Clinical Commentary Review

The Role of Atypical Infections and Macrolide Therapy in Patients with Asthma

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For many years, the clinical benefit of macrolide use has been recognized in specific groups of patients with pulmonary disease. Dramatic improvement in survival of patients with diffuse panbronchiolitis is the most striking example of successful macrolide use as well as treatment of community acquired pneumonia caused by the atypical bacteria *Mycoplasma, Chlamydophila,* and *Legionella*. There also has been documentation of reduction in the exacerbation rate and of improvement in quality of life in patients with cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, and reduction in post–lung transplantation bronchiolitis frequency. There has long been an interest in treating patients with severe asthma by using macrolides, but research results have not shown consistent clinical benefit in their use in the "general" population of patients with severe asthma. Rather, the successful use of macrolides seems to be in those patients with either documented *Mycoplasma* or *Chlamydophila* infection, or noneosinophilic asthma. Patients with neutrophil predominant phenotype severe asthma tend to show a decline in exacerbation rate, improved peak expiratory flows, and improved quality of life when treated with macrolides. This article will review the use of macrolides in the treatment of asthma. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:511-7)**

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Asthma is a disorder of the airways characterized by airway hyperresponsiveness and airflow obstruction, with clinical manifestations of cough, wheeze, chest tightness, dyspnea, and mucus production, which occur because of airway inflammation and results from complex host (genetic) and environmental (irritants, infection, and allergens) interactions. The incidence of asthma is increasing in most areas of the world, perhaps in part as a result of changes in the environment. In addition to air pollution, infection may play an important role. Previous publications stress the role of viral illnesses in causing most asthma exacerbations but that may simply be because atypical bacteria are difficult to culture. Evidence of bacterial pathogens in the airways of patients with asthma has been reported in an increasing number of studies, as has been their association with acute and chronic asthma and future asthma diagnosis.[1-6] There is evidence that atypical respiratory pathogens such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* may contribute to the pathogenesis of stable asthma and asthma exacerbations.[7] Macrolides have become the antibiotic of choice to treat most patients with asthma and those suspected with subacute bacterial infections (SBI) (low-grade infection without an elevated white blood cell count, elevated temperature, or radiographic infiltrate) caused by these bacteria. However, recent clinical studies and research have focused on the "non-antimicrobial" effects of macrolide therapy. Because macrolides have both antibiotic (bacteriostatic) and anti-inflammatory (interference of the innate and adaptive immune system) properties,[8] the immunomodulatory effects of macrolides may help explain their benefit in specific patient phenotypes with severe asthma. Because macrolides are now the most commonly prescribed antibiotic class, with an average of 2 to 3 prescriptions per person annually estimated by the Center for Disease Dynamics, Economics and Policy,[9] careful use for patients with severe asthma is important to prevent further antibiotic resistance.

ROLE OF BACTERIAL INFECTIONS IN ASTHMA PATHOGENESIS AND CONTROL

At birth, both the innate and adaptive parts of the immune system are immature and continue to develop throughout the first years of life. The hygiene hypothesis is that humans are born with a Th2 (allergic) phenotype and need an early trigger, such as a bacterial infection, to shift the immune status toward a Th1 (nonallergic) phenotype. Thus, children exposed early in life to a variety of bacterial and fungal pathogens have a lower risk of developing asthma and allergies than those who lack such exposure. Ege et al[10] compared children living on farms with those in a reference group with respect to the prevalence of asthma as related to microbial exposure. Samples from mattress dust were screened for bacterial DNA and for bacterial and

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Abbreviations used
ACT- Asthma Control Test
BAL- Bronchoalveolar lavage
BHR- Bronchial hyperresponsiveness
DPB- Diffuse panbronchiolitis
GER- Gastroesophageal reflux
HRV- Human rhinovirus
SBI- Subacute bacterial infection

fungal cultures. The frequency of samples positive for bacteria and fungi was higher for children living on farms. These children, who had higher levels of microbial exposure, demonstrated much greater protection from developing asthma. Caudri et al,[11] in 2009, demonstrated that children with early day care exposure had more wheezing in the first years of life but less wheezing and steroid use (both inhaled and oral steroids) between 4 and 8 years of age. After the age of 8 years, early day care was not protective for asthma symptoms, allergic sensitization, or airway hyperresponsiveness.

The importance of timing of bacterial versus allergen exposure was documented by Chu et al[12] in a murine model. These investigators evaluated the effects of different timing of airway *M pneumoniae* infection and allergen exposure on bronchial hyperresponsiveness (BHR), lung inflammation, and the protein levels of Th1 (IFN-γ) and Th2 (IL-4) cytokines in bronchoalveolar lavage (BAL) fluid. If the *Mycoplasma* infection occurred 3 days before allergen sensitization and challenge, then the infection reduced the BHR and lung inflammation; this was accompanied by a significant induction of Th1 responses (increased IFN- γ) and decreased Th2 IL-4 production. However, when *Mycoplasma* infection occurred 2 days after allergen exposure, the infection initially produced a temporary reduction of BHR, only to be followed by increased BHR, lung inflammatory response, and IL-4 levels, which result in a long-term chronic asthma model. Analysis of these data indicates that the *Mycoplasma* infection could modulate both physiological and immunologic responses in a murine asthma model, which lends further support to the asthma hygiene hypothesis. Moreover, in 2005, Chu et al[13] demonstrated that *M pneumoniae* infection caused increased collagen deposition in the airways of mice in which infection was preceded by allergic sensitization. At 42 days after infection, this remodeling occurred, but it did not occur more acutely at 14 days. However, in mice with allergy and that were not infected, there was no increased airway collagen deposition, which suggests that, over the long term, *M pneumoniae* infection could modulate airway collagen deposition and induce remodeling.

Influenza virus, respiratory syncytial virus, and rhinovirus infection appear to play a role in increased asthma risk.[14] The question remains, once asthma is present, how do viral infections produce an exacerbation? Although there is no evidence that asthmatics have more colds caused by human rhinovirus (HRV) that non-asthmatics, it appears that HRV is the most common cause of viral—induced asthma exacerbations.[15,16] Recently, Kennedy et al showed that asthmatic children who had naturally acquired HRV infections did not have different viral loads compared to adults with or without asthma who were infected with HRV experimentally.[16] Asthma symptoms may persist for weeks, even months in spite of standard asthma controller therapy. Holgate[17] has emphasized that the airway epithelium in the asthmatic is abnormal, and when exposed to HRV it releases more pro-inflammatory mediators compared to normal epithelium. The impaired virus elimination and production of cell death also appears to be related to a defective production of interferon which is responsible for initiating apoptosis and viral clearance in normal epithelial cells.[18]

Similar to viruses, atypical bacteria such *as M pneumoniae* and *C pneumoniae* are capable of causing significant epithelial inflammation.[19] The very nature of infection with these agents, which, in the case of *C pneumoniae* is a chronic intracellular inflammatory process and in the case of *M pneumoniae* is persistent epithelial damage, makes them ideal candidates to produce chronic symptoms and poor asthma control. *Mycoplasma* is transmitted by droplet spread and has an average incubation period of 21 days. The bacterial pathogenicity involves its cytoadherence to the respiratory mucosa. The bacteria interact with respiratory epithelial cells by binding to various host cell receptors, including sulfated glycolipids.[20] Once attached, *M pneumoniae* induces the generation of superoxide radicals and inhibits catalase, which leads to oxidative stress in the host cell. In addition, *Mycoplasma* also induces the production of proinflammatory cytokines, such as IL-8 and TNF by interacting with Toll-like receptors. The infection eventually leads to several pathologic changes, including loss of cilia, metabolic derangements, and cell death.[21]

C pneumoniae is an obligate intracellular pathogen that is transmitted by person-to-person spread of respiratory sections, with an incubation time of 3 to 4 weeks. *C pneumoniae* exists in 2 forms, the replicating reticulate bodies and the infective elementary bodies. After being released into the extracellular environment, the elementary bodies interact with respiratory epithelial cells, which leads to phagosome formation and subsequent intracellular replication.[21] *C pneumoniae* increases the endothelial nuclear factor with subsequent upregulation of inflammatory adhesion molecules, such as IL-8 and platelet-derived growth factor.[22]

ANTIBIOTIC AND ANTI-INFLAMMATORY PROPERTIES OF MACROLIDES

Macrolides are a group of clinically useful antibiotics derived from *Streptomyces* species. Structurally, they contain a 14-, 15-, or 16-membered lactone ring to which 1 or more sugars are attached. Macrolides are bacteriostatic and interfere with protein synthesis. Although the exact mechanism of action may vary, depending on the specific macrolide, the primary action is thought to be the dissociation of peptidyl—transfer RNA from ribosomes during translocation. Macrolides bind to 50S ribosomes of bacteria and inhibit transpeptidation and translocation of nascent peptides.[23] The original group of macrolides consists of the 14-membered lactone ring and includes erythromycin, clarithromycin, roxithromycin, and troleandomycin. These drugs are well absorbed from the gastrointestinal tract, have excellent tissue penetration, and have broad efficacy against many respiratory pathogens. The second group consists of 15-membered ring antibiotics with the addition of a nitrogen element and are known as azalides; this group includes azithromycin. The third group is of those antibiotics with a 16-membered ring and with a monobasic charge; included in this group are spiramycin, josamycin, and midecamycin. Ketolides are a new class of macrolides, contain a 14-membered ring, and have a much broader