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International Journal of Antimicrobial Agents 29 (2007) 485–493

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Review

The role of antibiotics in asthma

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Received 17 November 2006; accepted 21 November 2006

Abstract

There is increasing evidence that atypical respiratory pathogens such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* may contribute to the pathogenesis of both stable asthma and asthma exacerbations. It is postulated that these organisms may contribute to inflammation in the airways possibly by activating inflammatory mechanisms in the respiratory tract.

The macrolide class of antibiotics may have a part to play in the management of asthma by exerting anti-inflammatory effects on the chronically inflamed airways in addition to their anti-infective action. The ketolide antibiotics may also have similar properties.

This paper discusses the role of these antibiotics in the management of asthma.

Keywords: Asthma; Asthma exacerbations; Atypical bacterial infection; Macrolide antibiotic

1. Introduction

Asthma is a complex multifactorial disease involving interactions between genetic susceptibility and exposure to environmental factors such as allergens, pollutants and lower respiratory tract infections. The latter are felt to be involved at various levels in the natural history of asthma. Acute viral infections (e.g. rhinovirus, coronavirus, respiratory syncytial virus [RSV], parainfluenza virus, influenza virus, and adenovirus) have been associated with asthma exacerbations both in children and in adults [1,2]. Acute bacterial infections with atypical pathogens (such as *Mycoplasma* [*M.*] *pneumoniae* and *Chlamydophila* [*C.*] *pneumoniae*) have also been associated with acute asthma exacerbations, whereas chronic infection with these agents may play a role in persistent asthma. The mechanisms associating the presence of microorganisms in the airways and asthma has not been fully investigated, but likely involve increased susceptibility to infection in asthma, with the presence of infection augmenting inflammation in the lower airways. It is likely, but as yet unproven, that repeated acute infections and/or chronic infections play a role in disease progression, via increased inflammation resulting in airway 'remodelling'. Should this be confirmed, antimicrobial therapy may have a role in this disease by interrupting a vicious cycle of infection–disease progression.

Evidence from everyday clinical practice indicates that antimicrobials are indeed commonly prescribed in patients with asthma both in Europe [3] and the United States [4]. Interestingly, this attitude finds little support from current guidelines. The recent National Asthma Education and Prevention Program Expert Panel Report indicates that antibiotics are not currently recommended for the treatment of acute asthma exacerbations except when fever, purulent sputum or clear evidence of infection are present [5]. This advice is based on the only two randomised, double-blind, placebo-controlled, parallel-group trials testing routine antibiotic administration in addition to standard care to adult [6] or paediatric [7] populations with asthma exacerbations, that were published at the time of writing. Both of these rather old studies found no association between antibiotic treatment and improvement in any asthma outcome. It must however be noted that both studies were small, and employed penicillin

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doi:10.1016/j.ijantimicag.2006.11.029

derivatives, to which atypical pathogens such as *M. pneumoniae* and *C. pneumoniae* show extremely poor responses.

2. Asthma and infections

Asthmatic individuals have increased susceptibility to rhinovirus infection [8] and risk of invasive bacterial infection [9]. The mechanisms of increased susceptibility to infection in asthma have been better elucidated in two recently published articles [10,11]. The authors show deficient rhinovirus induction of interferon-β [10] and of interferon-λs in asthmatic primary bronchial epithelial cells and of interferon-λs, also in alveolar macrophages, which was highly correlated with rhinovirus-induced asthma exacerbation severity, airway inflammation and virus load in vivo [11]. In relation to bacterial infections, lipopolysaccharide induction of interferon-λs in asthmatic macrophages was also deficient and correlated with exacerbation severity [11]. These data identify novel mechanisms of susceptibility to infection in asthma and suggest new approaches to prevention and/or treatment of asthma exacerbations.

3. Bacteria in asthma

C. pneumoniae and *M. pneumoniae* infections have been associated with asthma. An association between asthma and *C. pneumoniae* infection was first put forward by Hahn et al. [12] in the early 1990s. *M. pneumoniae* infection may be associated with longlasting dry cough, and an association with asthma symptoms has been suggested [13,14]. The main problem that hampers the full understanding of the possible association between *C. pneumoniae* and *M. pneumoniae* infection and asthma is the lack of standardised, sensitive, and specific diagnostic methods [15,16].

3.1. Acute asthma

Information linking *M. pneumoniae* or *C. pneumoniae* infection to acute asthma exacerbations has been gathered both for adults and children.

3.1.1. Children

A relationship between acute infection with atypical pathogens and acute asthma exacerbations in children has been sought in several controlled and uncontrolled studies [17–22]. The vast majority of studies were concordant in finding an association between atypical bacterial infection and asthma exacerbations. Rates of identification varied between 4.5% and 25% of asthma episodes for *C. pneumoniae*, and 5% to 22.5% for *M. pneumoniae*.

These findings suggest a relationship between childhood asthma and acute *M. pneumoniae* or *C. pneumoniae* infection. In children, with wheezing, the incidence of acute *M. pneumoniae* and *C. pneumoniae* infections increases with age and occurs mainly after 5 years of age.

3.1.2. Adults

Studies employing serology, culture and molecular biology to identify acute atypical infection have been carried out in adult patients presenting with asthma exacerbations [12,23–31]. Evidence of atypical infection was found in most, but not all of these studies. Interestingly, in one trial a serological association between *C. pneumoniae* and acute asthma was found only with anti-heat shock protein (HSP) 10 antibodies and not with traditional serological markers [28]. Lieberman et al. [29] found that *M. pneumoniae* but not *C. pneumoniae* was associated with hospitalisation for acute exacerbation of bronchial asthma. In the study by Wark et al. [27] over one-third of patients with acute severe asthma showed a rise in *C. pneumoniae*-specific antibodies consistent with acute infection, reinfection, or reactivation of latent infection with the microorganism. These subjects exhibited a more intense inflammatory response (as assessed by sputum total cell count, neutrophil count, and eosinophil cationic protein levels) compared with subjects with acute asthma who did not show an increase in *C. pneumoniae* antibody levels.

Overall, available studies in adults and children suggest that acute *C. pneumoniae* and/or *M. pneumoniae* infection may play a significant role in asthma exacerbations.

3.2. Chronic asthma

In addition to acute exacerbations, the role of *M. pneumoniae* and *C. pneumoniae* in the pathogenesis of chronic asthma has also been extensively investigated. Accumulating evidence from sero-epidemiological studies has shown that many asthmatics have elevated antibody levels to *C. pneumoniae* [32] and *M. pneumoniae* [33]. It has been proposed that both pathogens cause occult chronic lower airway inflammation. Consequently, an association between these pathogens and chronic asthma has been hypothesised [34].

3.2.1. Children

Trials addressing the possible relationship between atypical infection and persistent asthma in children have found both positive [18,21,35–37] and negative results [38]. Cunningham et al. [18], in a large prospective study on school-age children with asthma, showed that chronic *C. pneumoniae* infection was common in this population occurring in around one-quarter of children, furthermore, the frequency of asthma exacerbations reported by each child during the 13 months of the study was positively associated with the levels of secretory IgA towards *C. pneumoniae*. The authors suggested that the inflammatory response to chronic *C. pneumoniae* infection may interact with allergic inflammation to increase asthma symptoms, however, given our recent knowledge [10,11], it is also possible that chronic *C. pneumoniae* infection is a marker of increased susceptibility to infection, and therefore to infection-associated exacerbations.

Moreover, there is strong evidence suggesting that serologic evidence of *C. pneumoniae* and *M. pneumoniae* in children hospitalised with acute exacerbations of asthma is associated with persistent asthma symptoms [21].

Perhaps the most persuasive evidence comes from a recent study in children in which *C. pneumoniae* was detected by PCR and culture in bronchoalveolar lavage collected from 42 asthmatic children undergoing bronchoscopy [37]. Of these 28 (67%) and 14 (33%) samples were PCR- and culture-positive, respectively. Elevation of total IgE was strongly associated with lavage culture positivity for *Chlamydia*. These data require confirmation in larger numbers of children and comparison with control subjects, but indicate that viable *C. pneumoniae* organisms are frequently present in the lung lavage fluid from asthmatic paediatric patients.

3.2.2. Adults

A large number of controlled and uncontrolled trials have investigated the role of *C. pneumoniae* and *M. pneumoniae* in adult patients with chronic asthma [12,33,38–52]. Once again, serology was the most commonly employed diagnostic method. Most trials did observe an association between atypical infection and chronic asthma, with negative results being recorded in the minority of cases [38].

Kraft et al. [44] have shown that asthmatic patients exhibit evidence of *M. pneumoniae* airway colonisation/infection with significantly greater frequency than non-asthmatic subjects. In a large study involving 430 subjects with symptoms suggestive for asthma, rhinitis and allergy [46], logistic regression analysis controlling for age, sex and smoking showed that asthma was significantly associated with elevated IgG antibody levels to *C. pneumoniae*. More interestingly, when atopics and non-atopics were analysed separately, an even stronger relationship with longstanding asthma was obtained in the non-atopic group (OR 6.0, 95% CI 2.1–17.1). These data indicate the involvement of the microorganism in the development of non-atopic asthma.

Most reported studies have investigated prevalence of positive serology for atypical bacteria in asthma and control populations; however, a possible association between chronic atypical bacterial infection and asthma severity in adults has also been hypothesised. In an uncontrolled study, Black et al. [52] describe 619 asthmatic subjects in whom IgG and IgA antibodies to *C. pneumoniae* were associated with asthma severity markers. A positive association was found between antibodies to *C. pneumoniae* and the use of high-dose inhaled steroids, higher daytime symptom scores, and an inverse association with FEV_1 as percentage of predicted. A controlled study by Huitinen et al. [48] also found an inverse correlation between *C. pneumoniae* antibody titres (HSP 60 IgA) and FEV_1 values.

Martin et al. [33] reported one of the most comprehensive evaluations of the role of both *C. pneumoniae* and *M. pneumoniae* infections in patients with chronic asthma. In their study, 31 of 55 asthmatic patients had positive polymerase chain reaction (PCR) results for *Mycoplasma* ($n = 25$) or *Chlamydia* species ($n = 6$), which were mainly found on lung biopsy specimens or in lung lavage fluid. On the contrary, only 1 of 11 normal control subjects had positive PCR results for *Mycoplasma* species.

The high number of positive studies associating *C. pneumoniae* and *M. pneumoniae* and chronic stable asthma and the correlation between increasing antibody titres to these organisms and increasing asthma severity support the existence of a relationship between atypical infection and chronic asthma, these studies have recently been reviewed in more detail [53].

4. New-onset asthma

Given the positive findings regarding infection with atypical organisms and exacerbations of previously diagnosed asthma or chronic asthma, an interesting speculation is whether infection with these bacteria may be associated with new-onset asthma in previously healthy subjects. Regrettably, a limited number of studies have addressed this issue. Hahn et al. [12] found that 4 of 19 patients with acute *C. pneumoniae* infection subsequently developed asthma. In a 9-year study period, the same group later found 10 patients with de novo wheezing and evidence of acute infection. Five of these patients went on to develop chronic asthma [54]. Conversely, other studies on newly diagnosed asthma in both children [55] and adults [56,57] failed to identify associations with *C. pneumoniae* antibody titres.

M. pneumoniae infection has also been associated with initial onset of bronchial asthma in some studies [58]. In a recent study, 50% of 51 children had evidence of *M. pneumoniae* infection at the time of their first asthma attack [22].

Current evidence is insufficient to support or refute the role of atypical pathogens in new-onset asthma [53].

5. Biological basis for the involvement of atypical pathogens in asthma and chronic airway inflammation

Serologic evidence for increased atypical bacterial infections in asthma has been increasing steadily for 15 years and has been more recently supported by increased detection of the organisms themselves, mostly with molecular methods. A biologic basis for increased susceptibility to atypical bacterial infections however, is only just beginning to emerge. Studies in mouse models of *C. pneumoniae* pneumonitis revealed dramatically increased pathology in IFN-γR–/– mice [59] and more recently it has been shown that IFN-γ secretion by bone-marrow-derived macrophages controls infection and importantly, that this is IFN-βα dependent [60,61]. The recent discovery of the type III (λ) IFNs and the realisation that they have almost identical properties in innate immunity to the type I (αβ) IFNs, coupled with the demonstration that individuals with asthma have deficient type III

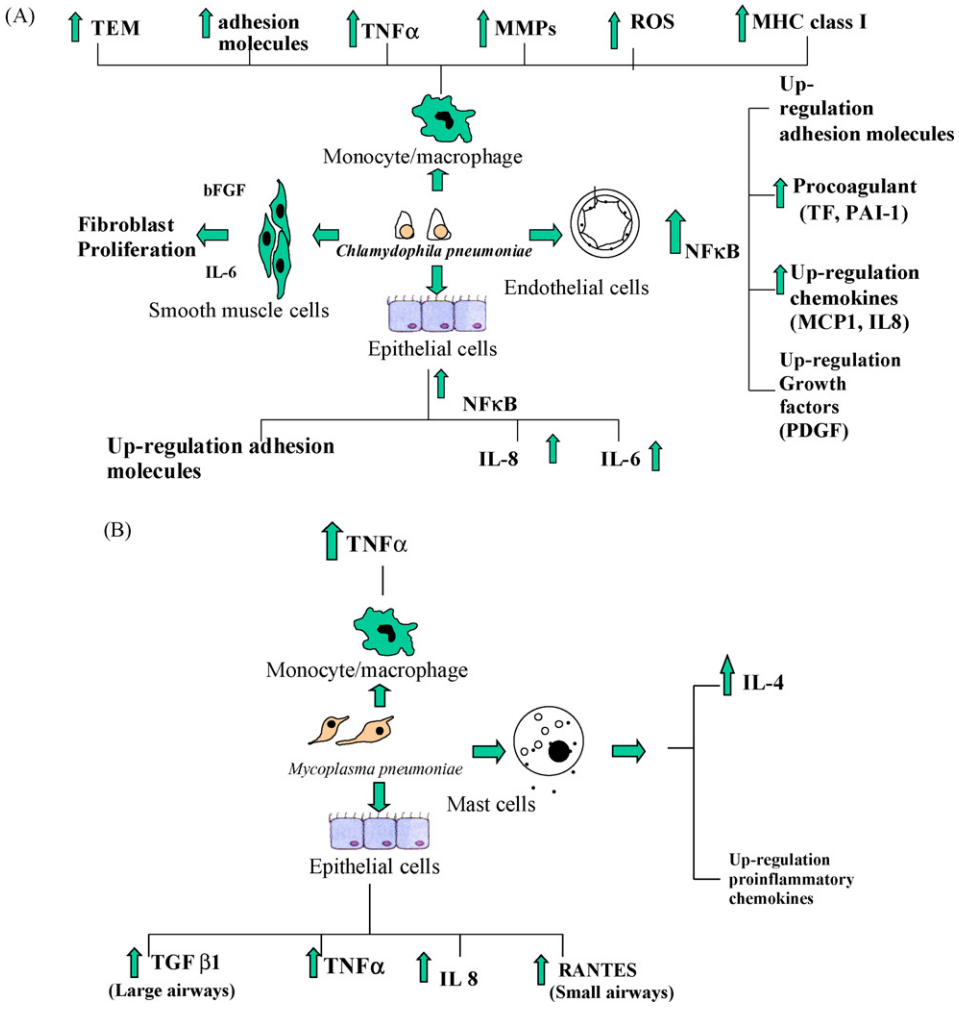

Fig. 1. Interactions between *Chlamydophila pneumoniae* (A) and *Mycoplasma pneumoniae* (B) and different cell types present in the airways. TEM = transendothelial migration; MMPs = matrix metalloproteinases; NF = nuclear factor; MCP = monocyte chemotactic protein; BFG = basic fibroblast growth factor; TF = tissue factor; PAI 1 = plasminogen activator inhibitor 1; TNF-α = tumour necrosis factor-α; MCP = monocyte chemotactic protein; TGF-β1 = transforming growth factor-β1; RANTES = regulated upon activition normal T cell expressed and secreted.

IFN production in macrophages in response to both viral and bacterial stimuli [11], provides an important likely explanation for increased susceptibility to atypical bacterial infection in asthma. Further study to determine whether macrophages from individuals with asthma also have deficient type I IFN production in response to bacterial stimuli, and to determine whether type III IFNs are also important in host defence against *C. pneumoniae* infections, and both type I and type III IFNs against *M. pneumoniae*, will be required to confirm this theory.

There is thus increasing evidence for increased frequency/persistence of atypical bacterial infections in asthma and recent evidence provides a rational biological basis for this increased susceptibility. It is therefore important to understand the consequences of both more severe acute and of chronic atypical bacterial infections on both airway inflammation and airway remodelling in asthma. Investigation in this field has so far concentrated mainly on *C. pneumoniae*, whereas less information is available for *M. pneumoniae*. The mechanisms regulating the possible role of atypical pathogens in causing acute or sustaining persistent airway inflammation have recently been reviewed [53,62]. Both *C. pneumoniae* and *M. pneumoniae* infection may participate in the pathogenesis of asthma at different levels of the airways by interacting with numerous cellular elements within the lung (mast cells, epithelium, endothelium, macrophages, smooth muscle). Fig. 1 summarises currently known interactions between *C. pneumoniae* and *M. pneumoniae* and different cell types present in the airways.

6. Use of antibiotics in asthma patients with atypical bacterial infection

The evidence described above presents an increasingly strong case for a role for atypical bacterial infection in asthma

patients, both as a contributing cause of exacerbations and in sustaining or increasing the severity of chronic asthma. Eradication of atypical bacteria from the airways could therefore become an important aspect of asthma treatment. In addition to providing important evidence regarding asthma treatment, trials testing the clinical efficacy of antimicrobial therapy active against *C. pneumoniae* and *M. pneumoniae* in asthma patients would also provide further evidence for the role of atypical bacterial infection in this disease.

Antibiotics exerting activity against atypical bacteria, such as macrolides (including the azalide azithromycin), the ketolide telithromycin, tetracyclines and fluoroquinolones would be logical candidate drugs. To date, clinical trials in asthma have mostly employed macrolides and ketolides due to their favourable tolerability/safety profile and excellent intracellular accumulation characteristics. Most studies have been in chronic stable asthma, while a single recent study has also examined efficacy in acute asthma exacerbations.

6.1. Chronic stable asthma

Hahn treated 46 asthmatic patients seropositive for *C. pneumoniae* with doxycycline, azithromycin or erythromycin for a median period of 4 weeks [63]. Mean FEV_1 increased 12.5% after treatment. However, the study had no placebo group, and subjects received a wide variety of additional medications at varying doses, thus decreasing the validity of these results. Black et al. [64] performed a multicentre, randomized, double-blind, placebo-controlled trial that studied the effect of 6 weeks treatment with roxithromycin (150 mg twice daily) in subjects with asthma and serological evidence of *C. pneumoniae* infection. Follow-up was continued for 6 months following treatment interruption. The authors observed significant improvement in evening PEF values at the end of treatment, but the difference between the groups diminished thereafter. It has been suggested that reinfection after cessation of treatment resulted in the loss of benefit during follow-up or that suppression, rather than eradication, of *C. pneumoniae* was obtained during the treatment phase [33].

A Cochrane review of macrolide usage in chronic asthma has been performed [65]. Ninety-five candidate studies were initially identified, but due to the entry criteria employed (randomised placebo-controlled study of macrolide therapy of >4 weeks duration) only five studies (for a total of 357 patients) were eventually included in the meta-analysis. The authors found an overall positive effect on symptoms and eosinophilic markers of inflammation following macrolide therapy in asthma patients.

A further trial not included in the above meta-analysis studied 55 patients with chronic, stable asthma treated with clarithromycin 500 twice a day, or placebo for 6 weeks [66]. In patients with PCR-positivity for *M. pneumoniae* or *C. pneumoniae*, macrolide treatment improved FEV_1 and reduced airway tissue expression of IL-5. Similar improvements were not observed in those receiving placebo, or in those receiving macrolide therapy but without evidence of infection, suggesting that the treatment effect was related to antimicrobial, not anti-inflammatory activity. *Mycoplasma* and *Chlamydia* organisms were still present in the airways of seven asthmatic subjects after treatment with clarithromycin, and two subjects had positive PCR findings after treatment only. The authors suggested that macrolides, being bacteriostatic, had difficulty in eradicating these organisms and, moreover, that this difficulty may result in a chronic state of infection/colonisation. Experimental evidence for this suggestion may be derived from a study by Kutlin et al. [67] testing prolonged treatment with azithromycin, clarithromycin or levofloxacin on *C. pneumoniae* in a continuous-infection model. They observed that 30-day treatment with these agents at concentrations comparable to those achieved in the epithelial lining fluid reduced but did not eliminate *C. pneumoniae* in continuously infected HEp-2 cells. These data suggest that the dosage and duration of antibiotic therapy currently being used may not be sufficient to eradicate a putative chronic *C. pneumoniae* infection.

Recently, in a further study also not included in the meta-analysis, 45 adult patients with mild/moderate asthma were treated one 600-mg azithromycin tablet daily for 3 consecutive days, followed by 600 mg weekly for an additional 5 weeks or placebo. Treatment with azithromycin resulted in improved asthma symptom scores over a 3-month post-treatment follow-up period, using a non-validated score measuring symptoms and daily activities on a 5-point scale [68]. Positive IgA (but not IgG) to *C. pneumoniae* at baseline was associated with more severe asthma symptoms during follow-up, but treatment groups were too small to determine whether treatment effects were restricted to those with evidence of infection.

Finally, in the only study in children, and also not in the meta-analysis, Esposito et al. [69] studied 352 children, aged 1–4 years, with recurrent LRTIs, including wheezing and acute bronchitis. Patients were randomised to receive azithromycin (10 mg/kg/day for 3 days weekly, for 3 weeks) together with symptom-specific agents or symptom-specific agents alone. In the first month, clinical success was significantly more frequent among the patients who had received azithromycin and this difference was significant only for the group of patients with serology and/or PCR evidence of atypical bacterial infections in nasopharyngeal specimens, however, this study was not placebo controlled and may therefore be subject to bias.

6.2. Acute asthma exacerbations

A multicentre, double-blind, randomised, placebo-controlled clinical study assessed the efficacy of oral telithromycin 800 mg once daily for 10 days as a supplement to standard of care treatment for adult patients with acute exacerbations of asthma. Assessment of *C. pneumoniae* and/or *M. pneumoniae* infection by culture, serology and PCR was included [70]. Compared with placebo, telithromycin-treated patients had clinically relevant and

significantly greater reductions in asthma symptoms over the treatment period, larger improvements from baseline to the end of treatment in all PFTs, including FEV_1, a faster median time to 50% reduction in symptom severity (5 days versus 8 days), and a greater proportion of completely symptom-free days during the treatment period (16% versus 8%). This study demonstrated statistically significant and clinically substantial benefits associated with ketolide antibiotic treatment in acute exacerbations of asthma. In this population 61% of patients had evidence of *C. pneumoniae* and/or *M. pneumoniae* infection and the effect of telithromycin on FEV_1 was statistically significant in patients with documented infection at baseline and not in those patients without evidence of infection. However, the magnitudes of treatment effects on FEV_1 were similar in the infection-positive and -negative groups, and the lack of statistical significance in the latter could simply relate to the smaller numbers of patients in that group. Further, there were no differences between infection-positive and -negative groups in terms of the other study outcomes, so that the mechanisms of benefit remain unclear.

7. Limits of current studies and suggestions for further trials

The main limits of the studies reported in the literature are related to patient population size, severity of asthma studied and atypical bacterial diagnostic tests applied. In general most studies studied mild/moderate asthma and treatment effects that were observed were small. No study was designed and powered for subgroup analyses (infected versus non-infected, steroid versus non-steroid treatment, severe versus mild asthma, etc.) and this approach has limited usefulness of the results obtained and has hampered interpretation of the studies.

The most important issue is probably related to the definition of 'infected asthmatics', as logic suggests and some studies have indicated [66,69] that treatment effects are likely to be greatest/only observed in those who are infected with atypical bacteria at the time treatment is given. Serology may be useful retrospectively in defining acute infection if good paired serum samples are available, however, it will clearly not be useful in making acute treatment decisions unless decisions can be made on a single acute sample. The TELICAST study suggested a single estimation of IgM [70] may be useful, but further studies are clearly required to confirm this. Serology certainly has a lower specificity and sensitivity when applied to chronic infection, as most adults have been previously exposed and high IgG levels are therefore a poor indication of current bacterial presence. It is possible though, that IgA may prove a more useful assessment than IgG [68]. Molecular biology techniques are more specific and sensitive but should be used on the right sample. Applying a PCR on sputum is probably better than using a pharyngeal swab specimen in acute infection/reactivation, but obtaining good-quality samples is difficult [70], and sputum contains PCR inhibitors, so appropriate processing is required. Sputum PCR has not yet been studied in the context of chronic infection. PCR of peripheral blood mononuclear cells is so far the best biological approach for detection of chronic infection, but this method does not confirm the site of infection. In addition, molecular methods are not standardised and a great deal of further work is required before they could be considered clinically useful.

It is also important to define the most sensitive endpoints when studying asthma outcomes. In-clinic pulmonary function tests [64,66] and patient-reported symptom scores [68] are outcomes that have proven useful in placebo-controlled studies of chronic asthma to date, quality of life and use of rescue therapy may also be useful, but there are insufficient data to determine which of these outcomes is the most sensitive to change. Exacerbation frequency is also an important clinical outcome that has not been studied in chronic asthma. In terms of acute exacerbations studies, again in-clinic pulmonary function tests and patient-reported symptom scores are the only outcomes that have proven useful in the only placebo-controlled study reported to date [70]. No data are published on the use of quality of life questionnaires during acute asthma, but this may be a new important end point for future studies.

There is a clear and urgent need for further studies investigating the role of therapy directed against atypical bacterial infections in both acute and chronic stable asthma, these studies must be well-designed randomised placebo-controlled studies. Most studies in stable asthma to date have studied mild/moderate asthma. Given the potential risks of generation of resistance when using long-term antibiotic therapy, and the potential benefits in terms of response to currently available therapies and the potential for relief of burden of disease, we believe studies in moderate/severe asthma are warranted.

In addition, the known anti-inflammatory activity of macrolides and ketolides can hamper the evaluation of the 'antibacterial' activity of these drugs, thus studies need to be large and adequately powered for subgroup analyses of 'infected' versus 'non-infected' subjects. Methodologies to define infection need to be as comprehensive as possible, and preferably should use both newer serological techniques including IgM and perhaps IgA, as well as molecular techniques, preferably on respiratory samples. Studies in both acute exacerbations of asthma and in chronic stable asthma need to be performed in both children and adults.

8. Conclusions

A growing body of clinical evidence indicates that atypical pathogens such as *C. pneumoniae* and *M. pneumoniae* may contribute to the pathogenesis of both acute exacerbations of asthma and chronic stable asthma. It is also likely that chronic persistent infection with and/or frequent reactivation of these agents may contribute to ongoing inflammation in

the airways and possibly therefore to long-term remodelling. However, definitive demonstration of a causal association between atypical bacterial infection and asthma is still lacking. It may be that some patients with asthma (particularly in the setting of impaired innate immune responses) are more prone to infection with these agents, and the increased burden of infection may contribute to disease severity and progression. In vitro studies have identified a number of mechanisms associated with chronic *C. pneumoniae* and *M. pneumoniae* atypical bacterial infection that may contribute to maintaining chronic airway inflammation. Both bacterial elements activate transcription factors, thus priming most cellular elements in bronchial tissue (epithelium, endothelium, monocytes/macrophages, smooth muscle cells), resulting in a cascade of cytokine release and adhesion molecule up-regulation, which favours cellular influx into the airways, persistent inflammation, and airway remodelling.

Evidence has accumulated indicating that macrolide antibiotics as a class may exert properties that promote and sustain reparative processes in chronically inflamed airways. These properties, distinct from antimicrobial activity, have been termed 'anti-inflammatory'. Anti-inflammatory effects are manifested at lower doses and usually after several weeks of treatment. Several animal inflammation models, in vitro studies using human cell cultures, and clinical studies have better defined the possible mechanisms through which macrolides exert anti-inflammatory activities, although large-scale, double-blind, randomised studies are needed to define the true clinical impact of this down-regulation of host inflammatory responses.

Treatment trials have been instituted to test whether including specific antibiotic classes targeted towards atypical bacteria would be associated with better clinical outcomes compared to standard medication for asthma. Ideally, both short-term indicators (e.g. recovery from an exacerbation) and long-term indicators (number of exacerbations, progression of disease) should be followed. Data from the limited number of studies carried out so far indicate that treatment with macrolides is associated with some benefit in both clinical and functional terms, although perhaps only in patients with documented atypical infection and provided that treatment be prolonged for several weeks. A key question is whether even prolonged antibiotic treatment is capable of truly eradicating *C. pneumoniae* and *M. pneumoniae* or rather simply temporarily suppresses the infection, which is then refuelled by long-standing reservoirs. The single study in acute exacerbations with a ketolide antibiotic also showed clear benefit, and further studies with macrolides and ketolide antibiotics in acute asthma exacerbations are required.

In summary, should additional research confirm preliminary results, therapeutic decisions regarding asthma patients will in the future include the potential addition of antimicrobial agents. Clearly, a better definition of patient subsets most likely to benefit from this treatment, optimal agents, timing and duration of therapy are essential before antimicrobial treatment may be recommended outside clinical research trials.

References

[1] Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 1995;310:1225–9.

[2] Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. BMJ 1993;307:982–6.

[3] Wahlstrom R, Hummers-Pradier E, Lundborg CS, et al. Variations in asthma treatment in five European countries: judgement analysis of case simulations. Fam Pract 2002;19:452–60.

[4] Glauber JH, Fuhlbrigge AL, Finkelstein JA, et al. Relationship between asthma medication and antibiotic use. Chest 2001;120:1485–92.

[5] National Asthma Education and Prevention Program. Use of antibiotics to treat asthma exacerbations. J Allergy Clin Immunol 2002;110:S180–3.

[6] Graham VA, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. Lancet 1982;1:418–20.

[7] Shapiro GG, Eggleston PA, Pierson WE, et al. Double-blind study of the effectiveness of a broad spectrum antibiotic in status asthmaticus. Paediatrics 1974;53:867–72.

[8] Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. Lancet 2002;359:831–4.

[9] Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med 2005;352:2082–90.

[10] Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005;201:937–47.

[11] Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med 2006;12:1023–6.

[12] Hahn DL, Dodge RW, Golubjatnikov R. Association of *Chlamydia pneumoniae* (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. JAMA 1991;266:225–30.

[13] Hammerschlag MR. *Mycoplasma pneumoniae* infections. Curr Opin Infect Dis 2001;14:181–6.

[14] Waites KB, Talkington DF. *Mycoplasma pneumoniae* and its role as a human pathogen. Clin Microbiol Rev 2004;17:697–728.

[15] Dowell SF, Peeling RW, Boman J, et al. Standardizing *Chlamydia pneumoniae* assays: recommendations from the Centers for Disease Control and Prevention (USA) and the Laboratory Centre for Disease Control (Canada). Clin Infect Dis 2001;33:492–503.

[16] Kuo CC, Jackson LA, Campbell LA, Grayston JT. *Chlamydia pneumoniae* (TWAR). Clin Micro Rev 1995;8:451–61.

[17] Emre U, Roblin PM, Gelling M, et al. The association of *Chlamydia pneumoniae* infection and reactive airway disease in children. Arch Pediatr Adolesc Med 1994;148:727–32.

[18] Cunningham AF, Johnston SL, Julious SA, et al. Chronic *Chlamydia pneumoniae* infection and asthma exacerbations in children. Eur Respir J 1998;11:345–9.

[19] Freymuth F, Vabret A, Brouard J, et al. Detection of viral, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections in exacerbations of asthma in children. J Clin Virol 1999;13:131–9.

[20] Esposito S, Blasi F, Arosio C, et al. Importance of acute *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections in children with wheezing. Eur Respir J 2000;16:1142–6.

[21] Thumerelle C, Deschildre A, Bouquillon C, et al. Role of viruses and atypical bacteria in exacerbations of asthma in hospitalized children: a prospective study in the Nord-Pas de Calais region (France). Pediatr Pulmonol 2003;35:75–82.

[22] Biscardi S, Lorrot M, Marc E, et al. *Mycoplasma pneumoniae* and asthma in children. Clin Infect Dis 2004;38:1341–6.

[23] Seggev JS, Lis I, Simantov R, et al. *Mycoplasma pneumoniae* is a frequent cause of exacerbation of bronchial asthma in adults. Ann Allergy 1986;57:263–5.
[24] Allegra L, Blasi F, Centanni S, et al. Acute exacerbations of asthma in adults: role of *Chlamydia pneumoniae* infection. Eur Respir J 1994;7:2165–8.
[25] Cook PJ, Davies P, Tunnicliffe W, et al. *Chlamydia pneumoniae* and asthma. Thorax 1998;53:254–9.
[26] Miyashita N, Kubota Y, Nakajima M, et al. *Chlamydia pneumoniae* and exacerbations of asthma in adults. Ann Allergy Asthma Immunol 1998;80:405–9.
[27] Wark PA, Johnston SL, Simpson JL, et al. *Chlamydia pneumoniae* immunoglobulin A reactivation and airway inflammation in acute asthma. Eur Respir J 2002;20:834–40.
[28] Betsou F, Sueur JM, Orfilla J. Anti-*Chlamydia pneumoniae* heat shock protein 10 antibodies in asthmatic adults. FEMS Immunol Med Microbiol 2003;35:107–11.
[29] Lieberman D, Lieberman D, Printz S, et al. Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. Am J Respir Crit Care Med 2003;167:406–10.
[30] Meloni F, Paschetto E, Mangiarotti P, et al. Acute *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections in community-acquired pneumonia and exacerbations of COPD or asthma: therapeutic considerations. J Chemother 2004;16:70–6.
[31] Green RM, Custovic A, Sanderson G, et al. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. BMJ 2002;324:763.
[32] von Hertzen LC. Role of persistent infection in the control and severity of asthma: focus on *Chlamydia pneumoniae*. Eur Respir J 2002;19:546–56.
[33] Martin RJ, Kraft M, Chu HW, et al. A link between chronic asthma and chronic infection. J Allergy Clin Immunol 2001;107:595–601.
[34] Lemanske Jr RF. Is asthma an infectious disease? Chest 2003;123(Suppl 3):385S–90S.
[35] Gil JC, Cedillo RL, Mayagoitia BG, Paz MD. Isolation of *Mycoplasma pneumoniae* from asthmatic patients. Ann Allergy 1993;70:23–5.
[36] Emre U, Sokolovskaya N, Roblin PM, et al. Detection of anti-*Chlamydia pneumoniae* IgE in children with reactive airway disease. J Infect Dis 1995;172:265–7.
[37] Webley WC, Salva PS, Andrzejewski C, et al. The bronchial lavage of pediatric patients with asthma contains infectious *Chlamydia*. Am J Respir Crit Care Med 2005;171:1083–8.
[38] Mills GD, Lindeman JA, Fawcett JP, et al. *Chlamydia pneumoniae* serological status is not associated with asthma in children or young adults. Int J Epidemiol 2000;29:280–4.
[39] Hahn DL, Golubjatnikov R. Asthma and chlamydial infection: a case series. J Fam Pract 1994;38:589–95.
[40] Bjornsson E, Hjelm E, Janson C, et al. Serology of *Chlamydia* in relation to asthma and bronchial hyperresponsiveness. Scand J Infect Dis 1996;28:63–9.
[41] Hahn DL, Peeling RW, Dillon E, et al. Serologic markers for *Chlamydia pneumoniae* in asthma. Ann Allergy Asthma Immunol 2000;84:227–33.
[42] Biscione GL, Corne J, Chauhan AJ, Johnston SL. Increased frequency of detection of *Chlamydophila pneumoniae* in asthma. Eur Respir J 2004;24:745–9.
[43] Sävykoski T, Harju T, Paldanius M, et al. *Chlamydia pneumoniae* infection and inflammation in adults with asthma. Respiration 2004;71:120–5.
[44] Kraft M, Cassell GH, Henson JE, et al. Detection of *Mycoplasma pneumoniae* in the airway of adults with chronic asthma. Am J Respir Crit Care Med 1998;158:998–1001.
[45] Tuuminen T, Edelstein I, Punin A, et al. Use of quantitative and objective enzyme immunoassays to investigate the possible association between *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* antibodies and asthma. Clin Microbiol Infect 2004;10:345–8.
[46] von Hertzen L, Töyrylä M, Gimishanov A, et al. Asthma, atopy and *Chlamydia pneumoniae* antibodies in adults. Clin Exp Allergy 1999;29:522–8.
[47] Gencay M, Rüdiger JJ, Tamm M, et al. Increased frequency of *Chlamydia pneumoniae* antibodies in patients with asthma. Am J Respir Crit Care Med 2001;163:1097–100.
[48] Huittinen T, Hahn D, Anttila T, et al. Host immune response to *Chlamydia pneumoniae* heat shock protein 60 is associated with asthma. Eur Respir J 2001;17:1078–82.
[49] Falck G, Gnarpe J, Hansson L-O, et al. Comparison of individuals with and without specific IgA antibodies to *Chlamydia pneumoniae*. Respiratory morbidity and the metabolic syndrome. Chest 2002;122:1587–93.
[50] Foschino Barbaro MP, Resta O, Aliani M, et al. Seroprevalence of chronic *Chlamydia pneumoniae* infection in patients affected by chronic stable asthma. Clin Microbiol Infect 2002;8:358–62.
[51] von Hertzen L, Vasankari T, Liippo K, et al. *Chlamydia pneumoniae* and severity of asthma. Scand J Infect Dis 2002;34:22–7.
[52] Black PN, Scicchitano R, Jenkins CR, et al. Serological evidence of infection with *Chlamydia pneumoniae* is related to the severity of asthma. Eur Respir J 2000;15:254–9.
[53] Johnston SL, Martin RJ. *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*: a role in asthma pathogenesis? Am J Respir Crit Care Med 2005;172:1078–89.
[54] Hahn DL, McDonald R. Can acute *Chlamydia pneumoniae* respiratory tract infection initiate chronic asthma? Ann Allergy Asthma Immunol 1998;81:339–44.
[55] Korppi M, Paldanius M, Hyvarinen A, et al. *Chlamydia pneumoniae* and newly diagnosed asthma: a case-control study in 1 to 6-year-old children. Respirology 2004;9:255–9.
[56] Larsen FO, Norn S, Mordhorst CH, et al. *Chlamydia pneumoniae* and possible relationship to asthma. Serum immunoglobulins and histamine release in patients and controls. APMIS 1998;106:928–34.
[57] Routes JM, Nelson HS, Noda JA, Simon FT. Lack of correlation between *Chlamydia pneumoniae* antibody titers and adult-onset asthma. J Allergy Clin Immunol 2000;105:391–2.
[58] Yano T, Ichikawa Y, Komatu S, et al. Association of *Mycoplasma pneumoniae* antigen with initial onset of bronchial asthma. Am J Respir Crit Care Med 1994;149:1348–53.
[59] Rottenberg ME, Gigliotti Rothfuchs AC, Gigliotti D, et al. Role of innate and adaptive immunity in the outcome of primary infection with *Chlamydia pneumoniae*, as analyzed in genetically modified mice. J Immunol 1999;162:2829–36.
[60] Rothfuchs AG, Gigliotti D, Palmblad K, et al. IFN-alpha beta-dependent. IFN-gamma secretion by bone marrow-derived macrophages controls an intracellular bacterial infection. J Immunol 2001;167:6453–61.
[61] Rothfuchs AG, Trumstedt C, Mattei F, Schiavoni G, et al. STAT1 regulates IFN-alpha beta- and IFN-gamma-dependent control of infection with *Chlamydia pneumoniae* by nonhemopoietic cells. J Immunol 2006;176:6982–90.
[62] Blasi F, Cosentini R, Tarsia P, Allegra L. Potential role of antibiotics in the treatment of asthma. Curr Drug Targets Inflamm Allergy 2004;3:237–42.
[63] Hahn DL. Treatment of *Chlamydia pneumoniae* infection in adult asthma: a before–after trial. J Fam Pract 1995;41:345–51.
[64] Black PN, Blasi F, Jenkins CR, et al. Trial of roxithromycin in subjects with asthma and serological evidence of infection with *Chlamydia pneumoniae*. Am J Respir Crit Care Med 2001;164:536–41.
[65] Richeldi L, Ferrara G, Fabbri LM, Gibson PG. Macrolides for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford, UK: Update Software; 2003.
[66] Kraft M, Cassell GH, Pak J, Martin RJ. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: effect of clarithromycin. Chest 2002;121:1782–8.

[67] Kutlin A, Roblin PM, Hammerschlag MR. Effect of prolonged treatment with azithromycin, clarithromycin, or levofloxacin on *Chlamydia pneumoniae* in a continuous-infection model. Antimicrob Agents Chemother 2002;46:409–12.

[68] Hahn DL, Plane MB, Mahdi OS, Byrne GI. Secondary outcomes of a pilot randomized trial of azithromycin treatment of asthma. PLoS Clin Trials 2006;1:e11. doi:10.1371/journal.pctr.0010011.

[69] Esposito S, Bosis S, Faelli N, et al. Role of atypical bacteria and azithromycin therapy for children with recurrent respiratory tract infections. Pediatr Infect Dis J 2005;24:438–44.

[70] Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. The effect of telithromycin in acute exacerbations of asthma: the TELICAST study. N Engl J Med 2006;354:1589–600.