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REVIEW

Long-term macrolide maintenance therapy in non-CF bronchiectasis: Evidence and questions

Charles S. Haworth [a,*], Diana Bilton [b], J. Stuart Elborn [c]

[a] Cambridge Centre for Lung Infection, Papworth Hospital, Cambridge, CB23 3RE, UK
[b] Department of Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK
[c] Centre for Infection and Immunity, Queen's University of Belfast, 97 Lisburn Road, Belfast, BT9 7BC, Northern Ireland, UK

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Summary
Macrolide antibiotics have anti-inflammatory and immunomodulatory properties in addition to antibacterial activity. Until recently, only a small number of studies evaluating macrolides in patients with non-cystic fibrosis (CF) bronchiectasis had been published. These were open-label, uncontrolled, short-duration studies that included small numbers of patients. However, these studies suggested that macrolides can reduce exacerbation frequency, reduce sputum volume, and improve lung function in patients with non-CF bronchiectasis.

Three recently published randomised, double-blind, placebo-controlled studies showed that macrolides (azithromycin or erythromycin) taken for between 6 and 12 months led to significant reductions in exacerbation rate and reduced the decline in lung function. In all studies, macrolides were generally well tolerated.

The advantages of macrolide maintenance therapy need to be balanced against the risks, which include emergence of bacterial resistance, cardiotoxicity and ototoxicity. In addition, a key need is the consistent definition of endpoints for studies in non-CF bronchiectasis, particularly the definition of exacerbation, to allow systematic data analysis. Existing studies on the use of low-dose macrolides in non-CF bronchiectasis are encouraging, but further studies are needed to define the optimal agent, dose, duration for treatment, and the patients likely to benefit and long-term safety.

* Corresponding author. Tel.: +44 (0)1480 364656; fax: +44 (0)1480 364330.
E-mail address: charles.haworth@papworth.nhs.uk (C.S. Haworth).

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Introduction

Bronchiectasis describes the pathological condition of abnormally dilated airways [1]. Cystic fibrosis (CF) is one of the leading inherited causes of bronchiectasis but there are numerous other causes, including a post-infectious aetiology (e.g. after pneumonia, pertussis, or *Mycobacterium* infection), connective tissue disease, allergic bronchopulmonary aspergillosis, immunodeficiency, autoimmune conditions, congenital ciliary defects or foreign body aspiration [1—3]. In 26—53% of patients, bronchiectasis is idiopathic and has no known cause [1—3].

Bronchiectasis is increasing in prevalence in developing countries and in some indigenous groups in affluent countries [4—6]. With the increased life expectancy of the global population, there is also greater risk of chronic illness, including bronchiectasis, worldwide. Bronchiectasis is commonly reported in developed countries, with prevalence increasing with age [1]. The term 'non-CF bronchiectasis' has been used to describe the group of patients with bronchiectasis caused by conditions other than CF [7].

The pathophysiology of bronchiectasis involves irreversible dilation and damage to the bronchial walls (conducting airways) as a consequence of repeated infection and subsequent inflammation. Mucociliary clearance is impaired, so the airways are vulnerable to repeated colonisation by pathogens [7]. Chronic infection promotes further neutrophilic inflammation, leading to a vicious cycle of infection and inflammation in the permanently damaged airways. Patients present with persistent cough, chronic daily sputum production and recurrent chest infections [1]. Estimates suggest that the airways of almost all patients with bronchiectasis are chronically infected with pathogenic bacteria, even among those who are clinically stable [8]. The most common infecting pathogens are *Haemophilus influenzae* (47—55%) and *Pseudomonas aeruginosa* (12—26%) [1]. Bacterial load correlates with inflammatory response, with greater numbers of neutrophils, and higher concentrations of neutrophil degradation products and inflammatory markers [1,9].

Recent studies using pyrosequencing have demonstrated a much greater diversity than was previously appreciated, including many anaerobic species. The significance of these is yet to be determined [8,10,11].

The aims of management of non-CF bronchiectasis in adults are to identify and treat any underlying causes in order to prevent disease progression; to maintain and improve pulmonary function; to reduce exacerbation frequency and severity; and to improve health-related quality of life (HRQoL) by reducing symptoms and exacerbations [7]. Management strategies include airway clearance techniques, inhaled hyperosmolar agents, mucolytics, inhaled corticosteroids, short- and long-term antibiotics (either oral or nebulised) and surgery: though the evidence base for most of these is poor [1,7]. Patient education is also a key component of non-CF bronchiectasis management and should focus on interventions that improve quality of life (QoL) and reduce exacerbation frequency along with the implementation of action plans to improve the recognition and treatment of acute exacerbations [7].

The treatment of non-CF bronchiectasis has generally consisted of treatments with proven efficacy in CF or other diseases (e.g. chronic obstructive pulmonary disease [COPD]), but this is by no means a sound strategy, as evidenced by the study of recombinant human deoxyribonuclease [12]. This treatment for CF was not only ineffective in patients with idiopathic bronchiectasis, but potentially harmful [12] and should not be used in this patient population [7].

The British Thoracic Society guidelines on the management of non-CF bronchiectasis highlight the current evidence gaps, which limit recommendations for chronic management strategies [7]. Bronchiectasis may not respond