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Management of Chronic Rhinosinusitis in Children with Cystic Fibrosis and Primary Ciliary Dyskinesia

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Introduction

Chronic rhinosinusitis (CRS) significantly impacts physical health and quality of life in children. Symptoms, especially in children with complex mucocilliary disorders, may be debilitating and result in respiratory compromise with decreased pulmonary function. While there is no consensus in the literature regarding precise optimal medical therapy for pediatric CRS, medical management typically includes some combination of long-term oral antibiotics, nasal steroids, antihistamines, leukotriene inhibitors, topical nasal antibiotics, hypertonic saline rinses, and oral steroids. Children who fail medical therapy are often referred to Otolaryngology for further guidance and possible surgical intervention. Surgical intervention may include mucosal biopsies to narrow the differential diagnosis, adenoidectomy, or endoscopic sinus surgery including polypectomy. This chapter will discuss the medical and surgical management of CRS in children with complex mucocilliary disorders, specifically cystic fibrosis (CF) and primary ciliary dyskinesia (PCD).

Background

Cystic Fibrosis (CF) is an autosomal recessive disorder with an estimated incidence of 1 in 2000 Caucasians (overall 1 in 30,000 people), with a carrier rate of 1 in 20 in Caucasians. Chromosome 7q31 encodes a protein product, specifically a chloride channel otherwise known as cystic fibrosis transmembrane conductance regulator (CFTR) which is defective in patients with the mutation. The most common CF mutation is known as ΔF508, although nearly 1000 CF mutations have been identified. This abnormal CFTR protein contributes to decrease in mucociliary clearance despite normal ciliary ultrastructure and beat frequency. Chloride ion transport plays a critical role in mucus hydration. For many children with CF, mucus stasis leads to obstruction of the natural ostia of the sinuses, causing mucosal inflammation, entrapped secretions, and ultimately bacterial colonization.

Colonization with the organisms *Pseudomonas aeruginosa* and *Staphylococcus aureus* are most commonly seen in the setting of CF. *Pseudomonas aeruginosa* may actually produce pyocianin which, in vitro, slows ciliary beating. The prevalence of sinusitis in patients with CF may approach nearly 100% (Tandon et al. 2003). Nasal polyposis may occur after age 5 and usually before age 20 (Gysin et al. 2000). Nearly half of patients with CF have CRS for greater than 3 months per calendar year (Gysin et al. 2000), experiencing symptoms which may include rhinorrhea, postnasal drip, anosmia, facial pain, and sleep disorders.

Primary Ciliary Dyskinesia (PCD) is an autosomal recessive disorder with an estimated incidence of 1 in 15,000-20,000 births. PCD consists of defects in ciliary bending resulting in decreased mucociliary clearance. The paranasal sinuses, middle ear, and large airways are lined by ciliated epithelium. Cilia consist of nine peripheral microtubular doublets surrounding a central pair of microtubules that are critical for mucociliary clearance of secretions. Normal ciliary bending results from displacement of adjacent microtubular doublets, which is mediated by adenosine triphosphatase activity. Each dynein generates ciliary movement by means of microtubule sliding.

Healthy human cilia move in a rapid, rhythmic, wavelike motion. In PCD this motion is disrupted, resulting in ciliary immotility and an uncoordinated response with limited bending. To assess for abnormal cilia, samples may be obtained by nasal biopsy of the inferior turbinates, adenoids, or bronchial brush biopsy, with investigation of ciliary beat frequency as well as specific ultrastructural examination for features such as absence of dynein arms (Leigh 2003, Stilllwell et al 2011), absence of radial spokes, or absence of central pair of microtubules in patients with the above clinical features. Up to 20% of children with PCD may have normal ciliary ultrastructure. Biological markers such as nasal NO have been considered for PCD screening. NO has been associated with up regulation of ciliary beat frequency possibly related to stress induced activation of NOS3 enzyme (Davis ME et al. 2001), leading to the hypothesis that decreases in NO may be a contributing factor to the primary ciliary defect (Li D et al. 2000). Mutations in DNAHI1 and DNAH5 genes have also been identified in individuals with abnormal ciliary function (Stillwell et al. 2011) in approximately one third of confirmed cases. Although genetic testing is likely the gold standard for diagnosis of PCD, not all mutations are known or screened for commercially.

Clinical differentiation of sinusitis between PCD and CF may be challenging since many symptoms overlap (**Table 1**). However, physical examination signs such as chronic otitis media, chronic productive cough, and a history consistent of recurrent respiratory infections and bronchiectasis, rhinitis, sinusitis, bronchitis, and pneumonia, are more generally associated with PCD. Kartagener's, a triad of rhinosinusitis, chronic bronchitis with bronchiectasis, and situs inversus may occur in approximately 50% of PCD patients. Specifically, chronic nasal congestion and abundant watery to mucoid nasal secretions starting from the first day of life and rhinitis are common reasons for these children to visit the otolaryngologist especially in the neonatal period, with nasal polyps occurring in approximately 18% to one third of patients with PCD (Leigh 2003, Yoo et al. 2004) most often starting in adolescence (Barbato et al 2009). Purulent nasal secretions are observed in both PCD and CF during active infections and are typically transported by gravity or airflow due to decreased ciliary clearance. Sinusitis with radiographic changes may be seen as early as 6 months of age in children with PCD (Yoo et al. 2004). Interestingly, the severity of symptoms has not been shown to correlate with ultrastructural defects (Barbata et al. 2009) in PCD. The most frequently isolated organism in children with PCD is *H. influenzae*, followed by *S. pneumoniae, S. aureus, P. aeruginosa,* and *Escherichia coli*. In contrast, the most

Table 1: Overview of CF and PCD general characteristics

	Cystic Fibrosis	**Primary Ciliary Dyskinesia**
Defect	Absence of migration of CFTR membrane protein	Microtubule (Dynein arm defect, radial spoke, microtubular transposition defect)
Inheritance	Autosomal Recessive Chromosome 7, DeltaF508 most common	Autosomal Recessive (?Chromosome 6/7)
Prevalence	1 in 2000 Caucasian, 1 in 30,000 persons	1 in 15,000-20,000
Diagnostic Tests	Two positive Sweat Chloride Tests > 60 mEq/L; Genetic testing	Saccharin; Nasal NO levels; Ciliary biopsy with evaluation of ultrastructure and motility by electron microscopy; Genetic testing
Presence of Sinonasal Polyps	6-48%	18-33%

frequently isolated organisms in children with CF are *P. aeruginosa* and *S. aureus*.

Although ideally children are referred for otolaryngology consultation after a mucociliary disorder has already been diagnosed, sometimes CRS is the most prominent feature, having never been formally evaluated for PCD or CF. Diagnostic testing for suspected mucociliary disorders in children with CRS should include immunoglobulins and subclasses, immunologic response to common vaccinations, chest x-ray, age-appropriate pulmonary function tests, sweat chloride testing (CF), and ciliary biopsy with assessment of mucociliary clearance, measurement of ciliary beat frequency, and ultrastructural defects in cilia. Occasionally testing for CF genotype may be required, particularly in the setting of borderline-high sweat chloride responses. Tests of mucociliary clearance may be difficult to perform in very young children. In children older than age 12, saccharin or technetium-labelled albumin may be placed on the inferior turbinate. The time taken for the patient to taste the saccharin is then measured and in healthy patients is less than 1 hour; when radiolabelled albumen in preferred, mucocilliary clearance is measured by a gamma counter (Meeks et al. 2000). Visualization of cilia to differentiate from CF may be undertaken by light microscopy, but should be performed with minimum of 6 weeks following resolution of a respiratory infection for the most accurate results (Meeks et al. 2000). Epithelial cell brushings from the inferior or middle turbinate or biopsies may be performed for examination under electron microscopy for this purpose.

Medical management

General consensus for medical management of CRS in children with CF and PCD is limited. Moreover, because of the rare incidence of PCD, management of CRS in these children is historically modeled after successful treatment described for CF patients. For the purpose of this chapter, management for the two entities will be described concurrently.

Medical management for PCD and CF in the past has consisted of hydration, physical therapy, postural drainage, bronchodilators, antibiotics, interval influenza and pneumococcal vaccines, and routine IV gamma globulin (Parsons et al. 1993). Encouraging regular exercise is important to mobilize mucous and secretions. In PCD, 59% of patients reported recurrent rhinosinsusitis, with an average age of diagnosis age 6.8 years (Sommer et al) compared to nearly 90-100 % of patients with CF. Aerosols such as recombinant human rhDNase, hypertonic saline, or mannitol have questionable effectiveness in PCD (Barbato et al. 2009) and CF. Case reports of PCD patients have used nebulized isotonic NaCl solution with DNase therapy with improved respiratory outcomes, possibly from decreased viscosity from DNA disintegrating from neutrophils in sputum (Berge et al. 1999, Raynor et al. 2000, Tandon et al. 2003). In CF patients specifically, DNAse therapy may decrease the need for revision endoscopic sinus surgery (Raynor et al. 2000). Short beta-agonists have been shown to increase ciliary beat frequency in normal cilia in vitro, but studies are lacking in patients with PCD.

There is general anecdotal agreement for PCD and CF, that routine hypertonic 7% nasal saline irrigations (Mainz et al. 2009) and possibly topical antibiotic lavages for CF patients (Davidson et al. 1995) and anticholinergics for PCD (Barbata et al. 2009, Yoo et al. 2004) improve symptoms. Prolonged macrolide antibiotics for PCD patients and possibly CF patients (Mainz et al. 2009) until symptoms abate may be beneficial for chronic nasal congestion and recurrent sinusitis, but studies are lacking. Macrolides inhibit neutrophil migration and oxidative burst leading to neutrophil apoptosis, thus decreasing mucous viscosity (Hand et al. 1990) in PCD patients, while topical tobramycin in CF patients may be beneficial although studies are scant in regards to CRS. Medical management for CF includes nasal steroids to reduce poly size and load, inhaled glucocorticoids, and prolonged macrolide therapy for their anti-inflammatory properties. Antibiotics to treat CF related organisms which include *P. aeruginosa* and *S. aureus* include aminoglycosides and quionolones. Other acceptable antibiotic choices include piperacillin, ceftazidime, cefsulodin, and imipenem. Antibiotic lavages delivered topically via the nose may have some effectiveness in treating bacterial infections, particularly in the setting of colonization without significant systemic symptoms.

Inhaled nitric oxide may even be bacteriostatic to *S. aureus* as well as improve ciliary beat frequency (Macinelli et al. 1983). The role of topical nasal steroids and antihistamines in these patients is unclear (Stillwell at al. 2011, Yoo et al. 2004), but approximately 50% of patients with PCD and nasal polyposis respond to oral corticosteroids (Yoo et al. 2004). Fewer CF patients respond to topical steroids since nasal polyps in these patients are histologically dominated by neutrophils (Mainz et al. 2009), but may actually respond to ibuprofen (Lindstrom et al. 2007). Topical decongestants (Mainz et al. 2009) may be maintained for up to 4 weeks with acute exacerbations (Yoo et al. 2004), but may cause rebound worsening congestion.

Emerging therapies to modify mucous viscosity in patients with PCD include L-arginine, topical hypertonic saline, mannitol, and uridine-5'-triphosphate

(UTP). UTP may improve chloride ion transport and goblet cell degranulation, thus improving ciliary clearance, while hypertonic saline may improve mucus hydration and stimulate prostaglandin E2 production (Yoo et al. 2004). Manuka honey may have biofilm penetration and thus be helpful in preventing *S.aureus* and *P. aeruginosa* colonization in PCD (Lusby et al. 2005).

Surgical management

Indications for surgery in CF sinusitis include nasal obstruction, polyposis, headache and/or facial pain, lateral nasal wall medialization, pulmonary exacerbations that correlate with sinusitis, and declining pulmonary function tests in the setting of CT evidence of sinusitis that is refractory to medical therapy (Shatz et al. 2006). Studies evaluating outcomes after endoscopic sinus surgery for PCD are scant at best, and outcomes data must be derived from studies evaluating CF patients. Moreover, surgical outcomes for CRS in either CF or PCD have been heterogeneously reported and have been routinely determined in non-randomized, single-institution case series and cohorts. Likewise, outcome measures vary among studies and are more often non-validated and subjective.

At our institution, surgical recommendations for children with CF and PCD are based on the confluence of findings from the best available evidence as well as the individual patient's course, symptoms, and needs. The importance of establishing realistic goals and expectations for outcomes of surgery for children with CF and PCD cannot be overstated. Preoperatively, we discuss with families the risk of recurrence, need for further surgery, and likelihood of some persistent symptoms even in the short-term. Together, with the patient and family, we aim to establish attainable goals of surgical management, which may include the following: improvement in nasal airway and breathing, clearance and lavage of inspissated mucous to alleviate facial pain and headache, allowance for more easily administered antimicrobial therapy through topical nasal administration (thereby avoiding oral or IV antibiotics in some circumstances), less frequent exacerbation of acute rhinosinusitis with symptoms occurring for a shorter period of time, or improvement of lower airway symptoms with decreased occurrence and length and frequency of hospital admissions. We stress to the families that management of CRS in the setting of mucociliary disease is unlikely to be uniformly achieved in a single successful course of therapy, but will rather require a longitudinal relationship among the patient, the family, and the otolaryngologist with expectation for implementing some combination of medical and surgical management as symptoms dictate. Likewise, surgical recommendations are always made following interdisciplinary discussion and consideration of risks and benefits with the treating pulmonologist, immunologist, and pediatrician.

Surgical management of CRS in CF and PCD typically consists of endoscopic sinus surgery and debridement of sinonasal polyps. Surgical removal of nasal polyps in isolation may result in relief of nasal obstruction, but symptoms generally recur within 18 months in 60% of patients and is considered overall ineffective (Crockette DM et al. 1987). When polypectomy is combined with endoscopic maxillary antrostomy and ethmoidectomy, the recurrence rate may be reduced to as low as 10% (Crockette DM et al. 1987). In one study of children with

PCD, over 86% of patients underwent either x-ray or computed tomography for evaluation of the sinuses, with 69% ultimately undergoing surgical intervention (Sommer et al. 2010). Endoscopic surgical intervention is generally recommended in the setting of polyposis, entrapped secretions, with facial pain, headache, fevers, and frequent exacerbations of pulmonary disease (Tandon et al. 2003). We have found use of the Hydrodebrider® Irrigation System (©2012 Medtronic, Inc.) extremely beneficial and superior to standard lavage in clearing inspissated secretions intraoperatively from the paranasal sinuses.

Endoscopic sinus surgery benefits patients in the short term, but unfortunately studies have shown that symptoms often abate in up to half of patients, and frequently recur in 2-4 years (Rowe-Jones et al. 1996, Keck et al. 2007). An important yet understudied benefit of endoscopic sinus surgery may be improved postoperative delivery of topical medications, including hypertonic saline or topical antibiotic irrigations.

Prior to considering endoscopic sinus surgery in children with CF, coagulation profile should be sought since patients may have hepatic involvement and impaired absorption of vitamin K, which should be corrected preoperatively. Regarding surgical anatomy, CF patients have been found to have increased incidence of hypoplastic and aplastic sinuses, with fewer pneumatization variants such as Haller or Agger nasi cells. Observation such as bowing of the maxillary sinus medial wall and resoprtion of the uncincate process is not uncommon (Tandon et al. 2003). In children with CRS without CF or PCD, adenoidectomy is often an effective alternative, first-line surgical treatment (Rosefeld RM 1995). Although the effectiveness of adenoidectomy in children with CF or PCD has not been widely reported or evaluated, this procedure may still have utility, particularly in children with PCD who present for surgical consultation at younger ages. On the contrary, children with CF are most often first evaluated for symptomatic CRS during school-age or adolescent years when adenoid hypertrophy and colonization is less likely to be a precipitating factor in CRS.

Adequate control of CRS is critical to improving upper and lower respiratory symptoms for children with mucociliary disorders. Control of CRS may also ultimately improve eustachian tube dysfunction and recurrent pneumonia. Parsons et al. in 1993 originally described a case series of 3 patients who underwent functional endoscopic sinus surgery for PCD with success and ultimate improvement in respiratory symptoms. Extent of surgery varied from minimal functional procedure to eliminate obstructions caused at the osteometal complex to total sphenoethmoidectomy and enlargement of all natural ostia. Keck et al. in 2007 performed a prospective non randomized clinical trial performing endonasal polypectomy, infudibulotomy, meatal antostromy, ethmoidectomy on 26 children with CF. In this study, polyp and Likert symptom scales both deceased with complete remission of nasal polyposis seen in 21% of patients, improved polyp score in 54% of patients, and a recurrence rate of 15%. (Keck et al. 2007). Similar results were obtained by Jones et al in 1993 with improvement in nasal obstruction and purulent nasal discharge symptoms.

The need for revision endoscopic surgery ranges from 47-72 percent within

the first 2 years (Shatz et al. 2006). A combination of endoscopic surgery and antimicrobial lavage has been shown to reduce need for revision surgery to 10-22% during the first 2 years after initial surgery (Moss et al. 1995). Children refractory to multiple endoscopic procedures have had improvement in symptoms and polyp load by a combined surgical approach consisting of revision functional endoscopic sinus surgery, Caldwell-Luc, and medial maxillectomy (Shatz et al. 2006). Out of 15 children studied by Shatz et al in Israel, there was a significant decrease in the number of hospitalizations, intravenous antibiotics courses, increased mean FEV1 from 70.2% to 89.3%, and marked clinical improvement in several patients. Four patients did not have recurrence of sinonasal polyposis for over 10 years (Shatz et al 2006). Furthermore, it has been demonstrated that after adjusting for socioeconomic status, mean FEV1% predicted and FEV1% improve following endoscopic sinus surgery, but are decreased for children from lower socioeconomic backgrounds regardless of surgical intervention (Kovell et al. 2011). In contrast, endoscopic sinus surgery has also been shown in several studies not to markedly change pulmonary function or have an impact on microbial pathogens, but did reduce hospital admission for 6 months postoperatively (Jarett et al. 2004, Osborn et al. 2011, Rosbe et al. 2001), and reduced hospital admissions per year from 2.12/year to 1.94/year postoperatively (Jones et al. 1993). Improvement in activity level and olfactory function has also been shown post-operatively following endoscopic sinus surgery (Nishioka et al. 1995).

Conclusion

Management of CRS in children with CF and PCD is complex and multifaceted (**Table 2**).

Table 2: Summary of proposed therapies for CRS in children with CF and PCD

	Cystic Fibrosis	Primary Ciliary Dyskinesia
Hypertonic Saline	*	*
rhDNase	*	*
Macrolide Antibiotics	*	*
Inhaled NO	N/A	*
Oral Corticosteroids	*	*
Ibuprofen	*	N/A
Topical Abx	*	*
Prolonged Oral Antibiotics	*	*
UTP	N/A	*
Adenoidectomy	N/A	*
Inferior antrostomy	N/A	*
Endoscopic Sinus Surgery (which may include): maxillary antrostomy & ethmoidectomy, polypectomy, infudibulotomy	*	*

*Suggested proposed therapy

In general, uniform, multi-institutional, prospective or controlled data as to long-term effectiveness of medical/surgical therapy for CRS in CF or PCD is lacking. Endoscopic sinus surgery is frequently performed in children with PCD or CF, however outcome measures for success are variable, and need for recurrent surgery is common. Treatment for CRS in these children should mirror the best available evidence but also be tailored for the individual child. Realistic expectations as to the course of CRS treatment and outcomes for children with CF or PCD should be established at baseline, with emphasis on shared-decision making in treatment decisions, realistic goals of therapy, and a longitudinal relationship with the patient, family, otolaryngologist, and surrounding specialists.

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