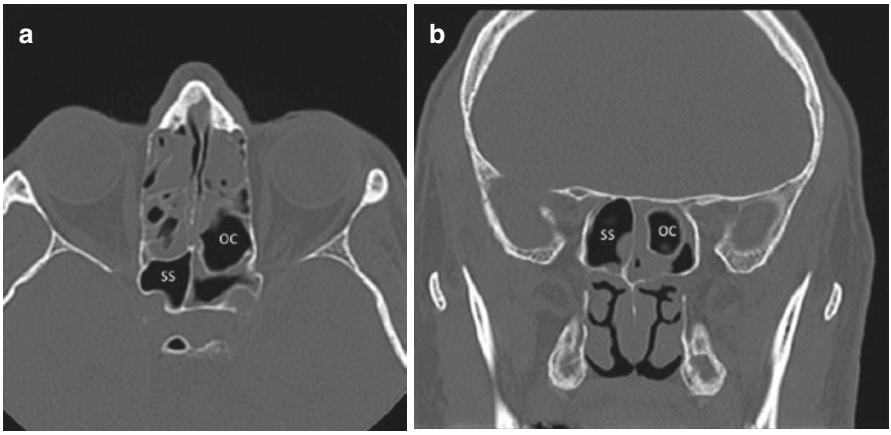


Fig. 4.5 Onodi cell. (**a**) Axial CT, (**b**) coronal CT (SS, sphenoid sinus; OC, Onodi cell)

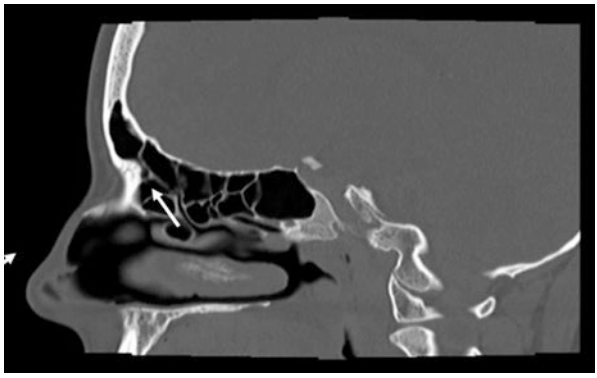


Fig. 4.6 Sagittal CT image demonstrating the frontal sinus outflow tract (arrow)

frontal recess (Fig. 4.6). The boundaries of the frontal recess are the agger nasi cell anteriorly, the lamella of the ethmoid bulla posteriorly, the orbit laterally, and the middle turbinate medially. The drainage of the frontal sinus can be obstructed by an enlarged or diseased ethmoid bulla, suprabullar cell, or agger nasi cell.

Imaging Modalities for Sinus Disease

Sinus disease is exceedingly common in patients imaged for any reason. Studies have demonstrated that >50% of adult patients with viral upper respiratory tract infection (URTI) have abnormal maxillary sinus radiographs [9]. It is not uncommon to see opacification of multiple sinuses and air-fluid levels in those with uncomplicated acute viral infection [9]. In children with MRI obtained for other neurologic indications, the prevalence of imaging abnormalities of the sinuses on

MRI was 45% [10]. Additionally, a different disease pattern has been identified in pediatric patients with sphenoid and posterior ethmoid abnormalities identified more commonly versus maxillary sinus abnormalities in adults with acute rhinosinusitis [10]. In a study investing the impact of uncomplicated URTI, MRI scans were obtained in 60 children (average age 5.7 years) within 6 days of onset of URTI symptoms [11]. Sixty percent of children had maxillary or ethmoid abnormalities, with 35% in the sphenoid, and 18% in the frontal sinus. The MRI correlated well with symptoms, and when a second MRI on 26 of the children was completed, MRI findings were improved regardless of current clinical symptoms. This same group also showed that 68% of symptomatic children with URTI and 42% of healthy children had significant sinus abnormalities on MRI [11]. The incidence of sinus abnormalities is even higher in very young patient populations and reaches nearly 100% in a study of infants who had a cold in the 2 weeks preceding a head CT obtained for other reasons [12]. Although those pediatric patients who are asymptomatic may have imaging changes, there is also significant evidence that imaging findings correlate with clinical signs and symptoms. Manning et al. had pediatric patients undergoing imaging for *non-sinus* reasons examined with rhinoscopy in addition to symptom collection from patients just before imaging [13]. Forty-seven percent of these patients had sinus abnormalities. There was a correlation between the presence of respiratory symptoms and imaging, and this group suggests that sinus abnormalities on imaging reflect ongoing or resolving URTI or allergic inflammation, and not necessarily rhinosinusitis [13]. It is imperative to remember that abnormalities on sinus CT or MRI are exceedingly common in pediatric patients and unless obtained for surgical planning, interpretation as an incidental finding should be taken with caution.

Imaging Signs of Rhinosinusitis

An air-fluid level is the most typical imaging finding; however, it is only present in 25–50% of patients with acute rhinosinusitis [14]. Figure 4.7 shows a Waters' view sinus X-ray with an air-fluid level in the maxillary sinus. Unfortunately, there is little correlation with X-ray results and CT imaging, and clinical utility of X-ray is limited [15]. CT imaging has better anatomical delineation and an improved assessment of inflammation and possible complications. Peripheral mucosal thickening, air-fluid levels, gas bubbles within the fluid, and obstruction of the ostiomeatal complexes are recognized findings. Figures 4.8 and 4.9 demonstrate a CT with partial opacification in addition to an air-fluid level in the right maxillary sinus. Rhinitis (almost always associated with sinusitis) is characterized by thickening of the turbinates with obliteration of the surrounding meatus.

Bhattacharyya et al. have reported on the diagnostic accuracy of CT in pediatric chronic rhinosinusitis [16]. They compared a total of 66 pediatric patients (mean age, 8 years) with CRS and exhibited a mean Lund-Mackay [17, 18] score of 10.4 (95% confidence interval, 9.2–11.5); 192 control patients (mean age, 9 years) exhibited a

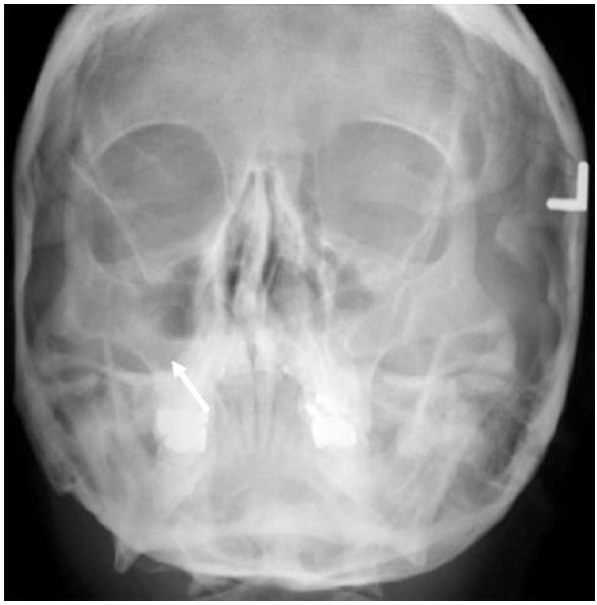


Fig. 4.7 Frontal Waters' view of the paranasal sinuses demonstrates thickening and a fluid level (arrow) in the right maxillary sinus and mucosal thickening of the left maxillary sinus

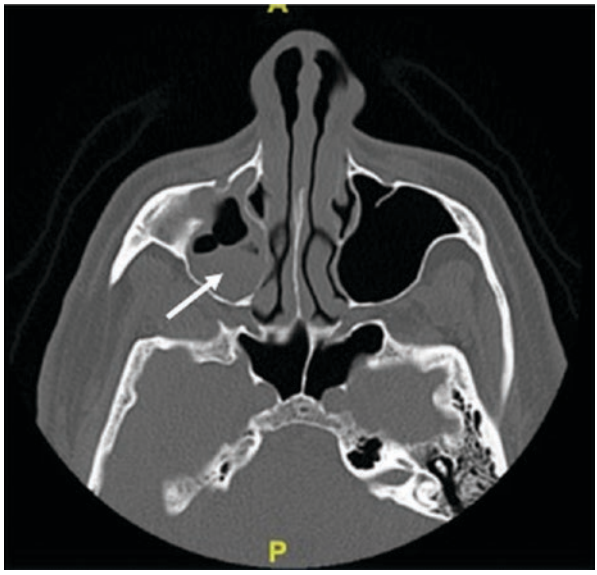


Fig. 4.8 Axial CT image with bone windowing demonstrating right maxillary sinus with peripheral mucosal thickening, air-fluid levels, and gas bubbles within the fluid (arrow)

mean Lund-Mackay score of 2.8 (95% confidence interval, 2.4–3.2). Adopting a Lund-Mackay score cutoff of 5 to represent CRS, the CT scan demonstrated a sensitivity and specificity of 86% and 85%, respectively. Lund-Mackay scores of 2 or less have an excellent negative predictive value, whereas Lund-Mackay scores of 5 or greater have an excellent positive predictive value (i.e., strongly indicate true dis-

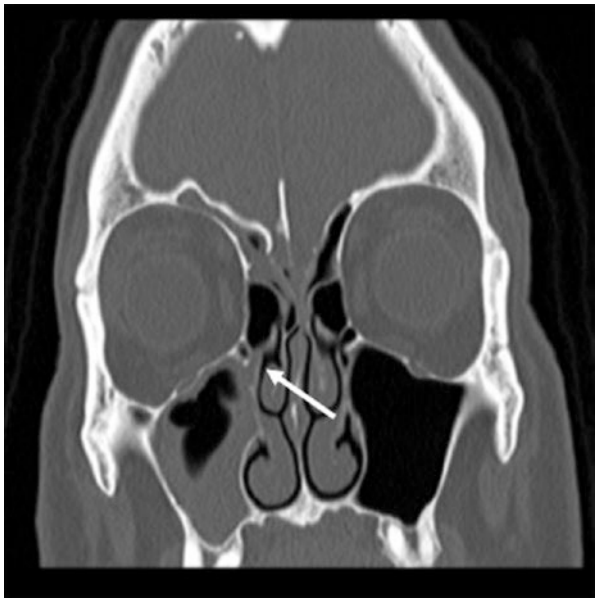


Fig. 4.9 Coronal CT with partial right maxillary sinus opacification and obstruction of the ostiomeatal complex (arrow)

ease). The Lund-Mackay [18] radiologic staging score of chronic rhinosinusitis (range 0–24) assigns each sinus a score of 0 (no abnormality), 1 (partial opacification), or 2 (complete opacification) for each sinus on each side, while the ostiomeatal complex is assigned a score of either 0 (not obstructed) or 2 (obstructed).

Complications of Rhinosinusitis

According to the AAP guideline, clinicians should obtain a contrast-enhanced CT scan of the paranasal sinuses and/or an MRI with contrast whenever a child is suspected of having orbital or central nervous system complications of acute bacterial rhinosinusitis [3] (Evidence Quality: B; Strong Recommendation by the AAP) or as referenced from the ACR appropriate criteria in (Table 4.2). The most common complication of acute rhinosinusitis involves the orbit in children with ethmoid sinusitis who are younger than 5 years [19–21]. Orbital complications should be suspected when the child presents with a swollen eye, especially if accompanied by proptosis or impaired function of the extraocular muscles. Orbital complications of acute rhinosinusitis have been divided into five categories, as first defined by Chandler: preseptal cellulitis, subperiosteal abscess, orbital cellulitis, orbital abscess, and cavernous sinus thrombosis [22]. Intracranial complications of acute rhinosinusitis, which are less common than orbital complications, have a higher morbidity and mortality than those involving the orbit. Intracranial complications include meningitis, subdural empyema, epidural empyema, dural venous thrombosis, and brain

Table 4.2 Indications for imaging in pediatric patients with clinical concern of orbital or intracranial complication. Initial imaging

Procedure	Appropriateness category	Relative radiation level
CT head and paranasal sinuses with IV contrast	Usually appropriate	☢☢☢
MRI head and paranasal sinuses without and with IV contrast	Usually appropriate	O
MR venography head with IV contrast	May be appropriate	O
CT venography head with IV contrast	May be appropriate	☢☢☢☢
CTA head with IV contrast	May be appropriate	☢☢☢☢
MR venography head without and with IV contrast	May be appropriate	O
MR venography head without IV contrast	May be appropriate	O
MRA head without IV contrast	May be appropriate	O
MRA head with IV contrast	May be appropriate	O
CT head and paranasal sinuses without and with IV contrast	Usually not appropriate	☢☢☢☢
CT head and paranasal sinuses without IV contrast	Usually not appropriate	☢☢☢
MRI head and paranasal sinuses without IV contrast	Usually not appropriate	O
X-ray paranasal sinuses	Usually not appropriate	☢

abscess [19]. Defects in the frontal sinus communicate with the anterior cranial fossae leading to intracranial complications (Fig. 4.10). In general, the contrast-enhanced CT scan has been the preferred imaging study when complications of rhinosinusitis are suspected. However, there are documented cases in which a contrast-enhanced CT scan has failed to identify cases with intracranial complications [23]. For orbital and intracranial complications, MRI with contrast has some advantages [24]. Preseptal cellulitis can be identified on CT scan with thickening of the eyelid, and the postseptal fat will not be involved. With subperiosteal abscess, you will often see a fluid collection between the bone and periorbita, adjacent to the affected sinus. Early infections may be difficult to identify with only subtle changes seen in the medial orbital fat plane [25]. As the infection progresses, the abscess will become rim enhancing and crescent shaped. In pediatric patients, this is most often contiguous with one of the ethmoid sinuses [25, 26]. With orbital cellulitis, there is inflammation within the orbit without discrete abscess formation. Although CT is generally adequate, weighted MRI will be more sensitive to inflammation and can help with differentiation of orbital cellulitis from orbital inflammatory syndrome or lymphoid lesions [27]. When pus develops within the orbit, this is defined as an orbital abscess, and it is caused by the progression of cellulitis or by local abscess spread. CT will demonstrate a discrete abscess (Fig. 4.11) [28]. MRI with contrast

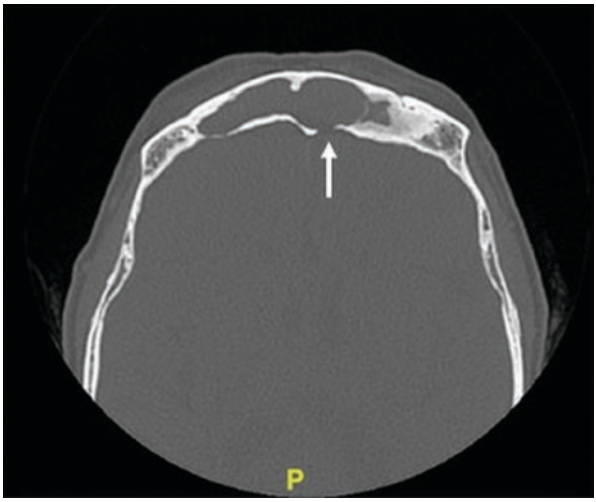


Fig. 4.10 Axial CT with bone window, demonstrating a dehiscence (arrow) noted through the posterior table of the left frontal sinus

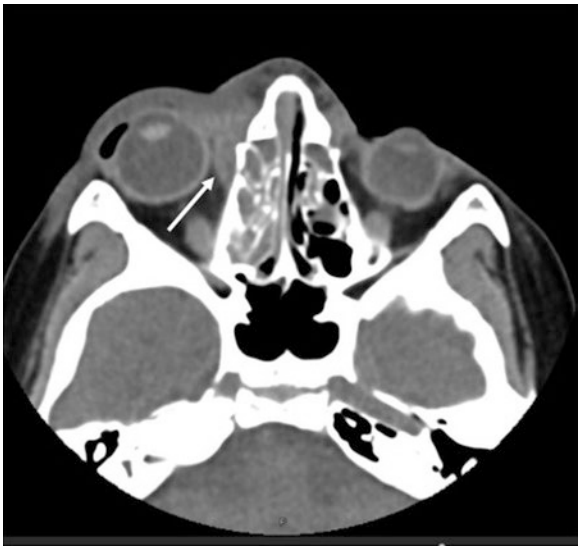


Fig. 4.11 Axial CT with right rim enhancing subperiosteal abscess (arrow), adjacent sinusitis of the right ethmoid sinuses

will show T2 hyperintensity and rim enhancement in addition to restricted diffusion [29]. With spread of infection through the valveless orbital venous system, cavernous sinus thrombosis can develop with serious clinical consequences including proptosis, chemosis, and bilateral cranial nerve deficits [30]. Filling defects in the cavernous sinus can be seen in both CT and MRI; however, the diagnosis with imaging is often difficult because acute thrombosis can be isointense [31]. Dilation of the superior ophthalmic vein and enhancement of the lateral cavernous sinus borders are further imaging clues [32].

Pott's Puffy Tumor (Frontal Sinus Osteomyelitis)

One possible complication of untreated acute frontal sinusitis is a Pott's puffy tumor. Blockage of the frontal sinus outflow tract can result in abscess formation inside the frontal sinus with erosion of the abscess either through the anterior bony lamina to form a subperiosteal pericranial abscess associated with "puffiness" of the forehead, through the posterior bony lamina resulting in an epidural abscess or through the orbital plate of the frontal bone into the superior orbit resulting in an extraconal orbital abscess (Fig. 4.12). The primary presenting features of a Pott's puffy tumor depend on the location, but often include severe headache and fever.

The imaging option of choice is a contrast-enhanced CT scan of the sinuses, which will demonstrate opacification of the frontal sinus [33–35]. CT gives excellent bony detail and is excellent at demonstrating cortical destruction and periosteal reactions [35]. If there is suspicion for a concurrent intracranial complication, then a contrast-enhanced MRI should be obtained. On inspection during surgical drainage of these abscesses, the bone can appear moth-eaten, characteristic of osteomy-

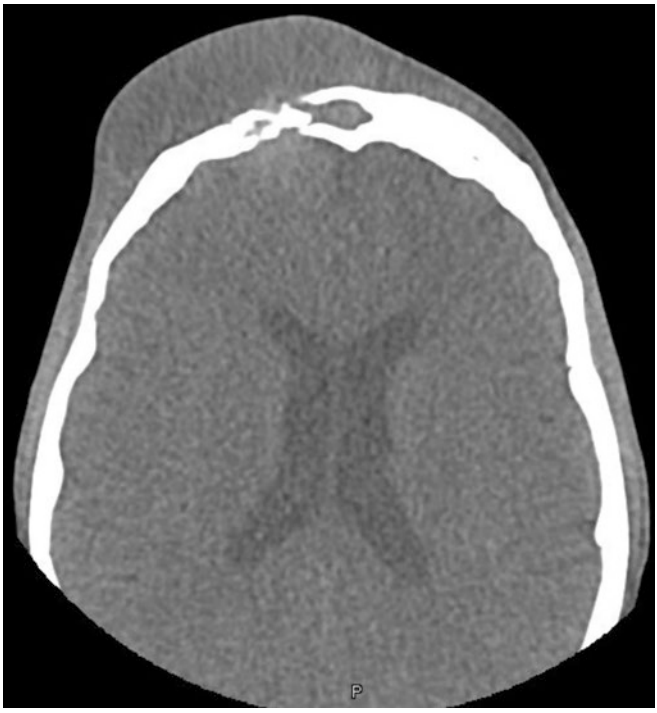


Fig. 4.12 Pott's puffy tumor. 18-year-old presenting with right frontal sinusitis with associated cortical breakthrough resulting in a subperiosteal abscess into the right frontal soft tissues

elitis. This is apparent on contrasted MRI of the sinuses by the characteristic hypointensity of the bone marrow on T1 imaging (Normal bone marrow is hyperintense on T1 imaging) [35].

Cystic Fibrosis

Cystic fibrosis is a systemic disease caused by an autosomal-recessive mutation in a single gene (CFTR) on chromosome 7 that encodes a critical chloride ion transporter which is necessary for the normal function of epithelia in the respiratory tract, paranasal sinuses, pancreas, biliary tract, GI tract, male reproductive tract, and sweat glands. The most common mutation is the F508delG mutation. CF is most common among Caucasians of Northern European descent, with a frequency of 1:2000 live births [36]. Affected mucosal surfaces accumulate high concentrations of sodium, chloride, and mucin, which results in impaired mucociliary clearance despite normal ciliary anatomy and function [36]. The life expectancy of patients with cystic fibrosis has increased significantly as medical science has progressed, with the current median life expectancy being 40.7 years. Chronic pansinusitis is a universal finding in patients with cystic fibrosis, and management of sinus disease throughout the patient's lifetime is important. Furthermore, children with cystic fibrosis commonly present with nasal polyps, which is uncharacteristic of chronic rhinosinusitis in children and should always raise the suspicion of cystic fibrosis. There is controversy as to whether management of paranasal sinus disease has downstream effects on lower respiratory tract disease, with some – but not all – studies showing some benefit [37].

Obstruction is common at the osteomeatal complex and at the sphenoethmoid recess (Fig. 4.13). Patients with CF often, but not always, have hypoplastic frontal and sphenoid sinuses. It characteristically presents with thick secretions causing sinus opacification, which are hypodense on CT, hypointense on T1 MRI, and hyperintense on T2 MRI [38, 39]. There are often osteitic changes present which can lead to increased sinus wall thickness. The inspissated mucus can have a heterogeneous appearance, resembling that of fungal rhinosinusitis which is an important differential. The sinuses can be so poorly aerated that mucoceles can form in 16% of cases [36, 40, 41], causing medial expansion of the lateral nasal wall and subsequent nasal airway obstruction in the case of maxillary sinus mucoceles, or orbital symptoms in the case of ethmoidal mucoceles. The upper respiratory tract of patients with CF is frequently colonized with a variety of pathogenic bacteria, most commonly *Pseudomonas aeruginosa* and *Staphylococcus aureus,* and these mucoceles can therefore become infected and form mucopyoceles [41]. In the case of a frontal mucopyocele, this can potentially erode through the bony limits of the

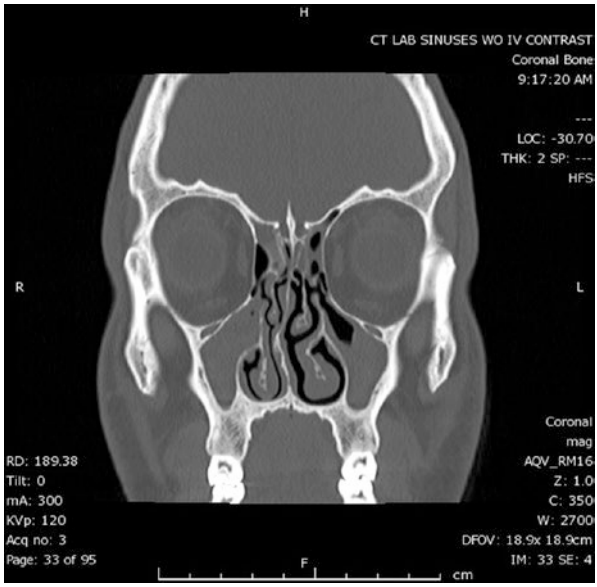


Fig. 4.13 Cystic fibrosis patient with small but completely opacified bilateral maxillary sinuses associated with osseous wall remodeling suggestive of chronic and recurrent sinusitis

frontal sinus and form a Pott's puffy tumor. Sinonasal polyposis is also frequently found in patients with cystic fibrosis, in anywhere from 33% to 57% [37].

Allergic Fungal Sinusitis

Allergic fungal sinusitis (AFS) is subtype of CRS with a predominant eosinophilic component. It is pathologically similar to allergic bronchopulmonary aspergillosis [42]. AFS age of onset is generally earlier and is therefore not infrequently seen in the pediatric sinusitis patient. Medical management of AFS is difficult and surgical intervention is commonly indicated in these patients. In addition to the presence of polyps, there are characteristic CT findings including hyperattenuated areas of accumulated eosinophilic mucin (Fig. 4.14) [43]. These imaging finds are a component of the diagnostic criteria for AFS [44]. Expansile lesions of the sinus cavities and demineralization are also seen. Twenty to thirty percent of AFS patients can present with bony erosion on CT; in this case, invasive fungal sinusitis must also be considered. MRI can be a valuable adjunctive study in AFS. On MRI, the eosinophilic mucin will appear hypointense on T2-weighted MRI due to high concentration of metal present in fungal organisms including iron and magnesium (Fig. 4.14) [45]. T1-weighted MRI can also have hypoattenuation but can also have mixed signal intensities.

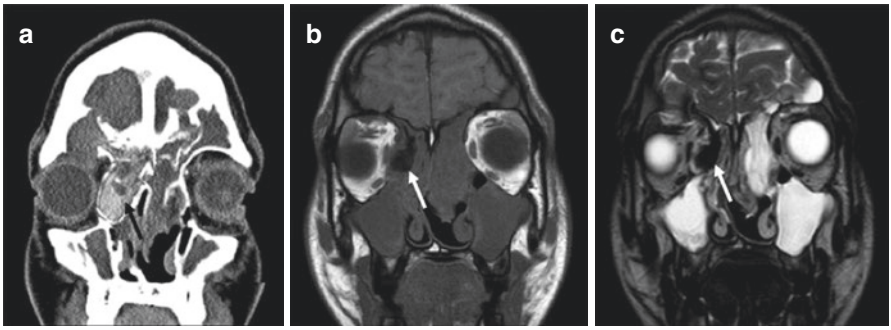


Fig. 4.14 Allergic fungal sinusitis. (**a**) Coronal CT demonstrating patient with left mucocele and characteristic areas of hyperintensity which correspond to fungal mucin on the right (arrow). (**b**) T1 MRI with hypoattenuated area corresponding to fungal elements. (**c**) T2 MRI demonstrating signal void in the area of mucin. Mucocele on the left with hyperattenuation for comparison

References

1. Lin EC. Radiation risk from medical imaging. Mayo Clin Proc. 2010;85(12):1142–6; quiz 1146.
2. McAlister WH, Parker BR, Kushner DC, et al. Sinusitis in the pediatric population. American College of Radiology. ACR Appropriateness Criteria. Radiology. 2000;215. Suppl:811–8.
3. Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262–80.
4. Wolf G, Anderhuber W, Kuhn F. Development of the paranasal sinuses in children: implications for paranasal sinus surgery. Ann Otol Rhinol Laryngol. 1993;102(9):705–11.
5. Willner A, Lazar RH, Zalzal GH. Endoscopic treatment of concha bullosa in children. Oper Tech Otolayngol Head Neck Surg. 1996;7:289–92. https://doi.org/10.1016/S1043-1810(96)80049-2.
6. Zeifer B. Pediatric sinonasal imaging: normal anatomy and inflammatory disease. Neuroimaging Clin N Am. 2000;10(1):137–59, ix.
7. Kantarci M, Karasen RM, Alper F, Onbas O, Okur A, Karaman A. Remarkable anatomic variations in paranasal sinus region and their clinical importance. Eur J Radiol. 2004;50(3):296–302.
8. Kim HU, Kim SS, Kang SS, Chung IH, Lee JG, Yoon JH. Surgical anatomy of the natural ostium of the sphenoid sinus. Laryngoscope. 2001;111(9):1599–602.
9. Gwaltney JM, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med. 1994;330(1):25–30.
10. Gordts F, Clement PA, Destryker A, Desprechins B, Kaufman L. Prevalence of sinusitis signs on MRI in a non-ENT paediatric population. Rhinology. 1997;35(4):154–7.
11. Kristo A, Uhari M, Luotonen J, et al. Paranasal sinus findings in children during respiratory infection evaluated with magnetic resonance imaging. Pediatrics. 2003;111(5 Pt 1):e586–9.
12. Glasier CM, Mallory GB, Steele RW. Significance of opacification of the maxillary and ethmoid sinuses in infants. J Pediatr. 1989;114(1):45–50.
13. Manning SC, Biavati MJ, Phillips DL. Correlation of clinical sinusitis signs and symptoms to imaging findings in pediatric patients. Int J Pediatr Otorhinolaryngol. 1996;37(1):65–74.
14. Som PM, Curtin HD. Head and neck imaging. 4th ed. St. Louis: Mosby; 2004. https://doi.org/10.1148/radiol.2331042535.

15. McAlister WH, Lusk R, Muntz HR. Comparison of plain radiographs and coronal CT scans in infants and children with recurrent sinusitis. AJR Am J Roentgenol. 1989;153(6):1259–64.
16. Bhattacharyya N, Jones DT, Hill M, Shapiro NL. The diagnostic accuracy of computed tomography in pediatric chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2004;130(9):1029–32.
17. Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? Otolaryngol Head Neck Surg. 2007;137(4):555–61.
18. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology. 1993;31(4):183–4.
19. Brook I. Microbiology and antimicrobial treatment of orbital and intracranial complications of sinusitis in children and their management. Int J Pediatr Otorhinolaryngol. 2009;73(9):1183–6.
20. Sultész M, Csákányi Z, Majoros T, Farkas Z, Katona G. Acute bacterial rhinosinusitis and its complications in our pediatric otolaryngological department between 1997 and 2006. Int J Pediatr Otorhinolaryngol. 2009;73(11):1507–12.
21. Wald ER. Periorbital and orbital infections. Infect Dis Clin N Am. 2007;21(2):393–408.. vi
22. Chandler JR, Langenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. Laryngoscope. 1970;80(9):1414–28.
23. McIntosh D, Mahadevan M. Failure of contrast enhanced computed tomography scans to identify an orbital abscess. The benefit of magnetic resonance imaging. J Laryngol Otol. 2008;122(6):639–40.
24. Younis RT, Anand VK, Davidson B. The role of computed tomography and magnetic resonance imaging in patients with sinusitis with complications. Laryngoscope. 2002;112(2):224–9.
25. Handler LC, Davey IC, Hill JC, Lauryssen C. The acute orbit: differentiation of orbital cellulitis from subperiosteal abscess by computerized tomography. Neuroradiology. 1991;33(1):15–8.
26. Greenberg MF, Pollard ZF. Medical treatment of pediatric subperiosteal orbital abscess secondary to sinusitis. J AAPOS. 1998;2(6):351–5.
27. Kapur R, Sepahdari AR, Mafee MF, et al. MR imaging of orbital inflammatory syndrome, orbital cellulitis, and orbital lymphoid lesions: the role of diffusion-weighted imaging. AJNR Am J Neuroradiol. 2009;30(1):64–70.
28. Jain A, Rubin PA. Orbital cellulitis in children. Int Ophthalmol Clin. 2001;41(4):71–86.
29. Sepahdari AR, Aakalu VK, Kapur R, et al. MRI of orbital cellulitis and orbital abscess: the role of diffusion-weighted imaging. AJR Am J Roentgenol. 2009;193(3):W244–50.
30. Ebright JR, Pace MT, Niazi AF. Septic thrombosis of the cavernous sinuses. Arch Intern Med. 2001;161(22):2671–6.
31. Razek AA, Castillo M. Imaging lesions of the cavernous sinus. AJNR Am J Neuroradiol. 2009;30(3):444–52.
32. Wang A-G, Liu J-H, Shyong M-P, Yen M-Y. Magnetic resonance imaging in chronic cavernous sinus thrombosis. Neuro-Ophthalmology. 2000;23(1):29–34.
33. Lee YJ, Sadigh S, Mankad K, Kapse N, Rajeswaran G. The imaging of osteomyelitis. Quant Imaging Med Surg. 2016;6(2):184–98.
34. Huijssoon E, Woerdeman PA, van Diemen-Steenvoorde RA, Hanlo PW, Plötz FB. An 8-year-old boy with a Pott's puffy tumor. Int J Pediatr Otorhinolaryngol. 2003;67(9):1023–6.
35. Tsai B-Y, Lin K-L, Lin T-Y, et al. Pott's puffy tumor in children. Childs Nerv Syst. 2010;26(1):53–60.
36. Solares CA, Citardi MJ, Budev M, Batra PS. Management of frontal sinus mucoceles with posterior table erosion in the pretransplant cystic fibrosis population. Am J Otolaryngol. 2007;28(2):110–4.
37. Gergin O, Kawai K, MacDougall RD, et al. Sinus computed tomography imaging in pediatric cystic fibrosis: added value? Otolaryngol Head Neck Surg. 2016;155(1):160–5.
38. Eggesbø HB, Søvik S, Dølvik S, Kolmannskog F. CT characterization of inflammatory paranasal sinus disease in cystic fibrosis. Acta Radiol. 2002;43(1):21–8.
39. Eggesbø HB, Dølvik S, Stiris M, Søvik S, Storrøsten OT, Kolmannskog F. Complementary role of MR imaging of ethmomaxillary sinus disease depicted at CT in cystic fibrosis. Acta Radiol. 2001;42(2):144–50.

40. Qureishi A, Lennox P, Bottrill I. Bilateral maxillary mucoceles: an unusual presentation of cystic fibrosis. J Laryngol Otol. 2012;126(3):319–21.
41. Horesh E, Colin AA, Casiano R, Wester ST. An atypical presentation of sinus mucopyocele in a pediatric cystic fibrosis patient. Clin Ophthalmol. 2015;9:821–4.
42. Manning SC, Vuitch F, Weinberg AG, Brown OE. Allergic aspergillosis: a newly recognized form of sinusitis in the pediatric population. Laryngoscope. 1989;99(7 Pt 1):681–5.
43. Zinreich SJ, Kennedy DW, Malat J, et al. Fungal sinusitis: diagnosis with CT and MR imaging. Radiology. 1988;169(2):439–44.
44. Bent JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994;111(5):580–8.
45. Aribandi M, McCoy VA, Bazan C. Imaging features of invasive and noninvasive fungal sinusitis: a review. Radiographics. 2007;27(5):1283–96.

Chapter 5
Microbiology of Pediatric Sinusitis

Phillip R. Purnell and Michele M. Carr

Introduction

The upper respiratory tract, including the sinuses, is colonized by a mixture of normal bacterial flora and opportunistic pathogenic organisms. When the system is affected by a viral infection, the microflora and immune response can be altered such that an acute bacterial infection can develop. The vast majority of patients with viral upper respiratory infection will have a coincident viral sinus infection. The most common viruses involved in acute rhinosinusitis include adenovirus, rhinovirus, influenza, and parainfluenza. In adults, 0.5–2% of these patients will develop acute bacterial rhinosinusitis (ABRS) after viral infection [1, 2]. In pediatric patients, this estimate is much higher, from 5% to 13% of patients [3, 4]. Viral sinusitis is thought to precede approximately 80% of ABRS while 20% is related to allergic inflammation [5]. ABRS is most commonly associated with aerobic bacteria including *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. While ABRS lasts less than 4 weeks, subacute rhinosinusitis lasts from 4 to 12 weeks, and chronic rhinosinusitis (CRS) is defined as lasting more than 12 weeks. Estimates of the progression of ABRS to CRS in pediatric patients are currently unknown. While ABRS is generally unimicrobial, current work with CRS demonstrates a complicated interaction between multiple bacterial species. Additionally, the bacteria associated with CRS may be resistant to conventional medical therapies. CRS may also be complicated by fungal infection. A thorough understanding of the basic microbiology of sinusitis drives proper antimicrobial selection and appropriate patient care. This chapter will focus on the current concepts in microbiology of ABRS and CRS in pediatric patients.

P. R. Purnell · M. M. Carr (✉)
Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA
e-mail: Michele.carr@hsc.wvu.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_5

Normal Flora

The bacteria causing sinusitis are likely to originate from the nasal cavity. Purulent nasal discharge isolated from pediatric patients shows a higher rate of known pathogens including the aerobes *S. pneumoniae*, *H. influenza*, and *M. catarrhalis* [6]. In healthy children, the most commonly isolated bacteria from middle meatus cultures were *H. influenza* (40%), *M. catarrhalis* (34%), and *S. pneumonia* (50%) [7], demonstrating that these bacteria are present even in the healthy state, suggesting that viral or allergic processes may allow proliferation of otherwise commensal bacteria. *S. aureus* has been shown to be a common isolate in pediatric nasal swabs, even in healthy patients [8]; this is important to note in light of increasing data implicating *S. aureus* as a possible pathogenic bacteria in ABRS, especially methicillin-resistant strains [9, 10].

Acute Bacterial Rhinosinusitis

ABRS is defined by the presence of two or more symptoms of nasal discharge, obstruction, facial pain/pressure, or hyposmia/anosmia lasting up to 4 weeks. Various factors including environment, host immune factors, viral infection, and allergy can affect the microbiology of an infection. Viruses are the most common cause of acute rhinosinusitis and after viral infection, bacterial growth can occur. This may be due to immune alterations allowing proliferation of otherwise dormant bacterial species, ostial obstruction caused by virally induced inflammation, and increased local adherence of bacteria [11]. Rhinovirus, adenovirus, parainfluenza, and influenza are commonly implicated in early viral sinusitis [12]. After the viral infection, a secondary bacterial infection can develop, which complicates the clinical course. This occurs in 5–13% of pediatric patients [4, 13]. In a study of 294 pediatric patients aged 6–35 months, ABRS complicated 8% of viral upper respiratory tract infections [14]. The presence of rhinovirus correlated with progression to ABRS. The most common bacteria associated with ABRS are similar in pediatric and adult patients; these include *S. pneumonia*, *H. influenza*, *M. catarrhalis*, and Group A beta-hemolytic strep [15]. Chlamydia and mycoplasma have also been associated with ABRS in children, although much less commonly [16]. In the transition from acute to subacute sinusitis, almost identical bacterial species have been identified in serial maxillary sinus aspirations including *S. pneumonia*, *H. influenza*, and *M. catarrhalis* [17]. In the transition to chronic sinusitis, the common aerobes are identified first, followed by anaerobes including *Bacteroides* and *Peptostreptococcus*, which are both normally identified in the oropharynx [18]. In 2000, the pneumococcal vaccine was introduced and widely used in the United States; this dramatically decreased the incidence of *S. pneumonia*-associated ABRS and increased the percentage of *H. influenza* isolated. It is important to note that these data were collected in the adult population, although it was primarily the

pediatric population receiving the vaccination [19]. Brooks et al. studied nasopharyngeal cultures from pediatric patients before and after the introduction of the 7-valent pneumococcal vaccine [20]. They demonstrated that in acute maxillary sinusitis, *S. pneumonia* isolates declined by 18% and *H. influenza* increased by 8%. The vaccination also significantly altered the serotype of pneumococcus isolated in sinusitis. Serotype 19A, which was not included in the 7-valent vaccine, became the most prominent isolate in pediatric CRS patients and was associated with antibiotic resistance [21]. With introduction of the 13-valent pneumococcal vaccine, which contains antigens to serotype 19A, the isolated serotypes continue to evolve as does antimicrobial resistance [22].

The majority of microbiological data in pediatric acute sinusitis was obtained via maxillary sinus aspiration. A study done by Wald et al. with a total of 50 pediatric patients who had clinical and radiographic evidence of acute sinus disease (a total of 79 sinus aspirates) showed that in 70% of patients, at least one sinus was infected [23]. The study demonstrated the predominance of *S. pneumoniae* (37%), *H. influenza* (25%), and *M. catarrhalis* (25%) in ABRS, with very few anaerobes or staphylococci isolated in this study [24]. In addition, 12% of the patients had beta-lactamase-producing bacterial infection. Microbiological studies of acute sinusitis are highlighted in Table 5.1. There have been no recent studies using sinus aspiration in pediatric patients with ABRS due to its invasive nature, despite its being regarded as the best way to obtain an accurate sinus culture. There have been multiple studies comparing the utility of middle meatus sampling as an alternative to the invasive sinus puncture [25]. A meta-analysis pooling data from 126 adults with ABRS showed endoscopic cultures had a sensitivity of 80.9% and specificity of 90.5% [25]. When endoscopic cultures were taken from pediatric patients with CRS, the sensitivity was 75% and specificity 99% [26]. Groups have also tried to correlate the results of nasal cultures with maxillary sinus aspiration. In adults, the nasal culture only correlates with sinus aspiration between 40% and 60% of the time [27]. In pediatric patients, there is even lower correlation between nasopharyngeal cultures or throat cultures and sinus aspiration, with less than 25% of nasopharyngeal cultures correlating with the organism present in the sinus [24]. This highlights the lack of data available for ABRS using sterile technique and sinus aspiration; therefore, several groups have advocated using acute otitis media bacteriology as a proxy for ABRS [28, 29].

Recently some studies show increased methicillin-resistant *S. aureus* (MRSA) prevalence in pediatric ABRS, while others have found no change [30]. Association with increased clinical complications including facial and orbital cellulitis has been demonstrated by multiple studies [30, 31]. Despite the recent data suggesting increasing presence of *S. aureus* isolated in sinusitis patients, its role as a pathogen is still debated. In a group of 250 children with complicated sinusitis requiring surgery, there was no change in MRSA prevalence from 2004 to 2014 [32]. There was, however, poorer clinical outcome (as measured by persistent ocular physical exam findings) over time in the patients with MRSA, but no increased intracranial or extracranial complications [31]. Several other case studies have examples of *S. aureus*-related complications [32–34]. As others have

Table 5.1 Percentage of recovery of organisms from pediatric patients with chronic sinusitis

Author, year	Number of patients	Patient ages (years)	*S. pneumonia*	*H. influenza*	*M. catarrhalis*	*S. aureus*	Coagulase-negative *Staphylococcus*	α-Hemolytic strep (viridians)	*Peptostreptococcus*	*Fusobacterium*	*Bacteroides*	*Prevotella*	Anaerobes
Wald 1981 [24][a]	30	1 to 16	41	27	22								
Brook 1981 and 1995 [68, 94][a]	40	6 to 16		3		6			23	11	10	12	12
Wald 1984 [23]	50	1 to 16	37	25	25								
Otten 1988 [82]	141	3 to 10	26	48	7	6							
Wald 1989 [17]	40	2 to 12	35	31	23								
Tinkelman 1989 [83]	35	10 mo to 16	29	29	14	11							
Goldenhersh 1990 [66]	12	3 to 9			50								
Muntz 1991 [84]	105	9 mo to 17	7	7	7	19		23					6
Orobello 1991 [85]	39	15 mo to 19	1	4		12	24	19					4
Erkam 1996 [69]	93	6 to 17	3	2	3	5		7	14	2	27		
Brook 2000 [86]	32	4 to 11	16	23	5	13			16	5		18	

Don 2001 [87]	70	10 mo to 15	16	42	18	11	16	26		1	3	7	
Slack 2001 [67]	119	0.8 to 14.5	19	24	17	3	6	6					
Tuncer 2004 [88]	30	4 to 12	15	10	5	30		10					
Ilki 2005 [89]	90	2 to 9	26	40	34	17							6
Adappa 2006 [90]	22	1.25 to 14.5						38					
Criddle 2008 [91]	23	6 mo to 6	18	18	27	9		18					
Hsin 2008 [26]	21	2 to 12	55	35	3	5	3	3					
Hsin 2010 [92]	165	4 to 16	14.0	19.5	5.3	9.3	13.0	20.8					8
Stokken 2014 [93]	41	4 to 17	9.8	4.9		19.5	22		2.4				14.6

[a]Wald [24] and Brook [68, 94] are pediatric patients with ABRS, not CRS

pointed out, *S. aureus* is commonly present in the nasal cavity of healthy children and its presence in endoscopic cultures assumes that there has been no contamination of the sample during the culturing process [35]. As of yet, there is no sufficient evidence to warrant *S. aureus* coverage for ABRS unless it is complicated sinusitis (as discussed below).

Odontogenic Sinusitis

Odontogenic ABRS is characterized by the absence of the most common bacteria associated with acute sinusitis. These sinus infections often result after dental procedures, maxillary dental infections, or facial trauma. In children presenting with periorbital cellulitis of odontogenic origin, anaerobic bacteria predominated, most commonly *Peptostreptococcus*, *Fusobacterium*, and *Prevotella* species, which are all considered normal oral flora but may be associated with dental disease [36, 37]. The total number of aerobic and anaerobic bacteria isolated in these children was also higher than in those with ABRS of non-odontogenic origin. More than half of the bacteria isolated in this study were beta-lactamase producers [36]. In adults, some studies have shown that up to 20% of sinusitis patients may have related odontogenic disease [38]. In odontogenic sinusitis cultures in these patients, similar ABRS-associated bacteria were isolated along in addition to increased numbers of gram-negative anaerobes, including *Peptostreptococcus* and *Prevotella* [38]. With the prevalence of anaerobes in these patients, appropriate antibiotic consideration is required.

Pediatric Nosocomial Sinusitis

The microbiology of pediatric nosocomial sinusitis is quite different from community acquired ABRS. Sinusitis is frequently found in intubated and critically ill patients. Incidence varies widely by study, but up to 80% of patients in the ICU have evidence of sinusitis. In the pediatric ICU, 44% of patients who had imaging for unrelated reasons had evidence of sinus disease and 69% of patients with endotracheal or nasogastric tube placement at the time of the imaging had sinusitis [39]. The use of nasogastric tubes, mechanical ventilation, and supine positioning puts these patients at risk for bacterial colonization of the sinuses [40, 41]. Those with facial trauma are at especially high risk for sinusitis [42, 43]. Bacterial colonization of the sinuses in the adult ICU patient is most commonly with *Pseudomonas*, *Proteus*, and *Acinetobacter* [44], with most studies showing the infrequent isolation of anaerobic bacteria [45, 46]. This is similar to what was isolated from pediatric ICU patients; however, anaerobic bacteria, including *Peptostreptococcus* and *Prevotella*, was found to be more prominent in pediatric patients in a study by Brook [47]. The most frequent aerobes isolated from these

patients were Pseudomonas and *S. aureus*. Seventy percent of the bacteria isolated in this study were also beta-lactamase producers. *Pseudomonas* and gram-negative rods seen in these nosocomial infections are similarly seen in immunocompromised patients and those with cystic fibrosis. These data highlight the importance of antibiotic coverage which includes beta-lactamase inhibition in these critically ill patients.

Complicated Sinusitis

Although intracranial and extracranial complications of sinusitis are rare in pediatric patients, they can lead to serious morbidity and even mortality. Children aged 2–10 are more commonly affected than neonates or infants. Systematic reviews have shown that the most common intracranial complications of sinusitis in pediatric patients are subdural empyema, epidural and cerebral abscesses, and meningitis [48]. These complications affect young adolescent males most frequently [48]. If the frontal sinus is involved, intracranial complications are 20 times more likely [49]. In studies which included pediatric patients, acute frontal sinusitis cultures showed the most common ABRS-associated bacteria: *S. pneumonia*, *H. influenza*, and *M. catarrhalis* [15, 50]. Cavernous sinus thrombosis is associated with a higher percentage of *S. aureus*, up to 70%, with *S. pneumoniae* and gram-negative anaerobes also identified [51]. In these patients, blood cultures are also commonly positive in approximately 70% of patients [52]. There are also several published cases of Aspergillus and Mucor associated with cavernous sinus thrombosis [53, 54].

Common complications of sinusitis in pediatric patients are orbital cellulitis, subperiosteal abscess, and orbital abscess [55]. Acute ethmoid sinusitis is associated with orbital infections [56]. Brook et al. described bacteria associated with periorbital cellulitis of odontogenic origin in pediatric patients [57]. Mixed aerobic and anaerobic bacteria were found in 50% of the patients. The aerobes isolated included alpha-hemolytic streptococci with the predominant anaerobic bacteria including gram-negative bacilli and *Peptostreptococcus* [57]. A recent retrospective chart review was completed in 129 hospitalized pediatric patients with acute ethmoid sinus disease, 47 of whom had subperiosteal orbital abscesses. They demonstrated that *Streptococcus* was the most frequently identified bacteria (60%) with *S. aureus* (12%) and anaerobes (12%) less frequently identified [58].

Chronic Rhinosinusitis

CRS can be a consequence of untreated or resistant ABRS, but multiple factors including anatomic abnormalities (maxillary hypoplasia and adenoid hypertrophy [59]), allergy [60], polyps, immunodeficiency [61], cystic fibrosis, ciliary

abnormalities, and nosocomial factors can all play a role. Previously microbiological studies in CRS were based on maxillary sinus cultures obtained through sinus aspiration. Newer molecular techniques, including PCR, mass spectrometry, and fluorescence in situ hybridization, have advanced the understanding of microbiological flora in CRS [62]. The majority of studies continue to be retrospective with 90 days or more of sinusitis symptoms and endoscopic or imaging evidence of sinusitis used as the criteria for sinus sampling. There is great variability in the methods used for collection of samples, multiple different areas sampled, varying history of previous antibiotic treatment, and patient selection bias in these studies [63]. Microbiological studies in pediatric CRS are highlighted in Table 5.1.

In pediatric and adult CRS, polymicrobial infections are more common than they are in ABRS [64]. In CRS, bacteria such as staphylococci, alpha-hemolytic streptococci, and anaerobes, including *Bacteroides* and peptostreptococci, have classically been identified. However, in more than 50% of the CRS studies, the same pathogens common in ABRS were recovered including *S. pneumonia*, *H. influenza*, and *M. catarrhalis* [65]. In pediatric allergy patients with CRS, the most commonly isolated bacteria was *M. catarrhalis* with 25% growing multiple organisms [66]. In 119 children with maxillary sinusitis >8 weeks, without cystic fibrosis or immunodeficiency, 67% of aerobic cultures were positive, most commonly for *H. influenza* (24%), *S. pneumonia* (19%), *M. catarrhalis* (17%), coagulase-negative *Staphylococcus* (6%), and alpha-hemolytic streptococci (6%) [67]. In 40 children with CRS studied by Brook et al., anaerobes were recovered in all of the culture-positive specimens [68], including gram-negative bacilli, gram-positive cocci, and *Fusobacterium*. In 93 endoscopically obtained pediatric maxillary sinus samples in patients with CRS, bacterial growth was present in 93% of samples, with anaerobes isolated in 93%. Anaerobes alone were isolated in 70% of the cases, most commonly Bacteroides species and gram-positive anaerobic cocci [69]. A 2010 study by Hsin et al. of 165 children with cultures obtained by maxillary sinus puncture showed isolates of alpha-hemolytic *Streptococcus* (21%), *H. influenza* (20%), *S. pneumoniae* (14%), coagulase-negative *Staphylococcus* (13%), and *S. aureus* (9%) [26]. This study demonstrated the changing bacteriologic profile in CRS and also demonstrated a high resistance rate to amoxicillin in *H. influenza*. Gram-negative enteric rods have been identified in 27% of CRS patients but were not recovered from control group non-CRS patients. These included *P. aeruginosa*, *Klebsiella pneumoniae*, and *Proteus* [70]. Invasive fungal sinusitis is rare in children and is associated with immunodeficiency, especially hematologic malignancies. Fungi including Mucor and Aspergillus are commonly identified in this subset of pediatric CRS [71].

Newer studies have brought to light the importance of the interaction between bacteria and the inflammatory response. Some groups have suggested that the inflammatory response is the principal driver of CRS while bacteria are simply bystanders which alter the immune response [72]. It is now widely thought that the persistent inflammatory response, rather than bacterial infection, may be the key factor increasing obstructive symptoms in children, and thus leading to persisting infection [63, 73].

Biofilm Formation in Chronic Rhinosinusitis

It has become apparent that bacterial biofilms play an important role in CRS development and the high rates of antibiotic resistance in these patients. Bacteria exist in planktonic and biofilm form. In biofilm formation, bacteria are able to produce an extracellular glycocalyx matrix of polysaccharides and proteins which forms a protective cover for the bacterial colony. These biofilm-forming colonies are generally polymicrobial, and with more organisms, the biofilm can become more resilient. The bacteria produce quorum-sensing molecules as the biofilm grows, and these can regulate gene and protein production in addition to regulating growth rate. Expression of proadhesion molecules and growth of pili contribute to stronger cellular interactions [74]. Biofilms are antibiotic protective and have been shown to increase minimal inhibitory concentrations of antibiotics from 100 to 1000 times [75]. The outer layer of the biofilm acts as a protective mechanism for the inner bacteria, so antibiotics targeting replication are not effective against the deeper bacteria [76]. These features of biofilms allow for persistent infection and long-term inflammatory reactions.

Lymphoid tissue in the upper airway may act as a bacterial reservoir that can promote biofilm formation. Biofilms have been found in the adenoid tissue of patients with otitis media and with recurrent upper respiratory infections [77, 78]. In pediatric patients with sinusitis, 79.3% of adenoids were colonized with bacteria, most commonly *H. influenza* (28.5%), *S. pneumonia* (21.7%), *S. pyogenes* (21.0%), and *S. aureus* (15.6%) [79]. The likelihood of bacterial isolation from the adenoid was also higher in those patients with worse radiographic sinusitis. When compared to patients with obstructive sleep apnea, patients with chronic rhinosinusitis have increased biofilm surface area. The CRS patients have 94.9% of their adenoid surface area covered with mature biofilm versus only 1.9% surface area coverage in patients with obstructive sleep apnea [80]. In adult patients with endoscopic sinus surgery for CRS, 78% of sinus mucosal specimens contained biofilms with *H. influenza*, *S. pneumonia*, and *S. aureus*. *P. aeruginosa* was not identified [81]. There have not been any studies looking at biofilm formation in the nasal mucosa of pediatric patients.

The majority of microbiological data of pediatric sinusitis suggests that it is similar to adult sinusitis. There have been a significantly larger number of studies in the adult sinusitis population, both acute and chronic. There remains a paucity of comprehensive sinusitis studies in pediatric patients, largely due to the invasive nature of appropriate sinus sampling. Data we do have show a variety of pathogenic organisms with minimal agreement between the studies. The reality is that there is likely a complex balanced interplay between microbes, inflammation, anatomy, and antibiotic treatment that determine health or disease with respect to the sinuses.

References

1. Gwaltney JM. Acute community-acquired sinusitis. Clin Infect Dis. 1996;23(6):1209–23; quiz 1224–5.
2. Puhakka T, Mäkelä MJ, Alanen A, et al. Sinusitis in the common cold. J Allergy Clin Immunol. 1998;102(3):403–8.

3. 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.
4. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. Pediatrics. 1991;87(2):129–33.
5. Fireman P. Diagnosis of sinusitis in children: emphasis on the history and physical examination. J Allergy Clin Immunol. 1992;90(3. Pt 2):433–6.
6. Brook I. Aerobic and anaerobic bacteriology of purulent nasopharyngitis in children. J Clin Microbiol. 1988;26(3):592–4.
7. 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(3):184–8.
8. Gordts F, Abu Nasser I, Clement PA, Pierard D, Kaufman L. Bacteriology of the middle meatus in children. Int J Pediatr Otorhinolaryngol. 1999;48(2):163–7.
9. Huang W-H, Hung P-K. Methicillin-resistant Staphylococcus aureus infections in acute rhinosinusitis. Laryngoscope. 2006;116(2):288–91.
10. Whitby CR, Kaplan SL, Mason EO, et al. Staphylococcus aureus sinus infections in children. Int J Pediatr Otorhinolaryngol. 2011;75(1):118–21.
11. Osur SL. Viral respiratory infections in association with asthma and sinusitis: a review. Ann Allergy Asthma Immunol. 2002;89(6):553–60.
12. Jacobs SE, Lamson DM, St George K, Walsh TJ. Human rhinoviruses. Clin Microbiol Rev. 2013;26(1):135–62.
13. 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(6):e1408–12.
14. Marom T, Alvarez-Fernandez PE, Jennings K, Patel JA, McCormick DP, Chonmaitree T. Acute bacterial sinusitis complicating viral upper respiratory tract infection in young children. Pediatr Infect Dis J. 2014;33(8):803–8.
15. Brook I. Bacteriology of acute and chronic frontal sinusitis. Arch Otolaryngol Head Neck Surg. 2002;128(5):583–5.
16. Savolainen S, Jousimies-Somer H, Kleemola M, Ylikoski J. Serological evidence of viral or Mycoplasma pneumoniae infection in acute maxillary sinusitis. Eur J Clin Microbiol Infect Dis. 1989;8(2):131–5.
17. Wald ER, Byers C, Guerra N, Casselbrant M, Beste D. Subacute sinusitis in children. J Pediatr. 1989;115(1):28–32.
18. Brook I, Frazier EH, Foote PA. Microbiology of the transition from acute to chronic maxillary sinusitis. J Med Microbiol. 1996;45(5):372–5.
19. 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 pneumococcal vaccine. J Med Microbiol. 2006;55.(Pt 7:943–6.
20. Brook I, Gober AE. Frequency of recovery of pathogens from the nasopharynx of children with acute maxillary sinusitis before and after the introduction of vaccination with the 7-valent pneumococcal vaccine. Int J Pediatr Otorhinolaryngol. 2007;71(4):575–9.
21. McNeil JC, Hulten KG, Mason EO, Kaplan SL. Serotype 19A is the most common Streptococcus pneumoniae isolate in children with chronic sinusitis. Pediatr Infect Dis J. 2009;28(9):766–8.
22. Olarte L, Hulten KG, Lamberth L, Mason EO, Kaplan SL. Impact of the 13-valent pneumococcal conjugate vaccine on chronic sinusitis associated with Streptococcus pneumoniae in children. Pediatr Infect Dis J. 2014;33(10):1033–6.
23. 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(2):297–302.
24. Wald ER, Milmoe GJ, Bowen A, Ledesma-Medina J, Salamon N, Bluestone CD. Acute maxillary sinusitis in children. N Engl J Med. 1981;304(13):749–54.

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(1):3–9.
26. Hsin C-H, Tsao C-H, Su M-C, Chou M-C, Liu C-M. Comparison of maxillary sinus puncture with endoscopic middle meatal culture in pediatric rhinosinusitis. Am J Rhinol. 2008;22(3):280–4.
27. 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(1):7–12.
28. Parsons DS, Wald ER. Otitis media and sinusitis: similar diseases. Otolaryngol Clin N Am. 1996;29(1):11–25.
29. Marchisio P, Ghisalberti E, Fusi M, Baggi E, Ragazzi M, Dusi E. Paranasal sinuses and middle ear infections: what do they have in common? Pediatr Allergy Immunol. 2007;18(Suppl 1):31–4.
30. Rujanavej V, Soudry E, Banaei N, Baron EJ, Hwang PH, Nayak JV. Trends in incidence and susceptibility among methicillin-resistant Staphylococcus aureus isolated from intranasal cultures associated with rhinosinusitis. Am J Rhinol Allergy. 2013;27(2):134–7.
31. Hamill CS, Sykes KJ, Harrison CJ, Weatherly RA. Infection rates of MRSA in complicated pediatric rhinosinusitis: An up to date review. Int J Pediatr Otorhinolaryngol. 2018;104:79–83.
32. Boucher H, Miller LG, Razonable RR. Serious infections caused by methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2010;51(Suppl 2):S183–97.
33. Martins A, Bordino L, Cohen D, Cruz D, Fitz Maurice Mde L, Spini RG. [Maxillary osteomyelitis secondary to rhinosinusitis in children: case report]. Arch Argent Pediatr. 2016;114(2):e87–90.
34. Kumar PS, Cunnion KM. Acute MRSA sinusitis with intracranial extension and marginal vancomycin susceptibility. Case Rep Pediatr. 2013;2013:153239.
35. 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(4):349–51.
36. Brook I. Sinusitis of odontogenic origin. Otolaryngol Head Neck Surg. 2006;135(3):349–55.
37. Brook I. Microbiology and management of endodontic infections in children. J Clin Pediatr Dent. 2003;28(1):13–7.
38. Puglisi S, Privitera S, Maiolino L, et al. Bacteriological findings and antimicrobial resistance in odontogenic and non-odontogenic chronic maxillary sinusitis. J Med Microbiol. 2011;60. (Pt 9:1353–9.
39. Moore BM, Blumberg K, Laguna TA, Liu M, Zielinski EE, Kurachek SC. Incidental sinusitis in a pediatric intensive care unit. Pediatr Crit Care Med. 2012;13(2):e64–8.
40. Holzapfel L, Chastang C, Demingeon G, Bohe J, Piralla B, Coupry A. A randomized study assessing the systematic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Influence of nosocomial maxillary sinusitis on the occurrence of ventilator-associated pneumonia. Am J Respir Crit Care Med. 1999;159(3):695–701.
41. George DL, Falk PS, Umberto Meduri G, et al. Nosocomial sinusitis in patients in the medical intensive care unit: a prospective epidemiological study. Clin Infect Dis. 1998;27(3):463–70.
42. Humphrey MA, Simpson GT, Grindlinger GA. Clinical characteristics of nosocomial sinusitis. Ann Otol Rhinol Laryngol. 1987;96(6):687–90.
43. Grindlinger GA, Niehoff J, Hughes SL, Humphrey MA, Simpson G. Acute paranasal sinusitis related to nasotracheal intubation of head-injured patients. Crit Care Med. 1987;15(3):214–7.
44. Balsalobre Filho LL, Vieira FMJ, Stefanini R, Cavalcante R, Santos Rde P, Gregório LC. [Nosocomial sinusitis in an intensive care unit: a microbiological study]. Braz J Otorhinolaryngol. 2011;77(1):102–6.
45. Holzapfel L, Chevret S, Madinier G, et al. Influence of long-term oro- or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: results of a prospective, randomized, clinical trial. Crit Care Med. 1993;21(8):1132–8.

46. Bert F, Lambert-Zechovsky N. Microbiology of nosocomial sinusitis in intensive care unit patients. J Infect. 1995;31(1):5–8.
47. Brook I. Microbiology of nosocomial sinusitis in mechanically ventilated children. Arch Otolaryngol Head Neck Surg. 1998;124(1):35–8.
48. Patel NA, Garber D, Hu S, Kamat A. Systematic review and case report: Intracranial complications of pediatric sinusitis. Int J Pediatr Otorhinolaryngol. 2016;86:200–12.
49. Hakim HE, Malik AC, Aronyk K, Ledi E, Bhargava R. The prevalence of intracranial complications in pediatric frontal sinusitis. Int J Pediatr Otorhinolaryngol. 2006;70(8):1383–7.
50. Ruoppi P, Seppä J, Nuutinen J. Acute frontal sinusitis: etiological factors and treatment outcome. Acta Otolaryngol. 1993;113(2):201–5.
51. Southwick FS, Richardson EP, Swartz MN. Septic thrombosis of the dural venous sinuses. Medicine (Baltimore). 1986;65(2):82–106.
52. Ebright JR, Pace MT, Niazi AF. Septic thrombosis of the cavernous sinuses. Arch Intern Med. 2001;161(22):2671–6.
53. Estrem SA, Tully R, Davis WE. Rhinocerebral mucormycosis: computed tomographic imaging of cavernous sinus thrombosis. Ann Otol Rhinol Laryngol. 1990;99(2 Pt 1):160–1.
54. Gelston CD, Durairaj VD, Simoes EA. Rhino-orbital mucormycosis causing cavernous sinus and internal carotid thrombosis treated with posaconazole. Arch Ophthalmol. 2007;125(6):848–9.
55. Kinis V, Ozbay M, Bakir S, et al. Management of orbital complications of sinusitis in pediatric patients. J Craniofac Surg. 2013;24(5):1706–10.
56. Soon VTE. Pediatric subperiosteal orbital abscess secondary to acute sinusitis: a 5-year review. Am J Otolaryngol. 2011;32(1):62–8.
57. Brook I. Microbiology of acute sinusitis of odontogenic origin presenting with periorbital cellulitis in children. Ann Otol Rhinol Laryngol. 2007;116(5):386–8.
58. Coudert A, Ayari-Khalfallah S, Suy P, Truy E. Microbiology and antibiotic therapy of subperiosteal orbital abscess in children with acute ethmoiditis. Int J Pediatr Otorhinolaryngol. 2018;106:91–5.
59. Milczuk HA, Dalley RW, Wessbacher FW, Richardson MA. Nasal and paranasal sinus anomalies in children with chronic sinusitis. Laryngoscope. 1993;103(3):247–52.
60. Smart BA. The impact of allergic and nonallergic rhinitis on pediatric sinusitis. Curr Allergy Asthma Rep. 2006;6(3):221–7.
61. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics. 1991;87(3):311–6.
62. Boase S, Foreman A, Cleland E, et al. The microbiome of chronic rhinosinusitis: culture, molecular diagnostics and biofilm detection. BMC Infect Dis. 2013;13:210.
63. Brook I. The role of antibiotics in pediatric chronic rhinosinusitis. Laryngoscope Investig Otolaryngol. 2017;2(3):104–8.
64. Wald ER. Microbiology of acute and chronic sinusitis in children and adults. Am J Med Sci. 1998;316(1):13–20.
65. Brook I. Microbiology of sinusitis. Proc Am Thorac Soc. 2011;8(1):90–100.
66. Goldenhersh MJ, Rachelefsky GS, Dudley J, et al. The microbiology of chronic sinus disease in children with respiratory allergy. J Allergy Clin Immunol. 1990;85(6):1030–9.
67. Slack CL, Dahn KA, Abzug MJ, Chan KH. Antibiotic-resistant bacteria in pediatric chronic sinusitis. Pediatr Infect Dis J. 2001;20(3):247–50.
68. Brook I, Yocum P. Antimicrobial management of chronic sinusitis in children. J Laryngol Otol. 1995;109(12):1159–62.
69. Erkan M, Ozcan M, Arslan S, Soysal V, Bozdemir K, Haghighi N. Bacteriology of antrum in children with chronic maxillary sinusitis. Scand J Infect Dis. 1996;28(3):283–5.
70. Nadel DM, Lanza DC, Kennedy DW. Endoscopically guided cultures in chronic sinusitis. Am J Rhinol. 1998;12(4):233–41.
71. Green KK, Barham HP, Allen GC, Chan KH. Prognostic factors in the outcome of invasive fungal sinusitis in a pediatric population. Pediatr Infect Dis J. 2016;35(4):384–6.

72. Kennedy JL, Borish L. Chronic rhinosinusitis and antibiotics: the good, the bad, and the ugly. Am J Rhinol Allergy. 2013;27(6):467–72.
73. Bhattacharyya N. The role of infection in chronic rhinosinusitis. Curr Allergy Asthma Rep. 2002;2(6):500–6.
74. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis. 2002;8(9):881–90.
75. Ceri H, Olson ME, Stremick C, Read RR, Morck D, Buret A. The Calgary Biofilm Device: new technology for rapid determination of antibiotic susceptibilities of bacterial biofilms. J Clin Microbiol. 1999;37(6):1771–6.
76. Post JC, Hiller NL, Nistico L, Stoodley P, Ehrlich GD. The role of biofilms in otolaryngologic infections: update 2007. Curr Opin Otolaryngol Head Neck Surg. 2007;15(5):347–51.
77. Galli J, Calò L, Ardito F, et al. [Bacterial biofilm identification in the rhinopharingeal mucosa of children with recurrent infection of the upper respiratory tract and otitis media]. Pediatr Med Chir. 2008;30(1):31–4.
78. Kania RE, Lamers GEM, Vonk MJ, et al. Characterization of mucosal biofilms on human adenoid tissues. Laryngoscope. 2008;118(1):128–34.
79. Shin KS, Cho SH, Kim KR, et al. The role of adenoids in pediatric rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2008;72(11):1643–50.
80. 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.
81. Dlugaszewska J, Leszczynska M, Lenkowski M, Tatarska A, Pastusiak T, Szyfter W. The pathophysiological role of bacterial biofilms in chronic sinusitis. Eur Arch Otorhinolaryngol. 2016;273(8):1989–94.
82. Otten FW, Grote JJ. Treatment of chronic maxillary sinusitis in children. Int J Pediatr Otorhinolaryngol. 1988;15(3):269–78.
83. Tinkelman DG, Silk HJ. Clinical and bacteriologic features of chronic sinusitis in children. Am J Dis Child. 1989;143(8):938–41.
84. Muntz HR, Lusk RP. Bacteriology of the ethmoid bullae in children with chronic sinusitis. Arch Otolaryngol Head Neck Surg. 1991;117(2):179–81.
85. Orobello PW, Park RI, Belcher LJ, et al. Microbiology of chronic sinusitis in children. Arch Otolaryngol Head Neck Surg. 1991;117(9):980–3.
86. Brook I, Yocum P, Shah K. Aerobic and anaerobic bacteriology of concurrent chronic otitis media with effusion and chronic sinusitis in children. Arch Otolaryngol Head Neck Surg. 2000;126(2):174–6.
87. Don DM, Yellon RF, Casselbrant ML, Bluestone CD. Efficacy of a stepwise protocol that includes intravenous antibiotic therapy for the management of chronic sinusitis in children and adolescents. Arch Otolaryngol Head Neck Surg. 2001;127(9):1093–8.
88. Tuncer U, Aydogan B, Soylu L, Simsek M, Akcali C, Kucukcan A. Chronic rhinosinusitis and adenoid hypertrophy in children. Am J Otolaryngol. 2004;25(1):5–10.
89. Ilki A, Ulger N, Inanli S, et al. Microbiology of sinusitis and the predictive value of throat culture for the aetiology of sinusitis. Clin Microbiol Infect. 2005;11(5):407–10.
90. Adappa ND, Coticchia JM. Management of refractory chronic rhinosinusitis in children. Am J Otolaryngol. 2006;27(6):384–9.
91. Criddle MW, Stinson A, Savliwala M, Coticchia J. Pediatric chronic rhinosinusitis: a retrospective review. Am J Otolaryngol. 2008;29(6):372–8.
92. Hsin C-H, Su M-C, Tsao C-H, Chuang C-Y, Liu C-M. Bacteriology and antimicrobial susceptibility of pediatric chronic rhinosinusitis: a 6-year result of maxillary sinus punctures. Am J Otolaryngol. 2010;31(3):145–9.
93. Stokken J, Gupta A, Krakovitz P, Anne S. Rhinosinusitis in children: a comparison of patients requiring surgery for acute complications versus chronic disease. Am J Otolaryngol. 2014;35(5):641–6.
94. Brook I. Bacteriologic features of chronic sinusitis in children. JAMA. 1981;246(9):967–9.

Part II
Sinusitis and Other Pediatric Issues

Chapter 6
The Role of Adenoids in Pediatric Sinusitis

Max April and Sara C. Gallant

Background

Up to 5–10% of upper respiratory infections in children are complicated by acute sinusitis [1, 2]. A subset of children are affected by chronic rhinosinusitis (CRS), but significant variation exists in definition of this disease in the pediatric population. In 2014, a panel selected by the American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HSNF) published a consensus statement (Table 6.1) that endeavored to elucidate definitions and management of pediatric CRS; the definition required at least 90 continuous days of 2 or more symptoms of purulent rhinorrhea, nasal obstruction, facial pain and pressure, or cough, as well as endoscopic or computed tomography (CT) findings consistent with CRS [3].

In keeping with the generally incomplete understanding of pediatric CRS, it remains unclear why a subset of children are more prone to CRS. Possible contributing etiologies include allergic rhinitis, anatomic obstruction of the ostiomeatal unit, susceptibility to upper respiratory tract infections, and ciliary dysfunction in the mucus membranes. Challenges that complicate the study of this process in children include age-dependent difficulty in communicating symptoms, difficulty of performing nasal endoscopy and obtaining targeted cultures in the less compliant pediatric population, and more recently minimization of computed tomography in pediatrics in an effort to spare children from long-term effects of radiation.

M. April (✉) · S. C. Gallant
Department of Otolaryngology–Head and Neck Surgery, NYU Langone Medical Center, New York, NY, USA
e-mail: max.april@nyumc.org

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_6

Table 6.1 Pediatric chronic rhinosinusitis: statements reaching consensus among AAO-HNS expert panel

	Statement
1	Pediatric chronic rhinosinusitis is defined as at least least 90 continuous days of 2 or more symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough and either endoscopic signs of mucosal edema, purulent drainage, or nasal polyposis and/or CT scan changes showing mucosal changes within the ostiomeatal complex and/or sinuses in a pediatric patient aged 18 years or younger
2	Management of children aged 12 years and younger with CRS is distinctly different than management of children aged 13 to 18 years old with CRS
3	**Nasal endoscopy (flexible or rigid) is appropriate in evaluating a child with CRS to document purulent drainage, mucosal edema, nasal polyps, and/or adenoid pathology (hyperplasia, infection)**
4	Management of the children with nasal polyps and CRS is distinctly different than management of children with CRS unaccompanied by nasal polyps
5	Allergic rhinitis is an important contributing fact or to PCRS, especially in older children
6	**Adenoiditis is an important contributing factor to PCRS, especially in younger children**
7	**The ability of adenoidsto serve as a bacterial reservoir for PCRS is independent of adenoid size**

Table listing statements about pediatric CRS for which a panel of experts organized by the AAO-HNS reached consensus. Adenoid-related statements are in shaded fields. Used with permission from [3]

The 2014 consensus panel identified that "adenoiditis is an important contributing factor to pediatric CRS, especially in younger children." The adenoid tissue is composed of a variably-sized mound of epithelial immune tissue located in the nasopharynx. It is part of Waldeyer's ring and is exposed to both airborne and ingested antigens due to its position in the upper airway. It can also harbor viruses and bacteria, which can inoculate the nasal and sinus mucosa or the middle ear causing infections. When adenoid tissue is enlarged, mass effect can cause nasal obstruction and voice abnormalities, as well as impaired drainage of secretions from the nasopharynx and nasal cavities. Adenoid tissue reaches a maximum size at the age 3–7 years and then begins to involute with increasing age.

There are several reports indicating that CRS symptoms may improve after children undergo adenoidectomy; a 2008 meta-analysis identified 9 papers that described efficacy of adenoidectomy in pediatric CRS. An estimated 69.3% of patients had post-adenoidectomy improvement in sinusitis symptoms including rhinorrhea, post-nasal drip, cough, congestion, antibiotic courses, and doctor's office visits, per caregiver report [4]. Adenoidectomy has become a common step in management of CRS in children who fail conservative medical management due to these noted improvements in symptoms postoperatively.

Pathophysiology: Adenoid Tissue and CRS

In children, the structural cause of nasal obstruction can be within the nasal cavity (e.g., inflamed or enlarged inferior turbinates or septal deviation) or within the nasopharynx, where adenoid hypertrophy may be the culprit. However, adenoidectomy is reported to improve CRS symptoms such as rhinorrhea, cough, post nasal drip, and halitosis, which cannot be explained if adenoidectomy's effectiveness is solely due to the removal of nasal and nasopharyngeal obstruction [4]. The mechanism by which it helps these symptoms may include but not be limited to elimination of an obstruction which causes secretion stasis by blocking drainage from the nasal cavities and nasopharynx, as well as elimination of a nidus for chronic bacterial colonization.

Adenoid tissue is known to harbor bacteria, particularly group A beta-hemolytic streptococcus, *H. influenzae*, and *S. aureus.* During upper respiratory infections or in cases of inflammatory conditions such as allergic rhinitis, impaired mucociliary function may allow these bacteria entry into the sinuses via the ostia.

A prospective study examining species and burden of pathogens in core adenoid tissue of children undergoing adenoidectomy for multiple reasons showed a strong positive correlation between level of sinonasal symptomatology in a given patient and the number of colony forming units and pathogens found in that patient's adenoid tissue, after adjustment for specimen weight and the effects of nasal obstruction symptoms [1].

Another study compared maxillary sinusitis severity based on preoperative Waters' view paranasal sinus radiographs, adenoid size based on lateral skull base radiographs, and adenoid bacteriology in children who underwent adenoidectomy for symptoms of adenoid hypertrophy. The most commonly isolated bacteria were *H. influenzae, S., pneumoniae,* and *S. pyogenes.* Bacterial isolation rate increased significantly according to the sinusitis grade, but there was no statistically significant correlation between sinusitis grade or adenoid bacteriology and adenoid to nasopharynx size ratio [5].

Otolaryngologists and other physicians should be aware of the bacteria's ability to form complex adherent communities known as biofilms on mucosal surfaces such as the adenoid. Individual planktonic bacteria communicate with each other and coalesce, subsequently adhering to surfaces using glycoconjugate moieties. An exopolysaccharide matrix is formed as the cells divide, and gradually the colony forms complex structures such as towers and water channels from a substance called extracellular polymeric substances (EPSs). These structures enhance survival of the bacteria within them; they help the bacteria eliminate waste, create a pH and oxygen tension gradient which allow maximum metabolic efficiency within the colony, and provide protection from mechanical forces, antibiotic treatment, and host defenses. Biofilms' resistance to the normal antibacterial functions of the immune system can lead to a sustained inflammatory response, which damages nearby mucosa without eradicating the bacterial infection. At intervals, biofilms

shed individual or clusters of metabolically active surface planktonic bacteria, which can then act as pathogens at separate loci. Thus, otolaryngologic diseases which involve biofilms often have a chronic time course and are characterized by antibiotic resistance and acute flare-ups [6].

Biofilms have been implicated in PCRS after having been identified in the paranasal sinus mucosa and in the adenoid tissue of pediatric patients with CRS. A study that used electron microscopy to compare the adenoid tissue removed from children with CRS and children requiring adenoidectomy for obstructive sleep apnea (OSA) found that the CRS-associated adenoid tissue had a mean of 94.9% surface coverage by mature biofilms, whereas the OSA-associated adenoid tissue had a mean of 1.9% coverage [7]. With biofilm presence in the adenoid tissue, intermittent shedding of active bacteria could intermittently seed the paranasal sinuses causing acute episodes of infection and chronic inflammation, as well as establishment of biofilms within the paranasal sinuses. Although consensus is that size of the adenoid does not seem to affect its ability to harbor bacteria [3], further extension into the nasal cavity due to hypertrophy could allow these shedding active bacteria to access the paranasal sinuses more easily due to closer proximity.

Several studies suggest that the adenoid plays its role in the immune system differently in patients with CRS than in those who undergo adenoidectomy for different indications. Adenoid tissue is composed largely of B and T lymphocytes, with a small component of plasma cells, covered with respiratory epithelium. Via this epithelium, the adenoid is thought to affect mucociliary clearance, secrete endogenous antimicrobial peptides (AMPs), and express pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) which in turn recognize pathogen-associated molecular patterns (PAMPs) which are presented to the mucosa. One small study compared levels of messenger RNA for selected genes of innate immunity in hypertrophic adenoid tissue removed from children with and without CRS. The study found that levels of RNA for SP-D, a mucosally secreted innate immunity protein that binds to pathogens and hastens clearance by antigen-presenting cells, were lower in the adenoidal epithelium of the patients who had CRS compared to those who had adenoid hypertrophy alone. On the other hand, levels of all common PRRs were not significantly different between the groups [8].

The adenoid tissues also secrete IgA, thus affecting mucosal surface protection. A study comparing adenoid tissue from children who underwent adenoidectomy for adenoid obstruction to tissue from children with otitis media with effusion (OME) or CRS showed lower IgA antibody staining in the children with or CRS [9].

A prospective study comparing surgically removed adenoid tissue from children with and without CRS found that the CRS patients' tissue expressed higher levels of tissue-remodeling associated cytokines like matrix metalloproteases (MMPs). These cytokines have been shown to be highly expressed in the nasal mucosa of CRS patients and are thought to play a major role in tissue remodeling and inflammation. The same study found that greater CRS severity as measured by radiographic plain film findings was significantly correlated with higher levels of activated inflammatory cells and cytokines in adenoid tissues [10].

Pediatric CRS has also been linked with asthma, which affects 2–20% of children [3]. The two diseases have similar pathophysiology – mast cells and eosinophils have been identified in the nasal mucosa of patients with allergic rhinitis and in the bronchial mucosa of patients with asthma. It is unclear whether the same inflammatory processes in the upper and lower airway tract cause both asthma and CRS as in the "united airway" hypothesis, or whether there is a more complicated interplay between differing inflammatory processes going on in the upper and lower airway.

A study comparing the expression of inflammatory cytokines in adenoid and sinus tissue sampled from children with CRS with or without asthma and from controls who were undergoing surgery for other pathologies showed an increase in select inflammatory cytokines and chemokines in sinus and adenoid tissues in children with CRS compared to controls, and higher levels of the same cytokines in the asthmatic CRS group when compared to the non-asthmatic CRS group [11].

Approaches to Treatment

Traditionally, the cornerstone of medical therapy for pediatric CRS has consisted of topical nasal steroid sprays, irrigations, and prolonged courses of broad-spectrum beta-lactamase stable antibiotics. Adjunct treatments may include systemic steroids, decongestants, allergy management, and antireflux medications. For children who fail medical management, the preferred approach to treatment is still evolving.

A prospective cohort study of 41 imaging-confirmed pediatric CRS patients from 1995 examined response based on caregiver surveys to a stepwise approach to refractory pediatric CRS treatment, consisting of a 2-month course of a beta-lactamase stable antibiotic (in addition to a prior 3-week course which was required for study inclusion), followed by adenoidectomy, and then ESS if indicated. Of note, out of 26 nonresponders to antibiotics, 10 progressed to adenoidectomy; in 16 patients, no adenoids were present so they went on to FESS. Two patients underwent FESS after failing adenoidectomy. Interestingly, there were no differences between groups in terms of number of sinus areas involved on CT. However, patients in the group that progressed to FESS were more likely to have asthma, allergic rhinitis, a longer duration of sinusitis, more total episodes of infection, and a greater number of symptoms. At 1-year follow-up, 88% of caregivers had had their expectations met. 13% of patients receiving antibiotics with or without adenoidectomy had expectations exceeded, whereas 50% of ESS patients did. All major symptoms were improved in 100% of ESS patients, compared with 75% of adenoidectomy patients and 67% of antibiotic patients. The groups of children as divided by final treatment did not differ significantly in terms of final outcomes, indicating a successful stepped approach [12].

The 2014 AAO-HNSF panel reached consensus that topical nasal steroid sprays and irrigations are beneficial for PCRS. The panel did not reach a consensus on an appropriate minimum antibiotic regimen for PCRS, but did reach consensus that 20, when compared to 10 days of antibiotics, may have a superior clinical effect and

that culture-directed antibiotic therapy might improve outcomes for PCRS patients who fail empiric antibiotic therapy targeted at common sinonasal pathogens. With regard to adenoidectomy, consensus was reached that adenoidectomy was an effective initial surgical therapy for patients aged up to 6 years; less consensus was obtained for patients aged 6–12 years, and no consensus could be reached regarding the role of adenoidectomy as first-line surgical treatment for patients older than 13 due to the absence of data in the literature surrounding adenoidectomy in this age group. When considering ESS, consensus was reached that it is best performed after failure of medical management, adenoidectomy, or both to control PCRS symptoms [3].

Several papers challenge this recommendation. A prospective study compared caregiver questionnaire-based outcomes at 6 and 12 months in patients with pediatric CRS who had failed 6 months of medical management and who underwent either adenoidectomy or ESS. Surgery was assigned in a nonrandomized fashion. As might be expected given the nonrandomized assignment of surgery, the ESS group had more severe disease based on CT findings as well as an older average age. After surgery, the ESS group reported more improvement in all symptoms except for nasal congestion and cough (which were similar) than the adenoidectomy group. 77% of patients who underwent ESS compared with 47% of patients who underwent adenoidectomy reported symptom improvement at 6 months. 3% of ESS patients compared with 40% of adenoidectomy patients went on to receive the other surgery due to refractory symptoms. Adjustment for age, sex, asthma, allergy, CT stage, and day care status with multivariate analysis showed that the rates of improvement in one or more of the questionnaire symptoms after ESS compared with adenoidectomy were still significant despite nonrandomization. Interestingly, this analysis also revealed asthma as the only other significant predictor of success after surgery. Of note, because all of these children had been referred after at least 6 months of medical therapy and had disease on CT scan, the sample patients may have had more severe disease than the general pediatric CRS population [13].

Adenoidectomy is not effective definitive treatment for all children with CRS. One study aimed at elucidating which children would have improvements in sinusitis after adenoidectomy grouped children by size of their adenoid and found that adenoidectomy improved sinusitis in 20% in the group with a small adenoid, 35% in the group with a medium adenoid, and 57% in the group with a large adenoid [14]. It is unclear why size may be predictive of clinical response; as is noted earlier in this chapter, several studies have suggested that bacterial burden of adenoid tissue is independent of its size [1, 5]. A larger adenoid may cause worse symptoms due to nasal obstruction factors or may cause worsened nasal cavity and ostiomeatal complex disease by creating a greater impediment to proper drainage and creating greater physical proximity of their bacterial loads to the sinonasal mucosa.

Endoscopic sinus surgery (ESS) can be safely performed in children by clinicians with adequate experience. However, in ESS as compared to adenoidectomy, there is a greater risk of serious complications such as periorbital injury, CSF leak, or other injury from the inherent nature of the procedure. In one paper comparing

groups undergoing ESS alone, adenoidectomy alone, and ESS in combination with adenoidectomy, the only surgical complications – minor orbital complications in 2.9% of patients – were related to an ESS procedure [2].

ESS also involves more resources than adenoidectomy; there is a more complicated list of endoscopic equipment, state-of-the-art surgery mandates the use of image guidance which can be expensive and requires a thin-cut CT scan with radiation, and OR times are longer than in adenoidectomy.

Previously cited reasons to avoid or delay ESS in children include fear of disrupting facial bone growth and difficulty of post-op debridement. The former concern was based on animal studies in which ESS was performed unilaterally and in which growth retardation was seen in the facial skeleton on the operated side. However, a 2002 comparison of pediatric patients who underwent ESS compared with those who were offered but refused ESS showed no difference in facial growth over a 10-year period [15]. Indeed, the panel which created the AAO-HNSF consensus statement on the topic of pediatric CRS agreed that there was lack of convincing evidence of this reason for avoiding ESS in children. The panel also agreed that good postoperative debridement is not necessary for successful results of ESS in PCRS [3].

One key question is whether adenoidectomy or ESS should be performed separately with one as the first line, or in tandem. Another prospective nonrandomized study compared children with refractory CRS who underwent ESS alone, adenoidectomy alone, or adenoidectomy and ESS in combination. Some patients in the ESS-alone group did better than the adenoidectomy alone, and some of the patients in the ESS and adenoidectomy group did better than children in the single modality groups. Adenoidectomy was successful at alleviating symptoms in 52% of cases, whereas ESS was successful in 75% and ESS with adenoidectomy successful in 87%. Multivariate analysis controlling for age, gender, asthma, allergy, severity of disease based on CT, cigarette smoke exposure, and day care attendance showed that ESS plus adenoidectomy was more effective than ESS alone. The authors of the study concluded therefore that children should be offered adenoidectomy alone or both adenoidectomy and ESS at once. They found that children with asthma who were exposed to cigarette smoke benefited the least from adenoidectomy alone and more from ESS and adenoidectomy together. They also noted that children under 6 years of age with low CT score and no asthma tended to have success from adenoidectomy alone, whereas children older than 6 years with a high CT score had a 96% success rate with combined ESS and adenoidectomy [2].

Another paper by the same lead author, this time retrospective, aimed to establish which children who underwent adenoidectomy for CRS were likely to fail to improve after this intervention and go on to require ESS after a period of time. Sixty-one out of 121 children failed to improve after adenoidectomy; 55 went on to undergo ESS. The mean time from adenoidectomy to ESS in those who required it was 24 months. Asthma and age of less than 7 years were predictive of earlier failure. The study did not compare characteristics of the failure group with characteristics of the group of all patients who underwent adenoidectomy for CRS [16].

Balloon sinuplasty is a relatively recently developed intervention which serves as a procedure that opens key sinus ostia without stripping mucosa and with less risk

to adjacent structures. A nonrandomized prospective study which compared symptom scores in children who underwent adenoidectomy alone with those who underwent adenoidectomy with targeted balloon sinuplasty found that 52.6% of children undergoing adenoidectomy had a significant score improvement 12 months after surgery compared with 80% of children who also underwent balloon catheter sinuplasty. There were no complications, suggesting that this can be a relatively safe and effective procedure in children. However, the procedure is described as being performed under general anesthesia for the pediatric population, which somewhat changes the calculation of risks and benefits of the procedure [17].

Summary/Recommendations

The authors of this chapter believe that endoscopy plays an important role in the diagnosis and treatment of pediatric CRS, not only for evaluation of mucosal edema, purulence, turbinate hypertrophy, and presence or absence of nasal polyps, but also for evaluation of adenoid hypertrophy and adenoiditis (Fig. 6.1). This was a

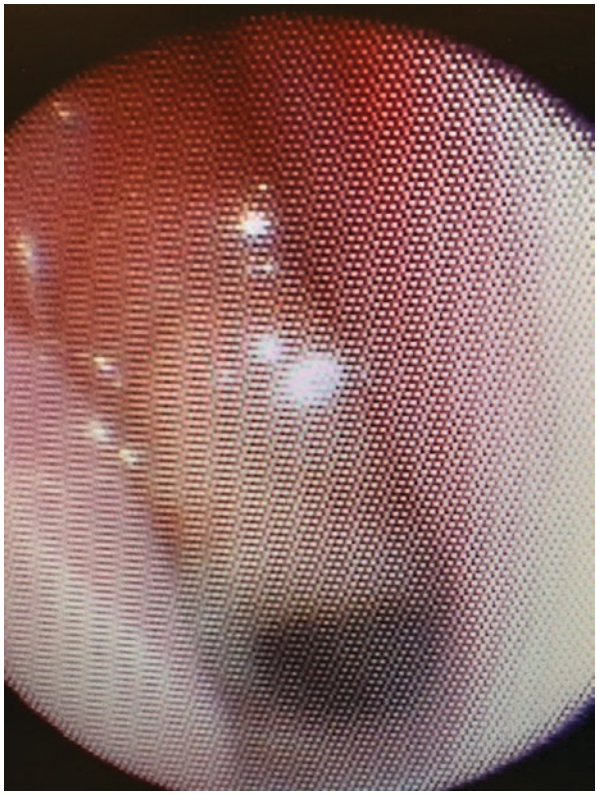


Fig. 6.1 Endoscopic evaluation of the adenoid allows the practitioner to identify hypertrophy and inflammation. In this 4-year-old patient, the adenoid tissue protrudes into the nasal cavity. It is covered in an exudate and is erythematous; the erythema extends to the posterior nasal septum

statement for which the AAO-HNSF panel also reached consensus [3]. Due to reports that adenoid size does not correlate with the extent to which adenoids harbor biofilms, obtaining lateral plain films to assess the adenoids is not recommended.

Primary medical management should include nasal saline rinses, topical nasal steroid sprays, and a trial of antibiotics. For patients who do not respond, adenoidectomy can be performed with the goal of disrupting and debriding the biofilm resident in the nasopharynx, as well as minimizing nasal obstruction.

Patient selection is important for good outcomes. Certain patients including those with craniofacial syndromes, cystic fibrosis, nasal polyposis, allergic fungal disease, immunodeficiency, and ciliary dyskinesia may have predisposing factors that suggest they will not respond well to adenoidectomy; for this reason, these causes should be considered and ruled out as indicated prior to initiation of treatment with procedures such as allergy evaluation, immunoglobulin deficiency workup, and sweat chloride testing. Recurrent episodes of pneumonia or bronchitis or, to a lesser degree, recurrent otitis media should prompt the otolaryngologist to pursue these studies. The presence or absence of asthma should also be noted, as the literature suggests that children with asthma tend to benefit more aggressive surgical treatment for CRS than adenoidectomy alone. Age also plays a role in patient selection; it is reflected in the clinical consensus statement by the expert panel that once children reach the age of 13, treatment approach to CRS tends to differ and ESS may be warranted earlier in the patient's course.

The size of the patients' adenoid is also important to assess for treatment plan development. For patients with a large adenoid that clearly extends into the nasal cavity, adenoidectomy seems to be a prudent first surgical step in treatment. For those with a small adenoid, it may be more efficient to proceed directly with ESS and adenoidectomy. However, if the inferior turbinates are enlarged, while the adenoid is small, adenoidectomy and inferior turbinate reduction may be trialed prior to performing ESS. In patients who have an intermediate amount of adenoid tissue, other patient factors such as age, symptomology, and parental preference help to shape the decision of whether to proceed with adenoidectomy alone or perform ESS (Fig. 6.2). These approaches may vary by patient. Though this framework for decision-making seems to work well for our patient population, it has not been formally measured or compared to other approaches.

We generally perform adenoidectomy using a powered curved microdebrider blade followed by suction monopolar cautery of the base. This approach efficiently removes adenoid tissue with the microdebrider blade, then uses suction monopolar cautery to simultaneously achieve good hemostasis and creates a smooth nasopharyngeal base to decrease crevices in which bacteria may collect and reestablish biofilms. The papers in the literature describe a variety of means of removing adenoid tissue, including curette and suction cautery; it is unclear whether removal technique affects outcomes, and these techniques have not been compared in the literature.

There are still many unanswered questions surrounding the role of adenoidectomy in pediatric CRS. There are relatively few papers on this topic, many of which are by the same few authors. There are also inherent difficulties in studying this

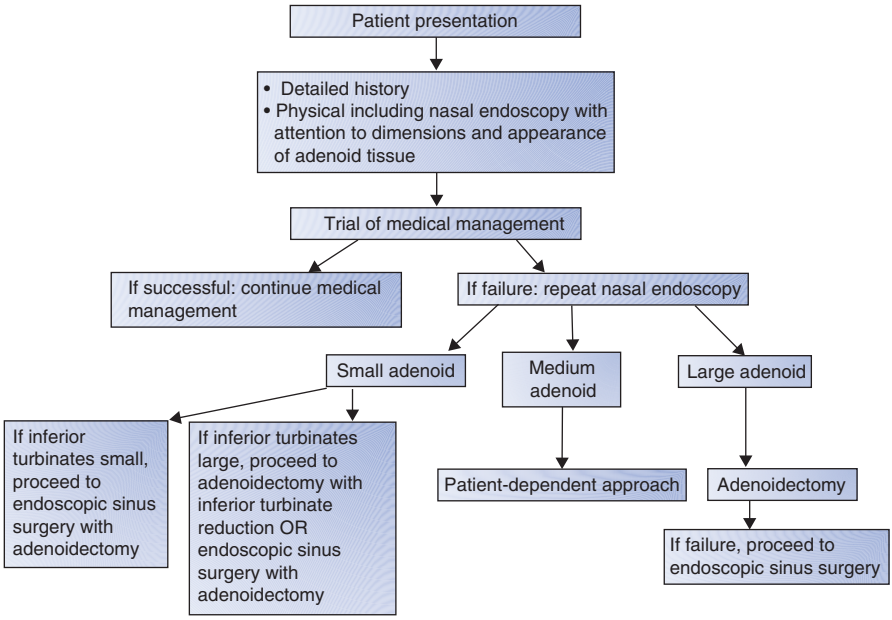


Fig. 6.2 Framework for decision-making

disease in this population. For example, the diagnosis of CRS requires both a specific symptomology as well as endoscopic or CT findings. However, due to difficulty of interviewing pediatric patients, many papers only look at caregiver surveys when assessing outcomes after adenoidectomy or ESS; this introduces a source of bias. Another issue with assessing response arises from the recent relative infrequency with which CT scans are obtained for children due to fears of exposing them to excess radiation. Also, there are few papers that note long-term results in CRS patients who undergo adenoidectomy. Future study should attempt to incorporate more objective measures of success in treatment, more patient cases, and longer follow-up periods.

References

1. Lee D, Rosenfeld RM. Adenoid bacteriology and sinonasal symptoms in children. Otolaryngol Head Neck Surg. 1997;116(3):301–7.
2. Ramadan HH. Surgical management of chronic sinusitis in children. Laryngoscope. 2004;114:2103–9.
3. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
4. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72:1541–5.

5. Shin KS, Cho S, Kim KR, et al. The role of adenoids in pediatric rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2008;72:1643–50.
6. Post JC, Hiller NL, Nistico L, et al. Curr Opin Otolaryngol Head Neck Surg. 2007;15(5):347–51.
7. Coticchia J, Zuliani G, Coleman C, et al. Biofilm surface area in the pediatric nasopharynx. Arch Otolaryngol Head Neck Surg. 2007;113:110–4.
8. Qu XP, Huang ZX, Sun Y, et al. Expression of innate immunity genes in epithelial cells of hypertrophic adenoids with and without pediatric chronic rhinosinusitis: a preliminary report. Chin Med J. 2015;128(21):2913–8.
9. Eun YG, Park DC, Kim SG, et al. Immunoglobulins and transcription factors in adenoids of children with otitis media with effusion and chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2009;73:1412–6.
10. Shin SY, Choi GS, Park HS, et al. Immunological investigation in the adenoid tissues from children with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2009;141:91–6.
11. Anfuso A, Ramadan H, Terrell A, et al. Sinus and adenoid inflammation in children with chronic rhinosinusitis and asthma. Ann Allergy Asthma Immunol. 2015;114(2):103–10.
12. Rosenfeld RM. Pilot study of outcomes in pediatric rhinosinusitis. Arch Otolaryngol Head Neck Surg. 1995;121:729–36.
13. Ramadan HH. Adenoidectomy vs endoscopic sinus surgery for the treatment of pediatric sinusitis. Arch Otolaryngol Head Neck Surg. 1999;125:1208–11.
14. Merck W. Pathogenetic relationship between adenoid vegetations and maxillary sinusitis in children. HNO. 1974;22(6):198–9.
15. Bothwell MR, Piccirillo JF, Lusk RP, et al. Long-term outcome of facial growth after functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2002;126(6):628–34.
16. Ramadan HH, Tiu J. Failures of adenoidectomy for chronic rhinosinusitis in children: for whom and when do they fail? Laryngoscope. 2007;117:1080–3.
17. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. Ann Otol Rhinol Laryngol. 2010;119(9):578–82.

Chapter 7
Allergy and Sinusitis

Sidrah M. Ahmad and Ahmad R. Sedaghat

Introduction

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are diseases that share common clinical and pathophysiological characteristics. Not surprisingly, AR and CRS are commonly comorbid, and each may impact the disease course of the other. AR, in particular, has been identified as one important risk factor and disease modifier for CRS [1].

AR is defined by characteristic symptomatology including nasal obstruction, rhinorrhea, pruritus, and sneezing that arises due to a type I hypersensitivity reaction against otherwise benign airborne environmental antigens, referred to as aeroallergens. In contrast, aeroallergen hypersensitivity refers to production of a type I hypersensitivity reaction that does not necessarily cause clinical symptoms, but is instead detected through allergy testing (skin or serological) [2]. This distinction is particularly important in understanding the clinical impact of an aeroallergen in the setting of a corresponding hypersensitivity. However, this distinction is also difficult to make in the setting of CRS.

S. M. Ahmad
Department of Surgery, Division of Otolaryngology, Stony Brook University Hospital, Stony Brook University School of Medicine, Stony Brook, NY, USA

A. R. Sedaghat (✉)
Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: ahmad.sedaghat@uc.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_7

Epidemiology

CRS affects up to 10% of the population in the United States and Western Europe [1, 3, 4]. The prevalence of CRS specifically in children is less well characterized, but analysis of data from a nationally representative database suggested that there were a total of 44.6 million outpatient physician visits for CRS in patients under 20 years of age in the United States between 2005 and 2012 [5, 6]. In contrast to CRS, AR is far more common. The prevalence of aeroallergen hypersensitivity and AR in the general pediatric population has been reported to be in the range of 10–40% [7, 8]. Previous studies have shown that aeroallergen hypersensitivity can be detected even in infants [9]. Patterns of hypersensitivity in children are similar to those observed in adults—with dust mites and trees being the most common perennial and seasonal hypersensitivities, respectively [9, 10]. Moreover, the prevalence of aeroallergen hypersensitivities in children with CRS is very similar to the prevalence of aeroallergen hypersensitivities in children with AR [11].

Patient Impact

AR has well-described clinical manifestations and downstream consequences, resulting in both direct and indirect costs that represent a major burden on society. The most prominent consequence of AR is related to the decreased quality of life (QOL) due to clinical symptoms suffered by patients, both adults and children [12–15]. Interestingly, the downstream systemic or extra-nasal symptoms of AR—such as poor sleep quality or facial discomfort—appear to be the symptoms associated with the greatest decreases in QOL [15].

The other downstream consequence of AR is related to the lost productivity that patients experience [14, 16]. In children, this directly translates to absenteeism and worse performance in school [14]. The costs of these clinical manifestations and downstream consequences of AR have been described to be billions of dollars annually [17, 18]. This includes direct costs associated with physician visits and medication usage as well as indirect costs associated with decreased productivity, which may equal or even exceed the direct costs.

CRS has similar effects on patients, leading to similarly high costs borne by the patient, the healthcare system, and society as a whole. Like AR, the primary consequence of CRS is decreased QOL. In both children and adults, the QOL detriment associated with CRS has been described to be comparable to that experienced by patients with other severe diseases such as asthma, rheumatoid arthritis, or diabetes [19, 20]. Like AR, the chronic symptoms of CRS—most prominently the systemic symptoms, such as poor sleep quality—appear to be most greatly associated with decreased QOL [21, 22]. CRS is also associated with substantial productivity losses related to missed work or school [23]. These manifestations and consequences of CRS are also associated with billions of

dollars in both direct and indirect costs [24] with up to 30% of these costs arising from care of children under 12 years of age [25].

Given the similar impacts of AR and CRS, and their common anatomic disease epicenter, it is not surprising that AR could potentially modulate the severity of CRS. AR has previously been shown to affect the disease course and downstream consequences of asthma, another inflammatory disease of the airway [26]. For example, AR is associated with more severe asthma and increased frequency of asthma exacerbations, while treatment of AR may also result in improved asthma outcomes [27–29]. It is not surprising then that AR has also been shown to negatively impact QOL in CRS, with some hypersensitivities potentially having a greater effect on CRS-specific QOL than others [30, 31], thereby serving as an important factor in direct and indirect CRS-related costs.

Pathophysiology: Immunologic

In addition to the epidemiologic association between AR and CRS, AR and CRS have been shown to have common inflammatory mechanisms. Unlike AR, which by definition is due to a very specific immunologic mechanism—a type I hypersensitivity reaction—CRS is a highly heterogeneous disease [32]. As CRS is defined based on clinical criteria [33] and not pathophysiology, it is not surprising that many different pathophysiologic mechanisms could converge upon the clinical phenotype defining CRS. However, it has long been known that a subset of CRS patients exhibits high levels of inflammatory mediators that are common to allergic and atopic immune conditions.

Allergy is defined pathophysiologically by a type I hypersensitivity reaction, which is characterized by recognition of allergens by specific IgE antibodies which then bind to the surface of and activate mast cells. Mast cell activation is accompanied by the release of inflammatory mediators including histamine and prostaglandins, which mediate the characteristic downstream symptoms of allergy. However, the inflammatory milieu in allergy is characterized by a pattern of inflammation that is referred to as type 2 T helper (Th2)-mediated inflammation, in reference to the types of CD4+ (helper) T cells that serve as the master regulators of the inflammation (Fig. 7.1) [34]. The Th2 response is characterized by the prototypical cytokines interleukin (IL-) 4, IL-5, and IL-13 that were initially identified to be produced by Th2 cells over three decades ago [35]. The Th2 response has been shown to have a prominent role in both allergic diseases and anti-parasitic immune responses. In the ensuing years since its initial discovery, a significant amount of insight has been gained into the Th2 inflammatory cascade. An important role for the epithelium and epithelial injury has been identified in the production of IL-25, IL-33, and TSLP, which may serve as prominent recruiters of cellular mediators of Th2 inflammation, including not only Th2 cells but also eosinophils, mast cells, and basophils [36]. More recent work has shown that epithelial injury is one important mechanism for the consequent inflammatory cascade that recruits Th2 inflammation in the nasal

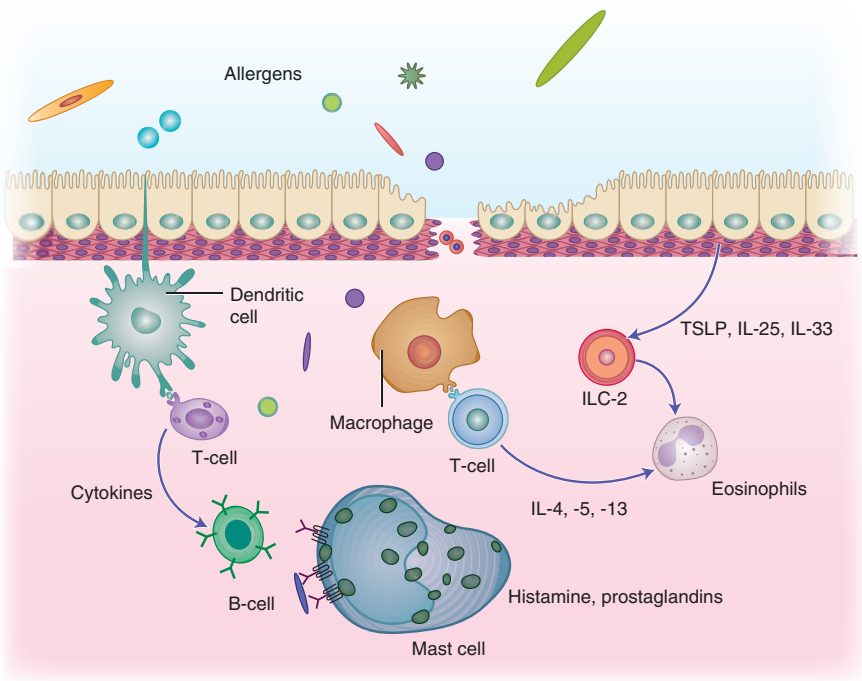


Fig. 7.1 Schematic showing the Th2 inflammatory pathway, which includes interactions between innate immunity (such as the epithelium, macrophages, dendritic cells, ILC-2 s, mast cells, and eosinophils) and adaptive immunity (including T cells and B cells)

mucosa during AR [37]. As noted above, the cytokines associated with the Th2 response include IL-4, IL-5, and IL-13. It has also been recently shown that these cytokines are produced by other inflammatory cells such as eosinophils and type 2 innate lymphoid cells in addition to Th2 cells [38], which can also serve to recruit additional inflammatory cells like mast cells, basophils, and IgE-producing plasma cells.

Cellular and molecular profiling of patients with CRS has demonstrated that a subset of CRS patients exhibit abnormally high levels of Th2 mediators in their sinonasal mucosa [39]. These Th2-skewed CRS patients have historically been found to have nasal polyps. Similar to AR, Th2 inflammation in CRS is associated with dysfunction of, or injury to, the sinonasal epithelium [40]. Increasingly sophisticated molecular profiling of sinonasal mucosa performed in conjunction with patients' clinical characteristics has led to more detailed subclassification of clinical presentations of CRS based on pathophysiology, referred to as "endotypes." Endotyping of CRS patients has shown that CRS patients with high levels of Th2 mediators in their sinonasal mucosa are more likely to have polyps, comorbid asthma, aeroallergen hypersensitivity, and increasingly recalcitrant disease [41, 42].

In the vast majority of CRS patients, the antigen (or allergen) that is driving the disease is not apparent and therefore cannot be targeted. However, in some instances, an allergen may be identified. For example, some CRS patients with strong Th2 responses have been found to have inflammation in their sinonasal mucosa that is reflective of an allergy-like responses to *Staphylococcus aureus* [41]. *S. aureus* may in fact be a dominant driving force in a subset of CRS patients [43]. However, it is possible that allergic inflammation in response to any number of microbes may lead to the development of CRS, as multiple studies have described disruption of the sinonasal microbiome in the setting of prominent Th2 inflammation [44, 45]. Allergic fungal rhinosinusitis is a subtype of CRS that is thought to be due to allergic inflammation specifically directed at fungal elements that commonly exist in the environment or that may be introduced into the paranasal sinuses [46]. Another clinical phenotype of CRS that has been more recently described in the literature has been referred to as "central compartment atopic disease" (CCAD) [47, 48]. CCAD describes a subset of CRS patients in whom the sites of mucosal inflammation, i.e., active disease, are objectively identified to be within the areas of the paranasal sinuses closest to the nasal cavity. In these patients, in whom physical exam findings of polypoid changes to the middle turbinates are noted, there is a high prevalence of aeroallergen hypersensitivity. The pattern of objective disease distribution appears to be in areas that would be most exposed to aeroallergens, and as such CCAD is thought to be one form of CRS that is driven by allergy.

Pathophysiology: Anatomic

In addition to specifically driving the underlying inflammation in CRS and promoting common inflammatory responses that may aggravate a patient's CRS, AR plays a role in the development and persistence of CRS through other mechanisms. One simplistic explanation for the development of CRS is through blockage of the sinus drainage pathways with subsequent mucus retention and oxygen depletion that inhibits ciliary function and promotes bacterial growth (Fig. 7.2a). AR is associated with mucosal edema in the nasal cavity and proximal regions of the paranasal sinuses, which may be one cause of sinus outflow obstruction. Previous work has also demonstrated that AR may serve as a premorbid condition to CRS [49]. Subsequent work following patients with AR found that the presence of variants of normal sinonasal anatomy known to cause sinus outflow obstruction, such as infraorbital ethmoid air cells, was associated with the subsequent development of CRS [50, 51]. These results support the notion that allergic inflammation may contribute to the development of CRS by further constricting already narrow sinus outflow tracts (Fig. 7.2b).

The obstruction of sinus outflow tracts due to allergic inflammation may also be a risk factor for recurrent acute bacterial rhinosinusitis [52, 53]. Acute bacterial rhinosinusitis complicates 4–6% of all upper respiratory tract infections in children [54]. Its etiopathogenesis is thought to be related to obstructed sinus outflow with

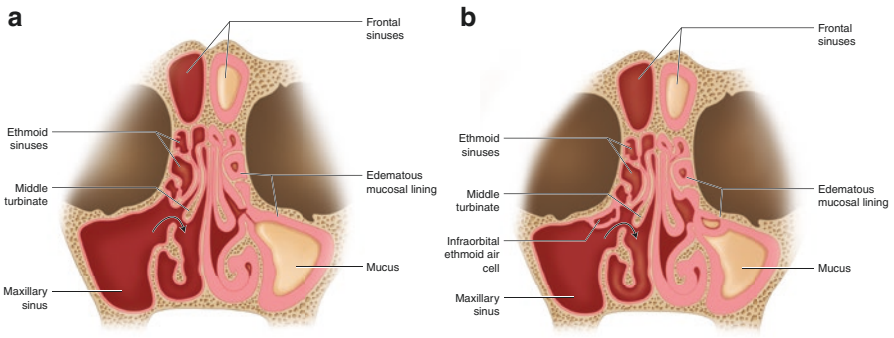


Fig. 7.2 Schematic showing, on a coronal section through the paranasal sinuses, (**a**) obstruction of normal mucociliary clearance (left) by mucosal edema within normal sinus outflow tracts (right) and (**b**) further obstruction of normal mucociliary clearance (left) by mucosal edema within the outflow tract of a maxillary sinus with the obstructive anatomic variant referred to as an infraorbital ethmoid air cell (right)

stasis of mucus that is increased in production in the setting of an upper respiratory tract infection. This obstruction may arise from the sinonasal inflammatory response that normally occurs in an upper respiratory tract infection but may be more likely if there is increased sinonasal mucosal edema at baseline due to AR.

Interestingly, the number of aeroallergen hypersensitivities has not been found to be significantly associated with rhinosinusitis. In patients with AR, an increased number of aeroallergen hypersensitivities were not associated with the development of CRS [55, 56]. These results in total suggest that the role of allergy in the development of rhinosinusitis is complex and not determined solely by how atopic a patient may be.

Treatment and Controversies

The mainstay of treatment for both CRS and AR is medical management. Level 1 evidence supports the use of intranasal saline irrigations and intranasal corticosteroids for treatment of both CRS and AR [57–60]. However, to date there is insufficient evidence to support the use of treating allergies with antihistamines, antileukotrienes, or immunotherapy, for the management of CRS [1, 61]. As such, these treatment modalities can be considered as options for the treatment of CRS but may or may not be beneficial [1].

Given the increasing knowledge of the heterogeneous nature of CRS, it is not surprising that allergy-specific treatments are not universally effective for CRS. For example, only approximately half of CRS patients have polyps (as a reflection of a Th2 inflammatory skew), and only approximately half of all CRS patients may have an aeroallergen hypersensitivity [11, 30]. Moreover, aeroaller-

gen hypersensitivity—the presence of positive allergy testing—does not necessarily translate to allergy, which implies a functional significance for the hypersensitivity. This functional significance for hypersensitivity is detected as the presence of nasal symptoms by the patient with AR. However, in the setting of CRS, which is defined by chronic nasal symptoms, it is unclear whether those nasal symptoms arise due to hypersensitivity or some other inflammatory process in the sinonasal mucosa. Making matters more confusing is the possibility that breakdown of the sinonasal epithelium in the setting of CRS may predispose CRS patients to development of hypersensitivity—hence the higher prevalence compared to the general population—but not necessarily with downstream clinical significance [62, 63]. Although some subsets of CRS patients have been identified, such as those with allergic fungal rhinosinusitis or CCAD, for whom allergy may play an important role in their sinonasal disease and therefore serve as a therapeutic target, at present it is still not possible to identify all CRS patients whose disease is at least partly driven by allergy and would therefore benefit from allergy-specific treatments.

Conclusions

AR and CRS are diseases that are linked through epidemiologic association, common clinical presentation, and common pathophysiologic mechanisms. AR may contribute to the development and persistence of CRS. However, because CRS is a pathophysiologically heterogeneous disease, the manner in which AR may contribute to the CRS disease process from patient-to-patient still cannot be fully appreciated. Development of means for identifying patients for whom allergy plays a dominant role in their CRS disease process is still needed for accurately determining which CRS patients will most benefit from allergy-specific treatments.

References

1. Orlandi RR, et al. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(Suppl 1):S209.
2. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on practice parameters in allergy, asthma and immunology. American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol. 1998;81(5 Pt 2):478–518.
3. Benson V, Marano MA. Current estimates from the National Health Interview Survey, 1992. Vital Health Stat. 1994;10(189):1–269.
4. Hastan D, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy. 2011;66(9):1216–23.
5. QuantPsyc: quantitative psychology tools.
6. Gilani S, Shin JJ. The burden and visit prevalence of pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2017;157(6):1048–52.

7. Meltzer EO, et al. Burden of allergic rhinitis: results from the pediatric allergies in America survey. J Allergy Clin Immunol. 2009;124(3 Suppl):43.
8. Wright AL, et al. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics. 1994;94(6 Pt 1):895–901.
9. Sheehan WJ, et al. Age-specific prevalence of outdoor and indoor aeroallergen sensitization in Boston. Clin Pediatr. 2010;49(6):579–85.
10. Sedaghat AR, et al. Characterization of tree allergy prevalence in children younger than 4 years. Ann Allergy Asthma Immunol. 2014;112(4):388–9.
11. Sedaghat AR, Phipatanakul W, Cunningham MJ. Characterization of aeroallergen sensitivities in children with allergic rhinitis and chronic rhinosinusitis. Allergy Rhinol (Providence). 2014;5(3):143–5.
12. Kim SK, Jo MW, Kim SH. Health-related quality of life by allergy symptoms in elementary school students. Health Qual Life Outcomes. 2018;16(1):93.
13. Nathan RA. The burden of allergic rhinitis. Allergy Asthma Proc. 2007;28(1):3–9.
14. Blaiss MS, et al. The burden of allergic rhinitis and allergic rhinoconjunctivitis on adolescents: a literature review. Ann Allergy Asthma Immunol. 2018;121(1):43–52 e3.
15. Hoehle LP, et al. Association between symptoms of allergic rhinitis with decreased general health-related quality of life. Am J Rhinol Allergy. 2017;31(4):235–9.
16. Vandenplas O, et al. Impact of rhinitis on work productivity: a systematic review. J Allergy Clin Immunol Pract. 2018;6(4):1274–86 e9.
17. Meltzer EO, Bukstein DA. The economic impact of allergic rhinitis and current guidelines for treatment. Ann Allergy Asthma Immunol. 2011;106(2 Suppl):12.
18. Zuberbier T, et al. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. Allergy. 2014;69(10):1275–9.
19. Cunningham MJ, Chiu EJ, Landgraf JM, Gliklich RE. The health impact of chronic recurrent rhinosinusitis in children. Arch Otolaryngol Head Neck Surg. 2000;126(11):1363–8.
20. DeConde AS, Soler ZM. Chronic rhinosinusitis: epidemiology and burden of disease. Am J Rhinol Allergy. 2016;30(2):134–9.
21. Hoehle LP, et al. Symptoms of chronic rhinosinusitis differentially impact general health-related quality of life. Rhinology. 2016;54(4):316–22.
22. Speth MM, et al. Changes in chronic rhinosinusitis symptoms differentially associate with improvement in general health-related quality of life. Ann Allergy Asthma Immunol. 2018;121:195.
23. Campbell AP, et al. Depression symptoms and lost productivity in chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2017;118(3):286–9.
24. Caulley L, et al. Direct costs of adult chronic rhinosinusitis by using 4 methods of estimation: results of the US Medical Expenditure Panel Survey. J Allergy Clin Immunol. 2015;136(6):1517–22.
25. Ray NF, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol. 1999;103(3. Pt 1):408–14.
26. Shtraks JP, Toskala E. Manifestations of inhalant allergies beyond the nose. Otolaryngol Clin N Am. 2017;50(6):1051–64.
27. Kang HR, et al. Risk factors of asthma exacerbation based on asthma severity: a nationwide population-based observational study in South Korea. BMJ Open. 2018;8(3):e020825.
28. Yilmaz O, et al. Allergic rhinitis may impact the recovery of pulmonary function tests after moderate/severe asthma exacerbation in children. Allergy. 2014;69(5):652–7.
29. Baiardini I, et al. Effects of mometasone furoate on the quality of life: a randomized placebo-controlled trial in persistent allergic rhinitis and intermittent asthma using the Rhinasthma questionnaire. Clin Exp Allergy. 2011;41(3):417–23.
30. Hoehle LP, et al. A contemporary analysis of clinical and demographic factors of chronic rhinosinusitis patients and their association with disease severity. Ir J Med Sci. 2018;187(1):215–21.
31. Yamasaki A, et al. Cockroach hypersensitivity is associated with greater severity of chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2017;119(5):469–70.

32. Bachert C, et al. ICON: chronic rhinosinusitis. World Allergy Organ J. 2014;7(1):25. eCollection 2014.
33. Rosenfeld RM, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. 2015;152(2. Suppl):S39.
34. Wambre E, James EA, Kwok WW. Characterization of CD4+ T cell subsets in allergy. Curr Opin Immunol. 2012;24(6):700–6.
35. Mosmann TR, et al. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol. 1986;136(7):2348–57.
36. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of Type 2 immunity. Immunity. 2015;43(1):29–40.
37. Papazian D, Hansen S, Wurtzen PA. Airway responses towards allergens - from the airway epithelium to T cells. Clin Exp Allergy. 2015;45(8):1268–87.
38. Zhu J. T helper 2 (Th2) cell differentiation, type 2 innate lymphoid cell (ILC2) development and regulation of interleukin-4 (IL-4) and IL-13 production. Cytokine. 2015;75(1):14–24.
39. Van Zele T, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy. 2006;61(11):1280–9.
40. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. Annu Rev Pathol. 2017;12:331–57.
41. Tomassen P, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol. 2016;137(5):1449–56 e4.
42. Van Zele T, et al. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy. 2014;28(3):192–8.
43. Bachert C, et al. Role of staphylococcal superantigens in upper airway disease. Curr Opin Allergy Clin Immunol. 2008;8(1):34–8.
44. Chalermwatanachai T, et al. Chronic rhinosinusitis with nasal polyps is characterized by dysbacteriosis of the nasal microbiota. Sci Rep. 2018;8(1):7926.
45. Mahdavinia M, et al. The nasal microbiome in patients with chronic rhinosinusitis: analyzing the effects of atopy and bacterial functional pathways in 111 patients. J Allergy Clin Immunol. 2018;142(1):287–90 e4.
46. Hoyt AE, et al. Allergic fungal rhinosinusitis. J Allergy Clin Immunol Pract. 2016;4(4):599–604.
47. DelGaudio JM, et al. Central compartment atopic disease. Am J Rhinol Allergy. 2017;31(4):228–34.
48. Hamizan AW, et al. Allergic phenotype of chronic rhinosinusitis based on radiologic pattern of disease. Laryngoscope. 2018;128:2015.
49. Tan BK, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2013;131(5):1350–60.
50. Sedaghat AR, et al. Risk factors for development of chronic rhinosinusitis in patients with allergic rhinitis. Int Forum Allergy Rhinol. 2012;2(5):370–5.
51. Sedaghat AR, et al. Sinonasal anatomic variants and asthma are associated with faster development of chronic rhinosinusitis in patients with allergic rhinitis. Int Forum Allergy Rhinol. 2013;3(9):755–61.
52. Blaiss MS. Pediatric allergic rhinitis: physical and mental complications. Allergy Asthma Proc. 2008;29(1):1–6.
53. Veskitkul J, et al. Clinical characteristics of recurrent acute rhinosinusitis in children. Asian Pac J Allergy Immunol. 2015;33(4):276–80.
54. Wald ER, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132:e262.
55. Sedaghat AR, Phipatanakul W, Cunningham MJ. Atopy and the development of chronic rhinosinusitis in children with allergic rhinitis. J Allergy Clin Immunol Pract. 2013;1(6):689–91 e1–2.
56. Sedaghat AR, et al. Aeroallergen sensitivities and development of chronic rhinosinusitis in 13 adults who initially had allergic rhinitis. Clin Otolaryngol. 2017;42(2):487–90.

57. Chong LY, et al. Saline irrigation for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016;4:CD011995.
58. Chong LY, et al. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016;4:CD011996.
59. Head K, et al. Saline irrigation for allergic rhinitis. Cochrane Database Syst Rev. 2018;6:CD012597.
60. Al Sayyad JJ, et al. Topical nasal steroids for intermittent and persistent allergic rhinitis in children. Cochrane Database Syst Rev. 2007;(1):CD003163.
61. DeYoung K, et al. Systematic review of immunotherapy for chronic rhinosinusitis. Am J Rhinol Allergy. 2014;28(2):145–50.
62. Steelant B, et al. Restoring airway epithelial barrier dysfunction: a new therapeutic challenge in allergic airway disease. Rhinology. 2016;54(3):195–205.
63. Schleimer RP, et al. Epithelium: at the interface of innate and adaptive immune responses. J Allergy Clin Immunol. 2007;120(6):1279–84.

Chapter 8
Rhinosinusitis and Asthma in Children

Ahmad Salaheddine Naja, Ahmad R. Sedaghat, and Wanda Phipatanakul

Introduction

The upper and lower respiratory tracts may be considered as a single morphological and functional unit. Physiologically, the role of the upper airway includes the protection of the lower airway by conditioning the inhaled air through filtration, humidification, and warming. There is growing evidence that inflammatory diseases of the airway, such as allergic rhinitis, chronic rhinosinusitis (CRS), and bronchial asthma, are manifestations of the same or similar pathological processes but in different parts of the respiratory tract. These diseases frequently have the same triggers: aeroallergens, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), irritants, and viral and bacterial infections. The concept of a "unified airway" has been proposed as an integrated term to cover the relationship between the upper and lower airways as well as their mutual effects on each other.

Inflammatory airways diseases, including allergic rhinitis, rhinosinusitis, and asthma, are major diseases of public health importance in children, especially in developed countries. The prevalence of asthma in children under the age of 18 in the United States increased from 8.7% in 2001 to 9.7% in 2009 and then decreased to 8.3% in 2013 [1, 2]. According to the Pediatric Allergies in America survey in 2009, 13% of children in the United States had a health-care provider-confirmed diagnosis

A. S. Naja
Department of Surgery, American University of Beirut Medical Center, Beirut, Lebanon

A. R. Sedaghat
Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

W. Phipatanakul (✉)
Division of Allergy and Immunology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA
e-mail: Wanda.Phipatanakul@childrens.harvard.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_8

of allergic rhinitis, with 61% of them having been diagnosed before the age of 6 years [3]. Acute and chronic rhinosinusitis in the pediatric population account for 7 million, 1.6 million, and 5.6 million ambulatory visits per annum, respectively, as reported in the National Ambulatory Medical Care Surveys [4].

Pediatric Rhinosinusitis

Rhinosinusitis refers to inflammation of the nasal and sinus mucosa, which are contiguous with each other. Symptoms of rhinitis, which include rhinorrhea, nasal obstruction, nasal discharge, and sneezing, are also present in rhinosinusitis. Rhinosinusitis can be divided into acute and chronic depending on the duration of the disease. Acute rhinosinusitis usually lasts less than 4 weeks and is usually an infectious process, caused by a viral or bacterial infection. According to American Academy of Pediatrics (AAP) and the Infectious Diseases Society of America [5, 6], acute bacterial rhinosinusitis (ABRS) should be suspected in a child with any of the following three presentations:

(i) Persistent symptoms or signs compatible with acute rhinosinusitis, including nasal discharge of any quality or daytime cough or both, lasting for ≥10 days without any evidence of clinical improvement
(ii) Onset with severe symptoms or signs of high fever (≥39 °C [102 °F]) and purulent nasal discharge or facial pain lasting for at least 3 consecutive days at the beginning of the illness
(iii) "Double worsening"—symptoms or signs including fever, daytime cough, headache, or increase in nasal discharge following a typical viral upper respiratory infection (URI), lasting 5–6 days, and which were initially improving but then acutely worsened

Common risk factors for ABRS include viral upper respiratory tract infection and allergic rhinitis. Commonly involved pathogens in ABRS include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

According to a consensus statement from an expert panel of otorhinolaryngologists, pediatric chronic rhinosinusitis (CRS) is defined as at least 90 continuous days of symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough with corresponding endoscopic and/or radiographic findings in a patient who is 18 years or younger [7]. In younger children, adenoid disease is an important predisposing factor, irrespective of adenoid size. In children, symptoms are mostly limited to symptoms suggestive of allergic rhinitis, such as nasal congestive symptoms, and a high degree of suspicion is required to make a diagnosis of CRS [8]. Initial presenting symptoms include cough and nasal discharge. Headache and sinus tenderness are less common symptoms. The etiology of CRS in children is poorly understood, and several factors may play a role in it including allergy, microbes, and genetic susceptibility. Cystic fibrosis, primary ciliary dyskinesia, and immunodeficiency are systemic conditions associated with CRS and must be ruled out in a child

who has CRS. The presence of nasal polyps in children with CRS, in particular, should raise suspicion for evaluation of cystic fibrosis with sweat chloride and/or genetic testing. Gastroesophageal reflux disease may also be associated with the worsening of CRS [9].

CRS is diagnosed based on clinical, endoscopic, and radiographic findings. Nasal endoscopy is recommended as the first line of diagnostic investigation for pediatric CRS [7]. Though children are less tolerant to an endoscopic examination of the nasal cavity and sinuses, it should be attempted as it allows direct visualization of the sinonasal mucosa for signs of inflammation, polyps, and assessment for adenoid hypertrophy or adenoiditis without the radiation exposure associated with imaging modalities. If radiographic imaging is pursued, computed tomography (CT) of the nose and paranasal sinuses is the imaging modality of choice to look for mucosal thickening and fluid collection in the sinuses. One previous study has suggested that head CT scans in childhood may be associated with a slightly increased but low absolute risk of malignancy due to radiation exposure [10]. However, this study was based on historic CT scan protocols that exposed children to as much as 20 times the radiation doses as are used in today's sinus CT scans [11]. Formal allergy testing should be also considered in children with CRS particularly in those with a history of allergic triggers.

CRS in children is commonly associated with adenoid hypertrophy [12]. The adenoid may be an important site for harboring bacteria implicated in the pathogenesis of pediatric CRS as nasopharyngeal and sinus cultures from children with CRS frequently grow the same pathogens. However, the role of adenoid size ("hypertrophy") in isolation as a causative factor of pediatric CRS is controversial. While the presence of adenoid inflammation may be a strongly associated factor for CRS in younger children, this association is present irrespective of the size of adenoid.

Epidemiological Associations

The epidemiological and pathological associations between the inflammatory conditions of the airway—allergic rhinitis, rhinosinusitis, and asthma—have been reported time and again in the medical literature. The "Atopic March," also referred to as the allergic march, refers to the development of allergic rhinitis and asthma, preceded by the development of atopic dermatitis and food allergy that occurs very early in childhood. Allergic rhinitis is very common in children with asthma and vice versa [13]. In a large study of 10,954 US children aged 3–17 years, 1202 (10.4%) children were found to have asthma, and these children were more likely to have hay fever/respiratory allergies with a prevalence difference (PD) of 30.5%, eczema or skin allergies (PD = 14.1%), sinusitis (PD = 11.3%), food or digestive allergies (PD = 10.4%), and difficulty with emotions, concentration, behavior, or getting along with others (PD = 7.9%) [14]. Bronchial hyperreactivity (BHR) is seen in about 80% of children with allergic rhinitis, even in the absence of a history of wheezing, and it may be an important risk factor for future development of

asthma [15–17]. The strong association of asthma and allergic rhinitis is particularly pertinent in this discussion since allergic rhinitis is highly prevalent and a risk factor for recurrent episodes of acute rhinosinusitis and is very closely associated within chronic rhinosinusitis [18–21].

Acute Rhinosinusitis

Acute flares in nasal and sinus disease have been reported to affect pulmonary status in asthmatics [22]. In fact, recurrent acute rhinosinusitis is one risk factor for acute asthma exacerbations [23]. Much of the work related to acute sinus exacerbations and asthma, however, has been performed in patients with CRS. In adult CRS patients, the frequency of acute exacerbations of CRS has been shown to be associated with both decreased asthma control and greater patient-reported productivity losses in asthmatics [24, 25].

Chronic Rhinosinusitis

Chronic rhinosinusitis has a close epidemiological and pathophysiological association with bronchial asthma. Even in the absence of nasal allergy, CRS may be associated with increased risk of late-onset bronchial asthma [26]. Much of the established associations between asthma and CRS have been established in adults. Comorbid CRS and asthma have been shown in multiple ways to be associated with worse outcomes with respect to each other. CRS is associated with more frequent asthma exacerbations [27]. Asthmatics with CRS also have more emergency room visits and total health-care visits than asthmatics without CRS [28]. Approximately 85–90% of patients with asthma have abnormal findings on CT scans of the sinuses [29]. Radiological evidence of CRS, even without any obvious sinonasal symptoms, in patients with asthma is associated with significantly lower FEV1 and FEV1/FVC ratio, and these patients were more likely to have a poor quality of life [30]. The nature of the association between CRS and asthma has been shown to be a relative one, whereby the status of one disease reflects the status of the other. For example, the burden of CRS symptoms is associated with worse asthma control, including an increasing need for systemic corticosteroid usage for asthma [31, 32]. In other words, worsening CRS status is associated with worsening asthma status. Similarly, the frequency of acute exacerbations of CRS has been negatively associated with the level of asthma control in asthmatic CRS patients, irrespective of the baseline CRS symptom severity [24]. Acute exacerbations of CRS also appear to have a dominant effect on asthmatic CRS patients, associating with lost productivity (missed work and/or school), which is in contrast to non-asthmatic CRS patients [25, 33]. Comorbid asthma is also associated with worse clinical outcomes with respect to CRS. The severity of asthma is positively associated with greater

radiological severity of CRS, and asthma is also associated with nasal polyposis [34]. Asthmatics have also been found to generally have a greater burden of CRS symptomatology than CRS patients without asthma [35].

Pathogenesis

The entire respiratory tract can behave as one functional unit in response to irritants or antigenic stimulation. Studies have shown that when an allergen is deposited in either the nose or bronchi, inflammatory responses are initiated in distant sites of the respiratory tract. The nasobronchial reflex is one such phenomenon where exposure of nasal mucosa to irritants or cold air leads to bronchoconstriction. Introduction of an allergen into a segmental bronchus in patients with allergic rhinitis induces nasal inflammation [36]. These phenomena suggest that inflammatory mediators produced at one site in the airway may play a role in the pathogenesis of disease at other sites in the airway. While inflammatory mediators produce airway obstruction by vasodilation and mucosal edema in the upper respiratory tract, bronchoconstriction is responsible for obstruction in the lower respiratory tract. Blockage of the ostia through which the sinonasal secretions drain by mucosal edema may contribute to the development of recurrent acute or chronic inflammation in the paranasal sinuses.

The nasal mucosa and the bronchial mucosa are lined with a pseudostratified ciliated columnar epithelium which has a protective barrier function. Genetic/anatomic defects of the epithelium can potentially serve as pathogenic factors in chronic inflammatory diseases of both the upper and lower airways. Patients with asthma and/or CRS with nasal polyps have been shown to have altered intercellular tight junctions between epithelial cells [37, 38]. This is likely due to the effects of pro-inflammatory cytokines such as IFN-gamma and IL-4 or viral infections such as rhinovirus [39]. Disruption of tight junctions leads to penetration of inhaled allergens or microbial products into the subepithelial space activating pro-inflammatory responses that may serve to drive persistence of chronic inflammation in the upper and lower airway mucosa. The inflammatory response in the nasal mucosa is more severe in children with CRS and concomitant asthma compared with non-asthmatic children with CRS. In asthmatic children with CRS, sinomucosal expression of tumor necrosis factor-alpha and adenoid levels of epidermal growth factor, eotaxin, fibroblast growth factor-2, growth-related oncogene, and platelet-derived growth factor-AA was significantly higher. Posterior nasal drainage of mucopurulent secretions in sinusitis has also been proposed as a potential exacerbating factor for bronchial asthma [40]. These findings collectively have indicated that treatment of concomitant sinus disease may be an important component of managing childhood asthma [41].

Treatment

Given the close clinical and pathophysiologic relationships between sinusitis and asthma, it has long been suspected, and more recently shown, that successful treatment of sinusitis could positively impact pulmonary outcomes in asthmatic patients. As acute rhinosinusitis is a largely self-limited disease process, the evidence supporting the treatment of sinusitis as an indirect means of addressing asthma has been derived through the study of CRS patients. Initial treatment of CRS in children consists of medical management with intranasal corticosteroid sprays and nasal saline irrigation as there is level 1 evidence for both of these treatments. Use of these medications may lead to improvement of asthma status as well. For example, use of intranasal corticosteroids in patients with allergic rhinitis has been shown to decrease bronchial hyperresponsiveness and hospital visits related to asthma [42, 43]. Other therapies targeting allergic inflammation, given the high prevalence of allergy in CRS, include antihistamine nasal sprays and leukotriene antagonists such as montelukast. Montelukast has been previously reported to potentially have a beneficial effect in CRS with polyps [44]. Leukotriene modifiers may have an additional benefit of directly treating asthma as well. In allergic patients, immunotherapy may be considered. Immunotherapy has been shown to have benefit for allergic asthma [45]. In contrast, the efficacy of immunotherapy for CRS patients with aeroallergen hypersensitivity is still not established [46]. More than likely, there are CRS patients whose disease is driven by aeroallergen hypersensitivity, while others have coincidental hypersensitivity but not true allergy. It remains unclear how to differentiate these patients. For patients with nasal polyposis, newer nasal sprays that deliver medicine high up in the nasal cavity may be helpful, though not studied in children. Vitamin D insufficiency is associated with adverse outcomes and poor disease control in asthma [47, 48]. Vitamin D3 supplementation, however, should be cautiously used in patients with vitamin D deficiency, asthma, and sinonasal disease. It has not been shown to reduce the rate of asthma treatment failures, and in Black populations, it may be associated with a higher risk of asthma exacerbations in patients with sinus disease [49, 50].

Antibiotics may also be of benefit in cases where symptoms or signs are indicative of an infectious etiology. The choice of antibiotics should ideally be culture-directed—derived from endoscopically guided cultures of the middle meatus or the nasopharynx. If antibiotics are indicated, there is no consensus for the duration. Because current treatment guidelines recommend 10–14 days of culture-directed antibiotics for uncomplicated acute rhinosinusitis, antibiotics for CRS are generally given for a longer duration. However, even for adults, antibiotics for CRS are not recommended for longer than 3 weeks. Additionally, if GERD is present, antireflux therapy should be initiated.

In CRS patients who fail appropriate medical management, surgical treatment options targeting the paranasal sinuses exist. As the adenoid frequently harbors bacteria implicated in CRS, adenoidectomy is a reasonable option for children with CRS refractive to medical therapy, irrespective of the severity of airway obstruction

[12]. While removing the adenoids, a maxillary sinus wash may also be done concomitantly to improve success rates [51]. Functional endoscopic sinus surgery (FESS) is intended to restore the natural ventilation and drainage pathways of the paranasal sinuses at the ostiomeatal complex. Although not yet well-studied in children, FESS in adult asthmatic CRS patients has been shown to have a secondary benefit of improving asthma control and asthma-related quality of life [52]. Moreover, FESS has been shown to reduce the frequency of asthma attacks and the number of hospitalizations and improves symptom control in subjects [53, 54].

Aspirin exacerbated respiratory disease (AERD), also known as Samter's triad, is the combination of asthma, chronic rhinosinusitis with nasal polyposis, and sensitivity to aspirin and other NSAIDs clinically characterized by nasal congestion and bronchoconstriction [55, 56]. This occurs because of an imbalance between leukotrienes and prostaglandins due to acquired changes in arachidonic acid metabolism. Exposure to any COX-1 inhibitor exacerbates the underlying pro-inflammatory and anti-inflammatory imbalances and leads to these upper airway and lower airway symptoms within 30–120 minutes. Treatment involves administration of a leukotriene antagonist (montelukast/zafirlukast) and avoidance of all NSAIDs [57]. Omalizumab has been shown to control respiratory symptoms in AERD [58]. Aspirin desensitization can be considered if NSAIDS cannot be withdrawn because of coexisting inflammatory conditions [59]. Treatment of the underlying aspirin sensitivity through aspirin desensitization will have a benefit in improving both CRS and comorbid asthma since in AERD, the asthma and CRS are driven by the same pathophysiologic mechanism.

Finally, there are several novel agents currently being studied for the treatment of nasal polyposis, CRS, and/or AERD including omalizumab (anti-IgE), mepolizumab (anti-IL-5 agent), dupilumab (anti-IL-4Rα agent), prasugrel ($P2Y_{12}$ antagonist), and ifetroban (TP receptor antagonist) [60]. These are shown in Table 8.1. Anti-IgE agent omalizumab has been shown to have clinical efficacy in improving the symptomatology, quality of life, and nasal endoscopic findings in patients with nasal polyps and asthma [61]. Mepolizumab is a humanized monoclonal antibody that binds to IL-5, preventing it from binding to the IL-5 receptor on eosinophils, which is an important step for the differentiation of eosinophils. As eosinophils are the dominant cell type found in eosinophilic asthma and nasal polyps, mepolizumab was studied in these conditions and was found to have a significant effect on asthma control and reduction of nasal polyp size, respectively [62, 63]. Subcutaneous dupilumab has shown efficacy in, and is now FDA approved for, the management of adult patients with CRS and nasal polyposis refractory to intranasal corticosteroids. Compared with placebo, the use of subcutaneous dupilumab led to significant improvements in the endoscopic nasal polyp score, the Lund-Mackay CT score, the 22-item SinoNasal Outcome Test score, and the sense of smell assessed by the University of Pennsylvania Smell Identification test in CRS patients [64]. Further studies are required in children to explore the utility of subcutaneous dupilumab in this set of patients. $P2Y_{12}$ receptor antagonist prasugrel has been previously studied in AERD patients, but was not shown to have a significant effect on attenuations of aspirin-induced symptoms [65]. However, in a small subset of patients with AERD

Table 8.1 Newer biologics used in treatment of upper airway disease and asthma

Agent	Mechanism of action	Study population	Study effect
Omalizumab	Anti-IgE monoclonal antibody	Adult patients having nasal polyposis with comorbid asthma ($n = 24$)	Significant improvement in nasal endoscopic polyp score, CT Lund-Mackay score, airway symptoms, and disease-specific quality of life
Mepolizumab	Anti-Ig 5 monoclonal antibody	Adult patients with severe nasal polyposis (grade 3 or 4 or recurrent after surgery) ($n = 30$)	Significant reduction in nasal polyp size
Dupilumab	Anti-IL-4Rα monoclonal antibody	Adult patients with chronic rhinosinusitis and nasal polyposis refractory to intranasal corticosteroids ($n = 60$)	Significant improvements in the endoscopic nasal polyp score, the Lund-Mackay CT score, the 22-item SinoNasal Outcome Test score, and the sense of smell assessed by the University of Pennsylvania Smell Identification test
Prasugrel	$P2Y_{12}$ receptor antagonist	AERD patients who underwent aspirin challenges ($n = 40$)	No significant effect, but in a small subset of patients with AERD ($n = 5$) who had greater baseline platelet activation and milder upper airway symptoms during aspirin provocations, complete attenuation of aspirin-induced symptoms was noticed

who had greater baseline platelet activation and milder upper airway symptoms during aspirin provocations, it completely attenuated the aspirin sensitivity reaction. More studies are therefore still needed to identify patients with AERD who might benefit from prasugrel.

Knowledge Gaps

Much of the studies that highlight the relationship between sinusitis and asthma have been performed in adults. The epidemiological associations and effects of treatment of rhinosinusitis on asthma control and vice versa need to be studied in greater depth in the pediatric population to frame evidence-based guidelines suitable to this group of patients. Studies using targeted biological agents and immunotherapy may have a significant role, although not yet fully characterized, in the treatment of CRS patients as these agents may be potentially beneficial in reducing inflammation throughout the respiratory tract.

Disclosure Statement All authors have no direct financial interest in subject matter or materials discussed in article or with a company making a competing product. Dr. Phipatanakul would like to acknowledge NIH funding K24 AI 106822 for research into the content described in this chapter.

References

1. Akinbami LJ, Simon AE, Rossen LM. Changing trends in asthma prevalence among children. Pediatrics. 2016;137(1):e20152354.
2. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breysse PN. Vital signs: asthma in children - United States, 2001-2016. MMWR Morb Mortal Wkly Rep. 2018;67(5):149–55.
3. Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, Sheth KK, et al. Burden of allergic rhinitis: results from the pediatric allergies in America survey. J Allergy Clin Immunol. 2009;124(3. Suppl):S43–70.
4. Gilani S, Shin JJ. The burden and visit prevalence of pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2017;157(6):1048–52.
5. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–112.
6. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262–80.
7. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
8. Ramadan HH. Chronic rhinosinusitis in children. Int J Pediatr. 2012;2012:573942.
9. Phipps CD, Wood WE, Gibson WS, Cochran WJ. Gastroesophageal reflux contributing to chronic sinus disease in children: a prospective analysis. Arch Otolaryngol Head Neck Surg. 2000;126(7):831–6.
10. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380(9840):499–505.
11. Sedaghat AR, Gray ST, Kieff DA. In response to preapproval of sinus computed tomography for otolaryngologic evaluation of chronic rhinosinusitis does not save health care costs. Laryngoscope. 2014;124(12):E471–2.
12. Neff L, Adil EA. What is the role of the adenoid in pediatric chronic rhinosinusitis? Laryngoscope. 2015;125(6):1282–3.
13. Ciprandi G, Caimmi D, Miraglia Del Giudice M, La Rosa M, Salpietro C, Marseglia GL. Recent developments in United airways disease. Allergy Asthma Immunol Res. 2012;4(4):171–7.
14. Mirabelli MC, Hsu J, Gower WA. Comorbidities of asthma in U.S. children. Respir Med. 2016;116:34–40.
15. Braman SS, Barrows AA, DeCotiis BA, Settipane GA, Corrao WM. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. Chest. 1987;91(5):671–4.
16. Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. J Allergy Clin Immunol. 1999;104(3 Pt 1):534–40.
17. Ciprandi G, Cirillo I. The lower airway pathology of rhinitis. J Allergy Clin Immunol. 2006;118(5):1105–9.
18. Sedaghat AR, Gray ST, Chambers KJ, Wilke CO, Caradonna DS. Sinonasal anatomic variants and asthma are associated with faster development of chronic rhinosinusitis in patients with allergic rhinitis. Int Forum Allergy Rhinol. 2013;3(9):755–61.
19. Sedaghat AR, Gray ST, Wilke CO, Caradonna DS. Risk factors for development of chronic rhinosinusitis in patients with allergic rhinitis. Int Forum Allergy Rhinol. 2012;2(5): 370–5.
20. Sedaghat AR, Phipatanakul W, Cunningham MJ. Atopy and the development of chronic rhinosinusitis in children with allergic rhinitis. J Allergy Clin Immunol Pract. 2013;1(6):689–691. e1-2.
21. Sedaghat AR, Phipatanakul W, Cunningham MJ. Prevalence of and associations with allergic rhinitis in children with chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2014;78(2):343–7.

22. Kuiper JR, Hirsch AG, Bandeen-Roche K, Sundaresan AS, Tan BK, Schleimer RP, et al. Prevalence, severity, and risk factors for acute exacerbations of nasal and sinus symptoms by chronic rhinosinusitis status. Allergy. 2018;73(6):1244–53.
23. Dougherty RH, Fahy JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype. Clin Exp Allergy. 2009;39(2):193–202.
24. Banoub RG, Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Relationship between chronic rhinosinusitis exacerbation frequency and asthma control. Laryngoscope. 2017;128(5):1033–8.
25. Phillips KM, Bergmark RW, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Chronic rhinosinusitis exacerbations are differentially associated with lost productivity based on asthma status. Rhinology. 2018;56(4):323–9.
26. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67(1): 91–8.
27. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol. 2012;129(5):1229–35.
28. Bhattacharyya N, Kepnes LJ. Additional disease burden from hay fever and sinusitis accompanying asthma. Ann Otol Rhinol Laryngol. 2009;118(9):651–5.
29. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. J Allergy Clin Immunol. 2001;107(1):73–80.
30. Sahay S, Gera K, Bhargava SK, Shah A. Occurrence and impact of sinusitis in patients with asthma and/or allergic rhinitis. J Asthma. 2016;53(6):635–43.
31. Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Association of severity of chronic rhinosinusitis with degree of comorbid asthma control. Ann Allergy Asthma Immunol. 2016;117(6):651–4.
32. Phillips KM, Hoehle LP, Bergmark RW, Campbell AP, Caradonna DS, Gray ST, et al. Chronic rhinosinusitis severity is associated with need for asthma-related systemic corticosteroids. Rhinology. 2017;55(3):211–7.
33. Campbell AP, Hoehle LP, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Symptom control in chronic rhinosinusitis is an independent predictor of productivity loss. Eur Ann Otorhinolaryngol Head Neck Dis. 2018;135(4):237–41.
34. Pearlman AN, Chandra RK, Chang D, Conley DB, Tripathi-Peters A, Grammer LC, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. Am J Rhinol Allergy. 2009;23(2):145–8.
35. Hoehle LP, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. A contemporary analysis of clinical and demographic factors of chronic rhinosinusitis patients and their association with disease severity. Ir J Med Sci. 2018;187(1):215–21.
36. 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(6):2051–7.
37. Leonardi S, Vitaliti G, Marseglia GL, et al. Function of the airway epithelium in asthma. J Biol Regul Homeost Agents. 2012;26:S41–8.
38. Soyka MB, Wawrzyniak P, Eiwegger T, Holzmann D, Treis A, Wanke K, et al. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-γ and IL-4. J Allergy Clin Immunol. 2012;130(5):1087–96.e10.
39. 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(12): 1271–81.
40. Slavin RG. Asthma and sinusitis. J Allergy Clin Immunol. 1992;90:534–7.
41. Anfuso A, Ramadan H, Terrell A, Demirdag Y, Walton C, Skoner DP, et al. Sinus and adenoid inflammation in children with chronic rhinosinusitis and asthma. Ann Allergy Asthma Immunol. 2015;114(2):103–10.

42. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3):466–76.
43. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. J Allergy Clin Immunol. 1993;91(1 Pt 1):97–101.
44. Kieff DA, Busaba NY. Efficacy of montelukast in the treatment of nasal polyposis. Ann Otol Rhinol Laryngol. 2005;114(12):941–5.
45. Chelladurai Y, Suarez-Cuervo C, Erekosima N, Kim JM, Ramanathan M, Segal JB, et al. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. J Allergy Clin Immunol Pract. 2013;1(4):361–9.
46. DeYoung K, Wentzel JL, Schlosser RJ, Nguyen SA, Soler ZM. Systematic review of immunotherapy for chronic rhinosinusitis. Am J Rhinol Allergy. 2014;28(2):145–50.
47. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. J Allergy Clin Immunol. 2010;126(1):52–8.e5.
48. Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A, et al. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. Am J Respir Crit Care Med. 2012;186(6):508–13.
49. Castro M, King TS, Kunselman SJ, Cabana MD, Denlinger L, Holguin F, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. JAMA. 2014;311(20):2083–91.
50. Jiao J, King TS, McKenzie M, Bacharier LB, Dixon AE, Codispoti CD, et al. Vitamin D3 therapy in patients with asthma complicated by sinonasal disease: secondary analysis of the vitamin D add-on therapy enhances corticosteroid responsiveness in asthma trial. J Allergy Clin Immunol. 2016;138(2):589–92.e2.
51. Ramadan HH, Cost JL. Outcome of adenoidectomy versus adenoidectomy with maxillary sinus wash for chronic rhinosinusitis in children. Laryngoscope. 2008;118(5):871–3.
52. Schlosser RJ, Smith TL, Mace J, Soler ZM. Asthma quality of life and control after sinus surgery in patients with chronic rhinosinusitis. Allergy. 2017;72(3):483–91.
53. Vashishta R, Soler ZM, Nguyen SA, Schlosser RJ. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. Int Forum Allergy Rhinol. 2013;3(10):788–94.
54. Ehnhage A, Olsson P, Kölbeck K-G, Skedinger M, Stjärne P, NAFS Study Group. One year after endoscopic sinus surgery in polyposis: asthma, olfaction, and quality-of-life outcomes. Otolaryngol Head Neck Surg. 2012;146(5):834–41.
55. Samter M, Beers RF. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. Ann Intern Med. 1968;68(5):975–83.
56. Nabavi M, Esmaeilzadeh H, Arshi S, Bemanian MH, Fallahpour M, Bahrami A, et al. Aspirin hypersensitivity in patients with chronic rhinosinusitis and nasal polyposis: frequency and contributing factors. Am J Rhinol Allergy. 2014;28(3):239–43.
57. Christie PE, Smith CM, Lee TH. The potent and selective sulfidopeptide leukotriene antagonist, SK&F 104353, inhibits aspirin-induced asthma. Am Rev Respir Dis. 1991;144(4):957–8.
58. Porcaro F, Di Marco A, Cutrera R. Omalizumab in patient with aspirin exacerbated respiratory disease and chronic idiopathic urticaria. Pediatr Pulmonol. 2017;52(5):E26–8.
59. 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.
60. Lam K, Kern RC, Luong A. Is there a future for biologics in the management of chronic rhinosinusitis? Int Forum Allergy Rhinol. 2016;6(9):935–42.

61. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013;131(1):110–6.e1.
62. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189–97.
63. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011;128(5):989–95.e1–8.
64. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous Dupilumab on Nasal Polyp Burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA. 2016;315(5):469–79.
65. Laidlaw TM, Cahill KN, Cardet JC, Murphy K, Cui J, Dioneda B, et al. A trial of type 12 purinergic (P2Y12) receptor inhibition with prasugrel identifies a potentially distinct endotype of patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2018;143(1):316–24.e7.

Chapter 9
Chronic Rhinosinusitis in Children with Cystic Fibrosis

Nour Akil and Austin S. Rose

Introduction

Chronic rhinosinusitis (CRS) encompasses a spectrum of disease characterized by inflammatory and infectious processes that affect the nasal cavity and paranasal sinuses [1–3]. CRS in children is considered unique, due to the differences in predisposing factors and anatomy seen between children and adults. One of the most important underlying disease states to consider in the evaluation and work-up of CRS in children is cystic fibrosis (CF).

CF is an autosomal recessive genetic disease with 2500 to 3500 new diagnoses in the United States annually [4]. This multisystem disorder is associated with significant morbidity and mortality, often due to its respiratory complications. The disease is caused by abnormal chloride transport through the CF transmembrane conductance regulator (CFTR) protein. This disruption in anion transport at the surface of epithelial cells leads to increased sodium and water absorption, dehydration of mucosal surfaces, and thickening of secretions with increased risk of infection and neutrophilic inflammation.

CFTR is present in multiple cell types in a variety of organs, including the lungs, sinonasal mucosa, intestine, and pancreas. The CFTR gene was discovered in 1989 and is present on the long arm of chromosome 7, at position 7q31.2. Today, there are over 2000 described mutations affecting CFTR quantity and/or function, and patients with CF demonstrate a wide spectrum of clinical manifestations. This

N. Akil
Division of Pediatric Pulmonary, University of North Carolina School of Medicine, Chapel Hill, NC, USA
e-mail: nonour@email.unc.edu

A. S. Rose (✉)
Department of Otolaryngology–Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC, USA
e-mail: austin_rose@med.unc.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_9

phenotypic diversity, however, is not fully explained by genotype. Disease severity and the organ systems affected are influenced by a number of other factors such as modifier genes, the environment, and lifestyle [5, 6].

Over time, CF-related sinus disease has gained increased attention due to its clear negative impact on patients' morbidity and quality of life (QOL). In the sinuses, as in other affected organs, impaired mucociliary clearance leads to a retention of secretions, inflammation of mucosal linings, and secondary bacterial colonization. Along with CRS, children with CF are at increased risk of nasal polyp formation, which can further obstruct sinus openings and, when large enough, block the normal flow of air through the nasal passages [7]. Finally, in addition to the direct effects of sinus disease on patients with CF, there is increasing evidence that sinonasal secretions are aspirated into the lungs, contributing to chronic lung infection and inflammation [8]. This is consistent with the unified airway model, a concept that views the upper and lower airways as a single functional entity. With a similar pseudostratified, ciliated, columnar epithelium, they are subject to the same inflammatory and infections processes. Furthermore, disease states of either the upper or lower airway tracts are likely to impact each other. In CF sinus disease, the primary concern is for aspiration of chronically infected postnasal drainage, resulting in secondary pulmonary exacerbations, bronchopneumonia, and decreased lung function.

A comprehensive understanding of CRS is paramount in treating pediatric patients with CF. In these children, the specific medical and surgical treatments employed will be different, as will expectations for improvement in their symptoms and QOL. Recommendations will also vary based on the manifestations of sinonasal disease and the degree of severity in each patient. This chapter will focus on the evaluation and management of CRS in children with CF and present a framework for surgical decision-making in these challenging patients.

Classification of CRS

Rhinosinusitis can be considered a spectrum of disease characterized by concurrent inflammatory and infectious processes which affect the nasal passages and the contiguous paranasal sinuses. Diagnosis and management are aided by the classification of this diverse condition into categories based primarily on the duration of symptoms. The definition of CRS has largely been accepted as the persistence of characteristic signs and symptoms beyond 12 weeks. Such an extended period of chronic symptoms may also be punctuated by episodes of acute exacerbations.

Pediatric rhinosinusitis, whether acute or chronic, should be considered a unique condition due to differences in predisposing factors and in the anatomy of the sinuses between children and adults. In addition, the sinus cavities of children with CF are often relatively small, further complicating CRS and its treatment in these patients. Woodworth et al. found that CF patients homozygous for the most common CFTR mutation (F508del) had a greater incidence of hypoplastic or underdeveloped sinuses [9]. It remains unclear, however, whether this anatomical difference is due to the chronically poor aeration of the sinuses during development that is characteristic of CF or the underlying genetic defect itself.

Pathophysiology

Along with the nasal passages, the paranasal sinuses serve to filter, warm, and humidify inspired air. Sinuses grow in size and shape throughout childhood and are key in reducing the overall weight of the human skull. The frontal sinuses are the last to fully develop and generally reach adult size by puberty.

Normal function of the sinuses depends on patent ostia, including the important common pathway of drainage and aeration known as the osteomeatal complex (OMC, see Fig. 9.1), as well as normal mucous secretion and ciliary function. In CF, mucociliary flow in the sinuses is disrupted due to thickened secretions. In addition, physical obstruction of the sinus ostia due to nasal polyps may lead to further retention of secretions and blockage of air exchange, resulting in hypoxia of the sinus mucosa and secondary bacterial infection.

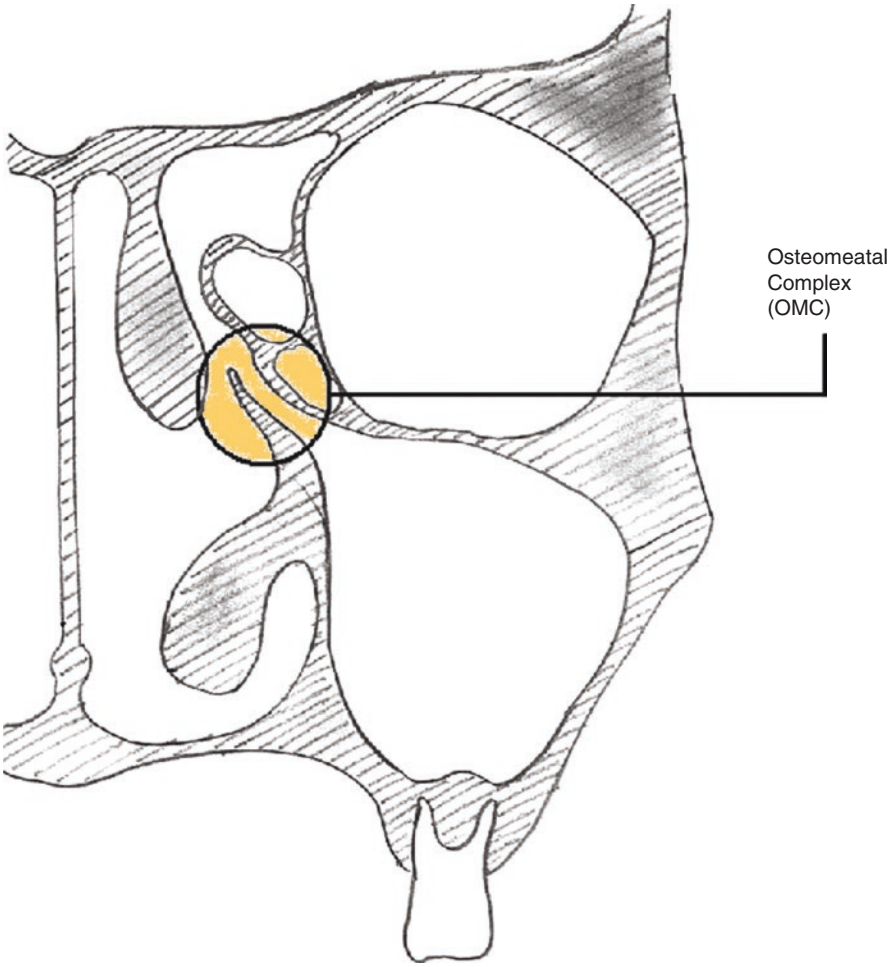


Fig. 9.1 Diagram of the osteomeatal complex (OMC)

Traditionally, normal sinuses, unlike other areas of the upper aerodigestive tract, have been thought to be sterile and without a normal and possibly protective microbial population. A few recent studies, however, suggest otherwise. Abreu et al. describe a reduced diversity of sinus microbes in patients with CRS in comparison to healthy controls. They also used a murine model of CRS to demonstrate the possible protective effects of one organism in particular – *Lactobacillus sakei* [10]. While many questions remain, these findings may support a new paradigm in which the disturbance of normal sinus microbial populations proves an important factor in the pathogenesis of CRS. Given their frequent though necessary use in children with CF, antibiotics may play a role, along with the underlying disease, in the disruption of normal sinus flora.

A host of other innate and environmental factors are also involved in contributing to the common pathophysiologic pathways in CRS. Local or anatomic factors include direct sinus obstruction due to anatomic abnormalities such as the presence of concha bullosa, septal deviation, nasal polyposis, trauma, and foreign bodies. Conditions contributing to mucosal inflammation and secondary obstruction include URI, bacterial infection, allergy, and gastroesophageal reflux disease (GERD). GERD in particular is known to be prevalent in children with CRS [11], and, in a retrospective study, Bothwell et al. demonstrated a significant decrease in the need for sinus surgery among children on anti-reflux therapy [12]. In addition to allergens, environmental irritants such as air pollutants or tobacco smoke may at times play a role in chronic mucosal inflammation.

Bacterial infection has long been considered a key component of CRS, and the pathogens found in children are generally similar to those in adults. The common isolates associated with CRS include those found in acute sinusitis (*Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *nontypeable Haemophilus influenzae*), as well as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and anaerobes. A systematic review of the literature by Møller et al. found *Staphylococcus aureus* most commonly isolated from the nose and sinuses of CF patients, followed by *Pseudomonas aeruginosa*, coagulase negative staphylococci, and *Haemophilus influenzae* [13]. The possible role of relatively ubiquitous fungi in the CRS inflammatory response has also been proposed, though remains controversial [14].

Recent evidence has also supported the role of bacterial exotoxins and biofilm formation in the pathogenesis of CRS. Exotoxins are released by bacteria and may contribute to a symptomatic immune response. In particular, Wang et al. demonstrated the presence of staphylococcal exotoxin and its effect on T cells in CRS patients with nasal polyps [15]. Biofilms form when bacteria aggregate on surfaces within an external matrix of polysaccharides, nucleic acids, and proteins. In CRS, biofilm formation may decrease the efficacy of antimicrobials by as much as a hundredfold, allowing bacteria to thrive for prolonged periods of time within the nose and sinus cavities. In 2005, Sanclement et al. used electron microscopy to demonstrate the presence of biofilms in sinus biopsies from 80% of patients undergoing functional endoscopic sinus surgery (FESS) for CRS, while none were seen in healthy controls [16]. Other studies have reported the presence of biofilms in ade-

noid tissue from patients with chronic infectious disease of the upper airways including CRS [17]. Recent research on topical medications in the treatment of CF has focused on bacterial biofilm-associated chronic sinusitis caused by *Pseudomonas aeruginosa* [18]. The literature suggests that both exotoxins and biofilms may be important factors in the role of bacterial infection in both CRS and CF CRS in particular.

Genetics

More than 2,000 unique CFTR variants have been identified. Deletion of a phenylalanine at position 508 (F508del) is the most common mutation accounting for approximately 70% of CF alleles worldwide. A large spectrum of additional known mutations account for the remainder of CF cases. Thus, most CF genotypes are rare, and only approximately 20 mutations constitute a frequency ≥0.1% [19]. Historically, CFTR mutations were categorized into different classes according to their molecular defect. There are seven classes that differ in CFTR anion channel production, processing, function, or stability [20]. These CFTR protein channel defect classes and associated mutation examples are presented in Table 9.1. CFTR nonsense or splicing mutations abrogate CFTR production (Class I). Missense mutations, such as F508del, impair CFTR folding (Class II). Moreover, mutation Classes III to VI comprise mutations that produce CFTR chloride channels that reach the cell surface, but are not fully functional. In Class III, CFTR regulation is altered, reducing the probability the channel is open. In Class IV, CFTR has a diminished ion conductance. Class V mutations result in reduced amounts of functional CFTR. Class VI mutations decrease the stability of CFTR, resulting in a shorter residence time of CFTR at the apical membrane. Finally, Class VII mutations result in no production of CFTR mRNA. Even though this classification system is considered an oversimplification, it remains the most widely known model.

Table 9.1 CFTR protein channel defect classes and associated mutations [87]

CFTR defect classes	Description	Associated mutation examples	% CF patients with mutation on at least one allele
I	No protein	G542X, W1282X, R553X	22%
II	No traffic	F508del, N1303K, I507del	88%
III	Impaired gating	G551D, S549N	6%
IV	Decreased conductance	D1152H, R347P, R117H	6%
V	Less protein	3272-26A→G	5%
VI	Less stable	c.120del123	1–2%
VII	No mRNA	Dele2,3(21kb), 1717-1G→A	1–2%

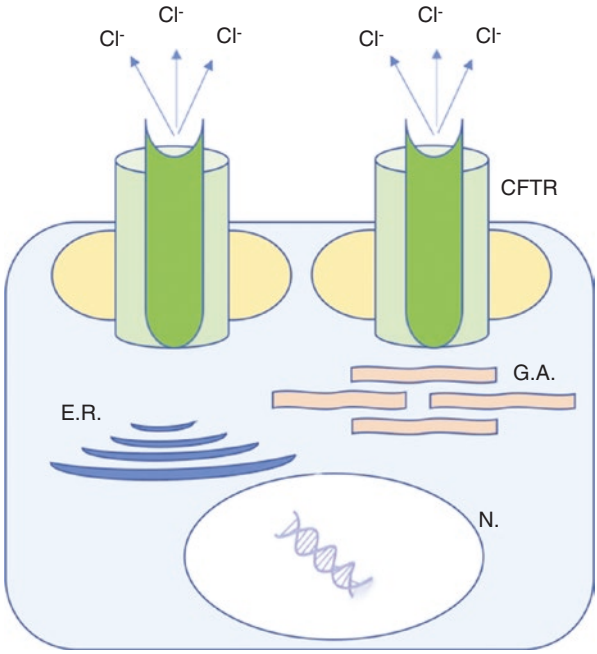


Fig. 9.2 Diagram of a normal epithelial cell (N, nucleus; ER, endoplasmic reticulum; GA, Golgi apparatus; CFTR, cystic fibrosis transmembrane conductance regulator protein)

An illustration of a normal epithelial cell is compared with a demonstration of the different CF defect classes in Figs. 9.2 and 9.3, respectively.

It is important to identify a CF patient's specific mutation if possible, as genotype affects disease severity [21] as well as response to treatment with various CFTR modulator therapies. However, alone it does not accurately predict symptomatology and progression in CF-related sinus disease. A study published in 2017 showed that genotype is not related to the severity of CF CRS. In addition, there was no significant relationship between genotype and control of symptoms following surgery [22].

Diagnosis

Careful history and physical examination is clearly important in the evaluation of CF-associated sinus disease. The symptoms of CRS in children are different than in adult patients and include persistent cough, as well as prolonged anterior and posterior nasal drainage, congestion, low-grade fever, irritability, and behavioral difficulties. Headache, especially in the frontal area, is a less common complaint among children than in adults. Interestingly, although two-thirds of CF patients describe a decreased sense of smell, only 10–15% complain specifically of sinonasal symptoms [23]. This may be due to the insidious nature of the disease and chronic nature of CRS in children with CF.

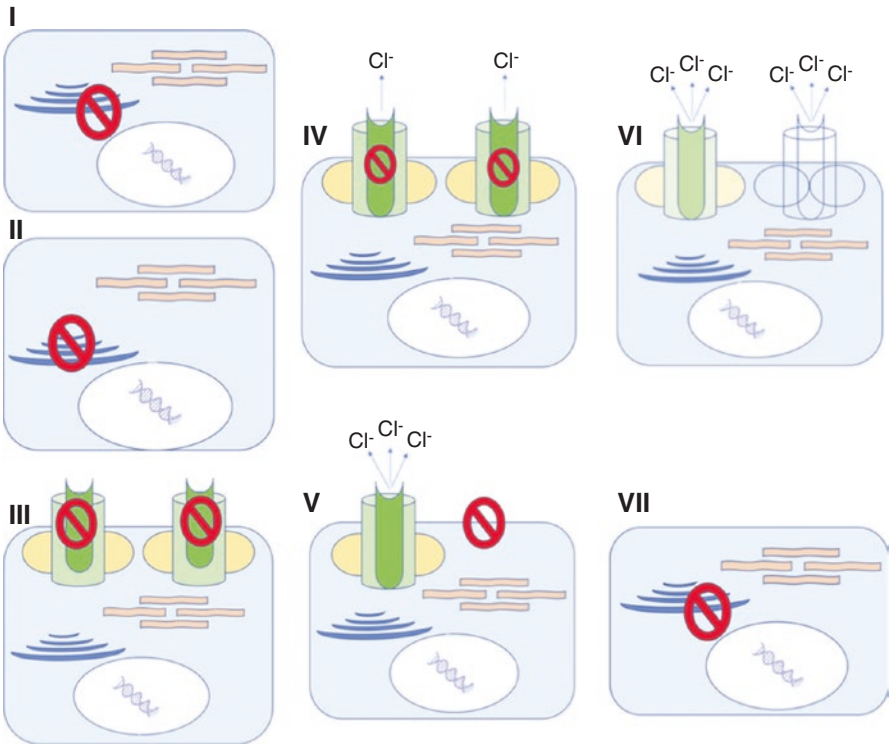


Fig. 9.3 Overview of CFTR defect classes. Class I: No protein synthesis due to degradation of abnormal mRNA. Class II: Defective protein folding leading to its protease destruction. Class III: Nonfunctional CFTR channels. Class IV: Decreased ion conductance through CFTR. Class V: Insufficient CFTR quantity. Class VI: Unstable transmembrane CFTR leading to fast turnover. Class VII: Large deletion leads to production of severely truncated polymerase

Physical examination should include a complete head and neck evaluation. Anterior rhinoscopy should be performed with a nasal speculum or otoscope using a large ear speculum. Characteristic findings include mucosal erythema and irritation, thickened nasal mucous, polyps, and frank purulent drainage. Otolaryngologists will usually include fiber-optic sinonasal endoscopy as part of their examination, allowing for improved visualization of the middle meatus, a common site of polyps, or purulent drainage from the maxillary and ethmoid sinuses (Fig. 9.4). Endoscopy is also useful for visualization of the posterior nasal cavity, nasopharynx, and adenoid tissue.

The radiologic evaluation of children with suspected CRS, including those with underlying CF, is generally reserved for those with disease refractory to medical management. Plain films, computed tomography (CT), and magnetic resonance imaging (MRI) have all been used in the evaluation of chronic sinusitis; however, CT scanning is generally considered the study of choice (Fig. 9.5). CT provides a

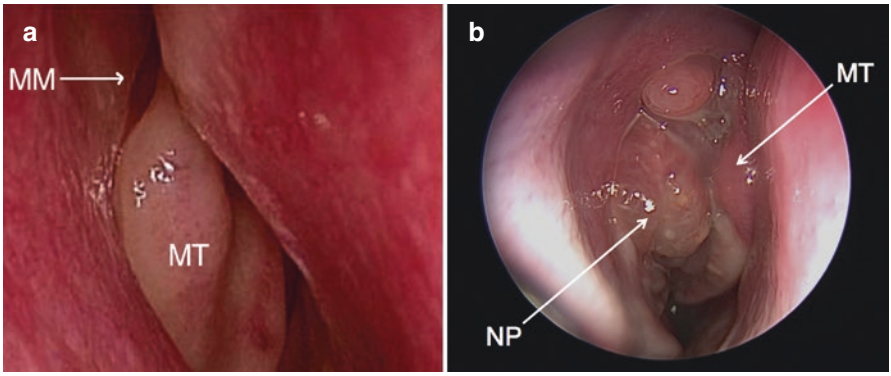


Fig. 9.4 (**a**) Normal sinonasal endoscopic view of the middle turbinate (MT) and middle meatus (MM). (**b**) Endoscopic exam in a child with CF demonstrating nasal polyps

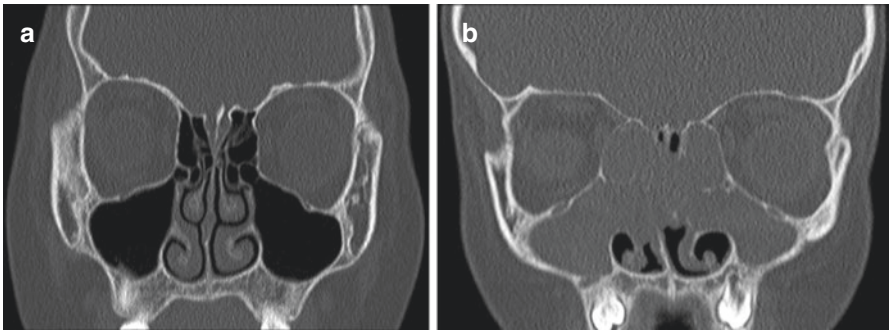


Fig. 9.5 (**a**) A normal coronal CT scan of the sinuses. (**b**) A coronal CT scan of the sinuses in a child with CF and associated CRS, demonstrating mucosal thickening and nasal polyposis

much higher resolution of bone and soft tissue without the interference of overlying structures in comparison to plain radiography [24].

Recent literature has supported restraint in the use of CT imaging in children due to concerns of excess radiation exposure [25]. In evaluating CRS, most otolaryngologists advocate CT scans of the sinuses only when making a decision regarding surgical intervention. These scans can also be used intraoperatively, without additional radiation exposure, for image guidance to help reduce the risk of complications during sinus surgery. In a 2012 clinical consensus statement for the American Academy of Otolaryngology-Head and Neck Surgery Foundation, Setzen et al. reported a strong consensus (>75% of the panel) for the statement "CT imaging is indicated in pediatric patients for chronic sinusitis when medical management and/or adenoidectomy have failed to control symptoms" [26].

When evaluating a child with symptoms of CRS, one should always consider the possibility of underlying disease, such as CF, as a contributing factor. Other disorders impacting normal sinonasal function include allergy, primary ciliary

dyskinesia (PCD), autoimmune vasculitic disease such as eosinophilic granulomatosis with polyangiitis (EGPA), and a variety of immune deficiencies.

Further Evaluation

Beyond history taking and physical examination, the further work-up and evaluation of CF patients with suspected chronic sinusitis should include the following:

- *Bacterial cultures* can evaluate for specific pathogens and help guide antimicrobial treatment. Sinus aspirates for culture-directed treatment can be obtained via sinus trephination or intraoperatively. Cultures from the middle meatus are generally easier to obtain in most cases and have relatively high predictive value in the diagnosis of bacterial sinusitis [27].
- *Imaging* – CT scanning of the sinuses is recommended for children with CF CRS refractory to medical management, nasal obstruction due to polyps, or decreases in pulmonary function.
- *Pediatric otolaryngology referral* is recommended for children with CF and suspected CRS refractory to medical management. A pediatric otolaryngologist with experience in sinus disease can facilitate further evaluation and treatment, such as fiber-optic sinonasal endoscopy as well as surgical intervention including adenoidectomy and, if necessary, FESS.

In 1938, Dr. Dorothy Anderson was the first to describe cystic fibrosis of the pancreas [28]. It wasn't until 1953 when the sweat electrolyte defect in CF was discovered. Six years later, the sweat chloride test was created. In the 1960s, diagnosis of cystic fibrosis was made by sweat test and biopsies of the small intestine. In 1989, the CF gene was identified and given the name CFTR [29]. Full CFTR sequencing started to become available in the 2000s.

Over the years, it became clear that early diagnosis and treatment of CF were critical for improved nutritional and pulmonary outcomes. Hence, newborn screening was developed and became the mainstay of diagnosis. In the United States, all 50 states and the District of Columbia screen newborns for CF in the first 2 to 3 days of life. CF newborn screening is based on the serum level of immunoreactive trypsinogen (IRT). IRT is produced by the pancreas and is normally found in small amounts in the blood stream. IRT levels are high in patients with CF, prematurity, stressful delivery, and other conditions. Some states only test IRT levels on the first blood test, while other states conduct both an IRT and a DNA test.

If IRT is elevated on the newborn screening, then a sweat chloride test is recommended for confirmation. CFTR-related metabolic syndrome (CRMS) was proposed to describe infants with a positive newborn screen but who do not meet diagnostic criteria for CF. These children have elevated trypsinogen levels and a sweat chloride value not in the defining range for CF or fewer than two CF disease-causing mutations in the CFTR gene. The exact clinical implications of a CRMS diagnosis remain unclear. While these patients do not have cystic fibrosis, they may

develop similar signs and symptoms, with a milder clinical course than CF patients. There are thus far no studies addressing prevalence and severity of sinus disease in patients with CRMS.

Medical Treatment

It should be appreciated that few randomized controlled trials or systematic reviews of the literature exist with recommendations for the treatment of CRS in children, especially in those with concurrent CF [30]. Much of what is known, therefore, is based on findings in adult populations or studies of acute sinusitis. For example, a recent review of the Cochrane and PubMed databases by Makary and Ramadan revealed no randomized controlled studies comparing medical treatment with FESS, or other surgical procedures, for CRS in children [31].

The medical management of CRS has traditionally included combinations of antihistamines, decongestants, nasal saline irrigation, topical nasal steroids, and oral antibiotics. In a survey of pediatric otolaryngologists in 2005, Sobol et al. reported that 95% of respondents used antibiotics in the treatment of CRS, 90% prescribed topical steroids, and 68% recommended nasal saline sprays or irrigations for their patients [32]. Antihistamines and decongestants are commonly used in suspected sinusitis for their role in reducing mucosal edema, as well as to treat any component of the underlying allergy. Yet, in a recent Cochrane systematic review of acute sinusitis, no significant evidence was found to support the use of antihistamines or decongestants [33].

Nasal saline sprays, or irrigations when tolerated, are also used in the treatment of CRS and are thought to help primarily in the clearance of sinonasal secretions, pathogens, and debris. While the Cochrane review could not support any recommendations in regard to nasal saline irrigation either, a number of studies have demonstrated some degree of efficacy in CRS. In a prospective study of 40 children, Wei et al. demonstrated a significant improvement in both quality of life (QOL) and CT scan Lund-Mackay scores after 6 weeks of once-daily nasal saline irrigation [34]. Other reviews of the literature also support a clinical benefit from the use of topical nasal saline [35]. For the most part, nasal saline sprays or irrigations are well tolerated in children with minimal side effects. Some have proposed that hypertonic saline solutions are preferred in children with CF CRS due to their relative ability to hydrate mucous secretions. Hypertonic saline, however, can cause irritation of mucosal linings, and recent studies have not supported any significant benefit [36].

Topical nasal steroids suppress mucosal inflammation and are also therefore widely used in the treatment of CRS in children. Examples include fluticasone propionate, which is widely available in generic form, and mometasone furoate, which is indicated for use in nasal congestion due to allergic rhinitis for children age 2 and older. Evidence is limited but supports the use of both intranasal and systemic corticosteroids in the treatment of sinusitis, either alone or in combination with antibiotic therapy [37, 38]. The use of topical nasal steroids is generally preferred for

children with CRS due to their low systemic bioavailability. Systemic side effects are rare, with minor epistaxis the most commonly reported complication [39]. Though controversial, nasal steroids may also have a role in combination with surgery, as part of a postoperative and preventative medical regimen along with nasal saline. While Dijkstra et al. found no effect on the recurrence of CRS symptoms or nasal polyps following FESS [40], others have demonstrated a decreased need for revision surgery in CRS patients treated with topical nasal steroids postoperatively [41]. In CF, there have been mixed findings in regard to the treatment of nasal polyps with topical nasal steroid sprays. While Weber et al. demonstrated improvement in 57.14% of patients with CF and nasal polyps treated with topical corticosteroids [42], a systematic review by Beer et al. found only some effect in reducing the size of nasal polyps, but concluded there was no clear evidence for using topical steroids in patients with cystic fibrosis and nasal polyposis [43].

The use of antibiotics in treating acute sinusitis is generally accepted with recommended courses ranging from 10 to 14 days. In CRS, the available evidence suggests that a longer duration of treatment (from 3 to 12 weeks) is necessary to achieve any significant benefit [44]. In the absence of culture data, amoxicillin-clavulanate remains a good choice for first-line treatment. In CF CRS, however, antibiotic choices should address common pathogens including *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Antibiotic treatment has been shown to decrease sinonasal bacterial colonization in CF patients, in particular when combined with surgery [45]. Long-term macrolide treatment (12 weeks) may also be of benefit in CRS patients with low IgE levels [46] and is commonly used in children with sinonasal disease secondary to CF in which inflammation is primarily neutrophilic.

While oral and intravenous (IV) routes are frequently used in the administration of antibiotics in CF CRS, the potential for topical antibiotic therapy has also gained recent attention [14]. Nebulized inhalational antibiotic agents are used routinely in the treatment of CF-related pulmonary disease. The theory is that topical treatment, via spray, nebulizer, or irrigation, should serve to deliver a high concentration of antibiotic directly to the sinonasal mucosa while minimizing systemic side effects. While recent reviews have not supported the use of topical antibiotics for CRS, a number of studies have reported symptomatic improvement [47, 48]. Uren et al. treated 16 patients with surgically recalcitrant CRS and endoscopic cultures positive for *Staphylococcus aureus.* After 3 weeks of twice daily topical mupirocin, 12 patients were improved symptomatically with 15 demonstrating an improvement in endoscopic findings and negative cultures [49]. Based on these results, the use of mupirocin in postoperative nasal saline irrigations, when *Staphylococcus aureus* is found on intraoperative sinus cultures, has become more widespread both in CRS and CF CRS patients. In addition, Mainz et al. demonstrated, in a randomized controlled trial, that topical intranasal tobramycin treatment of *Pseudomonas aeruginosa* in CF patients resulted in a decrease of bacterial quantity and significantly improved QOL based on sinonasal outcome test (SNOT-20) survey scores [50].

So far there has been little evidence that topical antibiotics are effective in reducing biofilm formation though, perhaps surprisingly, regression of biofilms has been reported in CRS patients following 8 weeks of treatment with oral clarithromycin

[51]. While topical antibiotic treatment is not currently recommended in most cases of CRS, initial findings do seem to warrant further study. Questions regarding dosage, length of therapy, optimal method of delivery, and the potential for combination with other treatments remain to be answered. In summary, topical nasal steroids, nasal saline, and systemic antibiotics when necessary remain the medical treatments of choice for CRS in children with CF based on the best evidence to date.

Treatment of CF-Related Pulmonary Disease

In addition to treating pathogens of the upper and lower airways with appropriate antibiotics, a major part of CF therapy is directed toward managing the effects of defective CFTR proteins on various organs. Airway inflammation and mucous plugging cause significant morbidity and mortality in patients with cystic fibrosis. In the 1950s, iodides, oral streptokinase or streptodornase, and intramuscular or inhaled pancreatic trypsin were used to thin the mucous secretions of CF patients. In 1993, dornase alfa (Pulmozyme®) was approved by the US Food and Drug Administration (FDA) for patients with CF, age 5 and older. Dornase alfa is inhaled recombinant human deoxyribonuclease (DNase) and was the first truly effective mucus thinner. Though not used routinely due to cost, the benefits of intranasal dornase alfa in CF CRS have also been demonstrated. A systematic review by Shah et al. found that topical intranasal dornase alfa appeared to improve sinonasal symptoms in CF patients to a greater degree than saline alone [52].

As for airway clearance, chest physical therapy and pressure vibrations remain widely used. By the 1990s, the benefit of exercise for mucous mobilization and clearance was also appreciated. In 2009, clinical trials showed that oral azithromycin, used as an anti-inflammatory agent, led to improved lung function and weight gain in CF patients with chronic *Pseudomonas aeruginosa* infection. It also decreased their rate of hospital admissions due to pulmonary exacerbations. High-dose ibuprofen is another anti-inflammatory medication that is used for patients with CF under age 18.

CFTR Modulators

CFTR modulators are molecules that bind to the CFTR protein to enhance function and/or structural stability. Ivacaftor (Kalydeco®) was the first CFTR modulator to be approved for clinical use. Ivacaftor is a potentiator of CFTR channel activity. In clinical trials, ivacaftor therapy resulted in lower sweat chloride and improvements in lung function, QOL, and nutritional indices in patients with CF with the G551D mutation [53–56]. In 2012, the FDA approved ivacaftor for patients age 12 and older with the G551D mutation, which represents approximately 4%–5% of the CF population. From 2013 to 2015, approval was expanded to include patients age 6

years or older and those with other gating mutations. Even with the expanded indication, only about 10% of patients with CF in the United States carry mutations responsive to ivacaftor.

In 2015, the combination drug ivacaftor/lumacaftor (Orkambi®) was approved for CF patients with two copies of F508del [57]. Lumacaftor corrects defective CFTR folding. The proposed mechanism of action of the combination is to restore CFTR trafficking and activity. Consequently, this medication acts to counter fluid secretion defects in affected organs. Studies have demonstrated improvement in lung function, nutrition, and QOL. The benefits are modest, however, when compared to those observed with ivacaftor [57, 58]. In 2018, tezacaftor/ivacaftor (Symdeko®) was approved for patients older than 12 years and homozygous for the F508del mutation or with one mutation that responds to tezacaftor/ivacaftor. This combination improves processing and trafficking of defective CFTR by suppressing folding defects [59]. Clinical trials showed that tezacaftor/ivacaftor improved lung function and QOL and had less side effects than the ivacaftor/lumacaftor combination [60–62].

While these results are certainly promising, the effect of CFTR modulators on sinus disease in CF patients is still unclear. There are no published studies comparing sinus disease before and after initiation of CFTR modulator therapy. However, molecular studies do suggest an increase in ciliary beat frequency and mucociliary clearance in human sinonasal epithelial cell cultures [63].

Surgical Treatment

When prolonged efforts at medical therapy have failed, pediatric patients with persistent CRS are referred to an otolaryngologist for further evaluation and possible surgical intervention. In children with CF, pediatric otolaryngology should be consulted early, as up to 60% of CF patients will ultimately undergo some form of sinus surgery [64]. It should be remembered, however, that perioperative morbidity in CF patients may be higher due to pulmonary disease and a higher rate of coagulopathy resulting in part from impaired vitamin K absorption. Clearly, surgery for CRS in CF is not curative, and deciding whether a child is a good candidate for FESS can be challenging. As no standard criteria or clinical practice guidelines currently exist, we propose a framework of three primary indications for surgical intervention based on clinical experience at our institution and various degrees of support in the literature thus far (Table 9.2).

Though indications and outcomes may differ, the array of surgical procedures utilized in CF patients is generally similar to that used in children with CRS alone. Adenoidectomy is the first line of surgical treatment and is often performed even prior to radiologic imaging with CT. Large adenoids may physically disrupt the normal mucociliary clearance of the nasal cavity and sinuses, though adenoid tissue of any size is thought to act as a reservoir for bacteria. Evidence also suggests frequent biofilm formation on adenoid tissue in children with CRS [65]. A 2008 meta-analysis of adenoidectomy in children with rhinosinusitis found an overall rate of clinical improvement of approximately 70%, consistent with prior studies [66]. In

Table 9.2 Proposed framework for surgical decision-making in CF CRS

Indication	Findings	Intervention	Evidence
1. Nasal obstruction due to nasal polyposis	Physical exam, fiber-optic sinonasal endoscopy, CT scan	Endoscopic nasal polypectomy	Fetta et al. [76]
2. CRS symptoms refractory to medical management	H&P, fiber-optic sinonasal endoscopy, CT scan	Adenoidectomy FESS	Khalid et al. [78] Liang et al. [79]
3. Impaired pulmonary function, episodes of bronchopneumonia	PFTs, input from Pediatric Pulmonology team, history of pulmonary exacerbations/ hospitalizations	Adenoidectomy - Functional endoscopic sinus surgery (FESS)	Khalfoun et al. [82] Rosbe et al. [83] Shatz et al. [84] Osborn et al. [85]

teenage children, adenoid tissue may tend to recede and become less clinically relevant. For this age group, endoscopic sinus surgery, either with or without treatment of adenoid tissue, may be considered more frequently as an acceptable initial surgical procedure [67].

The goal of sinus surgery beyond adenoidectomy is generally to enlarge the natural ostia or openings of the sinuses, while preserving normal mucosa, in an effort to reestablish normal aeration and mucociliary function. Surgical intervention may also include the removal of any obstructive or diseased tissue such as nasal polyps. A CT scan is often obtained at this point to demonstrate persistent sinus disease despite maximal medical therapy and for a careful review of sinonasal anatomy prior to surgery. CT data is also commonly used for intraoperative image guidance in children undergoing FESS.

In recent years, the refinement of fiber-optic endoscopes has allowed for most sinus surgery to be performed endoscopically. In children, the most common procedure is "limited" FESS and involves widening of the natural ostium of the maxillary sinus along with a limited or anterior ethmoidectomy. Some surgeons, however, recommend complete removal of the anterior and posterior ethmoid cells, resulting in a larger, better-aerated, and well-mucosalized ethmoid cavity. Others favor addressing all sinuses affected by disease including the sphenoid sinuses and, when fully developed, the frontal sinuses. Virgin et al. recommend more aggressive widening of the maxillary antrostomy or modified endoscopic medial maxillectomy in CF CRS patients. Their study of 22 patients found significantly reduced symptom scores at 60 days and up to 1 year postoperatively. While the forced expiratory volume in 1 second (FEV1) did not change on average, endoscopic scores and number of hospitalizations due to pulmonary exacerbations were significantly reduced [68].

More recently, balloon dilation of sinus ostia, known as balloon catheter sinuplasty (BCS), has been reported as an alternative to conventional FESS. In children, this is primarily used for treatment of the maxillary sinus and has been described both alone and in combination with other procedures such as adenoidectomy and

ethmoidectomy [69]. BSC is still being evaluated for its efficacy in children with CRS. In CF patients, where larger and more lasting sinus openings are warranted, its role is likely to remain limited.

While surgery is clearly indicated for complications of acute sinusitis, its role in CRS is less clear. Sinus surgery in CRS, and CF CRS in particular, is probably best thought of as an adjuvant treatment to medical therapy, with the aim of improving sinus function. Parents should be counseled in regard to reasonable expectations for symptomatic improvement, as children will remain prone to URI, allergy, and other underlying factors. A reduction in the frequency and severity of symptoms is a reasonable goal, and many children will benefit from continued medical management, including topical nasal steroids and saline postoperatively. In fact, the enlargement of sinus ostia achieved by sinus surgery may also serve to improve the delivery and efficacy of topical treatments such as nasal steroid sprays and saline irrigations [70].

The majority of studies on the effectiveness of FESS for pediatric CRS are retrospective, though demonstrate significant clinical improvement for CRS refractory to medical management and adenoidectomy. In 2009, Siedek et al. reported a 76% rate of improvement in both CRS symptoms and overall QOL [71]. In a review of 11 studies, Makary and Ramadan found a success rate for pediatric FESS ranging from 82% to 100% [31]. Results also seem to be lasting, with one study demonstrating the symptomatic benefits of FESS over medical therapy as far out as 10 years [72].

Though quite safe, the potential complications of endoscopic sinus surgery include bleeding, infection, recurrent disease, cerebrospinal fluid leak, and orbital injury including hematoma and loss of vision. Despite concerns among some, however, cephalometric measurements by Van Peteghem and Clement found no impact of FESS on facial growth in children with CF [73]. In the Makary and Ramadan review, an overall complication rate was estimated at 1.4% [31]. In this study, no cases of cerebrospinal fluid leak or major orbital injury such as hematoma or blindness were reported, supporting the relative safety of FESS in children. Further reducing the risk of complications, intraoperative CT-image guidance has quickly become a routine adjunct to pediatric FESS and may also facilitate more complete removal of diseased tissue (Fig. 9.6).

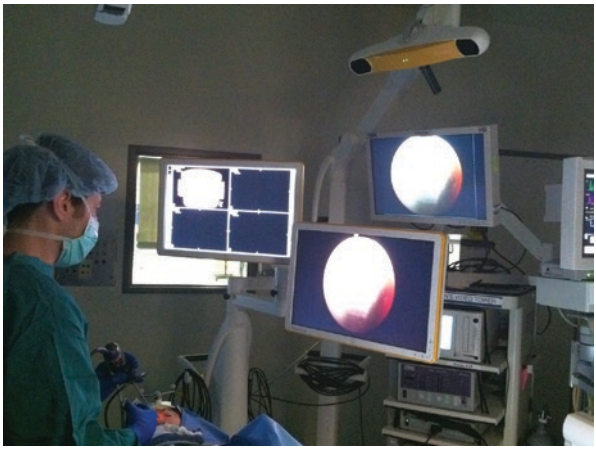


Fig. 9.6 Endoscopic sinus surgery with use of intraoperative CT-image guidance

While not curative, and with up to 50% of children with CF undergoing FESS requiring further surgery [74], there appears to be an important role for surgical intervention in many cases. A review of the most recent literature supports a proposed framework of indications for surgery in children with both CF and CRS.

Surgical Decision-Making in CF CRS

At some point in their lifetime, 25–30% of CF patients will develop recurrent *nasal polyposis* [42]. Small nasal polyps or polypoid tissue may arise in the middle meatus, obstructing the natural outflow of the ethmoid, frontal, and maxillary sinuses at the OMC. In addition, nasal polyps may grow to the point of obstructing nasal airflow along the floor of the nasal cavity. Interestingly, vitamin D_3 deficiency may be associated with an increased prevalence of nasal polyps in children with CF [75]. While medical treatment including topical or systemic corticosteroids can be helpful in the management of symptoms associated with nasal polyps, surgical resection is clearly effective. In most cases, this is achieved endoscopically using Blakesley forceps or a powered microdebrider. Fetta et al. reported significantly improved postoperative QOL in CRS with nasal polyps in children both with and without CF [76]. As might be expected, patients with CF experienced a higher rate of recurrence, though the burden of additional surgery was outweighed by the benefits of revision FESS in these children. The presence of nasal polyposis obstructing either sinus ostia or nasal airflow appears to be a strong indication for recommending surgical intervention such as FESS with endoscopic nasal polypectomy.

Although characteristic findings on physical exam, endoscopy, and CT scan are present in up to 90% to 100% of children with CF [64], only 10–15% of these children complain of *CRS symptoms*. Approximately 2–3% of pediatric CF patients undergo surgery each year for sinus disease [77], however, raising an important question: How should one decide on the need for surgical intervention in children with CF CRS? While abnormal findings on endoscopy and CT scan are present in most patients, reported symptoms such as cough, low-grade fever, purulent rhinorrhea or postnasal drainage, and facial pain or pressure are clearly late findings. Complaints of classic CRS symptoms such as these, therefore, should be considered a sign of advanced disease – when refractory to medical management, surgical intervention including adenoidectomy and FESS is indicated. In a case-controlled study of 20 adult patients with CF, postoperative endoscopic findings and QOL were both significantly improved following FESS for sinus disease [78]. Likewise, a retrospective review of 24 studies by Liang et al. supported universal improvement of sinonasal symptoms following sinus surgery in both pediatric and adult CF patients [79]. It could not be concluded from this review, however, if FESS had any impact on lower airway disease.

The final aspect to consider in a proposed model for surgical decision-making in CF CRS is the degree to which sinonasal disease contributes to bronchopneumonia and *impaired pulmonary function*. It seems reasonable to assume that chronically

infected paranasal sinuses and associated postnasal drainage may lead to intermittent aspiration and contamination of the lower airways. A number of studies support this conclusion. Choi et al., for example, demonstrated a high correlation between pretransplant sinus cultures and posttransplant bronchoalveolar lavage (BAL) cultures in 141 CF patients undergoing lung transplant [80]. Aanæs et al. likewise found persistent sinonasal pathogens despite negative BAL cultures in CF patients with intermittent lung colonization, suggesting the need for control of sinonasal infection in preventing pulmonary disease [81]. Both studies support the concept of the unified airway theory.

The second part of this vital question regards the effect, if any, of surgical intervention in CF CRS on pulmonary function. The literature thus far demonstrates mixed findings in this regard. In a retrospective chart review of 181 patients, Khalfoun et al. report a reversal of declining FEV1 1 year after FESS in CF patients with moderate to severe lung disease (FEV1 < 80%) [82]. Rosbe et al. looked at 66 patients that underwent a total 112 FESS procedures. While there was no significant difference postoperatively in pulmonary function testing (PFT) or steroid requirements, the results did indicate a reduced need for hospitalization in the 6-month period following surgery [83]. Shatz et al. found that a relatively aggressive surgical approach including FESS, a Caldwell-Luc procedure, and medial maxillectomy resulted in significantly improved QOL, reduced need for IV antibiotics, and fewer admissions to the hospital [84]. FEV1 was also improved on average at 6 months postoperatively. Alternatively, Osborn et al. followed 41 children with CF for 12 months after FESS and found no consistent effect on PFT results or significant impact on lower respiratory tract microbial pathogens. In almost 50% of cases, positive cultures were identical in both the preoperative and postoperative specimens [85].

While important for nasal polyposis and CRS symptoms, it appears unclear at this time whether surgical intervention in CF patients is beneficial in terms of improved pulmonary function. A systematic review by Crockett et al. concluded there was little high-level evidence regarding surgical interventions in patients with CRS and CF [86]. Further prospective studies, in greater numbers of patients, will be needed to better evaluate the effects of surgery including FESS on pulmonary function in children with CF.

Summary

CRS in children with CF is a challenging condition from the standpoint of management and decision-making in treatment. The evidence supports combined therapeutic approaches including both medical and, when necessary, surgical options. As the pathogenesis becomes clearer through ongoing basic science research, our ability to treat CRS in children with CF both effectively and safely will continue to improve. The effect of surgery on lung pathogens and pulmonary function is an important area for further investigation, as is the possible benefit of topical intranasal

antimicrobial therapy and CFTR modulators. Future prospective studies will add to our understanding of CF CRS and help to further shape the model for surgical decision-making outlined above. Regardless of future developments, careful history, physical examination, imaging when necessary, and judgment will remain vital in the diagnosis and management of this disease, as will close communication and cooperation between pediatricians and their colleagues in pediatric pulmonology and otolaryngology.

Acknowledgments The authors would like to thank Dr. Terry L. Noah, MD, and Dr. Charles R. Esther, Jr., MD, PhD, of the UNC Division of Pediatric Pulmonology for their input and careful review of our manuscript. We greatly appreciate their time and assistance. We would also like to thank Dr. Hassan Ramadan, MD, and Dr. Fuad Baroody, MD, for their guidance and inspiration in the field of pediatric rhinology, as well as the opportunity to contribute to this outstanding book.

References

1. Anand VK. Epidemiology and economic impact of rhinosinusitis. Ann Otol Rhinol Laryngol Suppl. 2004;193:3–5.
2. 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.
3. Lusk R. Pediatric chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2006;14:393–6.
4. Tipirneni KB, Woodworth BA. Medical and surgical advancements in the management of cystic fibrosis chronic rhinosinusitis. Curr Otorhinolaryngol Rep. 2017;5(1):24–34.
5. Li W, Soave D, Miller MR, Keenan K, Lin F, Gong J, Chiang T, et al. Unraveling the complex genetic model for cystic fibrosis: Pleiotropic effects of modifier genes on early cystic fibrosis-related morbidities. Hum Genet. 2014;133(2):151–61.
6. Corvol H, Blackman SM, Boëlle PY, Gallins PJ, Pace RG, Stonebraker JR, et al. Genome-wide association meta-analysis identifies five modifier loci of lung disease severity in cystic fibrosis. Nat Commun. 2015;6(1):8382.
7. Feuillet-Fieux MN, Lenoir G, Sermet I, Elie C, Djadi-Prat J, Ferrec M, et al. Nasal polyposis and cystic fibrosis (CF): review of the literature. Rhinology. 2011;49(3):347–55.
8. Nelson J, Karempelis P, Dunitz J, Hunter R, Boyer H. Pulmonary aspiration of sinus secretions in patients with cystic fibrosis. Int Forum Allergy Rhinol. 2018;8(3):385–8. https://doi.org/10.1002/alr.22043.
9. 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.
10. Abreu NA, Nagalingam NA, Song Y, Roediger FC, Pletcher SD, Goldberg AN, Lynch SV. Sinus microbiome diversity depletion and Corynebactrium tuberculostearicum enrichment mediates rhinosinusitis. Sci Transl Med. 2012;12:4(151):151ra124.
11. Phipps CD, Wood E, Gibson WS, Cochran WJ. Gastroesophageal reflux contributing to chronic sinus disease in children. Arch Otolaryngol Head Neck Surg. 2000;126:831–6.
12. Bothwell MR, Parsons DS, Talbot A, Barbero GJ, Wilder B. Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngol Head Neck Surg. 1999;121(3):255–62.
13. Møller ME, Alanin MC, Grønhøj C, Aanæs K, Høiby N, von Buchwald C. Sinus bacteriology in patients with cystic fibrosis of primary ciliary dyskinesia: a systematic review. Am J Rhinol Allergy. 2017;31(5):293–8.

14. Comstock RH, Lam K, Mikula S. Topical antibiotic therapy of chronic rhinosinusitis. Curr Infect Dis Rep. 2010;12:88–95.
15. Wang M, Shi P, Chen B, Zhang H, Jian J, Chen X, et al. The role of superantigens in chronic rhinosinusitis with nasal polyps. ORL J Otorhinolaryngol Relat Spec. 2008;70(2):97–103.
16. Sanclement JA, Webster P, Thomas J, Ramadan HH. Bacterial biofilms in surgical specimens of patients with chronic rhinosinusitis. Laryngoscope. 2005;115(4):578–82.
17. Calò L, Passàli GC, Galli J, Fadda G, Paludetti G. Role of biofilms in chronic inflammatory diseases of the upper airways. Adv Otorhinolaryngol. 2011;72:93–6.
18. Klodzińska SN, Priemel PA, Rades R, Mørck Nielsen H. Inhalable antimicrobials for treatment of bacterial-associated sinusitis in cystic fibrosis patients: challenges and drug delivery approaches. Int J Mol Sci. 2016;17(10):1688–707.
19. Sosnay PR, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Gentet. 2013;45(10):1160–7.
20. Veit G, Avramescu RG, Chiang AN, Houck SA, Cai Z, Peters KW, et al. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. Mol Biol Cell. 2016;27(3):424–33.
21. MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the cystic fibrosis foundation patient registry. Ann Intern Med. 2014;161(4):233–41.
22. Abuzeid WM, Song C, Fastenberg JH, Fang CH, Ayoub N, Jerschow E, et al. Correlations between cystic fibrosis genotype and sinus disease severity in chronic rhinosinusitis. Laryngoscope. 2017;128(8):1752–8.
23. Aanaes K, Johansen HK, Slov M, Buchvald FF, Hjuler T, Pressler T, et al. Clinical effects of sinus surgery and adjuvant therapy in cystic fibrosis patients: can chronic lung infections be postponed? Rhinology. 2013;51(3):222–30.
24. Leo G, Triulzi F, Incorvaia C. Sinus imaging for diagnosis of chronic rhinosinusitis in children. Curr Allergy Asthma Rep. 2012;12(2):136–43.
25. Brenner DJ, Hall EJ. Computed tomography – an increasing source of radiation exposure. N Engl J Med. 2007;357:2277–84.
26. Setzen G, Ferguson BJ, Han JK, Rhee JS, Cornelius RS, Froum SJ, et al. Clinical consensus statement: appropriate use of computed tomography for paranasal sinus disease. Otolaryngol Head Neck Surg. 2012;147(5):808–16.
27. Elwany S, Helmy SA, El-Reweny EM, Harfoush R, Sobhy A. Endoscopically directed middle meatal cultures vs computed tomography scans in the diagnosis of bacterial sinusitis in intensive care units. J Crit Care. 2012;27(3):315:1–5.
28. Andersen D. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study. Am J Dis Child. 1938;56:344–99.
29. Kerem B, Rommens J, Buchanan J, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science. 1989;245:1073–80.
30. Thomas M, Yawn B, 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.
31. Makary CA, Ramadan HH. The role of sinus surgery in children. Laryngoscope. 2013;00:1–5.
32. 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;115:78–80.
33. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. Cochrane Database Syst Rev. 2012;9:CD007909.
34. 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(9):1989–2000.
35. Khianey R, Oppenheimer J. Is nasal saline irrigation all it is cracked up to be? Ann Allergy Asthma Immunol. 2012;109(1):20–8.

36. Corcoran TE, Godovchik JE, Donn KH, Busick DR, Goralski J, Locke LW, et al. Overnight delivery of hypertonic saline by nasal cannula aerosol for cystic fibrosis. Pediatr Pulmonol. 2017;52(9):1142–9.
37. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. Cochrane Database Syst Rev. 2009;4:CD005149.
38. Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar CB, Perera R, et al. Systemic corticosteroids for acute sinusitis. Cochrane Database Syst Rev. 2014;3:CD008115.
39. Skoner D. Update of growth effects of inhaled and intranasal corticosteroids. Curr Opin Allergy Clin Immunol. 2002;2(1):7–10.
40. Dijkstra MD, Ebbens FA, Poublon RM, Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. Clin Exp Allergy. 2004;34(9):1395–400.
41. 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(5):1017–23.
42. Weber SAT, Iyomasa RM, Corrêa CC, Florentino WNM, Ferrari GF. Nasal polyposis in cystic fibrosis: follow-up of children and adolescents for a 3-year period. Braz J Otorhinolaryngol. 2017;83(6):677–82.
43. Beer H, Southern KW, Swift AC. Topical nasal steroids for treating nasal polyposis in people with cystic fibrosis. Cochrane Database Syst Rev. 2015;6:CD008253.
44. 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;50:1–12.
45. Aanaes K, von Buchwald C, Hjuler T, Skov M, Alanin M, Johansen HK. The effect of sinus surgery with intensive follow-up on pathogenic sinus bacteria in patients with cystic fibrosis. Am J Rhinol Allergy. 2013;27(1):e1–4.
46. Adelson RT, Adappa ND. What is the proper role of oral antibiotics in the treatment of patients with chronic sinusitis? Curr Opin Otolaryngol Head Neck Surg. 2013;21(1):61–8.
47. Scheinberg PA, Otsuji A. Nebulized antibiotics for the treatment of acute exacerbations of chronic rhinosinusitis. Ear Nose Throat J. 2002;81:648–52.
48. Vaughan WC, Carvalho G. Use of nebulized antibiotics for acute infections in chronic sinusitis. Otolaryngol Head Neck Surg. 2002;127:558–68.
49. Uren B, Psaltis A, Wormald PJ. Nasal lavage with mupirocin for the treatment of surgically recalcitrant chronic rhinosinusitis. Laryngoscope. 2008;118:1677–80.
50. Mainz JG, Schädlich K, Schien C, Michl R, Schelhorn-Neise P, Koitschev A, et al. Sinonasal inhalation of tobramycin vibrating aerosol in cystic fibrosis patients with upper airway Pseudomonas aeruginosa colonization: results of a randomized, double-blind, placebo-controlled pilot study. Drug Des Devel Ther. 2014;10(8):209–17.
51. Tatar EC, Tatar I, Ocal B, Korkmaz H, Saylam G, Ozdek A, et al. Prevalence of biofilms and their response to medical treatment in chronic rhinosinusitis without polyps. Otolaryngol Head Neck Surg. 2012;146(4):669–75.
52. Shah GB, De Keyzer L, Russell JA, Halderman A. Treatment of chronic rhinosinusitis with dornase alfa in patients with cystic fibrosis: a systematic review. Int Forum Allergy Rhinol. 2018;8(6):729–36.
53. Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, et al. Cystic Fibrosis Foundation Pulmonary Guidelines. Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. Ann Am Thorac Soc. 2018;15(3):271–80.
54. Accurso F, Rowe S, Clancy J, Boyle MP, Dunitz JM, Durie PR, et al. Effect of Vx-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med. 2010;363:1991–2003.
55. Davies JC, Wainwright C, Canny G, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med. 2013;187:1219–25.

56. McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). Lancet Respir Med. 2014;2:902–10.
57. Wainwright CE, Elborn J, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med. 2015;373:220–31.
58. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the cystic fibrosis questionnaire-revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic pseudomonas aeruginosa airway infection. Chest. 2009;135:1610–8.
59. Ren HY, Grove DE, De La Rosa O, Houck SA, Sopha P, Van Goor F, et al. VX-809 corrects folding defects in cystic fibrosis transmembrane conductance regulator protein through action on membrane-spanning domain 1. Mol Biol Cell. 2013;24(19):3016–24.
60. Donaldson SH, Pilewski JM, Griese M, Cooke J, Viswanathan L, Tullis E, et al. Tezacaftor/ivacaftor in subjects with cystic fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. Am J Respir Crit Care Med. 2018;197(2):214–24.
61. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. N Engl J Med. 2017;377(21):2024–35.
62. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med. 2017;377(21):2013–23.
63. Conger BT, Zhang S, Skinner D, Hicks SB, Sorscher EJ, Rowe SM, et al. Comparison of cystic fibrosis transmembrane conductance regulator (CFTR) and ciliary beat frequency activation by the CFTR modulators genistein, VRT-532, and UC_{CF}-152 in primary sinonasal epithelial cultures. JAMA Otolaryngol Head Neck Surg. 2013;139(8):822–7.
64. Ramsey B, Richardson MA. Impact of sinusitis in cystic fibrosis. J Allergy Clin Immunol. 1992;90(3,Pt2):547–52.
65. Coticchia J, Zuliani G, Coleman C, Carron M, Gurrola J, Haupert M, 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.
66. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72(10):1541–5.
67. Ramadan HH. Surgical management of chronic sinusitis in children. Laryngoscope. 2004;114(12):2103–9.
68. Virgin FW, Rowe SM, Wade MB, Gaggar A, Leon KJ, Young KR, et al. Extensive surgical and comprehensive postoperative medical management for cystic fibrosis chronic rhinosinusitis. Am J Rhinol Allergy. 2012;26(1):70–5.
69. Ramadan HH, McLaughlin K, Josephson G, Rimell F, Bent J, Parikh SR. Balloon catheter sinuplasty in young children. Am J Rhinol Allergy. 2010;24:e54–6.
70. Mainz JG, Koitschev A. Management of chronic rhinosinusitis in CF. J Cyst Fibros. 2009;8(Suppl 1):S10–4.
71. 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;73:741–5.
72. Smith TL, Kern R, Palmer JN, Schlosser R, Chandra RK, Chiu AG, et al. Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study with 1-year follow-up. Int Forum Allergy Rhinol. 2013;3(1):4–9.
73. Van Peteghem A, Clement PA. Influence of extensive functional endoscopic sinus surgery (FESS) on facial growth in children with cystic fibrosis. Comparison of 10 cephalometric parameters of the midface for three study groups. Int J Pediatr Otorhinolaryngol. 2006;70(8):1407–13.

74. Rowe-Jones JM, Mackay IS. Endoscopic sinus surgery in the treatment of cystic fibrosis with nasal polyposis. Laryngoscope. 1996;106(12, Pt. 1):1540–4.
75. Konstantinidis I, Fotoulaki M, Iakovou I. Vitamin D_3 deficiency and its association with nasal polyposis in patients with cystic fibrosis and patients with chronic rhinosinusitis. Am J Rhinol Allergy. 2017;31(6):395–400.
76. Fetta M, Tsillis NS, Segas JV, Nikolopoulos TP, Vlastarakos PV. Functional endoscopic sinus surgery improves quality of life in children suffering from chronic rhinosinusitis with nasal polyps. Int J Pediatr Otorhinolaryngol. 2017;100:145–8.
77. Virgin FW. Clinical chronic rhinosinusitis outcomes in pediatric patients with cystic fibrosis. Laryngoscope Investig Otolaryngol. 2017;2(5):276–80.
78. Khalid AN, Mace J, Smith TL. Outcomes of sinus surgery in adults with cystic fibrosis. Otolaryngol Head Neck Surg. 2009;141(3):358–63.
79. Liang J, Higgins TS, Ishman SL, Boss EF, Benke JR, Lin SY. Surgical management of chronic rhinosinusitis in cystic fibrosis: a systematic review. Int Forum Allergy Rhinol. 2013;3(10):814–22.
80. Choi KJ, Cheng TZ, Honeybrook AL. Correlation between sinus and lung cultures in lung transplant patients with cystic fibrosis. Int Forum Allergy Rhinol. 2018;8(3):389–93.
81. Aanaes K. Bacterial sinusitis can be a focus for initial lung colonization and chronic lung infection in patients with cystic fibrosis. J Cyst Fibros. 2013;12(Suppl 2):S1–20.
82. Khalfoun S, Tumin D, Ghossein M, Lind M, Hayes D Jr, Kikby S. Improved lung function after sinus surgery in cystic fibrosis patients with moderate obstruction. Otolaryngol Head Neck Surg. 2018;158(2):381–5.
83. Rosbe KW, Jones DT, Rahbar R, Lahiri T, Auerbach AD. Endoscopic sinus surgery in cystic fibrosis: do patients benefit from surgery? Int J Pediatr Otorhinolaryngol. 2001;61(2):113–9.
84. Shatz A. Management of recurrent sinus disease in children with cystic fibrosis: a combined approach. Otolaryngol Head Neck Surg. 2006;135(2):248–52.
85. 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.
86. Crockett DJ, Wilson KF, Meier JD. Perioperative strategies to improve sinus surgery outcomes in patients with cystic fibrosis: a systematic review. Otolaryngol Head Neck Surg. 2013;149(1):30–9.
87. De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016;4(8):662–74.

Chapter 10
Sinusitis and Immunodeficiency in Children

Randa Barazi and Zeina Korban

Introduction

Chronic rhinosinusitis (CRS) is known to have a significant impact on the quality of life and incurs a financial burden on the healthcare system [1]. CRS is a heterogeneous disorder that is classified into two main subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRSwNP is associated with more severe disease in adults [2]. However, pediatric CRS is defined as subjective and objective signs of sinonasal symptoms that last for more than 90 days. Treatment can be challenging and involves medical and surgical therapy.

Patients with CRS are usually evaluated for underlying conditions such as ciliary dysfunction, anatomical abnormalities, allergies, and more recently, immunodeficiency [3].

Immunodeficiency is common in patients with CRS and was found in 13% of patients with recurrent CRS and 23% of patients with difficult-to-treat CRS. ∗ Immune deficiencies should be considered in patients who are refractory to medical and surgical therapy, despite optimal management [4].

Immunodeficiencies can be primary immunodeficiencies, which are usually inherited immune disorders, and secondary immune deficiencies that occur as a consequence of events.

Patients with immunodeficiencies often present with more frequent and severe infections with unusual organisms, and the immune system should be evaluated in patients who have frequent exacerbations of CRS [5].

CRS is most commonly associated with humoral immunodeficiency (antibody deficiency), with a prevalence of 8%–34% of specific antibody deficiency

R. Barazi · Z. Korban (✉)
Department of Otolaryngology Head and Neck Surgery, American University of Beirut Medical Center, Beirut, Lebanon
e-mail: zk27@aub.edu.lb

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_10

(SAD).[4]CVID (common variable immune deficiencies) and SAD represent the most commonly encountered humoral deficiencies in patients with CRS.

We know that the prevalence of nasal polyps among pediatric patients is lower when compared to adults. However, no studies show a difference in the types of immune deficiencies between adult and pediatric CRS [6].

This chapter will primarily focus on immune deficiencies (primary and secondary) in pediatric CRS and will address the various types, methods of screening, and treatment recommendations.

Diagnosis

Workup

Diagnosing underlying immune deficiencies can be challenging. A detailed family and medical history should always be the starting point particularly in patients who present with recurrent bronchopulmonary infections, sinusitis, and gastroenteritis. Inquiry regarding prior therapy with immunosuppressive medications, chemotherapy, and history of autoimmune disease should always be incorporated. The presence of prior positive cultures with encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis*) can raise a flag (Table 10.1) [5]. Frequency of infections and hospitalization records should be evaluated as well.

Physical examination is crucial, and the presence of associated lymphadenopathy, skin granulomas, and splenomegaly in addition to sinonasal and lung findings aids in diagnosing underlying immune deficiencies.

A compass of laboratory tests should be performed including a complete blood count (CBC) with differential, quantitative immunoglobulin levels (IgG, IgA, and IgM), IgE levels, and pneumococcal antibody titers pre and post vaccines. Additional testing may be needed to further evaluate responses to polysaccharide vaccines. IgG subclasses can also be assessed. Immunoglobulin level 2 standard deviations (SD) below age-adjusted means are considered low (Table 10.2) [7].

Table 10.1 Evaluation details

Age at presentation
Sex
Sinus surgery
Family history
Antibiotic use
Sinopulmonary infections
Recurrent diarrhea
Prior positive cultures
Recurrent ear infections
Recurrent tube otorrhea

Table 10.2 Immunoglobulin levels in primary and secondary immunodeficiencies

	IgG	IgA	IgM
SAD[a]	Normal	Normal	Normal
SIGAD	Normal	Absent	Normal
CVID	Low	Low	Normal or low
Secondary immunodeficiency	Low	Normal	Normal

[a]Low vaccine response

Additional clues to raise the suspicion of an immunodeficiency include i) hypergammaglobulinemia (elevated gamma globulin) and HIV infection, particularly levels >30 g/L; (ii) very low IgE levels, which can prompt the diagnosis of an antibody deficiency; and (iii) idiopathic thrombocytopenic purpura (ITP), which can be associated with primary or secondary immune deficiencies [8].

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases (PID) comprise more than 300 disorders [9]. PID are inherited disorders that are grossly divided into immunodeficiency involving B cells (humoral immunity), T cells (cellular immunity), phagocytes (innate immunity), the complement system (innate immunity), or some combination of factors [10]. We will mainly discuss the antibody deficiencies that are most commonly associated with chronic rhinosinusitis.

Common Variable Immunodeficiency (CVID)

CVID is characterized by hypogammaglobulinemia and recurrent bacterial infections in patients older than 2 years of age. It includes a group of heterogeneous disorders. In 2015, the International Consensus Document on CVID published the diagnostic criteria for this condition [11]:

(1) The patient must have at least one characteristic clinical manifestation of CVID (infection, autoimmunity, or lymphoproliferation), (2) low IgG (at least two measurements more than 3 weeks apart), (3) low IgA or low IgM, (4) for those patients whose IgG is more than 100 mg/dL, demonstrate an inadequate response to at least one T-dependent or T-independent antigen, (5) exclude other causes of hypogammaglobulinemia, and (6) genetic studies for monogenic forms of CVID.

The pathophysiology for CVID is loss of B-cell function. The dysfunction can be at a different level of the B-cell cycle: (1) B-cell production, (2) B-cell maturation or survival, (3) B-cell activation and proliferation, (4) at the germinal center, and (5) post-germinal center [10].

CVID has a broad clinical presentation and symptoms of antibody deficiency that might not present until the second, third, or fourth decade of life.

Sinopulmonary infections are common in patients with CVID, predominantly with *Streptococcus* and *Haemophilus* species. Multiple studies show that the prevalence of CRS in CVID is high reaching 82%. These patients tend to present with high Lund-Mackay scores, and a CT scan of the sinuses is urged once CVID is suspected. The maxillary sinus is primarily affected, and this is seen in 33% of patients [12].

CVID entails high morbidity and mortality with respiratory failure, infection, and malignancy as contributors. The introduction of immunoglobulin replacement therapy has reduced the incidence of infections and improved quality of life [13].

SAD

SAD is a primary immunodeficiency associated with a qualitative defect in antibody function. Patients are unable to make specific antibodies in response to polysaccharide antigens.

Patients with SAD should have the following diagnostic criteria: (1) older than 2 year (2) recurrent respiratory tract infections, (3) normal immunoglobulin and IgG subclass levels, and (4) impaired response to pneumococcal capsular polysaccharide (23 valent unconjugated pneumococcal vaccine). A protective antibody level ($\geq$1.3 μg/mL) in 7 or more of 14 pneumococcal serotypes is considered an appropriate response. In addition, patients with SAD have lower levels of IgA [10].

Based on the degree of nonresponsiveness to a polysaccharide vaccine thus antibody concentrations, SAD is stratified into four different phenotypes (i.e., mild, moderate, severe, and memory) depending on the age of the patient [10].

- Mild: a concentration of >1.3 μg/mL for >50% of the serotypes if <6 years old, and >1.3 μg/mL for >70% of the serotypes if >6 years old
- Moderate: a concentration of >1.3 μg/mL for <50% of the serotypes if <6 years old, and > 1.3 μg/mL for <70% of the serotypes if >6 years old
- Severe: a concentration of >1.3 μg/mL for two or less serotypes across all age groups
- Memory: loss of immunologic memory within 6 months [14]

Patients with the mild phenotype have higher IgG levels than those with more severe phenotypes. As regards IgA and IgM levels, no difference is seen between the different phenotypes. Asthma is more common in patients with moderate SAD. However, no difference is seen between the different SAD classes as regards allergic rhinitis, nasal polyps, and sinus surgery.

The severity of SAD is not directly associated with the severity of sinus disease. Patients with severe SAD have lower Lund-Mackay scores.

Patients with SAD and CRS tend to have more frequent infections and require more antibiotic courses than patients who have an adequate response especially when severe or moderate SAD is present [15].

Sinopulmonary infections are common, and the frequency is lower in patients with mild SAD. However, CRS patients with mild SAD and CRS patients without SAD were comparable with regard to antibiotic courses. Therefore, it is important to classify SAD into its phenotypes since this will affect management, has direct clinical relevance, and will help avoid treating patients with mild SAD with unnecessary medications, antibiotics, and lifelong immunoglobulin replacement [16]. In addition, it will warn physicians to frequently monitor severe SAD patients, since they will require more aggressive treatment protocols.

Selective IgA Deficiency

Immunoglobulin A (IgA) is the first line of defense in the upper airway mucosa [5]. Selective IgA deficiency (SIGAD) is defined as a serum IgA level of less than 7 mg/dL with normal serum IgG, IgM levels, and no other major immune defects in patients older than 4 years [10]. SIGAD is the most common primary immunodeficiency, and many patients are asymptomatic and don't present with recurrent sinopulmonary infections. The pathogenesis of SIGAD lies in a defective IgA transport system [10].

The role of IgA in CRS has been studied, and SIGAD is reported in CRS patients. In patients with CRSwNP, decreased levels of IgA to *Staphylococcus aureus* enterotoxin B have been reported [16].

CD8± T Lymphocyte Deficiency

This entity should be considered when dealing with difficult-to-treat CRS patients. The pathogenesis lies in a defective gene (CD8A or tapasin-binding protein (TAPBP)) that leads to altered major histocompatibility complex class I (MHC1) function of circulating CD8 + T lymphocytes contributing to the development of refractory/severe CRS [10]. These patients usually present at a younger age, needing surgery early in their disease, and have a greater number of surgeries [10].

IgG Subclass Deficiency

The diagnosis of IgG subclass deficiency is considered in patients with recurrent infections, one or more IgG subclass levels less than 2 SD below the age-adjusted mean with normal total IgG level, and normal total concentrations of IgM and IgA

[10]. Many patients can be asymptomatic, making the IgG subclass deficiency a laboratory finding and not a disease. The most common subclass deficiencies presenting with recurrent infections are IgG4 deficiency, followed by IgG2 deficiency, then IgG3 deficiency, and finally IgG1 deficiency [17]. This is controversial since some studies show that IgG2 is mostly prevalent in the pediatric population and IgG3 in the adult population.

A combination of one IgG subclass deficiency with another IgG subclass or an IgA deficiency is also common [17]. Recurrent upper respiratory infections are common in patients with IgG3 deficiency since IgG3 is responsible for the immune response against *Moraxella catarrhalis* and *Streptococcus pyogenes* [18]. IgG subclass deficiencies are noted in patients with asthma, CRSwNP, allergic rhinitis, and recurrent upper and lower airway infections especially with underlying allergies or autoimmune diseases [19, 20].

Secondary Immunodeficiencies

Secondary immunodeficiencies are immunodeficiencies that occur as a consequence of other diseases or medications. They can be the result of malignancies (non-Hodgkin lymphoma, CLL, etc.), medications (antimalarial agents, rituximab, corticosteroid, chemotherapy, anticonvulsant, etc.), and infections (HIV, EBV, etc.) [10]. The prevalence of secondary immunodeficiencies is rising due to the increased use of immunosuppressive/chemotherapeutic agents [10]. Patients tend to be older than patients with primary immunodeficiencies. Secondary immunodeficiency patients usually have antibody deficiencies, and most of them have hypogammaglobulinemia (low IgG and normal IgM and IgA) with a smaller proportion having a specific or subclass defect [10].

The molecular mechanisms of secondary antibody deficiencies are still unknown and most likely depend on the cause of deficiency.

Treatment

Treatment for patients with CRS and underlying immunodeficiencies entails medical and surgical therapy. Medical management always precedes invasive procedures when dealing with the pediatric population. Treatment of CRS varies, and maximal medical therapy usually includes oral antibiotics, topical antibiotics, oral steroids, nasal steroids, and saline irrigations. In patients with antibody deficiencies, early treatment is advised with reports that prophylactic antibiotics can aid in reducing exacerbations. Culture-based treatment is recommended to avoid resistance [21].

Immunoglobulin Replacement Therapy

According to the clinical practice guidelines published by the American Academy of Otolaryngology – Head and Neck Surgery, the role of intravenous immunoglobulin replacement therapy on CRS in adult patients with humoral immunodeficiency is still an area of research [22].

In the pediatric population, immunoglobulin replacement is indicated in patients with chronic infections and immunodeficiency, failing other therapies like prophylactic antibiotics and vaccination [10, 23].

It can be administered to patients with both primary and secondary immunodeficiencies except for IgA deficiency as the commercial preparations of IVIG are low in IgA [23].

Many studies have shown that IVIG (intravenous immunoglobulins) in primary immunodeficiency (SAD, CVID) results in significant reduction in the frequency of antibiotic administration for pneumonia, bronchitis, and sinusitis in children [22].

A study by *Walsh* et al. looked at IVIG in patients with primary versus secondary immunodeficiency and showed that it reduces serious and non-serious infections in both primary and secondary immunodeficiency groups [24]. On the other hand, *Quinti* et al. showed that IVIG does not decrease the prevalence of CRS in patients with CVID [22]. The latter has also been supported by *Keswani* et al. [15]. In the pediatric population, high-dose (500–600 mg/kg) IVIG has revealed superior outcomes than lower doses (150 mg/kg) [22].

Immunoglobulin can be administered intravenously or subcutaneously, and the treatment dose frequency is individualized according to severity and frequency of infections [22, 23]. Immunoglobulin levels are usually followed to determine the length of IVIG treatment [10]. Nonetheless, we need to keep in mind that despite IVIG treatment, complications may persist [22].

Surgery

Endoscopic sinus surgery (ESS) is reserved when maximal medical therapy fails and is discussed elsewhere in the text. The goal is to achieve wide antrostomies and cavities to allow for delivery of medications, reduce the inflammatory load, and restore function. Patients with immunodeficiencies benefit similarly post ESS when compared to immunocompetent patients with respect to symptom scores and quality of life. The role of adenoidectomy should also be considered in the pediatric population, and this also is discussed separately in the text. A lower threshold for surgery is advisable to avoid life-threatening infections and consequent complications [7, 8, 25].

There are still no standardized treatment guidelines for these patients, and further research is warranted. Close follow-up is key, and patients may require multiple surgeries to achieve a positive outcome.

Conclusion

Patients with refractory CRS should always be evaluated for underlying immunodeficiencies (primary or secondary). This includes a comprehensive family and personal history, serum immunoglobulin levels, and functional antibody responses. SAD and CVID remain the most commonly encountered humoral deficiencies. Underlying immune defects are varied, and more studies are now focused to understand their pathophysiology and role in CRS. Medical therapy and endoscopic sinus surgery are crucial early in the disease process to minimize long-term comorbidities that may ensue as well as frequent infections and hospitalizations. New targeted therapies are in progress that may improve clinical outcomes.

References

1. Rudmik L, Smith TL. Quality of life in patients with chronic rhinosinusitis. Curr Allergy Asthma Rep. 2011;11:247–52.
2. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. J Allergy Clin Immunol. 2011;128:693–707.
3. Rha YH, Choi SH. Predisposing factors associated with chronic and recurrent Rhinosinusitis in childhood. Allergy Asthma Immunol Res. 2012;4(2):80–4.
4. Odat H, Alqudah M. Prevalence and pattern of humoral immunodeficiency n chronic refractory sinusitis. Eur Arch Otorhinolaryngol. 2016;273(10):3189–93.
5. Bonilla FA, Khan DA, Ballas ZK. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136:1186–205.
6. Mahdavinia M, Grammar LC III. Chronic rhinosinusitis and age: is the pathogenesis different? Expert Rev Anti-Infect Ther. 2013;11:1029–40.
7. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. Ann Allergy Asthma Immunol. 2014;113:347–85.
8. Holding S, Jolles S. Current screening approaches for antibody deficiency. Curr Opin Allergy Clin Immunol. 2015;15:547–55.
9. Bousfiha A, Jeddane L, Picard C, Ailal F, et al. The 2017 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol. 2018;38:129–43.
10. Chiarella SE, Grammar LC. Immune deficiency in chronic rhinosinusitis: screening and treatment. Expert Rev Clin Immunol. 2017;13(2):117–23.
11. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, et al. International Consensus Document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract. 2016;4(1):38–59.
12. Angulo-Pérez G, Vivar-Acevedo E, Vargas-Aguayo A, et al. Prevalence, location and tomographic severity of chronic rhinosinusitis in adult patients with common variable immunodeficiency. Rev Alerg Mex. 2015;62:15–21.
13. Resnick ES, Moshier EL, Godbold JH, et al. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119:1650–7.
14. Orange JS, Ballow M, Stiehm ER, 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.
15. Keswani A, Mehtora N, et al. The clinical significance of Specific Antibody Deficiency (SAD) severity in Chronic Rhinosinusitis (CRS). J Allergy Clin Immunol Pract. 2017;5(4):1105–11.

16. Hupin C, Rombaux P, Bowen H, et al. Downregulation of polymeric immunoglobulin receptor and secretory IgA antibodies in eosinophilic airway diseases. Allergy. 2013;68:1589–97.
17. Stiehm ER. The four most common pediatric immunodeficiencies. J Immunotoxicol. 2008;5(2):227–34.
18. Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. Clin Exp Immunol. 2009;159:344–50.
19. Oxelius VA, Hanson LA, et al. IgG3 deficiency: common in obstructive lung disease. Hereditary in families with immunodeficiency and autoimmune disease. Monogr Allergy. 1986;20:106–15.
20. Kim JH, Park HJ, et al. Immunoglobulin G subclass deficiency is the major phenotype of primary immunodeficiency in a Korean adult cohort. J Korean Med Sci. 2010;25:824–8.
21. Ryan MW, Brooks EG. Rhinosinusitis and comorbidities. Curr Allergy Asthma Rep. 2010;10:188–93.
22. Mazza JM, Lin SY. Primary immunodeficiency and recalcitrant chronic sinusitis: a systematic review. Int Forum Allergy Rhinol. 2016;6(10):1029–33.
23. Finocchi A, Angelini A, Chini L, Di Cesare S, Cancrini C, Rossi R, et al. Evaluation of the relevance of humoral immunodeficiencies in a pediatric population affected by recurrent infections. Pediatr Allergy Immunol. 2002;13:443–7.
24. Walsh JE, Gurrola JG II, Graham SM, Mott SL, Ballas ZK. Immunoglobulin replacement therapy reduces chronic rhinosinusitis in patients with antibody deficiency. Int Forum Allergy Rhinol. 2017;7:30–6.
25. Dao AM, Rereddy SK, Wise SK, et al. Management of non-invasive rhinosinusitis in the immunosuppressed patient population. Laryngoscope. 2015;125:1767–71.

Chapter 11
Pediatric Rhinosinusitis and Gastroesophageal Reflux

Lauren Sowa and Fuad M. Baroody

Introduction

A relationship between pediatric chronic rhinosinusitis and gastroesophageal reflux has been speculated, though a true cause-and-effect relationship has yet to be solidified. The goal of this chapter is to present a review of the literature and show some of the conclusions drawn by more recent studies.

GERD

In a recent 2018 update of Clinical Practice Guidelines, the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition define gastroesophageal reflux (GER) as "the passage of gastric contents into the esophagus with or without regurgitation" [1]. It becomes broadened to gastroesophageal reflux disease (GERD) when this process causes symptoms or complications that impact a child's daily life in a pathologic manner, specifically noting esophagitis or strictures. Studies quote estimates that between 10% and 60% of infants suffer from GER at age 6 months, which later declines to less than 5–10% by age 1 year. Furthermore, within this group, it is estimated that ~25% are asymptomatic and that 8% have nasopharyngeal reflux [2, 3]. In most cases, GER resolves spontaneously by age 2; if this is not the case, then it is generally considered pathologic and is

L. Sowa · F. M. Baroody (✉)
Section of Otolaryngology-Head and Neck Surgery and Department of Pediatrics, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA
e-mail: fbaroody@surgery.bsd.uchicago.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_11

labeled as GERD [4]. This decline is thought to be related to maturity of the lower esophageal sphincter over time, as well as to the transition from a predominantly liquid to a more solid diet by 18–24 months of age [2, 3, 5, 6]. In general, by age 1.5–2 years, the prevalence of GER in the pediatric population normalizes to that of the adult population at around 10–20% [7].

Symptoms of gastroesophageal reflux present differently depending on a child's age. In younger infants, common signs include back arching, crying, regurgitation, and overall irritability. It is important to note that up to 50% of infants younger than 4 months will regurgitate feeds at least once per day, which is considered normal [1]. In older children, it is more common that they complain of symptoms such as heartburn or regurgitation. GER has also been associated with several processes that are commonly seen in pediatric populations, namely, asthma, bronchitis, and failure to thrive, and hematemesis, though the aforementioned updated guidelines shift away from attributing respiratory and laryngeal symptoms to GER [4, 8]. Furthermore, it is prominently seen in children with comorbid conditions such as cystic fibrosis, prematurity, and neurologic impairment. In addition, it has been found that environmental factors, such as exposure to cigarette smoke or certain medical interventions commonly used in neonatal units, such as theophylline and caffeine, can potentially increase a child's risk of developing GERD [6].

The extraesophageal symptoms of GER/GERD, such as chronic cough, stridor, recurrent respiratory infections, aspiration, or apneic events, are frequently the reason for referral to a subspecialist for evaluation. The nonspecific nature of these signs/symptoms further enforces the importance of a complete history and physical examination by both pediatricians and subspecialists (e.g., gastroenterologists, otolaryngologists) prior to pursuing more involved diagnostic testing. Validated questionnaires have been developed over the last several years to aid physicians in diagnosing GER/GERD; those used to assess infant populations have been much less successful in predicting presence of disease or predicted response to therapy as compared to those used in older children and adolescents [1, 9–12].

Of the multiple existing diagnostic tests, including 24-hour pH-probe monitoring, motility studies/manometry, endoscopy, barium contrast radiography, and gastric/esophageal ultrasound, pH probe monitoring plus or minus intraluminal impedance monitoring is favored in the diagnosis of GER/GERD, though the results of these studies tend to not correlate with the severity of symptoms. Rather, they provide quantitative data related to acid exposure, with an episode being defined as a drop in intraesophageal pH below 4.0 [1]. The addition of multiple intraluminal impedance monitoring allows for additional information regarding acidic versus nonacidic reflux. Neither, however, has been shown to have a highly sensitive or specific correlation with symptom severity. Endoscopy (EGD) with biopsy is not considered diagnostic for GERD, since patients with GER/GERD can have symptoms but still produce negative mucosal biopsies for esophagitis. It is considered helpful in diagnosing other causes of esophagitis such as eosinophilic esophagitis (EoE), Crohn's, or candidal esophagitis.

In the infant population, non-pharmacologic modalities of treatment are considered first line. These include post-feeding positioning changes, which involves

side-lying or (in more severe cases) prone positioning following feeds, thickening of breastmilk or formula to slow transit, and changing to non-milk formulas to test for milk protein allergy [6]. In older children, lifestyle modifications are also considered first line, including dietary changes, weight loss, and smoking/alcohol cessation.

Pharmacologic therapy is typically reserved for infants and children who have failed conservative therapy. Medications are classified as histamine antagonists (H2 blockers), proton pump inhibitors, or prokinetic agents. H2 blockers include famotidine, ranitidine, and cimetidine; these are well-tolerated by infants and children of all ages and have minimal side effects. They are effective at acid suppression, but have been known to have a dissipating level of effectiveness after 6 weeks of use [13, 14]. Proton pump inhibitors have been shown to be more effective at acid suppression and expediting healing of erosive disease. They are not widely approved for use in children younger than 1 year of age, though off-label use has increased over the last several years [1, 13]. Prokinetic agents include metoclopramide, erythromycin, and cisapride, which aim to combat delayed gastric emptying by improving esophageal peristalsis. Evidence is lacking regarding the effectiveness of these agents in treating GERD; they have, however, been shown to cause prolonged QTc and therefore present potential cardiac risk. Subsequently, cisapride has been removed from circulation since the late 1990s. Additionally, dopaminergic dysregulation and pyloric stenosis have been associated with prolonged use of metoclopramide and erythromycin, respectively [15, 16]. In the neonatal population, low-dose erythromycin ethylsuccinate is sometimes used as a prophylactic treatment for feeding intolerance. In a large, retrospective cohort study of 348 neonatal intensive care units (NICU), over 20,000 neonates who had received metoclopramide, erythromycin, or both were reviewed to compare adverse events associated with each treatment. Adverse events (AE) included electrolyte abnormalities, necrotizing enterocolitis (NEC), cardiac arrhythmias, and pyloric stenosis. Metoclopramide was more commonly used by a large margin and also showed a higher incidence of AE (with the exception of pyloric stenosis) as compared to erythromycin, especially in younger and lower birth weight infants [17]. In a small placebo-controlled study in 2001, authors found that in low birth weight neonates, low-dose erythromycin administered 30 minutes before feedings led to shorter times to reach full feeds as compared to placebo [18]. However, a more recent randomized, double-blinded, placebo-controlled study using multichannel intraluminal impedance (MII) monitoring to diagnose GERD in neonates compared a 7-day course of erythromycin ethylsuccinate with placebo and found no significant reduction in the number of reflux events. The use of MII ensures that acidic and nonacidic reflux could be measured and was able to associate episodes with symptoms [19]. The above studies emphasize that, though they may have potential benefit in small populations, there is no definitive advantage to using prokinetic agents in the setting of GERD or feeding intolerance especially considering their less than optimal side-effect profile.

In infants, convincing evidence of an indication for empiric reflux therapy is limited. Moreover, it is thought that a 2-week trial of an H2 blocker is warranted,

though improvement in symptoms cannot be definitively attributed to pharmacologic therapy versus spontaneous resolution with aging and growth [1]. In children and older adolescents who fail conservative therapy, a trial of PPI for 2–4 weeks is recommended, with the option to continue for 2–3 months followed by an appropriate wean if improvement is seen [20]. If not, referral to a pediatric gastroenterologist is warranted.

For infants refractory to all proposed nonpharmacologic and pharmacologic treatments, surgical treatment for GERD involves Nissen fundoplication to create increased pressure at the lower esophageal sphincter, thereby preventing both pathologic and physiologic reflux [12].

Pathophysiology of Sinusitis and GERD

In a large case control study out of Texas Children's Hospital, 1980 children with gastroesophageal reflux disease and 7920 controls were selected via diagnostic codes. In these patients, ages 2–18 years, the number of cases with a concurrent diagnosis of sinusitis was significantly higher in children with GERD (4.19%) compared to the control group (1.35%) [21]. Attempts to confirm this relationship between the two pathologies have been made using such methods as nasopharyngeal pH probe, multichannel impedance monitoring, and measurement of serum biomarkers [22–28]. From this, several theories exist that attempt to explain the mechanism by which GERD might contribute to sinusitis.

Pepsin A, a known reliable biomarker for reflux, has been widely used as an indicator for the presence of gastric reflux in the upper aerodigestive tract [24, 27]. In children, several studies have examined the possible effect of reflux on acute otitis media by measuring pepsin in middle ear aspirates versus serum [29, 30]. It has also been utilized in studies of laryngeal epithelium, specifically in *in vitro* porcine models, to show that enzymatically active pepsin is present in the larynx following reflux events [25]. A later study by the same group evaluated human biopsy tissue from both patients with no clinical signs/symptoms of reflux and those with a score of 8 or higher on the Reflux Symptom Index questionnaire. Laboratory analysis showed that pepsin in both acidic and nonacidic refluxate contributed to cell damage. Furthermore, in tissue samples with known squamous metaplasia, pepsin was found to increase cell proliferation and potentially contribute to neoplastic changes [26]. Regarding sinusitis, a recent study from Sichuan University in China examined adult patients with CRS (both with and without polyps) versus controls using several molecular techniques to measure levels of pepsin A in nasal and polypoid tissue. They found that washings from 60% of tissues from patients with CRS contained appreciable levels of pepsin A as compared to only 11% in controls. This suggests that those patients with CRS also have evidence of GERD [24].

Another area of research involves the presence of *H. pylori* in nasal tissue. As part of a systematic literature review exploring a prognostic relationship between CRS and GERD, ten case control studies were examined in which the primary

outcome was presence of *H. pylori* in sinonasal tissue. CRS was defined using international consensus criteria in a majority of these studies. In four of these studies, 87.5% of patients with *H. pylori* also had GERD. Overall, an increased odds ratio of *H. pylori* in patients with CRS of 2.88 was observed, with a prevalence of 31.7% [7]. Only one of these studies, however, included an exclusively pediatric population. Furthermore, it was pointed out that *H. pylori* studies are difficult to interpret as no true gold-standard test exists. Another small study by Koc and colleagues noted the presence of *H. pylori* in polypoid tissue but not in middle turbinate nasal mucosa during concha bullosa excision surgeries in patients without polyps using ELISA, suggesting a potential association between the pathology of nasal polyposis in CRS and a pathogen known to cause GERD [31, 32]. Morinaka et al. performed a similar study of 19 patients and used PCR to detect *H. pylori* in nasal and maxillary sinus tissue of patients undergoing surgery for CRS. Of the two in which it was detected, the bacteria was also found in samples from the gastrointestinal tract, proposing that simultaneous colonization of sinonasal and gastrointestinal tissues with *H. pylori* is seen in patients with CRS. However, this study was limited by lack of a control group [33]. Furthermore, all of the above studies preferentially look at adult populations, which limits their applicability to the pediatric population and warrants further investigation.

The most frequently hypothesized mechanism to explain an association between CRS and GERD has to do with nasopharyngeal reflux and irritation, causing delayed mucociliary clearance. In CRS, delayed mucociliary clearance is typically caused by an insult, such as allergens, viral antigens, or pollutants, which thereby causes mucosal edema and thick secretions [34]. This leads to stasis and subsequent inflammation and infection within the sinuses. Similar theories have been used to establish relationships between GERD and other upper airway infections, including acute otitis media [35–37]. In both children and adults, several groups have speculated that direct extension of refluxed gastric contents into the nasopharynx could lead to enough inflammation to cause the signs and symptoms of CRS [38]. To further support this claim, Contencin and colleagues performed a small study involving 31 infants and children to examine nasopharyngeal pH. Thirteen of the patients had chronic rhinitis or rhinopharyngitis, and 18 served as asymptomatic controls [8]. Using a nasopharyngeal pH probe, he found that the average pH was lower and the overall number of episodes with pH below 6 higher in the group with nasal symptoms as compared to controls. Though limited by low power, this study was one of the earliest to propose a relationship between GERD and CRS in children, specifically in relation to direct extension of reflux contents into the nasopharynx [8].

Carr and colleagues followed by performing a retrospective study of children under 2 and demonstrated the presence of reflux in 42% of children undergoing adenoidectomy as compared to 7% of those undergoing tympanostomy tube placement alone, suggesting that adenoid hypertrophy and adenitis may have some relation to irritation from reflux contents and not just biofilm, which has been previously described [35]. The diagnosis of GERD in this study was inconsistent among participants and included a single episode of reflux on scintiscan, decreased emptying on a barium swallow, 24-hour pH probe study showing pH less than 4 for 6% of the

time, esophageal biopsies showing inflammatory cells, or signs of reflux laryngitis on laryngoscopy. This, in conjunction with its small sample size, was a major limitation of this study [39]. This idea is consistent with the most recent Clinical Consensus Statement on Pediatric Rhinosinusitis, which considers adenoid disease to be more contributory to CRS in younger children as compared to allergic rhinitis, which is more significant in older children [40]. A subsequent study of children ages 6 months to 5 years with sinonasal symptoms examined maxillary cultures, esophageal biopsies, and adenoidectomy specimens to establish a pathologic relationship between CRS and GERD [41]. Younger patients were more likely to have positive antral cultures or esophageal biopsies independent of one another, while older children were more likely to have positive results simultaneously. Aside from this, authors noted that overall 40% of their patients, who were chosen based on nasal complaints, ultimately were found to have a diagnosis of GERD even in the absence of overt reflux symptoms.

A more recent adult study involved the use of the validated Sino-Nasal Outcome Test (SNOT-20) and saccharin test for mucociliary clearance to demonstrate that GERD may contribute to decreased mucociliary clearance [42]. Fifty patients with diagnosed GERD by endoscopic evaluation underwent testing. Results showed that, of the 74% of patients who had abnormal mucociliary clearance times (MCT), patients were more likely to have extraesophageal symptoms of GERD (i.e., cough, hoarseness) as opposed to typical lower digestive tract symptoms of GERD (i.e., heartburn, belching, etc.) [42]. These patients with longer MCT also had higher SNOT-20 scores, though this was not statistically significant. The authors theorized that perhaps the effect of GERD on the nasal mucosa was not local inflammation from direct extension as previously speculated, but rather a potentially neurally mediated reflex via the vagus nerve in response to stimulation in the esophagus. This theory stems from a previously established reflex described by Schan and colleagues, who showed that esophageal acid causes tightening of the bronchopulmonary system and ultimately decreased peak expiratory flow via a vagally mediated pathway [43]. This was further investigated by Wong and colleagues using stimulation with both HCl and normal saline at the level of the gastroesophageal junction, which ultimately resulted in increased nasal mucous production and nasal symptom scores [31, 44]. This suggests that esophageal stimulation with gastric acid may evoke a neurogenically mediated response causing nasal symptoms and pathology.

Treatment

Several small studies have demonstrated a trend in which treatment with a proton-pump inhibitor (PPI) improved CRS symptoms in adults [45–47]. However, limited evidence exists to support reflux therapy in the setting of pediatric chronic rhinosinusitis. In a prospective study conducted by Phipps et al., 30 pediatric patients (ages 2–18) with CRS who underwent a 24-hour dual pH probe were examined. They found that 63% of them had significant esophageal reflux. Within

this group, 32% also had nasopharyngeal reflux. Nasopharyngeal episodes with pH less than 4.0 did not always correlate with esophageal pH, but they did correlate with symptoms such as cough. Of these children, 79% experienced improvement in rhinosinusitis symptoms after medical treatment of GERD [48]. Bothwell and colleagues performed a retrospective study that examined the effectiveness of treatment with reflux therapy in 30 children with CRS. All 30 patients had been deemed candidates for FESS but had also undergone pH probe testing. Following a course of treatment for a mean of 8.2 months, improvement in symptoms related to CRS was measured at 89% which obviated the need for a surgical procedure. Those who did require surgery were found to have larger agger nasi cells and obstructive frontal outflow anatomy on CT scan. This study estimated that approximately 50% of patients with GERD have silent disease and show predominantly extraesophageal symptoms. The downfall of this study, however, is that it lacks a control group due to its retrospective nature [49]. Both of the above studies can also be criticized due to the lack of a placebo group which would shed light on potential improvement of CRS symptoms in children with growth and the passage of time (natural history of the disease).

Conclusions

Based on the current available literature, there appears to be some correlation between CRS and GERD in the pediatric population. Whether the cause-and-effect relationship has to do with direct extension of reflux, neurogenically mediated secretory reactions, or some combination of various factors is unclear. Recent studies have suggested that, with appropriate clinical history, pediatric patients treated with anti-reflux medications have shown improvement in CRS symptoms. However, these studies have been low in power and lack prospective, blinded design. Because of this, it is currently not recommended to empirically treat children with CRS with reflux medication in the absence of overt GERD symptoms. Additionally, further investigation into the significance of symptoms in different age groups should be performed given that the nature of both pathologies appears to vary between patients ages 0–2 and 3–18.

References

1. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric gastroesophageal reflux clinical practice guidelines. J Pediatr Gastroenterol Nutr. 2018;66(3):516–54.
2. Keles B, Ozturk K, Arbag H, Gunel E, Ozer B. Frequency of pharyngeal reflux in children with adenoid hyperplasia. Int J Pediatr Otorhinolaryngol. 2005;69(8):1103–7.
3. Vandenplas Y, Sacré-Smits L. Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old. J Pediatr Gastroenterol Nutr. 1987;6(2):220–4.

4. Shepherd RW, Wren J, Evans S, Lander M, Ong TH. Gastroesophageal reflux in children. Clin Pediatr (Phila). 1987;26(2):55–60.
5. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy: a pediatric practice-based survey. Arch Pediatr Adolesc Med. 1997;151(6):569–72.
6. Henry SM. Discerning differences: Gastroesophageal reflux and gastroesophageal reflux disease in infants. Adv Neonatal Care. 2004;4(4):235–47.
7. Leason SR, Barham HP, Oakley G, Rimmer J, DelGaudio JM, Christensen JM, et al. Association of gastro-oesophageal reflux and chronic rhinosinusitis: systematic review and meta-analysis. Rhinology. 2017;55(1):3–16.
8. Contencin P, Narcy P. Nasopharyngeal pH monitoring in infants and children with chronic rhinopharyngitis. Int J Pediatr Otorhinolaryngol. 1991;22(3):249–56.
9. Orenstein SR, Shalaby TM, Cohn JF. Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire. Clin Pediatr (Phila). 1996;35(12):607–14.
10. Orenstein SR, Kartan R, Cohn JF, Shalaby TM. Reliability and validity of an infant gastroesophageal reflux questionnaire. Clin Pediatr (Phila). 1993;32(8):472–84.
11. Aggarwal S, Mittal SK, Kalra KK, Rajeshwari K, Gondal R. Infant gastroesophageal reflux disease score: reproducibility and validity in a developing country. Trop Gastroenterol. 2004;25(2):96–8.
12. Størdal K, Johannesdottir GB, Bentsen BS, Sandvik L. Gastroesophageal reflux disease in children: association between symptoms and pH monitoring. Scand J Gastroenterol. 2005;40(6):636–40.
13. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Coletti RB, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 2001;32(Suppl2):S1–31.
14. Wilder-Smith CH, Ernst T, Gennoni M, Zeyen B, Halter F, Merki HS. Tolerance to oral H2-receptor antagonists. Dig Dis Sci. 1990;35(8):976–83.
15. Dalby-Payne JR, Morris AM, Craig JC. Meta-analysis of randomized controlled trials on the benefits and risks of using cisapride for the treatment of gastroesophageal reflux in children. J Gastroenterol Hepatol. 2003;18(2):196–202.
16. Vandenplas Y. Management of paediatric GERD. Nat Rev Gastroenterol Hepatol. 2014;11(3):147–57.
17. Ericson JE, Arnold C, Cheeseman J, Cho J, Kaneko S, Wilson E, et al. Use and safety of erythromycin and metoclopramide in hospitalized infants. J Pediatr Gastroenterol Nutr. 2015;61(3):334–9.
18. Oei J, Lui K. A placebo-controlled trial of low-dose erythromycin to promote feed tolerance in preterm infants. Acta Paediatr. 2001;90(8):904–8.
19. Ballengee CR, Davalian F, Conaway MR, Sauer CG, Kaufman DA. Erythromycin and reflux events in premature neonates. J Pediatr Gastroenterol Nutr. 2018;67(6):720–5.
20. Björnsson E, Abrahamsson H, Simrén M, Mattsson N, Jensen C, Agerforz P, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006;24(6):945–54.
21. El-Serag HB, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. Gastroenterology. 2001;121(6):1294–9.
22. Greifer M, Ng K, Levine J. Impedance and extraesophageal manifestations of reflux in pediatrics. Laryngoscope. 2012;122(6):1397–400.
23. Katle EJ, Hatlebakk JG, Grimstad T, Kvaloy JT, Karmhus Steinsvag S. Gastro-oesophageal reflux in patients with chronic rhinosinusitis investigated with multichannel impedance - pH monitoring. Rhinology. 2017;55(1):27–33.

24. Wang J, Yu Z, Ren J, Xu Y, Zhang Y, Lei L, et al. Effects of pepsin A on heat shock protein 70 response in laryngopharyngeal reflux patients with chronic rhinosinusitis. Acta Otolaryngol. 2017;137(12):1253–9.
25. Johnston N, Dettmar PW, Bishwokarma B, Lively MO, Koufman JA. Activity/stability of human pepsin: implications for reflux attributed laryngeal disease. Laryngoscope. 2007;117(6):1036–9.
26. Johnston N, Yan JC, Hoekzema CR, Samuels TL, Stoner GD, Blumin JH, et al. Pepsin promotes proliferation of laryngeal and pharyngeal epithelial cells. Laryngoscope. 2012;122(6): 1317–25.
27. Ren J, Zhao Y, Wang J, Ren X, Xu Y, Tang W, et al. PepsinA as a marker of laryngopharyngeal reflux detected in chronic rhinosinusitis patients. Otolaryngol Head Neck Surg. 2017;156(5):893–900.
28. DiBaise JK, Huerter JV, Quigley EM. Sinusitis and gastroesophageal reflux disease. Ann Intern Med. 1998;129(12):1078.
29. Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall JP, Pearson JP. Reflux of gastric juice and glue ear in children. Lancet. 2002;359(9305):493.
30. Lieu JE, Muthappan PG, Uppaluri R. Association of reflux with otitis media in children. Otolaryngol Head Neck Surg. 2005;133(3):357–61.
31. Lupa M, DelGaudio JM. Evidence-based practice. Reflux in sinusitis. Otolaryngol Clin N Am. 2012;45(5):983–92.
32. Koc C, Arikan OK, Atasoy P, Aksoy A. Prevalence of Helicobacter pylori in patients with nasal polyps: a preliminary report. Laryngoscope. 2004;114(11):1941–4.
33. Morinaka S, Ichimiya M, Nakamura H. Detection of Helicobacter pylori in nasal and maxillary sinus specimens from patients with chronic sinusitis. Laryngoscope. 2003;113(9):1557–63.
34. Heath J, Hartzell L, Putt C, Kennedy JL. Chronic rhinosinusitis in children: pathophysiology, evaluation, and medical management. Curr Allergy Asthma Rep. 2018;18(7):37.
35. Chang AB, Cox NC, Faoagali J, Cleghorn GJ, Beem C, Ee LC, et al. Cough and reflux esophagitis in children: their co-existence and airway cellularity. BMC Pediatr. 2006;6:4.
36. Ulualp SO, Toohill RJ. Laryngopharyngeal reflux: state of the art diagnosis and treatment. Otolaryngol Clin N Am. 2000;33(4):785–802.
37. Önal Z, Çullu-Çokuğraş F, Işıldak H, Kaytaz A, Kutlu T, Erkan T, et al. Evaluation of the likelihood of reflux developing in patients with recurrent upper respiratory infections, recurrent sinusitis or recurrent otitis seen in ear-nose-throat outpatient clinics. Turk J Pediatr. 2015;57(3):258–65.
38. DelGaudio JM. Direct nasopharyngeal reflux of gastric acid is a contributing factor in refractory chronic rhinosinusitis. Laryngoscope. 2005;115(6):946–57.
39. Carr MM, Poje CP, Ehrig D, Brodsky LS. Incidence of reflux in young children undergoing adenoidectomy. Laryngoscope. 2001;111(12):2170–2.
40. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
41. Nation J, Kaufman M, Allen M, Sheyn A, Coticchia J. Incidence of gastroesophageal reflux disease and positive maxillary antral cultures in children with symptoms of chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2014;78(2):218–22.
42. Delehaye E, Dore MP, Bozzo C, Mameli L, Delitala G, Meloni F. Correlation between nasal mucociliary clearance time and gastroesophageal reflux disease: our experience on 50 patients. Auris Nasus Larynx. 2009;36(2):157–61.
43. Schan CA, Harding SM, Haile JM, Bradley LA, Richter JE. Gastroesophageal reflux-induced bronchoconstriction. An intraesophageal acid infusion study using state-of-the-art technology. Chest. 1994;106(3):731–7.
44. Wong IW, Rees G, Greiff L, Myers JC, Jamieson GG, Wormald P-J. Gastroesophageal reflux disease and chronic sinusitis: in search of an esophageal-nasal reflex. Am J Rhinol Allergy. 2010;24(4):255–9.

45. Megale SRMCL, Scanavini ABA, Andrade EC, Fernandes MIM, Anselmo-Lima WT. Gastroesophageal reflux disease: its importance in ear, nose, and throat practice. Int J Pediatr Otorhinolaryngol. 2006;70(1):81–8.
46. Pincus RL, Kim HH, Silvers S, Gold S. A study of the link between gastric reflux and chronic sinusitis in adults. Ear Nose Throat J. 2006;85(3):174–8.
47. 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.
48. Phipps CD, Wood WE, Gibson WS, Cochran WJ. Gastroesophageal reflux contributing to chronic sinus disease in children: a prospective analysis. Arch Otolaryngol Head Neck Surg. 2000;126(7):831–6.
49. Bothwell MR, Parsons DS, Talbot A, Barbero GJ, Wilder B. Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngol Head Neck Surg. 1999;121(3):255–62.

Chapter 12
Pediatric Sinusitis and Adenoiditis

Angela M. Donaldson

Anatomy and Function of Adenoid

The adenoids are located in the nasopharynx between the fossa of Rosenmuller. The adenoids along with tonsillar tissue make up the lymphatic tissue of Waldeyer's ring. Adenoids are part of the mucosa-associated lymphoid tissue (MALT), which is populated by T lymphocytes, B lymphocytes, macrophages, and plasma cells. In the adenoid region, approximately 50–60% of the cells are B lymphocytes. The role of this lymphatic tissue is to initiate an immune response to particular antigens found on the mucosal surface [1, 2]. The main function of MALT is to produce and transport IgA across mucosal epithelium. The location of the adenoid tissue, as well as their adaptive immunity function, has made many scholars consider this tissue to be a reservoir for viruses, bacteria, and allergens [1, 3].

Adenoid Hypertrophy

Normal adenoid vegetation reaches its most prominent size, between the ages of 2 and 7, before it gradually regresses [2, 4]. Abnormal enlargement of adenoid tissue may result from multiple conditions such as physiologic changes, viral or bacterial infection, and potentially gastroesophageal reflux. Studies have found that the two most significant risk factors for the presence of adenoid hypertrophy are allergic rhinitis and cigarette smoke exposure at home [4]. Additionally, allergic diseases including atopic dermatitis and asthma have been associated with adenoid hypertrophy [5].

A. M. Donaldson (✉)
Department of Otorhinolaryngology Head and Neck Surgery, Mayo Clinic Jacksonville, Jacksonville, FL, USA

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_12

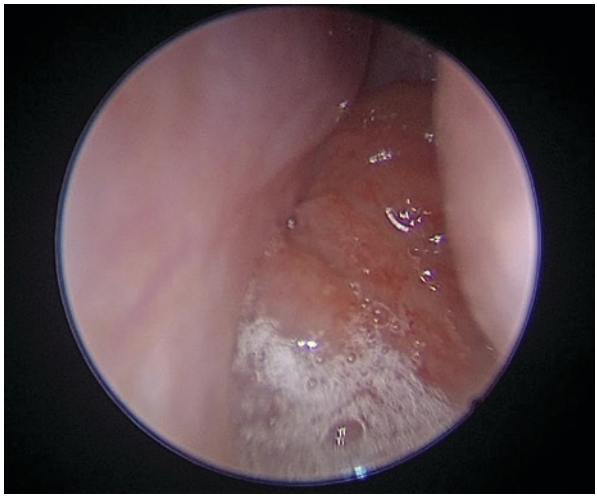


Fig. 12.1 Endoscopic view of adenoid hypertrophy extending past the torus tubarius to the vomer

Multiple modalities have been used to assess the amount of nasopharyngeal obstruction. In 1985, Cohen and Konak described a grading system using lateral neck plain films, measuring the distance between the pharyngeal tubercles and the maximum convexity of the adenoid tissue [6]. With the increased familiarity of endoscopic techniques in the pediatric population, several endoscopic grading scales have been suggested (Fig. 12.1). Parikh used the relationship between the adenoids and anatomic landmarks, such as the soft palate, torus tubarius, and vomer, while others used a percentage of choanal obstruction to create adenoid hypertrophy grading scales [7].

Symptoms of Adenoiditis and Sinusitis

In the pediatric population, viral upper respiratory infections are common, with an average of 6–8 per year. However, only 5–13% of these infections become bacterial sinus infections [8, 9]. Both chronic adenoiditis and chronic rhinosinusitis (CRS), in the pediatric population, can have similar symptoms, making it challenging to determine the correct diagnosis on history alone. Based on a 2014 consensus statement, pediatric (CRS) diagnostic criteria include 90 or more uninterrupted days of sinonasal symptoms, congestion, cough, nasal drainage, and/or facial pain and pressure [8]. These symptoms have also been described in the setting of adenoiditis. Multiple studies, however, have shown a correlation between adenoiditis and otitis media with or without effusion. Therefore, one potential distinguishing factor in chronic adenoiditis is a history of chronic or recurrent otitis media [10].

Adenoid Bacteriology

Pathogenic bacteria have been isolated from the nasopharynx of healthy children, as transient or normal microbiome flora. One example of this is a study by Lee and Rosenfeld. While they identified at least one bacterial pathogen in all 84 samples of adenoid tissue they procured, 63% of the specimens collected did not have a concentration of bacteria that met statistical significance for infection [3]. One explanation for this is that mucin covering the nasopharynx mucosa may function as receptor molecules for *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. The mucin, therefore, prevents adhesion to the epithelial surface and penetration into the mucosa leading to a penetrating infection [11]. The most common organisms found in the adenoid area include *Neisseria* spp., *Streptococcus pyogenes*, *Haemophilus influenzae*, *Staphylococcus aureus*, Actinomyces, Bacteroides, Peptostreptococcus, and *Fusobacterium* spp.

Adenoid Bacteriology and Adenoid Hypertrophy

Most studies have found that adenoid hypertrophy does not correlate with adenoid bacteriology. Several investigators have published results noting significantly higher bacterial concentrations in adenoid tissue removed for chronic or recurrent adenoiditis as compared to adenoid hypertrophy [12]. One study looking at biofilms on the adenoid mucosa in patients with CRS and OSA reported a mean biofilm colonization of 94% in the CRS group, as compared to 1.9% in the OSA group [13].

Theories Behind Adenoid Causes of Chronic Sinusitis

Adenoid Hypertrophy

There have been many theories postulating the adenoids role in the pathogenesis of chronic rhinosinusitis. Adenoid hypertrophy has been considered a potential contributing factor to sinusitis. Some believed that tissue obstruction of the nasopharynx led to secretion stasis and set up a reservoir for bacteria in the adenoid tissue. Multiple studies have demonstrated that there is no significant association between adenoid size and quantity of bacterial load [14]. Fukuda et al. looked at 404 children and measured their adenoid-nasopharyngeal (AN) ratio. They found no significant difference in AN ratio when comparing the quality and quantity of nasal secretions and severity of sinusitis on plain film X-ray [15]. Shin followed this study in 2008, looking at sinusitis grade, adenoid size, and adenoid bacteriology. This study also found no statistically significant correlation between sinusitis

grade and adenoidal-nasopharyngeal ratio. It is important to note that Shin's group used Water's view of plain films to evaluate sinusitis, which has largely fallen out of favor [12].

Adenoid Bacterial Reservoir

There is a strong consideration that adenoid tissue acts as a bacterial reservoir, slowing mucociliary clearance, which may contribute to sinonasal symptoms [16]. The theory is that when the nasal mucosa has an altered local host resistance such as upper respiratory infection (URI), the bacteria may flourish and exacerbate sinonasal symptoms. Lee and Rosenfeld found a strong correlation between the severity of sinus symptoms on a questionnaire and quantitative bacteriology on adenoid tissue specimens [3]. Another study noted that isolated bacteria rates increased with greater severity of sinusitis on plain film, which supports the theory of adenoid tissue as a reservoir of bacteria [12]. However, not all evidence supports this theory. One study looked at maxillary sinus microbiology and adenoid bacteriology. When they compared cultures from maxillary sinus aspirates and the adenoid tissue of the same patient, they did not find a correlation between the bacterial growths on cultures obtained in the adenoid compared to the maxillary sinus. In fact, 100% of the adenoid tissue samples had bacteria growth, but only 47% of the sinus aspirates grew bacteria [14].

Adenoid Biofilms

The classic theory described bacteria as adhering to the mucosa of the nasopharynx, then travelling to the sinus ostia before growing and causing infection. Coticchia presented an alternative theory in which a known or common sinus pathogen enters the nasopharynx, colonizes, and creates a biofilm [13]. Once the biofilm is created, it starts to shed individual cells of bacteria which then reenter and reinfect the sinus cavity. Biofilm formation on the adenoid tissue has been identified in multiple studies. This biofilm model does rely on the assumption that both the nasopharynx and ostiomeatal complex has some level of inflammation and reduction in mucociliary clearance at the time of reinfection. Oral antibiotics may be given at that point which typically lead to a temporary clinical improvement, but the biofilm remains resistant [13].

Diagnostic Testing

The current best practice guidelines published in 2015 recommend an endoscopy or CT scan for the evaluation of patients presenting with nasal congestion, nasal drainage, cough, and headache [17]. Flexible nasopharyngoscopy is the

most common endoscopic instrument used to evaluate this pediatric population. Some studies suggest nasopharyngeal culture is also helpful in the diagnosis [8, 18]. There is some variability in the timing of obtaining a CT scan, given the potential risk related to radiation exposure. Some physicians elect to defer ordering a CT scan until there is evidence of both medical and adenoidectomy failure. Most studies use Bhattacharyya et al. distinction on Lund-Mackay score to assess the severity of the disease. This study found that there is an 86% sensitivity and 87% specificity of having CRS when the Lund-Mackay score was >/=5. There was also a strong negative predicative value of having CRS, if the Lund-Mackay score was less than 2 [19]. Most studies have used >5 or < 5 as the parameters for diagnosing a patient with CRS versus chronic adenoiditis [19, 20]. Chronic adenoiditis has also been diagnosed by evidence of infection and/or inflammation of the adenoid tissue on nasal endoscopy without evidence of discharged from the middle meatus [21]. Additionally, the most recent consensus statement recommended against the use of radiologic imaging, especially lateral plain films, in the evaluation of adenoids in children with CRS. Based on the current evidence, radiologic imaging provides limited information on adenoid size alone [8].

Treatment of Chronic Adenoiditis and Chronic Rhinosinusitis

Medical Management

Medical management includes nasal saline irrigation, nasal steroids, and antibiotics. The consensus statement did note that 20 days of oral antibiotics produced superior results in this population, based on the theory that pediatric CRS is a more advanced disease in comparison to adults [8].

Surgical Management

Surgical management includes adenoidectomy, endoscopic sinus surgery, and most recently balloon sinuplasty. These procedures can be performed alone or in combination. Studies have found that adenoidectomy alone was effective in children up to 12 years of age, as the initial procedure after failing medical therapy. However, children age 6–12 have had less consistent success with adenoidectomy alone [8]. Adenoidectomy in CRS is believed to work by reducing the number of pathologic organisms in the nasopharynx that may contribute to sinus infection.

A meta-analysis from Brietzke showed that 50–75% of children had symptomatic improvement after adenoidectomy alone [22]. In this study, the mean age was 5.8,

with follow-up of 1–9 months. Other studies have looked at differences in symptom improvement based on surgical technique. One study found that there was a significant improvement with endoscopic sinus surgery (ESS) compared to adenoidectomy when assessing improvement in nasal discharge and headache. In this study, nasal congestion and cough had similar results in improvement for both techniques [23].

The literature also describes certain outliers that may not benefit from adenoidectomy. A study by Ramadan et al. found that patients with asthma and chronic adenoiditis had a lower success rate with adenoidectomy alone, when compared with children without asthma. They also found that those children with CRS and asthma did very poorly when treated with adenoidectomy alone [24]. Adenoidectomy may also not be the treatment of choice for patients with comorbidities such as cystic fibrosis, immunodeficiency, nasal polyps, and ciliary dyskinesia [16, 20].

Complementary Medicine

More recently, the use of Hyaluronic acid nasal saline has been suggested as a possible complementary therapy to surgical intervention [25]. In 2017, there was a study published by Pignatro et al., looking at the endoscopic and clinical benefits of hyaluronic acid in children with chronic adenoiditis. The study found that hyaluronic acid topical therapy significantly improved postnasal drip, swollen nasal mucosa, anterior, nasopharyngeal, and ostiomeatal secretions, and degree of severe adenoid hypertrophy [26].

Conclusion

The symptoms of chronic adenoiditis and chronic rhinosinusitis in the pediatric population are very similar. Endoscopic evaluation and CT scan of the sinus are helpful and recommended to decipher these two disease processes. Nasal endoscopy showing adenoid inflammation and drainage without inflammation or obstruction of the ostiomeatal complex is more consistent with chronic adenoiditis. Using the Lund-Mackay scoring system, patients with true CRS typically have a score >/= 5, while those with chronic adenoiditis have scores <5. Multiple theories have been used to describe the correlation between adenoid and sinusitis. The literature most strongly supports the hypothesis that biofilms are associated with adenoiditis and sinusitis and adenoid hypertrophy is not related to the severity of sinusitis. Adenoidectomy alone has a greater than 50% improvement in sinonasal symptoms, and should be considered the first choice intervention. Special consideration is given to asthmatics, and patients with cystic fibrosis, immunodeficiency, and ciliary dysmotility disease, as these patients tend to have poorer results with adenoidectomy alone.

References

1. Cesta MF. Normal structure, function, and histology of mucosa-associated lymphoid tissue. Toxicol Pathol. 2006;34(5):599–608.
2. Marseglia GL, Caimmi D, Pagella F, Matti E, Labó E, Licari A, et al. Adenoids during childhood: the facts. Int J Immunopathol Pharmacol. 2011;24(4 Suppl):1–5.
3. Lee D, Rosenfeld RM. Adenoid bacteriology and sinonasal symptoms in children. Otolaryngol Head Neck Surg. 1997;116(3):301–7.
4. Berçin AS, Ural A, Kutluhan A, Yurttaş V. Relationship between sinusitis and adenoid size in pediatric age group. Ann Otol Rhinol Laryngol. 2007;116(7):550–3.
5. Evcimik MF, Dogru M, Cirik AA, Nepesov MI. Adenoid hypertrophy in children with allergic disease and influential factors. Int J Pediatr Otorhinolaryngol. 2015;79(5):694–7.
6. Cohen D, Konak S. The evaluation of radiographs of the nasopharynx. Clin Otolaryngol Allied Sci. 1985;10(2):73–8.
7. Parikh SR, Coronel M, Lee JJ, Brown SM. Validation of a new grading system for endoscopic examination of adenoid hypertrophy. Otolaryngol Head Neck Surg. 2006;135(5):684–7.
8. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
9. Marseglia GL, Pagella F, Klersy C, Barberi S, Licari A, Ciprandi G. The 10-day mark is a good way to diagnose not only acute rhinosinusitis but also adenoiditis, as confirmed by endoscopy. Int J Pediatr Otorhinolaryngol. 2007;71(4):581–3.
10. Marseglia GL, Pagella F, Caimmi D, Caimmi S, Castellazzi AM, Poddighe D, et al. Increased risk of otitis media with effusion in allergic children presenting with adenoiditis. Otolaryngol Head Neck Surg. 2008;138(5):572–5.
11. Marseglia GL, Poddighe D, Caimmi D, Marseglia A, Caimmi S, Ciprandi G, et al. Role of adenoids and adenoiditis in children with allergy and otitis media. Curr Allergy Asthma Rep. 2009;9(6):460–4.
12. Shin KS, Cho SH, Kim KR, Tae K, Lee SH, Park CW, et al. The role of adenoids in pediatric rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2008;72(11):1643–50.
13. Coticchia J, Zuliani G, Coleman C, Carron M, Gurrola J 2nd, Haupert M, 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.
14. Tuncer U, Aydogan B, Soylu L, Simsek M, Akcali C, Kucukcan A. Chronic rhinosinusitis and adenoid hypertrophy in children. Am J Otolaryngol. 2004;25(1):5–10.
15. Fukuda K, Matsune S, Ushikai M, Imamura Y, Ohyama M. A study on the relationship between adenoid vegetation and rhinosinusitis. Am J Otolaryngol. 1989;10(3):214–6.
16. Ramadan HH, Tiu J. Failures of adenoidectomy for chronic rhinosinusitis in children: for whom and when do they fail? Laryngoscope. 2007;117(6):1080–3.
17. Neff L, Adil EA. What is the role of the adenoid in pediatric chronic rhinosinusitis? Laryngoscope. 2015;125(6):1282–3.
18. Kosikowska U, Korona-Głowniak I, Niedzielski A, Malm A. Nasopharyngeal and adenoid colonization by Haemophilus influenzae and Haemophilus parainfluenzae in children undergoing adenoidectomy and the ability of bacterial isolates to biofilm production. Medicine (Baltimore). 2015;94(18):e799.
19. Bhattacharyya N, Jones DT, Hill M, Shapiro NL. The diagnostic accuracy of computed tomography in pediatric chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2004;130(9):1029–32.
20. Makary CA, Ramadan HH. Sinus and upper airway surgery in children. Curr Allergy Asthma Rep. 2018;18(5):32.
21. Marzouk H, Aynehchi B, Thakkar P, Abramowitz T, Goldsmith A. The utility of nasopharyngeal culture in the management of chronic adenoiditis. Int J Pediatr Otorhinolaryngol. 2012;76(10):1413–5.

22. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72(10):1541–5.
23. Ramadan HH. Adenoidectomy vs endoscopic sinus surgery for the treatment of pediatric sinusitis. Arch Otolaryngol Head Neck Surg. 1999;125(11):1208–11.
24. Ramadan HH, Makary CA. Can computed tomography score predict outcome of adenoidectomy for chronic rhinosinusitis in children. Am J Rhinol Allergy. 2014;28(1):e80–2.
25. Torretta S, Marchisio P, Rinaldi V, Carioli D, Nazzari E, Pignataro L. Endoscopic and clinical benefits of hyaluronic acid in children with chronic adenoiditis and middle ear disease. Eur Arch Otorhinolaryngol. 2017;274(3):1423–9.
26. Pignataro L, Marchisio P, Ibba T, Torretta S. Topically administered hyaluronic acid in the upper airway: a narrative review. Int J Immunopathol Pharmacol. 2018;32:2058738418766739.

Suggested Reading

Brambilla I, Pusateri A, Pagella F, Caimmi D, Caimmi S, Licari A, et al. Adenoids in children: advances in immunology, diagnosis, and surgery. Clin Anat. 2014;27(3):346–52.
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.
Haapaniemi JJ. Adenoids in school-aged children. J Larngol Otol. 1995;109(3):196–202.
Lusk RP, Bothwell MR, Piccirillo J. Long-term follow-up for children treated with surgical intervention for chronic rhinosinusitis. Laryngoscope. 2006;116(12):2099–107.
Lusk RP, Stankiewicz JA. Pediatric rhinosinusitis. Otolaryngol Head Neck Surg. 1997;117(3 Pt 2):S53–7.
Mora R, Dellepiane M, Crippa B, Guastini L, Santomauro V, Salami A. Ribosomal therapy in the treatment of recurrent acute adenoiditis. Eur Arch Otorhinolaryngol. 2010;267(8):1313–8.
Pereira L, Monyror J, Almeida FT, Almeida FR, Guerra E, Flores-Mir C, Pachêco-Pereira C. Prevalence of adenoid hypertrophy: a systematic review and meta-analysis. Sleep Med Rev. 2018;38:101–12.
Saedi B, Sadeghi M, Mojtahed M, Mahboubi H. Diagnostic efficacy of different methods in the assessment of adenoid hypertrophy. Am J Otolaryngol. 2011;32(2):147–51.
Takahashi H, Honjo I, Fujita A, Kurata K. Effects of adenoidectomy on sinusitis. Acta Otorhinolaryngol Belg. 1997;51(2):85–7.

Part III
Medical Treatment of Rhinosinusitis

Chapter 13
Antibiotics: Intranasal and Systemic for Treatment of Sinusitis in Children

Zachariah K. Chandy, Elisabeth H. Ference, and Jivianne T. Lee

Introduction

Bacterial rhinosinusitis is a common condition affecting the pediatric population. The use of antibiotics for the treatment of pediatric acute and chronic bacterial rhinosinusitis is widespread. However, treatment regimens vary greatly and there is limited evidence regarding the use of antibiotics for pediatric rhinosinusitis. Many professional organizations [including the Infectious Disease Society of America (IDSA), American Academy of Pediatrics (AAP), American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF)] as well as the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS) have sought to evaluate the current literature and provide evidence-based guidelines to aid in the treatment of pediatric acute and chronic rhinosinusitis (CRS). We review these guidelines, as well as the underlying literature, in this chapter.

Z. K. Chandy
Department of Head and Neck Surgery, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA

E. H. Ference (✉)
Rick and Tina Caruso Department of Otolaryngology–Head and Neck Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA
e-mail: elisabeth.ference@med.usc.edu

J. T. Lee
Department of Head and Neck Surgery, University of California Los Angeles Medical Center and David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_13

Bacteriology

In 1984, Wald et al. analyzed the bacteriology of acute rhinosinusitis in pediatric patients from maxillary sinus aspirates under sedation [1]. The most common bacteria cultured were *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and nontypeable *Haemophilus influenzae*. Following the advent and use of the pneumococcal vaccine, the bacteriology of sinusitis has not been subsequently evaluated due to the relative invasiveness of maxillary sinus aspirations. Assumptions of the current trends of bacteriology in acute sinusitis are based on acute otitis media, because tympanocentesis is more readily performed and is believed to reflect sinonasal bacteria. Table 13.1 summarizes the bacteriology of acute and chronic rhinosinusitis based on recent evidence. In studies of cultures from acute otitis media following the use of the pneumococcal vaccine, the three most common bacteria remained *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and nontypeable *Haemophilus influenzae* [2]. However, the proportion of *Streptococcus pneumoniae* has decreased, as would be expected with the use of the vaccine. The proportion of *Streptococcus pneumoniae* and *Haemophilus influenzae* are now equivalent, while *Moraxella catarrhalis* is still a distant third. Approximately 20% of *Streptococcus pneumoniae* cultured is penicillin non-susceptible, whereas 32% of *Haemophilus influenzae* and all *Moraxella catarrhalis* produce beta-lactamase.

In 2010, Hsin et al. attempted to characterize the bacteriology of pediatric CRS after the pneumococcal vaccine was administered [3]. Maxillary sinus aspirates of children with CRS undergoing aspiration and irrigation were analyzed. Alpha-hemolytic *Streptococcus* was the most commonly found at 20.8%, followed by *Haemophilus influenzae* (19.5%), *Streptococcus pneumoniae* (14.0%), coagulase-negative *Staphylococcus* (13.0%), *Staphylococcus aureus* (9.3%), and anaerobes (8.0%). To further evaluate the effect of the pneumococcal vaccine on the bacteriology of CRS, McNeil et al. analyzed sinus cultures that grew *Streptococcus pneumoniae* following endoscopic sinus surgery [4]. Ninety-six percent were found to be non-vaccine serotypes. Seventy-five percent were found to be non-susceptible to penicillin, while 21% were not susceptible to cefotaxime. Given that the exact rates of the susceptibility of bacteria differ by location, use of local antibiogram may be beneficial when deciding antibiotic choice.

In summary, when suspecting acute bacterial rhinosinusitis, the antibiotic chosen should cover *Streptococcus pneumonia*, *Moraxella catarrhalis*, and *Haemophilus*

Table 13.1 Bacteriology of acute and chronic rhinosinusitis

Acute rhinosinusitis	*Streptococcus pneumoniae* (28–36%) *Haemophilus influenzae* (19–34%) *Moraxella catarrhalis* (19–30%)
Chronic rhinosinusitis	*Haemophilus influenzae* (19.5%) *Streptococcus pneumoniae* (14.0%) *Coagulase-negative Staphylococcus* (13.0%) *Staphylococcus aureus* (9.3%) Anaerobes (8.0%)

influenzae. In CRS, additional coverage should be provided for alpha-hemolytic Streptococcus, coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and anaerobes.

Cultures

Obtaining satisfactory cultures in pediatric patients is challenging. Given the relative invasiveness of obtaining cultures in children, the merits of culture-guided treatment remain questionable. Per the EPOS and AAO-HNSF guidelines, cultures are not essential in uncomplicated acute or chronic rhinosinusitis [5, 6]. However, for patients who have not responded to empiric therapy within 2–3 days, have severe illness, an associated complication, or are immunocompromised, culture-directed treatment is warranted.

Maxillary sinus aspiration is the gold standard culture technique. In the pediatric population, this often requires general anesthesia which limits its utility. Several studies have demonstrated a robust association with endoscopically guided middle meatal cultures, especially when suction aspiration is used rather than culture swabs (Fig. 13.1) [3, 7, 8]. In contrast, blind nasopharyngeal swabs have demonstrated a poor association with maxillary sinus aspirates [9]. If cultures are required, EPOS recommends the use of endoscopically guided middle meatal cultures in patients who can tolerate rigid endoscopy in the clinic [5]. For those who cannot tolerate clinic procedures and require anesthesia, EPOS recommends the use of maxillary sinus aspiration over middle meatal cultures since sinus irrigations can be performed simultaneously. Balloon catheter devices can be used for dilation and irrigation of the sinuses; however, there are currently no available culture traps which can be loaded onto the balloon catheters.

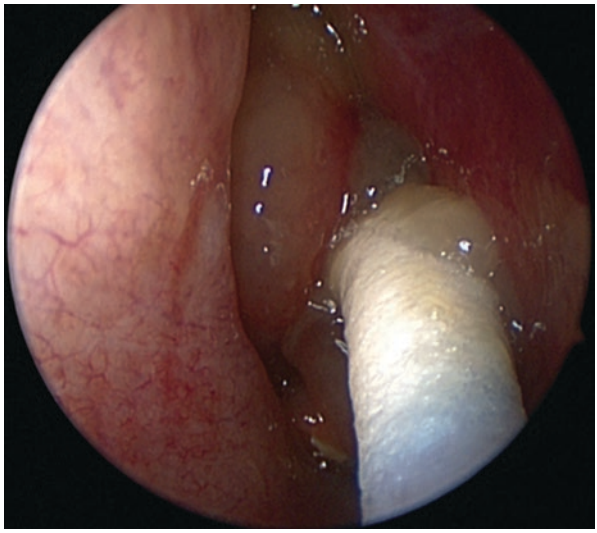


Fig. 13.1 Endoscopically guided middle meatus culture

Oral Antibiotics in Acute Rhinosinusitis

The use and timing of antibiotic therapy in acute uncomplicated bacterial rhinosinusitis remains controversial. The current literature is limited by the difficulty of differentiating patients with viral upper respiratory infection (URI) from those with bacterial rhinosinusitis. Based on guidelines, a diagnosis of acute bacterial rhinosinusitis can be made and differentiated from viral URI if symptoms last greater than 10 days, if the symptoms are severe at onset (concurrent nasal discharge and fever greater than 39 Celsius for at least 3 days), or if symptoms worsen after a period of initial improvement [5, 10]. Given viral URIs may improve without treatment, including patients with viral rather than bacterial illnesses may skew results to suggest less need for antibiotic therapy.

Wald et al. performed a randomized, double-blinded study with strict inclusion criteria for acute bacterial rhinosinusitis to further delve into this issue [11]. Inclusion criteria included pediatric patients with persistent symptoms for greater than 10 days, worsening symptoms, or severe symptoms. This criterion was used to select for patients with probable acute bacterial sinusitis, while excluding patients with viral URIs. Patients were treated with amoxicillin/clavulanate versus placebo, stratified based on the severity of illness, and followed for 14 days. Of those treated with amoxicillin/clavulanate, 50% reported improvement, while 14% had treatment failure. Of those treated with placebo, 14% had improvement, while 68% had treatment failure. This study demonstrates the relative benefit of antibiotics in improving final treatment success. A second randomized controlled trial comparing treatment with cefitoren, a cephalosporin, or amoxicillin/clavulanate in pediatric patients with acute rhinosinusitis found no significant difference in improvement rates at 14 days between antibiotic groups (78.8% for cefitoren and 84.7% with amoxicillin/clavulanate) [12]. The rate of adverse events, most commonly diarrhea, was substantial (18.1% with amoxicillin/clavulanate; 4.5% with cefitoren).

Based on the above studies, different professional organizations have offered conflicting advice (summarized in Table 13.2). Given the significant difference in improvement between the antibiotic group and placebo group when strict inclusion criteria were used, the IDSA guidelines suggest the immediate use of antibiotics when the diagnosis of acute bacterial rhinosinusitis is made [13]. The goal is to provide faster recovery and reduce the risk of potential complications. On the contrary, the EPOS guidelines suggest that although antibiotics may improve the speed and rate of improvement, acute bacterial rhinosinusitis may improve irrespective of treatment [5]. In addition, it cites the non-zero adverse reaction rate as a potential issue with the widespread use of antibiotic. The EPOS guidelines endorse symptomatic treatment of uncomplicated acute bacterial rhinosinusitis, while reserving antibiotics for those with preexisting conditions or those who develop complications of acute rhinosinusitis. The AAP has also made recommendations regarding oral antibiotic treatment [10]. The guidelines suggest the use of oral antibiotics for patients with severe symptoms or worsening symptoms to reduce the risk of orbital and intracranial complications. For those with mild or moderate symptoms, the

Table 13.2 Oral antibiotic recommendations for acute bacterial rhinosinusitis

Professional organization	Antibiotic choice	Duration
IDSA	First line: Amoxicillin/clavulanate Non-type 1 hypersensitivity to penicillin: Cephalosporin and Clindamycin Type 1 hypersensitivity to penicillin: Levofloxacin	10–14 days
EPOS 2012	First line: Amoxicillin, Amoxicillin/clavulanate, or Cephalosporin If penicillin allergy: Azithromycin, Clarithromycin, or Trimethoprim/sulfamethoxasole Anaerobes: Clindamycin	Duration of therapy not specified
AAP	First line: Amoxicillin Amoxicillin/clavulanate for patients younger than 2 years old, with severe symptoms, or recent antibiotics Non-type 1 hypersensitivity to penicillin: Third-generation cephalosporin (Cefdinir or Cefuroxime) Type 1 hypersensitivity to penicillin: Levofloxacin or Cefixime with Clindamycin or Linezolid	7 days following complete clinical improvement with a minimum of 10 days duration

Oral antibiotic recommendations for acute bacterial rhinosinusitis
IDSA Infectious disease society of America, *EPOS* 2012 European Position Paper on Rhinosinusitis and Nasal Polyps 2012, *AAP* American Academy of Pediatrics

guidelines advocate for the use of oral antibiotics or an observational period of 72 hours. The observational period is advocated given patients may improve without therapy, as the use of antibiotics is not without adverse effects.

Regarding choice of antibiotic therapy, the IDSA guidelines recommend the use of amoxicillin/clavulanate over amoxicillin, given the high rates of beta-lactamase producing bacteria [13]. In addition, the guidelines do not recommend the use of azithromycin, clarithromycin, trimethoprim/sulfamethoxazole, or cephalosporins given the high rates of resistance seen in *Streptococcus pneumoniae* and *Haemophilus influenzae*. In children with non-type 1 hypersensitivity to penicillin, dual therapy with a third-generation cephalosporin and clindamycin may be considered. With a Type 1 hypersensitivity to penicillin, the guidelines suggest the use of levofloxacin. However, care must be taken with the use of fluoroquinolones in pediatric patients due to the possibility of arthropathy [14]. Based on current evidence, the guideline does not endorse empiric methicillin-resistant *Staphylococcus aureus* coverage.

The EPOS guidelines advise the use of amoxicillin (40 mg/kg/day or 80 mg/kg/day) initially [5]. Amoxicillin/clavulanate and cephalosporins are alternative first-line choices, especially if concerned for beta-lactamase producing bacteria. If patient has noted allergies to these medications, alternatives are azithromycin, clarithromycin, and trimethoprim/sulfamethoxasole. If there is concern for possible anaerobes, clindamycin is an option.

Similar to the EPOS guidelines, the AAP recommends amoxicillin 45 mg/kg/day as first-line therapy in uncomplicated acute rhinosinusitis [11]. In locations with greater than 10% prevalence of non-susceptible *Streptococcus pneumonia*, amoxicillin 80–90 mg/kg/day is recommended to increase sinus concentrations to overcome the resistance attributed to penicillin-binding proteins. Amoxicillin-clavulanate 80–90 mg/kg/day is first-line therapy for patients younger than 2 years old, patients who have recently used antibiotics, or patients with severe symptoms to cover beta-lactamase generating bacteria. For patients with non-type 1 penicillin allergies, a third-generation cephalosporin (cefdinir or cefuroxime) is recommended. For those patients with Type 1 sensitivity to penicillin, levofloxacin or a combination of cefixime (a third-generation cephalosporin) with clindamycin or linezolid can be used. Trimethoprim-sulfamethoxazole and azithromycin are not recommended based on bacterial resistance patterns.

The appropriate duration of treatment for acute rhinosinusitis in children is unclear because randomized trials are limited. Most of the current evidence is based on adult studies. A meta-analysis by Falagas analyzed 12 adult studies comparing short course therapy up to 7 days versus long course therapy defined as 2 days greater than short course therapy for the same antibiotic at the same daily dosage [15]. The study found no difference in outcomes or relapse rate of infection between the two course durations. Based on this evidence, the IDSA guideline recommends the duration of treatment to be 5–7 days in adults [13]. Given the lack of evidence, they weakly suggest the duration of treatment to be at least 10–14 days in pediatric patients. The EPOS guidelines do not suggest an exact duration of therapy [5]. The AAP advocates for oral antibiotic use to be continued for 7 days following complete clinical improvement with a minimum of 10 days to avoid prolonged antibiotic courses [11]. Additional randomized trials to better define the appropriate duration of therapy in children are necessary.

Oral Antibiotics in Chronic Rhinosinusitis

Although widespread, the literature supporting the use of oral antibiotics for pediatric CRS is limited. Otten et al. performed a double-blinded, randomized study analyzing the effectiveness of oral antibiotics for use specifically in chronic sinusitis [16]. Seventy-five children with purulent rhinosinusitis for 3 months underwent sinus aspiration and washout followed by randomization into treatment with cefaclor or placebo for 1 week. At 6 weeks, there was no statistically significant difference in resolution of sinusitis clinically or on radiograph (64.8% resolution in cefaclor group versus 52.5% in placebo group; $p = 0.28$). Given pretreatment with sinus aspiration and washout and the short duration of therapy, it is difficult to draw definitive conclusions regarding oral antibiotics use in pediatric CRS.

Due to the limitations in evidence, the choice of antibiotic is often based on treatment regimens for pediatric acute rhinosinusitis. There is also limited evidence regarding the optimal duration of therapy. The EPOS guidelines suggest there is no

current evidence to support short duration of antibiotics in pediatric CRS [5]. The guidelines advocate for longer course duration, despite limited evidence, given the likely equivalence to adult chronic sinusitis. The AAO-HNSF pediatric sinusitis consensus guidelines support longer course durations as well [6]. The panel reached a consensus that 20 days are superior to 10 days of antibiotic therapy. The consensus statement also recommends culture-direct antibiotics for patients who have not responded to prior medical therapy.

Intravenous Antibiotics

Prior studies have examined the use of intravenous (IV) antibiotics for pediatric rhinosinusitis and found complications of long-term venous access without significant benefit. In a retrospective analysis, 70 children with chronic sinusitis who had failed a 3–4 week course of oral antibiotics were treated in a stepwise approach with IV antibiotics plus maxillary sinus irrigation with or without adenoidectomy, followed by endoscopic sinus surgery and IV antibiotics if there was insufficient improvement [17]. Given the inclusion of both surgical and antibiotic intervention, it is not possible to know the relative contribution of IV antibiotics compared to maxillary sinus irrigation to the patients' improvement. There was equivocal response rate between patient who received IV antibiotics plus sinus irrigation and those who received IV antibiotics with irrigation and adenoidectomy. IV antibiotics included cefuroxime (43%), ampicillin (31%), ticaracillin (21%), ceftriaxone (3%), and vancomycin (1%). Treatment was not without adverse complications. Fourteen percent of patients developed complications including superficial thrombophlebitis (9%), dislodged catheter requiring venotomy (1%), serum sickness (1%), pseudomembranous colitis (1%), and drug fevers (1%). In a similar retrospective analysis, 22 children with CRS who failed medical therapy were treated with maxillary sinus aspiration, irrigation, adenoidectomy, and IV antibiotic therapy until resolution of symptoms [18]. One hundred percent of patients had initial clinical improvement after IV therapy, while 77% had complete resolution at 12 months. Although these two studies are encouraging, the benefits of IV antibiotics are difficult to ascertain due to concurrent interventions including maxillary aspiration, irrigation, and adenoidectomy. In addition, both studies lack a control group. The EPOS guidelines suggest, based on the current evidence, there is no justification for the use of IV antibiotics in routine pediatric chronic rhinosinusitis [5].

Although infrequent, intraorbital and intracranial complications of sinusitis (orbital cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombosis) can be clinically severe. Therefore, prompt treatment is of the utmost importance. Per the EPOS and AAP guidelines, early initiation of broad spectrum IV antibiotics covering aerobes and anaerobes is recommended [5, 11]. The AAP specifically recommend vancomycin with piperacillin-tazobactam, ampicillin-sulbactam, or ceftriaxone to cover penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *S. Aureus* [11]. If clinically improving and afebrile for

48 hours, the patient can be transitioned to equivalent oral antibiotics [5]. The guidelines suggest surgical drainage of abscess if clinically worsening (fevers, changes in visual acuity or color vision, ophthalmoplegia, or large abscess greater than 1 ml in volume) or if no improvement after 48 hours.

Overall, pediatric patients with complications of sinusitis or significant comorbidities (cystic fibrosis, ciliary dyskinesis, immunodeficiencies) may benefit from IV antibiotics. In addition, IV antibiotics can be valuable if cultures grow bacteria with resistance to oral antibiotics or if sinusitis has been refractory to medical and surgical management. However, the benefit of intravenous therapy must be weighed against the risks of an indwelling catheter.

Antibiotic Irrigations

Daily saline irrigations have proven beneficial amongst pediatric patients with CRS. Nasal irrigations are believed to improve clearance of the sinuses and can be used to deposit medications, such as antibiotics, onto the sinus mucosa (Fig. 13.2).

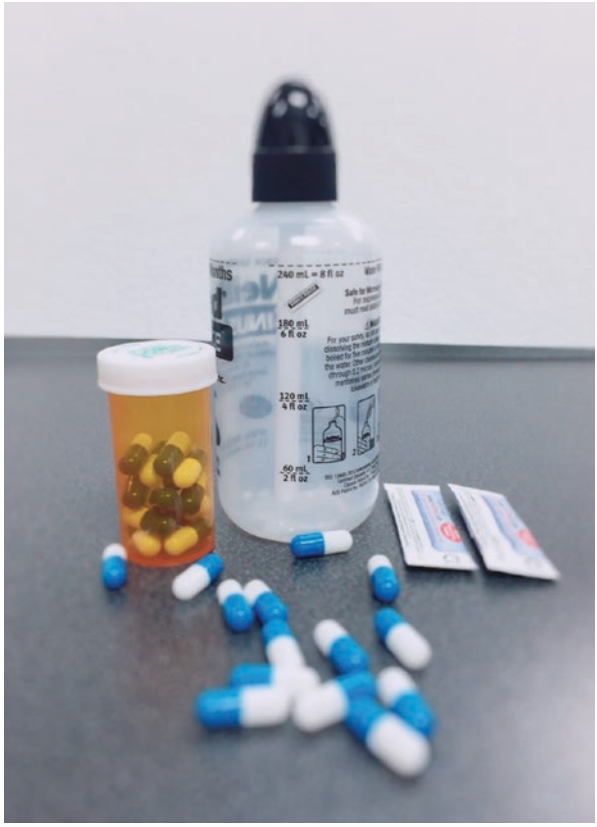


Fig. 13.2 Antibiotic antral irrigation. (Courtesy of advanced RX)

It has been postulated that intranasal antibiotic irrigation can provide the benefits of antibiotics without toxic side effects by avoiding high systemic levels of oral or IV antibiotics [19, 20].

Currently, studies of antibiotic irrigations in the pediatric population are limited. Wei et al. performed a prospective, double-blinded cohort study with the goal of comparing the treatment outcomes of pediatric patients with chronic rhinosinusitis using daily saline irrigations compared to saline irrigations with low dose gentamycin solution (80 mg gentamycin/1000 ml normal saline) [19]. The study enrolled 40 children and followed them over the course of 6 weeks. In both groups, there was a noted improvement of quality of life scores and Lund-MacKay Computed Tomography scores following treatment. However, there was no statistical difference between groups. In this limited sample of non-operated patients, gentamycin nasal irrigation did not provide improved efficacy over saline irrigation alone. However, a minimum ostial diameter of approximately 3 mm may be necessary to ensure that the sinus can be successfully irrigated with saline solution [21]. Therefore, pediatric patients with unoperated sinuses may not benefit significantly from topical antibiotics due to the inability of the solution to reach the sinus mucosa.

A literature review of the current adult and pediatric evidence concluded that antibiotic irrigations may be most beneficial when used following endoscopic sinus surgery in a culture-directed manner [20]. However, given the limited evidence in the pediatric population, it is difficult to draw direct recommendations for use of nasal antibiotics irrigations in children. Some topical antibiotics, such as tobramycin and gentamycin, may have ototoxic effects, which have not been adequately studied. Moreover, little is known about dosing for pediatric patients given that sinus size and mucosal surface area changes rapidly during childhood based on pneumatization and midface growth. Based on the limited available evidence to date, the AAO-HNSF did not reach consensus regarding the use of topical antibiotic irrigation for the pediatric population [6]. The other professional organizations did not specifically comment or advocate for the use of antibiotic antral irrigations in the pediatric population. More studies analyzing alternative antibiotic antral irrigations with varying dosages and with measurement of subsequent serum levels would be valuable to determine the efficacy of antibiotic antral irrigations and the degree of systemic absorption.

Pediatric patients with cystic fibrosis often undergo tobramycin nebulizer therapy when *Pseudomonas* is cultured in the lungs. The nebulized tobramycin can be inhaled through a nasal mask, thus theoretically providing deposition of the tobramycin into the sinuses. However, prior studies have found that in the adult population, administration of topical antibiotics via a nebulizer or spray technique has not shown significant clinical benefit while administration via irrigation methods has shown promise [22, 23]. The EPOS guidelines do not recommend topical antibiotics as first-line therapy for patients with cystic fibrosis based on limitations in evidence. Further studies are needed regarding the use of topical antibiotic irrigations in patients with cystic fibrosis as an adjunct to inhaled pulmonary nebulizers and as a way to reduce sinus colonization by bacteria such as *Pseudomonas* and *Staphylococcus aureus* [5].

Conclusion

Although controversial, the use of empiric oral antibiotics is recommended for pediatric acute and chronic bacterial rhinosinusitis. Culture-directed therapy is reserved for patients who do not respond to initial treatment. Based on the current evidence, intravenous antibiotics should be reserved for patients with complications of sinusitis or comorbidities, while intranasal antibiotic irrigations may be beneficial in pediatric patients who previously have undergone sinus surgery and have failed routine medical management.

References

1. Wald ER, Reilly JS, Casselbrant M, Ledesma-Medina J, Milmoe GJ, Bluestone CD, et al. Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. J Pediatr. 1984;104(2):297–302.
2. Casey JR, Adlowitz DGPM. New patterns in otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2010;29:304–9.
3. Hsin CH, Su MC, Tsao CH, Chuang CY, Liu CM. Bacteriology and antimicrobial susceptibility of pediatric chronic rhinosinusitis: a 6-year result of maxillary sinus punctures. Am J Otolaryngol. 2010;31(3):145–9.
4. McNeil JC, Hulten KG, Mason EO, Kaplan SL. Serotype 19A is the most common streptococcus pneumoniae isolate in children with chronic sinusitis. Pediatr Infect Dis J. 2009;28(9):766–8.
5. 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.
6. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
7. Orobello PW Jr, Park RI, Belcher LJ, Eggleston P, Lederman HM, Banks JR, et al. Microbiology of chronic sinusitis in children. Arch Otolaryngol Head Neck Surg. 1991;117(9):980–3.
8. Hsin C-H, Tsao C-H, Su M-C, Chou M-C, Liu C-M. Comparison of maxillary sinus puncture with endoscopic middle meatal culture in pediatric rhinosinusitis. Am J Rhinol. 2008;22(3):280–4.
9. 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.
10. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262–80.
11. Wald ER, Nash D, Eickhoff J. Effectiveness of amoxicillin/clavulanate potassium in the treatment of acute bacterial sinusitis in children. Pediatrics. 2009;124(1):9–15.
12. Poachanukoon O, Kitcharoensakkul M. Efficacy of cefditoren pivoxil and amoxicillin/clavulanate in the treatment of pediatric patients with acute bacterial rhinosinusitis in Thailand: a randomized, investigator-blinded, controlled trial. Clin Ther. 2008;30(10):1870–9.
13. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–112.

14. Committee on Infectious Diseases. The use of systemic fluoroquinolones. Pediatrics. 2006;118(3):1287–92.
15. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. Br J Clin Pharmacol. 2009;67(2):161–71.
16. Otten HW, Antvelink JB, Ruyter de Wildt H, Rietema SJ, Siemelink RJG, Hordijk GJ. Is antibiotic treatment of chronic sinusitis effective in children? Clin Otolaryngol Allied Sci. 1994;19(3):215–7.
17. Don DM, Yellon RF, Casselbrant ML, Bluestone CD. Efficacy of a stepwise protocol that includes intravenous antibiotic therapy for the management of chronic sinusitis in children and adolescents. Arch Otolaryngol Head Neck Surg. 2001;127(9):1093–8.
18. Adappa ND, Coticchia JM. Management of refractory chronic rhinosinusitis in children. Am J Otolaryngol. 2006;27(6):384–9.
19. 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(9):1989–2000.
20. Lee JT, Chiu AG. Topical anti-infective sinonasal irrigations: update and literature review. Am J Rhinol Allergy. 2014;28:29–38.
21. Grobler A, Weitzel EK, Buele A, Jardeleza C, Cheong YC, Field J, et al. Pre- and postoperative sinus penetration of nasal irrigation. Laryngoscope. 2008;118(11):2078–81.
22. Lim M, Citardi MJ, Leong J-L. Topical antimicrobials in the management of chronic rhinosinusitis: a systematic review. Am J Rhinol. 2008;22(4):381–9.
23. Rudmik L, Hoy M, Schlosser RJ, Harvey RJ, Welch KC, Lund V, et al. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2013;3(4):281–98.

Chapter 14
Saline Irrigation in Pediatric Rhinosinusitis

Friederike S. Luetzenberg and Julie L. Wei

Introduction

Chronic rhinosinusitis (CRS) is considered the fifth most common chronic illness in the USA, with a reported up to 15% of the population being affected [1, 2]. The global incidence rate is a bit more variable and ranges from 1% to 11% [3, 4]. In pediatric CRS, specifically, 0.5–10% of upper viral infections are thought to progress to acute rhinosinusitis (ARS) with a subsequent undefined proportion advancing to CRS [5]. It is, therefore, not surprising that CRS accounts for the chief complaint in approximately 27 million office and emergency room visits in the USA annually [6]. This prevalence combined with a probably of patients with CRS being five times more likely to be prescribed medication than patients without CRS has created a huge economic burden; in fact, the healthcare cost associated with CRS is estimated to be $5–$8 billion per year with additional loses accruing due to decreased productivity at work and school [2, 6]. Mucosal thickening on CT imaging demonstrates that CRS is not an infectious process, but rather an inflammatory disease. Hence, common management approach using antibiotics and/or antihistamine and topical nasal steroid spray, for resumed infectious or allergic causes of these symptoms, results in observed unresolved persistent daily symptoms in children.

F. S. Luetzenberg
University of Central Florida College of Medicine, Orlando, FL, USA
e-mail: fluetzenberg@knights.ucf.edu

J. L. Wei (✉)
Pediatric Otolaryngology/Audiology, Department of Surgery, Nemours Children's Hospital, Orlando, FL, USA

Otolaryngology-Head Neck Surgery, University of Central Florida College of Medicine, Orlando, FL, USA
e-mail: Julie.wei@nemours.org

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_14

Nasal saline irrigation has been shown over decades to significantly relieve symptoms associated with CRS and improve patient's quality of life. Although awareness and slowly increasing practice of daily saline rinses appear relatively new in the Western world, it has been considered a "hygiene" practice which can be traced back as far as 1000 BC to the ancient Hindus of Ayurveda [7]. Continuing along the timeline, in the fifteenth century, the Far Eastern yoga tradition of Hatha Yoga Pradipika practiced *Jala neti*, meaning nasal cleansing with (salt)water, and created the *neti pot*, a popular device still used today [8, 9]. The first mentioning of nasal irrigation in the Western world, however, was not until 1895 when the *British Medical Journal* reported on this "new" phenomenon [8]; and it took another 80 years before the introduction of nasal rinses in the USA [7]. Today nasal saline irrigation is commonly accepted as an adjunctive therapy for conditions such as CRS, but its benefits as the primary first-line treatment may still be questioned by many. Furthermore, many physicians and patients may be confused as to what saline solution to use and with what device to best apply it. This chapter aims to share the past and current best evidence on the efficacy of nasal saline irrigations, what to use, and how to use it when treating pediatric CRS.

Physiology

In a normal setting, the upper respiratory system possesses mucociliary clearance, also known as the mucociliary escalator, which comprises the interplay between ciliated epithelium and daily mucus secretions [10]. The nasal passage and all structures are covered by mucous membrane, which provides large surface area with rich underlying venous plexus to optimize warming of air, humidification, and secretion of mucus constantly to protect the airway from foreign particles. There is mucociliary clearance which propels fine particles toward the pharynx and such are then swallowed [11]. The mucus layer consists of two distinct layers—the gel and sol layer [10]. The superficial gel layer is a thick, more viscous constituent, with various antibodies and proteins to trap and eliminate foreign microorganisms and matter. The sol layer, in contrast, is the deeper, more serous constituent which bathes the ciliated epithelium allowing the appropriate cilia motion [10]. Cilia move in a concerted and active beating pattern, known as ciliary beat frequency, which under normal circumstances beat at about 13 Hz in vitro [11]. The beating motion moves the mucus layers synchronously in one direction. The interplay between well-functioning cilia and adequate amount of mucus is *critical* in order to clear the nasal passages appropriately.

In CRS, there is a defect in the mucociliary transport system, as has been repeatedly shown with using saccharin tests in multiple studies [11, 12], the two possible culprits being either the mucus or the cilia. Studies suggest that there is no significant difference in primary ciliary beat frequency between patients with CRS and normal controls which would lead to the disease [13]. In fact, one study concluded that the presence of CRS may eventually lead secondary cilia dyskinesia due to the

chronic disease process and, therefore, not be implicated in the origin of the disease [14]. The acquired ciliary defects, now displaying decreased ciliary beat frequency, however, slow the mucociliary clearance even more, feeding into the vicious disease cycle. This leads to the conclusion that initially the nasal mucus secretions themselves are responsible for the "sinusitis," which are later joined by progressively slowing cilia. This is important to keep in mind when considering the usefulness of nasal irrigation as a treatment for CRS.

While western culture may focus solely on infectious and allergic causes of mucociliary dysfunction, there are many physiologic factors which are important for good mucociliary clearance: the number of cilia, their structure, activity, and coordinated movement. Optimum functionality of mucociliary clearance presupposes a temperature of 37.0 °C (98.6 °F) and absolute humidity of 44 mg/dm^3 corresponding to a relative humidity of 100%. Under the condition of insufficient temperature and humidity, after a short time the ciliary cells suspend their transport function. Under such circumstances, bacterial germinal colonization is facilitated [15].

Based on these physiologic requirements for optimal mucociliary clearance, it is conceivable that nasal symptoms may in fact be commonly a result of suboptimal conditions for physiologic function of the nose. When chronically exposed to indoor and/or outdoor environments which have inadequate humidity, external cold temperatures, and exposure to indoor air heating or wood-burning heat, prolonged geographic winter seasons, prevalence of nasal congestion, "stuffiness," and perception of "blockage" can be expected. In children, an additional common cause is temporary mucociliary clearance disturbance due to acute viral upper respiratory tract illness. However, even after viral illness is over, persistent suboptimal mucociliary clearance may continue due to the factors listed above.

There are additional factors which may disturb mucus secretion in the upper respiratory tract. Normal nasal physiology involves "nasal cycle" of intermittent congestion and decongestion of contralateral nasal passages due to an increase in blood flow and vasodilation of mucous membrane of inferior turbinate, versus a decrease in blood flow and vasoconstriction in the other, respectively [16]. It has been hypothesized that the nasal cycle may contribute to the mucociliary clearance and protection against respiratory infections. Soane et al. showed that the mucociliary clearance was 2.5 times greater in the patient nostril during the nasal cycle than in the congested nostril [17], indicating once again increased mucus secretions in the hinderance of the mucociliary escalator and the potential for microorganisms and foreign particles to stay in one's nostril longer.

Furthermore, the climate of one's geographical location may contribute to the amount of mucus secreted. Nasal passages are naturally warm moist environments, which means that depending on what the outside environment presents, during inspiration and expiration, the air properties need to be adjusted. As such, a comprehensive study on climate zones and subsequent nasal functioning extrapolated that cool-dry air requires the most inspiratory modifications, whereas hot-wet air requires the most expiratory modifications [18]. In terms of CRS, the setting of cold-dry environment may dehydrate one's nose, leading to mucostatsis and

decreased mucociliary clearance [19, 20]. On the other extreme, however, hot-wet air may increase the perception congestion due to the sheer static overhydration of the nasal passages [21]. Based on all the factors presented, in order to effectively treat nasal symptoms and dysfunction, mucociliary clearance must be optimized while an excessive amount of mucus minimized. These are the reasons why nasal saline irrigation should be used frequently and often as the primary method to restore mucociliary clearance and optimal nasal physiology.

Nasal irrigation has been shown to be effective at improving the symptoms of CRS, and it does so by enhancing the impaired mucociliary clearance. On one hand, saline rinses are effective at washing out mucus with its entrapped debris and microorganisms by decreasing the viscosity of the gel layer, taking care of the copious amounts of mucus [22]—the big culprit in decreased mucociliary clearance in CRS discussed previously. On the other hand, the effectiveness of saline irrigation on ciliary beat frequency appears to be a bit controversial. Although no significant decline in ciliary beat frequency has been reported to exist initially, the later inhibited, perhaps even overwhelmed, cilia does beat more slowly [13, 23]. This means, however, that simply slowed cilia has the potential to regain its beating capabilities with a little help. Studies have demonstrated that airway cilia are stimulated by ATP-dependent intracellular calcium release and inhibited by extracellular sodium blocking the ATP-gated channels permeable to calcium [22, 24, 25]. This alone would lead one to question the efficacy of saline solutions on ciliary beat frequency, in general. Interestingly enough, however, there have been numerous reports on saline, specifically saline with higher tonicities, stimulating ciliary beat frequency. As such, Wabnitz et al. found that 3% saline increases ciliary beat frequency within 5 minutes after administration in comparison to physiologic saline, but it does not affect the measurements between hypertonic and normal saline after 60 minutes [22]. Increasing hypertonicity further then leads to ciliostasis in in vitro tissue from CRS patients without comorbidities, which is reversible at 7% tonicity but irreversible at 14% tonicity [26]. On the contrary, in the presence of normal saline or hypotonic saline, ciliary beat frequency has been shown to remain constant or even decrease [26, 27]. This may lead to the speculation that the positive effects of saline irrigation may in fact not be due to an alteration in ciliary beat frequency, but mainly in the properties of the mucus layer. The previously increased viscosity of the gel layer may be decreased by the additional fluid, with higher osmolarities attracting larger quantities of fluid from adjacent compartments [22]. The decreased viscosity, in turn, would lead to improved mucociliary clearance and increased ciliary beat frequency by sheer regained ease of motility. If, however, inhibiting sodium ions were to be removed from the solution, the solution may affect the actual ciliary beat frequency after all; exactly this was done in a study by Bonnomet et al. The study compared the effects of non-diluted seawater, diluted seawater, and normal saline, in addition to a control group, on ciliary beat frequency [28]. The seawater solutions were isotonic after removing NaCl but preserving the water's natural minerals at full capacity and one-third, respectively. Similar to the above-mentioned decrease in ciliary beat frequency in the presence of normal saline, normal saline reduced half of the cultures ciliary beat frequency to be indeterminable [28]. Non-diluted and

diluted seawater, however, both improved ciliary beat frequency significantly in comparison to normal saline and the control group, with non-diluted seawater significantly outperforming diluted seawater as well [28]. From a physiological standpoint, saline as well as seawater solutions show to be efficacious in improving CRS-related symptoms but due to diverging underlying mechanisms.

Patients

Although the use of saline nasal irrigation has been well established for the treatment of CRS in adults, few studies have been published on usage in children. This may be one factor why saline irrigation is underutilized and under "prescribed" by clinicians. There is one study which reported that up to 63% of children who suffer from chronic respiratory complaints may have CRS, suggesting under appreciation for an association between pulmonary and nasal dysfunction especially the "sinopulmonary reflex" [29]. The greatest barrier to the trial of saline irrigation in the pediatric population appears to be the same assumption by both physicians and parents: that "the child will not tolerate the treatment" [6, 30]. The perception of impaired tolerability precedes the willingness to try nasal saline irrigations and, hence, underutilization as first-line treatment for chronic nasal symptoms including for children who may progress to develop CRS. In fact, Jeffe and colleagues found that only 28% parents believed their child would tolerate the nasal rinse but supposed the tolerability would improve once the child was older [6]. This begs the questions, is saline irrigation safe for younger children and do they accept the treatment well? Two studies reviewed the use of saline nasal irrigation in children and recruited participants as young as 2 or 3 years of age. In both studies, authors found no significant differences in tolerability between age groups [6, 30]. Even when taken duration of treatment into consideration, children as young as 4 years old accepted and tolerated saline irrigations well for as long as six continuous weeks [2]. While the use of saline irrigation in a toddler may require more parental involvement and be more challenging compared to self-administration in a teenager, children may be more adaptable than expected by clinicians. A study by Chirico et al. showed that saline irrigations are even safe and well-accepted in neonates and infants [31, 32]. While the use of saline in neonates was not specific for CRS, it did demonstrate safe utilization of saline in early childhood. Minimal adverse effects have been reported in few participants regardless of age at application. These include sensation of "burning" during irrigation, ear fullness, few nose bleeds, and cough [30, 33]. In all cases, the benefits have been reported to outweighed risks and adverse effects.

Their symptoms necessary to establish a diagnosis of pediatric CRS are labeled "fuzzy" by most studies. However, Brietzke et al. published a consensus statement on pediatric CRS in 2014, and defined pediatric CRS as children who have "at least 90 continuous days of 2 or more symptoms purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough and either endoscopic signs of mucosal edema or

purulent drainage, and/or CT scan changes showing mucosal changes in a patient who is 18 years or younger" [34]. The most common comorbidities include allergic rhinitis, asthma, and gastroesophageal reflux—although these have been no consensus on gastroesophageal reflux being a contributory factor in pediatric CRS [2, 34]. Other factors such as cystic fibrosis and nasal polyps will be discussed later on.

Regardless of where in the disease process on this continuum of persistent symptoms, studies integrating cross-national treatment recommendations, assessing practice compliance with published guidelines, as well as national position papers on rhinosinusitis all support saline irrigation as first-line treatment in numerous countries [9, 35, 36]. Both adult and pediatric patients are likely to seek care first from their primary care provider. A 2017 study from the UK reported that while there is increased use of saline irrigation, authors stated that only 1% of surveyed CRS patients reported current use of saline rinses [35], yet Gulliford et al. reported a median of 91% of patients being prescribed systemic oral antibiotics for a diagnosis of rhinosinusitis by their primary care provider [37]. Not only have antibiotics been reported to be ineffective in the treatment of CRS, their continued use when not indicated continues to increase antibiotic resistance globally. Similarly, surveys of the American Rhinologic Society and American Society of Pediatric Otolaryngologists showed that nasal steroid sprays are used by slightly more physicians than saline irrigations and that 57% of physicians still administer oral antibiotics [38, 39]. What warrants consideration is also the prominent use of nasal steroids. Parents, caretakers, and even patients have been reported to develop reservations about long-term use of steroids, or "cortisone phobia" reported by Kaschke [9]. As a non-pharmacological agent without side effects, the use of nasal saline irrigations as first-line treatment for CRS will minimize the need for dependence on medications including nasal steroid and others.

Adenoidectomy has been a procedure believed to be appropriate and effective for children with CRS [38, 39]. It is so common that 63% of the aforementioned survey participants stated they performed three or more adenoidectomies for pediatric CRS monthly [38]. The most concerning long-term consequence being discussed here is the continued facial skeletal development in young children and the impact the surgery may have on it [30, 34]. Even if that is unlikely to be a concern, recent recommendations by both the Food and Drug Administration (FDA), supported by American Society of Anesthesiology (ASA), on minimizing exposure of general anesthesia in early childhood for elective surgeries, supports more judicious decision making and recommendation for surgical intervention. The FDA cautions that repeated or lengthy surgical procedures may affect the child's brain development, as indicated by numerous animal studies [40]. The ASA supported this statement by pointing towards studies showing difficulties in learning or behavior following prolonged or repeated exposure to anesthetics in children, yet a potential negative impact on cognitive development was to remain uncertain [41]. Specific guidelines for medical versus surgical interventions have already been established in countries such as the UK that state medical management needs to be employed for at least 3 months before a surgical referral [35]. Additionally, in the USA many insurance companies require preoperative confirmation of hypertrophied adenoids in children

under the age of 5, using CT or office-based awake nasopharyngoscopy before approving surgical coverage [42–44], adding either radiation exposure or emotional distress to the child's disease process should surgery be considered.

Most studies reporting significant symptom and quality of life improvements used saline irrigations daily for 4–8 weeks [2, 30, 45, 46]. Children were instructed to rinse their noses one to three times per day, and regardless of whether saline was used alone or in conjunction with another therapy, such as anti-histamines, or irrigating post-surgically, the scores were improved when compared to therapies without saline [47–49]. Efficacy and improved outcome from daily use over multiple weeks has been reported by Hong et al., as in their study the poorly compliant children showed significantly less improvement in comparison to the more compliant children [30]. The most common outcomes reported in studies assessing the efficacy of saline irrigation included subjective reports of symptom relief in terms of nasal congestion, nasal secretions, cough, and emotional stress, as well as objective measures using sinonasal or other Quality of Life surveys and or opacification on CT scans [1, 2, 33]. After completion of treatment, many studies reported that patients continued to use the irrigation on an as needed basis with continued efficacy [2, 6]. Pham et al. reported on long-term outcomes using saline irrigation in children, and found that less than 10% of subjects with pediatric CRS required endoscopic sinus surgery due to persistent symptoms [2]. A review of saline irrigation after endoscopic surgery of paranasal sinuses showed reduced edema, crusting, and secretions after creating sufficient sinus ostial openings when irrigations were employed [48].

In addition to its effectiveness when treating pediatric CRS, use of saline irrigation for the treatment of symptoms due to allergic rhinosinusitis (ARS) warrants mentioning even if controversial. Few studies have focused the use of saline rinses in pediatric ARS, but Wang and colleagues showed an increase in Quality of Life scores and decrease in ARS symptoms in children after adding daily saline irrigation to standard treatment for 3 weeks [50]. However, the European guidelines on the treatment of ARS continue to exclude nasal saline irrigation as a recommended treatment option. A more recent publication considering American as well German databases came to the conclusion that it may not be appropriate yet to indorse saline rinses in cases of ARS based on the lack of previous substantiated study results demonstrating significant benefits in comparison to standard therapies alone [9]. It is, therefore, necessary to expand the research on saline rinses in ARS before consensus is achieved.

How to Use and Types of Irrigation Devices

Once providers and patients agree to a trial of nasal saline irrigation, both need to know how and which device to use. The most effective method of using saline agree on using a device which can deliver large-volume solutions (>100 ml) at low pressures and is easy to use [9, 48, 51, 52]. Although not distinguishing between

volumes, a study adding a radioactive solution to saline and measuring solution distribution within the sinuses showed that nasal douching was significantly more effective than nasal spray and a nebulizer [53]. As mentioned already, the greatest barrier in using saline rinses in children is the assumption by both parents and physicians that the child will not tolerate its use [6, 30]. It is important for healthcare providers to explain to parents and caretakers that the majority of children will likely need a few days and multiple attempts before getting used to saline irrigation. Jeffe et al. reported that only 14% of children accepted the irrigation after the first attempt, yet 73% accepted it within 1 week of continuous use as reported by the parents [6]. Thus, to be successful parents and children need to be encouraged to keep trying and appropriate expectations are set. Second, it may be beneficial to not only explain or demonstrate the technique of irrigation devices, but also have the child do a "test-run" in the office to confirm understanding and execution prior to going home [52]. This way, parents' doubts may also be alleviated by watching their child performing the task on their own. The greatest barrier reported by children is the cumbersomeness of applying the irrigation every day [30]. Given easy access to social media, specifically "You Tube," children, parents, and physicians/providers can easily reference or view the actual irrigation on personal electronic devices and phones.

Devices and techniques are plentiful, but the head position achieving the greatest distribution of solution appears to be the vertex down position (Fig. 14.1). If this can physically not be accomplished, the nose-to-sink position would be the next best option [48]. Based on the senior author's clinical experience, in children it is best and least traumatic for both patients and parents to use the nose-to-sink position and minimize choking and sensation of "drowning" as preschool aged children often have not mastered "breath-holding" and swimming.

Based on various efficiencies reported in studies, squeeze bottles and Neti pots seem to deliver the best results; but what do patients say? Based on a comprehensive Amazon.com search (Fig. 14.2), reviewing available systems and their reviews, the squeeze bottle and Neti pot are the most popular, with the squeeze bottle winning the race by a small margin. Both devices are reusable after sufficient cleaning and

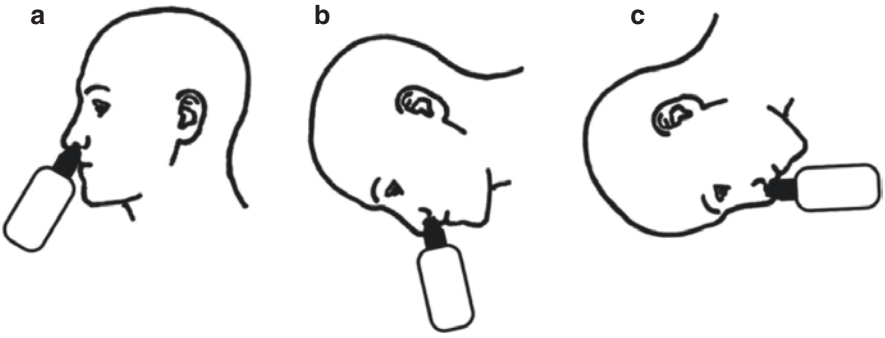


Fig. 14.1 The position of the head during irrigation: (**a**) neutral upright position, (**b**) nose-to-sink position, and (**c**) vertex down position [48]

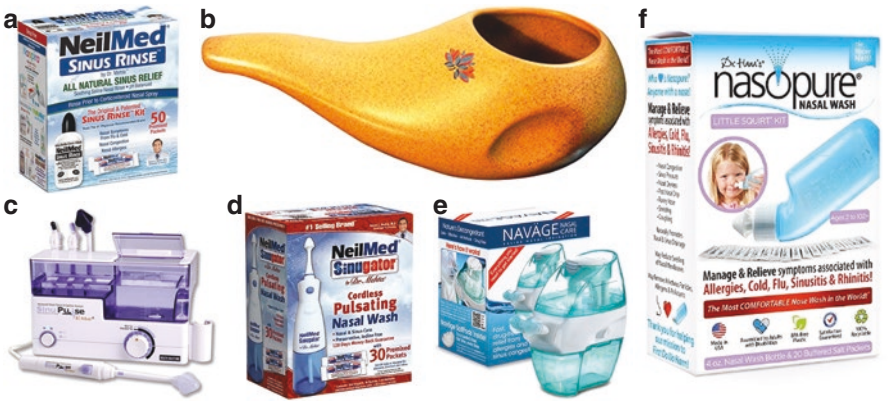


Fig. 14.2 Irrigation systems (advertising images): (**a**) NeilMed Sinus Rinse, squeeze bottle [54]. (**b**) Ceramic Neti Pot [56]. (**c**) SinuPulse Advanced Nasal Sinus Irrigation System [57]. (**d**) NeilMed Sinugator Pulsating Nasal Watch [59]. (**e**) Navage Nasal Irrigation [58]. (**f**) Nasopure squeeze bottle for kids [60]

affordable; the squeeze bottle can be purchased for $10.39, and it comes with the plastic bottle and 50 premixed packets [54]; the Neti pot is available in stainless steel or ceramic constructions, and according to the instructions, patients can use either Neti-pot salt or non-ionized salt mixed with water [55, 56]. The device costs between $20 and $30, but the stainless steel version may exhibit rusting if not cleaned properly.

Other devices which also received overall good reviews are a fully automated, electric irrigation system, a NeilMed pulsating nasal wash that the description compares to an electric toothbrush, and a recent "Navage system" pushes the solution in one nostril and sucks the irrigant out the other nostril as compared to only pushing the solution in and passively allowing irrigant to come out. This has been gaining favor with patients and families, especially in children. The electric irrigation system and Navage are in a head-to-head competition when it comes to overall customer ratings; at $70–$80, the biggest critique of the electric system is its ease of breaking for some customers [57], whereas at $90 the Navage system loses points for continuously requiring the purchase of fitting pods at an additional expense [58]. The NeiMed pulsating nasal wash loses the race in terms of customer reviews based on the poor construction and short life of the device; at about $25, it is not the most expensive apparatus available, but for the customers the negatives outweighed the positives in this case [59]. For children, in particular, the squeeze bottle kits are available as a pediatric version, which is a 4-ounce bottle instead of the 8-ounce bottle, and allows smaller hands greater ease of control and use for children to self-irrigate [60]. Neti pots, although not available as a distinct pediatric Neti pot, can also be used by children themselves. Even though "it may look scary" children are capable of using them safely once they try [61]. The Navage system, however, is cleared by the FDA and Health Canada only for children ages 12 and older [62].

For instructional purposes on a children's level, these YouTube videos show children performing and explaining how to use a squeeze bottle and a Neti pot. If your child is afraid to try using a saline irrigation system, it may help watching another child do it also.

- Squeeze bottle https://www.youtube.com/watch?v=uK6YWj85huI
- Neti pot https://www.youtube.com/watch?v=2V3DtOJM23g

Lastly, there is a concern about bacterial contamination of the devices due to their repeated use and subsequent introduction of the bacteria into the nasal airways. Upon investigating the devices bacterial flora, studies found that bacteria did in fact grow quite rapidly inside the apparatuses post usage [51, 63]. Interestingly, however, the solution in the bottle did not get contaminated [64]. In order to exercise best practices and be on the safe side, it is recommended to microwave the devices prior to every use. Although microwave duration of 120 seconds at 700 watts exhibited the best disinfection results, the plastic of the squeeze bottle began deforming [51]. Thus, the recommendation settled on 90 seconds at 700 watts to achieve the best balance between cleaning and preserving the bottle. It is critical for parents and caretakers to be fully aware of any risks associated with the use of microwave and the heating of plastic objects, especially risk of burns due to any solutions being "microwaved." If any microwave is used, we are referring only to the cleaning of the devices, NEVER for the act of irrigating. Besides using a microwave, devices should be cleaned after every use, using hot water and antibacterial soap [65]. Furthermore, nasal irrigation should only be performed with sterile or distilled water purchased in stores [66]. Tap water which has been boiled for 3–5 minutes and cooled to lukewarm temperature is a good alternative; previously boiled water to be used within 24 hours can be stored in a closed container [66]. Non-boiled tap water has the potential to contain amoeba which, upon rinsing one's nose, can enter the brain and cause detrimental neurological infections. Although this is extremely rare, two deaths in 2011 may have reportedly been related to the use of Neti pots with non-bailed tap water [67].

Tonicity of Irrigation Solution

Physiological mechanism of nasal saline irrigations and how different tonicities affect the components of mucociliary clearance has been discussed earlier. However, there has been a long-standing debate on the optimal tonicity of the irrigation solution. Overall, isotonic as well as slightly hypertonic solutions have been reported most commonly to be both safe and effective in reducing the symptoms related to pediatric CRS. Shoseyov and colleagues compared 0.9% normal saline with 3.5% hypertonic saline in children with CRS [45]. Both groups exhibited significant improvements in a decrease of post-nasal drip and nasal secretions with no

statistically significant difference between groups. Only the cough and radiological scores saw greater improvements with the hypertonic solution [45]. Considering that both groups experienced significant symptom relief and increased comfort, the authors did not conclude one solution to be advantageous over the other. For children to accept and use these rinses comfortably, however, hypertonic irrigation was associated with higher reporting of nasal burning and irritation [9, 45]. Even at 3.5% children reported nasal discomfort for the first 3–4 days of irrigation [45]; the burning and itching sensation ceased subsequently but can initially cause potential distress in both children and parents. When using hypertonic saline rinses, it is therefore recommended not to exceed 3.5%, with 2% appearing to be a nice, effective compromise in the middle [9]. Concentrations greater than 3.5% can lead to severe irritation and harmful effects on mucociliary clearance [9]. Hypotonic solutions, on the other hand, have not been effective in increasing mucociliary clearance [9, 22]. Thus, choosing between normal and slightly hypertonic saline may depend on the patient's comfort and experience with the solution. As both tonicities have shown to be effective and safe for pediatric CRS, parents can rest assured by the possibility of adjusting the tonicity if necessary.

Besides tonicity, saline irrigations for CRS have also been investigated in combination with a number of additives. Probably the most popular combination, saline with topical steroids—steroid irrigations—was comprehensively reviewed for the use in CRS after endoscopic sinus surgery. This meta-analysis included 12 studies and concluded that steroid irrigation did not differ from saline irrigation alone in terms of symptom relief, quality of life, and endoscopic findings [49]. A recent study reported a clinical significance in favor of adding budesonide to high-volume saline rinses as compared to saline alone for treating adults with CRS; they, however, failed to establish a statistically significant difference between outcomes in the two groups and presented inconsistent methods and results, leading to an inconclusive report [68]. Thus, the addition of steroids to nasal rinses is not warranted. Similarly, adding antibiotics to nasal rinses does not improve the efficacy of the irrigation. A study comparing saline only to saline plus gentamicin rinses exhibited equally positive results for improved CT and quality of life scores [33]. The antibiotics did not add any benefits to the irrigation, and it is therefore not necessary to expose children to further antibiotics. Continuing this trend, adding an anti-fungal to nasal irrigations does not contribute any additional benefits. Although there have been theories implementing the possibility of fungal spores contributing to CRS, multiple studies have shown that an additive antifungal medication, such as amphotericin B, does not increase the efficacy of nasal rinses over saline alone [69, 70]. Use of antifungal agents may be helpful for a specific population of children with "allergic fungal sinusitis," which is most prevalent in the south and southeast. More will be discussed on AFS in the next section. Altogether, it appears that saline by itself is just as effective as saline with any of the described additives at relieving symptoms, improving endoscopic scores as well as the quality of life and, therefore, mitigates the need of subjecting children with CRS to these medications.

Special Considerations

Some patients may not exhibit the most classical presentation of CRS, such as the presence of nasal polyps, and some may have an underlying disease in which CRS is just one of the presenting symptoms; these special situations, also, deserve our attention. Upon performing an endoscopic examination, a portion of patients may have CRS with nasal polyps, clinical consensus statement agreed that CRS with nasal polyps in children should be treated differently than CRS without polyps [34]. In fact, the vast majority of research shows that topical corticosteroid irrigations are favored in the presence of nasal polyps [36, 71, 72]. In comparison to simple CRS, in which steroid solutions did not achieve results different from saline only rinses, CRS with nasal polyps benefits from the addition of corticosteroids. Two comprehensive meta-analyses representing the current clinical positions in the USA as well as in Europe showed that the use of topical steroid rinses with, again, large volume, low-pressure devices attained the greatest reduction in polyp size and was, therefore, recommended [36, 73].

CRS is also commonly present in patients with cystic fibrosis (CF). The disease mechanism of CRS in CF is different, however, than in "normal" CRS. CF patients possess a mutated cystic fibrosis transmembrane conductance regulator gene which affects chloride ion channel function in the nose, leading to very viscous, desiccated mucus, impairing the mucociliary clearance severely [74, 75]. This, in turn, leads to increased infections and inflammation. Whereas in non-CF CRS, physiologic or hypertonic saline irrigations have both shown to be effective, in CF-CRS patients this debate is still controversial. Some studies say that CF-CRS is preferably combated with hypertonic saline rinses [76, 77]. As described earlier, the hypertonicity attracts even more fluid to the applied area, which is even more so needed in the markedly dried-out mucus in CF. This benefit of hypertonic saline may be balanced by the potential adverse effects of burning and itching children may experience. On the other hand, some studies show that physiological saline is just as efficacious as hypertonic saline [77] and that especially in pediatric patients, the effects of hypertonic saline are not as great as in adult patients [76]. Physiologic saline may, therefore, still be beneficial in terms of removing mucus and crusts and has improved quality of life scores significantly in comparison to no nasal irrigation.

The final special form of CRS deserving our attention is allergic fungal rhinosinusitis or allergic fungal sinusitis (AFS); here, eosinophilic mucin with fungal hyphae is present in the nasal airways [78]. While in CRS with nasal polyps and CF CRS a trial of conservative medical treatment is recommended before advancing to surgical interventions [36, 74], in AFS, surgical treatment should be the first line of treatment followed by additive medical therapies [36]. Post-surgically, AFS appears to benefit from a similar medical intervention as CRS with nasal polyps—namely topical corticosteroid irrigations [36, 78]. This was shown by two extensive literature reviews discussing the recommended treatment of AFS. One review even presented that steroid irrigations reduced the recurrence rate of AFS from 50% with no treatment to 15% with treatment [36]. Recent studies have begun investigating the

utility of adding fluconazole to saline irrigations to treat AFS sinuses with a topical antifungal postoperative. Although the evidence is limited, 75% of patients using topical antifungal irrigation showed disease improvement after 3 months of continuous use in one study [79], and only 10% of patients had a recurrence of AFS after 9 months of antifungal irrigation in another study [80]. Thus, although additives to saline irrigations may not show increased benefits in simple CRS, the addition of corticosteroids may be warranted in under special circumstances.

Conclusion

Saline irrigation is safe and appropriate as both first-line treatments for pediatric chronic rhinosinusitis. Despite current and past research evidence demonstrating efficacy, it is likely still underutilized in children. Increase in awareness and use may result from newly available and a variety of commercial irrigation devices.

References

1. Wei JL. Chronic nasal dysfunction in children: Allergic rhinitis? Infectious? What to do if neither? Curr Opin Otolaryngol Head Neck Surg. 2015;23(6):491–8.
2. Pham V, Sykes K, Wei J. Long-term outcome of once daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. Laryngoscope. 2014;124(4):1000–7.
3. Kim JH, Cho C, Lee EJ, Suh YS, Choi BI, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in South Korea according to diagnostic criteria. Rhinology. 2016;54(4): 329–35.
4. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy. 2011;66(9):1216–23.
5. Gallant JN, Basem JI, Turner JH, Shannon CN, Virgin FW. Nasal saline irrigation in pediatric rhinosinusitis: a systematic review. Int J Pediatr Otorhinolaryngol. 2018;108:155–62.
6. Jeffe JS, Bhushan B, Schroeder JW Jr. Nasal saline irrigation in children: a study of compliance and tolerance. Int J Pediatr Otorhinolaryngol. 2012;76(3):409–13.
7. Psaltis AJ, Foreman A, Wormald PJ, Schlosser RJ. Contamination of sinus irrigation devices: a review of the evidence and clinical relevance. Am J Rhinol Allergy. 2012;26(3):201–3.
8. Barham HP, Harvey RJ. Nasal saline irrigation: therapeutic or homeopathic. Braz J Otorhinolaryngol. 2015;81(5):457–8.
9. Achilles N, Mosges R. Nasal saline irrigations for the symptoms of acute and chronic rhinosinusitis. Curr Allergy Asthma Rep. 2013;13(2):229–35.
10. Bronchiectasis Toolbox. Airway clearance in the normal lung. http://bronchiectasis.com.au/physiotherapy/principles-of-airway-clearance/airway-clearance-in-the-normal-lung. Accessed 21 Mar 2018.
11. Rusznak C, Devalia JL, Lozewicz S, Davies RJ. The assessment of nasal mucociliary clearance and the effect of drugs. Respir Med. 1994;88(2):89–101.
12. Sakakura Y, Majima Y, Harada T, Hattori M, Ukai K. Nasal mucociliary transport of chronic sinusitis in children. Arch Otolaryngol Head Neck Surg. 1992;118(11):1234–7.
13. Braverman I, Wright ED, Wang CG, Eidelman D, Frenkiel S. Human nasal ciliary-beat frequency in normal and chronic sinusitis subjects. J Otolaryngol. 1998;27(3):145–52.

14. Al-Rawi MM, Edelstein DR, Erlandson RA. Changes in nasal epithelium in patients with severe chronic sinusitis: a clinicopathologic and electron microscopic study. Laryngoscope. 1998;108(12):1816–23.
15. Williams R, Rankin N, Smith T, Galler D, Seakins P. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. Crit Care Med. 1996;24(11):1920–9.
16. Kahana-Zweig R, Geva-Sagiv M, Weissbrod A, Secundo L, Soroker N, Sobel N. Measuring and characterizing the human nasal cycle. PLoS One. 2016;11(10):e0162918.
17. Soane RJ, Carney AS, Jones NS, Frier M, Perkins AC, Davis SS, et al. The effect of the nasal cycle on mucociliary clearance. Clin Otolaryngol Allied Sci. 2001;26(1):9–15.
18. Maddux SD, Yokley TR, Svoma BM, Franciscus RG. Absolute humidity and the human nose: a reanalysis of climate zones and their influence on nasal form and function. Am J Phys Anthropol. 2016;161(2):309–20.
19. Astrand AB, Hemmerling M, Root J, et al. Linking increased airway hydration, ciliary beating, and mucociliary clearance through ENaC inhibition. Am J Physiol Lung Cell Mol Physiol. 2015;308(1):L22–32.
20. Harvard Health Publishing. What to do about sinusitis. 2018. https://www.health.harvard.edu/diseases-and-conditions/what_to_do_about_sinusitis. Accessed 21 Mar 2019.
21. Zhao K, Blacker K, Luo Y, Bryant B, Jiang J. Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance. PLoS One. 2011;6(10):e24618.
22. 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(5):803–5.
23. Nuutinen J, Rauch-Toskala E, Saano V, Joki S. Ciliary beating frequency in chronic sinusitis. Arch Otolaryngol Head Neck Surg. 1993;119(6):645–7.
24. Friedman M, Hamilton C, Samuelson CG, et al. Dead Sea salt irrigations vs saline irrigations with nasal steroids for symptomatic treatment of chronic rhinosinusitis: a randomized, prospective double-blind study. Int Forum Allergy Rhinol. 2012;2(3):252–7.
25. Friedman M, Vidyasagar R, Joseph N. A randomized, prospective, double-blind study on the efficacy of dead sea salt nasal irrigations. Laryngoscope. 2006;116(6):878–82.
26. Boek WM, Keles N, Graamans K, Huizing EH. Physiologic and hypertonic saline solutions impair ciliary activity in vitro. Laryngoscope. 1999;109(3):396–9.
27. Luk CK, Dulfano MJ. Effect of pH, viscosity and ionic-strength changes on ciliary beating frequency of human bronchial explants. Clin Sci (Lond). 1983;64(4):449–51.
28. Bonnomet A, Luczka E, Coraux C, de Gabory L. Non-diluted seawater enhances nasal ciliary beat frequency and wound repair speed compared to diluted seawater and normal saline. Int Forum Allergy Rhinol. 2016;6(10):1062–8.
29. Nguyen KL, Corbett ML, Garcia DP, et al. Chronic sinusitis among pediatric patients with chronic respiratory complaints. J Allergy Clin Immunol. 1993;92(6):824–30.
30. Hong SD, Kim JH, Kim HY, Jang M-S, Dhong H-J, Chung S-K. Compliance and efficacy of saline irrigation in pediatric chronic rhinosinusitis. Auris Nasus Larynx. 2014;41(1):46–9.
31. Chirico G, Quartarone G, Mallefet P. Nasal congestion in infants and children: a literature review on efficacy and safety of non-pharmacological treatments. Minerva Pediatr. 2014;66(6):549–57.
32. Chirico G, Beccagutti F. Nasal obstruction in neonates and infants. Minerva Pediatr. 2010;62(5):499–505.
33. 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(9):1989–2000.
34. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
35. Philpott C, Erskine S, Smith R, et al. Current use of baseline medical treatment in chronic rhinosinusitis: data from the National Chronic Rhinosinusitis Epidemiology Study (CRES). Clin Otolaryngol. 2018;43(2):509–24.

36. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol. 2012;50(Suppl23):1–298.
37. Gulliford MC, Dregan A, Moore MV, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ Open. 2014;4(10):e006245.
38. Beswick DM, Messner AH, Hwang PH. Pediatric chronic rhinosinusitis management in rhinologists and pediatric otolaryngologists. Ann Otol Rhinol Laryngol. 2017;126(9): 634–9.
39. Beswick DM, Ramadan H, Baroody FM, Hwang PH. Practice patterns in pediatric chronic rhinosinusitis: a survey of the American Rhinologic Society. Am J Rhinol Allergy. 2016;30(6):418–23.
40. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. 2016; https://www.fda.gov/Drugs/DrugSafety/ucm532356.htm. Accessed 21 Mar 2019.
41. American Society of Anesthesiologists. ASA Response to the FDA Med Watch Warning - December 16, 2016. 2016; https://www.asahq.org/advocacy/fda-and-washington-alerts/washington-alerts/2016/12/asa-response-to-the-fda-med-watch. Accessed 7/26/18.
42. AmeriHealth Caritas Pennsylvania. Clinical policy title: tonsillectomy and (or) adenoidectomy in children less than 5 years old 2016; https://www.amerihealthcaritaspa.com/pdf/provider/resources/clinical/policies/110304-tonsillectomy-or-adenoidectomy-children-less-than-5-years-old.pdf. Accessed 21 Mar 2019.
43. Keystone First. Clinical policy title: tonsillectomy and (or) adenoidectomy in children less than 5 years old 2016; https://www.keystonefirstpa.com/pdf/provider/resources/clinical/policies/tonsillectomy-and-adenoidectomy-children-less-than-5.pdf. Accessed 21 Mar 2019.
44. Emblem Health. Tonsillectomy/adenoidectomy. 2018; https://www.emblemhealth.com/~/media/Files/PDF/_med_guidelines/MG_Tonsilectomy_Adenoidectomy.pdf. Accessed 7/26/18.
45. Shoseyov D, Bibi H, Shai P, Shoseyov N, Shazberg G, Hurvitz H. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. J Allergy Clin Immunol. 1998;101(5):602–5.
46. Cho HJ, Min HJ, Chung HJ, et al. Improved outcomes after low-concentration hypochlorous acid nasal irrigation in pediatric chronic sinusitis. The Laryngoscope. 2016;126(4):791–5.
47. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev. 2007;3:Cd006394.
48. de Paiva Leite SH, Douglas RG. How does sinus surgery affect topical irrigation distribution? Curr Opin Otolaryngol Head Neck Surg. 2018;26(1):21–6.
49. Yoon HY, Lee HS, Kim IH, Hwang SH. Post-operative corticosteroid irrigation for chronic rhinosinusitis after endoscopic sinus surgery: A meta-analysis. Clin Otolaryngol. 2018;43(2):525–32.
50. Wang Y-H, Yang C-P, Ku M-S, Sun H-L, Lue K-H. Efficacy of nasal irrigation in the treatment of acute sinusitis in children. Int J Pediatr Otorhinolaryngol. 2009;73(12):1696–701.
51. Nikolaou E, Mitsi E, Ferreira DM, Bartolo A, Leong SC. Assessing the ideal microwave duration for disinfection of sinus irrigation bottles-A quantitative study. Clin Otolaryngol. 2018;43(1):261–6.
52. Lin SY, Baugher KM, Brown DJ, Ishman SL. Effects of nasal saline lavage on pediatric sinusitis symptoms and disease-specific quality of life: a case series of 10 patients. Ear Nose Throat J. 2015;94(2):E13–8.
53. Wormald PJ, Cain T, Oates L, Hawke L, Wong I. A comparative study of three methods of nasal irrigation. Laryngoscope. 2004;114(12):2224–7.
54. Neil Med Sinus Rinse Complete Kit. https://www.amazon.com/dp/B000RDZFZ0/?coliid=IH03ZN5IJCTCI&colid=321ZX3Y1FRJZB&psc=0&ref_=lv_ov_lig_dp_it. Accessed 21 Mar 2019.

55. Neti Pot | Nasal Wash System | Nasal Rinse | Sinus Rinse (18 Oz.) made of high quality Unbreakable Stainless Steel for Sinus Congestion (Ayurvedic JalNeti). https://www.amazon.com/dp/B01IJWECFY/?coliid=I2F096IKQCT685&colid=321ZX3Y1FRJZB&psc=0&ref_=lv_ov_lig_dp_it. Accessed 21 Mar 2019.
56. Sattvic path ergonomically designed hand-made ceramic neti pot, clay brown. https://www.amazon.com/dp/B00YTEPKJ4/ref=sspa_dk_detail_4?pd_rd_i=B00YTEPKJ4&pd_rd_wg=XT1Wf&pd_rd_r=3QSWP2NP25GVPEWFXCXK&pd_rd_w=XpYQ4&th=1. Accessed 21 Mar 2019.
57. Sinupulse elite advanced nasal sinus irrigation system. https://www.amazon.com/dp/B001CWT4JI/?coliid=IO2DMNWKELPR&colid=321ZX3Y1FRJZB&psc=0&ref_=lv_ov_lig_dp_it. Accessed 21 Mar 2019.
58. Navage nasal irrigation basic bundle: navage nose cleaner and 18 SaltPods. https://www.amazon.com/dp/B074HGG576/?coliid=ICB1VKP0GODP&colid=321ZX3Y1FRJZB&psc=0&ref_=lv_ov_lig_dp_it. Accessed 21 Mar 2019.
59. NeilMed Sinugator Cordless Pulsating Nasal Wash with 30 Premixed Packets. https://www.amazon.com/dp/B005UO6NRA/?coliid=I3GRR29E3N5MLN&colid=321ZX3Y1FRJZB&psc=0&ref_=lv_ov_lig_dp_it. Accessed 21 Mar 2019.
60. Dr. Hana's Nasopure "The Nicer Neti Pot for Kids | Little Squirt Kit | 4 Ounce Bottle with 20 Buffered Salt Packets | Nasal Irrigation for Natural Allergy Relief. https://www.amazon.com/Nasopure-Nicer-Sinus-Rinse-Ounce/dp/B002D6RJSK. Accessed 21 Mar 2019.
61. Williams D. Mom nose best: Neti pots for kids. 2009; https://inhabitat.com/inhabitots/neti-pots-for-kids-are-you-kidding-me/. Accessed 21 Mar 2019.
62. Navage nasal care: frequently asked questions. https://www.navage.com/category-s/37.htm#children. Accessed 21 Mar 2019.
63. 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(4):458–63.
64. 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(3):197–9.
65. Cleveland Clinic. Safe Neti pot use: 3 tips. https://health.clevelandclinic.org/safe-neti-pot-use-3-tips/. Accessed 21 Mar 2019.
66. U.S. Food and Drug Administration. Is rinsing your sinuses with neti pots safe? https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm316375.htm. Accessed 21 Mar 2019.
67. Live Science. 'Brain-eating amoeba' infections prompt warning about neti pots. https://www.livescience.com/22626-brain-eating-amoeba-neti-pots.html. Accessed 21 Mar 2019.
68. Tait S, Kallogjeri D, Suko J, Kukuljan S, Schneider J, Piccirillo J. Effect of budesonide added to large-volume, low-pressure saline sinus irrigation for chronic rhinosinusitis. JAMA Otolaryngology-Heand & Neck Surgery. 2018;144(7):605–12.
69. Jiang RS, Twu CW, Liang KL. Efficacy of nasal irrigation with 200 mug/mL amphotericin B after functional endoscopic sinus surgery: a randomized, placebo-controlled, double-blind study. Int Forum Allergy Rhinol. 2018;8(1):41–8.
70. 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(6):1122–8.
71. Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract. 2016;4(4):565–72.
72. Harvey RJ, Snidvongs K, Kalish LH, Oakley GM, Sacks R. Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. Int Forum Allergy Rhinol. 2018;8(4):461–70.
73. Rudmik L, Soler ZM. Medical therapies for adult chronic sinusitis: a systematic review. JAMA. 2015;314(9):926–39.

74. Mainz JG, Koitschev A. Management of chronic rhinosinusitis in CF. J Cyst Fibros. 2009;8(Suppl 1):S10–4.
75. Le C, McCrary HC, Chang E. Cystic fibrosis sinusitis. Adv Otorhinolaryngol. 2016;79:29–37.
76. Trimble AT, Whitney Brown A, Laube BL, et al. Hypertonic saline has a prolonged effect on mucociliary clearance in adults with cystic fibrosis. J Cyst Fibros. 2018;17(5):650–6.
77. Tipirneni KE, Woodworth BA. Medical and surgical advancements in the management of cystic fibrosis chronic rhinosinusitis. Curr Otorhinolaryngol Rep. 2017;5(1):24–34.
78. Gan EC, Thamboo A, Rudmik L, Hwang PH, Ferguson BJ, Javer AR. Medical management of allergic fungal rhinosinusitis following endoscopic sinus surgery: an evidence-based review and recommendations. Int Forum Allergy Rhinol. 2014;4(9):702–15.
79. Jen A, Kacker A, Huang C, Anand V. Fluconazole nasal spray in the treatment of allergic fungal sinusitis: a pilot study. Ear Nose Throat J. 2004;83(10):692–694–5.
80. Khalil Y, Tharwat A, Abdou AG, et al. The role of antifungal therapy in the prevention of recurrent allergic fungal rhinosinusitis after functional endoscopic sinus surgery: a randomized, controlled study. Ear Nose Throat J. 2011;90(8):E1–7.

Chapter 15
Medical Treatment of Pediatric Rhinosinusitis: Focus on Intranasal and Systemic Corticosteroids

Fuad M. Baroody

Rhinosinusitis is a commonly encountered problem in both pediatric and otorhinolaryngologic practices with a recent increase in the diagnosis of acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) in both adult and pediatric patients. This is likely a consequence of an improved understanding of the etiology, pathophysiology, and microbiology of the disease. The exact prevalence of the disease in children is difficult to determine as only a small percentage of cases present to the physician's office. A recent analysis of national survey databases between 2005 and 2012 showed that CRS accounted for 5.6 million visits per year among patients 0–20 years of age [1]. CRS was diagnosed in 2.1% of all visits, ARS in 0.6% and as comparators, allergic rhinitis in 2.6%, upper respiratory tract infections (URI) in 8% and otitis media in 6.7%. In a Swedish population-based study of 3112 adolescents, Westman and colleagues estimated the 12-month prevalence of CRS based on questionnaire to be 1.5% and, after clinical follow-up with objective confirmation, to be 0.3–0.8% [2]. Prevalence of radiologically confirmed rhinosinusitis in patients presenting with chronic respiratory complaints is much higher and approaches 30–60% depending on the sinuses involved with younger children having a higher rate of abnormal imaging than older adolescents [3, 4].

The mainstay of treatment of rhinosinusitis in children is medical with nasal saline irrigation, antibiotics, and anti-inflammatory therapy with corticosteroids as the most common therapies. In this chapter, we will present the evidence, when available, that supports the use of these agents in the treatment of both acute and chronic rhinosinusitis in the pediatric age group.

F. M. Baroody (✉)
Section of Otolaryngology-Head and Neck Surgery and Department of Pediatrics, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA
e-mail: fbaroody@surgery.bsd.uchicago.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_15

Intranasal Saline

Acute Rhinosinusitis Saline nasal irrigation has become mainstream in the treatment of rhinosinusitis in adults based on the presumption that it helps to clear debris and secretions from the nasal cavity. There is one trial in children that shows that adding saline versus placebo to decongestants and antibiotics in children with ARS resulted in greater improvement in nasal airflow and quality of life as well as better improvement of total symptom score [5]. Despite the lack of strong evidence, nasal saline irrigations are safe and are recommended if tolerated by the child with ARS.

Chronic Rhinosinusitis A Cochrane review analyzed randomized controlled trials in which saline was evaluated in comparison with either no treatment, a placebo, as an adjunct to other treatments, or against other treatments [6]. Overall there was evidence that saline is beneficial in the treatment of the symptoms of CRS when used as the sole modality of treatment. In a more recent trial, Wei and colleagues enrolled 40 children with CRS in a randomized, prospective, double-blind study comparing once daily irrigation with saline or saline/gentamicin for 6 weeks [7]. There were statistically significant improvements in quality of life scores at 3 and 6 weeks and a reduction of CT scores after 6 weeks in both groups with no significant difference between the groups, suggesting that the addition of gentamicin to saline irrigations provided no additional benefit. Contrary to what parents may think, saline irrigations were well tolerated by more than 80% of children and adolescents and when questioned, over 70% of patients/parents thought there was an improvement in nasal symptoms with irrigation [8]. Based on the above, saline nasal irrigation has become a mainstay of therapy of CRS in the pediatric age group [9].

Antibiotics

Acute Rhinosinusitis In the context of an upper respiratory tract infection, ARS can be diagnosed if there are persistent symptoms for more than 10 days, worsening of symptoms after initial improvement (double sickening), or severe symptoms at onset. The American Academy of Pediatrics guidelines recommend starting antibiotics when there is a severe onset of symptoms or worsening after initial improvement [10]. For persisting symptoms beyond 10 days, the guidelines recommend starting antibiotics or offering another 3 days of observation before doing so as symptoms might improve spontaneously [10]. A meta-analysis of randomized controlled trials evaluating antibiotic treatments for ARS, in which 3 of the 17 evaluated studies were performed in the pediatric age group, shows that antibiotics were associated with a higher rate of cure or improvement compared to placebo [11]. The rate of resolution of symptoms was faster with antibiotics in most randomized controlled trials. There are also a few trials where treatment with antibiotics in patients with ARS shows no added benefit over placebo [12, 13].

When considering antibiotic choices, one should keep in mind that over the past one to two decades, increasing resistance to antimicrobials has emerged among the organisms that are encountered in common upper respiratory infections in the pediatric age group. Furthermore, the routine use since 2000 of the 7-valent and, more recently, the 13-valent pneumococcal conjugate vaccine has been associated with a decrease in recovery of *S. pneumoniae* and an increase in recovery of *H. influenzae* [10, 14]. Extrapolating from what is known related to acute otitis media, it is estimated that *S. pneumoniae* and *H. influenzae* are currently each responsible for 30% of cases of ARS in children and *M. catarrhalis* for approximately 10%, also assuming that a quarter of aspirates, if done, would be sterile [10]. Risk factors for the presence of amoxicillin resistant organisms remain age under 2, recent antibiotic usage (within 30 days) and daycare attendance. Based on the above, the first-line treatment for uncomplicated ARS in a patient without risk factors remains amoxicillin at 45 mg/kg/day administered twice daily. Double that dose can be used in communities with higher incidences of *S. pneumoniae* resistance. In patients with severe disease or with risk factors for resistance, high dose amoxicillin clavulanate is recommended (dosed at 80–90 mg/kg/day of the amoxicillin component) and is also given twice daily. If the child will not tolerate PO antibiotics, ceftriaxone IV or IM at 50 mg/kg/day given as a single dose can be dosed for 1–3 days before switching to PO antibiotics to finish the course. Cephalosporins can be used in case of penicillin allergy and the favorite choices are cefdinir, cefuroxime, or cefpodoxime [15]. In case of lack of responsiveness and the suspicion of resistant organisms, a combination of clindamycin (or linezolid) and cefixime will provide the most comprehensive coverage for resistant *S. pneumoniae* and *H. influenzae*. Quinolones could also be used in exceptional circumstances [16]. Resistance trends of pneumococcus and *H. influenzae* to trimethoprim/sulfamethoxazole and azithromycin render their use unjustifiable in the treatment of ARS in patients with penicillin allergy [17, 18]. Duration of treatment varies widely, and a reasonable length would be for 7 days after the disappearance of symptoms, which usually averages about 10 days of therapy [10].

Chronic Rhinosinusitis There is no good evidence in the literature to support the use of antibiotics for CRS in children. Two clinical trials conducted by the same group do not show significant differences between treatment with placebo and systemic antibiotics in children with clinical criteria commensurate with CRS [19, 20]. The EPOS 2012 guidelines conclude as follows: "available data does not justify the use of short-term oral antibiotics for the treatment of CRS in children (Strength of recommendation: B)" [21]. In contrast, the consensus statement by the American Academy of Otolaryngology-Head and Neck Surgery supported the conclusion that "20 consecutive days of antibiotic therapy may produce a superior clinical response in pediatric CRS patients compared to 10 days of antibiotic therapy" [9]. In general clinical practice, antibiotics are used frequently as part of maximal medical management in children with CRS and treatment durations vary between 2 and 4 weeks. In many of these instances, treatment targets acute exacerbations on top of pre-existing chronic disease. The choice of antibiotics is similar to that described above for ARS.

Intravenous antibiotic therapy for resistant CRS has been advocated as an alternative to surgical intervention. Few studies evaluate this option [22] and they are limited by the presence of multiple variables that make it difficult to ascertain that the positive effect seen in CRS was related to the IV antibiotic use per se. Therefore, intravenous antibiotics are not routinely advocated for the treatment of CRS in children and are essentially reserved to treat the complications of ARS.

Intranasal Corticosteroids

Acute Rhinosinusitis The evidence for using INCS in acute rhinosinusitis is developing. Studies in adults with acute rhinosinusitis suggest that INCS may provide an additive benefit (versus placebo) when used in addition to antibiotic therapy [23, 24].

In the pediatric age group, Barlan et al. conducted a double-blind placebo-controlled trial in 89 children (age 1–15 years) with acute rhinosinusitis [25]. To be included in the study subjects had to have two of three major criteria (purulent nasal discharge, cough, purulent pharyngeal drainage) or one major and two minor criteria (facial pain, periorbital edema, earache, tooth pain, sore throat, headache, increased wheeze, fever, foul breath for more than 7 days). The children also had to have a positive Waters radiograph with complete opacification of the maxillary sinus or mucoperiosteal thickening >4 mm. All were treated with oral antibiotics; 43 also received intranasal budesonide (50 mcg), whereas 46 received a placebo saline spray. Budesonide was associated with greater improvements in nasal discharge and cough by the second week of treatment, but by the end of 4 weeks, both groups had a comparable improvement in symptom scores. In another pediatric study, children with ARS were treated with amoxicillin clavulanate with or without INCS and were stratified according to allergic rhinitis status [26]. There was no added benefit of using INCS in the patients with ARS without allergic rhinitis but in the rhinosinusitis with allergic rhinitis group, using an INCS improved the efficacy over the group with antibiotics alone.

Nayak and colleagues evaluated the effectiveness and safety of mometasone furoate nasal spray (MFNS) at two dose regimens as adjunctive treatment with oral antibiotics for ARS in a mixed population of adults and children (8–78 years of age) [27]. The diagnosis of ARS was made if the patients had purulent rhinorrhea with at least one moderate/severe nasal symptom (purulent rhinorrhea, congestion, post nasal drip, sinus headache, facial pain, cough). They also had to have the diagnosis confirmed by a CT scan. The study was multicenter, double-blind placebo controlled and enrolled 967 outpatients. All participants received amoxicillin/clavulanate for 21 days and either MFNS 200 mcg twice daily, MFNS 400 mcg twice daily or placebo nasal spray as adjunctive therapy. Both doses of MFNS resulted in significantly greater improvements in total symptom score compared to placebo which was significant by Day 4 of therapy and continued to be effective till day 21 of treat-

ment. Of note, is that both doses of MFNS used exceed the recommended dosage for allergic rhinitis in adults (200 mcg once daily) and children under age 12 years (100 mcg once daily).

To investigate the efficacy of INCS as monotherapy for ARS, Meltzer and colleagues conducted a randomized, placebo-controlled, double-blind, double-dummy trial in 981 patients older than 12 years with ARS [28]. Subjects were randomized to MFNS 200 mcg once daily or twice daily for 15 days, amoxicillin 500 mg three times daily for 10 days, or respective placebo. Subjects were recruited based on having uncomplicated rhinosinusitis based on symptoms (rhinorrhea, postnasal drip, nasal congestion/stuffiness, sinus headache, and facial pain/pressure/tenderness on palpation over the paranasal sinuses) for more than 7 days. The primary endpoint was mean (AM/PM) major symptom score over the 15-day treatment period. Mometasone furoate nasal spray 200 mcg twice daily (twice the allergic rhinitis dose) was significantly superior to placebo and amoxicillin at improving major symptom score. Starting on day 2, MFNS 200 mcg twice daily improved total symptom score throughout treatment versus amoxicillin and placebo. Although significantly superior to placebo, MFNS 200 mcg once daily was not superior to amoxicillin for the primary or secondary efficacy endpoints. In this study, amoxicillin was not shown to be more effective than placebo in controlling major symptom scores, a fact that has been previously demonstrated in placebo-controlled studies performed in both adults [29] and children [13].

In another prospective, randomized trial, children with ARS were treated with either antibiotics (amoxicillin clavulanate) and intranasal decongestants (xylometazoline) for 2 weeks ($n = 45$), or large volume low pressure nasal saline + fluticasone propionate combination (400 mcg of fluticasone diluted in 120 ml of saline twice daily) for 3 weeks ($n = 46$) [30]. Children in both treatment groups improved at the 21-day time point compared to baseline, and there were no significant differences between the groups in clinical scores, nasal peak inspiratory flow, or the radiologic resolution of ARS by Waters views.

Symptom scores tended to improve more quickly in the steroid irrigation group as a reduction from baseline was statistically significant at the 7-day time point whereas the antibiotic group symptom scores achieved significance compared to baseline at day 14. The only concern with this study is the use of saline irrigation in one arm but not in the other as it is conceivable that the more rapid improvement in the group with saline/steroid irrigations occurred because of the mechanical clearance effect of saline irrigation, not that of the intranasal steroid. Indeed, in children with CRS, saline nasal irrigation alone has been shown to be effective in resolving symptoms and CT findings of disease and the addition of gentamicin to the irrigation did not yield additional benefit [7].

Thus, there is some evidence in children that INCS are effective as adjuvants to antibiotics in the treatment of uncomplicated ARS, with one study showing the benefit specific to patients with concomitant allergic rhinitis. In studies including older children and adults, again the benefit of adding INCS to antibiotics was demonstrated but the doses of INCS used were higher than those approved for the treatment of allergic rhinitis in the pediatric age group. Finally, there is some evidence

supporting a high dose of INCS as monotherapy in patients with uncomplicated ARS. However, generalizing these conclusions to younger children is not justified in the absence of more evidence.

Chronic Rhinosinusitis INCS have become an important aspect of the treatment algorithm in light of increasing recognition of inflammation in the etiology of CRS. In a recent survey of pediatric otolaryngologists, Beswick and colleagues reported that 96% used nasal steroid sprays, 93% nasal saline irrigations, 91% oral antibiotics, and 43% oral steroids for maximal medical management of CRS in children [31]. In a similar survey of members of the American Rhinologic Society, the most frequently used therapies for maximal medical management of CRS in children were saline irrigation (97%), intranasal steroids (98%), oral antibiotics (90%), and oral steroids (72%) [32].

A Cochrane review evaluated the efficacy of intranasal steroids in CRS [33]. Eighteen randomized, controlled trials were included, with a total of 2738 participants. Fourteen studies had participants with nasal polyps and four studies had participants without nasal polyps. Only one study was conducted in children. Therefore, most evidence is inferred from patients with nasal polyps and does show some improvement in favor of intranasal steroids, especially as relates to the symptom of nasal congestion. The pediatric study included in this Cochrane review was primarily evaluating the safety of mometasone furoate nasal spray (MFNS) in children with nasal polyps [34]. Subjects aged 6–11 years with bilateral nasal polyps received MFNS 100 mcg once or twice daily or placebo; those aged 12–17 years received MFNS 200 mcg once or twice daily or placebo. Safety measures included a change in 24-h urinary free cortisol from baseline and change in 24-h urinary free cortisol. There were no differences between the treatment groups or placebo attesting to the safety of the intranasal steroid. Although the study was not powered for efficacy, information about polyp size, nasal symptoms, and investigator-evaluated therapeutic response was reported. MFNS given twice daily was associated with the greatest response in polyp size, congestion, and anterior rhinorrhea/postnasal drip. Groups that received MFNS once and twice daily showed numerically greater improvement in congestion compared with placebo. Moreover, subjects who received MFNS twice daily had better investigator assessed therapeutic response compared with those who received a placebo.

In the United States, it is the author's experience that most children with CRS present without nasal polyposis and the most frequent presentation of nasal polyps in children is in the context of cystic fibrosis or allergic fungal rhinosinusitis. Thus, the data from the above study are not very applicable to the typical presentation of pediatric CRS in the United States. However, the efficacy of INCS in CRS with/without polyps in adults, as well as their favorable safety profile, supports the recommendation that they be part of first-line therapy in children with CRS [9, 21].

Safety of INCS Most of the data available about the safety of INCS are from studies in patients with allergic rhinitis. The most common side effects are a result of local irritation and include dryness, burning, stinging, blood tinged secretions, and

epistaxis. The incidence of epistaxis with different preparations ranges from 4% to 8% over short treatment periods (2–12 weeks) with no differences between placebo and active therapy [35, 36]. In studies carried over a year, epistaxis is as high as 20% [37, 38]. Septal perforations are rare complications of INCS [39]. A systematic review of 34 published articles looking at biopsy studies in patients with allergic rhinitis or CRS using INCS did not show evidence of atrophy but a significant reduction in the odds ratio for the development of squamous metaplasia in patients using INCS, suggesting a favorable effect [40]. Studies in adults and children evaluating effects of INCS on the hypothalamic pituitary axis show no adverse effects [38, 41–52]. Although there has been a report of an association between the use of INCS and the development of posterior subcapsular cataracts [53], a systematic review of controlled trials did not demonstrate a clinically relevant impact of INCS on either ocular pressure, glaucoma, lens opacity, or cataract formation [54]. The effect of INCS on children's growth has been investigated in controlled studies using both knemometry in short-term studies (2–4 weeks) and stadiometry in long-term (12 months) studies. A meta-analysis of eight randomized controlled trials with appropriate controls showed that, compared to children using placebo, mean growth was significantly lower among children using INCS in trials using knemometry ($n = 4$) and that there was no significant growth difference in studies using stadiometry ($n = 4$) [55]. The data suggest that INCS might have deleterious effects on short-term growth in children, but the heterogeneity in the stadiometry studies makes the effects on long-term growth suppression unclear. Therefore, when using INCS in younger children, it is advisable to use the newer preparations that have been approved for the younger age groups (mometasone, fluticasone) and monitor growth carefully.

Systemic Steroids

Systemic steroids have also been used in children with CRS because of their potent anti-inflammatory properties. Ozturk and colleagues treated children with CRS with amoxicillin clavulanate for 30 days and with either a prednisone taper course for 15 days or placebo [56]. The steroid taper was given at the beginning of therapy. Compared to placebo, treatment with steroids resulted in significant improvements in CT scan score as well as symptoms of cough, nasal obstruction, postnasal discharge and total symptom score. In another study, primarily performed to evaluate mechanisms of inflammation in CRS, 30 children with asthma and CRS (mean age 9.1 years) were studied prospectively [57]. Sixteen were allergic and 14 were nonallergic. CRS diagnosis was confirmed by endoscopy showing purulence in the osteomeatal unit. All children were treated with amoxicillin-clavulanate and fluticasone propionate aqueous nasal spray (100 mcg daily) for 14 days; as well as a short taper course of oral corticosteroids for 10 days (deflazacort 1 mg/kg daily for 2 days, 0.5 mg/kg daily for 4 days, and 0.25 mg/kg daily for 4 days). Nasal lavage cytokine levels and cytology were evaluated before and after therapy. The results showed

normalized endoscopy in 25 children after treatment, a reduction in levels of IL4 in nasal lavages, as well as a significant reduction of the nasal inflammatory infiltrate in all the children. Although this study showed an improvement in clinical CRS after therapy, it is hard to glean the relative efficacy of systemic steroid administration as there was no placebo group and multiple other therapies were administered concomitantly. Therefore, evidence is scarce in support of systemic steroids in the treatment of CRS in the pediatric age group but using short courses is often added to other standard therapies.

In summary, corticosteroids are potent anti-inflammatory agents and are commonly utilized as adjuncts in the treatment of ARS and CRS in children. Antibiotics are frequently utilized and saline irrigations should be routinely included in the treatment of the child with chronic sinus problems.

References

1. Gilani S, Shin JJ. The burden and visit prevalence of pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2017;157(6):1048–52.
2. Westman M, Stjärne P, Bergström A, Kull I, Toskala E, Cardell LO, Wickman M, Holmström M. Chronic rhinosinusitis is rare but bothersome in adolescents from a Swedish population-based cohort. J Allergy Clin Immunol. 2015;136(2):512–4.
3. Van der Veken P, Clement PA, Buisseret T, Desprechins B, Kaufman L, Derde MP. CAT-scan study of the prevalence of sinus disorders and anatomical variations in 196 children. Acta Otorhinolaryngol Belg. 1989;43(1):51–8.
4. Nguyen KL, Corbett ML, Garcia DP, Eberly SM, Massey EN, Le HT, et al. Chronic sinusitis among pediatric patients with chronic respiratory complaints. J Allergy Clin Immunol. 1993;92(6):824–30.
5. Wang YH, Yang CP, Ku MS, Sun HL, Lue KH. Efficacy of nasal irrigation in the treatment of acute sinusitis in children. Int J Pediatr Otorhinolaryngol. 2009;73(12):1696–701.
6. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane database of systematic reviews (Online). 2007(3):CD006394.
7. 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(9):1989–2000.
8. Jeffe JS, Bhushan B, Schroeder JW Jr. Nasal saline irrigation in children: a study of compliance and tolerance. Int J Pediatr Otorhinolaryngol. 2012;76(3):409–13.
9. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head and Neck Surg. 2014;151(4):542–53.
10. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 year. Pediatrics. 2013;132(1):e262–80.
11. Falagas ME, Giannopoulou KP, Vardakas KZ, Dimopoulos G, Kara-georgopoulos DE. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. Lancet Infect Dis. 2008;8(9):543–52.
12. Kristo A, Uhari M, Luotonen J, Ilkko E, Koivunen P, Alho OP. Cefu-roxime axetil versus placebo for children with acute respiratory infection and imaging evidence of sinusitis: a randomized, controlled trial. Acta Paediatr. 2005;94(9):1208–13.
13. Garbutt JM, Goldstein M, Gellman E, Shannon W, Littenberg B. A randomized, placebo-controlled trial of antimicrobial treatment for children with clinically diagnosed acute sinusitis. Pediatrics. 2001;107(4):619–25.

14. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis mediasix to eight years after introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2010;29(4):304–9.
15. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. Otolaryngol Head Neck Surg. 2007;136(3):340–7.
16. Grady R. Safety profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis J. 2003;22(12):1128–32.
17. 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(3):511–9.
18. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in *Haemophilus influenzae*. Clin Microbiol Rev. 2007;20(2):368–89.
19. Otten FW, Grote JJ. Treatment of chronic maxillary sinusitis in children. Int J Pediatr Otorhinolaryngol. 1988;15(3):269–78.
20. 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(3):215–7.
21. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;23:1–298.
22. Don DM, Yellon RF, Casselbrant ML, Bluestone CD. Efficacy of a stepwise protocol that includes intravenous antibiotic therapy for the management of chronic sinusitis in children and adolescents. Arch Otolaryngol Head Neck Surg. 2001;127(9):1093–8.
23. Meltzer EO, Charous BL, Busse WW, Zinreich SJ, Lorber RR, Danzig MR, The Nasonex Sinusitis Group. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. J Allergy Clin Immunol. 2000;106(4):630–7.
24. Dolor RJ, Witsell DL, Hellkamp AS, Williams JW Jr, Califf RM, Simel DL, Ceftin and Flonase for Sinusitis (CAFFS) Investigators. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. JAMA. 2001;286(24):3097–105.
25. Barlan IB, Erkan E, Bakir M, Berrak S, Başaran MM. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Ann Allergy Asthma Immunol. 1997;78(6):598–601.
26. Wan KS, Wu WF, Chen TC, Wu CS, Hung CW, Chang YS. Comparison of amoxicillin + clavulanate with or without intranasal fluticasone for the treatment of uncomplicated acute rhinosinusitis in children. Minerva Pediatr. 2015;67(6):489–94.
27. Nayak AS, Settipane GA, Pedinoff A, Charous BL, Meltzer EO, Busse WW, et al. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. Ann Allergy Asthma Immunol. 2002;89(3):271–8.
28. 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.
29. Bucher HC, Tschudi P, Young J, Periat P, Welge-Luussen A, Zust H, et al. Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis: a placebo-controlled, double-blind, randomized trial in general practice. Arch Intern Med. 2003;163:1793–8.
30. Tugrul S, Dogan R, Baki ES, Meric A, Ozturan O. The use of large volume low pressure nasal saline with fluticasone propionate for the treatment of pediatric acute rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2014;78:1393–9.
31. Beswick DM, Messner AH, Hwang PH. Pediatric chronic rhinosinusitis management in rhinologists and pediatric otolaryngologists. Ann Otol Rhinol Laryngol. 2017;126(9):634–9.
32. Beswick DM, Ramadan H, Baroody FM, Hwang PH. Practice patterns in pediatric chronic rhinosinusitis: a survey of the American Rhinologic Society. Am J Rhinol Allergy. 2016;30(6):418–23.

33. Chong LY, Head K, Hopkins C, Philpott C, Schilder AGM, Burton MJ. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016;4:CD011996.
34. Chur V, Small CB, Stryszak P, Teper A. Safety of mometasone furoate nasal spray in the treatment of nasal polyps in children. Pediatr Allergy Immunol. 2013;24:33–8.
35. Maspero JF, Rosenblut A, Finn A Jr, 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.
36. Meltzer EO, Tripathy I, Maspero JF, Wu W, Philpot E. Safety and tolerability of fluticasone furoate nasal spray once daily in paediatric patients aged 6-11 years with allergic rhinitis: subanalysis of three randomized, double-blind, placebo-controlled, multicentre studies. Clin Drug Investig. 2009;29:79–86.
37. Rosenblut A, Bardin PG, Muller B, Faris MA, Wu W, Caldwell MF, Fokkens WJ. Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. Allergy. 2007;62:1071–7.
38. 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.
39. Lanier B, Kai G, Marple B, et al. Pathophysiology and progression of nasal septal perforation. Ann Allergy Innumol. 2007;99:473–80.
40. Verkerk MM, Bhatia D, Rimmer J, Earls P, Sacks R, Harvey RJ. Intranasal steroids and the myth of mucosal atrophy: a systematic review of original histological assessments. Am J Rhinol Allergy. 2015;29:3–18.
41. Van AA, Bronsky EA, Dockhorn RJ, Grossman J, Lumry W, Meltzer EO, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone diproprionate. J Allergy Clin Immunol. 1993;91:1146–54.
42. Brannan MD, Herron JM, Reidenberg P, Affrime MB. Lack of hypothalamic-pituitary- adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray administered to patients with allergic rhinitis. Clin Ther. 1995;17:637–47.
43. Vargas R, Dockhorn RJ, Findlay SR, Korenblat PE, Field EA, Kral KM. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol. 1998;102:191–7.
44. Howland WC 3rd, Dockhorn R, Gillman S, Gross GN, Hille D, Simpson B, et al. A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis. J Allergy Clin Immunol. 1996;98:32–8.
45. Nayak AS, Ellis MH, Gross GN, Mendelson LM, Schenkel EJ, Lanier BQ, et al. The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis. J Allergy Clin Immunol. 1998;101:157–62.
46. Galant SP, Melamed IR, Nayak AS, Blake KV, Prillaman BA, Reed KD, et al. Lack of effect of fluticasone propionate aqueous nasal spray on the hypothalamic- pituitary-adrenal axis in 2- and 3-year-old patients. Pediatrics. 2003;112:96–100.
47. Kim K, Weiswasser M, Nave R, Ratner P, Nayak A, Herron J, et al. Safety of once-daily ciclesonide nasal spray in children 2 to 5 years of age with perennial allergic rhinitis. Pediatric Asthma Allergy Immunol. 2007;20:229–42.
48. Chervinsky P, Kunjibettu S, Miller DL, Prenner BM, Raphael G, Hall N, Shah T. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2007;99:69–76.
49. Patel D, Ratner P, Clements D, Wu W, Faris M, Philpot E. Lack of effect on adult and adolescent hypothalamic-pituitary-adrenal axis function with use of fluticasone furoate nasal spray. Ann Allergy Asthma Immunol. 2008;100:490–6.
50. Weinstein S, Qaqundah P, Georges G, Nayak A. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in children aged 2 to 5 years with perennial allergic rhinitis: a randomized,

double-blind, placebo-controlled study with an open-label extension. Ann Allergy Asthma Immunol. 2009;102:339–47.
51. Tripathy I, Levy A, Ratner P, Clements D, Wu W, Philpot E. HPA axis safety of fluticasone furoate nasal spray once daily in children with perennial allergic rhinitis. Pediatr Allergy Immunol. 2009;20:287–94.
52. Hampel FC Jr, Nayak NA, Segall N, Small CJ, Li J, Tantry SK. No hypothalamic-pituitary-adrenal function effect with beclomethasone dipropionate nasal aerosol, based on 24-hour serum cortisol in pediatric allergic rhinitis. Ann Allergy Asthma Immunol. 2015;115(2):137–42.
53. Liu A, Manche EE. Bilateral posterior subcapsular cataracts associated with long-term intranasal steroid use. J Cataract Refract Surg. 2011;37:1555–8.
54. Ahmadi N, Snidvongs K, Kalish L, Sacks R, Tumuluri K, Wilcsek G, Harvey R. Intranasal corticosteroids do not affect intraocular pressure or lens opacity: a systematic review of controlled trials. Rhinology. 2015;53(4):290–302.
55. Mener DJ, Shargorodsky J, Varadhan R, Lin SY. Topical intranasal corticosteroids and growth velocity in children: a meta-analysis. Int Forum Allergy Rhinol. 2015;5:95–103.
56. 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(2):348–52.
57. Tosca MA, Cosentino C, Pallestrini E, Riccio AM, Milanese M, Canonica GW, Ciprandi G. Medical treatment reverses cytokine pattern in allergic and nonallergic chronic rhinosinusitis in asthmatic children. Pediatr Allergy Immunol. 2003;14:238–41.

Part IV
Surgical Treatment of Rhinosinusitis

Chapter 16
Adenoidectomy and Sinus Lavage

Habib G. Zalzal, Chadi A. Makary, and Hassan H. Ramadan

Introduction

Chronic rhinosinusitis (CRS) is estimated to affect up to 12% of the population in the United States, with nearly $1.8 billion spent on treating children under 12 years of age annually [1]. Duration of sinus disease symptoms differentiates between acute rhinosinusitis (12 weeks or less) and CRS (more than 12 weeks) [2]. Symptoms include nasal blockage, obstruction, congestion, or discharge (anterior or posterior nasal drip), alongside facial pain, pressure, and cough [2–4]. Symptomatology should also correlate with positive findings on physical examination, nasal endoscopy, or computed tomography (CT) scan. The pathogenesis of CRS is not fully understood but thought to be multifactorial [2, 3, 5]. Biofilms, viral and bacterial infections, anatomical abnormalities, and chronic adenoiditis may contribute to this chronic disease pathophysiology [4].

Adenoid tissue, as a result of chronic adenoiditis or recurrent inflammation causing hypertrophy, can act as a bacterial reservoir and lead to symptoms similar to CRS [6, 7]. In 2008, Shin et al. examined adenoid size and bacteriology in relation to pediatric CRS, with bacteria isolated from adenoid tissue in 79.3% of specimens [7]. The rate of bacterial isolation from adenoid cultures correlated with the severity of sinus disease on Waters' view X-ray imaging [7]. Such bacteria include *Streptococcus pneumoniae*, *non-typeable Haemophilus influenzae*, and *Moraxella catarrhalis*, which are common for both otitis media and sinusitis in both children and adults [6]. A 2007 study by Coticchia et al. found that the surface area of the adenoids covered by biofilm in patients with CRS (94.9%) was much higher than in

H. G. Zalzal · C. A. Makary
Department of Otolaryngology–Head and Neck Surgery, West Virginia University School of Medicine, Morgantown, WV, USA

H. H. Ramadan (✉)
Department of Otolaryngology, West Virginia University School of Medicine, Morgantown, WV, USA
e-mail: hramadan@hsc.wvu.edu

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_16

patients who had sleep apnea (1.9%) [8]. They concluded that biofilm along the adenoid explained the cycle of recurrent CRS despite medical therapy and recommended mechanical debridement to remove the nidus of infection [8, 9].

The 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS), the 2014 American Academy of Otolaryngology (AAO) clinical consensus statement on pediatric CRS, and the 2016 International Consensus Statement on Allergy and Rhinology (ICAR) all made statements on the difficulty differentiating CRS from chronic adenoiditis due to the similarity of presentation in young children [2, 3, 5]. The relationship between adenoiditis and pediatric CRS was proven by the correlation of bacteria isolated from the middle meatus and the adenoid, with significant reduction of recurrent sinusitis after adenoidectomy [6, 10]. Due to the role that adenoids play in both chronic adenoiditis and CRS, current guidelines recommend that adenoidectomy be the first-line surgical intervention for children with either condition (Table 16.1) [2, 3, 5].

Table 16.1 Selected statements regarding adenoids and pediatric CRS

2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)	
Position	Statement
Consensus	The adenoids are a prominent contributor to CRS in young children, and there exists a role of adenoid removal in younger children from a bacteriologic and immunologic perspective
Consensus	The most supported surgical approach to the child with CRS who has failed maximal medical therapy is an initial attempt at an adenoidectomy with a maxillary sinus wash plus/minus balloon dilation in the child without cystic fibrosis, nasal polyposis, or allergic fungal sinusitis
2014 American Academy of Otolaryngology (AAO) Clinical Consensus Statement	
Position	Statement
Consensus	Adenoidectomy is an effective first-line surgical procedure for children up to 6 years of age with chronic rhinosinusitis (CRS)
Consensus	Adenoidectomy is an effective first-line surgical procedure for children aged 6–12 years with CRS
Consensus	Adenoidectomy can have a beneficial effect in patients with pediatric CRS that is independent of endoscopic sinus surgery (ESS)
Consensus	Tonsillectomy (without adenoidectomy) is an ineffective treatment for CRS
No Consensus	Adenoidectomy is an effective first-line surgical procedure for children aged 13 years and older with CRS
2016 International Consensus Statement on Allergy and Rhinology (ICAR)	
Position	Statement
Consensus	Adenoiditis can have a very similar clinical presentation to chronic rhinosinusitis, making differentiation difficult in the pediatric age group
Consensus	Adenoidectomy should be considered a first-line therapy for medically refractory, uncomplicated pediatric RS, given its simplicity, low risk profile, and effectiveness
Consensus	Plain X-rays have no role in pediatric chronic rhinosinusitis, in patients suspected to have sinus disease; the only mechanism to distinguish adenoiditis from rhinosinusitis is CT scan. However, it should be reserved when surgery is considered rather than for diagnostic purposes
Consensus	Adenoidectomy alone is an effective treatment for PCRS; it is strong in children up to 6 years old and supported through 12 years of age
Consensus	The role of adenoid tissue in CRS may be obstructive and/or serve as a reservoir for bacterial growth

Treatment

Medical and surgical therapy for pediatric CRS is variable and wide-ranging. Several consensus statements have attempted to pinpoint the best algorithm for treatment of this condition [2, 3, 5]. Poorly controlled sinus disease results in significant detriments to quality of life, particularly regarding nasal breathing, sense of smell, and overall well-being. Finding the appropriate balance between medical and surgical therapy for chronic sinus infections in children is important.

The anatomy of the paranasal sinuses develops throughout childhood. Uniform surgical treatment of sinus disease is, as a result, difficult to adopt because of this dynamically changing sinonasal anatomy. The presence of adenoid tissue in children complicates their clinical symptomatology through chronic infection and/or chronic hypertrophy. Chronic inflammation of the sinuses can lead to nasopharyngeal lymphoid overgrowth and subsequent adenoiditis and adenoid hypertrophy. This interferes with upper airway airflow and can lead to the symptoms of nasal obstruction, congestion, and rhinitis seen in patients with CRS. Compared to adults, the presence of adenoid tissue complicates the decision-making process in children.

Medical therapy remains first-line treatment for pediatric CRS due to its effectiveness for a large percentage of patients. Optimal medical therapy differs among practitioners, but most physicians start with oral antibiotics, nasal saline irrigations, intranasal corticosteroid spray, and other allergy therapies [2, 3, 5, 11]. Guidelines suggest that at least 3 weeks of antibiotics use is sufficient to determine whether a patient's CRS symptoms will resolve, although no good evidence exists to support this length of therapy [2, 3, 5]. Nasal saline rinses are effective, and adherence in children is reasonable [12]. Intranasal corticosteroid use is effective with a low risk compared to oral corticosteroid use [4]. The majority of children will improve with optimal medical therapy [11]. If treatment with oral antibiotics and adjunct nasal sprays fails, surgical intervention is indicated (Table 16.2) [5].

Role of Imaging for Pediatric Chronic Rhinosinusitis

The EPOS, AAO, and ICAR consensus statements encourage a role for CT scan of the sinuses as a main imaging modality for both children and adults with CRS [2, 3, 5]. Plain X-rays, however, are no longer recommended as these do not correlate with CT findings in patients with CRS [3, 5]. Regarding the utility of CT scans, it is important to realize that abnormalities may be present in the sinuses with the absence of disease, particularly in the setting of the developing sinus [13]. CT scans have been associated with an increased risk of leukemia and brain cancer relative to the dose of radiation and number of studies performed [14]. Due to the risk of radiation exposure, every effort should be made to minimize use of scans in children [9].

Nevertheless, CT scans are useful in differentiating CRS from chronic adenoiditis in children. Bhattacharyya et al. in 2004 looked at utilizing Lund-Mackay scoring to determine a difference between patients with chronic adenoiditis and CRS. From their work, children with a score of 5 or more had a high sensitivity (86%) and specificity (85%) of having CRS [15]. Children with a CT score of 2 or less had an excellent negative predictive value for CRS, enabling the likely diagnosis of chronic adenoiditis in patients with CRS-like symptoms [15].

Adenoidectomy

Adenoidectomy as an operation dates back to February 1868, when Hans Wilhelm Meyer first described the lymphoid structure in an article entitled *On the Adenoid Vegetations in the Nasopharyngeal Cavity* [16]. Its initial utility was for treatment of otitis, and Meyer devised a sharp ring knife to fit through the nose into the nasopharynx. Meyer subsequently used his finger in the mouth to control cutting in the nasopharynx [16]. While adenoidectomy has evolved significantly from its initial debut two centuries ago, the basic technique has remained unchanged.

The current technique involves a McIvor mouth gag placed to open the patient's mouth, and a nasopharyngeal mirror to examine the nasopharynx after retraction of the soft palate with red rubber catheters [6]. Using either hot (electrocautery, coblation) or cold (adenoid curette, microdebridement) technique, adenoid tissue is subsequently removed with several swipes against the posterior nasopharynx under indirect mirror visualization [6]. A 2007 survey found that the most popular instruments currently were suction electrocautery, coblation, and then cold dissection followed by electrocautery [17]. While cold technique using adenoid curettage results in less operating time, it may cause more blood loss when compared to electrocautery or coblation [6, 17]. Although a relatively simple procedure, significant complications, both immediate (bleeding, Grisel syndrome, or inflammatory torticollis) and delayed (velopharyngeal insufficiency), may occur and should be addressed with the patient's family prior to the procedure [6]. A small subset of patients may require a revision adenoidectomy due to adenoid regrowth, particularly children who underwent the procedure at a young age, have a diagnosis of acid reflux, or have recurrent otitis [18].

As mentioned previously, adenoidectomy reached consensus by the EPOS, AAO, and ICAR as an effective first-line surgical treatment for children up to 6 years with CRS, with support for kids up to 12 years of age [2, 3, 5]. While previous research has shown that independent effectiveness of adenoidectomy can vary, a 2008 meta-analysis examined clinical outcome of patients who underwent adenoidectomy for refractory CRS [9, 19]. In this study, 69.3% of children improved completely with adenoidectomy alone from their CRS symptoms [19]. Other studies, however, have reported a roughly 50% failure rate of adenoidectomy for CRS [9, 20]. A 2007 retrospective analysis by Ramadan et al. found that patients

with asthma and those with age less than 7 years were predictors of earlier failure rate, eventually requiring salvage functional endoscopic sinus surgery (FESS) later [20]. Gender, Lund-Mackay stage, and allergy status had no bearing on failure time or rate [20].

Adenoidectomy is also recommended for children with chronic adenoiditis without CRS, particularly in patients under 13 years [5]. When children have chronic adenoiditis and CRS, the success rate of adenoidectomy falls significantly [21]. A 2014 study by Ramadan et al. looked at children who failed optimal medical treatment of CRS. Patients were divided into two groups based on Lund-Mackay scoring: children who had a CT score greater than 5 were in the chronic adenoiditis with CRS group and those who has a CT score of less than 5 were in the chronic adenoiditis group. This study showed that patients with both chronic adenoiditis and CRS had a success rate of 43% following adenoidectomy, while those with chronic adenoiditis alone had a success rate of 65% [21].

Similar to their 2007 study, Ramadan et al. also found an increased failure rate in asthmatic children. Children with asthma in the chronic adenoiditis and CRS group had a success rate of 28%, while those in the chronic adenoiditis group had a 53% success rate following adenoidectomy [21]. The unified airway theory has led to the idea that CRS and asthma coexist in patients at a higher frequency than the prevalence of each in the general population [21–23]. The sequence of disease and parallel inflammatory pathways involved suggest progressive manifestations of a common disease process affecting both the upper and lower airways [23]. Ramadan et al. believed that when adenoidectomy alone was performed on asthmatics with symptoms of CRS, those children usually did not have a good outcome, and revision surgery, or FESS, was usually warranted to address their sinuses [21].

Sinus Lavage

Sinus lavage, or maxillary antral lavage, is a procedure in which a cannula is inserted into the maxillary sinus via the inferior meatus or within the middle meatus via the maxillary ostium. If placed correctly, nasal saline solution will irrigate and drain secretions of the sinus. The procedure is particularly effective in patients with acute or chronic maxillary sinusitis resistant to medical therapy [24]. In children, due to likely intolerance of cannula placement, the procedure is recommended to occur under sedation. While no age minimum exists, special attention is warranted during pediatric antral lavage as the maxillary sinus floor does not reach its maximum inferior dimension until around 16 years of age [25]. Insertion of the cannula towards the suspected anatomic location of the maxillary sinus may not be consistent for all age and gender groups [25].

Sinus lavage is frequently performed in conjunction with adenoidectomy as it has been theorized to improve the outcome in children with CRS. Some studies have even suggested that a postoperative course of intravenous antibiotics based on

cultures obtained from the wash also improves outcomes [26, 27]. However, it is questionable whether this improvement is from the sinus lavage alone, from the intravenous antibiotics alone, or from a combination of both interventions [26, 27].

A 2008 study by Ramadan et al. analyzed 60 children who underwent adenoidectomy with and without sinus lavage for CRS [28]. Children enrolled in the study had chronic symptoms with clinical evidence (physical examination and CT scan) of CRS for at least 6 months or more than 6 episodes of acute rhinosinusitis over a 1-year period. No postoperative intravenous antibiotics were used in this study. Improvement was measured using postoperative questionnaire. At 1 year postoperatively, 87.5% of children who underwent adenoidectomy with sinus lavage improved compared to 60.7% of patients who underwent adenoidectomy alone [28]. Children with severe CRS based on Lund-Mackay scoring (score greater than 6) also had similar improvement (93% vs. 60%) [28]. Follow-up study by Criddle et al. in 2008 also found similar results for the efficacy of sinus irrigation [29].

Despite the aforementioned research, few other studies have analyzed sinus lavage as an adjunct therapy for pediatric CRS. As a result, the AAO could not reach a consensus that the current evidence supported a role for antral irrigation in managing selected children with CRS [5].

Practice Patterns for Treatment of Pediatric Chronic Rhinosinusitis

Referral patterns typically affect whether a CT scan would be ordered for treatment of CRS in children. Pediatric otolaryngologists are more likely to perform adenoidectomy before obtaining a scan, whereas rhinologists are more likely to obtain a scan before any surgical treatment [30]. Additionally, pediatric otolaryngologists were more likely to avoid use of CT imaging over the past decade compared to rhinologists, but this may be likely due to practice patterns more than anything [30].

Both pediatric otolaryngologists and rhinologists were more likely to perform adenoidectomy as part of initial surgical management. Additionally, both pediatric otolaryngologists and rhinologists were likely to perform adenoidectomy alone versus adenoidectomy with sinus lavage. However, rhinologists on average performed sinus lavage in conjunction with adenoidectomy more frequently than pediatric otolaryngologists (31% vs. 18% respectively) [30].

Table 16.2 Treatment Protocol for Children with chronic rhinosinusitis

Sinonasal Symptoms	Medical Therapy		Surgical Therapy
- Nasal obstruction - Rhinorrhea - Post-Nasal drip - Pressure - Cough - ± Facial Pressure	→ - Oral Antibiotics - Nasal Saline Irrigations - Intranasal Corticosteriod Spray - Antihistamines - Decongestants / Mucolytics - Hydration - ± Consider Sinus Culture	Persistence of Symptomology →	- First Line: Adenoidectomy ± Sinus Lavage - Depending on age ± CT Scan depending on age and severity of symptomology - Endoscopic Sinus Surgery

Conclusion

There are many details to be conscious of when performing surgery upon the pediatric nasopharynx and paranasal sinuses. The presence of adenoid tissue in young children complicates treatment selection, as symptoms typically associated with CRS could also be secondary to chronic adenoiditis. Nevertheless, three major multinational committees have all agreed that adenoidectomy should be first-line therapy after failure of optimal medical management. Although sinus lavage has efficacy in what is in the current literature, more evidence is needed before its use can be widely adopted, as only few rhinologists regularly use this adjunct treatment in children. As a surgical therapy, adenoidectomy is a safe and efficacious stepping stone prior to more invasive paranasal surgeries in children with CRS and chronic adenoiditis.

Disclosures The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

References

1. Beule A. Epidemiology of chronic rhinosinusitis, selected risk factors, comorbidities, and economic burden. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2015;14:Doc11.
2. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;23:1–298.
3. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(Suppl 1):S22–S209.
4. Makary CA, Ramadan HH. Sinus and upper airway surgery in children. Curr Allergy Asthma Rep. 2018;18(5):32.
5. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151:542–53.
6. Ungkanont K, Myers EN, et al. "Adenoidectomy." Operative otolaryngology: head and neck surgery. 3rd ed. Philadelphia: Elsevier; 2018. p. 1341–6.
7. 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;72:1643–50.
8. 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;133:110–4.
9. Neff L, Adil EA. What is the role of the adenoid in pediatric chronic rhinosinusitis? Laryngoscope. 2015;125(6):1282–3.
10. Elwany S, El-Dine AN, El-Medany A, et al. Relationship between bacteriology of the adenoid core and middle meatus in children with sinusitis. J Laryngol Otol. 2011;125:279–81.
11. Lusk R. Pediatric Chronic Rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2006;14(6):393–6.
12. Jeffe JS, Bhushan B, Schroeder JW. Nasal saline irrigation in children: a study of compliance and tolerance. Int J Pediatr Otorhinolaryngol. 2012;76(3):409–13.
13. Rizzi MD, Kazahaya K. Pediatric chronic rhinosinusitis: when should we operate? Curr Opin Otolaryngol Head Neck Surg. 2014;22(1):27–33.
14. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380:499–505.

15. Bhattacharyya N, Jones DT, Hill M, Shapiro NL. The diagnostic accuracy of computed tomography in pediatric chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2004;130(9):1029–32.
16. Ruben RJ. The adenoid: Its history and a cautionary tale. Laryngoscope. 2017;127(Suppl 2):S13–28.
17. Kadhim AL, Spilsbury K, Semmens JB, et al. Adenoidectomy for middle ear effusion: a study of 50,000 children over 24 years. Laryngoscope. 2007;117(3):427–33.
18. Dearking AC, Lahr BD, Kuchena A. Factors associated with revision adenoidectomy. Otolaryngol Head Neck Surg. 2012;146(6):984–90.
19. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72:1541–5.
20. Ramadan HH, Tiu J. Failures of adenoidectomy for chronic rhinosinusitis in children: for whom and when do they fail? Laryngoscope. 2007;117:1080–3.
21. Ramadan HH, Makary CA. Can computed tomography score predict outcome of adenoidectomy for chronic rhinosinusitis in children. Am J Rhinol Allergy. 2014;28(1):e80–2.
22. Feng CH, Miller MD, Simon RA. The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis. Am J Rhinol Allergy. 2012;26(3):187–90.
23. Steinke JW. The relationship between rhinosinusitis and asthma sinusitis. Curr Allergy Asthma Rep. 2006;6:495–501.
24. Ramadan HH, Owens RM, Tiu C, et al. Role of antral puncture in the treatment of sinusitis in the intensive care unit. Otolaryngol Head Neck Surg. 1998;119(4):381–4.
25. Lorkiewicz-muszyńska D, Kociemba W, Rewekant A, et al. Development of the maxillary sinus from birth to age 18. Postnatal growth pattern. Int J Pediatr Otorhinolaryngol. 2015;79(9):1393–400.
26. Buchman CA, Yellon RF, Bluestone CD. Alternative to endo- scopic sinus surgery in the management of pediatric chronic sinusitis refractory to oral antimicrobial therapy. Otolaryngol Head Neck Surg. 1999;120:219–24.
27. Don DM, Yellon RF, Casselbrant ML, Bluestone CD. Efficacy of stepwise protocol that includes intravenous antibiotic therapy for the management of chronic sinusitis in children and adolescents. Arch Otolaryngol Head Neck Surg. 2001;127:1093–8.
28. Ramadan HH, Cost JL. Outcome of adenoidectomy versus adenoidectomy with maxillary sinus wash for chronic rhinosinusitis in children. Laryngoscope. 2008;118:871–3.
29. Criddle MW, Stinson A, Savliwala M, et al. Pediatric chronic rhinosinusitis: a retrospective review. Am J Otolaryngol. 2008;29(6):372–8.
30. Beswick DM, Messner AH, Hwang PH. Pediatric chronic rhinosinusitis management in rhinologists and pediatric otolaryngologists. Ann Otol Rhinol Laryngol. 2017;126(9):634–9.

Chapter 17
Balloon Sinuplasty in Children

Elisabeth H. Ference and Hassan H. Ramadan

Introduction

BCD devices have become an important tool in the surgical management of pediatric CRS in recent years. BCD has grown tremendously in popularity since its introduction in 2006, and in 2011 nearly 12% of all pediatric sinus surgery involved BCD [1, 2]. BCD may be associated with less mucosal and anatomic disruption, therefore minimizing synechiae formation and ostial stenosis and thus the need for postoperative debridements or revision (Table 17.1). The BCD devices are single use and disposable, and so may lead to increased surgery costs without a significant decrease in operating room time [1, 2]. This chapter reviews the evidence for safety and efficacy of BCD in pediatric patients and discusses pearls and pitfalls of the technique.

History

As with many surgical devices, BCD was first approved and used for adult patients before being studied in pediatric patients. BCD of the frontal sinuses was initially described by Lanza in 1993 using a Fogarty balloon, and the initial cadaveric and clinical studies utilizing a dedicated sinus device were presented in 2005 shortly before FDA approval [3–5]. The first long-term single-arm uncontrolled observational study, called the CLEAR study, enrolled 109 non-polyp adult patients unresponsive to medical therapy who underwent BCD alone or using a hybrid

E. H. Ference (✉)
Rick and Tina Caruso Department of Otolaryngology–Head and Neck Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA
e-mail: elisabeth.ference@med.usc.edu

H. H. Ramadan
Department of Otolaryngology, West Virginia University, School of Medicine, Morgantown, WV, USA

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_17

Table 17.1 Advantages and disadvantages of balloon catheter dilation (BCD) devices for pediatric patients

Advantage	Disadvantage
Less distortion of anatomy and mucosal disruption	Cost of disposable instruments increase total cost of procedure
Minimized synechiae formation and ostial stenosis	Contraindicated in patients with osteoneogenesis, nasal polyposis, or extensive mucosal disease
Decreased need for postoperative debridements	Hybrid technique necessary in patients with complex pneumatization patterns to avoid worsening obstruction
Possible decreased blood loss	Surgeon must be able to perform traditional surgery if balloon catheter dilation fails
Possible use in critically ill patients and patients with complications of acute or chronic sinusitis	No device available for ethmoid sinus
Surgical tool for dissection of difficult-to-reach frontal recess cells	Poor results in patients with hypoplastic sinuses
For teenagers able to cooperate, possible use in office setting with minimal anesthetic requirements	Unclear efficacy in patients with immunodeficiency or other comorbidities
Can be used as adjuvant to adenoidectomy	Unclear benefit in children compared to endoscopic sinus surgery

method [6–8]. The cohort was initially followed for 24 weeks and in later publications for 1 and 2 years, with findings of improvement in SNOT-20 and 94% maxillary, 92% frontal, and 86% sphenoid patency at 1 year [6–8]. Two randomized controlled trials, as well as meta-analyses, found no significant difference in quality of life or revision rate between BCD and traditional endoscopic sinus surgery, with decreased postoperative recovery time in patients who underwent BCD [9–13].

Studies in the adult population have shown a technical success rate of 97.5%; SNOT-20 outcome improvement at 6-, 12-, and 24-month follow-up; and statistically significant reductions in work/school days missed, physician/nurse visits, acute infections, and antibiotic prescriptions [10]. However, the studies included patients with limited disease severity (maxillary disease with or without anterior ethmoid disease only) and excluded patients with polyposis, fungal disease, and deviated septum. For example, in the XprESS study, which is one of the few to include patients with sphenoid and frontal disease, 48% of patients had a baseline Lund-Mackay score of less than or equal to 3 and 34% had scores between 3 and 8 [14].

Evidence in Pediatric Patients

BCD was first described for pediatric use in 2009 by Dr. Ramadan [15, 16]. Follow-up studies have sought to evaluate larger, multicenter cohorts of patients, to define when the use of the BCD is most efficacious, and to compare it to traditional techniques (Table 17.2).

Table 17.2 Summary of available research on pediatric balloon catheter dilation

Year	Author	Type	Comparison groups	Sample size	Age range (years)	Outcome measure for improvement of symptoms[b]	Maximum length of follow-up	Reported complications
2010	Ramadan	Prospective, nonrandomized	BCD with or without adenoidectomy versus adenoidectomy alone	49	2–11 (mean 7.7)	SN-5	52 weeks	None (unable to dilate hypoplastic sinuses)
2012	Ramadan	Prospective, single-armed	BCD after adenoidectomy	26	4–12 (mean 9.0)	SN-5	1 year	None
2015	Wang	Prospective, nonrandomized	BCD with or without adenoidectomy versus continued medical therapy	96	7–12 (mean 9.3)	SN-5, VAS	1 year	1 patient with periorbital swelling without hematoma in BCD group
2016[a]	Thottam	Retrospective	BCD and ethmoidectomy without adenoidectomy versus ESS without adenoidectomy	28	3–18 (mean 9.3)	Reported symptoms, medication use	2 years	None
2017	Soler	Prospective, single-armed	BCD with or without adenoidectomy or other adjuvant procedures	50	2–21 (mean 6.6)	SN-5, SNOT 22 (age > 12), RSI, revision rate	0.5 years	None
2017	Liu	Prospective, single-armed	BCD without adenoidectomy	30		VAS, CT, nasal endoscopy, nonvalidated questionnaire	1 year	3 patients with synechiae

Abbreviations: *SN*-5 Sinus and Nasal Quality of Life Survey, *SNOT*-22 22-item Sino-Nasal Outcome Test, *RSI* rhinosinusitis symptom inventory, *VAS* visual analogue scale, *CT* computed tomography, *BCD* balloon catheter dilation, *ESS* endoscopic sinus surgery

[a]Update of 2012 study using same cohort of patients by same research group

[b]Primary outcome measures of some of the included studies were technical success and complication rate

Safety

The safety and feasibility of BCD in pediatric patients was initially investigated in a study of 30 children aged 4–16 years with CRS who had failed medical management [16]. The procedure was successful in 91% of sinuses (51 of 56 attempted sinuses), and the failures occurred in four hypoplastic maxillary sinuses and one frontal sinus. Thirteen (43%) had concurrent adenoidectomy. There were no complications or side effects. The results of this study were encouraging, except for the case of hypoplastic sinuses. While the study utilized fluoroscopy, most BCD systems currently utilize transillumination and thus remove the risk of radiation.

Possible complications of BCD include postoperative bleeding, orbital injury, skull base injury, and lack of improvement. Dilation in the wrong location, for example, in a suprabullar cell or other anatomic variations of frontal recess pneumatization, can lead to worsened obstruction or no improvement. A recent review of the Department of Defense database found that 7.8% of adult patients had post-dilation complications, most commonly bleeding or pain greater than expectation [17]. Interestingly, two patients with the most serious complications (orbital chemosis and proptosis and facial subcutaneous emphysema) had baseline Lund-Mackay scores of 0 [17].

A study using a commercial insurance database which included pediatric and adult patients found a BCD complication rate of 5.26% compared to 7.35% for conventional ESS and a revision rate of 7.98% for BCD compared to 16.85% for ESS [18]. There was no data on the severity of disease prior to surgery, which may be the underlying cause for the higher revision rate in the ESS group. Patients aged 6 years or younger were excluded due to the high rates of adjuvant adenoidectomy. The complication rate for patients aged 7–18 was not reported separately due to the low number; however, there was no statistically significant difference in the odds of complications in pediatric patients compared to older patients based on a multivariable regression model. Patients aging 7–12 did have lower odds of revision compared to patients over 60, but there was no difference in the odds of revision between patients aging 13–18 and older patients. Reported complications included CSF leak, pneumocephalus, orbital complications, and severe bleeding. Therefore, these risks should be discussed with patients and their families, especially when a frontal sinus dilation is planned.

Efficacy

Adenoidectomy has been the initial surgical intervention in the treatment of pediatric CRS and is successful in approximately 50% or greater of operated children [19]. Removal of the adenoids may be successful due to adenoiditis or because the adenoids serve as a bacterial reservoir. Prior studies suggested that antral irrigations improve the efficacy of adenoid surgery, especially in patients with asthma or high

computed tomography (Lund-Mackay) score [20]. BCD systems also allow for targeted irrigation of the sinuses, and therefore it was theorized that BCD would also improve the efficacy of adenoidectomy alone in improving pediatric rhinosinusitis either via dilation of the sinus or by irrigation.

The first study suggesting efficacy of BCD in pediatric patients was by Ramadan et al. in 2010 [21]. A prospective, nonrandomized study evaluated 49 children ages 4 through 11. Of the 49 children, 30 underwent BCS, and 24 of the 30 (80%) had improvement in their symptoms after 12 months of follow-up compared with 10 of the 19 patients (52.6%) who underwent adenoidectomy alone. In subgroup analysis on multivariable regression, BCD was more effective than adenoidectomy in older children, but there was no difference based on asthma status or computed tomography score (Lund-Mackay system). Some of the patients underwent irrigation in addition to dilation, and therefore it is not possible to discern which mechanism led to the improvement. A multicenter study from the same year which only evaluated patients undergoing BCD with or without irrigation found that of 32 children ages 2 through 11 who underwent BCD, 79% had moderate or significant improvement after 12 months based on SN-5 score [15]. A third single-arm study from China found that in 30 children, 61 of 65 (94%) of sinuses were successfully ballooned with statistically significant improvement in visual analogue score (VAS), computed tomography, and endoscopic findings 1 year after the procedure [22]. Only BCD was performed in these patients, as those with adenoidal hypertrophy were excluded. None of these studies had any major complications, although the last reported synechiae in three (10%) of patients [22]. In summary, these three studies suggest that BCD is feasible and may have better outcome than adenoidectomy alone or offer improvement without adjunct adenoidectomy.

Further research sought to identify the utility of balloons for specific patient populations and combined with certain adjunct procedures. Ramadan et al. examined use of balloons in children with continued chronic rhinosinusitis despite prior adenoidectomy [23]. The study was a single-arm, prospective study of 26 children ages 4–12 years (mean 9 years) with a mean Lund-Mackay score of 7.3 who had persistent symptoms of chronic rhinosinusitis despite medical therapy and prior adenoidectomy. Children had undergone an allergy evaluation, immunoglobulin deficiency workup, and sweat chloride test when indicated. Surgical success, defined as a decrease of more than 0.5 on postoperative SN-5 score, was achieved in 81% of children after either maxillary sinus BCD alone or a hybrid procedure (BCD with anterior ethmoidectomy in four patients) or BCD with revision adenoidectomy (two patients). Three patients had a contralateral ESS maxillary antrostomy for a hypoplastic sinus or failed cannulation with the balloon device. In a separate analysis which excluded patients who underwent a hybrid procedure, the change was still statistically significant. Unpublished 3-year follow-up data of the cohort found that 78.9% of patients maintained their benefit and did not require further surgical intervention for CRS [24].

The largest and most recent study of pediatric BCD was performed by Soler et al. and was again a single-arm study but was prospective and multicenter, including both community and tertiary referral centers. It included 50 children ages 2–21 years

old with CRS who had failed medical management and who were followed for 6 months after surgery. All 157 sinus dilations were successful, with no device-related complications, and 93% of patients had clinical improvement defined as a difference of one or more on SN-5. The combination of procedures performed was mixed, with 60% of patients undergoing concurrent procedures most commonly adenoidectomy (42% of patients). Other adjuvant procedures included inferior turbinate reduction, ethmoidectomy, septal surgery, and unrelated procedures such as tonsillectomy and tympanostomy tube placement. Eight children, all older than 12, underwent procedures in an office setting under local anesthesia. No difference in symptom control was identified in children who underwent BCD alone versus children who underwent BCD with adenoidectomy, turbinate surgery, or ethmoidectomy. Multivariate regression found that improvements in SN-5 scores were maintained despite controlling for numerous factors, including the performance of adjunctive procedures, suggesting that balloon dilation in and of itself contributes to efficacy. Of note, there was no control group, and participants were not randomized to procedure type; therefore, causality could not be proven [25]. Moreover, survey data alone was used to determine improvement rather than postoperative imaging or endoscopy [25]. Review and oversight by the FDA was provided for this study, and data were used to obtain FDA clearance for the expanded indication for treating maxillary sinuses in children 2 years and older and frontal and sphenoid sinuses in children 12 years and older.

In contrast, a randomized, blinded study by Gerber and Kennedy found no difference in symptoms scores in children who underwent adenoidectomy with inferior or middle meatal puncture with a curved 18 gauge needle versus those who underwent adenoidectomy and BCD [26]. Both groups had aspiration and irrigation of the sinus performed with approximately 15–25 mL of saline. The study included 25 patients between ages 2 and 12 years old who had previously failed medical management. Both groups improved in overall mean symptom scores compared to baseline, and there was no additional benefit seen in the balloon sinuplasty group during short- or long-term follow-up.

BCD Versus Medical Management

A nonrandomized, controlled study was performed by Wang et al. comparing BCD to ongoing management of a cohort of 79 children aged 7–12 years in China who failed medical therapy. All participants had been treated with at least 2 years of medical therapy. Parents were given the choice between continued medical management and balloon catheter dilation with or without adenoidectomy. Adenoidectomy was performed for all patients with significant nasal obstruction, sleep symptoms, or repeated episodes of otitis media. The medically managed control group had improvement as measured by SN-5 and VAS scores at 3 months but

no significant improvement at 12 months. The improvement in surgically managed group remained superior to that of the medically managed group at all time points. One patient in the surgically managed group had periorbital swelling which resolved without sequela by the seventh postoperative day. Of note, the study did not state what percentage of patients in the surgical group underwent adenoidectomy and did not perform any statistical analysis controlling for the performance of adenoidectomy.

BCS Versus FESS

In the adult literature, the REMODEL study comparing BCD with FESS showed similar symptom relief in adults with CRS disease limited to the maxillary and anterior ethmoid sinuses [10]. Thottam et al. compared BCD with FESS in the pediatric population through a retrospective chart review [27, 28]. A cohort of 15 patients underwent BCD and 16 patients FESS, with an age range of 3–17 and mean age of 9.3 years, and were followed at 2–4 weeks after the procedure then at variable lengths 4 months or more later. Outcome was based on subjective impression of patients per the blinded chart reviewer with success defined as improvement in one or more preoperative sinus complaints [28]. The difference in outcome was not found to be statistically significant, with 62.3% of ESS patients and 80% of BCD patients reporting improvement in their overall sinus symptoms [28]. Patients who underwent BCD had a greater decrease in reported antibiotic use compared to those who underwent FESS [28]. A follow-up study 2 years later found that in 28 of the original patients, there continued to be no long-term significant difference in outcome (73.3% of FESS and 76.9% of BCD with improvement), and both groups had significant decrease in individual symptoms and medication use [27]. The analysis is limited by the retrospective nature of the study and its reliance on subjective improvement based on medical record documentation.

Expanded Indications

BCD has been found to be a useful surgical tool in other situations or in cases of difficult anatomy. It can be utilized in critically ill patients who require sinus ostia dilation and irrigation to improve infection with minimal bleeding. It can even be performed at bedside in the ICU setting for patients too unstable for transfer to the operating room [29]. BCD is also an important adjunct to traditional instrumentation in patients with difficult anatomy due to superior or lateral frontal sinus cells (Fig. 17.1). These cells can be crushed by the balloon and then the walls removed using traditional instrumentation. This “hybrid” approach avoids an open surgical

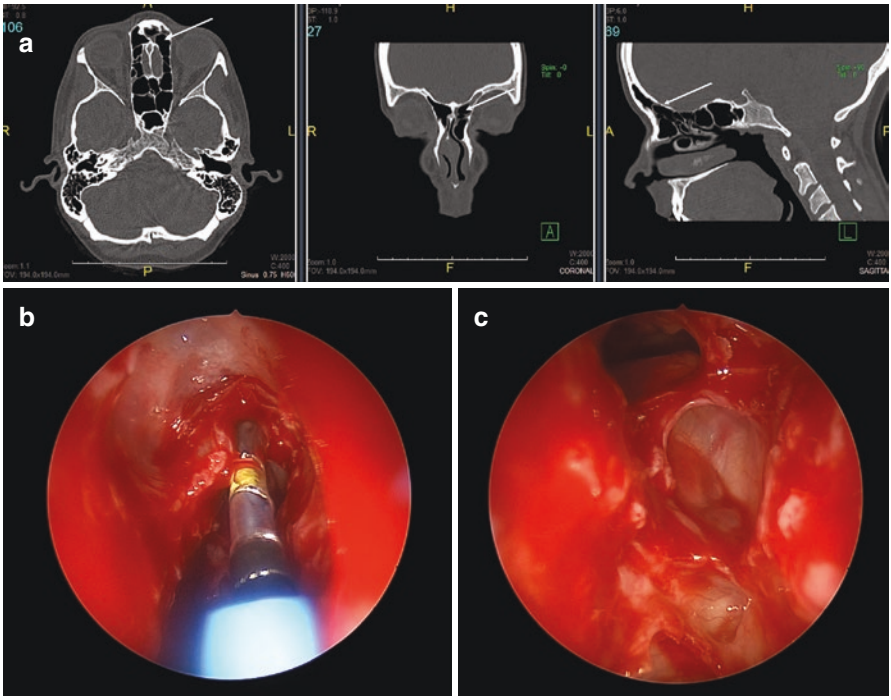


Fig. 17.1 (**a**) Triplanar view of difficult frontal bullar cell (white arrow) which can be removed using a hybrid approach of balloon catheter dilation followed by traditional endoscopic techniques to remove the crushed cell walls. (**b**) Balloon being deployed between the frontal beak and the anterior wall of the frontal bullar cell. (**c**) Visualization of the frontal sinus anteriorly and the inside of the frontal bulla cell posteriorly before the walls of the frontal bullar cell are removed with traditional frontal instruments

approach and increases the efficiency of endoscopic surgery [30]. In the office, BCD can also be used to alleviate postoperative stenosis and avoid revision surgery, although this indication is limited in the young pediatric population due to difficulty with tolerating office endoscopy and procedures [31].

Roland et al. reported on a case of BCD of the frontal sinus and intravenous antibiotics in a 12-year-old patient with an epidural abscess who experienced complete resolution of his abscess on imaging at 6 weeks without the need for craniotomy [32]. In cases of complications of acute sinusitis, BCD may prevent the need for endoscopic sinus surgery and/or trephination in a severely infected and edematous field. BCD allows for drainage of the infected sinus and irrigation. However, it can be difficult to access the sinus with a guidewire in an acutely inflamed patient, and surgeons must be able to transition to traditional endoscopic techniques if minimally invasive technology fails (Fig. 17.2).

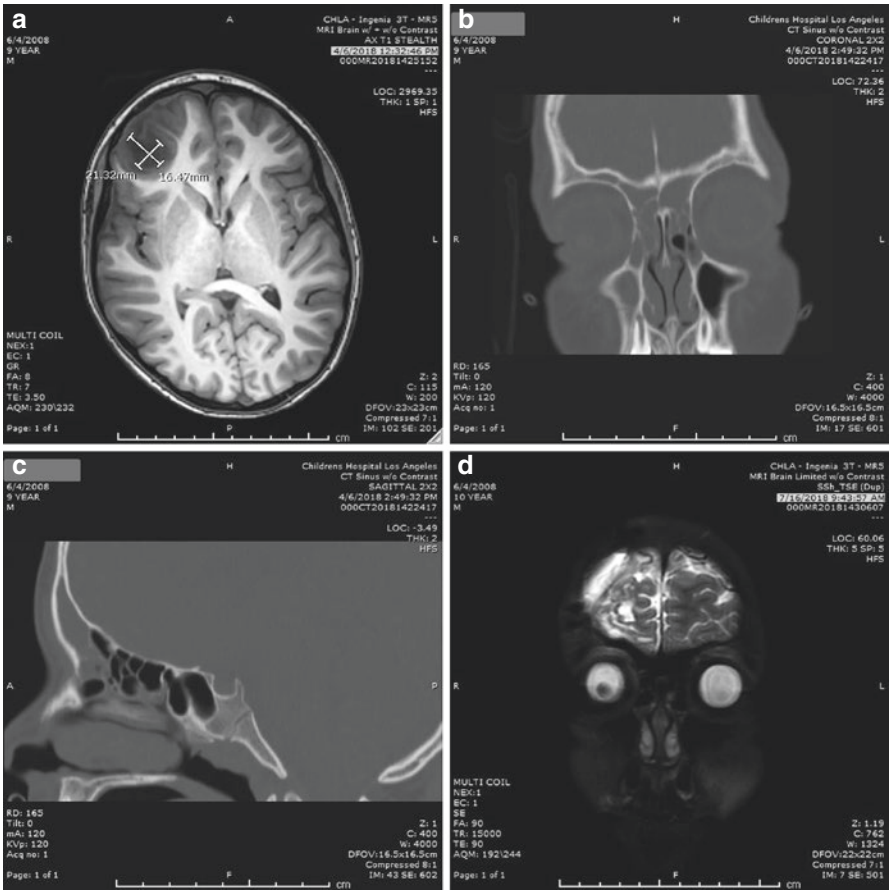


Fig. 17.2 Example of a case of balloon catheter dilation used for complications of pediatric sinusitis. (**a**) T1 MRI showing a right frontal lobe parenchymal abscess and cerebritis associated with right frontal extracerebral empyema (now shown) and pansinusitis. (**b**) Coronal CT scan with pansinusitis. A balloon was able to be passed into the right frontal sinus, and the sinus was irrigated, but the balloon could not be passed into the left frontal sinus which was therefore opened with traditional endoscopic sinus techniques. (**c**) A sagittal CT scan showing complex pneumatization of the left fontal sinus, making balloon catheter dilation difficult. Therefore, surgeons must be prepared to use either balloon catheter dilation or traditional techniques to achieve drainage of the sinus. (**d**) Follow-up coronal T1 MRI 3 months later showing bilateral clear frontal sinuses

Controversy

Controversy regarding BCD has occurred due to issues regarding reimbursement and interaction with industry. In the adult population, BCD can be performed in the office, and therefore a greater percentage of the fees are paid to the surgeon compared to performing a similar procedure in a hospital-based operating room [6–8, 33–35]. There has been a significant increase in utilization of the technology since

its introduction, and therefore use of the technology has faced scrutiny both by otolaryngologists and by payers [2, 36–40]. Two studies have found an association between industry payments and frequency with which surgeons utilize BCD [41, 42]. However, these studies are cross sectional and cannot prove causality.

Multiple factors, including patient preference for minimally invasive techniques, likely exist for the rapid uptake and popularity of the technology. The minimally invasive technique decreases persistent parental and physician concerns regarding facial growth. However, there have previously been multiple negative studies examining growth after endoscopic sinus surgery (ESS) utilizing both photographic and radiographic techniques, and no studies have evaluated facial growth after BCD [43, 44].

A research group led by Dr. PJ Wormald found that patients with larger maxillary antrostomies had decreased nitric oxide levels after surgery compared to patients with smaller ostia size [45]. Preserving nitric oxide levels within the sinuses may be a benefit of BCD compared to ESS as nitric oxide can improve ciliary function and maintain an antimicrobial environment [45, 46]. Further research is necessary to determine the extent of surgery required to improve pediatric CRS.

Both the EPOS 2012 and a recent Clinical Consensus Statement have not found conclusive effectiveness of balloon dilation in children and suggested that future research is necessary [19, 47]. Many of the studies described above have been single-armed, without a medically managed control group. An ideal study would include control arms with sham procedures to control for the placebo effect. Such rigorous studies are expensive to conduct, challenge the limits of physician equipoise, and face difficulties with patient recruitment due to desire for or against a surgical intervention [48].

It is unknown whether the dilation of the sinus itself or the irrigation of the sinus may lead to improvement in pediatric CRS. The article by Gerber and Kennedy discussed in the efficacy section found no difference in improvement among patients who underwent adenoidectomy with sinus irrigation via an inferior or middle meatal window puncture with a needle versus BCD and irrigation [26]. The study is small with only 25 patients but was powered to 80%. Further studies are therefore necessary to determine if specific groups of children will most benefit from the addition of BCD to adenoidectomy with irrigation for CRS. An epidemiology study found that pediatric patients with asthma have greater odds of having BCD compared to pediatric patients without asthma [1]. This practice is supported by a study by Ramadan which reports that pediatric patients with asthma are less likely to derive benefit from adenoidectomy alone [49]. However, a study in adult patients found that after maxillary antrostomy, CRS symptoms of asthmatic patients improved equally to CRS symptoms of non-asthmatic patients but only for asthmatic patients who underwent traditional sinus surgery, not BCD [50]. It remains unclear if pediatric patients with asthma and CRS would benefit more from BCD or traditional ESS as an adjunct to adenoidectomy.

BCD may not be an appropriate choice of technique for patients with nasal polyposis, antrochoanal polyposis, ciliary dyskinesia, immunodeficiency, cystic fibrosis, or allergic fungal sinusitis because traditional techniques with larger antrostomies may be necessary to open the affected sinus and decrease mucosal disease burden.

There have been no studies of BCD in these patient populations, and research is needed regarding the role, if any, of balloon technology for these diseases.

BCD may be challenging or impossible in patients with hypoplastic sinuses, complex pneumatization patterns, or significant osteoneogenesis [16]. Therefore, a surgeon performing BCD should be able to perform endoscopic procedures if BCD is unable to achieve the desired result.

Technique

In most young pediatric patients, general anesthesia is required for BCD. Teenagers may be able to tolerate the procedure under local anesthesia. The nose is decongested with pledgets and local anesthetic (either topical gel or injections). Balloons of various diameters and lengths are available, and no studies have compared the efficacy of competing devices. In both Acclarent Inc. (Menlo Park, CA) and Entellus Medical (Plymouth, MN) BCD systems, initial access is obtained by endoscopic placement of a guidewire, while the Medtronic (Minneapolis, MN) includes only the catheter device. For maxillary sinuses, the guide catheter is inserted behind the lower uncinate process angled toward the lateral inferior recess of the sinus in line with the natural ostia (Fig. 17.3). For frontal sinuses, the catheter is inserted behind the superior uncinate angled toward the superior medial aspect of the orbit (Fig. 17.4). For the sphenoid sinus, the catheter is inserted medial to the middle turbinate angled toward the inferior portion of the superior turbinate in line with the ostia (Fig. 17.5). The flexible guidewire is then advanced through the catheter if the system includes one.

Position is then confirmed with direct visualization or image guidance in case of the sphenoid or with transillumination or image guidance for the frontal and maxil-

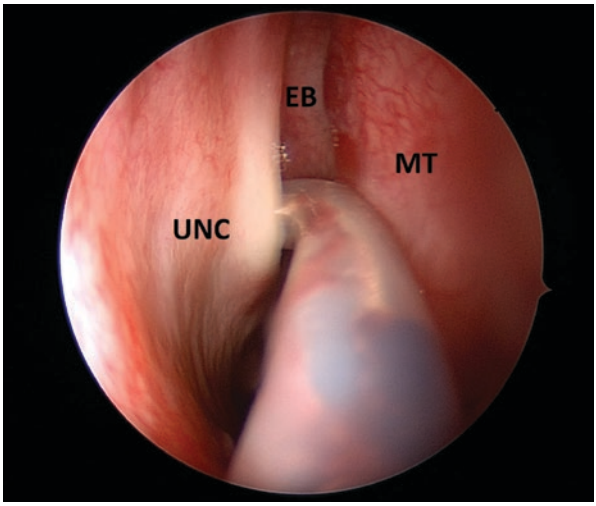


Fig. 17.3 For the right maxillary sinus balloon dilation, the guide catheter can be seen inserted between the uncinate process (UNC) and the ethmoid bulla (EB) angled toward the natural ostia (MT middle turbinate)

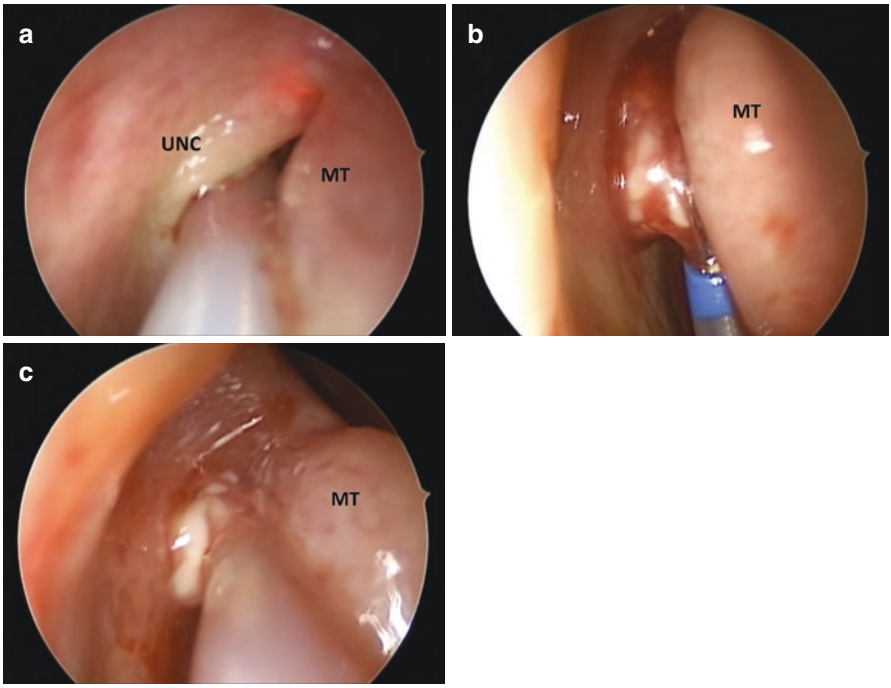


Fig. 17.4 (**a**) For the right frontal sinus, the catheter is inserted behind the superior uncinated angled toward the frontal ostia. The light of the guidewire is visible as it is threaded superiorly. (**b**) Purulence was obtained with balloon dilation in this patient with right frontal sinusitis. (**c**) The sinus is further irrigated until only clear fluid is seen (UNC, MT)

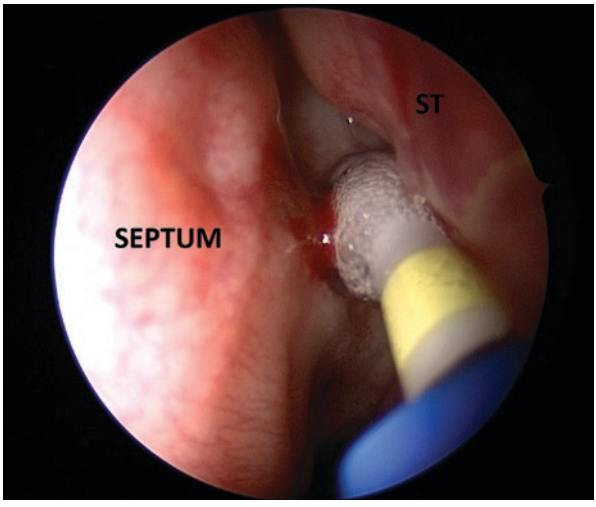


Fig. 17.5 For the left sphenoid sinus, the balloon device is inserted medial to the middle turbinate and superior turbinate in line with the natural ostia (ST septum)

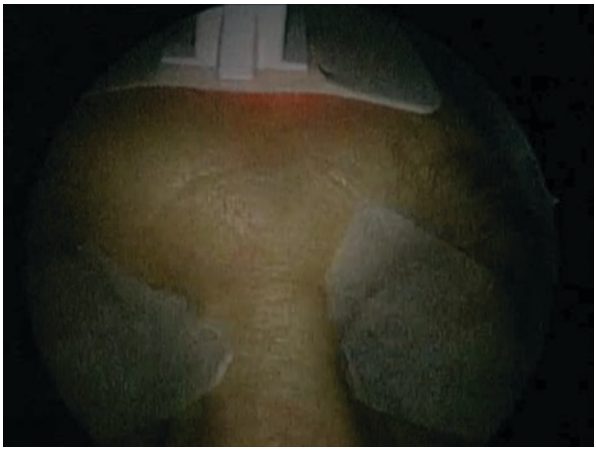


Fig. 17.6 Position in the frontal sinus is confirmed with transillumination of the forehead

lary sinuses (Fig. 17.6). For the frontal sinus, it is important to see the illumination superiorly and/or laterally because illumination only in glabella/medial canthus area may indicated that the wire is in a frontal cell. If illumination cannot be seen in the maxillary sinus, the guidewire should be rotated and the upper lip should be lifted as the illumination may occur sublabially in patients with a low maxillary sinus floor. For the sphenoid sinus, an initial dilation can be performed in the sphenoethmoid recess in order to better visualize the ostia, and then the catheter and guidewire can be advanced under direct visualization.

The balloon is advanced over the guidewire and positioned across the ostia of the sinus. It is then inflated per the manufacturer's instructions, and multiple dilations can be performed. For the frontal sinus, multiple dilations can be performed using the measurement markers on the balloon delivery device to ensure the entire frontal recess is completely opened. For the maxillary sinus, the balloon can be partially retracted out of the ostia and inflated to ensure that the uncinate is medialized away from the natural ostia. Most systems also include the ability to irrigate the sinus directly through the catheter channel once the guidewire is retracted. After inflation and irrigation, the device is removed. Nasal packing is not necessary and is at the discretion of the surgeon but can be used to medialize the middle turbinate if needed.

Adenoidectomy can be performed either transorally with a headlamp and mirror, transorally using an endoscope, or transnasally using an endoscope. Anterior ethmoidectomy can be performed at the time of BCD, both in the operating room or in the office.

Conclusion

BCD is an important addition to the surgical treatment of pediatric CRS. Multiple studies have found it to be a safe technique, although the efficacy compared to traditional ESS cannot be determined based on the current evidence [47]. Future

studies are necessary to determine the long-term efficacy of BCD with and without adjuvant procedures, to examine BCD in expanded indications such as in complications of acute sinusitis, and to analyze the comprehensive cost of the procedure.

References

1. Ference EH, Schroeder JW, Qureshi H, Conley D, Chandra RK, Tan BK, et al. Current utilization of balloon dilation versus endoscopic techniques in pediatric sinus surgery. Otolaryngol Head Neck Surg. 2014;151(5):852–60.
2. Ference EH, Graber M, Conley D, Chandra RK, Tan BKBK, Evans C, et al. Operative utilization of balloon versus traditional endoscopic sinus surgery. Laryngoscope. 2015;125(1):49–56.
3. Lanza D. Postoperative care and avoiding frontal recess stenosis. Abstr Int Adv Sinus Symp. 1993;
4. 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.
5. 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.
6. 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 Neck Surg. 2008;139(3_suppl_1):S38–46.
7. Kuhn FA, Church CA, Goldberg AN, Levine HL, Sillers MJ, Vaughan WC, et al. Balloon catheter sinusotomy: one-year follow-up—outcomes and role in functional endoscopic sinus surgery. Otolaryngol Neck Surg. 2008;139(3_suppl_1):S27–37.
8. Bolger WE, Brown CL, Church CA, Goldberg AN, Karanfilov B, Kuhn FA, et al. Safety and outcomes of balloon catheter sinusotomy: a multicenter 24-week analysis in 115 patients. Otolaryngol Neck Surg. 2007;137(1):10–20.
9. Achar P, Duvvi S, Kumar BN. Endoscopic dilatation sinus surgery (FEDS) versus functional endoscopic sinus surgery (FESS) for treatment of chronic rhinosinusitis: a pilot study. Acta Otorhinolaryngol Ital. 2012;32(5):314–9.
10. Chandra RK, Kern RC, Cutler JL, Welch KC, Russell PT. REMODEL larger cohort with long-term outcomes and meta-analysis of standalone balloon dilation studies. Laryngoscope. 2016;126(1):44–50.
11. Cutler J, Bikhazi N, Light J, Truitt T, Schwartz M, REMODEL Study Investigators. Standalone balloon dilation versus sinus surgery for chronic rhinosinusitis: a prospective, multicenter, randomized, controlled trial. Am J Rhinol Allergy. 2013;27(5):416–22.
12. Bikhazi N, Light J, Truitt T, Schwartz M, Cutler J, REMODEL Study Investigators. Standalone balloon dilation versus sinus surgery for chronic rhinosinusitis: a prospective, multicenter, randomized, controlled trial with 1-year follow-up. Am J Rhinol Allergy. 2014;28(4):323–9.
13. Levy JM, Marino MJ, McCoul ED. Paranasal sinus balloon catheter dilation for treatment of chronic rhinosinusitis. Otolaryngol Neck Surg. 2016;154(1):33–40.
14. Gould J, Alexander I, Tomkin E, Brodner D. In-office, multisinus balloon dilation: 1-year outcomes from a prospective, multicenter, open label trial. Am J Rhinol Allergy. 2014;28(2):156–63.
15. Ramadan HH, McLaughlin K, Josephson G, Rimell F, Bent J, Parikh SR. Balloon catheter sinuplasty in young children. Allergy Rhinol. 2010;1(2).:ajra.2010.24.34.
16. Ramadan HH. Safety and feasibility of balloon sinuplasty for treatment of chronic rhinosinusitis in children. Ann Otol Rhinol Laryngol. 2009;118(3):161–5.
17. Laury AM, Bowe SN, Stramiello J, McMains KC. Balloon dilation of sinus ostia in the Department of Defense: diagnoses, actual indications, and outcomes. Laryngoscope. 2017;127(3):544–9.

18. Chaaban MR, Rana N, Baillargeon J, Baillargeon G, Resto V, Kuo Y-F. Outcomes and complications of balloon and conventional functional endoscopic sinus surgery. Am J Rhinol Allergy. 2018; https://doi.org/10.1177/1945892418782248.
19. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;(23).: 3 p preceding table of contents, 1-298.
20. Ramadan HH, Cost JL. Outcome of adenoidectomy versus adenoidectomy with maxillary sinus wash for chronic rhinosinusitis in children. Laryngoscope. 2008;118(5):871–3.
21. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. Ann Otol Rhinol Laryngol. 2010;119(9):578–82.
22. Liu J, Zhao Z, Chen Y, Xu B, Dai J, Fu Y. Clinical curative effect and safety of balloon sinuplasty in children with chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2017;100:204–10.
23. Ramadan HH, Bueller H, Hester ST, Terrell AM. Sinus balloon catheter dilation after adenoidectomy failure for children with chronic rhinosinusitis. Arch Otolaryngol Neck Surg. 2012;138(7):635.
24. Makary CA, Ramadan HH. Sinus and upper airway surgery in children. Curr Allergy Asthma Rep. 2018;18(5):32.
25. Nishioka GJ. Finding clinical efficacy with balloon sinus dilation in pediatric chronic rhinosinusitis patients. Int Forum Allergy Rhinol. 2017;7(6):629–30.
26. Gerber ME, Kennedy AA. Adenoidectomy with balloon catheter sinuplasty: a randomized trial for pediatric rhinosinusitis. Laryngoscope. 2018;128:2893. https://doi.org/10.1002/lary.27270.
27. Thottam PJ, Metz CM, Kieu MC, Dworkin J, Jagini J, Bangiyev JN, et al. Functional endoscopic sinus surgery versus balloon sinuplasty with ethmoidectomy: a 2-year analysis in pediatric chronic rhinosinusitis. Indian J Otolaryngol Head Neck Surg. 2016;68(3):300–6.
28. Thottam PJ, Haupert M, Saraiya S, Dworkin J, Sirigiri R, Belenky WM. Functional endoscopic sinus surgery (FESS) alone versus balloon catheter sinuplasty (BCS) and ethmoidectomy: a comparative outcome analysis in pediatric chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2012;76(9):1355–60.
29. 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(4):596–8.
30. Hathorn IF, Pace-Asciak P, Habib A-RR, Sunkaraneni V, Javer AR. Randomized controlled trial: hybrid technique using balloon dilation of the frontal sinus drainage pathway. Int Forum Allergy Rhinol. 2015;5(2):167–73.
31. Luong A, Batra PS, Fakhri S, Citardi MJ. Balloon catheter dilatation for frontal sinus ostium stenosis in the office setting. Am J Rhinol. 2012;22(6):621–4.
32. Roland LT, Wineland AM, Leonard DS. Balloon frontal sinuplasty for intracranial abscess in a pediatric acute sinusitis patient. Int J Pediatr Otorhinolaryngol. 2015;79(3):432–4.
33. Batra PS. Evidence-based practice. Otolaryngol Clin N Am. 2012;45(5):993–1004.
34. Levine SB, Truitt T, Schwartz M, Atkins J. In-office stand-alone balloon dilation of maxillary sinus ostia and ethmoid infundibula in adults with chronic or recurrent acute rhinosinusitis: a prospective, multi-institutional study with-1-year follow-up. Ann Otol Rhinol Laryngol. 2013;122(11):665–71.
35. Levine HL, Sertich 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;117(4):263–70.
36. Svider PF, Sekhsaria V, Cohen DS, Eloy JA, Setzen M, Folbe AJ. Geographic and temporal trends in frontal sinus surgery. Int Forum Allergy Rhinol. 2015;5(1):46–54.
37. Svider PF, Darlin S, Bobian M, Sekhsaria V, Harvey RJ, Gray ST, et al. Evolving trends in sinus surgery: what is the impact of balloon sinus dilation? Laryngoscope. 2018;128(6):1299–303.
38. Calixto NE, Gregg-Jaymes T, Liang J, Jiang N. Sinus procedures in the Medicare population from 2000 to 2014: a recent balloon sinuplasty explosion. Laryngoscope. 2017;127(9):1976–82.

39. Chaaban MR, Baillargeon JG, Baillargeon G, Resto V, Kuo Y-F. Use of balloon sinuplasty in patients with chronic rhinosinusitis in the United States. Int Forum Allergy Rhinol. 2017;7(6):600–8.
40. Piccirillo JF, Payne SC, Rosenfeld RM, Baroody FM, Batra PS, DelGaudio JM, et al. Clinical consensus statement: balloon dilation of the sinuses. Otolaryngol Neck Surg. 2018;158(2):203–14.
41. Eloy JA, Svider PF, Bobian M, Harvey RJ, Gray ST, Baredes S, et al. Industry relationships are associated with performing a greater number of sinus balloon dilation procedures. Int Forum Allergy Rhinol. 2017;7(9):878–83.
42. Fujiwara RJT, Shih AF, Mehra S. Cross-sectional analysis of the relationship between paranasal sinus balloon catheter dilations and industry payments among otolaryngologists. Otolaryngol Neck Surg. 2017;157(5):880–6.
43. Bothwell M, 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.
44. 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.
45. Kirihene RK, Rees G, Wormald PJ. The influence of the size of the maxillary sinus ostium on the nasal and sinus nitric oxide levels. Am J Rhinol. 2002;16(5):261–4.
46. Lee ER, Nadaraja GS. Evaluating the role of balloon sinuplasty in the treatment of pediatric chronic rhinosinusitis. Curr Otorhinolaryngol Rep. 2017;5(4):229–34.
47. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
48. Soler ZM, Rosenbloom JS, Skarada D, Gutman M, Hoy MJ, Nguyen SA. Response to: finding clinical efficacy with balloon sinus dilation in pediatric chronic rhinosinusitis patients. Int Forum Allergy Rhinol. 2017;7(6):631.
49. Ramadan HH. Surgical management of chronic sinusitis in children. Laryngoscope. 2004;114(12):2103–9.
50. Koskinen A, Myller J, Mattila P, Penttilä M, Silvola J, Alastalo I, et al. Long-term follow-up after ESS and balloon sinuplasty: comparison of symptom reduction and patient satisfaction. Acta Otolaryngol. 2016;136(5):532–6.

Chapter 18
Endoscopic Sinus Surgery for Pediatric Patients

Judd H. Fastenberg, Michael S. Weinstock, and John P. Bent

Introduction

The role of pediatric sinus surgery in the treatment of sinusitis continues to evolve. In the 1990s, there was growing enthusiasm that endoscopic sinus surgery (ESS) may represent a primary treatment for pediatric chronic rhinosinusitis (PCRS). Now, with a greater understanding of the role of medical management, the modality is utilized more selectively. ESS is considered a safe and effective intervention for a range of different acute and judiciously selected chronic pediatric sinus disorders.

Indications and Outcomes

The general indications for pediatric ESS fall into several distinct categories, including PCRS unresponsive to appropriate medical therapy, management of "complicated" PCRS (such as patients with comorbid immunodeficiencies, primary ciliary dyskinesia, and cystic fibrosis), symptomatic mucoceles, antrochoanal polyps,

J. H. Fastenberg (✉)
Department of Otorhinolaryngology–Head and Neck Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

M. S. Weinstock
Department of Otorhinolaryngology–Head and Neck Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

J. P. Bent
Department of Otolaryngology–Head and Neck Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Department of Otolaryngology, Children's Hospital at Montefiore, Bronx, NY, USA

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_18

allergic fungal rhinosinusitis (AFRS), and complications of acute bacterial rhinosinusitis (ABRS). The outcomes of surgical intervention vary significantly based on these indications.

PCRS Unresponsive to Medical Therapy

PCRS, which affects approximately 8% of the pediatric population, represents the most common indication for ESS [1]. The condition is defined as at least 90 continuous days of two or more of the four cardinal pediatric rhinosinusitis symptoms (nasal obstruction, purulent nasal discharge, facial pain/pressure, or cough), *in addition to* endoscopic or radiographic evidence of disease in a patient 18 years of age or younger [2]. Medical management of PCRS is generally tailored to the individual patient and may include a combination of topical and systemic therapies; however, there is no overwhelming consensus defining "appropriate" or "maximal" therapy. In general, otolaryngologists should prescribe antibiotics of at least 3 weeks' duration (optimally culture-guided) in combination with at least a month of continuous daily nasal steroid spray and nasal saline rinses for difficult PCRS. This medical regimen often obviates the need for surgery, especially when topical steroids are administered effectively. Surgeons should also consider evaluation for both food and environmental allergies before surgery.

The pathophysiologic contribution of chronic adenoiditis to chronic sinusitis is well recognized, and therefore adenoidectomy plays a significant role in the surgical treatment paradigm for PCRS. Adenoidectomy alone can be an effective surgical treatment for the appropriate patient. In a 2008 meta-analysis, Brietzke and Brigger demonstrated that adenoidectomy alone led to an improvement in 70% of patient patients with a mean age of under 6 years [3]. Ramadan et al. reported the safety and feasibility of balloon catheter dilation (BCD) in which 51/56 sinuses were successfully dilated. Their group later demonstrated that BCD in conjunction with adenoidectomy led to a higher percent of children with ≥0.5 reduction in SN-5 than adenoidectomy alone (80% vs. 53%) at 1-year follow-up, although their adenoidectomy alone cohort was less symptomatic, leaving the results less persuasive for critics [4, 5]. A subsequent prospective, multi-institutional trial of BCD for the management of uncomplicated PCRS demonstrated a clinically and statistically significant improvement in symptom control without any related adverse events [6]. Despite evidence of efficacy, there remains no clear definition regarding which pediatric patients are more appropriate for BCD versus concomitant procedures such as adenoidectomy, turbinate surgery, or ESS [7]. Our experience has been that PCRS can be markedly improved by adenoidectomy alone in the vast majority of cases, especially when PCRS exists in the setting of chronic adenoiditis with or without adenoid hypertrophy, which is shown in Figs. 18.1 and 18.2. We do not typically combine adenoidectomy with any sinus surgery unless the adenoid appears minimally hypertrophic.

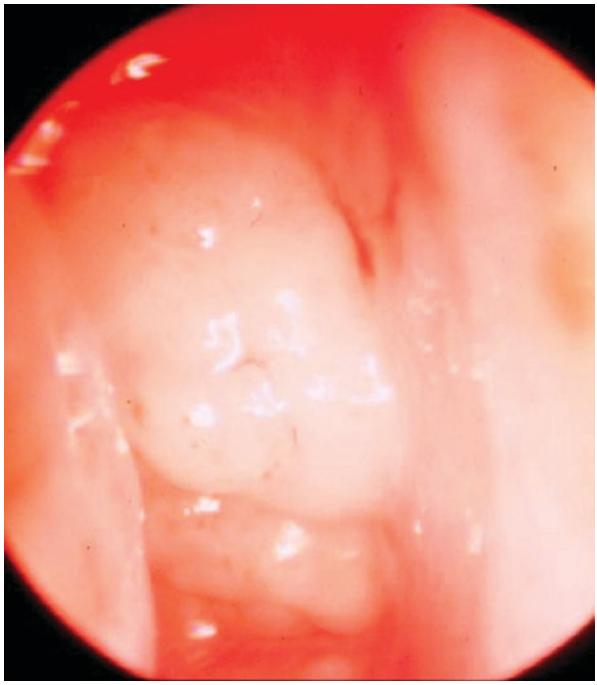


Fig. 18.1 Adenoid hypertrophy

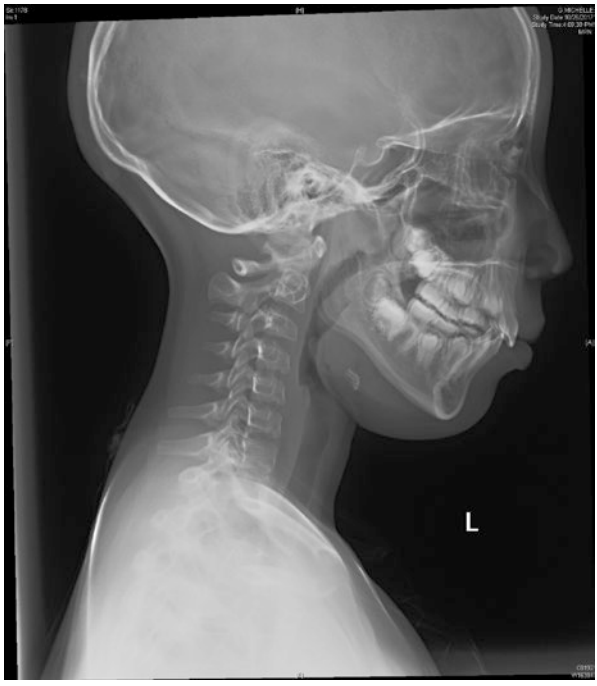


Fig. 18.2 Lateral neck X-ray demonstrating adenoid hypertrophy

Several studies have also demonstrated that ESS is an effective surgical treatment for uncomplicated PCRS. In a 2013 systemic review, Makary et al. found that ESS has a success rate ranging from 82% to 100% in improving symptoms and/or quality of life with an extracted complication rate of 1.4% [8]. A separate systemic review and meta-analysis that focused on both patients with uncomplicated PCRS and those with disease complicated by comorbid conditions such as cystic fibrosis and primary ciliary dyskinesia demonstrated a similar success rate of 71%–100% [9]. One should recognize that these relatively favorable percentages apply to carefully selected patients who did not respond to extensive medical therapy and that surgery has no role as first-line treatment in PCRS.

Complicated PCRS

Certain conditions such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and primary immunodeficiencies may predispose patients to PCRS and complicate both their surgical and medical management. Several studies have demonstrated that ESS is safe in pediatric patients with CF [10] and that combined ESS and medical therapy may help eradicate pathogenic bacteria from the sinuses of these patients and contribute to improved lung function status and delay in gram-negative lung infections [11, 12]. Similar studies have demonstrated similar ESS safety in patients with PCD, as well as the potential benefit of ESS in eradicating pathogens from the sinuses, which otherwise may serve as a bacterial reservoir that can contribute to secondary lung infections [13]. Despite these positive results, surgery will not rid the patient of their underlying vulnerability, revision surgery is commonly needed, and pernicious symptoms typically persist, so expectations should be adjusted accordingly.

Symptomatic Mucoceles, Antrochoanal Polyps, and Fungal Sinusitis

As with ESS in the adult population, there are several sinonasal diagnostic entities that are appropriate for primary surgical intervention with the addition of concomitant medical management. These include expansile mucoceles that can cause complications such as orbital and/or skull base erosion, large obstructive antrochoanal polyps, and AFRS (Fig. 18.3).

Complications of Acute Bacterial Rhinosinusitis

Complications of acute bacterial rhinosinusitis (ABRS) may result in devastating sequellae if not emergently managed. Emergent CT or MRI imaging should be ordered for any patient in whom there is clinical concern for either an orbital

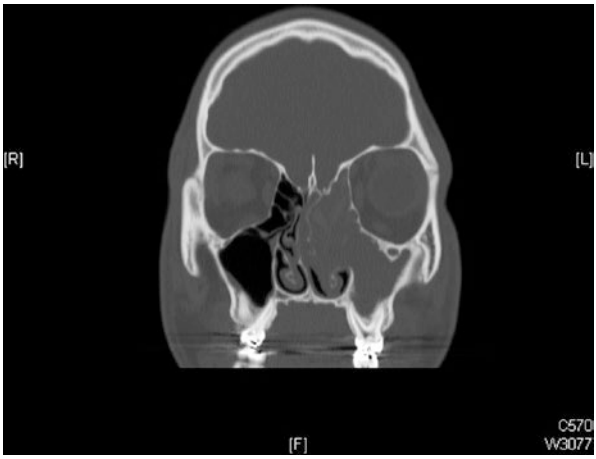


Fig. 18.3 Coronal CT consistent with left-sided AFRS

Table 18.1 Complications of sinusitis

Intracranial	Extracranial
Frontal bone osteomyelitis with abscess	Preseptal cellulitis
Epidural abscess	Orbital cellulitis
Subdural abscess	Subperiosteal abscess
Intraparenchymal abscess	Orbital abscess
Meningitis	Cavernous sinus thrombosis

complication (preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, or cavernous sinus thrombosis) or intracranial complication (meningitis, epidural, subdural, or intraparenchymal abscess, frontal bone osteomyelitis, and abscess formation) (Table 18.1). The patient's clinical status, medical history, severity of infection, and imaging findings may help differentiate patients who require urgent surgical intervention from those who can safely undergo a trial of broad-spectrum intravenous antibiotics and possibly avoid or delay surgery. Several retrospective studies have demonstrated the safety and effectiveness of ESS in the setting of orbital complications [14, 15]. Interestingly, a database study from 2015 investigating trends in orbital complications of pediatric rhinosinusitis in the USA found that the prevalence of cases requiring hospitalization has decreased, while the proportion of cases undergoing surgical intervention has increased [16].

Technique

Surgical Technique

Pediatric ESS is performed under general anesthesia with the patient supine with the head elevated from 0° to 30°. Initial vasoconstriction is typically performed with topical oxymetazoline (0.05%) pledgets. Proper labeling and close care must

be taken to not inadvertently inject topical solutions. The eyes must be protected from corneal abrasion by closing the lids with plastic tape or Tegaderm dressings; they should be kept in the surgical field when the face is prepped and draped, so that any movement, bruising, or swelling is immediately recognized. Sometimes gentle palpation of the eye helps define if the lamina papyracea remains intact. Injection of 1% lidocaine with 1:100,000 epinephrine is then typically performed with a 25-gauge needle in several areas, including the axilla of the middle turbinate, along the uncinate process and maxillary line, the face of the ethmoid bulla, and the region of the sphenopalatine artery. The extent of local anesthetic injection is largely dependent on the breadth of the planned surgery. Care should be taken to not exceed the total amount of local anesthetic in children (7 mg/kg of 1% lidocaine with epinephrine or 4.5 mg/kg for 1% lidocaine alone).

Maxillary Sinus

Surgery typically begins by addressing the maxillary sinus with a middle meatal antrostomy. This may be done with either a 0° or 30° rigid endoscope, with the latter permitting better visualization. Scope size is determined by the size of the nasal cavity—4 mm should be used unless they will not safely fit, in which case 2.7/3 mm scopes are necessary. Uncinectomy is the first step. Proper performance sets the tone for the remainder of the procedure and helps avoid surgical failure and orbital or lacrimal complications [17]. Most surgeons are comfortable with various techniques of uncinectomy, including the anterior-to-posterior "classical" technique described by Stammberger [18] or a posterior-to-anterior technique such as the "swing door" described by Wormald [19]. The former is performed by making an incision with the sharp end of an elevator or a sickle knife at uncinate's insertion into the lateral nasal wall, which should be softer in comparison to the firmer, most anterior lacrimal bone where the nasolacrimal duct is located. The latter technique is performed by identifying the free edge of the uncinate process and then introducing a backbiting instrument and cutting Blakesley forceps to first remove the midsection of the bone. The posterior-to-anterior technique should be utilized in the presence of atelectatic maxillary sinuses to avoid injury to the orbit. Once the uncinate is removed and the natural ostium is identified, the maxillary ostium can be enlarged to allow the surgeon to remove any maxillary sinus contents and easily irrigate the sinus when necessary.

In most ESS for PCRS, especially children in the first decade of life, the surgeon should be aiming to aerate the maxillary sinus only, possibly in combination with opening the anterior-inferior-medial surface of the ethmoid bullae. As such, it is not always typically worth removing the entire uncinate, in that the superior portion may remain intact. It is critical to remove the inferior uncinate to get an adequate opening of the natural maxillary sinus ostium. Furthermore, one must be very careful not to confuse a commonly seen patent posterior fontanelle ostium with the natural ostium. The natural ostium is difficult or impossible to visualize with a 0° telescope, whereas a posterior fontanelle ostium is not, so if one easily sees an

opening into the maxillary sinus with a 0° telescope, it is probably not the natural ostium. To avoid injury to the lacrimal ducts, the natural ostium should be enlarged posteriorly or not at all. Often removing the uncinate alone is sufficient. If the surgeon chooses to enlarge the ostium posteriorly, this should be done with great care, as it is easy to inadvertently tear the sinus mucosa off the roof of the orbit, which will collapse the sinus and its opening in a way that can be difficult to rectify. To minimize this risk, the surgeon will often opt to sharply divide the mucosa in the posterior aspect of the ostium.

Ethmoid Sinuses

The need for and extent of ethmoidectomy in pediatric patients is largely dictated by the extent of disease as demonstrated by CT scan findings and patient symptoms. Often the uncinate is plastered against and occluding the ethmoid's drainage pathways, and uncinectomy alone alleviates ethmoid congestion. In other instances, simply opening an approximate 5–10 mm window into the bullae provides adequate drainage. In young children, it is rarely necessary to dissect back to the basal lamella of the middle turbinate and even less necessary to perform posterior ethmoid surgery.

The full extent of the ethmoid bulla should be visible following complete uncinectomy. The bulla can be entered with a J-curette or similar instrument, usually inferomedially along the natural drainage pathway (Fig. 18.4). Anterior ethmoid

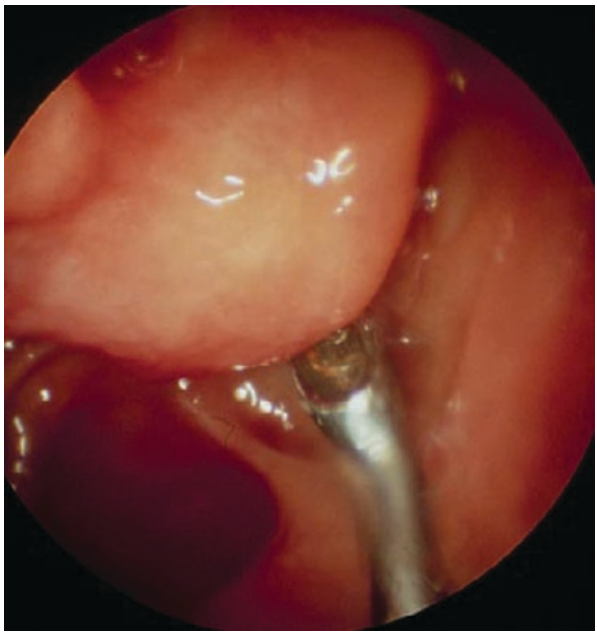


Fig. 18.4 Ethmoid bullectomy

cells are then removed with either hand instruments such as an up-biting Blakesley forceps or carefully with a powered instrument such as the microdebrider. Retro and/or supra-bullar cells can then be addressed if indicated, as may be the case in adolescents or unusual cases. In the unlikely event that posterior ethmoidectomy is performed, a J-curette or similar instrument may be placed through the basal lamella. Care must be taken to ensure that an adequate middle turbinate strut is maintained inferiorly to prevent instability that could contribute to postoperative turbinate lateralization. The lamina papyracea is identified laterally. The skull base is identified posteriorly and then is traced superiorly and anteriorly toward the area of the frontal recess. Septations may be left along the lamina and skull base, although the extent of removal is determined largely by the preference of the operating surgeon. Typically, the only reason to be performing comprehensive ethmoid surgery in children would be for AFS or polyposis.

Sphenoid Sinus

The sphenoid sinus rarely needs to be addressed during ESS, even when there is involved disease based on the CT scan. Particularly in young children, the sphenoid is very small and is affected by dependent drainage from the more anterior sinuses. For children under 10 years of age, unless they have fungal debris in their sphenoid or a suppurative complication, the sphenoid should not be addressed during initial sinus surgery. Adolescent patients sometimes follow patterns seen with adults, in that they may have chronic or acute sphenoid disease requiring targeted surgical intervention. In these cases, a sphenoidotomy may be performed either through a transnasal or transethmoidal technique. The latter is typically employed when an ethmoidectomy is also being performed as part of the surgery. The former is performed by first lateralizing the middle turbinate and identifying the superior turbinate. The sphenoid os is found just inferomedially to this structure. After identification through either technique, the ostium is enlarged using instruments such as a mushroom punch, which may necessitate partial removal of the inferior aspect of the superior turbinate. Removal of contents and irrigation of the sinus can then be performed. Care is taken to avoid damage to vital structures such as the carotid artery and optic nerve, which are typically located laterally. It is critical to review imaging and check for bony dehiscence of either structure preoperatively.

Frontal Sinus

The frontal sinus is fully developed by the age of 15. As a result, pediatric patients will have variable degrees of sinus pneumatization and development. Frontal sinusitis is usually not a problem in most children with uncomplicated CRS under the

age of 12 [20]. If the sinus is involved, as with the sphenoid, uncinectomy, possibly with maxillary antrostomy and limited anterior ethmoidectomy, will often allow the frontal sinuses to drain and aerate spontaneously. In these cases, one would want to take care to remove the uncinate up to its most superior attachment, in addition to the part that obstructs the maxillary and ethmoid sinuses. In the atypical cases when directed frontal sinusotomy is indicated, conservative opening with either Draf I or Draf IIA sinusotomy is typically sufficient.

Septum

Septoplasty is only performed in the case of significant obstruction, preventing access to the sinuses or causing significant nasal obstruction. We proceed with targeted and conservative septoplasty, either through an open or endoscopic technique, but in most cases we are able to leave mild to moderate septal deviation untreated and still obtain excellent results. Although there are favorable results of large series of septoplasty in children, such as from Crysdale et al. who modified in the quadrangular cartilage through an open rhinoplasty approach, there is no consensus regarding the risks of the surgery, and therefore many are reluctant to perform the surgery given that nasal growth centers are at risk, at least hypothetically. There is no evidence to suggest that isolated septoplasty will be helpful for PCRS.

Concha Bullosa

Resection of concha bullosa cells (pneumatization of the middle turbinate) may be performed by removing the lateral aspect of the cell with either hand or powered instruments. The surgeon should take care to sharply divide the lateral component prior to removal to avoid trauma to the middle turbinate's medial component or its vertical attachment to the skull base. Similarly, one should use sharp techniques in detaching the posterior extent of the concha bullosa to avoid tearing more tissue than desired and risk bleeding where sphenopalatine branches course across the lateral nasal wall.

The indication for concha excision correlates with size. Removal of the lateral extent of the concha bullosa, especially larger cells, leads to markedly easier sinus surgery. The concha functions like an intranasal space expander, and with its lateral wall gone, the middle meatus can be several times larger than usual, which greatly enhances visibility and maneuverability. Because removal of smaller concha bullosa cells may not add much advantage and could risk middle meatal adhesions, they should be approached judiciously. However, it should be noted that there is no evidence to suggest that concha bullectomy contributes to improved outcomes.

Image Guidance

Image-guided surgery (IGS) is an important adjunct tool that may help surgeons perform safer and more comprehensive sinus surgery. While it is not a substitute for sound knowledge of anatomy, critical decision-making, or technical experience, for well-trained otolaryngologists, it may help increase surgeon confidence and reduce fear of complications involving the orbit or brain. Although the technology has become commonplace, the use of image guidance is not mandatory or standard of care. It is therefore used on a case-by-case basis at the discretion of the operating surgeon. The American Academy of Otolaryngology lists seven relative indications for use of image guidance, including the presence of distorted anatomy (Table 18.2). Given the varying degrees of development and pneumatization of pediatric sinuses, IGS may be particularly useful for these cases. Furthermore, complications of ABRS such as orbital complications should also necessitate use of the tool. On the other hand, the most common and appropriate pediatric ESS procedures, uncinectomy with conservative middle meatal antrostomy and anterior ethmoidectomy, benefit relatively less from image guidance. We usually do not use IGS for these procedures and find that the challenge is not anatomic orientation but rather a very narrow space that often bleeds easily as a result of chronic inflammation.

Postoperative Care

Patients should be instructed to start nasal saline irrigations shortly after surgery. The use of postoperative antibiotics and steroids should be tailored to the patients based on the clinical situation and the indication for surgery. Survey studies have demonstrated wide variation in surgeon preferences in regard to prescribing patterns [21].

Table 18.2 Position statement: Intraoperative use of computer-aided surgery (approved 2002, revised 2014)

1. Revision sinus surgery
2. Distorted sinus anatomy of development, 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. CSF rhinorrhea or conditions where a skull base defect is present
7. Benign and malignant sinonasal neoplasms

Follow-Up

Postoperative care of the sinonasal cavity is critical for optimal surgery outcomes. This includes postoperative debridement, which may help prevent undesired sequellae such as synechiae and early ostia closure. The main aims of debridements are to lyse early adhesions and remove blood clot, spacers, packing, or stents placed at the time of initial surgery. Whereas adults can frequently tolerate this procedure in the office setting, most pediatric patients cannot. Surgeons should therefore be prepared to debride pediatric patients in the operating room under general anesthesia if recovery is not proceeding as planned and prepare parents for this possibility as part of the preoperative consent. These "second look" procedures, typically performed 2–3 weeks following the initial surgery, were at one time common but are not frequently necessary and therefore have fallen out of favor [22–24]. If patients allow for adequate examination in the office and the sinonasal cavity appears to be healing well, allowing "biological dressings" to remain in place may be the best option with continued use of moisture and irrigations to facilitate nasal hygiene and healing. Furthermore, Ramadan et al. demonstrated that treatment with intravenous dexamethasone during initial ESS may reduce maxillary mucosal edema, ethmoid scarring, and incidence of maxillary ostia closure, thus decreasing the need for second-look procedures [23].

Midface Growth

Although 12% of sinus surgeons in one study reported that they avoid performing ESS in pediatric patients out of concern for facial growth retardation [25], several contemporary studies have refuted this concern [26–28]. Early concern likely stemmed from older evidence that other facial surgeries, such as septoplasty, cleft palate repair, and repair of mandibular fractures, may lead to such issues [29–31]. A 1995 study by Mair et al. then demonstrated that, in piglets undergoing unilateral sinus surgery, the ipsilateral maxillary and ethmoid sinuses reached only 57% and 65% of the size of the nonoperated side, respectively [32]. Fortunately, more recent investigations have provided reassurance that these risks do not apply to humans. Specifically, prospective studies have demonstrated that there is no statistically significant change in sinus volumes or cephalometric parameters in patients who underwent ESS compared to those who did not [26–28].

Conclusions

Pediatric endoscopic sinus surgery (ESS) is a safe and effective intervention for select pediatric sinus disorders, including both chronic and acute conditions. Outcomes and rates of success vary significantly, largely due to a lack of consensus

on indications, technique, concurrent medical therapy, as well as postoperative management. While adenoidectomy plays a critical role in the surgical treatment of PCRS, and, more recently, BCD has generated interest and encouraging preliminary results, further study is necessary to standardize an evidence-based surgical paradigm and to identify which pediatric patients would benefit most from surgical intervention.

References

1. Kay DJ, Rosenfeld RM. Quality of life for children with persistent sinonasal symptoms. Otolaryngol Head Neck Surg. 2003;128(1):17–26.
2. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
3. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008;72(10):1541–5.
4. Ramadan HH. Safety and feasibility of balloon sinuplasty for treatment of chronic rhinosinusitis in children. Ann Otol Rhinol Laryngol. 2009;118(3):161–5.
5. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. Ann Otol Rhinol Laryngol. 2010;119(9):578–82.
6. Soler ZM, Rosenbloom JS, Skarada D, Gutman M, Hoy MJ, Nguyen SA. Prospective, multicenter evaluation of balloon sinus dilation for treatment of pediatric chronic rhinosinusitis. Int Forum Allergy Rhinol. 2017;7(3):221–9.
7. Gudis DA, Soler ZM. Update on pediatric sinus surgery: indications and outcomes. Curr Opin Otolaryngol Head Neck Surg. 2017;25(6):486–92.
8. Makary CA, Ramadan HH. The role of sinus surgery in children. Laryngoscope. 2013;123(6):1348–52.
9. Vlastarakos PV, Fetta M, Segas JV, Maragoudakis P, Nikolopoulos TP. Functional endoscopic sinus surgery improves sinus-related symptoms and quality of life in children with chronic rhinosinusitis: a systematic analysis and meta-analysis of published interventional studies. Clin Pediatr (Phila). 2013;52(12):1091–7.
10. Tumin D, Hayes D Jr, Kirkby SE, Tobias JD, McKee C. Safety of endoscopic sinus surgery in children with cystic fibrosis. Int J Pediatr Otorhinolaryngol. 2017;98:25–8.
11. Aanaes K, von Buchwald C, Hjuler T, Skov M, Alanin M, Johansen HK. The effect of sinus surgery with intensive follow-up on pathogenic sinus bacteria in patients with cystic fibrosis. Am J Rhinol Allergy. 2013;27(1):e1–4.
12. Alanin MC, Aanaes K, Hoiby N, et al. Sinus surgery postpones chronic Gram-negative lung infection: cohort study of 106 patients with cystic fibrosis. Rhinology. 2016;54(3):206–13.
13. Alanin MC, Aanaes K, Hoiby N, et al. Sinus surgery can improve quality of life, lung infections, and lung function in patients with primary ciliary dyskinesia. Int Forum Allergy Rhinol. 2017;7(3):240–7.
14. Segal N, Nissani R, Kordeluk S, et al. Orbital complications associated with paranasal sinus infections - a 10-year experience in Israel. Int J Pediatr Otorhinolaryngol. 2016;86:60–2.
15. Sciarretta V, Dematte M, Farneti P, et al. Management of orbital cellulitis and subperiosteal orbital abscess in pediatric patients: a ten-year review. Int J Pediatr Otorhinolaryngol. 2017;96:72–6.
16. Capra G, Liming B, Boseley ME, Brigger MT. Trends in orbital complications of pediatric rhinosinusitis in the United States. JAMA Otolaryngol Head Neck Surg. 2015;141(1):12–7.
17. Richtsmeier WJ. Top 10 reasons for endoscopic maxillary sinus surgery failure. Laryngoscope. 2001;111(11 Pt 1):1952–6.

18. Stammberger H. An endoscopic study of tubal function and the diseased ethmoid sinus. Arch Otorhinolaryngol. 1986;243(4):254–9.
19. Wormald PJ, McDonogh M. The 'swing-door' technique for uncinectomy in endoscopic sinus surgery. J Laryngol Otol. 1998;112(6):547–51.
20. CA M. Pediatric sinus surgery for chronic rhinosinusitis. Oper Tech Otolaryngol Head Neck Surg. 2018;29(2):89–93.
21. Fang CH, Fastenberg JH, Fried MP, Jerschow E, Akbar NA, Abuzeid WM. Antibiotic use patterns in endoscopic sinus surgery: a survey of the American Rhinologic Society membership. Int Forum Allergy Rhinol. 2018;8(4):522–9.
22. Walner DL, Falciglia M, Willging JP, Myer CM 3rd. The role of second-look nasal endoscopy after pediatric functional endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg. 1998;124(4):425–8.
23. Ramadan HH. Corticosteroid therapy during endoscopic sinus surgery in children: is there a need for a second look? Arch Otolaryngol Head Neck Surg. 2001;127(2):188–92.
24. Younis RT. The pros and cons of second-look sinonasal endoscopy after endoscopic sinus surgery in children. Arch Otolaryngol Head Neck Surg. 2005;131(3):267–9.
25. Beswick DM, Ramadan H, Baroody FM, Hwang PH. Practice patterns in pediatric chronic rhinosinusitis: a survey of the American Rhinologic Society. Am J Rhinol Allergy. 2016;30(6):418–23.
26. 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.
27. 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.
28. Van Peteghem A, Clement PA. Influence of extensive functional endoscopic sinus surgery (FESS) on facial growth in children with cystic fibrosis. Comparison of 10 cephalometric parameters of the midface for three study groups. Int J Pediatr Otorhinolaryngol. 2006;70(8):1407–13.
29. Verwoerd CD, Urbanus NA, Nijdam DC. The effects of septal surgery on the growth of nose and maxilla. Rhinology. 1979;17(2):53–63.
30. Bernstein L. The effect of cleft palate operations on subsequent growth of the maxilla. Laryngoscope. 1968;78(9):1510–65.
31. McGuirt WFSP. Mandibular fractures: their effect on growth and dentition. Arch Otolaryngol Head Neck Surg. 1987;113(3):257–61.
32. Mair EA, Bolger WE, Breisch EA. Sinus and facial growth after pediatric endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg. 1995;121(5):547–52.

Chapter 19
Septoplasty and Turbinate Reduction in Children

Christian P. Soneru, Charles A. Riley, and David A. Gudis

Introduction

As in the adult patient, nasal obstruction may significantly affect quality of life and contribute to other disease processes such as obstructive sleep apnea (OSA) in the pediatric patient. Although there are multiple possible causes of nasal obstruction, structural issues such as a nasal septal deviation (NSD) and inferior turbinate hypertrophy (ITH) are frequently discovered in the workup of a child who presents with nasal obstruction. Nasal obstruction from any cause often leads to obligate mouth breathing which has been associated with dental malocclusion and abnormalities of craniofacial development [1–3]. Obligate mouth breathing caused specifically by NSD has also been shown to be associated with craniofacial and dental anomalies [4, 5]. The historical controversies over concern for the effects of pediatric septoplasty on craniofacial growth may cause apprehension for the surgeon. However, recent research demonstrates that septoplasty performed using meticulous technique does not result in long-term craniofacial growth abnormalities. Although septoplasty and inferior turbinate reduction have no role in the management of chronic sinusitis [6], they have been shown to be very effective in treating nasal obstruction in the pediatric patient.

C. P. Soneru · C. A. Riley · D. A. Gudis (✉)
Department of Otolaryngology - Head and Neck Surgery, Columbia University Irving Medical Center, New York, NY, USA

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_19

Anatomy

The septum is made of mucoperichondrial and mucoperiosteal flaps that envelope the quadrangular cartilage and bony septum, comprised of the perpendicular plate of the ethmoid bone, the vomer, and the crests of the maxillary and palatine bones. The main difference between the pediatric and adult septum is in the proportion of the septum made up of cartilage. An anatomic study has shown that the cartilaginous portion of the septum reaches adult dimensions by 2 years of age, with subsequent growth due to expansion of the bony parts of the septum [7]. The inferior turbinate consists of a bony core covered by mucosa and vascularized erectile submucosal tissue. It is formed by the embryonic maxilloturbinal, which develops as a projection from the lateral nasal wall. Unlike the other turbinates, the inferior turbinate is not considered to be of ethmoid origin embryologically. The inferior turbinate attaches to the lateral nasal wall just below the middle turbinate, from just posterior to the pyriform aperture anteriorly to just anterior to the choanae posteriorly [8].

Evaluation of the Septum and Inferior Turbinate in the Pediatric Patient

A thorough head and neck exam with particular attention to anterior rhinoscopy and a thorough nasal endoscopy is optimal to determine the cause or causes of nasal obstruction. Although NSD and ITH commonly contribute to pediatric nasal obstruction, adenoid hypertrophy is often found concurrently. Furthermore, congenital nasal masses must be ruled out. Not all practitioners perform routine nasal endoscopy; in a survey of pediatric otolaryngologists on the evaluation and management of the pediatric patient with bilateral nasal obstruction, plain film was used more frequently in younger age groups while fiberoptic nasal endoscopy was used more often in older age groups [9]. The authors hypothesized that this was because fiberoptic endoscopy is more difficult to perform and adenoid hypertrophy is more likely in the younger patient (ages 3–6). If adenoid hypertrophy is suspected, a lateral neck plain film may be helpful. If the examination raises concern for a nasal mass, computed tomography (CT) scan and magnetic resonance imaging (MRI) should also be performed.

Full evaluation of the pediatric patient who presents with nasal obstruction must also consider allergic and nonallergic rhinitis. Allergic rhinitis is among the most common chronic conditions of childhood [10] with well-defined clinical symptoms and management guidelines [11, 12]. In a study of children and adolescents with moderate-to-severe persistent allergic rhinitis who were treated with daily intranasal steroids and oral antihistamines or leukotriene receptor antagonists for at least 2 months, nonresponders to medical therapy showed a higher prevalence of objective NSD and severe ITH compared to patients who responded to medical therapy.

This study highlights the importance of appropriate follow-up, a thorough physical exam, and a broad differential diagnosis in pediatric patients who present with nasal obstruction [13].

Consideration must also be given to the possibility of concurrent sleep disordered breathing. It has been shown that nasal obstruction may contribute to OSA [14]. Although adenotonsillar hypertrophy is the most common cause of OSA in children, a significant portion of children have persistent apnea or hypopnea after tonsillectomy and adenoidectomy [15]. A subset of these patients has nasal obstruction due to an NSD and/or ITH, indicating the importance of a thorough exam prior to embarking on surgery.

Pediatric Septoplasty: Effect on Facial Growth

Although septoplasty is one of the most common procedures performed by otolaryngologists on adults, it has been a controversial area in the pediatric population because early animal studies demonstrated craniofacial growth abnormalities following septal resection. In a study from 1858, examining anatomic parameters after resection of the cartilaginous nasal septum in growing animals, the hard palate was found to be significantly shorter in the anterior-to-posterior direction [16]. In a study several decades later, Landsberger resected the anterior septum in a young canine model and discovered that the nasal cavity floor was higher than normal 6 months later [17], resulting in the hypothesis that growth of the septum affected the position of the hard palate. A later study on the effects of resection of the cartilaginous septum and mucoperichondrium in growing rabbits found underdevelopment of the nasal and premaxillary bones with the extent and severity of deformity proportional to the extent of the septal defect [18]. More recently, animal studies have found no effect on facial growth if the mucoperichondrial flaps were preserved during septoplasty, with studies performed on both canine pups [19] and growing ferrets [20].

Following these promising findings with mucoperichondrial flap preservation in animal models, human studies began appearing which confirmed the lack of effect on craniofacial growth. Both Jugo [21] and Triglia et al. [22] performed external septoplasty in children and did not find any serious alterations on craniofacial growth based on subjective visual assessment. Studies utilizing anthropometric measurements provided a more objective analysis. Bejar et al. [23] compared postoperative anthropometric measurements in 28 children who underwent external septoplasty to normative data and found that most measurements were similar to normal averages. Although the nasal dorsal length was decreased in this cohort postoperatively, it is unclear if this was attributable to surgery as measurements were not routinely made preoperatively. To build on these findings, El-Hakim et al. [24] compared preoperative to postoperative measurements in 26 pediatric patients undergoing external septoplasty. Although nasal dorsum length and nasal tip protrusion were decreased postoperatively, the differences were not statistically significant.

With regard to conservative endonasal septoplasty, one study of 44 pediatric patients found no significant differences in anthropometric measurements compared to normal values when taken at an average of 12.2 years following surgery [25].

Pediatric Septoplasty: Indications

Based on the available research, current evidence suggests that pediatric septoplasty with careful preservation of the mucoperichondrial flaps can be performed without altering craniofacial growth. In addition, there is evidence that untreated obligate mouth breathing may lead to dental malocclusion and craniofacial growth disturbance. Therefore, a septoplasty should be considered in the child with an NSD that is associated with obligate mouth breathing or obstructive sleep apnea. To date, there is no consensus based on the published data that defines the minimum age to perform a septoplasty. However, several authors have advocated a minimum age of five [26] or six [23, 27] years in children with severe nasal obstruction caused by NSDs. Other studies have advocated for closed reduction of severe NSDs in the neonatal period as malocclusion was frequently found if left untreated [5, 28]. In neonates, NSDs can occur due to trauma in utero or during birth and may be associated with important clinical implications including failure to thrive or respiratory distress. These can be ameliorated with closed reduction within the first few weeks of life. Finally, with the expansion of endoscopic endonasal skull base surgery in the pediatric population, septoplasty may be indicated for access to certain skull base pathologies [29].

Pediatric Septoplasty: Outcomes

Several studies have evaluated outcomes after pediatric septoplasty. Dispenza et al. performed a retrospective study of 46 patients (aged 4–12) who underwent endonasal septoplasty or closed septorhinoplasty and were followed for an average of 10 years [30]. Of the 16 patients with isolated NSDs, only 1 patient (6.3%) developed a recurrence postoperatively. Of the remaining patients with combined nasal and septal deformity, a lower rate of recurrent NSD was identified in those treated with septorhinoplasty (14.7%) relative to septoplasty alone (25%), although no statistical analysis was performed. In a study evaluating postoperative quality of life, Yilmaz et al. followed 35 patients with a mean age of 13.4 years for 12 months after endonasal septoplasty and found significant improvements in both nose obstruction symptom evaluation (NOSE) and visual analog scale (VAS) [31]. A second study of 28 patients found significant improvements postoperatively in the VAS as well as in the Sinus and Nasal Quality of Life Survey (SN-5), a quality of life instrument validated in the pediatric population [32].

Pediatric Septoplasty: Technique

A variety of operative techniques can be utilized to correct an NSD in the pediatric patient. Although closed septal repositioning does not have much use in managing a deviated nasal septum in the adult patient, it may be efficacious in the pediatric patient, particularly in the setting of an acutely displaced septum as a result of trauma [26]. A Boies elevator or Asch forceps may be used in this situation. Targeted endoscopic septoplasty may also be performed. In the setting of small, isolated spurs, the spur may be resected without flap elevation [26], although resection of mucoperichondrium must be kept to a minimum. The majority of septal spurs can be managed safely via an endoscopic approach with a small mucoperichondrial flap raised over the deviated bone and cartilage only (Figs. 19.1 and 19.2). Alternatively, a standard Killian or hemitransfixion incision may be made and a mucoperichondrial flap raised. Once the deviated cartilage is isolated, straightening may be achieved with relaxing incisions along the convex side of the deviation. If cartilage needs to be removed to achieve an adequate nasal airway, it is important to reimplant any straight pieces of bone and cartilage [24] or to flatten or crush pieces of deviated cartilage and reimplant them between the mucoperichondrial flaps. At the conclusion of the procedure, an absorbable quilting suture and/or Silastic splints may be used to reapproximate the mucoperichondrial flaps.

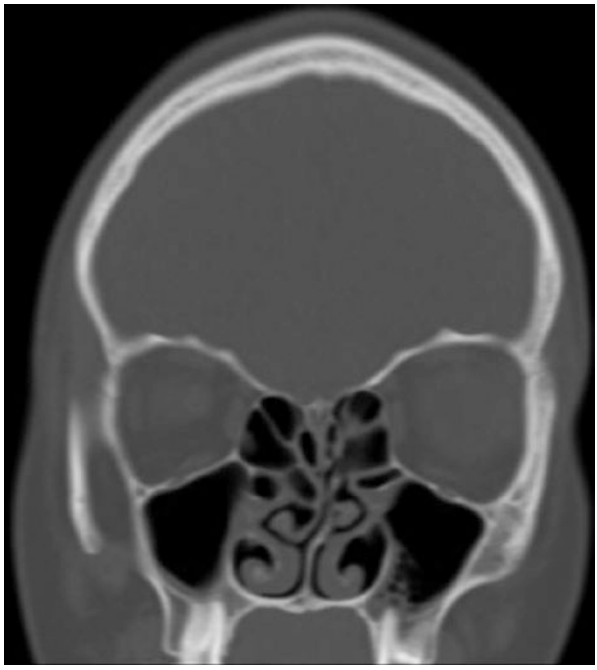


Fig. 19.1 Image from a coronal CT scan of a pediatric patient with a severely deviated septum toward the left side. Patient presented with chronic left-sided nasal obstruction

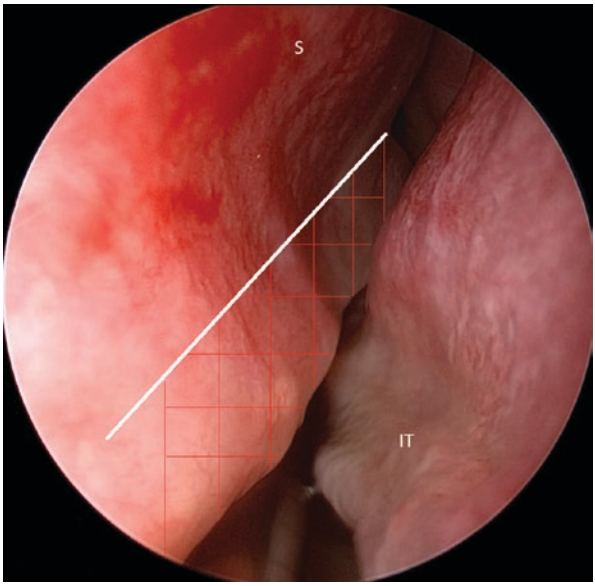


Fig. 19.2 An endoscopic view of the left nasal cavity demonstrating a septal deviation compromising the nasal airway. This deviation can be removed safely via an endoscopic approach with a small mucoperichondrial flap raised over the deviated bone and cartilage only. Only the deviated cartilage and bone (red-checked area) should be removed. Any straight pieces of bone and cartilage are replaced between the mucoperichondrial flaps. The septal bone and cartilage above the white line are not removed. (S Septum, IT Inferior turbinate)

Surgery on the Inferior Turbinate

ITH is a very common cause of pediatric nasal obstruction (Fig. 19.3). Often found concurrently with allergic rhinitis, medical therapy may include intranasal corticosteroid sprays, oral leukotriene receptor antagonists, antihistamines (oral or intranasal), and immunotherapy in the appropriate patient. If medical treatments fail to achieve symptomatic relief, surgery on the inferior turbinates may be performed, with the goal of expanding the nasal airway while preserving the mucosa of the turbinate to minimize crusting and preserve function. Inferior turbinate reduction may be performed as an isolated procedure or in conjunction with adenotonsillectomy, adenoidectomy, endoscopic sinus surgery, or septoplasty.

There are several surgical options to treat inferior turbinate hypertrophy. Partial and total turbinectomy were once the procedures of choice [33] but have largely been replaced by mucosal-sparing techniques due to the concerns for postoperative pain, crusting, bleeding, and atrophic rhinitis [34]. Lasers have also been used for destruction of hypertrophic mucosa of the inferior turbinate, most commonly with the carbon dioxide (CO2) and neodymium:yttrium-aluminum garnet (Nd:YAG) lasers. However, this technique has largely fallen out of favor given the risks of persistent crusting, atrophy, and synechiae formation [35].

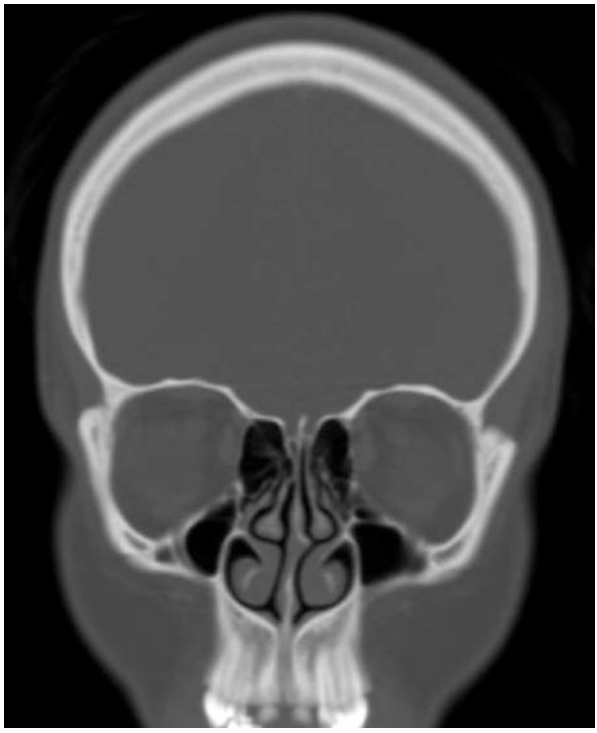


Fig. 19.3 Coronal CT demonstrating bilateral inferior turbinate hypertrophy. This patient failed appropriate medical therapy

Results from early studies have led to the adoption of mucosal-sparing techniques. Submucosal resection is a mucosal-sparing option in which the submucosal tissue is removed with or without bone removal. Monopolar electrocautery with Bovie may be performed in the submucosal tissue but creates high temperatures and often thermal damage to the mucosal layer. A more recent development is radiofrequency ablation, which uses a submucosal radiofrequency delivered by bipolar current to create a plasma field that ablates soft tissue and creates necrosis at a lower temperature, therefore preserving the overlying mucosa. As the area of necrosis heals, the lesion contracts, leading to a reduction in size of the inferior turbinate [36]. In addition to research demonstrating long-term benefits in adults [37], it has been shown to be effective and safe in the pediatric population [38]. Microdebrider-assisted inferior turbinoplasty (MAIT) is another option [39]. After the inferior turbinate is infiltrated with local anesthetic, a vertical incision is made at the head of the inferior turbinate. A submucosal tunnel is then created with sharp dissection, and a straight microdebrider is applied through the incision. Lower-profile microdebrider blades specifically designed for this procedure have been developed (Inferior Turbinate Blade; Medtronic Corporation, Minneapolis, MN; Fig. 19.4). The incision site is then cauterized if needed, and typically no nasal packing is necessary.

Multiple comparisons of the various surgical techniques have been performed for managing inferior turbinate hypertrophy in the adult patient. A systematic review and meta-analysis of studies comparing radiofrequency ablation and MAIT found

Fig. 19.4 Inferior turbinate blade attachment for microdebrider (Medtronic Inc., Minneapolis, MN) allows for submucousal resection of hypertrophic inferior turbinate tissue

patient improvement with both techniques, although the largest, highest-quality studies favored MAIT [40]. For the pediatric population, there have been relatively few studies evaluating outcomes of inferior turbinate surgery. A review of the literature performed in 2009 identified 11 articles in which turbinate surgery was performed in pediatric patients with nasal congestion refractory to medical management [41]. Each article identified in this review evaluated techniques popular at the time of the article's publication, with the earlier studies reporting on partial or total turbinectomy and the more recent studies reporting on radiofrequency ablation and microdebrider use. Overall, 50–94% of participants improved subjectively, although the heterogeneity of the outcome measures did not allow for meta-analysis. Since that time, two other studies have been performed. Cheng et al. evaluated 51 children with obstructive sleep apnea and nasal congestion due to persistent severe allergic rhinitis refractory to medical therapy, of which 28 underwent adenotonsillectomy (AT) alone and 23 underwent adenotonsillectomy with concurrent MAIT [42]. When compared to the cohort that underwent AT alone, the cohort that underwent AT and MAIT showed significantly greater improvements postoperatively with respects to apnea-hypopnea index, acoustic rhinometry, and subjective quality of life. The second study was a retrospective review from a single academic institution of 107 children who underwent surgery on the inferior turbinate [43]. Procedures included radiofrequency ablation (67.3%), MAIT (17.8%), and partial turbinate resection (19.6%). Revision inferior turbinate surgery was performed in 7.5% of all patients with no significant difference between the surgical techniques used at the initial procedure. Based on a telephone survey utilizing a 5-point Likert scale taken at a median of 4.55 years after the procedure, the authors found that 70% of patients were satisfied or extremely satisfied with the procedure, with no difference between the various surgical techniques.

Although there is limited evidence on the long-term benefits of inferior turbinate surgery in pediatric patients, a survey of pediatric otolaryngologists discovered that 81% of respondents performed the procedure, with 47% of preferring coblation, 16% using MAIT primarily, and the remainder preferring other techniques [44]. This high rate is likely due at least in part to the safety of pediatric turbinate surgery, with an overall complication rate of around 4% based on the largest review [41]. The complications in this study consisted of intranasal synechiae (62%) and postoperative epistaxis (34%). Inferior turbinate reduction has also not been shown to increase the complication rate when performed concurrently with adenoidectomy [45] or AT [46].

Conclusion

Septoplasty and inferior turbinate reduction may be performed safely and effectively in the pediatric patient with nasal obstruction due to a deviated nasal septum and inferior turbinate hypertrophy refractory to medical therapy. Historical concerns regarding craniofacial developmental abnormalities have been alleviated, as recent publications have demonstrated no effect on facial growth if mucoperichondrial septal flaps are preserved. Proper surgical technique and patient selection optimizes chances for a successful outcome and improved quality of life.

References

1. Linder-Aronson S. Adenoids: their effect on mode of breathing and nasal airflow and their relationship to characteristics of the facial skeleton and the dentition. A biometric, rhinomanometric and cephalometro-radiographic study on children with and without adenoids. Acta Otolaryngol Suppl. 1970;265:1–132.
2. Luzzi V, Di Carlo G, Saccucci M, et al. Craniofacial morphology and airflow in children with primary snoring. Eur Rev Med Pharmacol Sci. 2016;20(19):3965–71.
3. Bresolin D, Shapiro PA, Shapiro GG, Chapko MK, Dassel S. Mouth breathing in allergic children: its relationship to dentofacial development. Am J Orthod. 1983;83(4):334–40.
4. D'ascanio L, Lancione C, Pompa G, Rebuffini E, Mansi N, Manzini M. Craniofacial growth in children with nasal septum deviation: a cephalometric comparative study. Int J Pediatr Otorhinolaryngol. 2010;74(10):1180–3.
5. Pentz S, Pirsig W, Lenders H. Long-term results of neonates with nasal deviation: a prospective study over 12 years. Int J Pediatr Otorhinolaryngol. 1994;28(2–3):183–91.
6. Brietzke S, Shin J, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
7. Van Loosen J, Van Zanten GA, Howard CV, Verwoerd-Verhoef HL, Van Velzen D, Verwoerd CD. Growth characteristics of the human nasal septum. Rhinology. 1996;34(2):78–82.
8. Mynatt RG, Sindwani R. Surgical anatomy of the paranasal sinuses. In: Stucker FJ, de Souza C, Kenyon GS, Lian TS, Draf W, Schick B, editors. Rhinology and facial plastic surgery. Berline: Springer; 2009.
9. Kohlberg GD, Stewart MG, Ward RF, April MM. Evaluation and management of pediatric nasal obstruction: a survey of practice patterns. Am J Rhinol Allergy. 2016;30:274–8.
10. Izquierdo-Dominguez A, Valero AL, Mullol J. Comparative analysis of allergic rhinitis in children and adults. Curr Allergy Asthma Rep. 2013;13:142–51.
11. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update. Allergy. 2008;63:8–160.
12. Montoro J, Del Cuvillo A, Mullol J, et al. Validation of the modified allergic rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. Allergy. 2012;67:1436–42.
13. Marino-Sanchez FS, Valls-Mateus M, Ruiz-Echevarria K, Alobid I, Cardenas-Escalante P, Jimenez-Feijoo R, Lozano-Blasco J, et al. Nasal obstructive disorders induce medical treatment failure in pediatric persistent allergic rhinitis (the NODPAR study). Pediatr Allergy Immune. 2017;28:176–84.
14. Suratt PM, Turner BL, Wilhoit SC. Effect of intranasal obstruction on breathing during sleep. Chest. 1986;90:324–9.

15. Lipton AJ, Gozal D. Treatment of obstructive sleep apnea in children: do we really know how? Sleep Med Rev. 2003;7:61–80.
16. Fick L. Uber die Ursachen der Knochenforman: Experimental Untersuchung. Wigand GH: Gottingen; 1858.
17. Landsberger R. Die triebende Krafte zur Dehnung und Streckung des Gesichtschadels. Zahnarztliche Runschau. 1929;23:978–90.
18. Sarnat BG, Wexler MR. Growth of the face and jaws after resection of the septal cartilage in the rabbit. Am J Anat. 1966;118:755–67.
19. Bernstein L. Early submucous resection of nasal septal cartilage: a pilot study in canine pubs. Arch Otolaryngol. 1973;97(3):273–8.
20. Cupero TM, Middleton CE, Silva AB. Effects of functional septoplasty on the facial growth of ferrets. Arch Otolaryngol Head Neck Surg. 2001;127(11):1367–9.
21. Jugo SB. Total septal reconstruction through decortication (external) approach in children. Arch Otolaryngol Head Neck Surg. 1987;113(2):173–8.
22. Triglia JM, Cannoni M, Pech A. Septorhinoplasty in children: benefits of the external approach. J Otolaryngol. 1990;19(4):274–8.
23. Bejar I, Farkas LG, Messner AH, Crysdale WS. Nasal growth after external septoplasty in children. Arch Otolaryngol Head Neck Surg. 1996;122:816–21.
24. El-Hakim H, Crysdale WS, Abdollel M, Farkas LG. A study of anthropometric measures before and after external septoplasty in children: a preliminary study. Arch Otolaryngol Head Neck Surg. 2001;127:1362–6.
25. Tasca I, Compadretti GC. Nasal growth after pediatric septoplasty at long-term follow-up. Am J Rhinol Allergy. 2011;25:e7–e12.
26. Christophel JJ, Gross CW. Pediatric Septoplasty. Otolaryngol Clin N Am. 2009;42:287–94.
27. Crysdale WS, Walker PJ. External septorhinoplasty in children: patient selection and surgical technique. J Otolaryngol. 1994;23:28–31.
28. Sooknundun M, Kacker SK, Bhatia R, Deka RC. Nasal septal deviation: effective intervention and long term follow-up. Int J Pediatr Otorhinolaryngol. 1986;12(1):65–72.
29. Chivukula S, Koutourousiou M, Snyderman CH, Fernandez-Miranda JC, Gardner PA, Tyler-Kabara EC. Endoscopic endonasal skull base surgery in the pediatric population. J Neurosurg Pediatr. 2013;11:227–41.
30. Dispenza F, Saraniti C, Sciandra D, Kulamarva G, Dispenza C. Management of nasoseptal deformity in childhood: long-term results. Auris Nasus Larynx. 2009;36:665–70.
31. Yilmaz MS, Guven M, Akidil O, Kayabasoglu G, Demir D, Mermer H. Does septoplasty improve the quality of life in children? Int J Pediatr Otorhinolaryngol. 2014;78:1274–6.
32. Lee VS, Gold RM, Parikh SR. Short-term quality of life outcomes following pediatric septoplasty. Acta Otolaryngol. 2017;137(3):293–6.
33. Segal S, Eviatar E, Berenholz L, Kessler A, Shlamkovitch N. Inferior turbinectomy in children. Am J Rhinol. 2003;17(2):69–73.
34. Nurse LA, Duncavage JA. Surgery of the inferior and middle turbinates. Otolaryngol Clin N Am. 2009;42(2):295–309.
35. Janda P, Stroka R, Baumgartner R. Laser treatment of hyperplastic inferior nasal turbinates: a review. Lasers Surg Med. 2001;28:404–14.
36. Utley DS, Goode RL, Hakim I. Radiofrequency energy tissue ablation for the treatment of nasal obstruction secondary to turbinate hypertrophy. Laryngoscope. 1999;109:683–6.
37. Bhattacharyya N, Kepnes LJ. Clinical effectiveness of coblation inferior turbinate reduction. Otolaryngol Head Neck Surg. 2003;129:365–71.
38. Bitar MA, Kanaan AA, Sinno S. Efficacy and safety of inferior turbinate coblation in children. J Laryngol Otol. 2014;128(Suppl 2):S48–54.
39. Friedman M, Tanyeri H, Lim J, Landsberg R, Caldarelli D. A safe, alternative technique for inferior turbinate reduction. Laryngoscope. 1999;109(11):1834–7.

40. Acevedo JL, Camacho M, Brietzke SE. Radiofrequency ablation turbinoplasty versus microdebrider-assisted turbinoplasty: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2015;153(6):951–6.
41. Leong SC, Kubba H, White PS. A review of outcomes following inferior turbinate reduction surgery in children for chronic nasal obstruction. Int J Pediatr Otorhinolaryngol. 2010;74:1–6.
42. Cheng PW, Fang KM, Su HW, Huang TW. Improved objective outcomes and quality of life after adenotonsillectomy with inferior turbinate reduction in pediatric obstructive sleep apnea with inferior turbinate hypertrophy. Laryngoscope. 2012;122(12):2850–4.
43. Arganbright JM, Jensen EL, Mattingly J, Gao D, Chan KH. Utility of inferior turbinoplasty for the treatment of nasal obstruction in children: a 10-year review. JAMA Otolaryngol Head Neck Surg. 2015;141(10):901–4.
44. Jiang ZY, Pereira KD, Friedman NR, Mitchell RB. Inferior turbinate surgery in children: a survey of practice patterns. Laryngoscope. 2012;122:1620–3.
45. Langille M, El-Hakim H. Pediatric inferior turbinoplasty with or without adenoidectomy: preliminary report on improvement of quality of life, symptom control, and safety. Otolaryngol Head Neck Surg. 2011;40:420–6.
46. Yuen SN, Leung PP, Funamura J, Kawai K, Roberson DW, Adil EA. Complications of turbinate reduction surgery in combination with tonsillectomy in pediatric patients. Laryngoscope. 2017;127:1920–3.

Chapter 20
Postoperative Management of Pediatric Sinusitis

Jason R. Rudman, Douglas M. Nguyen, Mikhaylo Szczupak, and Ramzi T. Younis

Introduction

Pediatric chronic rhinosinusitis (CRS) is characterized by at least 90 continuous days of two or more of the following symptoms in patients younger than 18 years: purulent rhinorrhea, nasal obstruction, facial pressure/pain, cough, endoscopic signs of mucosal edema, purulent drainage, nasal polyposis, and/or CT scans showing mucosal changes of the ostiomeatal complex [1]. Obstruction of the ostiomeatal complex is thought to be a starting point for sinus disease in the pediatric population, leading to negative pressure in the nasal cavity, excess mucus production, and retention in the sinuses that leads to infection [2]. Pediatric CRS is a significant burden on the healthcare system and patient quality of life. 8.3–9.3% of children were found to meet clinical criteria for sinusitis by their primary pediatricians [3, 4]. In the USA alone, there are 3.7–7.5 million visits for CRS per year in patients aged 0–20 years [5].

Surgical intervention is typically reserved for CRS resistant to medical management. Functional endoscopic sinus surgery (FESS) is a procedure meant to restore the patency of the sinus ostia that drain the paranasal sinuses, improve airflow through the nose, and allow for delivery of topical medications. Meta-analysis demonstrates that FESS reduces CRS-related symptoms with a success rate of 92% with low incidence of adverse events in the pediatric population [6]. Recurrence of symptoms and the need for revision FESS are challenges to the surgical management of CRS. Fortunately, revision FESS is rarely required in children. Ramadan

J. R. Rudman · M. Szczupak · R. T. Younis (✉)
Department of Otolaryngology–Head and Neck Surgery, University of Miami Miller School of Medicine, Miami, FL, USA
e-mail: Jason.rudman@jhsmiami.org

D. M. Nguyen
Department of Otolaryngology, University of Miami Miller School of Medicine, Miami, FL, USA

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_20

et al. reported a revision rate of 13% in the pediatric population, with the most common reasons including adhesions, maxillary ostium stenosis, missed maxillary sinus ostium, deviated septum, and mucocele [7]. Other risk factors include asthma, younger age, sinonasal polyposis, and history of allergic rhinitis [8, 9].

Ensuring the best outcomes and reducing the need for revision surgery after FESS require diligent postoperative follow-up and optimal medical management. In fact, one of the primary goals of FESS is to allow for improved delivery of topical sinonasal therapy. In this chapter, the authors discuss the available evidence for optimal postoperative care after FESS including topical and systemic therapies as well as sinonasal debridement in the pediatric patient. Special considerations in the cystic fibrosis (CF) patient are addressed, followed by a brief discussion of surgical complications for which to monitor in the postoperative period.

Management after Functional Endoscopic Sinus Surgery (FESS)

Postoperative care is integral to the success of any sinus surgery and has been shown in the adult population to optimize clinical outcomes [10]. The goals of postoperative care in the pediatric patient with chronic sinusitis are the same as in the adult: reduce mucosal inflammation and infection, improve short- and long-term patient symptoms, and maintain patent nasal cavities and sinus ostia. The challenge in the pediatric population is two-fold: (1) a lack of high-quality research defining optimal management in the post-FESS pediatric population and (2) poor tolerance of in-clinic nasal debridement, a standard part of postoperative care in the adult population. Nevertheless, pediatric FESS has become a more widespread part of pediatric CRS management over the last three decades. A growing body of research and clinical experience has shed light on optimizing postoperative care in the pediatric CRS population, helping to minimize the need for revision endoscopic sinus surgery.

Topical Therapy after FESS

Nasal Saline Irrigation

Saline nasal irrigation remains a mainstay of medical management in pediatric rhinosinusitis. It acts by reducing viscosity of sinonasal mucus, clearing debris and allergens, and reducing bacterial load. A retrospective cohort study of 144 medically managed CRS pediatric patients between 2003 and 2012 showed that once-daily nasal saline irrigation is effective as a first-line treatment for CRS by reducing the need for FESS [11]. Once-daily saline rinses in children are well tolerated, with greater than 90% compliance over a six-week period [12]. In the adult population,

postoperative saline irrigations are universally recommended [13]. Six randomized clinical trials support the use of postoperative nasal saline irrigation, showing improved symptom scores and improved endoscopic outcomes after FESS [10, 14–18]. Less clear is the exact volume and frequency of nasal irrigation or douching. In adults, some authors suggest high-volume (250 mL) rinses starting on postoperative day 1, frequently at first (3–6 times daily) and then reducing the frequency after a few weeks (1–3 times daily) [19]. In children, once-daily irrigations have shown efficacy and high tolerability in the medical therapy of CRS, making it the currently preferred regimen for postoperative nasal saline irrigations by many surgeons. There is no dedicated prospective clinical trial in the pediatric population addressing the efficacy of postoperative saline irrigations in improving outcomes or preventing need for revision surgery, but a favorable benefit to risk ratio and excellent tolerability make it an integral part of postoperative nasal care.

Nasal Saline Spray

Saline spray is commonly recommended in the postoperative period as a means of maintaining nasal humidification to facilitate mucociliary clearance. Hypertonic saline spray and isotonic saline spray have both shown efficacy in treating CRS in the pediatric population [20]. Postoperative pediatric studies are limited. However, to assess the effect of saline spray on symptomatology in the immediate post-op period, Pinto et al. performed a prospective randomized controlled trial in adults after FESS. Twenty adult patients received isotonic nasal saline spray, 20 received hypertonic saline spray, and 20 used no spray. There was no significant difference in sinonasal symptoms during the 5-day post-op study period, concluding that nasal saline, administered as a spray, has no efficacy in improving symptoms in the immediate post-op period [18].

Topical Antibiotics

In the non-cystic fibrosis (CF) pediatric population, good evidence is lacking for the efficacy of topical antibiotics after sinus surgery in improving outcomes. A randomized clinical trial in 34 children with medically managed CRS compared once-daily nasal saline irrigations to saline mixed with gentamicin over a 6-week period. This showed over 90% adherence to each regimen over 6 weeks, with a similar increase in quality of life scores on the Sinonasal 5 (SN-5) Survey with either regimen. Lund-Mackay scoring of pre- and posttreatment computed tomography (CT) showed clinically significant improvement within each group, but no statistical difference between the saline and gentamicin/saline group. The authors conclude that due to the excellent tolerance, compliance, and effectiveness of either irrigation, either should be used as first-line treatment in pediatric CRS. Given the lack of clinical or radiologic improvement with gentamicin/saline compared to saline alone, this small study fails to show any benefit in adding a topical antibiotic.

To date, there are no prospective studies in the postoperative CRS pediatric population addressing topical antibiotic therapy, with the notable exception of the CF population. Topical antibiotic rinses like tobramycin have shown some promise in reducing the need for revision FESS in these postoperative CF patients (see section "Topical Antibiotics").

Nasal Steroids

Application of topical medicine through the nostrils does not imply delivery to the sinuses. One of the goals of FESS is to increase the amount of topical rinses and medications, including corticosteroid spray, that reaches the paranasal sinus mucosa [21]. Sinus ostium size is an important factor for topical drug distribution [22], and proper techniques for delivery also play a role [21].

A consensus statement on pediatric chronic rhinosinusitis by the AAO-HNSF in 2014 reached consensus that daily, topical nasal steroid sprays are beneficial adjunctive medical management for CRS [1]. No pediatric study to date has specifically examined the role of nasal steroids in the immediate postoperative period in improving surgical outcomes. However, an adult corollary meta-analysis found that adult postoperative endoscopic scores were significantly better in the corticosteroid group, and recurrence rates were lower in cases of CRS with nasal polyps who underwent ESS [23]. Mometasone furoate nasal spray improves wound healing, especially in cases with nasal polyps [24]. Steroid nasal irrigation does not induce adverse effects related to systemic absorption, but beneficial effects of additional steroids in saline irrigation were insignificant when measuring endoscopic score and CRS-related quality of life improvement in postoperative adult patients [25].

Nasal steroid sprays have an excellent safety record over at least three decades of use. Concerns about systemic absorption or growth retardation have not materialized. Second-generation intranasal corticosteroids that are currently in use, like mometasone and fluticasone, have systemic bioavailability levels of less than 1%. Side effects are typically mild and consist of epistaxis and nasal irritation, making these medications generally well tolerated [26].

Systemic Therapy

Systemic Steroids

Consensus on the use of systemic steroids by sinus surgeons varies by type of training and years of practice [27]. A randomized control trial showed perioperative prednisone improved endoscopic appearance in adult patients with nasal polyposis without any adverse events [28]. Despite the evidence, standard practice of postoperative systemic steroids is debated. Perioperative systemic steroids should be considered for moderate to severe CRS and nasal polyposis at high risk for postoperative complications. With care taken, a short course of postoperative systemic steroids

could be considered to minimize mucosal inflammation during the healing process to prevent excess mucosal edema and crusting.

Oral Antibiotics

Many authors advocate for a short course of postoperative oral antibiotics to reduce the sinonasal bacterial load, reduce inflammation, and enhance appropriate healing after FESS. The first-line therapy is amoxicillin/clavulanate (Augmentin). In a patient with severe penicillin allergy, azithromycin can be considered. In those with non-anaphylactic penicillin reaction, cefdinir is recommended [29]. Specific guidelines for length of treatment, dosing, or even whether antibiotics are indicated cannot be provided due to a lack of high-quality evidence.

However, when even minimal nasal packing or splints are placed at the time of surgery, oral antibiotics with *Staphylococcus* coverage are absolutely indicated for the duration of the nasal packing to prevent the rare but life-threatening complication of toxic shock syndrome (TSS). This syndrome is characterized by fever, diffuse maculopapular rash, desquamation of the palms or soles, and hypotension [30, 31]. If present, this complication typically develops within a few days of the surgery and is treated aggressively with IV antistaphylococcal antibiotics, hydration, and removal of any contributing foreign body like nasal packing.

Adjuvant Postoperative Oral Medications

There is debate on the efficacy of either antihistamines or leukotriene receptor antagonists in pediatric CRS. Nevertheless, these therapies may be reasonable for children with documented allergic rhinitis or CRS patients with asthma consistent with continuing medical management. Treatment for allergic rhinitis before surgery showed higher success rates postoperatively in children [32]. In adults, adjuvant montelukast postoperatively significantly improved sinonasal outcomes, particularly in cases with eosinophilic CRS with nasal polyposis and allergic fungal sinusitis [33]. There are no studies on postoperative effect of antihistamines or leukotriene receptor antagonists specific to the pediatric population. Decongestants have not reached widespread use due to concern over systemic absorption, blood pressure, and rebound epistaxis. Intraoperatively, decongestants help to improve visualization of the surgical field, reduce estimated blood loss, and do not confer a higher rate of postoperative rebound epistaxis [34].

In-Office Debridement Versus "Second-Look" Surgery

Traditionally, sinonasal debridement after endoscopic sinus surgery was considered critical to prevent synechiae (obstructive mucosalized scar bands formed by bridging clots in the postoperative nasal cavity), to remove obstructive nasal crusting and

mucus, as well as to optimize mucosal healing to prevent stenosis of sinus ostia. In adults, in-clinic debridement remains the mainstay of postoperative care after FESS and is often done 1 and 3 weeks post-op, after which there is more variability based on surgeon preference and patient factors.

In older and cooperative children, in-clinic debridement remains an important part of routine post-FESS care. However, nasal debridement of a young or noncooperative child is not recommended in the clinic setting. Some surgeons choose, therefore, to perform sinonasal debridement under general anesthesia in the operating room as a planned "second-look" procedure 2–4 weeks after the initial surgery. During this second look, all crusting and thick mucus is removed, synechiae are lysed, nasal packing is removed, and stenosed sinus ostia may be widened.

Despite these advantages, the value of a second-look procedure has been called into question. The additional trip to the operating room requires a second session of general anesthesia, the negative effects of which have been suggested recently in the anesthesiology literature [35]. Together with the additional consequences of the financial cost and time away from school, the routine practice of a second look has been called into question since 1997 when Mitchell et al. showed equivalent short-term symptom outcomes (12.1 months, range 6–22 months) in 50 consecutive pediatric patients undergoing FESS in 1994–1995 who subsequently did or did not undergo a second look [36].

Data on outcomes after ESS debridement differs between adults and pediatrics. In adults with CRS, multiple level 1b studies show that routine postoperative sinonasal debridement significantly improved symptoms and endoscopic outcomes. Based on the body of evidence, postoperative debridement is recommended in adults [37–39]. On the contrary, the pediatric literature has several studies that demonstrate postoperative debridement to be not necessary in children and to have no improvement in long-term surgical success rates [36, 40]. In 2014, an AAO-HNSF consensus statement concluded that "postoperative debridement after ESS for Pediatric CRS is not essential for treatment success." Surgeons may consider a more selective approach to second-look nasal debridement in children at higher risk for surgical failure, like those with CF, immotile cilia, and immunodeficiencies and those undergoing revision sinus surgery [36].

Cystic Fibrosis: Postoperative Management

Children with CF and immotile cilia syndrome frequently suffer from CRS that is resistant to medical management due to thick secretions and poor mucociliary clearance. Therefore, many will undergo FESS. At the time of surgery, many authors recommend more extensive operations than would typically be performed in children with uncomplicated CRS. Endoscopic maxillary mega-antrostomy or medial maxillectomy allows for large antrostomies to facilitate gravity-dependent mucus clearance and improve delivery of postoperative topical medications [41, 42]. The pathophysiology, treatment, and outcomes of pediatric CRS in CF are

sufficiently different from non-CF CRS to warrant a separate discussion of postoperative treatment strategies.

Second-Look Procedure

As discussed in section "In-Office Debridement Versus "Second-Look" Surgery," second-look procedures have fallen out of favor in most pediatric CRS patients; however, none of the studies looked specifically at patients with CF; caution must be taken in applying the conclusions from non-CF patients to this group with its unique pathophysiology. Therefore, no recommendation can be provided at this time on the utility of a second-look debridement in the pediatric CF population [43].

Postoperative Topical Therapy

Saline and Corticosteroids

Multiple noncontrolled case seriesreport postoperative use of saline irrigation, saline spray, and topical intranasal corticosteroids as routine part of care after FESS in CF patients. In CF patients that have undergone lung transplantation, chronic sinonasal *Pseudomonas* colonization and infection predispose to allograft infection. Holzmann showed that in these patients, FESS followed by daily nasal isotonic saline irrigation significantly reduced the incidence of pneumonia and tracheobronchitis [44]. No control was incorporated, so the role of postoperative saline cannot be extrapolated from this study.

To date, there have been no controlled studies in the CF population for these therapies. However, given the overall safety, tolerance, and proven efficacy in the non-CF FESS population, nasal saline irrigations and intranasal corticosteroid sprays remain a mainstay of postoperative therapy.

Topical Antibiotics

Several case series without controls in the adult and pediatric CF literature show good results with post-FESS topical irrigations with antibiotics like tobramycin (80 mL/250 mL normal saline) but with no comparison group [45]. Controlled studies examining the efficacy of topical antibiotics in this population are lacking.

One case series including both children and adults with CF has demonstrated interesting results with endoscopic sinus surgery and serial antimicrobial lavage (ESSAL) with 40 mg tobramycin (1 mL) [46]. In this approach, irrigation catheters are placed in each maxillary antrostomy during FESS, and the catheter is sutured to the floor of the nasal vestibule, with one end exiting the nare through which antimicrobial

irrigations can subsequently be delivered three times daily for the first 7–10 days after sinus surgery. At the first follow-up clinic visit, the catheters are removed and the patient continues normal postoperative topical nasal saline use. If symptoms persist or recur, a catheter is replaced in the maxillary sinus for another 7–10 courses of lavage. CF patients undergoing ESSAL showed a significantly decreased need for repeat surgery compared to controls at both 1 year (10% vs 47%) and 2 years (22% vs 72%) after surgery. The results are promising in that they demonstrate efficacy of sinonasal lavage in reducing or delaying the need for revision surgery; a serious limitation in the pediatric group however is the presence of a catheter that extends out of the nose and may be poorly tolerated by children and certainly will be difficult to replace in the clinic if symptoms persist or recur after removal of the initial catheter. Additionally, with no direct comparison arm, the benefit of the topical antibiotic cannot be assessed compared to saline lavages alone.

Dornase Alfa

Extracellular DNA from lysed neutrophils may contribute to the high viscosity of sinonasal mucus in CF patients with CRS. When applied topically to the nasal cavity, recombinant human deoxyribonuclease, or dornase alfa, reduces mucus viscosity by cleaving extracellular DNA in sinonasal secretions. It has shown significant pulmonary improvement when used as a nebulizer in children with CF [47].

A case series of twenty CF patients who underwent FESS, five of whom subsequently received inhaled dornase alfa (age range 11 years to 25 years), showed that dornase alfa may lead to fewer revision surgeries over a 3-year period. There was no change in pulmonary function tests between the two groups [48].

To better determine the benefit of post-FESS dornase alfa in CF patients, Cimmino et al. performed a double-blind, randomized clinical trial in 24 CF patients, including adults and children, after FESS. Half were randomized to receive 2.5 mg of inhaled dornase alfa nasally, while the other half received inhaled hypotonic saline. Therapy was initiated 1 month after surgery for a 12-month period. The authors found that the dornase alfa group had significant improvement in nasal symptoms and endoscopic appearance at both 24 and 48 weeks compared to control. The authors conclude that dornase alfa is safe and effective at 1 year after surgery [49].

In summary, dornase alfa may be considered a tool for extending the effects of FESS in children with CF. The cost-effectiveness and long-term benefit remain unknown [43].

Topical Gene Therapy

Gene therapy shows promise as a near-future strategy for the treatment of CF by introducing normal CF transmembrane conductance regulator (CFTR) into the affected epithelium. A phase II randomized, double-blind, placebo-controlled clinical trial introduced an adeno-associated CFTR viral vector—tgAAVCF—into a

maxillary sinus of 23 post-FESS CF patients, with the other maxillary sinus receiving placebo. At 3 months, the therapy was shown to be safe. Disappointingly, the results at 3 months posttreatment showed equivalent outcomes in the treated group and placebo group based on rate of relapse of recurrent sinusitis. At the time of publication, no definitive evidence supports topical gene therapy for treatment of chronic sinusitis in children with CF [50].

Postoperative Systemic Therapy

Oral Steroids and Oral Antibiotics

Postoperative use of culture-directed oral antibiotics and, to a lesser extent, oral steroids is common for CF patients [41, 51, 52]. Most studies addressing these therapies are case series without corresponding controls. Evidence-based recommendations on systemic steroids and antibiotics after FESS in CF patients cannot be provided at this time due to a lack of quality studies.

IV Antibiotics

A relatively large prospective, non-randomized, uncontrolled clinical trial demonstrated that an aggressive regimen of FESS and postoperative adjuvant therapy (2 weeks of antipseudomonal IV antibiotics followed by 6 months of topical antibiotic nasal irrigations) was effective in reducing the frequency of pulmonary CF pathogen colonization 1 year after surgery. With no comparison arm, the exact role of FESS, IV antibiotics, and topical antibiotics cannot be determined from this study [53].

Oral Antihistamines and Decongestants

Oral antihistamines and decongestants are generally discouraged as they may increase the viscosity of mucus and decrease mucociliary clearance, exacerbating the underlying cause of disease in this patient population.

Avoiding Triggering Factors in the Postoperative Period

Pediatric CRS is a medical disease with complex and myriad underlying causative factors. With this in mind, the aims of surgery are largely to allow for improved medical management of the underlying disease. Integral to surgical success is treatment of the underlying disease and avoidance of predisposing factors.

Second-Hand Smoke and Environmental Irritants

Secondhand smoke and environmental irritants predispose to recurrent sinus infections by impairing sinonasal ciliary function [54]. Both asthma and rhinosinusitis occur more frequently in children exposed to tobacco smoke. FESS in children exposed to secondhand smoke has worse outcomes [40]. Therefore, in addition to preoperative avoidance, the importance of smoking cessation and avoidance in the postoperative period must be imparted to the child's guardians.

Allergic Rhinitis

Referral for allergy testing and immunotherapy should be considered if allergic rhinitis is suspected to contribute to the child's CRS. This is often done prior to surgery but can be considered after FESS.

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease is found in 63% of pediatric patients with CRS, showing a high association but lacking definitive causality. The exact relationship remains a contentious debate. Treatment of reflux has been found to be effective in reducing sinus disease [55]; however, no causal relationship was shown in randomized, controlled studies in the pediatric CRS population [56]. A recent consensus statement by a nine-member panel of fellowship-trained pediatric otolaryngologists or rhinologists published by AAO-HNSF in 2014 states, "Empiric treatment for GERD is not a beneficial adjunctive medical therapy for (Pediatric) CRS." The panel did not reach consensus regarding a contribution of GERD in the pathogenesis of CRS in the pediatric population [1].

Conclusion

Functional endoscopic sinus surgery has been an effective tool in treating pediatric sinusitis refractory to medical therapy. Additionally, postoperative care is of the utmost importance to bridge surgical therapy with future medical treatment for chronic rhinosinusitis. The goal in the postoperative period is to shorten recovery time and improve patient's sinus disease. Close follow-up and continuing medical management are two essential aspects to realize these goals. The extent of pediatric sinus surgery varies based on anatomy, etiology, and symptoms. As such, postoperative care must also be personalized. The clinician should assess the benefits and

risks of postoperative topical and systemic options to maximize the results of endoscopic sinus surgery while minimizing the risk for revision surgery.

An important part of postoperative counseling is to remind parents that the child will still have viral URIs periodically, which have overlapping symptoms with CRS. These URIs do not imply surgical failure.

The lack of high-quality postoperative pediatric studies for chronic sinusitis is an obstacle in assessing the best methods for care in the postoperative period. Further research is needed to refine the extent of benefit and risk these options may give.

References

1. Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542–53.
2. Shahid SK. Rhinosinusitis in children. ISRN Otolaryngol. 2012;2012:851831.
3. Aitken M, Taylor JA. Prevalence of clinical sinusitis in young children followed up by primary care pediatricians. Arch Pediatr Adolesc Med. 1998;152(3):244–8.
4. Kakish KS, Mahafza T, Batieha A, Ekteish F, Daoud A. Clinical sinusitis in children attending primary care centers. Pediatr Infect Dis J. 2000;19(11):1071–4.
5. Gilani S, Shin JJ. The burden and visit prevalence of pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2017;157(6):1048–52.
6. Rizzi MD, Kazahaya K. Pediatric chronic rhinosinusitis: when should we operate? Curr Opin Otolaryngol Head Neck Surg. 2014;22(1):27–33.
7. Ramadan HH. Revision endoscopic sinus surgery in children: surgical causes of failure. Laryngoscope. 2009;119(6):1214–7.
8. 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.
9. Chan KH, Winslow CP, Abzug MJ. Persistent rhinosinusitis in children after endoscopic sinus surgery. Otolaryngol Head Neck Surg. 1999;121(5):577–80.
10. Rudmik L, Smith TL. Evidence-based practice: postoperative care in endoscopic sinus surgery. Otolaryngol Clin N Am. 2012;45(5):1019–32.
11. Pham V, Sykes K, Wei J. Long-term outcome of once daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. Laryngoscope. 2014;124(4):1000–7.
12. 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(9):1989–2000.
13. Weber RK, Hosemann W. Comprehensive review on endonasal endoscopic sinus surgery. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2015;14:Doc08.
14. Freeman SR, Sivayoham ES, Jepson K, de Carpentier J. A preliminary randomised controlled trial evaluating the efficacy of saline douching following endoscopic sinus surgery. Clin Otolaryngol. 2008;33(5):462–5.
15. Fooanant S, Chaiyasate S, Roongrotwattanasiri K. Comparison on the efficacy of dexpanthenol in sea water and saline in postoperative endoscopic sinus surgery. J Med Assoc Thail. 2008;91(10):1558–63.
16. Liang KL, Su MC, Tseng HC, Jiang RS. Impact of pulsatile nasal irrigation on the prognosis of functional endoscopic sinus surgery. J Otolaryngol Head Neck Surg. 2008;37(2):148–53.
17. Pigret D, Jankowski R. Management of post-ethmoidectomy crust formation: randomized single-blind clinical trial comparing pressurized seawater versus antiseptic/mucolytic saline. Rhinology. 1996;34(1):38–40.

18. Pinto JM, Elwany S, Baroody FM, Naclerio RM. Effects of saline sprays on symptoms after endoscopic sinus surgery. Am J Rhinol. 2006;20(2):191–6.
19. Staffieri A, Marino F, Staffieri C, Giacomelli L, D'Alessandro E, Maria Ferraro S, et al. The effects of sulfurous-arsenical-ferruginous thermal water nasal irrigation in wound healing after functional endoscopic sinus surgery for chronic rhinosinusitis: a prospective randomized study. Am J Otolaryngol. 2008;29(4):223–9.
20. Shoseyov D, Bibi H, Shai P, Shoseyov N, Shazberg G, Hurvitz H. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. J Allergy Clin Immunol. 1998;101(5):602–5.
21. Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. Otolaryngol Head Neck Surg. 2008;139(1):137–42.
22. Grobler A, Weitzel EK, Buele A, Jardeleza C, Cheong YC, Field J, et al. Pre- and postoperative sinus penetration of nasal irrigation. Laryngoscope. 2008;118(11):2078–81.
23. Pundir V, Pundir J, Lancaster G, Baer S, Kirkland P, Cornet M, et al. Role of corticosteroids in functional endoscopic sinus surgery--a systematic review and meta-analysis. Rhinology. 2016;54(1):3–19.
24. Jorissen M, Bachert C. Effect of corticosteroids on wound healing after endoscopic sinus surgery. Rhinology. 2009;47(3):280–6.
25. Yoon HY, Lee HS, Kim IH, Hwang SH. Post-operative corticosteroid irrigation for chronic rhinosinusitis after endoscopic sinus surgery: a meta-analysis. Clin Otolaryngol. 2018;43(2):525–32.
26. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. J Investig Allergol Clin Immunol. 2012;22(1):1–12.
27. Arianpour K, Svider PF, Guys N, Shenouda K, Folbe E, Hsueh WD, et al. Incorporation of antibiotics and systemic steroids by sinus surgeons: is there widespread consensus? Int Forum Allergy Rhinol. 2018;8(9):1034–40.
28. 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(11 Pt 2 Suppl 115):1–28.
29. Makary CA, Ramadan HH. The role of sinus surgery in children. Laryngoscope. 2013;123(6):1348–52.
30. Younis RT, Gross CW, Lazar RH. Toxic shock syndrome following functional endonasal sinus surgery: a case report. Head Neck. 1991;13(3):247–8.
31. Barbour SD, Shlaes DM, Guertin SR. Toxic-shock syndrome associated with nasal packing: analogy to tampon-associated illness. Pediatrics. 1984;73(2):163–5.
32. Ramadan HH, Hinerman RA. Outcome of endoscopic sinus surgery in children with allergic rhinitis. Am J Rhinol. 2006;20(4):438–40.
33. Yelverton JC, Holmes TW, Johnson CM, Gelves CR, Kountakis SE. Effectiveness of leukotriene receptor antagonism in the postoperative management of chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(3):243–7.
34. Korkmaz H, Yao WC, Korkmaz M, Bleier BS. Safety and efficacy of concentrated topical epinephrine use in endoscopic endonasal surgery. Int Forum Allergy Rhinol. 2015;5(12):1118–23.
35. Warner DO, Zaccariello MJ, Katusic SK, Schroeder DR, Hanson AC, Schulte PJ, et al. Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: the Mayo Anesthesia Safety in Kids (MASK) Study. Anesthesiology. 2018;129(1):89–105.
36. Mitchell RB, Pereira KD, Younis RT, Lazar RH. Pediatric functional endoscopic sinus surgery: is a second look necessary? Laryngoscope. 1997;107(9):1267–9.
37. Bugten V, Nordgard S, Steinsvag S. Long-term effects of postoperative measures after sinus surgery. Eur Arch Otorhinolaryngol. 2008;265(5):531–7.
38. Bugten V, Nordgard S, Steinsvag S. The effects of debridement after endoscopic sinus surgery. Laryngoscope. 2006;116(11):2037–43.

39. Rudmik L, Soler ZM, Orlandi RR, Stewart MG, Bhattacharyya N, Kennedy DW, et al. Early postoperative care following endoscopic sinus surgery: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2011;1(6):417–30.
40. Ramadan HH. Corticosteroid therapy during endoscopic sinus surgery in children: is there a need for a second look? Arch Otolaryngol Head Neck Surg. 2001;127(2):188–92.
41. Virgin FW, Rowe SM, Wade MB, Gaggar A, Leon KJ, Young KR, et al. Extensive surgical and comprehensive postoperative medical management for cystic fibrosis chronic rhinosinusitis. Am J Rhinol Allergy. 2012;26(1):70–5.
42. Cho DY, Hwang PH. Results of endoscopic maxillary mega-antrostomy in recalcitrant maxillary sinusitis. Am J Rhinol. 2008;22(6):658–62.
43. Crockett DJ, Wilson KF, Meier JD. Perioperative strategies to improve sinus surgery outcomes in patients with cystic fibrosis: a systematic review. Otolaryngol Head Neck Surg. 2013;149(1):30–9.
44. Holzmann D, Speich R, Kaufmann T, Laube I, Russi EW, Simmen D, et al. Effects of sinus surgery in patients with cystic fibrosis after lung transplantation: a 10-year experience. Transplantation. 2004;77(1):134–6.
45. Halvorson DJ, Dupree JR, Porubsky ES. Management of chronic sinusitis in the adult cystic fibrosis patient. Ann Otol Rhinol Laryngol. 1998;107(11 Pt 1):946–52.
46. Moss RB, King VV. Management of sinusitis in cystic fibrosis by endoscopic surgery and serial antimicrobial lavage. Reduction in recurrence requiring surgery. Arch Otolaryngol Head Neck Surg. 1995;121(5):566–72.
47. Suri R, Metcalfe C, Lees B, Grieve R, Flather M, Normand C, et al. Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial. Lancet. 2001;358(9290):1316–21.
48. Raynor EM, Butler A, Guill M, Bent JP 3rd. Nasally inhaled dornase alfa in the postoperative management of chronic sinusitis due to cystic fibrosis. Arch Otolaryngol Head Neck Surg. 2000;126(5):581–3.
49. Cimmino M, Nardone M, Cavaliere M, Plantulli A, Sepe A, Esposito V, et al. Dornase alfa as postoperative therapy in cystic fibrosis sinonasal disease. Arch Otolaryngol Head Neck Surg. 2005;131(12):1097–101.
50. Wagner JA, Nepomuceno IB, Messner AH, Moran ML, Batson EP, Dimiceli S, et al. A phase II, double-blind, randomized, placebo-controlled clinical trial of tgAAVCF using maxillary sinus delivery in patients with cystic fibrosis with antrostomies. Hum Gene Ther. 2002;13(11):1349–59.
51. 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.
52. Marks SC, Kissner DG. Management of sinusitis in adult cystic fibrosis. Am J Rhinol. 1997;11(1):11–4.
53. Aanaes K, Johansen HK, Skov M, Buchvald FF, Hjuler T, Pressler T, et al. Clinical effects of sinus surgery and adjuvant therapy in cystic fibrosis patients - can chronic lung infections be postponed? Rhinology. 2013;51(3):222–30.
54. Goldsmith AJ, Rosenfeld RM. Treatment of pediatric sinusitis. Pediatr Clin N Am. 2003;50(2):413–26.
55. Bothwell MR, Parsons DS, Talbot A, Barbero GJ, Wilder B. Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngol Head Neck Surg. 1999;121(3):255–62.
56. El-Serag HB, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. Gastroenterology. 2001;121(6):1294–9.

Chapter 21
Failure of Surgical Treatment in Children with Chronic Rhinosinusitis

Anne S. Lowery and Frank W. Virgin

Introduction

Chronic rhinosinusitis (CRS) in the pediatric population is a taxing problem emotionally, behaviorally, and financially, not only for the patient but also for family members [1]. Otolaryngologists often turn to surgical management of CRS following the failure of maximal medical management. The goals for surgical management of CRS in children are to improve quality of life, alleviate sinus symptoms, and prevent complications including anosmia, sepsis, orbital or intracranial abscess, cavernous sinus thrombosis, and meningitis [1]. In patients with cystic fibrosis, primary ciliary dyskinesia, and reactive airway disease, an additional goal of aggressive surgical management of CRS is improving pulmonary function [2].

There is growing support in the literature for adenoidectomy and functional endoscopic sinus surgery (FESS) for the management of pediatric chronic rhinosinusitis (CRS) that is refractory to medical management. Promising data show that surgical interventions have positive effects not only on symptoms but also on patient-reported quality of life [3–5]. However, despite the known benefits of surgical management of CRS, surgical failures do occur.

A. S. Lowery
Vanderbilt University School of Medicine, Nashville, TN, USA

Surgical Outcomes Center for Kids, Vanderbilt University Medical Center, Nashville, TN, USA

F. W. Virgin (✉)
Department of Otolaryngology-Head and Neck Surgery, Vanderbilt University Medical Center, Nashville, TN, USA

Surgical Outcomes Center for Kids, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: frank.w.virgin@vumc.org

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_21

Definition of Failure

The failure of surgical management for children with CRS can be defined as failure to improve sinonasal symptoms, quality of life, the need for revision surgery, and disease recurrence.

Chronic rhinosinusitis is commonly associated with nasal obstruction, facial pain and pressure, postnasal drip, headache, and cough. Quality of life measures describe the net consequence of associated illness on physical, social, and emotional well-being [6]. Quality of life measures are more commonly being used to evaluate the overall impact of a disease process on a patient and to evaluate the benefits of treatment. Several instruments have been utilized to assess the effectiveness of surgical CRS management in children [7]. However, the SN-5 is the only CRS quality of life instrument validated in pediatric patients [8]. Failure to improve subjective symptoms or objective quality of life measures, as reported by the patient or caregiver, is considered a failure of surgical management.

Revision surgery is defined as any further surgical intervention for CRS after the primary operation. This can include secondary adenoidectomy, nasal polypectomy, or revision FESS. A large national retrospective study conducted by Chaaban et al. assessed a total of 16,040 patients, both pediatric and adult, with CRS between 2011 and 2014 and found that the 6-month revision rate was 16.85% for FESS [9].

Recurrence of disease is defined as the return of CRS symptoms after a period of disease remission. Recurrence may also be based on endoscopic findings postoperatively, which include purulent nasal discharge, crust, synechiae formation, and recurrent polyps.

In children with cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and asthma, a goal of surgery, in addition to improvement of symptoms and overall quality of life, is improvement in pulmonary function [10]. Failure to improve pulmonary function is also considered a failure of surgical management in this patient population [11].

Patient Groups at Risk for Failure

Multiple factors have been shown to increase the risk of surgical failure. While surgical success has been reported to be between 71% and 100%, children with systemic or genetic diseases are often excluded from analysis [12–14]. Surgical failure is often a reflection of the difficulties of underlying disease and condition.

Smoke Exposure

Cigarette smoke has a negative impact on mucociliary clearance in the sinuses leading to sinusitis [15]. A retrospective study over 10 years by Siedek et al. evaluated the outcomes of FESS. The analysis found that children and adolescents

who started or continued to smoke had significantly worse symptom outcomes when compared to their non-smoking counterparts [4]. Negative effects of smoking on surgical success is not only limited to primary exposure. Ramadan et al. found that children with secondary smoke exposure had a 70% symptom resolution following FESS, compared to 90% symptom resolution in children not exposed to smoking [16]. In addition, Kim et al. found that when assessing for recurrence or persistence of disease 6 months postoperatively using endoscopic findings, children with indirect smoking exposure had significantly poorer outcomes [17].

Age

Surgical failure has been demonstrated to occur earlier and more frequently in younger children. Chan et al. conducted a retrospective review of children with prior sinus surgery who were referred to a subspecialty sinus clinic. A total of 217 patients were seen during the study time. Fifteen patients had surgery prior to presentation to the clinic. Fourteen patients had sufficient data for analysis. In this small group, they found that children who had their first procedure at an age <4.8 years were more likely to require additional surgical management [18]. Similarly, Ramadan in a retrospective review found that children who were 6 years and younger had a 20% revision rate compared to 9% in children who were 6 years and older. In this study, 17 of the 23 children who required two or more revisions were under 6 years old, suggesting that younger children have higher incidence of surgical failure and more revisions overall [19]. Additionally, another study by Ramadan et al., investigating adenoidectomy failure, found that children younger than 7 years had a mean adenoidectomy failure time of 15 months compared to 27.5 months for those older than 7 years. Younger children under age 7 were more likely to require salvage FESS earlier than children older than 7 years [20]. Chan et al. hypothesized that the anatomic site of failure is the osteomeatal complex (OMC). In younger children, the small distance between adjacent structures, combined with postsurgical edema of mucosal surfaces, may be more likely to lead to synechiae formation and persistent inflammation [18].

Asthma

In children with chronic rhinosinusitis, 35–65% also have concomitant asthma [21]. Asthma and CRS have been characterized pathologically by eosinophilic inflammation involving the respiratory mucosa [21]. In a prospective study by Ramadan evaluating adenoidectomy versus FESS, and versus a combination of adenoidectomy and FESS, asthmatic children had a 62% success rate after surgery, compared to 80% overall success in children without asthma. When independently evaluating the different surgical methods, asthmatic children had worse outcomes

with adenoidectomy alone, 37% success versus 65% in non-asthmatic counterparts. Similar success rates were achieved with FESS alone or FESS and adenoidectomy, 71% versus 79% and 82% versus 90%, respectively [14].

Allergic Fungal Sinusitis

Children with allergic fungal sinusitis (AFS) have a hypersensitivity to fungi. This patient group has been found to have an increased need for revision surgery. In a study by Younis et al., evaluating patients with AFS, 22% of patients required revision surgery and 19% of those required a second revision surgery [22]. These revision rates are higher than the national average published by Chaaban et al. [9].

Cystic Fibrosis

Surgical intervention in the CF population is focused not only on improving overall symptoms and quality of life but also on pulmonary function and exacerbations. Although sinus surgery has demonstrated a positive effect on symptoms and quality of life, surgical intervention has not clearly demonstrated a positive impact on pulmonary function [3]. Madonna et al. investigated the pulmonary status of CF patients after sinus surgery and found that there was no significant improvement [23]. In addition, Rosbe et al. found that in CF patients, there was no change in the postoperative oral or inhaled steroid use and no change in pulmonary function as measured by forced vital capacity (FVC) and forced expiratory volume in the first second of expiration (FEV_1) [24]. Similarly, Osborn et al. noted no change in pulmonary function post FESS [25]. Finally, Fetta et al. found that polyp recurrence was 30.7% in the general pediatric population but reached 75% in children with CF [26].

Cilia Motility Defect

Ciliary dysfunction, such as in Kartagener's syndrome or primary ciliary dyskinesia (PCD), impairs mucociliary clearance and increases the susceptibility to rhinosinusitis [27]. Younis et al. found that every patient with immotile cilia syndrome required repeat surgery 3–5 years after the first operation [28]. Alanin et al. in a prospective study investigated the effect of FESS on symptoms of CRS in the PCD population. They found that while there was a significant improvement in sinonasal symptoms as assessed by the SNOT-22 score, there was no difference in pulmonary function, assessed via FEV_1 and FVC, pre- and post surgery.

Immunodeficiency

Children with immunodeficiency, either inherited or acquired, have extremely poor surgical outcomes. Despite being on maximal medical therapy, prophylactic antibiotic therapy, and intravenous immunoglobulin therapy (IVIG), 83% of children who are immunosuppressed required revision surgery within 3–5 years after the first FESS [28]. Ritter et al., in a retrospective cohort of 34 immunosuppressed children with underlying malignancies who underwent FESS for acute rhinosinusitis, found 19 of 34 had acute invasive fungal rhinosinusitis (AIFR). Fifty-six percent of those patients died at the end of follow-up, at an average of 30 months, with 10 mortalities directly attributed to their infections. Despite aggressive diagnostic and therapeutic approach with empirical antifungal therapy and immediate FESS based on imaging findings and high clinical suspicion, outcomes were poor with high mortality especially in those with AIFR [29]. In a study with Yakirevitch et al., evaluating the outcomes of surgery for pediatric AIFR found that patients underwent an average of two endoscopic procedures and 4 of 13 patients underwent open surgery [30].

Methods for Reducing Failure

Surgical failures in the management of pediatric CRS occur. Through preoperative identification of risk factors, appropriate goals and expectations of surgery can be set. A thorough evaluation of the patient, including environmental exposures, genetic disorders, and systemic illness, is crucial to ensuring mutual understanding between the surgeon, patient, and guardian.

There is no consensus on the appropriate postoperative management of pediatric patients following FESS. A variety of treatments have been utilized in an attempt to improve postoperative outcomes. These include perioperative steroids, postoperative steroids and antibiotics, stents, nasal irrigations, and second-look procedures. A more conservative approach to postoperative care may achieve similar results as compared to more aggressive approaches such as through a second-look endoscopy under general anesthesia [31].

Postoperative care is likely important in determining surgical outcomes; however, evidence for this is limited in the pediatric patient population. Intranasal packing is frequently utilized in an attempt to prevent postoperative hemorrhage and synechiae formation between the middle turbinate and lateral nasal wall. Kimmelman et al. compared hyaluronic acid packing versus no packing in 10 patients requiring bilateral FESS. The primary outcomes included synechia formation, middle meatal stenosis, mucosal status, and mucosal regeneration and were rated on a four-point outcome scale. Overall, at the end of 5 weeks, patients with hyaluronic packing had less synechia (2.3 vs. 1.2) and middle meatal stenosis (2.2 vs. 1.3) than those without packing [32]. Miller et al., in a blinded randomized control trial of 37 patients requiring bilateral FESS for CRS, compared absorbable hyaluronic acid stents

versus standard nonabsorbable packing. They reported that there was no significant difference between absorbable and nonabsorbable packing in postoperative synechiae rates in adults [33]. However, because of the relative smaller size of the middle meatus in children, the theorized synechiae rates are higher in the pediatric population [34]. In a prospective study, Hu et al. evaluated the effectiveness of an absorbable hyaluronic acid packing material after FESS in children. At 3-week follow-up, 35% of the packed sinuses and 43% of the unpacked sinuses had synechiae. The mean synechiae score at first visit for those with hyaluronic acid packing was 0.48 ± 0.72, and that for the unpacked sinuses was 0.70 ± 0.91 ($p < 0.05$). However, at 8- and 12-week follow-up, there was no difference between the two groups in the severity of adhesions, granulation tissue formation, infection rate, and patency of the maxillary sinus ostia. The conclusion of this study was that while packing is not necessary for routine FESS, it should be considered in children who are predisposed to develop postoperative hemorrhage or adhesions and revision surgery with preexisting adhesions [35].

Patients with systemic disease such as CF, primary ciliary dyskinesia, immunodeficiency, asthma, and allergic fungal sinusitis face higher rates of surgical failure when compared to pediatric CRS patients without comorbidity. Promising new research suggest aggressive medical therapy in the mucociliary-impaired population is essential to the success of overall disease management. Virgin et al. described a surgical approach consisting of FESS and bilateral modified endoscopic medial maxillectomy (MEMM) combined with postoperative medical treatment consisting of culture-directed antibiotics, low-dose prednisone, saline irrigations, topical steroids, and antibiotics. Symptoms measured by total SNOT-22 scores were significantly reduced at 60-day and 1-year follow-up. In addition, they also showed that hospital admissions secondary to pulmonary exacerbations were significantly improved compared to years prior to surgery (2.0 vs. 3.2) [36]. Other proponents for aggressive postoperative medical therapy include Alanin et al. who examined 24 pediatric and adult patients with primary ciliary dyskinesia (PCD). Patients underwent FESS with bronchoalveolar lavage. Postoperative management consisted of topical saline irrigation, topical nasal steroid spray, and topical colistin irrigation if *Pseudomonas aeruginosa*-positive sinus cultures were discovered. At 1-year follow-up, significant improvements in symptoms and quality of life were reported [37]. Similarly, Aanaes et al. reported a prospective study evaluating 58 pediatric and adult CF patients who underwent FESS. Adjuvant medical therapy included colistin sinus irrigation at the time of surgery, 2 weeks of broad-spectrum IV antibiotics, 6 months of topical nasal steroid spray, nasal saline, and colistin sinus irrigation. The study demonstrated that pathogenic bacteria were eradicated from the sinuses at 6 months follow-up in 41% of patients who underwent the combination of ESS and intense medical therapy [38]. Furthermore, Raynor et al. conducted a retrospective chart review and found that CF patients postoperatively managed with nasally inhaled dornase alfa had fewer revision FESS when compared to non-dornase alfa-treated patients over the course of 3 years (1.6 vs. 3.2) [39]. While further studies are needed to solidify the optimal postoperative management, maximal medical management postoperatively may be beneficial for surgical outcomes.

Conclusion

As our understanding of pediatric rhinosinusitis continues to evolve, it is critical to understand the indications and effectiveness of medical and surgical therapies in this population. When proposing surgical treatment, it is important to consider risk factors that may be associated with poorer outcomes so that the surgeon may give realistic expectations of recurrence, revision, and resolution of disease.

References

1. Rudnick EF, Mitchell RB. Improvements in quality of life in children after surgical therapy for sinonasal disease. Otolaryngol Head Neck Surg. 2006;134(5):737–40.
2. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease with associated reactive airway disease in children. Pediatrics. 1984;73(4):526–9.
3. Virgin FW. Clinical chronic rhinosinusitis outcomes in pediatric patients with cystic fibrosis. Laryngoscope Investig Otolaryngol. 2017;2(5):276–80.
4. 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.
5. Nishioka GJ, Barbero GJ, Konig P, Parsons DS, Cook PR, Davis WE. Symptom outcome after functional endoscopic sinus surgery in patients with cystic fibrosis: a prospective study. Otolaryngol Head Neck Surg. 1995;113(4):440–5.
6. Kay DJ, Rosenfeld RM. Quality of life for children with persistent sinonasal symptoms. Otolaryngol Head Neck Surg. 2003;128(1):17–26.
7. Xie DX, Wu J, Kelly K, Brown RF, Shannon C, Virgin FW. Evaluating the sinus and nasal quality of life survey in the pediatric cystic fibrosis patient population. Int J Pediatr Otorhinolaryngol. 2017;102:133–7.
8. Ni JS, Kompelli AR, Nguyen SA, Schlosser RJ, Clemmens C, Soler ZM. The sinus and nasal quality of life survey (SN-5) in the management of pediatric chronic rhinosinusitis: a systematic review and meta-analysis. Int J Pediatr Otorhinolaryngol. 2018;111:162–9.
9. Chaaban MR, Rana N, Baillargeon J, Baillargeon G, Resto V, Kuo YF. Outcomes and complications of balloon and conventional functional endoscopic sinus surgery. Am J Rhinol Allergy. 2018; https://doi.org/10.1177/1945892418782248.
10. Magit A. Pediatric rhinosinusitis. Otolaryngol Clin N Am. 2014;47(5):733–46.
11. Alanin MC, Johansen HK, Aanaes K, Hoiby N, Pressler T, Skov M, et al. Simultaneous sinus and lung infections in patients with primary ciliary dyskinesia. Acta Otolaryngol. 2015;135(1):58–63.
12. Vlastarakos PV, Fetta M, Segas JV, Maragoudakis P, Nikolopoulos TP. Functional endoscopic sinus surgery improves sinus-related symptoms and quality of life in children with chronic rhinosinusitis: a systematic analysis and meta-analysis of published interventional studies. Clin Pediatr (Phila). 2013;52(12):1091–7.
13. 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.
14. Ramadan HH. Surgical management of chronic sinusitis in children. Laryngoscope. 2004;114(12):2103–9.
15. Benninger MS. The impact of cigarette smoking and environmental tobacco smoke on nasal and sinus disease: a review of the literature. Am J Rhinol. 1999;13(6):435–8.
16. Ramadan HH, Hinerman RA. Smoke exposure and outcome of endoscopic sinus surgery in children. Otolaryngol Head Neck Surg. 2002;127(6):546–8.

17. Kim HY, Dhong HJ, Chung SK, Chung YJ, Min JY. Prognostic factors of pediatric endoscopic sinus surgery. Int J Pediatr Otorhinolaryngol. 2005;69(11):1535–9.
18. Chan KH, Winslow CP, Abzug MJ. Persistent rhinosinusitis in children after endoscopic sinus surgery. Otolaryngol Head Neck Surg. 1999;121(5):577–80.
19. Ramadan HH. Revision endoscopic sinus surgery in children: surgical causes of failure. Laryngoscope. 2009;119(6):1214–7.
20. Ramadan HH, Tiu J. Failures of adenoidectomy for chronic rhinosinusitis in children: for whom and when do they fail? Laryngoscope. 2007;117(6):1080–3.
21. Poddighe D, Brambilla I, Licari A, Marseglia GL. Pediatric rhinosinusitis and asthma. Respir Med. 2018;141:94–9.
22. Younis RT, Ahmed J. Predicting revision sinus surgery in allergic fungal and eosinophilic mucin chronic rhinosinusitis. Laryngoscope. 2017;127(1):59–63.
23. Madonna D, Isaacson G, Rosenfeld RM, Panitch H. Effect of sinus surgery on pulmonary function in patients with cystic fibrosis. Laryngoscope. 1997;107(3):328–31.
24. Rosbe KW, Jones DT, Rahbar R, Lahiri T, Auerbach AD. Endoscopic sinus surgery in cystic fibrosis: do patients benefit from surgery? Int J Pediatr Otorhinolaryngol. 2001;61(2):113–9.
25. 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.
26. Fetta M, Tsilis NS, Segas JV, Nikolopoulos TP, Vlastarakos PV. Functional endoscopic sinus surgery improves the quality of life in children suffering from chronic rhinosinusitis with nasal polyps. Int J Pediatr Otorhinolaryngol. 2017;100:145–8.
27. Vlastos I, Athanasopoulos I, Mastronikolis NS, Panogeorgou T, Margaritis V, Naxakis S, et al. Impaired mucociliary clearance in allergic rhinitis patients is related to a predisposition to rhinosinusitis. Ear Nose Throat J. 2009;88(4):E17–9.
28. Younis RT, Lazar RH. Criteria for success in pediatric functional endonasal sinus surgery. Laryngoscope. 1996;106(7):869–73.
29. Ritter A, Fischer S, Yaniv E, Hadar T, Soudry E, Shai D, et al. Acute rhinosinusitis in immunosuppressed children: diagnostic and therapeutic management. Pediatr Infect Dis J. 2017;36(4):e80–6.
30. Yakirevitch A, Barg AA, Bedrin L, Primov-Fever A, Wolf M, Migirov L. Acute invasive fungal Rhinosinusitis in children with hematologic malignancies: outcome of surgical treatment. Pediatr Hematol Oncol. 2015;32(8):568–75.
31. 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(1):15–8.
32. Kimmelman CP, Edelstein DR, Cheng HJ. Sepragel sinus (hylan B) as a postsurgical dressing for endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2001;125(6):603–8.
33. Miller RS, Steward DL, Tami TA, Sillars MJ, Seiden AM, Shete M, et al. The clinical effects of hyaluronic acid ester nasal dressing (Merogel) on intranasal wound healing after functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2003;128(6):862–9.
34. Stankiewicz JA. Comments about postoperative care after endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg. 2002;128(10):1207–8.
35. Hu KH, Lin KN, Li WT, Huang HM. Effects of meropack in the middle meatus after functional endoscopic sinus surgery in children with chronic sinusitis. Int J Pediatr Otorhinolaryngol. 2008;72(10):1535–40.
36. Virgin FW, Rowe SM, Wade MB, Gaggar A, Leon KJ, Young KR, et al. Extensive surgical and comprehensive postoperative medical management for cystic fibrosis chronic rhinosinusitis. Am J Rhinol Allergy. 2012;26(1):70–5.
37. Alanin MC, Aanaes K, Hoiby N, Pressler T, Skov M, Nielsen KG, et al. Sinus surgery can improve quality of life, lung infections, and lung function in patients with primary ciliary dyskinesia. Int Forum Allergy Rhinol. 2017;7(3):240–7.

38. Aanaes K, von Buchwald C, Hjuler T, Skov M, Alanin M, Johansen HK. The effect of sinus surgery with intensive follow-up on pathogenic sinus bacteria in patients with cystic fibrosis. Am J Rhinol Allergy. 2013;27(1):e1–4.
39. Raynor EM, Butler A, Guill M, Bent JP 3rd. Nasally inhaled dornase alfa in the postoperative management of chronic sinusitis due to cystic fibrosis. Arch Otolaryngol Head Neck Surg. 2000;126(5):581–3.

Part V
Complications

Chapter 22
Pediatric Intracranial Complications from Sinusitis

Osama Hamdi, Connor M. Smith, Caitlin E. Fiorillo, and Diego Preciado

Introduction

Infections of the paranasal sinuses in children frequently result in acute complications outside of the sinuses such as orbital infections, facial (Fig. 22.1) or intracranial abscesses, and infected thrombophlebitis [1, 2]. Orbital cellulitis (OC) represents a group of conditions ranging from periorbital inflammation to subperiosteal and orbital abscess (SPA/OA) and cavernous sinus thrombosis.

Intracranial complications include epidural abscess, subdural empyema, meningitis, encephalitis, intracerebral abscess, and dural sinus thrombosis. Fortunately, intracranial complications from sinusitis have decreased dramatically in the post-antibiotic era. The incidence of these complications in patients admitted with the diagnosis of sinusitis, however, remains at around 3% [3, 4]. As opposed to adults, the classic triad of fever, headache, and altered mental status is often absent in children [3, 5]. Without a heightened level of suspicion, these complications can go unrecognized, untreated, or undertreated in children, resulting in serious morbidity and mortality.

In children that initially present with these infectious complications, it is unclear whether surgically addressing the intranasal sinus source externally or endoscopically

O. Hamdi · C. M. Smith
Division of Pediatric Otolaryngology, Children's National Health System, Washington, DC, USA

C. E. Fiorillo
Department of Pediatric Otolaryngology, Children's National Medical Center, Children's National Health System, Washington, DC, USA

D. Preciado (✉)
Department of Pediatric Otolaryngology, Children's National Health System, The George Washington University School of Medicine, Washington, DC, USA
e-mail: dpreciad@cnmc.org

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0_22

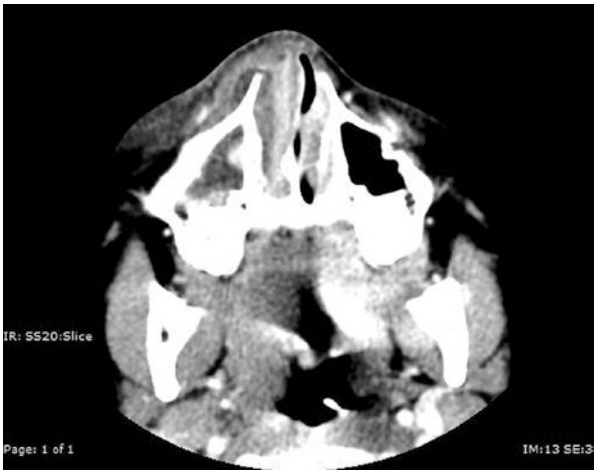


Fig. 22.1 A 6-year-old male presented with right facial swelling concerning for abscess. On CT scan, found to have acute sinusitis with intranasal abscess spreading onto the maxilla

Table 22.1 The Chandler Classification divides orbital complications into five groups based on progressive severity

Stage	Description
I	Inflammatory edema (preseptal cellulitis)
II	Orbital cellulitis
III	Subperiosteal abscess
IV	Orbital abscess
V	Cavernous sinus thrombosis

Reprinted with permission from Chandler et al. [9]

at the time of abscess drainage influences ultimate outcome. This chapter will review the latest literature on the subject as well as propose management algorithms for children with these conditions.

Orbital Complications

OC most commonly results as a complication of acute sinusitis and can lead to disastrous outcomes if not appropriately treated. It is thought to occur by the spread of infection either by direct extension through the thin lamina papyracea, via local thrombophlebitis, or by way of infected thromboemboli [6–8]. The Chandler Classification system was described in 1970 by Chandler et al. and continues to be widely used to categorize patients with orbital complications into 5 groups (Table 22.1, Fig. 22.2) [9].

Four hundred sixty-five patients were treated at Children's National Medical Center over a seven-year period with a diagnosis of OC. 40% of these patients were evaluated in the emergency room and discharged. Of the 276 patients admitted to the hospital, 70 (25%) had or went on to develop CT-proven SPOA. Forty-seven patients (67%) were successfully treated medically, while 23 patients (33%)

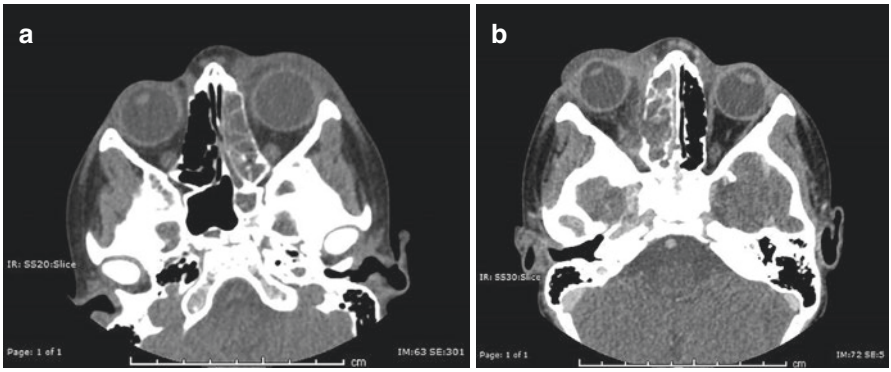


Fig. 22.2 (**a**) Chandler Classification 1. Preseptal cellulitis. Arrow indicates approximate position of orbital septum that acts as a barrier to spread of infection. (**b**) Chandler Classification 2. Postseptal cellulitis

underwent surgical intervention. Patients successfully treated medically were younger and had smaller abscesses than those treated surgically.

Although our institution does not have a strict management algorithm for this condition, patients were cared for in a standard fashion, and an ophthalmology consultation was ordered for all cases. To assess the need for operative intervention, the following criteria were used: large abscess (subjective size determination), decrease in visual acuity or other concerns on ophthalmologic exam, and worsening clinical picture or failure to improve despite 24–48 hours of appropriate medical therapy (Fig. 22.3) [10, 11]. Then the decision to use endoscopic, open, or combined approach was based on CT findings, abscess location, and attending judgment. No differences in outcome based on surgical approach were demonstrated in this retrospective study.

While the exact role and timing of surgical intervention for SPOA remains controversial, it appears clear that many smaller abscesses in younger patients are amenable to medical treatment with close observation and serial ophthalmologic examinations (Fig. 22.4). In our retrospective series, 44/54 (81%) of patients with an abscess smaller than 10 mm were successfully treated medically, while 12/13 (92%) of those larger than 10 mm underwent surgical intervention. Others have also reported on the successful medical management of small abscesses in patients without visual compromise. Starkey and Steele reported 7 cases of SPOA with 6 of 7 successfully treated medically but did not specify specific size criteria [12]. Garcia and Harris applied management criteria to 37 patients with SPOA who were all less than 9 years old. Twenty-nine patients met the nine criteria for medical management, which included medial location and small or moderate size of abscess. In their study, size was subjectively determined based on CT scan review. Twenty-seven of the 29 patients were successfully managed without surgical intervention [13, 14]. Oxford and McClay reported on 43 patients with SPOA, 18 of whom resolved with medical management. Patients managed medically had abscesses that were significantly smaller than those who had surgical intervention (width 0.25 vs. 1.46 cm,

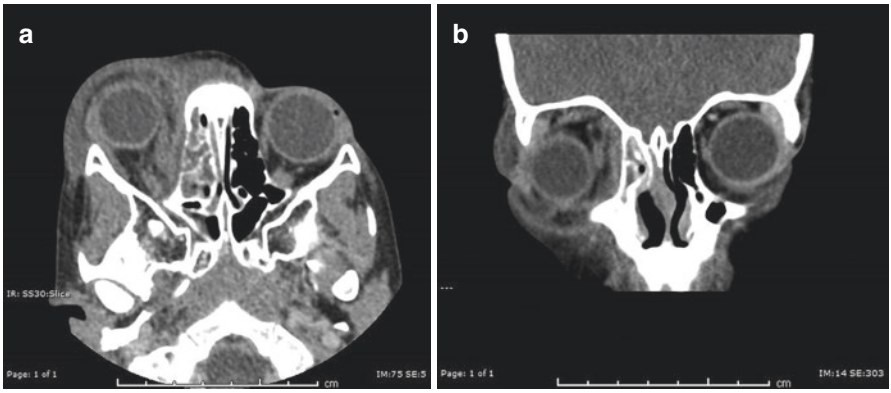


Fig. 22.3 A 4-year-old male presented with fevers, headache, and periorbital edema after an upper respiratory infection. On initial CT scan, noted to have acute right maxillary and ethmoid sinusitis with a 4 mm medial subperiosteal abscess on (**a**) coronal and (**b**) sagittal that worsened on IV antibiotics. Patient taken to OR for drainage

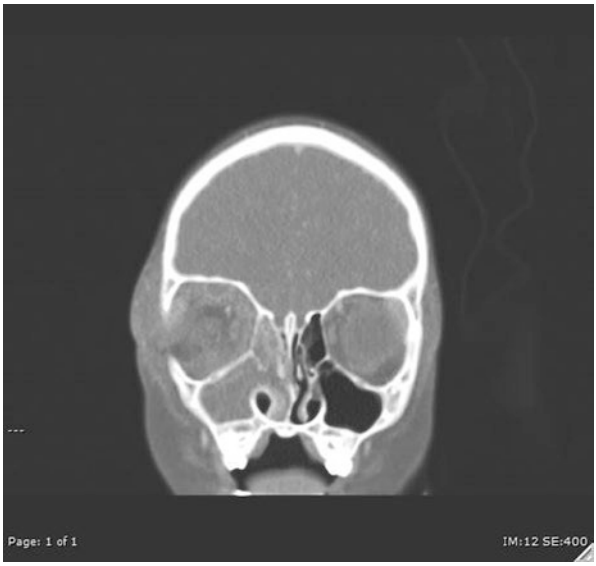


Fig. 22.4 Same patient as in Fig. 22.3. Had initial improvement that then worsened. Repeat CT scan demonstrated a new superior subperiosteal abscess that was managed with IV antibiotics

$p < 0.001$). They concluded that patients with small, medial SPOA without ocular signs are amenable to medical management. Oxford and McClay also proposed criteria for medical management of medial SPOA that includes abscess width less than 4 mm [10]. Greenberg et al. reviewed management of 25 cases of SPOA and concluded that medial SPOA secondary to sinusitis in children under the age of 6 are highly amenable to medical treatment alone. In their study, abscess size categories were arbitrarily determined and no treatment recommendations based on size were given [15].

Our data support that patients younger than 6 years of age more often present with less extensive disease and are more likely to be successfully treated medically. This is consistent with the literature. Harris reported on 37 cases of CT-proven SPOA and showed that patients younger than 9 years old were more likely to improve without surgery and had less complex infections than older patients [14]. Israele and Nelson's review of the literature showed that patients with periorbital cellulitis were younger than those with OC, which supports the idea that older patients are more likely to present with more complex infections [16]. Brown et al., in their series of 42 patients with SPOA, also showed that patients treated medically were younger than those who underwent surgical drainage (5.1 vs. 11 years, $p < 0.0001$) [17].

In our series, patients who underwent surgical intervention had a significantly longer hospital stay than those patients treated medically. This is consistent with the surgical group having a more extensive disease process and is supported in the literature. Jackson and Baker reported on 39 patients with OC, 19 of whom were less than 20 years old. The average stay in the hospital was longer for patients treated surgically than those treated medically (13.4 vs. 9.4 days) [7]. Nageswaran reported 41 cases of OC, including 34 cases of subperiosteal abscess. Twenty-nine patients underwent surgical intervention. The average length of stay in their study was also longer for the surgical group (6.5 vs. 4.2 days, $p = 0.011$) [18]. Similarly, Oxford and McClay showed that nonsurgical patients had a shorter hospital stay than surgical patients (4.3 vs. 5.8 days, $p = 0.038$) [10]. Brown also demonstrated shorter hospitalization for patients with SPOA treated medically (6.5 vs. 9.6 days, $p = 0.011$) [17].

The recent literature supports more conservative management of small SPOA secondary to sinusitis in younger patients without visual compromise. The majority of SPOA less than 10 mm in size were successfully treated medically. Some older patients may also be candidates for medical management; however, a low threshold should exist for surgical intervention given the tendency for older pediatric patients to present with more advanced infections.

Intracranial Infections

Intracranial complications are potentially devastating consequences of pediatric sinusitis. Their diagnosis requires a heightened level of suspicion, and their management requires close collaboration between multiple specialties, including otolaryngology, neurosurgery, and infectious disease. Multiple recent series have described their experience with intracranial complications and find that with prompt and aggressive management, prognosis can be favorable [5, 19–21]. In our series, 22% of patients admitted to the hospital with intracranial infections during the study period were found to have sinusitis. Of these, only 8 (38.1%) children presented with signs or symptoms suggestive of sinusitis, such as nasal congestion, purulent rhinorrhea, and periorbital or forehead edema. This finding is in agreement with our

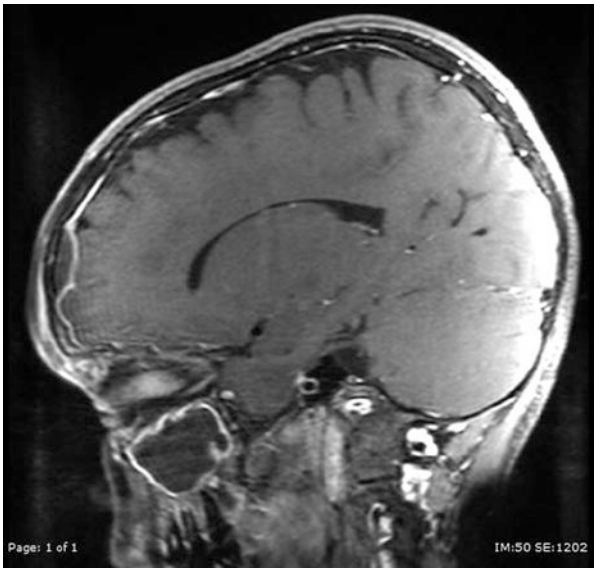


Fig. 22.5 A 10-year-old male presented with fever and headache for 5 days without sinonasal symptoms. He was found to have acute right pansinusitis and a right frontal epidural empyema seen on this T1-weighted MRI with contrast. He was treated with endoscopic sinus surgery and neurosurgical drainage of the empyema

previous report [3] and others [20–23] and reinforces the notion that in children, one has to be suspicious of the sinuses being the source of intracranial infections even in the absence of nasal symptoms (Fig. 22.5).

The majority of patients with intracranial complications from sinusitis are male presenting in their teenage years [4, 8, 24, 25]. Adolescent patients may be more vulnerable to intracranial complications from sinusitis because of the significant growth of the frontal sinuses and increased vascularity of the diploic venous system associated with this stage of development [4, 26, 27]. Germiller et al. looked at 25 patients of mean age of 13.2, being treated for intracranial complications. Their study consisted of 76% adolescents and 76% male [20]. A recent series on intracranial complications of sinusitis reported by T.K. Nicoli et al. found six patients with frontal sinusitis, with a median age of 21 years, five of whom were men and one a woman. They also attributed this increased vulnerability in male adolescents to the developing blood supply of the sinus and highlighted anatomical differences in development of men as a reason for their increased predisposition (Fig. 22.6) [28].

Subdural abscesses were the more commonly found intracranial complication associated with sinusitis in our series (Fig. 22.7). This profile was also seen in studies by Bradley et al. [1] and Singh et al. [10]. Our previous publication [3] and more recent series, however, have described epidural abscesses as being the most frequent intracranial complication of sinusitis [20, 25, 29]. In congruence with the literature, our experience has been that patients with subdural abscesses tended to present with significant and obvious neurologic symptoms and signs and, as a consequence, may have sought or been brought to medical attention earlier. Half of the patients with epidural abscesses and 21% of those with subdural abscesses were managed successfully with conservative neurosurgical treatment and parenteral antibiotics.

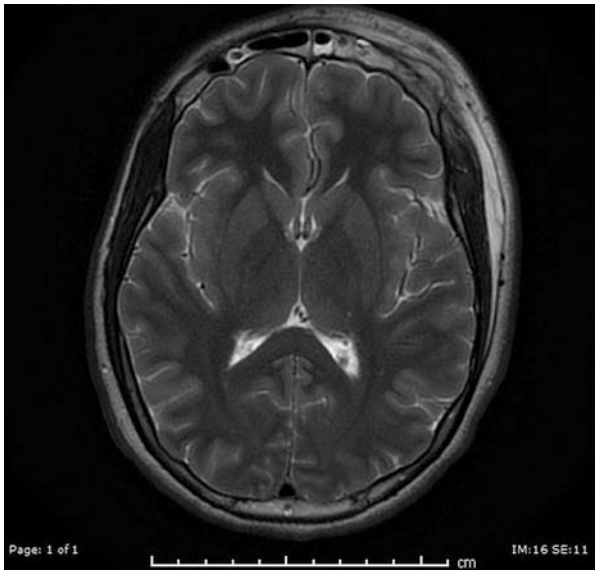


Fig. 22.6 A 14-year-old male presented with 24 hours of headache followed by left periorbital edema. T2-weighted MRI demonstrated acute left maxillary, ethmoid, and frontal sinusitis with a frontal subperiosteal abscess or "Pott's puffy tumor." He was taken to OR for incision and drainage of abscess and endoscopic sinus surgery

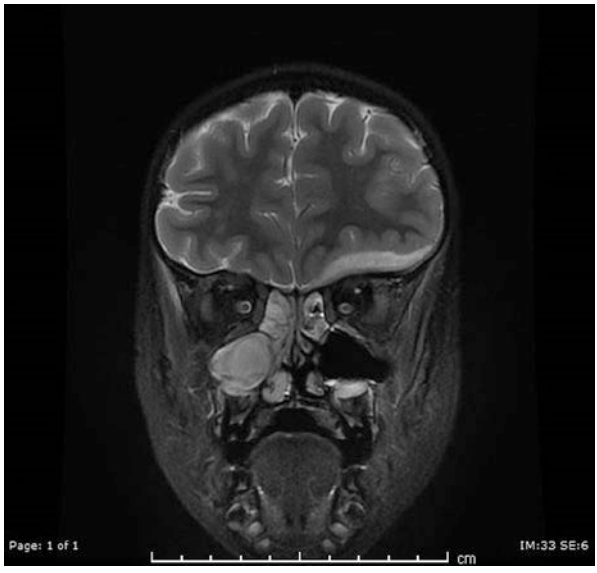


Fig. 22.7 A 7-year-old presented with meningitic signs and fever after 2 weeks of upper respiratory tract symptoms. She was found to have acute right sinusitis with a left frontotemporal subdural empyema, secondary encephalitis, and cavernous sinus thrombosis

It is to be noted that those with subdural abscesses that were managed without craniotomy had small, focal collections and showed rapid clinical improvement with parenteral antibiotics.

Parenteral antibiotics were administered to all children with suspected intracranial complications of sinusitis. A combination of a penicillin or vancomycin, metronidazole, and a third-generation cephalosporin is chosen because of the ability to

penetrate into inflamed central nervous system tissue and adequate empiric broad-spectrum coverage. Therapy was adjusted as culture and sensitivity results became available. Parenteral antibiotics are typically continued for a period of 4–8 weeks. Patients with intracranial abscesses are also treated with intravenous phenytoin.

Since our report in 1995, ESS has become a readily available, useful tool in the surgical management of children with acute and chronic sinusitis. Its precise therapeutic role, however, in the management of children with intracranial complications from sinusitis is perhaps less defined. Some propose that aggressive use of ESS should be instituted in nearly all patients with intracranial complications from sinusitis and that its use can result in improved overall outcomes [20]. In our previous series, we highlighted the importance of frontal sinus cranialization and exenteration as a "single-stage" procedure at the time of neurosurgical craniotomy if the frontal sinus was found to be the infectious source and the posterior table was deficient [3]. In general, studies of surgical management for intracranial complications of sinusitis are limited by relatively small patient samples and the fact that outcomes are for the most part favorable; therefore, statistical analyses need to be interpreted with caution. Given the lack of a randomized protocol, and selection of surgical treatment modality employed based upon patient characteristics, one cannot draw any conclusions on whether early or aggressive ESS or frontal sinus trephination make a substantial impact in the rate of favorable outcomes in these patients. The only way to prove this definitively is with a strictly defined prospective, randomized protocol comparing those undergoing ESS or trephination at the time of craniotomy vs. those undergoing only craniotomy. Such a study has yet to be performed.

Changing Nature of Complications Since the Advent of the Prevnar Vaccine

In a recent report, we compared 49 patients with OC and/or SPOA/OA in the pre-PCV7 era with 59 patients from the post-PCV7 era. We found that although PCV7 vaccination eliminated *S. pneumoniae* as an etiologic pathogen in acute sinusitis complications in our series, there was a parallel and significant increase in *S. aureus*, including an increase in the prevalence of MRSA associated with orbital infections related to acute sinusitis.

Seeing that there has been an increased incidence of orbital infections from MRSA pathogens and given that patients with OC and SPOA/OA have a significantly increased risk of morbidity if they are not treated aggressively in a timely manner, it is prudent to treat patients with these infections with broad-spectrum antibiotics that cover MRSA until specific culture information becomes available [30].

No studies have been done to date noting the effect of the PCV13 vaccine on acute sinusitis patients. However, both Olarte L et al. [31] and Lindstrand et al. [32] assessed the impact of PCV13 on chronic sinusitis in children. Olarte observed 91 cases of chronic sinusitis with positive cultures for *S. pneumonia*, and 61 (67%) isolates were non-PCV13 serotypes. Despite a decrease in *S. pneumoniae* isolation

in children with chronic sinusitis in the post PCV13 era, there was a significant increase in isolation of the anaerobic organism, *Prevotella spp*. ($P = 0.02$) [31]. Lindstrand et al. found a 66% lower risk of hospitalization for sinusitis following PCV7 and PCV13 vaccination in children <2 years of age [32].

In our series, we found that the most commonly isolated bacteria in intracranial and orbital infections related to sinusitis in the post-PCV7 era were *S. aureus* (42%), anaerobes (20%), and *Strep. intermedius* (12%) [30].

Similar findings were found by Barry Seltz et al. in a study that looked at 94 children with orbital infections. They found that *Streptococcus anginosus (15%)* was the most common cause of infection followed by *S. aureus (9%)*, *S0 pyogenes (6%)*, and *S. pneumoniae (4%)* [33].

Health-Care Costs of Sinusitis Complications

Not only do intracranial complications as a result of sinusitis present with pathological burdens on the patient, they also result in a significant financial burden on the family. Work by Mahalingam-Dhingra et al. looked at 5440 patients with orbital cellulitis and assessed the different variables that impact the cost of treatment at their institution. They found that the mean (SE) total charges associated with a patient diagnosed with orbital cellulitis in 2006 were $16,444 ($805.40). This charge can be further broken down to assess the difference in these patients that were treated surgically and those that were not. They found that 12.4% of their total cohort required surgical intervention. In patients that required surgical management, they found that the mean (SE) total charge was $41,009 ($2971.9) compared to their nonsurgical counterparts at $13,008 ($716.8). While the charges of the operation led to an increased total charge for these patients, they found that they also have a longer mean (SE) stay at the hospital of 7.1 (0.38) days compared to 3.4 (0.11) days for the nonsurgical patients. This longer hospital stay synchronously adds to the increase in the charge burden on these patients. Though this data was collected at this specific institution, it is important to note that normative data found that hospitals found in western geographic regions had higher surgical rates for patients with orbital and periorbital infections. This was also found to be true in hospitals located in urban areas. Thus, there is a steep cost of care for patients with intracranial complications that result from sinusitis, particularly for those that require surgical management [34].

References

1. Bradley PJ, Manning KP, Shaw MD. Brain abscess secondary to paranasal sinusitis. J Laryngol Otol. 1984;98:719–5.
2. Maniglia AJ, VanBuren JM, Bruce WB, Bellucci RJ, Hoffman SR. Intracranial abscesses secondary to ear and paranasal sinuses infections. Otolaryngol Head Neck Surg. 1980;88:670–80.

3. Lerner DN, Choi SS, Zalzal GH, Johnson DL. Intracranial complications of sinusitis in childhood. Ann Otol Rhinol Laryngol. 1995;104:288–93.
4. Clayman GL, Adams GL, Paugh DR, Koopmann CF Jr. Intracranial complications of paranasal sinusitis: a combined institutional review. Laryngoscope. 1991;101:234–9.
5. Adame N, Hedlund G, Byington CL. Sinogenic intracranial empyema in children. Pediatrics. 2005;116:e461–7.
6. Wald ER. Periorbital and orbital infections. Infect Dis Clin N Am. 2007;21(2):393–408, vi.
7. Jackson K, Baker SR. Clinical implications of orbital cellulitis. Laryngoscope. 1986;96(5):568–74.
8. Wiatrak. Orbital subperiosteal abscess. In: Cotton R, Myer C, editors. Practical pediatric otolaryngology. Philadelphia: Lippincott-Raven; 1999. p. 978–82.
9. Chandler JR, Langenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. Laryngoscope. 1970;80(9):1414–28.
10. Oxford LE, McClay J. Medical and surgical management of subperiosteal orbital abscess secondary to acute sinusitis in children. Int J Pediatr Otorhinolaryngol. 2006;70(11):1853–61.
11. Sobol SE, Marchand J, Tewfik TL, Manoukian JJ, Schloss MD. Orbital complications of sinusitis in children. J Otolaryngol. 2002;31(3):131–6.
12. Starkey CR, Steele RW. Medical management of orbital cellulitis. Pediatr Infect Dis J. 2001;20(10):1002–5.
13. Garcia GH, Harris GJ. Criteria for nonsurgical management of subperiosteal abscess of the orbit: analysis of outcomes 1988-1998. Ophthalmology. 2000;107(8):1454–6; discussion 1457–8.
14. Harris GJ. Subperiosteal abscess of the orbit. Age as a factor in the bacteriology and response to treatment. Ophthalmology. 1994;101(3):585–95.
15. Greenberg MF, Pollard ZF. Medical treatment of pediatric subperiosteal orbital abscess secondary to sinusitis. J AAPOS. 1998;2(6):351–5.
16. Israele V, Nelson JD. Periorbital and orbital cellulitis. Pediatr Infect Dis J. 1987;6(4):404–10.
17. Brown CL, Graham SM, Griffin MC, Smith RJ, Carter KD, Nerad JA, et al. Pediatric medial subperiosteal orbital abscess: medical management where possible. Am J Rhinol. 2004;18(5):321–7.
18. Todman MS, Enzer YR. Medical management versus surgical intervention of pediatric orbital cellulitis: the importance of subperiosteal abscess volume as a new criterion. Ophthalmic Plast Reconstr Surg. 2011;27:255–9.
19. Nageswaran S, Woods CR, Benjamin DK Jr, Givner LB, Shetty AK. Orbital cellulitis in children. Pediatr Infect Dis J. 2006;25(8):695–9.
20. 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.
21. Glickstein JS, Chandra RK, Thompson JW. Intracranial complications of pediatric sinusitis. Otolaryngol Head Neck Surg. 2006;134:733–6.
22. Giannoni C, Sulek M, Friedman EM. Intracranial complications of sinusitis: a pediatric series. Am J Rhinol. 1998;12:173–8.
23. Jones NS, Walker JL, Bassi S, Jones T, Punt J. The intracranial complications of rhinosinusitis: can they be prevented? Laryngoscope. 2002;112:59–63.
24. Singh B, Van Dellen J, Ramjettan S, Maharaj TJ. Sinogenic intracranial complications. J Laryngol Otol. 1995;109:945–50.
25. Gallagher RM, Gross CW, Phillips CD. Suppurative intracranial complications of sinusitis. Laryngoscope. 1998;108:1635–42.
26. Johnson DL, Markle BM, Wiedermann BL, Hanahan L. Treatment of intracranial abscesses associated with sinusitis in children and adolescents. J Pediatr. 1988;113:15–23.
27. Bluestone CD, Steiner RE. Intracranial complications of acute frontal sinusitis. South Med J. 1965;58:1–10.

28. Nicoli TK, Oinas M, Niemelä M, Mäkitie AA, Atula T. Intracranial Suppurative complications of sinusitis. Scand J Surg. 2016;105(4):254–62.
29. Herrmann BW, Forsen JW Jr. Simultaneous intracranial and orbital complications of acute rhinosinusitis in children. Int J Pediatr Otorhinolaryngol. 2004;68:619–25.
30. Peña MT, Preciado D, Orestes M, Choi S. Orbital complications of acute sinusitis changes in the post–pneumococcal vaccine era. JAMA Otolaryngol Head Neck Surg. 2013;139(3):223–7.
31. Olarte L, Hulten KG, Lamberth L, Mason EO, Kaplan SL. Impact of the 13-valent pneumococcal conjugate vaccine on chronic sinusitis associated with Streptococcus pneumoniae in children. Pediatr Infect Dis. 2014;J33:1033–6.
32. Lindstrand A, Bennet R, Galanis I, et al. Sinusitis and pneumonia hospitalization after introduction of pneumococcal conjugate vaccine. Pediatrics. 2014;134:e1528–36.
33. Seltz LB, Smith J, Durairaj VD, Enzenauer R, Todd J. Microbiology and antibiotic management of orbital cellulitis. Pediatrics. 2011;127(3):e566–72.
34. Mahalingam-Dhingra A, Lander L, Preciado DA, Taylormoore J, Shah RK. Orbital and periorbital infections: a national perspective. Arch Otolaryngol Head Neck Surg. 2011;137(8):769–73.

Index

H. H. Ramadan, F. M. Baroody (eds.), *Pediatric Rhinosinusitis*,
https://doi.org/10.1007/978-3-030-22891-0