Paediatric and Adult Bronchiectasis: Monitoring, cross-infection, role of multi-disciplinary teams and self-management plans

Authors: Vidya Navaratnam[1,2], Douglas L Forrester[3], Kah Peng Eg[4], Anne B Chang[2,5]

1) Division of Epidemiology and Public Health, University of Nottingham, UK
2) Child Health Division, Menzies School of Health Research, Darwin, NT, Australia
3) Department of Respiratory Medicine, Royal Darwin Hospital, Darwin, NT, Australia
4) Respiratory and Sleep Unit, Department of Paediatrics, University of Malaya, Kuala Lumpur, Malaysia
5) Department of Respiratory and Sleep Medicine, Children's Health Queensland, Queensland University of Technology, Brisbane, Queensland, Australia

Correspondence to:

Dr Vidya Navaratnam

Nottingham Respiratory Research Unit

Clinical Sciences Building, Nottingham City Hospital

Hucknall Road

Nottingham NG5 1PB

UK

vidya.navaratnam@nottingham.ac.uk

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Abstract

Bronchiectasis is a chronic lung disease associated with structurally abnormal bronchi; clinically manifested by a persistent wet/productive cough, airway infections and recurrent exacerbations. Early identification and treatment of acute exacerbations is an integral part of monitoring and annual review, in both adults and children, to minimise further damage due to infection and inflammation. Common modalities used to monitor disease progression include clinical signs and symptoms, frequency of exacerbations and/or number of hospital admissions, lung function (FEV_1 %predicted), imaging (radiological severity of disease) and sputum microbiology (chronic infection with *P. aeruginosa*). There is good evidence that these monitoring tools can be used to accurately assess severity of disease and predict prognosis in terms of mortality and future hospitalisation. Other tools that are currently used in research settings such as health-related quality of life questionnaires, magnetic resonance imaging and lung clearance index can be burdensome and require additional expertise or resource, which limits their use in clinical practice. Studies have demonstrated that cross-infection, especially with *P. aeruginosa* between patients with bronchiectasis is possible but infrequent. This should not limit participation of patients in group activities such as pulmonary rehabilitation, and simple infection control measures should be carried out to limit the risk of cross-transmission. A multi-disciplinary approach to care which includes respiratory physicians, chest physiotherapists, nurse specialists and other allied health professionals are vital in providing holistic care. Patient education and personalised self-management plans are also important despite limited evidence it improves quality of life or frequency of exacerbations.

(247 words)

Bronchiectasis: Monitoring, cross-infection, MDT care

Introduction

Bronchiectasis is a chronic suppurative lung disease characterised by abnormal dilatation of the bronchial tree, which is generally irreversible in adults.[1] Repeated and/or chronic infection with recurrent respiratory exacerbations (predominantly infectious) and airway damage are hallmarks of the disease,[2] which if left unabated leads to decline in lung function[3] and respiratory failure.[4] Data suggest that the burden of disease on secondary care services is increasing worldwide.[5, 6] There is a pressing need to ensure accurate assessment, and optimal management, both pharmacological and non-pharmacological, to reduce morbidity and mortality and improve quality of life of these patients. This involves multiple facets and includes disease-monitoring, preventing cross-infection, personalised self-management plans and a multi-disciplinary approach, which is the focus of this review. Unless specified, bronchiectasis refers to that unrelated to cystic fibrosis (CF).

Monitoring

Monitoring in bronchiectasis is important to identify complications, prevent cross infection and to aid treatment decisions so as to maintain lung function, ensure early treatment and reduce exacerbation frequency, and improve quality of life (QoL). These require an assessment of symptoms and their impact on QoL, concordance with treatment and any other concerns as an integral part of each review,[7] with a variety of different modalities (summarised in Table 1), briefly described below.

Clinical symptoms and signs

Monitoring of clinical features related to exacerbations may prompt earlier treatment and reduce disease progression. Establishing the patients' baseline (which can be altered after initial diagnosis and treatment) so as to enable the detection of new symptoms is clinically important and

also used in clinical trials.[8] These symptoms include changes to sputum colour and volume, dyspnoea and haemoptysis. Amongst adults with bronchiectasis, clinical features such dyspnoea is reported in over 80% of individuals[9] and is associated with reduced FEV_1 and radiological extent of bronchiectasis.[10] Studies have also shown that sputum colour can predict bacterial infection[11] and is associated with bronchial inflammation.[12] However, there are limited data on changes to daily symptoms during the natural history of bronchiectasis and timing of the changes seen around exacerbations. An observational UK cohort study reported that changes to cough, breathlessness and sputum colour were the most prevalent symptoms at initiation of antibiotic treatment for exacerbations.[13] There was also an association between symptom burden and fall in peak expiratory flow rate.[13] Recently, a consensus statement for defining exacerbations in adults for clinical trials was developed: "a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 hours: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required".[14]

In children who are unable to expectorate and who may not have a continuous cough but only one that occurs during exacerbations or disease progression, the above symptoms are not applicable but instead, a change in cough quality (from dry to wet) and/or frequency/severity are markers of an exacerbation (when acute) or deterioration in bronchiectasis (when chronic and unaltered with optimal treatment).[15] Other paediatric specific features include growth failure.[16]

Signs of disease progression include new development of digital clubbing, chest wall abnormality, development of secondary cardiac disease (pulmonary hypertension signs e.g. loud P2, cardiac failure). In addition, monitoring of extrapulmonary of co-morbidities and/or complications should be part of a clinical review. There is a multitude of possible co-morbidities/complications; the more common and treatable ones are listed in Table 2.

Health related QoL (HR-QoL) measures and disease severity

HR-QoL measures are mainly used in research settings as they can be burdensome and difficult to administer in routine clinical practice. Commonly used HR-QoLs in respiratory disease include St George's Respiratory Questionnaire (SGRQ), Leicester Cough Questionnaire (LCQ) and the Quality of life Questionnaire-Bronchiectasis (QOL-B).[17] QOL-B is the first bronchiectasis-specific, HR-QoL for adults[18], whilst SGRQ and LCQ were developed for other respiratory conditions but have been shown to be valid in assessing HRQoL in bronchiectasis.[19, 20] To date, there have been no comparative studies to investigate which HRQoL questionnaire is best.

Given the difficulties of direct reporting for children of pre-school age, parent-proxy reporting is often the practice of choice. Parent-proxy cough-specific QoL (PC-QoL)[21] is the tool commonly used in paediatric studies.[22] For older children (>7 years), a child self-reporting instrument, chronic cough-specific QoL (CC-QoL) questionnaire [23] is a more reliable and sensitive HRQoL from the child's perspective.[23]

The Bronchiectasis Severity Index (BSI)[24], FACED[25] and e-FACED[26] have been developed and validated in adults with bronchiectasis to define the disease severity and prognosticate outcomes (hospitalisation and mortality). Recently, the Bronchiectasis Aetiology Comorbidity Index (BACI) was developed and validated to accurately predict which patients were at higher risk of death at 5 years and hospitalisations.[27] BACI also was able to predict frequency of exacerbations and HRQoL as measured by SGRQ.[27] More detail on these scoring systems are set out in Review 1. None of these scoring systems can be validly applied in children.

Imaging

The sensitivity of chest radiographs (CXR) for diagnosing bronchiectasis is poor, varying between 37% (compared to a bronchogram[28]) to 87.8% (compared to high resolution computed tomography[HRCT]).[29] It logically follows that CXR is also insensitive in monitoring disease progression.[7] Studies amongst adults with CF demonstrated that CXR changes correlate poorly in acute exacerbations.[30]

HRCT is currently the 'gold standard' for diagnosing and assessing the degree and anatomic extent of bronchiectasis,[7, 31] although multi-detector CT (MDCT) scans are more sensitive (c.f. HRCT) in detecting bronchiectasis.[32, 33] In a study that compared serial HRCT and functional changes in 48 adults with bronchiectasis (median interval between scans was 28 months), 56.3% of individuals had HRCT features consistent with progression of disease and changes to disease severity was better detected on HRCT compared to FEV_1.[34] Radiation burden limits the use of serial chest CT scans in monitoring, especially in children who are approximately 10 times as sensitive to the effects of radiation as adults[7] but as low dose CT scans are increasingly improving, this may be a future monitoring tool.

The role of magnetic resonance imaging (MRI) as a non-invasive, radiation free imaging modality is increasingly proposed, with one study suggesting that 3-T MRI was just as effective as HRCT in assessing extent and severity of bronchiectasis in 30 children and 11 young adults with bronchiectasis.[35] In young children with CF (age range 0-6 years), MRI can detect bronchiectatic changes from the first year of life and response to treatment of exacerbations.[36] In adults, hyperpolarised ^{3}He MRI reported abnormal ventilation defects in patients with bronchiectasis (n=15) and none in controls (n=15).[37] There was also evidence of improvement in ventilation defects in approximately half the patients with bronchiectasis following airway clearance treatment.[37] The high cost and expertise required to acquire and interpret the images currently limits its use in clinical

practice. Furthermore, evidence of the role of MRI in monitoring radiological progression and detecting response to therapies in bronchiectasis is still lacking.

Pulmonary function tests (PFTs)

International guidelines suggest that spirometry should be performed at diagnosis[7, 31] and be repeated at least annually in adults under secondary care follow up[7] and at each review in children,[31] although spirometry can be insensitive in children.[38] Airflow obstruction is the most common pattern seen on spirometry.[39] Restrictive or a mixed patterns are also found, as is normal values (in mild bronchiectasis).[40, 41] FEV_1% predicted is the spirometric index most strongly associated with mortality[24, 25] and hospital admission.[24] Adult patients with FEV_1 <30% predicted had an almost 4.5 times higher mortality and 1.5 times higher risk of hospital at 4 years.[24] Another study demonstrated that FEV_1<50% predicted was associated with 5 times higher mortality at 5 years.[25] This has resulted in FEV_1 being a key component in bronchiectasis severity scores.[24, 25] The lack of data on paediatric scoring systems makes it unclear if FEV_1 is as useful a prognostic marker in children.

There is little information on the role of other PFT indices in monitoring the natural history of bronchiectasis. One study using data from a cohort of 111 adults with bronchiectasis[4] described that pulmonary function indices associated with mortality were higher residual volume (RV)/Total Lung Capacity (TLC) ratio (RR 1.03, 95%CI 1.01-1.04), lower TLC (RR 0.95, 95%CI 0.93-0.98) and lower transfer coefficient for the lung for carbon monoxide (Kco) (RR 0.96, 95%CI 0.94-0.98).[4] A small study (n=27) found that mean six-minute walk distance (6MWD) had a stronger correlation with HR-QoL measures then spirometric indices,[42] whilst a Chinese study described higher mortality in those with a lower 6MWD at baseline.[43] Baseline 6MWD of survivors was 467.9±77.1 metres compared to 363.7±126.7 metres in those who had died 6 years later.[43] Our literature search revealed no published data on non-spirometric lung function indices in the paediatric population.

There is renewed interest in the use of the Lung clearance index (LCI), from multiple breath washout tests, as an early marker of detecting early airway disease. While it is likely more sensitive than spirometry, its role is unclear, and unlikely the same as in cystic fibrosis.[44, 45]

Lower Airway Microbiology

Guidelines recommend that all children and adults with bronchiectasis have an assessment[7] and surveillance[31] of lower respiratory tract microbiology, although no clear guidance on its frequency was provided. Monitoring sputum characteristics (colour, volume) is also useful as sputum colour can predict bacterial infection[11] and is associated with bronchial inflammation.[12] In children who do not expectorate, microbiology monitoring poses another layer of complexity as bronchoalveolar lavage is required and thus this is usually not done unless there is a deterioration in the child's clinical's state. Some centre use cough swabs or induced sputum but there is controversy with regards to its accuracy, even in CF.[46]

Microbiological surveillance is important to detect acquisition of pathogens (e.g. *P.aeruginosa, mycobacterium, aspergillus),* which can be eradicated.[47, 48] These pathogens *are* associated with accelerated lung function decline[49, 50] and poor outcomes.[4, 51, 52] The predominant pathogen isolated in children is *Haemophilus influenzae.*[53-56] In adults *H. influenzae* is frequently isolated, followed by *P. aeruginosa*.[57, 58] Summary of a roundtable discussion amongst clinicians with an interest in bronchiectasis revealed varying frequencies of sputum microbiological surveillance in clinical practice.[59]

Much can be learned from data relating to other lung diseases and some potential pitfalls avoided. Genetic sequencing techniques for identifying bacterial species in sputum has improved our understanding of lung flora and in the future, may be feasible enough to be used to assess 'new infections'. For example, *P. aeruginosa* is more widespread in the sputum of patients admitted with

exacerbations of chronic obstructive pulmonary disease than was previously thought and acquisition is associated with exacerbation.[60] Individuals with CF have a tendency to pick up a strain of *P. aeruginosa* which they become chronically infected with throughout their life but which may be displaced by an epidemic strain.[61, 62] However, there is still no consensus on how to define "chronic infection[63] although it is important to classify patients with regards to their infection status as this relates to disease progression and segregation of patients based on lower airway microbiology.

Use of other markers (e.g. anti-pseudomonal antibodies as a surrogate marker for *P. aeruginosa)* to monitor lower airway microbiology have been studied. Using a commercially available "anti-PA IgG" ELISA, a study of 408 individuals suggests clinical utility for initial diagnosis of chronic infection (n=60; sensitivity 95%, specificity 74.4%) and monitoring of treatment response to first isolation of *P. aeruginosa* (n=38).[64] However there is still insufficient data to recommend its use in clinical practice.

Exacerbations

Another paper in this series focuses on exacerbations; clinicians should be cognisant that monitoring for exacerbations and its frequency is important as exacerbations are an independent predictor of lung function decline[49, 65] and impair QoL in adults[65, 66] and children.[67] Frequency of exacerbations is incorporated into severity scoring models (e.g. BSI[24] and E-FACED[68]) and the 'frequent exacerbator' phenotypes (>2-3 exacerbations/year) have higher mortality.[68, 69]

Cross-infection

As patients with bronchiectasis are often chronically infected by various pathogens,[70] and new infections can lead to persistent airway inflammation resulting in further lung damage and deterioration in lung function, prevention of cross-infection (transmission of pathogens between patients) is an increasing concern, as it also is in CF. Cross-infection can potentially occur in clinics, hospitals and social events (e.g. camps, schools, work).

The follow-up of these patient groups varies worldwide, with some centres sharing clinics for both CF and non-CF patient groups. Recent published data from the European Bronchiectasis Registry suggest that across Europe 45% of adults with bronchiectasis are managed in centres with shared facilities with adults with CF and 10% of bronchiectasis patients are followed up in CF clinics.[71] In CF, evidence of cross-infection with pathogens such as *Methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Burkholderia cepacia complex* and *Mycobacterium abscessus*[72-75] has led to guidelines recommending limiting contact between patients and setting clinics based on the patients' bacteriology of clinical isolates.[76]

The limited published data on cross-infection in people with bronchiectasis have, to date, investigated the risk of cross-infection of *P. aeruginosa* strains. Two United Kingdom (UK)-based studies and a Spanish study suggest minimal risk of cross-infections in their cohorts.[77-79] One UK study[77] investigated the risk of cross-infection amongst adults with bronchiectasis where patients were cared for separately and at a distance from the regional CF centre. Isolates collected from 36 patients analysed using two genotyping methods found an absence of dominant clones of *P. aeruginosa,* leading the authors to conclude there was little evidence of cross-infection.[77] More recently, a study of 93 adults with bronchiectasis from 16 England and Wales centres analysed 189 isolates of *P. aeruginosa* from sputum samples using whole genome sequencing.[78] The distribution of *P. aeruginosa* lineages found in the isolates was broadly representative of the *P. aeruginosa* population, with no data to suggest widespread transmissible strains amongst the population

studied.[78] The Spanish study used PCR fingerprinting on 64 *P. aeruginosa* isolates from 16 adults with bronchiectasis; 56% of patients harboured only one clone and 31.5% carried two clones. The genetic dissimilarity between the clones suggested that cross infection was unlikely to have occurred.[79]

However, the possibility of the occurrence of cross transmission of *P. aeruginosa* amongst patients with bronchiectasis was raised by two other UK studies. A study using 144 isolates of *P. aeruginosa* from the sputum of 84 adults with bronchiectasis, and analysed using multiple-locus variable number tandem repeat typing reported that three individuals acquired epidemic strains of *P. aeruginosa*, likely from the CF population during inpatient stays.[80] There was no evidence of cross-infection of non-epidemic strains between patients with bronchiectasis.[80] The second study[81] of segregated CF and unsegregated bronchiectasis cohorts with shared facilities used sputum derived isolates from 46 bronchiectasis and 22 CF adults. The authors[81] found that cross infection occurred in 3 out of 46 of the unsegregated non-CF individuals but the differences in strain distribution made cross-transmission between patients with CF and bronchiectasis unlikely, despite sharing of facilities.[81] Within the paediatric population, there is only one published case report of a 14-year-old boy with bronchiectasis (secondary to chronic aspiration) infected by an epidemic strain of *P. aeruginosa*, identical to the strain which was found in four CF patients with whom he shared a room during his in-patient stay.[82]

In summary, these data depict the possibility of cross-infection with *P. aeruginosa* within the bronchiectasis population and between individuals with CF and bronchiectasis. However, such incidents are infrequent. Furthermore, there is insufficient evidence of new acquisition of *P. aeruginosa* as all individuals included in the studies above were already infected with *P. aeruginosa*. There are no studies examining cross-infection of micro-organisms other than *P. aeruginosa* in people with bronchiectasis and further research in this area is needed. A recent position statement by the European Bronchiectasis Network (EMBARC), EMBARC/ELF patient advisory group and European Reference Network (ERN-Lung) Bronchiectasis Network concluded that current evidence suggests

cross-infection is uncommon[83] and the benefits of group activities such as pulmonary rehabilitation[84] outweigh any theoretical risk of cross-transmission of pathogens.[83]

While much may be learned and applied from CF-based studies, the cystic fibrosis transmembrane receptor (CFTR) dysfunction in CF leads to a fundamentally different microbiological niche[85] compared to non-CF bronchiectasis for a number of reasons such as the different sputum composition, increased chloride and DNA levels and reduced airway fluid glutathione, and neutrophil dysfunction contribute to an environment with different selection pressures and thus different traits in the bacterial populations.[86] However, the serious nature of the consequences and robust evidence of global transmission of epidemic strains of *P. aeruginosa* between individuals with CF[87] makes the authors loathe to ignore simple infection control measures to reduce cross-infection. Use of face masks at appropriate times greatly reduces the risk of transmission between individuals[88] in clinical settings and should be adopted where practicable.

Role of the Multi-disciplinary team (MDT)

Multidisciplinary care is defined as when healthcare professionals from across disciplines work together to provide comprehensive care aiming to meet the needs of the patient.[89] Providing holistic care for patients with bronchiectasis to control symptoms, reduce exacerbations, preserve lung function and maintain quality of life requires input from all members of the multi-disciplinary team. Good practice guidelines recommend that as a minimum, patients be managed by a respiratory physiotherapist and nurse specialist alongside a chest physician.[7] There are no published data investigating the role of MDT care in patients with bronchiectasis, particularly with regards to cost-effectiveness. Evidence behind guidelines for MDT care in bronchiectasis is extrapolated from COPD. A Cochrane review found that MDT approach to patients with COPD improved not just exercise tolerance and quality of life, but also hospital admissions due to exacerbations and length of stay in hospital.[90] There was however, no effect on mortality.[90] We also found no information available on

the impact of telemedicine in the management of patients with bronchiectasis. Below we discuss aspects of MDT care with the largest evidence base.

Chest physiotherapists and pulmonary rehabilitation

Airway clearance techniques are widely used in treating patients with bronchiectasis, as discussed in another paper in this series. There is wide variety of techniques that are age, preference and co-morbidity dependent- thus specialised chest physiotherapists are an essential team member. Chest physiotherapists are also usually the leaders of pulmonary rehabilitation.

Nutritionists

There are limited studies on anthropological measurements, assessment of macro- and micro-nutrition or nutritional supplementation in individuals with bronchiectasis. Nevertheless, nutritional issues may occur especially in those with severe disease and thus, nutritionists are part of the MDT. An Australian study retrospectively reviewed longitudinal data from 52 children with bronchiectasis over 3-5 years and described improvements in BMI z-scores per annum over 3 years, but no further change at five year follow up (n=25).[65] Similar to the findings of a London cohort[91], children with worse spirometry (FEV_1<80% predicted) at baseline were associated with a lower BMI.[65] Amongst 98 Turkish adults with bronchiectasis had a mean BMI of 27.62 (SD 6.36), and a lower BMI was strongly associated with mortality.[92] However, a Spanish study of 76 adults reported no difference in mean BMI between patients who had rapid decline in lung function compared to those who did not.[49]

Nurse specialist and nurse-led care

Within a MDT, the nurse specialist is often the first point of contact for patients. In most teams, the nurse specialist has the key role of an integrated approach to chronic disease management e.g. COPD and diabetes, as well as leading health education. In some centres, a nurse-led care approach is used. However, a recent systematic review evaluating the safety and efficacy of nurse-led care amongst adults with bronchiectasis included only one RCT,[93] a UK study crossover trial with 80 adults with bronchiectasis who were treated for 12 months by a specialist nurse or doctor, who then crossed over to the other clinician for the next 12 months.[94] There was no difference in mean FEV_1 between the groups and no differences in other clinical outcomes or HR-QoL measures, but patients in the nurse-led care group had higher hospital admissions.[94] Further analyses by the authors of the systematic review demonstrated no difference in the number of exacerbations requiring treatment with antibiotics.[93] Although initially the nurse-led care group had higher treatment costs, by the end of the trial, these were equitable.[93, 94]

Our literature search also revealed a non-randomised pilot study of specialist nurse-led cognitive behavioural therapy (CBT) in adult patients with longstanding and severe bronchiectasis. [95] There were no differences in levels of anxiety and depression between the groups.[95] There was a marked difference in SGRQ scores between the groups at the baseline; likely due to selection bias as "sicker" patients chose to be in the control group. The difference in SGRQ scores between the groups remained at the end of the study, but was lower in the CBT group. [95] The shuttle test distance in the CBT group was higher both pre-and post -intervention. [95] This study raises the possibility of CBT playing a role in improving overall health in adults with bronchiectasis, but severe limitations of its design mean more robust clinical trials need to be carried out before firm conclusions can be drawn.

Self-management plans

Educating individuals with bronchiectasis, including explanation of their condition, how to recognise infective exacerbations and the importance of treatment, as well as a personalised management plan with approaches and options to treatment is recommended.[7, 96] Qualitative studies have highlighted that patients felt that information available was lacking, there was a need for accessible information outside the specialist clinic setting and increasing resources could equip patients to manage their disease more effectively.[97, 98] A study using focus groups found that although patients had conflicting views on the meaning of self-management, most were comfortable with the opportunity to self-manage their condition, especially if it helps avoid admission to hospital.[99]

A systematic review assessed the efficacy, cost-effectiveness and adverse effects in self-management interventions amongst people with bronchiectasis that included two adult-based RCTs.[100] One was a proof of concept RCT comparing usual care with an expert patient programme described no differences in SGRQ total scores between the groups post-intervention, at three or six months after intervention.[101] The other RCT of early rehabilitation, self-management and usual care (six weeks of intervention) compared to usual care in adults with chronic respiratory disease, which included 20 individuals with bronchiectasis.[102] Amongst the subset of participants with bronchiectasis[102] there was a trend in improvement in mean SGRQ scores for both groups, but this did not meet statistical significance at six weeks, 3 or 12 months follow up.[100] Although the mean difference in SGRQ scores between the groups exceeded the minimum clinical important difference[103] the lack of power from the small sample size (n=20) means conclusions are unable to be drawn.[100] The authors of the systematic review concluded that there is insufficient evidence to determine if self-management interventions impact HR-QoL or exacerbations.[100]

Conclusion

In summary, current evidence suggests a low risk of cross-infection of *P. aeruginosa* in bronchiectasis. At present the benefits of group participation activities such as pulmonary rehabilitation and structured exercise programmes likely outweigh the risks of possible cross-transmission of pathogens, but more evidence is required. Further research and consistent terminology surrounding infection status, particularly with regards to chronic *P. aeruginosa* infection are also lacking. A validated and universally adopted classification of infections will help guide treatment and prognosis in and individual clinical setting, and facilitate research into future therapies, clinical governance and quality assurance.

There are a wide range of modalities available for disease monitoring, but the cost and expertise involved in some of these tools may limit their use as part of routine care. There is also a lack of clarity on optimal frequency of monitoring and the role of telemedicine in the follow-up of stable patients. Despite multi-disciplinary care and self-management being part of good practice guidelines, there is a paucity of evidence. Until more evidence is obtained in the neglected field of bronchiectasis, practice should be based on national guidelines.

Table 1: Modalities used for monitoring patients with bronchiectasis.

Test for monitoring	Major Findings	Advantage	Limitation	Evidence	
				Children	**Adults**
Symptoms and signs	Increased sputum volume, change in sputum purulence, chest pain, dyspnoea	Easy to recognise	Insensitive, dependent of patients' recall	Change of cough characteristics with exacerbations, associations of symptoms and signs with other markers of bronchiectasis severity.[104, 105]	Sputum colour can predict bacterial infection[11] and is associated with bronchial inflammation.[12]
Quality of life measures	St George's Respiratory Questionnaire (SGRQ),[19] Leicester Cough Questionnaire (LCQ)[20] have been validated in patients with bronchiectasis. Quality of life bronchiectasis (QOL-B) is a disease specific questionnaire.[18]	Widely available	Not routinely used in clinical practice	Parent-proxy cough-specific QoL (PC-QoL) used in pre-school children.[21] Chronic cough-specific QoL (CC-QoL) questionnaire for older children able to self-report.[23] Relationship between QoL measures and other bronchiectasis markers of severity. [22]	A systematic review found currently used HRQoL measures valid and reliable in bronchiectasis.[17]
Spirometry	Decrease in FEV_1	Widely available, easy to use in follow up	In mild disease, spirometry values are normal. Can be difficult to obtain from young children (aged < 5 years)	Several cohort studies comparing chest CT scan with spirometry[38, 91] and/or description of lung function in cohorts	FEV_1 associated with disease severity as measured by BSI [24] and FACED.[25]
Transfer coefficient of the lung for carbon monoxide (Kco)	Reduced Kco	Widely used in clinical practice	Difficult obtaining reproducible measurements due to cough	No data available	Lower Kco was associated with a slight reduction in mortality (RR 0.96, 95% CI 0.94-0.98)[4]
Total lung capacity (TLC)	Reduced TLC	Widely used in clinical practice	Different methods in measuring TLC	No evidence	Lower TLC found to be associated with slightly reduced risk of death (RR 0.95,

					95% CI 0.93-0.98)[4]
Six-minute walk test (6MWT)	Reduced distance usually seen at six minutes (6MWD)	Good measure of functional status in chronic respiratory disease	Can be influenced by external factors e.g. skeletal muscle dysfunction	No evidence	Moderate correlation between 6MWD and FEV_1 and FVC percent predicted. [42] No association with HRCT severity of bronchiectasis. [42] Strongly associated with HRQoL measures. [19] Shorter 6MWD associated with higher mortality. [43]
Lung clearance Index (LCI)	Higher values seen in patients with bronchiectasis	Non-invasive, repeatable.	Time intensive to obtain, limited availability, research tool	No reliable data in bronchiectasis unrelated to CF. LCI may be more sensitive than spirometry in children with CF.[106]	Inconsistent results.[44, 45] However, maybe more sensitive measure compared to FEV_1. [107] Associated with spirometric airflow obstruction.[108]
Chest radiograph	Increased linear markings, crowding of bronchi, mucous plugs, bronchial wall thickening, tram tracking	Low cost, highly available, low radiation dose	Can be normal	CXR is of little diagnostic value in children[109]	Poor correlation between infective exacerbations and radiographic changes.[30]
High resolution computed tomography (HRCT)	Various bronchiectasis radiology score e.g. Bhalla, Webb reflecting increasing severity of bronchial wall dilatation, bronchial wall thickening, signet ring. Change from cylindrical to varicose to cystic bronchiectasis	Current gold standard for diagnosis	Radiation burden limits the use in monitoring radiological progression	A broncho-arterial ratio > 0.8 is considered diagnostic of bronchiectasis.[110] Relationship between radiological scores and other markers of bronchiectasis severity.[38, 111]	Relationship between radiological scores and other markers of bronchiectasis severity.[112]
Magnetic Resonance Imaging (MRI)	Ventilation defect percent	Radiation free	Time and cost associated with image	Requires validation for	In patients with CF, changes seen on 3He MRI

	in areas of bronchiectasis	imaging modality	acquisition may limit the use to tertiary centres	diagnosis and monitoring	strongly correlated with abnormalities seen on HRCT and spirometry.[113] A small study (n=15) in people with bronchiectasis showed that structure-function abnormalities seen on hyperpolarised ^{3}He MRI correlated well with CT changes.[37]
Sputum microbiology	*Haemophilus influenzae* is common in children [53-56]. In adults *H. influenzae* and *P.aeruginosa* are commonly isolated.[57 58]	Widely used in clinical practice	Multiple bacterial species can be isolated in a single sputum sample. Difficulty in obtaining samples in pre-school children	Limited data describing lower microbiology in children with bronchiectasis. *P. aeruginosa* is uncommon in children with bronchiectasis.[54]	*P. aeruginosa* strongly associated with lung function decline,[49] disease severity [24, 25] and mortality.[4]
Exacerbations	Change in sputum volume and/or colour, increasing breathlessness and/or reduced exercise tolerance, lethargy, malaise, haemoptysis. International guidelines long term antibiotics (inhaled or oral) if a patient has 3 or more exacerbations a year.[31, 84, 114]		Varying definitions of exacerbation have been used in studies.	Wet cough and cough severity were the best predictors of exacerbations in children.[15] Respiratory viruses were detected in almost 50% of exacerbations in children. [115] Frequency of exacerbations requiring hospitalisation was associated with rapid decline in lung function.[65]	*P. aeruginosa* is associated with more frequent exacerbations.[116] Frequent exacerbations are associated with higher disease severity and mortality.[68, 69]

Table 2: Common co-morbidities/complication in bronchiectasis

Co-morbidities/complications as part of treatable traits [47, 48]	Main symptoms and signs
Asthma-like disease[117]	Breathlessness, wheeze, chest tightness, cough (especially at night), diurnal variation in peak flow recording.
Chronic obstructive pulmonary disease[118]	Productive cough, breathlessness (especially on exertion), wheeze, hyperinflation, air trapping. Fixed airflow obstruction on spirometry
Gastro-oesophageal reflux [119]	Heartburn, epigastric pain, chest discomfort, regurgitation
Sinusitis[120]	Nasal obstruction/congestion, anterior/posterior rhinorrhoea, anosmia, headache, facial pain/pressure. Nasal polyps, mucopurulent discharge, oedematous middle meatus
Ischaemic heart disease[121]	Central chest pain (on exertion or at rest) radiating to the jaw and/or left arm, shortness of breath
Anxiety and/or depression[122]	Feelings of apprehension or dread, poor concentration, insomnia and/or sleep disturbance, anhedonia, low mood, poor appetite, lethargy
Hypoxaemia	Breathlessness on exertion and/or at rest, lethargy, tachycardia, confusion, desaturation on exertion, peripheral cyanosis
Pulmonary hypertension[123]	Dyspnoea on exertion and/or at rest, syncope, chest pain, fatigue, peripheral oedema, peripheral or central cyanosis
Urinary incontinence[124, 125]	Stress incontinence (leaking urine during extra sudden pressure e.g. coughing, laughing, exercise), urge incontinence, overflow incontinence
Dental disease[126]	Halitosis, red, swollen, bleeding, receding gums, sensitive teeth
Sleep disordered breathing[127]	Unrefreshed sleep, excessive daytime somnolence, early morning headaches, fatigue, lethargy, nocturia, weight gain

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