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Mini-symposium: Primary Ciliary Dyskinesia

Treatment recommendations in Primary Ciliary Dyskinesia

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EDUCATIONAL AIMS

The reader will come to appreciate that:

- Clinicians should be aware that there are currently no evidence-based treatments for PCD
- Most recommendations for medical treatments and airway clearance are extrapolated from CF and non-CF bronchiectasis literature
- Daily airway clearance and antibiotic treatment of infectious exacerbations are the cornerstone of PCD treatment
- Routine screening should include pulmonary function testing, microbiological surveillance of sputum, audiometry testing, and health prevention strategies such as routine vaccinations for pneumococcus and influenza virus

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SUMMARY

Primary Ciliary Dyskinesia (PCD) is a rare heterogenic disorder leading to significant respiratory morbidity. Health-care providers who treat PCD must familiarize themselves with recommended treatment strategies. However, most of the treatments recommended in PCD have been extrapolated from cystic fibrosis (CF) and non-CF bronchiectasis literature. Mainstays of therapy are reviewed in detail, and should include at a minimum: regular airway clearance, routine microbiological surveillance, antibiotic treatment for pulmonary exacerbation, and health vaccinations. This review summarizes both medical and surgical pulmonary treatment considerations, as well as recommendations for the integration of non-pulmonary subspecialty care in the management of PCD.

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As an orphan disease, Primary Ciliary Dyskinesia (PCD) has historically been lacking in clinical trials evaluating therapeutics and management. To date, there are no evidence-based treatment guidelines informed by randomized clinical trials in patients with PCD. Accordingly, most current treatment recommendations in PCD are extrapolated from the cystic fibrosis (CF) and non-CF bronchiectasis literature. This narrative review represents a detailed evaluation of literature identified in PubMed and Cochrane databases, with a focus on clinical trials in CF and non-CF bronchiectasis, observational studies in PCD, and expert opinion of the authors. Given the broad nature of our topic and the lack of clinical trials in patients with PCD, we did not conduct focused systematic reviews and evidence grading of individual interventions.

INTRODUCTION

Before embarking on the treatment of PCD, the initial task of verifying correct diagnosis is paramount in this frequently misdiagnosed disease. As addressed in other portions of this mini-symposium, a thorough diagnostic evaluation should be performed to rule out alternative etiologies including, but not limited to: CF, immune deficiency, aspergillus or tuberculosis infection, chronic gastro-esophageal reflux with aspiration, and alpha1-antitrypsin deficiency [1]. Once a diagnosis of PCD has been ascertained, it should be recognized that treatment recommendations are based on biological rationale and extrapolated from other diseases associated with bronchiectasis (Figure 1). Further,

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consideration must be given to individual patient characteristics and preferences in order to optimize treatment plans.

AIRWAY CLEARANCE

Due to the underlying impairment of mucociliary clearance in PCD, regular airway clearance should be a mainstay of treatment. In comparison to CF, persons with PCD have a preserved or improved cough clearance [2,3] affording better opportunity to rid the airways of excessive mucus and potentially pathogenic bacterial burden. In addition to forced cough and breathing techniques, a variety of manual devices also exist to aid in chest physiotherapy and mucus clearance. These include positive expiratory pressure valves, and mouthpiece or chest wall oscillating devices. Each of these oscillating devices is used to improve airway-opening and loosen and thin mucus, followed by forced expiration with cough to complete mucus clearance. A recent meta-analysis in CF comparing multiple forms of oral and chest wall physiotherapy demonstrated no superior form of chest physiotherapy over another in outcome measures of forced expiratory volume in 1 second (FEV_1), frequency of exacerbations, or patient satisfaction [4]. Patient age, experience, and preference should all be taken into consideration in recommending forms of airway clearance or modalities. Irrespective of the chosen modality, routine daily performance of airway clearance is advised, and should be reviewed frequently with patients. Exercise should also be routinely recommended in PCD. Decreased pulmonary function in PCD has been associated with poor exercise tolerance [5] and it is conversely expected that routine exercise may improve lung function. Indeed, performing exercise prior to airway clearance may enhance mucociliary clearance. In a study of children with PCD, exercise was shown to be superior to short acting bronchodilator use resulting in superior peak expiratory flow rates [6]. A regimen of exercise and airway clearance may thus produce the most beneficial effects, and should be the foundation of treatment.

MEDICAL THERAPIES (TABLE 1)

Antibiotics & Microbial Surveillance

Patients with PCD should have routine clinical visits with surveillance of microbial organisms through sputum cultures and in those that are not able to expectorate, oropharyngeal cultures. Culture results will help in treatment of specific pathogens that are known to cause deterioration (in other chronic suppurative lung diseases) and potentially lead to bronchiectasis. In the pediatric and adult population, 2 to 4 visits per year are recommended. During clinical visits, an oropharyngeal swab or sputum culture should be obtained to screen for bacterial organisms which frequently also affect patients with CF, including *Pseudomonas aeruginosa*, and acid fast bacilli such as non-tuberculous mycobacteria. It is advisable for sputum and oropharyngeal cultures to be processed in a similar fashion to CF sputum cultures with biannual to quarterly "routine" bacterial cultures, and a minimum of annual culture testing for acid-fast bacilli. However, patients with PCD also have predominance of sputum culture growth with *Staphylococcus aureus*, *Streptococcus pneumonia* and nontypeable *Haemophilus influenza* [7,8]. In certain laboratories, culture processing for CF sputa may not select for these organisms. It may be advisable to request particular attention to organisms such as *Streptococcus pneumonia* and *Haemophilus influenza* in PCD sputa based on the specific laboratory processing the sample.

In the case of acute respiratory exacerbations of PCD, antibiotics should be used, and the selection of antibiotics should be tailored

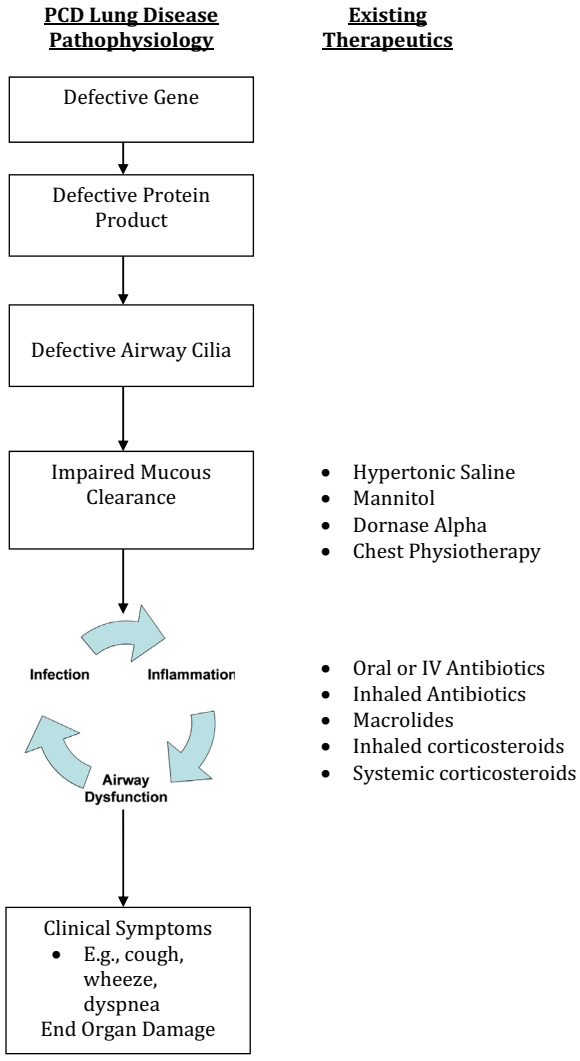

Figure 1. Pulmonary Pathophysiology and Therapeutic Options.

toward culture history and microbial sensitivity. Acute exacerbations may be defined similarly as in CF or non-CF bronchiectasis by hallmark symptoms such as: an increase or change in wet cough and/or cough severity, sputum color, chest pain, dyspnea, and/or hemoptysis [9]. A decrease in lung function may also indicate presence of a pulmonary exacerbation. Whereas mild exacerbations may be treated with oral antibiotics and increased aggressive airway clearance, either severe or refractory exacerbations may require intravenous antibiotics and inpatient hospitalization. A duration of 14-21 days of total antibiotic therapy is recommended in PCD, as is typically performed in analogous respiratory diseases such as CF [10,11] and non-CF bronchiectasis [12]. It is recommended that airway clearance is augmented during the treatment period to accelerate mucus and bacterial clearance from the airways [10].

Inhaled Antibiotics & Eradication of Pseudomonas aeruginosa

There have been no studies of inhaled antibiotic use in PCD. However, extrapolating from the CF experience in eradication of *Pseudomonas aeruginosa* [13], use of inhaled tobramycin (300 mg nebulized twice daily) for a 28 day period should be considered upon the first evidence of *Pseudomonas aeruginosa* growth. Nebulized gentamicin (80 mg inhaled twice daily) may also be

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