

## RESEARCH LETTER

## Research priorities in bronchiectasis

Taking a network approach, we have identified research priorities in non-cystic fibrosis bronchiectasis. We discuss these in the context of increasing recognition of bronchiectasis and increasing mortality rates.

Bronchiectasis is defined by damaged dilated bronchi that presents clinically as chronic sputum production with recurrent respiratory infections. Conditions as diverse as cystic fibrosis (CF), previous lung infections, rheumatoid arthritis, inflammatory bowel disease, immune deficiencies and gastro-oesophageal reflux are associated with bronchiectasis, and impact on the management and outcome.<sup>1</sup> With the exception of cystic fibrosis, there is a striking paucity of research into bronchiectasis. As a consequence, there are large gaps in our knowledge of the pathogenesis of the disease, and the evidence base for effective management is poor. Ground-breaking research into bronchiectasis was supported by the UK Medical Research Council in the 1950s, but the development of antibiotics has perhaps led to the perception that significant bronchiectasis is rare, and when identified, is easily managed and not clinically particularly important. Both perceptions are wrong. In the USA, the current prevalence of adult bronchiectasis was estimated at 52/100 000,<sup>2</sup> suggesting there are at least 30 000 bronchiectasis patients in the UK. However, accurate data are lacking, and in just nine UK centres, 5000 patients with bronchiectasis are under regular follow-up suggesting the true prevalence is even higher. Furthermore, bronchiectasis is not a benign process, but has a significant morbidity and mortality.<sup>3 4</sup> In the national British Thoracic Society (BTS), 2011 audit patients with bronchiectasis had an annual exacerbation rate of 2.6, and local data from UK centres suggest hospital admissions for treatment of bronchiectasis and bed occupancy are both rising. Bronchiectasis has wider relevance for respiratory medicine as it is associated with asthma, interstitial lung disease and chronic obstructive pulmonary disease (COPD). In the latter, it correlates with more persistent infections, prolonged hospital admissions and increased healthcare costs.<sup>2</sup> Unfortunately, the treatment of bronchiectasis remains largely empirical, or extrapolated from other respiratory conditions, such as CF and COPD,<sup>1</sup>

although very recent controlled trials confirming the efficacy of prophylactic macrolide regimens in bronchiectasis have demonstrated that clinical research into bronchiectasis is possible.<sup>5</sup> There is a clear and urgent need for additional research into bronchiectasis to help reduce the growing clinical burden of this neglected disease.

While there are many studies that need to be undertaken, the research priorities can be simply categorised into the following three areas:

1. Epidemiology. Accurate data on the age and sex-related incidence, prevalence and comorbidities is essential in order to identify the size of the clinical burden, and which subjects are most at risk of bronchiectasis and, potentially, could indicate previously unsuspected aetiological factors. Prospective healthcare utilisation data and the mortality from the disease (or from associated comorbidities) are needed to fully define the severity of the clinical problem. This may also identify where improved management could impact the most on health, or identify which patient subgroups need closest follow-up and will assist effective commissioning of healthcare for patients with bronchiectasis.
2. Pathogenesis. The cause of bronchiectasis is only defined in ~50% of patients, and the variability in severity and clinical progression in addition to the opportunity to treat the underlying cause, make research into this area a priority. Translational studies of mucociliary function, systemic and mucosal immunity are required to identify potential causes or exacerbators of bronchiectasis. We need to take advantage of modern immunological techniques and new findings that have improved our understanding of host/pathogen interactions. Adequately powered genetic studies are necessary to assess the susceptibility of the host to bronchiectasis, its progression and to infection with particular pathogens. Further microbial research is needed to elucidate drivers of exacerbations and the progression of bronchiectasis, for instance, specific pathogen research, such as *Pseudomonas* virulence determinants necessary for chronic infection in bronchiectasis, and the investigation and the composition and perturbation of airway polymicrobial communities with molecular techniques. Similarly, the role of viruses and fungi needs to be assessed in driving exacerbations or chronic disease progression, with the former

having an established role in COPD exacerbations, but with no conclusive data available in bronchiectasis.

3. Management. The recent BTS bronchiectasis guidelines are dominated by low-grade evidence and limited controlled trial data, mandating further clinical trials for both 'established' and newer therapies. Widely used therapies, such as inhaled corticosteroids, have a poor evidence base in bronchiectasis, yet may carry a risk of pneumonia. Airway clearance techniques, a cornerstone of therapy, are supported by some trial data, yet the optimum method remains unclear. The appropriate duration of antibiotics for exacerbations is unknown, and could potentially be individualised if biomarkers that monitor treatment response can be identified. We need more trials to define the patient groups most likely to benefit from the different antibiotic prophylaxis regimens, duration of treatment, and to assess their effects on bacterial resistance or microbiome content. There is also a pressing need to investigate whether early identification of acquisition of *Pseudomonas* (perhaps using molecular techniques), followed by an optimal eradication regimen results in reduced morbidity, or slows disease progression. Epidemic strains of *Pseudomonas* have led to significant morbidity in CF, yet we lack data on whether cross-infection is similarly a problem for bronchiectasis.

Fortunately, several recent developments will help improve research into bronchiectasis. First, technological advances, such as microarrays, rapid and relatively cheap whole-genome sequencing are now available and will help answer some of the important aetiological and pathogenesis questions. Direct sequencing of microbial nucleic acid from sputum provides very detailed data on the microbial content of the airways, and will allow monitoring of longitudinal bacterial airways ecology and in response to therapeutic interventions. Second the pharmaceutical industry has started significant development programmes into combating airway infection with novel inhaled antibiotic preparations. Additional development streams include novel inhaled mucolytics and therapies targeting neutrophilic inflammation (the probable main driver for airway damage). Recent experiences with clinical trials have shown that patients with bronchiectasis are highly engaged in clinical research, suggesting that rapid advances are likely. Third, the

recent BTS guidelines and successive UK national audits in bronchiectasis care in 2010 and 2011 have helped support and define an increasing interest in bronchiectasis from physicians and researchers alike, while highlighting the lack of high-quality research data, and the consequent significant variations in clinical practice. A major impediment to effective research has been the heterogeneity of bronchiectasis due to significant variability in aetiology and clinical courses. Only through collaborative research between several centres can enough patients representing particular subgroups of bronchiectasis be recruited for authoritative clinical trials and translational studies. To that end, nine centres within the UK have formed the Bronchiectasis Research & Academic Network aiming to construct a comprehensive database of well-characterised bronchiectasis patients to support translational research into the areas described above. The registry will also facilitate clinical trials in bronchiectasis and help make the UK a key destination for trials of new therapies. In the USA, a similar national bronchiectasis registry has already been established by the US COPD Foundation, and has recruited over 1200 patients across multiple centres. More registries across the globe encompassing genetic, environmental and microbiological variability will be needed to make significant improvements in our understanding and effective management of patients with bronchiectasis.

As the research and evidence base improves for bronchiectasis, a key challenge is ensuring that these patients are getting the best possible care, and that new research findings are translated into patient management. Although many patients remain stable and might be adequately managed in primary care and general respiratory services, a network of

specialised centres for patients with complex bronchiectasis would both stimulate research and improve patient care. This model works well for complex asthma. The need for specialised bronchiectasis care has already been recognised for some subgroups, with specialist commissioning of the care for patients with primary ciliary dyskinesia in the UK. Other patients with bronchiectasis who might benefit from management in centres with specialist expertise include those with rapidly progressive disease, or who are infected with opportunistic, but recalcitrant pathogens, such as resistant Gram-negative bacteria, *Aspergillus* species and non-tuberculous mycobacteria. The recognition by commissioners of healthcare of the need for specialised care for some patients with bronchiectasis will ensure that any innovations identified by new research are translated into clinical practice.

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**Acknowledgements** We acknowledge the support and comments from the UK Bronchiectasis Research & Academic Network (BRAN) in writing this article; (1) D Bilton, R Wilson, Royal Brompton Hospital, (2) A Hill Edinburgh Royal Infirmary, (3) A Sullivan Birmingham, (4) T Wilkinson Southampton University, (5) JS Elborn, J Bradley Belfast City Hospital, (6) J Hurst University College London, (7) J Duckers Llandough Hospital, Wales, (8) A Floto, C Howarth and J

Foweraker, Papworth Hospital, Cambridge, (9) T Small, K Hester, Freeman Hospital Newcastle upon Tyne.

**Contributors** The authors (ADS, JB and ML) drafted and revised the opinion piece. The collaborators reviewed and advised on the contents.

**Funding** ADS acknowledges a HEFCE Clinical Academic Senior Lecturership and Newcastle NIHR Biomedical Research Centre in Ageing grant support. ML was supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London. UCLH/UCL receive funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme and work in Professor Brown's laboratory is supported by the Medical Research Council, Rosetrees Trust, and the Wellcome Trust.

**Disclaimer** The views expressed in this publication are those of the authors and not necessarily those of the NHS, The National Institute for Health Research or the Department of Health.

**Competing interests** None.

**Provenance and peer review** Not commissioned; internally peer reviewed.

**To cite** De Soya A, Brown JS, Loebinger MR, *et al.* *Thorax* Published Online First: 14 December 2012 doi:10.1136/thoraxjnl-2012-202893

Received 18 October 2012

Revised 18 October 2012

Accepted 23 November 2012

*Thorax* 2012;0:1–2.

doi:10.1136/thoraxjnl-2012-202893

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