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Effects of Atypical Infections with Mycoplasma and Chlamydia on Asthma

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Asthma is a common condition characterized by inflammation, intermittent airflow obstruction, and bronchial reactivity. There are many factors that contribute to the pathogenesis of asthma and play a role in exacerbations and disease severity. Examples include underlying host susceptibility, atopy, environmental exposures, and respiratory infections. Viruses such as rhinovirus, coronavirus, respiratory syncytial virus, and human metapneumovirus are frequently detected in patients with asthma flares and are believed to be the most common trigger for exacerbations.[1,2] However, there is emerging evidence to suggest that atypical bacterial infections are positively correlated with asthma exacerbations, chronic asthma, and severity of disease. This article discusses *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, and reviews studies evaluating their possible role in asthma. Significant limitations due to difficulties with sampling and detection exist in evaluating atypical bacterial infections in the lung.

MYCOPLASMA PNEUMONIAE AND RESPIRATORY DISEASE

Mycoplasma pneumoniae is an atypical bacterium that is transmitted by contact with respiratory droplets. The average incubation period is 21 days. *M pneumoniae* is a frequent cause of respiratory disease in humans. The pathogenic mechanism of the bacterium involves its association or cytoadherence with the respiratory mucosa. The bacteria interact with the host cells through an attachment structure that is

composed of multiple subunits that bind to various host cell receptors including sulfated glycolipids.[3] Once attached, *M pneumoniae* induces the generation of super-oxide radicals and inhibits catalase, leading to oxidative stress in the host cell. *M pneumoniae* infection also induces the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-8, in part through engage-ment of Toll-like receptors (TLRs).[3] Infection ultimately leads to various pathologic changes to the respiratory epithelium including loss of cilia, metabolic derangements, and sloughing.

The immune response to *M pneumoniae* is multifactorial and includes innate signaling through TLRs, opsonization, phagocytosis, and adaptive immune responses such as antibody production and activation of TH_{17} cells.[3] Clinically, some individuals clear the bacteria whereas others only partially eradicate it, leading to a chronic low-level infection. Evidence suggests that established allergic airway inflammation may hinder clearance of the pathogen. Using a mouse model, Wu and colleagues[4] found that TLR2 expression was down-regulated in the presence of allergic inflammation and *M pneumoniae* infection. Recently, Wu and colleagues[5] also reported that low-dose *M pneumoniae* infection enhanced underlying allergic lung inflammation and augmented the T-helper 2 (Th2) response to allergen. By contrast, high-dose *M pneu-moniae* infection attenuated the allergic response. Furthermore, Hoek and colleagues[6] demonstrated that rodent mast cells release IL-4 when cocultured with *M pneumo-niae*, suggesting that *M pneumoniae* infection may promote allergic inflammation. Lastly, Chu and colleagues[7] found that *M pneumoniae* infection of allergen-sensitized mice resulted in an increase in airway collagen deposition. These animal studies suggest that *M pneumoniae* infection in the lung may play a role in asthma develop-ment, pathology, and disease activity.

CHLAMYDOPHILA PNEUMONIAE AND RESPIRATORY DISEASE

Chlamydophila pneumoniae is an obligate intracellular pathogen that is transmitted by person-to-person contact through respiratory secretions. The incubation period is 3 to 4 weeks. Many individuals remain asymptomatic during *C pneumoniae* infection whereas others develop sinopulmonary disease. *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 respi-ratory epithelial cells, leading to phagosome formation and subsequent intracellular replication. In the lungs, *C pneumoniae* infection has been shown to increase endothe-lial nuclear factor (NF)-κB with subsequent up-regulation of inflammatory adhesion molecules, chemokines such as IL-8, and platelet-derived growth factor.[8] Epithelial cell adhesion molecules are also increased, leading to an influx of inflammatory cells. In addition, *C pneumoniae* may participate in airway remodeling through promotion of fibroblast proliferation driven in part by IL-6 and other growth factors.[8] Similarly to *M pneumoniae* infection, the immune response to *C pneumoniae* is multifactorial and includes innate, humoral, and cell-mediated immune mechanisms.

Pulmonary infection with *C pneumoniae* may also contribute to asthma develop-ment and disease pathology. Chen and colleagues[9] infected BALB/c mice with *C pneumoniae* intranasally, and found that repeated infection increased IL-4 gene expression and airway subepithelial basement membrane thickening, both features of atopic asthma. Using a murine model, Blasi and colleagues[10] demonstrated that intranasal infection with *C pneumoniae* resulted in sustained airway hyperresponsive-ness as measured by methacholine challenge with barometric plethysmography. Recently, Bulut and colleagues[11] established that *C pneumoniae* heat shock protein

60 (cHSP60) contributed to the development of acute lung inflammation in mice, and concluded that cHSP60 may play a role in both acute and chronic lung inflammation. These animal studies suggest a mechanism by which *C pneumoniae* infection in the lung may contribute to the development and pathologic manifestation of asthma.

DIAGNOSIS OF ATYPICAL BACTERIAL INFECTIONS

There are significant limitations and challenges in diagnosing atypical bacterial infections in the lung. Current techniques include culture, antigen detection, serology, and polymerase chain reaction (PCR). Culturing atypical bacteria is time-intensive and technically difficult. Other methods for detection include enzyme immunoassays (EIA), enzyme-linked immunosorbent assays (ELISAs), and microimmunofluorescence.[3] For *C pneumoniae*, detection of IgM antibodies typically at 2 to 3 weeks after infection or a fourfold increase in IgG antibodies in convalescent sera suggests acute infection. For *M pneumoniae*, the EIA is frequently used to compare acute and convalescent sera looking for a fourfold increase in antibody titers. PCR detection of atypical bacteria is more sensitive, but there is a lack of standardization and availability. In addition, the correlation between these different diagnostic tests is fairly low.[12] A definitive diagnosis may require invasive tissue sampling, which is infrequently performed. Due to the lack of standardized tests and discordance between detection methodologies, there are limitations in the ability to accurately detect atypical bacterial infections of the lung, which subsequently affects the conclusions that can be drawn from available studies evaluating the role of atypical bacteria and asthma. Emerging techniques such as multiplex PCR and microfluidic platforms for *M pneumoniae* may provide methods for fast and sensitive diagnosis.[13]

ATYPICAL BACTERIAL INFECTIONS AND ACUTE EXACERBATIONS

In many studies, atypical bacterial infections are positively correlated with acute asthma exacerbations. For years there have been reports of a potential link between atypical infections and asthma. In 1970, Berkovich and colleagues[14] examined children with asthma and found evidence of *M pneumoniae* infection in 18% of asthma exacerbations. In 2004, Johnston and Martin[15] reviewed 12 studies looking at *C pneumoniae* and *M pneumoniae* infections and acute asthma flares, and found that 9 of the 12 studies demonstrated an association between infection and exacerbations. Several studies supporting a role of atypical bacterial infections in asthma exacerbations are now discussed here.

In a study of 74 mild to moderate adult asthmatics with acute exacerbations, Allegra and colleagues[16] reported that 20% of subjects had seroconverted to one or more viral or atypical bacterial pathogens as evidenced by a fourfold increase in titers during the 6-month study period. Evidence of atypical bacterial infection was found in 11% of subjects, 88% of which were caused by *C pneumoniae.* In contrast, only 9% of subjects with acute exacerbations had evidence of viral infection. A limitation of the study was that PCR methodologies were not available for diagnosis.

Miyashita and colleagues[17] evaluated 168 adults with asthma exacerbations and 108 matched controls, and found a significant increase in *C pneumoniae* infection in the asthmatic group as well as an increase in *C pneumoniae*–specific IgG and IgA in the asthmatics as compared with controls. The investigators subsequently concluded that *C pneumoniae* infection may contribute to asthma exacerbations. Furthermore, Cunningham and colleagues[18] evaluated 108 children with asthma, and obtained nasal aspirates and sera if there was a significant decrease in peak flow or an increase in respiratory symptoms. Of note, children with recurrent

exacerbations were more likely to remain PCR-positive for *C pneumoniae* and have more than 7 times greater levels of *C pneumoniae*–specific IgA levels. Cunningham and colleagues postulated that the higher antibody response to *C pneumoniae* in subjects with increased asthma flares compared with those with fewer exacerbations could represent an increase in prevalence of infection or differential immune response to the bacterium.

In 2002, Lieberman and colleagues[19] performed a prospective study looking at 100 patients who were admitted to the hospital for asthma exacerbations. Subjects younger than 18 years and those with evidence of infiltrate by chest imaging were excluded. Blood samples from the subjects and age-matched controls were obtained at admission and 3 to 5 weeks later for serologic testing. The frequency of acute infections with various pathogens including viruses, bacteria, and atypical bacteria were compared between the asthma and control groups. Significant findings include the detection of influenza A in 11% of asthmatics versus 2% of controls, and positive serologic tests for *M pneumoniae* in 18% of hospitalized asthmatics compared with 3% of controls. There was no difference in detection of *C pneumoniae* between the 2 groups. Again, the study is limited by serologic diagnosis of infections, but the investigators concluded that *M pneumoniae* infection is correlated with asthma exacerbations requiring hospitalization.

A prospective analysis of 58 patients presenting to the emergency department with an asthma exacerbation revealed serologic evidence of an acute atypical infection with either *C pneumoniae*, *M pneumoniae*, or both in 38% of subjects.[20] The investigators obtained peak flow measurements at presentation and spirometry at follow-up, and found a significant reduction in peak flow and forced expiratory flow in 1 second (FEV$_1$) in the asthmatic group with atypical bacterial infections compared with the asthmatics without atypical bacterial infection. In addition, those presenting with severe asthma as defined by an initial peak expiratory flow (PEF) of less than 50% of predicted were more likely to have serologic evidence of acute atypical bacterial infection, with an odds ratio (OR) of 4.29.[20] Specific limitations of the study that are addressed in the publication include difficulties with diagnosis using serology, small sample size, and use of percent predicted instead of personal best for peak flow recordings. Despite these limitations, the results support an association between atypical bacterial infections and increased functional impairment during acute asthma exacerbations.

To evaluate the role of atypical bacterial infections in pediatric asthma exacerbations, Biscardi and colleagues[21] prospectively studied subjects who were admitted to hospital with severe asthma flares. Nasopharyngeal samples were obtained at admission and evaluated for the presence of a variety of respiratory viruses and for *C pneumoniae* and *M pneumoniae*. Acute infection was diagnosed by either elevation of specific IgM at initial serology or a 4-fold increase in IgG titers at follow-up. The subjects were divided into 3 groups for data analysis. Group 1 included 119 subjects with acute exacerbation of asthma. Group 2 consisted of 51 subjects presenting with their first onset of wheezing. Group 3 comprised 152 controls with chronic, stable asthma without exacerbation in the previous 6 months and/or allergic rhinitis. In group 1, *M pneumoniae* was found in 24 subjects (20%) and *C pneumoniae* was detected in 4 (3.4%) subjects during exacerbation. In the new-onset wheeze group, *M pneumoniae* was detected in 26 subjects (50%), a statistically significant difference when compared with group 1, and *C pneumoniae* was identified in 4 (8.3%). In the control group, only 8 (5.2%) had evidence of *M pneumoniae*. At 1-year follow-up, 62% of subjects in group 2 who had been diagnosed with an atypical infection had recurrence of asthma compared with only 27% of noninfected subjects in that group. This study also supports the potential role of atypical bacterial infections during acute asthma exacerbations and,

interestingly, demonstrated that *M pneumoniae* infection was present in a large proportion of children presenting with their first asthma attack.

One of the hallmarks of asthma exacerbations is increased mucous production. The asthmatic airway expresses increased levels of the major mucin protein MUC5AC compared with nonasthmatic controls. Kraft and colleagues[22] reported that airway epithelial cells from patients with asthma demonstrated increased MUC5AC expression following *M pneumoniae* infection. In their study, bronchoscopy with airway brushings was performed on 11 asthmatic subjects and 6 nonasthmatic controls with subsequent culture of airway epithelial cells at an air-liquid interface with and without *M pneumoniae*. MUC5AC mRNA and protein expression were measured using PCR and ELISA techniques. The investigators found a significant increase in MUC5AC mRNA and protein expression in the asthmatic cells that were exposed to *M pneumoniae* and that this increase was attenuated by coculture with an NF-κB or TLR2 inhibitor.[22] Kraft and colleagues subsequently postulated that the increased mucin expression in asthmatic epithelial cells in response to *M pneumoniae* likely involves TLR2 signaling and NF-κB activation. Similarly, Morinaga and colleagues[23] also found that *C pneumoniae* infection of airway epithelial cells led to an increase in MUC5AC expression that could be reduced by treatment with macrolides and ketolides. This study also concluded that both ERK (extracellular signal-related kinase) and NF-κB were involved in MUC5AC production triggered by *C pneumoniae.* Various human studies support the potential role of atypical bacterial infections in acute exacerbations of asthma.

ATYPICAL BACTERIAL INFECTIONS AND THE DEVELOPMENT OF ASTHMA

The data supporting the role of atypical bacterial infections in the development of asthma is less clear. Zaitsu[24] compared 103 first-time wheezing infants and toddlers with 64 healthy controls. Seroconversion to *C pneumoniae* was significantly higher in the wheezing subjects than in controls (44.7% and 17.2%, respectively). Among the wheezing patients, those who progressed to developing asthma were statistically more likely to have a family history of allergic diseases and higher total IgE. Furthermore, wheezing patients with *C pneumoniae* infection were also more likely to develop asthma than those without infection (relative risk 2.9).[24]

In 2000, Kim and colleagues[25] investigated whether *M pneumoniae* infection led to impaired lung function. Thirty-eight children hospitalized for *M pneumoniae* lung infection and 17 control children with *M pneumoniae* upper respiratory infections without lung involvement completed high-resolution chest computed tomography (CT) 1.0 to 2.2 years after infection. Of note, 37% of the *M pneumoniae* infection group compared with 12% of the control group exhibited abnormal CT findings including bronchial wall thickening and air trapping, which contributes to airflow obstruction.

A population-based adult cohort study followed subjects for 15 years and investigated whether *C pneumoniae* infection conferred a risk of developing asthma or reduced lung function as compared with those without serologic evidence of *C pneumoniae*.[26] Although atypical bacterial infection did not increase the risk for development of asthma, the investigators found that subjects with chronic *C pneumoniae* infection and nonatopic asthma experienced a faster decline in FEV_1 compared with other asthmatics without chronic infection. These findings suggest that atypical bacterial infections may contribute to the development of airflow obstruction. However, It must be noted that several published studies do not support an association between atypical bacterial infection and the development of new-onset obstructive lung

disease.[27,28] Consequently, further studies are needed to clarify the role of atypical bacterial infections in the development of asthma.

ATYPICAL BACTERIAL INFECTIONS, CHRONIC ASTHMA, AND SEVERITY OF DISEASE

Several studies support a correlation between atypical bacterial infections and chronic stable asthma. In 2001, Martin and colleagues[29] looked for evidence of infection with either *M pneumoniae* or *C pneumoniae* by PCR in 55 patients with chronic asthma and nonasthmatic controls, and found that more than 50% of asthmatics were positive for atypical bacteria as compared with 9% of controls. PCR-positive asthmatics also had a greater number of tissue mast cells, which raises the possibility that atypical bacterial infection of a previously sensitized host might augment underlying allergic inflammation, a finding that Wu and colleagues[5] described in a murine model of allergic asthma. Gencay and colleagues[30] evaluated 33 adult subjects with chronic stable asthma and matched controls for serologic evidence of infection with *C pneumoniae*. Significant findings include evidence of chronic *C pneumoniae* infection, as defined by *C pneumoniae*–specific IgG of 1:512 or more and IgA of 1:40 or more, in 18.2% of asthmatics versus 3% of controls.

In addition, evidence suggests that atypical bacterial infections may also alter the severity of chronic asthma. In the review by Johnston and Martin[15] of atypical infections and asthma, 16 of 20 studies supported a role for atypical infections in chronic asthma and several found an association between infection and severity of disease. In 1998, Hahn and colleagues[31] described 3 steroid-dependent asthmatics with serologic evidence for recent *C pneumoniae* infection who were able to discontinue oral steroids following antibiotic therapy for atypical bacteria.

Although based on a small group, the investigators[31] questioned whether these subjects' atypical bacterial infection contributed to steroid dependency and severity of disease. This idea was further evaluated by Black and colleagues[32] who examined 619 asthmatics for serologic evidence of *C pneumoniae* infection and collected clinical information including severity of symptoms, number and frequency of hospitalizations, and use of asthma medications. The investigators found a correlation between the use of high-dose inhaled steroids with increased *C pneumoniae* IgG and IgA titers. In addition, those with elevated *C pneumoniae* IgG had lower FEV_1 compared with percent predicted. Although it is unclear whether the use of high-dose inhaled steroids is a risk factor for developing atypical bacterial infections in the lung, these findings highlight the possibility that atypical infections may influence the severity of chronic asthma. Black and colleagues[32] propose that proinflammatory cytokines such as TNF-α and RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted) induced by the infection may contribute to disease severity.

In a prospective study of a Finnish cohort, subjects with nonatopic asthma with serologic evidence of *C pneumoniae* experienced a faster decline in FEV_1 than matched asthmatics without infection.[26] In addition, Ten Brinke and colleagues[33] followed 101 severe asthmatics in a cross-sectional study and determined that nonatopic asthmatics with serologic evidence of *C pneumoniae* infection had significantly greater estimated decline in postbronchodilator FEV_1/vital capacity. Put simply, *C pneumoniae* infection worsened the airflow obstruction, which may be explained in part by infection-related airway remodeling and inflammation.[33] Cook and colleagues[34] measured antibody titers to *C pneumoniae* in 123 acute asthmatics and 1518 nonasthmatic controls who were admitted to hospital.[34] Although antibody titers suggesting acute infection were not different between the groups, *C pneumoniae*

antibody titers suggesting prior infection were found in 34.8% of those with chronic, severe asthma compared with 12.7% of controls with adjusted odds ratio of 3.99.

Chlamydial antigens such as HSP60 are responsible for activation of the host inflammatory cascade in response to infection. Immune responses directed against cHSP have been associated with the development of various inflammatory conditions including ocular and pelvic disease. Hahn and Peeling[35] tested for antibody responses to a cHSP60 fragment in adult asthmatics and 52 nonasthmatic controls who were exposed to *C pneumoniae*, and found that immunoreactivity to the cHSP60 fragment was associated with increased airflow limitation as defined by lower postbronchodilator FEV_1. It is postulated that host immune responses to cHSP may contribute to airway pathology, thus worsening disease severity. Several human studies including those outlined here suggest an association between atypical bacterial infections and severity of asthma.

EFFECTS OF ANTIBIOTICS ON ATYPICAL BACTERIA IN ASTHMA

Although studies suggest a role for atypical bacterial infections in asthma exacerbations, chronic asthma, and severity of disease, the use of antibiotics such as macrolides directed against them is still under investigation and is not routinely practiced. The mechanism by which antibiotics such as macrolides affect asthma is not well understood and is likely to be multifactorial. If atypical bacterial infections contribute to asthma, one can imagine how antibiotic-mediated clearance of the bacteria may be beneficial. The effects of macrolides likely extend far beyond their antimicrobial properties. Numerous studies have characterized the anti-inflammatory effects of macrolides, which include reduction in bronchial epithelial cell production of endothelin-1 (ET-1), down-regulation of adhesion molecules altering local inflammation, inhibition of airway mucous production, and reduction of proinflammatory cytokines such as IL-8.[36–39] Some of the human trials that have sought to investigate the effects of antibiotic therapy for atypical infections in asthma are outlined in this section.

Asthmatics with a current exacerbation were enrolled in a double-blind, placebo-controlled, randomized trial (TELICAST) investigating the efficacy of telithromycin during acute asthma flares.[40] A total of 278 acute asthmatics were enrolled and treated with standard care plus 10 days of either telithromycin or placebo. Culture, serology, and PCR techniques were used to evaluate for *M pneumoniae* or *C pneumoniae*. The primary outcomes were symptom scores and morning PEFs. Sixty-one percent of subjects had evidence of atypical bacterial infection. Symptom scores improved significantly in the treatment group; however, there was no difference in morning peak flows. Spirometry was obtained at various time points including baseline, end of treatment, and at 6 weeks. At the end of treatment, the FEV_1 improved by 0.63 L in the telithromycin group compared with 0.34 L in the control group ($P = .001$); however, this difference was no longer seen at 6 weeks. On subgroup analysis, it appears that the improvement in FEV_1 at the end of treatment compared with controls was only significant in those with evidence of atypical infection. The TELICAST trial demonstrated temporary clinical improvement following use of antimicrobials during asthma exacerbations, but raised many questions including who would benefit from therapy, whether the benefits outweigh potential adverse events, and the mechanism of action of antimicrobials in this setting.

Horiguchi and colleagues[41] examined the effects of sparfloxacin on 26 asthmatics with serologic evidence of *C pneumoniae*. The subjects were seen in an outpatient clinic and randomized to sparfloxacin, a respiratory quinolone that covers atypical

bacteria, or no treatment for a total of 21 days. Of note, the treatment subjects reported a decrease in symptoms, less rescue medication use, and improved morning peak flows. Although it suggests that antimicrobial therapy can improve asthma, this study is limited by the small sample size and bias that may be introduced from non-blinded treatment. Black and colleagues[42] performed a randomized, double-blind, placebo-controlled trial (CARM study) evaluating the use of roxithromycin in asthmatics with serologic evidence of *C pneumoniae*. The study included 232 subjects who participated in a 2-week run-in period, 6 weeks of treatment with either roxithromycin or placebo, and 24 weeks of follow-up. The primary end points included asthma symptom scores and the change in mean PEF. Following treatment there was no difference in symptom scores, but the roxithromycin group experienced a greater increase in mean evening PEF (15 L/min) compared with placebo (3 L/min), which was no longer seen at 3 months. This trial demonstrated a transient effect on evening PEF following antibiotic therapy.

In 2001, Kraft and colleagues[43] studied the effects of clarithromycin on 55 subjects with chronic asthma. The subjects completed methacholine challenges, spirometry, chest radiography, and upper and lower airway sampling, which included PCR analysis for *M pneumoniae* and *C pneumoniae*. The subjects were randomized to receive clarithromycin or placebo for 6 weeks with subsequent evaluation of lung function and measurement of inflammatory mediators. Significant findings include evidence of *M pneumoniae* and/or *C pneumoniae* in 56% of asthmatics. PCR-positive treatment subjects experienced an increase in FEV_1 (2.50 ± 0.16 to 2.69 ± 0.19 L; $P = .05$) that was not found in PCR-negative subjects in the treatment group or in controls. The investigators analyzed bronchoalveolar lavage samples for cytokine expression, and found a reduction in TNF-α, IL-5, and IL-12 mRNA in the PCR-positive asthmatics treated with clarithromycin and a reduction in TNF-α and IL-12 mRNA in treated subjects who were PCR-negative. There were no changes noted in inflammatory cytokines in the placebo group. Kraft and colleagues concluded that clarithromycin improved lung function in patients with evidence of atypical bacteria in addition to reducing pulmonary inflammatory cytokines in both PCR-positive and -negative subjects.

Studies also support a beneficial role of macrolides in asthmatics that is independent of infection with atypical bacteria. Simpson and colleagues.[44] treated severe, refractory asthmatics without known *M pneumoniae* or *C pneumoniae* colonization with clarithromycin or placebo for 8 weeks and found improved quality-of-life scores and reduced sputum IL-8 in the treated subjects. The investigators speculated that macrolides may provide effective adjunctive treatment, especially for those with severe asthma and presumed neutrophilic disease, primarily because of their anti-inflammatory properties. Although some studies suggest a possible therapeutic benefit from use of antimicrobials in asthma, it remains unclear as to who would benefit from therapy and whether any improvement in lung function or symptoms can be sustained. The most recent Cochrane review in 2005 to evaluate the effects of macrolides for chronic asthma cited insufficient evidence to currently recommend their use.[45] This topic clearly requires further investigation to better understand the role of antimicrobial therapy in asthma.

SUMMARY

Taken together, these studies suggest that *C pneumoniae* and *M pneumoniae* infections are frequently present in acute exacerbations and chronic asthma. In addition, there is mounting evidence to suggest that atypical bacterial infections may also affect

the severity of disease, although a causal role for the development of asthma has not been proved. Significant limitations exist in diagnosing atypical bacterial infections in the lung because of difficulties with sampling and lack of standardized detection methodologies. Numerous animal and human studies have outlined mechanisms by which atypical bacterial infections may contribute to airway obstruction through promotion of allergic airway inflammation and airway remodeling. Additional trials are needed to clarify the role of antimicrobials for atypical bacteria in asthma. As our understanding of the role of atypical infections in asthma expands, antimicrobial and anti-inflammatory therapies targeted for specific asthma phenotypes may provide new therapeutic options.

ACKNOWLEDGMENTS

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