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Is there a role for antibiotics?

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Abstract:
Atypical bacteria (Mycoplasma pneumoniae and Chlamydophila pneumoniae) are thought to be inflicted in the pathogenesis and precipitation of acute asthma. Past and current infections with these organisms were found more frequently in asthmatics compared to healthy controls. It was suggested that atypical infections could precipitate acute asthma attacks in previously healthy individuals. This has raised the question of whether or not to add antibiotics to the management, especially macrolides. This review highlights the natural history of these organisms and their role in acute asthma of children. The current literature about role of antibiotics in acute asthma is summarized.

Introduction

Mycoplasma pneumoniae (*M. pneumoniae*) and *Chlamydophila pneumoniae* (*C. pneumoniae*) are important etiological agents responsible for human respiratory tract diseases. These atypical microorganisms received much attention regarding their role in bronchial asthma pathogenesis [1]. These agents infect the human bronchial tree, causing ciliary dysfunction and epithelial damage. *M. pneumoniae* and *C. pneumoniae* species are able to generate proinflammatory cytokines both in-vivo and in-vitro. Persistent infection with both agents has been implicated in the progression or induction of asthma and other pulmonary diseases [2]. A body of literature has been published about the role of these atypical bacteria in stable asthma, mainly in adults. However, research regarding the effect of these bacteria in pathogenesis of acute asthma in children has been scarce.

This review highlights the key points known about these organisms in relation to acute asthma of children and the role of antibiotics in the treatment.

Microbiological background

In 1944, *M. pneumoniae* was first isolated and described from a patient with primary atypical pneumonia by Eaton et al [3]. It only infects humans and cholesterol is essential for its growth. It lacks a cell wall and so it is

pleomorphic. *M. pneumoniae* grows slowly and its growth is more prominent in presence of excess nitrogen and carbon dioxide. *M. pneumoniae* is transmitted via respiratory droplets. Reproduction occurs in Mycoplasmas by "binary fission", temporally linked with duplication of the attachment organelle, which migrates to the opposite pole of the cell during replication and before nucleoid separation [4*]. C. pneumoniae* (previously known as *Chlamydia pneumoniae*) first gained attention in early 1980's. They are very small gram-negative bacteria that are obligate intracellular parasites. *C. pneumoniae* (strain Taiwan acute respiratory agent or TWAR) is an important cause of pneumonia. During one epidemic, up to half of the pneumonia cases have been found to be caused by this organism [5]. Most infections, however, are mild or asymptomatic. Recurrent infections are common, since the memory immunity elicited by *C. pneumoniae* is short-lived and only partial. A characteristic feature of all Chlamydia is their tendency to persist [6].

M. Pneumoniae and C. pneumoniae in respiratory diseases

Infection with *M. pneumoniae* can produce long-term impairment in airway functions, even in asymptomatic children. Tsolia et al [7] studied 75 children with community-acquired pneumonia and found that the most common bacterial pathogen was *Mycoplasma pneumoniae* (35% of cases), mixed infections were documented in 35% of patients and the majority had a viral-bacterial combination. In an Italian multicenter study, Principi et al [8] investigated 613 children aged 2-14 years hospitalized for community-acquired lower respiratory tract infections (LRTIs). Serum samples were obtained on admission and after 4-6 weeks to assay the titers of *M. pneumoniae* and *C. pneumoniae* antibodies. Acute *M. pneumoniae* infections in 210 patients (34.3%) and acute *C. pneumoniae* infections in 87 (14.1%) were diagnosed. Fifteen of the 18 children with *M. pneumoniae* and/or *C. pneumoniae* infections whose treatments were considered clinical failures 4-6 weeks after enrollment did not

receive macrolides. *M. pneumoniae* and *C. pneumoniae* were detected in children hospitalized with severe pneumonia. Samransamruajkit et al [9] investigated children with severe pneumonia and found that 25% of cases were positive for *M. pneumoniae*, 15% were positive for *C. pneumoniae* and 7.6% were positive for both. *M. pneumoniae* infection has been found in 10 to 40% of patients with community-acquired pneumonia, with even higher proportion during epidemics.

Regarding chronic asthma, it appears that the timing of atypical bacterial infections in relation to allergen challenges determines the effect on asthma pathogenesis. Chu et al [10] conducted studies on mice and reported that *M. pneumoniae* infection prior to allergen exposure was protective against allergic responses, including decreased airway hyperreactivity, lung inflammation and interleukin 4 (IL-4) productions. In contrast, if the infection occurred after allergen exposure, it was found to enhance allergic responses. Patel et al [11] examined bronchoalveolar lavage (BAL) fluid for *C. pneumoniae* and interleukin-8 (IL-8) using polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay from two groups of asthmatic children with an average age of 8 and 8.7 years, respectively. In the first group, six (33%) were PCR-positive for *C. pneumoniae* and IL-8 from *C. pneumoniae*-positive samples was 3.3-fold higher compared with negative samples (p = 0.003). Comparable results were obtained from the second group. They concluded that undiagnosed *C. pneumoniae* infections in children might contribute to poorly controlled asthma via induction of IL-8 production.

The role of atypical bacteria in cystic fibrosis is less well established, and there appears to be a lack of published papers in the literature addressing this subject, especially in children. Janahi et al [12] stated that Mycoplasma infection should be considered in rapidly deteriorating cystic fibrosis patients, even if they were on macrolides. Infection with *C. pneumoniae* is associated with acute exacerbations in cystic fibrosis patients and it

can trigger the production of IgE specific to *C. pneumoniae*, and this might result in bronchial hyperreactivity [13].

M. Pneumoniae and C. pneumoniae in pediatric acute asthma

Acute *M. pneumoniae* and *C. pneumoniae* respiratory infections might be involved in acute wheezing and/or asthma attacks in children. Esposito et al [14] studied 71 children aged 2-14 yrs with an acute episode of wheezing and 80 matched healthy controls. Specific antibodies and nasopharyngeal aspirates for detection of *M. pneumoniae* and *C. pneumoniae* were obtained on admission and after 4-6 weeks. Acute *M. pneumoniae* and *C. pneumoniae* infections were detected significantly more frequently in children with wheezing than in controls.

In patients infected with one of the two pathogens, a history of recurrent wheezing was significantly more frequent. In follow-up, among non antibiotic-treated children, those with acute *M. pneumoniae* and/or *C. pneumoniae* infection showed a significantly higher recurrence of wheezing (p=0.03). That study emphasized the significant relationship of atypical bacterial infections with wheezing in children, especially in those with history of recurrent episodes. In a recent study by Wood et al [15], researchers enrolled 143 children (53 with acute asthma) over 20 month-period with multiple follow-ups. They detected *M. pneumoniae* using community-acquired respiratory distress syndrome (CARDS) toxin antigen capture and PCR as well as IgG and IgM levels directed against CARDS toxin and P1 adhesin. They found that *M. pneumoniae* was detectable in 64% of children with acute asthma. Previously, Ou et al [16] demonstrated serologic evidence of *M. pneumoniae* infection in 23% of acute asthmatic children with previous history of asthma, and in 45% of acute asthmatics experiencing their first attack. Hanhan et al [17] investigated the relation between *M. pneumoniae* and status asthmaticus in children. They reviewed all patients admitted to pediatric intensive care over one year with this condition. They found that 42% were *M. pneumoniae* positive. Those patients were more

likely to have one or more infiltrates in their chest x-rays.

M. pneumoniae products that provoke allergic inflammation are still unclear. Krishnan et al [18] reported that Mycoplasmas secrete ADP-ribosylating and vacuolating toxin (CARDS toxin), which is a 68 kilodaltons protein with high binding affinity to human surfactant. These properties lead to inflammatory processes in airways, ciliostasis, tissue injury and disruption of tissue integrity. The process by which CARDS toxin enters target cells might be through the CARDS toxin being bound to mammalian cell surfaces and being internalized rapidly in a dose and time-dependent manner through a clathrin-mediated pathway. Medina et al [19] exposed naive mice to a single dose of recombinant CARDS (rCARDS) toxin responded with an inflammatory response consistent with allergic diseases. rCARDS toxin induced 30-fold increase of Th-2 cytokines (IL-4 and IL-13) and up to 80-fold increase of Th-2 chemokines, together with airways eosinophilia, T and B cells infiltration and mucus glandular metaplasia. The inflammatory responses correlated with toxin-dependent increase in airway hyperreactivity. Researchers suggested that rCARDS toxin is capable of inducing allergic-type inflammation in naive animals and might represent a causal factor in *M. pneumoniae*-associated acute asthma.

C. pneumoniae infections, whether detected by positive cultures, serologic methods or PCR, were able to trigger acute attacks of wheezing in asthmatic children. Glucocorticoids could enhance reactivation of persistent respiratory *C. pneumoniae* to an active growth phase; this leads to increased production of inflammatory cytokines and precipitates acute asthma [20]. *C. pneumoniae* infections might be underestimated due to atypical clinical presentations and difficulties in laboratory diagnosis. Chlamydial association with acute asthma in children has been reported in different parts of the world with varying prevalence. In Poland, Szczepanik et al [21] studied 30 children suffering from bronchial asthma exacerbations and demonstrated anti- *C.*

pneumoniae antibodies in 13.3% of them. In Argentina, Maffey et al [22] reported that 2% of acute asthmatic children had serologic evidence of *C. pneumoniae*. However, Sato [23] reported a prevalence of 48.4% in Japanese acute asthmatic children. It appears that the prevalence varies widely according to geographic region and climate.

Is there a role for antibiotics in acute asthma?

In 2001, Graham et al [24] conducted a meta-analysis and concluded that the role of antibiotics in the treatment of acute asthma was difficult to assess from the current literature at that time. After that, few clinical trials have emerged addressing this subject. Fonseca et al [25] evaluated the effect of clarithromycin on inflammatory markers levels in children with acute attacks of recurrent wheezing. They reported that nasopharyngeal concentrations of tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) and interleukin-10 (IL-10) were significantly and persistently lower in children given clarithromycin compared to controls. There was a greater effect of clarithromycin on nasopharyngeal cytokine concentrations in patients with evidence of *M. pneumoniae* or *C. pneumoniae* infections. However, there were no significant differences detected in serum cytokines for children treated with clarithromycin compared to controls. Koutsoubari et al [26] conducted a study on 40 school-aged children with acute asthma exacerbations. Children were randomized to receive clarithromycin for three weeks in addition to the standard exacerbation treatment. The microbial trigger of exacerbations was assessed by serology and PCR. They found that children in the clarithromycin group had significantly more symptom-free days and less total number of periods with loss of control during the follow-up period, compared to controls.

Johnston et al [27] found the ketolide telithromycin to reduce acute asthma symptoms among adult patients receiving telithromycin than among those receiving placebo. However, there was no significant relationship between bacteriologic status and the response to acute asthma treatment. Brusselle et al [28] investigated the role of azithromycin on exacerbation-prone adults with severe asthma. They found that azithromycin did not reduce the rate of severe exacerbations. However, there was significant reduction in the primary endpoint rate in azithromycin-treated patients with non-eosinophilic severe asthma.

Bébéar et al [29] conducted a 2-year longitudinal study to investigate the role of M. pneumoniae infections in 168 and 20 hospitalized children and adults, respectively, with asthma exacerbation compared with outpatients (88 children and 48 adults) with chronic asthma (without an exacerbation). The prevalence of *C. pneumoniae* and respiratory viruses was also assessed. They found that *M. pneumoniae* infection was more prevalent in children with chronic asthma (13.6%) compared with children with exacerbation (7.1%), while the reverse was true in adults (6.3 vs. 10.0%, respectively). However, these differences were not statistically significant. Acute *C. pneumoniae* infection was identified in 3.9% of children and 7.4% of adults. Children seen for chronic asthma were significantly more likely to be infected with *C. pneumoniae* than children hospitalized for an asthma exacerbation. No differences in the outcome parameters were identified between *M. pneumoniae*-infected and noninfected patients. Researchers concluded that *M. pneumoniae* does not play a direct role in the pathogenesis of pediatric acute or chronic asthma.

Tang et al [30] investigated whether serum procalcitonin (PCT) can be utilized to guide the use of antibiotics in the treatment of acute asthma. A randomized-controlled trial including 225 asthmatics was held. Serum PCT levels, and other inflammatory biomarkers of all patients were measured. In addition to the standard treatment, the control group received antibiotics according to the attending physicians' discretions, while the patients in the PCT group were treated with antibiotics according to serum PCT concentrations. Antibiotics usage was strongly discouraged when the PCT

concentration was below 0.1 µg/L; discouraged when the PCT concentration was between 0.1 µg/L and 0.25 µg/L; or encouraged when the PCT concentration was above 0.25 µg/L. Researchers found that the probability of antibiotic usage in the PCT group (46.1%) was lower than that in the control group (74.8%)(p< 0.001). PCT and IL-6 showed good diagnostic significance for bacterial asthma (p = 0.003). They concluded that serum PCT concentration could be used to effectively determine if acute asthma patients have bacterial infections in the respiratory tract, and to guide the use of antibiotics in the treatment of acute asthma exacerbations.

Up to the author's knowledge, the current literature so far is not enough and further randomized-controlled trials are needed in order to build evidence. Antibiotic use in acute asthma should remain consensus-driven until more research is conducted.

Conclusion

The role of *M. pneumoniae* and *C. pneumoniae* in pathogenesis and precipitation of acute asthma in children appears to be substantial. Antibiotic use for acute asthma should remain individualized until further evidence emerges.

Conflict of interest

None declared. No funds were received for the preparation of this review.

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