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Medical and Surgical Advancements in the Management of Cystic Fibrosis Chronic Rhinosinusitis

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Abstract

Purpose of review—The purpose of this review is to provide otolaryngologists with the most up-to-date advancements in both the medical and surgical management of CF-related sinus disease.

Recent findings—Recent studies have supported more aggressive CRS management, often with a combination of both medical and surgical therapies. Comprehensive treatment strategies have been shown to reduce hospital admissions secondary to pulmonary exacerbations in addition to improving CRS symptoms. Still, current management strategies are lacking in both high-level evidence and standardized guidelines.

Summary—The unified airway model describes the bi-directional relationship between the upper and lower airways as a single functional unit and suggests that CRS may play a pivotal role in both the development and progression of lower airway disease. Current strategies for CF CRS focus primarily on amelioration of symptoms with antibiotics, nasal saline and/or topical medicated irrigations, and surgery. However, there are no definitive management guidelines and there remains a persistent need for additional studies. Nevertheless, otolaryngologists have a significant role in the overall management of CF, which requires a multi-disciplinary approach and a combination of both surgical and medical interventions for optimal outcomes of airway disease. Here we present a review of currently available literature and summarize medical and surgical therapies best suited for the management of CF-related sinus disease.

Keywords

sinusitis; cystic fibrosis; surgical therapy; drug therapy; chronic sinusitis; modified medial maxillectomy; ivacaftor; endoscopic sinus surgery; CFTR

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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Introduction

Cystic fibrosis (CF) affects 1 in 2,500–3,500 newborns annually and is the commonest lethal genetic disease among Caucasians with a prevalence of 30,000 in the United States alone.^{1,2} The deadly disorder is characterized by widespread multi-organ pathology resulting from chronic stasis of inspissated mucus and includes both upper and lower respiratory complications, gastrointestinal obstruction, exocrine pancreatic dysfunction, biliary blockage, and frequently, absence of the vas deferens in males.³ CF is caused by genetic mutations of the CF transmembrane conductance regulator (CFTR) protein located at the q31 locus⁴ on the long arm of chromosome 7, which encodes a cell surface anion channel responsible for chloride (Cl⁻) and bicarbonate (HCO₃) transportation.⁵ Of the classes of CFTR mutations, the F508del is the most common and represents a three-nucleotide deletion resulting in the absence of phenylalanine at position 508.² Consequently, lack of phenylalanine leads to production of a misfolded protein that cannot be transported to the cell surface.¹ Although a variety of mutations exist, each class ultimately results in some degree of defective anion transport at the apical surface of epithelial cells leading to increased sodium and water absorption at the luminal surface. As such, exocrine secretions become thick, viscous, and prone to inflammation and infection.⁶ In the airways, this translates to impaired mucociliary clearance (MCC) and a predisposition to persistent bacterial colonization with abundant neutrophilic infiltration.^{7,8}

Although pulmonary demise is the most common cause of death, the majority of patients with CF invariably develop chronic rhinosinusitis (CRS) due to infected, mucous-filled sinuses and marked swelling of sinonasal mucosa.^{9,10} In fact, up to 100% of CF patients will have sinonasal pathology demonstrated on clinical and/or radiographic examination.⁴ Additionally, some two-thirds exhibit nasal polypsis (NP), which further complicates CRS management.¹¹ Despite this, CF patients have a relatively low incidence of self-reported CRS symptoms at less than 20%.¹² Symptoms of CRS are debilitating and classically include headache, facial pain, nasal obstruction, congestion, and chronic nasal discharge.^{13–16} Moreover, sinus anatomy is often abnormal in CF patients with many exhibiting pansinus hypoplasia or aplasia, which only further contributes to CF sinus disease.¹⁷

The combination of infected, inspissated mucous, abnormal sinus anatomy, and lack of definitive treatment consequently translates into reductions in quality of life (QOL) for these patients. Current strategies for managing CRS in CF patients focus on symptomatic amelioration with antibiotics, topical irrigations, and surgery. However, there is no definitive cure and prevention methods are both controversial and lacking. In addition, management of CF-related sinus disease varies greatly and the indications, timing, and degree of medical versus surgical management are not universally defined. Despite CRS being a classic finding in CF, its significance has been relatively overlooked as a secondary, QOL outcome in comparison to the most important treatment outcome in these patients: improved lung function. While average life expectancy has dramatically increased over the past several decades, patients with CF continue to experience a significantly reduced QOL and premature mortality with a median survival of only 33.4 years.¹⁸ Improvements in the management of CF-related lung disease have been the primary driving force behind life

expectancy; however, there is evidence that CRS may affect more than just QOL since the unified airway model suggests it contributes to the bacterial seeding of the lower airway and the ultimate progression to pulmonary demise.¹⁹

The Unified Airway Model

There is a critical relationship between the upper and lower airways, collectively referred to as the unified airway. This so-called unified airway model views the entire respiratory system as a single functional unit consisting of the nose, sinuses, larynx, trachea, and distal lung.²⁰ As a single entity consisting of the same pseudostratified, ciliated, columnar epithelium, the unified airway is uniformly subjected to the same inflammatory and infectious insults and suggests that CF represents a bi-directional pathological process whereby diseases of the upper airway affect those of the lower airway, and vice versa.^{2,9,21} This concept is underscored by clinical reports of pulmonary exacerbation frequently following acute sinonasal infection and similar bacteria in the upper and lower airways.^{22–25} For example, cultures from bronchoalveolar lavage (BAL) and the nasal cavity frequently have concordance rates of up to 80%.^{26–28} Additionally, there are genotypic and phenotypic similarities between post-transplant BAL and paranasal sinus aspirate cultures in CF patients.^{24,29–33} Therefore, it is highly plausible that the sinuses behave as bacterial reservoirs and, in patients with CF, represent the initial source of disease transmission to the distal airways (Figure 1).²

The bi-directional unified airway is further supported by previous reports suggesting that treatment of CF-related sinus disease with sinus surgery results in reduced pulmonary disease.^{2,19,34,35} This is particularly true for asthma, which is seen with higher prevalence in CF patients (~20% vs 5–8% in the general population), especially those undergoing ESS (up to 42%).^{36,37} In fact, patients with asthma often experience increased difficulty in stabilizing their reactive airways when concurrently afflicted by CRS.³⁸ In these patients, successful medical and/or surgical treatment of CRS results in significantly improved airway control with a reduction of asthma medications, exacerbations, and improved lung function.³⁹ Similarly, aggressive treatment of CF-related sinus disease may result in improved lung outcomes for these patients. The study of CF-related sinus disease and its pathogenic role in the unified airway are increasingly important considering the leading cause of both morbidity and mortality continues to be airway disease due to pulmonary infection and inflammation.⁴⁰

Chronic Rhinosinusitis in CF

Defective anion transport secondary to CFTR dysfunction causes decreased airway surface liquid depth with a resultant increase in mucus viscosity by a factor 30–60 times higher than that seen in non-CF patients.^{41–45} Inflammation and inspissated secretions congest sinus ostia, consequently leading to hypoxia and mucosal edema, which further impairs MCC.⁴⁶ The chronic cycling of inflammation and remodeling promote neutrophil-predominant polyp formation, which only continues to increase with age.⁴⁷ In contrast to that seen in CF patients, NP observed in the general population is predominantly eosinophilic with T-helper cell mediated type-2 inflammatory cytokines.^{46,48}

Both the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS)⁴⁹ and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012)⁵⁰ outline the most commonly referenced criteria for CRS, defining it as persistent sinonasal inflammation lasting at least 12 weeks, often with two or more of the following symptoms:

- nasal blockage,
- obstruction,
- congestion,
- nasal discharge,
- +/- facial pain/pressure
- +/- decreased/loss of smell^{49,50}

While these symptoms alone have a high sensitivity for CRS, they are relatively non-specific.⁴⁹ Therefore, a diagnosis of CRS must be additionally accompanied by objective findings consistent with inflammatory and/or mucosal changes with positive endoscopic and/or computed tomography (CT) findings, which frequently demonstrate at least one of the following:

- nasal polyps, and/or
- mucopurulent discharge,
- edema/mucosal obstruction,
- mucosal changes.^{49,50}

Despite two-thirds of CF patients describing a reduced sense of smell and 80% meeting the standard CRS criteria, only 10–15% explicitly complain of sinonasal symptoms.⁵¹

Underreporting of CRS symptoms in this population is common and whether this represents acclimation to chronic disease or lack of severity relative to other CF-related symptoms remains uncertain.⁴⁶ Therefore, it is especially important to use specific questioning and QOL questionnaires in CF patients, such as the Rhinosinusitis Outcome Measure-31 and Sinonasal Outcome Test-22 (SNOT-22) for adults or Sinonasal-5 for children.²¹

Aside from subjective self-reported questionnaires, nasal endoscopy and radiographic imaging with CT may aid in the diagnosis of CF CRS.^{52–54} Nasal endoscopy classically reveals thick mucoid discharge with bilateral polyposis.²¹ While scoring systems such as Lund-Mackay or Nair can be used to evaluate mucosal disease on sinus CT, they do not correlate to clinical symptoms and, perhaps more importantly, fail to predict efficacy of surgical intervention.⁵⁵ However, some CFTR genotype mutations are associated with more severe CT findings. For example, class I–III CFTR mutations present with more advanced sinus hypoplasia, opacification, and osteitis of maxillary sinus wall.⁵⁶ While CT scanning in this population is important due to the myriad of anatomical differences, it should be limited in children and is most beneficial during intra-operative sinus navigation.^{57,58}

Medical Management of CF-related CRS

While there are no universally accepted treatment guidelines for CRS, management often begins with conservative therapy for patients with and without CF. In fact, little conclusive evidence exists on the management of CRS in general, with even less data regarding the specific efficacy and treatment dosing strategies for CF-related CRS.⁵⁹ Nevertheless, there have been a number of recent studies to demonstrate favorable outcomes with medical management in this population. The most frequently studied regimens include nasal saline irrigation, antibiotics, topical steroids, dornase alfa, ivacaftor, and ibuprofen.^{4,21}

Nasal Saline Irrigations

Nasal saline irrigation is typically used as an adjunct to medical therapy and to help remove secretions of inspissated mucus and crusting from the upper airways.^{21,60} While no conclusive evidence currently supports the use of nasal saline specifically for CF CRS, a recent Cochrane meta-analysis concluded that use of isotonic (0.9%) saline irrigation in non-CF patients resulted in symptomatic improvement and amelioration of disease-specific QOL outcomes when compared to no treatment.^{61,62} While many saline delivery options are available, the squeeze bottle/neti pot devices represent the best available delivery to the paranasal sinuses²¹, which is further improved following ESS.⁶³

Some studies advocate use of hypertonic saline because of favorable effects seen in CF-related lung disease and in non-CF patients with CRS. Hypertonic saline causes reduced mucus viscoelasticity, improved mucociliary clearance and decongestion secondary to dissolution of mucus ionic bonds and osmosis, which allows rehydration of airway secretions.^{64,65} In non-CF patients with CRS, a recent Cochrane review concluded that there is some benefit in disease-specific QOL with use of daily, large-volume (150mL), mildly hypertonic (2%) nasal saline irrigation in comparison to placebo.⁶⁶ However, recently published data from a multicenter, double-blind, randomized controlled trial found that sinonasal inhalation with hypertonic saline (NaCl 6.0%) applied with vibrating aerosols was not superior to isotonic (NaCl 0.9%) nasal saline irrigation in patients with CF-related CRS.⁶⁴ Additionally, hypertonic saline (6 to 7%) is often associated with an increase of adverse reactions due to its irritating properties on sinonasal mucosa, which provokes cough and airway obstruction.^{62,67} As such, use of hypertonic saline may be less efficacious due to a lack of tangible evidence and any previously perceived benefits may be limited by poor patient compliance secondary to its irritating effects.^{60,68}

Corticosteroids

Generally speaking, topical steroids are the standard of care for reducing mucosal inflammation in patients with non-CF CRS, particularly those with allergic CRS or those with eosinophil-mediated NP.⁶⁹ On the contrary, both NP and CRS in CF patients are characterized by an abundance of neutrophils, which has a less robust response to nasal steroids.⁶⁰ Nonetheless, topical steroids have shown some benefit in NP management⁷⁰, with one double-blind, randomized controlled trial demonstrating a reduction in polyp size after administration of betamethasone nasal drops when compared to placebo.⁷¹ However, no studies have demonstrated symptomatic improvement in CF CRS despite improvement in

NP.^{50,70} Still, low absorption topical steroid rinses (i.e., mometasone, budesonide) are routinely prescribed for both CF and non-CF related CRS given their beneficial anti-inflammatory properties and low side effect profile.²¹ Of note, budesonide has not been shown to produce any significant effects on the hypothalamic-pituitary axis.^{72,73} As such, evidence regarding the use of topical steroids in CF-related sinus disease is inconclusive and thus warrants future high-level clinical studies.^{71,74,75}

Non-CF patients with CRS have demonstrated significant improvements with a short, 2–4 week course of systemic oral corticosteroids.⁷⁶ While beneficial in this population, there is little comprehensive research regarding their therapeutic effects in patients with CF-related sinus disease. Furthermore, use of systemic corticosteroids should be carefully limited and reserved for acute exacerbations due to their unfavorable metabolic side effects, which is observed with higher prevalence in the CF population due to baseline pancreatic dysfunction.

Antibiotics

Chronic airway infection secondary to opportunistic bacterial colonization is typical for patients with CF and antibiotic treatment should be directed at common CF microbes such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*.⁶⁰ While there is widespread support for inhalation antibiotics (i.e., tobramycin, colistin, aztreonam) in CF-related lung disease, there is a relative paucity of high-level evidence to support their use in the upper airways.⁷⁷ However, use of intensive antibiotic therapy has been particularly beneficial during the postoperative period in eradication of chronic sinonasal bacterial colonization.²² In one study, adjuvant therapy consisted of 2 weeks of intravenous (IV) antibiotics, 6 months of colistin nasal irrigations, and 12 months of topical nasal steroids.²² While extensive, results were promising with two-thirds of patients exhibiting no pathogenic bacteria from maxillary-ethmoidal complex cultures for a period of 6-months post-ESS.²² Furthermore, the prevalence of noncolonized patients had increased by 150%.²² Additionally, a recent double-blind, randomized placebo-controlled study demonstrated significant improvements in a validated QOL questionnaire with a concomitant decrease in *P. aeruginosa* following 28 days of tobramycin nasal inhalation.⁷⁸ Another study showed prolonged improvement of sinus aeration on serial sinus magnetic resonance imaging (MRI) with use of 20mg tobramycin.⁷⁹ In addition, use of postoperative topical aminoglycosides with nasal irrigation resulted in reduced recurrence of CF-related sinus exacerbation and infection due to *P. aeruginosa*,⁸⁰ as well as improved control of CRS for up to two years.²⁸ Topical antibiotics provide a favorable alternative to traditional oral therapies due to their reduced incidence for systemic side effects with the added benefit of reaching higher concentrations within the paranasal sinuses.⁵⁹

Oral antibiotics, particularly macrolides, have also been studied in the therapeutic management of CRS, however, their use is uniquely distinct from their more well-known antimicrobial properties.⁶⁰ 14- and 15-member ringed macrolides (clarithromycin, erythromycin, azithromycin) promote tissue repair by inducing neutrophil chemotaxis, reducing cytokine and mucus production, and improving the clearance of airway secretions, which ultimately results in down-regulation of immune and inflammatory responses.⁶⁰ In

patients without CF, this translates into reduced nasal secretions, postnasal drip, and improvements in nasal obstruction.⁸¹ Furthermore, the use of azithromycin has been shown to decrease pulmonary deterioration and reduce airway inflammation.^{60,82} Still, further studies are required to accurately evaluate their anti-inflammatory properties in the CF upper airway.⁸³

Dornase Alfa

Dornase alfa, a mucolytic agent consisting of recombinant human deoxyribonuclease, has demonstrated several significant improvements in regard to patient symptoms, rhinoscopy, and overall lung function.⁸⁴ When administered via nebulized inhalation, the major advantage of this medication rests in its ability to reduce mucus viscosity by cleaving extracellular, long-chain DNA that accumulates in CF airways as a result of extensive neutrophil degradation.^{60,85} In CF patients over age 5, dornase alfa has demonstrated significantly improved lung function as measured by forced expiratory volume in one second (FEV1)⁸⁶, as well as decreased incidence of pulmonary exacerbations.^{85,86} Moreover, bronchial inhalation of dornase alfa has been shown to reduce the annual rate of pulmonary deterioration in a number of trials.^{86–91} A recent double-blind, placebo-controlled cross-over trial concluded that vibrating sinonasal inhalation of dornase alfa results in symptom and QOL improvement in patients with CF-related CRS.⁸ In this trial, nasal inhalation of dornase alfa via Pari-Sinus™ device demonstrated significant improvement in QOL as evidenced by improved overall sinonasal outcome test (SNOT-20) scores when compared to isotonic saline ($p=0.017$).⁸ Like many novel therapies, however, the availability of dornase alfa for treatment of CRS is currently limited by cost.

Ivacaftor

Until recently, the only available treatments for progressive lung disease were those that targeted secondary effects of mutant CFTR⁹² rather than directly targeting the dysfunctional protein itself. However, recent advances in molecular genetics have allowed researchers to better understand the complicated functions and production of the CFTR Cl⁻ channel, which has led to groundbreaking discoveries and promising improvements in medical therapy. Ivacaftor (Kalydeco [VX-770], Vertex Pharmaceuticals Inc.), a CFTR potentiator, is one such drug that improves the open probability of the defective Cl⁻ channel in patients with at least one copy of the mutant G551D-CFTR allele or other less common gating mutations (non-G551D class III mutations).^{92,93} In contrast to the majority of mutations that cause CF, the G551D mutation allows transportation of the CFTR protein to the apical cell surface, but with a faulty functioning Cl⁻ channel.⁹⁴ When combined with routine standard of care, ivacaftor improves lung function by approximately 10% with a significant 47% reduction in the annual rate of percent-predicted FEV1 (ppFEV1) deterioration.^{95–97} While this novel pharmacologic therapy is undoubtedly revolutionary, it is limited by a number of factors. The G551D-CFTR mutation is only present in 4–5% of patients with CF.^{98,99} The drug is also exceptionally expensive, costing upwards of \$300,000 per year.¹⁰⁰ Nevertheless, the clinical benefits afforded to this subset of CF patients are enormous and it is likely they will experience a lower rate of lung transplantation compared to those receiving traditional care as a consequence of less severe pulmonary involvement.¹⁰⁰ A recent case report by Chang et al.¹⁰¹ demonstrated reversal of CF CRS with both subjective and objective findings after

treatment with ivacaftor. The patient experienced rapid resolution of sinonasal symptoms within four weeks, but encountered prompt recurrence of sinus disease upon treatment cessation.¹⁰¹ CT imaging demonstrated no evidence of frontal or maxillary sinus disease after a period of 10 months.¹⁰¹ Additionally, pulmonary symptoms were significantly improved after only three months and demonstrated an increased FEV₁ from 72% to 90% of predicted and reduced thickening of bronchial mucosa on chest CT.¹⁰¹

Newer gene therapies are currently being studied to target more common forms of CF. For example, combination drug lumacaftor/ivacaftor (Orkambi™ [VX-809], Vertex Pharmaceuticals Inc.) was recently FDA-approved to treat patients 12 and older with two copies of the F508del, the most common CFTR mutation, present in about two-thirds of mutant alleles.¹⁰² The combination drug, consisting of both a corrector (lumacaftor) and potentiator (ivacaftor), enhances lung function by significantly improving ppFEV1 by approximately 3% and reducing pulmonary exacerbations in patients with CF, both of which are important predictors of survival.^{93,103} Furthermore, homozygotes with two mutant F508del alleles exhibit 40% reduction in the yearly rate of pulmonary deterioration. Although respiratory symptoms were not significantly ameliorated, lumacaftor/ivacaftor demonstrated significant improvements to body mass index, which is often reduced in these patients.¹⁰⁴ While such cutting-edge therapies have yet to be evaluated for their effects on the upper airways, it is reasonable that they will provide similar relief to the CFTR-mediated mucosal abnormalities seen in CF sinus disease.^{21,105} As such, the benefits of novel therapeutics may outweigh their exorbitant costs and have set a precedent on the importance of targeting the underlying genetic defect. Importantly, CFTR modulators are also beginning to make their way into clinical studies and represent potential future therapies for mucociliary clearance defects in patients with non-CF CRS.^{44,45,106–116}

Ibuprofen

While not widely studied for the treatment of CRS in any population, high-dose ibuprofen has slowed progression of CF-related lung disease in pediatric patients.¹¹⁷ In CF patients with NP, a retrospective study of high-dose ibuprofen led to complete resolution of NP in all 12 patients at some point during the course of treatment.¹¹⁸ However, the vast majority experienced polyp recurrence upon ibuprofen cessation and nearly half additionally required ESS for more definitive treatment.¹¹⁸ Observed effects are likely due to cyclooxygenase inhibition and resultant suppression of neutrophil migration and activation.⁸³ While some favorable outcomes were observed with high-dose ibuprofen, its use is probably limited due to the fact that polyps are likely to recur following cessation of ibuprofen and the unfavorable side effects associated with high-dose therapy.

Surgical Management of CF-related CRS

While there are no standardized criteria supporting ESS versus pharmacologic treatment in CF-related CRS, surgical intervention is generally reserved for those who have failed more conservative medical therapy. Current literature reports that ESS is performed in 20–60% of patients with CF^{16,119,120} and results in both symptomatic and endoscopic improvement.¹²¹ A retrospective review of 24 studies recently reported universal improvement of sinonasal

symptoms following sinus surgery, which was evaluated with use of validated questionnaires or subjective reports.¹²² Due to intrinsic defects in the sinonasal mucosa of CF patients, primary outcomes have traditionally focused on QOL measures based on improved symptoms of nasal airway obstruction, sinonasal purulence, sense of olfaction, and overall activity level.¹²³ Aside from symptomatic improvement, however, endoscopic appearance and pulmonary function testing (PFT) have been the next most commonly reported outcomes for measuring the efficacy of surgical intervention.¹²² In the review by Liang et al., endoscopic improvements in CF-related CRS were evident in more than 50% of studies based on assessments of polyposis, edema, mucopurulence, crusting, and/or scarring.¹²² Additional studies report that ESS ultimately results in reduced rates of pulmonary exacerbation by reducing the number of hospitalizations in the 6-month post-operative period.³⁵

In non-CF patients with CRS, traditional ESS techniques are relatively straightforward with the primary goal of widening sinus ostia by removing obstructive nasal polyps to allow improved sinus drainage and adequate penetration of topical medications.⁶⁰ However, there a number of studies supporting more aggressive surgical strategies in CF patients due to the high rate of revision surgery and the ability to achieve better control of sinonasal bacteria.^{39,124,125} This is particularly true for the maxillary sinus, which remains a recurrent problem in CF patients due to superiorly located ostia.^{125,126} These patients often experience persistent mucopurulence despite “adequate” maxillary antrostomies, which serve as a reservoir for chronic infection throughout the airways.⁵⁷ One study suggests modified endoscopic medial maxillectomy (MEMM) improves the effectiveness of nasal irrigations, delivery of topical treatments, and permits better debridement in the clinic (Figure 2).¹²⁶ Results of this study demonstrated significantly improved symptom scores measured by SNOT-22 questionnaires up to 12 months postop ($p<0.0001$), as well as significantly reduced Lund-Kennedy endoscopy scores up to one year.¹²⁶ While there was no significant change in FEV1%, hospital admissions from pulmonary exacerbations were significantly reduced ($p<0.05$).¹²⁶ A similar study of CF children by Shatz et al.¹²⁷ evaluated the outcomes of a combined surgical approach in comparison to ESS alone. The combined approach, consisting of ESS, Caldwell-Luc procedure, and medial maxillectomy, demonstrated significantly improved QOL while reducing the need of IV antibiotics and rate of inpatient hospitalizations.¹²⁷ Additionally, there was a significant improvement in FEV₁ at six months.¹²⁷ Overall, a systematic review of operative approaches in CF patients concluded that large maxillary mega-antrostomies or modified medial maxillectomies provide improved QOL and sinus symptom scores, lowered the frequency of inpatient hospitalizations, and reduced the need for IV antibiotics.¹²⁵

Several studies have additionally recommended ESS in patients undergoing lung transplantation¹²⁷ due to high bacterial concordance rates between bronchoalveolar lavage and nasal cultures and the unfavorable effects associated with bacterial seeding of transplanted lungs.²⁸ For example, it is thought that chronic sinonasal bacterial colonization results in bronchiolitis obliterans or allograft rejection.⁸³ Persistent CF sinonasal pathogens despite negative BAL cultures in intermittently lung-colonized patients¹²⁴ also suggests that the sinuses represent a more permanent bacterial focus than the lungs and supports the need for adequate control of upper airway disease.¹²⁴

Although there is clear evidence to suggest the benefits of ESS, relapse rates can be as high as 50% after only 1.5–2 years¹²⁸, with some studies citing recurrence in 46–100% of patients after a period of 2–4 years.⁷⁸ Patients with more severe NP at initial presentation are significantly more likely to require revision ESS.¹²⁹ Relapse and recurrence are especially common when surgical intervention is incomplete⁸⁰ or when adjunct treatment with antibiotics is inadequate.⁸ In fact, there is evidence to suggest that ESS followed by intensive post-operative medical therapy results in eradication of pathogenic sinonasal bacteria for up to 12 months.²² In the aforementioned study, adjuvant therapy consisted of 2 weeks of IV antibiotics, 6 months of colistin nasal irrigations, and 12 months of topical nasal steroids.²² Two-thirds of subjects in the study exhibited no pathogenic bacteria from maxillary-ethmoidal complex cultures for a period of 6-months post-ESS.²² Furthermore, the prevalence of noncolonized patients had increased by 150%.²² Therefore, it is essential to stress the importance of routine follow-up in this population to ensure adequate postoperative adjuvant therapy and, ultimately, optimize surgical outcomes.

Still, there are several limitations to evaluating efficacy outcomes in ESS. According to Liang et al., 46% of studies combined both adults and children, thus precluding assessment of each individual group.¹²² Furthermore, no studies had high-level evidence and 87.5% (21/24) consisted of level 4 evidence, with only 12.5% level 3b evidence.¹²² It is important to appreciate that ESS does not provide a definitive cure in these patients due to intrinsic mucosal defects characterized by an abundance of inflammation and bacterial pathogens.¹²⁶ Therefore, optimal management of CF CRS is likely to be of most benefit when combined with ancillary treatments such as medication, mechanical, and physical therapies.¹²⁶

Conclusions

Despite lack of high-level evidence in this population subset, it remains clear that CF patients require specialized management of their sinus disease as a means to both prevent CRS progression and improve pulmonary outcomes. While there are no ‘gold standards’ in the treatment of CF-related sinus disease, it often includes combination therapy with both medical and surgical intervention. Recent evidence supports extensive ESS, such as MEMM, followed by intensive post-operative medical therapy, but overall high-level evidence is lacking. Future randomized, controlled trials with long-term follow-up are required to delineate any potential universal treatment guidelines. As the life expectancy and prevalence of CRS continue to increase in this population, optimal management should consist of multi-disciplinary teams that include otolaryngologists, particularly those familiar with CF-related sinus disease.

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Figure 1. Transnasal endoscopic views of a cystic fibrosis patient with mucopurulence emanating from the left sphenoidal recess (A) and left maxillary antrostomy (B) extending to the nasopharynx (C). The sinuses may serve as a bacterial reservoir where overflowing mucopurulence may lead to recurrent pulmonary exacerbations.

Figure 2.

Coronal computed tomography scan (A) through the mid-maxillary sinuses demonstrates complete filling of the dependent portion of the sinus bilaterally. A 3 month postoperative transnasal endoscopic view of the left maxillary sinus (B) where a modified endoscopic medial maxillectomy has been performed shows no mucopurulence. This patient had a comprehensive approach to their disease including “large hole” surgery, culture-directed antibiotics, topical tobramycin/mupirocin/mometasone irrigations BID, and aggressive postoperative debridement.