REVIEW

Mycoplasma pneumoniae and its role in asthma

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Mycoplasma pneumoniae (*M pneumoniae*), primarily recognised as a causative agent of community-acquired pneumonia has recently been linked to asthma. An infection with *M pneumoniae* may precede the onset of asthma or exacerbate asthma symptoms. Chronic infection with *M pneumoniae* has been suspected to play a part in some patients with asthma. The role of immunoglobulin E-related hypersensitivity and induction of T helper type 2 immune response leading to inflammatory response in *M pneumoniae*-infected patients with asthma have also been proposed. Use of macrolides in reducing asthma symptoms only in *M pneumoniae*-infected patients supports the use of macrolides in patients with asthma having *M pneumoniae* infection. As macrolides are both antimicrobial and anti-inflammatory drugs, the therapeutic role of their biphasic nature in reducing asthma symptoms needs further attention in clinical research.

Asthma is defined as a chronic inflammatory disease of airways characterised by airways hyper-responsiveness to a multiplicity of stimuli, reversible airway limitation and chronic eosinophilic infiltration of the airways.[1] The pathogenesis of asthma seems to be the result of a complex mixture of genetic and environmental influences. The role of respiratory tract infections in the pathogenesis of asthma is well established. Several viruses have been implicated in the exacerbation of asthma. Also, in childhood, certain viral infections have been thought to be responsible for the inception of asthma.[2] Respiratory viral infections caused by rhinoviruses, coronaviruses, influenza, parainfluenza and respiratory syncytial viruses (RSVs) are important triggers of asthma episodes.[3] By using polymerase chain reaction (PCR) and culture, viruses were detected in 80% of episodes of wheeze or reduced peak flow in 9–11-year-olds with asthma. Rhinoviruses accounted for 61% of the viruses detected, coronaviruses 16%, influenza 9%, parainfluenza 9% and RSV 5%. RSV infection, although detected in only 5% of asthma episodes is known to be a potent cause of wheezing, particularly in infancy,[3] although much is still unknown about the mechanisms involved and why some pathogens are more potent inducers of wheeze than others.

Recently, the role of atypical pathogens—*Chlamydia pneumoniae* (*C pneumoniae*) and *Mycoplasma pneumoniae* (*M pneumoniae*) in asthma has become an active area of investigation.[4] Serological studies in adults with asthma suggest a possible role for *C pneumoniae* in the pathogenesis of severe asthma.[5] A recent report evaluated a group of adults with chronic asthma by serology, multiple airways culture and PCR specific for *C pneumoniae*. Of the 55 patients with asthma evaluated, 7 were positive for PCR and 18 had positive serological results.[6]

M pneumoniae, primarily recognised as a causative agent of community-acquired pneumonia has recently been linked to asthma in various ways: an infection with the organism may precede the onset of asthma, exacerbate asthma or make control more difficult.[4] The growing importance of these pathogens remains ill understood and undefined because of the lack of awareness and the lack of rapid and specific diagnostic techniques. The existing data are not conclusive, but suggestive enough to drive studies evaluating them as possible mechanisms in the pathogenesis of asthma. This review looks at the current literature on the role of *M pneumoniae* in bronchial asthma.

M pneumoniae in exacerbation of asthma

M pneumoniae has been suspected as a factor for the exacerbation of asthma for a long time. The first prospective study that directly relates viral and mycoplasmal infection to recurrent episodes of wheezing in children with asthma has been reported by Berkovich *et al*[7] in 1970. Serological evidence of infection with either *M pneumoniae* and respiratory virus was detected in 27 of 84 (32%) patients. Huhti *et al*[8] reported 63 patients after severe episodes of acute asthma, of which 19% had associated viral or mycoplasma infections. In another series of 95 adults with bronchial asthma, 20 (21%) had evidence of recent mycoplasmal infection during exacerbation of disease.[9] These figures were further supported by various recent studies. In a serologically based prospective study by Lieberman *et al*,[10] 18% of patients hospitalised for an acute exacerbation of bronchial asthma, were found to have acute infection with *M pneumoniae*. In another study by Biscardi *et al*,[11] 20% (24/119) of the patients with previously diagnosed asthma were found to have acute *M pneumoniae* infection during the current exacerbation. Of the 51 patients experiencing their first episode, acute *M pneumoniae* was proved in 26 (50%) of the patients.[11] In other series, serological evidence of *M pneumoniae* was found in 3.3–15% patients hospitalised for an acute exacerbation of asthma.[12 13] Therefore, from the current literature, it seems that *M pneumoniae* is an important trigger for the acute exacerbation of asthma, accounting for 3.3–50% of exacerbations.

Abbreviations: BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; RSV, respiratory syncytial virus

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M pneumoniae: role in initial onset

Although mycoplasmal airways infection often exacerbates bronchial asthma, the cause of the initial onset of asthma remains unclear. It has been hypothesised that early life community-acquired pneumonia caused by *M pneumoniae* is associated with increased asthma prevalence. Yano *et al*[14] in 1994, for the first time described a patient in whom previous acute mycoplasmal respiratory infection led to initial onset of bronchial asthma. The patient had an immediate positive skin test for *M pneumoniae* antigen and showed the presence of immunoglobulin (Ig)E antibody specific for *M pneumoniae* antigen in serum. Further, a bronchial inhalation challenge test with partially purified *M pneumoniae* antigen was found positive.

In a follow-up study by Mok *et al*,[15] of 50 children with *M pneumoniae* respiratory illness, five developed clinical signs of asthma. All five, however, had a family and personal history of atopy. Therefore, in children with an atopic constitution, such infections may trigger allergic sensitisation.[16] In a study by Sutherland *et al*,[17] 35 patients with a history of community-acquired pneumonia were evaluated by questionnaire 7–9 years after episodes of pneumonia. Patients with a history of atypical pneumonia showed increased asthma prevalence.[17] Current and past asthma prevalence was 55% in patients with atypical bacteria. There have been reports of patients presenting with acute infection by *M pneumoniae*, followed by development of asthma and marked improvement in lung function and asthma symptoms with antimicrobial treatment directed against these organisms.[14] It seems that acute infection with *M pneumoniae* can initiate asthma in some previously asymptomatic patients; however, for a quantitative role of these bacteria as asthma initiators, additional information should be acquired before definitive conclusions can be drawn.

Chronic infection and asthma

Chronic *M pneumoniae* respiratory infections have been hypothesised to play a part in asthma. In humans, *M pneumoniae* is reported to commonly be detectable by culture of the respiratory tract up to several months after recovery from acute pneumonia. Even after treatment with effective antibiotics, *M pneumoniae* can still be cultured from respiratory secretions. Pulmonary structural abnormalities suggestive of small airways obstruction were observed 1–2 years after pneumonia due to *M pneumoniae*, with considerably increased frequency as compared with controls.[18] Persistence of infection with this organism results in decreased expiratory flow rates and increased airways hyper-responsiveness in individuals without asthma.[19] A possible mechanism is that the organism is difficult to eradicate, as macrolides are bacteriostatic, which results in the chronic state of infection.[20]

Mok *et al*,[15] also showed an impairment in pulmonary function in 50 children with a history of *M pneumoniae* respiratory tract infection. The maximum expiratory flow at 50% of vital capacity was markedly reduced in the group who had a history of *M pneumoniae* infection and did not change with inhalation of a helium oxygen mixture, suggesting small airways obstruction. These tests were performed from 1.5 to 9.5 years after the infection, suggesting that *M pneumoniae* infection may impair pulmonary function despite lack of symptoms and underlying lung disease.

To study the potential of *M pneumoniae* to establish chronic respiratory infections with associated pulmonary disease, a murine model was investigated.[18] BALB-C mice were intranasally inoculated with *M pneumoniae. M pneumoniae* was detected in bronchoalveolar lavage (BAL) in 70% and 22% of mice at 109 and 530 days after inoculation, respectively. At 530 days, 78% of the mice inoculated with *M pneumoniae* showed abnormal histopathology characterised by peribronchial and perivascular mononuclear infiltrates. Serum anti-*M pneumoniae* IgG was detected in all the mice inoculated with *M pneumoniae* and was inversely correlated to the histopathology score 530 days after inoculation. Noticeably increased airways methacholine reactivity in *M pneumoniae*-inoculated mice was observed as compared with controls at 245 days, and increased airways obstruction at 530 days. A similar mouse model of chronic respiratory infection with *Mycoplasma pulmonis*, a natural pathogen of rodents, has been previously established,[21] and it has been shown that rats chronically infected with *M pulmonis* develop lung fibrosis accompanied by changes in lung compliance. Treatment with dexamethasone was shown to reverse the chronic inflammatory airways disease induced by *M pulmonis* and to reduce the colony forming units of *M pulmonis* in the respiratory tract of rats.

Most of the studies have shown the association of *M pneumoniae* in asthma by isolation of the organism in throat swabs and serological documentation. If *M pneumoniae* is a causal factor in chronic asthma, then this organism should be present in the lungs of certain individuals with stable, chronic asthma. Recently, in a preliminary study by Kraft *et al*,[22] 18 patients with stable chronic asthma were evaluated to determine the presence of *M pneumoniae* in upper and lower airways by PCR and compared with those without asthma. *M pneumoniae* was shown in 10 of 18 patients with asthma; in 9 of the 10 patients, the organism was detected in BAL and bronchial biopsy specimens. In a further extension to this study, 55 patients with chronic stable asthma were compared with 11 normal controls using PCR. A large number of patients—that is, 25 of 55 patients, showed the presence of *M pneumoniae* in their airways, with the distinguished feature of an increased number of mast cells.[6] PCR-positive patients with asthma had increased airways expression of tumour necrosis factor α, interleukin (IL) 4 and IL5 compared with PCR-negative patients with asthma. Further treatment with clarithromycin was associated with improved lung function and with decreased levels of these cytokines only in *M pneumoniae* PCR-positive patients.[19 23]

Although the current literature is scanty, it supports the possibility that *M pneumoniae* may be present initially and persist for months in normal people and in patients with asthma, resulting in deceased pulmonary function and subsequent development of asthma in some cases. Also, studies suggest that a large number of patients with asthma continue to harbour *M pneumoniae* in their airways. This led to increased cytokine production, which may cause a continuing inflammatory response and affect asthma control. It also seems reasonable to conclude that, in patients with asthma, the airflow limitation may be much more in *M pneumoniae*-infected patients and could lead to poorer asthma control.

Pathophysiology

The pathophysiological mechanisms by which the pathogen contributes to the development of asthma-related symptoms and to the onset and exacerbation of asthma are not fully understood.

Although the interaction of mycoplasmas with respiratory epithelial cells is a critical early phase of pathogenesis, little is known about the cascade of events initiated by infection of respiratory epithelial cells by mycoplasmas. Effects of mycoplasmal infections on airways seems to be multifactorial, and involve a complex interplay of airways inflammation and IgE-mediated hypersensitivity, in addition to features of individual patients such as atopic predisposition.

Role of cytokines

The role of T lymphocytes in the pathogenesis of asthma has also been reported. It was recently shown that the release of

type 2 cytokines, including IL4 and IL5, is increased in patients with asthma, whereas the level of type 1 cytokine interferon-Y production is normal or low.[24] A type 2 cytokine profile has also been mentioned in RSV infection, and may therefore explain its association with the subsequent development of asthma. However, recent studies of RSV have shown that only IL5 seems to be essential for the development of airways hyper-responsiveness.[25 26] Children with wheezing and acute *M pneumoniae* infection have a specific cytokine profile characterised by a marked increase in serum levels of IL5.[24] *M pneumoniae*-positive patients with asthma also had increased airways expression of tumour necrosis factor α, IL4 and IL5.[23] Further, in the murine model (BALB-C mice), infection with *M pneumoniae* resulted in increased airways hyper-responsiveness. The associated lung pathology was primarily a neutrophilic infiltrate at day 3, followed by a reduction in neutrophils and an increase in macrophages by day 21. Interferon-Y, a T helper type 1 cytokine was suppressed at days 3 and 7 compared with the saline solution-treated controls, suggesting a T helper type 2 response that was associated with hyper-responsiveness.[6]

The above findings suggest that *M pneumoniae* infection may result in a T helper type 2 predominant airways disease, with hyper-responsiveness that mimics asthma in a murine model. The findings also support the relationship between IL5 secretion and infection due to *M pneumoniae*. A better understanding of the immune response is needed to understand the pathophysiological mechanisms contributing to the development of asthma.

IgE-related hypersensitivity

The immediate type of hypersensitivity to microbes has also been suggested to play a part in infectious exacerbation for bronchial asthma.[27] T helper type 2 cells produce IL4, IL5 and IL13, which promote IgE production and eosinophil function, both of which may play a part in the pathogenesis of asthma. Indeed, many studies have shown that eosinophilic inflammation associated with hypersecretion of mucus is dependent on the presence of T helper type 2 cells in the lung.[28] Tipirneni *et al*[29] detected IgE to *M pneumoniae* in 5 of 152 patients with asthma and other atopic diseases; however, the pathogenic role of mycoplasmal IgE was not discussed. There is a possibility that mycoplasmal infection led to the destruction of respiratory mucosal cells and facilitated the penetration of antigens into the mucosa; the patient become atopic to other allergens, in addition to *M pneumoniae* allergen, after this infection.[14] Laitinen *et al*,[30] suggested that such infection denuded the epithelial surface and exposed irritant receptors. As mycoplasma are antigenic and can initiate an antibody response, it is possible that IgE attach to mast cells and then interact with *M pneumoniae* antigen, which in turn stimulates histamine release to cause airway obstruction.[31] Thus, mycoplasmal infection may contribute to the recurrent episodes of wheezing by non-specifically predisposing the patient to the production of IgE, thereby predisposing it to type 1 immediate hypersensitivity asthmatic reaction. Alternatively, it is also possible that the latent mycoplasmal infection undetectable by usual methods may have contributed to the development of wheeze through specific IgE-mediated sensitisation, in addition to another possibility that mycoplasma-specific IgE could be provided with epitopes that cross-react with components of the airways.[14]

Treatment: effect of macrolides

Macrolides are well known for their antibacterial properties. However, data confirm that macrolides also possess anti-inflammatory properties that may contribute to clinical benefits observed in patients with airways inflammation.[32–35] Macrolides seems to modulate inflammatory activity by inhibiting inflammatory cell chemotaxis, cytokine synthesis, adhesion molecule expression and reactive oxygen species production.[33] The effectiveness of these drugs seems to be limited to 14-membered and 15-membered macrolides. The relative ineffectiveness of 16-membered ring macrolides compared with that of 14-membered ring molecules, despite relatively comparable antimicrobial activity, also suggest a mechanism that is unrelated to antimicrobial activity.[36]

Interest in the immunomodulatory effect of macrolides began with the observation that the use of troleandomycin as adjunctive treatment in patients with steroid-dependent asthma improved asthma symptoms, and the patients were able to discontinue concomitant treatment with oral steroids.[32] This spurred interest in the potential benefits of their long-term application in a variety of chronic pulmonary diseases—cystic fibrosis, bronchiectasis, chronic bronchitis, sinusitis, chronic obstructive pulmonary disease and diffuse panbronchiolitis.[34 35 37 38] Bronchiolitis obliterans organising pneumonia may be another disease that can benefit from such treatment.[39]

The treatment of diffuse panbronchiolitis is the most striking example of the benefits of macrolides. Before the introduction of macrolide treatment, the 10-year survival rate was reported to be 12–50%, but since the introduction of macrolide treatment, the 10-year survival rate is >90%.[32] In diffuse panbronchiolitis, the role of macrolides seems to be mainly anti-inflammatory by altering the cytokines. These advances occurred in patients where the disease had improved without eliminating bacteria, including cases where *Pseudomonas aeruginosa* was involved. In cystic fibrosis and panbronchiolitis, at least partly, macrolides act by altering the biofilm of Gram-negative organisms such as pseudomonas.[32 35 38] The benefits for community-acquired pneumonia are consistent, and higher, when a macrolide is given with another atypical agent than if the atypical agent is given alone, suggesting a non-antibacterial benefit. Repeatedly throughout the literature, macrolide-containing regimens have been associated with lower mortality and lower length of hospital stay than other types of monotherapies or combination therapies.[38]

A considerable amount of data describing additional effects associated with macrolide treatment to improve asthma symptoms has been gathered. Several reports have suggested that macrolides such as erythromycin and troleandomycin favourably affect the clinical status of patients with chronic asthma.[40 41] In a study by Miyatake *et al*,[41] 10 weeks of treatment with erythromycin was shown to markedly decrease bronchial hyper-responsiveness, as shown by the analysis of 23 patients with asthma. In another study, relatively short-tem treatments (<3 months) with oral erythromycin and roxithromycin, two macrolide antibiotics, were associated with considerable improvement in bronchial hyper-reactivity in patients with asthma.[41 42] In another study, Amasayu *et al*[43] showed, in patients with mild to moderate asthma, that 8 weeks of clarithromycin (200 mg twice daily) treatment improved asthma symptoms and decreased sputum eosinophils and serum eosinophil cationic protein. There were also modest improvements in bronchial hyper-responsiveness. Spector *et al*[40] also reported that troleandomycin, a macrolide derivative, has favourable effects on bronchial responsiveness in patients with bronchial asthma. Recently, a new immunosuppressant, FK-506, the chemical structure of which belongs to macrolides, as does erythromycin, was shown to suppress T lymphocytes.[44] Additionally, Konno *et al*[45] showed that macrolides decreased pulmonary expression of tumour necrosis factor, IL3, IL4 and IL5 in a murine model. Macrolides have also been shown to decrease mucus production and bronchial hyper-responsiveness in vitro.[42 46] Beneficial effects of these drugs are considered to be dependent on the anti-inflammatory action on airways inflammation.

There is a controversy about whether macrolides alter the metabolism of glucocorticoides or whether these effects are due to its antimicrobial property. Earlier studies have suggested possible interaction between macrolides and corticosteroids, causing increased concentration of steroids. This is unlikely in the cases reported by Garey *et al*,[47] as patients were able to discontinue prednisone entirely after long-term treatment with oral clarithromycin. In their report of three patients, two of them were able to discontinue prednisone after 12 months of clarithromycin, 500 mg twice daily. The third patient was able to taper prednisone to 5 mg twice daily. The salutary effects of clarithromycin were observed only after several weeks of continuous treatment, whereas the prednisone dose was being tapered. Also, Fost *et al*[48] recently showed that clarithromycin did not affect the pharmacokinetics of prednisone. It is also reported that these agents could also lead to a reduction in airways inflammation by decreasing the transcription of mRNA for a variety of cytokines and inhibiting IL8 release by eosinophils and therefore improving symptoms and pulmonary function. These effects are not caused by bronchodilatation, elevation of serum theophylline level or steroid sparing mechanism.[49]

Recently, a study was carried out by Kraft *et al*[19] to see the effect of clarithromycin on lung function of both *M pneumoniae*-infected and uninfected patients. They found that treatment with clarithromycin resulted in a marked improvement in forced expiratory volume in 1 s and reduced airways tissue expression of IL5, but only in *M pneumoniae*-positive patients. This improvement was not seen in patients who received clarithromycin but have negative findings for *M pneumoniae*. No change in the degree of sinus disease was shown after clarithromycin treatment; thus, it may affect airways directly. To check the effect of antibiotics on *M pneumoniae*, a mouse model was developed. In this mouse model, treatment with cethromycin greatly reduced *M pneumoniae* culture titres in BAL samples, cytokine and chemokine concentration in BAL samples, histological inflammation in the lungs and disease severity.[50]

The above findings show that macrolides could be useful in reducing airways inflammation and therefore improve symptoms and pulmonary function in *M pneumoniae*-infected patients. However, it is too early to conclude that macrolides could be useful in the treatment of occult infection in asthma because of their antimicrobial activity. Indeed, they may be useful because of their anti-inflammatory nature.

CONCLUSION

The available clinical literature supports the role of *M pneumoniae* in exacerbation and initial onset of asthma. It also suggests that the treatment of patients with asthma, who are *M pneumoniae*-positive, with macrolides reduces asthma symptoms as well. However, the exact mechanism of macrolides in reducing asthma symptoms in *M pneumoniae*-infected patients needs to be elucidated before developing any firm conclusion, as macrolides are both antibacterial and anti-inflammatory agents. Additional studies are warranted to understand the pathophysiological and therapeutic importance of these findings for a better understanding of the role of *M pneumoniae* at the cellular level.

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REFERENCES

1 **McFadden ER Jr**. Asthma. In: Fauci AS, Braunwald E, Isselbacher KJ, *et al*, eds. *Harrison's principles of internal medicine*.14th edn. New York: Mc-Graw Hill Health Professions Division, 1998.
2 **Lemanske RF**. Is asthma an infectious disease. *Chest* 2003;**123**:385S–90S.
3 **Johnston SL**. Is Chlamydia pneumoniae important in asthma? The first controlled trial of therapy leaves the question unanswered. *Am J Respir Crit Care Med* 2001;**164**:513–14.
4 **Macdowell AL**, Bacharier LB. Infectious triggers of asthma. *Immunol Allergy Clin North Am* 2005;**25**:45–66.
5 **Johnston SL**, Pattemore PK, Sanderson S, *et al*. Community study of role of viral exacerbations of asthma in 9–11 year old children. *BMJ* 1995;**310**:1225–9.
6 **Martin RJ**, Kraft M, Chu HW, *et al*. A link between chronic asthma and chronic infection. *J Allergy Clin Immunol* 2001;**107**:595–601.
7 **Berkovich S**, Millian SJ, Snyder RD. The association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. *Ann Allergy* 1970;**28**:43–9.
8 **Huhti E**, Mokka T, Nikoskelainen J, *et al*. Association of viral and mycoplasma infections with exacerbations of asthma. *Ann Allergy* 1974;**33**:145–9.
9 **Seggev JS**, Lis I, Siman-Tov R, *et al*. Mycoplasma pneumoniae is a frequent cause of exacerbation of bronchial asthma in adults. *Ann Allergy* 1986;**57**:263–5.
10 **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.
11 **Biscardi S**, Lorrot M, Marc E, *et al*. Mycoplasma pneumoniae and asthma in children. *Clin Infect Dis* 2004;**38**:1341–6.
12 **Friedek D**, Ekiel A, Szulakowski P, *et al*. Antibodies seroprevalence of Mycoplasma pneumoniae antigens in patients with bronchial asthma. *Wiad Lek* 2002;**55**:158–63.
13 **Meloni F**, Paschetto E, Mangiarotti P, *et al*. Acute Chlamydia pneumoniae and Mycoplasma pneumoniae infections in community acquired pneumonia and exacerbation of COPD or asthma; therapeutic considerations. *J Chemotherapy* 2004;**16**:70–6.
14 **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.
15 **Mok JYQ**, Waugh PR, Simpson H. Mycoplasma pneumoniae infection: a follow up study of 50 children with respiratory illness. *Arch Dis Child* 1979;**54**:506–11.
16 **Frick OL**, German DF, Milles J. Development of allergy in children, association with virus infections. *J Allergy Clin Immunol* 1979;**63**:228–41.
17 **Sutherland ER**, Brandorff JM, Martin RJ. Atypical bacteria pneumonia and asthma risk. *J Asthma* 2004;**41**:863–8.
18 **Hardy RD**, Jafri HS, Olsen K, *et al*. Mycoplasma pneumoniae induces chronic respiratory infection, airway hyperreactivity, and pulmonary inflammation: a murine model of infection-associated chronic reactive airway disease. *Infect Immun* 2002;**70**:649–54.
19 **Kraft M**, Cassell GH, Pak J, *et al*. Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. *Chest* 2002;**121**:1782–8.
20 **Luby JP**. Pneumonia caused by Mycoplasma pneumoniae. *J Infect Dis* 1991;**135**:673–722.
21 **Bowden JJ**, Schoeb TR, Lindsey JR, *et al*. Dexamethasone and oxytetracycline reverse the potentiation of neurogenic inflammation in airways of rats with Mycoplasma pulmonis infection. *Am J Respir Crit Care Med* 1994;**150**:1391–401.
22 **Kraft M**, Cassell GH, Henson JE, *et al*. Detection of Mycoplasma pneumoniae in the airways of adults with chronic asthma. *Am J Respir Crit Care Med* 1998;**158**:998–1001.
23 **Kraft M**, Cassell GH, Duffy LB, *et al*. Mycoplasma and Chlamydia are present in the airways of chronic stable asthmatics [abstract]. *Am J Respir Crit Care Med* 1999;**159**:A517.
24 **Esposito S**, Droghetti R, Bosis S, *et al*. Cytokine secretion in children with acute Mycoplasma pneumoniae infection and wheeze. *Pediatr Pulmonol* 2002;**34**:122–7.
25 **Schwarze J**, Cieslewicz G, Hamelmann E, *et al*. IL-5 and eosinophils are essential for the development of airway hyperresponsiveness following acute respiratory syncytial virus infection. *J Immunol* 1999;**162**:2997–3004.
26 **Schwarze J**, Cieslewicz G, Joetham A, *et al*. Critical roles for interleukin-4 and interleukin-5 during respiratory syncytial virus infection in the development of airway hyperresponsiveness after airway sensitization. *Am J Respir Crit Care Med* 2000;**162**:380–6.
27 **Pauwels R**, Verscharegan G, van der Stareaten M. IgE antibodies to bacteria in patients with bronchial asthma. *Allergy* 1980;**35**:665–9.
28 **Wills-Karp M**. Immunologic basis of antigen induced airwayhyperresponsiveness. *Annu Rev Immunol* 1999;**17**:255–81.
29 **Tipirneni P**, Moore BS, Hyde JS, *et al*. IgE antibodies to Mycoplasma pneumoniae in asthma and other atopic diseases. *Ann Allergy* 1980;**45**:1–7.

30 **Laitinen LA**, Elkin RB, Jacobs L, *et al*. Changes in bronchial reactivity after administration of live attenuated influenza virus. *Am Rev Respir Dis* 1976;**113**:194–8.
31 **Gil JC**, Cedillo RL, Mayagoitia BG, *et al*. Isolation of Mycoplasma pneumoniae from asthmatic patients. *Ann Allergy* 1993;**70**:23–5.
32 **Rubin BK**, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest* 2005;**125**:71S–78S.
33 **Tamaoki J**. The effects of macrolides on inflammatory cells. *Chest* 2004;**125**:41S–51S.
34 **Gotfried MH**. Macrolides for the treatment of chronic sinusitis, asthma and COPD. *Chest* 2004;**125**:52S–61S.
35 **Kudoh S**, Azuma A, Yamamoto M, *et al*. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998;**157**:1829–32.
36 **Shirai T**, Sato A, Chida K. Effect of 14-membered ring macrolide therapy on chronic respiratory tract infections and polymorphonuclear leukocyte activity. *Intern Med* 1995;**34**:469–74.
37 **Wozniak Wozniak DJ**, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on Pseudomonas aeroginosa. *Chest* 2004;**125**:62S–69S.
38 **Amsden GW**. Anti-inflammatory effects of macrolides - an unappreciated benefit in the treatment of community acquired respiratory tract infections and chronic inflammatory pulmonary conditions. *J Antimicrobial Chemotherapy* 2005;**55**:10–21.
39 **Stover DE**, Mangino D. A treatment alternative for bronchiolitis obliterans organizing pneumonia. *Chest* 2005;**128**:3611–17.
40 **Spector SL**, Katz FH, Farr RS. Troleandomycin: effectiveness in steroid-dependent asthma and bronchitis. *J Allergy Clin Immunol* 1974;**54**:367–79.
41 **Miyatake H**, Taki F, Taniguchi H, *et al*. Erythromycin reduces the severity of bronchial hyperresponsiveness in asthma [comments]. *Chest* 1991;**99**:670–3.
42 **Shimizu T**, Kato M, Mochizuki H, *et al*. Roxithromycin reduces the degree of bronchial hyperresponsiveness in children with asthma. *Chest* 1994;**106**:458–61.
43 **Amayasu H**, Yoshida S, Ebana S, *et al*. Clarithromycin suppresses bronchial hyper responsiveness associated with eosinophilic inflammation in patients with asthma. *Ann Allergy Asthma Immunol* 2000;**84**:594–8.
44 **Kino T**, Hatanaka H, Miyata S, *et al*. FK-506, a novel immunosuppressant isolated from a streptomyces. *J Antibiotics* 1987;**40**:1256–65.
45 **Konno S**, Asano K, Kurokawa M, *et al*. Antiasthmatic activity of a macrolide antibiotic, roxathriomycin: analysis of possible mechanism in vitro and in vivo. *Int Arch Allergy Immunol* 1994;**105**:308–16.
46 **Goswami SK**, Kivity S, Marom Z. Erythromycin inhibits respiratory glycoconjugate secretion from human airways in vitro. *Am Rev Respir Dis* 1990;**141**:72–8.
47 **Garey KW**, Rubinstein I, Gotfried MH, *et al*. Long term clarithromycin decreases prednisone requirements in elderly patients with prednisone dependent asthma. *Chest* 2000;**118**:1826–7.
48 **Fost DA**, Leung DY, Martin RJ. Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol* 1999;**103**:1031–5.
49 **Cazzola M**, Matera MG, Blasi F. Macrolides and occult infection in asthma. *Curr Opin Pulm Med* 2004;**10**:7–14.
50 **Rios AM**, Mejias A, Chavez-Bueno S, *et al*. Impact of cethromycin (ABT-773) therapy on microbiological, histologic, immunologic, and respiratory indices in murine model of Mycoplasma pneumoniae lower respiratory infection. *Antimicrob Agents Chemother* 2004;**48**:2897–904.