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Invited Commentary

AZALEA Trial Highlights Antibiotic Overuse in Acute Asthma Attacks

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Asthma affects more than 300 million people worldwide, causing variable symptoms of cough, chest tightness, and exertional or nocturnal dyspnea due to chronic inflammation of the lower airways and bronchial hyperresponsiveness. Acute episodes of worsening respiratory symptoms, called acute exacerbations or asthma attacks, can be life-threatening, and in-



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duce important costs, encompassing both direct health care expenses and indirect costs due to absence from work or school. For many decades, asthma attacks have been treated with inhaled short-acting bronchodilators and systemic corticosteroids. There is thus a need for novel therapies which—as add-on treatment to systemic corticosteroids—could hasten clinical and functional recovery in patients experiencing an asthma attack and prevent complications.

In this issue of *JAMA Internal Medicine*, Johnston et al¹ report the results of the Azithromycin Against Placebo for Acute Exacerbations of Asthma (AZALEA) trial. In this multicenter, randomized, double-blind, placebo-controlled study in the United Kingdom, they investigated the macrolide azithromycin as a supplement to standard treatment in adult patients presenting to emergency departments (EDs) with an acute asthma exacerbation. Patients were mainly recruited from secondary care hospitals and needed to be enrolled within 48 hours of initial presentation to medical care. Importantly, all patients received a course of oral or systemic corticosteroids. A total of 199 asthma patients (mean age, 40 years; 70% female) were randomized to azithromycin 500 mg daily for 3 days or matching placebo. The primary outcome, that is, diary card asthma symptom score 10 days after randomization, was not different between the azithromycin and placebo groups. Likewise,

there were no significant between-group differences in secondary outcomes such as quality-of-life questionnaires, lung function measurements during the exacerbation, or time to a 50% reduction in asthma symptoms. Therefore, addition of azithromycin to standard medical care for acute asthma exacerbations did not result in a statistically or clinically significant benefit. Adverse events were infrequent in both treatment groups, with more gastrointestinal adverse events in the azithromycin group compared with placebo. No data are provided on secondary ED visits or hospital (re-)admissions.

In contrast, the Telithromycin, *Chlamydomphila*, and Asthma (TELICAST) study has demonstrated clinical benefit of treatment with telithromycin (800 mg daily for 10 days) vs placebo in acute asthma exacerbations.² However, severe adverse reactions including liver toxicity limit the use of telithromycin in clinical practice. Why did the AZALEA trial have negative results, whereas the TELICAST study seemed to have positive results? First, there is a crucial difference in trial design: all patients randomized in the AZALEA trial were required to receive systemic corticosteroid treatment, whereas only 34% of randomized patients received corticosteroids in the TELICAST study. Because the beneficial effects of macrolides might be partially attributed to their anti-inflammatory properties, it is difficult to demonstrate benefit on top of the powerful anti-inflammatory effects of systemic corticosteroids, leading to predictably negative results in the AZALEA study as opposed to the TELICAST study. Second, in the AZALEA study only 5% of the azithromycin-treated patients tested positive for current infection with *Chlamydomphila pneumoniae* or *Mycoplasma pneumoniae*, whereas in the TELICAST study 60% of telithromycin-treated patients had a positive IgM test result for one of these atypical organisms. Because both

studies used similar methods of sampling and serological testing, the different prevalences of *C pneumoniae* infection might have contributed to the different outcomes between the 2 trials. Third, a selection bias occurred in the AZALEA trial because only 199 of 4582 screened patients were randomized, limiting the external validity of the study. Intriguingly, 2044 patients (45% of the enrolled population) were excluded from the trial because they had already received antibiotics. We speculate that patients with an asthma attack who were judged eligible to receive antibiotics by their treating physician would have had a higher likelihood of response to azithromycin treatment than those who were not prescribed antibiotics. Last, the AZALEA study might have had negative results because of the heterogeneity of chronic asthma and acute asthma exacerbations. Long-term therapy with low-dose azithromycin has been shown to be efficacious in preventing exacerbations in several neutrophilic chronic airway diseases, such as cystic fibrosis, bronchiectasis, diffuse panbronchiolitis, chronic obstructive pulmonary disease (COPD), and noneosinophilic severe asthma.³ However, subgroup analysis of the AZALEA study revealed no significant benefit of azithromycin in patients with low blood eosinophil levels.

An important finding of the AZALEA study is the high use of antibiotics in adult patients with acute asthma exacerbations, despite the facts that Cochrane reviews have not found sufficient evidence in favor of antimicrobial treatment of acute asthma and that treatment guidelines recommend against routine use of antibiotic therapy. Inappropriate use of antibiotics for acute asthma has been documented in EDs in several countries including the United States, where 22% of acute asthma visits resulted in an antibiotic prescription, and is likely to contribute to increased bacterial antibiotic resistance.⁴ Restricting the use of antibiotics to those patients with acute exacerbations who will benefit the most is therefore paramount. Because clinical symptoms and signs are nonspecific, accurate biomarkers in blood, sputum, or exhaled breath (eg, volatile organic compounds) that confirm or exclude the presence of bacterial respiratory tract infections – ideally as point-of-care tests – are desirable. Two Chinese studies of serum procalcitonin-guided antibiotic therapy in severe acute asthma exacerbations in EDs suggest that this biomarker strategy might

allow the reduction of unnecessary antibiotic use without apparent harm, but also the more widely available C-reactive protein testing could be used to guide antibiotic therapy by distinguishing pneumonia from asthma exacerbations.⁵

Asthma is a heterogeneous syndrome, encompassing different clinical and inflammatory phenotypes (eg, eosinophilic vs noneosinophilic asthma).⁶ These asthma characteristics in the stable state influence the risk of future exacerbations, as well as their frequency and severity. Importantly, acute asthma exacerbations are also heterogeneous. Although viral infections of the respiratory tract are the most frequent cause of asthma attacks, many different agents may trigger acute exacerbations: bacterial infections, allergens, drugs, outdoor air pollution, smoking, weather changes, and emotional distress. It is tempting to speculate that azithromycin treatment is less likely to benefit patients with eosinophilic acute exacerbations elicited by noninfectious triggers. Recently, as a way toward precision medicine of chronic airway diseases, encompassing asthma and COPD, the concept of “treatable traits” has been launched for chronic management in the stable state.⁷ Applying the treatable traits approach additionally to acute exacerbations of chronic airway diseases might facilitate personalized medicine. Indeed, the current health care use-based definitions of acute exacerbations of asthma (ie, systemic corticosteroids) and COPD (ie, antibiotics and/or systemic corticosteroids) seem too arbitrary to us.

In conclusion, the AZALEA trial demonstrated no benefit of short-term treatment with azithromycin in addition to oral or systemic corticosteroids in adult patients presenting with an acute asthma exacerbation at EDs of secondary care hospitals. Yet the most striking finding of the study is the overuse of antibiotics in patients with asthma attacks. To tackle this problem, at least 4 strategies need to be combined: (1) raising awareness among health care professionals and patients; (2) implementing the recommendations of asthma guidelines not to use antibiotics routinely in asthma exacerbations; (3) performing large trials in primary and secondary care to investigate which patients with asthma attacks might benefit from antibiotic treatment, and (4) validating known biomarkers (C-reactive protein, procalcitonin) and developing novel biomarkers for guiding targeted antibiotic therapy.

ARTICLE INFORMATION

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