

# Update on Primary ciliary dyskinesia

## Journal of Paediatrics and Child Health

Evie Alexandra Robson <sup>1,4</sup>, Philip Chetcuti <sup>1</sup>, Robert Anthony Hirst <sup>2</sup>, Hannah M. Mitchison <sup>3</sup>, Eduardo Moya <sup>1</sup>, Daniel Peckham <sup>4</sup>, Philip J. Robinson <sup>5</sup>, Andrew Rutman <sup>2</sup>, Christopher O'Callaghan <sup>2,6</sup>

<sup>1-</sup> *The North of England Primary Ciliary Dyskinesia Management Service, Leeds General Infirmary, Great George street, Leeds, LS1 3EX, 0113 3926335*

<sup>2-</sup> *Centre for PCD Diagnosis and Research, Department of Infection, Immunity and Inflammation, RKCSB, University of Leicester, Leicester LE2 7LX, UK*

<sup>3-</sup> *Genetics and Genomic Medicine, University College London, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH*

<sup>4-</sup> *Centre for Respiratory Medicine, St James' University Hospital, Beckett St, Leeds, West Yorkshire LS9 7TF*

<sup>5-</sup> *PCD Service, Respiratory Medicine, Royal Children's Hospital, Victoria, Parkville 3052, Australia*

<sup>6-</sup> *Respiratory, Critical Care & Anaesthesia, UCL Great Ormond Street Hospital Institute of Child Health, University College London WC1N 1EH, UK*

Corresponding author: Evie Robson MBBS MRCPCH MSc

E mail: [evie.robson@nhs.net](mailto:evie.robson@nhs.net)

Word count: 3974

Keywords:

- Primary Ciliary Dyskinesia
- Cilia
- PCD
- Kartagener
- Bronchiectasis
- Chronic cough

---

## **Abstract**

*PCD is a rare autosomal recessive disorder of ciliary function. It is characterised by progressive sino-pulmonary disease, fertility problems and disorders of organ laterality. Clinical phenotype and disease course can vary significantly. A daily chronic wet cough that never goes away is invariably present, with most suffering from persistent and significant rhinosinusitis. Middle ear effusion and hearing difficulty are seen in a proportion of patients. Bronchiectasis is reported in approximately 70% of children.*

*Diagnosis can be difficult requiring specialist centre input. In patients with a suggestive clinical phenotype a combination of nasal nitric oxide, high-speed video microscopy analysis for ciliary beat frequency and pattern, and transmission electron microscopy analysis of ciliary ultrastructure are performed as appropriate. In populations studied genetic defects have been identified in approximately 60% of cases, with many genes yet to be discovered.*

*There is no evidence on which to base guidelines of clinical management and most treatment regimens are extrapolated from those used in Cystic Fibrosis. Specialist care by respiratory and ENT specialists is recommended. Current respiratory management focuses on physiotherapy and exercise to help compensate for defective mucociliary transport together with identification and treatment of infection.*

*On going international collaboration is key in being able to better understand a disease of such heterogeneity and to produce best practice guidance for standardised clinical care.*

---

## Defining the disease

Primary Ciliary Dyskinesia (PCD) is a rare autosomal recessive disorder characterized by abnormal ciliary function, leading to progressive sino-pulmonary disease, reduced fertility and disorders of organ laterality. The prevalence of PCD is approximately 1:20,000 live births although this varies significantly between ethnic groups. A prevalence of 1:2,200 has been reported in a highly consanguineous UK Asian population.

Large numbers of ciliated cells are present in the respiratory tract, brain ventricles and aqueducts, testicular efferent ducts and fallopian tubes. Ciliated cells are the dominant cell type in human airways (up to  $10^9$  cilia per  $\text{cm}^2$ ). Normal cilia have 9 peripheral microtubular doublets and a central pair arrangement. The key axonemal components are the outer dynein arms and inner dynein arms, motors and radial spokes and the nexin dynein regulatory complex. Each cilium will beat in a coordinated fashion over a million times each day, providing mucociliary clearance and innate lung defence. In PCD, mucociliary clearance is absent or markedly impaired due to abnormal ciliary movement. Reduced Generation of Multiple Motile Cilia (previously known as Ciliary Aplasia), is a rare disease entity, currently grouped with PCD, in which there are highly reduced numbers of cilia that can either be motile or have motility defects. Patients with this condition appear to present with a more severe clinical course of recurrent and chronic airway infection.

*Situs Inversus* totalis occurs in approximately 45% of confirmed cases of PCD but is not seen in patients with central microtubular defects such as ciliary transposition. Kennedy and colleagues (2007) reported 6.3% of patients to have heterotaxy (as defined by any thoraco-abdominal asymmetry other than *situs inversus*). In this group, there is a small but significant increase in prevalence of complex congenital heart disease. Rare associations of PCD include hydrocephalus, polycystic kidney disease and retinitis pigmentosa. The sperm tail has a similar structure and motor system to that of cilia. As a result, males with PCD will have marked sub-fertility or infertility. In women, defective ciliary function affecting the reproductive tract may sometimes affect fertility and potentially increase the risk of ectopic pregnancies.

## Course of the disease

Primary Ciliary Dyskinesia is a genetically heterogeneous condition with variable clinical phenotypes. Patients invariably present with chronic rhino-sinusitis, a daily wet sounding cough, recurrent pulmonary infections and inflammation of the respiratory tract. Glue ear is very common and can cause significant hearing loss in young children. In 2014, Dell and colleagues reported that 91% of their PCD population had a history of neonatal respiratory distress. This is much higher than the UK experience.

Radiological features of PCD are characterised by bronchiectasis, peri-bronchial thickening, mucous plugging, consolidation and air trapping. Bronchiectasis is more predominant in the middle and lower lobes and Magnin and colleagues (2012) reported evidence of

bronchiectasis in 70% of children on first CT scan (mean age 8.7 years). The true prevalence of structural lung disease in this age group remains unclear as not all children with PCD have CT scans.

Abnormal lung function is common in PCD and is associated with an obstructive pattern with a reduction in both FEV<sub>1</sub> and FEF<sub>25-75</sub>. A systematic review by Goutaki and colleagues (2015) reported a mean FEV<sub>1</sub> of 58% (range 35-77%) and 78% (range 73-88%) in adults and children respectively.

The natural history and disease progression of PCD is poorly defined with conflicting reports in the literature describing a wide variability in longitudinal change in lung function and disease progression. Marthin and colleagues (2010) assessed the change in lung function in 74 patients. Over a three-year study period, 34% of patients lost more than 10% of FEV<sub>1</sub>, 57% were stable, and 10% improved by more than 10%. An earlier report from the same centre by Ellerman and Bisgaard (1997) reported lung function was maintained over many years following diagnosis in both children and adults. These variations in the course of lung function did not correlate with age of diagnosis or baseline lung function. In a UK report of 151 adults, Shah and colleagues (2016) reported a decline of 0.49% predicted FEV<sub>1</sub> per year in adult patients, compared with 5.6% and 2.35% in subjects with cystic fibrosis and non-CF bronchiectasis respectively. Deterioration in lung function occurs in some individuals before diagnosis and it appears this can be stabilised with appropriate treatment.

In adult patients there is a wide spectrum of lung function impairment and radiological disease severity. Expert opinion suggests poor correlation between CT findings and spirometry, (Maglione (2012)). Lung clearance index is an alternative and more sensitive marker of airways disease in conditions such as cystic fibrosis. However in PCD, lung clearance index does not appear to correlate with either spirometry or high resolution CT findings. Further work is required to determine its place in assessment.

Shah and colleagues (2016) found that *Pseudomonas aeruginosa* colonisation may be a marker of disease severity, rather than a predictor of disease progression. Colonisation is shown to correlate with age, impairment in FEV<sub>1</sub> at diagnosis and extent of bronchiectasis, but did not correlate with change in lung function over time. These findings differ to those of the clinical course of cystic fibrosis. *P. aeruginosa* colonisation appears much less common in patients with PCD than with cystic fibrosis. Alanin and colleagues (2015) found 39% of 107 patients with PCD met the criteria for chronic *P.aeruginosa* infection at least once. In contrast, by adulthood, approximately 80% patients with cystic fibrosis are colonised with *P.aeruginosa*.

The prognosis of PCD varies significantly and children can develop severe lung disease. A study by Noone and colleagues (2003) evaluated 78 patients with PCD whose ages ranged between 0-73 years. While decline in lung function for the whole cohort was 25 to 50% less than that reported in cystic fibrosis, 25% of individuals were classified as having severe disease.

## Diagnosis

Unlike cystic fibrosis, newborn screening for PCD is not available and as such most presentations are as a result of the recognition of suggestive symptomatology. A diagnosis of PCD is often delayed due to lack of recognition of such signs and symptoms and diagnosis in adulthood is not uncommon, especially when *situs inversus* is not present. A European survey in 2010 by Kuehni and colleagues, reported median age at diagnosis to be 5.3 years, lower in children with *situs inversus* and in children attending tertiary respiratory centres.

Diagnostic algorithms for PCD vary significantly between countries. There is no “gold-standard” test for PCD, hence European consensus guidelines (2009) recommend a combination of tests including recognition of a clinical phenotype, nasal nitric oxide screening, high-speed video microscopy analysis of ciliary beat frequency and pattern, and transmission electron microscopy analysis of ciliary ultrastructure. The nationally funded diagnostic services for the UK (Leicester, Royal Brompton and Southampton) have used this approach since 2006. In addition they undertake ciliated cell culture to help in the diagnosis of rare or previously unreported phenotypes. Genetic testing is increasingly used but its availability in diagnostic testing varies significantly between countries.

## Clinical Phenotype

The British Thoracic Society guidelines, (2008) define chronic cough in children as lasting more than 8 weeks. The most important clinical feature suggestive of a PCD diagnosis from a detailed history includes a wet sounding cough that has ‘always been there’ and is present every day even when the child is well. Most older children and adults will also expectorate sputum. Notably cough is present in the neonatal period. Table 1 highlights well-defined clinical features that may be present.

Table 1. Important clinical features suggesting a diagnosis of PCD

• Unexplained, prolonged neonatal respiratory distress
• Recurrent airway infections
• Persistent daily wet cough that ‘has always been there’
• <i>Situs inversus</i>
• Persistent rhinorrhoea, often present from the neonatal period
• Chronic sinusitis
• Sibling or family member with PCD
• Parental consanguinity
• Chronic otitis media with effusion
• Conductive hearing loss (often improving in teenage years)
• Reduced fertility
• Cardiovascular malformation
• Polysplenia or asplenia

In children with chronic respiratory symptoms other causes should be considered and excluded as appropriate e.g. cystic fibrosis, immunodeficiency, structural airway abnormalities and aspiration. The differential diagnosis of chronic productive cough from the BTS guidelines 2008, are included in table 2:

• Asthma
• Post-nasal drip/ allergic rhinitis
• Persistent endobronchial infection
• Cystic Fibrosis
• Immune Deficiency
• Recurrent aspiration
• Anatomical disorders including: • Tracheo/ bronchomalacia, airway compression, tracheoesophageal fistula or laryngeal cleft.
• Retained inhaled foreign body
• Psychogenic cough
• Interstitial lung disease
• Tuberculosis
• Whooping cough

In PCD chronic secretion retention in the upper respiratory tract predisposes to infection in the middle ear, nose and facial sinuses. Morgan and colleagues (2016) reported that chronic otitis media with effusion affects up to 80% of children and is often persistent, with fluctuation through adulthood. Hearing loss is common and is usually mild to moderate but can be profound. It does, however, usually spontaneously resolve in teenage years. Most centres do not recommend use of aural ventilation tube insertion, as prolonged ear discharge may ensue and persistent tympanic perforation may be seen. Nasal congestion is extremely common and nasal polyps can occur over time with chronic sinusitis, with impaired sense of smell reported by some. Chronic rhinosinusitis has a major impact on quality of life.

Dell and colleagues (2016) showed that children with PCD had lower health-related quality-of-life scores than children with cystic fibrosis, in comparing overall respiratory symptoms, of 63.7 and 77.8 respectively (scores 0-100). Interviews highlighted the importance of the impact of respiratory and sinus symptoms on daily living. Several items of significance in PCD included runny nose, nasal congestion, chronic otitis media, difficulty hearing, speech delay and in some cases, special accommodation in the classroom.

A full clinical examination is important, including general health and nutrition status, and full ENT examination. Digital clubbing is uncommon in patients with PCD. Late recognition of dextrocardia is not uncommon due to failure to auscultate on the right side of the chest where the apex lies.

It can be difficult to determine if children with PCD are worse due to an infection as unlike most children with cystic fibrosis or bronchiectasis due to other causes whose cough disappears when well, the 'PCD' wet sounding cough never goes away. Although chest X-rays are requested in PCD they may be normal and do not exclude underlying bronchiectasis. As with other respiratory problems in childhood, spirometry is performed when the child is old enough, on a regular basis. A sputum sample or cough swab should be taken in order to determine microbiology and guide antibiotic therapy.

## Specific diagnostic Investigations

Several predictive tools have been developed to aid in earlier recognition and appropriate referrals to PCD centres. Investigators at seven North American sites in the Genetic Disorders of Mucociliary Clearance Consortium defined four clinical features to be statistically predictive of PCD. These included laterality defect; unexplained neonatal respiratory distress; early-onset, year-round nasal congestion; and early-onset, year-round wet cough. In the UK, Behan and colleagues (2016) developed a diagnostic prediction tool called PICADAR (Primary Ciliary Dyskinesia Rule), which showed good sensitivity and specificity of 0.9 and 0.75 respectively.

Listed below are the tests undertaken to help diagnose patients with PCD.

### Nasal Nitric Oxide

High-speed video microscopy analysis and transmission electron microscopy are technically demanding investigations. Nasal nitric oxide has been established as a non-invasive screening tool for PCD and should be used as part of the diagnostic work-up. It can be measured in most, but not all children over 5 years of age and allows early assessment in respiratory units. Nasal obstruction or the inability to perform the test, are not uncommon reasons for failure.

Nasal NO levels are low in the vast majority (usually <100 ppb), but not in all patients with PCD. While emerging portable analysers have resulted in an increased access to nasal nitric oxide measurements, values fluctuate according to the equipment and technique used. There is no current consensus over exact thresholds to constitute cut off values.

### High-speed video microscopy analysis

Ciliary function can be assessed by high-speed video microscopy analysis of ciliary beat frequency and ciliary beat pattern. The technique requires highly trained individuals experienced in recognising different beat patterns and has been adopted by many countries worldwide. The test can help identify patients with PCD in whom electron microscopy is normal and where a genetic defect has not been identified. Abnormalities of pattern associated with PCD include static, slow, rotating, stiff, hyper-frequent and vibrating cilia.

Subtle functional defects are increasingly recognised to cause disease. Reference ranges for ciliary beat frequency vary and in our laboratory, range between 10-15Hz. It is important that individual laboratories standardise their technique and obtain their own normal values. In 2009, Stannard and colleagues performed high-speed video microscopy analysis and electron microscopy on nasal tissue from 371 patients referred to Leicester Royal Infirmary for diagnostic assessment, in order to determine the ability of ciliary beat frequency and ciliary pattern analysis to predict electron microscopy-diagnosed PCD. High-speed video microscopy analysis was found to be highly sensitive and specific. The group recognised the existence of a phenotype where no ultrastructural abnormality could be detected on electron microscopy, ciliary beat frequency was high, but ciliary pattern analysis was abnormal. These findings highlight the continued need for a combination approach in the diagnostic process.

Analysis of cilia can be particularly difficult due to secondary damage but this is vastly reduced if nasal brushings are taken 4 weeks or more after a viral upper respiratory tract infection.

### Transmission electron microscopy

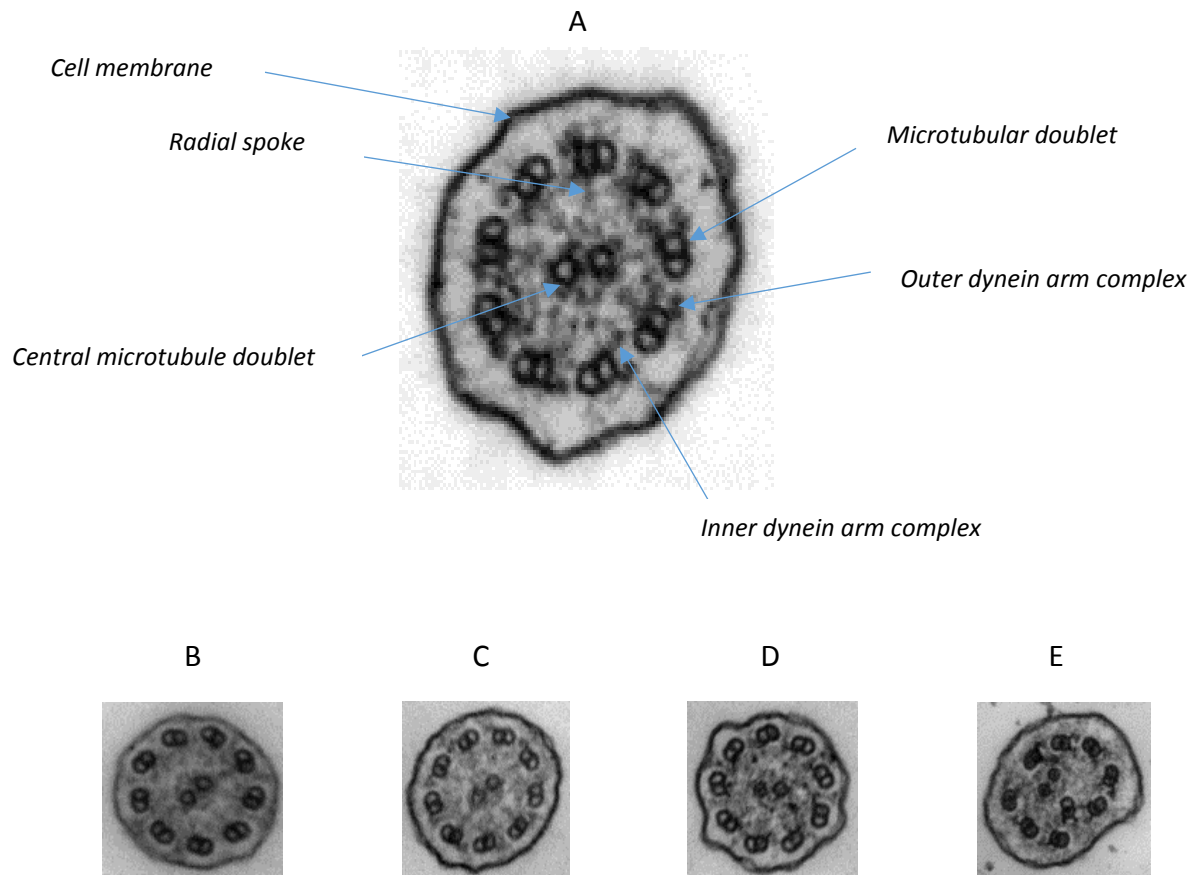
Transmission electron microscopy allows the visualisation of the ciliary ultrastructure. Correct identification of PCD ultrastructural defects requires highly trained and experienced staff and findings can be influenced by inflammation and infection of ciliated epithelium.

Defects in ciliary components can cause cilia to be static or to beat dyskinetically. Lucas and colleagues (2016) reported that the most common defects affect the outer dynein arms and a combination of the inner and outer dynein arms. Inner dynein arm defects with microtubular disorganisation have been reported in approximately 15% of PCD cases. Isolated inner dynein arm defects are seen but currently no genetic mutations have been identified that cause this phenotype. Central pair and microtubular defects occur less frequently.

Axonemal structural analysis by transmission electron microscopy remains an effective test for PCD as it is highly specific in confirming a diagnosis and shows an excellent correlation with genotype. Previous research has suggested that in up to 20% of PCD cases the axonemal structure looks normal, although in our experience the figure is lower.



Figure 1. Typical transmission electron microscopy axonemal cross sections of normal cilia (A), and from patients with PCD: lack of dynein arms (B), lack of inner dynein arms (C), lack of outer dynein arms (D) and microtubule transposition defect (E).



## Ciliated cell Culture

Ciliated epithelium can be re-analysed following culture and re-differentiation of the epithelial cells using an air-liquid interface technique. In 2014, Hirst and colleagues showed that post-culture samples clarified the diagnostic status, and in a number of subjects, enhanced the ability to make a diagnosis. High-speed video microscopy results suggestive of PCD are confirmed either by repeat brushings or culturing of the epithelial cells and reanalysis.

Although 2009 guidelines suggested potential adjuncts to diagnosis including immunofluorescence labelling of cilia proteins, radioaerosol mucociliary clearance and genotyping, they have not been incorporated into the UK diagnostic algorithm.

Pulmonary radioaerosol MCC is described as a technique based on characterising the clearance patterns of inhaled radioaerosol tracer. This is however, non-specific to PCD and therefore of limited use as a diagnostic tool.

## Genetics

PCD is inherited in an autosomal recessive fashion. In 1999 Pennarun and colleagues described the identification of the first PCD-causing genetic mutation. Since then there have been rapid advances in the understanding of the underlying genetic defects responsible for PCD. To date, over 30 genes have been described as being associated with a PCD phenotype and this is felt to account for approximately 60% of diagnosed cases. It is interesting to reflect on the recent advances in mutation-specific therapy in cystic fibrosis, that this condition has mutations in one known gene and encompasses approximately 27 exons. PCD as mentioned is associated with mutations in at least 30 separate genes encompassing over 700 exons. With over 250 proteins in the cilium, (Ostrowski and colleagues, 2002), and additional proteins involved in the cytoplasmic assembly and or transport of dyneins, there is potential for a large number of gene mutations still to be identified.

The association between genetic defects and ciliary ultrastructure and function are increasingly well established, although the links between genetics and clinical phenotype remain largely unknown. International data collection is underway in order to aid understanding and tailor individualised management. Current genotype and phenotype correlations have demonstrated that lung disease patterns appear variable across all ciliary ultrastructural and genotypic groups. Knowles and colleagues (2014), reported the association of biallelic mutations in RSPH1 while more mild disease and CCDC39/ CCDC40 have been linked to more severe disease, as described by Davis and colleagues (2015).

Table 3. A list of the more common genes affected in PCD and description of their mutational consequence within the ciliary axoneme or cell.

<b>Protein function</b>	<b>Gene/protein name</b>
ODA proteins	<u>DNAH5, DNAI1, DNAI2, DNAL1, NME8, DNAH11</u>
ODA-associated proteins that enable ODA docking and attachment to the axoneme	<u>CCDC114, CCDC151, ARMC4, TTC25, CCDC103</u>
Molecular ruler proteins	<u>CCDC39, CCDC40</u>
Nexin dynein regulatory complex proteins	<u>CCDC65, CCDC164, GAS8</u>
Central pair proteins	<u>HYDIN</u>
Radial spoke proteins	<u>RSPH1, RSPH3, RSPH4A, RSPH9, DNAJB13</u>
Cytoplasmic assembly of cilia	<u>DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5, LRRC6, ZMYND10, SPAG1, C21orf59</u>
Multiciliogenesis proteins. Mutations associated with RGMC	<u>CCNO, MCIDAS</u>

*ODA= Outer Dynein Arm, RGMC=Reduced Generation Motile Cilia*

Mutation screening using multigene panels and next-generation sequencing allows genotyping and may help with the diagnosis with certain PCD phenotypes where ultrastructure is normal.

## Summary

Accuracy of diagnostic testing was assessed by Jackson et al in 2016, using data from 654 patients referred for PCD diagnostics. Their work highlighted the importance of a combined approach for diagnostic investigations. High-speed video microscopy alone had excellent accuracy, but required significant expertise and often repeated sampling or cell culture. Transmission electron microscopy alone was found to be specific but missed 21% of cases. Nasal nitric oxide ( $\leq 30$  nLmin<sup>-1</sup>) was useful in combination with high-speed video microscopy analysis. In isolation nasal nitric oxide screening at this cut-off would miss approximately 10% of cases. The group reported a high accuracy with combination testing which remains the requirement. Recent reports of PCD gene mutations associated with inconclusive high-speed video microscopy analysis or transmission electron microscopy studies highlights the need for highly skilled and experienced microscopists to ensure accurate diagnosis for this significantly heterogeneous disease, and also the increasing availability of genetic testing to aid in diagnostics. A current priority is in standardization of methods used and reporting of tests. Evidence-based guidelines for diagnostic testing are under development through the European Respiratory Society PCD Task Force-

With the discovery of a growing number of mutations, patients with recognized genes can be offered genetic counselling and extended family screening in high-risk populations.

## Lack of awareness

There is a lack of awareness of PCD among the medical profession. A study by Behan and colleagues (2016) reported patients experience on the diagnostic process of PCD. Thirty-five percent had visited their doctor on more than 40 occasions with symptoms prior to referral for PCD testing. Ninety-seven percent of patients considered it very important to improve awareness of PCD among medical practitioners.

## Management

A national management service was set up in four UK centres in 2013. This is commissioned by the NHS to provide a specialist multidisciplinary team annual review and advice service for children in England. Currently there is very limited evidence to base guidelines for the treatment of PCD and management has largely been extrapolated from other respiratory diseases, in particular cystic fibrosis. Given the different pathophysiology of PCD and cystic fibrosis, an evidence base for PCD management should be seen as a priority.

Clinical evaluation of patients with PCD is difficult as patients almost invariably have a persistent wet sounding cough which contrasts with most children with cystic fibrosis or

non-CF bronchiectasis where the cough diminishes or clears completely with treatment. Clinical assessment relies on monitoring changes in cough and sputum production, clinical wellbeing, lung function and culture of pathogens. Deterioration in these parameters will often require antibiotic treatment and more intensive airway clearance. A major aim of treatment is to improve where possible and to maintain lung function. This involves approaches outlined below.

## Airway clearance

Optimisation of mucociliary clearance is a cornerstone for current management strategies. There is presently no evidence to support the use of any particular airway clearance device or technique and physiotherapy should be tailored to the individual, which may aid compliance. Routine exercise is strongly encouraged.

## Mucolytics

Both cystic fibrosis and PCD are associated with neutrophilic airway inflammation and the release of neutrophil DNA within secretions. In cystic fibrosis, there are multiple clinical trials showing significant improvement in lung function, quality of life and reduced pulmonary exacerbation following daily nebulisation of recombinant human rDNAse. It is not, however recommended in non-CF bronchiectasis as it has been found to be ineffective. It has not been formally studied in PCD.

Hypertonic saline at 3-7% is recommended for use in cystic fibrosis. There is no evidence-based research to support its use.

## Microbiology

Polineni and colleagues (2016) suggested that sputum and cough swab specimens should be processed to the same standards and protocols as for cystic fibrosis specimens. This includes using the appropriate media and monitoring for bacteria such as *Pseudomonas aeruginosa* and atypical Mycobacteria. *Staphylococcus aureus*, *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* are often the predominant bacteria in the sputum of patients with PCD.

There is no evidence supporting the use of inhaled antibiotics in PCD, although they are often tried based on evidence extrapolated from cystic fibrosis clinical trials. Eradication therapy is advised if *P. aeruginosa* is cultured. Data supporting the use of low-dose macrolides in non-CF bronchiectasis has resulted in the wide use of low dose Azithromycin although no trials have been undertaken in PCD.

Pneumococcal and annual influenza vaccines are recommended.

## Otitis media and hearing

Chronic Otitis media with effusion, (glue ear) can significantly affect quality of life, hearing, language development and school performance. In the UK and Europe hearing aids are advocated for those with hearing defects as insertion of ventilation tubes appears to be associated with discharge from the ear and in some, persistent perforation of the eardrum. The natural history of hearing problems is for the majority to have considerable improvement in hearing during teenage years with many no longer requiring hearing aids.

Chronic rhinosinusitis is a significant burden for patients. Sino-nasal irrigation, often referred to as nasal douching, can remove mucus, bacteria and biofilm from the sinuses and reduce oedema. Many patients report benefit but again research evidence of benefit is lacking. The use of topical steroids and antibiotics has not been evaluated. Evidence for the use of endoscopic sinus surgery in severe cases is also lacking.

## In Conclusion

Research is clearly needed and due to small patient numbers the establishment of International PCD registries should facilitate evaluation of management options. International and multidisciplinary collaborations will be key to this. The USA based PCD foundation, investigators and clinicians are developing a network of PCD clinical centres to coordinate efforts in North America and Europe, in order to improve knowledge and care.

The UK and USA website support groups are:

- [www.pcdsupport.org.uk](http://www.pcdsupport.org.uk)
- [www.pcdfoundation.org](http://www.pcdfoundation.org)

## Practice points

- PCD is a progressive condition, which may result in significant morbidity.
- A high index of suspicion is required in children with a persistent, wet sounding cough, that is present every day and who also have nasal symptoms, with or without *situs* anomalies.
- PCD should be considered in a term neonate with unexplained, prolonged respiratory distress.
- Diagnosis is often delayed, with evidence of bronchiectasis in children.
- Children and adults need specialist respiratory and ENT care. This will also facilitate evidence-based trials on a multicentre basis.
- There is an on-going requirement for international collaboration for evidence based disease management.

## Conflict of interest statement

The authors have no conflicts of interest in the production of this document.

## Acknowledgements

- Hannah M. Mitchison is a Great Ormond Street Hospital Children's Charity Reader in Molecular and Medical Genetics supported by Great Ormond Street Hospital Children's Charity
- Chris O'Callaghan is Professor of Respiratory and Paediatric Medicine and Head of Respiratory, Critical Care and Anaesthesia at the UCL Great Ormond Street Institute of Child Health, supported by Great Ormond Street Hospital Children's Charity and by Action Medical Research

## List of further reading sources

1. Goutaki M, Jose A, Meier B, Maurer E, Halbeisen F, Latzin P, Kuehni C. Lung function of patients with primary ciliary dyskinesia: A systematic review. *European Respiratory Journal* 2015 46: PA4518
2. Shah A, Shoemark A, MacNeill SJ, Bhaludin B, Rogers A, Bilton D, Hansell DM, Wilson R, Loebinger MR. A longitudinal study characterising a large adult primary ciliary dyskinesia population. *Eur Respir J* 2016;48:441-450
3. Anderson TN, Alanin MC, von Buchwald C, Nielsen LH. A longitudinal evaluation of hearing and ventilation tube insertion in patients with primary ciliary dyskinesia. *J Pediatr Otorhinolaryngol.* 2016 Oct;89:164-8
4. Dell SD, Leigh MW, Lucas JS, Ferkol TW, Knowles MR, Alpern A, Behan L, Morris AM, Hogg C, DunnGalvin A, Quittner AL. Primary Ciliary Dyskinesia: First Health-related Quality-of-Life Measures for Paediatric Patients. *Annals ATS* Vol 13, no;10,Oct 2016
5. Barbato A, Frischer T, Kuehni CE, Snijders D, Azevedo I, Baktai G, Bartoloni L, Eber E, Escribano A, Haarman E, Hesselmar B, Hogg C, Jorissen M, Lucas J, Nielsen KG, O'Callaghan C, Omran H, Pohunek P, Strippoli M-PF, Bush A. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. *Eur. Respir. J.* 2009; 34: 1264–1276.
6. Lucas JS, Paff T, Goggin P, Haarman E. Diagnostic Methods in Primary Ciliary Dyskinesia. *Paediatric Respiratory Reviews* 18(2016)8-17
7. Stannard WA, Chilvers MA, Rutman AR, Williams CD, O'Callaghan C. Diagnostic testing of patients suspected of primary ciliary dyskinesia. *Am J Respir Crit Care Med.* 2010 Feb 15;181(4):307-14
8. Hirst R.A, Jackson C.L, Coles J.L, Williams G, Rutman A, Goggin P.M, Adam E.C, Page A, Evans H.J, Lackie P.M, O'Callaghan C, Lucas J.S. Culture of Primary Ciliary Dyskinesia Epithelial Cells at Air-Liquid Interface Can Alter Ciliary Phenotype but Remains a Robust and Informative Diagnostic Aid. *PLoS ONE.* 2014 Feb 25;9(2):e89675

9. Pennarun G, Escudier E, Chapelin C, Bridoux A-M, Cacheux V, Roger G, Clement A, Goosens M, Amselem S, Duriez B. Loss-of-Function Mutations in a Human Gene Related to *Chlamydomonas reinhardtii* Dynein IC78 Result in Primary Ciliary Dyskinesia. *Am J Hum Genet.* 1999 Dec; 65(6): 1508-1519
10. Ostrowski L.E, Blackburn K, Radde K.M, Moyer M.B, Schlatzer D.M, Moseley A, Boucher R.C. A proteomic analysis of human cilia: identification of novel components. *Mol Cell Proteomics.* 2002 Jun;1(6):451-65
11. Knowles M.R, Ostrowski L.E, Leigh M.W, Sears P.R, Davis S.D, Wolf W.E, Hazucha M.J, Carson J.L, Olivier K.N, Sagel S.D, Rosenfeld M, Ferkol T.W, Dell S.D, Milla C.E, Randell S.H, Yin W, Sannuti A, Metjian H.M, Noone P.G, Noone P.J, Olson C.A, Patrrone M.V, Dang H, Lee H.S, Hurd T.W, Gee H.Y, Otto E.A, Halbritter J, Kohl S, Kircher M, Krischer J, Bamshad M.J, Nickerson D.A, Hilderbrandt F, Shendure J, Zariwala M.A. Mutations in RSPH1 cause primary ciliary dyskinesia with a unique clinical and ciliary phenotype. *Am J Respir Crit Care Med.* 2014 Mar 15;189(6):707-17
12. Davis S.D, Ferkol T.W, Rosenfeld M, Lee H.S, Dell S.D, Sagel S.D, Milla C, Zariwala M.A, Pittman J.E, Shapiro A.J, Carson J.L, Krischer J.P, Hazucha M.J, Cooper M.L, Knowles M.R, Leigh M.W. Clinical features of childhood primary ciliary dyskinesia by genotype and ultrastructural phenotype. *Am J Respir Crit Care Med.* 2015 Feb 1;191(3):316-24
13. Polineni D, Davis SD, Dell SD. Treatment recommendations in Primary Ciliary Dyskinesia. *Paediatric Respiratory Reviews* 18 (2016)39-45
14. Morgan LC, Birman CS. The impact of Primary Ciliary Dyskinesia on the upper respiratory tract. *Paediatric Respiratory Reviews* 18(2016)33-38
15. Lucas JS, Chetcuti P, Copeland F, Hogg, C, Kenny T, Moya E, O'Callaghan C, Walker WT. Overcoming challenges in the management of primary ciliary dyskinesia: The UK model. *Paediatric Respiratory Reviews* 15(2014) 142-145