

Is There a Role for Antibiotics in the Treatment of Asthma?

Involvement of Atypical Organisms

David L. Hahn

Dean Medical Center, Madison, Wisconsin, USA

Abstract

Emerging evidence suggests an association between some asthma and pulmonary infection by the atypical organisms *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, but a causal role for infection remains unproven and controversial. Most acute exacerbations of asthma are triggered by acute infections that are due to viral respiratory pathogens, not to bacteria or atypical organisms. Administration of antibiotics for acute exacerbations of asthma has been shown to be ineffective. Most evidence linking atypical infections to asthma is consistent with a promoting role for chronic infection in producing persistent asthma symptoms. Preliminary studies suggest that prolonged (≥ 6 weeks) administration of doxycycline or macrolides may eradicate *C. pneumoniae* from respiratory secretions and improve long term, not acute, asthma symptoms. Randomised, controlled trials are currently under way to investigate the effectiveness of these prolonged courses of macrolides and azalides (roxithromycin, clarithromycin and azithromycin) in adults with stable persistent asthma. Traditional courses (7 to 10 days) of any antibiotic are incapable of eradicating chronic *C. pneumoniae* or *M. pneumoniae* infection; furthermore, β -lactam and sulphonamide-based antibiotics that are commonly prescribed in acute respiratory syndromes are ineffective against these atypical organisms. Unless the goal is to treat documented sinusitis associated with asthma, it is inappropriate to prescribe traditional courses of any antibiotic for acute asthma exacerbations; whether longer courses of antibiotics should be prescribed to eradicate chronic atypical infections and decrease persistent asthma severity remains to be established.

In 1991 colleagues and I^[1] first reported that wheezing, asthmatic bronchitis and adult-onset asthma were associated with serological evidence for *Chlamydia pneumoniae* infection. Although acute infections were found to exacerbate and possibly even to initiate asthma in some cases, the preponderance of evidence from our study suggested that reinfection or chronic infection might have a causal association with asthma. This suggestion, that some asthma could be caused by infection, was

widely reported at the time. Subsequent investigations, based mainly on serological associations, have supported the possibility that *C. pneumoniae* could be related to asthma.^[2] Recently, *Mycoplasma pneumoniae* has also been added to the list of pathogens possibly contributing to asthma symptoms.^[3] That persistent infection with these organisms could produce chronic inflammation responsible for asthma symptoms is biologically plausible (table I). However, conclusive proof for such a causal as-

sociation is not established and there is no scientific basis currently for widespread recommendations regarding antibiotic treatment for asthma. Nevertheless, I am aware that antibiotics are being prescribed in acute exacerbations of asthma. The purpose of this article is to explain why antibiotics are not indicated for acute exacerbations of asthma even if a causal association is eventually proven.

1. Infection and Asthma: Potential Causal Relationships

At least 3 different causal pathways exist whereby infection could cause or affect asthma: initiation, exacerbation and promotion. Initiation refers to the ability of an environmental influence (in this case an infection) to produce asthma symptoms in a previously asymptomatic person. Exacerbation denotes that an infection temporarily intensifies already established asthma. Promotion indicates the ability of a chronic infection to persistently worsen asthma symptoms over a long period of time. In lay terms, persistent lung infection as a promoting

agent may be thought of as a 'hidden allergen', exposure to which the patient is entirely unaware.

Initiation of asthma can be expected to occur in about 1 adult patient per 1000 per year.^[4,5] Little is known about asthma initiation because the event is transient and hard to capture in scientific studies. Exacerbation is most widely thought of when speculating on what 'causes' asthma. It is now clear that the majority of asthma exacerbations in both children and adults are related to acute respiratory viral infections^[6,7] and that conventional courses of antibiotics are ineffective in asthma exacerbations.^[8] Examples of proposed promoting agents include persistent exposure to dust mite antigen and to atypical respiratory pathogens such as *C. pneumoniae* and *M. pneumoniae*. Identification (and removal) of asthma promoting agents offers perhaps the greatest current potential for lessening the disease burden due to asthma.

What role(s) might atypical infection play in asthma causation? Table II summarises current knowledge regarding *C. pneumoniae* and *M. pneumoniae* in the initiation, exacerbation and promo-

Table I. Atypical infection and asthma: epidemiology and biological plausibility

| | <i>Chlamydia pneumoniae</i> | <i>Mycoplasma pneumoniae</i> |
|--|---|--|
| Epidemiology | | |
| Prevalence | 50 to 90% of adults worldwide have evidence of previous exposure | Usually regarded as a childhood infection; adults also affected, prevalence uncertain |
| Acute infection | Mainly school children and young adults: causes upper respiratory infections, bronchitis and pneumonia but 70% are asymptomatic; postinfectious carriage documented | Mainly school children and young adults: causes upper respiratory infections, bronchitis and pneumonia, prevalence of asymptomatic infection uncertain; postinfectious carriage documented |
| Chronic infection | Acute reinfection common in adults; presence in circulating PBMCs documented; deep tissue infection common (e.g. atherosclerosis) | Recent evidence of lung carriage in adults, population prevalence uncertain |
| Biological plausibility | | |
| Cytokine production | Significant <i>in vitro</i> evidence | Some <i>in vitro</i> evidence |
| Inflammation in target organs | Established for other chlamydial infections (trachoma, tubal infertility); significant animal model evidence for <i>C. pneumoniae</i> | Indirect evidence from case reports (e.g. pulmonary fibrosis) |
| Bronchial hyperreactivity | One epidemiological study | Uncertain |
| IgE antibody | Several case series; documented in both adult and childhood asthma and cystic fibrosis with wheezing | Case reports |
| PBMCs = peripheral blood mononuclear cells. | | |

Table II. Atypical infection and asthma: potential causal relationships

| | <i>Chlamydia pneumoniae</i> | <i>Mycoplasma pneumoniae</i> |
|---------------------------|--|---|
| Initiation | Case series ^[5] | Case series ^[9,10] |
| Exacerbation ^a | Case series ^[1,11] | Many case series, e.g. ^[12,13] |
| Promotion | Evidence from epidemiological studies (over 4000 case/controls) reviewed elsewhere ^[2] and treatment case series ^[14,15] | Evidence from a bronchoscopic ^[9,16] and treatment study ^[17] |

a Most asthma exacerbations are associated with viral infections,^[6,7] not with atypical infections.

tion of asthma. The evidence regarding *C. pneumoniae* and asthma is more voluminous and has been recently reviewed elsewhere.^[2]

1.1 Initiation

It is a dramatic departure from current dogma to suggest that infections can initiate asthma. Nevertheless, research is currently being conducted on a role for acute respiratory syncytial virus (RSV) infection in the genesis of infant asthma. In adults, clinical reports have suggested that acute atypical infections appear to initiate asthma in some cases.^[5,9] If a role for infection as an asthma initiator is confirmed, then genetic susceptibility and/or other factors must also be involved, since many are infected but only some get asthma. It is unlikely that focusing treatment on the acute (initiating) infection will be the sole effective strategy in controlling disease, since acute infections are so prevalent, many are asymptomatic, and the initiating event is rarely appreciated at the time by medical caregivers. Development of effective vaccines against initiating pathogens has theoretical potential but may be difficult to achieve in practice.

1.2 Exacerbation

Although some acute exacerbations of asthma have been linked to atypical infection, the majority are due to viruses for which antibiotic treatment is not indicated.^[6,7] Furthermore, a microbiological study of acute *C. pneumoniae*, *M. pneumoniae* and respiratory virus infections in adults observed no preferential association between acute *C. pneumoniae* infection and wheezing exacerbations.^[18] It is also likely that some proportion of atypical infections that have been designated as 'acute' are

actually chronic infections incidentally discovered by sampling during acute viral illness.^[19,20]

1.3 Promotion

Do persistent atypical infections cause inflammation and persistent asthma in adults, and will eradication of infection lead to decreased inflammation and decreased asthma symptoms? This intriguing hypothesis has some preliminary support (table II). However, evidence from large, randomised, controlled trials must be available before generalised treatment recommendations can be formulated.

2. Antibiotic Treatment for Confirmed Atypical Infection

Available antibiotics that show *in vitro* activity against *C. pneumoniae* and *M. pneumoniae* include the tetracyclines, macrolides (including clarithromycin and the azalide azithromycin) and the newer quinolones. A novel class of macrolides that also show *in vitro* activity, termed ketolides, are not yet widely available for use. β -Lactams and sulphonamide-based antibiotics do not demonstrate effective *in vitro* activity, although penicillins can temporarily suppress replication of *C. pneumoniae*.

2.1 Acute Infection

Clinical experience suggests that tetracyclines, macrolides and newer quinolones can show clinical effectiveness in acute bronchitis and pneumonia caused by atypical pathogens, although relapse after a traditional 7- to 10-day course of therapy is commonly seen in cases of *C. pneumoniae* infection. Therefore, 14 to 21 days of treatment have been recommended when *C. pneumoniae* infection is

known or suspected. Post-treatment persistence of *C. pneumoniae* and *M. pneumoniae* has been documented even after clinical cure (see table I). This observation underscores the potential for these atypical organisms to produce chronic infection even after resolution of acute respiratory symptoms.

2.2 Chronic Infection

It is now known that *C. pneumoniae* chronically infects the majority of adults with atherosclerosis^[21] and an uncertain proportion of patients with asthma and chronic obstructive pulmonary disease.^[2] A surprisingly high proportion of children with asthma may also be chronically infected.^[20,22] The prevalence of chronic *M. pneumoniae* infection in children and adults remains to be established. Currently, trials are under way using 3 to 12 months of azithromycin therapy to determine whether treatment is effective in the secondary prevention of heart disease.^[23] In asthma, a preliminary report of a randomised, controlled trial revealed that 6 weeks of clarithromycin therapy (500mg twice daily) was effective in improving forced expiratory volume in 1 second (FEV₁).^[17] An open-label noncontrolled trial also reported clinical and spirometric (FEV₁) improvement with 4 to 6 weeks of azithromycin (1000mg once weekly).^[15] These studies do not address the question whether long term microbial eradication was achieved, however. A single case report documented that *C. pneumoniae* was eradicated from bronchoalveolar lavage fluid after 5 weeks of treatment with azithromycin 1000mg administered once weekly.^[24]

3. Antibiotic Treatment for Asthma?

In 1961, a primary care study reported the apparent clinical effectiveness of troleandomycin administration for 'infectious asthma'.^[25] Later research in academic medical settings focused on the 'steroid-sparing effect' of troleandomycin but these subsequent findings do not explain the apparent clinical effectiveness in the (steroid-naive) primary care asthma patient population. The concept

of infectious asthma fell into disuse during the 1970s and 1980s but was reintroduced in 1995^[26] to denote adult asthma beginning after an acute respiratory illness. This modern version of the infectious asthma syndrome was associated subsequently with markers for *C. pneumoniae* infection, resurrecting the question whether antibiotic treatment would affect the natural history of asthma.^[5]

Indeed, uncontrolled clinical observations suggest that *C. pneumoniae* infection in asthma may be clinically relevant and that randomised, controlled trials are justified. In 1994, Emre et al.^[14] reported that asthma was improved following microbiological eradication of *C. pneumoniae* infection in culture-positive children. In 1995, Hahn^[15] reported similar observations in adults with asthma. Both studies found that clinical response to antibiotics was more likely to be observed in patients with milder disease, or in patients with a shorter duration of asthma and less evidence of fixed obstruction. More recently, significant clinical improvement after antibiotics has been reported in patients with severe, steroid-dependent asthma.^[27] In these reports, the duration of antibiotic therapy varied from a few weeks to more than 3 months (median 4 to 6 weeks). Macrolides (clarithromycin and azithromycin) and the tetracycline doxycycline appeared to be equally effective.

Recent evidence for persistent *M. pneumoniae* infection in the lungs of some adults with asthma suggests that more than 1 atypical organism could play a role in asthma.^[3] Indeed, preliminary results of a randomised, controlled trial of 6 weeks of macrolide therapy in adults with asthma support this possibility.^[16,17]

The suggested beneficial effect of antibiotics against asthma in this group of studies cannot be explained by anti-inflammatory properties of macrolides, since asthma improvement (i) persisted after discontinuation of antibiotic treatment, (ii) was correlated with microbial eradication and (iii) was not observed in polymerase chain reaction (PCR) negative individuals receiving macrolides.

4. Summary and Conclusions

Observations from primary care settings suggest that a surprisingly high proportion of asthma, particularly of adult onset, may begin after respiratory illnesses attributable to infection, and that persistent infection by *C. pneumoniae* could play a role in asthma. Other recent evidence suggests that *M. pneumoniae* could also contribute. However, more evidence from randomised, controlled trials must be available before generalised recommendations for or against antibiotic treatment for asthma can be formulated. Since conventional courses of antibiotics are not effective against chronic atypical infection, future studies should explore the effects on asthma of prolonged courses of appropriate antibiotics mentioned earlier.

There is no established role for antibiotics in the treatment of acute exacerbations of asthma. Most acute exacerbations are virally induced and conventional courses of antibiotics will be largely ineffective against chronic atypical infections. Likewise, antibiotics are ineffective for most acute bronchitis in persons with normal lung function.^[28] Nevertheless, antibiotics are being prescribed for the majority of acute asthma exacerbations in my own multispecialty group practice in particular (Luskin A, Bukstein D. unpublished observations) and also in the majority of uncomplicated acute bronchitis in adults^[29] in general. Perhaps the high prevalence of antibiotic prescribing in acute asthma exacerbations is a specific manifestation of the larger problem of antibiotic overprescribing for virally induced respiratory illness in general. Another possibility is that the emerging evidence linking atypical infections and asthma has been misinterpreted. Thus, I emphasise that the use of antibiotics in the treatment of acute exacerbations of asthma currently represents inappropriate prescribing that can contribute to emergence of antibiotic-resistant bacteria. A future role for antibiotics against chronic infection is possible but requires further study.

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Correspondence and offprints: Dr *David L. Hahn*, Arcand Park Clinic, 3434 East Washington Ave, Madison, WI 53704, USA.

E-mail: dlhahn@facstaff.wisc.edu