

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 cytoadhesion 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)-1 β and resultant inflammation.¹¹ CARDS can also bind surfactant protein A (SP-A)¹² and interacts with a host protein annexin A2¹³ 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 cytoadherence-induced inflammation through TLR4 and autophagy pathways.¹⁸

Clearance of *M pneumoniae* from the lung is primarily through macrophage activation, requiring MyD88-NF- κ B 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

example, in murine models, airway hyperresponsiveness (AHR) can be induced by *M pneumoniae* infection by inducing increased mast cell burden.²² The *M pneumoniae* CARDS toxin can induce and exacerbate experimental asthma.^{23,24} Particularly in the setting of allergic airway sensitization, *M pneumoniae* infection can cause AHR,²⁵ airway inflammation,²⁶ wheeze,²⁷ airway mucin expression,^{28,29} and remodeling through collagen deposition.³⁰

The existing literature also provides strong evidence that, indeed, *M pneumoniae* infection induces type-2 inflammation in humans, particularly in the setting of allergic disease or asthma. For example, in subjects with *M pneumoniae* pneumonia, bronchoalveolar lavage (BAL) sampling has revealed induction of type-2 inflammatory cytokines,³¹ eosinophilia,³² and abnormal cellular responses.³³ In those with atopic disease or asthma, *M pneumoniae* infection markedly induced eosinophils³⁴ and eosinophil-associated cytokines.^{35–37} Asthmatics seem disproportionately affected by severe disease,³⁸ perhaps related to defective SHP-1 in airway epithelial cells of asthmatics, resulting in enhanced inflammatory response to *M pneumoniae* infection.³⁹ The importance of TLRs as a receptor for *M pneumoniae* infection and severity is illustrated by increased expression of TLR2 and TLR4 on peripheral blood dendritic cells from children with asthma compared with those without asthma or *M pneumoniae* infection.⁴⁰ Notably, and perhaps related, airway tissue analyses reveal increased expression of TLR2, 3, and 4 and TSLP in fatal asthma.⁴¹

***Mycoplasma pneumoniae* and Asthma in Humans**

With data supporting the contribution of *M pneumoniae* to airway inflammation and type-2 inflammation, the relationship between asthma and *M pneumoniae* infection cannot be discounted. Indeed, the contribution of airway *M pneumoniae* infection to development, chronicity, and severity of asthma has been long studied and previously reviewed.^{42–45} However, despite the breadth of published literature, guidelines for the evaluation and treatment of *M pneumoniae* in asthma have not been established, due in large part to heterogeneity among studies and challenges due to diagnostic techniques. This article presents relevant studies in human subjects, which attempt to elucidate the relationship between asthma development, severity, and *M pneumoniae* infection.

Onset of wheeze or asthma

Although direct causation has not been established, atypical infection is correlated with asthma development⁴⁶ or the onset of wheezing. Indeed, in pediatric cohorts, *M pneumoniae* infection is diagnosed in higher frequencies among those with acute wheezing associated with febrile upper respiratory tract infection⁴⁷ and can be related to structural changes seen on cross-sectional imaging of the lung.⁴⁸ Those with *M pneumoniae* lower respiratory infections without preexisting asthma may have persistently impaired lung function years later.¹ In light of the high frequency of *M pneumoniae* exposure and variability of infection, a nonselected longitudinal cohort study may be a more powerful tool to study the contribution of *M pneumoniae* to development of asthma and wheeze.

Chronic asthma, exacerbations, and severity

Acute or prior *M pneumoniae* infection is frequently detected in children and adults with diagnosed asthma, seemingly more frequently than in those without asthma. Further, *M pneumoniae* may be implicated in refractory disease or asthma exacerbations, thereby conferring significant disease morbidity and severity. Studies assessing the presence of *M pneumoniae* infection in the pediatric and adult populations are listed in [Table 1](#).

Table 1
Studies evaluating *Mycoplasma pneumoniae* role in chronic asthma, exacerbations, and/or severity

Reference	Population	Type of Study, Number (N) of Subjects	Testing Method	Outcome
Pediatric Studies				
Smith-Norowitz et al, ¹²¹ 2013	Stable asthmatics	Cohort, N = 36	Serologic	Higher concentrations of anti- <i>M pneumoniae</i> IgM in asthmatics compared with nonasthmatic controls
Bebear et al, ¹²² 2014	Chronic asthma, exacerbations	Cohort, N = 168, N = 88	Serologic and blood PCR	<i>M pneumoniae</i> detected in 13.6% with chronic asthma, 7% of asthma exacerbations
Fonseca-Aten et al, ¹²³ 2006	Exacerbations of wheeze or asthma seen in the emergency room	Cohort, N = 43	Nasopharyngeal PCR	<i>M pneumoniae</i> infection in 48% by PCR-based methods, and coinfection with <i>C pneumoniae</i> in 9 by PCR and/or serology
Wood et al, ¹²⁴ 2013	Acute or refractory asthma	Cohort, N = 143	Serologic	<i>M pneumoniae</i> detected in 64% of subjects with acute asthma, 65% with refractory asthma, and 56% of healthy controls
Biscardi et al, ⁸¹ 2004	Hospitalization for acute severe asthma or wheeze	Cohort, N = 352	Serologic	<i>M pneumoniae</i> detected in 20% of those with preexisting asthma, 50% of those for whom the hospitalization represented the initial asthma presentation, 5% in stable asthmatic controls

Adult Studies				
Bebear et al, ¹²² 2014	Chronic asthma, exacerbations	Cohort, N = 68	Serologic and blood PCR	<i>M pneumoniae</i> detected in 6.3% with chronic asthma, 10% of asthma exacerbations
Kraft et al, ¹²⁵ 1998	Chronic stable asthma	Cohort, N = 29	Blood and respiratory tract culture, PCR	Half of the asthmatic group had <i>M pneumoniae</i> detected from the lower airway by PCR, compared with 1 in the nonasthmatic group
Martin et al, ¹²⁶ 2001	Chronic stable asthma	Cohort, N = 55	Blood and respiratory tract culture, PCR	<i>M pneumoniae</i> identified in 45% of asthmatics
Lieberman et al, ¹²⁷ 2003	Hospitalization for acute asthma	Cohort, N = 100	Serology	18% had evidence of acute <i>M pneumoniae</i> infection; clinical parameters suggested that these subjects had more severe exacerbations
Peters et al, ¹²⁸ 2011	Refractory asthmatics	Cohort, N = 64	Respiratory and blood serology, antigens	52% had evidence of <i>M pneumoniae</i> : <i>M pneumoniae</i> antigens, antibodies against CARDS toxin and P1 adhesin

Abbreviations: Ig, immunoglobulin; PCR, polymerase chain reaction.

CHLAMYDOPHILA PNEUMONIAE

Chlamydomphila pneumoniae, formerly known as *Chlamydia pneumoniae*, is a common human respiratory pathogen. This ubiquitous, obligate intracellular microorganism is transmitted via the respiratory route and widely distributed, with seropositivity noted in well more than half of adults. Most *C pneumoniae* infections are asymptomatic or mildly symptomatic; however, a significant proportion of individuals suffer more severe illnesses such as upper respiratory tract infection, community-acquired pneumonia, and bronchitis. The clinical course of *C pneumoniae* infections can be expected to follow a biphasic timeline, with chronic cough for several weeks after resolution of the initial infectious syndrome. *C pneumoniae* infection has also been linked to coronary atherosclerosis, bronchiectasis, chronic obstructive pulmonary disease, Alzheimer disease, and multiple sclerosis. Despite the evidence of widespread infection from *C pneumoniae* in the general population, genetic susceptibility and/or differences in immune responsiveness may be responsible for the spectrum of disease severity and sequelae.⁴⁹

Chlamydomphila pneumoniae Pathogenicity

Chlamydial organisms have a unique biphasic developmental cycle wherein the transmissible agent, the dense and metabolically inactive elementary body, transforms on host-cellular endocytosis to become the metabolically active reticulate body. After the acute infection, *C pneumoniae* can achieve a latent, metabolically inert state in which it does not multiply but remains viable. However, during this state of chronic infection or colonization, the *C pneumoniae* can continue to produce its heat shock protein 60 (HSP60), a highly immunogenic protein that can induce a pronounced inflammatory response through TLR2, TLR4,^{50–52} and cytosolic pathogen recognition receptors,⁵³ effectively inducing the transcription factor NF- κ B⁵⁴ and subsequent downstream proinflammatory events. HSP60 has also been shown to directly stimulate peripheral blood lymphocyte proliferation and interferon (IFN)- γ secretion, and induce T helper (Th)1 polarization through dendritic cell-expressed signals.^{55,56} Furthermore, *C pneumoniae* can induce inflammatory activity through host NLRP3 signaling, leading to IL-1 β upregulation.^{57–60} Finally, *C pneumoniae* can inhibit proliferation of activated human T cells through apoptotic and pyroptotic pathways.⁶¹ Chronic *C pneumoniae* infection in a murine model⁶² induced bronchus-associated lymphoid tissue, classically and alternatively activated macrophages, and pulmonary fibrosis.

Experimental and Mechanistic Models of Chlamydomphila pneumoniae and Asthma

Similar to *M pneumoniae*, there is a relationship between *C pneumoniae* infection and the induction of an asthmatic phenotype and type-2 inflammation. In particular, early-life *C pneumoniae* respiratory infections in mice have been shown to irreversibly modify immunity, confer risk for asthma, and impair lung physiology.^{63–66} *C pneumoniae* infection in mice can induce immunoglobulin (Ig)E production,⁶⁷ lung eosinophilia, IL-5 production, mucus cell hyperplasia, and AHR.⁶⁸ Interestingly, neutrophilic inflammation^{68,69} is often induced in these models and identified in human BAL,⁷⁰ similar to that seen in neutrophilic asthma. *C pneumoniae* can further contribute to airway inflammation through the production of MUC5AC mucin⁷¹ and to airway remodeling through the matrix metalloproteinases^{72,73} and vascular endothelial growth factor.^{73,74} However, the degree of infection of *C pneumoniae*^{75,76} or mast cell burden⁷⁷ may be related to risk of antigen sensitization and airway inflammation.

***Chlamydophila pneumoniae* and Asthma in Humans**

Onset of wheeze or asthma

C pneumoniae has been repeatedly identified in and associated with initial asthma presentation. Diagnosis of acute *C pneumoniae* infection in pediatric cohorts, followed longitudinally, is associated with wheezing⁷⁸ and incident diagnosis of asthma.^{78,79} Data support a role of repeated or chronic *C pneumoniae* infection in children with recurrent respiratory symptoms.⁸⁰ Diagnosis of asthma is also associated with *C pneumoniae* in both children⁸¹ and adults.^{82,83}

Chronic asthma, exacerbations, and severity

Literature suggests *C pneumoniae* infection is detected more frequently among asthmatics than nonasthmatics, further supporting theories implicating *C pneumoniae* in asthma pathogenesis. Further, *C pneumoniae* infection has been implicated in severity of asthma through contribution to exacerbations. *C pneumoniae* is also implicated in poor asthma control, worse quality of life, and lung function decline, which all contribute to severity of asthma. Studies measuring these effects are shown in [Table 2](#).

MACROLIDES FOR ASTHMA

The effect of macrolide therapy on asthma may be due to a direct antibacterial effect, particularly against the atypical bacteria *M pneumoniae* and *C pneumoniae*; however, the impact of these drugs on corticosteroid pharmacokinetics or as direct immunomodulatory therapy is potentially significant. This article discusses the evidence supporting use of macrolides to treat asthma irrespective of infection status, the use of macrolides in asthmatics with evidence of atypical infection, and the impact of macrolide therapy as steroid-sparing therapy.

Use of Macrolides in Asthma, Irrespective of Atypical Infection

In clinical trials of macrolide therapy for asthma irrespective of atypical infection status, benefit is not clear. Although trials have showed some improvement in AHR^{84,85} or quality of life^{86,87} in adult persistent asthmatics, these benefits were inconsistent. Macrolide therapy has been shown to affect airway inflammation in asthmatics, in both noneosinophilic⁸⁸ and aspirin-exacerbated respiratory disease phenotypes.⁸⁹

Bacterial infection can induce asthma exacerbation, suggesting antibacterial therapy may reduce exacerbation rates. The Azithromycin for prevention of exacerbations in severe asthma (AZISAST) trial⁹⁰ was a randomized, double-blinded, placebo-controlled study of low-dose, long-term azithromycin as add-on therapy to inhaled corticosteroids and long-acting beta-2 agonists in adult subjects with exacerbation-prone severe asthma. Although the primary outcome, rate of exacerbations, and/or LRTI requiring antibiotics, was not different between the treatment groups, a predefined subgroup analysis according to blood cellular phenotype identified relative benefit of azithromycin in the noneosinophilic severe asthma phenotype. *M pneumoniae* or *C pneumoniae* status was not assessed in these participants.

Macrolides as Steroid-Sparing Agents for Asthma

Interest in the use of macrolides as steroid-sparing therapy in severe asthma has been ongoing for decades. The macrolide troleandomycin was shown in several studies^{91–93} to improve clinical and laboratory markers of asthma, as well as aid in steroid dose reduction; other studies found little benefit.^{94,95} Clarithromycin was used in a small cohort to reduce steroid requirements and improve quality of life.⁹⁶

Table 2
Studies evaluating *Chlamydophila pneumoniae* role in chronic asthma, exacerbations, and/or severity

Reference	Population	Type of Study, Number (N) of Subjects	Testing Method	Outcome
Pediatric Studies				
Fonseca-Aten et al, ¹²³ 2006	Exacerbations of wheeze or asthma seen in the emergency room	Cohort, N = 43	Nasopharyngeal PCR	<i>C pneumoniae</i> identified in 12 (28%) of acute exacerbations
Awasthi et al, ¹²⁹ 2012	Hospitalization for asthma exacerbation, or uncontrolled asthma in clinic	Cohort, N = 89	Serologic	25% of asthmatic children presenting with exacerbations in the hospital had evidence of <i>C pneumoniae</i> , compared with 7% of those with uncontrolled asthma presenting to clinic
Adult Studies				
Lieberman et al, ¹²⁷ 2003	Hospitalization for acute asthma	Cohort, N = 100	Serologic	8 subjects had evidence of acute <i>C pneumoniae</i> infection
Kraft et al, ¹²⁵ 1998	Chronic stable asthma	Cohort, N = 29	Blood and respiratory tract culture, PCR	Half of the asthmatics were seropositive for <i>C pneumoniae</i>
Martin et al, ¹²⁶ 2001	Chronic stable asthma	Cohort, N = 55	Blood and respiratory tract culture, PCR	<i>C pneumoniae</i> identified in 13% of asthmatics using PCR, compared with no <i>C pneumoniae</i> in the upper airways of controls
Bebear et al, ¹²² 2014	Chronic asthma, exacerbations	Cohort, N = 68	Serologic and blood PCR	<i>C pneumoniae</i> was present in 10% of children and 6% of adults with chronic asthma
Biscione et al, ¹³⁰ 2004	Spouse pairs of 1 atopic asthmatic, 1 nonatopic nonasthmatic	Cohort, N = 148	Nasopharyngeal	<i>C pneumoniae</i> was detected in 6.4% of asthmatics, 2.3% of the nonasthmatic spouses

Miyashita et al, ¹³¹ 1998	Acute exacerbation	Cohort, N = 276	Serologic	Evidence of <i>C pneumoniae</i> by IgG and/or IgA in 9% of asthmatics compared with 3% of controls
Allegra et al, ¹³² 1994	Outpatient asthma exacerbations	Cohort, N = 74	Serologic	9% were found to be infected by <i>C pneumoniae</i>
Black et al, ¹³³ 2000	Asthmatics	Cohort, N = 619	Serologic	Higher antibody titers were associated with more severe asthma
Huittinen et al, ¹³⁴ 2001	Asthmatics	Cohort, N = 619	Serologic	Antibodies against <i>C pneumoniae</i> HSP60 were associated with asthma, levels of IgA antibodies were inversely associated with lung function
Hahn et al, ¹³⁵ 2001	Asthmatics	Cohort, N = 138	Serologic	27% of asthmatic subjects were <i>C pneumoniae</i> HSP60 seropositive vs 8% of controls, <i>C pneumoniae</i> HSP60 seropositivity correlated with lower FEV1
Pasternack et al, ¹³⁶ 2005	New diagnosis of asthma	Longitudinal cohort, N = 245	Serologic	Neither baseline <i>C pneumoniae</i> status nor seroconversion was related to incident asthma; however, nonatopic asthmatics with positive <i>C pneumoniae</i> serology had a faster rate of lung function decline than noninfected subjects with or without asthma

Abbreviation: FEV1, forced expiratory volume in 1 second.

However, in none of these studies was *M pneumoniae* or *C pneumoniae* status reported. The mechanism by which troleandomycin may improve corticosteroid effectiveness was elucidated by Szefer and colleagues,⁹⁷ wherein pharmacokinetic studies demonstrate reduced elimination of methylprednisolone in the presence of troleandomycin. Finally, Strunk and colleagues,⁹⁸ with the Childhood Asthma Research and Education Network, sought to determine whether azithromycin or montelukast could be used as inhaled steroid-sparing therapy in children ages 6 to 18 years old with moderate to severe asthma. This study was discontinued early after futility analysis demonstrated no difference among the treatment groups.

Use of Macrolides in Asthma, with Respect to Atypical Infection

For those asthmatics with evidence of *C pneumoniae* or *M pneumoniae* infection, however, treatment with an appropriate macrolide may lead to symptom improvement or reduction of inflammation. Similarly, for those with asthma exacerbations and evidence of *C pneumoniae* or *M pneumoniae* infection, macrolide therapy may be beneficial. Studies assessing the impact of antibiotic therapy on *C pneumoniae* or *M pneumoniae* infection in asthma are described in [Table 3](#).

A Cochrane Database systematic review was performed to determine whether macrolides are effective in the management of patients with chronic asthma.⁹⁹ Twenty-three studies met inclusion criteria of randomized, placebo-controlled clinical trials involving both children and adult subjects with chronic asthma treated with macrolides for more than 4 weeks. The investigators concluded that, although existing evidence does not show macrolides to be better than placebo for most clinical outcomes, they may affect some measures of lung function, and the possible benefit of macrolides in subjects with noneosinophilic asthma based on subgroup analyses in 2 of the included studies may require further investigation. Further recommendations were not given because the evidence was determined to be of very low quality due to heterogeneity among subjects and interventions, imprecision, and reporting biases. Clearly, additional clinical trials are needed in this area to address impact of atypical infection evaluation and treatment among the severe asthmatic, frequent exacerbator, or non-eosinophilic asthmatic phenotype.

MICROBIOME OF THE ASTHMATIC LUNG

The respiratory mucosa, once thought to be sterile, is known to host a large variety of commensal bacteria, which are proposed to contribute to the maintenance of immune homeostasis and protection from disease.^{100–103} It is estimated that more than 10,000 different microbial species live in and on humans, representing 100 trillion organisms existing in a symbiotic relationship, most of which are bacterial. The airway microbiome likely develops in early life, may be altered by diet or antibiotic exposure, and is related to the gut microbiome. Similarly, the gut microbiome develops in early life, with a rapid increase in diversity that seems necessary for health¹⁰⁴ and is susceptible to alterations through diet and antibiotic therapy.

The hygiene hypothesis proposes that reduction in the diversity and quantity of microbial exposure confers risk for the development of atopic disease and inflammation.^{105–107} Indeed, in individuals with asthma, abnormal microbiological characteristics have been identified in the gut,^{108–110} upper airway,¹¹¹ and lower airway.

The degree and nature of the contribution of lung microbiome to severity of asthma is not yet clear. Marri and colleagues¹¹² reported alterations in the microbial composition of induced sputum of asthmatics that were similar among asthmatics suffering from mild or severe disease but distinguished asthmatics from normal controls. Huang

Table 3
Clinical trials of macrolide therapy for asthma, with respect to *Mycoplasma pneumoniae* or *Chlamydomphila pneumoniae* infection status

Reference	Population	<i>M pneumoniae</i> or <i>C pneumoniae</i> Assessment	N	Intervention	Outcomes
Kraft et al, ¹³⁷ 2002	Stable adult asthma	<i>M pneumoniae</i> or <i>C pneumoniae</i> on PCR	N = 55	Clarithromycin or placebo for 6 wk	Improvement in FEV ₁ in those with infection, with reduction in BAL cytokine expression, particularly TNF- α , IL-5, and IL-12
Black et al, ¹³⁸ 2001	Adult asthma	Elevated <i>C pneumoniae</i> antibody titers	N = 232	Roxithromycin or placebo for 6 wk	Those receiving treatment had greater improvement in morning and evening peak expiratory flow rates
Hahn et al, ¹³⁹ 1995	Adult asthma, moderate to severe	<i>C pneumoniae</i> antibodies	N = 46	Doxycycline, azithromycin, or erythromycin for 4 wk	Half of subjects had clinical improvement, measured by pulmonary function or symptom scores
Sutherland et al, ¹⁴⁰ 2010	Adult asthma, mild to moderate uncontrolled	<i>M pneumoniae</i> or <i>C pneumoniae</i> on PCR	N = 92	Clarithromycin or placebo for 16 wk	PCR-negative subjects had no benefit by asthma control questionnaire, PCR-positive group was underpowered
Emre et al, ¹⁴¹ 1994	Children with acute wheezing	<i>C pneumoniae</i> antibodies	N = 159	Erythromycin or clarithromycin for standard course	For wheezing with <i>C pneumoniae</i> antibodies, treatment led to eradication of infection and improvement in clinical outcomes
Fonseca-Aten et al, ¹²³ 2006	Children with acute wheezing	<i>M pneumoniae</i> or <i>C pneumoniae</i> on PCR	N = 43	Clarithromycin or placebo for standard course	No differences were noted between the treatment groups, even among those with infection; however, nasal aspirate concentrations of TNF- α , IL-1 β , and IL-10 decreased after treatment
Johnston et al, ¹⁴² 2006	Adults with acute asthma exacerbation	<i>M pneumoniae</i> or <i>C pneumoniae</i> on PCR, culture or antibodies	N = 278	Telithromycin or placebo for 10 d	The treatment group had improvement in symptoms and lung function, not restricted to the 61% of participants positive for <i>C pneumoniae</i> or <i>M pneumoniae</i>

Abbreviation: TNF, tumor necrosis factor.

and colleagues¹¹³ identified differences in the bronchial airway microbiota to be associated with suboptimally controlled asthma and bronchial hyperresponsiveness.

However, literature supports a significant association between asthma severity and changes in microbiota profiles. Huang and colleagues¹¹⁴ studied severe asthma, identifying specific microbiota of the bronchial brushings to be associated with inflammatory processes such as the relationship of Proteobacteria and Th17 gene expression. Green and colleagues¹¹⁵ identified dominant bacterial profiles, particularly *Moraxella*, *hemophilus*, or streptococcal species, in the airway associated with severe airway obstruction and airway neutrophilia. Goleva and colleagues¹¹⁶ identified an impact of gram-negative bacteria on corticosteroid resistance in asthma.

As anticipated, antibiotic therapy affects the airway microbiome in asthma. Slater and colleagues¹¹⁷ treated 5 adult subjects with moderate to severe persistent asthma with 6 weeks of daily azithromycin therapy. Microbiome samples were obtained from the lung via BAL before and after therapy. In this pilot study, the investigators reported decreased bacterial richness after treatment, with reduction in *Pseudomonas*, *Haemophilus*, and *Staphylococcus* spp.

Therefore, aberrations of the microbiome in asthmatics not only contribute to the development and perpetuation of abnormal inflammation in asthma^{118,119} but, theoretically, could confer susceptibility to infections such as *M pneumoniae* and *C pneumoniae*. Further, knowledge of the abnormal microbiome patterns and manipulation thereof will likely lead to novel therapies.¹²⁰

SUMMARY

Understanding of the impact of atypical bacterial infection on the development of asthma and contribution to severity is based on mostly associative evidence, supported by translational and mechanistic experiments. Future clinical trials examining the impact of atypical infection, or treatment of that infection, on asthma severity will require careful phenotyping of participants. Longitudinal cohort studies seeking to understand the contribution of these atypical bacteria to the development or severity of asthma will be challenged to study these infections in the setting of the host's microbiota.

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