ELSEVIER

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

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Review

The role of antibiotics in asthma

Francesco Blasi [a], Sebastian L. Johnston [b,*]

[a] *Institute of Respiratory Diseases, University of Milan, IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy*

[b] *Department of Respiratory Medicine, National Heart and Lung Institute, Imperial College London, London W2 IPG, UK*

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

* Corresponding author. Tel.: +44 20 7594 3764; fax: +44 20 7262 8913.
E-mail address: s.johnston@imperial.ac.uk (S.L. Johnston).

0924-8579/$ – see front matter © 2006 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.
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.