



Macrolides in the treatment of asthma

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Purpose of review

This review summarizes the importance of macrolide therapy in the treatment of asthma, discusses macrolide mechanisms of action, and outlines new clinical data supporting their use. The effects of macrolides on both the innate and adaptive immune responses are discussed.

Recent findings

Subacute bacterial infection with both typical and atypical organisms contributes to poor asthma control. Identification of pathogens using polymerase chain reaction (PCR) and cultures from bronchoscopic samples directs antibiotic therapy and improves asthma control. PCR identification of *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* in asthmatics best identifies the macrolide responsive phenotype.

Summary

Because of their effect on protein synthesis, macrolides have both antimicrobial and anti-inflammatory properties. Both mechanisms appear to be important in their clinical efficacy in treating a wide variety of pulmonary disorders, including asthma.

Keywords

asthma, *Chlamydophila pneumoniae*, fiberoptic bronchoscopy, macrolides, *Mycoplasma pneumoniae*

INTRODUCTION

Asthma is a disorder of the airways characterized by airway hyperresponsiveness and airflow obstruction with clinical manifestations of cough, wheeze, chest tightness, dyspnea, and mucus production. This occurs because of airway inflammation resulting from complex host (genetic) and environmental (irritants, infection, and allergens) interactions.

For physicians, the monumental challenge remains to identify those factors most important in causing asthma and preventing adequate asthma control. Identification of different asthma phenotypes by hierarchical cluster analysis clearly emphasizes the clinical heterogeneity in severe asthma and the need for new approaches to identify those factors responsible for poor asthma control [1]. Numerous publications have emphasized the role of viral infections, with or without coexisting bacterial infections, in causing asthma exacerbations [2–8]. An increasing body of evidence exists suggesting that chronic or subacute infection with atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* may be responsible for poor asthma control in a subset of asthmatic patients [9–11]. When these organisms are identified by bronchoscopic PCR studies, treatment with macrolide antibiotics results in better asthma control

[12,13]. In contrast, patients with suboptimally controlled asthma in the Asthma Clinical Research Network (ACRN) study, without PCR evidence of mycoplasma or chlamydophila infection, who were treated with clarithromycin showed no significant improvement in asthma control. Additional studies to identify the ‘macrolide responsive asthmatic’ are needed.

Macrolides have become the antibiotic of choice to treat most asthmatic patients with *M. pneumoniae* and *C. pneumoniae* subacute bacterial infections (SBIs; low-grade infection without elevated white blood cell count, elevated temperature, or radiographic infiltrate). Macrolides have both antibiotic (bacteriostatic) and anti-inflammatory (interference of the innate and adaptive immune system) properties [14]. It remains unknown which of these mechanisms are more important in treating many lung

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KEY POINTS

- *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae* are atypical mycobacteria that contribute to poor asthma control in some patients.
- Macrolide antibiotics are effective in improving asthma control in patients with documented infection using PCR techniques from bronchoscopic samples.
- Macrolides have both antimicrobial (bacteriostatic) and anti-inflammatory (effects on innate and adaptive immune systems) properties by altering protein synthesis.

conditions, including asthma. It appears that PCR identification of mycoplasma and chlamydomphila through bronchoscopic techniques [biopsy, brush, and bronchoalveolar lavage (BAL)] best defines this asthma phenotype and which patients will best respond to macrolide therapy [12^a].

ROLE OF VIRAL AND BACTERIAL INFECTIONS IN ASTHMA PATHOGENESIS AND CONTROL

At birth, both the innate and adaptive parts of the immune system are immature and continue to develop throughout the first years of life. The hygiene hypothesis, simply stated, suggests that children exposed to a variety of bacterial and fungal pathogens have a lower risk of developing asthma and allergies than those who lack such exposure. Ege *et al.* [15] compared children living on farms with those in a reference group with respect to prevalence of asthma as related to microbial exposure. Samples from mattress dust were screened for bacterial DNA and bacterial and fungal cultures. The frequency of samples positive for bacteria and fungi was higher for children living on farms. These children, who had higher levels of microbial exposure, demonstrated much greater protection from developing asthma.

A similar protective response has been seen in a murine model of allergic asthma when mice were preinfected with mycoplasma prior to allergen exposure. Chu *et al.* [16] evaluated the effects of different timing of airway *M. pneumoniae* infection on bronchial hyperresponsiveness (BHR), lung inflammation, and the protein levels of Th1 [interferon (IFN)- γ] and Th2 [interleukin (IL)-4] cytokines in bronchoalveolar lavage fluid. If the mycoplasma infection occurred 3 days prior to allergen sensitization and challenge, the infection reduced the BHR and lung inflammation (Fig. 1a and b). This was accompanied by a significant induction of Th1

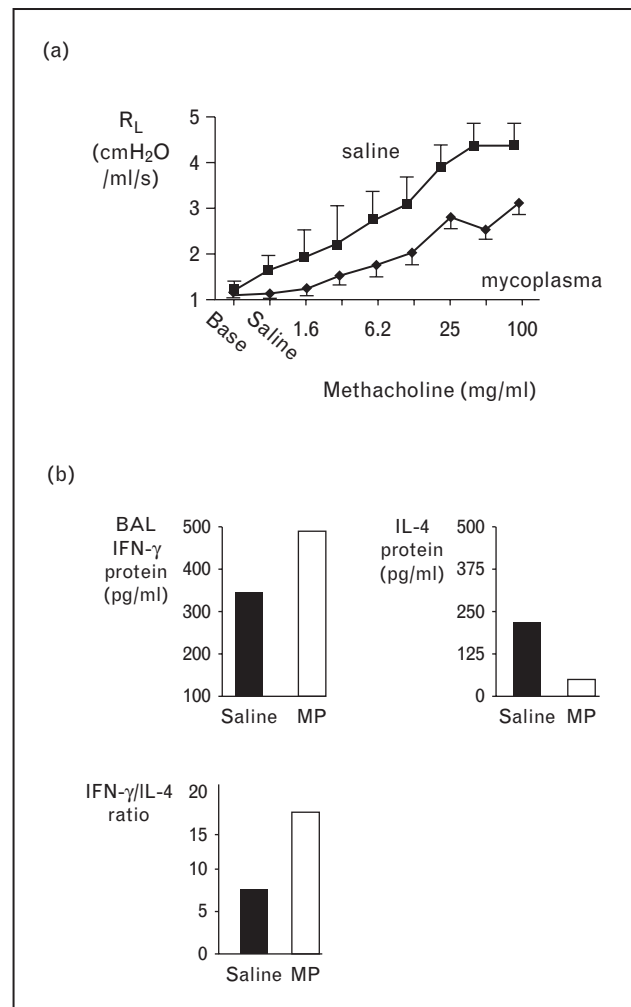


FIGURE 1. Murine model of asthma: mycoplasma infection precedes allergen exposure. (a and b) In this murine model of allergic asthma, if a mycoplasma respiratory infection precedes allergen sensitization and challenge, airway hyperresponsiveness is decreased (methacholine challenge; a). This is because of increased Th1 [interferon (IFN)- γ] inflammation and decreased Th2 [interleukin (IL)-4] inflammation. Thus, the ratio favors nonallergic, Th1 cytokines (b). BAL, bronchoalveolar lavage; Base, baseline; MP, *Mycoplasma pneumoniae*; R_L , lung resistance [16].

responses (increased IFN- γ and decreased IL-4 production). On the other hand, when mycoplasma infection occurred 2 days following allergen exposure, the infection initially produced a temporary reduction of BHR, only to be followed by an increased BHR, lung inflammatory response, and IL-4 levels (Fig. 2a and b). These data suggest that mycoplasma infection could modulate both physiological and immunological responses in a murine asthma model, lending further support to the asthma hygiene hypothesis.

There is a well established correlation between childhood upper respiratory viral infections and

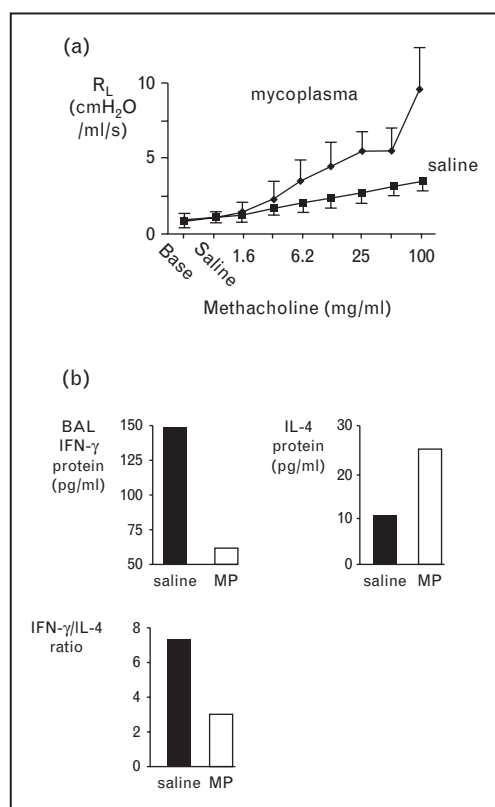


FIGURE 2. Murine model of asthma: allergen exposure precedes mycoplasma infection. (a and b) In this murine model, the mycoplasma respiratory infection follows the allergen sensitization and challenge. This sequence of events produces increased airway hyperresponsiveness (methacholine challenge, a) and increased allergic Th2 inflammation profile (b). BAL, bronchoalveolar lavage; Base, baseline; IFN, interferon; IL, interleukin; MP, *Mycoplasma pneumoniae* [16].

increased asthma risk [2]. Influenza virus, respiratory syncytial virus, and rhinovirus infection appear to play a role in increased asthma risks [3]. The question remains, once asthma is present, how do viral infections produce an exacerbation? In addition to allergens and air pollutants (irritants), some exacerbations are thought to be related to infection. Because culture techniques are limited, especially for viruses, specific infectious causes are difficult to confirm. PCR technology has allowed for the identification of numerous viruses and it appears that the human rhinovirus (HRV) most commonly contributes to viral-induced exacerbations [2]. Although there is no evidence that asthmatics have more colds than nonasthmatics [17], symptoms may persist for weeks, even months, in spite of standard asthma controller therapy. Holgate [18] has emphasized that the airway epithelium in the asthmatic is abnormal, and when exposed to HRV it releases more proinflammatory mediators

compared to normal epithelium. The impaired virus elimination and production of cell death also appears to be related to a defective production of interferon, which is responsible for initiating apoptosis and viral clearance in normal epithelial cells [19].

The recent review by Papadopoulos *et al.* [7] reports that because of the susceptibility of the asthmatic airway to respiratory viruses, 40–80% of asthma exacerbations in both children and adults are caused by viral infections. These exacerbations are frequently prolonged and associated with neutrophil as well as eosinophil influx into the airways [20]. Using cultured epithelial cells, Wark *et al.* [21] demonstrated impaired virus elimination and increased cytotoxic cell death as a consequence of defective IFN- β and IFN- λ production. These two cytokines are responsible for initiating apoptosis and viral clearance by normal epithelial cells as well as activating a large range of protective antiviral pathways. Thus, it is possible that a genetic deficiency in IFN production is partially responsible for increased susceptibility of the asthmatic airways to common cold viral infection. More recently, it has been shown that asthmatic epithelial cells release more proinflammatory mediators [22], which are selectively suppressed *in vitro* by exogenously added IFN- β [23].

Although viral infections and those caused by bacteria are usually considered separately, little is known about the role of secondary bacterial infections producing lingering and more severe symptoms during an exacerbation [8]. Adult asthmatics frequently receive an antibiotic in addition to systemic corticosteroids with an acute exacerbation, although controlled studies confirming antibiotic efficacy are lacking.

Typical bacterial infection (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) do not cause the type of airway epithelial inflammation that viral or atypical bacterial infections do, although there is evidence that colonization of the posterior nasopharynx with *S. pneumoniae* or *H. influenzae* in childhood increases asthma risk later in life [24].

Similar to viruses, atypical bacteria such as *M. pneumoniae* and *C. pneumoniae* are capable of causing significant epithelial inflammation [25]. The very nature of infection with these agents, which in the case of *C. pneumoniae* is a chronic intracellular inflammatory process and in the case of *M. pneumoniae* is persistent epithelial damage, makes them ideal candidates to produce chronic symptoms and poor asthma control. Mycoplasma is transmitted by droplet spread and has an average incubation period of 21 days. The bacterial pathogenicity involves its cytoadherence to the respiratory

mucosa. The bacteria interact with respiratory epithelial cells by binding to various host cell receptors including sulfated glycolipids [26]. Once attached *M. pneumoniae* induces the generation of superoxide radicals and inhibits catalase, leading to oxidative stress in the host cell. In addition, mycoplasma also induces the production of proinflammatory cytokines such as IL-8 and tumor necrosis factor (TNF) by interacting with Toll-like receptors. The infection eventually leads to several pathologic changes including loss of cilia, metabolic derangements, and cell death [27].

C. pneumoniae is an obligate intracellular pathogen that is transmitted by person-to-person spread of respiratory secretions with an incubation time of 3–4 weeks. *C. pneumoniae* exists in two forms, the replicating reticulate bodies and the infective elementary bodies. After being released into the extracellular environment, the elementary bodies interact with respiratory epithelial cells, leading to phagosome formation and subsequent intracellular replication [27]. *C. pneumoniae* increases endothelial nuclear factor with subsequent upregulation of inflammatory adhesion molecules such as IL-8 and platelet-derived growth factor [28].

ROLE OF ANTIBIOTICS IN MODIFYING THE CLINICAL EXPRESSION OF ASTHMA

Upper respiratory tract infections and acute bronchitis are the most common reasons for visits to a primary care physician's office. Even though most of these are viral in cause, antibiotics are frequently prescribed. In individuals with no underlying lung disease such as asthma or chronic obstructive pulmonary disease (COPD), antibiotics have not been proven to be effective in controlled clinical trials [29]. On the other hand, in patients with acute exacerbations of COPD, antibiotic therapy reduces the symptoms of cough, sputum production, and shortness of breath [30]. In patients with asthma exacerbations, routine antibiotic therapy has not been shown to reduce symptoms or improve pulmonary function. There continues to be a paucity of data from randomized, double-blind, placebo-controlled trials for the use of antibiotics to treat acute exacerbations of asthma. Two older studies by Shapiro and Graham (total of 121 patients) showed that penicillin-based antibiotic therapy, in addition to bronchodilators and corticosteroids, produced no improvement in forced expiratory volume in 1 s (FEV₁), symptoms scores, and duration of hospital stay [31,32].

Over the past decade, there has been a marked increase in the use of macrolide antibiotics to treat asthma exacerbations. In 2006, Johnston

et al. [33] conducted a multicenter, double-blind, placebo-controlled clinical trial to evaluate the efficacy of a 10-day course of telithromycin, 800 mg/day, in 278 adults with acute asthma. Patients receiving telithromycin demonstrated significantly greater improvement in asthma symptom scores ($P=0.04$) and symptom-free days ($P=0.006$) compared with those taking placebo during the 10-day treatment period. They also noted greater improvement in FEV₁ ($P=0.001$) by day 10, but there was no significant improvement in home-measured peak expiratory flow rates. Those not receiving antibiotics improved more slowly; however, at day 42 of the follow-up period they had similar lung function as those who did. In this study, relapse rates were similar in the placebo and treatment groups. Unfortunately, detailed information about documenting the presence of *C. pneumoniae* and *M. pneumoniae* by serologic analysis, PCR, and cultures is not available as related to the macrolide group versus the placebo group.

Atypical bacteria such as *M. pneumoniae* and *C. pneumoniae* are associated with acute exacerbations of asthma and contribute to long-term poorly controlled asthma [27]. Previous studies have documented that up to 30–40% of patients with persistent symptoms following a chest infection or bronchitis will have evidence of mycoplasma or chlamydia infection [11,34]. Because of this and other reports, the ACRN designed a study to evaluate the efficacy of macrolide therapy (clarithromycin) in suboptimally controlled asthmatics who were on low-dose fluticasone for 4 weeks and had an Asthma Control Questionnaire score of at least 1.5 [35]. Patients had bronchoscopy and endobronchial biopsies for PCR studies to detect *M. pneumoniae* or *C. pneumoniae*. Ninety-two patients were randomized and only 12 had PCR evidence for infection. Because of the small number with PCR positivity, the group data were analyzed together and the addition of clarithromycin did not improve asthma control or lung function for the entire group. Airway hyperresponsiveness was improved, increasing the methacholine PC20 by 1.2 ± 0.5 ($P=0.02$) in the entire study population. However, in spite of this reduction in airway hyperreactivity, the lack of clinical improvement suggests that the routine addition of macrolide therapy to uncontrolled asthmatics on low-dose inhaled corticosteroids (ICSs) offers little additional benefit.

To further evaluate the microbiological environment in uncontrolled asthmatics on low-dose ICS therapy, Huang *et al.* [9], using molecular methods of bacterial 16S ribosomal RNA detection, reported that people with asthma had a greater lower

respiratory bacterial load than normal individuals. They also had greater numbers of pathogenic bacteria, especially *Haemophilus* species. Those patients exhibiting a significant decrease in BHR after clarithromycin treatment had greater pretreatment airway bacterial diversity than nonresponders. Similarly, Hilty *et al.* [36] using the same technique found large quantities of Proteobacteria, particularly *Haemophilus* species in both asthmatics and patients with COPD.

When subacute bacterial infections are recognized, and specific pathogens are identified in the setting of poor asthma control, directed antibiotic therapy may reduce symptoms and improve pulmonary function. A recent study evaluated 58 refractory asthmatics with bronchoscopy, visual evaluation of the upper and lower airways, endobronchial biopsies, brushes and BAL for cell counts, histology, cultures, and PCR studies [12[•]]. Using information from these samples, five clinical phenotypes were observed as the major reason(s) for poor asthma control: gastroesophageal reflux, SBI, tissue eosinophilia, combination (gastroesophageal reflux plus SBI, gastroesophageal reflux plus tissue eosinophilia, SBI plus tissue eosinophilia, or gastroesophageal reflux plus SBI plus tissue eosinophilia), and nonspecific. The importance of recognizing multiple potential exacerbating factors comes from the combination group who, until all causes were treated, showed no significant improvement. Of the 25 out of 58 patients with SBI, specific pathogens were identified by culture or PCR studies (Table 1). Thirteen patients had positive PCR for mycoplasma (10 patients) or chlamydophila (three patients) using a combination of BAL (nine

positive), endobronchial biopsy (three positive), and endobronchial brush (two positive), with one being positive in BAL and brush. The 13 patients had significant improvement in % predicted FEV₁ and Asthma Control Test (ACT) following 6 months of macrolide therapy. Of interest, the other 12 patients with a variety of bacterial pathogens also showed significant improvement in ACT and % predicted FEV₁ with culture-directed antibiotic therapy. All 25 patients' results are demonstrated in Fig. 3. Although additional studies to confirm these results are needed, it appears that specific identification of pathogens using bronchoscopy to obtain samples identifies a group of asthmatic patients who best respond to antibiotic therapy.

ANTIBIOTIC AND ANTI-INFLAMMATORY PROPERTIES OF MACROLIDES

Macrolides are a group of clinically useful antibiotics derived from *Streptomyces* species. Structurally, they contain a 14-membered, 15-membered, or 16-membered lactone ring to which one or more sugars are attached. Macrolides are bacteriostatic and interfere with protein synthesis. Although the exact mechanism of action may vary, depending on the specific macrolide, the primary action is thought to be the dissociation of peptidyl-tRNA from ribosomes during translocation. Macrolides bind to 50S ribosomes of bacteria and inhibit transpeptidation and translocation of nascent peptides [37].

The original group of macrolides consists of the 14-membered lactone ring and includes erythromycin, clarithromycin, roxithromycin, and troleandomycin (Table 2) [38]. These drugs are well absorbed from the gastrointestinal tract, have excellent tissue penetration, and have broad efficacy against many respiratory pathogens. The second group consists of a 15-membered ring with the addition of a nitrogen element and are known as azalides, and includes azithromycin. The third group are those with a 16-membered ring with a monobasic charge and include spiramycin, josamycin, and midecamycin. Ketolides are a newer class of macrolides, contain a 14-membered ring and have a much broader spectrum and acid resistance compared to other macrolides. Telithromycin, a ketolide, was widely used in the United States to treat acute sinusitis and purulent bronchitis, until several reports of death from liver failure and deaths in patients with myasthenia gravis curtailed its use.

Because of their ability to penetrate polymorphonuclear leukocytes, macrolides are readily accessible at the sites of inflammation. Newer macrolides

Table 1. Twenty-five patients with subacute bacterial infection contributing to poor asthma control	
No. of patients	Bacteria ^a
1	<i>Acinetobacter</i>
1	Methicillin-resistant <i>Staphylococcus aureus</i>
1	Methicillin-sensitive <i>Staphylococcus aureus</i>
1	<i>Alcaligenes xylosoxidans</i>
1	<i>Moraxella catarrhalis</i>
2	Alpha hemolytic streptococci
2	<i>Stenotrophomonas maltophilia</i>
3	<i>Pseudomonas aeruginosa</i>
3	<i>Haemophilus influenzae</i>
3	<i>Chlamydophila pneumoniae</i>
10	<i>Mycoplasma pneumoniae</i>

Data from [12[•]].
^aThree patients had positive cultures/PCR studies for more than one organism.

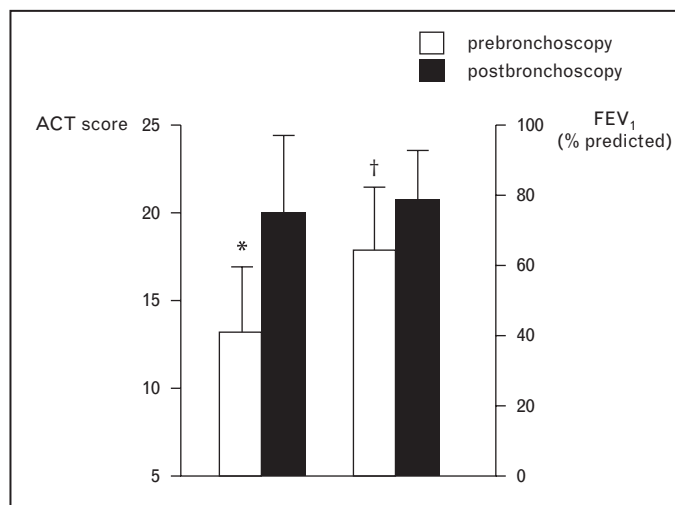


FIGURE 3. The Asthma Control Test (ACT) score and percentage predicted forced expiratory volume in 1 s (FEV₁) in patients with subacute bacterial infection prebronchoscopy and 4–6 months postculture and PCR-directed therapy. * $P \leq 0.0004$; † $P \leq 0.00005$ [12[■]].

such as azithromycin accumulate intracellularly leading to an intracellular concentration that is 26 times higher than erythromycin in macrophages [14].

In addition to their antimicrobial action, macrolides possess anti-inflammatory properties that may contribute to clinical improvement in many patients with chronic airway inflammation [39].

The clinical efficacy of the ‘anti-inflammatory properties’ of macrolides was originally described by Kudoh in 1987 [40,41], who used them to treat diffuse panbronchiolitis (DPB). This condition is characterized by a diffuse, chronic, neutrophilic airway inflammation involving the bronchiolar and

centrilobular regions. Patients with DPB develop cough, sputum production, bronchiectasis, and colonization with pathogens, in particular, *Pseudomonas*. With macrolide therapy, the 10-year survival increased from 12% to greater than 90%. Because serum levels of erythromycin were well below minimal inhibitory concentrations for detected pathogens in patients with DPB, it was postulated that there was an additional anti-inflammatory effect.

Because of their effect on protein synthesis, macrolides alter many aspects of the lung–microorganism–environmental interface including effects on the biofilm and quorum sensing, as well as bacterial adherence, mobility, and toxins [42[■]].

Table 2. Structural differences in common and newer macrolides

Structure	Common macrolides	Newer macrolides
14-Membered ring	Erythromycin, clarithromycin ^{a,b} Roxithromycin, troleandomycin ^{b,c}	
15-Membered ring	Azithromycin ^{b,d}	
16-Membered ring		Spiramycin Josamycin Midecamycin
Ketolide ^e	Telithromycin	Cethromycin

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^aClarithromycin differs from erythromycin by the methylation of a hydroxyl group in the lactone ring.

^bThese modifications in structure result in better gastrointestinal tolerability, better tissue penetration, increased half-life, and decreased risk of interaction with other drugs metabolized by the cytochrome P-450 enzyme system [39].

^cTroleandomycin is the acetylated ester of the macrolide oleandomycin and is structurally related to erythromycin.

^dAzithromycin is an azalide, which differs from erythromycin by the addition of a nitrogen atom into the lactone ring.

^eKetolides are a newer class of semisynthetic derivatives of erythromycin, derived by substituting the cladinose sugar with a keto group and attaching a cyclic carbamate group in the lactone ring. These modifications result in a much broader spectrum than other macrolides and increased activity against macrolide-resistant bacteria because of their ability to bind at two sites at the bacterial ribosome.

The biofilm is an aggregate of microorganisms, connected by a polysaccharide matrix that protects bacteria from phagocytosis and suppresses the effect of many antibiotics and the normal ciliary action of epithelial cells. Macrolides alter the matrix by inhibiting polysaccharide synthesis [43], and this change allows for enhanced phagocytosis and clearance of bacteria by alveolar macrophages [44].

Quorum sensing occurs when bacteria use mutual communication to coordinate the expression of genes. These genes can produce biofilm formation and stimulate IL-8 production, causing neutrophil influx with additional inflammation. Macrolides appear to interfere with this process by reducing transcription of quorum sensing genes [45].

Adherence of bacteria to mucosal surfaces and respiratory epithelial cells is an important initial event in the pathogenesis of airway inflammation. Macrolides produce decreased adherence of many pathogens, which may partially explain their efficacy in patients colonized with *Pseudomonas* [46]. In addition to blocking adherence, macrolides impair the mobility of *Pseudomonas* by inhibiting the production of flagellin, the major constituent of bacterial flagella. The decreased bacterial mobility facilitates phagocytosis by alveolar macrophages [47].

Bacteria produce toxins. These toxins are cytotoxic enzymes and include elastase, protease, and phospholipase that contribute to pathogenicity. Macrolides suppress the production of bacterial toxins, thus reducing their virulence [48].

Innate immunity

Cytokines are hormone-like proteins that are important in the immune response. These mediators can initiate, perpetuate, and eventually downregulate inflammation. Chemokines are cytokines with chemotactic capacity. Proinflammatory cytokines such as IL-1, IL-2, IL-4, IL-6, IFN- γ , TNF- α , and granulocyte macrophage colony-stimulating factor and chemokines (e.g. IL-8) regulate the immune response through positive feedback [42²²]. Anti-inflammatory cytokines, such as IL-10, prostaglandins, and TGF- β attenuate the immune response through a negative-feedback system. In general, macrolides inhibit the synthesis and/or secretion of proinflammatory cytokines, while increasing the release of anti-inflammatory cytokines [49].

Alveolar macrophages are scavengers and play a key role in inflammation by phagocytizing apoptotic cells, bacteria, and other inflammatory debris. Macrolides enhance all of these macrophage activities [50].

Neutrophils also play a key role in airway inflammation and accumulate at the site of inflammation. Many lung transplantation patients with early bronchiolitis and bronchiectasis develop severe neutrophilic inflammation and bronchiolitis obliterans. Vanaudenaerde *et al.* [14] described a subset of these patients who demonstrated an excellent clinical response to macrolide therapy. Prior to macrolide treatment, these patients all had increased neutrophils and IL-8 in the BAL. Following therapy, there was a significant mean increase in FEV₁ (13%) as well as a significant decrease of both BAL neutrophils and IL-8. In this group, it appears that macrolides specifically reduce inflammation by inhibiting components of the innate immune system.

Adaptive immunity

Not only do macrolides have an effect on the innate immune system, but they also have an impact on cellular immunity through T-cell regulation and antigen presentation [42²²]. Long-term use of macrolide antibiotics reduces the number of lymphocytes in the BAL fluid of patients with DPB to normal levels [51]. In addition, there is augmentation of the apoptosis of activated lymphocytes, thus reducing inflammation [52]. Macrolides appear to have a suppressive effect on the proinflammatory cytokine production by T cells [53]. Although current data clearly outlines the importance of macrolides in altering the innate immune response, data are now emerging to demonstrate their effect on adaptive immunity.

CONCLUSION

Macrolide antibiotics are well known for their antibiotic and anti-inflammatory characteristics. It has been well documented that, in addition to allergens and environmental irritants, subacute infections with atypical bacteria including *M. pneumoniae* and *C. pneumoniae* contribute to poor asthma control. The routine addition of macrolide antibiotics in uncontrolled asthmatics has not been shown useful in reducing symptoms and improving lung function. On the other hand, documentation of infection with PCR studies from bronchoscopy samples (biopsy, brushing and BAL) can identify an asthma phenotype that has a favorable response to macrolide therapy.

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Conflicts of interest

R.J.M. has done consultancy work and/or received travel support and/or honoraria for attendance at speaking

activities and/or advisory boards for Teva, Merck, AstraZeneca, Genentech/Novartis, KaloBios, Graceway, Shering, and LEK; and received research grants from the NHLBI (murine and human models); and received royalties from UpToDate. J.T.G.Jr has done consultancy work and/or received travel support and/or honoraria for attendance at speaking activities and/or advisory boards for Merck, AstraZeneca, Genentech, and GlaxoSmithKline. D.R.R. has done consultancy work and/or received travel support and/or honoraria for speaking activities for Genentech and AstraZeneca.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 93).

1. Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181:315–323.
2. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010; 376:826–834.
3. Dulek DE, Peebles RS Jr. Viruses and asthma. *Biochim Biophys Acta* 2011; 1810:1080–1090.
4. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol* 2010; 125:1178–1187; quiz 1188–1179.
5. Kloefer KM, Gern JE. Virus/allergen interactions and exacerbations of asthma. *Immunol Allergy Clin North Am* 2010; 30:553–563, vii.
6. Lee SL, Chiu SS, Malik PJ, *et al.* Is respiratory viral infection really an important trigger of asthma exacerbations in children? *Eur J Pediatr* 2011; 170:1317–1324.
7. Papadopoulos NG, Christodoulou I, Rohde G, *et al.* Viruses and bacteria in acute asthma exacerbations: a GA(2) LEN-DARE systematic review. *Allergy* 2011; 66:458–468.
8. Rosenthal LA, Avila PC, Heymann PW, *et al.* Viral respiratory tract infections and asthma: the course ahead. *J Allergy Clin Immunol* 2010; 125:1212–1217.
9. Huang YJ, Nelson CE, Brodie EL, *et al.* Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. *J Allergy Clin Immunol* 2011; 127:372–381; e371–e373.
10. Specjalski K, Jassem E. *Chlamydomphila pneumoniae*, *Mycoplasma pneumoniae* infections, and asthma control. *Allergy Asthma Proc* 2011; 32:9–17.
11. Sutherland ER, Martin RJ. Asthma and atypical bacterial infection. *Chest* 2007; 132:1962–1966.
12. Good J, Kolakowski C, Groshong S, *et al.* Refractory asthma: importance of ■ bronchoscopy to identify phenotypes and direct therapy. *Chest* 2011; doi: 10.1378/chest.11-0741 [Epub ahead of print].
This study uses data from fiberoptic bronchoscopy to identify specific asthma phenotypes. In patients with subacute bacterial infection, culture and PCR directed therapy improves both asthma symptoms (ACT) and pulmonary function (FEV₁). Postbronchoscopy directed therapy also improved other phenotypes.
13. Kraft M, Cassell GH, Pak J, *et al.* *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: effect of clarithromycin. *Chest* 2002; 121:1782–1788.
14. Vanaudenaerde BM, Vos R, Meyts I, *et al.* Macrolide therapy targets a specific phenotype in respiratory medicine: from clinical experience to basic science and back. *Inflamm Allergy Drug Targets* 2008; 7:279–287.
15. Ege MJ, Mayer M, Normand AC, *et al.* Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011; 364:701–709.
16. Chu HW, Honour JM, Rawlinson CA, *et al.* Effects of respiratory *Mycoplasma pneumoniae* infection on allergen-induced bronchial hyperresponsiveness and lung inflammation in mice. *Infect Immun* 2003; 71:1520–1526.
17. Pattermore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I: Epidemiology. *Clin Exp Allergy* 1992; 22:325–336.
18. Holgate ST. The sentinel role of the airway epithelium in asthma pathogenesis. *Immunol Rev* 2011; 242:205–219.
19. Matsumoto M, Oshiumi H, Seya T. Antiviral responses induced by the TLR3 pathway. *Rev Med Virol* 2011; 21:67–77.
20. Fraenkel DJ, Bardin PG, Sanderson G, *et al.* Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. *Am J Respir Crit Care Med* 1995; 151:879–886.
21. 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; 201:937–947.
22. Wark PA, Grissell T, Davies B, *et al.* Diversity in the bronchial epithelial cell response to infection with different rhinovirus strains. *Respirology* 2009; 14:180–186.
23. Cakebread JA, Xu Y, Grainge C, *et al.* Exogenous IFN-beta has antiviral and anti-inflammatory properties in primary bronchial epithelial cells from asthmatic subjects exposed to rhinovirus. *J Allergy Clin Immunol* 2011; 127:1148–1154; e1149.
24. Bisgaard H, Hermansen MN, Buchvald F, *et al.* Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med* 2007; 357:1487–1495.
25. Andersen P. Pathogenesis of lower respiratory tract infections due to *Chlamydia*, *Mycoplasma*, *Legionella* and viruses. *Thorax* 1998; 53:302–307.
26. Waites KB, Balish MF, Atkinson TP. New insights into the pathogenesis and detection of *Mycoplasma pneumoniae* infections. *Future Microbiol* 2008; 3:635–648.
27. Metz G, Kraft M. Effects of atypical infections with *Mycoplasma* and *Chlamydia* on asthma. *Immunol Allergy Clin North Am* 2010; 30:575–585; vii–viii.
28. Blasi F, Tarsia P, Aliberti S. *Chlamydomphila pneumoniae*. *Clin Microbiol Infect* 2009; 15:29–35.
29. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA* 1997; 278:901–904.
30. Daniels JM, Snijders D, de Graaff CS, *et al.* Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 181:150–157.
31. Graham VA, Milton AF, Knowles GK, *et al.* Routine antibiotics in hospital management of acute asthma. *Lancet* 1982; 1:418–420.
32. Shapiro GG, Eggleston PA, Pierson WE, *et al.* Double-blind study of the effectiveness of a broad spectrum antibiotic in status asthmaticus. *Pediatrics* 1974; 53:867–872.
33. Johnston SL, Blasi F, Black PN, *et al.* The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006; 354:1589–1600.
34. Martin RJ, Kraft M, Chu HW, *et al.* A link between chronic asthma and chronic infection. *J Allergy Clin Immunol* 2001; 107:595–601.
35. Sutherland ER, King TS, Icitovic N, *et al.* A trial of clarithromycin for the ■ treatment of suboptimally controlled asthma. *J Allergy Clin Immunol* 2010; 126:747–753.
This ACRN designed study evaluated 92 patients with uncontrolled asthma on low-dose fluticasone with bronchoscopy and endobronchial biopsies for PCR identification of *M. pneumoniae* and *C. pneumoniae*. The addition of clarithromycin did not improve lung function or reduce symptoms for the entire group. Unfortunately, only 12 patients had positive PCR studies so the group was too small for separate statistical analysis.
36. Hilty M, Burke C, Pedro H, *et al.* Disordered microbial communities in asthmatic airways. *PLoS One* 2010; 5:e8578.
37. Jain R, Danziger LH. The macrolide antibiotics: a pharmacokinetic and pharmacodynamic overview. *Curr Pharm Des* 2004; 10:3045–3053.
38. Friedlander AL, Albert RK. Chronic macrolide therapy in inflammatory airways diseases. *Chest* 2010; 138:1202–1212.
39. Jaffé A, Bush A. Anti-inflammatory effects of macrolides in lung disease. *Pediatr Pulmonol* 2001; 31:464–473.
40. 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; 157:1829–1832.
41. Kudoh S, Uetake T, Hagiwara K, *et al.* Clinical effects of low-dose long-term erythromycin chemotherapy on diffuse panbronchiolitis. *Nihon Kyobu Shikkan Gakkai Zasshi* 1987; 25:632–642.
42. Altenburg J, de Graaff CS, van der Werf TS, *et al.* Immunomodulatory effects ■ of macrolide antibiotics. Part 1: Biological mechanisms. *Respiration* 2011; 81:67–74.
This is an outstanding review of the immunomodulatory efforts of macrolide antibiotics. Excellent references are cited and the reader will gain a new appreciation for the current and future application of macrolide therapy.
43. Kondoh K, Hashiba M, Baba S. Inhibitory activity of clarithromycin on biofilm synthesis with *Pseudomonas aeruginosa*. *Acta Otolaryngol Suppl* 1996; 525:56–60.
44. Ichimiya T, Yamasaki T, Nasu M. In-vitro effects of antimicrobial agents on *Pseudomonas aeruginosa* biofilm formation. *J Antimicrob Chemother* 1994; 34:331–341.
45. Nalca Y, Janssch L, Bredenbruch F, *et al.* Quorum-sensing antagonistic activities of azithromycin in *Pseudomonas aeruginosa* PAO1: a global approach. *Antimicrob Agents Chemother* 2006; 50:1680–1688.
46. Tsang KW, Ng P, Ho PL, *et al.* Effects of erythromycin on *Pseudomonas aeruginosa* adherence to collagen and morphology in vitro. *Eur Respir J* 2003; 21:401–406.

47. Kawamura-Sato K, Iinuma Y, Hasegawa T, *et al.* Effect of subinhibitory concentrations of macrolides on expression of flagellin in *Pseudomonas aeruginosa* and *Proteus mirabilis*. *Antimicrob Agents Chemother* 2000; 44:2869–2872.
48. Kita E, Sawaki M, Oku D, *et al.* Suppression of virulence factors of *Pseudomonas aeruginosa* by erythromycin. *J Antimicrob Chemother* 1991; 27:273–284.
49. Culic O, Erakovic V, Parnham MJ. Anti-inflammatory effects of macrolide antibiotics. *Eur J Pharmacol* 2001; 429:209–229.
50. Xu G, Fujita J, Negayama K, *et al.* Effect of macrolide antibiotics on macrophage functions. *Microbiol Immunol* 1996; 40:473–479.
51. Mukae H, Kadota J, Kohno S, *et al.* Increase in activated CD8⁺ cells in bronchoalveolar lavage fluid in patients with diffuse panbronchiolitis. *Am J Respir Crit Care Med* 1995; 152:613–618.
52. Kadota J, Mizunoe S, Kishi K, *et al.* Antibiotic-induced apoptosis in human activated peripheral lymphocytes. *Int J Antimicrob Agents* 2005; 25:216–220.
53. Williams AC, Galley HF, Watt AM, *et al.* Differential effects of three antibiotics on T helper cell cytokine expression. *J Antimicrob Chemother* 2005; 56:502–506.