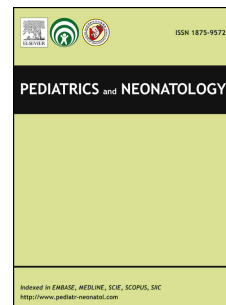


Journal Pre-proof

Non-Cystic Fibrosis Bronchiectasis in children and adolescents: neglected and emerging issues

Marco Poeta, Marco Maglione, Melissa Borrelli, Francesca Santamaria



PII: S1875-9572(19)30522-4

DOI: <https://doi.org/10.1016/j.pedneo.2019.09.013>

Reference: PEDN 973

To appear in: *Pediatrics & Neonatology*

Received Date: 22 March 2019

Revised Date: 16 July 2019

Accepted Date: 24 September 2019

Please cite this article as: Poeta M, Maglione M, Borrelli M, Santamaria F, Non-Cystic Fibrosis Bronchiectasis in children and adolescents: neglected and emerging issues, *Pediatrics and Neonatology*, <https://doi.org/10.1016/j.pedneo.2019.09.013>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2019, Taiwan Pediatric Association. Published by Elsevier Taiwan LLC. All rights reserved.

Review Article

Non-Cystic Fibrosis Bronchiectasis in children and adolescents: neglected and emerging issues.

Marco Poeta*, Marco Maglione*, Melissa Borrelli and Francesca Santamaria.

Department of Translational Medical Sciences, Section of Pediatrics, Federico II University, Naples, Italy.

* MP and MM contributed equally to the article as first authors.

Running title: Pediatric Non-Cystic Fibrosis Bronchiectasis

Corresponding Author:

Francesca Santamaria, MD; Department of Translational Medical Sciences, Federico II University, Via Pansini 5, 80131-Naples, Italy.

Phone: +39 081 746 3495

Fax: +39 081 7463116

Email: santamar@unina.it

Francesca Santamaria is member of EU-funded COST Action BEAT-PCD (BM1407).

Review Article

Non-Cystic Fibrosis Bronchiectasis in children and adolescents: neglected and emerging issues.

Marco Poeta*, Marco Maglione*, Melissa Borrelli and Francesca Santamaria.

Department of Translational Medical Sciences, Section of Pediatrics, Federico II University, Naples, Italy.

* MP and MM contributed equally to the article as first authors.

Running title: Pediatric Non-Cystic Fibrosis Bronchiectasis

Corresponding Author:

Francesca Santamaria, MD; Department of Translational Medical Sciences, Federico II University, Via Pansini 5, 80131-Naples, Italy.

Phone: +39 081 746 3495

Fax: +39 081 7463116

Email: santamar@unina.it

Francesca Santamaria is member of EU-funded COST Action BEAT-PCD (BM1407).

Review Article

**Non-Cystic Fibrosis Bronchiectasis in Children and Adolescents:
Neglected and Emerging Issues.**

Running title: Pediatric Non-Cystic Fibrosis Bronchiectasis

Journal Pre-proof

Abstract

Pediatric non-cystic fibrosis (CF) bronchiectasis is characterized by endobronchial suppuration, airway neutrophilic inflammation and poor mucus clearance and is associated with persistent productive cough due to recurrent airway infections. Most recommendations are based on expert opinion or extrapolated from CF practice. The present narrative review aims to address some issues on the management of children or adolescents with non CF-bronchiectasis that still require attention, and analyze what available literature offers to reply to open questions. We focused on the potential offered by technological advances on lung disease assessment through novel chest imaging techniques and new or old pulmonary function tests. We also summarized the main novelties in the disease prevention and treatment. Finally, a novel diagnostic algorithm is proposed, that might help physicians in the daily clinical decision-making process. Future directions for research on pediatric non-CF bronchiectasis should include larger study populations and longer prospective clinical trials, as well as new clinical and laboratory endpoints to determine the underlying mechanisms of lung disease progression and support the role of new and existing treatments.

Key Words: adolescents; bronchiectasis; children; chronic cough; suppurative lung disease

1. Introduction

Three clinical entities, associated with endobronchial suppuration, neutrophilic inflammation and poor mucus clearance, have been merged under the spectrum of pediatric suppurative lung disorders, i.e., protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD) and bronchiectasis.¹ While PBB is a syndrome with isolated persistent wet cough resolving after 2–4 weeks of oral antibiotics and with normal chest imaging (except for occasional peribronchial thickening), bronchiectasis in childhood is defined as the presence of persistent or recurrent (>3) episodes of chronic (>4 weeks) productive cough, sometimes with coarse crackles and digital clubbing, associated with the chest computed tomography (CT) finding of a ratio between the inner airway and the outer vessel diameter ≥ 0.80 .¹ In between PBB and bronchiectasis, there is CSLD, which defines patients with clinical symptoms of bronchiectasis without its radiographic features.¹ As etiology and clinical features of bronchiectasis and CSLD largely overlap, the conditions have been frequently referred to simply as CSLD, yet the absence of CT abnormalities makes a crucial difference.

The global burden of pediatric bronchiectasis is unknown, although extrapolation of published data suggests that prevalence ranges from 0.2–735 cases per 100 000 children.² Indeed, heterogeneity of definitions, limited access to diagnostic technology in some areas, and lack of epidemiologic data from developing countries make a precise assessment of prevalence unreliable.³ What is clear is that low-income populations have a higher incidence of bronchiectasis, generally of infectious origin, with early severe manifestations particularly amongst Australian, Pacific Islands and Alaskan native people.² In high-income countries a major cause is cystic fibrosis (CF), whereas within non-CF conditions epidemiologic data are less consolidated. Although reported prevalence is affected by the local diagnostic facilities, primary immune deficiencies (PID),

chronic/recurrent aspiration, postinfectious entities, primary ciliary dyskinesia (PCD) and airways malformations represent the most common causes everywhere.^{2, 4-8} Undeniably, a relevant proportion of cases are probably classified as idiopathic because of insufficient awareness of the underlying etiology and/or limited availability of diagnostic resources (for example, those for ciliary motility and structure defects). Should this be confirmed, the prevalence of the disorder could significantly change.

Management of non-CF bronchiectasis has long been based on expert opinion or derived from CF. However, in the last decade some recommendations on pediatric non-CF bronchiectasis or specific disorders were published.⁴⁻⁶ These generally focus on diagnostic approach, clinical monitoring and treatment for stable disease and exacerbations. Nevertheless, issues such as clinical applicability of biomarkers, development of decision-making algorithms, quality of life (QoL) evaluation, emerging lung function or structure assessment technologies, and therapeutic challenges remain poorly addressed, leaving a number of questions unanswered.

In the present narrative review we focus on some “neglected” aspects and analyze what available literature offers to reply to open questions. Furthermore, we present an algorithm to help clinicians in moving from the initial diagnosis to the identification of the underlying etiology.

2. Old and new biomarkers

Relevance of biomarkers is crucial in clinical practice for screening, early diagnosis or disease monitoring, and in research as outcome measures. Blood measurements may not reflect what happens in the airways, so lung biomarkers are usually detected through bronchoalveolar lavage (BAL). Biofilms produced by respiratory pathogens were isolated

in BAL from non-CF bronchiectasis children even when BAL-defined infection was absent.⁹ Nevertheless, the need for general sedation and the potential risks of BAL limit its use, particularly in pediatric settings where a long-term follow-up is required.

Collection of exhaled breath condensate (EBC) provides a non-invasive method to assess lower airway biomarkers that is more suitable for children than BAL. In CF and non-CF bronchiectasis, EBC contains high levels of matrix metalloproteases, which correlate with worse spirometry and high resolution CT (HRCT).¹⁰ Interestingly, the application of metabolomics to EBC also showed how nuclear magnetic resonance spectroscopy discriminates healthy subjects from CF and PCD patients.¹¹ In EBC from PCD children, 8-isoprostane, a marker of oxidative stress, is increased,¹² and nitric oxide (NO) metabolites are similar to controls, despite reduced nasal NO (nNO).¹³ It is hoped that further studies will clarify the role of EBC metabolic profiling in the characterization of bronchiectasis with different etiology.

Induced sputum is a safe, non-invasive tool for sampling secretions from the lower airways particularly in non-expectorating young children.¹⁴ Unfortunately, it was rarely applied to pediatric non-CF bronchiectasis and further studies should be encouraged, especially when BAL is not feasible.

In the field of non-invasive biomarkers a relevant role has been gained by NO.¹⁵ Measurement includes fractional exhaled NO (FeNO) and the less widespread nNO. FeNO analysis is well validated in the assessment of asthma control, but its application to other conditions is less studied. Similarly, despite a growing body of evidence supporting the utility of nNO in the diagnostic work-up of several disorders, current literature indicates its major application in PCD screening.⁴ In PCD, nNO is markedly reduced for unclear reasons but may be normal in cases with subtle beating abnormalities of cilia.⁵ Indeed, low nNO levels are also permissive for PCD airway colonization by non-typeable *Haemophilus*

influenzae (NTHi).¹⁶ An official guideline has concluded that nNO helps to address further testing or support the diagnosis of patients with atypical phenotypes and/or normal ciliary ultrastructure, but a definite diagnosis of PCD cannot be based on nNO alone.⁴

3. Functional and structural lung disease assessment

Unlike other organs which can be easily monitored through imaging or function tests, e.g., kidney or liver, lung is far more elusive, particularly in children. Therefore, to assess and monitor lung function and structure, the development of reliable non-invasive tools represents a priority in pediatrics and a remaining challenge.

3.1 Lung Function

Wide diffusion, low cost and non-invasiveness make spirometry a valuable tool for assessing efficacy of treatment and monitoring pulmonary deterioration.^{17, 18} Nevertheless, spirometry fails to detect early disease and peripheral airways changes of some conditions.¹⁹ There is also increasing recognition that in CF and non-CF bronchiectasis HRCT lung changes may occur despite normal spirometry.²⁰ Spirometry is also limited by the need of patient's cooperation. Indeed, virtually no data are available in non-CF preschoolers, though PCD abnormalities are evident in infancy.¹⁷ The static lung volumes determination may be useful as well, but the limited diffusion of such a technique and an even higher need for patients' cooperation compared to spirometry strongly affect the application of plethysmography in children. A study of 17 children with postinfectious bronchiectasis undergoing the multiple helium dilution technique demonstrated increased residual volume and residual volume/total lung capacity ratio.²¹

Lung clearance index (LCI), a non-effort-dependent technique also applicable to young children, is increased in many conditions, such as CF and asthma, and increasing

evidence supports its role as an earlier marker of distal airway impairment compared to spirometry.²² Data in adult bronchiectasis are less conclusive as one study excluded that LCI is useful for short-term assessment of the response to antibiotics.²³ Evidence in children mainly derives from PCD literature which showed that LCI is very sensitive in detecting structural and functional abnormalities even in the presence of normal FEV₁.^{24–26} Conversely, a comparative study of LCI, HRCT and spirometry concluded that LCI is not a sensitive test of airway disease in advanced PCD as it does not correlate with HRCT.²⁷ Because of these controversial results, LCI is not listed in the diagnostic work-up, but more studies should be encouraged. Finally, fraction of end-expiratory oxygen (F_{EO2}) measured by a fast-response analyzer connected to a pneumotachometer was recently proposed as a non-invasive test to evaluate O₂ tension of distal airways.²⁸ The F_{EO2} in CF was found to be significantly lower than in PCD, possibly given the thinner PCD airways secretions compared to CF mucus plugs, supporting a potential application of this procedure for screening PCD in cases with bronchiectasis.

3.2 Lung structure

An accurate assessment of lung structure is crucial for identifying bronchiectasis,¹ but CT is criticized for its ionizing radiation burden. Alternative techniques have been investigated and an increasing body of literature has become available particularly for chest magnetic resonance imaging (MRI) and, to a lesser extent, for electric impedance tomography (EIT).

MRI has been repeatedly proposed as reliable radiation-free technique in several disorders and the diffusion of high-field 3.0-T MRI has partially overcome technical problems such as long acquisition times, need for patient cooperation, respiratory and cardiac motion artifacts, and low signal-to-noise ratio due to low proton density of the

lung.²⁹ Good agreement between chest high-field MRI and HRCT and significant correlation with pulmonary function have been found, with good-to-excellent sensitivity and specificity.³⁰ Moreover, functional MRI has been proposed to assess lung perfusion (i.e., the dynamic contrast-enhanced MRI with intravenous gadolinium) or lung mechanics (by a spirometer-controlled technique), or lung ventilation with inhaled hyperpolarized gases, or to evaluate both perfusion and ventilation without contrast media (by the Fourier decomposition procedure),²⁹ but studies of pediatric non-CF bronchiectasis are few. A recent study of functional MRI in PCD children and adults has supported the use of chest MRI sequences without the need for contrast agents or breathing manoeuvres.³¹

EIT is a strongly function-oriented radiations-free imaging modality whose applications in pediatrics are raising growing interest,³² but robust studies in non-CF bronchiectasis are lacking. However, future EIT application in pediatric respiratory medicine might provide valuable information on chest regional changes.

4. Quality of Life assessment tools

Monitoring chronic respiratory diseases has traditionally focused on periodical assessment of clinical, functional and imaging outcomes.¹ However, these parameters are inadequate to evaluate how disease impacts on children's everyday life.³³ Therefore, the role of QoL, particularly health-related QoL (HRQoL), has increasingly gained relevance in the management of pediatric disorders. This determined an effort in standardizing HRQoL evaluation tools; hence disease-specific questionnaires for pediatric patients or their parents were developed.^{34, 35} QoL is strongly affected by the respiratory condition both in terms of physical and mental functioning.³³ In non-CF bronchiectasis, parental distress is high, with mental health worse than in CF parents, which is probably due to less intensive interaction with healthcare professionals.³⁶

Most studies assessing QoL in non-CF bronchiectasis have used tools originally designed for chronic cough, which, although informative, may be incomplete.³³ Recently, the QoL Questionnaire-Bronchiectasis was developed as the first specific tool for non-CF bronchiectasis with good reproducibility and reliability in adults.³⁴ Nevertheless, as the heterogeneity of non-CF bronchiectasis mitigates against the development of a comprehensive patient-reported outcome measure, QoL questionnaires have been recently validated for specific conditions.³⁵ Particularly, whereas tools of QoL in children with bronchiectasis secondary to PID or chronic aspiration are lacking, an HRQoL measure was developed for PCD children that takes into account general aspects common to chronic lung disorders and specific issues of this population (i.e., sinus/ear disease).³⁷ Despite these advances, evidence of QoL in children is still limited. Further application of new tools designed for specific diseases will lead towards a better assessment of QoL.

5. Therapeutic strategies: areas of certainty and new challenges

Disappointingly, most of the pediatric literature on treatment of non-CF bronchiectasis is composed of reviews with recommendations^{1, 5} or is extrapolated from CF.³⁸ Nevertheless, despite the lack of controlled clinical trials, few guidelines have addressed the treatment of children.^{6, 39, 40} At any age, the primary goals of bronchiectasis management are to prevent premature respiratory decline, to suppress airway infections minimizing exacerbations, to reduce morbidity and mortality, and to improve HRQoL.¹ Core prescriptions include daily airway clearance techniques (ACT) and pulmonary rehabilitation programs as well as measures of infection control and prevention.

5.1 Airway clearance techniques and pulmonary rehabilitation programs

Pulmonary rehabilitation programs and ACTs including manual chest physiotherapy with percussion and vibration, postural drainage, autogenic drainage, active cycle breathing, positive expiratory pressure (PEP) devices and mechanical cough assist have been exhaustively described in CF and in adult disorders.^{41–43} Current international guidelines recommend ACT as part of routine management in non-CF bronchiectasis,^{6, 39, 40} even though the evidence basis is sparse.^{41–43} In the last two decades few pediatric trials have been published,^{44–47} but the small sample size, the short study periods and, at least for some, the absence of a comparison group make it difficult to claim superiority of a specific mode (**Table 1**). As aerobic fitness is a cardiorespiratory prognostic measure, exercise would be also beneficial, but pediatric publications in non-CF bronchiectasis are limited.^{21, 48, 49} Actually, training and frequent revision by a respiratory therapist are mandatory to reach the goal of mobilizing secretions and interrupt the vicious cycle of inflammation and infection, and a personalized plan including clear written advice should be tailored to individual needs. Despite the limited number of evidence-based studies, some key practice points should be kept in mind and recommended (**Table 2**). Finally, as adherence can be suboptimal, novel approaches to measures adherence in children and adolescents should be encouraged (Clinical Trial: NCT02906826).

5.2 Pharmacological treatment

The pathogens colonization of lower airways is associated with more severe and frequent exacerbations and fuels the vicious cycle of infection>inflammation>lung damage that further increases bacterial growth.¹ Antibiotics reduce airway bacterial load and consequently should interrupt the vicious cycle. Adult and pediatric guidelines recommend oral or intravenous antibiotic course for at least 10–14 days, prescribed on the basis of known or suspected pathogens colonization.^{6, 39, 40} Macrolides have been used in a

number of pediatric short- or long-term randomized controlled trials (RCT) of non-CF bronchiectasis (**Table 3**).^{50–53} The non-inferiority of azithromycin *versus* amoxicillin-clavulanate was shown in a recent RCT, suggesting that macrolides may be alternatively used for treating non-severe exacerbations in children with non-CF bronchiectasis who have penicillin hypersensitivity or poor adherence to twice-daily antibiotic administration.⁵⁴

Guidelines suggest prescription of inhaled antibiotics in patients with frequent exacerbations and *Pseudomonas aeruginosa* infections, or when macrolides are contraindicated.^{6, 39, 40} Regrettably, pediatric studies evaluating inhaled antibiotics (aminoglycosides; colistin; aztreonam), or bronchodilators, or hyperosmolar agents (hypertonic saline or mannitol) are lacking. Also, inhaled mucolytics such as recombinant human DNase have been evaluated in very small case series or anecdotal reports.⁵⁵ Apparently, there is no role for oral or inhaled glucocorticoids in bronchiectasis, other than the treatment of atopic conditions or of allergic aspergillosis.¹ Despite this, most of these agents continue to be used in the daily practice, and this is a stimulus to promoting further research.

A relevant question about treatment of pediatric non-CF bronchiectasis is what the future holds. A clinical trial of azithromycin in PCD children and adults is under way, and results are awaited to clarify whether maintenance macrolides affect lung function and symptoms.⁵⁶ Another PCD study has recently found that in epithelial cells co-cultured with NTHi the association of azithromycin *plus* a cephalosporin-3'-diazeniumdiolate NO donor prodrug significantly decreased NTHi viability, suggesting that exogenous NO *plus* antibiotics might be a novel therapeutic approach.¹⁶ As airways colonization may be complicated by bacterial biofilm, a study of non-CF adults showing superior antimicrobial efficacy of inhaled antibiotic nanoparticles compared to inhaled native antibiotics opens the door for innovative biomedical treatment of biofilm infections.⁵⁷

5.3 Surgical strategies

Resection of the affected area also by video-assisted thoracoscopy is safe at any age. A recent meta-analysis showed benefits of lung resection in non-CF bronchiectasis with low mortality, acceptable morbidity and significant improvements in symptoms.⁵⁸ Indeed, many surgical studies have important limitations including the efficacy assessment through only roughly defined clinical features, the absence of a control group in most of them, and the involvement of mixed populations of children and adults. Interestingly, approximately 60% of the studies have been conducted in Middle Eastern populations (especially, Turkey and Iran) who, apparently, are not investigated for genetic disorders other than CF.⁵⁸ Therefore, we cannot exclude that in developing countries the higher frequency of surgery is due to inadequate or delayed start of medical treatment or to a late/missed diagnosis of specific disorders. Indeed, considering the high frequency of consanguinity in this geographic area, many bronchiectasis cases defined as “postinfectious” may actually hide an unidentified genetic etiology due to lack of local availability of certain investigations (for instance, cilia microscopy, motility or genetics; immunological studies).³ Surgery indications include failure of conservative treatment, recurrent hemoptysis or destroyed lung parenchyma. Overall, although symptoms may decrease or disappear after resection, surgical treatment remains controversial and high caution should be exercised concerning the decision, especially in children. A priority remains that conservative strategies should be started as soon as possible, avoiding unnecessary surgery, or at least restricting its indications to patients who fail to improve after medical treatment. Finally, transplantation is also a well-established treatment for end-stage bronchiectasis, but there are no reports in non-CF pediatric bronchiectasis.

5.4 Prevention of infections

Seasonal influenza and pneumococcal vaccines are recommended for people with bronchiectasis.^{1, 6} Interestingly, a recent RCT of children with PBB, CSLD or non-CF bronchiectasis showed the effectiveness of the 10-valent pneumococcal-*H. influenzae* protein D conjugate vaccine (PHiD-CV) in terms of reduction in antibiotic courses, respiratory symptoms and hospitalized exacerbations and significant immune response also towards NTHi.⁵⁹ Furthermore, the effectiveness towards NTHi has been microbiologically confirmed on samples of BAL fluids and nasopharyngeal swabs of children with chronic cough who received a primary course of two PHiD-CV doses compared to 7- or 13-valent pneumococcal vaccine.⁶⁰ In pediatric non-CF bronchiectasis there are no studies on *Pseudomonas aeruginosa* vaccines, but these might have a role in the difficult airways infection control.

6. Diagnostic algorithm

In most cases, managing children with non-CF bronchiectasis means dealing with rare conditions that require specialist referral to provide standardized approaches. Nevertheless, before expert consultation, patients are managed by primary care health professionals who are seldom trained and confident enough to assess the disease correctly. In this scenario, structured pathways for clinical decision-making have been published, including diagnostic procedures and even indications or timing for specialist referral of a number of specific conditions laying under the umbrella of pediatric non-CF bronchiectasis. Actually, a more comprehensive algorithm embracing non-CF bronchiectasis as a clinical syndrome and orientating the diagnostic approach towards specific etiologies is lacking. We propose a diagnostic pathway to guide clinicians towards the identification of the specific etiology of the disorder (**Figure**). When facing a child or adolescent with clinical features and confirmed HRCT evidence of bronchiectasis, we first

suggest exclusion of the genetic disorders that primarily involve the respiratory tract and the host's defense against pathogens, i.e., CF, PCD, and primary immune defects. Once these have been excluded, we propose a cluster of additional diagnostic tests to investigate bronchiectasis and suggest how to manage cases when the work-up is inconclusive. As with all algorithms, it does not substitute clinical judgment, especially considering phenotypical heterogeneity of non-CF bronchiectasis, but it may provide a systematic approach to it.

7. Conclusions

It has already become widely accepted that the management of pediatric non-CF bronchiectasis should no longer be dependent upon extrapolating from CF or adult disorders experience. A lot still needs to be done, but we trust the path is set. For instance, as mutations underlying specific disorders, such as PID or PCD, are increasingly identified,^{61, 62} the possibility of individualized treatment primarily including gene therapy is rising.

Regrettably, non-CF bronchiectasis is still understudied in children, and it still suffers neglect in some areas and also relevant emerging issues need to be addressed. Overall, diagnostic tests in pediatric pulmonology require high expertise. To overcome difficulties in the procedure and interpretation of results in non-CF bronchiectasis, novel networks such as ERN Lung⁶³ and BEAT-PCD (COST Action BM 1407)⁶⁴ have been developed to improve access to diagnosis and treatment of non-CF bronchiectasis and PCD, respectively.

Future research should include larger study populations and RCTs, as well as new clinical and laboratory endpoints, in order to determine the underlying mechanisms of lung disease progression and identify the predictors of exacerbations, to investigate, whenever

possible, the correlations of genotype and phenotype and to support the role of new preventive and therapeutic strategies.

Journal Pre-proof

Figure Diagnostic approach to children with clinical features and radiological diagnosis of bronchiectasis.

Figure legend: CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastro-esophageal reflux disease; TEF, trachea-esophageal fistula; GI, gastrointestinal; PPD, purified protein derivative; PCR, polymerase chain reaction; BAL, bronchoalveolar lavage; MRI, magnetic resonance imaging; CT, computed tomography.

Journal Pre-proof

REFERENCES

1. Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. *Lancet* 2018;**392**:866–79.
2. McCallum GB, Binks MJ. The epidemiology of chronic suppurative lung disease and bronchiectasis in children and adolescents. *Front Pediatr* 2017;**5**:27.
3. Kapur N, Karadag B. Differences and similarities in non-cystic fibrosis bronchiectasis between developing and affluent countries. *Paediatr Respir Rev* 2011;**12**: 91–6.
4. Lucas JS, Barbato A, Collins SA, Goutaki M, Behan L, Caudri D, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. *Eur Respir J* 2017;**49**. pii: 1601090.
5. Shapiro AJ, Zariwala MA, Ferkol T, Davis SD, Sagel SD, Dell SD, et al. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol* 2016;**51**:115–32.
6. Chang AB, Bell SC, Torzillo PJ, King PT, Maguire GP, Byrnes CA, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand; Thoracic Society of Australia and New Zealand guidelines. *Med J Aust* 2015;**202**:21–3.
7. Downard CD, Calkins CM, Williams RF, Renaud EJ, Jancelewicz T, Grabowski J, et al. Treatment of congenital pulmonary airway malformations: a systematic review from the APSA outcomes and evidence based practice committee. *Pediatr Surg Int* 2017;**33**:939–53.
8. Boesch RP, Daines C, Willging JP, Kaul A, Cohen AP, Wood RE, et al. Advances in the diagnosis and management of chronic pulmonary aspiration in children. *Eur Respir J* 2006;**28**:847–61.

9. Marsh RL, Thornton RB, Smith-Vaughan HC, Richmond P, Pizzutto SJ, Chang AB. Detection of biofilm in bronchoalveolar lavage from children with non-cystic fibrosis bronchiectasis. *Pediatr Pulmonol* 2015;**50**:284–92.
10. Karakoc GB, Inal A, Yilmaz M, Altintas DU, Kendirli SG. Exhaled breath condensate MMP-9 levels in children with bronchiectasis. *Pediatr Pulmonol* 2009;**44**:1010–6.
11. Montuschi P, Paris D, Montella S, Melck D, Mirra V, Santini G, et al. Nuclear magnetic resonance-based metabolomics discriminates primary ciliary dyskinesia from cystic fibrosis. *Am J Respir Crit Care Med* 2014;**190**:229–33.
12. Zihlif N, Paraskakis E, Tripoli C, Lex C, Bush A. Markers of airway inflammation in primary ciliary dyskinesia studied using exhaled breath condensate. *Pediatr Pulmonol* 2006;**41**:509–14.
13. Csoma Z, Bush A, Wilson NM, Donnelly L, Balint B, Barnes PJ, et al. Nitric oxide metabolites are not reduced in exhaled breath condensate of patients with primary ciliary dyskinesia. *Chest* 2003;**124**:633–8.
14. Jochmann A, Artusio L, Robson K, Nagakumar P, Collins N, Fleming L, et al. Infection and inflammation in induced sputum from preschool children with chronic airways diseases. *Pediatr Pulmonol* 2016; **51**:778–86.
15. Manna A, Montella S, Maniscalco M, Maglione M, Santamaria F. Clinical application of nasal nitric oxide measurement in pediatric airway diseases. *Pediatr Pulmonol* 2015;**50**:85–99.
16. Walker WT, Jackson CL, Allan RN, Collins SA, Kelso MJ, Rineh A, et al. Primary ciliary dyskinesia ciliated airway cells show increased susceptibility to *Haemophilus influenzae* biofilm formation. *Eur Respir J* 2017;**50**. pii: 1700612.

17. Halbeisen FS, Goutaki M, Spycher BD, Amirav I, Behan L, Boon M, et al. Lung function in patients with primary ciliary dyskinesia: an iPCD Cohort study. *Eur Respir J* 2018;**52**. pii: 1801040.
18. Twiss J, Stewart AW, Byrnes CA. Longitudinal pulmonary function of childhood bronchiectasis and comparison with cystic fibrosis. *Thorax* 2006;**61**:414–8.
19. Santamaria F, Montella S, Tiddens HAWM, Guidi G, Casotti V, Maglione M, et al. Structural and functional lung disease in primary ciliary dyskinesia. *Chest* 2008;**134**:351–7.
20. Maglione M, Bush A, Montella S, Mollica C, Manna A, Esposito A, et al. Progression of lung disease in primary ciliary dyskinesia: is spirometry less accurate than CT? *Pediatr Pulmonol* 2012;**47**:498–504.
21. Swaminathan S, Kuppurao KV, Somu N, Vijayan VK. Reduced exercise capacity in non-cystic fibrosis bronchiectasis. *Indian J Pediatr* 2003;**70**:553–6.
22. Downing B, Irving S, Bingham Y, Fleming L, Bush A, Saglani S. Feasibility of lung clearance index in a clinical setting in pre-school children. *Eur Respir J* 2016;**48**:1074–80.
23. Grillo L, Irving S, Hansell DM, Nair A, Annan B, Ward S, et al. The reproducibility and responsiveness of the lung clearance index in bronchiectasis. *Eur Respir J* 2015;**46**:1645–53.
24. Green K, Buchvald FF, Marthin JK, Hanel B, Gustafsson PM, Nielsen KG. Ventilation inhomogeneity in children with primary ciliary dyskinesia. *Thorax* 2012;**67**:49–53.
25. Boon M, Vermeulen FL, Gysemans W, Proesmans M, Jorissen M, De Boeck K. Lung structure-function correlation in patients with primary ciliary dyskinesia. *Thorax* 2015;**70**:339–45.
26. Nyilas S, Bauman G, Pusterla O, Sommer G, Singer F, Stranzinger E, et al. Structural and functional lung impairment in primary ciliary dyskinesia. Assessment with magnetic

- resonance imaging and multiple breath washout in comparison to spirometry. *Ann Am Thorac Soc* 2018;**15**:1434–42.
27. Irving SJ, Ives A, Davies G, Donovan J, Edey AJ, Gill SS, et al. Lung clearance index and high-resolution computed tomography scores in primary ciliary dyskinesia. *Am J Respir Crit Care Med* 2013;**188**:545–9.
28. Mendelsohn L, Wijers C, Gupta R, Marozkina N, Li C, Gaston B. A novel, noninvasive assay shows that distal airway oxygen tension is low in cystic fibrosis, but not in primary ciliary dyskinesia. *Pediatr Pulmonol* 2019;**54**:27–32.
29. Ciet P, Tiddens HA, Wielopolski PA, Wild JM, Lee EY, Morana G, et al. Magnetic resonance imaging in children: common problems and possible solutions for lung and airways imaging. *Pediatr Radiol* 2015;**45**:1901–15.
30. Montella S, Maglione M, Bruzzese D, Mollica C, Pignata C, Aloj G, et al. Magnetic resonance imaging is an accurate and reliable method to evaluate non-cystic fibrosis paediatric lung disease. *Respirology* 2012;**17**:87–91.
31. Smith LJ, West N, Hughes D, Marshall H, Johns CS, Stewart NJ, et al. Imaging lung function abnormalities in primary ciliary dyskinesia using hyperpolarized gas ventilation MRI. *Ann Am Thorac Soc* 2018;**15**:1487–90.
32. Vogt B, Löhr S, Zhao Z, Falkenberg C, Ankermann T, Weiler N, et al. Regional lung function testing in children using electrical impedance tomography. *Pediatr Pulmonol* 2018;**53**:293–301.
33. Nathan AM, de Bruyne JA, Eg KP, Thavagnanam S. Review: quality of life in children with non-cystic fibrosis bronchiectasis. *Front Pediatr* 2017;**5**:84.
34. Quittner AL, O'Donnell AE, Salathe MA, Lewis SA, Li X, Montgomery AB, et al. Quality of life questionnaire-bronchiectasis: final psychometric analyses and determination of minimal important difference scores. *Thorax* 2015;**70**:12–20.

35. Behan L, Leigh MW, Dell SD, Dunn Galvin A, Quittner AL, Lucas JS. Validation of a health-related quality of life instrument for primary ciliary dyskinesia (QOL-PCD). *Thorax* 2017;**72**:832–9.
36. Carotenuto M, Esposito M, Di Pasquale F, De Stefano S, Santamaria F. Psychological, cognitive and maternal stress assessment in children with primary ciliary dyskinesia. *World J Pediatr* 2013;**9**:312–7.
37. Dell SD, Leigh MW, Lucas JS, Ferkol TW, Knowles MR, Alpern A, et al. Primary ciliary dyskinesia: first health-related quality-of-life measures for pediatric patients. *Ann Am Thorac Soc* 2016;**13**:1726–35.
38. El Maraachli W, Conrad DJ, Wang AC. Using cystic fibrosis therapies for non-cystic fibrosis bronchiectasis. *Clin Chest Med* 2016;**37**:139–46.
39. Al-Jahdali H, Alshimemeri A, Mobeireek A, Albanna AS, Al Shirawi NN, Wali S, et al. The Saudi Thoracic Society guidelines for diagnosis and management of noncystic fibrosis bronchiectasis. *Ann Thorac Med* 2017;**12**:135–61.
40. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;**65** Suppl 1: i1–58.
41. Muñoz G, de Gracia J, Buxó M, Alvarez A, Vendrell M. Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial. *Eur Respir J* 2017;**51**:1701926.
42. Lee AL, Burge AT, Holland AE. Airway clearance techniques for bronchiectasis. *Cochrane Database Syst Rev* 2015;**11**:CD008351.
43. Lee AL, Button BM, Tannenbaum EL. Airway-clearance techniques in children and adolescents with chronic suppurative lung disease and bronchiectasis. *Front Pediatr* 2017;**5**:2.

44. Santamaria F, Celentano L, Buonpensiero P, Sarnelli P, Caterino M, Raia V. Positive expiratory pressure treatment: efficacy in pulmonary diseases. *J Pediatr* 1998;**133**:717–8.
45. Indinnimeo L, Tancredi G, Barreto M, De Castro G, Zicari AM, Monaco F, et al. Effects of a program of hospital-supervised chest physical therapy on lung function tests in children with chronic respiratory disease: 1-year follow-up. *Int J Immunopathol Pharmacol* 2007;**20**:841–5.
46. Gurses HN, Ayhan B, Demir R, Ozyilmaz S. The effects of inspiratory muscle training on respiratory muscle strength and pulmonary functions in children with bronchiectasis. *Eur Respir J* 2013;**47** Suppl 57:5064.
47. Gokdemir Y, Karadag-Saygi E, Erdem E, Bayindir O, Ersu R, Karadag B, et al. Comparison of conventional pulmonary rehabilitation and high-frequency chest wall oscillation in primary ciliary dyskinesia. *Pediatr Pulmonol* 2014;**49**:611–6.
48. Valerio G, Giallauria F, Montella S, Vaino N, Vigorito C, Vigorito C, et al. Cardiopulmonary assessment in primary ciliary dyskinesia. *Eur J Clin Invest* 2012;**42**: 617–22.
49. Madsen A, Green K, Buchvald F, Hanel B, Nielsen KG. Aerobic fitness in children and young adults with primary ciliary dyskinesia. *PLoS One* 2013;**8**:e71409.
50. Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. *Eur Respir J* 1997;**10**:994–9.
51. Yalçın E, Kiper N, Özçelik U, Doğru D, Firat P, Sahin A, et al. Effects of claritromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. *J Clin Pharm Ther* 2006;**31**:49–55.
52. Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, et al. Long-term azithromycin for Indigenous children with non-cystic fibrosis bronchiectasis or chronic

- suppurative lung disease (Bronchiectasis Intervention Study): a multi-centre, double-blind, randomised controlled trial. *Lancet Respir Med* 2013;**1**:610–20.
53. Masekela R, Anderson R, Gongxeka H, Steel HC, Becker PJ, Green RJ. Lack of efficacy of an immunomodulatory macrolide in childhood HIV related bronchiectasis: a randomised, placebo-controlled trial. *J Antivir Antiretrovir* 2013;**5**:044–9.
54. Goyal V, Grimwood K, Byrnes CA, Morris PS, Masters IB, Ware RS, et al. Amoxicillin-clavulanate versus azithromycin for respiratory exacerbations in children with bronchiectasis (BEST-2): a multicentre, double-blind, non-inferiority, randomised controlled trial. *Lancet* 2018;**392**:1197–206.
55. El-Abiad NM, Clifton S, Nasr SZ. Long-term use of nebulized human recombinant DNase1 in two siblings with primary ciliary dyskinesia. *Respir Med* 2007;**101**:2224–6.
56. Kobbernagel HE, Buchvald FF, Haarman EG, Casaulta C, Collins SA, Hogg C, et al. Study protocol, rationale and recruitment in a European multi-centre randomized controlled trial to determine the efficacy and safety of azithromycin maintenance therapy for 6 months in primary ciliary dyskinesia. *BMC Pulm Med* 2016;**16**:104.
57. Serisier DJ, Bilton D, De Soyza A, Thompson PJ, Kolbe J, Greville HW, et al. Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial. *Thorax* 2013;**68**:812–7.
58. Fan LC, Liang S, Lu HW, Fei K, Xu JF. Efficiency and safety of surgical intervention to patients with Non-Cystic Fibrosis bronchiectasis: a meta-analysis. *Sci Rep* 2015;**5**:17382.
59. O'Grady KF, Chang AB, Cripps A, Mulholland EK, Smith-Vaughan H, Wood N, et al. The clinical, immunological and microbiological impact of the 10-valent pneumococcal-Protein D conjugate vaccine in children with recurrent protracted bacterial bronchitis, chronic suppurative lung disease and bronchiectasis: A multi-centre, double-blind, randomised controlled trial. *Hum Vaccin Immunother* 2018:1–12.

60. Hare KM, Smith-Vaughan HC, Leach AJ, Pizzutto SJ, McCallum GB, Chang AB. Reduced nontypeable *Haemophilus influenzae* lower airway infection in children with chronic endobronchial suppuration vaccinated with the 10-valent pneumococcal *H. influenzae* protein D conjugate vaccine. *Vaccine* 2018;**36**:1736–42.
61. Platt C, Geha RS, Chou J. Gene hunting in the genomic era: approaches to diagnostic dilemmas in patients with primary immunodeficiencies. *J Allergy Clin Immunol* 2014;**134**:262–8.
62. Lai M, Pifferi M, Bush A, Piras M, Michelucci A, Di Cicco M, et al. Gene editing of DNAH11 restores normal cilia motility in primary ciliary dyskinesia. *J Med Genet* 2016;**53**:242–9.
63. Humbert M, Wagner TO. Rare respiratory diseases are ready for primetime: from Rare Disease Day to the European Reference Networks. *Eur Respir J* 2017;**49**:1700085.
64. Rubbo B, Behan L, Dehlink E, Goutaki M, Hogg C, Kouis P, et al. Proceedings of the COST action BM1407 inaugural conference BEAT-PCD: translational research in primary ciliary dyskinesia - bench, bedside, and population perspectives. *BMC Proc* 2016;10 Suppl 9:66.

Table 1 Summary of pediatric trials on airway clearance techniques or pulmonary rehabilitation in non-cystic fibrosis bronchiectasis.

Intervention	Main results	Comments
Positive expiratory pressure mask ⁴⁴	Significant improvement of pre- <i>versus</i> post- treatment regional lung ventilation. No change of pre- <i>versus</i> post- treatment FEV ₁	8-week trial in 6 children No comparison group not undergoing airway clearance techniques.
Supervised physiotherapy ⁴⁵	Significant thoracic gas volume decrease and FEV ₁ improvement <i>versus</i> unsupervised controls.	1-month trial in 24 children. No comparison group not undergoing airway clearance techniques.
Inspiratory-threshold loading device and cough training ⁴⁶	Significantly improved pulmonary function and respiratory muscle strength in treated <i>versus</i> untreated subjects.	8-week trial (abstract)
Postural drainage, percussion and vibration <i>versus</i> high-frequency chest wall oscillation ⁴⁷	Significantly improved pulmonary function, no desaturation and no differences between methods. Both methods efficient, chest wall oscillation more comfortable.	Controlled randomized crossover study of 2 methods in 24 children with primary ciliary dyskinesia. Efficiency and comfort measured subjectively. Short study period.

Table 2 Key practice points for pulmonary rehabilitation programs and airways clearance techniques in children and adolescents with non-cystic fibrosis bronchiectasis.

- Consider the patient age and the etiology of the disorder
- Individualize the treatment
- Educate the patient and the family, also with clear written advice on actions to take if symptoms deteriorate
- Be ready to change the treatment, if needed
- Develop a scheduled written follow-up plan
- Set a cluster of goals to be reached, e.g., improvement of spirometry or exercise test
- Start as soon as possible

Table 3 Summary of randomized controlled trials with different macrolides in pediatric non-cystic fibrosis bronchiectasis.

	Main results	Comments
Roxithromycin ⁵⁰	No change in FEV ₁ , airway responsiveness, sputum purulence and leucocytes	Double-blind placebo randomized controlled trial of twice-daily dose treatment for 12 weeks.
Clarithromycin ⁵¹	Significant decrease in cytokine, neutrophils and sputum volume. Significant increase of sputum macrophage ratios. No significant change in FEV ₁	Randomized controlled trial of 12 weeks treatment.
Azithromycin ⁵²	Reduced rate of exacerbations and improved weight-for-age z-score.	Increased macrolide resistance in nasopharynx pathogens in a randomized controlled trial of once-weekly dose treatment for 12–24 months.
Erithromycin ⁵³	No significant change in the number of exacerbations No improvement in lung function No impact on the levels of cytokines.	Double-blind placebo randomized controlled trial assessing efficacy of once-daily dose treatment for 52 weeks to children with HIV-related bronchiectasis.

