**Abstract (185/200 words)**

**Introduction:** Primary ciliary dyskinesia (PCD) is a rare heterogeneous disorder, usually inherited as an autosomal recessive condition bur X-linked inheritance is also described. Abnormal ciliary function in childhood leads to neonatal respiratory distress in term infants, persistent wet cough, bronchiectasis, chronic rhinosinusitis, and hearing impairment; approximately 50% of patients have *situs inversus*. There is paucity of evidence for treating PCD, hence consensus guidelines are predominantly influenced by knowledge from cystic fibrosis (CF). Extrapolation of evidence from other diseases is inappropriate since differences in pathophysiology, morbidity and prognosis risk treatment failure and lack of adherence.

**Areas covered:** Review authors searched PubMed and Cochrane data bases for publications relating to management of children with PCD. Because of the paucity of data we emphasise the need for well-designed clinical trials with PCD patients, rather than reliance on evidence from other diseases.

**Expert commentary:** The evidence for treatment of PCD is poor, and management is often extrapolated from studies of patients with CF or chronic rhinosinusitis. However, much work is underway to improve the situation and international consortia and networks are conducting well-designed projects to inform the management of children with PCD.

**Key Words:** primary ciliary dyskinesia, PCD, Kartagener, therapy, management, microbiology, transition, rare diseases, review

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**Abbreviations**

active cycle of breathing technique: ACBT

acute otitis media: AOM

chronic rhino-sinusitis CRS

cystic fibrosis: CF

cystic fibrosis transmembrane conductance regulator: CFTR

ear, nose and throat doctor: ENT

endoscopic sinus surgery ESS

European Respiratory Society: ERS

high resolution computer tomography: HRCT

international PCD cohort study: iPCD

lung clearance index: LCI

mucociliary clearance: MCC

nasal polyps: NP

otitis media with effusion OME

recombinant human DNase: rhDNase

positive expiratory pressure: PEP

primary ciliary dyskinesia: PCD

QOL questionnaires for PCD: QOL-PCD

ventilation tubes: VT

# Introduction

Primary ciliary dyskinesia (PCD) is a genetically and clinically heterogeneous disorder, usually inherited as an autosomal recessive condition [1]. Abnormal ciliary function leads to slow onset neonatal respiratory distress in term infants, persistent wet cough, bronchiectasis, chronic rhinosinusitis (CRS), fertility issues and conductive hearing impairment. A little less than 50% of patients have *situs inversus* and congenital heart disease has been reported to occur in 5% of children [2]. Whilst there is little data relating to the long-term outcomes for patients with PCD, it is evident that disease progression is highly variable, with some patients maintaining reasonably good lung function and quality of life into later adulthood, whilst others have worse outcomes leading to respiratory failure and lung transplantation [3-5].

The prevalence of PCD is not clearly established, but it is estimated to affect approximately 1:10,000 Europeans [1], with a significantly higher incidence in populations with closed genetic pools [6]. A European survey of PCD specialists found that only a small fraction of expected PCD patients had been diagnosed [7], and an international survey of patients reported that 37% of patients had visited a doctor with PCD related symptoms more than 40 times before being referred for testing [8]. The reasons for under-diagnosis are multi-factorial. Paediatricians rarely see a case, and their awareness of PCD is therefore limited. Symptoms are non-specific, and only patients with situs inversus, a rare condition in the general population, are diagnosed at an earlier age [7]. There is no gold standard diagnostic test and diagnosis therefore depends on a combination of tests including nasal nitric oxide, high-speed video microscopy, transmission electron microscopy, genetic testing and immunofluorescence staining of ciliary proteins [9]. These diagnostic tests are highly specialised and patients often need to travel considerable distances to attend a diagnostic centre.

As with other ‘orphan diseases’, the evidence base for therapeutics and management is lacking, hence consensus guidelines are generally based on clinical trials involving patients with cystic fibrosis (CF) and small observational studies in PCD [10,11]. Extrapolation of evidence from other diseases is regrettable since differences in pathophysiology, morbidity and prognosis might lead to treatment failure, lack of adherence and side effects. Moreover we need to consider the heterogeneous nature of PCD; therapies that work in some patients might not work in all. In this review, we discuss current management strategies for children with PCD emphasising the urgent need for methodologically-sound, randomised clinical trials to enhance the evidence base for treatment. Since the management of PCD is predominantly based on experience from patients with CF, we discuss similarities and differences between these diseases throughout the review. The manuscript is not a systematic review but provides the authors’ expert knowledge of the disease area; in preparation for the review we searched PubMed and Cochrane data bases for publications relating to management of children with PCD.

# Pathophysiology of PCD and CF

PCD is characterised by a failure of mucociliary clearance (MCC) and is usually inherited in an autosomal recessive pattern, with X-linked inheritance also reported. Biallelic mutations in >35 cilia related genes have been proven to cause PCD (listed in [12]); these genes only account for ≈65% of cases, so many more genes have yet to be discovered [12]. The mutations lead to abnormal ciliary beating which is usually but not always associated with abnormal ciliary ultrastructure seen by transmission electron microscopy. The dysfunctional cilia prevent efficient MCC [13,14].

Cystic fibrosis is also an autosomal recessive disorder which leads to impaired MCC, but the underlying pathophysiology differs from PCD. CF is the result of mutations in one gene causing dysfunction of only one protein, the cystic fibrosis transmembrane conductance regulator (CFTR). Despite the identification of over 2000 mutations in the CFTR gene, at least one copy of the commonest mutation (p.Phe508del) is found in over 90% of CF patients in the UK. CF therefore contrasts markedly with PCD where a number of genes are causative and each of genes may carry a large number of different mutations. There will therefore be a much higher degree of heterogeneity between PCD patients than CF patients. The net result of CFTR dysfunction is abnormal chloride efflux from the epithelial cell with associated abnormalities in sodium influx and defects in bicarbonate transport [15-17]. However, abnormal CFTR also appears to have intracellular effects that result in impaired mucociliary transport and defects in innate immunity [18].

Although inflammation in CF airways may be present from birth [19], CF patients have preserved MCC in early life [20]. This is in contrast to PCD where MCC is a primary defect, absent from birth. It has been suggested that MCC becomes impaired in CF only after a “2nd hit” [20]. Using piglet models of CF, particle clearance was shown to be identical to wild-type airways at baseline but following cholinergic mucus stimulation, the mucus strands remained abnormally tethered to the submucosal glands and prevented clearance [21,22]. Impaired MCC in CF can therefore start following infection or inflammation.

Studies directly comparing CF and PCD are limited. Mucus from CF and PCD patients was compared by Bush *et al* who found that IL-8 concentrations were significantly higher in PCD patients, but with no differences in physical or transport properties of the mucus [23].This is contrary to the idea that CF mucus viscosity accounts for more severe airway inflammation and failure of MCC, instead supporting the theory mentioned above that it is abnormal tethering of mucus to the epithelium that may inhibit airway clearance in CF. Ratjen *et al* compared inflammation in CF and PCD sputum from children with respiratory exacerbations. Neutrophils were more abundant, with higher neutrophil elastase activity in PCD than CF sputum. Interestingly, this was responsive to oral antibiotic treatment in PCD but not in CF [24].

It is also known that nasal nitric oxide levels differ in the PCD and CF airways. Whilst CF patients have lower nasal NO levels than healthy subjects, this is still much higher than that seen in PCD [25]. The causes and downstream effect of this difference in NO is not entirely clear, but might result in differing response to infection/inflammation in the airways of PCD and CF patients.

# Management of children with primary ciliary dyskinesia

There is no cure for PCD and management therefore aims to optimize health, social and psychological wellbeing whilst preventing progression of lung damage. There have been few clinical trials in PCD and management is empirically based on other diseases such as CF and CRS. Consensus guidelines are based on the experience of specialist centers in Europe and North America [10,11]. Patients should be looked after in specialist PCD centers by a multidisciplinary team which includes as a minimum a pediatric pulmonologist, an ear nose and throat (ENT) doctor and respiratory physiotherapists [9,10]. In this review we will discuss pulmonary management, which is based on airway clearance and treatment of infections, and ENT management of rhinosinusitis and ear disease. We then review the options for monitoring disease in children with PCD. We will also discuss the role of a transition program to prepare the child and family for transfer to adult services.

## 3.1.Lower airway clearance therapy

Since impaired MCC is the fundamental problem in patients with PCD, therapies to facilitate mucus clearance from the airways are central to reducing stasis of secretions, occurrence of infections, atelectasis, inflammation and progressive lung disease. A respiratory physiotherapist should tailor the airways clearance technique to the individual, taking into consideration the age of the child, patient preference, ability, mucus properties and disease severity. Regular review by a physiotherapist will allow the technique to be adapted as needed e.g. transition from parent delivery of treatment to independent methods, change of techniques where adherence is an issue. Airway clearance is usually recommended twice daily with increased sessions during exacerbations; this can be a significant burden to families [26,27] and poor compliance can be an issue. Unlike CF, impaired MCC is present from birth. With newborn screening, CF patients are usually diagnosed before MCC has been discussed, and it has been questioned whether airway clearance should be started in asymptomatic infants at diagnosis [28]. In contrast, PCD patients are usually symptomatic from birth [29], are often referred for diagnostic testing late and the diagnostic process can be protracted [7,8]; therefore airway clearance therapy should undoubtedly be started as soon as a diagnosis of PCD is thought likely.

A range of airway clearance interventions are available including breathing techniques, manual techniques, positioning, positive expiratory pressure (PEP) adjuncts and oscillatory-PEP [30]. Combinations of techniques are often used, for example a combination of active cycle of breathing technique (ACBT) can be used in combination with an oscillatory-PEP device. ACBT aims to improve ventilation throughout the airways and mobilize mucus from smaller to large airways from where it can be expectorated using a cough. PEP aims to open airways, improving ventilation of small airways, whilst the oscillatory device causes vibrations in the airway which are thought to improve mucus flow and enhance clearance. A recent systematic review found only one clinical study which compared different airway clearance techniques in PCD patients [30]. A randomized cross-over design was used to compare high frequency chest wall oscillation (vest therapy) for five days at home, with postural drainage percussion and vibrations performed by a physiotherapist for 5 days in a hospital setting [31]. Both groups had improved lung function but there was no significant difference between techniques.

A number of nebulized treatments have been shown to assist mucus clearance in patients with CF. As already discussed, the pathologies underlying PCD and CF are different, and treatments to alter the properties of mucus and its clearance may not be similarly effective. For example recombinant human DNase (rhDNase) lyses neutrophil DNA which originates mainly from decaying neutrophils at sites of airway inflammation. There is good evidence for its use in CF [32] but the support for use in PCD is limited to a few case reports [33,34]. Importantly a large study of patients with non-CF bronchiectasis showed faster decline in FEV1 and more frequent exacerbations in patients who received rhDNase in comparison to those treated with placebo [35]. Until a well-designed study is undertaken in PCD the role of rhDNase is therefore unclear and not generally recommended.

Osmotic agents such as hypertonic saline are also used in CF to assist with mucus clearance as an adjunct to airways clearance therapy. Recently the first randomized clinical trial in PCD [36], explored the effect of hypertonic saline on the quality of life (QOL) of 22 adults in a double-blind cross over trial. At the time of the trial there was no disease specific QOL measure and results were therefore based on the St George’s Respiratory questionnaire (SGRQ) which was not designed for patients with PCD. The study showed no significant effect of hypertonic saline on SGRQ score. However the study population was small particularly given the non-specific outcome measure, and larger studies are required using outcome measures which are validated in PCD [26,37,38].

Two studies have suggested that aerobic fitness might be reduced in children with PCD [39,40]. Since exercise is good for general wellbeing, and might assist bronchodilation [41] it is important to encourage PCD patients to exercise regularly. However there is no evidence that exercise adequately clears airway secretions of PCD patients and it should be used in combination with, not as an alternative to, airway clearance therapies.

*3.2. Management of airway infections*

We will firstly review what is known about the microbiology of the PCD airway, and will then discuss management strategies.

*Haemophilus influenzae* is the most frequently isolated pathogen from the airways of PCD patients [5,42-44]. It infects 40-80% of PCD patients annually [42], while *Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, Achromobacter xylosoxidans and Burkholderia spp* are less prevalent [42,43]. Non-tuberculous mycobacteria may be cultured in up to 10% of PCD patients [5,45]. In cross-sectional studies *Pseudomonas aeruginosa* has been isolated in approximately 10% of PCD patients [5,43,45]. Recent studies have found increasing prevalence of *P. aeruginosa* with age and dominance in adults [3,42]. Data is limited but increasing bacterial diversity with age has been reported [42]. A strong age dependent bacteriology also occurs in CF, but in contrast to PCD the bacterial diversity decreases with age [46].

The reported prevalence of chronic infection with *P. aeruginosa* varies in PCD with reports ranging from 5% to 39% [4,42,43,47]. This might partly reflect the lack of consensus about the definition of chronic infection for PCD; the Leeds Criteria are widely used to define chronic infection in CF, and a consensus approach is also warranted for PCD to aid guidelines on strategies for antibiotic therapy and for comparing and designing clinical studies. According to the 2013 European Cystic Fibrosis patient registry approximately 33% of patients with CF are chronically infected with *P. aeruginosa* [201]. PCD patients colonized or infected with *P. aeruginosa* have poorer pulmonary function than other PCD patients [4,47] indicating that it is a major pathogen not only in CF but also in PCD.

Patients with CF can house a bacterial reservoir in their sinuses and concordant bacteriology in the upper and lower airway is frequent [48-50]. Furthermore, lung re-colonization from the sinuses is frequently observed in lung-transplanted CF patients [51,52]. Chronic rhinosinusitis (CRS) is almost universal in PCD and bacterial sinusitis has been reported in 88% of PCD patients with CRS [53]. PCD sinuses can house a variety of pathogens, although *P. aeruginosa* is the dominant pathogen presumably also functioning as a bacterial reservoir leading to lung colonization and infection [53,54].

Recently it was shown that 10 out of 12 (83%) PCD patients kept the same *P. aeruginosa* clone type for a prolonged period, similar to findings in CF patients [55-58]. To acquire more knowledge about persistence and adaptation of pathogenic microorganism in PCD more frequent sampling of sputum is needed e.g. every second month [58]. In a retrospective longitudinal study, it was reported that chronic *P. aeruginosa* infection was cleared for at least one year in 29 out of 42 patients (69%) [42]. This finding raises important questions of whether eradication had really been successful: was the quality of the sputum samples optimal, was the rate of sputum sampling too sparse, or were PCD patients really able to clear persistent infections?

Management of airway infection in PCD including surveillance, prophylaxis, segregation and treatment is currently without any evidence and is based on expert opinions, often extrapolated from experience with CF [10,11]. Consensus guidelines recommend surveillance cultures of expectorated sputum or oropharyngeal cough swabs 2-4 times a year [10,11]. The impact of sampling frequency of respiratory tract cultures is currently unresolved in CF [59,60] and there is no evidence in PCD, but it inevitably influences likelihood of detection of new pathogens, load of therapy and the ability to differentiate chronic and non-chronic infection. More frequent sampling will undoubtedly increase the detection of pathogens. The 2013 Infection Control Guideline for CF recommendation is quarterly lower airway sample cultures, or more frequently if clinically indicated [59]. Whilst the current information for PCD is based on weak and inconsistent data sets from few centres, it seems reasonable to follow guidance from CF.

Minimizing exposure to respiratory pathogens and other infections is probably important, whether this relates to hospitalization, visits to the pulmonary outpatient clinic or day care settings in infancy and early childhood. Patients with PCD should receive pneumococcal immunisation as part of the normal immunisation programme and annual influenza vaccine [10,11]. Recommendations on the use of prophylactic oral antibiotics are disputable, but they are used in some centres and further discussed below. Chronic prophylactic therapy with azithromycin has been previously investigated in CF [61,62] and non-CF bronchiectasis [63,64] showing positive effect and is currently under prospective investigation by the BESTCILIA consortium [65].

In a small study of 12 patients from a clinic of 125 (10%) PCD patients, cross infection with P*. aeruginosa* was not observed, but this does not prove that cross-infection is not a risk in PCD [57]. Larger multi-center studies, with more frequent sampling might improve the evidence for cross-infection and help determine whether strict segregation is warranted.

Eradication strategies following positive cultures are currently based on expert opinions [10,11]. Although the need for antibiotic treatment for patients with simultaneous symptoms of infection and positive cultures for respiratory pathogens is not contentious, indications for treatment modalities such as chronic suppressive oral or inhaled antibiotics, or treatment based on positive cultures without simultaneous sign of exacerbation or disease progression are by no means certain.

Furthermore, treatment of respiratory infections reflects experience from CF without accounting for possible differences in side-effect profiles between patient groups with respect to specific antibiotic drugs and dosages used. Recommended doses for CF are often substantially higher than those recommended in other diseases with the risk of imposing toxic effects to PCD patients. Given the above-mentioned premises, it is unclear whether the management of PCD can be transferred directly from CF. *P. aeruginosa* can establish persistent lung infections in PCD exhibiting exactly the same pattern as in CF lung infections [57]. Adaptive mutations optimize pathogen fitness by modification of virulence factors required for survival in both CF and PCD patients [56,57,66]. In PCD patients *P. aeruginosa* isolated from the lungs showed convergent evolution in eight genes like *P. aeruginosa* isolated from CF patients e.g. related to antibiotic resistance, quorum sensing, motility, type III secretion and mucoidity. Therefore, until further evidence is available it seems logical to follow the same guidelines for management, i.e. surveillance, segregation and treatment as in CF, with modifications to the dose of antibiotics. However, if there were evidence to support that infections in PCD are more easily eradicated than CF, a less aggressive approach to infection prevention and control could be justified. Well-designed epidemiological studies and randomised trials are needed to examine this further.

*3.3. Additional treatments of the lower airway*

A number of additional treatments including bronchodilators, inhaled corticosteroids, mannitol and N-acetylcysteine are sometimes used in patients without evidence [67]. These treatments, which are generally used based on experience from CF and non-CF bronchiectasis, have recently been discussed in a comprehensive review by Polineni [68]. In the opinion of the authors of our manuscript, given the lack of evidence for any treatments in PCD it is reasonable to trial these treatments in individual cases following assessment by a paediatric pulmonologist, with careful review of response to treatment.

Similarly, evidence for surgical intervention is limited to a small retrospective, case-control study of 5 adults who underwent lobectomy and 7 who did not have surgery [69]. Patients who had undergone surgery had worse lung function, but it is not possible to say whether this was caused by the surgery, or whether it prompted surgical intervention. Lung transplantation is an option in patients with end stage disease, and has been performed in a number of patients. Transplantation will require advanced planning particularly in patients with situs abnormalities.

*3.4. Management of sinonasal disease*

Sinonasal disease is ubiquitous in patients with PCD, mostly represented by chronic rhinosinusitis (CRS). CRS is a hallmark of PCD, affecting ≥70% of patients [4,70-73]. Symptoms include nasal obstruction, decreased sense of smell, pain, coughing and nasal discharge. CRS can be very debilitating, affecting QOL [26,38]. Abnormal sinus development, hypo- or aplasia, is found in >50% of adult patients with PCD [74]. Nasal polyps (NP) are prevalent in up to 50% of adult PCD patients [4] and may appear in childhood [47,53].

Currently, CRS management in PCD focuses on relieving symptoms. Therapeutic strategies are inspired from CRS treatment in the general population and CF. These include sinonasal irrigation with saline, topical nasal steroids and antibiotics. Anecdotally, sinonasal irrigation with iso- or hypertonic saline is a beneficial and safe method for assisting upper airway clearance in PCD, as it is in the general population [75,76]. Nasal irrigation can remove stagnant mucus and it is inexpensive, well tolerated and practical [75-77].

Topical steroids have a well-documented positive effect in the general CRS patients [75,76], and it may be reasonable to believe that administration can also reduce mucosal inflammation and polyps in PCD. However, topical steroids have no clear effect on CF patients with NP, presumably because airway inflammation in CF is dominated by neutrophils [78] and this is also the case in PCD [23,24].

Management of sinonasal exacerbation is based on antimicrobial therapy which can be guided by middle meatus culture. Prophylactic antibiotics (either local or oral) for long-term sinonasal therapy have not been evaluated in PCD. However, therapy with macrolides is effective in treating CRS without nasal polyps in the general population [75] and is potentially beneficial in treating PCD patients with CRS as well.

Endoscopic sinus surgery (ESS) can ventilate and drain the sinuses and is a well-established CRS treatment, improving QOL in patients with CRS including CF where medical therapy has failed [75,76]. Only a few studies have evaluated the potential benefits of CRS treatment with ESS in PCD and they consistently show subjective benefit [53,79,80]. Importantly recent studies suggest that the sinuses may function as a bacterial reservoir causing repeated lower airway infection and advocate that ESS can eradicate pathogenic sinus bacteria and thereby protect the lower airways [53,54].

*3.5.Management of otologic disease*

Conversely to CF, otologic manifestations are frequent in PCD, affecting up to 100% of children <12 years of age [72,81-84]. The natural history of otologic disease tends to improve with age [81,85,86]. The cardinal otologic features include recurrent acute otitis media (AOM), otitis media with effusion (OME) and chronic otitis media [72,81,83,86]. Cholesteatoma has been documented in a few patients with PCD [84,86,87]. Both recurrent AOM and persistent OME appear between 2 and 3 years but, unlike the general population, they continue until the age of 6 to 8 years and commonly persist in adulthood [81,86,88]. A moderate conductive hearing loss is reported in PCD patients with OME, mainly before 12 years [81] which may impair speech acquisition.

The management of otologic disease in children with PCD is extrapolated from studies of the general population since interestingly otologic problems in cystic fibrosis are very infrequent. It aims to improve hearing and prevent possible sequel such as delayed speech acquisition, tympanic membrane atelectasis and retraction pockets.

Conservative treatment includes courses of oral antibiotics in case of recurrent AOM [72]. The choice of antibiotics is guided by the prevalence of bacteria in AOM, focusing on *S. pyogenes*, *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. In cases of recalcitrant acute otitis, a myringostomy is considered in order to obtain middle ear fluid for culture. Continuous alternating antibiotics have not been specifically studied but it does not appear to prevent complications of AOM [86].

In the general population, insertion of ventilation tubes (VT), possibly combined with adenoidectomy, is indicated for restoration of hearing in children with persistent bilateral OME and prevention of further middle ear infections in children suffering from recurrent AOM [89]. In PCD children, the use of VT is controversial since recurrent mucopurulent ear discharge after VT insertion is described in 30% of PCD patient while it concerns less than 5% of the general paediatric population [81,86]. The European Respiratory Society Consensus Statement recommends against placement of VT in patients with PCD, and advises to watch for spontaneous resolution of OME which may occur in the teenage years [10]. Hearing aids may be required in case of hearing loss which is impacting on education or speech development.

Antibiotics for ear discharge in children with VT should focus on the most common bacteria causing acute otitis media [90]. In case of ear discharge occurring after VT insertion, local antibiotics are usually prescribed but there is no study addressing this treatment in PCD. In the general paediatric population, a recent Cochrane systematic review found moderate to low-quality evidence that antibiotic eardrops (with or without corticosteroid) are more effective than oral antibiotics, corticosteroid eardrops and no treatment in children with ear discharge following VT insertion [89]. Potential ototoxicity of ototopical antibiotics should be kept in mind; this is a concern in general when prescribing local antibiotics for treatment of ear discharge but the risk is higher in PCD as ear discharge may require longer treatment and patient may have pre-existing sensorineural hearing loss.

Tympanic membrane perforation and extrusion following VT insertion is more common in children with PCD than in the general pediatric population [86]. Tympanic membrane perforation requires myringoplasty once the middle ear is healed. Healing may be partial in PCD and the chances of successful surgical outcomes are likely to be lower than in the general population.

Similarly to CF patients, anaesthesia in PCD patients requires techniques that prevent anaesthetic-related morbidity during the post-operative period [91]. Meticulous respiratory preparation includes intensive physiotherapy and, if needed, antibiotics and aerosolized medications. Myringotomy and VT insertion is a relatively short procedure that does not involve the airway directly. The post-operative period can be eventful and merits careful monitoring.

# Monitoring of disease in children with PCD

Clinical outcome measures should give the clinician or researcher insight into the patient’s current disease status and how this has changed from the previous assessment. There are a wide range of potential outcome measures for PCD patients (Table 1) the relevance of which will depend on the setting they are measured, i.e. research study or clinic, and the frequency and practicality of undertaking the measurement. Here we consider several of these in more depth. We will consider monitoring of lung function, structural lung disease, ENT and quality of life in children with PCD.

*4.1.Monitoring Lung Function*

Spirometry, and in particular forced expiratory volume in 1 second (FEV1), is routinely used in clinically practice for monitoring PCD patients, as it is widely available and quick to perform. However, it is effort dependent and therefore generally only possible in children over 5 years of age. Whilst predicted values are widely available these are not specific to all ethnic groups, in particular to patients from South Asia in whom the prevalence of PCD can be high [6,92]. Furthermore, spirometry lacks sensitivity in detecting early structural lung disease progression evident on high resolution computer tomography (HRCT) scan [93], and peripheral airway disease as detected in lung clearance index [94-97]. In the experience of the authors, FEV1can be highly variable in stable PCD patients even on the same day. This is presumably due to variable obstruction caused by secretions with cough clearance between first and following attempts. To be meaningful as an outcome within patient variability needs to be understood.

Lung clearance index derived from a multiple breath wash-out technique expresses ventilation inhomogeneity. It can be performed in all ages, as it only requires tidal breathing, and changes little with age. However measurements are reliant on the dispersal of the inhaled gas throughout the lungs and, as it will not enter obstructed areas of the lung, has the potential to underestimate disease severity. It has been widely studied in CF patients and has been demonstrated to be more sensitive in detecting early disease than FEV1 and correlates better with changes on chest HRCT scans [98,99]. However the literature on its use in PCD is mixed with some showing a correlation with FEV1, whilst others not, and no correlation to HRCT findings [94-97].

*4.2. Monitoring Structural Lung Disease*

Most PCD clinics undertake routine CXR, annually or every few years, as they are readily available, cheap and involve a minimal radiation burden [10,11]. However, CXRs are not sensitive for early structural changes of disease. Due to concern over the radiation exposure most centres use HRCT in PCD patients when clinically indicated, with few using it routinely. Published literature concerning structural lung disease in both CF and PCD, has principally concentrated on changes evident on HRCT. Data is conflicting whether lung disease is worse in CF than PCD [100,101]. Whilst all lobes are effected in CF, there is relative sparing of the upper lobes in patients with PCD [100]. Typical changes seen in both diseases include bronchiectasis, peribronchial thickening, mucus plugging, atelectasis and consolidation/ collapse. Significantly more information in this area is available from patients with CF, due in part to the ability to detect the condition by newborn screening and the clinical drive to detect and potentially prevent or retard the onset of early lung disease. The desire for periodic assessment of structural lung disease to aid in this assessment has resulted in qualitative and, more recently, quantitative scoring systems for CF lung disease allowing longitudinal assessment of changes in structural disease as well as uniformity between reviewers [102-104]. Two commonly used scoring systems derived for assessment of structural CF lung disease, Brody and Bhalla, were derived by descriptive reviews of structural changes seen on HRCT scans from a heterogeneous group of patients with CF with subsequent construction of a scoring system [102,103]. Refinement of the systems over ensuring years has led to reliable, validated scoring systems used not only in clinical care but also as end points for intervention trials. Probably the most commonly employed scoring system for both these end points is the modified Brody score which entails the scoring of 5 different parameters: bronchiectasis, mucous plugging, peribronchial thickening, parenchymal changes of consolidation and ground glass thickening and focal air trapping; several reports of structural lung disease in PCD have employed the use of a modified Brody score to describe and quantitate structural changes [100,101,105]. This of course assumes that structural changes in PCD are similar if not identical to those seen in CF, and the assumption has as yet not been ratified.

Up to 70% of infants with PCD are reported to have evidence of neonatal respiratory difficulty despite birth at term. Mullowney *et al* previously described the high incidence of upper lobe disease associated with this presentation [29]; in a case control study of 46 infants subsequently diagnosed as having PCD, 70% of the 23 infants in whom a chest X-ray had been performed showed evidence of lobar collapse – 75% of which occurred in the upper lobes. This high level of upper lobe disease, interestingly in contrast to the relative sparing of upper lobes in HRCT scans in older children with PCD, is distinctly different from reports of lung disease at diagnosis in infants with CF detected by new born screening. In a group of 57 infants with CF detected by newborn screening, Sly *et al* reported 80% of HRCT scans at a median age of 3.6 months had evidence of structural lung disease including 19% with bronchial dilatation, 45% with bronchial wall thickening, and 67% with gas trapping [106]. Lobar collapse was not reported.

Several investigators have described structural changes seen on HRCT scans from older patients with PCD. Jain *et al* reviewed 26 HRCT scans from children with PCD, and found that while the previously reported changes seen in CF were also evident in PCD, there was relative sparing of upper lobes from disease, particularly bronchiectasis [105]. Overall severity scores, assessed using the CF derived modified Brody score were highest for the middle and lingular lobes. A further study evaluated the lung disease in 20 children and adults with PCD by a modified Brody composite HRCT scan score to assess the prevalence of the structural abnormalities [100]. They also attempted to correlate HRCT scan scores with spirometry findings and clinical data. Bronchiectasis was seen in 80% of cases while peribronchial thickening (80%) mucous plugging (75%); parenchymal changes (65%) were also seen commonly. Mosaic perfusion was the least common abnormality and was seen in only 45% of cases. The total HRCT scan score was significantly related to age and lung function including both FEV1 and FVC.

A study of structural changes on HRCT scans in 20 adolescents with PCD reported bronchiectasis (70%), mucous plugging (70%), peribronchial thickening (90%), parenchymal abnormalities (65%), and hyperinflation (50%) [107]. HRCT scores, using a combined modified Brody and Bhalla scoring system, significantly increased (i.e. worse disease) with age, and were negatively correlated to PaO2, FVC, FEV1, and FEF25-75% longitudinal changes. Similar findings were described in a study from Israel which compared lung function and HRCT changes assessed, again using a Brody score, between children with PCD and 2 groups of CF patients, pancreatic sufficient (CF-PS) and pancreatic insufficient (CF-PI). The severity of structural lung disease was similar for PCD and CF-PS and significantly worse in CF-PI [101].

The desire to avoid the radiation doses associated with HRCT imaging has led some investigators to consider non-radiation based imaging techniques such as magnetic resonance imaging (MRI) scanning to assess structural changes. Montella *et al,* in a study of 41 subjects with non-CF chronic lung disease including 14 patients with PCD, found that MRI scanning had good agreement with paired HRCT scans in describing features of suppurative lung disease including bronchiectasis and mucous plugging [108]. Further development of this technique may aid examination of longitudinal changes over time in PCD as well as being a useful assessment tool for short term intervention therapy trials. To date no studies have reported the use of hyperpolarizing gas MRI, Helium3 or Xenon, in the assessment of lung disease in PCD.

*4.3.Monitoring ENT diseases*

An annual ENT evaluation is a minimum for monitoring ear and sinus disease in children with PCD. Considering the high incidence of hearing impairment in PCD, evaluation of audition is usually done at diagnosis and can be repeated annually in case of ear disease. Hearing is measured with open field audiogram and pure tone audiogram respectively before and after 6 years. In case of sensorineural hearing impairment, auditory evoked potentials are useful to evaluate the auditory nerve functioning. Ear or sinus imaging is not classical part of ENT monitoring of children with PCD. Sinus CT (classical or cone-beamed) is indicated prior to performing ESS. Nasal function testing (i.e. rhinomanometry and olfactory testing) can be proposed, especially in case of nasal polyps, in order to objectively measure nasal congestion and its consequence on olfaction.

*4.4.Monitoring Health Related Quality of Life*

PCD effects the physical, psychological and social well-being of patients and their families [109]. Health-related quality of life (QOL) questionnaires allow measurement of the patient’s perceptions of the impact of their disease. There are a number of generic questionnaires which have been used as outcomes measures in PCD patients e.g. St George’s Respiratory Questionnaire and Sino-Nasal Outcome Test (SNOT-22) [109]. Disease-specific outcome measures for CF (CFQ-R) and bronchiectasis (QOL-B) have also been used as outcome measure for PCD patients [36,109]. However, these questionnaires were not designed for use in PCD patients, and have often not been validated in the age-groups in which they have been used. PCD-specific QOL questionnaires (QOL-PCD) were therefore developed and validated for children and adults [26,37,38]. QOL-PCD have been translated into a number of languages and are being used in a number of studies. In the future, the QOL-PCD will not only be used as an important outcome measure in research of PCD patients but also in the routine monitoring of their disease progression.

# Transition of patients from paediatric to adult care

Transition is a gradual process of empowerment that equips young people with the skills and knowledge necessary to manage their own medical condition in preparation for adult services. In all chronic conditions a good transition from paediatric to adult services is necessary to optimise long-term outcomes of young people [110]. This is particularly important in a rare condition such as PCD where adult specialist services are limited and many health care professionals have not heard of the condition. The lack of a specialist PCD adult service can lead to patients being mismanaged in respiratory services or general practice. In the experience of the authors young adult patients report that having left paediatric services they may be advised to stop physiotherapy between exacerbations, be prescribed vitamins in accordance with CF guidelines, struggle to get sputum microbiological assessment and struggle to get antibiotics to treat exacerbations.

Ensuring young people have the knowledge to become “expert patients” with a good understanding of the management of PCD and skills to negotiate with physicians may serve to reduce morbidity [110,111]. They should have a good understanding of their condition, their medications, and how to access medical services (e.g. how to get prescriptions and fertility advice). A good transition programme should be holistic, not only addressing medical aspects of care, but also ‘healthy living’, careers options, bullying etc.

Transition can be facilitated by a simple tool; “Ready Steady Go” is a structured generic transition programme which has been recommended by the National Institute for Health and Care Excellence UK as an example of good practice [110] [202]. The programme is used as a framework to guide transition by all four national PCD centres in England [9], where it has been tailored to meet the needs of children with PCD. The programme begins around the age of 11 when children are moving to senior school, thereby taking more responsibility for other aspects of their lives. This allows plenty of time to address all aspects of daily life, in bite size pieces, whilst preparing the child and family for transfer to adult services at 16-18 years [110]. Alongside this, the English Service provides a “PCD folder” for each child from diagnosis with sections for all aspects of their care including diagnostic information, Family Support Group information, audiology, cardiac, annual reviews, discharge summaries, school, disability living allowance etc. This encourages the family to keep all their child’s information in one place and is a useful resource should the child need to be seen in a non-PCD centre. It also ensures that as the young person moves to adult services they have a comprehensive record of their clinical journey.

# Expert commentary

The evidence for treatment of PCD is poor, and management is often extrapolated from studies of patients with CF or chronic rhinosinusitis. However, much work is underway to improve the situation. Collaborations between PCD clinicians and scientists are strong, and in recent years a number of major advances have been made to improve care of children with PCD. We are now ready for methodologically robust clinical trials to be conducted in PCD patients. Moreover, scientists are actively seeking novel treatments. The first randomised clinical trial in PCD was recently published [36], and the first commercially funded clinical trial is in progress (CLEAN-PCD [203])

Two recent European Respiratory Society (ERS) task forces, various national and international consortia, EU-FP7 funded BESTCILIA and a current international network BEATPCD, have been particularly fruitful for advancing the field. An ERS taskforce (ERS TF 2007-9) provided evidence of the disparity in diagnosis and treatment across Europe [7,67] and published a consensus statement for the diagnosis and treatment of children with PCD [10]. A second ERS Task Force (2014-16) published the first evidence-based guideline for the diagnosis of PCD [12], and investigated patient perspectives about diagnosis, treatment and research [8]. In North America the PCD Foundation has similarly developed a consensus statement for the diagnosis and management of patients with PCD [11]. BESTCILIA (2012-15), led to the development of a European PCD registry [112], the international PCD cohort (iPCD) with over 3000 patients [113], a randomized-controlled clinical trial to investigate azithromycin to prevent respiratory exacerbations [65] and the development and validation of quality of life questionnaires, QOL-PCD [26,37,38]. National and international consortia have been particularly successful in advancing our understanding of PCD genetics [9,12,45]. BEAT-PCD (COST Action BM1407) is an EU-funded network of clinicians and scientists, coordinating research from basic science to clinical research, with the ultimate aim of finding treatments that lead to measurable improvements in long-term outcome of patients with PCD [114][205]. An important focus of the network is to establish the evidence, and gain expert consensus for the key components to underpin clinical trials which are currently missing e.g. definition of a respiratory exacerbation.

In addition to existing research networks and collaborations, PCD will benefit from a new clinical network. In December 2016 the European Commission approved 23 European Reference Networks (ERNs) for rare diseases, including one for rare respiratory diseases; ERN-LUNG [115]. The ERN-LUNG is a network of healthcare providers, including a core group of PCD reference centres dedicated to providing and promoting excellence in diagnosis and care of patients across Europe.

# Five-year view:

Over the coming years, we anticipate that a number of clinical trials will contribute to evidence based guidelines for the management of PCD. Importantly, iPCD is positioned to deliver epidemiological evidence of practice that might be associated with better clinical outcomes that can then be examined in randomised trials. Examples of studies might include evaluation of different airway clearance techniques, effectiveness of nasal steroids, efficacy of ventilation tubes, and *P. aeruginosa* eradication studies.

We anticipate significant advances as our understanding of the genetics and pathophysiology of PCD grows, and new technologies relating to genetics studies and novel therapies emerge. A number of research groups are searching for novel therapies including gene therapy. In an *ex vivo* proof of concept study, a DNAh11 mutation was corrected using transcription activator-like effector nucleases (TALENs) [116]. However, experience of gene therapy in CF has been relatively disappointing and would be considerably more complicated in PCD given the large number of associated genes. Other novel treatments such as read-through drugs may prove beneficial and knowledge gained from molecular studies might contribute to a personalised medicine approach as is emerging for patients with CF.

In addition, microbiology and infection prevention and control guidelines will need special attention in relation to PCD. Networks such as BEATPCD are facilitating researchers to share knowledge, samples and models which will hopefully expedite pre-clinical research. The close collaboration of scientists and clinicians should then ease the pipeline to clinical trials. With the new ERN-LUNG PCD reference centres, we anticipate that all patients in Europe should have access to diagnostic and care facilities which adhere to ERS Guidelines [12], will be included in the European PCD registry [112], and will have the opportunity to participate in well-designed clinical trials [115].

# Key issues (bullet points summarizing the review)

* Lower airway clearance therapy is critical to improve mucus clearance in children with PCD. Given the absence of evidence for any method, or that a particular method is superior, physiotherapists should individualise the treatment based on individual need and patient preference.
* There is no evidence that mucolytics or osmotic agents improve mucus clearance. However, case reports suggest that patients might benefit, therefore well designed clinical trials are needed.
* There is no evidence for or against cross-infection between patients with PCD, but this is perhaps due to lack of surveillance and poor data. The pathogens infecting PCD patients are similar to those implicated in CF and, in the authors’ opinions, in the absence of evidence to the contrary, segregation and other measures to prevent cross-infection should align to measures used in CF patients.
* Studies to assess antimicrobial treatments are urgently needed: prophylaxis, treatments of exacerbation, treatment of asymptomatic cultures and eradication of *P. aeruginosa*.
* Chronic rhinosinusitis affects most patients with PCD, but evidence for treatments is lacking. Randomised trials are needed to investigate the effect of nasal rinsing, non-steroidal drugs and topical nasal steroids, on the upper airways in PCD, as well as studies to investigate the role of surgical intervention.
* Management of serous otitis media is controversial in PCD, and well-designed studies are needed to determine whether conservative or surgical treatment is superior.

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| --- | --- |
| T**able 1 – Monitoring children with PCD in clinical practice and for research** | |
| **Clinical**   * Mortality * Exacerbation rate * Admission rate   **Growth**   * Height * Weight * Body Mass index * Bioelectrical impedance analysis   **Lung function**   * Spirometry * Plethysmography * Lung Clearance Index   **Questionnaires**   * QOL-PCD (age appropriate version) | **Sputum & bronchoalveolar lavage**   * Bacteriology and antibiotic resistance * Viruses, fungi & non-tuberculous mycobacterium culture   **ENT functions**   * Audiogram (age appropriate) * Auditory evoked potentials * Rhinomanometry (after 6 years) * Olfactory tests   **Radiology**   * Chest X-ray * Chest High Resolution computer tomography scan * Magnetic resonance imaging * Sinus and ear high resolution computer tomography scan |

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