

Review

Chronic Rhinosinusitis with Nasal Polyposis in People with Cystic Fibrosis

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Abstract: Cystic fibrosis (CF) is an autosomal recessive disorder that results in deranged ion transport and affects multiple organ systems, including the upper and lower respiratory tracts. People with CF (PwCF) often develop chronic rhinosinusitis (CRS) with or without nasal polyposis. CRS can significantly decrease quality of life for PwCF and can lead to more frequent pulmonary exacerbations. The management of CRS in PwCF is different from that in individuals without CF. Novel therapies have emerged in the last several years that have drastically altered the progression of both pulmonary and sinonasal disease in people with CF. It is critical for providers who manage CF-related CRS to understand the unique characteristics and challenges that coincide with this disease process. This review article aims to provide readers with an overview of the pathophysiology of CF and to summarize best practice strategies for the management of CF-related CRS.

Keywords: chronic rhinosinusitis; nasal polyposis; cystic fibrosis; highly effective modulator therapy

1. Cystic Fibrosis: Background and Overview

Cystic fibrosis (CF) is an autosomal recessive disorder that is most common among individuals of northern European descent, yet affects people of all ethnic and racial backgrounds [1]. CF is caused by variants in the CF transmembrane conductance regulator (CFTR) gene, which encodes a complex chloride channel and regulatory protein that is expressed on the surface of epithelial cells that line the respiratory tract and exocrine glands [2,3]. CF causing variants result in deranged ion transport across multiple organ systems, including the upper airway, lower airway, and gastrointestinal system [4–6]. Research efforts have traditionally focused on improving lung function, as pulmonary disease is the predominant cause of early mortality among people with CF (PwCF) [7]. However, as treatment options have improved and life expectancy has increased for PwCF, a new emphasis has been placed on improving quality of life (QOL), which includes managing the sinonasal manifestations of CF [8,9]. Furthermore, in line with the unified airway theory, the paranasal sinuses may serve as a reservoir for pulmonary infections [10–13]. Thus, treating sinonasal disease is an important factor in optimizing pulmonary status in PwCF.

The upper airway manifestations of CF result from an abnormal electrolyte concentration in nasal secretions, leading to reduced water content and inspissated mucus [14,15]. The hyperviscosity of nasal secretions and impaired mucociliary clearance predisposes PwCF to develop chronic bacterial infections and inflammation, which can then lead to chronic rhinosinusitis (CRS) with or without nasal polyposis [8,15–17]. Although the majority of PwCF are identified through newborn screening, some individuals are not diagnosed with CF until much later in life. Consequently, evaluation for CF should be considered in adult patients with CRS and a history of pulmonary infections.

Nearly all adults with CF have radiologic or endoscopic findings of sinus inflammation; however, only a minority report typical symptoms of CRS [3,15,18–21]. Because of minimal reporting, CF-related CRS (CF-CRS) is thought to be underdiagnosed and undertreated,



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although awareness of this disease complication is increasing [18]. At present, there are no universally accepted diagnostic criteria for CF-CRS; however, patient-reported symptoms and objective findings on nasal endoscopy or imaging are frequently utilized to make the diagnosis [22,23].

Olfactory dysfunction (OD) is one of the hallmark features of CRS and is estimated to occur in up to 80% of non-CF individuals with CRS [24]. Among PwCF, the prevalence of OD is estimated at 63% to 94% [4,25,26]. The mechanism of OD among PwCF is not fully understood but is likely associated with chronic, lifelong inflammation near the olfactory apparatus in the superior nasal cavity. OD may be related to inflammation of the olfactory cleft, nasal polyps, chronic infections, and/or prior functional endoscopic sinus surgery (FESS) [27]. PwCF often do not report subjective olfactory impairment when queried, which is frequently discordant with their objective olfactory testing results [4,27]. This discordance may be due to a response shift or inadvertent deprioritization of olfactory-related QOL, as the global symptom burden PwCF endure is high; however, further investigation on this topic is needed [27,28].

2. Chronic Rhinosinusitis with Nasal Polyposis in People with Cystic Fibrosis

CRS is a heterogeneous process that consists of multiple phenotypes and endotypes. CRS with nasal polyposis (CRSwNP) is one of the main phenotypes of CRS and makes up approximately 30% of cases in non-CF individuals (Figure 1) [29]. CRSwNP in people without CF (Pw/oCF) typically presents between 40 and 60 years of age and is usually bilateral in nature [29,30]. The prevalence of nasal polyposis among adults with CF has been estimated at 32% to 44% [31–34], while the prevalence in pediatric patients is approximately 45% to 57% [3,35–37]. Additionally, the prevalence of CRSwNP among pediatric patients with CF increases with age—nasal polyposis has been diagnosed in 18% of patients younger than six years and 45% of adolescents [37]. Modest differences in prevalence rates across age are likely due to variation in sampling in different cohorts.

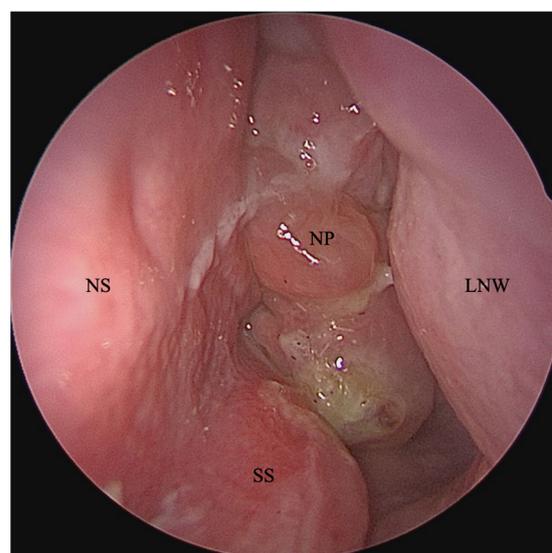


Figure 1. Left nasal cavity endoscopy images from a person with chronic rhinosinusitis with nasal polyposis. Abbreviations: NS = nasal septum; SS = septal spur; NP = nasal polyps; LNW = lateral nasal wall.

Although the endoscopic and radiologic appearance of nasal polyposis is often similar among PwCF and Pw/oCF, different mechanisms are involved in the development of these inflammatory lesions in these two populations. Endotypes refer to distinct immunologic pathways that lead to CRS. In general, CRSwNP is considered a type 2 eosinophilic inflammatory response [38]. However, recent studies have demonstrated that endotypes may vary based on race and geographic location. For instance, Pw/oCF with CRSwNP who identify

as white are more likely to have eosinophilic-predominance, while those who identify as Asian are more likely to show neutrophilic inflammation [38–40]. Such differences are likely a result of variation in genetic ancestry that impact immune response to stimuli. Although studies on endotypes in nasal polyps in PwCF are limited, CF-CRS is commonly associated with neutrophilic inflammation [41–43]. The pathogenesis of CF-CRSwNP is not well understood; however, research has identified associations between the presence of nasal polyposis and factors such as pulmonary colonization with *Pseudomonas aeruginosa* and severe CFTR variants [44,45].

3. Management of Nasal Polyps in People with Cystic Fibrosis

Until recently, treatments for PwCF were primarily focused on treating the end-organ manifestations of CF [46]. For CF-CRS, management has typically involved a combination of topical and systemic medical therapies followed by sinus surgery for medically refractory disease (Table 1) [13,18].

Table 1. Summary of treatments for cystic fibrosis-related chronic rhinosinusitis and their effects on nasal polyps.

	Treatment for Cystic Fibrosis-Related Chronic Rhinosinusitis	Mechanism	Effect on Nasal Polyps
Local Therapies	Dornase-alpha	Cleaves extracellular DNA, resulting in decreased secretion viscosity and improved mucociliary clearance.	None
	Nasal saline irrigations	Clears retained mucus and pathogens from the paranasal sinuses.	None
	Topical corticosteroids	Decreases inflammation of the sinonasal mucosa.	Reduction in polyps
	Topical antibiotics	Treats bacterial infections, which results in decreased inflammation of the paranasal sinuses.	Unknown
	Endoscopic sinus surgery	Improves ventilation of the paranasal sinuses, removes polyps, and allows for improved delivery of topical medications postoperatively.	Reduction in polyps
Systemic Therapies	Oral antibiotics	Treats bacterial infections of the paranasal sinuses.	Unknown
	Oral corticosteroids	Decreases inflammation of the sinonasal mucosa.	Possible reduction in polyps, although evidence is limited
	Highly effective modulator therapy	Significantly improves CFTR dysfunction.	Reduction in polyps

Several topical therapies exist to treat CF-CRS with or without nasal polyposis. Dornase-alpha is an effective pulmonary and sinonasal treatment that selectively cleaves extracellular DNA that is produced through the degradation of neutrophils [47–49]. This medication results in decreased viscosity of secretions and improved mucociliary clearance. Nasally inhaled dornase-alpha results in improved sinonasal symptoms; however, its impact on pulmonary function and radiographic and endoscopic findings of CRS is variable [48,50,51]. The use of intranasal dornase-alpha does not appear to significantly affect the presence or size of nasal polyps in CF-CRS [50].

Nasal saline irrigations (NSI) are another common treatment for CRS in both PwCF and Pw/oCF. A randomized controlled trial demonstrated that both hypertonic and isotonic saline led to small improvements in sinonasal symptom burden assessed via the 22-Item SinoNasal Outcome Test among PwCF, although this was not specific to CF-CRSwNP [52]. There is no evidence showing that NSI alone improves nasal polyps; however, clearing the paranasal sinuses of retained mucus and pathogens may help decrease inflammation along the sinonasal mucosa [53].

Topical corticosteroids can be helpful in treating CF-CRS, especially in patients with nasal polyposis [18]. A randomized controlled trial showed a reduction in nasal polyps but no change in symptom score among patients treated twice daily with topical betamethasone for six weeks [54]. Another study found that nasally inhaled beclomethasone resulted in improvement in nasal obstructive symptoms among PwCF-CRS without nasal polyposis and resulted in a reduction in nasal polyps among CF-CRSwNP [55].

Topical antibiotics have also shown promising results in the treatment of CF-CRS, specifically with regard to patient-reported outcomes and need for revision sinus surgery [56–58]. Two randomized controlled trials on CF-CRS demonstrated improved patient-reported outcome measures after treatment with topical tobramycin [56,58]. However, these studies were not specifically designed to examine the effect on nasal polyposis.

In addition to topical therapies, there is a role for systemic medications in the treatment of CF-CRS. Oral antibiotics are a mainstay of treatment in this population, as PwCF suffer from recurrent infections of the respiratory tract [13]. Oral corticosteroids are often used for short-term management of CRSwNP in Pw/oCF; however, data on their use in CF-CRSwNP are limited [8,13]. The Cystic Fibrosis Foundation recommends against the routine use of chronic systemic corticosteroids for CF-CRS [18]. It is possible that PwCF with CRSwNP may benefit from short-term systemic corticosteroids in certain cases; however, oral corticosteroids must be used with caution in PwCF, as there is a high prevalence of CF-related diabetes [13,53].

For individuals with medically refractory disease, FESS continues to have an important role in treating CF-CRSwNP. Individuals who remain symptomatic after appropriate medical therapy are candidates for FESS. Multiple studies have demonstrated that FESS leads to improved sinonasal symptoms and QOL [59–62]. Compared to Pw/oCF, FESS in PwCF may be more extensive given the need for larger drainage pathways to facilitate clearance of tenacious mucus and instillation of topical medications after surgery. Specifically, maxillary mega-antrostomy (also known as endoscopic medial maxillectomy), Draf 3 frontal sinusotomy, and sphenoid nasalization can be used to facilitate drainage of the sinus cavities [18]. Individuals with CF-CRSwNP should be counseled that nasal polyps are likely to recur because poor mucociliary clearance remains even after surgical intervention [53]. These individuals may require multiple surgical procedures over their lives. Surgery and medical therapies should be used in conjunction to improve individuals' QOL.

4. The Impact of Highly Effective Modulator Therapy on Sinusitis and Nasal Polyps

Unlike the aforementioned medications that treat the downstream effects of CFTR dysfunction, highly effective CFTR modulator therapy (HEMT) partially reverses the underlying CFTR defect by impacting the CFTR protein. Since the discovery of the CFTR gene in 1989, over 2000 variants in the gene have been identified [63,64]. Each of these gene variants is associated with a specific class, which describes the type of CFTR protein defect incurred by a given variant [64]. Knowledge of the various types of CFTR defects has allowed for the development of targeted therapies.

CFTR modulators consist of potentiators and correctors. Potentiators augment gating of the channel, while correctors improve the processing and trafficking of CFTR, resulting in chloride channel presence at the surface of epithelial cells [65,66]. In 2011, ivacaftor, a CFTR potentiator, became the first CFTR modulator to be approved for PwCF with the G551D mutation [67]. While this medication was highly effective for a small percentage of PwCF, the majority of PwCF were not variant-eligible to take this medication. Since then, additional modulators and combinations of medications have been developed and approved by regulatory bodies for PwCF. The most recent HEMT to be approved was elexacaftor-tezacaftor-ivacaftor (ETI), which is a three-drug combination of two correctors and one potentiator that has been shown to significantly improve lung function, nutritional outcomes, and overall QOL among individuals with at least one copy of F508del, the most common CFTR variant [65,68,69]. Based on in vitro response of additional variants, the approved use of ETI has subsequently been expanded [70].

More recent studies have shown that ETI is efficacious in treating CF-CRS. Specifically, ETI has been shown to significantly improve patient-reported sinonasal outcomes, reduce sinus opacification on computed tomography (CT) scans, and reduce nasal polyp burden on nasal endoscopy (Figure 2) [71–73]. In contrast to these improvements CRS severity, treatment with ETI did not lead to improvement in olfactory dysfunction among PwCF—specifically, CT opacification of the olfactory cleft and Smell Identification Test (SIT) scores did not improve [27]. It is possible that earlier intervention with HEMT may improve or prevent olfactory dysfunction; additional studies are needed to investigate this theory.

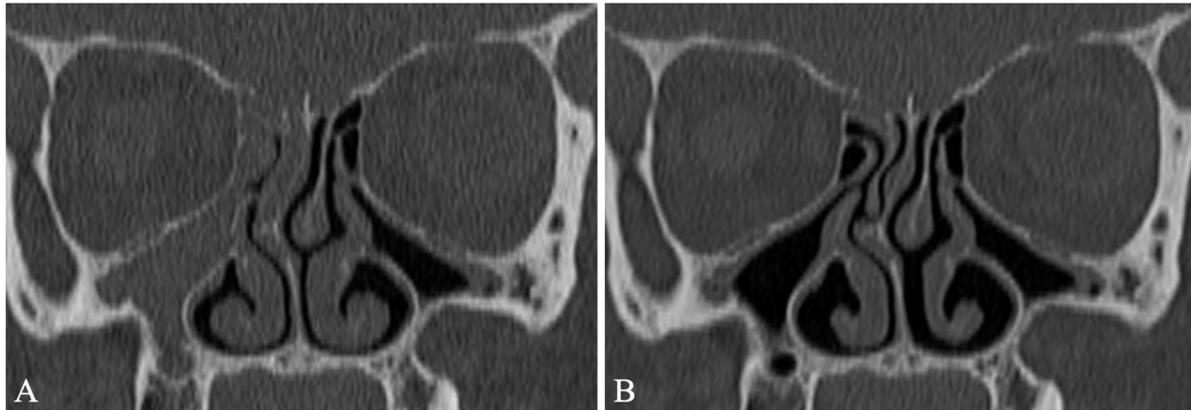


Figure 2. Coronal sinus computed tomography images of a person with cystic fibrosis before (A) and after six months (B) of elexacaftor/tezacaftor/ivacaftor treatment. This twice daily oral therapy leads to an improvement (decrease) in sinus opacification.

Given the extrapulmonary benefits of HEMT, the utility of this medication in the post-lung transplantation setting is an area of ongoing research. A study by Benninger et al. found that of the nine adult PwCF who were initiated on ETI after lung transplantation, eight (88.9%) had improvement in subjective sinonasal symptoms [74]. A study by Hayes et al. found that three of five pediatric patients (60%) treated with HEMT after lung transplantation reported improvement in CRS-related symptoms [75]. A multi-institutional study found that among CF lung transplant recipients, the most common reason for ETI initiation in the post-transplant setting was sinonasal disease (68%) [76]. Although HEMT may be helpful in managing the extrapulmonary manifestations of CF after lung transplantation, the initial clinical trials on HEMT excluded transplant recipients; thus, providers need to be aware of the risks, specifically the potential for drug–drug interactions with CFTR modulators and transplant medications [75]. Furthermore, the use of HEMT represents a significant paradigm shift for the management of CF-CRS, and as such, use of the aforementioned conventional therapies is likely to change over time.

5. Unique Considerations for Managing Chronic Rhinosinusitis in the Pediatric Population

The diagnosis and treatment of CRS in children and adolescents with CF is nuanced and differs somewhat from that of the adult population. Compared to adults, pediatric patients may not be as well-equipped to express their concerns and often report minimal sinonasal symptoms, despite significant sinonasal disease on imaging studies [77,78]. Additionally, CT imaging is useful in evaluating sinonasal disease burden; however, this imaging modality exposes individuals to radiation. CT imaging should be used judiciously in all individuals, including children [79]. Magnetic resonance imaging, which does not expose individuals to ionizing radiation, may also be considered [80].

In both children and adults, medical management is the first line treatment for CF-CRS. In addition to the local and systemic therapies that treat the end-organ manifestations of CF-CRS, HEMT has been shown to improve CRS outcomes in PwCF. However, not all

PwCF are candidates for HEMT—eligibility depends on age, genotype, and the absence of other co-morbidities such as end-stage liver disease. ETI was recently approved for use in children with eligible variants ≥ 2 years of age and ivacaftor alone was approved for use in infants with eligible variants as young as one month of age [81,82]. Future studies in young children, such as those being done in conjunction with the Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function in Infants and Young Children (BEGIN, NCT04509050), will be crucial for understanding how HEMT impacts sinonasal outcomes when initiated early in life.

If sinonasal symptoms and inflammation persist despite appropriate medical therapy, FESS is a treatment option. FESS has been shown to be safe in the pediatric population and studies have demonstrated that surgery leads to decreased sinonasal symptoms and improved QOL in both adults and children with CF [83–85]. FESS in the pediatric population is unique. The paranasal sinuses are incompletely formed at birth and continue to develop throughout childhood, though sinus hypoplasia remains common in the CF population. As such, all sinus cavities are often not fully pneumatized in children and adolescents, particularly in those with CF. Underpneumatization of the sinuses alters surgical planning and may limit the extent of FESS. Prior studies in animal models have raised concerns about midface development in pediatric patients undergoing FESS [86,87]. However, two studies in human subjects found no significant impact on facial development in children who underwent FESS [88,89]. Taken together, this information suggests that surgery can be considered in carefully selected pediatric patients with CF-CRS with refractory disease. Some authors propose waiting until a child is older to embark on surgery [89].

The postoperative management after ESS in children with CF can be challenging, as many pediatric patients are unable to tolerate in-office debridements. Because of this limitation, many physicians have advocated for a second-look debridement procedure a few weeks after the initial surgery. A study by Helmen et al. found that second-look debridements did not impact rates of sinonasal exacerbations or need for revision ESS; however, patients who underwent debridement in the operating room did experience a longer time interval until their first pulmonary exacerbation compared to those who did not undergo debridement (113.9 versus 47.4 days) [90]. Data on the optimal treatments for CF-CRS in the pediatric population are limited, and more robust studies on this topic are needed.

6. Future Directions in the Management of Cystic Fibrosis-Related Chronic Rhinosinusitis with Nasal Polyposis

CF is a complex disease that affects multiple organs; therefore, PwCF should be treated by multidisciplinary care teams that include otolaryngologists with experience managing this challenging disease process. Additionally, research teams comprised of experts from a broad range of specialties are helpful to ensure all aspects of this disease are investigated.

An active area of research involves understanding the role of biologic therapies for the treatment of CRSwNP in Pw/oCF. There are currently three monoclonal antibodies that are approved in the United States for the treatment of CRSwNP, all of which target the type 2 immune pathway. At this time, none of the biologic medications are approved for use in PwCF. Additionally, since the majority of PwCF have neutrophilic polyps, it is unlikely that the current biologic medications would be of benefit in this population. However, studies have also demonstrated that CF-CRSwNP is a heterogeneous entity, and often involves eosinophilic infiltrates [91]. Thus, the immune pathways implicated in CF-CRSwNP are not fully understood, and future research should investigate whether there is a role for the use of biologic medications in treating this disease.

Personalized medicine involves understanding the unique characteristics of each individual and their disease process. Prior studies have failed to demonstrate a reliable correlation between subjective and objective measures of CF-CRS; thus, it is important for providers to consider all measures of sinonasal disease severity when managing CF-CRS [92,93]. Additionally, it is important for providers to be mindful of the impact that an

individual's treatment burden can have on their QOL. One study found that the average person with CF spends 108 min per day on CF treatment activities [94]. Providers should consider the challenges associated with specific treatment regimens and discuss these factors with PwCF in their care. Although treatment options for PwCF have drastically improved in the last decade, there is still much progress to be made to optimize quality and quantity of life in this population. Furthermore, HEMT is not available for all PwCF; for those individuals who are ineligible or intolerant of HEMT, novel therapeutic options to treat CRS are needed.

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References

1. Walters, S.; Mehta, A. Chapter 2: Epidemiology of cystic fibrosis. In *Cystic Fibrosis*, 3rd ed.; Hodson, M., Ed.; Taylor & Francis Group: London, UK, 2007; pp. 21–45.
2. O'Sullivan, B.P.; Freedman, S.D. Cystic fibrosis. *Lancet* **2009**, *373*, 1891–1904. [[CrossRef](#)] [[PubMed](#)]
3. Yung, M.W.; Gould, J.; Upton, G.J.G. Nasal polyposis in children with cystic fibrosis: A long-term follow-up study. *Ann. Otol. Rhinol. Laryngol.* **2002**, *111 Pt 1*, 1081–1086. [[CrossRef](#)] [[PubMed](#)]
4. Di Lullo, A.M.; Iacotucci, P.; Comegna, M.; Amato, F.; Dolce, P.; Castaldo, G.; Cantone, E.; Carnovale, V. Cystic Fibrosis: The Sense of Smell. *Am. J. Rhinol. Allergy* **2020**, *34*, 35–42. [[CrossRef](#)]
5. Mall, M.A.; Galiotta, L.J.V. Targeting ion channels in cystic fibrosis. *J. Cyst. Fibros.* **2015**, *14*, 561–570. [[CrossRef](#)] [[PubMed](#)]
6. Bock, J.M.; Schien, M.; Fischer, C.; Naehrlich, L.; Kaeding, M.; Guntinas-Lichius, O.; Gerber, A.; Arnold, C.; Mainz, J.G. Importance to question sinonasal symptoms and to perform rhinoscopy and rhinomanometry in cystic fibrosis patients. *Pediatr. Pulmonol.* **2017**, *52*, 167–174. [[CrossRef](#)]
7. *Cystic Fibrosis Foundation Patient Registry, 2021 Annual Data Report*; Cystic Fibrosis Foundation: Bethesda, MD, USA, 2022.
8. Tipirneni, K.E.; Woodworth, B.A. Medical and Surgical Advancements in the Management of Cystic Fibrosis Chronic Rhinosinusitis. *Curr. Otorhinolaryngol. Rep.* **2017**, *5*, 24–34. [[CrossRef](#)]
9. Johnson, B.J.; Choby, G.W.; O'Brien, E.K. Chronic rhinosinusitis in patients with cystic fibrosis—Current management and new treatments. *Laryngoscope Investig. Otolaryngol.* **2020**, *5*, 368–374. [[CrossRef](#)] [[PubMed](#)]

10. Illing, E.A.; Woodworth, B.A. Management of the upper airway in cystic fibrosis. *Curr. Opin. Pulm. Med.* **2014**, *20*, 623–631. [[CrossRef](#)]
11. Alanin, M.C.; Aanaes, K.; Høiby, N.; Pressler, T.; Skov, M.; Nielsen, K.G.; Taylor-Robinson, D.; Waldmann, E.; Krogh Johansen, H.; von Buchwald, C. Sinus surgery postpones chronic Gram-negative lung infection: Cohort study of 106 patients with cystic fibrosis. *Rhinology* **2016**, *54*, 206–213. [[CrossRef](#)]
12. Johansen, H.K.; Aanaes, K.; Pressler, T.; Nielsen, K.G.; Fisker, J.; Skov, M.; Høiby, N.; von Buchwald, C. Colonisation and infection of the paranasal sinuses in cystic fibrosis patients is accompanied by a reduced PMN response. *J. Cyst. Fibros.* **2012**, *11*, 525–531. [[CrossRef](#)]
13. Safi, C.; Zheng, Z.; Dimango, E.; Keating, C.; Gudis, D.A. Chronic Rhinosinusitis in Cystic Fibrosis: Diagnosis and Medical Management. *Med. Sci.* **2019**, *7*, 32. [[CrossRef](#)] [[PubMed](#)]
14. Doull, I.J. Recent advances in cystic fibrosis. *Arch. Dis. Child.* **2001**, *85*, 62–66. [[CrossRef](#)]
15. Liang, J.; Higgins, T.; Ishman, S.L.; Boss, E.F.; Benke, J.R.; Lin, S.Y. Medical management of chronic rhinosinusitis in cystic fibrosis: A systematic review: Medical Management of CRS in CF. *Laryngoscope* **2014**, *124*, 1308–1313. [[CrossRef](#)]
16. Suy, P.; Coudert, A.; Vrielynck, S.; Truy, E.; Hermann, R.; Ayari-Khalfallah, S. Evolution of sinonasal clinical features in children with cystic fibrosis. *Int. J. Pediatr. Otorhinolaryngol.* **2019**, *124*, 47–53. [[CrossRef](#)]
17. Hulka, G.F. Head and Neck Manifestations of Cystic Fibrosis and Ciliary Dyskinesia. *Otolaryngol. Clin. N. Am.* **2000**, *33*, 1333–1341. [[CrossRef](#)] [[PubMed](#)]
18. Kimple, A.J.; Senior, B.A.; Naureckas, E.T.; Gudis, D.A.; Meyer, T.; Hempstead, S.E.; Resnick, H.E.; Albon, D.; Barfield, W.; Benoit, M.M.; et al. Cystic Fibrosis Foundation otolaryngology care multidisciplinary consensus recommendations. *Int. Forum Allergy Rhinol.* **2022**, *12*, 1089–1103. [[CrossRef](#)] [[PubMed](#)]
19. Ramsey, B.; Richardson, M. Impact of sinusitis in cystic fibrosis. *J. Allergy Clin. Immunol.* **1992**, *90*, 547–552. [[CrossRef](#)]
20. Le, C.; McCrary, H.C.; Chang, E. Cystic Fibrosis Sinusitis. *Adv. Otorhinolaryngol.* **2016**, *79*, 29–37. [[CrossRef](#)] [[PubMed](#)]
21. Spielman, D.B.; Beswick, D.M.; Kimple, A.J.; Senior, B.A.; Aanaes, K.; Woodworth, B.A.; Schlosser, R.J.; Lee, S.; Cho, D.; Adappa, N.D.; et al. The management of cystic fibrosis chronic rhinosinusitis: An evidenced-based review with recommendations. *Int. Forum Allergy Rhinol.* **2022**, *12*, 1148–1183. [[CrossRef](#)]
22. Beswick, D.M.; Schlosser, R.J. Chronic rhinosinusitis in people with Cystic Fibrosis: Expanding evidence and future directions. *J. Cyst. Fibros.* **2022**, *21*, 737–738. [[CrossRef](#)]
23. Rosenfeld, R.M.; Piccirillo, J.F.; Chandrasekhar, S.S.; Brook, I.; Kumar, K.A.; Kramper, M.; Orlandi, R.R.; Palmer, J.N.; Patel, Z.M.; Peters, A.; et al. Clinical Practice Guideline (Update): Adult Sinusitis. *Otolaryngol. Head. Neck Surg.* **2015**, *152* (Suppl. S2), S1–S39. [[CrossRef](#)] [[PubMed](#)]
24. Ahmed, O.G.; Rowan, N.R. Olfactory Dysfunction and Chronic Rhinosinusitis. *Immunol. Allergy Clin. N. Am.* **2020**, *40*, 223–232. [[CrossRef](#)]
25. Lindig, J.; Steger, C.; Beiersdorf, N.; Michl, R.; Beck, J.F.; Hummel, T.; Mainz, J.G. Smell in cystic fibrosis. *Eur. Arch. Otorhinolaryngol.* **2013**, *270*, 915–921. [[CrossRef](#)] [[PubMed](#)]
26. Beswick, D.M.; Humphries, S.M.; Balkissoon, C.D.; Strand, M.; Miller, J.E.; Khatiwada, A.; Vladar, E.K.; Lynch, D.A.; Taylor-Cousar, J.L. Olfactory dysfunction in people with cystic fibrosis with at least one copy of F508del. *Int. Forum Allergy Rhinol.* **2022**, *12*, 963–966. [[CrossRef](#)] [[PubMed](#)]
27. Beswick, D.M.; Humphries, S.M.; Balkissoon, C.D.; Strand, M.; Vladar, E.K.; Ramakrishnan, V.R.; Taylor-Cousar, J.L. Olfactory dysfunction in cystic fibrosis: Impact of CFTR modulator therapy. *J. Cyst. Fibros.* **2022**, *21*, e141–e147. [[CrossRef](#)]
28. Schwartz, C.E.; Andresen, E.M.; Nosek, M.A.; Krahn, G.L. RRTC Expert Panel on Health Status Measurement. Response shift theory: Important implications for measuring quality of life in people with disability. *Arch. Phys. Med. Rehabil.* **2007**, *88*, 529–536. [[CrossRef](#)]
29. Stevens, W.W.; Schleimer, R.P.; Kern, R.C. Chronic Rhinosinusitis with Nasal Polyps. *J. Allergy Clin. Immunol. Pract.* **2016**, *4*, 565–572. [[CrossRef](#)]
30. Fokkens, W.J.; Lund, V.J.; Hopkins, C.; Hellings, P.W.; Kern, R.; Reitsma, S.; Toppila-Salmi, S.; Bernal-Sprekelsen, M.; Mullol, J.; Alobid, I.; et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* **2020**, *58* (Suppl. S29), 1–464. [[CrossRef](#)]
31. Hadfield, P.J.; Rowe-Jones, J.M.; Mackay, I.S. The prevalence of nasal polyps in adults with cystic fibrosis. *Clin. Otolaryngol.* **2000**, *25*, 19–22. [[CrossRef](#)]
32. Cimmino, M.; Cavaliere, M.; Nardone, M.; Plantulli, A.; Orefice, A.; Esposito, V.; Raia, V. Clinical characteristics and genotype analysis of patients with cystic fibrosis and nasal polyposis. *Clin. Otolaryngol Allied Sci.* **2003**, *28*, 125–132. [[CrossRef](#)]
33. Kerrebijn, J.D.; Poublon, R.M.; Overbeek, S.E. Nasal and paranasal disease in adult cystic fibrosis patients. *Eur. Respir. J.* **1992**, *5*, 1239–1242.
34. De Gaudemar, I.; Contencin, P.; Van den Abbeele, T.; Munck, A.; Navarro, J.; Narcy, P. Is nasal polyposis in cystic fibrosis a direct manifestation of genetic mutation or a complication of chronic infection? *Rhinology* **1996**, *34*, 194–197.
35. Triglia, J.M.; Nicollas, R. Nasal and sinus polyposis in children. *Laryngoscope* **1997**, *107*, 963–966. [[CrossRef](#)]
36. Sliker, M.G.; Schilder, A.G.M.; Uiterwaal, C.S.P.M.; van der Ent, C.K. Children with cystic fibrosis: Who should visit the otorhinolaryngologist? *Arch. Otolaryngol. Head Neck Surg.* **2002**, *128*, 1245–1248. [[CrossRef](#)] [[PubMed](#)]

37. Schraven, S.P.; 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*, 181–186. [[CrossRef](#)] [[PubMed](#)]
38. Akdis, C.A.; Bachert, C.; Cingi, C.; Dykewicz, M.S.; Hellings, P.W.; Naclerio, R.M.; Schleimer, R.P.; Ledford, D. Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J. Allergy Clin. Immunol.* **2013**, *131*, 1479–1490. [[CrossRef](#)] [[PubMed](#)]
39. Zhang, N.; Van Zele, T.; Perez-Novó, C.; Van Bruaene, N.; Holtappels, G.; DeRuyck, N.; Van Cauwenberge, P.; Bachert, C. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. *J. Allergy Clin. Immunol.* **2008**, *122*, 961–968. [[CrossRef](#)]
40. Mahdavinia, M.; Suh, L.A.; Carter, R.G.; Stevens, W.W.; Norton, J.E.; Kato, A.; Tan, B.K.; Kern, R.C.; Conley, D.B.; Chandra, R.; et al. Increased noneosinophilic nasal polyps in chronic rhinosinusitis in US second-generation Asians suggest genetic regulation of eosinophilia. *J. Allergy Clin. Immunol.* **2015**, *135*, 576–579. [[CrossRef](#)]
41. Bachert, C.; Zhang, N.; Cavaliere, C.; Weiping, W.; Gevaert, E.; Krysko, O. Biologics for chronic rhinosinusitis with nasal polyps. *J. Allergy Clin. Immunol.* **2020**, *145*, 725–739. [[CrossRef](#)]
42. Hamilos, D.L. Chronic Rhinosinusitis in Patients with Cystic Fibrosis. *J. Allergy Clin. Immunol. Pract.* **2016**, *4*, 605–612. [[CrossRef](#)]
43. Van Zele, T.; Claeys, S.; Gevaert, P.; Van Maele, G.; Holtappels, G.; Van Cauwenberge, P.; Bachert, C. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy* **2006**, *61*, 1280–1289. [[CrossRef](#)]
44. Feuillet-Fieux, M.N.; Lenoir, G.; Sermet, I.; Elie, C.; Djadi-Prat, J.; Ferrec, M.; Magen, M.; Couloigner, V.; Manach, Y.; Lacour, B.; et al. Nasal polyposis and cystic fibrosis(CF): Review of the literature. *Rhinology* **2011**, *49*, 347–355. [[CrossRef](#)]
45. Henriksson, G.; Westrin, K.M.; Karpati, F.; Wikstroim, A.C.; Stierna, P.; Hjelte, L. Nasal Polyps in Cystic Fibrosis. *Chest* **2002**, *121*, 40–47. [[CrossRef](#)] [[PubMed](#)]
46. Clancy, J.P.; Jain, M. Personalized medicine in cystic fibrosis: Dawning of a new era. *Am. J. Respir. Crit. Care Med.* **2012**, *186*, 593–597. [[CrossRef](#)]
47. Koch, C.; Høiby, N. Pathogenesis of cystic fibrosis. *Lancet* **1993**, *341*, 1065–1069. [[CrossRef](#)]
48. Cimmino, M.; Nardone, M.; Cavaliere, M.; Plantulli, A.; Sepe, A.; Esposito, V.; Mazzarella, G.; Raia, V. Dornase Alfa as Postoperative Therapy in Cystic Fibrosis Sinonasal Disease. *Arch. Otolaryngol. Head Neck Surg.* **2005**, *131*, 1097. [[CrossRef](#)]
49. Yang, C.; Montgomery, M. Dornase alfa for cystic fibrosis. *Cochrane Database Syst. Rev.* **2021**, *3*, CD001127. [[CrossRef](#)] [[PubMed](#)]
50. Mainz, J.G.; Schien, C.; Schiller, I.; Schädlich, K.; Koitschev, A.; Koitschev, C.; Riethmüller, J.; Graepler-Mainka, U.; Wiedemann, B.; Beck, J.F. Sinonasal inhalation of dornase alfa administered by vibrating aerosol to cystic fibrosis patients: A double-blind placebo-controlled cross-over trial. *J. Cyst. Fibros.* **2014**, *13*, 461–470. [[CrossRef](#)] [[PubMed](#)]
51. Shah, G.B.; De Keyzer, L.; Russell, J.A.; Halderman, A. Treatment of chronic rhinosinusitis with dornase alfa in patients with cystic fibrosis: A systematic review: Dornase alfa for CRS CF patients. *Int. Forum Allergy Rhinol.* **2018**, *8*, 729–736. [[CrossRef](#)]
52. Mainz, J.G.; Schumacher, U.; Schädlich, K.; Hentschel, J.; Koitschev, C.; Koitschev, A.; Riethmüller, J.; Prenzel, F.; Sommerburg, O.; Wiedemann, B.; et al. Sino nasal inhalation of isotonic versus hypertonic saline (6.0%) in CF patients with chronic rhinosinusitis—Results of a multicenter, prospective, randomized, double-blind, controlled trial. *J. Cyst. Fibros.* **2016**, *15*, e57–e66. [[CrossRef](#)]
53. Mainz, J.G.; Koitschev, A. Pathogenesis and management of nasal polyposis in cystic fibrosis. *Curr. Allergy Asthma Rep.* **2012**, *12*, 163–174. [[CrossRef](#)]
54. Hadfield, P.J.; Rowe-Jones, J.M.; Mackay, I.S. A prospective treatment trial of nasal polyps in adults with cystic fibrosis. *Rhinology* **2000**, *38*, 63–65.
55. Donaldson, J.D.; Gillespie, C.T. Observations on the efficacy of intranasal beclomethasone dipropionate in cystic fibrosis patients. *J. Otolaryngol.* **1988**, *17*, 43–45. [[PubMed](#)]
56. Mainz, J.G.; Schädlich, K.; Schien, C.; Michl, R.; Schelhorn-Neise, P.; Koitschev, A.; Koitschev, C.; Keller, P.M.; Riethmüller, J.; Wiedemann, B.; 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. Dev. Ther.* **2014**, *8*, 209–217. [[CrossRef](#)] [[PubMed](#)]
57. Moss, R.B.; King, V.V. 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*, 566–572. [[CrossRef](#)]
58. Di Cicco, M.; Alicandro, G.; Claut, L.; Cariani, L.; Luca, N.; Defilippi, G.; Costantini, D.; Colombo, C. Efficacy and tolerability of a new nasal spray formulation containing hyaluronate and tobramycin in cystic fibrosis patients with bacterial rhinosinusitis. *J. Cyst. Fibros.* **2014**, *13*, 455–460. [[CrossRef](#)]
59. Lazio, M.S.; Luparello, P.; Mannelli, G.; Santoro, G.P.; Bresci, S.; Braggion, C.; Gallo, O.; Maggiore, G. Quality of Life and Impact of Endoscopic Sinus Surgery in Adult Patients With Cystic Fibrosis. *Am. J. Rhinol. Allergy.* **2019**, *33*, 413–419. [[CrossRef](#)] [[PubMed](#)]
60. Khalid, A.N.; Mace, J.; Smith, T.L. Outcomes of sinus surgery in adults with cystic fibrosis. *Otolaryngol. Head Neck Surg.* **2009**, *141*, 358–363. [[CrossRef](#)]
61. Taylor, R.J.; Miller, J.D.; Rose, A.S.; Drake, A.F.; Zdanski, C.J.; Senior, B.A.; Ebert, C.S.; Zanation, A.M. Comprehensive quality of life outcomes for pediatric patients undergoing endoscopic sinus surgery. *Rhinology* **2014**, *52*, 327–333. [[CrossRef](#)]
62. Ayoub, N.; Thamboo, A.; Habib, A.R.; Nayak, J.V.; Hwang, P.H. Determinants and outcomes of upfront surgery versus medical therapy for chronic rhinosinusitis in cystic fibrosis: Chronic rhinosinusitis in cystic fibrosis. *Int. Forum Allergy Rhinol.* **2017**, *7*, 450–458. [[CrossRef](#)]

63. Kerem, B.; Rommens, J.M.; Buchanan, J.A.; Markiewicz, D.; Cox, T.K.; Chakravarti, A.; Buchwald, M.; Tsui, L.C. Identification of the cystic fibrosis gene: Genetic analysis. *Science* **1989**, *245*, 1073–1080. [CrossRef]
64. Middleton, P.G.; Taylor-Cousar, J.L. Development of elexacaftor–tezacaftor–ivacaftor: Highly effective CFTR modulation for the majority of people with Cystic Fibrosis. *Expert. Rev. Respir. Med.* **2021**, *15*, 723–735. [CrossRef] [PubMed]
65. Middleton, P.G.; Mall, M.A.; Dřevínek, P.; Lands, L.C.; McKone, E.F.; Polineni, D.; Ramsey, B.W.; Taylor-Cousar, J.L.; Tullis, E.; Vermeulen, F.; et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N. Engl. J. Med.* **2019**, *381*, 1809–1819. [CrossRef] [PubMed]
66. Boyle, M.P.; De Boeck, K. A new era in the treatment of cystic fibrosis: Correction of the underlying CFTR defect. *Lancet Respir. Med.* **2013**, *1*, 158–163. [CrossRef] [PubMed]
67. Ramsey, B.W.; Davies, J.; McElvaney, N.G.; Tullis, E.; Bell, S.C.; Dřevínek, P.; Griese, M.; McKone, E.F.; Wainwright, C.E.; Konstan, M.W.; et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N. Engl. J. Med.* **2011**, *365*, 1663–1672. [CrossRef]
68. Heijerman, H.G.M.; McKone, E.F.; Downey, D.G.; Van Braeckel, E.; Rowe, S.M.; Tullis, E.; Mall, M.A.; Welter, J.J.; Ramsey, B.W.; McKee, C.M.; et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: A double-blind, randomised, phase 3 trial. *Lancet* **2019**, *394*, 1940–1948. [CrossRef]
69. Keating, D.; Marigowda, G.; Burr, L.; Daines, C.; Mall, M.A.; McKone, E.F.; Ramsey, B.W.; Rowe, S.M.; Sass, L.A.; Tullis, E.; et al. VX-445-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *N. Engl. J. Med.* **2018**, *379*, 1612–1620. [CrossRef] [PubMed]
70. Trikafta United States Prescribing Information. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212273s004lbl.pdf (accessed on 10 May 2023).
71. Stapleton, A.L.; Kimple, A.J.; Goralski, J.L.; Nouraie, S.M.; Branstetter, B.F.; Shaffer, A.D.; Pilewski, J.M.; Senior, B.A.; Lee, S.E.; Zemke, A.C. Elexacaftor-Tezacaftor-Ivacaftor improves sinonasal outcomes in cystic fibrosis. *J. Cyst. Fibros.* **2022**, *21*, 792–799. [CrossRef]
72. DiMango, E.; Overdeest, J.; Keating, C.; Francis, S.F.; Dansky, D.; Gudis, D. Effect of highly effective modulator treatment on sinonasal symptoms in cystic fibrosis. *J. Cyst. Fibros.* **2021**, *20*, 460–463. [CrossRef]
73. Beswick, D.M.; Humphries, S.M.; Balkissoon, C.D.; Strand, M.; Vladar, E.K.; Lynch, D.A.; Taylor-Cousar, J.L. Impact of Cystic Fibrosis Transmembrane Conductance Regulator Therapy on Chronic Rhinosinusitis and Health Status: Deep Learning CT Analysis and Patient-reported Outcomes. *Ann. Am. Thorac. Soc.* **2022**, *19*, 12–19. [CrossRef]
74. Benninger, L.A.; Trillo, C.; Lascano, J. CFTR modulator use in post lung transplant recipients. *J. Heart Lung Transplant.* **2021**, *40*, 1498–1501. [CrossRef]
75. Hayes, D.; Darland, L.K.; Hjelm, M.A.; Mansour, H.M.; Wikenheiser-Brokamp, K.A. To treat or not to treat: CFTR modulators after lung transplantation. *Pediatr. Transplant.* **2021**, *25*, e14007. [CrossRef]
76. Ramos, K.J.; Guimbellot, J.S.; Valapour, M.; Bartlett, L.; Wai, T.H.; Goss, C.H.; Pilewski, J.M.; Faro, A.; Diamond, J.M. Use of elexacaftor/tezacaftor/ivacaftor among cystic fibrosis lung transplant recipients. *J. Cyst. Fibros.* **2022**, *21*, 745–752. [CrossRef]
77. Gallant, J.N.; Mitchell, M.B.; Virgin, F.W. Update on sinus disease in children with cystic fibrosis: Advances in treatment modalities, microbiology, and health-related quality-of-life instruments. *Curr. Opin. Otolaryngol. Head Neck Surg.* **2018**, *26*, 417–420. [CrossRef]
78. Gentile, V.G.; Isaacson, G. Patterns of sinusitis in cystic fibrosis. *Laryngoscope* **1996**, *106*, 1005–1009. [CrossRef] [PubMed]
79. Gergin, O.; Kawai, K.; MacDougall, R.D.; Robson, C.D.; Moritz, E.; Cunningham, M.; Adil, E. Sinus Computed Tomography Imaging in Pediatric Cystic Fibrosis: Added Value? *Otolaryngol. Head Neck Surg.* **2016**, *155*, 160–165. [CrossRef] [PubMed]
80. Sommerburg, O.; Wielpütz, M.O.; Trame, J.P.; Wuennenmann, F.; Opdazaite, E.; Stahl, M.; Puderbach, M.U.; Kopp-Schneider, A.; Fritsching, E.; Kauczor, H.; et al. Magnetic Resonance Imaging Detects Chronic Rhinosinusitis in Infants and Preschool Children with Cystic Fibrosis. *Ann. Am. Thorac. Soc.* **2020**, *17*, 714–723. [CrossRef] [PubMed]
81. Goralski, J.L.; Hoppe, J.E.; Mall, M.A.; McColley, S.A.; McKone, E.; Ramsey, B.; Rayment, J.H.; Robinson, P.; Stehling, F.; Taylor-Cousar, J.L.; et al. Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2 Through 5 Years with Cystic Fibrosis and at Least One F508del Allele. *Am. J. Respir. Crit. Care Med.* **2023**, *208*, 59–67. [CrossRef] [PubMed]
82. Kalydeco United States Prescribing Information. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203188s0221_207925s003lbl.pdf (accessed on 10 May 2023).
83. Macdonald, K.I.; Gipsman, A.; Magit, A.; Fandino, M.; Massoud, E.; Witterick, I.J.; Hong, P. Endoscopic sinus surgery in patients with cystic fibrosis: A systematic review and meta-analysis of pulmonary function. *Rhinology.* **2012**, *50*, 360–369. [CrossRef] [PubMed]
84. Liang, J.; Higgins, T.S.; Ishman, S.L.; Boss, E.F.; Benke, J.R.; Lin, S.Y. Surgical management of chronic rhinosinusitis in cystic fibrosis: A systematic review: Surgical management of CRS in CF. *Int. Forum Allergy Rhinol.* **2013**, *3*, 814–822. [CrossRef] [PubMed]
85. Chaaban, M.R.; Kejner, A.; Rowe, S.M.; Woodworth, B.A. Cystic Fibrosis Chronic Rhinosinusitis: A Comprehensive Review. *Am. J. Rhinol. Allergy* **2013**, *27*, 387–395. [CrossRef]
86. Pirsig, W. Growth of the deviated septum and its influence on midfacial development. *Facial Plast. Surg.* **1992**, *8*, 224–232. [CrossRef] [PubMed]
87. Verwoerd-Verhoef, H.L.; Verwoerd, C.D.A. Surgery of the lateral nasal wall and ethmoid: Effects on sinonasal growth. *Int. J. Pediatr. Otorhinolaryngol.* **2003**, *67*, 263–269. [CrossRef]

88. Bothwell, M.R.; Piccirillo, J.F.; Lusk, R.P.; Ridenour, B.D. Long-Term Outcome of Facial Growth after Functional Endoscopic Sinus Surgery. *Otolaryngol. Head Neck Surg.* **2002**, *126*, 628–634. [[CrossRef](#)]
89. Van Peteghem, A.; Clement, P.A.R. Influence of extensive functional endoscopic sinus surgery (FESS) on facial growth in children with cystic fibrosis. *Int. J. Pediatr. Otorhinolaryngol.* **2006**, *70*, 1407–1413. [[CrossRef](#)]
90. Helmen, Z.M.; Little, R.E.; Robey, T. Utility of Second-Look Endoscopy with Debridement After Pediatric Functional Endoscopic Sinus Surgery in Patients with Cystic Fibrosis. *Ann. Otol. Rhinol. Laryngol.* **2020**, *129*, 1153–1162. [[CrossRef](#)]
91. Steinke, J.W.; Payne, S.C.; Chen, P.G.; Negri, J.; Stelow, E.B.; Borish, L. Etiology of Nasal Polyps in Cystic Fibrosis: Not a Unimodal Disease. *Ann. Otol. Rhinol. Laryngol.* **2012**, *121*, 579–586. [[CrossRef](#)]
92. Beswick, D.M.; Humphries, S.M.; Miller, J.E.; Balkissoon, C.D.; Khatiwada, A.; Vladar, E.K.; Ramakrishnan, V.R.; Lynch, D.A.; Taylor-Cousar, J.L. Objective and patient-based measures of chronic rhinosinusitis in people with cystic fibrosis treated with highly effective modulator therapy. *Int. Forum Allergy Rhinol.* **2022**, *12*, 1435–1438. [[CrossRef](#)]
93. Eischen, E.; Gliksmann, M.F.; Segarra, D.; Murtagh, R.D.; Ryan, L.E.; Parasher, A.K.; Tabor, M.H. Correlation between CT imaging and symptom scores in cystic fibrosis associated chronic rhinosinusitis. *Am. J. Otolaryngol.* **2023**, *44*, 103858. [[CrossRef](#)]
94. Sawicki, G.S.; Sellers, D.E.; Robinson, W.M. High Treatment Burden in Adults with Cystic Fibrosis: Challenges to Disease Self-Management. *J. Cyst. Fibros.* **2009**, *8*, 91–96. [[CrossRef](#)]

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