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*Bronchiectasis: What We Don’t Know Yet But Should.*

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Bronchiectasis: What we don't know yet but should

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Abstract

Bronchiectasis is a chronic lung disease characterized by airway dilatation, mucus retention and recurrent lower respiratory tract infections. Bronchiectasis has a significant morbidity and an appreciable mortality rate and is increasing in prevalence. Despite this there are still significant knowledge gaps in our understanding of the epidemiology, pathophysiology, prognosis and optimal treatments in bronchiectasis. This review highlights selected key knowledge gaps in bronchiectasis. Addressing these gaps in knowledge could improve the disease burden both to patients and to healthcare systems. Coordinated research networks and large database cohorts of patients ready to participate in both observational and intervention studies will be needed to improve our treatment options.
 Bronchiectasis: What we don't know yet but should

Introduction

Bronchiectasis is increasingly recognised as both a primary disease and as a complication of other common diseases such as asthma and chronic obstructive pulmonary disease (COPD). There is a paucity of data on the epidemiology, pathophysiology and optimal treatment approaches in this patient population. Data does suggest, however, that the incidence of bronchiectasis is increasing, with a corresponding increase in mortality rates. Marked heterogeneity exists in the aetiologies of bronchiectasis and these may result in different therapeutic targets. Significant knowledge gaps remain and there is a continuing need to systematically coordinate our research endeavours to enable us to deliver a step-change in bronchiectasis management from empirical to evidence-based therapies. Networks are developing to capture large patient cohorts allowing better understanding of the disease process and its management (e.g. PROGNOSIS, EMBARC (www.bronchiectasis.eu) and BronchUK (www.bronch.ac.uk). Multidisciplinary and cross-national efforts in epidemiology, microbiology, genetics, immunology, basic science and epithelial biology in conjunction with the pharmaceutical industry will help to tackle these knowledge gaps and deliver effective new therapies to the clinic. Selected research areas that such collaborative efforts may undertake are discussed in this article.

Definition and Diagnosis of Bronchiectasis

Bronchiectasis, also referred to as non-cystic fibrosis bronchiectasis, is characterised by irreversible airway dilatation with clinical features including cough, chronic sputum
production, haemoptysis, dyspnoea and chronic rhinosinusitis. Patients report recurrent hospital admissions, reduced quality of life and fatigue.\textsuperscript{1,2,3,4} The ‘vicious cycle’ hypothesis describes how a combination of host susceptibility and environmental insult leads to progressive airway damage and dilatation.\textsuperscript{5} Defects in host immune response can also contribute to chronic infection and inflammation.\textsuperscript{6}

Whilst bronchiectasis is quite frequently seen in COPD and in some cases of chronic asthma, it unclear if there is causality or co-association between these conditions. Recognised aetiologies include post-infection, immunodeficiency syndromes, inflammatory bowel disease, connective tissue diseases, Primary Ciliary Dyskinesia (PCD), Young’s syndrome, and inhalation of a foreign body. A significant proportion of cases, up to 50%, will have idiopathic bronchiectasis.\textsuperscript{7-10} Investigations to identify associated conditions may include genetic testing for cystic fibrosis, Aspergillus precipitins, immunological profile, and sputum microbiology.\textsuperscript{9} Defining the aetiology leads to management changes for both children and adults with bronchiectasis.\textsuperscript{7,10,11}

To confirm clinical suspicions, high resolution computed tomography scanning (HRCT) is required.\textsuperscript{12} Studies acknowledge that a clinical scenario highly suggestive of bronchiectasis may not correlate with a ‘positive’ HRCT, which raises questions about the links between clinical symptoms and the pathophysiological processes involved.\textsuperscript{7,8} It has also been shown in two case-series that approximately 15% of radiologically diagnosed patients had their bronchiectasis diagnosis refuted on re-read of their scans.\textsuperscript{8,13}

The comparison of airway and accompanying artery diameter in order to establish presence of airway dilatation has been described pathologically.\textsuperscript{14} The same comparison is used to look for airway dilatation on HRCT scans.\textsuperscript{15} Bronchial wall thickening is also well described in bronchiectasis imaging (Figures 1 and 2). When bronchiectasis and COPD co-exist or overlap, understanding which process drives this is challenging. Gatheral et al studied the impact of
COPD-related bronchiectasis and showed the presence of bronchiectasis to be associated with increased infections and hospitalisations regardless of bronchial wall thickness. Difficulty remains in defining COPD-driven bronchiectasis or idiopathic bronchiectasis in an ex-or current smoker. A catch-all term, Bronchiectasis and COPD overlap syndrome (BCOS), has been suggested.

Table 1 Known unknowns in definitions and diagnosis

Key: There are several unknowns in the definitions and diagnosis of bronchiectasis. ABPA denotes allergic bronchopulmonary aspergillosis and NTM non tuberculous mycobacterial disease.

| 1) | What are the false positive and false negative rates of bronchiectasis on chest HRCT? |
| 2) | Can computerized algorithms help define bronchiectasis and monitor airway caliber changes on HRCT? |
| 3) | What is the natural history of suspected bronchiectasis patients with a “normal” HRCT? How many progress to bronchiectasis within 5 years? |
| 4) | What are the minimal set of aetiological investigations? (see figure 2) |
| 5) | Does HRCT have any role in monitoring response to treatment? (see figure 3) |
| 6) | Does air trapping/ mosaicism pattern on HRCT predict a better response to anti-inflammatory treatments? (see Figure 4) |
| 7) | How good are HRCT patterns at directing investigations into aetiology such as ABPA or NTM disease? |
| 8) | What role is there for HRCT in helping define causes for recurrent exacerbations? |
| 9) | What clinical features suggest extended aetiological testing (e.g. Cystic Fibrosis genotyping, extended immunology testing) is undertaken? |
| 10) | What symptoms or clinical features in common respiratory diseases such as COPD and asthma should prompt HRCT scanning to exclude coexistent bronchiectasis? |

**Epidemiology**

Reported rates of bronchiectasis are likely to be inaccurate due to misdiagnosis (as other common respiratory disorders, e.g. asthma or COPD) and missed diagnosis (e.g. with
overlapping diagnoses such as BCOS and asthma-bronchiectasis overlap syndrome (ABOS). Data across multiple healthcare systems suggest prevalence is increasing.\textsuperscript{18-21} Recent population-based estimates of prevalence in Germany suggested an overall rate of 67/100,000, increasing to 228/100,000 population in men aged 75-84.\textsuperscript{20} Prior data from the US support these findings with an even higher overall annual prevalence of 370/100,000 person-years and 537/100,000 person-years in women aged 80-84.\textsuperscript{21} We are unsure if rising prevalence is due to increased pick-up rates with greater access to HRCT scanning, or if it represents a real increase in disease burden. Irrespective of the cause of increasing rates of bronchiectasis, we are still left with a conundrum: why is bronchiectasis not rapidly declining with improving health, nutrition, access to childhood vaccination and antibiotic therapy?

Establishing aetiological causality in bronchiectasis also presents ongoing uncertainties: separating idiopathic bronchiectasis from post-infectious bronchiectasis is challenging. Accuracy in categorisation is important as some aetiological subgroups encountered in clinical practice are excluded from interventional studies.\textsuperscript{22,23} A recent UK primary care database study suggested that HIV infection was a more common aetiological cause of bronchiectasis than previously reported.\textsuperscript{21} This may reflect greater rates of HRCT scanning in this population, perhaps advocating wider use of HRCT in other “at risk” groups. High rates of bronchiectasis in COPD have also been reported (as high as 40%), yet this is likely to be influenced by which sub-population of COPD patients are investigated, i.e. “chronic bronchitis recurrent exacerbators” or all other phenotypes of COPD (such as emphysema without exacerbations).\textsuperscript{9,16} The fact that the conditions known to overlap with bronchiectasis (COPD and asthma) are so prevalent could translate into a large increase in identification of cases of bronchiectasis.

Several unknowns are listed in table 2

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\begin{tabular}{|l|}
\hline
1) Is there a genuine increase in prevalence or simply an improved diagnostic rate or change in diagnostic thresholds on HRCT? \\
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4
| 2) Do aetiologies vary between developing and developed nations? |
| 3) Which aetiologies are associated with a poorer outcome/ early mortality? |
| 4) Is there good inter-observer correlation when aetiological causes of bronchiectasis are attributed? |
| 5) Can we develop more robust aetiological definitions that work in clinical practice? |
| 6) Which aetiologies benefit from targeted specific treatment? |
| 7) Is there an impact of national programs of pneumococcal vaccination on rates of bronchiectasis? |

**Prognosis**

Until recently, prognosis data has been dominated by single-centre studies, often from specialised centres. Available data from across the UK suggests an increasing mortality rate at 3%/year. Two prognostic scoring indices providing estimates of mortality and hospitalisations over a 4-5 year period have recently been published: the FACED score (Forced expiratory volume 1 second, Age, Colonisation by *Pseudomonas aeruginosa*, Extent (number of lobes affected) and Dyspnoea, Spain) and the Bronchiectasis Severity Index (BSI, Edinburgh). The latter was internationally validated across 4 centres (UK, Belgium, and Italy). It has many components similar to the FACED with additional factors consisting of weighting for prior healthcare use and persistent infection with “other pathogens.” Neither, however, have been tested outside of Europe or in developing nations and we do not know how interventions such as Pseudomonas eradication may alter such prognostic indices.

**Table 3 Known unknowns in Bronchiectasis prognosis**

Key: FACED score and Bronchiectasis severity index (BSI) scores

| 1) Are there differences between the FACED and BSI prognostic scores in utility and accuracy? |
| 2) What factors will influence uptake and use of prognostic indices into routine clinical practice? |
3) Will clinicians alter management based on “high risk” scoring in such systems and what treatment intensification might be applied in “high risk” patients?

4) Do these scoring indices work effectively across different healthcare systems?

5) Do different aetiologies confer different prognoses? How does BCOS (Bronchiectasis and COPD overlap syndrome) affect the performance of the scoring indices?

6) What is the impact of comorbidities on prognosis? Should we be assessing all patients with bronchiectasis for prevalent comorbidities?

7) Can these prognostic scores help transplant referral and predict mortality over a transplant window of 1-2 years?

8) Does the mortality rate or hospitalisation risk fall if Pseudomonas is “eradicated” and their FACED or BSI score falls?
Pathogenesis and microbiology

Cole’s continuous and self-perpetuating vicious cycle hypothesis provides a useful model of bronchiectasis pathophysiology to this day. Treatment is targeted at interrupting the interconnecting processes of failed mucus clearance, airway bacterial colonisation, airway inflammation and airway structural damage in an attempt to break this cycle and prevent disease progression.

Airway inflammation is dominated by neutrophils, with impaired mucociliary clearance and failure of neutrophil opsonophagocytic killing. Since these neutrophils are believed to be normal prior to their arrival in the airway, it is likely that the airway inflammatory milieu itself impairs bacterial clearance. Neutrophil elastase (NE) is associated with reduced opsonisation of pathogens, further promoting pro-inflammatory cytokine release. NE also slows ciliary beat frequency and promotes mucus hypersecretion via activation of the MUC5AC gene. Further mechanisms of immune dysfunction include failure to clear apoptotic cells and T cell infiltration, particularly Th17 cells. Much more work, however, is needed before targeted anti-cytokine therapies can be trialled.

Patients with bronchiectasis frequently develop acute infective pulmonary exacerbations characterised by symptoms of fever, purulent sputum, and dyspnoea, with associated adverse effects on both morbidity and quality of life. Frequent exacerbations may contribute to the progressive decline of lung function, though both the aetiology and pathophysiology of exacerbations remains poorly understood. Studies using classical microbial culture techniques in stable state bronchiectasis report Haemophilus influenzae (14–47% of cases), Pseudomonas aeruginosa (5–31%), and Streptococcus pneumoniae (2–14%) as the most frequently isolated pathogens.
Bronchiectatic airways may become ‘colonised’ by *P. aeruginosa* with ‘repeated positive sputum cultures over a defined period of time’. Conflicting data exist on the independent contribution of *P. aeruginosa* to long term prognosis. Whether *P. aeruginosa* drives disease progression or is simply a marker of existing severe disease remains in question. A recent meta-analysis of 3683 bronchiectasis patients demonstrated *P. aeruginosa* colonisation in 21.4% of patients, which was associated with a 3-fold increase in mortality and a 7-fold increase in hospitalisation rates.\(^{35}\) In this analysis, 8 different methods of defining *P. aeruginosa* colonisation in bronchiectasis studies were identified. The word ‘colonisation’ is misleading and perhaps ‘persistent infection’ should be adopted more widely.

Although there are numerous studies in CF regarding the transmissibility of epidemic strains of *P. aeruginosa* and *Mycobacterium abscessus*, cross-infection data in bronchiectasis are very limited.\(^{36-38}\) The 2010 BTS guidelines failed to comment on this evidence gap leaving it unclear as to whether or not bronchiectasis patients with *P. aeruginosa* should be segregated as is recommended in CF infection control guidelines.\(^9\) Most cross infection studies in bronchiectasis are single centre and focus on *P. aeruginosa* with limited longitudinal sampling.\(^{39-41}\) These often lack a robust description of the clinical environment, e.g. are facilities shared with patients who have CF and carry known CF epidemic strains? In a case series of 40 patients from a UK adult bronchiectasis clinic without strict segregation, using two genotyping techniques to cross validate findings, no single common “epidemic strain” was found.\(^{39}\) However certain common strains found widely within the natural environment, e.g. *Pseudomonas* Clone C did infect patients raising the possibility of environmental acquisition in the bronchiectasis population.\(^{39}\)
Pujana et al, examined 16 patients with 64 *P. aeruginosa* isolates. Despite the limited discrimination potential of DNA fingerprinting, cross-infection or common source, acquisition was absent.\(^{40}\) In another study of 125 isolates taken from 31 patients attending a bronchiectasis clinic in Spain, pulsed field gel electrophoresis suggested that certain strains may be predominant within a clinic setting.\(^{41}\)

On balance there are no strong data suggesting widespread *P. aeruginosa* epidemic strains as a cause of clinical decline in bronchiectasis; why this is so different to CF remains unknown.

Whilst *P. aeruginosa* colonisation is associated with reduced lung function, a longitudinal study demonstrated *P. aeruginosa* infection across all stages of airflow limitation, highlighting the importance of rigorous sputum surveillance protocols in all bronchiectasis patients even those with “mild” airflow limitation.\(^{42}\)

Further known unknowns are the correct definition and the therapies for bacterial eradication, with huge variations noted between different healthcare systems and countries. Is it possible to fully eradicate *P. aeruginosa*? One retrospective study suggested that 34% of *P. aeruginosa* colonised patients subsequently became culture negative on follow-up; however, it is impossible to determine if this was true eradication or failure of successful *in vitro* culture using classical techniques.\(^{42}\) The capability of *P. aeruginosa* to form biofilms protects it from both the immune system and systemically delivered antibiotics. It also rapidly adapts to chronic infection in the lung and readily develops antimicrobial resistance.\(^{27}\) Why resistance rates appear lower than reported for CF remains unclear.
BTS guidelines for bronchiectasis recommend eradication treatment for new isolation of *P. aeruginosa*. However, some patients may spontaneously clear the organism without treatment. A recent RCT evaluating the efficacy of 3 months nebulised tobramycin following intravenous antibiotics on initial isolation of *Pseudomonas aeruginosa*, showed Pseudomonas-free rates of 54.5% in treatment group versus 29.4% in placebo group. These eradication rates are, however, significantly lower than those reported in CF, further confirming the different pathobiology of these two conditions.

We have few data on microbiology outside Europe and Australasia and there is also a definite lack of data describing the impact of organisms other than *P. aeruginosa* in bronchiectasis, in particular in those colonised with the most common bronchiectasis pathogens such as *H. influenzae*. Recent reports suggest that *Haemophilus* infected patients do have a worse outcome compared to non-colonised patients, but to a lesser extent than *P. aeruginosa*. A recent post-hoc analysis of the BLESS trial suggested that in patients without *P. aeruginosa* airway infection, erythromycin did not significantly reduce exacerbations and actually promoted displacement of *H. influenzae* by more macrolide-tolerant pathogens including *P. aeruginosa*. These findings argue for a cautious approach to chronic macrolide use in patients without *P. aeruginosa* airway infection.

Significant recent advances in our understanding of bronchiectasis have arisen through culture-independent microbiological techniques which allow a comprehensive analysis of polymicrobial bacterial communities in the lung. Detection of uncultivable microorganisms has challenged our understanding pathogenesis, progression and management of bronchiectasis. These technologies reveal colonisation with organisms previously not recognised by culture-based studies like *Veillonella* sp., *Prevotella* sp. and *Neisseria* spp. Loss
of microbiome diversity, with dominance of one or a few species, is associated with worse lung function and increased exacerbations.\textsuperscript{46, 47} An inverse relationship between the abundance of \textit{P. aeruginosa} and that of \textit{H. influenzae} within the bronchiectasis lung bacterial community, suggests a progression in microbial states.\textsuperscript{47}

The role of viruses and air pollution whilst described in other disease areas is poorly studied in bronchiectasis. Exacerbations in bronchiectasis are frequently managed with antibiotics; however, viral infections may also be significant in many cases. Recent data suggests that respiratory viruses may play a crucial role in triggering bronchiectasis exacerbations.\textsuperscript{48}

\textbf{Table 4 Selected known unknowns in bronchiectasis microbiology}

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<tr>
<td>1)</td>
<td>What is the best and most acceptable definition of bacterial ‘colonisation’ or ‘eradication’?</td>
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<td>2)</td>
<td>\textit{Does P. aeruginosa} always drive disease progression or is it a marker of disease severity?</td>
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<td>3)</td>
<td>What is the clinical relevance of a single isolate of \textit{P. aeruginosa} and when should treatment be initiated?</td>
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<td>4)</td>
<td>What factors make \textit{P. aeruginosa} more likely to occur (or persist) in some patients and not others?</td>
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<td>5)</td>
<td>\textit{Does chronic infection with P. aeruginosa} always contribute to lung function decline?</td>
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<td>6)</td>
<td>Why does \textit{Pseudomonas} appear to have lower resistance rates and lack of significant epidemic strain infections in bronchiectasis than seen in CF?</td>
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<td>7)</td>
<td>\textit{Can we successfully eradicate P. aeruginosa}? What do we consider to be a successful eradication? Does this have any impact on disease outcomes?</td>
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<tr>
<td>8)</td>
<td>\textit{Is there a pattern of polymicrobial colonisation} that can be identified? \textit{Is there an inverse relationship} between \textit{H. influenzae} and \textit{P. aeruginosa} and is \textit{this} related to extent of lung damage?</td>
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<td>9)</td>
<td>\textit{Can the microbiome be manipulated} to confer a better clinical outcome?</td>
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Treatment

There are a number of widely used current therapies in bronchiectasis - to our knowledge none are specifically licensed for the treatment of bronchiectasis. We will limit discussion to antimicrobials though note there are many unknowns in the utility and best regimens for anti-inflammatory treatments, physiotherapy and mucolytics in bronchiectasis. Many therapies developed and now used for CF do not readily translate across into bronchiectasis, e.g. nebulised aztreonam, now licensed for CF, has two “negative” phase III trials in bronchiectasis.49 This was also seen for the inhaled mucolytic mannitol.50 It is entirely plausible that good therapies for bronchiectasis have been inadvertently but inappropriately discarded due to unintended sub-optimal trial designs translated over from the CF literature.

Perhaps the greatest evidence of efficacy for treatments currently used in bronchiectasis is for prolonged or long term macrolide (LTM) antibiotics with three large scale studies consistently showing an effect in exacerbation reduction with either long term azithromycin 500mg thrice weekly, 250mg daily or 400mg BD of erythromycin (BLESS, BAT and EMBRACE trials).51-53 Several recent meta-analyses including these studies and various smaller scale studies both confirmed the role for long term macrolides in exacerbation prevention.54-57 There were no clear effects on pathogen clearance or eradication but statistical if not clinically significant improvements in FEV1 and QoL measures were observed. Unfortunately a consistent theme, where measured, was the statistically significant increase in macrolide resistance. The evidence for macrolides in preventing exacerbations in recurrent exacerbators is strong. The role of LTM in patients with high symptom burdens but without frequent exacerbations is unclear. In our experience, many of these report symptomatic improvement with LTM. However, many questions remain over the use of long term macrolides (Table 5).
Table 5 Known unknowns with Long term macrolides (LTM)

Key: Whilst there are a number of good quality studies of LTM in bronchiectasis, there are still several unanswered questions:

| 1) | Do long term macrolides (LTM) have an acceptable long term safety profile in an elderly comorbid population? |
| 2) | Does macrolide associated increased antimicrobial resistance in the upper airway flora translate into a later increase in the rate of resistance in the general population or of refractory pneumonia? |
| 3) | What are best markers of LTM response and how soon after treatment should patients be monitored/treatment stopped? |
| 4) | Can LTM responders be identified by any patient characteristic or biomarker in advance or is a therapeutic trial needed? |
| 5) | Can we withdraw macrolides after “stabilizing” a patient and if so what period of time does this take? |
| 6) | Should chronic macrolide therapy be restricted to patients with frequent exacerbations and high severity index scores or is there a rationale for using them in highly symptomatic but non exacerbating “lower risk” patients? |
| 7) | How do we define partial response to macrolides? Do patients not responding to one macrolide respond to switching to an alternative macrolide or dose escalation? |
| 8) | Can LTM treatment holidays be applied to patients across a range of disease severities in Spring/Summer months? |
| 9) | Do the differing macrolides offer similar efficacy but differing adverse event profiles, e.g. ototoxicity, cardiac conduction defects and/or resistance induction rates? |

Chronic inhalational antibiotics (CIA) are widely used in bronchiectasis and until recently, the evidence base was scant. A single centre single-blind study of gentamicin produced marked reductions in exacerbations; multicenter double-blind follow on studies may help truly define the utility of this therapy in daily practice.\textsuperscript{58} Data from a large multicenter international trial of nebulised ultrafine colistin delivered by an intelligent breath activated nebuliser was particularly notable even though the study failed to reach its primary endpoint. This landmark study demonstrated a significant proportion of trials participants were non-compliant. When a \textit{per protocol} analysis was conducted limiting the analysis to patients defined as compliant at 80% or more of prescribed therapy, there was a significant exacerbation reduction effect. These
observations, along with others, suggest we have issues in defining the appropriate target population, the optimal outcome measures and in ensuring that non-compliance does not impair study outcomes.59

Phase II studies have suggested a possible role for dry powder inhaled ciprofloxacin and nebulised liposomal ciprofloxacin with a reduction in bacterial load.60,61 Both are now in phase III development programs.

One key challenge will be to understand the implications of “resistant” strains in CIA therapy. Firstly, the breakpoints established for antimicrobials that are currently used to define resistance or sensitivity probably have little relevance to the biofilm mode of growth, nor the very high concentrations possible within the lung with CIA. Secondly, long term CIA therapy will likely select a sub-population of resistant bacteria. If, however, the suppression of sensitive strains results in a clinically meaningful reduction in total bacterial load, the emergence (or selection) of resistant strains may be acceptable.

There are significant uncertainties in the role of either inhaled or oral long term antibiotics. There are no studies randomising patients to LTM as compared to CIA. One uncertainty for the future will be where such new therapies fit in in comparison to long term macrolides? Commonly, there is a patient preference for LTM given these are easier to fit into a treatment regimen. Clinicians may well however prefer to limit LTM use and target pathogens with inhaled therapies. Shared decision making will ultimately improve patient adherence.

**Table 6 Known unknowns in chronic inhaled antimicrobial (CIA) therapy:**

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<td><strong>1)</strong></td>
<td>Is CIA therapy an ‘add-on’ to LTM or a first choice before LTM? Do patient characteristics define which approach to take first?</td>
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<tr>
<td><strong>2)</strong></td>
<td>What are patients’ preferences in LTM vs IA as first line therapies?</td>
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<tr>
<td><strong>3)</strong></td>
<td>What is the optimal CIA regimen? Daily? Monthly cycles? Alternating CIA agents?</td>
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<tr>
<td><strong>4)</strong></td>
<td>Are there predictors of CIA adverse events such a bronchospasm? Are CIA therapy test dose trials needed in all patients?</td>
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Adherence and education

For some patients with bronchiectasis, multiple medical treatments can be required. Some of these, such as nebulised treatments and airway clearance regimes, can be particularly burdensome in terms of a regular time commitment. It makes sense that for treatments to be effective they need to be taken as prescribed, but what do we know about deviations from the prescribed regime and what effect this has in bronchiectasis? One recent study looked at treatment adherence in bronchiectasis and found that over a 1 year period just over 50% of participants were adherent to inhaled antibiotics and other respiratory treatments and 41% adherent to airway clearance techniques. Less than 20% of the cohort were adherent to all treatments.62 Adherence to inhaled antibiotics was associated with significantly fewer exacerbations.

A high degree of adherence seems to be beneficial at least when it comes to inhaled antibiotics, so promoting treatment adherence and educating patients about this is important. The BTS guidelines recommend patient education about treatments and self-management but no specific information or educational packages are recommended.9 Qualitative studies highlight that patients feel that lack of information is one of the barriers to self-management and describe the importance of information in improving patients’ confidence and in developing the skills to live with and manage their condition.63, 64 Factors predicting adherence to treatment in bronchiectasis include patients’ beliefs about treatments, perceived treatment burden and number of prescribed treatments.65 Further work to develop a behaviour change intervention to promote adherence to treatment in bronchiectasis offers hope.66
Developing an understanding of patients’ and their carers’ information and education needs and how these could be addressed may offer a key advance. A variety of packages have been developed for use in COPD yet there remains to be an evidenced based intervention designed for use in this patient population.

Conclusions

Patients with bronchiectasis and clinicians managing them are unable to achieve optimal patient care until major gaps in our understanding of the disease pathophysiology, prognosis and optimal treatment regimens are advanced. Collaborative working and harnessing the enthusiasm and engagement of a patient population that has been frustrated by delays in diagnosis and empirical treatment into both observational and interventional studies will be crucial to achieving this. After the recently noted increases in bronchiectasis prevalence, the renewed enthusiasm from the life sciences industry for intervention studies in bronchiectasis and international collaborative efforts in bronchiectasis are both timely and desperately needed.

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References


