Pediatric ENT Infections

Cemal Cingi
Emin Sami Arısoy
Nuray Bayar Muluk
Editors

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Editors
Cemal Cingi
Department of Otorhinolaryngology
Faculty of Medicine
Eskişehir Osmangazi University
Eskişehir, Turkey

Nuray Bayar Muluk
Department of Otorhinolaryngology
Faculty of Medicine
Kırıkkale University
Kırıkkale, Turkey

Emin Sami Arısoy
Division of Pediatric Infectious Diseases
Department of Pediatrics
Faculty of Medicine
Kocaeli University
Kocaeli, Turkey

ISBN 978-3-030-80690-3 ISBN 978-3-030-80691-0 (eBook)
https://doi.org/10.1007/978-3-030-80691-0

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Preface

We, the editors, are deeply honored and humbled for the opportunity to provide the *Pediatric Ear, Nose, and Throat Infections* textbook to physicians and healthcare providers working in this field as a comprehensive and up-to-date reference book, which will be available both online and in printed format.

Humankind, world history, and, more recently, globalization have sarcastically failed at equally scattering health opportunities and solutions for all children on behalf of a fair life in all corners of the world. In this context, during the last century, morbidity and mortality rates in children due to infectious diseases have been dramatically reduced in high-income countries. On the other side, pediatric infectious diseases in low- and middle-income countries remain among the leading causes of morbidity and mortality. Children in these countries also experience disproportionate rates of ear, nose, and throat (ENT) infections, often with more frequency and severity than those in the high-income world.

The knowledge and experience in the field of pediatric ENT infections are widening, deepening, and ever-changing. And so are the responsibilities and roles of physicians and other healthcare providers. The goal of preparing the *Pediatric Ear, Nose, and Throat Infections* is to provide a comprehensive, evidence-based, up-to-date reference book presenting current medical information required in the daily practice for those who care for children with infections in the ENT area and related issues. With the release of *Pediatric Ear, Nose, and Throat Infections*, we have aimed to guide the family physician, pediatrician, pediatric infectious diseases expert, and ENT specialists in the diagnosis and treatment of these conditions and to manage the neonate, infant, children, and adolescents with optimal care and outcomes, no matter what part of the world they live in.

Total 222 author colleagues from 34 countries collaborated with their willingness, enthusiasm, cooperation, effort, and time dedicated to preparing this book. The *Pediatric Ear, Nose, and Throat Infections* could not have been created without the mentorship, professional expertise, co-authorship, and enthusiastic support of our authors, including worldwide-known experts in the fields of pediatric infectious diseases and otorhinolaryngology. We have been exceptionally fortunate to have been able to work with them and count on their collaboration. Not enough words could be written to sufficiently express our heartfelt gratitude towards them.

Finally, we would like to wholeheartedly thank our teachers, mentors, parents, and families for providing us education, guidance, encouragement, help, patience, time, and a convenient environment in support of our intellectual aims and work.

Eskişehir, Turkey
Kocaeli, Turkey
Kırıkkale, Turkey
October 29, 2021

Cemal Cingi
Emin Sami Arısoy
Nuray Bayar Muluk

Contents

Part II Symptoms and Signs

Nasal and Paranasal Sinus Infections in Children with Cystic Fibrosis

41

Ali Seyed Resuli, Cemal Cingi, and Glenis Scadding

41.1 Introduction

Cystic fibrosis (CF) is a chronic disease that involves multiple body systems and features repeated infective episodes affecting the bronchi, resulting in steadily worsening obstructive lung pathology and failure of the pancreas, which leads to malabsorption from the gut.

In the majority of cases of CF disorders of the sinuses and nose develop, resulting in referral to ENT specialists. It appears probable that the frequency and pathogenetic mechanism for other disorders affecting the head and neck, e.g. middle ear infections or pathology of the adenoids and tonsils, are little different in patients with CF from those without the condition [1, 2]. Interestingly, though, it seems that CF patients are less prone to otitis media than other people, although why this is so remains a mystery [3]. The focus of this chapter is disorders of the sinuses and nose in patients with CF [4].

CF is a genetic disorder with an autosomal recessive mode of inheritance. It involves mutated CF alleles on chromosome seven. The gene involved produces the CF transmembrane regulator (CFTR) protein, which transports chloride ions across the cellular outer membrane [5]. If this protein has defective function, chloride

A. S. Resuli (✉)
Department of Otorhinolaryngology, Faculty of Medicine, İstanbul Yeni Yüzyıl University, İstanbul, Turkey

C. Cingi
Department of Otorhinolaryngology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

G. Scadding
University College London, Royal National Throat, Nose, and Ear Hospital (Honorary Consultant Physician in Allergy and Rhinology), London, UK

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C. Cingi et al. (eds.), *Pediatric ENT Infections*,
https://doi.org/10.1007/978-3-030-80691-0_41

regulation by the mucosal epithelium of the airways and exocrine glands is abnormal, and a viscous layer of mucus pools in these regions [6].

The clinical presentation of CF is dominated by infections in the lower portion of the respiratory tree, as well as pancreatic failure. However, virtually all sufferers from this disorder also experience chronic rhinosinusitis, since mucus pooling also occurs in the sinuses and nose [7–10]. Such disease within the sinuses can produce a high level of morbidity in itself, in addition to a postulated negative effect on any lung pathology, and for this reason, ENT specialists are frequently called upon to assess and treat individuals suffering from CF [6].

41.2 Sinonasal Manifestations in Cystic Fibrosis

Rhinosinusitis refers to inflammation of the nasal lining, occurring in conjunction with inflammation of at least a single sinus. The pathogenesis involves multiple elements, notably dysfunctional mucociliary clearance, infection, atopy, swelling of the mucosa and, on occasion, atypical anatomical conformation of the nasal interior or the sinuses surrounding the nose [6, 10]. As estimated by looking at symptomatic occurrence, abnormal findings on physical examination and imaging, almost 100% of CF patients experience rhinosinusitis [8–10]. It is probable that sinus disorders are so common in individuals with CF because of the abnormal consistency of sinonasal mucus, which prevents effective drainage by the mucociliary mechanism. When the ostia become obstructed, the cilia are damaged, with the result that an inflammatory oedematous process is set in motion. This process is also driven by the presence of pathogenic bacteria, notably Pseudomonas, *Staphylococcus aureus* and non-typeable *Haemophilus influenzae*, which colonise the sinuses. These are respiratory pathogens of both upper and lower tract [11]. It has also been proposed by researchers that mutation of the CFTR allele may itself be an independent risk factor for sinonasal disorders, since even non-CF patients with chronic rhinosinusitis are more likely to possess a single mutated allele [12, 13].

The presenting complaints occurring with highest frequency in cases of sinusitis in patients with CF are stuffiness and pus-filled rhinorrhoea. Other symptoms that are frequent are cephalgia, oral breathing and abnormalities of olfaction. There is some variation in the usual findings from physical examination, but the constant features are pus-filled discharge and altered sinonasal lining, causing the nose to be blocked. In paediatric CF cases, anterior rhinoscopy or nasal endoscopy may identify polyps in as many as 86% of individuals. The exact figures reported by researchers differ, depending on the population studied and the composition of any groups compared [14–20]. There may be hypertrophy of the turbinates as well as hyperplastic lymphoid tissue in the back of the throat.

41.3 Clinical Evaluation

The history plays a key role in deciding how to manage CF patients with sinonasal disease, hence a meticulously detailed history focusing on symptoms affecting the nose and sinuses is required [4].

Features that need to be asked about within the history are as follows [21]:

- Blocked nose
- Deteriorating rhinorrhoea
- Pain over the face
- Deterioration in coughing
- Pyrexia

Between 90% and 100% of CF patients have imaging results indicating a sinus disorder [22–24], but polyp formation in the nose is less predictable, affecting between 6 and 67% of cases [2]. The frequency of nasal polyp formation increases with rising age. At the age of 6 years, 19% of cases have polyps that can be identified at endoscopy. By the age of 18 years, this figure has risen to 45% [25]. There is a higher frequency of polyps noted for patients who are homozygous for the delta f508 mutated allele [26].

A mere 10% of individuals with CF actually experience symptoms of sinusitis, such as pain, rhinorrhoea, pyrexia, or postnasal drainage [22]. Accordingly, the majority of cases where imaging shows sinusitis are asymptomatic. There are two ways to explain this situation: either the patient truly has no symptoms despite active pathology; or individuals may have mentally adjusted to such a situation and no longer perceive it as being abnormal [27].

In deciding to treat sinusitis, more emphasis is placed on the patient's reported symptoms than on the results of imaging investigations.

When taking a history, doctors should also enquire about lung-related symptoms. Not only is there a strong correlation between bacterial bronchitis and chronic sinusitis, but sinusitis also affects the degree of responsivity of the bronchial airways and the longevity of diseased periods. Also organisms are found in the sinuses before colonising the lungs (please find this reference). A declining ability to tolerate exercise is frequently associated with flare-ups of acute sinusitis or deterioration in chronic sinusitis [28, 29].

41.4 Physical Assessment

In the majority of cases, those referred to ENT specialists have already been diagnosed with CF and the aim of referral is to assess the need for surgical interventions on the sinus. Patients need to be examined physically in a detailed and comprehensive way so that the nasal cavity and sinuses can be assessed and any other factors predisposing to sinusitis may be identified.

When inspecting the face, the clinician may note broadening of the bridge of the nose, arising from chronic nasal polyp formation. Occasionally, a polyp may even be visible, emerging from the nostrils. Anterior rhinoscopic examination may reveal oedema of the turbinates, pus-filled rhinorrhoea and polyps within the nose. Endoscopic evaluation may allow visualisation of polyps that are blocking the

airway or the sinus ostium within the middle meatus. Pus may be seen discharging. It is not unusual to note the uncinate process projecting sufficiently to block part of the airway within the nose.

Assessment of the nasopharynx is similarly required. In a young patient, the adenoids may have hypertrophied and may be contributing to obstructed airflow within the nose. Just as with any other patient, CF sufferers need to have adenoidal hypertrophy treated prior to undertaking surgery on the sinuses [4].

41.5 Diagnosis

Sometimes CF may be diagnosed by an ENT specialist who notes the presence of multiple polyps in the nose of a paediatric patient with no other apparent health issues. On occasion, an individual with CF adapts to the condition to such an extent that they fail to present clinically at an early stage. Segal reports a frequency for CF of 1 in 16 children with nasal polyposis, but otherwise seemingly healthy [30]. The genetic abnormalities leading to CF vary, leading to a variety of severity in this disorder (pl find a reference).

CF children may be well grown and healthy looking therefore it is advisable to carry out the sweat chloride test on all paediatric cases presenting with polyp formation in the nose, to avoid missing a case of CF.

It is unusual, but possible, for paediatric cases of nasal polyposis to be seen in children who do not have CF. In such instances, the probable aetiology is allergic rhinitis of high severity, inflammatory responses linked to the Samter triad (asthma, intolerance of salicylates and polyp formation within the nose), Kartagener syndrome (organ reversal and non-motile cilia) or immune conditions of some other type. Diagnosis in such cases depends on thorough history-taking and physical examination, as well as the sweat test and a biopsy to examine the ciliary morphology, according to the presentation.

According to the research undertaken by Thamboo et al., the Sinonasal Outcome Test (SNOT-22), which consists of 22 questions, is suitable for screening paediatric CF cases for seemingly asymptomatic polyp formation within the nose. This research enrolled 37 children. If the SNOT-22 score was greater than 11, polyps could be accurately predicted 68.1% of the time, their absence predicted correctly 66.7% of the time, and the positive likelihood ratio was 1.82 [31].

41.5.1 CT Imaging

The degree of symptomatic discomfort and the severity as rated by CT imaging are only weakly correlated [32]. The symptomatic presentation is what guides how this condition is diagnosed and treated. The indications for undertaking CT imaging are to ascertain how extensive the condition is and to plan any surgical procedures. Axial and coronal sections are suitable, and no contrast agent is needed. CT should

be employed sparingly in a growing child because of potential harm from being exposed to a source of radiation. The resulting imagery has often been put in the most appropriate format to assist with operative interventions (see following text). Accordingly, if the clinician ordering CT suspects that operative intervention may be called for, liaison with an ENT specialist is recommended first.

The radiological findings consistent with chronic sinusitis are an opacified lumen, movement of the lateral wall of the nasal cavity medially in the area of the middle meatus, and the uncinate process appears decalcified. These appearances are seen in above 90% of patients with CF [33]. At endoscopy, the medially displaced lateral wall of the nose is evident, as seen radiologically, but until recently this phenomenon had not been quantified. However, Herovchon et al. [34] have now quantified the degree of displacement in research using CT imaging that measured the angles created by the uncinate process.

In some 12% of patients, the lateral wall of the nose protrudes medially, whilst the maxillary sinus contains thick mucus. These findings most resemble a mucocoele, which requires surgical intervention [21, 27].

The maxillary and ethmoid sinuses are frequently hypoplastic and contain little air in individuals with chronic sinusitis. Likewise, the frontal sinuses are underdeveloped [35]. It is frequent to note the absence of a hollow space in the frontal sinus in a CF patient who has reached adolescence [4].

41.5.2 Nitric Oxide

By filtering, warming, and humidifying inhaled air, the nasal cavity and turbinates play critical physiological roles. Nitric oxide (NO), a reactive oxygen species that spreads to the bronchi and lungs to cause bronchodilatory and vasodilatory effects, is continually released by paranasal sinuses and is part of the innate immune system, being toxic to bacteria and viruses. Nasal NO levels tend to be very low in CF, probably secondary to sinus obstruction (37). This, along with reduced mucociliary clearance may allow infection to occur. Replacement of NO is being tested currently. Low nasal NO levels may also alert the astute ENT surgeon to the possible diagnosis and can provide a marker of the effectiveness of sinus surgery (38).

41.6 Treatment

41.6.1 Nasal Douching

Nasal douching with saline may be helpful in removing allergens, pollutants and infective agents. In rhinosinusitis cases, especially in patients with cystic fibrosis, nasal douching helps clear infected secretions and may improve nasal patency **(39).** Seawater may be superior to saline (40).

41.6.2 Antimicrobial Pharmacotherapy

The bacteria responsible for nasal and sinus infections are different in cases of CF from those typically seen, hence antibiotic pharmacotherapy also differs. Whereas Pseudomonas occurs in virtually all cases with CF, this is not the case in non-CF patients.

Treatment of patients with CF using antibiotics typically aims to control pathogenic microbes that are found along the whole length of the respiratory tract. Antimicrobial pharmacotherapy may be informed by cultured material from the middle meatus or from sputum. The organisms which are most often isolated are *Pseudomonas aeruginosa* and *Staphylococcus aureus* [36]. Usually, antibiotic agents by mouth are prescribed prophylactically to individuals with CF for prevention of respiratory infections (upper or lower) or for management of already existing infections [37]. Although the employment of antibiotics by inhalation, notably tobramycin, colistin or aztreonam is commonplace, since these agents may lessen bacterial colonisation and thus offer improvements in pulmonary function, whether this treatment has any actual benefit in upper respiratory infections is unclear [38–40]. One problem here is the known ototoxicity of aminoglycosides, such as tobramycin. These agents produce sensorineural deafness and injury to the labyrinth, following prolonged use [41]. This situation alone should prompt the involvement of ENT specialists in management of CF. It is known that chronic rhinosinusitis can be effectively treated with antibiotics given by mouth in non-CF cases [42], hence there may be a reason to try the same in CF cases, too. One study found that the dimensions of polyps within the nose in CF patients were reduced following prolonged systemic pharmacotherapy using macrolide antibiotics [43].

41.6.3 Corticosteroids

The usual benefit from intranasal corticosteroids lies in their reducing swelling of the nasal lining and enhancing mucociliary drainage. This applies both acutely and for lengthier periods. Using oral corticosteroid treatment for a brief period may offer benefit in acute infective episodes. Furthermore, they potentially lessen blood loss during surgical procedures to remove nasal polyps if given before the procedure begins. Steroid treatment is commonplace in managing lung-related symptoms suffered by CF patients. It may help in reducing nasal and sinus symptoms, too, but there is a regrettable lack of evidence to reveal exactly how steroid therapy administered orally affects the symptoms of sinus disease in patients with CF. The Cochrane Collaboration have released a review summarising the evidence from a number of trials in which steroids were administered by mouth to CF sufferers. There were definite benefits in reducing the rate lung disease progressed, making admission to hospital for respiratory problems less common and giving a higher life quality. There was a lack of direct evidence on symptoms of disease in the nose and sinuses [44]. However, since it is recognised that steroids by mouth do offer benefits

in non-CF patients suffering from chronic sinusitis, it is not unreasonable to propose employing steroids for the treatment of sinusitis in CF cases, too [45, 46].

41.6.4 Other Therapies

Decongestant agents are less guaranteed to be beneficial. Antihistamine treatment not only lacks benefit but may even be harmful, since the secretions become even more viscid. In cases of CF, mucolytic agents typically offer no benefit. One exception to this principle is the employment of recombinant human deoxyribonuclease in infections of the lung and bronchi, where benefit has been shown. It reduces the viscoelasticity of sputum and improves breathing of (CF) patients [4].

41.6.5 Surgery

The evidence-base to support objective recommendations for when surgical interventions are appropriate in CF unfortunately does not yet exist. However, there are certain situations when it is reasonable to think about operative interventions, namely [4]:

- If the nose is significantly obstructed by intranasal polyp formation or the lateral wall of the nasal interior bulges medially, even despite aggressive pharmacotherapy, surgery may be appropriate.
- When it is noted at endoscopy or on CT imaging that the lateral wall of the nasal interior has shifted towards the midline, surgery may be warranted. This applies even if the patient has no symptoms of a blocked nose, since this phenomenon is highly likely to be due to a developing mucocele.
- Worsening of lung disease that seems to be linked to a deterioration in sinusitis, deterioration of lung function or decreased exercise tolerance, in spite of optimal pharmacotherapy, may be an indication for surgery.
- If no other cause than sinonasal disease can be ascribed to pain over the face or cephalgia, and this pain is reducing life quality.
- If the patient is dissatisfied with what has been achieved through optimal pharmacotherapy and remains troubled by nasal and sinus symptoms [27].

The situations in which operative interventions are contraindicated are as follows [4]:

- Obstructive lung disease of high severity, since general anaesthetics may be associated with intolerable risks.
- Deficiency of vitamin K and coagulation disorders of other causes. Patients with CF have inadequate activity by the pancreas and suffer from disorders of the liver and bile secretion. Thus, they may not absorb adequate vitamin K,

leading to a tendency to prolonged bleeding [47]. If the clotting profile performed prior to surgery indicates a lengthened prothrombin time (PT), the operation should not be undertaken until the PT has been brought back into the normal range.

- Hypoplasia of the sinus cavities may be considered relatively contraindicative for surgery. In CF patients, the maxillary, ethmoid and frontal sinuses may develop later than normal and contain less air than expected. It is common for hypoplasia affecting the sinuses to be noted on CT imaging. Given the additional risks that sinus hypoplasia imposes on surgical interventions, the imaging results need to be minutely checked and the operating surgeon should already have experience of this situation.

As with all patients presenting for sinus surgery, the approach in the past to CF cases was to employ simple polypectomy, open ethmoidectomy or the Caldwell-Luc method. Historically, polypectomy in CF cases has been associated with a decrease in symptoms at first but a greater than 80% risk that the lesions will recur [48–50]. More radical procedures, notably ethmoidectomy or Caldwell-Luc, offer a lower risk of recurrence of 45 to 60% in the two to eight years after the operation [46, 51]. As surgical interventions on the sinuses have developed in sophistication over the last few years, there has been increasing optimism that surgery can achieve higher success rates in CF cases, whilst becoming less invasive in nature. The safety and efficacy of surgery to the sinuses carried out endoscopically (ESS) has been demonstrated in numerous studies involving individuals suffering from CF [15, 52–57]. The benefits of ESS have been manifested as a decrease in nasal and sinus symptoms and a higher life quality in some studies [40, 57, 58], and as a lower risk of requiring redo operations than with conventional operations in others [59]. However, more radical types of operation on the sinuses may produce less benefit if the patient has CF. Georgalas et al. have recently published the results from a study of Draf type III (i.e. a modified Lothrop procedure done endoscopically) to drain the frontal sinus [60]. They examined long term outcomes, noting that, in their group of 122 cases, those patients who had CF were most at risk of the ostial entrance to the frontal sinus re-stenosing after surgery.

A procedure that possesses demonstrably equivalent efficacy to ESS in the treatment of chronic rhinosinusitis in patients without other disease is balloon catheter sinuplasty (BCS). This technique dates from 2006 [61]. Since its introduction, the technique has been specifically assessed in children with chronic rhinosinusitis to evaluate how efficacious and safe it is. Recently, results from research examining various cohorts suggest the technique is both safe and efficacious [62–65], whilst also benefitting from not requiring the excision of tissue, and preserving the integrity of the mucosae. It appears that BCS is especially suited for treating children with chronic rhinosinusitis, including those with CF. So far, studies focusing on the technique have not addressed CF cases in particular, but results from the use on other children are promising in terms of adding an extra option to the treatments clinicians have at their disposal to treat rhinosinusitis in paediatric CF cases.

41.6.6 Gene Therapy

This is a process in which a new, correct version of the CFTR gene is inserted into cells. Mutant copies of the CFTR gene remain, but the correct copy allows cells to make normal CFTR proteins. It is outwith the scope of this chapter, but more details can be found at https://www.cff.org/Research/Research-Into-the-Disease/Restore-CFTR-Function/Gene-Therapy-for-Cystic-Fibrosis

References

1. Cipolli M, Canciani M, Cavazzani M, et al. Ear disease is not a common complication in cystic fibrosis. Eur J Pediatr. 1993;152(3):265–6.
2. Halvorson DJ. Cystic fibrosis: an update for the otolaryngologist. Otolaryngol Head Neck Surg. 1999;120(4):502–6.
3. Haddad J Jr, Gonzalez C, Kurland G, et al. Ear disease in children with cystic fibrosis. Arch Otolaryngol Head Neck Surg. 1994;120(5):491–3.
4. Murray N. Sinonasal Manifestations of Cystic Fibrosis. In: Meyers AD (Ed). Medscape. Updated: May 23, 2019. https://emedicine.medscape.com/article/862538-overview (Accessed online at October 16, 2020).
5. Riordan JR, Rommens JM, Kerem BS, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989;245(4922):1066–73.
6. Oomen KP, April MM. Sinonasal manifestations in cystic fibrosis. Int J Otolaryngol. 2012;2012:789572. https://doi.org/10.1155/2012/789572.
7. Shatz A. Management of recurrent sinus disease in children with cystic fibrosis: a combined approach. Otolaryngology. 2006;135(2):248–52.
8. Tandon R, Derkay C. Contemporary management of rhinosinusitis and cystic fibrosis. Curr Opin Otolaryngol Head Neck Surg. 2003;11(1):41–4.
9. Cepero R, Smith RJH, Catlin FI, Bressler KL, Furuta GT, Shandera KC. Cystic fibrosis—an otolaryngologic perspective. Otolaryngology. 1987;97(4):356–60.
10. Kerrebijn JDF, Poublon RML, Overbeek SE. Nasal and paranasal disease in adult cystic fibrosis patients. Eur Respir J. 1992;5(10):1239–42.
11. Godoy JM, Godoy AN, Ribalta G, Largo I. Bacterial pattern in chronic sinusitis and cystic fibrosis. Otolaryngology. 2011;145:673–6.
12. Raman V, Clary R, Siegrist KL, Zehnbauer B, Chatila TA. Increased prevalence of mutations in the cystic fibrosis transmembrane conductance regulator in children with chronic rhinosinusitis. Pediatrics. 2002;109(1):E13.
13. Wang X, Moylan B, Leopold DA, et al. Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. J Am Med Assoc. 2000;284(14):1814–9.
14. Cuyler JP, Monaghan AJ. Cystic fibrosis and sinusitis. J Otolaryngol. 1989;18(4):173–5.
15. Triglia JM, Nicollas R. Nasal and sinus polyposis in children. Laryngoscope. 1997;107(7):963–6.
16. Slieker MG, Schilder AGM, Uiterwaal CSPM, Van der Ent CK. Children with cystic fibrosis: who should visit the otorhinolaryngologist? Arch Otolaryngol. 2002;128(11):1245–8.
17. Ryan MW. Diseases associated with chronic rhinosinusitis: what is the significance? Curr Opin Otolaryngol Head Neck Surg. 2003;11:41–4.
18. Yung MW, Gould J, Upton GJG. Nasal polyposis in children with cystic fibrosis: a long-term follow-up study. Ann Otol Rhinol Laryngol. 2002;111(12):1081–6.
19. Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope. 2005;115(12):2199–205.

20. Sakano E, Ribeiro AF, Barth L, Neto AC, Ribeiro JD. Nasal and paranasal sinus endoscopy, computed tomography and microbiology of upper airways and the correlations with genotype and severity of cystic fibrosis. Int J Pediatr Otorhinolaryngol. 2007;71(1):41–50.
21. Brihaye P, Clement PA, Dab I, Desprechin B. Pathological changes of the lateral nasal wall in patients with cystic fibrosis (mucoviscidosis). Int J Pediatr Otorhinolaryngol. 1994;28(2–3):141–7.
22. Cepero R, Smith RJ, Catlin FI, et al. Cystic fibrosis--an otolaryngologic perspective. Otolaryngol Head Neck Surg. 1987;97(4):356–60.
23. Neely JG, Harrison GM, Jerger JF, et al. The otolaryngologic aspects of cystic fibrosis. Trans Am Acad Ophthalmol Otolaryngol. 1972;76(2):313–24.
24. Shwachman H, Kulcycki LL, Mueller HL. Nasal polyposis in patients with cystic fibrosis. Pediatrics. 1962;30:389–401.
25. Schraven SP, Wehrmann M, Wagner W, Blumenstock G, Koitschev A. Prevalence and histopathology of chronic polypoid sinusitis in pediatric patients with cystic fibrosis. J Cyst Fibros. 2011;10(3):181–6.
26. Babinski D, Trawinska-Bartnicka M. Rhinosinusitis in cystic fibrosis: not a simple story. Intl J Ped Otorhinol. 2008;72:619–24.
27. Nishioka GJ, Cook PR. Paranasal sinus disease in patients with cystic fibrosis. Otolaryngol Clin N Am. 1996;29(1):193–205.
28. Ramsey B, Richardson MA. Impact of sinusitis in cystic fibrosis. J Allergy Clin Immunol. 1992;90(3 Pt 2):547–52.
29. Nishioka GJ, Barbero GJ, Konig P, et al. Symptom outcome after functional endoscopic sinus surgery in patients with cystic fibrosis: a prospective study. Otolaryngol Head Neck Surg. 1995;113(4):440–5.
30. Segal N, Gluk O, Puterman M. Nasal polyps in the pediatric population. B-ENT. 2012;8(4): 265–7.
31. Thamboo A, Santos RC, Naidoo L, Rahmanian R, Chilvers MA, Chadha NK. Use of the SNOT-22 and UPSIT to appropriately select pediatric patients with cystic fibrosis who should be referred to an otolaryngologist: cross-sectional study. JAMA Otolaryngol Head Neck Surg. 2014;140(10):934–9.
32. Sakano E, Ribeiro AF, Barth L, Neto AC, Ribeiro JD. Nasal and paranasal endoscopy computed tomography and microbiology of upper airways and the correlations with genotype and severity of cystic fibrosis. Intl J Ped Otorhinol. 2007;71:41–50.
33. April MM, Zinreich SJ, Baroody FM, Naclerio RM. Coronal CT scan abnormalities in children with chronic sinusitis. Laryngoscope. 1993;103(9):985–90.
34. Hervochon R, Teissier N, Blondeau JR, et al. Computed tomography description of the Uncinate process angulation in patients with cystic fibrosis and comparison with primary ciliary dyskinesia, nasal polyposis, and controls. Ear Nose Throat J. 2019;98(2):89–93.
35. Ledesma-Medina J, Osman MZ, Girdany BR. Abnormal paranasal sinuses in patients with cystic fibrosis of the pancreas. Radiological findings. Pediatr Radiol. 1980;9(2):61–4.
36. Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. Otolaryngol Head Neck Surg. 2001;125(3):265–9.
37. Anderson P. Emerging therapies in cystic fibrosis. Ther Adv Respir Dis. 2010;4(3):177–85.
38. 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.
39. Franche GLDS, Abreu E, Silva F, Saleh CDS. Bacteriology of the middle meatus aspirate in patients with cystic fibrosis. Braz J Otorhinolaryngol. 2007;73(4):494–9.
40. Shapiro ED, Milmoe GJ, Wald ER. Bacteriology of the maxillary sinuses in patients with cystic fibrosis. J Infect Dis. 1982;146(5):589–93.
41. Hansen CR, Pressler T, Koch C, Høiby N. Long-term azitromycin treatment of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection; an observational cohort study. J Cyst Fibros. 2005;4(1):35–40.

42. Pai VB, Nahata MC. Efficacy and safety of aerosolized tobramycin in cystic fibrosis. Pediatr Pulmonol. 2001;32(4):314–27.
43. Westerman EM, Le Brun PPH, Touw DJ, Frijlink HW, Heijerman HGM. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. J Cyst Fibros. 2004;3(1):23–8.
44. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. Am J Respir Crit Care Med. 2008;178(9):921–8.
45. Tan KHV, Mulheran M, Knox AJ, Smyth AR. Aminoglycoside prescribing and surveillance in cystic fibrosis. Am J Respir Crit Care Med. 2003;167(6):819–23.
46. Cheng K, Ashby D, Smyth R. Oral steroids for cystic fibrosis. Cochrane Database Syst Rev. 2000;2:CD000407.
47. Rashid M, Durie P, Andrew M, et al. Prevalence of vitamin K deficiency in cystic fibrosis. Am J Clin Nutr. 1999;70(3):378–82.
48. Shwachman H, Kulzycki LL, Mueller HL, Flake CG. Nasal polyposis in patients with cystic fibrosis. Pediatrics. 1962;30:389–401.
49. Jaffe BF, Strome M, Khaw KT, Shwachman H. Nasal polypectomy and sinus surgery for cystic fibrosis a 10 year review. Otolaryngol Clin N Am. 1977;10(1):81–90.
50. Crockett DM, McGill TJ, Healy GB, Friedman EM, Salkeld LJ. Nasal and paranasal sinus surgery in children with cystic fibrosis. Ann Otol Rhinol Laryngol. 1987;96(4):367–72.
51. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. Ann Intern Med. 2011;154(5):293–302.
52. Keck T, Rozsasi A. Medium-term symptom outcomes after paranasal sinus surgery in children and young adults with cystic fibrosis. Laryngoscope. 2007;117(3):475–9.
53. Albritton FD, Kingdom TT. Endoscopic sinus surgery in patients with cystic fibrosis: an analysis of complications. Am J Rhinol. 2000;14(6):379–85.
54. Schulte DL, Kasperbauer JL. Safety of paranasal sinus surgery in patients with cystic fibrosis. Laryngoscope. 1998;108(12):1813–5.
55. Cuyler JP. Follow-up of endoscopic sinus surgery on children with cystic fibrosis. Arch Otolaryngol. 1992;118(5):505–6.
56. 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. Otolaryngology. 1995;113(4):440–5.
57. Jones JW, Parsons DS, Cuyler JP. The results of functional endoscopic sinus (FES) surgery on the symptoms of patients with cystic fibrosis. Int J Pediatr Otorhinolaryngol. 1993;28(1):25–32.
58. Khalid AN, Mace J, Smith TL. Outcomes of sinus surgery in adults with cystic fibrosis. Otolaryngology. 2009;141(3):358–63.
59. Moss RB, King VV. Management of sinusitis in cystic fibrosis by endoscopic surgery and serial antimicrobial lavage: reduction in recurrence requiring surgery. Arch Otolaryngol. 1995;121(5):566–72.
60. Georgalas C, Hansen F, Videler WMJ, Fokkens WJ. Long term results of Draf type III, (modified endoscopic Lothrop) frontal sinus drainage procedure in 122 patients: a single Centre experience. Rhinology. 2011;49:195–201.
61. Stewart AE, Vaughan WC. Balloon sinuplasty versus surgical management of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2010;10(3):181–7.
62. Ramadan HH. Safety and feasibility of balloon sinuplasty for treatment of chronic rhinosinusitis in children. Ann Otol Rhinol Laryngol. 2009;118(3):161–5.
63. Ramadan HH, McLaughlin K, Josephson G, Rimell F, Bent J, Parikh SR. Balloon catheter sinuplasty in young children. Am J Rhinol Allergy. 2010;24(1):e54–6.
64. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. Ann Otol Rhinol Laryngol. 2010;119(9):578–82.
65. Sedaghat AR, Cunningham MJ. Does balloon catheter sinuplasty have a role in the surgical management of pediatric sinus disease? Laryngoscope. 2011;121:2053–4.