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Journal of Cystic Fibrosis Volume 8 Suppl 1 (2009) S10–S14

Journal of Cystic Fibrosis

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Management of chronic rhinosinusitis in CF ☆

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Abstract

Routine CF management often does not include upper airway (UAW) assessment although CFTR defects equally affect the sinonasal mucosa. Up to 50% of CF patients have chronic rhinosinusitis (CRS) and/or nasal polyps, and almost 100% reveal UAW abnormalities on CT scan. CRS impairs quality of life. UAW dysfunction in filtering, humidifying, and warming inspired air affects lower airways and the UAW is a potential site of first colonization and a reservoir for opportunistic bacteria. Therefore, UAW pathology substantially affects overall health in CF.

Standard treatments are scarce and mostly lack evidence. Nasal douche can remove mucus and crusts. Recently, delivery of dornase alfa using a vibrating aerosol has shown potential as treatment for CF-related CRS. Surgery is indicated when conservative approaches fail but postoperative relapse is frequent.

In summary, upper airway involvement in CF is undertreated and requires prospective investigation and an interdisciplinary consensus on diagnosis and therapy.
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Keywords: Rhinosinusitis; Upper airways; Cystic fibrosis; Surgery; Conservative therapy: Consensus

1. Introduction

Thirty years ago cystic fibrosis (CF) regularly led to death during the first decade of life. Patients were severely malnourished and, like today, the principal reason for reduced life expectancy was pulmonary deterioration due to chronic infection with opportunistic bacteria e.g. *Pseudomonas aeruginosa* (*P.a.*). Since then, standardised aggressive treatment has improved life expectancy enormously. As a consequence, "secondary symptoms" like upper airway (UAW) involvement and its impact on the course of the disease and quality of life (QoL) are coming into the focus of CF care.

The CFTR defect affects the upper airway mucosa like the lower airways, so that the paranasal sinuses (PS) are almost universally involved in CF [1–3]. Rhinosinusitis (RS) symptoms with or without nasal polyps are therefore a hallmark of the disease. Predominant clinical signs are chronic nasal congestion, rhinorrhoea with anterior or postnasal drip, mouth breathing, anosmia, facial pain and sleep disorders [4,5].

The self-reported incidence of RS symptoms in CF is as low as 10% without specific questioning [6]. However, on careful evaluation, up to half of patients suffer from chronic rhinosinusitis (CRS) (>3 months of symptoms per year) [2–4] and another third report intermittent RS symptoms. Indeed, computed tomography (CT) scans of the PS are pathologic in almost all patients, although this is sometimes limited to hypoplastic frontal sinuses [7]. Thus, a high index of suspicion and meticulous evaluation are needed to diagnose symptoms and signs of sinonasal disease in CF.

2. Impact of rhinosinusitis on CF health

RS in CF is assumed to be the result of the underlying CFTR defect and bacterial infection that lead to inflammation and thickening of the sinus mucosa and hypersecretion of

☆ Paper presented during the symposium "Striving for excellence: optimizing CF patient care today" at the 3st European Cystic Fibrosis Conference, Prague, 13 June 2008.

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mucus. RS requires significant health care resources due to difficulties in treatment. The health burden it imposes is generally high: in non-CF patients QoL measures of bodily pain and social functioning are significantly worse for CRS patients than patients with congestive heart failure, angina, chronic obstructive pulmonary disease (COPD) or back pain [8].

Besides impairing QoL, CRS may influence CF-related health much more than expected by causing nutritional and bronchopulmonary problems. As the senses of smell and taste are strongly correlated, olfactory disorders, which are a frequent symptom of CRS, can aggravate nutritional problems. Thus, CRS may negatively influence appetite [2] and nutritional status in patients who must struggle to consume up to 150% of the generally recommended calories per day.

Pulmonary disease is still the primary cause of premature death in most CF-patients [9]. In healthy airways more than 7000 L of air is inspired per day and is water-saturated up to 100%, filtered and warmed to body temperature within one passage through the airways [10]. Dysfunction of the UAW results in bronchial inhalation of cold, dry and non-filtered air, which negatively affects lower airway (LAW) function and increases hyper-reactivity as in asthma [11].

Chronic pulmonary infection with *P.a.* plays a central role in the progression of CF lung disease. There is increasing evidence that the UAW is a site of first colonization and a reservoir for chronic persistence of *P.a.* [12–14]; the same *P.a.* strains are found in sputum and UAW specimens [13], and the same *P.a.* clones have been identified in the sputum and bronchoalveolar lavage fluid of CF lung transplant patients before and after they received presumably *P.a.*-free lungs [14]. These genetically identical bacteria are thought to originate from the patients' trachea or UAW. Recent studies have shown the persistence of *P.a.* in human UAW as biofilm-forming units [15].

3. Assessment of UAW involvement in CF

Basic clinical assessment of the UAW can easily be performed in a few minutes. The appearance of the epithelium and the patient's breathing pattern give some essential information about sinonasal status: mouth breathing indicates nasal obstruction, often combined with thick purulent anterior and posterior discharge (postnasal drip); broadening of the nasal dorsum [1] may be the result of expanding sinonasal polyposis during growth of the facial features.

An otoscope, routinely used by paediatricians for inspection of the tympanon, can be employed for anterior rhinoscopy. Mucosal status, secretions or crusts can be assessed, e.g. pale mucosa with transparent secretions indicates allergic rhinitis, reddish mucosa indicates viral infection, and purulent discharge indicates bacterial CRS. Pronounced polyposis can also be detected and the overall adequacy of UAW ventilation can be assessed without special apparatus [1,5].

Little information is gained from plain radiographs and the gold standard of sinonasal radiographic imaging is a CT scan, especially for planning surgical interventions. Magnetic resonance imaging (MRI) allows better differentiation of mucosa, polyps and retained secretions than CT but does not display osseous structures [16] and requires more time and cost.

An ear, nose and throat (ENT) specialist should be consulted at the latest when troublesome sinonasal symptoms persist longer then 12 weeks. In fact, an annual ENT consultation is advisable but is most often not part of routine CF care. On the other hand, only an ENT specialist with expertise in CF can serve as a meaningful extension of a CF management team. The ENT specialist should be proficient with differential diagnosis of CF-related RS, including recurrence rates and responsiveness to therapeutic measures.

3.1. Conservative treatment

Therapeutic regimens for CF-related RS are scarce and often lack systematic evaluation. A recent European consensus on rhinosinusitis and nasal polyps gives an extensive general overview of conservative and surgical therapeutic options [5].

Conservative measures are regarded as the initial, less aggressive step in treatment. Although there are some studies concerning different conservative treatment modalities in non-CF CRS patients, very few studies are focused on CF patients and there is therefore very little evidence for the efficacy or dosage of medical treatments for CF-related RS [2]. This presentation focuses on treatments which the authors consider to be of special interest in CF patients.

3.1.1. Nasal saline irrigations

Nasal douches or saline sprays are usually applied as an adjunct to medical treatment in order to remove secretions and crusts from the upper airways. Physiologic saline (0.9%) or buffered hypertonic saline (which additionally contains $NaHCO_3$ and K_2SO_4 as main components and sparse amounts of other ions) is used. Nasal douche is commonly performed while the soft palate is elevated, with 125 mL of fluid for each nostril [17]. A recent Cochrane review [18] concludes that saline irrigation is better than no treatment for improving symptoms and disease-specific quality of life scores in non-CF patients. Although there is evidence that moderately hypertonic solutions improve mucociliary clearance, an advantage of hypertonic over isotonic saline on symptoms is less evident. While there may be some added clinical benefit, this is balanced by patient intolerance. No information can be provided regarding the delivery, dosage frequency or volume of nasal lavage [18] and there are no data regarding nasal application of hypertonic saline in CF patients.

3.1.2. Nasal decongestants

Nasal decongestants (oxymetazoline, phenylephrine and xylometazoline) decrease congestion of the inferior turbinate [19] but do not directly affect the maxillary or ethmoid sinuses. Rebound congestion may occur after use for more then a week, causing physical dependence on the medication

or iatrogenic rhinitis [20]. Thus, decongestants should be applied only as short term medication in acute exacerbations of RS.

3.1.3. Topical steroids

Long term administration of topical steroids is a standard treatment for allergic CRS and eosinophil-dominated nasal polyposis in adults and children [5]. Although CF-related nasal polyps are histologically dominated by neutrophils, which do not respond to steroids, positive effects on CF-related nasal polyps have been reported in smaller studies [21, 22]. This may be the result of the common anti-inflammatory effect of steroids. Larger obstructing polyps usually require surgery [23]. We recommend the application of topical steroids in perioperative care and in CF-related nasal polyps but this field requires further investigation.

3.1.4. Topical antibiotics

The effect of antibiotic treatments in acute and chronic RS unrelated to CF has been evaluated in a Cochrane review [24]. Chronic airway infection in CF is a special entity involving colonization with opportunistic bacteria e.g. *Staphylococcus aureus* and *P.a.* Therefore, CF-specific therapeutic regimens may be required.

Addition of antibiotics to the last portion of nasal lavage in the postoperative care of CF patients has reduced recurrence rates [13]. There are also reports of nasal inhalation of antibiotics by non-CF [25] and CF [26] patients. However, standard nebulisation techniques are generally not expected to reach crucial areas in the UAW due to the narrowness of the sinus orifices. The novel PARI SINUS™ nebulizer designed for sinonasal deposition could give a new perspective to this field (see below).

3.1.5. Macrolides

Macrolides with 14- and 15-membered rings down-regulate immune and inflammatory responses and promote tissue repair by influencing neutrophil chemotaxis and infiltration, inflammatory cytokine production, mucus production, and the transportability of airway secretions. This mechanism is distinct from their antimicrobial properties. The clinical benefit of macrolides in non-CF patients with CRS includes decreased nasal secretion and postnasal drip, and improvement in nasal obstruction [27].

Azithromycin is commonly used to treat *P.a.*-related CF lung disease. Long-term, prospective, double-blind placebo-controlled (DBPC) clinical studies are required to establish the utility of macrolides in the treatment of CF-related CRS [28].

3.1.6. Ibuprofen

Recent studies describe the positive effect of chronic high-dose ibuprofen treatment on the progression of lung disease in children with CF [29]. A small series of CF patients with nasal polyposis who received ibuprofen all reported absence of nasal polyps at some point during treatment, although 42% subsequently required endoscopic sinus surgery for polyposis [30]. More testing is needed to determine if ibuprofen ameliorates CF polyposis.

3.1.7. Dornase alfa

Dornase alfa reduces mucus viscoselasticity and promotes mucus clearance by cleaving long-chain DNA, a viscous substance that reaches high concentrations in CF airway secretions as a result of neutrophilic degradation. Clinically, it reduces the risk of pulmonary exacerbations and improves FEV_1 [31] as well as the annual rate of decline in lung function [32,33] in CF patients over 5 years old.

A DBPC study in early postoperative CF-related CRS reported that nasal symptoms were better controlled by dornase alfa than by isotonic saline when inhaled using a conventional nebuliser: there was significant improvement in rhinoscopic findings as well as FEV_1 [34]. However, the paranasal sinuses are cavities communicating with the nose only via narrow ducts, and therefore surgical enlargement of the orifices is believed to be obligatory to permit conventional nebulisers to deliver drugs to the sinus mucosa.

Aerosols can potentially enter sinus cavities when a pressure gradient is induced by a vibrating air flow [35]. This principle was implemented in the PARI SINUS™, a novel device that targets drug delivery to the PS via a pulsating aerosol with a frequency of approximately 44.5 Hz [36]. In a small (5 patients) DBPC cross-over pilot study we assessed the suitability of endpoints for a larger trial of dornase alfa delivered using the PARI SINUS™ as conservative therapy for CF-related CRS. We found that dornase alfa significantly improved the Sino-Nasal Outcome Test-20 (SNOT-20) score, a QoL measure specific for CRS symptoms [37]. Further research will determine whether this novel conservative approach fulfils its initial promise.

3.2. Surgical therapy

Therapy of chronic nasal obstruction in CF patients relies heavily on surgical measures when conservative approaches fail. In the short term, surgery leads to significant improvement of primary symptoms, e.g. nasal airway obstruction, purulent nasal discharge and olfactory function, as well as secondary symptoms, e.g. activity level [38]. However, these benefits persist in only half of the population [1,39], and recur in 46–100% of patients within 2–4 years [40]. Recurrence seems to be less frequent with more aggressive surgery or with a combination of surgical and conservative measures [13]. Unfortunately DBPC studies on the pre- and/or post-operative management of such patients are missing.

The endoscopic technique employed for nasal sinus surgery in non-CF patients is widely standardised and aims to enlarge the natural sinus opening and remove obstructing polyps. In contrast to classical functional endoscopic sinus surgery, a more aggressive approach is used in CF patients. Surgery also requires meticulous medical aftercare and endoscopic monitoring. Nevertheless, resection of nasal landmarks such as the middle or lower turbinate does not alleviate CRS symptoms.

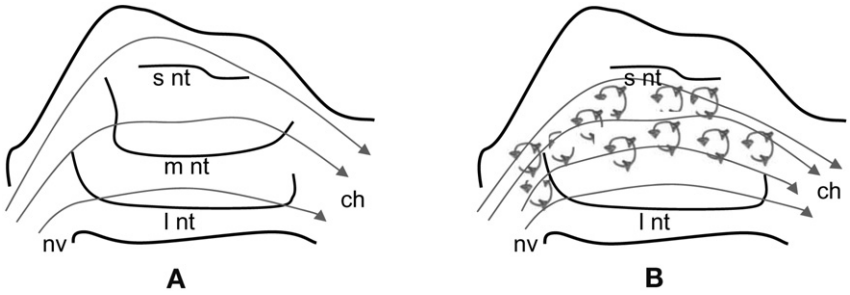

Diagram of nasal landmarks (in black) including the orificium = nasal valve (*nv*), the superior-, middle-, and lower nasal turbinates (*s/m/l nt*) and the choanal area (*ch*). Nasal flow pattern (in grey) with laminar and turbulent nasal inspiratory flow. A: flow pattern with intact nasal airways achieving maximal contact of the inspired air to nasal surfaces. B: flow pattern after surgical resection of the middle nasal turbinate resulting in very high flow rates in some areas and loss of ventilation in others. Adapted from Grützenmacher [46].

On the contrary, this may lead to pathological intranasal airflow patterns (Fig. 1), causing irregular aeration of the nasal mucosa. Thus, some focal areas of UAW mucosa may dry out, leading to discomfort and development of nasal crusts that may further hinder physiological airflow patterns.

Because the recurrence rate after ENT surgery is so high, we suggest that prevention of CRS is as important in CF as optimization of surgery, and that both require a strategy for conservative care of the UAW. Standardised prospective studies of specific surgical techniques versus outcomes are required to assess their effectiveness in CF-related polyposis.

4. Discussion and conclusions

The nasal passages and PS are integral parts of the airways [41]. The strong relationship between CRS and lung disease emphasises the concept of "united airways", which is already accepted in the treatment of common nasal polyposis [11]. In patients with asthma, pulmonary disease is much more difficult to stabilize when they have concomitant CRS [11] and asthma control is significantly improved with medical and/or surgical therapy of UAW disease. The Allergic Rhinitis and its Impact on Asthma working group [42,43], in collaboration with the WHO, has issued a state-of-the-art review and recommendations on the link between rhinitis and asthma. Similar recommendations have been published for upper airway involvement in COPD [44].

In CF patients, potential bidirectional communication between upper and lower airways makes the simultaneous assessment and treatment of all respiratory disease foci mandatory [45]. In contrast to asthma and COPD, pulmonary infection with *P.a.* plays a central role in the progression of CF lung disease.

Due to the lack of available evidence, the evaluation of conservative and surgical therapeutic options for CF-related CRS requires prospective, blinded studies and systematic evaluation of conservative UAW treatments to be of maximum practical utility. This goal can be achieved by integrating standard criteria for assessing UAW symptoms into routine patient examinations in CF centres and the development of guidelines by an interdisciplinary working group comprised of CF clinicians, otorhinolaryngologists, microbiologists and other interested specialists.

Acknowledgements

The work of Sheila McKenzie, who edited this manuscript into idiomatic English of suitable length, was funded by Roche.

Conflict of interest statement

The study on sinonasal inhalation with dornase alfa was supported by Hoffmann-La Roche, Germany and Pari Corp., Germany. This did not influence the study design or the collection, analysis and interpretation of data. We confirm herewith, that the manuscript objective was not influenced by the support received from the above-mentioned companies.

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