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The Management of Cystic Fibrosis Chronic Rhinosinusitis: An Evidenced-Based Review with Recommendations

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Abstract

Background: Cystic fibrosis (CF) chronic rhinosinusitis (CRS) has emerged as a distinct diagnostic entity, unique from other endotypes of CRS in its presentation, pathophysiology, diagnosis, treatment, and outcomes. As the sinonasal health of this patient population may have broad effects on pulmonary health and quality of life, a comprehensive understanding of the diagnostic and therapeutic approach to CF CRS is essential. Recognizing recent scientific advances and unique treatment modalities specific to this challenging patient population, this

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review systematically evaluates the scientific literature and provides an evidenced-based review with recommendations (EBRR) for fundamental management principles of CF CRS.

Methods: A systematic review of the literature was performed. Studies evaluating interventions for the management of CF CRS were included. An iterative review process was implemented in accordance with EBRR guidelines. A treatment recommendation was generated based on an assessment of the benefits, harms and the overall grade of evidence.

Results: This review evaluated the published literature on five unique topics. Each of the following therapeutic categories was investigated explicitly with regard to treatment outcomes in patients with CF CRS: 1) nasal saline; 2) intranasal corticosteroids (INCS); 3) topical antibiotics; 4) cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy; and 5) endoscopic sinus surgery (ESS).

Conclusion: Based on the currently available evidence, nasal saline, ESS, and CFTR modulators are *recommended* in the management of CF CRS when appropriate. INCS and topical antibiotics are *options.* Clinical judgment and experience are essential in caring for patients with this uniquely challenging disorder.

Keywords

chronic rhinosinusitis; cystic fibrosis; pediatric rhinology; topical therapy for chronic rhinosinusitis; endoscopic sinus surgery; medical therapy of chronic rhinosinusitis; Irrigations

Introduction

Cystic fibrosis (CF) chronic rhinosinusitis (CRS) has emerged as a distinct diagnostic entity, unique from other endotypes of CRS in its presentation, diagnosis, treatment, and outcome. Nearly all patients with CF exhibit sinonasal manifestations of CF.[1-4] The dysfunctional cystic fibrosis transmembrane regulator (CFTR) protein results in impaired anion transport across the epithelial surface. This defect results in thickened secretions with impaired mucociliary clearance that affects both the upper and lower airways and leads to severe sinonasal and pulmonary sequalae. Interestingly, despite radiographic evidence of sinonasal disease in nearly all patients with CF, only a minority of patients report classic symptoms associated with CRS.[5,6] Nevertheless, 62.5% of patients meet the diagnostic criteria for CRS when standard definitions of CRS are applied, requiring both symptoms and objective findings for diagnosis.[7] These patients manifest a uniquely challenging endotype of CRS, frequently refractory to repeated medical and surgical intervention. The management of these patients has traditionally been based upon principles of other CRS endotypes, but a distinct approach should be considered for CF CRS.

Comprehensive management of CF CRS is essential to control sinonasal symptoms, optimize respiratory health, and improve quality of life. Increasing evidence supports the unified airway principle whereby the upper and lower respiratory tracts are integrally related and constitute one interconnected organ system.[8] In patients with CF, sinonasal cultures correlate with pulmonary cultures, and the sinuses may serve as a reservoir for bacterial reinfection following lung transplantation.[9-11] Moreover, pulmonary exacerbations are temporally associated with declines in sinonasal quality of life.[12] There is conflicting

data on whether CF CRS management, including endoscopic sinus surgery (ESS), can improve pulmonary function.[13-19]

The severity of CF CRS varies significantly over a poorly defined spectrum. While nearly all patients with CF exhibit some findings of sinonasal inflammation, not all patients require intervention. Some patients require therapy for management of primarily sinonasal symptoms, while others undergo surgery to eradicate bacterial colonization following lung transplantation.

The purpose of this study is to evaluate the published literature specific to the management of CF CRS to determine evidence-based recommendations regarding the treatment of this unique patient population. These recommendations are targeted towards patients with CF CRS who specifically require intervention. Even while focusing on CF CRS, it is important to recognize that CF is a complex multi-organ system disease. The approach to the patient with CF is complex, and optimal management requires the collaboration and expertise of a multidisciplinary team to carefully weigh different therapeutic options and minimize the overall burden of care for these patients and their families.

Methods

The development of this guideline was performed in adherence to the methodology outlined by Rudmik and Smith for the generation of an evidenced-based review with recommendations (EBRR).[20]

A group of 12 authors with clinical and research experience in the management of CF CRS was assembled. Before beginning the literature review process, we carefully reviewed the following three instruments: 1. Clinical practice guideline manual[21]; 2. Appraisal of Guidelines Research & Evaluation (AGREE) instrument[22]; and 3. Conference on Guideline Standardization (COGS) report.[23]

The purpose and target of the review were outlined (Table I). We then generated a list of commonly implemented treatment modalities (Table II). A systematic review of the literature was initiated using the PubMed, EMBASE, and Cochrane databases. Each of the listed treatment modalities was separately explored by performing a title and abstract search of each database with the terms “cystic fibrosis” and the named treatment. To maximize the search results, the “or” function was utilized with synonyms for each search term, as outlined in Table II. Results were reviewed according to title and abstract. Inclusion criteria of studies were as follows: 1. Patient(s) with cystic fibrosis; 2. Use of the designated treatment modality; 3. Any metric of sinonasal health or quality of life. Because of the diagnostic dilemma unique to CF CRS in which patients with CF almost always have CRS evident on CT or endoscopy even in the absence of symptoms, all patients with CF in these studies were included without necessarily requiring a diagnosis of CRS by criteria established for non-CF CRS. We included patients of all ages due to the paucity of data available. After the initial screening of title and abstracts, literature meeting the designated inclusion and exclusion criteria underwent full-text review to determine suitability for inclusion. All available literature published through January 2021 was included for review.

Previously performed systematic reviews were utilized to identify any additional relevant literature not identified through the initial screening.

All included papers were reviewed, and the level of evidence (LOE) was determined in accordance with the Oxford Centre for Evidence-Based Medicine 2011 guidelines, with the exception of case reports, which were categorized as level 5.[24] The characteristics of each study were tabulated. The aggregate grade of evidence and treatment recommendations were generated. The recommendations were established in accordance with the American Academy of Pediatrics strategy, as outlined in Table III.[25]

Two authors (D.B.S. and D.A.G.) wrote the initial draft of the manuscript. Each of the other authors then critically reviewed the manuscript individually. Specifically, they reviewed the data, identified any additional studies to be included, and provided an independent recommendation in an effort to optimize the quality of the manuscript. After all authors reviewed the manuscript, a group meeting was established to resolve any conflicts.

Results

Nasal Saline

Despite the extensive evidence supporting the use of nasal saline irrigations in pediatric and adult CRS[26-28], there is very little data specific to patients with CF CRS. A total of four studies regarding the use of nasal saline in patients with CF CRS were included, as summarized in Table IV.

A randomized control trial by Mainz et al. compared inhaled hypertonic saline (6.0%) versus isotonic saline (0.9%) and found significant symptomatic improvement in both groups, as measured by the SNOT-20 score.[29] However, one therapy was not found to be superior to the other. A more recent survey of otolaryngology and pulmonology providers who care for patients with CF CRS demonstrated consensus that nasal saline irrigations should be a component of maximal medical therapy for CF CRS.[30] Farzal et al. surveyed 427 otolaryngologists, pulmonologists, CF patients, and CF caregivers regarding CF CRS management. 67% of prescribers advocated the use of isotonic nasal saline irrigations, while 29% recommended the use of hypertonic saline. Of the surveyed CF patients and caregivers, 65% of patients reported actually using irrigations, and the majority of them used irrigations combined with steroids or antibiotic rinses.[31]

Aanaes et al. investigated the extent of nasal saline delivery following ESS in patients with CF.[32] Saline was mixed with a radioactive tracer and delivered via a NeilMed Sinus Rinse© kit in an upright position, and patients were then immobilized in a supine position. Dynamic SPECT/CT (Single-Photon Emission Computed Tomography) was then performed on 10 patients immediately following irrigation. Fluid was not detected in any of the sphenoid or frontal sinuses. Tracer was identified in the ethmoid and maxillary sinuses but did not contact all mucosal surfaces, with only 23% of the fluid-filled maxillary sinuses. 10/24 (41.7%) of scanned maxillary sinuses exhibited improvement in fluid volume as compared with their preoperative scans. The results of this study suggest suboptimal delivery of topical sinonasal medications via nasal saline irrigations.

Several studies included in other sections of this review incorporated the use of nasal saline as a part of a comprehensive treatment plan alongside other interventions. The studies included in this section were restricted to those specifically investigating the effect of nasal saline on CF CRS. Nevertheless, it is important to acknowledge the wide body of literature supporting the use of nasal saline in patients with non-CF CRS.[26-28,33]

Summary of evidence for nasal saline use in CF CRS—Aggregate quality of evidence: C (Level 2: 1 study, Level 4: 1 study, Level 5: 2 studies)

Benefit: Clearance of inspissated secretions, microbes, and debris

Harm: Potential nasal irritation, epistaxis, middle ear effusions, and increased burden of care

Cost: Low

Benefit-Harms Assessment: Preponderance of benefit over harm

Value Judgement: Limited evidence in CF-specific patient population, but extensive evidence for management of CRS. Commonly used as a medium for delivery of topical medications such as corticosteroids and antibiotics.

Policy level: Recommendation

Intervention: Recommend the use of nasal saline in patients with CF CRS.

Intranasal Corticosteroids

Four studies evaluated the use of INCS specifically in patients with CF CRS, as summarized in Table V. The highest quality, double-blinded randomized control trial was conducted by Hadfield et al. and assessed the use of betamethasone nasal drops twice daily for six weeks in patients with CF and nasal polyps. Only 22 of 46 patients completed the trial and were included in the analysis. They demonstrated a statistically significant reduction in polyp size without a clear improvement in sinonasal symptoms compared with the placebo group.[34] Sinonasal symptoms did improve with treatment, but there was no significant difference between the placebo and treatment groups. Reported side effects included epistaxis and a burning/tingling sensation but did not require discontinuation of therapy.

Costantini et al. observed a similar reduction in polyp size and also noted decreased nasal resistance on rhinomanometry, but changes in symptoms were not measured.[35] This study evaluated 14 children with CF and nasal polyps treated for two months with intranasal beclomethasone dipropionate. Dosing ranged from 50 mcg twice daily in children younger than four years old to 100 mcg three times daily in older children. Follow-up examination at the conclusion of therapy demonstrated significantly reduced nasal resistance on rhinomanometry.

This finding was preserved two months after therapy completion, despite a slight non-significant increase in resistance. Reduction or disappearance of polyps on anterior rhinoscopy was demonstrated in 85.7% of patients.

Notably, an early study by Donaldson et al. demonstrated improvement in sinonasal symptoms in two separate cohorts of CF patients: those with CRS with nasal polyposis (CRSwNP) and those with CRS without nasal polyposis (CRSsNP).[36] Over half of those with polyps also experienced a size reduction. Three patients with polyps progressed to requiring surgery, two of whom reported poor medication adherence. Only one patient reported an adverse event of pain requiring temporary cessation of use.

In a prospective cohort study, Zemke et al. examined factors associated with worse sinonasal outcomes in those with CF CRS who previously had endoscopic sinus surgery.[37] Nasal steroid use was associated with a 9-point lower SNOT-22 score, exceeding the minimal clinically important difference (MCID), as well as a 2.24 point lower modified Lund Kennedy nasal endoscopy score. In contrast, CF-related diabetes and comorbid allergic rhinitis were associated with worse sinonasal symptoms and endoscopic grade. The authors also observed that patients who presented for CRS exacerbation were more likely to present with a pulmonary exacerbation at the subsequent visits (odds ratio 2.07, p=0.059).

Beclomethasone dipropionate and betamethasone are the only two INCS formulations that have been studied in the CF patient population. No studies have investigated differences in effectiveness or adverse effects between nasal spray versus sinus irrigation delivery methods.

Several studies included in other sections of this review incorporated the use of INCS as a part of a comprehensive treatment plan following other interventions such as ESS. The studies included in this section were restricted to those specifically investigating the effect of INCS alone on CF CRS.

Summary of evidence for topical corticosteroid use in CF CRS—Aggregate quality of evidence: C (Level 2: 1 study, Level 3: 2 studies, Level 4: 1 study)

Benefit: Improvement in sinonasal symptoms, reduction in inflammation, edema, and polyp size, with improved endoscopic appearance.

Harm: Potential epistaxis, dryness, nasal discomfort, low risk of systemic absorption, increased burden of care

Cost: Low

Benefit-Harms Assessment: Balance of benefit and harm in patients with CF CRS

Value Judgement: Consider disease severity and burden of care when determining optimal delivery method

Policy level: Option

Intervention: Consider INCS use for patients with CF CRS

Topical Antibiotics

A total of eight studies were included, as summarized in Table VI. A retrospective study by Moss and King in 1995 investigated the effect of postoperative antimicrobial lavages (most commonly tobramycin) on the need for revision surgery. During surgery, catheters were secured into the maxillary sinuses to allow for irrigation for 7-10 days postoperatively with subsequent irrigations every month. Patients who received serial antimicrobial lavages were significantly less likely to require revision surgery over 2 years (22% vs. 72%, p=0.003).

In a prospective cohort study of 33 patients with CF CRS, Zemke et al. examined which factors were associated with sinonasal outcomes, as measured by the SNOT-22 and disease severity on imaging.[37] 27 of 33 patients used one or more of the following sinonasal topical antibiotics in nasal saline irrigations: aminoglycoside, ciprofloxacin, mupirocin, and vancomycin. Other patients used inhaled antibiotics including: aztreonam, colistimethate, and tobramycin. Neither sinonasal nor inhaled topical antibiotics were associated with better or worse SNOT-22 score, modified Lund-Mackay score, or incidence of CRS exacerbations.

A randomized control trial by Mainz et al. evaluated the effect of inhaled tobramycin via the PARI Sinus™ nebulizer daily for 28 days.[38] Patients in the tobramycin group exhibited a 6.67±4.71 point decrease in SNOT-20 score, while those in the placebo group experienced an increase of 3.34±2.12 points. There was no significant change in nasal endoscopy or in FEV-1. Serum concentrations of tobramycin remained low. Adverse events included one patient who experienced a change in hearing.

Aanaes et al. conducted a prospective cohort study evaluating sinonasal cultures in patients after undergoing ESS who were treated with an intensive postoperative care regimen, including intravenous antibiotics for two weeks and nasal saline irrigations with antibiotics for 6 months. The antibiotic rinses were only utilized when patients had sinonasal cultures susceptible to colistimethate sodium. After six-month follow-up, 66 of 98 cultures were negative, with 41% of patients having no bacterial regrowth bilaterally. They did not report any other sinonasal or pulmonary outcomes.[39]

Two studies published by Christian von Buchwald's group prospectively followed 106 patients with CF CRS and evaluated pulmonary and sinonasal outcomes in the short and long term (≥3 years).[15,40] Patients underwent ESS followed by IV antibiotics for 2 weeks and topical antibiotics. These interventions were performed to manage symptomatic CF CRS or in search of an infectious focus for those with increasing lower airway culture positivity or declining pulmonary function. After one year follow-up, a significant improvement in SNOT-22 and HRQoL surveys was noted, but these findings were not sustained upon long-term follow-up (median 52 months). According to the Leeds criteria,[41] there was a significant improvement in pulmonary infection status, even after 3-year follow-up with an overall increase in the number of non-colonized patients.[15] Twenty-seven patients had an improved lung infection status. Overall, pulmonary functions status decreased from FEV-1 81% to 75% and FVC 92% to 88%. However, in the subgroup of 27 patients with improved pulmonary infection status, lung function was preserved. Halvorson et al. investigated the effect of sinonasal tobramycin irrigations in addition to surgery. One-third

of patients had negative sinonasal cultures after treatment.[42] Given the combined nature of these interventions, it is difficult to isolate the effect of topical antibiotics.

Aanaes et al. prospectively evaluated the use of topical antibiotics combined with autologous platelet-rich fibrin in 10 patients with CF CRS.[43] Colistin and ciprofloxacin were combined with the autologous platelet-rich fibrin and delivered at the conclusion of ESS. Tobramycin was used in one patient to address recurrent MRSA infections. In 8/9 (88.9%) of patients with positive pseudomonal cultures at the time of surgery, cultures were negative for pseudomonas on follow-up ≥12 days later. They measured sinonasal antibiotic concentrations postoperatively and were present in the majority of patients for ≥ 7 days.

The available data supports the use of topical antibiotics for select patients with CF CRS because it may improve sinonasal symptoms and eradicate bacterial colonization. Many studies frequently combine topical antibiotics with other interventions, so the impact is difficult to isolate. It is important to recognize that there is limited data to support the use of a specific regimen, including a standard antibiotic, dose, delivery mechanism, or duration of treatment.

Summary of evidence on topical antibiotic use in CF CRS

Aggregate quality of evidence: C (Level 2: 1 study, Level 3: 5 studies, Level 4: 2 studies)

Benefit: Potential improvement of sinonasal symptoms, eradication of bacterial colonization

Harm: Potential systemic absorption and ototoxicity, discomfort, mucosal irritation

Cost: Moderate; increased out-of-pocket expenses due to the need for medication compounding

Benefit-Harms Assessment: Balance of benefit and harm in patients with CF CRS

Value Judgement: Evidence suggests the greatest benefit in the treatment of patients who have had prior surgery

Policy level: Option

Intervention: Consider the use of topical antibiotic irrigation for patients with CF CRS who have positive sinonasal cultures and uncontrolled disease.

CFTR Modulators

CFTR modulators are a class of medications that improve the function of the CFTR protein through various mechanisms. Various CFTR modulators exist, and certain medications combine modulators with differing mechanisms of action to achieve maximal effect.[44] Dual CFTR modulator therapy exhibited modest improvements in pulmonary function in patients with certain genotypes, while ivacaftor alone is highly effective for individuals with gating mutations.[45] More recently developed triple CFTR modulator therapy combines three different medications (elexacaftor, tezacaftor, and ivacaftor) and is effective in patients with delta F-508 mutations. This therapy has resulted in significant clinical improvements

in patients with respect to pulmonary function, body mass index, frequency of pulmonary exacerbation, and quality of life.[46] A total of twelve studies evaluating CFTR modulator therapy were included in this review, as summarized in Table VII.

Ivacaftor Therapy

The initial evidence regarding the impact of CFTR modulator therapy on CF CRS was published as case reports. Patients with CF CRS who initiated ivacaftor, the first CFTR modulator approved by the Federal Drug Administration (FDA), were noted to have improvement or resolution of sinonasal symptoms and radiographic findings.[47-50] In 2015, Sheikh et al. noted significant improvements in sinonasal disease of 12 patients following the initiation of ivacaftor as measured by CT scan at one year.[51] Following treatment, no patients had persistent severe sinonasal disease on imaging; however, sinonasal symptoms were not assessed.

Mccormick et al. conducted a prospective cohort study evaluating the effect of ivacaftor on sinonasal symptoms by measuring SNOT-20 in 153 patients.[52] They found a significant improvement in SNOT-20 score with a decrease of 0.21 at 6 months, but this did not exceed the minimal clinically important difference of 0.8.

Gostelie et al. evaluated 8 patients with CF CRS treated with ivacaftor for 2 months.[53] These patients exhibited a significant improvement in sinonasal symptoms with an associated improvement in Lund-Kennedy scores, although 2 patients were noted to have increased edema on endoscopy. Lund-Mackay scores significantly improved in the bilateral maxillary and anterior ethmoid sinuses. They also observed a significant increase in nasal nitric oxide levels.

Elexacaftor/Tezacaftor/Ivacaftor Therapy

Three studies have investigated the effects of elexacaftor/tezacaftor/ivacaftor therapy on sinonasal disease in CF patients. A case series by Douglas et al. evaluated 25 patients who exhibited a significant improvement in SNOT-22 score (−10.18), which exceeded the MCID of 8.[54] DiMango et al. prospectively evaluated sinonasal symptoms in 43 patients on elexacaftor/tezacaftor/ivacaftor therapy and observed a 10.4 point reduction in SNOT-22 and a 22.7 improvement in the respiratory domain of the CF related quality of life (CFQ-R) metric, both of which exceeded their respective MCIDs.[55] The extra-nasal domain of the SNOT-22 score correlated to the respiratory domain of the CFQ-R.[56]

Beswick et al. demonstrated that elexacaftor/tezacaftor/ivacaftor was associated with substantial improvements in sinus CT opacification via machine learning analysis and Lund Mackay evaluation, mean 15.3 point improvement in SNOT-22 total scores, and improvements in health utility value and productivity loss in a prospective cohort of 25 patients with CF.[57]

Given the robust improvements in CF CRS with highly effective modulator therapy, this treatment may prove to be helpful in the post-lung transplantation population. This is an area of active investigation.

Southern et al. performed a systematic review of randomized control trials evaluating any type of CFTR modulator therapy and noted a significant increase in quality of life and in FEV-1, but no increase in sinonasal adverse events compared to placebo.[58]

Summary of evidence for CFTR modulator use for CF CRS—Aggregate quality of evidence: C (Level 1: 1 study; Level 3: 4 studies, Level 4: 3 studies; Level 5: 4 studies)

Benefit: CFTR modulators improve sinonasal and respiratory quality of life with improvement in objective metrics of CRS, including CT and nasal endoscopy scores.

Harm: Lumacafator-ivacafator was associated with transient shortness of breath and blood pressure increase in some patients; Possible medication interactions or increase in liver function tests; Risk of cataract development in pediatric patients; No other major increase in the risk of serious adverse events in patients using CFTR modulator therapy

Cost: High monetary cost, approximately $300,000/year without insurance coverage

Benefit-Harms Assessment: Preponderance of benefit over harm

Value Judgement: Evaluate the overall clinical picture and CF severity with a multidisciplinary CF team to weigh benefits versus costs.

Policy level: Recommend

Intervention: Recommend CFTR modulator use for patients with a responsive genotype and refractory CF CRS in consideration with a multidisciplinary care team.

Endoscopic Sinus Surgery

A total of fifty-three studies evaluating ESS in patients with CF CRS were included, as summarized in Table VIII. The earliest evidence in support of exclusively endoscopic sinus surgery for patients with CF CRS was published in 1991 by Duplechain et al., who retrospectively assessed outcomes of pediatric patients undergoing ESS for CF (14 patients) and non-CF (18 patients) CRS.[59] Multiple case series published in the 1990s demonstrated improvement in sinonasal symptoms in patients with CF CRS who underwent ESS with differing rates of symptom recurrence or need for revision surgery.[1,60-63]

A study by Moss and King published in 1995 demonstrated the superiority of ESS combined with postoperative antimicrobial lavage compared with conventional non-endoscopic sinus surgery when evaluating the need for revision surgery.[64]

ESS in Pediatric CF CRS

In 1997, Triglia and Nicollas compared outcomes of pediatric patients undergoing ESS for CF CRS versus non-CF CRS with a mean follow-up of 3.7 years. Of those with CF CRS, 68% reported improvement in rhinorrhea, and 84% had decreased nasal obstruction, which was comparable to those without CF. Those with CF had higher recurrence rates, with 16% experiencing major polyp recurrence and 32% having minor polyp recurrence within 1 year.[65]

In 2002, Yung et al. retrospectively reviewed the outcomes of 23 pediatric patients with CF CRS and noted that of the 12 who required ESS, there was a subjective improvement in olfaction and nasal obstruction with variable effects on rhinorrhea and postnasal drip.[66] All patients ultimately experienced recurrence of polyps. Seven of 12 patients required revision surgery, and the mean interval time between surgeries was 4 years. In 2003, Clement published a case series of pediatric patients with CF CRS managed with ESS.[67] Upon 6-month follow-up, a dramatic improvement was noted in nasal obstruction and headache. More modest improvement was noted in sleep quality, rhinorrhea, and recurrent acute sinusitis episodes, with 20-65% of patients still experiencing symptoms postoperatively. Taylor et al. performed a prospective study comparing outcomes of pediatric ESS in those with and without CF. In those with CF, a parent reported survey demonstrated a significant improvement in sinonasal quality of life following surgery. Self-reported SNOT-16 and PedsQLTM scores were also improved, but this finding was not statistically significant.[68] Di Cicco et al. reported outcomes of endoscopic management of sinonasal mucoceles in 9 patients with CF CRS and noted improvement in sinonasal symptoms without mucocele recurrence.[69]

ESS and Sinonasal Outcomes in CF CRS

In 2007, a prospective cohort study was published by Keck and Rozsasi, demonstrating significant improvement in all sinonasal symptom domains after ESS, with the exception of olfaction. There was also a statistically significant 50% decrease in the grade of polyps on endoscopic nasal evaluation postoperatively.[70] McMurphy et al. retrospectively evaluated the effect of ESS on Lund-Mackay scores and found no significant change postoperatively.[71] In 2008, Fuchsmann et al. retrospectively assessed outcomes of ESS in CF CRS.[72] Mean follow-up was 3 years, and patients experienced a reduction in nasal obstruction, pain, and rhinorrhea. Forty percent of patients had a recurrence of polyps, and 30% required revision surgery.

Khalid et al. performed a retrospective case-control study comparing patients with CF vs. non-CF CRS.[73] Patients with CF CRS experienced a significant reduction in sinonasal symptoms and improvement in quality of life after surgery. The improvement in postoperative quality of life in CF patients is comparable to patients without CF after one year. Rickert et al. demonstrated that patients with a higher preoperative polyp grade are significantly more likely to require revision surgery.[74]

In 2014, Savastano et al. published a retrospective study evaluating the effectiveness of “extensive endoscopic sinus surgery” in adult patients with CF CRS. A significant reduction in both SNOT-22 and Lund-Mackay scores was observed 6 months to 2 years after surgery.[75] Cho and Hwang reported improved efficacy of endoscopic maxillary mega-antrostomy in alleviating sinonasal symptoms in patients with previously unsuccessful surgery (mean follow-up: 11 months).[76] Lee et al. compared the effectiveness of complete versus limited ESS in 57 patients with CF CRS. They found a significant reduction in oral antibiotic usage after complete versus limited ESS, but no significant change in hospitalization or IV antibiotic usage was observed two years aftery surgery. Postoperatively, there was a greater reduction in the rate of pulmonary function decline in those who received

complete ESS, but this finding did not reach statistical significance.[77] This is an important finding, as many of the other included studies in this review evaluated the effects of limited ESS, addressing only some of the paranasal sinuses.

Brook et al. investigated the effect of CFTR mutation type on the need for ESS in those ≥18 years old.[78] Patients with more severe CFTR mutations (class I-III) had higher Lund-Mackay scores and were more likely to ultimately undergo ESS; however, their SNOT-22 score was not significantly worse than those with milder CFTR mutations (classes IV-VI). Abuzeid et al. investigated outcomes associated with CFTR mutation severity and found significant improvement in SNOT-22 in the overall cohort, but no difference between high and low-risk CFTR mutation types with respect to postoperative SNOT-22.[79] With the widespread introduction of highly effective modulator therapy starting in 2019 (elexacaftor/tezacaftor/ivacaftor), additional studies will be needed to investigate postoperative outcomes in patients on these medications.

ESS Safety in Patients with CF CRS

Schulte et al. evaluated the safety of sinus surgery in 15 patients with CF CRS and did not observe any surgical or anesthetic complications.[80] Tumin et al. evaluated the safety of ESS and the duration of hospitalization after surgery in 213 pediatric CF patients versus 821 non-CF patients.[81] CF patients were significantly more likely to require prolonged hospitalization >1 day (30% versus 9%). However, they did not have higher rates of 30-day readmission or 30-day reoperation compared with non-CF patients, suggesting an overall comparable safety profile for CF patients undergoing ESS.

Soudry et al. found that 46% of patients required postoperative hospitalization with an average duration of 1.4 days. They retrospectively analyzed many clinical factors to determine those associated with a need for hospital admission following ESS. On univariate analysis, hospitalization was associated with a history of ≥4 prior ESS, surgery time>2.5 hours, blood loss>150 ml, severe postoperative pain, and larger narcotic requirement. However, on multivariate analysis, only severe postoperative pain (score ≥ 7/10) was associated with the need for overnight admission.[82] Maggiore et al. found significant anatomic differences between CF and non-CF patients, but no significant increase in surgical complication rate associated with ESS.[83] Spielman et al. demonstrated the feasibility of avoiding general anesthesia and performing revision in-office ESS in patients with CF CRS.[84]

ESS Effect on Pulmonary Function—Conflicting evidence exists regarding the effect of ESS on pulmonary function in patients with CF CRS. Multiple retrospective studies demonstrate no significant change in PFTs following ESS.[85-90] In 2012, Virgin et al. prospectively studied the impact of ESS with modified endoscopic medial maxillectomy and found significant improvements in sinonasal symptoms and endoscopy scores with a decrease in hospitalization secondary to pulmonary exacerbations, but they did not find evidence of a substantial change in pulmonary function up to one year postoperatively.[91] In a retrospective case-controlled trial evaluating 40 patients two years after ESS, Dadgostar et

al. also did not find any significant change in postoperative pulmonary function (FEV-1) or in the number of pulmonary exacerbations.[92]

Halvorson et al. performed a controlled retrospective cohort study investigating the effects of surgery compared with medical management.[42] Postoperative FVC and FEV-1 were significantly improved. Patients also noted improvement in sinonasal symptoms and exercise tolerance at 3 months postoperatively. However, all patients had recurrence of polyps within 18 months of surgery. Lazio et al. retrospectively analyzed outcomes of ESS in adult patients with CF CRS and similarly demonstrated a significant improvement in SNOT-22 from 44 preoperatively to 7, six months postoperatively. On long-term 24 month follow-up, there was a trend toward improved lung function with an increase in FVC from 76 preoperatively to 87 ($p=0.07$); FEV-1 increased from 66.5 to 81.5 ($p=0.55$).[93]

A retrospective cohort study by Becker et al. investigated risk factors predictive of a need for revision surgery and found that elevated preoperative Lund-Mackay score on the initial CT scan was the only factor associated with a need for future revision surgery.[94] Notably, Becker et al. also observed a modest increase in postoperative pulmonary function.

Kovell et al. demonstrated an improvement in specific pulmonary function metrics 1-2 years after ESS compared with CF patients who did not undergo surgery.[95] More specifically, in a multivariate analysis, they found that patients who underwent ESS had a significant increase in FEV1% predicted and FVC% predicted 1-2 years postoperatively, although these findings were not uniform at all time points.

Henriquez et al. evaluated postoperative outcomes in 15 patients one year after surgery. They found that there was a significant reduction in the number of days hospitalized postoperatively. Still, there was no significant change in pulmonary function or IV antibiotic use.[96] Halderman et al. evaluated pulmonary function after ESS and found a significant improvement in FEV-1 compared with preoperative values, only at the 6-month time mark.[97] Percent predicted FEV-1 (ppFEV-1) was significantly improved at the 6, 9, and 12-month time points compared with preoperative values. Patients homozygous for delta-F508 had improved change in ppFEV-1 compared with the group as a whole, suggestive of differences associated with different genotypes.

As previously described above, two studies published by Christian von Buchwald's group prospectively followed 106 patients with CF CRS.[15,40] There was also a significant improvement in pulmonary infection status one year following ESS with postoperative IV and topical antibiotics, although pulmonary function decreased slightly. Khalfoun et al. retrospectively performed a mixed-effects linear regression analysis stratifying those with CF CRS based on mild versus moderate-severe disease defined by an FEV-1 cutoff of 80%.[98] Those with preoperative FEV-1 <80% exhibited a reversal of the negatively sloped trajectory for FEV-1 prediction one year postoperatively, suggestive of an improvement in lung function in those with more severe disease preoperatively. In the largest study to-date, Kawai et al. retrospectively assessed pulmonary function for one year postoperatively in 188 patients, who underwent 427 surgeries.[99] They stratified patients by the severity of their lung disease. There was a significant improvement in FEV-1 postoperatively in all patients whose

baseline FEV-1 was <80%. In those with severe pulmonary disease, an 8.1% improvement was observed. They identified a 3.0% increase in those with moderate disease.

Ayoub et al. retrospectively evaluated patients with CF CRS who underwent upfront ESS as opposed to those managed medically or who received delayed ESS.[100] Importantly, all 3 groups achieved similar SNOT-22 scores regardless of surgery timing. Those who underwent surgical management exhibited worse sinonasal and pulmonary disease. There was no improvement in pulmonary function, as measured by FEV-1. Those managed medically exhibited stable to improved pulmonary function, while those who underwent ESS exhibited decreasing FEV-1 48 months postoperatively.

ESS in the Lung Transplant Population

Choi et al. revealed a significant correlation between sinus cultures before lung transplantation with bronchoalveolar lavage cultures of the newly allografted lungs, suggesting that the sinuses serve as a reservoir for bacteria, leading to future colonization and pulmonary infection.[10] Leung et al. evaluated the effectiveness of performing ESS (bilateral maxillary antrostomy and partial ethmoidectomy) prior to lung transplantation but found that 87% of patients exhibited recolonization with pseudomonas soon after lung transplantation (median time = 19 days).[101] In contrast, Holzmann et al. investigated the impact of sinus surgery following lung transplantation. They found a significant correlation between sinonasal and pulmonary culture results with a lower incidence of pneumonia in patients whose sinus surgery was “successful,” as defined by three or fewer positive sinonasal cultures.[102] Luparello et al. assessed CF patients status post lung transplantation to compare outcomes between those who underwent ESS and those who did not. Six months after ESS, they observed a substantial reduction in SNOT-22 (41 → 7, p=0.003) and Lund-Kennedy scores(10 → 2, p = 0.02); postoperative FEV-1 and FVC at 24 months were improved but not statistically significant.[103] Two studies by Vital et al. evaluated bacterial colonization rates in patients undergoing ESS after recovering from lung transplantation. 53% of patients who underwent ESS with subsequent nasal saline irrigations did not have chronic sinonasal bacterial colonization. ESS was instrumental in eradicating pre-transplant pulmonary pseudomonas in 62% of patients.[19] They demonstrate a significant correlation between sinonasal colonization and pulmonary infection of the allografted lungs.[18,19] Persistent airway pseudomonal infection post-transplant was a risk factor for bronchiolitis obliterans stage 1 and 2. Patients with persistent airway pseudomonal colonization had lower survival rates compared to those who underwent successful eradication.[18] Aanaes et al. conducted a prospective cohort study evaluating sinonasal cultures in patients after undergoing ESS who were treated with an intensive postoperative care regimen, including intravenous antibiotics for two weeks and nasal saline irrigations with antibiotics for 6 months. After six-month follow-up, 66 of 98 cultures were negative, with 41% of patients having no bacterial regrowth bilaterally.[14]

Summary of evidence for endoscopic sinus surgery use for CF CRS—

Aggregate quality of evidence: Level B (Level 3: 13 studies, Level 4: 40 studies)

Benefit: Improvement in sinonasal symptoms; potential eradication of colonization

Harm: Anesthesia risks, potential surgical complications: bleeding, infection, low risk of orbital/skull base injury

Cost: high

Benefit-Harms Assessment: preponderance of benefit over harm

Value Judgement: Evidence suggests the greatest benefits in those with severe sinonasal symptoms refractory to medical therapy; mixed outcomes data exist on the effect of ESS on pulmonary function; few studies rigorously control for the effects of CFTR modulator therapy

Policy level: Recommend

Intervention: Recommended for patients with persistent sinonasal symptoms despite medical therapy; Option to eradicate sinonasal colonization, especially after lung transplantation

Discussion

This review was undertaken to aid clinicians with management recommendations for CF CRS. Sinonasal disease in the CF population worsens not only quality of life but also lower airway disease. The goal of these recommendations is to provide a concise review of studies directed at treatment outcomes of CF CRS, such that these summarized findings can serve as a foundation when considering management decisions for patients with CF. An established, rigorous methodology was applied to this review, including a robust literature search.[20] Given the few number of studies on all interventions except ESS, the search was intentionally broad and included studies on adults and pediatric patients with CF.

Overall, the existing evidence was sufficient to recommend most interventions assessed in this review (Table IX). The grade of evidence was relatively low (B or C) for the treatments evaluated, highlighting both the need to review existing evidence in a systematic manner and identifying an important evidence gap in CF CRS. Many included studies utilize a version of multidisciplinary guideline definitions of CRS when evaluating CF patients; however, there is no uniformly accepted definition of CRS in the CF population.[104,105] Given the known disparity between patient symptoms, which are reported to varying degrees, and the near universal presence of sinonasal inflammation on imaging or nasal endoscopy, this area merits further consideration.[106]

The current review used an iterative process, which has been embraced by documents including International Consensus Statements in several areas of rhinology.[104,107,108] Many of the studies were conducted prior to the widespread availability of highly effective modulator therapy; as initial studies have demonstrated that this treatment substantially improves CF CRS severity in the short term, we anticipate that recommendations will evolve over time. There is a lack of evidence regarding the combination of surgery with CFTR modulator therapy. For CFTR modulator candidates, this therapy may preclude the need for surgery and thus surgery should not be performed immediately following initiation of modulator therapy, as some patients may have near resolution of symptoms without surgery.

Based on the response to the highly effective modulator therapy, the current CF treatment burden and need for surgery may be reduced in the near future.[109]

It is important to note that the use of topical antibiotics and INCS is listed as an *option*, in the context of having limited Grade C evidence. Further high quality studies are needed to clarify the role of these therapies. The use of nasal saline is *recommended* in spite of overall low quality evidence. There are some benefits and low risk associated with this treatment in patients with CF CRS. The use of saline irrigations is better studied in patients with non CF CRS, in whom there is substantial evidence supporting the use of this treatment.[26-28,33]

The evidence supports a recommendation of CFTR modulators for the management of CF CRS. Pulmonologists with experience in CF generally prescribe and manage these novel pharmacotherapies. The authors advise that the administration of these therapeutics be in conjunction with the patient's primary CF provider. The care of this multisystem disorder is complex, and collaboration and shared decision-making should include the patient, the primary treating pulmonologist, and all members of the care team.

Conclusion

This review evaluates the use of five different therapeutic interventions in the management of CF CRS. The literature supports the use of nasal saline, CFTR modulators, and endoscopic sinus surgery in managing patients with CF CRS. Based on the available data, these interventions receive a grade of *Recommend* for use in the appropriate patient. The evidence regarding the use of topical antibiotics and topical corticosteroids reveals a near equal balance of benefit to harm and is of relatively low quality, and thus their use is an *Option.* Clinical judgment, experience, and consultation with a multidisciplinary team are essential in the management of this patient population, as not all patients with CF CRS necessarily require or will benefit from each of these interventions. Overall, the grade of evidence was relatively low for most interventions, identifying a literature gap and need for further investigation. Conflicting data exist, and additional research is needed regarding the effect of CF CRS treatment on pulmonary outcomes.

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Conflicts of Interest:

DMB: consultant, Trinity Sciences

BAW: consultant to Cool Medical, Smith and Nephew, and Medtronic

BAS: Vice President for Corporate Development and Strategy, American Rhinologic Society

DYC: National Institutes of Allergy and Infectious disease (K08AI146220), Triological Society Career Development Award, and Cystic Fibrosis Foundation K08 Boost Award (CHO20A0-KB)

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Table I:

Review Characteristics

Purpose	Outline the evidence regarding the management of chronic rhinosinusitis (CRS) in patients with cystic fibrosis (CF) to promote an evidence-based treatment strategy.
Goal	Systematically review the literature and provide recommendations regarding the optimal management of CRS in patients with CF.
Focus	Disease: CRS Population: Adult or pediatric patients with CF Interventions: Medical and surgical therapeutic interventions
Intended Users	Clinicians, including otolaryngologists, pulmonologists, and pediatricians, who care for patients with CF CRS.

Table II:

Treatment options

Treatment modalities	Search terms
Nasal saline	Cystic fibrosis AND (nasal saline OR nasal irrigation * OR nasal lavage)
Intranasal corticosteroids	Cystic fibrosis AND (intranasal steroid * OR nasal steroid * OR corticosteroid * OR glucocorticoid * OR budesonide OR mometasone OR fluticasone)
Topical antibiotics	Cystic fibrosis AND (topical antibiotic * OR tobramycin OR polymyxin E OR amikacin OR colistin OR gentamicin OR vancomycin OR levofloxacin) AND (Haemophilus OR aspergillus OR pseudomonas OR MRSA OR *Staphlyococcus Aureus*)
CFTR modulators	Cystic fibrosis AND (ivacaftor OR elexacaftor OR tezacaftor)
Endoscopic sinus surgery	Cystic fibrosis AND sinus AND surgery

* denotes a wildcard truncation character to include both singular and plural Terms were searched in the title and abstract fields.

Table III:

Grades of Evidence and Basis of Recommendations

Grade	Research quality	Preponderance of benefit over harm	Balance of benefit and harm
A	Well-designed RCTs	Strong recommendation	Option
B	RCT with minor limitations; Overwhelming consistent evidence from observational studies	Strong recommendation or recommendation	Option
C	Observational studies (case control and cohort design)	Recommendation	Option
D	Expert opinion; Case reports; Reasoning from first principles	Option	No recommendation

RCT – randomized control trial

Table IV:

Summary of evidence on nasal saline

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
Mainz[29]	2016	RCT	2	69 patients	CF CRS	Inhaled NaCl 0.9% versus Inhaled NaCl 6.0%	**1** SNOT-20 **2** Rhinomanometry **3** Inflammatory markers in nasal lavage	Both treatment groups exhibited a significant improvement in SNOT-20, but one treatment was not significantly better than the other. There was a nonsignificant improvement in rhinometry.
Aanaes[32]	2018	Case series	4	12 patients	CF CRS	Nasal saline with radiotracer delivered after ESS	**1** Dynamic SPECT scan to measure sinonasal delivery of nasal saline following ESS	10/24 maxillary sinuses exhibited improvement compared with preoperative levels. No saline reached the frontal or sphenoid sinuses. Fluid reached the ethmoid sinuses and the maxillary sinuses were 23% filled, on average.
Jayawardena[30]	2020	Survey of providers	5	175 respondents who care for patients with CF CRS	Otolaryngologists and pulmonologists	Survey regarding the management of CF CRS	**1** Achieving consensus of ≥75% agreement amongst respondents	93% of respondents felt that maximal medical management of CF CRS should include nasal saline irrigations
Farzal[31]	2021	Survey of providers/ patients	5	427 respondents including providers, patients, and caregivers	Otolaryngologists, pulmonologists, CF patients, CF caregivers	Survey regarding the management of CF CRS	**1** Nasal saline irrigation usage	67% of prescribers advocate isotonic nasal saline irrigations, while 29% recommend hypertonic saline irrigations.

CF: cystic fibrosis; CRS: chronic rhinosinusitis; RCT: randomized control trial; SNOT-20: 20 item Sino-Nasal Outcome Test

Table V:

Summary of evidence for intranasal corticosteroid use in CF CRS

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
Donaldson[36]	1988	Retrospective cohort study	3	30	CF CRS	Beclomethasone dipropionate: 2 puffs twice daily with subsequent adjustment	**1** Sinonasal symptoms **2** Polyp size	11/13 patients without polyps reported improvement in symptoms. 11/16 patients with polyps had symptoms, and all improved on medication. Of the 16 patients with polyps: 7 resolved, 3 regressed, 4 had no change, and 2 increased.
Costantini[35]	1990	Case series	4	14	CF CRS	Beclomethasone dipropionate spray: 2-3x/day x 2 months	**1** Anterior rhinoscopy **2** Rhinomanometry	Significant reduction in nasal resistance after 2 months. 85.7% of patients demonstrated a “reduction or disappearance” of polyps.
Hadfield[34]	2000	RCT	2	46	CF CRS	Betamethasone nasal drops: twice daily x 6 weeks versus placebo	**1** Sinonasal symptoms via visual analog scale **2** Lund-Mackay endoscopic score	22/46 patients completed trial, demonstrating a significant reduction in polyp size. No significant difference in sinonasal symptoms between groups.
Zemke[37]	2019	Prospective cohort study	3	33	CF CRS	“Nasal steroids”	**1** SNOT-22 **2** Modified Lund-Kennedy CT score	48.5% of the study population used INCS, which was associated with significantly lower SNOT-22 and modified Lund-Kennedy scores.

CF: cystic fibrosis; CRS: chronic rhinosinusitis; RCT: randomized control trial; SNOT-22: 22 item Sino-Nasal Outcome Test

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Table VI:

Summary of evidence on topical antibiotic use in CF CRS

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint		Conclusion
Moss[64]	1995	Retrospective study	4	51	CF CRS	Postoperative antimicrobial lavages	**1**	Surgical recurrence rate	Operative recurrence rate = 72% in the standard treatment group vs. 22% in those receiving postoperative antimicrobial lavages after 2-year follow-up.
Halvorson[42]	1998	Retrospective study	3	16	CF CRS (age≥18)	"Medical Management" vs. "Medical management" + Surgery + postop tobramycin irrigations	**1** **2** **3** **4**	Sinonasal cultures Sputum cultures FEV-1/FVC Sinonasal symptoms	Unable to assess the isolated effect of topical antibiotics directly because they were combined with surgery. 2/6 patients had negative sinonasal cultures after treatment.
Aanaes[40]*	2013	Prospective cohort study	3	106	CF CRS	ESS + IV abx x 2 weeks + topical nasal abx/steroids	**1** **2** **3**	Sinonasal symptoms Upper/lower airway bacterial colonization rates Pulmonary function	After 1 year f/u, there was a significant reduction in SNOT-22 with improved HRQoL. A significant reduction in lower airway cultures was observed after surgery. There was a clinically small but significant reduction in FVC and FEV-1.
Aanaes[14]	2013	Prospective cohort study	3	58	CF patients with CRS, recent lung transplant, or worsening lung function.	ESS followed by IV abx x 2 weeks and by saline irrigations with colistimethate sodium x 6 months	**1**	Sinonasal culture	At 6 month follow-up, 41% of patients had no bacterial regrowth bilaterally.
Mainz[38]	2014	RCT	2	9	CF patients with pseudomonal colonization of the lower airway	Inhaled tobramycin versus saline via the PARI Sinus™ nebulizer once daily x 28 days	**1** **2** **3** **4**	SNOT-20 Nasal Endoscopy Nasal lavage/culture PFTs	Patients using aerosolized sinonasal tobramycin had a significantly lower SNOT-20 score exceeding the MCID. No change in nasal endoscopy grade or in PFTs. 67% had a decrease in *P. aeruginosa* colonization.
Alanin[15]*	2017	Prospective cohort	3	106	CF CRS	ESS + IV abx x 2 weeks + topical nasal steroids/abx	**1** **2** **3**	Lower airway bacterial colonization PFTs Sinonasal quality of life	After ≥3-year f/u, SNOT-22 was not significantly changed, but HRQOL was worse. There was a significant improvement in lung infection status with fewer positive cultures but worsened PFTs
Zemke[37]	2019	Prospective cohort study	3	33	CF CRS	Topical antibiotics (Aminoglycoside,	**1**	SNOT-22	81.8% of the population used some form of sinonasal antibiotic rinse. In a

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
						ciprofloxacin, mupiricon, or vancomycin)	**2** Modified Lund-Kennedy CT score	logistic regression, this factor was not associated with sinonasal outcomes.
Aanaes[43]	2021	Case series	4	10	CF CRS	Topical antibiotic (colistin, ciprofloxacin, or tobramycin) mixed with autologous platelet-rich fibrin delivered at the conclusion of ESS	**1** Pseudomonas colonization **2** Sinonasal antibiotic concentration	8/9 patients with pseudomonal colonization at the time of surgery had negative cultures ≥ 12 days after surgery. The majority of patients had detectable sinonasal antibiotic levels for more than 7 days.

* same patient population; CF: cystic fibrosis; CRS: chronic rhinosinusitis; ESS – endoscopic sinus surgery; FEV-1: forced expiratory volume in one second; FVC: forced vital capacity; IV Abx – intravenous antibiotics; MCID – minimal clinically important difference; RCT: randomized control trial; SNOT-20: 20 item Sino-Nasal Outcome Test; SNOT-22: 22 item Sino-Nasal Outcome Test

Table VII:

Summary of evidence on CFTR modulators

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
Hayes[47]	2014	Case report	5	1	CF CRS	ivacaftor	**1** CT sinus **2** Sinonasal symptoms	Resolution of sinonasal symptoms with radiographic improvement.
Vreede[48]	2015	Case report	5	1	CF CRS	ivacaftor	**1** CT sinus **2** Sinonasal symptoms	Improvement in sinonasal symptoms and radiographic severity.
Sheikh[51]	2015	Case-series	4	12	CF	ivacaftor	**1** CT Sinus rating: normal - severe	Decrease in radiographic severity of sinus disease in all patients.
Chang[49]	2015	Case report	5	1	CF CRS	ivacaftor	**1** CT sinus **2** Sinonasal symptoms **3** Nasal voltage/pH **4** Airway surface liquid viscosity	Resolved sinonasal symptoms and resolution of radiographic sinus disease. Increased airway surface pH and decreased viscosity.
McCormick[52]	2019	Prospective cohort	3	153	CF CRS	ivacaftor	**1** SNOT-20	Statistically significant improvement in SNOT-20 score, but less than the MCID. The greatest impact was found on the rhinologic, psychologic, and sleep domains.
Douglas[54]	2020	Case Series	4	25	CF	elexacaftor/ tezacaftor/ ivacaftor	**1** SNOT-22	Significant improvement in SNOT-22 exceeding the MCID.
Gostelie[53]	2020	Case Series	4	8	CF CRS	ivacaftor	**1** Modified Lund-Mackay score **2** Sinonasal symptoms **3** Nasal nitric oxide **4** Nasal Endoscopy	Significant improvement in radiographic severity of CRS and nitric oxide levels. After 2 months, sinonasal symptoms and endoscopic severity improved.
Pallin[50]	2020	Case report	5	1	CF CRS	ivacaftor	**1** SNOT-22 **2** CFQ-R	Improvement in SNOT-22 and CFQ-R respiratory domain scores that exceed MCID.
Southern[58]	2020	Systematic review of RCTs	1	2959	CF	CFTR corrector monotherapy, dual therapy, or triple therapy	**1** Quality of life **2** FEV-1 **3** Pulmonary exacerbations	CFTR corrector dual and triple therapy was associated with improved quality of life and FEV-1 with fewer pulmonary exacerbations. No difference in sinonasal or other adverse events compared with the placebo group.

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
							4 Adverse events	
DiMango[55]*	2021	Prospective cohort	3	43	CF	elexacaftor/ tezacaftor/ ivacaftor	**1** SNOT-22 **2** CFQ-R	Significant improvement in SNOT-22 and respiratory domain of the CFQ-R exceeding the MCID.
DiMango[56]*	2021	Prospective cohort	3	43	CF	elexacaftor/ tezacaftor/ ivacaftor	**1** SNOT-22 **2** CFQ-R **3** Correlation between SNOT-22 + CFQ-R	Correlation between the extra-nasal domain of SNOT-22 with the respiratory domain of CFQ-R.
Beswick[57]	2021	Prospective cohort	3	25	CF CRS	elexacaftor/ tezacaftor/ ivacaftor	**1** Sinus CT opacification **2** SNOT-22 **3** Health Utility Value **4** Presenteesim, Absenteeism, Activity Impairment	Improvements in sinus CT opacification via machine learning analysis and productivity loss; clinically meaningful improvements in sinonasal QOL and health utility

* same patient population

CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire–Revised; CRS: chronic rhinosinusitis; CT – computed tomography; FEV-1: forced expiratory volume in one second; MCID – minimal clinically important difference; RCT: randomized control trial; SNOT-20: 20 item Sino-Nasal Outcome Test; SNOT-22: 22 item Sino-Nasal Outcome Test

Table VIII:

Summary of Evidence on Endoscopic Sinus Surgery

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
Duplechain[59]	1991	Retrospective controlled cohort	3	32	**1** Pediatric CF CRS **2** Pediatric non-CF CRS	ESS	**1** Sinonasal symptoms **2** School absenteeism	Majority of patients had improvement in sinonasal symptoms and a reduction in the number of school days missed but did not report CF-specific outcomes.
Cuyler[60]	1992	Case series	4	10	**1** Pediatric CF CRS **2** Pediatric CF without CRS	ESS	**1** Sinonasal symptoms **2** Follow-up CT scan	Patients with CRS underwent ESS and reported a partial improvement in symptoms but all demonstrated recurrent disease on follow-up CT scans.
Jones[61]	1993	Case series	4	17	CF CRS	ESS	**1** Sinonasal symptoms **2** Hospitalization	Significant improvement in sinonasal quality of life, but no significant change in the number of hospitalizations.
Nishioka[62]	1995	Prospective cohort	3	26	CF CRS	ESS	**1** Sinonasal symptoms **2** Polyp recurrence	Significant improvement in nasal obstruction, drainage, and olfaction. 46% of patients had a recurrence of nasal polyps.
Moss[64]	1995	Retrospective controlled cohort	3	51	**1** Nonendoscopic sinus surgery **2** ESS with irrigation catheter placement	Nonendoscopic vs. ESS with recurrent antimicrobial lavage	**1** Need for revision surgery	At 2 year f/u, the need for revision surgery was 72% in conventional group vs. 22% after ESS + antimicrobial lavage.
Gentile[1]	1996	Case series	4	14	CF CRS	ESS	**1** Sinonasal symptoms	All patients had improvement in nasal obstruction and headache
Rowe-Jones[63]	1996	Retrospective cohort	4	46	CF CRS	ESS	**1** Return of symptoms to preoperative level **2** Need for revision surgery **3** Sinonasal symptoms	There was a 50% chance of requiring revision surgery or having symptoms return to preoperative levels (average f/u 28 months). 87% of patients had improvement or resolution of symptoms.
Triglia[65]	1997	Retrospective controlled cohort	3	46	**1** Pediatric CRS **2** Pediatric CRS + asthma **3** Pediatric CF CRS	ESS	**1** Sinonasal symptoms **2** Polyp recurrence	27 children with CF CRS underwent ESS. 68% reported improvement in rhinorrhea and 84% had decreased nasal obstruction. 16% had major polyp recurrence within 1 year.

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
Madonna[85]	1997	Case series	4	15	CF CRS	ESS	**1** PFTs **2** Sinonasal symptoms	PFTs were not significantly improved following ESS, but all patients experienced initial improvement in sinonasal symptoms.
Halvorson[42]	1998	Retrospective controlled cohort	3	16	CF CRS (age >18)	"Medical Management" vs. "Medical management" + ESS	**1** PFTs **2** Sinonasal symptoms **3** Exercise tolerance **4** Polyp recurrence	Postoperative improvement in PFTs, sinonasal symptoms, and exercise tolerance at 3 months postoperatively. All patients had a recurrence of polyps.
Schulte[80]	1998	Retrospective cohort	4	23	CF CRS	Sinus surgery (endoscopic or traditional)	**1** Complications **2** Recurrent sinonasal symptoms **3** Revision surgery	No surgical or anesthesia complications. 86% of patients developed recurrent symptoms and 71% required revision surgery.
Rosbe[86]	2001	Retrospective cohort	4	66	CF CRS	ESS	**1** PFTs **2** Inhaler/steroid use **3** Hospitalized days	ESS had no significant impact on PFTs or inhaler/steroid use.
Yung[66]	2002	Case series	4	12	Pediatric CF CRS	ESS	**1** Sinonasal symptoms **2** Polyp recurrence **3** Revision surgery	All patients experienced a subjective improvement in olfaction and nasal obstruction. Polyps recurred in all patients and 7 required revision surgery.
Clement[67]	2003	Case series	4	21	Pediatric CF CRS	ESS	**1** Sinonasal symptoms	Upon 6 month f/u, a dramatic improvement was noted in nasal obstruction and headache. More modest improvement was noted in sleep quality, rhinorrhea, and recurrent acute sinusitis episodes.
Holzmann[102] *	2004	Retrospective cohort	4	37	CF CRS	ESS s/p lung transplantation	**1** Sinonasal cultures **2** BAL cultures **3** Pneumonia incidence **4** Bronchiolitis obliterans incidence	Significant correlation between positive sinonasal and BAL cultures as well as between negative sinonasal and BAL cultures. Patients with ≤3 positive sinus cultures had a lower incidence of pneumonia.

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
Jarrett[87]	2004	Case series	4	17	Pediatric CF CRS	ESS	**1** PFTs **2** Ideal body weight	No significant change in pulmonary function tests or ideal body weight was sustained following ESS.
Di Cicco[69]	2005	Case series	4	9	Pediatric CF CRS with mucocele	ESS	**1** Sinonasal symptoms **2** Mucocele recurrence	All patients had improvement in sinonasal symptoms with no mucocele recurrence.
Becker93	2007	Retrospective cohort	4	81	CF CRS	ESS	**1** Risk factors for recurrent surgery **2** PFTs	Elevated preoperative Lund-Mackay score increases the risk for revision surgery. Mild improvement in postoperative pulmonary function testing was observed.
Keck[70]	2007	Prospective cohort	3	26	CF CRS	ESS	**1** Sinonasal symptoms (Total rhinosinusitis symptom score) **2** Endoscopic grading	Significant decrease in all sinonasal symptoms except olfaction. The severity of polyps on endoscopic grading decreased by 50% after surgery.
McMurphy[71]	2007	Retrospective controlled cohort	3	45	CF CRS	ESS	**1** Lund-Mackay score	No significant change in Lund-Mackay score.
Fuchsmann[72]	2008	Retrospective cohort	4	26	CF CRS	ESS	**1** Sinonasal symptoms **2** Polyp recurrence	Reduction in nasal obstruction, pain, and rhinorrhea. 40% of patients had recurrence of polyps and 30% required revision surgery (mean f/u=3 years)
Cho[76]	2008	Retrospective cohort	4	28	Recalcitrant maxillary sinusitis (26% CF)	Endoscopic maxillary mega-antrostomy	**1** Sinonasal symptoms **2** Revision surgery **3** Surgical complications	74% reported complete resolution of symptoms, 26% reported partial resolution. No complications or revision surgery required (mean f/u: 11-months).
Leung[101]	2008	Retrospective cohort	4	87	CF CRS	ESS prior to lung transplantation	**1** Sinonasal cultures **2** BAL cultures **3** Time to recolonization	87% of patients had recolonization of the lower airway with pseudomonas after lung transplantation when ESS was performed pre-transplant. Median time to recolonization was 19 days.
Khalid[73]	2009	Case-control study	4	40	CF CRS vs. non-CF CRS	ESS	**1** Sinonasal symptoms **2** Quality of life	Patients with CF CRS experience improvements in sinonasal symptoms and quality of life following ESS. Neither group showed significant

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint		Conclusion
							3	Endoscopic exam	improvement in endoscopic exam after surgery.
Rickert[74]	2010	Prospective cohort	3	49	CF CRS	ESS	**1** **2**	Modified Malm polyp grade Revision surgery	After a mean f/u of 7.3 years, patients with higher polyposis grade preoperatively were more likely to require revision surgery.
Osborn[88]	2011	Retrospective cohort	4	41	CF CRS	ESS	**1** **2**	PFTs Respiratory tract microbial pathogens	ESS did not affect PFTs or respiratory tract microbial pathogens.
Kovell94	2011	Retrospective cohort	4	62	CF CRS	ESS vs. medical management	**1** **2**	PFTs Medicaid insurance status	1-2 years postoperatively, patients in the surgical cohort had more significant improvement in some PFT metrics.
Henriquez95	2012	Retrospective cohort	4	15	CF CRS	ESS	**1** **2** **3**	PFTs IV antibiotic use Hospitalized days	1 year after surgery, a significant reduction in the number of hospitalized days was observed. There was no significant difference in PFTs or IV antibiotic use.
Kempainen[89]	2012	Retrospective cohort	4	32	CF CRS	ESS	**1** **2** **3**	PFTs IV antibiotic use Hospitalized days	No significant difference in FEV-1 and FVC up to one year after surgery. No difference in IV antibiotic usage or hospitalization rates.
Virgin90	2012	Prospective cohort	3	22	CF CRS	ESS (including modified endoscopic medial maxillectomy)	**1** **2** **3** **4**	Sinonasal symptoms Lund-Kennedy score PFTs Hospital admissions	Significant improvement in SNOT-22 and Lund-Kennedy scores up to 1 year postoperatively. No change in FEV-1, hospitalizations secondary to pulmonary exacerbations were decreased.
Aanaes[14]	2013	Prospective cohort	3	58	CF patients with CRS, recent lung transplant, or worsening lung function.	ESS followed by IV abx x 2 weeks and by saline irrigations with colistimethate sodium x 6 months	**1**	Sinonasal culture	At 6 month follow-up, 41% of patients had no bacterial regrowth bilaterally.
Aanaes[40]*	2013	Prospective cohort	3	106	CF CRS	ESS + IV abx x 2 weeks + topical nasal abx/ steroids	**1**	Sinonasal symptoms	After 1 year f/u, there was significant reduction in SNOT-22 with improved HRQoL. A significant decrease in lower

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Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
							2 Upper/lower airway bacterial colonization rates **3** Pulmonary function	airway cultures was observed after surgery. There was a clinically small but significant reduction in FVC and FEV-1.
Vital[18]*	2013	Retrospective cohort	4	77	CF CRS s/p lung transplant	ESS	**1** Upper/lower airway bacterial colonization	ESS after lung transplantation led to eradication rates ranging from 33-100%, depending on the pathogen. A significant correlation was observed between sinonasal colonization and lung allograft infection.
Vital[19]*	2013	Retrospective cohort	4	94	CF patients s/p lung transplant	ESS + nasal saline irrigations	**1** Upper/lower airway pseudomonal colonization **2** Bronchiolitis obliterans	The presence of pseudomonas in the upper and lower airways was correlated. Lower airway colonization was eradicated in 62% of patients with sinus surgery post-transplant. Patients with persistent pseudomonal colonization had a higher risk of bronchiolitis obliterans and death.
Savastano[75]	2014	Prospective cohort	3	33	Adult CF CRS	ESS	**1** SNOT-22 **2** Lund-Mackay score	SNOT-22 and Lund-Mackay scores significantly improved postoperatively from mean 30.5 to 13.8 and 18.0 to 7.8 after 2 years, respectively. There was no correlation between these two metrics.
Soudry[82]	2014	Retrospective cohort	4	33	CF CRS	ESS	**1** Need for postoperative admission **2** Factors associated with requiring hospitalization	46% of patients required inpatient admission following ESS. On logistic regression, severe postoperative pain (≥7/10 score) was the only predictor of admission.
Taylor[68]	2014	Prospective controlled cohort	4	21	Pediatric CF CRS vs. non-CF CRS	ESS	**1** Sinonasal symptoms **2** Preoperative nasal endoscopy **3** Preoperative Lund-Mackay	Significant improvement in parent-reported sinonasal quality of life, but not self-reported measures. Preoperative nasal endoscopy and Lund-Mackay scores correlated with Pearson correlation = 0.51.
Alanin[15]*	2017	Prospective cohort	3	106	CF CRS	ESS + IV abx x 2 weeks + topical	**1** Lower airway bacterial colonization	After ≥3-year f/u, SNOT-22 was not significantly changed, but HRQOL was worse. There was

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
						nasal steroids/abx	**2** PFTs **3** Sinonasal quality of life	a significant improvement in lung infection status with fewer positive cultures but worsened PFTs
Ayoub[100]	2017	Retrospective controlled cohort	4	136	CFS CRS	Medical management vs. upfront ESS vs. delayed ESS	**1** SNOT-22 **2** PFTs	Despite the timing, all 3 groups exhibited similar postoperative SNOT-22 scores. PFTs worsened over time in both surgical groups but remained stable in those managed medically.
Brook[78]	2017	Retrospective cohort	4	115	Adult CF CRS	ESS	**1** SNOT-22 **2** Lund-Mackay Score **3** CFTR mutation type	Patients with severe CFTR mutation types (class I-III) were more likely to have a higher Lund-Mackay score and undergo ESS.
Halderman96	2017	Retrospective cohort	4	25	Adult CF CRS	ESS	**1** Pulmonary function **2** CFTR genotype **3** IV abx usage	Heterogenous results. Significant improvement in FEV-1 at 6-months and in ppFEV-1 at 6, 9, and 12 months. Patients homozygous for delta f-508 had higher ppFEV-1 compared with the group.
Tumin[81]	2017	Retrospective controlled cohort	4	1034	Pediatric CF CRS	ESS	**1** Prolonged hospitalization **2** Hospital readmission **3** Reoperation	CF patients were more likely to require prolonged hospitalization >1 day but did not have higher rates of readmission or unplanned reoperation within 30 days.
Abuzeid[79]	2018	Retrospective cohort	4	49	Adult CF CRS	ESS	**1** CFTR genotype **2** SNOT-22	Significant improvement in SNOT-22 for the entire cohort, but no difference between high and low-risk CFTR genotype subgroups.
Choi[10]	2018	Retrospective cohort	4	141	CF CRS	Lung transplantation	**1** Pre- and post-transplant nasal and BAL cultures	There was a significant correlation between pre-lung transplant sinus cultures and post-lung transplant BAL cultures.
Kanjanaumporn99	2018	Retrospective controlled cohort	4	141	**1** Adult CF CRS with bronchiectasis	ESS	**1** SNOT-22 **2** PFTs	A significant reduction in SNOT-22 score was noted in patients with CF with 3-year f/u. No significant change in postoperative PFTs were noted in the entire cohort.

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
					2 Adult non-CF CRS with bronchiectasis			
Khalfoun97	2018	Retrospective cohort	4	131	CF CRS	ESS	**1** PFTs	In those with moderate-severe pulmonary function (FEV-1<80%), ESS was associated with a reversal of the negative slope in the predicted trajectory of FEV-1 one year after surgery.
Lazio92	2019	Retrospective controlled cohort	4	54	Adult CF CRS	ESS	**1** SNOT-22 **2** Lund-Kennedy Score **3** PFTs	Patients undergoing ESS exhibited a significant reduction in SNOT-22 and Lund-Kennedy score 6 months postoperatively. There was no significant change in PFTs.
Luparello[103]	2019	Retrospective controlled cohort	4	23	Adult CF CRS s/p lung transplant	ESS vs. no ESS	**1** SNOT-22 **2** Lund-Kennedy Score **3** PFTs	There was a significant reduction in SNOT-22 and Lund-Kennedy scores 6 months after ESS. Postoperative FEV-1 and FVC at 24 months were improved but not statistically significant.
Lee[77]	2020	Retrospective controlled cohort	4	57	CF CRS	Limited vs. Complete ESS	**1** Oral/IV abx use **2** Hospitalization **3** Rate of lung function change	Significant reduction in oral antibiotic usage after complete vs. limited ESS. No significant difference in IV abx use, hospitalization, or rate of lung function change.
Dadgostar91	2021	Retrospective controlled cohort	4	40	CF CRS	ESS	**1** Pulmonary exacerbations **2** PFTs **3** Hospitalization	There was a significant increase in the number of days hospitalized 2 years postoperatively. No significant change in FEV-1 or pulmonary exacerbations.
Kawai98	2021	Retrospective controlled cohort	4	188	CF CRS: **1** Mild pulmonary disease **2** Moderate pulmonary disease	ESS	**1** PFTs	In those with severe pulmonary disease (FEV-1<40%), there was a significant increase in FEV-1 after ESS (mean 8.1). In those with moderate pulmonary disease (FEV-1: 40-70%), FEV-1 significantly increased by 3.0% postoperatively.

Study	Year	Study Design	LOE	Number of Subjects	Study Groups	Intervention	Primary Endpoint	Conclusion
					3 Severe pulmonary disease			
Maggiore[83]	2021	Retrospective controlled cohort	4	147	**1** Adult CF CRS **2** Non-CF CRS	ESS	**1** Anatomic differences **2** Surgical complications **3** Length of hospitalization for ESS	No significant difference in surgical complications in CF vs. non-CF patients, but CF patients had a significantly longer hospital stay for ESS.
Spielman[84]	2021	Case series	4	5	Adult CF CRS	Revision ESS (in-office)	**1** Surgical complications **2** Feasibility of in-office revision ESS for CF CRS	There were no surgical complications following revision in-office ESS. In addition, in-office ESS permitted outpatient surgery without general anesthesia.

* same patient population; Abx – antibiotics; BAL – bronchoalveolar lavage; CFTR – cystic fibrosis transmembrane regulator protein; ESS – endoscopic sinus surgery; FEV-1 – forced expiratory volume; f/u – follow-up; HRQoL – Health Related Quality of Life survey; PFTs – pulmonary function tests; ppFEV-1 – percent predicted FEV-1; SNOT-22: 22 item Sino-Nasal Outcome Test

Table IX:

Summary of Recommendations

Intervention	Grade of evidence	Balance of benefit to harm	Recommendation
Nasal saline	C	Benefit	Recommend
Topical corticosteroids	C	Equal	Option
Topical antibiotics	C	Equal	Option
CFTR modulators	C	Benefit	Recommend
Endoscopic sinus surgery	B	Benefit	Recommend