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ORIGINAL ARTICLE

Cystic Fibrosis Foundation otolaryngology care multidisciplinary consensus recommendations

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Abstract

Background: Cystic fibrosis (CF) is a multisystem disease that often requires otolaryngology care. Individuals with CF commonly have chronic rhinosinusitis but also present with hearing loss and dysphonia. Given these manifestations of CF, otolaryngologists are frequently involved in the care of patients with CF; however, there is limited consensus on optimal management of sinonasal, otologic, and laryngologic symptoms.

Methods: The Cystic Fibrosis Foundation convened a multidisciplinary team of otolaryngologists, pulmonologists, audiologists, pharmacists, a social worker, a nurse coordinator, a respiratory therapist, two adults with CF, and a caregiver of a child with CF to develop consensus recommendations. Workgroups developed draft recommendation statements based on a systematic literature review, and a ≥80% consensus was required for acceptance of each recommendation statement.

Results: The committee voted on 25 statements. Eleven statements were adopted recommending a treatment or intervention, while five statements were formulated recommending against a specific treatment or intervention. The committee recommended eight statements as an option for select patients in certain circumstances, and one statement did not reach consensus.

Conclusion: These multidisciplinary consensus recommendations will help providers navigate decisions related to otolaryngology consultation, medical and surgical management of CF-CRS, hearing, and voice in individuals with CF. A collaborative and multidisciplinary approach is advocated to best care for our patients with CF. Future clinical research is needed utilizing standardized, validated outcomes with comprehensive reporting of patient outcome, effects of modulator therapies, and genetic characteristics to help continue to advance care, decrease morbidity, and improve the quality of life for individuals with CF.

KEYWORDS
chronic rhinosinusitis, cystic fibrosis, dysphonia, evidence-based medicine, FESS, sinus, voice and allergy

1 | PURPOSE AND BACKGROUND

Biallelic pathogenic variations of the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene result in CF. Although mortality of CF is generally a result of the dysfunction of the CFTR in the pulmonary epithelium, the CFTR is expressed throughout the reproductive, gastrointestinal, and sinonasal mucosa.[1–3] Aberrant chloride

TABLE 1 Ototoxic medications frequently taken by individuals with CF

Ototoxic medications specific to CF care			
Medication class	**Specific drug**	**Administration route**	**Relevant references**
Aminoglycosides	Tobramycin Amikacin	Intravenous	11,120,121
Aminoglycosides	Tobramycin Amikacin	Inhaled	13,122,123
Glycopeptides	Vancomycin	Intravenous	124,125
Macrolides	Azithromycin Erythromycin Clarithromycin	Intravenous/oral	126–129
Nonsteroidal anti-inflammatory drugs	Aspirin Ibuprofen Naproxen	Oral	130,131

Abbreviation: CF, cystic fibrosis.

transport in the sinonasal mucosa results in impaired mucociliary clearance, persistent infections, and chronic rhinosinusitis (CRS).[4]

CF-related CRS (CF-CRS) is a diffuse form of CRS secondary to mucociliary dysfunction.[5] Imaging studies and nasal endoscopies performed in individuals with CF universally have findings consistent with CRS; however, less than half of individuals complain of sinonasal symptoms.[6] Thus, many patients with CF-CRS are undiagnosed and untreated or undertreated. When patients are diagnosed with CF-CRS, there are few data to support optimal medical therapy and there is significant variability in surgical management; however, it is well known from the general CRS literature that CRS significantly decreases quality of life[7] and there is concern that untreated CF-CRS may contribute to pulmonary decline.

As a consequence of recurrent respiratory infections, patients with CF are frequently taking systemic antibiotics that can have ototoxic (cochleotoxic/vestibulotoxic) effects (Table 1). High-frequency sensorineural hearing loss, tinnitus, and/or balance issues are a potential side effect of aminoglycosides, which are the primary treatment for *Pseudomonas aeruginosa*.[8] Additionally, macrolides are commonly used for immunomodulatory and antimicrobial properties and have known ototoxic effects, particularly when paired with an aminoglycoside or loop diuretic.[9,10] Clinically, the prevalence of hearing loss in individuals with CF is considerably higher than age-matched control populations, and hearing loss is typically worse in patients with more lifetime courses of intravenous antibiotics.[11,12] A recent study by Elson et al[13] showed that 53% of patients with CF treated for ≥5 years with inhaled aminoglycosides exhibited hearing abnormalities. The combined use of both inhaled and intravenous aminoglycosides (or other ototoxic agents) may further increase the risk for developing ototoxicity and needs further investigation. Permanent hearing loss is associated with depression, social isolation, and cognitive decline in both children and adults,[14—16] and these consequences may be partially reversible with early intervention and hearing restoration (ie, hearing aids[17]). Preserving hearing in children is crucially important for speech, emotional, and social development. Thus, it is critical to identify hearing loss to facilitate hearing rehabilitation and to take into account hearing status for future antimicrobial selection. Although some medications (platinum-based chemotherapies) have clear protocols for monitoring ototoxic effects, there is no widely accepted guidance for ototoxicity monitoring (cochleotoxic/vestibulotoxic) of systemic antibiotic therapies in the CF population.

Recognizing the importance of sinonasal, auditory, and speech concerns in children and adults with CF and lack of well-defined treatment strategies, the Cystic Fibrosis Foundation (CFF) created a task force to develop recommendations for children and adults with CF regarding their sinonasal and otologic disease. As noted throughout the guidelines and in the systematic review (Supplemental File 1), there is limited level 1 or level 2 evidence to support clinical management of sinonasal, auditory, and speech concerns of the individuals with CF. Generally, the current literature is limited to single-institution cohort studies and case-control studies. Given the quality of evidence available to answer the relevant questions, the committee agreed to issue recommendations for an intervention, recommendations against an intervention, or described an intervention as an option for select patients. Statements that were listed as options were intended to be left to the discretion of the individual CF provider, patient, and particular clinical scenario.

This document is not meant to be interpreted as a standard of care. It is intended to provide insight into common decisions and problems, weigh the evidence when available, and provide recommendations. Our statements do not take into account all of the unique factors leading to decisions for individuals with CF that must be considered by the care team for each individual patient.

2 | METHODS

The CFF guidelines steering committee identified otolaryngology as an area that would benefit from input by a multidisciplinary panel of experts and patients. The CFF then invited a multidisciplinary team of adult and pediatric otolaryngologists, pulmonologists, audiologists, pharmacists, a social worker, a nurse coordinator, a respiratory therapist, two adults with CF, and a caregiver of a child with CF to a multidisciplinary committee meeting in June 2019 to determine the scope of the work and develop clinically relevant questions to address. The committee was divided into four workgroups focused on pediatric sinus disease, adult sinus disease, hearing, and other topics. At the end of this meeting, 24 questions were identified that served as the basis for a literature search (Supplemental File 1).

Once the literature search was completed and reviewed, the workgroups developed draft recommendations. The committee reconvened virtually in November 2020 through two video conferences to iteratively revise and vote on the draft recommendation statements. An a priori voting threshold of 80% agreement of all committee members was used for approval of statements as routinely utilized by the CFF.[18–20] Committee members who were unable to attend both video conferences were provided with a recording of the meeting and voted by email. Five of 29 committee members had a conflict of interest on statement 18, which focused on CFTR modulators. Those five committee members were excluded from the review of the evidence and voting on that statement.

The manuscript was provided for review by the committee before distribution for public comment in May 2021. The committee reviewed and acknowledged and/or addressed each of the comments received during public comment. The same literature searches for each workgroup were replicated in July 2021 to ensure new publications addressing the PICO (population, intervention, control, and outcomes) questions had not been missed. Two articles were included in the conclusion based on this final literature review.

Many of the clinical questions selected by the committee had limited evidence. Given the lack of robust clinical evidence, the committee elected to issue three types of statements (Tables 2 and 3): (1) "recommends for"––the strongest positive statements are recommendations for specific interventions and generally apply to the majority of patients; (2) "recommends against"––the strongest negative statements are recommendations against a specific intervention and generally apply to the majority of patients; and (3) "acknowledges as an option"––these statements are based on a lower level of evidence and thought to apply to select patients and/or specific clinical situations or subpopulations (Table 3). With less evidence and less expert consensus, "options" are reasonable to consider as a potential topic for shared decision-making for children and adults with CF on a case-by-case basis.

One statement did not reach consensus and is shown in Table 4.

3 | RECOMMENDATIONS

Statements that had above an 80% consensus of the voting group and existing data are listed as recommendations (Table 2) and options (Table 3). In general, these recommendations apply broadly to the majority of children and adults with CF.

1. *The CFF recommends following CF infection control guidelines by otolaryngology teams caring for children and adults with CF*. Individuals with CF can acquire respiratory pathogens in health care centers. To prevent possible cross-infection, children and adults with CF should be evaluated in clinic settings in accordance with CFF guidelines.[18] Typical infection control guidelines in outpatient clinics recommend contact precautions for patients with a history of drug-resistant organisms; however, given the high prevalence of multidrug-resistant organisms in individuals with CF, the CFF suggests more stringent precautions. Recommended interventions include minimizing time in a common waiting area, encouraging patient use of a face mask in common clinic spaces, appropriate disinfection of equipment and examination rooms, and utilization of contact precautions (ie, gown and gloves) by all care team members.
2. *The CFF recommends otolaryngology consultation for children and adults with CF with persistent ear, nose, and throat symptoms*. Otolaryngologic repercussions of CF are prevalent and include sinus disease and otologic issues, among others. Several studies demonstrate that children and adults with CF are adversely impacted by upper airway manifestations of disease. CRS and sinonasal symptoms were found to be prevalent in an unbiased cross-sectional cohort of children with CF.[21] A cross-sectional study in adults with CF demonstrated similar findings.[22] This information is supported by data from the CFF Patient Registry.[23] Furthermore, individuals with CF are also at risk of ototoxicity from certain medications.

   Given the high prevalence of otolaryngologic symptoms and potential for treatment side effects in CF (ie, ototoxicity and dysphonia), the CFF recommends otolaryngology consultation for children and adults with CF who have persistent ear, nose,

TABLE 2 Cystic Fibrosis Foundation recommendations

#	CFF recommendations	Vote
1	The CFF recommends that CF infection control guidelines be followed for children and adults with CF being seen by an otolaryngology team.	100.00%
2	The CFF recommends otolaryngology consultation for children and adults with CF with persistent ear, nose, and throat symptoms.	100.00%
3	The CFF recommends the administration of a sinonasal quality-of-life tool to children and adults with CF (eg, SN-5 for ages 6–12 years and SNOT-22 for ages 13 or older), to identify sinonasal symptoms.	93.10%
4	The CFF recommends nasal saline irrigation for children and adults with CF with signs or symptoms of CRS.	100.00%
5	The CFF recommends the treatment of allergic rhinitis, including topical nasal corticosteroids, to improve nasal symptoms in children and adults with CF and concomitant allergic rhinitis.	100.00%
6	The CFF recommends endoscopic sinus surgery for children and adults with CF who have symptomatic CRS refractory to appropriate medical therapy.	100.00%
7	The CFF recommends that perioperative airway clearance therapy be continued as tolerated in children and adults with CF who undergo endoscopic sinus surgery for CRS.	100.00%
8	The CFF recommends baseline hearing study for ototoxic monitoring for all children and adults with CF in anticipation of receiving ototoxic therapies.	96.55%
9	The CFF recommends ototoxic monitoring annually for children and adults with CF who are exposed to ototoxic medications.	100.00%
10	The CFF recommends ototoxic monitoring following each course of intravenous ototoxic medications for children and adults with CF who already have any hearing loss.	89.66%
11	The CFF recommends voice evaluation and management for children and adults with CF and dysphonia (hoarseness).	100.00%
12	The CFF recommends against the routine use of systemic corticosteroids for CF-CRS in children and adults.	100.00%
13	The CFF recommends against the routine use of intranasal corticosteroids administered by nebulizers in children and adults with CF-CRS.	96.55%
14	The CFF recommends against performing routine endoscopic sinus surgery for children and adults with CF for the sole indication of declining lung function.	100.00%
15	The CFF recommends against performing routine adenoidectomy alone for the treatment of CRS in children with CF.	89.66%
16	The CFF recommends against performing routine balloon sinuplasty for children and adults with CF-CRS.	100.00%

The strongest positive statements of the multidisciplinary committee are recommendations for or against specific interventions. These recommendations generally apply to the majority of patients. Abbreviations: CF, cystic fibrosis; CF-CRS, cystic fibrosis–related chronic rhinosinusitis; CFF, Cystic Fibrosis Foundation; CRS, chronic rhinosinusitis; SN-5, 5-question Sinus and Nasal Quality of Life Survey; SNOT-22, 22-question Sino-Nasal Outcome Test.

and throat symptoms. Computed tomography may be beneficial to assess sinus disease in individuals with CF who have not undergone previous sinus surgery or where endoscopic examination cannot visualize all sinuses. However, the ultimate decision for radiographic imaging is dependent on the individual and the unique clinical scenario. Otolaryngologists can partner with CF specialists to manage these conditions optimally. This recommendation is aligned with several American and European guideline statements.[24–26]

3. *The CFF recommends the administration of a sinonasal quality-of-life tool to children and adults with CF to identify sinonasal symptoms.* Quality-of-life surveys can identify individuals with sinonasal symptoms who may benefit from referral or further management.[27] These instruments also provide longitudinal information regarding response to treatments, including endoscopic sinus surgery (ESS) and CFTR modulator therapy.[28,29] The caregiver-completed 5-question Sinus and Nasal Quality of Life Survey (SN-5) has been validated in a general pediatric population for ages 2 to 12 years and applied to children with CF.[21,30,31] The 22-question Sino-Nasal Outcome Test (SNOT-22) has been validated in a general adult population and is frequently used for adults with CF.[32–34] Age-appropriate measures can be obtained without the need for additional appointments. These patient-reported outcome measures can help direct additional management for children and adults with CF and be administered as part of routine multidisciplinary care.

TABLE 3 The Cystic Fibrosis Foundation options

#	CFF options	Vote
17	The CFF acknowledges surveillance visits with an otolaryngologist in the absence of ear, nose, and throat symptoms as an option.	86.21%
18	The ear, nose, and throat guidelines committee acknowledges the use of CFTR modulator therapy for treatment of CF-CRS when appropriate modulator therapy is available for age and genotype as an option.	100.00%
19	The CFF acknowledges the use of daily intranasal corticosteroid spray (INCS) for children and adults with CF-CRS as an option	100.00%
20	The CFF acknowledges extended sinus surgery in children and adults with CF and CRS refractory to appropriate medical therapy as an option.	100.00%
21	The CFF acknowledges perioperative intravenous antibiotics for children and adults with CF who undergo endoscopic sinus surgery for CRS after discussion with the multidisciplinary CF care team as an option.	100.00%
22	The CFF acknowledges the use of sinonasal topical antibiotic treatment in children and adults with CF who have previously had endoscopic sinus surgery as an option.	100.00%
23	The CFF acknowledges the use of intranasal dornase alfa nebulization for treatment of CRS in children and adults with CF.	89.66%
24	The CFF acknowledges ototoxic monitoring following each course of intravnous ototoxic medications as an option.	82.76%

These statements are based on a lower level of evidence and thought to apply to select patients and/or specific clinical situations or subpopulations. These "options" are reasonable to consider as a potential topic for shared decision making for children and adults with CF on a case-by-case basis. Abbreviations: CF, cystic fibrosis; CF-CRS, cystic fibrosis–related chronic rhinosinusitis; CFF, Cystic Fibrosis Foundation; CFTR, cystic fibrosis transmembrane conductance regulator; CRS, chronic rhinosinusitis; ESS, endoscopic sinus surgery.

4. *The CFF recommends nasal saline irrigation (NSI) for children and adults with CF with signs or symptoms of CRS*. Evidence supports the efficacy and favorable safety profile of NSI in the non–CF-CRS adult population.[4,35,36] A Cochrane systematic review of NSI for CRS demonstrated that it is well tolerated, and the benefits outweigh the risks; however, the relevance of these conclusions to the CF population is less clear.[37] Potential benefits of NSI include direct removal of secretions, irritants, allergens, purulence, and inflammatory mediators, which may decrease edema and improve mucociliary clearance. Potential mild adverse effects of NSI are uncommon and include nasal irritation and burning, epistaxis, ear pain, and headache.[7] No major adverse events from NSI were reported in a meta-analysis[37]; however, individuals with CF may be vulnerable to the introduction of pathogens to their sinonasal cavities. Also, while NSI is a low-cost intervention for CRS, patient-centered considerations of increasing the burden of care to perform NSI and to properly maintain equipment by individuals with CF need to be considered (patient advisory members, CFF workgroup, CF, and CRS guidelines). The optimal delivery method, saline concentration, frequency, or volume could not be determined based on the published literature; however, otolaryngologists routinely advocate for daily high-volume (≈240 mL) low-pressure isotonic irrigations. Patients should be advised that all irrigation devices require cleanliness and maintenance and that direct tap water should NOT be used for irrigation. The water used for irrigation should either be boiled or distilled to reduce bacterial contamination.[38]
5. *The CFF recommends the treatment of allergic rhinitis (AR), including with intranasal corticosteroid spray (INCS), to improve nasal symptoms in children and adults with CF and concomitant AR*. In some studies, over half of individuals with CF have evidence of concomitant allergic inflammation,[39] and nasal lavage fluid from individuals with CF was notable for the presence of elevated eosinophil cationic protein and leukotrienes.[40,41] The symptoms of AR can overlap significantly with symptoms of CRS in individuals with CF, with diagnostic testing not readily available in all clinical settings. There are limited data on the treatment of allergic disease in CF; however, the use of INCS is supported in numerous national and international AR guidelines, with a favorable safety profile.[42,43]
6. *The CFF recommends endoscopic sinus surgery (ESS) for children and adults with CF who have symptomatic CRS refractory to appropriate medical therapy*. Several studies demonstrate improved quality of life following sinus surgery in individuals with CF.[44–51] Within the reviewed studies, there is heterogeneity of study design, perioperative protocols, and postsurgical follow-up time. Of the limited prospective data available, SNOT-22 decreased with statistical significance at 12 months following surgical intervention.[47] Facial pain and headache follow-

ing surgical intervention demonstrated significant improvement during an average follow-up period of 23 months.[52] Prospective data also demonstrate symptom improvement in the pediatric population following ESS.[48] Retrospective data support overall improvement in sinonasal symptoms up to 48 months.[50]

7. *The CFF recommends that perioperative airway clearance therapy (ACT) be continued as tolerated in children and adults with CF-CRS who undergo endoscopic sinus surgery (ESS).* The United Kingdom's Cystic Fibrosis Trust standards of care guidelines recommend that children and adults with CF undergoing surgery have access to ACT perioperatively.[53] Per CFF guidelines, individuals with CF benefit from the use of nebulized dornase alfa and nebulized hypertonic saline.[54] Based on these recommendations, individuals with CF-CRS who undergo ESS should have access to ACT, nebulized dornase alfa, and nebulized hypertonic saline perioperatively. These therapies could be beneficial to avoid exacerbation in the perioperative period when pain medication and sedation is necessary. Furthermore, CFF recommends ACT be continued and increased during treatment for acute exacerbation of pulmonary disease.[55] Because no ACT modality has been demonstrated to be superior to another, ACT should be individualized based on patient, caretaker, and facility-specific considerations.[56]
8. *The CFF recommends that baseline audiological evaluations be obtained to monitor for ototoxicity for all children and adults with CF who may receive ototoxic therapies.* Individuals with CF are frequently prescribed oral, intravenous, or inhaled antibiotics to manage *P aeruginosa* or other bacterial infections. While many medications can have ototoxic effects (Table 1), the ototoxic effects of intravenous aminoglycoside administration leading to hearing, tinnitus, and/or balance issues are particularly well described.[12,57–61] Although it is presently unclear who will develop such ototoxicity, some data suggest that cumulative aminoglycoside exposure increases one's risk for progressive ototoxicity.[11,62] Hearing loss caused by intravenous aminoglycosides occurs initially in higher frequencies (>8 kHz) and may extend into lower frequencies over time in some patients.[63] While the link between intravenous aminoglycosides and ototoxicity is clear, a connection between nebulized aminoglycosides and objective hearing loss is less certain.[64,65] While there are no data to demonstrate that ototoxic monitoring can prevent ototoxicity or improve quality of life in individuals with CF, this recommendation is made because identifying individuals with preexisting hearing loss or new ototoxicity symptoms would potentially allow for selection of less ototoxic therapies. The CFF does not recommend any specific audiologic or vestibular testing but further discussion can be found in the Supplemental File, p. 81.
9. *The CFF recommends ototoxic monitoring annually for all children and adults with CF who are exposed to ototoxic medications.* As noted in statement 22, individuals with CF are frequently treated with ototoxic medications, especially intravenous aminoglycosides. The prevalence of hearing loss in individuals with CF is considerably higher than age-matched control populations.[11] Annual audiologic examinations to screen for ototoxic symptoms (hearing, tinnitus, or balance issues) in individuals undergoing treatment with known ototoxic medications are recommended and encouraged; this will allow clinicians to identify symptoms of ototoxicity earlier and consider less ototoxic antimicrobials when appropriate. Early identification of ototoxicity is also critical to facilitate a timely referral to audiology and ongoing ototoxicity management as needed (eg, aural rehabilitation and amplification strategies).
10. *The CFF recommends ototoxic monitoring for all children and adults with CF with established hearing loss following each course of ototoxic medications.* In individuals who already have documented sensorineural hearing loss, the CFF recommends monitoring for ototoxic effects after each course of ototoxic medications. In contrast to the broader recommendations in 24, this recommendation focuses on and includes only those individuals who already have documented hearing loss and aligns with the International Ototoxicity Management Working Group statement recommending posttreatment audiologic monitoring within 3 months of completing intravenous ototoxic treatment for individuals with CF.[66] This statement also supports that individuals with CF receive annual audiological evaluation (recommendation #9) to ensure their auditory function data are up-to-date before each new course of treatment.
11. *The CFF recommends voice evaluation and management for children and adults with CF with dysphonia (aka hoarseness).* There are no prospective studies to understand the effects of voice evaluation and treatment in patients with CF and dysphonia (hoarseness). However, two case-controlled studies including 102 patients demonstrated high rates of dysphonia in patients with CF.[67,68] These data suggested that people with CF had less favorable voice parameters for almost all voice measures, including subjective patient-reported Voice Handicap Index and GRBAS (grade, roughness, breathiness, asthenia, and strain) scale, and objective fundamental frequency, intensity, jitter, shimmer, and harmonics to noise ratio.

Dysphonia is associated with lower overall quality of life and difficulty communicating,[69] and treatment with voice therapy has been shown to be effective in patients without CF who have dysphonia.[70]

12. *The CFF recommends against the routine use of systemic corticosteroids for CF-CRS in children and adults*. There are no published studies evaluating systemic corticosteroids for CF-CRS. In individuals with CF (excluding those with asthma or allergic diseases), the Cystic Fibrosis Pulmonary Practice Guidelines for Chronic Medication for Maintenance of Lung Health recommend against chronic systemic corticosteroid administration to improve lung function or reduce exacerbations caused by adverse effects.[54,71]

    Several consensus statements and practice guidelines support the judicious use of short-term systemic corticosteroid therapy for non–CF-CRS to reduce symptoms, polyp size, and in the perioperative setting.[7,72,73] However, there is insufficient evidence to assess the effects of short-term systemic corticosteroid therapy in analogous situations for CF-CRS.

    In select cases, shared decision-making should be utilized to determine whether the benefits outweigh the risks of therapy. Future studies and follow-up are required to determine the impact of systemic corticosteroids on CF-CRS and overall health.

13. *The CFF recommends against the routine use of intranasal corticosteroids administered by nebulizers in children and adults with CF*. There are no published trials of intranasal corticosteroids administered by nebulizers for the treatment of CF-CRS to support routine use. The administration of topical corticosteroids by nebulization may result in increased absorption and therefore increased risk of systemic toxicity from corticosteroids, including impaired growth, decreased bone mineral density, diabetes, and cataracts. Individuals with CF are at risk for these corticosteroid-related adverse effects, which is part of the reason that published CF pulmonary guidelines have recommended against routine systemic and inhaled corticosteroids.[54,71] Further studies are needed to evaluate topical nasal corticosteroid administration by nebulization in individuals with CF and CRS, and there are likely select individuals whose unique circumstances and preferences are well served with nebulized corticosteroids.
14. *The CFF recommends against performing routine endoscopic sinus surgery (ESS) for children and adults with CF for the sole indication of declining lung function*. Although studies have shown that sinus surgery improves quality of life in individuals with CF-CRS, the effects of surgery are unclear on preventing declining lung function.[50,74–76] The study populations and the methods used to analyze pulmonary function are heterogeneous. A prospective study of 106 individuals with CF who had sinus surgery and postoperative topical antibiotics showed that there was no impact on the rate of decline in pulmonary function, but there did appear to be a decreased frequency of gram-negative lung infections.[74] In other retrospective cohort studies, it did not appear that sinus surgery resulted in statistically significant or clinically meaningful change in pulmonary function over time. Given the available evidence, the CFF recommends against performing routine ESS in children and adults with CF for the sole indication of declining lung function.
15. *The CFF recommends against performing routine adenoidectomy alone for the treatment of CF-CRS in children*. Adenoid inflammation and hypertrophy are often causes of CRS in children without CF.[77–79] Adenoids serve as a bacterial reservoir and cause posterior nasal obstruction.[77,78] Posterior nasal obstruction leads to mucus stasis, inflammation, and reduced mucociliary clearance.[79] Adenoidectomy is a first-line surgical option for refractory CRS in young children without CF[77]; however, the benefit of adenoidectomy for CF-CRS is uncertain, and, while adenoid hypertrophy may contribute to CF-CRS, it is unlikely to be a standalone cause. Further, children with mild to moderate CRS (without CF) have greater benefit from an adenoidectomy alone compared with children with severe CRS (without CF),[80] and, since children with CF-CRS typically have more severe CRS,[81,82] adenoidectomy alone is unlikely to adequately treat CF-CRS. Adenoidectomy may be considered as an adjunct procedure for pediatric patients with CF-CRS and there may be a role for adenoidectomy alone in children with CF and nasal obstruction without CRS.
16. *The CFF recommends against performing routine balloon sinuplasty for children and adults with CF-CRS*. Balloon sinuplasty has become a popular treatment for uncomplicated sinus disease in both adults and children without CF.[83] Balloon sinuplasty involves cannulating and dilating the natural ostium to improve mucociliary clearance from the maxillary, frontal, and/or sphenoid sinuses. It has been demonstrated to be safe and effective in the appropriately selected patient.[84–87] However, there currently exists no evidence to support its use in individuals with CF-CRS. A recent document, the American Academy of Otolaryngology Clinical Consensus Statement on Balloon Sinuplasty excluded individuals with CF from analysis and recommendations.[88] Individuals with CF-CRS have

inspissated purulent secretions, and typically have diffuse sinus disease impacting all sinuses.[82] Additionally, a large percentage of individuals with CF-CRS will have polyp disease (6%–48%), which is not adequately treated with balloon sinuplasty techniques.[89–92] Simple dilation of the natural ostium is unlikely to provide adequate and durable treatment of CF-CRS. Although routine use of balloon sinuplasty is not recommended in individuals with CF-CRS, there may be a role for this technique in appropriately selected situations.

Acknowledge as an option

In review of the available data, multiple topics had limited or no evidence regarding the clinical question. When there was general agreement of the committee that the benefits of an intervention would outweigh the risks for select patients, the committee voted to "acknowledge as an option." These interventions are considered reasonable clinical management for some patients and clinical scenarios but may not apply broadly to all children and adults with CF (Table 3). Further research to determine the applicability and efficacy of these interventions that were recommended as options continues to be needed.

17. *The CFF acknowledges surveillance visits with an otolaryngologist in the absence of ear, nose, and throat symptoms as an option*. While persistent, symptomatic ear, nose, and throat disease should prompt referral as discussed in statement 1, otolaryngologic surveillance for individuals without these symptoms is an option for patients and health care providers to consider. This acknowledgement of optional surveillance visits was influenced by the fact that only 10% to 50% of individuals with CF may complain of sinus symptoms,[23,93] asymptomatic surveillance visits may identify disease manifestations at an earlier stage or while asymptomatic. While the committee did not formally recommend an interval for subsequent surveillance visits it would be reasonable to consider these visits at different life stages (ie, childhood, adolescence, and as an adult). This potential benefit is balanced against increasing the burden of care on individuals with CF and/or their families and cost.
18. *The ear, nose, and throat guidelines committee acknowledges the use of CFTR modulator therapy for treatment of CF-CRS when appropriate CFTR modulator therapy is available based on age and genotype as an option*. While most individuals with CF initiate CFTR modulator therapy for pulmonary disease, the committee acknowledges considering CFTR modulator therapy for the isolated indication of CF-CRS. One prospective cohort study[29] demonstrated a significant improvement in individuals with CF with the G551D genotype receiving ivacaftor as assessed by the SNOT-20 questionnaire. More recently, a prospective cohort study demonstrated a significant improvement in CRS symptoms, as measured by the SNOT-22, in individuals with CF taking elexacaftor/tezacaftor/ivacaftor triple-modulator therapy.[94] There is emerging evidence that modulators can improve symptoms of CF-CRS and thus a patient with good lung function with symptomatic sinus disease refractory to other therapies (ie, NSIs and/or surgery) may benefit from modulator therapy independent of their lung disease. Consideration of modulator therapy for sinus disease should be implemented in coordination with multidisciplinary CF care teams after consideration of potential toxicity and costs with the potential benefit. It is likely that the impact of modulator therapy will need to be considered in further detail as more evidence becomes available.
19. *The CFF acknowledges the use of intranasal corticosteroid spray (INCS) for children and adults with CF-CRS as an option*. There is limited evidence for the medical management of CF-CRS, but there are data supporting the use of INCS for non–CF-CRS. A single Cochrane review suggested that in individuals with CF, INCS reduced polyp size but did not change symptom severity.[95] Another study demonstrated an improvement in nasal endoscopic score in adults with CF-CRS being treated with INCS.[96] The use of INCS for non–CF-CRS is widely recommended in multiple American and European clinical guidelines, and they are generally considered to be safe.[5,97,98] Given the overall limited evidence specifically demonstrating benefit in individuals with CF-CRS but recognizing their safety and efficacy for non–CF-CRS, the CFF recommends use of INCS as an option, acknowledging their use may provide therapeutic benefit for CF-CRS in some individuals. In particular, INCS may be more efferctive for the subset of individuals with CF who have nasal polyps. The option for use of INCS for CR-CRS (statement 19) differs from statement 5, which recommends treatment of AR including INCS because there are better data to support the use of INCS for AR than for CRS in the non–CF population.
20. *The CFF acknowledges extended sinus surgery in children and adults with CF and CRS refractory to appropriate medical therapy as an option*. In this document, "extended sinus surgery" refers to the modified endoscopic medial maxillectomy procedure (removal of the medial maxillary wall while leaving the head of the inferior turbinate and lacrimal system in place)[99–101]

and extended frontal sinus procedures (Draf 2b and Draf 3) where bone is drilled and removed to provide larger openings.[102] The purpose of these procedures is to decrease the accumulation of secretions, improve access for debridement of mucus and polypoid edema in the clinic, and increase delivery of NSIs and topical delivery of therapeutics.[103,104] Although benefits are demonstrated in five studies,[34,44,99,105,106] including improvements in forced expiratory volume in the first second of expiration, SNOT-22, and/or hospitalization rates, there is lack of comparative evidence to conventional functional ESS. Additionally, each patient's unique anatomy must be taken into account before extended procedures are considered. In general, extended procedures should be considered an option in revision surgeries where patients have specific problems that may benefit from more aggressive surgery––chronic crusting/pooling in the maxillary sinus, which may benefit from medial maxillectomies, or scarring of frontal sinuses that would benefit from extended frontal procedures. However, in select cases, extended procedures may be appropriate for primary surgery.

21. *The CFF acknowledges perioperative intravenous antibiotics for children and adults who undergo endoscopic sinus surgery (ESS) for CF-CRS after discussion with the multidisciplinary CF care team as an option*. The evidence is limited regarding perioperative intravenous antibiotics for individuals with CF who undergo sinus surgery for CRS. There is significant heterogeneity of cohorts and outcomes studied such as pulmonary function and symptom scores, as well as an overall lack of a protocolized approach.[44,47,74,75,107] The decision whether to use perioperative intravenous antibiotics should be made in consultation with the multidisciplinary CF care team. Considerations in the use of perioperative intravenous antibiotics should include whether empiric coverage of pathogens such as *P aeruginosa*, *Staphylococcus aureus*, and/or patient-specific culture-driven coverage is desired. Patient factors such as antimicrobial use history, allergies, and potential drug interactions should be considered in order to optimize benefit and minimize risk. In addition, consideration of the social and geographic situations may influence decision for perioperative intravenous antibiotics.
22. *The CFF acknowledges the use of sinonasal topical antibiotic treatment in children and adults with CF who have previously had ESS as an option*. There are few controlled trials of sinonasal topical antibiotics for CF-CRS. Two randomized controlled trials have shown improved patient-reported outcome measures (sinonasal quality of life or olfaction) using topical tobramycin.[108,109] Additionally, a prospective postoperative protocol in individuals with bacterial colonization using colistimethate irrigations demonstrated improvement in sinonasal quality of life and sinonsal cultures.[47] However, at least one study failed to establish an association between topical antibiotic use and sinonasal quality-of-life scores in individuals with CF following ESS.[96] Given the limited data and potential adverse effects, including development of antibiotic resistance, drug interactions, and systemic adverse reactions, the CFF acknowledges that sinonasal antibiotics may be a useful option in patients with previous sinus surgery for acute exacerbations, postoperative healing, and even routine use. The systemic absorption of tobramycin and colistin from sinus irrigation appears to be low or undetectable.[108,110] However, the degree to which irrigant may enter the middle ear via the eustachian tube and contribute to ototoxicity is unknown. To balance the benefits and potential risks, some clinicians recommend adding antibiotics on alternating months to a daily sinus saline irrigation regimen.
23. *The CFF acknowledges the use of intranasal dornase alfa nebulization for treatment of CRS in children and adults with CF as an option*. Intranasally nebulized dornase alfa has been shown to significantly improve sinonasal symptoms compared with saline alone in placebo-controlled studies.[111,112] Intranasal nebulization of dornase alfa appears safe with only minor side effects reported such as epistaxis.[113] The effect of intranasal dornase alfa on pulmonary function, sinus CT radiographic scores, and nasal endoscopic scores is less clear, and conflicting results have been demonstrated in the literature.[113] The high cost of dornase alfa remains a significant barrier prohibiting widespread use for the treatment of CF-CRS. Ultimately, larger controlled studies are necessary to understand the potential benefits of intranasal dornase alfa and to evaluate cost-effectiveness.
24. *The CFF acknowledges ototoxic monitoring for all children and adults with CF following each course of ototoxic medications as an option*. As noted in statements 8, 9, and 10, intravenous aminoglycosides and other antibiotics can cause hearing loss, tinnitus, and/or balance issues in individuals with CF. The CFF recommends, as an option, to monitor for these ototoxic effects after each course of ototoxic systemic medications in all individuals, while recognizing that this may place a significant burden on some individuals with CF and health care resources. This committee did not formally recommend a time frame for ototoxic monitoring; however, the International Ototoxicity Management Working Group recommends posttreatment

TABLE 4 Statements that did not reach consensus

#	No consensus	Vote
25	Should intranasal corticosteroids administered by irrigation versus no treatment with intranasal corticosteroids administered by irrigation be used in individuals with cystic fibrosis?	75.86%

audiologic monitoring within 3 months of completing an intravenous ototoxic treatment for individuals with CF.[66] Coordinating point of care options with your local audiology team may help alleviate this burden. As noted above in statements 8, 9, and 10, there are no published data showing that screening for ototoxicity will change or improve outcomes, but the knowledge that an individual is developing ototoxicity symptoms associated with treatments may potentially result in using alternative antibiotics. This ultimately may reduce new or progressive damage in hearing or balance resulting from treatment.

NO consensus

The committee was unable to come to a ≥80% consensus to recommend or recommend as an option the use of intranasal cordicosteroid by irrigation in individuals with CF (Table 4).

25. *Should intranasal corticosteroids (INC) administered by irrigation versus no treatment with INC administered by irrigation be used in individuals with CF?* There is insufficient evidence regarding the role of INC irrigation in individuals with CF-CRS, but potential benefits can be extrapolated from INC administered by spray or drops. Beer et al[95] demonstrated that topical betamethasone drops were associated with decreased polyp size but no change in subjective symptom scores. A prospective cohort study investigated factors predicting CRS severity in 33 adults with CF who had undergone prior sinus surgery.[96] The use of INC in this study resulted in a nonstatistically significant SNOT-22 reduction of nine points. Topical nasal corticosteroid drops and sprays have been associated with mild adverse effects, including nasal bleeding, burning, and tingling, compared with placebo.[95,114] With long-term corticosteroid use, there is concern for the development of adrenal suppression, adverse effects, or drug interactions, although the risk for INC is generally accepted to be low. There have been two case reports describing patients with CF-CRS who experienced drug interactions related to corticosteroid use, mostly implicating inhaled budesonide and not INC.[115,116] In general, the committee debated the utility of corticosteroids in CF-CRS, which is typically a neutrophilic inflammation compared with the majority of non–CF-CRS that has an eosinophilic inflammatory profile. Individuals with CF-CRS and nasal polyps may experience a better response to INC than the average individual with CF-CRS.

4 | CONCLUSIONS

No guidelines or specific recommendations can account for the myriad clinical circumstances leading to clinical decisions for individual patients. This document is to serve as guidance for clinicians managing complex clinical problems using a personalized approach and therefore should be considered in the overall context of the patient's clinical picture. This document is intended to provide best guidance on otolaryngology consultation, medical and surgical management of CF-CRS, hearing, and voice care in patients with CF, and we acknowledge the evidence is constantly evolving. For example, nearly all of the data evaluated predate the advent of highly effective modulator therapies.[117] The literature around the benefits of highly effective modulator therapy on sinonasal health and quality of life is evolving at a rapid pace.[118,119] As such, we expect that many of the recommendations made by the committee may change as new data become available.

This document also highlights the lack of evidence on which to make complex decisions for our patients with CF. As a result, we need to continue to manage these medically complex individuals from a multidisciplinary standpoint with our pulmonary colleagues. Future clinical research is needed utilizing standardized, validated outcomes with comprehensive reporting of patient outcome, effects of modulator therapies, and genetic characteristics to help continue to advance care, decrease morbidity, and improve the quality of life for individuals with CF.

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