Macrolides and Bronchiectasis
Clinical Benefit With a Resistance Price

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Bronchiectasis is a common condition. Although the true prevalence is unknown, the prevalence in the United States has been estimated to range from 4 per 100,000 in young adults to nearly 300 per 100,000 in persons 75 years and older. Although bronchiectasis is a pathological description, it describes a group of conditions of somewhat diverse etiology that result in impairment of innate immunity and chronic infection, which in turn result in bronchial damage and dilation of the airways. In general, when referring to the condition, cystic fibrosis (CF) is excluded for practical rather than scientific reasons and the condition is frequently identified as non–cystic fibrosis bronchiectasis.

Adults with bronchiectasis often have chronic cough and sputum production and frequently develop pulmonary exacerbations driven by infection. The cause of these events in bronchiectasis is not entirely clear, but they have an adverse effect on lung function, morbidity, and health-related quality of life (QOL). Treatment of patients with bronchiectasis is aimed at optimizing lung function and reducing the frequency of pulmonary exacerbations. However, treatment approaches have been extrapolated from other respiratory diseases such as chronic obstructive pulmonary disease (COPD) and CF, because few randomized controlled trials have been conducted to determine the specific treatment of bronchiectasis.

In this issue of JAMA, the results of the BLESS (Bronchiectasis and Low-dose Erythromycin Study) and BAT (Bronchiectasis and Long-term Azithromycin Treatment) trials, provide robust evidence for a beneficial effect of long-term macrolide maintenance therapy in patients with bronchiectasis. Given the paucity of evidence for treatments in bronchiectasis, the results of these studies and the recently published EMBRACE trial are welcome, because they provide a good evidence base for an effective therapy for bronchiectasis.

In the BLESS trial, 117 patients with a diagnosis of bronchiectasis were randomly assigned to receive erythromycin (400 mg) twice daily or placebo. In the BAT trial, 83 patients with bronchiectasis were randomly assigned to receive azithromycin (250 mg) daily or placebo. Patients recruited to the trials had experienced at least 2 (BLESS) or 3 (BAT) infective exacerbations in the year prior to study entry. Compared with placebo, the number of pulmonary exacerbations was significantly reduced by erythromycin in the BLESS trial (event rate, 1.29 vs 1.97; incidence rate ratio, 0.57 [95% CI, 0.42-0.77]; P = .003) and by azithromycin in the BAT trial (median number of exacerbations, 0 [interquartile range, 0-1] vs 2 [interquartile range, 1-3]; P < .001) at the end of the 12-month treatment period. Furthermore, both macrolides were superior to placebo with respect to improving lung function, and azithromycin also demonstrated a significant improvement in disease symptoms and QOL.

The results of these 2 studies confirm the results of the recently published EMBRACE trial, which reported a similar significant reduction in exacerbation frequency in patients who received azithromycin (500 mg) 3 times weekly for 6 months but no effect on lung function or QOL. A similar decrease in exacerbation frequency has also been reported for patients with COPD who received azithromycin (250 mg) daily. However, patients in the azithromycin group in the EMBRACE trial were more likely to have hearing decrements than those in the placebo group.

A major concern with the use of long-term maintenance antibiotics in treatment of respiratory disease is the emergence of new pulmonary pathogens and increased antimicrobial resistance among the airway microbiota. In both the BLESS and the BAT studies, extensive culture microbiology and antimicrobial sensitivity testing were performed to address these issues. There was no difference in microbiological profile between macrolide- and placebo-treated patients at baseline and after 1 year of treatment, suggesting that macrolide treatment did not result in the emergence of new pathogens. However, erythromycin significantly increased the proportion of macrolide-resistant commensals oropharyngeal streptococci, and azithromycin significantly increased macrolide resistance among respiratory pathogens including Haemophilus influenzae, Staphylococcus aureus, and Moraxella catarrhalis.

These findings are consistent with previous data from studies involving patients with COPD and patients with CF linking long-term macrolide exposure with significantly increased resistance among respiratory pathogens and oral flora. Furthermore, Malhotra-Kumar et al demonstrated that a single 3-day course of azithromycin increases macrolide resistance among the oral streptococcal flora from healthy volunteers, with this effect lasting for more than 180 days. These studies collectively suggest that the commensal airway microbiota could act as a reservoir of resistance for potentially pathogenic bacteria. A fur...
ther concern not addressed in either the BLESS or the BAT trials is that macrolide use may result in increased resistance to other antibiotics. For example, clindamycin resistance in a range of bacterial genera may be secondary to macrolide exposure, with 97% of CF-associated *Streptococcus milleri*-group organisms resistant to both a macrolide and clindamycin.14

A limitation of both the BLESS and the BAT trials is the focus on development of antibiotic resistance among “known pathogens” such as commensal oropharyngeal streptococci (BLESS) and *H influenzae*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae* (BAT). Furthermore, neither study used quantitative culture to determine if the reduced exacerbation rate in patients receiving macrolide treatment could be attributable to a decrease in either the total sputum bacterial load or the density of individual species.

In a recent study using quantitative aerobic and anaerobic culture as well as pyrosequencing to comprehensively define lung microbiota composition in clinically stable patients with bronchiectasis during an exacerbation, diverse microbiota communities were present, with bacteria from a range of genera including *Achromobacter*, *Stenotrophomonas*, *Prevotella*, *Veillonella*, and *Actinomyces* detected in addition to known pathogens.15 In clinically stable patients, there was some evidence that bacterial density in sputum was less in patients receiving long-term azithromycin treatment, suggesting that azithromycin had some effect on microbial load. It is not clear whether the diverse array of bacteria detected in the airways of patients with bronchiectasis all contribute to the underlying pathological process driving progressive lung damage.

However, the benefits of long-term macrolide treatment for individual patients with bronchiectasis need to be balanced with increasing concerns regarding the development of resistance to both macrolides and other antibiotics among airway microbiota. Further long-term longitudinal studies are required to better determine the relationship between maintenance macrolide treatment, the airway microbiome and resistome, and clinical efficacy in patients with bronchiectasis. A further potential problem is that macrolides may impair autophagy, an important process in the host response to infection with non-tuberculous mycobacteria.16 Chronic use of azithromycin may predispose to infection with a macrolide-resistant mycobacterium, which would limit treatment options in this difficult group of bacteria.

The important issues for clinicians are to determine which patients with bronchiectasis should be prescribed a macrolide and which macrolide should be used. In the trials in this issue of *JAMA*, patients were recruited if they had frequent exacerbations, defined as at least 2 (BLESS) or 3 (BAT) exacerbations in the previous year. Therefore, patients with bronchiectasis who have 2 or more exacerbations in the previous year should be considered for treatment. Erythromycin and azithromycin are both effective for reducing exacerbations and have similar effects on antimicrobial resistance. The effect of long-term macrolide use on antibiotic resistance in these patients is not clear but should dissuade clinicians from prescribing macrolides for patients whose clinical characteristics differ from those for whom a positive effect was seen in these studies. Macrolides also may have an adverse effect on liver function and on hearing, as well as prolongation of the QTc interval, with the results of a recent cohort study reporting a small absolute increase in cardiovascular deaths during 5 days of azithromycin therapy.17 Therefore a prudent approach would be to obtain a sputum culture and an electrocardiogram and to determine hearing and liver function prior to initiating treatment and at appropriate intervals thereafter. If sputum culture grows mycobacteria or there are abnormal findings on the other investigations, macrolide therapy should not be initiated or should be discontinued. Antibiotic resistance to common respiratory pathogens should also be monitored carefully, both in individual patients and in the community. Macrolides offer an important and now evidence-based treatment for bronchiectasis and, if used carefully, may help to improve QOL and reduce health care costs for patients with bronchiectasis.

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REFERENCES