RESEARCH TOPIC CLI6

Building an Integrated Framework for Bronchiectasis Exacerbations: phenotyping, endotyping, standard operating procedures, and individualized antibiotic duration

Research area
Medical Area

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Abstract
Project Summary
Bronchiectasis is a chronic inflammatory airway disease characterised by recurrent exacerbations, chronic infection, progressive structural lung damage, impaired quality of life, and frequent healthcare utilisation. Among all clinical events occurring in bronchiectasis, exacerbations are the most relevant dynamic expressions of disease instability, as they are associated with accelerated disease progression, greater symptom burden, increased hospitalisation risk, and repeated exposure to antibiotics. Recent European and international advances, including the growth of EMBARC (https://www.bronchiectasis.net) and the publication of updated ERS guidance, have improved the overall framework for bronchiectasis care, but the acute management of exacerbations remains one of the least evidence-based areas of the field. Current management of bronchiectasis exacerbations is still affected by two major limitations. First, exacerbations are clinically recognised but remain insufficiently characterised in terms of phenotype and endotype. Patients who present with apparently similar episodes of worsening symptoms may differ substantially in microbiology, inflammatory burden, severity, recovery kinetics, and risk of early recurrence. This heterogeneity is not yet adequately captured in routine practice, and there is no widely implemented framework to stratify exacerbations beyond simple clinical judgement. Second, antibiotic therapy, although central to management, is still largely prescribed according to fixed-duration approaches, especially around 14 days, despite limited direct evidence and despite the broader shift in respiratory infections toward more individualized, response-guided treatment strategies. The ATS/IDSA community-acquired pneumonia (CAP) framework, in particular, has shown that antibiotic duration can be safely tailored according to clinical stability rather than predefined prolonged courses, providing an important stewardship model for bronchiectasis research.
This PhD project is designed around the overarching goal of improving the understanding and management of bronchiectasis exacerbations through a combined clinical, organisational, observational, and translational programme. The project has two equally important and

closely interconnected components. The first is to improve the phenotypic and endotypic characterisation of bronchiectasis exacerbations and to use this knowledge to optimise the standard operating procedures (SOPs) through which exacerbations are recognised, monitored, and managed in clinical practice. The second is to develop an antimicrobial stewardship strategy focused on individualized antibiotic treatment, with specific emphasis on the correct duration of therapy, supported by a multicentre, pragmatic, randomized clinical study comparing individualized duration with standard-duration treatment.

The central idea is that management of bronchiectasis exacerbations should not be reduced to a single decision about how many days of antibiotics to prescribe. Instead, exacerbations should be understood as heterogeneous biological and clinical events that require better phenotyping, more structured monitoring, and individualized therapeutic strategies. Within this framework, antibiotic duration is not an isolated question but one of the most clinically actionable consequences of improved exacerbation characterisation. By combining detailed observational study of exacerbation trajectories with translational analyses and a pragmatic randomized stewardship trial, the project aims to generate a comprehensive framework for bronchiectasis exacerbation care, moving from descriptive heterogeneity to operational, evidence-based procedures.

The expected outcome is therefore broader than a trial on antibiotic duration alone. The project aims to deliver a multidimensional approach to exacerbation management in bronchiectasis, integrating phenotype, endotype, symptom evolution, microbiology, inflammatory signals, and treatment response into a clinically usable model. This model will support optimisation of antibiotic use, reduction of unnecessary exposure, and development of practical SOPs for exacerbation management in bronchiectasis care and future multicentre clinical research.

Scientific Background and Rationale

Bronchiectasis is now recognised as a major chronic respiratory disease with substantial morbidity and healthcare burden, and recurrent exacerbations are among the strongest drivers of poor outcomes. EMBARC data and other contemporary studies have shown that exacerbations are common, often recurrent, and strongly linked to quality-of-life impairment, hospitalisation, and long-term deterioration. Yet, despite their importance, exacerbations remain one of the least standardised domains of bronchiectasis care. The European Respiratory Society (ERS) guidelines provide an evidence-based general framework for management, but they also reflect the broader reality that several key aspects of exacerbation care still depend on expert consensus and local practice rather than high-quality comparative evidence. A first major gap concerns the biological and clinical heterogeneity of exacerbations. Although consensus definitions of bronchiectasis exacerbation exist and symptom-based tools such as the BEST diary have improved the ability to quantify symptom burden and recovery over time, exacerbations are still not routinely stratified according to phenotype or endotype. This is a major limitation, because not all exacerbations are biologically equivalent. Some may be predominantly driven by bacterial infection, others by inflammatory amplification, viral triggers, changes in airway microbiology, or combinations of these mechanisms. Likewise, some patients recover rapidly, whereas others show delayed resolution, treatment failure, or early relapse. A better understanding of exacerbation

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heterogeneity is therefore essential if management is to become more precise and more reproducible. A second major gap concerns how this heterogeneity should translate into clinical procedures. In most centres, SOPs for bronchiectasis exacerbations are not yet strongly anchored to structured assessment of symptom trajectories, microbiology, inflammatory markers, or response kinetics. Instead, management often remains reactive and empiric. This creates an important opportunity for healthcare research: if exacerbations can be better phenotyped and endotyped, then the resulting knowledge can be translated into more robust SOPs regarding reassessment, laboratory testing, follow-up intervals, escalation or de-escalation of therapy, and definition of clinical response. Within this broader agenda, antibiotic therapy is a particularly important and immediately actionable target. Short-term antibiotic treatment for bronchiectasis exacerbations remains a cornerstone of care, but the evidence supporting the optimal duration of treatment is limited. A 2019 review specifically concluded that there is a paucity of evidence for optimal antibiotic strategies in non-cystic fibrosis bronchiectasis exacerbations and long-term management, and argued that rationally designed studies using registry and population-based approaches are needed to optimise care. The same review noted that approximately 14 days remains the prevailing expert-consensus standard for exacerbations, despite the lack of strong comparative evidence.

This is where antimicrobial stewardship becomes central, but only as one part of a wider exacerbation-management programme. In bronchiectasis, patients are repeatedly exposed to antibiotics over time, and unnecessary prolongation of therapy may increase adverse effects, treatment burden, healthcare costs, and selective pressure for resistance. At the same time, shortening therapy indiscriminately would be unsafe. The relevant scientific question is therefore not simply whether shorter treatment is better, but which patients, in which type of exacerbation, and according to which response profile, can safely receive shorter therapy. This is fundamentally a question of exacerbation phenotyping and therapeutic individualisation.

There is already a strong conceptual precedent for individualized antibiotic duration in respiratory medicine. In community-acquired pneumonia, ATS/IDSA recommendations endorse shorter treatment courses guided by clinical stability rather than routine prolonged durations, demonstrating that response-based treatment can be both pragmatic and evidence-based. Bronchiectasis is clearly more heterogeneous than CAP, but this precedent is highly relevant: it supports the principle that treatment duration should be informed by patient recovery rather than habit alone.

Bronchiectasis-specific proof-of-concept data also support moving beyond a rigid 14-day paradigm. The randomized study by Bedi and colleagues explored a strategy of shortening intravenous antibiotic therapy based on bacterial load, showing that a shorter, biologically informed approach is feasible, even though bacterial load-guided management is not easily transferable to routine practice. A more scalable and clinically pragmatic model is to individualize therapy according to clinical stability, but to do so within a broader programme that also studies symptom trajectories, microbiology, inflammatory burden, and exacerbation endotypes.

Against this background, the present PhD is designed as an integrated programme on bronchiectasis exacerbations. Approximately half of the project is dedicated to improving the understanding of exacerbation phenotypes, endotypes, trajectories, and operational

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management, with the goal of refining SOPs. The other half is dedicated to antimicrobial stewardship, particularly the duration of antibiotic therapy, addressed through a multicentre, pragmatic, randomized study embedded within this larger conceptual framework. The rationale is that antibiotic duration can only be truly optimized if exacerbations themselves are better understood and better classified.

Central Hypothesis

Bronchiectasis exacerbations are heterogeneous clinical-biological events that can be more effectively managed through integrated phenotypic and endotypic characterisation, structured operational procedures, and individualized antibiotic strategies. A first hypothesis is that systematic assessment of exacerbation phenotype, symptom trajectory, microbiology, and inflammatory profile will identify clinically meaningful patterns of exacerbation behaviour and recovery. A second hypothesis is that this improved understanding can be translated into more robust and reproducible SOPs for exacerbation management. A third hypothesis is that, within this framework, individualized antibiotic duration based on patient response and clinical stability can reduce unnecessary antibiotic exposure without compromising clinical outcomes, thereby supporting a bronchiectasis-specific antimicrobial stewardship model.

Overall Aim

To improve the understanding and management of bronchiectasis exacerbations by integrating phenotypic and endotypic characterisation, optimisation of standard operating procedures, and individualized antibiotic treatment strategies, with a specific focus on the correct duration of antibiotic therapy within a multicentre pragmatic randomized study.

Specific Aims

- Aim 1: To characterise the clinical heterogeneity of bronchiectasis exacerbations through detailed phenotyping of symptoms, severity, microbiology, prior history, and short-term outcomes.
- Aim 2: To investigate the biological heterogeneity of bronchiectasis exacerbations through exploratory endotyping, including inflammatory and microbiological correlates of response and recovery.
- Aim 3: To define and refine a structured operational framework for the management of bronchiectasis exacerbations, including monitoring, reassessment, and response-based decision-making.
- Aim 4: To evaluate, within a multicentre pragmatic randomized study, whether individualized antibiotic duration based on clinical stability can reduce antibiotic exposure compared with standard-duration treatment without compromising safety and efficacy.
- Aim 5: To identify the phenotypic and endotypic factors associated with faster or slower clinical stability and with the need for shorter or longer antibiotic treatment.
- Aim 6: To translate the findings into practical SOPs for bronchiectasis exacerbation management, integrating exacerbation phenotyping, therapeutic monitoring, and antimicrobial stewardship principles.

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Research Plan

- Work Package 1: Clinical phenotyping of bronchiectasis exacerbations. This work package will focus on the detailed clinical characterisation of exacerbations, including symptom burden, sputum changes, dyspnoea, exacerbation history, baseline disease severity, and short-term clinical outcomes. Repeated symptom-based assessments, including validated tools where applicable, will be used to describe trajectories of recovery and to identify clinically meaningful patterns of exacerbation evolution. The aim is to move from a generic exacerbation label to a more structured and reproducible clinical phenotype framework.
- Work Package 2: Endotyping of exacerbations and translational profiling. This work package will explore the biological heterogeneity of exacerbations through analysis of blood and sputum samples collected during the acute event and follow-up. The goal is not to conduct stand-alone biomarker discovery, but to determine whether inflammatory and microbiological profiles are associated with symptom trajectories, treatment response, time to clinical stability, and risk of relapse. This component will support the broader objective of linking exacerbation biology to practical management decisions.
- Work Package 3: Optimisation of SOPs for bronchiectasis exacerbation management. This work package will translate observational and translational findings into a structured operational framework. It will focus on how exacerbations should be assessed, monitored, and re-evaluated in clinical practice, including the timing of follow-up, the role of symptom tools, microbiology, laboratory indices, and criteria for treatment response or concern. The aim is to develop a practical SOP-oriented model that can be used across centres and future collaborative studies.
- Work Package 4: Multicentre pragmatic randomized study on individualized antibiotic duration. This work package will evaluate whether a response-guided strategy based on clinical stability can safely reduce antibiotic exposure compared with usual standard-duration treatment. The study will focus on oral-antibiotic-treated bronchiectasis exacerbations and will assess antibiotic duration, total antibiotic exposure, clinical cure, treatment failure, recurrence, healthcare utilisation, and safety. The stewardship focus of the project is concentrated here, but within the broader conceptual framework of exacerbation management rather than as an isolated question.
- Work Package 5: Integration of exacerbation phenotype/endotype and stewardship into a unified management framework. The final work package will integrate the findings from the observational, translational, and randomized components into a single bronchiectasis exacerbation management framework. This will include recommendations on classification of exacerbation behaviour, identification of higher-risk recovery profiles, monitoring of response, and individualized antibiotic duration. The ambition is to generate a model that is clinically usable, methodologically grounded, and directly relevant to guideline development and future multicentre implementation.

Translational Dimension

The translational dimension of this PhD is designed to reinforce the clinical and procedural goals of the project rather than operate as a separate laboratory stream. The project begins from a healthcare need—improving the management of bronchiectasis exacerbations—and uses translational investigation to explain why exacerbations differ in severity, trajectory, and

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antibiotic requirements. Blood and sputum analyses will therefore be interpreted in the context of clinical phenotypes, symptom evolution, and treatment response, with particular interest in whether inflammatory and microbiological signatures help define exacerbation endotypes and recovery profiles. This gives the project its coherence: translational data support exacerbation stratification; stratification supports more robust SOPs; and these in turn support better antimicrobial stewardship, especially around individualized duration of therapy. In this way, the project moves across a full continuum from biology to bedside management and from bedside management to practical healthcare procedure.

Expected Impact

This project will deliver a broader and more clinically meaningful framework for bronchiectasis exacerbations than would be achieved by studying antibiotic duration alone. It will improve the understanding of exacerbation heterogeneity through phenotyping and exploratory endotyping, define more structured operational procedures for how exacerbations should be assessed and followed, and provide randomized evidence on individualized antibiotic duration as a stewardship strategy. Its expected outputs are therefore threefold. First, it will generate new knowledge on the clinical and biological heterogeneity of bronchiectasis exacerbations. Second, it will translate this knowledge into practical SOPs for exacerbation management. Third, it will provide evidence to support a more individualized and stewardship-oriented use of antibiotics, reducing unnecessary exposure while preserving patient safety and clinical effectiveness. In a field where exacerbation management remains dominated by expert opinion and repeated antibiotic use is common, this PhD has the potential to contribute meaningfully to both bronchiectasis care and responsible antimicrobial practice.

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