Chronic Infection and Severe Asthma

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KEYWORDS

• Severe asthma • Chronic infection • *Mycoplasma pneumoniae*
• *Chlamydophila pneumoniae* • Macrolides • Microbiome

KEY POINTS

- *Mycoplasma pneumoniae* can induce type 2 airway inflammation, which resembles asthma.
- *Chlamydophila pneumoniae* can induce profound systemic and local inflammation.
- Both *M pneumoniae* and *C pneumoniae* have been associated with the development, chronicity, and severity of asthma in humans.
- The use of macrolides in treatment of severe asthma, although controversial, may benefit those with confirmed atypical bacterial infection.
- The effect of the airway microbiome on the development and severity of asthma is an area of active research, with potential for high impact.

INTRODUCTION

The role of lung infection in the development, persistence, severity, and exacerbation of asthma has undergone investigation for decades. This article discusses current understanding of chronic bacterial infection in asthma as it pertains to pathogens, pathobiology, severity, and treatment. Future research will likely explore the impact of the lung microbiome because it may confer protection from asthma or contribute to development of disease.

MYCOPLASMA PNEUMONIAE

Mycoplasma pneumoniae is an extracellular atypical bacterium, transmitted by contact with respiratory droplets. *M pneumoniae* colonizes mucosal surfaces, predominantly of the respiratory tract. In addition to causing infectious disease, *M pneumoniae*

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exposure can induce a variety of autoimmune diseases. Importantly, *M pneumoniae* has been implicated in development of airway inflammation, development of asthma, and severity of asthma.

M pneumoniae contributes to community-acquired lower respiratory tract infection (LRTI) in children through the clinical syndromes of tracheobronchitis, pneumonia, and wheezing illnesses in both asthmatic and nonasthmatic children. Indeed, *M pneumoniae*-induced LRTI in children can cause wheezing in 40%[1] and has been identified as a pathogen in 19% of children older than 5 years with pneumonia.[2] In adults, *M pneumoniae* is a common cause of community-acquired pneumonia.[3] Although a systematic surveillance for *M pneumoniae* infection is not performed in the United States, data exist from outbreaks and were collected by the Centers for Disease Control and Prevention between 2006 and 2013,[4] through which macrolide resistance was identified in 10% of infections.

Mycoplasma pneumoniae Pathogenicity

M pneumoniae depends on a host for survival and replication. *M pneumoniae* has no cell wall and limited metabolic capacity; therefore, it depends on utilization of host cells for replication. *M pneumoniae* can have structural and functional effects through cytotoxic effects on ciliated cells. On exposure of a host cell, mainly of the respiratory epithelium, *M pneumoniae* projects a specialized attachment organelle, comprised of a filamentous core and adhesin-rich tip, which facilitates the cytadhesin necessary for the pathogen's survival.[5,6] This process is necessary for the development of lung inflammation associated with the infectious phenotype. *M pneumoniae* then synthesizes hydrogen peroxide and superoxide radicals, which induce cellular oxidative stress in the respiratory epithelium. However, the glycerol metabolic pathways, which may be responsible for cytotoxic effects and pathogenicity of oxidative stress,[7,8] have been identified and provide possible targets for development of novel therapies.[9] Interestingly, inhaled fluticasone may improve *M pneumoniae*-associated asthma through blocking adherence of *M pneumoniae* in the lung tissue, leading to prevention of subsequent inflammation-related physiologic effects.[10]

M pneumoniae can induce significant inflammation in the host. *M pneumoniae* produces a unique bacterial adenosine diphosphate (ADP)-ribosylating and vacuolating toxin, termed the community-acquired respiratory distress syndrome (CARDS) toxin, which can activate the NLRP3 inflammasome, leading to subsequent formation of interleukin (IL)-1β and resultant inflammation.[11] CARDS can also bind surfactant protein A (SP-A)[12] and interacts with a host protein annexin A2[13] which is involved in multiple cellular functions, including phagocytosis and tight junction maintenance.[14,15] *M pneumoniae* lipoproteins can initiate inflammation through toll-like receptor (TLR)-2,[16] thereby inducing IL-8 expression in airway epithelial cells.[17] Further, *M pneumoniae* causes cytadherence-induced inflammation through TLR4 and autophagy pathways.[18]

Clearance of *M pneumoniae* from the lung is primarily though macrophage activation, requiring MyD88-NF-kB signaling.[19] Polymorphisms of SP-A2 may affect binding of this protein to *M pneumoniae* and contribute to impaired clearance with disease susceptibility, as shown in a novel humanized transgenic mouse model.[20] Mast cells may play a role in protection from severe mycoplasma infection.[21]

Experimental and Mechanistic Models of Mycoplasma pneumoniae and Asthma

The association between *M pneumoniae* infection and asthma has been evaluated through in vitro and murine models. These experiments reveal a variety of mechanisms through which *M pneumoniae* and abnormal host responses to the infectious insult combine and additively contribute to the development or severity of asthma. For