Treatment to prevent exacerbations in bronchiectasis: macrolides as first line?

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Bronchiectasis exacerbations are defined by an increase in daily respiratory symptoms such as cough, sputum production, malaise, fatigue and breathlessness [1–3]. Symptoms accumulate over several days and can take weeks to resolve, with many patients never fully returning to baseline after therapy [4]. Patients with frequent exacerbations experience poorer quality of life and a markedly increased mortality [5–7]. Patients tend to continue to have frequent exacerbations over time unless therapy is initiated to prevent them [5]. Bronchiectasis guidelines such as those recently issued from the European Respiratory Society (ERS) and British Thoracic Society therefore rightly prioritise exacerbation prevention as perhaps the key objective of therapy, alongside improvement of patients' symptoms and quality of life [8–10].

The ERS guidelines published in 2017 made a number of recommendations for exacerbation prevention, including recommending airway clearance and pulmonary rehabilitation, mucoactive therapy in patients who have difficulty with mucus clearance and long-term antibiotic therapy [8–11, 12]. For long-term antibiotic therapy, macrolides were recommended for patients without *Pseudomonas aeruginosa* infection while inhaled antibiotics were recommended for patients with *P. aeruginosa* infection [8]. Inhaled bronchodilators were recommended for breathless patients, but inhaled corticosteroids (ICS) were not recommended, with the exception of patients with co-existing asthma and chronic obstructive pulmonary disease (COPD) [8].

All of these recommendations were conditional ("we suggest" rather than "we recommend") because of a lack of randomised controlled trials for most of these therapies. Despite these recommendations and the absence of evidence, ICS remain the most widely used pharmacotherapy for patients with bronchiectasis. In the US registry, 39% of patients and in European cohorts, 55% of patients were reported to be ICS users [13–15]. This is likely driven by the perceived overlap with other airways diseases, concerns about the adverse effects and potential development of resistance with long-term antibiotics, and about their availability, whereas ICS are largely cheap and widely available [16–20].

So how do we know which is the best maintenance therapy to introduce for the prevention of exacerbations in bronchiectasis?

In the absence of randomised clinical trials, observational data can provide important information about comparative effectiveness and safety as well as generating hypotheses that can be explored and investigated in future trials. In that regard, the contribution by Henkle *et al.* [21] in this issue of the *European Respiratory Journal* takes us a step closer to understanding first-line therapy for bronchiectasis patients.

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They studied 618 303 patients with a bronchiectasis diagnosis in the Medicare database, which provides insurance to adults over the age of 65 years. They sought to compare the relative benefit and safety of ICS and macrolides. Therefore, a subset of patients was identified and followed after the initial prescription of long-term preventative therapy; 83 589 patients received ICS and 6500 received macrolides between 2006 and 2014. Henkle *et al.* [21] assessed the risk of future exacerbations and hospitalisations using these data. Physician decisions are not random, and so there are often important confounders underlying a physician decision to favour ICS or macrolide. The authors accounted for this as far as possible by using a propensity score, which adjusted for the likelihood that a physician would prescribe one or the other, to produce two cohorts matched for observable patient characteristics and risk factors.

The results show a striking advantage of macrolide treatment over ICS in terms of exacerbation reduction and prevention of severe exacerbations. Patients taking ICS were 39% more likely to be hospitalised for respiratory infections and 56% more likely to have acute exacerbations in the adjusted models. Interestingly, there was no difference in mortality (adjusted hazard ratio 1.09), contrary to predictions given the established link between exacerbations and mortality [21].

The limitations of this type of study must be acknowledged. There is always the possibility that unmeasured confounders could account for some of the observed effect and there were differences in the groups at baseline, such as the frequency of respiratory consultations being higher in the macrolide group, that suggest possible bias by indication. The Medicare database is limited to individuals over the age of 65 years and the results of this study cannot be generalised to the whole bronchiectasis population since it is a disease that can affect patients at any age [22].

The authors interpreted their results as showing that ICS increased the risk of poor outcomes in bronchiectasis, but this study directly compared two treatments and found that macrolides were superior. This may have been due to a harmful effect of ICS, a highly beneficial effect of macrolides or a combination of both, but this study design did not allow a firm conclusion. Nevertheless, the results are plausible and consistent with what we know about both macrolide efficacy and ICS safety in bronchiectasis and other respiratory diseases [23–25]. Three randomised trials of 6 to 12 months' duration showed clear reductions in the frequency of exacerbations with macrolides, approximately halving the exacerbation rate within these populations [23–25]. A recent individual patient data meta-analysis confirmed this excellent efficacy for exacerbation reduction and demonstrated that this was consistent among nearly all patient subgroups [26]. Baseline exacerbation frequency, lung function, symptoms or quality of life did not impact upon efficacy [26].

The consistent efficacy being demonstrated for macrolides is in contrast to the data for inhaled antibiotics. The RESPIRE studies published in the *ERJ* in 2018 found benefit in terms of exacerbation frequency reduction of 39% in RESPIRE 1 14-day on/off arm, but did not demonstrate clear benefit in the other three arms of the trials [27–29]. Inhaled liposomal ciprofloxacin met its primary endpoint in ORBIT 4 but not in ORBIT 3 [30]. While the pooled data showing a significant reduction in exacerbation frequency suggests this medication would be a very useful addition to the treatment of chronic *P. aeruginosa* infection in bronchiectasis, the inconsistency between the two trials suggests we have not yet fully identified the phenotype that best responds to inhaled antibiotics.

The data presented in this issue of the *ERJ* further supports the cautious use of ICS in bronchiectasis. ICS appear to increase the risk of non-tuberculous mycobacteria (NTM), promote microbial overgrowth, may adversely effect neutrophilic inflammation and, to date, have not been shown to reduce exacerbation frequency in bronchiectasis [30–33]. In COPD, where the use of ICS in combination with bronchodilators is established, the field is moving towards targeted therapy [34]. ICS are effective against eosinophilic inflammation but do not have benefits for patients with predominantly neutrophilic inflammation, and may increase bacterial load or increase the risk of pneumonia [30–37]. This is potentially of concern in patients with bronchiectasis who have predominantly neutrophilic inflammation [38]. Nevertheless, eosinophilic subtypes of bronchiectasis are starting to be identified and a potential role for anti-eosinophil therapy in selected patients has been proposed [39, 40]. It remains to be tested, but sputum or blood eosinophils may represent a potential treatable trait to guide ICS use in bronchiectasis [41]. Possible responder populations could not be explored in the study by Henkle *et al.* [21] and should be the focus of future research. Bacterial load has emerged as a potential treatable trait for the guidance of inhaled antibiotic treatment [42]. Airway clearance [43, 44] and macrolides in contrast appear to be almost universal in their effectiveness in the frequent exacerbator population and may be considered for the moment as the first-line pharmacological intervention.

While the evidence clearly supports the use of macrolides as the preferred treatment for exacerbation prevention in bronchiectasis, there are significant challenges. The optimal dose and dosing regimens for use in bronchiectasis have not been identified [23–26]. Gastrointestinal and other adverse effects are

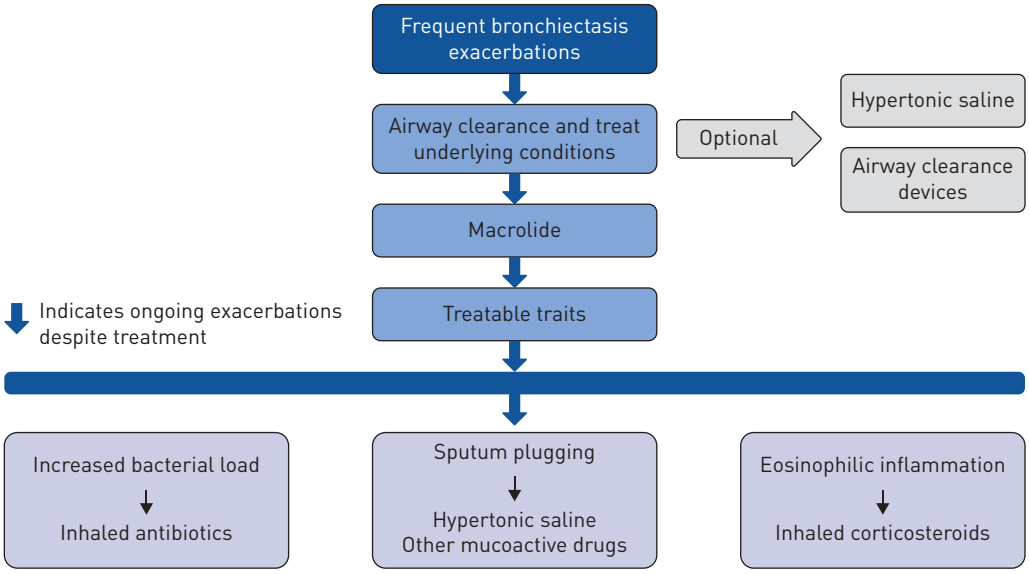

FIGURE 1 A simple schematic for exacerbation prevention in bronchiectasis.

relatively common [23–26]. Hearing loss was noted in a previous COPD trial, but this effect has not been evident in the much smaller bronchiectasis studies [45]. It nevertheless needs to be considered as a potential adverse effect in clinical practice. Antibiotic resistance emerges rapidly in the respiratory flora following macrolide treatment and changes in the microbiome are also observed, but the clinical significance of these changes in not known [23–26, 46–48]. Exclusion of non-tuberculous mycobacterial infection is recommended prior to treatment with macrolides because of the risk of inducing macrolide resistance and this is an issue of particular importance in populations with high NTM prevalence such as the USA. We have remarkably little information about what happens to patients with bronchiectasis treated with macrolides beyond the first 12 months. The data presented by Henkle *et al.* [21] is relatively reassuring when comparing macrolides to other widely used drugs such as inhaled corticosteroids, but prospective studies assessing outcomes beyond 12 months are also needed.

Figure 1 shows an outline of an "integrated exacerbation prevention algorithm" based on the ERS guidelines. It is suggested that all patients should receive airway clearance and appropriate treatment of underlying causes such as immunodeficiency or allergic bronchopulmonary aspergillosis, as well as important co-morbidities. In some patients, additional airway clearance interventions may be appropriate prior to initiating prophylactic treatment with antibiotics. Macrolides may be considered the preferred option for exacerbation prevention subject to the cautions described above. In patients that continue to exacerbate despite macrolide therapy, we endorse the concept of treatable traits, which should also be considered at every step of management.

Great progress has been made in a short period of time in bronchiectasis, with recent data establishing the impact of airway clearance, macrolides and inhaled antibiotics on exacerbation prevention. Important trials of mucoactive therapies, such as the UK CLEAR study, will inform on the efficacy of hypertonic saline or carbocisteine *versus* usual care in the near future [49]. A search of clinical trial registries indicates one ongoing randomised trial of inhaled corticosteroids (n=72) with a primary outcome of cough [50]. This study will be informative, but is unlikely to be powered to detect an effect on exacerbations or examine subgroups based on markers such as blood eosinophils. There is a clear need for a large randomised controlled trial in bronchiectasis powered for exacerbations and sufficient to identify subgroups of responders.

While awaiting such trials, the study by Henkle *et al.* [21] reminds us of the value of real-life data to study drug safety and effectiveness in clinical practice.

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