Bronchiectasis management in adults: state of the art and future directions

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Bronchiectasis is a rapidly developing field. This state of the art review highlights recent advancements in bronchiectasis management and emerging therapies. https://bit.ly/3yiipC0

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Abstract

Formerly regarded as a rare disease, bronchiectasis is increasingly recognised. A renewed interest in this disease has led to significant progress in bronchiectasis research. Randomised clinical trials (RCTs) have demonstrated the benefits of airway clearance techniques, inhaled antibiotics and long-term macrolide therapy in bronchiectasis patients. However, the heterogeneity of bronchiectasis remains one of the most challenging aspects of management. Phenotypes and endotypes of bronchiectasis have been identified to help find "treatable traits" and partially overcome disease complexity. The goals of therapy for bronchiectasis are to reduce the symptom burden, improve quality of life, reduce exacerbations and prevent disease progression. We review the pharmacological and non-pharmacological treatments that can improve mucociliary clearance, reduce airway inflammation and tackle airway infection, the key pathophysiological features of bronchiectasis. There are also promising treatments in development for the management of bronchiectasis, including novel anti-inflammatory therapies. This review provides a critical update on the management of bronchiectasis focusing on treatable traits and recent RCTs.

Introduction

Bronchiectasis is defined radiographically by permanent dilatation of the bronchi and clinically by cough, sputum production and recurrent chest infections [1, 2]. Previously considered an orphan disease [3], bronchiectasis is now recognised to be a common disease. In 2013, it was reported that prevalence had increased by 40% since 2003 and was as high as 566 per 100 000 persons [4–7]. The increased prevalence potentially results from increased awareness among physicians and a wider application of chest computed tomography (CT) scans in clinical practice. Prevalence data from most European and non-European countries have not been updated since 2013. Thus, the prevalence is likely to be much higher at the present time. Bronchiectasis is associated with high medical costs and increased mortality rate [4, 8–10].

The improved awareness of this disease has stimulated marked progress in bronchiectasis research. Multinational, multicentre, prospective cohorts are now established worldwide [11–16], advancing our understanding of bronchiectasis. An increase in translational research has improved disease understanding in areas such as airway inflammation, the microbiome and mucociliary dysfunction. Furthermore, randomised controlled trials (RCTs) have provided a higher level of evidence for the clinical management of bronchiectasis. In this review, we provide a state of the art overview of recent advancements in bronchiectasis management, including therapies under development.

Search strategy

The authors conducted a systematic review of the PubMed database up to February 2024 using the search term "bronchiectasis" with "treatment", "antibiotics", "physiotherapy", "macrolide", "anti-inflammatory",

"inhaled", "bronchodilators", "mucolytics", "Random*", "management" and "exacerbation". 5957 studies were initially identified, and eligibility was assessed by H. Choi and J.D. Chalmers. The search was supplemented by reviewing treatment options identified in the published international bronchiectasis guidelines and conducting updated searches for additional studies [17–21]. Developing treatment strategies were identified through searches of clinical trial registries.

Pathophysiology of bronchiectasis and goals of treatment

Traditionally, the pathophysiology of bronchiectasis has been explained by the "vicious cycle" model [22]. Impaired mucociliary clearance in dilated bronchi results in the accumulation of airway secretions that make an airway environment prone to chronic bacterial infection. In turn, this triggers an inflammatory response that causes abnormal airway remodelling and structural damage [23]. If the process occurs in a stepwise manner, it may be logical to stop the cycle by intervening with one of the three components: abnormal mucus, chronic infection or inflammation. However, treatment strategies targeting one component frequently fail in clinical practice.

In this regard, a "vicious vortex" model was proposed, and the model incorporated complex interactions among the three components of bronchiectasis [24]. For example, *Pseudomonas* infection does not only induce neutrophilic inflammation, but also directly affects mucociliary clearance through the action of ciliotoxins, such as pyocyanin, which slows down ciliary beat frequency [25, 26]. Bronchiectasis is an inflammatory disease and is associated with an imbalance between pro- and anti-inflammatory signalling, leading to the recruitment of inflammatory cells and, ultimately, a self-perpetuating cycle of inflammation [23, 27].

Treatment aims, therefore, are to improve mucus clearance from the airways, reduce inflammation and prevent and reduce the impact of infection. Successful treatment can mitigate the effects of lung damage, reduce airflow limitation, improve exercise capacity and reduce exacerbations.

Initial assessment

Patients with bronchiectasis are heterogeneous and, thus, their treatment must be individualised. Figure 1 summarises the principles of management of bronchiectasis. Following diagnosis based on high-resolution CT and the presence of the clinical syndrome [2], initial assessment of patients includes an assessment of the severity of symptoms, the frequency of exacerbations, lung function and microbiology, including bacterial, fungal and mycobacterial cultures. Patients with bronchiectasis frequently have comorbidities, with a median of four comorbidities per patient in one large international study. Comorbidities confer an increased risk of exacerbation or mortality [28]. Assessment of disease severity can include utilisation of validated severity tools such as the Bronchiectasis Severity Index and E-FACED [29, 30], but should also take into account parameters not included in the tools such as comorbidities, extent of symptoms and the underlying cause. Identifying patients at higher risk of deterioration is critical to guide initial therapy (figure 2).

Identifying and treating the underlying cause

The first step in bronchiectasis management is to identify an aetiology that may be treatable or influence management. Non-tuberculous mycobacterial (NTM) pulmonary disease, allergic bronchopulmonary aspergillosis (ABPA) and primary and secondary immunodeficiency are examples of underlying causes with specific treatments [17, 18, 31], while rheumatoid arthritis and primary ciliary dyskinesia (PCD) are examples of conditions that are associated with worse outcomes and differences in clinical phenotype which require a change in management [32, 33]. Table 1 shows details on the diagnosis and treatment of NTM pulmonary disease, ABPA, immunodeficiency and α_1-antitrypsin deficiency in bronchiectasis patients. Testing for other underlying causes arises from the detailed history. Patients with onset of disease during childhood or with specific clinical features such as infertility, severe rhinosinusitis/nasal polyps, severe disease accompanied by infection with *Pseudomonas aeruginosa* or *Staphylococcus aureus* or extrapulmonary features such as malabsorption may have a genetic cause of bronchiectasis such as PCD or cystic fibrosis (CF). A recent study reported that genome sequencing revealed an underdiagnosis of PCD in bronchiectasis where 12% of patients with severe bronchiectasis were found to have PCD [33]. Although specific treatment for PCD has not yet been established, its identification is important for more intensive airway clearance, management of upper airway disease, fertility counselling and cardiac investigations [34]. CF is infrequently diagnosed in adults but the availability of highly effective modulator therapy mandates that these cases are not missed. Although aetiological testing was performed by the treating clinician based on the testing recommended by consensus guidelines [17, 18], 38% of patients still had idiopathic bronchiectasis in a European multicentre cohort study [35]. Moreover, in a large proportion of aetiology, such as post-infective bronchiectasis, specific management targeting aetiology itself does not exist. Hence, the next step is to target the "treatable traits" of bronchiectasis: impaired mucociliary clearance, bacterial infection and airway inflammation (figure 1).

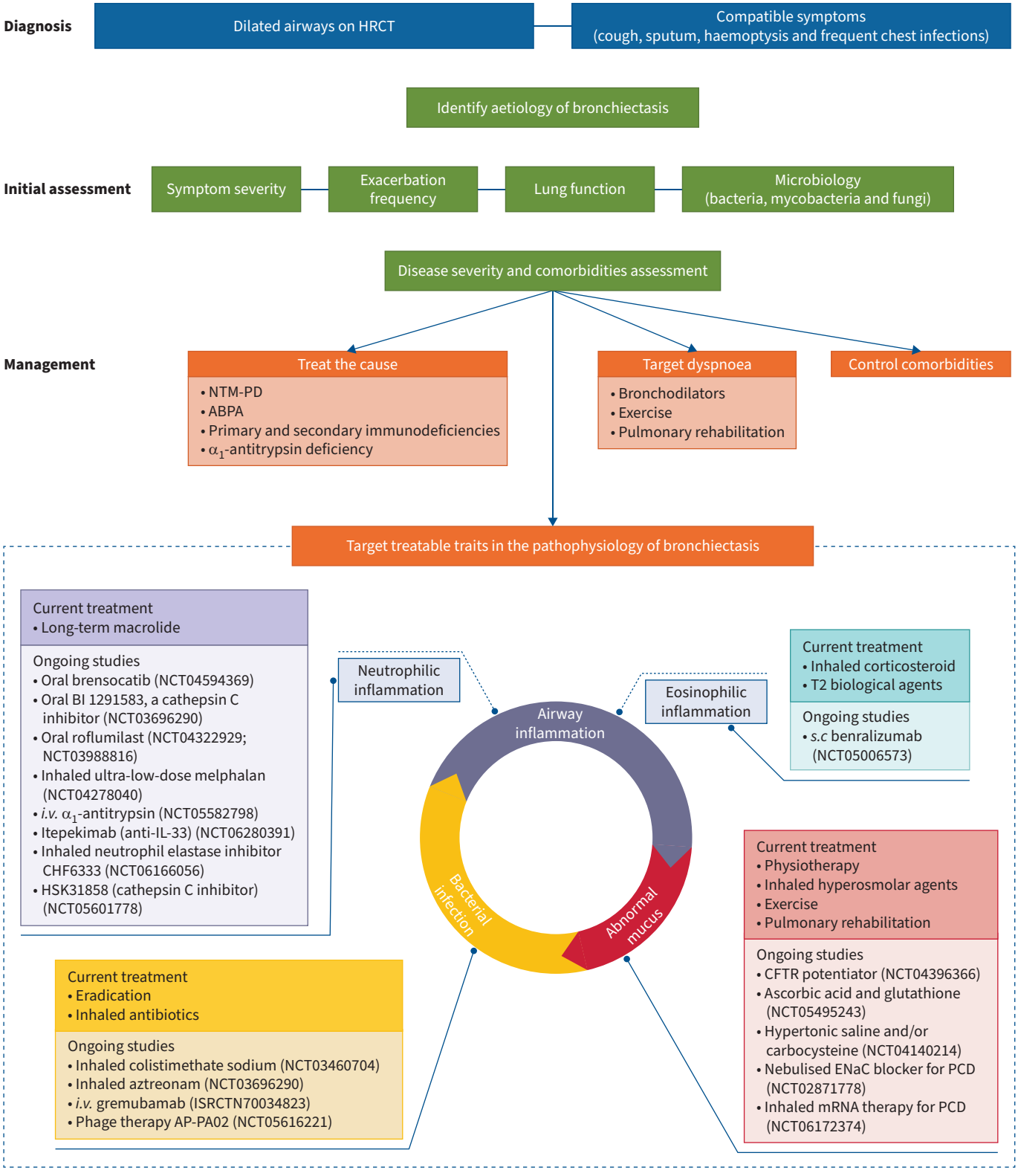

FIGURE 1 Summary of management points and ongoing studies (ClinicalTrials.gov and ISRCTN) in bronchiectasis. HRCT: high-resolution computed tomography; NTM-PD: non-tuberculous mycobacterial pulmonary disease; ABPA: allergic bronchopulmonary aspergillosis; IL: interleukin; *i.v.*: intravenous; T2: type 2; *s.c.*: subcutaneous; CFTR: cystic fibrosis transmembrane conductance regulator; ENaC: epithelial sodium channel; PCD: primary ciliary dyskinesia.

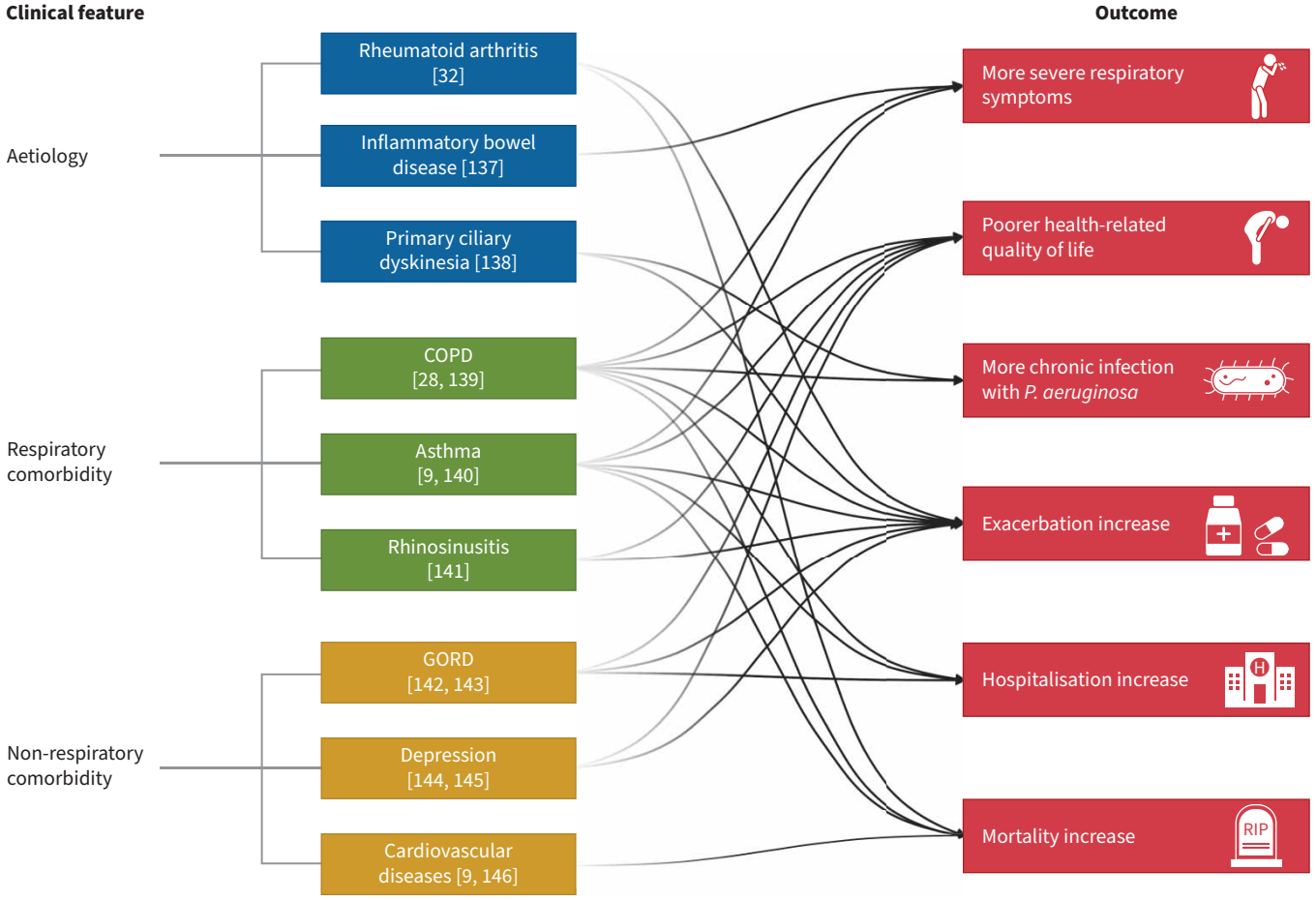

FIGURE 2 Clinical conditions associated with worse outcomes in patients with bronchiectasis. GORD: gastro-oesophageal reflux disease; *P. aeruginosa*: *Pseudomonas aeruginosa*.

Impaired mucociliary clearance

Airway clearance

The marked abnormalities in the mucus of bronchiectasis patients mandate that airway clearance is an absolute necessity in bronchiectasis management. Compared with healthy controls, mucus in bronchiectasis patients has higher mucin concentrations (both MUC5B and MUC5AC), and thus higher percent solids, higher osmotic pressure and increased elasticity and viscosity [36]. Furthermore, the abnormal mucus properties result in local hypoxia at the bronchial mucosa which further incites inflammation, increase in mucin concentration and worsen mucus properties [37]. Consequently, international guidelines recommend all patients with bronchiectasis receive instruction in airway clearance techniques taught by respiratory physiotherapists [17, 18, 38]. Unfortunately, evidence for this important aspect of care is somewhat lacking. Trials of airway clearance techniques are challenging to perform and as a result the majority of studies to date are small. Murray *et al*. [39] performed a randomised crossover trial in 20 patients who did not practice regular chest physiotherapy and compared 3 months of twice-daily airway clearance using an oscillatory positive expiratory pressure (PEP) device *versus* no physiotherapy. Upon study completion, regular airway clearance revealed significant improvements in the Leicester Cough Questionnaire (LCQ) score (median 1.3 improvement; p=0.002) and St George's Respiratory Questionnaire (SGRQ) total score (median 7.8 improvement; p=0.004), increased sputum volume and improved exercise capacity [39]. In addition, several small RCTs compared usual airway clearance, including the active cycle of breathing technique and autogenic drainage, with PEP devices, including Acapella (Smiths Medical, London, UK), Flutter (Scandipharm, Birmingham, AL, USA) and bubble-PEP [40–44]. Regular airway clearance resulted in increased sputum expectoration and improved health-related quality of life (HRQoL) in patients with bronchiectasis regardless of the clearance method.

TABLE 1 Diagnosis and treatment of treatable aetiologies in bronchiectasis

Aetiology	Diagnosis	Treatment	Comments
NTM pulmonary disease [17, 18, 133, 134]	Sputum culture for mycobacteria Microbiological test results compatible with NTM pulmonary disease: 1) the same NTM species is isolated in ⩾2 sputum cultures, 2) isolated in ⩾1 bronchial wash or lavage or 3) biopsy with mycobacterial histopathological features plus positive culture for NTM (or ⩾1 sputum or bronchial washings that are culture positive for NTM)	Combination of antibiotics for 12 months after sputum culture conversion Decided based on clinical symptoms, progression of radiological signs and knowledge of the infecting NTM species	ERS 2017 and BTS 2019 guidelines recommend mycobacterial sputum cultures in patients with bronchiectasis ATS/ERS/ESCMID/IDSA 2020 clinical practice guidelines for the treatment of NTM pulmonary disease
ABPA [17, 18, 135]	Total serum IgE test *Aspergillus*-specific IgG test *Aspergillus*-specific IgE test (or skin prick tests for *Aspergillus*)	Systemic corticosteroids Antifungal agents	ERS 2017 and BTS 2019 guidelines recommend ABPA testing in all patients with bronchiectasis
Immunodeficiency [17, 18]	Serum IgA, IgM and IgG Serum IgG subclass Peripheral blood lymphocyte subpopulations (including T-, B- and NK-cells) Pneumococcal IgG to vaccine response	Immunoglobulin replacement	ERS 2017 and BTS 2019 guidelines recommend serum IgA, IgM and IgG testing in all patients with bronchiectasis BTS 2019 guideline recommends pneumococcal IgG to vaccine response
A1AT deficiency [17, 18, 136]	Serum A1AT A1AT genetic testing	Intravenous augmentation of A1AT in countries where this is available	BTS 2019 guideline recommends A1AT deficiency testing in patients with coexisting basal panacinar emphysema ERS 2017 guideline states the presence of basal emphysema or early-onset airflow obstruction could suggest the need to exclude A1AT deficiency Portuguese 2016 guideline recommends A1AT deficiency testing in all patients with bronchiectasis (estimated prevalence is 1:2191 in Portugal)

NTM: non-tuberculous mycobacterial; ERS: European Respiratory Society; BTS: British Thoracic Society; ATS: American Thoracic Society; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; IDSA: Infectious Diseases Society of America; ABPA: allergic bronchopulmonary aspergillosis; NK: natural killer; A1AT: α_1-antitrypsin.

A recent RCT provided more long-term evidence for airway clearance. Munoz *et al.* [45] performed an RCT comparing 22 patients who underwent ELTGOL (slow expiration with the glottis opened in a lateral posture) twice a day for 12 months and 22 who performed placebo exercises. Despite the small sample size, the ability to gather long-term data and the ability to have a placebo control make this an important study in the airway clearance field. The ELTGOL group showed higher sputum volume (primary outcome), clinically significant improvement in the SGRQ and LCQ scores ($p<0.001$ for both) and reduced exacerbation ($p=0.042$) compared with those in the placebo group [45]. Notably, the results of the study emphasise that long-term airway clearance can ameliorate the clinical course of patients with bronchiectasis, beyond reducing daily symptoms and improving HRQoL.

Overall, studies have shown mixed results regarding which airway clearance technique is superior. This is likely due to the heterogeneity of bronchiectasis patients with regard to varying airway calibre, unique sputum properties and individual respiratory strength. From this perspective, the authors recommend that airway clearance management be tailored to the patient's needs, as the most effective airway clearance technique is one the patient will use consistently and successfully over time.

Airway clearance alone may be sufficient to manage patients' symptoms and improve their quality of life, but many patients have ongoing symptoms or exacerbations despite effective airway clearance. In this

situation, it is recommended to add additional symptomatic and/or preventative treatments in a stepwise manner until disease control is achieved.

Inhaled hyperosmolar agents and mucolytics

Mucoactive agents improve mucus hydration, reduce sputum viscosity and/or stimulate cough to aid mucus clearance. Available agents include oral mucolytic agents and nebulised hyperosmolar agents (mannitol and hypertonic saline). Oral mucolytics such as *N*-acetylcysteine, carbocysteine and erdosteine have achieved some success in the management of COPD [46] and are now being studied in bronchiectasis patients. Regarding nebulised hyperosmolar agents, small RCTs have compared hypertonic and isotonic saline as adjuncts to physiotherapy and revealed that hypertonic saline was more likely to ease sputum expectoration, improve lung function and enhance HRQoL [47–49]. However, an RCT investigating their long-term effects showed that nebulised hypertonic and isotonic saline had similar effects on exacerbation, sputum colonisation, HRQoL and forced expiratory volume in 1 s (FEV_1) over 12 months [50]. These results suggest that isotonic saline may benefit patients who cannot tolerate hypertonic saline. Notably, nebulised human recombinant DNase, although effective in CF, was poorly tolerated, ineffective and reduced FEV_1 in an RCT of bronchiectasis patients [51].

Inhaled dry mannitol powder was examined in two double-blind RCTs. The first study compared 231 patients on 320 mg of mannitol twice daily and 112 on a placebo for 12 weeks, followed by an open-label extension over 52 weeks to assess safety [52]. The study showed increased sputum weight in favour of mannitol, but no significant difference in the SGRQ. Because it was unclear whether the differences in sputum weight resulted from higher antibiotic use in the control group, a subsequent RCT focusing on exacerbations was conducted. The second study set the rate of exacerbations over 1 year as the primary outcome and enrolled patients who had two or more exacerbations in the previous 12 months [53]. The 52-week study included 233 patients who received 400 mg of mannitol twice daily and 228 who received a placebo. However, its primary end-point was not met (rate ratio of exacerbation 0.92, 95% CI 0.78–1.08; p=0.3) [53]. Despite its failure to achieve the primary end-point, *post hoc* analysis provided some insights. Gao *et al*. [54] classified patients enrolled in the study according to symptom burden using the SGRQ (>70: high symptom burden; 40–70: moderate; <40: low). In highly symptomatic patients, the proportion of patients remaining exacerbation-free for 12 months of treatment was significantly higher in the mannitol group (32.7% *versus* 14.6%; rate ratio 2.84, 95% CI 1.40–5.76; p=0.003) than in the placebo group; however, no benefit was evident in those with lower symptom burden [54]. These results emphasise the importance of a personalised medicine treatment strategy in bronchiectasis. Therapies seem to have more measurable benefits in highly symptomatic patients than in a larger undifferentiated bronchiectasis cohort.

Pulmonary rehabilitation and exercise tolerance

Exercise improves shortness of breath, reduces fatigue and raises endurance in bronchiectasis patients. Patients with significant breathlessness and those who cannot exercise independently should be referred for pulmonary rehabilitation. As in airway clearance, randomised trials of pulmonary rehabilitation in bronchiectasis are small but show a benefit. An 8-week pilot RCT that compared 30 bronchiectasis patients randomised to either pulmonary rehabilitation plus chest physiotherapy or chest physiotherapy alone demonstrated significantly improved exercise tolerance, including incremental shuffle walk (56.7 m; p=0.03) and endurance walk (193.3 m; p=0.01) tests, and HRQoL, including SGRQ and LCQ (8 and 2.6, respectively; p<0.001 for both) in patients who received pulmonary rehabilitation [55]. Remarkably, the improved outcomes persisted for 12 weeks after the pulmonary rehabilitation concluded. A subsequent RCT included 85 bronchiectasis patients: 42 randomised to 8 weeks of exercise training *versus* 43 controls. Exercise training increased both incremental shuttle and 6-min walk distance compared with the controls, although these improvements were not sustained at 6 or 12 months [56]. Additionally, exercise training reduced the exacerbation frequency (median 1 *versus* 2; p=0.012) and prolonged the time to first exacerbation (8 *versus* 12 months; p=0.047) compared with the control group [56].

A recent prospective observational study reinforced the importance of physical activity in bronchiectasis; it enrolled 64 bronchiectasis patients and objectively monitored their activity using armbands [57]. Patients who walked ⩽6290 steps per day or spent ⩾7.8 h per day in sedentary behaviour at baseline had an increased risk of bronchiectasis-related hospitalisation at 1-year follow-up [57]. Taken together, exercise should be emphasised in bronchiectasis patients to extend their exercise capacity, improve HRQoL and reduce exacerbations. Exercise must be continued to maintain long-term benefits [38, 58, 59].

Bacterial infection

Rationale

The rational for short- and long-term antibiotics is based on two scientific findings: 1) high airway bacterial loads correlate with airway and systemic inflammation and a greater risk of exacerbation in bronchiectasis patients [60], and 2) short- and long-term antibiotic treatments are associated with reductions in bacterial load and airway and systemic inflammation [60]. Among pathogens of chronic bacterial infection, *P. aeruginosa* infection, in particular, is associated with significantly worse outcomes in bronchiectasis patients. In a meta-analysis of 21 observational cohort studies (n=3683), *P. aeruginosa* infection correlated with higher mortality (OR 2.95, 95% CI 1.98–4.40), increased hospitalisations (OR 6.57, 95% CI 3.19–13.51) and exacerbations (mean difference 0.97 $year^{-1}$, 95% CI 0.64–1.30 $year^{-1}$) compared with infection with other pathogens or none [61]. These results were replicated in a European multicentre bronchiectasis study (n=2596), in which the prevalence of chronic *P. aeruginosa* infection was 15% [62]. However, the study showed that *P. aeruginosa* infection was independently associated with mortality primarily in patients with frequent exacerbations (hazard ratio (HR) 2.03, 95% CI 1.36–3.03) [62]. The frequent exacerbator with chronic *P. aeruginosa* infection is one of the most severe clinical phenotypes in bronchiectasis and some RCTs on inhaled antibiotics targeted this population.

The roles of other bacteria have also been examined in bronchiectasis patients. In a retrospective observational study of 167 patients, chronic *Stenotrophomonas maltophilia* infection conferred more exacerbations (rate ratio 1.42, 95% CI 0.96–2.12) and hospitalisations (rate ratio 2.08, 95% CI 1.00–4.29) than in patients without the organism [63]. *Staphylococcus aureus* was examined in a US registry study involving 830 bronchiectasis patients in which the prevalence was 11% [64]. Patients with *S. aureus* had more frequent exacerbations and poorer lung function than those with no prior *S. aureus* or Gram-negative infection; however, they had less frequent exacerbations and better lung function than those with Gram-negative infection [64]. Thus, *P. aeruginosa* and other Gram-negative organisms are the most clinically important pathogens in bronchiectasis. Naturally, this has resulted in the development of eradication and inhaled antibiotic therapy for bronchiectasis. Regular sputum cultures during both clinical stability and at exacerbations are important to guide therapy and identify new infection with *P. aeruginosa*.

New methods of detecting bacterial infection

Microbiome studies using bacterial 16S rRNA gene sequencing have provided more insight into bronchiectasis by characterising the abundance and diversity of microbial species and demonstrating a diverse microbial environment, while such information cannot be provided by traditional culture-dependent microbiology. In a recent microbiome study of 281 bronchiectasis patients by Dicker *et al*. [65], individual patient microbiome profiles were relatively stable over time, during exacerbations and during disease stability, consistent with previous microbiome studies [66, 67]. The study revealed that patients with dominant *Pseudomonas* in the microbiome profiles were at increased risk of all-cause mortality (HR 3.12, 95% CI 1.33–7.36) and had more frequent exacerbations (incidence rate ratio (IRR) 1.69, 95% CI 1.07–2.67) than patients with other dominant genera. Furthermore, the reduced microbiome diversity, assessed by α diversity (within-sample microbiome differences), correlated with increased disease severity, lower FEV_1 and more severe symptoms [65].

A recent study also used similarity network fusion approaches and metagenomics to integrate bacterial, fungal and viral data in sputum samples from 217 bronchiectasis patients [68]. In addition to reduced diversity, the study revealed that patients at the greatest risk of exacerbation have less complex microbial co-occurrence networks and a higher degree of antagonistic interactions in their airway microbiota [68]. These provocative results suggest that the relationships between bacteria in the bronchiectasis airway may be as, or more, important than the mere presence or absence of a single microbial group. Manipulating microbiomes by means other than antibiotics, probiotics and controlling host response in microbial environment [69, 70] will have therapeutic implications in the future.

Eradication

The European Respiratory Society (ERS) and British Thoracic Society (BTS) guidelines for adult bronchiectasis suggest that patients with a new isolation of *P. aeruginosa* should be offered eradication antibiotic treatment, despite low quality of evidence [17, 18, 71–73]. A recent systematic review and meta-analysis of observational studies reported that eradication treatment was associated with a 40% rate of clearing *P. aeruginosa* at 12 months. Efficacy was greater when systemic antibiotics were combined with an inhaled antibiotic (48% eradication rate) compared with systemic antibiotics alone (27% eradication rate) [74]. Therefore, current treatment recommendations suggest administration of a susceptibility guided oral fluoroquinolone or intravenous antipseudomonal antibiotics either with or followed by an inhaled antibiotic

for 6 weeks to 3 months as an eradication regimen. A prospective randomised study of eradication therapy compared with no eradication treatment and testing of different eradication regimens is warranted.

Inhaled antibiotics

Long-term suppressive use of inhaled antibiotics has been the most actively investigated therapeutic agent strategy for bronchiectasis in clinical trials. Inhaled antibiotics have the advantage of delivering higher concentrations of drugs to the airway, reducing systemic absorption and side-effects compared with oral or *i.v.* antibiotics [75]. The current evidence for the use of inhaled antibiotics, including ciprofloxacin, aztreonam, tobramycin, gentamicin and colistin, in bronchiectasis is summarised in table 2 [76–88].

A decade of phase 2 trials was followed by several large international phase 3 trials: AIR-BX, RESPIRE and ORBIT. The AIR-BX trial investigated aztreonam, an inhaled antibiotic licensed for CF treatment. AIR-BX1 (n=266) and AIR-BX2 (n=274) randomised patients to aztreonam or placebo over two treatment cycles of 28 days, with an off-treatment cycle in between [81]. The primary outcome was symptom improvement, measured using the Respiratory symptom domain of the Quality of Life Bronchiectasis (QOL-B) questionnaire after the first 28-day treatment. The primary outcome was only reached in AIR-BX2 (mean difference 4.6, 95% CI 1.1–8.2; p=0.011), and secondary end-points such as exacerbation were negative in both trials. Moreover, intolerance due to worsening dyspnoea and cough was a major issue. Active treatment was discontinued in 27 (20%) out of 134 aztreonam-treated patients in AIR-BX1 and in 10 (7%) out of 135 patients in AIR-BX2.

RESPIRE investigated a dry powder inhaled (DPI) formulation of ciprofloxacin in two identically designed trials: RESPIRE-1 (n=416) and RESPIRE-2 (n=521). Each trial studied 14- and 28-day on/off-treatment cycles of ciprofloxacin DPI administered twice daily *versus* placebo in a 2:1 allocation over a 48-week period [77, 78]. These trials included patients with *P. aeruginosa* and other bacteria, whereas most other inhaled antibiotic trials included only patients with *P. aeruginosa*. The primary outcomes were time to first exacerbation and frequency of exacerbations. Primary outcomes were only reached in the 14-day arm of RESPIRE-1: significantly prolonged time to first exacerbation (HR 0.53, 97.5% CI 0.36–0.80; p=0.0005) and reduced frequency of exacerbation (IRR 0.61, 97.5% CI 0.40–0.91; p=0.0061). However, these end-points were not met in the 28-day arm of RESPIRE-1 or in either arm of RESPIRE-2.

The ORBIT trials investigated liposomal formulations of ciprofloxacin, which aimed to improve tolerability through liposomal encapsulation of the drug, thus reducing the amount of free drug in contact with the pulmonary epithelium [79]. In phase 3 trials, ORBIT-3 (n=278) and ORBIT-4 (n=304) compared liposomal ciprofloxacin administered once daily with a placebo in a 2:1 ratio over 48 weeks [80]. The trials comprised six 56-day treatment cycles, with each cycle consisting of a 28 day on/off-treatment period. There was a significant prolongation of time to first exacerbation, a primary end-point, in ORBIT-4 (HR 0.72, 95% CI 0.53–0.97; p=0.032); however, this end-point was not met in either ORBIT-3 or pooled analysis of both trials.

More recently, three RCTs have investigated inhaled tobramycin in two different formulations: inhalation solution (TORNASOL and BATTLE studies) and dry powder (iBEST study). The TORNASOL trial (n=339), conducted in China, compared tobramycin inhalation solution and normal saline over 56 days (28 days on/off treatment) [83]. The study met its predefined co-primary end-point of a greater reduction in *P. aeruginosa* bacterial load (adjusted mean difference 1.74 $\log_{10}$CFU·mL^{-1}; p<0.001) and greater improvement in the Respiratory symptom domain of the QOL-B questionnaire (adjusted mean difference 7.91; p<0.001) on day 29. The BATTLE study (n=58) also compared tobramycin inhalation solution and placebo for 1 year [84]. The primary end-point of exacerbation frequency was not met (rate ratio 0.74, 95% CI 0.49–1.14; p=0.15). The iBEST phase 2 trial (n=107) investigated the efficacy of tobramycin inhalation powder, delivered by TOBI Podhaler (Novartis, Basel, Switzerland), and showed a reduction in *P. aeruginosa* bacterial load at all three doses; the higher the dose, the greater the reduction in bacterial load from baseline to day 29 (−2.5 $\log_{10}$CFU·mL^{-1} at 84 mg, −2.8 $\log_{10}$CFU·mL^{-1} at 140 mg and −3.8 $\log_{10}$CFU·mL^{-1} at 224 mg) (p<0.0001 for all) [85]. Overall, inhaled tobramycin was well tolerated, with the majority of study patients in these three studies achieving 88–94% compliance. The finding that inhaled tobramycin was well tolerated conflicts with the early phase 2 trial by Barker *et al.* [82] which showed that although inhaled tobramycin significantly reduced *P. aeruginosa* bacterial load, it was poorly tolerated and decreased FEV_1. The PROMIS trials of inhaled colistin have not yet been published but have been reported in abstract form, with PROMIS-I (ClinicalTrials.gov: NCT03093974) reporting a significant benefit of treatment [89] and PROMIS-II (ClinicalTrials.gov: NCT03460704) awaiting full results.

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TABLE 2 Summary of randomised controlled trials (RCTs) of inhaled antibiotics for bronchiectasis

Agent and study	Subjects (n)	Study design	Primary outcome	Duration	Study population	Main results	Safety
Ciprofloxacin DPI Wilson *et al.* (2013) [76]	A: 60 P: 64	Phase 2 double-blind RCT	Bacterial load	84 days (28-day treatment with follow-up)	⩾2 exacerbations in previous year; culture positive for target microorganisms	Mean difference in bacterial load −3.62 *versus* −0.27 $log_{10}CFU{\cdot}mL^{-1}$ (p<0.001); no significant differences in proportion of patients with exacerbations (36.7% *versus* 39.1%; p=0.6) and SGRQ (mean difference −3.56; p=0.059)	10% of patients developed resistance (MIC >4 $mg{\cdot}L^{-1}$) in the ciprofloxacin group; no difference in adverse events between groups
Ciprofloxacin DPI De Soyza *et al.* (2018) RESPIRE 1 [77]	14-day on/off A: 137 P: 68 28-day on/off A: 141 P: 70	Phase 3 double-blind RCT	Time to first exacerbation, frequency of exacerbations	12 months (14- or 28-day on/off-treatment cycles)	⩾2 exacerbation in previous year; culture positive for predefined microorganisms	14-day on/off cycle: significantly prolonged time to first exacerbation (median >336 *versus* 186 days; HR 0.53, 97.5% CI 0.36–0.80; p=0.0005); reduced frequency of exacerbation (IRR 0.61, 97.5% CI 0.40–0.91; p=0.0061); 28-day on/off cycle: no significant differences in primary end-points	No difference in adverse events between groups
Ciprofloxacin DPI Asakamit *et al.* (2018) RESPIRE 2 [78]	14-day on/off A: 176 P: 88 28-day on/off A: 171 P: 86	Phase 3 double-blind RCT	Time to first exacerbation, frequency of exacerbations	12 months (28-day on/off-treatment cycles)	⩾2 exacerbations in previous year; culture positive for predefined microorganisms	Missed primary end-point: prolonged time to first exacerbation (HR 0.87, 95% CI 0.62–1.21; p=0.40 in 14-day on/off and HR 0.71, 99% CI 0.39–1.27; p=0.051 in 28-day on/off) and reduced frequency of exacerbations (IRR 0.83, 95% CI 0.59–1.17; p=0.29 in 14-day on/off and IRR 0.55, 99% CI 0.30–1.02; p=0.001 in 28-day on/off)	No difference in adverse events between groups
Liposomal ciprofloxacin Serisier *et al.* (2013) ORBIT-2 [79]	A: 20 P: 20	Phase 2 double-blind RCT	Bacterial load after first 28-day treatment cycle with intervening 28-day off periods	24 weeks (three 28-day treatment cycles)	*P. aeruginosa*-colonised patients; ⩾2 exacerbations in previous 12 months	Reduction in *P. aeruginosa* bacterial load −4.2 *versus* −0.08 $log_{10}CFU{\cdot}mL^{-1}$ (p=0.002); reduced number of exacerbations in the active treatment group (OR 0.2, 95% CI 0.04–0.89; p=0.027)	No significant difference in MICs to ciprofloxacin at day 28; no increase in adverse events
Liposomal ciprofloxacin Haworth *et al.* (2019) ORBIT-3 and ORBIT-4 [80]	ORBIT-3 A: 183 P: 95 ORBIT-4 A: 206 P: 98	Phase 3 double-blind RCT	Time to first exacerbation	48 weeks (six 28-day on/off-treatment cycles)	⩾2 exacerbations in previous year; chronic *P. aeruginosa* infection	Median time to first exacerbation: 230 *versus* 158 days (HR 0.72, 95% CI 0.53–0.97; p=0.032) in ORBIT-4; 214 *versus* 136 days (HR 0.99, 95% CI 0.71–1.38; p=0.97) in ORBIT-3; and 222 *versus* 157 days (HR 0.82, 95% CI 0.65–1.02; p=0.074) in a pooled analysis of both trials	No difference in adverse events between groups
Aztreonam Barker *et al.* (2014) AIR-BX1 and AIR-BX2 [81]	AIR-BX1 A: 134 P: 132 AIR-BX2 A: 136 P: 138	Two phase 3 double-blind RCTs	QOL-B score at week 4	Two 28-day treatment courses with alternating 28 days off treatment	Positive sputum for *P. aeruginosa* or other Gram-negative organisms (excluding *H. influenzae*); FEV_1 >20% predicted; chronic sputum production	No difference in QOL-B at week 4 (mean difference 0.8, 95% CI −3.1–4.7; p=0.7 in AIR-BX1 and 4.6, 95% CI 1.1–8.2; p=0.011 in AIR-BX2); no difference in QOL-B in both studies at week 12 (p=0.56 in both studies); no difference in time to first exacerbation	Adverse events leading to discontinuation: AIR-BX1 22% *versus* 6%; AIR-BX2 10% *versus* 5%

Continued

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TABLE 2 Continued

Agent and study	Subjects (n)	Study design	Primary outcome	Duration	Study population	Main results	Safety
Tobramycin Barker *et al*. (2000) [82]	A: 37 P: 37	Phase 2 double-blind RCT	*P. aeruginosa* bacterial load at week 4	6 weeks (28-day treatment)	*P. aeruginosa*-colonised patients	Significant reduction in *P. aeruginosa* load (mean difference 4.56 $log_{10}CFU{\cdot}mL^{-1}$; p<0.01); 13/37 cleared *P. aeruginosa* from sputum; no significant change in FEV_1 (p=0.41)	Increased dyspnoea, chest pain and wheezing; new resistance to tobramycin in 4/36
Tobramycin Guan *et al*. (2022) TORNASOL [83]	A: 167 P: 172	Phase 3 double-blind RCT	*P. aeruginosa* bacterial load and QOL-B Respiratory symptoms score on day 29	16 weeks (two cycles of 28 days on/off treatment)	⩾1 exacerbations in previous 2 years; chronic *P. aeruginosa* infection	*P. aeruginosa* bacterial load mean difference 1.74 $log_{10}CFU{\cdot}mL^{-1}$ (p<0.001); QOL-B Respiratory symptom score mean difference 7.9 (p<0.001)	Adverse events leading to discontinuation: 6.2% (tobramycin) *versus* 2.8% (placebo)
Tobramycin Terpstra *et al*. (2022) BATTLE [84]	A: 26 P: 26	Phase 3 double-blind RCT	Frequency of exacerbation	12 months	⩾2 exacerbations in previous year; culture positive for predefined microorganisms	Missed primary end-point: rate ratio 0.74, 95% CI 0.49–1.14 (p=0.15)	8.8% of tobramycin group discontinued study due to respiratory symptoms in first 4 weeks
Tobramycin inhalation powder Loebinger *et al*. (2021) iBEST [85]	A: 86 P: 21	Phase 2 double-blind RCT	*P. aeruginosa* bacterial load on day 29	Treatment for 16 weeks plus follow-up for 8 weeks	*P. aeruginosa*-colonised patients	Primary end-point was met in all three doses: *P. aeruginosa* bacterial load ($log_{10}CFU{\cdot}mL^{-1}$) −2.5 at 84 mg (p=0.0004), −2.8 at 140 mg and −3.8 at 224 mg (p=0.0001 for all)	8.8% of tobramycin group discontinued study due to respiratory symptoms in first 4 weeks
Gentamicin Murray *et al*. (2011) [86]	A: 27 P: 30	Single-blind RCT	Bacterial load	12 months	Patients colonised with any pathogens in at least three sputum samples in the previous 12 months; 2 exacerbations in the previous year; able to tolerate test dose of gentamicin; FEV_1 >30% predicted; ex-smokers of >1 year; not on long-term antibiotics	Significant difference in bacterial load at 12 months (2.69 *versus* 7.67 $log_{10}CFU{\cdot}mL^{-1}$; p<0.0001); reduction in exacerbations (median 0 in gentamicin group *versus* 1.5 in saline group; p<0.0001); improved SGRQ and LCQ scores; reduced airway inflammation	Bronchospasm in 21.9%; two withdrawals; elevated serum gentamicin levels required dose reduction in one patient; no resistant isolates detected
Colistin Haworth *et al*. (2014) [87]	A: 73 P: 71	Phase 3 double-blind RCT	Time to first exacerbation	6 months	*P. aeruginosa*-colonised patients (⩾2 positive cultures in 12 months) and within 21 days of completing antipseudomonal antibiotics for exacerbation	Missed primary end-point (colistin 165 days *versus* placebo 111 days; p=0.11); improved SGRQ (mean difference −10.5; p=0.006); improved time to first exacerbation in patients taking >80% of doses	Five (7%) patients developed bronchoconstriction leading to discontinuation; no resistant strains at follow-up

DPI: dry powder inhaler; A: active; P: placebo; SGRQ: St George's Respiratory Questionnaire; MIC: minimum inhibitory concentration; HR: hazard ratio; IRR: incident rate ratio; *P. aeruginosa*: *Pseudomonas aeruginosa*; QOL-B: Quality of Life Bronchiectasis; *H. influenzae*: *Haemophilus influenzae*; FEV_1: forced expiratory volume in 1 s; LCQ: Leicester Cough Questionnaire.

The inconsistent results of recent inhaled antibiotic trials may be due to differences in patient selection or a lack of statistical power. Several trial programmes have shown discordant results in replicating phase 3 studies. A secondary analysis of the AIR-BX trial revealed improved symptoms in patients with high bacterial loads [90], which may guide the commencement of inhaled antibiotics in the future. Additionally, symptoms worsen during "off periods" when antibiotics are administered 28 days on and 28 days off, suggesting continuous administration may achieve better disease control [91–93]. We have recently reported a meta-analysis of 20 studies including 3468 participants. Overall, inhaled antibiotics were shown to be efficacious with a significant reduction in exacerbation frequency (rate ratio 0.78, 95% CI 0.68–0.91) and a much larger estimated reduction in severe exacerbations (rate ratio 0.48, 95% CI 0.31–0.74). Inhaled antibiotics were also associated with an improvement in symptoms measured using the QOL-B questionnaire and SGRQ [88]. However, potential downsides of this treatment include an increased treatment burden, such as inhalation time, and a higher risk of emergent antibiotic resistance. In real-world practice, inhaled antibiotics were used in approximately 8% of the EMBARC registry cohort (n=16 963) and the rate varied between 2% and 9% according to different European regions [35]. Predictive clinical parameters and/or biomarkers are needed to identify which patients will best respond to inhaled antibiotics.

Airway inflammation

Rationale and new methods of measuring airway inflammation

Recent advancements in molecular techniques have shed light on airway inflammation, which is an important axis in the pathophysiology of bronchiectasis. An observational study measured sputum neutrophil elastase activity in 381 bronchiectasis patients at baseline and during exacerbations [94]. Neutrophil elastase activity was significantly increased during exacerbations ($p=0.001$) and correlated with a higher frequency of exacerbations over a 3-year follow-up period ($p<0.001$). The key role of neutrophilic inflammation was also demonstrated in a proteomic study showing neutrophil extracellular traps and their components are key mediators of disease severity and predictive of exacerbations [95]. The integral role that neutrophilic inflammation plays in bronchiectasis pathophysiology is the rationale for a novel drug class, cathepsin C/dipeptidyl peptidase-1 (DPP1) inhibitors, currently in clinical trial that directly targets neutrophilic inflammation [96]. With the optimism that such novel drugs will soon become clinically available, the need of a point-of-care neutrophil elastase assay comes to the forefront. A lateral flow neutrophil elastase activity assay device to rapidly identify patients with bronchiectasis at an increased risk of airway infection and future exacerbation is under development [97]. Additionally, a point-of-care test measuring sputum myeloperoxidase, an abundant protein in neutrophils, showed that myeloperoxidase reflected the exacerbation status of bronchiectasis [98].

Long-term macrolide

Macrolide therapy is highly effective in reducing the frequency of exacerbations in bronchiectasis, believed to be due to its anti-inflammatory properties, although it is also possible that macrolides affect other constituents of the microbiome or quorum sensing in *P. aeruginosa* [68, 99, 100]. Thus, both the ERS and BTS bronchiectasis guidelines recommend long-term macrolide therapy for frequent exacerbators and those with chronic *P. aeruginosa* infection who have not improved with inhaled antibiotics [17, 18]. The benefit of chronic macrolide therapy was shown in three double-blind RCTs: EMBRACE, BLESS and BAT [101–103]. Subsequently, an individual patient data meta-analysis of the three trials (n=341) showed that macrolides reduced the frequency of exacerbation (IRR 0.49, 95% CI 0.36–0.66; $p<0.001$) and prolonged the time to first exacerbation (HR 0.46, 95% CI 0.34–0.61; $p<0.001$). The effect of macrolides was observed in all subgroups; notably, an increased benefit was observed in patients with *P. aeruginosa* infection (IRR 0.36, 95% CI 0.18–0.72; $p=0.004$) [104].

A major concern regarding long-term macrolide use is its potential influence on the composition of the respiratory microbiota in bronchiectasis. A secondary analysis of the BLESS trial suggested that long-term macrolide therapy may increase the relative abundance of *P. aeruginosa* in the respiratory microbiota of patients with bronchiectasis. However, no patients were colonised with *P. aeruginosa* in culture; therefore, the clinical importance of this finding remains unclear [105]. Other concerns regarding macrolides are the need to monitor gastrointestinal side-effects, the QT interval, risk of hearing deficits and the development of resistant NTM [106, 107]. Baseline ECG and sputum acid-fast bacillus culture are recommended prior to the commencement of macrolide therapy. The risk of tinnitus and hearing deficits should be discussed with the patient and consideration given to baseline audiogram. Macrolide was more commonly used in approximately 17% of the EMBARC registry cohort (n=16 963) compared with inhaled antibiotics, but the rate substantially varied between 1% and 24% according to different European regions [35].

Inhaled corticosteroids and biologics targeting type 2 inflammation

In the absence of concomitant asthma and/or ABPA, inhaled corticosteroids (ICS) are not universally endorsed by the international guidelines [17, 18]. ICS have not been shown to reduce the frequency of bronchiectasis exacerbations and they do not properly address the predominant neutrophilic inflammation that is central to bronchiectasis pathophysiology. Recently, however, an eosinophilic endotype of bronchiectasis that is distinct from asthma has been described. Tsikrika *et al*. [108], in a small study of cell counts from Greece, were among the first to identify a subset of patients with elevated sputum eosinophils in bronchiectasis. Subsequently, Shoemark *et al*. [109] coined the entity "eosinophilic bronchiectasis" in a multicentre European cohort by identifying a subset of bronchiectasis patients with elevated T-helper cell type 2 (Th2) cytokines in sputum and then demonstrating approximately 20% of patients have blood eosinophil counts >300 cells·μL^{-1} or sputum eosinophils >3% after exclusion of asthma and ABPA. We have further characterised this patient group by showing that Th2 cytokines are typically elevated in association with Th1/neutrophil markers in a mixed inflammatory subtype. This mixed inflammatory subtype correlated with increased exacerbation risk compared with patients with milder inflammatory subtypes [110]. Thus, most bronchiectasis patients classified as "eosinophilic bronchiectasis" would have overlapping evidence of neutrophilic inflammation, which should be considered when deciding treatment by clinicians.

In a *post hoc* analysis of an RCT, ICS resulted in a statistically significant reduction of the SGRQ (⩾4 points) in bronchiectasis patients with higher eosinophil counts (⩾3% or ⩾150 cells·μL^{-1}), although the ICS effect was not observed in other eosinophil groups [111, 112]. Moreover, another pooled *post hoc* analysis of two RCTs showed that ICS led to lower rates of exacerbation and hospitalisations in bronchiectasis patients with high eosinophil counts (⩾4%) [112–114]. These studies are limited by being *post hoc* with small sample sizes but are supported by extensive data showing eosinophils predict ICS response in other airway diseases.

The presence of an eosinophilic subtype of bronchiectasis raises the question of whether anti-Th2 biologics, which are highly effective in severe asthma, may have a role in eosinophilic bronchiectasis. The efficacy of anti-interleukin (IL)-5 or anti-IL-5 receptor monoclonal antibodies in severe eosinophilic bronchiectasis was reported in a case series (12 patients receiving mepolizumab and nine receiving benralizumab), which demonstrated marked improvements in exacerbation rate (median number of annual exacerbations, from 3 at baseline to 1 after 6 months of treatment) and lung function (median FEV_1 % pred, from 53% to 68%) [115]. Moreover, other studies investigating the efficacy of Th2 inflammation-targeting biologics in patients with severe uncontrolled asthma and bronchiectasis [116–118] also support their use in patients with asthma and associated bronchiectasis. In the meantime, additional work is necessary to properly define eosinophilic bronchiectasis. This includes addressing the repeatability of circulating eosinophils over time and clarifying the role of fractional exhaled nitric oxide [119–121]. Moving forward, as precision medicine strategies become more common place in bronchiectasis management, guidelines may recommend ICS for eosinophilic subtypes of bronchiectasis.

Bronchodilators

A survey of over 700 European patients with bronchiectasis found that 70% of patients described breathlessness as either difficult or very difficult [122]. Approximately half of the EMBARC registry cohort of 16 963 patients have an FEV_1 <80% predicted. Airflow obstruction is common and was reported in 35% of the patients [35]. A study performing detailed lung function in a cohort of 187 patients with bronchiectasis found airflow obstruction in 41%, but a higher proportion of patients also had air trapping reversibility and may respond to bronchodilator treatment even with "normal" spirometry [123]. Therefore, a trial of bronchodilators in patients with significant breathlessness is recommended by international guidelines [17, 18]. Randomised trials demonstrating efficacy are lacking.

Treating exacerbation

Definition of bronchiectasis exacerbation

Bronchiectasis exacerbations are watershed events in the natural history of the disease. Patients with frequent exacerbations have double the mortality rate compared with those who do not experience exacerbations [124]. In 2017, an international group of experts on bronchiectasis provided a uniform definition for clinical trials [125]. The consensus definition is: deterioration of three or more key symptoms for at least 48 h, in addition to a clinician's decision that a change in bronchiectasis treatment is required. The key symptoms are 1) cough, 2) sputum volume and/or consistency, 3) sputum purulence, 4) breathlessness and/or exercise intolerance, 5) fatigue and/or malaise, and 6) haemoptysis [125]. A clinician's decision to change treatment generally refers to the prescription of antibiotics.

Notably, the above definition was made for clinical trials, so a proportion of patients who are actually exacerbating do not meet those criteria in clinical practice. Research shows that a significant proportion of exacerbations are missed. In a study of 21 patients using a novel symptom diary, Artaraz *et al*. [126] showed that 23 out of 52 diary-detected exacerbations were not reported by the patients and were therefore not treated with antibiotics. Considering the detrimental effect of exacerbations in bronchiectasis patients [124, 127], widespread patient education to improve recognition of exacerbations is of paramount importance, particularly for those whose exacerbations are insufficiently severe to warrant hospital admission.

Antibiotic treatment for exacerbations

Bronchiectasis guidelines recommend antibiotics as the mainstay of treatment for bronchiectasis exacerbation. Based on expert opinion, the recommended duration of an antibiotic course is 14 days [17, 18]. However, shorter courses may be sufficient in cases of mild exacerbations or a rapid return to baseline condition, considering that an RCT demonstrated the non-inferiority of 10 *versus* 14 days in early responders to *i.v.* antibiotics in CF [128]. Additionally, the BTS guidelines recommend that suitable patients should have antibiotics to keep at home as part of their self-management plans [17]. This strategy guarantees prompt treatment of exacerbations but is not universally implemented because of concerns about antibiotic overuse. Exacerbation severity is typically determined by the site of care, with exacerbations requiring hospitalisation or home *i.v.* antibiotics regarded as severe and those managed as outpatients regarded as moderate. Severe exacerbations are usually managed with 14 days of *i.v.* antibiotics. Systemic corticosteroids are not recommended for bronchiectasis exacerbations in the absence of COPD or asthma [17, 18, 92].

A recent proof-of-concept study assessed the ability of bacterial load to guide the length of antibiotic administration during exacerbations. The study randomised 90 subjects to receive either a standard 14-day regimen or a flexible course guided by bacterial burden. 88% of patients whose length of antibiotic course was guided by bacterial load were able to stop treatment at day 8 [129]. The patients who received a standard 14-day course of antibiotics showed a non-significant trend for clinical improvement (improved HRQoL scores, reduced sputum volume and purulence) compared with the bacterial load-guided therapy. Paradoxically, despite receiving fewer days of antibiotics, the bacterial load-guided group had a longer time to next exacerbation compared with the patients who received a standard 14-day regimen [129]. A potential mechanism of such an effect is not known and may represent a chance finding. Therefore, more studies are needed to clarify the optimal duration of antibiotic treatment for bronchiectasis exacerbation. In fact, a singular recommendation is not likely to be appropriate for all patients given the overall heterogeneity of bronchiectasis patients. In addition, it is important to acknowledge that not all exacerbations require antibiotic treatment, as molecular methods do not identify bacteria in all cases. In some cases, exacerbations can be managed without antibiotics (*i.e.* by intensified airway clearance). Moving forward, this is an area of priority for future research.

A look to the future: new therapy, ongoing studies and precision medicine in bronchiectasis

A novel class of drugs that directly target neutrophilic inflammation in bronchiectasis has been developed. Neutrophil elastase and other neutrophil serine proteases are activated during neutrophil maturation in the bone marrow by cathepsin C/DPP1. Inhibitors of this enzyme are in advanced-phase clinical trial as novel anti-inflammatory treatments for bronchiectasis [130, 131]. The WILLOW phase 2 RCT of brensocatib, an oral reversible DPP1 inhibitor, enrolled patients with bronchiectasis in a 1:1:1 ratio to receive brensocatib 10 mg (n=82), 25 mg (n=87) or placebo (n=87) for 24 weeks. Brensocatib achieved the primary end-point of prolonged time to first exacerbation with 10 mg (HR 0.58, 95% CI 0.35–0.95; p=0.03) and 25 mg (HR 0.62, 95% CI 0.38–0.99; p=0.046) compared with that by placebo [96]. Brensocatib is currently in a phase 3 trial (ClinicalTrials.gov: NCT04594369). A similar compound, BI 1291583, is in a phase 2 clinical trial in bronchiectasis [132]. Randomised studies are also in progress testing biological treatments in eosinophilic (ClinicalTrials.gov: NCT05006573) and non-eosinophilic bronchiectasis (ClinicalTrials.gov: NCT06280391). Figure 1 summarises ongoing studies on other emerging treatments for bronchiectasis.

The heterogeneity of bronchiectasis precludes a one-size-fits-all management strategy. *Post hoc* analyses of previous clinical trials in bronchiectasis revealed clinically relevant subgroups of patients. For example, although both inhaled mannitol and inhaled aztreonam (AIR-BX) studies failed to meet their primary end-points [53, 81], *post hoc* analysis from each of the studies uncovered a subset of patients who benefitted from the study drug [54, 90]. Further analysis of such subsets may uncover “treatable traits”, or phenotypes and endotypes that may facilitate the recognition of patients who will benefit from certain therapies. Recent advancements in molecular techniques will make it possible to identify treatable traits. The objective of future bronchiectasis management is to employ targeted therapies toward specific treatable traits within mucus clearance, chronic bacterial infection and airway inflammation in accordance with the

TABLE 3 Suggested future research priorities in bronchiectasis (adapted from Aliberti *et al.* [122])

Evidence for current treatments
1) An RCT of *Pseudomonas* eradication therapy compared with symptomatic treatment
2) An RCT to determine the optimal duration of antibiotic treatment for bronchiectasis exacerbations
3) Biomarkers are needed to identify which patients respond optimally to inhaled antibiotics
4) An RCT of inhaled corticosteroids in bronchiectasis, including determining whether biomarkers such as blood eosinophil counts can guide treatment
5) Large-scale pragmatic trials of airway clearance techniques and pulmonary rehabilitation are required to establish a robust evidence base and the optimal mode of delivery for this intervention
Novel treatments and disease understanding
6) Development of novel strategies to modify the microbiome as alternatives to broad-spectrum antibiotics (including antibodies/vaccines, phage therapy and probiotics)
7) Development of novel therapeutics targeting neutrophilic inflammation/neutrophil extracellular traps to prevent exacerbations and improve symptoms
8) A large-scale genetic study of unselected patients with bronchiectasis is needed to identify underlying causes, find new causes of "idiopathic bronchiectasis" and to identify new therapeutic targets
9) Deep molecular endotyping of bronchiectasis incorporating proteomics, transcriptomics, microbiomics and other profiling is needed to understand the biological mechanisms underlying bronchiectasis and identify new biomarkers and targets
10) Studies of early bronchiectasis, including syndromes such as persistent bacterial bronchitis and the early stages of diseases such as primary ciliary dyskinesia, are needed to understand the initial molecular mechanisms leading to the development and progression of bronchiectasis

RCT: randomised controlled trial.

concept of precision medicine. There are many unanswered questions in the field of bronchiectasis. In 2016, the EMBARC consortium outlined 22 priority research topics [122]. Many have been addressed, such as the need for large-scale observational cohorts to study the natural history of bronchiectasis. Other areas still require further research. We have adapted these recommendations into 10 updated research recommendations: five on evidence for existing treatments and five related to novel treatments and disease understanding (table 3).

Conclusions

The fundamental goals of bronchiectasis treatment are to lessen the symptom burden, improve HRQoL, reduce exacerbations and prevent disease progression. With the increased awareness of the disease, bronchiectasis is finally receiving the attention that it deserves. Scientific research has improved our understanding of the pathophysiological mechanisms that drive the disease and there are an unprecedented number of clinical trials now available to our patients. With continued momentum, the concept of precision medicine in bronchiectasis will soon be a reality. Thus, the future for patients with bronchiectasis is promising.

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