Antibiotics for Asthma?

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(See the article by Biscardi et al. on pages 1341–6)

Asthma is a major public health problem, being the most common chronic illness of childhood and affecting nearly 5 million children in the United States [1]. One-third of children with asthma require emergency department care, nearly 50% of the yearly direct costs for asthma care are used to fund hospitalizations, and asthma is responsible for an estimated 11.8 million days of missed school each year [1–4]. It is likely that asthma is a multifactorial disease that is the result of an interplay between a genetic predisposition to allergic diseases and environmental factors. A growing body of evidence suggests that both acute viral infections (e.g., respiratory syncytial virus [RSV], parainfluenza virus, and influenza virus infections) and chronic infections (e.g., mycoplasma, chlamydia, and adenovirus infections) play a role in triggering allergic inflammation in the lower airways [5–10]. Although it has long been recognized that infections are associated with asthma exacerbations, the mechanisms by which infections effect changes in pulmonary function are not fully understood. Epidemiologic studies [11] suggest that acute viral infections in early infancy, such as RSV infection, may play a role in the development of an allergic diathesis. In addition, both clinical and observational studies support the association between viral infections and asthma exacerbations [12, 13]. Could treatment or prevention of specific infections interrupt the progression from mild or subclinical disease to more-severe phenotypic expression of reactive airway disease, including functional limitation?

Animal models and experimental infections in humans have afforded the opportunity to study the effect of infection, particularly viral infection, on lung inflammation and physiology. Although these infections have been shown to cause shifts in specific airway responsiveness, the mechanisms remain speculative [8, 14, 15]. Quite possibly, increases in airway inflammation alter the bronchoconstrictor response to methacholine and histamine, and the resultant inflammation may precipitate smooth muscle constriction, airway wall edema, mucus production, or a combination of these 3 factors, resulting in changes in airway reactivity. And although viruses, such as RSV, can alter the airway reactivity of normal individuals, the effect is much greater in asthmatic persons [16].

A prospective study [17] in this issue of Clinical Infectious Diseases provides further evidence of the association of infection with childhood asthma-related hospitalization. A total of 170 children aged 2–15 years were hospitalized with acute asthma and subdivided into 2 groups: group 1 contained 119 children with a known history of asthma, and group 2 contained 51 children who were hospitalized for their first asthma attack. Nasopharyngeal swab samples obtained from all children were tested for respiratory viruses (RSV, influenza virus, parainfluenza virus 1, 2, and 3, and adenovirus) by immunofluorescence and culture, but not by PCR. Mycoplasma pneumoniae and Chlamydia pneumoniae were tested for using PCR and serologic studies, but only children with positive serologic test results (i.e., detectable IgM or a 4-fold increase in IgG levels) were considered positive for M. pneumoniae or C. pneumoniae.

Nearly one-half of the children in the study [17] had an identified infection at the time of the asthma exacerbation. Viral infections with RSV or influenza virus A or B were more commonly seen in the children in group 1 (18 of whom had such infections) than in those in group 2 (only 2 of whom had such infection). M. pneumoniae, however, was identified as the most common pathogen associated with acute asthma exacerbations in both
groups. Overall, 29% of the children had *M. pneumoniae* detected during hospitalization for acute asthma. Moreover, 50% of the children in group 2 had *M. pneumoniae* identified at the time of their first asthma attack. Previous studies [10, 15, 18] report that recent or chronic infections with atypical pathogens such as *M. pneumoniae* and *C. pneumoniae* are associated with poorer disease control and higher rates of exacerbations. As would be expected, those with their first acute asthma exacerbation tended to be younger, and they accounted for ~30% of the hospitalizations. However, of those who underwent pulmonary function tests, <50% had a positive methacholine challenge test result, and those who had previous wheezing were also categorized as not having prevalent asthma. The children who received a diagnosis of asthma in this study [17] included a very heterogeneous group of patients, many of whom probably did not have asthma as defined by the National Heart Lung and Blood Institute guidelines [19, 20].

As Biscardi et al. [17] acknowledge, there are a number of limitations to their study. The contribution of viruses is likely underrepresented, because PCR studies were not performed. Also, neither rhinovirus (which has been reported to be associated with 25%–60% of acute asthma exacerbations in children) nor coronovirus (said to be associated with 15% of acute disease exacerbations and children) were studied [12]. In addition, questions about the specific laboratory studies remain. Would PCR studies for viral pathogens have increased the number of isolates detected? Were the optimal PCR primers used for the detection of both viral and atypical organisms? What was the sensitivity and specificity of each of these diagnostic tests? Was the “best” mycoplasma serologic testing method used? Did the test parameters vary between subjects of different ages? Would infectious agents have been detected in the same subjects during asymptomatic periods? Finally, it is noteworthy that there was not a good concordance between positive PCR results and positive results of serologic testing for *Mycoplasma* species.

Cumulatively, however, the data support that there are multiple infections associated with acute asthma exacerbations requiring hospital care. Although the relative importance of individual infections and coinfections (e.g., chronic atypical infections with acute viral infection) relating to asthma morbidity in children may be debated, a growing body of scientific evidence suggests that a variety of acute and chronic infections (probably most important in those who have a genetic predisposition to atopic diseases) may be associated with both the first phenotypic expression of disease in childhood and acute disease exacerbations and, additionally, may impact the natural history of childhood asthma. Although the numbers are small in this study, the frequency distribution of age and infection may shed some light on the relationship of particular pathogens to the disease risk in particular age groups. Obviously, given the limitations of this trial [17] and others previously published, additional research is needed.

Therapy for acute asthma has not changed in decades, and it is only in the last several years that new classes of drugs have been available. Although many studies have shown an association between particular infections and acute asthma exacerbations, causality has been more difficult to determine, and therapies aimed at eradication of infection are not available for many of the infections associated with acute asthma exacerbations. Specifically, what role does current or recent infection due to *Mycoplasma* species play in the interaction of allergen exposure leading to increased disease morbidity? Although those in this study with proven infection due to *Mycoplasma* or *Chlamydia* species received antibiotics, the impact of antimicrobial therapy is really unknown, because 62% of subjects nonetheless had relapses of asthma during the 1-year follow-up period. In addition, antibiotic administration was nonrandomized (those who did not receive antibiotics were not determined to have infection), and there were no systematic measures of acute disease severity reported. Although there have been several other studies to test the role of antimicrobial therapy in patients with asthma and infection due to *Mycoplasma* or *Chlamydia* species, these studies have been complicated by nonblinded study designs, the difficulty in eradicating *Mycoplasma* and *Chlamydia* species, and the known anti-inflammatory effects of macrolide antibiotics in patients with asthma [21–24]. Routine use of antibiotic therapy for the treatment of all acute asthma exacerbations would markedly increase the number of prescriptions given to children and would likely contribute to the rising rates of antibiotic resistance driven by large scale use of antibiotics. The definitive answer to the question regarding antibiotics and asthma must await carefully designed, adequately powered, double-blind, placebo-controlled, randomized, clinical trials with defined objective measures of acute disease severity.

In summary, new immunologic and microbiologic techniques are allowing us to further our understanding of the pathogenic role of infections in asthma. The effects of infections on the incidence and natural history of atopic diseases, including asthma, are complex, and they are likely the result of the interplay between specific pathogens, routes of infections, and the age of the genetically predisposed child. Improving our understanding of the role of these variables has important implications in both treating and preventing atopic diseases. The article by Biscardi et al. [17] in this issue of *Clinical Infectious Diseases* supports the consideration of testing for and treating atypical infections in childhood wheezing illness. However, although this study gives us additional information about the role of *Mycoplasma* species in wheezing illness, we are a long way from recommending routine testing for atypical infections and antimicrobial therapy for all acute wheezing episodes.
The real breakthrough will come when we have sensitive and specific bedside rapid diagnostic techniques to identify the pathogen and have interventions that rationally and specifically prevent or treat the asthmatic symptoms triggered by these agents. Until then, the treatment of many of these infections, because most of them are viral in nature, will remain empirical, with the mainstay of treatment being β-agonists and corticosteroids. This study [17] does point out that we should have raised clinical suspicion for and consider empirical treatment of suspected atypical infections in childhood wheezing illness. Whether outcomes will be altered, however, remains unknown.

References