sinusitis

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Review

A Systematic Review of the Treatment of Chronic Rhinosinusitis in Adults with Primary Ciliary Dyskinesia

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Abstract: Background: Primary ciliary dyskinesia (PCD) may be an underlying factor in some cases of refractory chronic rhinosinusitis (CRS). However, clinical management of this condition is not well defined. This systematic review examines the available evidence for the diagnosis and management of CRS in adults with PCD. Methods: A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Pubmed, EMBASE, and Cochrane database were queried for studies pertinent to treatment of PCD in adults. Two investigators performed eligibility assessment for inclusion or exclusion in a standardized manner. Results: Of the 278 articles identified, six studies met the criteria for analysis. These studies had a predominately low level of evidence. Medical therapy included oral antibiotics and nasal saline rinses. Endoscopic sinus surgery (ESS) was described in three of six studies. Outcomes measures were limited and included non-validated questionnaires, subjective reporting of CRS symptoms, and decreased preciptins against pseudomonas following ESS. Recommendation for a standardized therapeutic strategy was not possible with the available literature. Conclusion: A paucity of evidence is available to guide the treatment of PCD in the adult population. Further prospective studies are needed to determine the optimal diagnostic and management strategy for this condition.

Keywords: primary ciliary dyskinesia; kartagener's syndrome; chronic rhinosinusitis

1. Introduction

Primary ciliary dyskinesia (PCD) is a heterogeneous disorder of ciliary ultrastructure resulting in decreased mucociliary clearance. Ciliary immotility and defective ciliary ultrastructure were initially described by Afzelius in 1976 [1], with subsequent studies demonstrating uncoordinated or ineffective ciliary beat. These ciliary abnormalities result in chronic oto-sino-pulmonary disease including bronchiectasis, rhinitis, sinusitis, bronchitis, pneumonia, and chronic otitis media [2]. The triad of situs inversus, bronchiectasis, and rhinosinusitis, known as Kartagener's syndrome, occurs in approximately 50% of patients with PCD [2,3]. A rare disorder, PCD is thought to have an incidence of 1 per 10,000 to 20,000 births, though, current diagnostic and screening tests such as nasal nitric oxide, ciliary electron microscopy, molecular genetic panels, and ciliary motility studies are often difficult to interpret outside of highly skilled PCD centers [4–6].

Symptoms often begin shortly after birth and are chronic in duration. Sino-nasal symptoms vary but it is estimated that chronic rhinosinusitis (CRS) affects over 50% of patients with PCD, with 15%–40% suffering from nasal polyposis [7,8]. Symptoms of CRS in PCD may be debilitating,

as patients suffer from purulent nasal secretions and pansinusitis. Sinusitis may be missed in children due to lack of radiographic imaging [9]. Worsening pulmonary function and respiratory compromise may occur, with bronchiectasis appearing in nearly all adults. The findings of bronchiectasis with chronic sinusitis may be the most identifiable features in an adult with PCD without childhood diagnosis [6].

The treatment of CRS in adults with PCD is difficult given disparate literature and rare incidence of the disease. Adults with PCD are at high risk for pulmonary complications including bronchiectasis and aggressive treatment and monitoring may be necessary. Medical and surgical therapies may be utilized, but outcomes are poorly defined. Recent review on the management of CRS in children with PCD demonstrated similar challenges [10]. A systematic review was performed to evaluate the existing literature on the treatment and outcomes of CRS in adults with PCD.

2. Materials and Methods

A comprehensive, qualitative systematic review of English-language literature was conducted to investigate treatment of CRS in adults with PCD. A search was performed using Pubmed, EMBASE, and Cochrane CENTRAL database. Inclusion criteria for the literature search were defined using the Population, Intervention, Control, Outcome, Study Design (PICOS; Table 1) approach. Search was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection process [11]. The initial search included combined key terms and exploded Medical Subject Headings (MeSH) terms. MeSH terms addressed included: primary ciliary dyskinesia, Kartagener's syndrome, sinusitis, rhinitis, rhinosinusitis, functional endoscopic sinus surgery, and functional endoscopic sinus surgery (FESS).

Table 1. Population, Intervention, Control, Outcome, Study Design (PICOS) Inclusion Criteria.

Population	**Adult (>18 Years Old) Men and Women**
Intervention	Treatment of sinusitis in primary ciliary dyskinesia (PCD)
Control	No comparison group
Outcome	Results of treatment i.e., improvement or worsening of symptoms
Study Design	Case Report, Case Series, Cross-Sectional, Retrospective Cohort, Prospective Single-Arm Trial

Two investigators performed eligibility assessment for inclusion or exclusion in a standardized manner. Studies were included if they contained findings related to the medical or surgical treatment of CRS in adults with PCD. Duplicate records, review articles, articles without an abstract, and non-English articles were removed. Full text articles were reviewed and excluded if they contained pediatric patients only, if the article was unrelated to treatment of sinusitis in PCD, or lacked original patient data.

Data gathered from each article included study design, setting, type of therapy for CRS (medical or surgical), and treatment outcomes. Studies were assessed for bias by examining each study for design, source of patient data collection, and author's stated purpose for the study. Information collected from each article also included year of publication, authors, country of origin, patient population, and number of patients included. Findings were analyzed qualitatively for intervention, outcome assessment, results, and limitations. The level of evidence was determined according to guidelines defined by the Center for Evidence Base Medicine (CEBM) to provide an estimate of the strength of study design [12]. PRISMA guidelines were used for systematic literature review as seen in Figure 1.

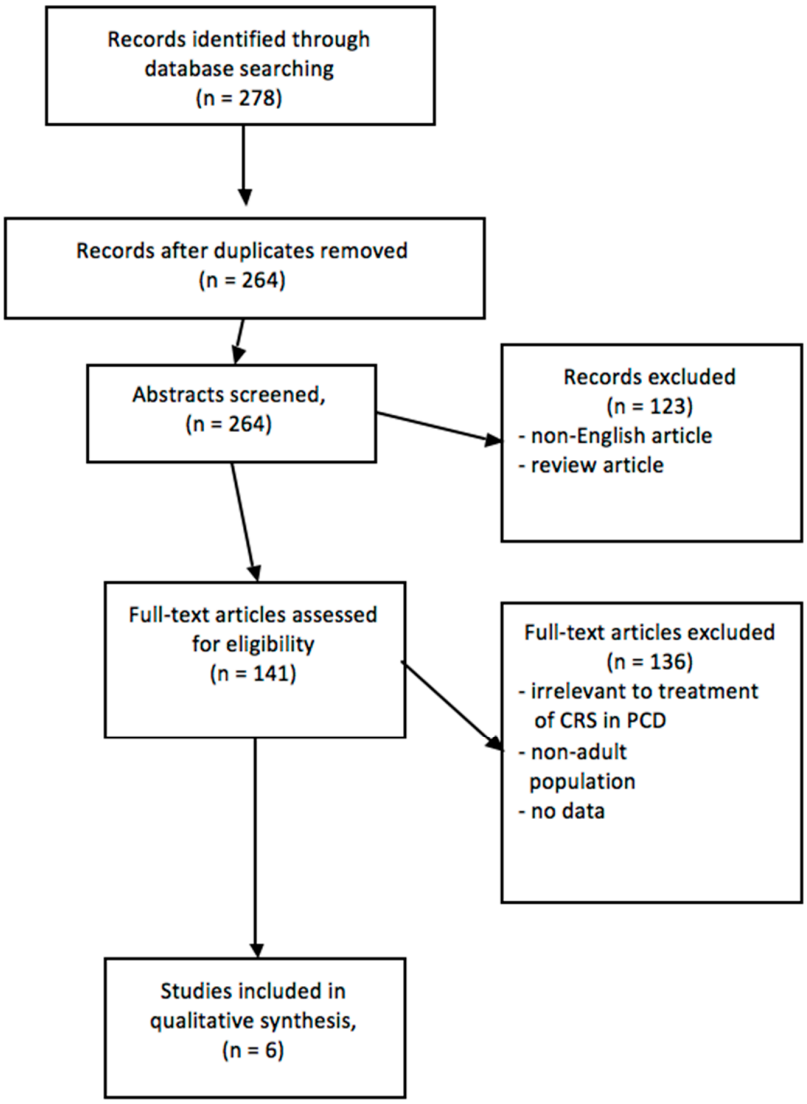

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram literature selection process. CRS: chronic rhinosinusitis; PCD: primary ciliary dyskinesia.

3. Results

The initial database query identified 278 articles. After screening and removal of duplicates, 141 articles were included for full-text review. A total of 136 articles were then excluded for irrelevance to treatment of CRS in PCD, non-adult population, or insufficient data. Manual searching of reference lists of the full text articles yielded no additional eligible studies. One study was published after the original search date and subsequently included. Six studies were included for qualitative analysis.

The six studies with direct thematic relevance to CRS in adult are summarized in Table 2. These manuscripts included one prospective single-arm trial [13], one retrospective cohort study [14], one cross-sectional study [7], two case series [15,16], and one case report [17]. The number of people included in each study ranged from one to 44. Antibiotic therapy was addressed in four studies, with two studies describing on treatment with long-term macrolides. Four studies addressed surgical treatment and outcomes including endoscopic sinus surgery. Outcome measures utilized for assessment included lung infection status (1 study), precipitins against pseudomonas (2 studies), author-created questionnaire (1 study), chest computerized tomography (CT) findings and/or pulmonary function (3 studies), arterial blood gases (1 study), and physical symptoms (5 studies).

Table 2. Summary of studies meeting criteria for qualitative analysis. CT, computerized tomography. FEV1, forced expiratory volume in 1 s. PCD, primary ciliary dyskinesia. PE, pressure equalization. SNOT: sinonasal outcome test.

Study	N	Setting	Level of Evidence	Intervention	Outcome Assessment	Results	Limitations
Alanin et al., 2016	24	Denmark	3	Endoscopic Sinus Surgery	SNOT-22, spirometry, precipitins, BMI, infection status of upper and lower airways	Improvement in CRS-related symptoms, reduced lung infection	Small, lacks control group
Alanin et al., 2015	8	Denmark	3	Endoscopic sinus surgery	Number of precipitins against *Pseudomonas* pre- and post-operatively	Reduced precipitins in $\frac{3}{4}$ patients after surgery	Small number of adults, pre and post-operative testing not performed in all patients
Kido et al., 2012	2	Japan	4	Long-term macrolide therapy	Chest CT findings, FEV1, physical symptoms	Improvement of outcome assessments in one case, decline in the other	Small case series
Mygind et al., 1983	27	Denmark	4	Antibiotics, nasal saline, sinus surgery, PE tube insertion	Physical symptoms	Improvement of sinonasal symptoms with antibiotics, nasal saline, and sinus surgery (Caldwell-Luc)	Case series, subjective outcome measures
Sommer et al., 2010	44	Germany	3	Antibiotic treatment, sinus surgery, tympanostomy tube placement	Questionnaire of treatment history in adults with PCD	19% needed antibiotics up to 10 times, 24% up to 30 times and 32% more than 30 times. 69% of patients underwent sinus surgery	Lack of age-specific data, non-validated questionnaire
Yoshioka et al., 2010	1	Japan	5	Long-term clarithromycin	Physical symptoms, pulmonary function, arterial blood gases, chest CT findings	Improvement in all outcome assessments	Single case report, subjective outcome measures

4. Discussion

There is a paucity of literature related to treatment and outcomes of CRS in adults with PCD. A recent consensus statement by the PCD Foundation noted the lack of randomized, controlled, or long-term prospective studies on CRS in PCD [6]. Data on outcomes of medical and surgical therapy is limited [6,10]. Standardized therapy has yet to be described, although the PCD foundation is making a strong effort towards a multi-disciplinary approach to improve long-term outcomes [6].

Medical management of CRS in adults with PCD is ill defined, and no consensus currently exists. Treatment of cystic fibrosis (CF), another recessive genetic disease with impaired mucociliary clearance, has been more substantially studied [18–22]. Intranasal glucocorticoids have been demonstrated to decrease nasal obstruction and nasal polyp size in CF patients [19]. Nasally nebulized dornase alfa, culture directed oral or systemic antibiotics, and topical antibiotic irrigation have all demonstrated benefit in CF patients after sinus surgery [20–22]. Less data is available for PCD, but current guidelines for general treatment of include daily chest physiotherapy and cardiovascular exercise as routine therapy, with antibiotics reserved for acute exacerbations [6,23,24]. Additionally, vaccination schedules should be followed, including annual influenza and pneumococcal vaccines [25,26]. General therapies utilized on an individual basis include inhaled or oral long-term suppressive antibiotics, inhaled hyperosmolar agents, deoxyribonuclease, and inhaled bronchodilators [6]. Long-term macrolide therapy has demonstrated some benefit in CRS patients [15,17], but robust data is lacking. Nasal saline is recommended for patients with CRS, and may improve symptoms in patients with PCD, although no studies exist examining their direct benefit.

A high percentage of PCD patients suffer from CRS and nasal polyposis, which can significantly affect quality of life. A recent study developed a metric to assess health-related quality of life in adults with PCD [27], demonstrating the multi-dimensional effects of the disease, including treatment burden and its effects on social and emotion functioning. Endoscopic sinus surgery (ESS) has been shown to help improve quality of life, lung infections, and lung function in adults with PCD [13], and the performance of ESS demonstrated benefit to children with PCD in one study [28], but outcomes in both children and adults are poorly defined, with high variation from study to study. The rarity of the disease makes long-term prospective studies difficult to perform, highlighting the need for multicenter data sharing. It is possible that ESS may decrease the need for numerous courses of antibiotics and allow for improved drug delivery for better disease control. However, the lack of evidence-based literature makes it difficult to provide any treatment recommendations or clinical practice guidelines.

Limitations of this review include the relatively small number of studies meeting inclusion criteria and low level of evidence based on CEBM criteria. The total number of patients in the studies was small (106) and dominated by single-institution case series. The limited number of studies and small sample size eligible for systematic review highlight the lack of available literature and may help guide further study. The use of a non-validated questionnaire further dampens the validity of treatment assessment. Validated outcome measures in future studies in this population are necessary to assess preoperative disease burden, response to medical and surgical treatment, and long-term outcomes. BESTCILIA, a European Commission funded consortium dedicated to improving care of PCD, is currently conducting a prospective study investigating long-term macrolide therapy in PCD patients [29]. Similar prospective studies will be needed to provide evidence for formal treatment recommendations.

5. Conclusions

The findings of this systematic review demonstrate a lack of evidence-based literature documenting the treatment and outcomes of PCD in adults. There is currently only one long-term prospective study of treatment of this rare disease. Efforts should be made toward a database for prospective data collection, which would allow for long-term multicenter studies investigating the treatment and outcomes of CRS in adults with PCD.

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Conflicts of Interest: The authors declare no conflict of interest.

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