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Management of the Upper Airway in Cystic Fibrosis

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Abstract

Purpose of Review—Upper airway disease engenders significant morbidity for patients with cystic fibrosis and is increasingly recognized as having a much greater role in pulmonary outcomes and quality of life than originally believed. Widespread disparate therapeutic strategies for cystic fibrosis chronic rhinosinusitis underscore the absence of a standardized treatment paradigm. This review outlines the most recent evidence-based trends in the management of upper airway disease in cystic fibrosis.

Recent Findings—The unified airway theory proposes that the sinuses are a focus of initial bacterial colonization which seeds the lower airway and may play a large role in maintaining lung infections. Mounting evidence suggests more aggressive treatment of the sinuses may confer significant improvement in pulmonary disease and quality of life outcomes in cystic fibrosis patients. However, there is a lack of high-level evidence regarding medical and surgical management of cystic fibrosis chronic rhinosinusitis that makes generalizations difficult.

Summary—Well designed clinical trials with long-term follow-up concerning medical and surgical interventions for cystic fibrosis sinus disease are required to establish standardized treatment protocols, but increased interest in the sinuses as a bacterial reservoir for pulmonary infections has generated considerable attention.

Keywords

chronic rhinosinusitis; cystic fibrosis; endoscopic sinus surgery; sinusitis; upper airway

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder related to deficiency or dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel, which is normally present and functional at the apical membranes of respiratory and exocrine glandular epithelium. Manifestations of CFTR deficiency include diabetes, malabsorption, male infertility, and increased susceptibility to airway bacterial infections [1,2]. Approximately, 30 000 people in the USA carry the diagnosis of CF, with the majority of patient morbidity and mortality attributable to pulmonary compromise. However, upper airway disease in the form of chronic rhinosinusitis (CRS) is nearly universal in this

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population and a common cause of morbidity. The unified airway theory links upper and lower airway disease and suggests that CRS may drive pulmonary exacerbations in patients with CF. In this review, we will describe the latest trends in the management of upper airway disease in CF.

Unified Airway

The concept of the unified airway model considers the entire respiratory system to represent a functional unit that consists of the nose, paranasal sinuses, larynx, trachea, and distal lung [3]. The upper and lower airways are composed of the same pseudostratified, ciliated, columnar epithelium and are thus affected by the same inflammatory and infectious processes. This intimate relationship has become increasingly recognized and studied. The prevalence of asthma in patients with CRS (approximately 20%) is much greater than that observed in the general population (5–8%) [4], and is even higher (42%) in patients who undergo endoscopic sinus surgery (ESS) [5]. Treatment of upper airway inflammation also appears to impact pulmonary outcomes in asthma as successful management of CRS results in decreased asthma medication, improved pulmonary function, and fewer exacerbations [6].

In CF, lack of functional CFTR impairs chloride and bicarbonate transport across the apical epithelium producing thickened secretions, dysfunctional mucociliary clearance, and chronic airway bacterial infection [7]. Akin to the relationship between CRS and asthma, aggressive treatment of CRS in CF could also provide better pulmonary outcomes. The acute escalation of sinonasal symptoms preceding a pulmonary exacerbation is an anecdotal relationship noted in CF patients that may suggest transmission of bacterial infection from the upper to the lower airway (Fig. 1). Support for this association includes studies establishing the presence of similar bacteria in pulmonary and sinonasal cultures [8–11]. In a recent study from Johansen et al. [11], a majority of CF patients were discovered to have sinus colonization with the identical genotype of *Pseudomonas aeruginosa* affecting the lung. Other research has confirmed that cultures of induced sputum were similar to sinonasal cultures removed during ESS [12]. In cases of lung transplantation in CF patients, a close association between post-transplantation bronchoalveolar lavage and paranasal sinus aspirate cultures has been recognized, with similarities in genotype and gene expression phenotypes [10,13–17]. These findings indicate the sinuses act as a bacterial reservoir for transmitting disease to the lower airways, making control of sinonasal infections a priority for improving pulmonary outcomes [18].

Chronic Rhinosinusitis in Cystic Fibrosis

Patients with classical CF have a high incidence of CRS with or without nasal polyps (NP) approaching 100% [19]. Imbalance of electrolyte transport from CFTR dysfunction reduces airway surface liquid depth and increases the viscosity of mucins in the airway 30–60 times higher than seen in patients without CF [20–24]. Tenacious secretions and tissue inflammation block sinus ostia, which results in hypoxia, mucosal edema, and additional impairment of mucociliary function [25]. Inflammation and remodeling promote the formation of NP that are present in up to 86% of patients with CF and increase in prevalence with age [26]. The formation of neutrophil-laden polyposis is primarily driven by

interleukin-8 in contrast to non-CF CRS with NP, which shows predominant eosinophilia and a T helper cell type 2-inflammatory cytokine profile [25,27].

The most commonly used criteria for CRS are from the European paper on rhinosinusitis [28] given as follows.

1. Inflammation of the nose and the paranasal sinuses with two or more symptoms for more than 12 weeks:
    a. nasal blockage,
    b. obstruction,
    c. congestion,
    d. nasal discharge,
    e. facial pain/pressure,
    f. reduction in olfaction,
2. with at least one of the following findings:
    a. nasal polyps,
    b. mucopurulent discharge,
    c. edema/mucosal obstruction,
    d. mucosal changes.

Individuals with CF commonly underreport their sinus symptoms despite a large burden of infection and inflammation. Whether this reflects an adaptation to the chronic disease, reduced severity of symptoms relative to pulmonary or gastrointestinal issues, or other unidentified explanation remains unknown [25]. Without specific questioning via quality of life questionnaires, only 10–15% of CF CRS patients volunteer their sinonasal symptoms even though two-thirds of patients report decreased olfaction and approximately 80% fulfill European paper on rhinosinusitis criteria for CRS [29&&]. This highlights the importance of utilizing questionnaires, such as the Rhinosinusitis Outcome Measure-31 and Sinonasal Outcome Test-22 for adult CRS patients and Sinonasal-5 for pediatric patients.

Less subjective diagnostic criteria for CF sinonasal disease include nasal endoscopy and radiographic imaging, primarily by computed tomography (CT) [30–32]. Nasal endoscopy usually reveals bilateral NP with thick nasal discharge and permits directed cultures of the sinuses for bacterial sensitivity analysis (Fig. 2). Traditional scoring methods to evaluate disease, such as the Lund–Mackay and Nair systems, do not predict surgical benefit [33]. Rasmussen *et al*. [33] found no correlation between CT scores and findings of purulence during ESS, pathogenic bacteria, or patient symptoms. Furthermore, bacteria and purulence were discovered in several cases with absent findings on CT scan. Notably, genotype influences sinonasal disease severity on CT scan images as class I-III CFTR mutations have worse sinus hypoplasia, opacification, and associated osteitis of the maxillary sinus wall compared with the less severe class IV and V mutations [34]. Indications for use of CT are especially critical to delineate for children to limit radiation exposure in this vulnerable

population. Cavel *et al.* [35] suggest that indications for imaging in pediatric patients should be limited to preoperative planning only, as imaging for disease evaluation was not found to modify clinical management. CT is an important tool for intraoperative navigation during ESS because of anatomical differences in CF patients, such as sinus hypoplasia [36, 37].

Therapeutic Management of the Upper Airway in Cystic Fibrosis

While there is insufficient data to form a consistent medical treatment paradigm for the CF upper airway, recent studies suggest a number of interventions have merit. Discussion of the latest evidence-based investigations regarding medical interventions for the CF upper airway are described below.

Dornase alfa

Cellular degradation of extensive neutrophils recruited to the respiratory epithelium releases large amounts of DNA into airway secretions causing increased viscosity. Dornase alfa (recombinant human deoxyribonuclease) cleaves this extracellular DNA and has been shown to improve pulmonary function and decrease respiratory exacerbations in CF patients when inhaled via nebulizer [38]. A randomized, prospective, double-blind trial investigating dornase alfa nasal inhalation after ESS demonstrated significant improvement in symptoms, rhinoscopic findings, and pulmonary function in patients receiving drug [39]. After a small pilot study revealed significant improvement in sinonasal symptoms [40], Mainz *et al.* [41&&] recently published the results of their double-blind, placebo-controlled crossover trial using nasal nebulized dornase alfa and demonstrated significant symptom reduction and improvement in pulmonary function. Administration of the drug for CRS is currently constrained by expense.

Nasal saline irrigations

Isotonic nasal saline irrigations remove inspissated secretions and crusting that accumulates from the underlying CF pathogenesis. Use of hypertonic saline has some theoretical benefit of decongestion by osmosis, but may not be as well tolerated [42]. A Cochrane meta-analysis concluded that quality of life in non-CF patients is improved with saline irrigation when compared with nontreatment [43]. Despite a lack of trials in CF patients, nasal saline irrigations are widely utilized because of extrapolated benefit from studies in non-CF patients and the value demonstrated in the pulmonary airways with nebulized hypertonic saline [44,45]. The squeeze bottle/neti pot devices provide the best saline irrigation delivery to the paranasal sinuses and irrigation delivery is greatly improved following ESS [46].

Corticosteroids

Therapeutic effects of systemic corticosteroids on CRS have not been well studied in CF patients. However, non-CF CRS with NP patients derive significant benefit from a short course (2–4 weeks) of oral corticosteroids [47]. Oral corticosteroids in CF patients should be limited to acute exacerbations and weighed against the potential risks given the prevalence of concomitant diabetes. Similarly, high-level evidence supports the use of topical corticosteroids to depress mucosal inflammation in non-CF CRS with and without NP

[48,49]. For neutrophil-mediated CF CRS with NP, topical corticosteroids have demonstrated mixed benefit [50–52]. One double-blind, placebo-controlled, randomized study by Hadfield *et al.* [52] revealed improvement in CF NP size with betamethasone nasal drops compared with placebo. However, the risk of bias was high in this study, as over 50% of patients did not complete follow-up [53]. Given the potential benefits of nasal saline irrigation as a delivery device, low absorption topical steroids (e.g., mometasone and budesonide) are commonly mixed with saline and prescribed for both non-CF and CF CRS. Topical steroid rinses with budesonide have demonstrated no alteration of the hypothalamic-pituitary axis in several studies [54,55]. Thus, low absorption topical steroid irrigations are a reasonable strategy in CF CRS, although further randomized controlled trials are warranted.

Antibiotics

Although there is strong evidence to support the use of inhalational antibiotics (tobramycin, colistin, and aztreonam) in CF pulmonary disease, large clinical trials for CF upper airway disease are lacking [56]. Recently, a small double-blind, placebocontrolled trial investigated sinonasal inhalation of tobramycin [57&]. Initial results showed positive effects on symptoms and decreased presence of *P. aeruginosa* in nasal lavages compared with saline irrigations [57&]. The use of topical antibiotics postoperatively has also been associated with reduced recurrence of CF sinus exacerbations [58] and improved control of sinus disease for 2 years following surgery [59]. Advantages of topical antibiotic therapy include avoidance of systemic side-effects of oral or intravenous antibiotics along with the ability to obtain higher concentration of antibiotics in the paranasal sinuses [60].

Ivacaftor

Dramatic advancements in understanding of the production, processing, and function of the CFTR channel have led to the discovery of small molecules that restore activity to the mutant CFTR protein and are now implemented for clinical treatment [61–63]. Ivacaftor was recently approved by the Food and Drug Administration for use in individuals age 6 and above with at least one copy of the G551D CFTR mutation [64]. However, the G551D mutation is present in only 4% of CF patients, the medication is costly, and requires long-term therapy [65]. Benefits of the drug on sinonasal symptoms in patients with the G551D mutation are currently being evaluated. Ivacaftor and other small molecules that target the CFTR protein exemplify a new paradigm shift in treatment that could provide relief of CFTR-mediated mucosal abnormalities that drive CF CRS pathogenesis [66,67].

Endoscopic Sinus Surgery in Cystic Fibrosis

Currently, there are no criteria for ESS versus medical management in CF CRS; thus, most clinicians make decisions for therapy based upon experience and patient complaints. The low incidence of self-reported symptoms despite radiographic and endoscopic evidence of sinus disease in the large majority of CF patients reveals the difficulties of establishing appropriate indications for surgical management. However, persistent symptoms despite a course of antibiotics (either during inpatient admission or provided on outpatient basis) are a well-established primary indication for surgical intervention. More aggressive strategies to treat asymptomatic individuals with surgery are garnering favor in certain centers because of

recent evidence that intervention with extensive surgical and medical management may help eradicate the bacterial reservoir in the sinuses and improve pulmonary outcomes (Fig. 3) [6,68&&]. Additionally, rising antipseudomonal immunoglobulin A (IgA) could potentially be used as an early supplemental tool to diagnose colonization with pseudomonas in the lungs and sinuses, thus impacting timing of surgical intervention [69].

Because of conflicting evidence and opinions regarding surgical indications, the percentage of CF patients requiring surgical management of their disease varies considerably according to where they obtain treatment. Virgin *et al.* [70&] analyzed CF patient data collected from the 29 largest pediatric hospitals in the USA. The frequency of ESS varied from 1 to 24% among centers during inpatient encounters and was more likely to be performed in larger CF centers and in patients less than 17 years of age. The authors attributed this to more consistent and aggressive care practices with regards to screening and treatment of CF-related comorbidities in larger centers dedicated to CF care.

Outcomes

Despite a lack of randomized, controlled trials, evidence suggests that ESS does impart significant attenuation of sinonasal symptoms. A systematic review of evidence-based sinus surgery outcomes noted that CF patients report improvement in quality of life measures following ESS, but at a lower rate and for shorter duration than non-CF CRS patients [71]. ESS also conferred significant benefit in both sinus symptoms and quality of life in CF children according to a recent meta-analysis [72].

Common consensus on the ‘gold standard’ of surgical therapy has not been established. Surgical approaches range from conservative measures such as removing obstructive NP to more aggressive interventions intended to provide better delivery of irrigations and other topical remedies [15,73&&]. Drainage and cleaning of the largest of the sinus cavities, the maxillary sinus, is particularly problematic due to superior location of the ostium that drains the sinus against gravity. To improve access, the modified endoscopic medial maxillectomy (also known as maxillary mega-antrostomy) procedure removes the medial maxillary wall, but does not sacrifice the head of the inferior turbinate or lacrimal system (Figs. 4 and 5). Accrual of secretions becomes less frequent, physical debridement of mucus and polypoid edema is easily accomplished in clinic, clearance of mucus is improved, and the cavity has increased access for nasal saline irrigations and topical delivery of therapeutics [74]. In a prospective observational study by the senior author (B.A.W.), extensive ESS and modified medial maxillectomies combined with a comprehensive postoperative medical management strategy (culture-directed antibiotics, oral steroid taper, topical steroid/antibiotic irrigations) was associated with marked improvement in sinus symptoms (Sinonasal Outcome Test-22 questionnaire) and objective findings (Lund–Kennedy scores) at 1 year of clinical follow-up [75]. There was a significant reduction in hospital admissions for pulmonary exacerbations in the year postsurgery compared with the year before, but no change in forced expiratory volume 1. Furthermore, a recent systematic review of perioperative approaches to improve ESS outcomes in the CF population concluded that large antrostomies provided improved quality of life and sinus symptom scores, lowered the frequency of inpatient hospitalizations, and reduced the need for intravenous antibiotics [76].

Further support for extensive surgical intervention with a regimented postoperative approach is derived from a prospective, intervention cohort study evaluating a treatment method that included extensive ESS followed by 2 weeks of intravenous antibiotics, 6 months of antibiotic (colistin) nasal irrigations, and 12 months of topical nasal steroids [8]. Criteria for intervention included not only patients with severe symptoms, but also those with recent lung transplantation (within a year) and patients with declining lung function and/or intermittently colonized lungs with increasing frequency of positive lower airway cultures regardless of antibiotic therapy. At 6 months, 67% of patients showed no growth of pathogenic bacteria including many patients who were deemed intermittently colonized or chronically infected prior to surgery [8]. In a follow-up study examining patients 1 year after the initiation of this surgical and medical intervention protocol, the prevalence of intermittently colonized patients had decreased by 38%, whereas noncolonized patients had increased by 150% as identified on pulmonary sputum samples [8].

Conclusion

The unified airway theory has stimulated pronounced interest in improving treatments for CF sinus disease because of the role the upper airway serves in seeding the lungs with pathogenic bacteria. A comprehensive strategy that includes extensive sinus surgery and regimented postoperative medical management is preferred, although there is minimal high-level evidence to provide consistent treatment recommendations that apply to all CF patients. Randomized, controlled trials with long-term follow-up are required to confirm efficacy of medical and surgical interventions for CF sinus disease.

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KEY POINTS

- The unified airway theory links upper and lower airway disease and suggests that CRS may drive pulmonary exacerbations in patients with CF.
- There are no universally accepted medical and surgical treatment protocols for the upper airway in CF because of a lack of high-level evidence.
- Regimented, aggressive management of the upper airway is a promising avenue for improving pulmonary outcomes and decreasing colonization with CF pathogens.

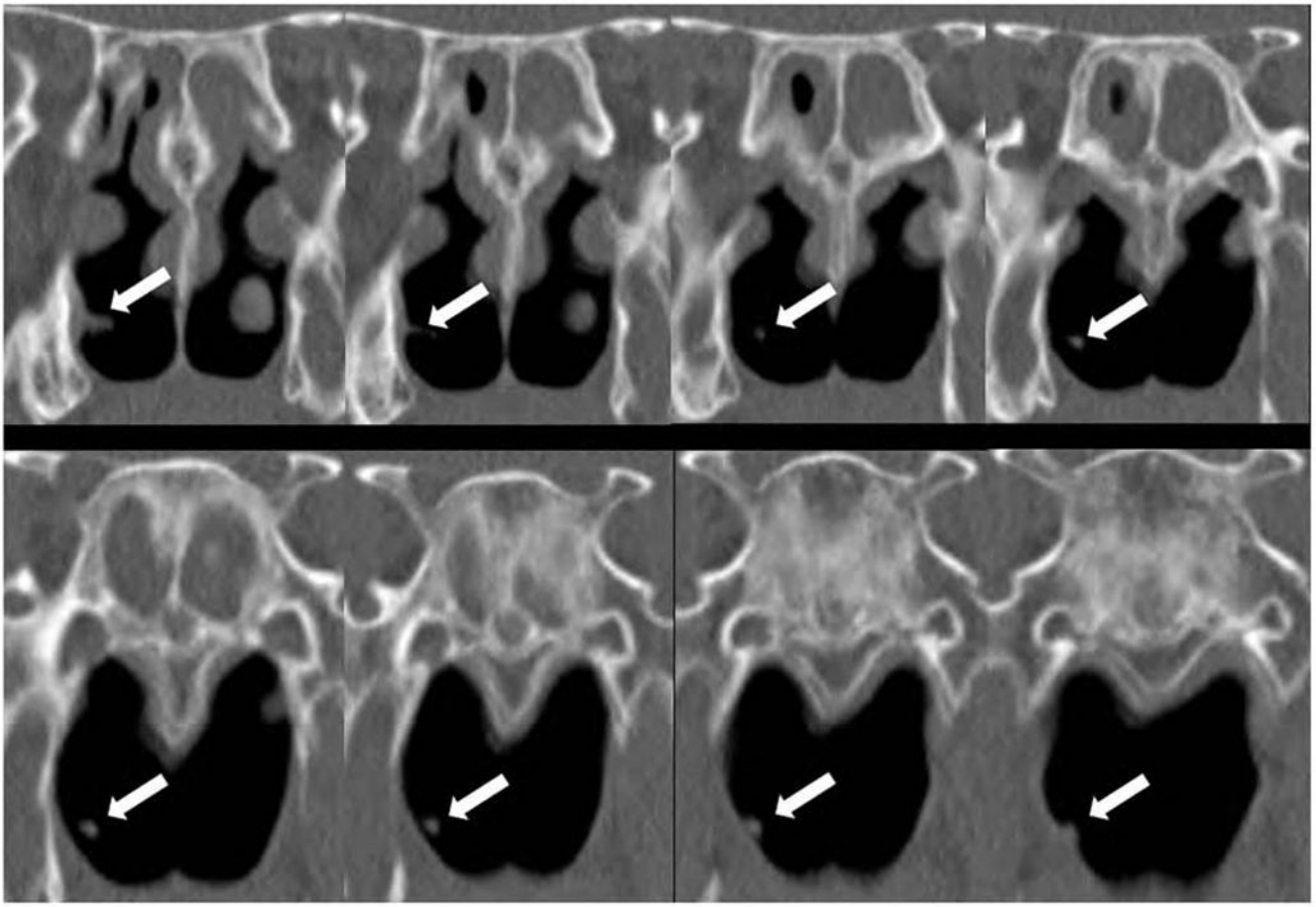

Figure 1.
Sequential coronal CT scans of the posterior nasal cavity revealing the tracking of sinus secretions from the right sinuses to the nasopharynx (left to right, top to bottom). Draining purulence frequently exacerbates cough and likely seeds the lower airway. CT, computed tomography.

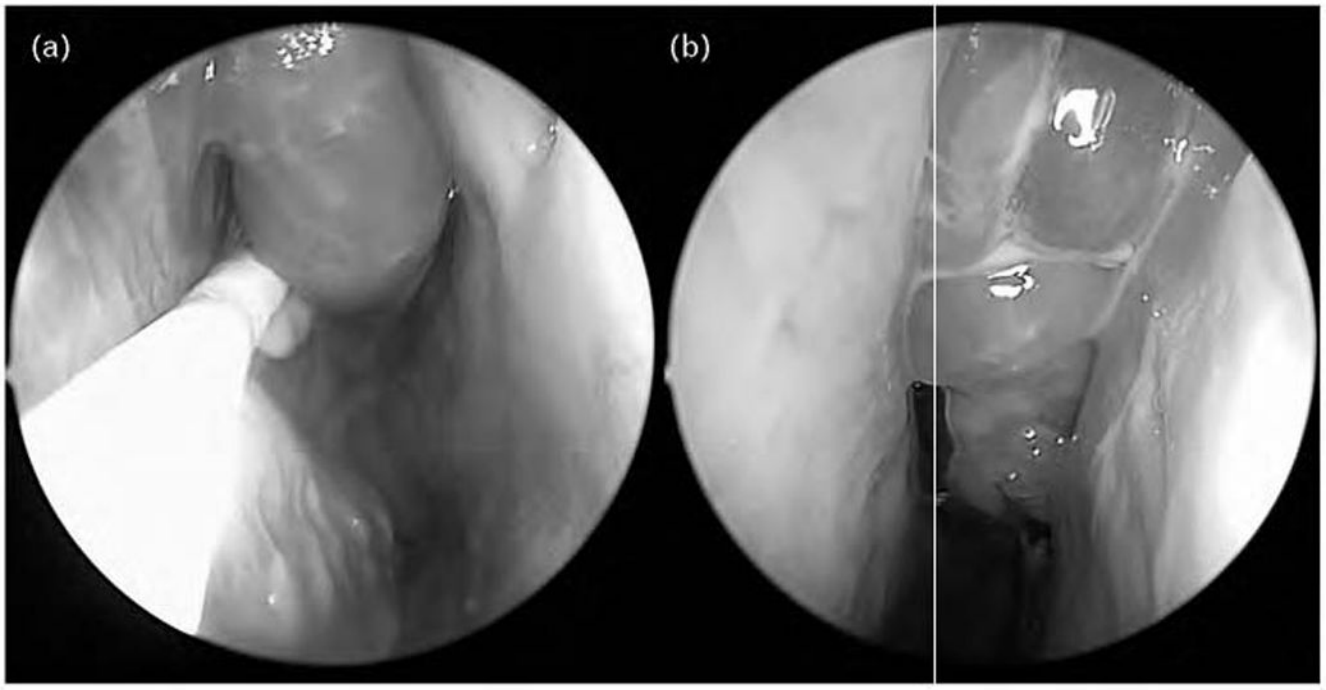

Figure 2.

Transnasal endoscopic views of the right (a) and left (b) nasal cavities of a CF patient. Note the extensive polyposis on both sides that would be difficult to discern without nasal endoscopic visualization. Culture of mucopurulent secretions is easily accomplished using rigid endoscopy as well. CF, cystic fibrosis.

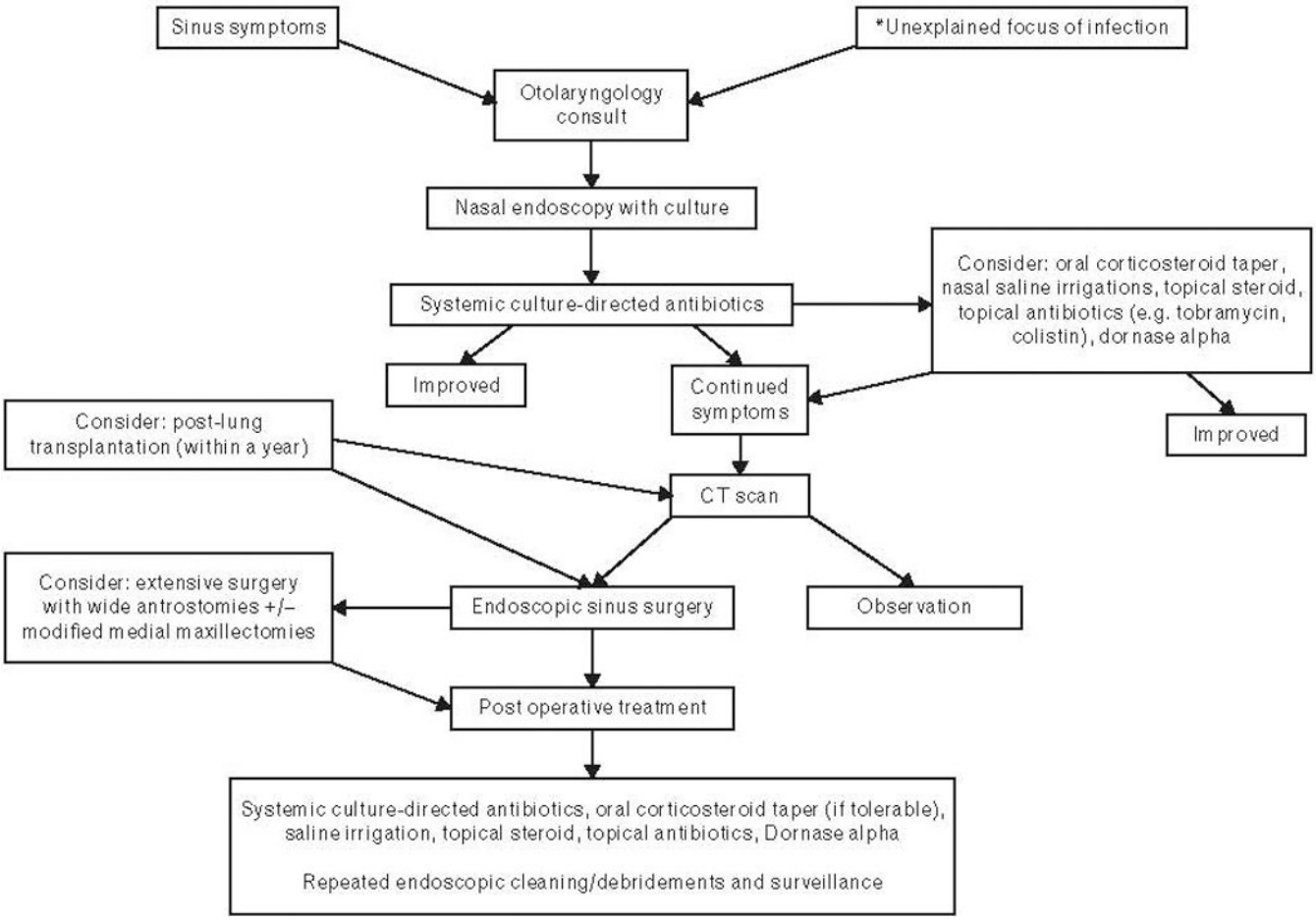

Figure 3.

Our suggested treatment algorithm based on the available evidence. CT, computed tomography.

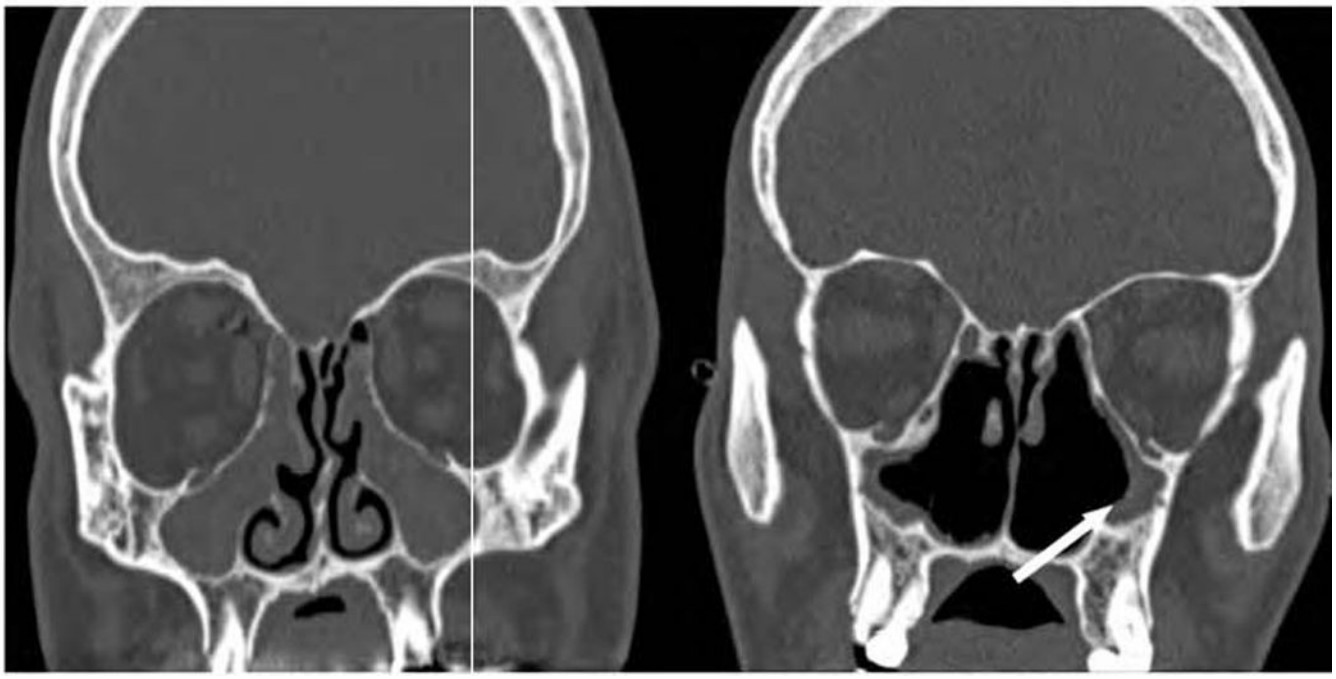

Figure 4.

Coronal CT scan demonstrating the preoperative appearance of a patient with CF after traditional maxillary antrostomies with completely opacified maxillary sinuses (Left). Postoperative appearance after endoscopic sinus surgery and bilateral modified endoscopic medial maxillectomies reveals complete marsupialization (arrow) of the maxillary sinus (Right). The coronal CT image is posterior to the anterior 1/3 of the inferior turbinate. CF, cystic fibrosis; CT, computed tomography. Reproduced with permission from [75].

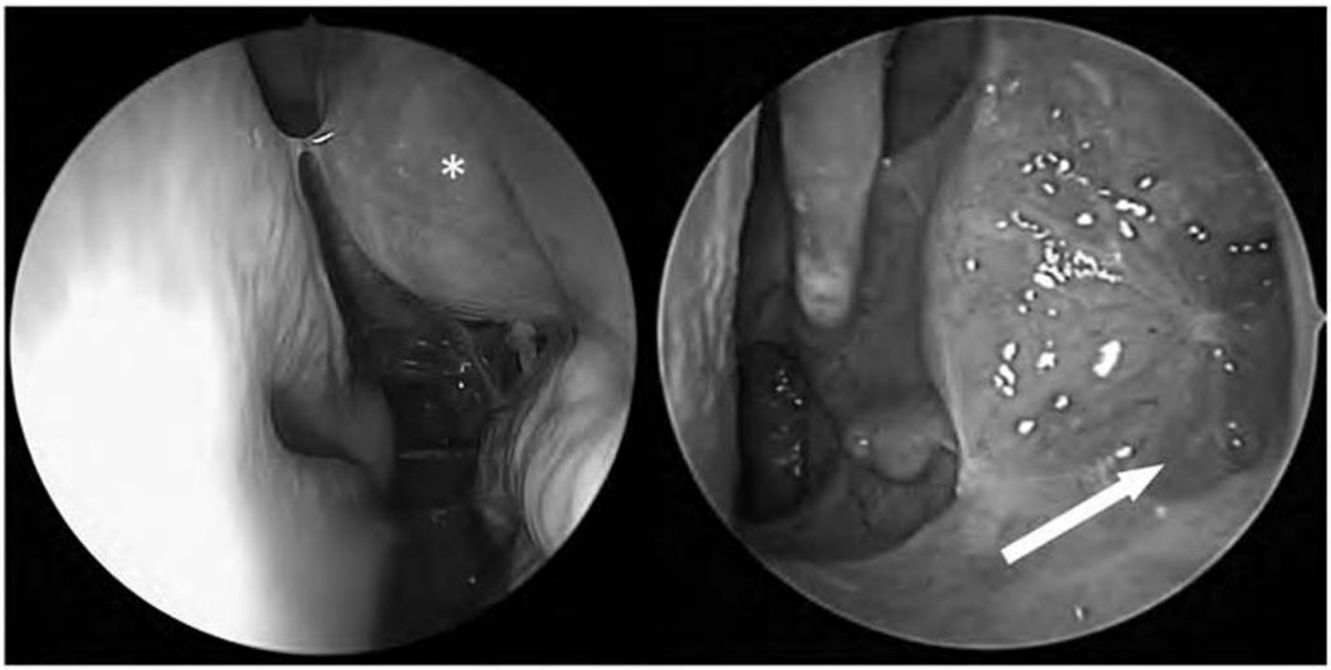

Figure 5.

Transnasal endoscopic view of the left nasal cavity before (left) and after (right) endoscopic sinus surgery with modified endoscopic medial maxillectomy. Note the nasal polyps () within the middle meatus and thick secretions preoperatively. A 30-degree endoscope is inserted past the anterior 1/3 of the inferior turbinate postoperatively revealing a well healed maxillary cavity with no secretions retained in the floor of the sinus (arrow). Reproduced with permission from [75].