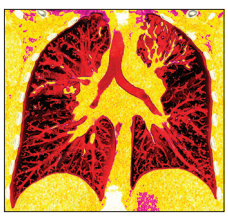
Developments and priorities in bronchiectasis research



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On July 1, 2023, we celebrated the second annual World Bronchiectasis Day. Increased recognition of bronchiectasis among health-care providers and the availability of chest CT in the past two decades have led to greater awareness of diagnostic signs and treatment options for this condition, which was previously thought of as an orphan disease. Furthermore, there is growing interest in bronchiectasis that is unrelated to cystic fibrosis (hereafter referred to as bronchiectasis), which has been neglected for many years despite its greater global burden.

One of the most important global developments in bronchiectasis in the past decade has been the establishment of international registries and international clinical research collaborations dedicated to bronchiectasis in adults, adolescents, and children. EMBARC was established in 2012[1] and the Children's Bronchiectasis Education Advocacy and Research Network (Child-BEAR-Net) was established in 2021 for children and adolescents with bronchiectasis.[2] These large-scale initiatives include collaborative registries and aim to raise awareness of the disease and advance research—including investigations into novel therapies and translational science—and have made substantial inroads into increasing the profile of bronchiectasis.

To guide management and improve the standard of care internationally, there are now international guidelines and quality standards for children, adolescents, and adults.[3–7] In addition to standardising and improving clinical care, international consensus statements have been agreed for the definitions of bronchiectasis in adults[8] and respiratory exacerbations in adults and in children and adolescents[9] for research purposes, thus facilitating comparisons between trials.

Although bronchiectasis is a condition traditionally thought to be permanent and progressive, challenging this concept, paediatric bronchiectasis has been shown to be reversible if there is a timely diagnosis and management plan.[6] Additionally, cystic fibrosis-related bronchiectasis has been shown to improve with cystic fibrosis transmembrane conductance regulator modulator therapy. A burning question is whether bronchiectasis identified in adults can be halted or improved, and this issue should remain a research priority for the decade ahead.

Another important question concerns the most effective treatments for bronchiectasis. Meta-analyses have confirmed clinical efficacy for both long-term antibiotics and macrolide therapy for reducing exacerbations.[10] Novel therapies are emerging, such as anti-inflammatory treatment with an inhibitor of dipeptidyl peptidase-1, which has been shown to prolong time to first exacerbation in a phase 2 trial.[11] Despite these advances, to date, there are no licensed therapies for bronchiectasis and future RCTs will aim to address this gap (panel). For example, we need to know who would benefit from chest clearance, mucoactive treatments, and treatments such as inhaled corticosteroids, long-acting β-2 agonists, and anti-cholinergic, anti-inflammatory, and anti-infective therapies. Additionally, the route of administration and duration of these treatments requires further study. Another advance in effective management has involved the definition of the first clinically relevant phenotypes and endotypes for bronchiectasis, based on patient characteristics and pathobiological mechanisms, which will continue to be developed in the years ahead.

Exacerbations of bronchiectasis have a major effect on both morbidity and mortality. The international guidelines[9] have helped to stratify exacerbations that might benefit from antibiotic therapy and provide management guidance, but the duration of treatment is not known. The consensus is that prolonged use of high-dose antibiotics is needed, but this concept has been challenged by the results of a trial of intravenous antibiotics for exacerbations in adults, in which treatment for 7 days was associated with an increased time to further antibiotic treatment compared with that for 14 days of treatment.[12] The National Institute for Health and Care Research SBIVA study will explore this shorter treatment duration in a UK-wide population.

The COVID-19 pandemic has highlighted the importance of viruses in bronchiectasis exacerbations and the effects of the public health measures in reducing these exacerbations, thus emphasising the value of vaccinations and social measures to reduce viral exposures. Additionally, the shift in the use of digital health-care technologies for patients with bronchiectasis due to COVID-19 cannot be neglected.

What then are the research priorities for the decade ahead? The international guidelines propose future

For more on the **European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC)** see https://www.bronchiectasis.eu/

For more on the **Child-BEAR-Net** see https://www.improvebe.org/

Panel: **Ongoing studies on the management of bronchiectasis***

Novel treatments specific for bronchiectasis

- A Proof of Concept Trial of Alpha-1 Antitrypsin Augmentation Therapy in Patients with Bronchiectasis (BATMAN; NCT05582798)
- A Randomised, Double-blind, Placebo-controlled, Parallel Group, Dose-finding Study Evaluating Efficacy, Safety and Tolerability of BI 1291583 bd Over at Least 24 Weeks in Patients with Bronchiectasis (AirleafTM; NCT05238675)
- A Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled, 52 Week, Phase III Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients with Non-Cystic Fibrosis Bronchiectasis (MAHALE; NCT05006573)
- A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects with Non-cystic Fibrosis Bronchiectasis – The ASPEN Study (NCT04594369)
- Anti-inflammatory Effects of Roflumilast Treatment for 12 Weeks in Stable-state Non-cystic Fibrosis Bronchiectasis (NCT04322929)

Precision medicine: description of phenotypes and endotypes

- The BRIDGE Study – Bronchiectasis Research Involving Databases, Genomics and Endotyping. An EMBARC2 and EMBARC3 Study (the primary aim is to describe the molecular endotypes that can guide treatment; NCT03791086)

Biomarkers and non-invasive diagnostic tests to guide diagnosis and treatment

- Assessment of an Exhaled Breath Test Using High-pressure Photon Ionization Time-of-flight Mass Spectrometry to Detect Bronchiectasis (NCT05293314)

Length of antibiotic treatment

- Seven versus Fourteen Days Antibiotics for Patients with Bronchiectasis Requiring Intravenous Antibiotics – The SBIVA Study (NIHR133876)

Role for mucolytics in bronchiectasis management

- Evaluating the Effect of Erdosteine on Respiratory Exacerbation Rate of Children and Adults with Bronchiectasis – A Double-blind, Randomised Controlled Trial (ACTRN12621000315819)

Airway clearance in bronchiectasis

- The Effectiveness of Airway Clearance in Bronchiectasis: A Prospective Cohort Study and Review of the Patient Experience (ACTRN12622001338752)

Prevention or reversibility of bronchiectasis

- The Effectiveness of Long-term Treatment with Azithromycin to Prevent Bronchiectasis and Recurrent Cough (LEAP-Cough) and Developing Individualised Approaches for Children with Chronic Wet Cough (ACTRN12623000098639)

EMBARC=European Multicentre Bronchiectasis Audit and Research Collaboration. *This panel is not an exhaustive list but aims to illustrate some of the important areas of ongoing research.

research studies in adults.[3-5] To overcome the scarcity of research priorities for children and adolescents with bronchiectasis, the Child-BEAR-Net undertook the development of a roadmap to guide health services on the needs of children with bronchiectasis and their parents, to reduce the disease burden and to improve long-term respiratory outcomes.[13] This roadmap highlights the need for further research on phenotyping and endotyping to facilitate the definition of personalised treatable traits and move towards a precision medicine approach to care—a plan that would benefit children, adolescents, and adults.

Despite the advances in the past decade, many ongoing clinical studies seek to reveal more completely the core tenets of bronchiectasis management (panel). Key areas of ongoing research include the investigation of novel drugs, the description of endotypes and phenotypes using large registry databases, and the role for other treatments. Biological mechanisms of bronchiectasis, the discovery of predictive biomarkers, and precision medicine are exciting areas of bronchiectasis research for the years ahead.

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