REVIEW ARTICLE

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Antimicrobial Therapy in Childhood Asthma and Wheezing

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Contents

Abstract

There is an increasing number of viral and bacterial pathogens suspected of contributing to asthma pathogenesis in childhood, making it more difficult for the practitioner to make specific therapy decisions. This review discusses the role of viruses, e.g. respiratory syncytial virus, human metapneumovirus, influenza viruses and rhinoviruses, as well as the role of the atypical bacteria *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*, as contributors to childhood asthma. Diagnosis, prevention, and therapy are discussed, including a summary of drugs, i.e. macrolide antibacterials, antivirals, and vaccine regimens already available, or at least in clinical trials. For the practitioner dealing with patients every day, drug regimens are assigned to the individual pathogens and an algorithm for the management of atypical infections in patients with asthma or recurrent wheezing is presented.

Besides hereditary and atopic predispositions, viral and atypical bacterial infection of the respiratory tract may contribute to the prevalence of asthmatic symptoms, either as a simple trigger for acute exacerbations or as a significant contributor to the pathogenesis of airway inflammation and hyperresponsiveness. This article focuses on these factors in childhood asthma and wheezing, and comments on diagnostic issues and available treatment options.

1. Asthma

Asthma has traditionally been defined on clinical grounds as a respiratory disease characterized by recurrent and reversible airway obstruction with wheezing, cough, and dyspnea. In recent years, our understanding of asthma has expanded, and the special impact of airway inflammation and, in severe cases, of airway remodeling on pathogenesis has led to a new definition which

describes asthma as a chronic inflammatory process in which a number of cells and cellular events are involved[1,2] (reviewed by Yang[3]).

Repeated measurements of FEV_1 (a general index of airway resistance) and PEF (which measures large airway resistance, which accounts for 80% of total resistance) have gained a global consensus to guide therapeutic interventions in patients >5 years of age. Bronchial hyperreactivity is defined as a 20% decrease in FEV_1 at ≤8 mg/mL methacholine challenge or >15% increase in FEV_1 after the administration of albuterol (salbutamol) in patients with baseline airflow obstruction (FEV_1 <70%) in whom a methacholine challenge cannot be performed.

Patients with asthma also exhibit elevated levels of fractionated exhaled nitric oxide, which can be utilized as a marker of airway inflammation. The measurement of fractionated exhaled nitric oxide has been shown to enhance the diagnosis of asthma, detect deterioration in the control of asthma, and monitor response to anti-inflammatory therapy, as levels decrease after inhaled corticosteroid treatment,[4] especially in individuals with asthma and atopy.[5] The measurement of fractionated exhaled nitric oxide may become an important tool in clinical practice.[6] Furthermore, an increase in the sputum-associated immune cell (in particular eosinophil) count should be taken into account during diagnosis, since it is believed to reflect underlying airway inflammation.[7-9] The eosinophil count can also be used to predict asthma control after the discontinuation of inhaled corticosteroids.[9]

2. Recurrent Wheezing versus Asthma in Early Childhood

The risk of subsequent asthma in an infant with a first episode of wheezing is difficult to predict, as nearly 90% of those events are triggered by viral infections,[10,11] in particular respiratory syncytial virus (RSV), human metapneumovirus (HMPV), parainfluenza virus (PIV), influenza virus (IV), rhinovirus, and adenovirus (ADV). HMPV and RSV in particular, but also rhinoviruses,[12] may contribute to acute exacerbations of asthma, and infection may represent the initial event in a history of asthma.

However, considering the plethora of viral agents the infant's immature immune system is confronted with after the shield of maternally derived antibodies has waned, recurrent wheezing may just be the consequence of recurrent infections or (in the cases of RSV and HMPV) even reinfections. In contrast to younger children, the majority of children aged ≥3 years who are hospitalized for acute wheezing show characteristics of atopy in their medical history.[3,10,11,13,14]

It is important, therefore, to emphasize that recurrent wheezing rarely results in the final diagnosis of asthma in children ≤3 years, as they may represent transient early wheezers. Although transient early wheezers were found to have normal-to-subnormal lung function at age 7 years, children with asthmatic symptoms already show significant impairment of expiratory flow volumes.[15] Any uncertainty, however, in the diagnosis of asthma in younger children must not result in undertreatment with anti-inflammatory (controller) drugs, in addition to short-acting β_2-adrenoceptor agonists (reliever drugs).[3,16]

2.1 Differential Diagnosis

Particularly in infants and young children, some important differential diagnoses have to be excluded before recurrent wheezing is attributed to bronchial hyperreactivity and asthma. In children who did not receive the full set of vaccinations in their first year of life, whooping cough should always be excluded and droplet precautions should be implemented as long as the results of *Bordetella pertussis* diagnostics are pending.

An aspirated foreign body may cause recurrent episodes of pulmonary infection. This makes it reasonable not only to confirm the clinical diagnosis of pneumonia with chest x-ray in hospitalized children, but also to control for the complete resolution of pulmonary infiltrates after 4–6 weeks. Cystic fibrosis should also be excluded (sweat test) in any child with severe recurrent respiratory tract infection.

The medical history of the patient may reveal prematurity and prolonged ventilator (supplemental oxygen) therapy with subsequent bronchopulmonary dysplasia. Gastroesophageal reflux disease (nocturnal attacks of wheezing and cough) may trigger recurrent wheezing and respiratory infections due to microaspirations. Sinusitis as a cause of posterior drainage-associated chronic cough should be considered in school age children with asthma symptoms.[17] Chronic persistent infection of the airways with atypical bacteria such as *Mycoplasma* spp. or *Chlamydophila* spp. may cause recurrent wheezing episodes;[18-20] beyond simple acute exacerbation, some recent lines of evidence suggest that infection with these atypical bacteria may play an additional role in the pathogenesis of asthma.[21]

3. Endogenous and Exogenous Risk Factors

As a result of continuous research, the number of potential risk factors (e.g. tobacco smoke, house dust mite, mould, pet or cockroach allergens, and genetic background of atopy) for the development of asthma is increasing (reviewed by Arruda et al.).[22]

Breastfeeding or, alternatively, the use of a documented hypoallergenic formula for at least 4–6 months seems to be protective.[23] This effect may be explained by the observation that maternal intake of the probiotic *Lactobacillus rhamnosus* GG

Table I. Overview of viral and bacterial pathogens that are considered contributory to childhood asthma and treatment options

Pathogen	Description	Diagnostic procedure	Therapy options	Comment
Viruses				
RSV	Paramyxovirus (RNA genome)	RT-PCR, culture, ELISA, IF	Ribavirin, palivizumab	Only in severely immunocompromised children[a]
HMPV	Paramyxovirus (RNA genome)	RT-PCR, culture, IF	None	
Influenza (A/B)	Orthomyxovirus (segmented RNA genome)	RT-PCR, culture, ELISA, IF	Oseltamivir, zanamivir	Oseltamivir should be administered in children with asthma and confirmed influenza
PIV	Paramyxovirus (RNA genome)	RT-PCR, culture, ELISA	Ribavirin	Only in severely immunocompromised children
Adenoviruses	Linear double-strand DNA genome	PCR, culture, ELISA	Cidofovir, ribavirin, vidarabine[b]	Only in severely immunocompromised children
Coronaviruses (SARS, hCoV-NL63)	RNA genome	RT-PCR	None	
Rhinoviruses	Picornavirus (RNA genome)	RT-PCR, culture, ELISA	Pleconaril, rupintrivir[c]	Only in severely immunocompromised children
hBoV	Parvovirus (linear single-strand DNA genome)	PCR	None	
Bacteria				
Chlamydophila pneumoniae		PCR, MIF, serology (IgM, IgG)	Prolonged course of clarithromycin or azithromycin (first-line) or doxycycline (children >8 years of age)	
Mycoplasma pneumoniae		PCR, serology (IgM, IgG)	Prolonged course of clarithromycin or azithromycin (first-line) or doxycycline (children >8 years of age)	

a Patients undergoing an allogenic blood stem cell or bone marrow transplantation. Premature infants on mechanical ventilation with severe bronchopulmonary dysplasia or hemodynamically unstable congenital heart disease (only anecdotal evidence from small case series for both indications in premature infants).

b In small series and clinical trials.

c In clinical trials (unlicensed).

ELISA = enzyme-linked immunosorbent assay; **hBoV** = human bocavirus; **hCoV-NL63** = human coronavirus NL63; **HMPV** = human metapneumovirus; **IF** = immunofluorescence; **Ig** = immunoglobulin; **MIF** = microimmunofluorescence; **PCR** = polymerase chain reaction; **PIV** = parainfluenza virus; **RSV** = respiratory syncytial virus; **RT-PCR** = reverse transcriptase polymerase chain reaction; **SARS** = severe acute respiratory syndrome.

during late pregnancy followed by administration of *L. rhamnosus* GG to the infant for the first 6 months of life significantly decreased the proportion of children with atopic eczema in the verum group.[24] Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics for prevention of atopic disease.[24,25] However, any protective effect of frequent early exposure to (potential) pathogens and infections on the prevalence of asthma has been questioned in further studies.[26,27] Thereby, only one prospective trial[28] fosters the hypothesis that antibacterial treatment in infancy is related to a higher risk of asthma later in life.[29,30]

Nevertheless, too many wheezing episodes in infants triggered by viral infection are treated with antibacterials, although the risk of bacterial superinfection is in general <5% (influenza excluded).[31-33] This misuse of antibacterials may have biased studies that evaluated antibacterial treatment in early infancy as a risk factor for subsequent asthma.[29] However, it should be noted that in contrast to this misuse, the sophisticated use of antibacterials, in particular macrolides, may downregulate prolonged inflammation, increase mucus clearance, prevent biofilm formation, and also decrease the bacterial virulence (reviewed by Shinkai and Rubin).[34]

4. Contributing Infections in Asthma and Wheezing

Table I summarizes pathogens that are suspected to exacerbate or contribute to the development of childhood asthma.

4.1 Viral Infections

For a long time it was believed that respiratory viruses were solely responsible for the 'common cold' and for serious airway disease only in high risk patients such as prematurely born infants, the elderly, and the immunocompromised. Subsequently, it was widely recognized that viral respiratory infections may cause severe lower respiratory tract disease in immunocompetent individuals.[35] In addition, viral respiratory tract infections are closely linked to wheezing in infancy and to hospitalization for acute wheezing before 3 years of age.[10,11,36,37] By comparison, a large majority of wheezing children aged 3–18 years display additional atopic characteristics that may be critical as a risk factor for hospitalization and an adverse response to viral infections, especially to rhinovirus, the most prevalent causative agent in this age group.[37] In asthmatic children, bronchial hyperresponsiveness after a single 'natural cold' has been found to last 5–11 weeks.[38] Beyond RSV and rhinovirus, the newly detected viruses HMPV, human coronavirus NL63 (hCoV-NL63), and human bocavirus may substantially contribute to acute asthma exacerbations.[39-44] The more severe clinical course of viral bronchiolitis in infants has been linked to inherited abnormalities of pulmonary function[45] and to certain risk factors like chronic lung disease of prematurity, hemodynamically relevant congenital heart disease, neurologic impairment, and immunodeficiency.[46]

In addition to acute aggravation of any pre-existing airway disease, RSV infection of the lower respiratory tract, in infants, severe enough to cause hospitalization has been linked to subsequent bronchial hyperreactivity, recurrent wheezing and asthma in school age children up to the age of 13 years.[13,14,47,48] Interestingly, children with recurrent wheezing after their first RSV bronchiolitis displayed elevated IgE antibodies against common respiratory and food allergens as well.[13,47] Thus, it has been speculated that lower respiratory tract infection with RSV triggers a general shift of the immune system in favor of atopy (dominance of T helper type 2 response, upregulating IgE production with higher levels of interleukin (IL)-4, IL5, IL10 and IL8 in bronchial secretions).[45,49-52] Similar changes in the immune system have been implicated for the devastating consequences of the first RSV immunization campaign with a formalin-inactivated RSV vaccine that resulted in severe and even lethal illness in the immunized children.[53]

In a series of recent publications on a retrospective study from the Kuopio University Hospital, Finland, rhinoviruses were detected in 27 (33%) of 81 respiratory samples from children who had been hospitalized for wheezing in infancy.[54] As single viral findings, rhinoviruses were associated with the development of asthma 7 years later ($p = 0.047$; odds ratio [OR], 4.14; 95% CI 1.02, 16.77 vs rhinovirus-negative cases [by logistic regression adjusted for age, sex, and atopic dermatitis on entry]). Korrpi et al.[55] reported on the same patients and compared children with RSV with those with rhinovirus infection. Oxygen saturation values were lower in children with RSV infection. There were no significant differences in respiratory rates or scores combining wheezing and retractions. The children with rhinovirus infection were older (median 13 vs 5 months) and presented more often with atopic dermatitis (OR, 16.7; 95% CI 2.22, 100) and blood eosinophilia (OR, 2.22; 95% CI 1.04, 50). The groups did not differ from each other with regard to total serum IgE. The risk of subsequent asthma was increased about 5-fold after RSV-induced wheezing, and ≥10-fold after rhinovirus-induced wheezing in the most recent patient collective.[56]

Lemanske et al. investigated the role of RSV infection in a prospectively followed (from birth to 3 years of age) cohort of 285 children at genetically high risk for developing allergic respiratory diseases.[12] When viral etiology was considered, first-year wheezing illnesses caused by rhinovirus infection were the strongest predictor of subsequent third-year wheezing (OR, 6.6; $p < 0.0001$). Moreover, 63% of the infants who wheezed during rhinovirus seasons continued to wheeze in the third year of life, compared with only 20% of all other infants (OR, 6.6; $p < 0.0001$). Also, similar mechanisms have been speculated to be active in severe bronchiolitis caused by rhinovirus,[57] but the evidence that rhinovirus-like RSV contributes to the pathogenesis of asthma in childhood is not as consistent and requires investigation in further prospective trials.

Juntti et al.[58] showed that children hospitalized for RSV infection in infancy still differed in interferon (IFN)-γ and soluble intercellular adhesion molecule-1 (sICAM-1) [CD54] production 6–10 years after the infection. Data from 51 children admitted to hospital for RSV infection during the first year of life suggested that the pathogenesis of asthma and wheezing after an early RSV infection may be different from that in children without an early RSV infection. The latent or chronic inflammatory state of the airways in asthmatic or atopic individuals may alleviate the infection with rhinovirus due to an increased expression of sICAM-1, hitherto known as the key receptor only for rhinoviruses and necessary for their adhesion to the respiratory epithelium.[59]

4.1.1 Diagnosis

The diagnostics of viral respiratory tract infections relies on different methods and, in general, depends on the skills and experiences of a virological laboratory.

Fortunately, some of the viruses causing respiratory infections can be cultivated in permissive cell cultures, provided that the necessary equipment and technology are available. However, as

the culture method is sometimes time-consuming and the viruses may be extremely difficult to recover, e.g. in the case of hCoV-NL63 and HMPV,[42-44,60] other more rapid diagnostic methods like reverse transcriptase polymerase chain reaction (RT-PCR) or antigen detection assays are preferred in clinical practice. Antigen detection by the enzyme-linked immunosorbent assay (ELISA) method is available for RSV, IV, PIV and ADV and provides a positive or negative result between 15 minutes and 3–6 hours. However, until such assays are developed for routine use for newly detected pathogens like HMPV or hCoV NL-63,[43] the method of choice is to detect the viral nucleic acid. Thus, PCR or RT-PCR plays a crucial role in the detection of newly detected viral respiratory pathogens. For most of these agents, however, it is still unknown how long the PCR remains positive in respiratory specimens after the cessation of the clinical illness.

Besides the high sensitivity of the RT-PCR/PCR, this method is advantageous in detecting additional infection by another virus, commonly described as co-infection. However, as the viral RNA may take 5–6 weeks to disappear from nasal mucus, e.g. after the onset of symptomatic respiratory infection by rhinoviruses,[61] it may not be clear which of the viruses detected is responsible for the clinical symptoms. Therefore, the duration of detection should be investigated, to avoid false positive PCR results, weeks or possibly months after the first infection.

4.2 Bacterial Infections

Any chronic respiratory tract infection may contribute to the aggravation of symptoms in patients with asthma, as the immunological response to the infection may foster the development of bronchial hyperreactivity, the inception of new atopic symptoms against common respiratory allergens, and the chronic inflammatory and remodeling process of the airways,[50,51] although the contribution to the latter remains highly speculative. On the other hand, chronic pulmonary inflammation and its deleterious effects on mucociliary clearance, drainage of mucus and cell debris and reduced airway patency enable the development of viral and bacterial superinfections.

There is a consensus that typical bacterial respiratory pathogens such as *Streptococcus pneumoniae* or *Haemophilus influenzae* have not been associated with the exacerbation or the inception of childhood asthma, and that the routine administration of β-lactams to patients with asthma exacerbations provides no significant benefit.[52,62]

The potential contribution of atypical bacteria, in particular *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, to the onset and persistence of childhood asthma is still a matter of ongoing debate.[52] Due to the extraordinary high incidence of viral respiratory infections in infants, the contribution of atypical bacterial pathogens to the inception of asthmatic symptoms in this age group might be underestimated.[52,63] A recently published review by Johnston and Martin[64]on this issue included nine studies in pediatric patients (table II), as well as other studies in adults. The main results of these trials in children are included in table II. Johnston and Martin came to the conclusion that in 15 out of 19 studies, a relationship was evident between asthma and infections with *M. pneumoniae* and *C. pneumoniae*.[64]

C. pneumoniae is a respiratory pathogen distributed worldwide, which causes conjunctivitis, pharyngitis, bronchitis and pneumonia (with pleural effusion in some cases). A subacute onset and a prolonged period of convalescence with ongoing malaise and cough are characteristic. While symptoms of acute sinusitis often accompany acute infection with *C. pneumoniae*, its causative role in chronic sinusitis in school age children has been questioned.[74] Nearly 10% of community-acquired pneumonias in children ≥5 years of age are caused by *C. pneumoniae*; the highest incidence is found in school-age children and adolescents, and about 50% of adults display serum IgG antibodies against the pathogen. It is an obligate intracellular parasitic bacterium which utilizes the energy metabolism of the human host cells for its replication. *C. pneumoniae* is transmitted by direct contact, droplets and (to a much lesser extent) by aerosol nuclei or fomites in conditions of high relative humidity. The incubation period is approximately 21 days,[52,75] and the attack rates are relatively low, even in family contacts. Infection with *C. pneumoniae* is usually followed by a specific immune response of IgM, IgG and IgA antibodies against certain bacterial antigens. This humoral immune response is not obligate; in particular, infants and young children may fail to mount sufficient antibodies in spite of culture-confirmed infection.[75-80] Thus, it is not clear whether the immune response can be used to differentiate between colonization and infection in young children.

Hahn et al. first observed in 1991[81] that 9 of 19 wheezing adults displayed serologic signs of an infection with *C. pneumoniae*. These findings were extended 5 years later when the same group suggested that the detection of IgA antibodies against *C. pneumoniae* corresponded with a higher probability of recent asthma symptoms.[82] Furthermore, in school-age children with wheezing, Cunningham et al.[67] observed an unusually high number of individuals with low-grade *C. pneumoniae* infection.

In contrast to viral respiratory infections, *C. pneumoniae* contributes only rarely to acute asthma exacerbations,[69] but an association between chronic infection with *C. pneumoniae* and the subsequent onset of asthma has been suggested by some authors. Nagy et al.[70] found a significantly higher risk of asthma in children infected with *C. pneumoniae* isolates with variant man-

Table II. A summary of studies investigating the contribution of the atypical bacteria *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* to childhood asthma[64]

Study (year)	Inclusion	Diagnostic methods	Results and comment
Emre et al.[65] (1994)	118 children with acute wheezing (emergency department); 41 healthy matched controls	Culture; serology, including IgG, IgM (MIF) and IgE (EIA)	*C. pneumoniae* in 11% (wheezers) vs 4.9% (controls) 7 (58.3%) of 12 children with positive cultures had no detectable antibody and only 3 (25%) children had serologic evidence of acute infection 9 (75%) of the infected patients experienced an improvement of their reactive airway disease after treatment with erythromycin or clarithromycin (culture switched to negative in 100%)
Emre et al.[66] (1995)	Culture-positive children with stable asthma (n = 14); 11 culture-negative asthmatic children; 11 culture-negative controls	Culture Serology, including IgG, IgM (MIF) and IgE (EIA)	IgE against *C. pneumoniae* was detected significantly more often in culture-positive asthmatic children than in culture-negative asthmatic children and in controls (86% vs 18% vs 22%; $p < 0.001$ and $p < 0.006$, respectively) The authors speculated that the production of specific IgE against *C. pneumoniae* may foster the development of asthma
Cunningham et al.[67] (1998)	Longitudinal study over 13 months in 96 children (aged 9–11y) with asthma; NPA routinely collected at defined intervals and in case of any clinical exacerbation (no controls)	PCR (NPA); EIA for secretory IgA	43 of 96 (45%) children with asthma displayed a positive *C. pneumoniae* PCR at least at one time point of the study *C. pneumoniae*-specific secretory IgA antibodies were >7 times greater in subjects who reported ≥4 exacerbations in the study ($p < 0.02$) *M. pneumoniae* was only detected in 4 of 357 samples (possibly related to the sensitivity of the PCR protocol)
Mills et al.[68] (2000)	198 subjects from a prospective birth cohort study at age 11y (n = 66) and at age 21y (n = 96)	Serology, including IgG and IgA (MIF)	No statistically significant correlation between symptoms suggestive of asthma in the previous 12 months and either IgG or IgA antibody levels. Individuals with high IgG titers (≥128) even showed a protective effect against ever having asthma (OR 0.29; CI 0.10, 0.87) Conclusion: *C. pneumoniae* is not a major risk factor
Esposito et al.[69] (2000)	71 children aged 2–14y with acute wheezing; 80 healthy matched controls. Clarithromycin administered at the discretion of the attending physician (15 mg/kg/day for 10 days)	PCR (NPA); serology using MIF for *C. pneumoniae* and EIA for *M. pneumoniae* (acute and convalescent after ≥4 weeks); skin prick test for common allergens to demonstrate atopy	*M. pneumoniae* in 22.5% (10% <4 years; 38.7% ≥5 years); in children with wheezing ≥5 years, significantly more often detected than in healthy controls (8.7%; $p = 0.0003$). Significantly more children with *M. pneumoniae* showed recurrent wheezing (93.7% vs 29.1% in pts without *M. pneumoniae* infection; $p < 0.001$) *C. pneumoniae* in 15.5% (10% <4 years; 22.6% ≥5 years); in children with wheezing ≥5 years, significantly more often detected than in healthy controls (0%; $p = 0.001$). Significantly more children with *C. pneumoniae* showed recurrent wheezing (72.7% vs 38.3% in pts without *C. pneumoniae* infection; $p = 0.04$) None of the pts infected and treated with clarithromycin (n = 11) but 69.2% of the pts infected but untreated (n = 13) showed a new episode of wheezing ($p = 0.0005$) in the following 3 months No significant difference in the prevalence of atopy between wheezing children with and without infection

Continued next page

Table II. Contd

Study (year)	Inclusion	Diagnostic methods	Results and comment
Esposito et al.[19] (2002)	25 children (aged 2–14y) with an acute episode of wheezing (15 with acute *M. pneumoniae* infection); 16 healthy matched controls (8 with laboratory evidence of asymptomatic acute *M. pneumoniae* infection)	PCR and serology using EIA for *M. pneumoniae*	In symptomatic children, IL-5 concentrations were significantly higher in those with acute *M. pneumoniae* infection ($p < 0.0001$). Children with acute *M. pneumoniae* infection and wheeze had higher IL-5 concentrations ($p < 0.0001$) IL-5 has been shown to be essential for the development of airway hyperresponsiveness in RSV infection[21]
Nagy et al.[70] (2003)	139 children with asthma; 174 healthy control subjects	Serology (ELISA); MBL variant alleles of the isolated *C. pneumoniae* strains (PCR)	Higher risk of asthma development in infected children with variant MBL alleles than infected children with normal MBL genotype. Especially high asthma risk in children with chronic or recurrent infection (positive results for both IgA and IgG; adjusted OR, 5.38; CI 1.75, 14.36; $p = 0.01$)
Thumerelle et al.[71] (2003)	82 symptomatic children (aged 2–16y) with ≥3 episodes of recurrent reversible wheezing; 27 asymptomatic asthmatic outpatients as controls	IF for influenza, RSV, PIV, ADV, and CV; PCR for rhinovirus and enterovirus; serology for *M. pneumoniae* and *C. pneumoniae*	Viral pathogens were diagnosed in 38% of symptomatic patients. Serology revealed a low prevalence of *M. pneumoniae* and *C. pneumoniae* infection in symptomatic patents of 5% each. Although atypical infections were linked to prolonged asthmatic symptoms, no correlation between infection and severity of chronic asthma or asthma exacerbations was found
Korppi et al.[72] (2004)	122 children aged 1–6y, treated for new asthma as inpatients or outpatients; 244 controls, matched by age, sex and municipality	MIF for *C. pneumoniae* and *C. trachomatis* antibodies; EIA for *C. pneumoniae* antibodies	IgG antibodies to *C. pneumoniae,* though common in 1- to 6-year-old children as detected by EIA (31–36%), did not differ between newly diagnosed asthma patients and controls The prevalence of IgA antibodies (EIA) was much lower (4–7%) but likewise not different between patients and controls
Biscardi et al.[18] (2004)	119 children (2–15y) with previously diagnosed asthma, hospitalized with exacerbation; 51 children with first asthma attack followed-up at 12 months; 152 children with stable asthma or allergic rhinitis as control group	PCR (NPA); serology (acute and convalescent after ≥4 weeks)	*M. pneumoniae* in 24 (20%); *C. pneumoniae* in 4 (3.4%) Subgroup with first asthma attack (n = 51): *M. pneumoniae* in 50% ($p < 0.01$); *C. pneumoniae* in 8.3% Control group: *M. pneumoniae* IgM in 5.2% ($p < 0.005$) Risk of recurrent wheezing was higher in first-attack children with *M. pneumoniae* or *C. pneumoniae* infection (62% vs 27%; $p < 0.05$). Conclusion: *M. pneumoniae* may play a role in the onset of asthma (50%) and increases the risk of recurrence
Webley et al.[73] (2005)	Blood and BAL samples from 70 pediatric patients undergoing flexible fiberoptic bronchoscopy (including 42 pts with asthma and 38 pts with various respiratory disorders); 70 matched control subjects without respiratory illness	PCR (BAL and blood); culture; electrochemiluminescence assay for IgE	44% of the BAL samples were PCR-positive for *Chlamydophila*, and 31% of the PCR-positive samples were positive when cultured on macrophages. Forty percent of the PCR-positive and 20% of the culture-positive samples, respectively, were from patients with asthma 34.3% of the blood samples were positive for *Chlamydophila* compared with 11% of 70 matched nonrespiratory controls ($p < 0.01$); 24% of the positive blood cultures from the respiratory group were from patients with asthma Elevation of total IgE was strongly associated with BAL culture positivity for *Chlamydophila* (77.3 vs 18.8%; $p < 0.0001$)

ADV = adenovirus; **BAL** = bronchoalveolar lavage; **CI** = 95% confidence interval; **CV** = coronavirus; **EIA** = enzyme immunoassay; **ELISA** = enzyme-linked immunosorbent assay; **IF** = immunofluorescence; **Ig** = immunoglobulin; **IL** = interleukin; **MBL** = mannose-binding lectin; **MIF** = microimmunofluorescence; **NPA** = nasopharyngeal aspirate; **OR** = odds ratio; **PCR** = polymerase chain reaction; **PIV** = parainfluenza virus; **pts** = patients; **RSV** = respiratory syncytial virus.

nose-binding lectin alleles (confirmed by PCR), in particular in those with chronic infection (confirmed by both positive IgG and IgA antibodies). Mills et al.,[68] however, could not determine a significant correlation between *C. pneumoniae* serology and asthma (table II). Because of its retrospective nature (antibodies were detected in stored serum samples), no results from culture or PCR were available to identify which patients harbored *C. pneumoniae* in their airways. In addition, only 22.9% of all individuals reporting asthma symptoms showed a bronchial hyperreactivity and the authors did not differentiate according to the two age groups (11 and 21 years; table II). The authors emphasized in their discussion that seroconversion is not universally associated with clinical infection and questioned the principle of assessing the effect of a respiratory infection on a chronic pulmonary disease simply by the measurement of antibody titers in serum.

On the contrary, two groups found an inverse correlation between *C. pneumoniae* respiratory tract infection and the inception of asthma or allergic rhinitis in children.[83,84] Such data about the role of *C. pneumoniae* in the inception and development of asthma in children are intriguing, but somewhat controversial; further well designed studies are needed. One recently published study[73] (table II) not only detected *C. pneumoniae* in bronchoalveolar lavage (BAL) samples from asthmatic children with PCR, but also confirmed the viability of the pathogen in culture, and correlated an elevated total level of IgE with lavage culture positivity for *C. pneumoniae*. The authors concluded that viable *C. pneumoniae* are frequently present in BAL specimens from symptomatic children with asthma.[73]

M. pneumoniae is a common pathogen in upper and lower airway infections including otitis media, pharyngitis,[85] tracheobronchitis and pneumonia in all age groups older than 12 months.[86] *M. pneumoniae* is an extracellular mucosal pathogen attached to the respiratory epithelium via a specific part of its cell, the organelle. The extent to which it invades and replicates intracellularly *in vivo* is not known.[21] The cellular and humoral immune response to the infection is responsible for clinical illness and airway injury. Acute infection is accompanied by lymphocyte proliferation and the release of tumor necrosis factor (TNF)-α, IFNγ, and various interleukins (IL2, IL4, IL5, IL6, IL8, IL10, and IL18).[21]

However, the distinct role of *M. pneumoniae* in asthma pathogenesis still has to be resolved.[16,50] Biscardi and colleagues[18] have reported the highest prevalence of *M. pneumoniae* infection; 50% of children with a first asthma attack, and 20% of children with previously diagnosed asthma and acute severe exacerbation. Although the authors searched for viruses, they did not use PCR methods and no immunofluorescence assay was available for the detection of rhinovirus, the most important viral pathogen in asthma exacerbations in school-aged children.[22,37,55,63]

4.2.1 Diagnosis

A series of very detailed investigations of the clinical, laboratory, and radiologic presentations of community-acquired pneumonia in children under the age of 5 years revealed that no combination of clinical signs, host acute phase response markers at any cut-off value, or radiologic findings reliably differentiates between bacterial and viral or between atypical and typical pneumonia in this age group.[72,87-89] Thus, microbiologic diagnostic efforts are indispensable to identify the responsible respiratory pathogen.

Initially, *C. pneumoniae* was designated as TWAR strain of *C. psittaci,*[90] but differences in DNA sequences, epidemiology, and also pathogenicity led to the actual classification of this pathogen. Furthermore, there is a high prevalence of IgG antibodies against *C. pneumoniae* in the general population (>50% in adults).[90] Thus, the laboratory diagnosis, in general, is based on serologic testing.

As a result of a consensus conference held at the Centers for Disease Control and Prevention, USA, Dowell and colleagues[91] concluded that acute infection with *C. pneumoniae* is accompanied by the appearance of IgM antibodies that can be detected 2–3 weeks after the onset of clinical symptoms. Thereafter, IgM antibodies are detectable up to 2–6 months and are replaced by low titers of IgG antibodies that firstly appear 6–8 weeks after infection. Dowell and colleagues concluded that the use of a single parameter will not lead to a complete diagnosis and that PCR, although not yet standardized, will be of increasing importance as a future tool for diagnosis. Furthermore, they stated that 'there are no wholly satisfactory serological methods for diagnosis of *C. pneumoniae* infection.'[91]

The PCR method for pathogen detection is of increasing importance for the second atypical bacterial pathogen related to asthma, *M. pneumoniae*. However, the major obstacle to the use of PCR as the single method for the detection of *M. pneumoniae* or *C. pneumoniae* is that it does not distinguish between viable and nonviable bacteria, for example after antibacterial chemotherapy.[92] Thus, at least one other method is recommended for the laboratory diagnosis of both infections.

The most frequently used method to detect specific antibodies in the majority of studies that investigated an association between asthma and *C. pneumoniae* infection is the microimmunofluorescence test.[64,91] Alternative serological assays have been described, but the lack of commercial availability and limited specificity (cross-reactive antibodies) have impeded their broader use in practice.[91,92]

The laboratory diagnosis of *M. pneumoniae* is more complex and even more difficult. Although *M. pneumoniae* can be cultivated on solid media, its growth is extremely slow (≥6 days), and the culturing methods are extremely insensitive. Thus, it is difficult to get a rapid diagnostic result with this method. However, *M. pneumoniae* can be isolated from swabs, retronasal aspirates, sputum, or BAL. In all cases where the subsequent culturing of the pathogen is required or desired, the specimen should be solved (i.e. material should be mixed with medium) in adequate transportation media. For rapid detection, the material can be investigated with enzyme immunoassays, oligonucleotide hybridization methods, or PCR assays.

While culturing on solid-phase media, middle-sized granulated colonies without the typical 'fried egg' appearance are formed. For orientation, *M. pneumoniae* can be identified via glucose cleavage reactions, hemadsorption, and hemolysis, and finally the identification procedure can be finished by a growth inhibition test and/or epifluorescence. Because of the insensitive culturing method and the difficulties of other methods, in addition to the direct or indirect detection of *M. pneumoniae*, serologic testing can and should be performed. Traditionally, such serologic detection of a *M. pneumoniae* infection was performed by complement fixation. This assay has the general limitations that it is: (i) impossible to differentiate antibody subclasses; (ii) lacks specificity; and thus, (iii) cannot differentiate between acute, chronic, or previous infections.[64] Meanwhile, the commonly used serologic test that replaced complement fixation is the ELISA method, which has the major advantage that there some assays commercially available and these tests specifically differentiate between different stages of the infection.[64]

All in all, the diagnosis of atypical respiratory tract infection is still laborious, sophisticated, expensive, and time consuming. There is an urgent need for sensitive, specific, standardized, and economically inexpensive diagnostic tests that can be used at the bedside or at least yield results within 2–6 hours.[18] Only if the pathogen can be easily identified and its detection can be definitely attributed to infection (vs colonization) will it be possible to confirm its role in the inception of the chronic inflammatory process; prospective randomized studies on the best therapeutic intervention can then be performed.[69] Modern multiplex PCR approaches detect an extended spectrum of pathogens in parallel, thereby reducing costs for material and personnel. Although this approach is intriguing, the 'reality check' of some published methods often yields much lower detection rates than expected. This problem will probably be overcome by the recent 'upgrade' of these multiplex assays as described by Khanna et al.[93] These authors developed the Pneumoplex®[1] assays that combine multiplex PCR and hybridization assays while being highly specific and highly sensitive.

5. Prevention and Treatment of Viral Infections

Almost 50 years after the first description of RSV, physicians attending children with viral respiratory tract disease and asthma are still awaiting the development of effective and economically inexpensive medications for the prevention and treatment of respiratory viral infections in infants.[45] For the majority of respiratory viruses there is no specific therapy available to impede infection or to inhibit viral replication in the infected host. In most cases, treatment is symptomatic with no specific intervention fighting the pathogen. In contrast to bronchiolitis in hospitalized infants and children without a history of asthma or recurrent wheezing,[31,94] the early administration of systemic corticosteroids represents the primary means of treatment in severe asthma exacerbations,[3,16] irrespective of any acute infection (the only exception is a varicella zoster virus infection in which systemic corticosteroids should only be given under systemic aciclovir coverage).

The neuraminidase inhibitors oseltamivir and zanamivir are active against influenza viruses and are available for the treatment of microbiologically confirmed influenza.[95] These substances inhibit the enzymatic activity of neuraminidase and are thought to prevent the release of newly budded progeny virions from the cell surface. The neuraminidase inhibitors have to be used very early (within the first 72 hours) during the course of the disease, or even as a chemoprophylaxis. Thus, a rapid laboratory diagnostic test that detects the viral RNA or the viral antigen is mandatory to guide decisions on treatment.

Another possibility to prevent influenza-triggered asthma is to prevent the infection by vaccination. Although this possibility is highly desirable, the major disadvantage is that vaccination targets actual influenza strains. In epidemic seasons, when new strains emerge (as most recently observed for the avian influenza virus H5N1), a new specific vaccine must be developed and, in general, is available only in the middle of the ongoing epidemic or for the next epidemic season. However, we strongly recommend vaccination of any high-risk group, especially those with an increased risk of asthma. In the near future, newer vaccine formulations and live, attenuated influenza vaccine strains[96-99] may complement current vaccination strategies.

A specific passive immunoprophylaxis and also a nonspecific antiviral therapy are available to prevent or treat infections with human RSV. The first option is immunoprophylaxis with

1 The use of trade names is for product identification purposes only and does not imply endorsement.

palivizumab, a humanized monoclonal antibody binding to the highly conserved F protein of both RSV-A and RSV-B subtypes.[32] The efficacy of palivizumab (mainly a significant reduction of the percentage of children who have to be rehospitalized with RSV infection in the first 24 months of life) was tested in two well-designed, prospectively randomized, double-blind multicenter studies.[100] However, the prophylactic use of this antibody is limited due to its high cost; thus, its application is recommended only for high-risk premature infants, for infants with hemodynamically relevant congenital heart disease,[46] and (not at the same level of evidence) in RSV-infected patients after allogenic blood stem cell transplantation.[101,102]

- Antiviral therapy for RSV infections is possible and sometimes successful with ribavirin, administered by the inhalation of aerosols from a small-particle aerosol generator. This therapy may be an option in the case of life-threatening RSV infections in mechanically ventilated premature infants or in severely immunocompromised children. In the latter group, ribavirin has been suggested as a treatment option in patients with severe influenza or parainfluenza virus infection.[102] Even in those high-risk populations, its routine use is controversial due to a lack of evidence of a significant benefit in randomized controlled studies, as well as cost issues, and potential toxicity (and teratogenicity) in both patients and exposed caregivers.[103] One study of ribavirin use in infants with severe bronchiolitis, observed a long-term benefit on subsequent airway hyperreagibility.[104] Even if this could be confirmed in further controlled trials, no valid clinical or laboratory parameter indicates which subgroup of patients will experience such a positive outcome.
- As reviewed by Weinberger,[52] a number of compounds are known to display only marginal cytotoxic effects while being highly active against RSV in inoculated tissue culture. Three compounds are already being tested in phase I or phase II trials: pleconaril, RSV 604 (A 60444), and RF I641.[52,105] However, neither ribavirin nor any of the new therapeutic agents active against RSV have been assessed or licensed for use in children with recurrent wheezing or asthma.[52]

The respiratory viruses most frequently detected in school-age children with asthma are the rhinoviruses. While no specific treatment against rhinoviruses is available yet, an increasing number of promising drug candidates are under development or even in the early phase of clinical trials. One of these drugs that has successfully passed a phase II clinical trial is rupintrivir,[106] a selective irreversible inhibitor of the rhinoviral 3C-protease which is administered intranasally. It is a peptidomimetic compound with poor aqueous solubility and low oral bioavailability in animals,[107] but it was well tolerated in healthy adult volunteers.[108] Pleconaril may be another future option for the treatment of rhinovirus infections as it inhibits the attachment of virus to host cell receptors and the uncoating of viral nucleic acid.[109] Pleconaril can be applied orally and is distributed to the upper and lower airways after enteral absorption. Infection with rhinoviruses, however, has not been a major inclusion criterion in clinical studies of pleconaril.[110]

ICAM-1 is an important cellular receptor for the attachment of rhinoviruses. There have been experimental approaches to inhibit the virus-receptor interaction by monoclonal antibodies or antagonistic molecules. One antibody-like compound CFY 196 is a recombinant antibody fusion protein and may be a promising candidate for further investigations and clinical trials. Another compound, sICAM-1 (tremacamra), consists of an ICAM-1 derivate in which the transmembrane and intracellular domains have been truncated.

Specific therapies or vaccinations are lacking for human metapneumovirus and respiratory coronaviruses. Furthermore, data on experimental usage of antivirals *in vitro* that should inhibit the replication of these viruses are ambivalent and not very promising, and even the development of specific vaccines has not yet been as successful as expected.

For human metapneumovirus, as for the other 'untreatable' viral pathogens, prospective controlled studies are needed to confirm or refute the efficacy of any therapeutic intervention in infants and children with recurrent wheezing, asthma, bronchiolitis, or pneumonia. It should be proven in prospectively randomized double-blind studies with sufficient power that a certain therapeutic intervention has a positive impact on illness severity (breath rate and oxygen saturation), length of inpatient care, and the necessity to admit the patient to the intensive care unit or to start mechanical ventilation. It is also important to identify evidence-based treatment methods to avoid the unjustified consumption of financial resources. In this context, systemic treatment with corticosteroids[31,111,112] or inhalation treatment with beta mimetics or adrenaline (epinephrine)[31,111,112] should be investigated critically. For example, in epidemiologic studies published up till 2005, 26–44% of all HMPV-infected hospitalized pediatric patients received systemic corticosteroids, and half of them were treated with bronchodilators. Due to the increasing number of clinically relevant viral respiratory pathogens and also the increasing number of newly developed antiviral drugs, the absolute prerequisite for a specific treatment remains a rapid and specific diagnostic approach.

Specific therapy options for viral infections are summarized in table I.

6. Treatment of Atypical Bacterial Infections

Taken together, results from Italy[69,113] and France[18] support the use of antimicrobials in patients with asthma and microbiologically confirmed *M. pneumoniae* or *C. pneumoniae* infection. Schmidt et al.[114] recently demonstrated that in children with therapy-refractory bronchitis or pneumonia, bronchial *C. pneumoniae* co-infection was associated with more severe disease. In their study, and others,[87,115] adequate antibacterial therapy for *C. pneumoniae* infection was shown to improve pulmonary function. Figure 1 presents an algorithm for the management of atypical pulmonary infections in patients with asthma or recurrent wheezing.

In this context, the principle aims of treatment are:

- The infection should be eradicated, not only suppressed.[79,80,116] However, this seems to be not so easy to achieve in *C. pneumoniae* infections. Therefore, some authors recommend an empirical second cycle of treatment if symptoms persist or recur.[90]
- Relief of acute symptoms in patients with acute infection should be prompt (those infections are self-limiting diseases in immunocompetent persons).
- The number and the severity of recurrent wheezing exacerbations during follow up should be reduced.[18,69]
- The inflammatory stimulus of chronic pulmonary infection with atypical pathogens on the underlying pulmonary disease should be stopped and the adverse effects of the cellular and humoral immune response on bronchial hyperreactivity should be contained.[19,21,113]

The microbiologic targets are obligate intracellular organisms (*C. pneumoniae*) or bacteria without a common Gram-positive/Gram-negative cell wall, rendering both pathogens *a priori* resistant to all β-lactams, glycopeptides, and carbapenems. In addition, *M. pneumoniae* is not susceptible to sulfonamides, rifampicin, or linezolid.

First-line agents for the treatment of infections due to *M. pneumoniae* or *C. pneumoniae* in children are the macrolides (erythromycin, clarithromycin, or roxithromycin) and the azalide azithromycin. Erythromycin and clarithromycin are available as intravenous preparations if the condition of the child does not allow oral medication. In children ≥8 years of age, intravenous doxycycline may be used as a feasible alternative, although there are no comparative studies on the use of doxycycline in children and adolescents besides its use in the treatment of tick-borne infections, melioidosis, or brucellosis.[117-120] However, at least in the US, azithromycin is available for intravenous use, but not clarithromycin, demonstrating that not only scientific reasons, but also individual local legal restrictions, may limit the use of an antimicrobial agent.

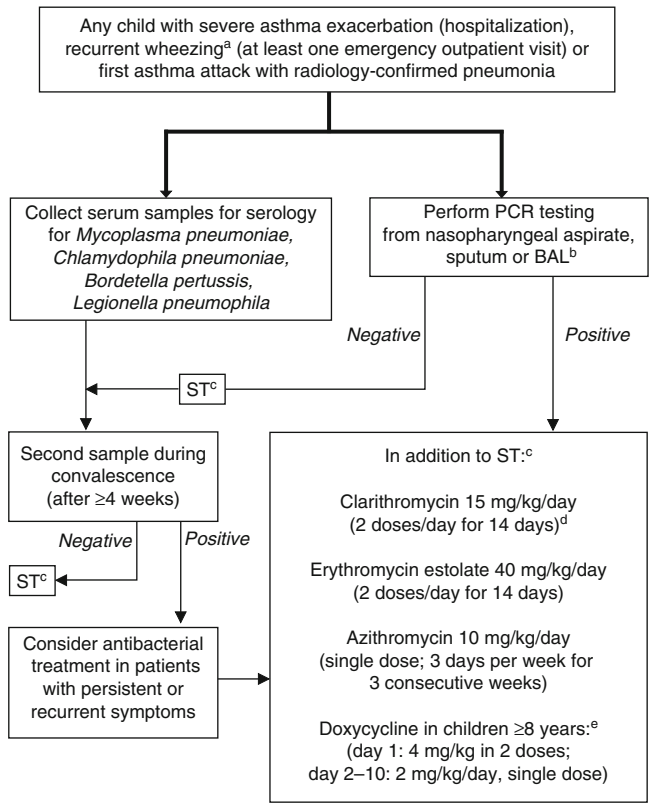

Fig. 1. Algorithm for the management of atypical infections in patients with asthma or recurrent wheezing. **BAL** = bronchoalveolar lavage; **PCR** = polymerase chain reaction; **ST** = standard therapy. **a** ≥3 episodes of reversible obstructive airway disease irrespective of any viral infection. **b** In intubated, mechanically ventilated patients. **c** Controller medication to be adjusted to the clinical severity of the symptoms (systemic/inhaled corticosteroids or montelukast).[3,16] To avoid an unnecessary increase in selective pressure and an increase in macrolide-resistant pathogens, community-acquired pneumonia in outpatients should be treated with amoxicillin/clavulanic acid or sulbactam/ampicillin or cefuroxime as first-line agents unless there are distinct features of atypical pneumonia in the medical history (i.e. a combination of subacute onset, low-grade fever, hoarseness, dry 'hacking' cough, malaise, myalgia, or headache). **d** Consider the use of systemic corticosteroids and intravenous immunoglobulins in any patient with extrapulmonary manifestations of *M. pneumoniae* disease (CNS, arthritis, nephropathy, or carditis). Fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin) and the ketolid telithromycin are third-line agents for the treatment of atypical pneumonia in pediatric patients with underlying immunodeficiency or life-threatening infections. **e** Do not use doxycycline against *B. pertussis* or *L. pneumophila* infection.

Third-line agents for the treatment of atypical pneumonia in severely immunocompromised children and adolescents are the fluoroquinolones (i.e. levofloxacin and moxifloxacin) or the ketolide telithromycin. Due to potential toxicities,[121] licensing issues and general considerations not to increase selective pressure on resistant pathogens,[122] the use of these agents is not standard in

children with recurrent wheezing or asthma, and are thus beyond the scope of this review.

From a microbiologic perspective, it seems reasonable to use clarithromycin (15 mg/kg/day in two doses for at least 14 days) as a first-line agent as it displays very promising *in vitro* sensitivity results, with minimum inhibitory concentrations ≤0.001–0.125 μg/mL (as do erythromycin and azithromycin). A prospective randomized study of 124 children treated with clarithromycin (tested against erythromycin ethylsuccinate 40 mg/kg/day in two or three divided doses in 110 patients) confirmed clinical and radiologic success in 98%, and an eradication of *M. pneumoniae* in 100% (n = 9).[123] *C. pneumoniae* was eradicated in 79% (culture). The gastrointestinal tolerability of clarithromycin seems to be better than that of erythromycin and it can be administered twice daily.

In contrast to azithromycin, the pharmacokinetic pattern of clarithromycin does not result in prolonged subtherapeutic plasma levels and an increased risk of subsequent colonization with macrolide-resistant pneumococci.[124-126] This clinically relevant observation has been refuted by others.[28] Arguments for the use of azithromycin are: it is highly active *in vitro*;[21] at least two randomized controlled trials in children confirmed its efficacy and safety against atypical community-acquired pneumonia;[127,128] children find the color and taste of the oral suspension of azithromycin agreeable; and the drug is well tolerated.[129] It is administered in a single daily dose. In addition, a substantial line of evidence suggests that azithromycin displays favorable immunomodulatory and anti-inflammatory effects in patients with chronic inflammatory pulmonary diseases like cystic fibrosis,[130,131] and bronchiolitis obliterans after stem cell transplantation.[132,133] Interestingly, Esposito et al.[113] investigated the use of azithromycin in children >8 years of age and with a physician's diagnosis of recurrent respiratory infections. Their results in the group of patients without an atypical bacterial infection demonstrated a significant benefit, which might have been related to the anti-inflammatory properties of azithromycin.

6.1 Drug Interactions

Treatment with erythromycin and, to a lesser, but still considerable extent, clarithromycin may result in clinically relevant, potentially toxic interactions with drugs that are (as the two macrolides) metabolized via hepatic cytochrome P450 microsomal enzymes.[129] Most relevant in patients with asthma is the profound elevation of theophylline plasma levels and the enhanced cardiotoxicity of antihistamines like terfenadine (prolonged QT interval, increased risk of ventricular arrhythmias, and torsade des pointes). Azithromycin does not interact with these enzymes and may be combined without subsequent problems, e.g. for example with cyclosporin after stem cell or organ transplantation.[134]

6.2 Duration of Treatment

No controlled trials are available on the optimal duration of treatment in childhood atypical bacterial tracheobronchitis or pneumonia. Considering the observation of persistent colonization after conventional treatment regimens, in particular in *C. pneumoniae* infections,[79,80,116] it seems reasonable to use a prolonged treatment schedule in children with asthma and confirmed atypical bacteria infection, as suggested by Esposito et al.[113] for azithromycin (i.e. 10 mg/kg/day for 3 days per week in 3 consecutive weeks). Alternatively, the use of clarithromycin for at least 14–21 days may be considered.[90] Further well designed, randomized and controlled trials are clearly needed to examine the effectiveness of different antibiotics against *M. pneumoniae* or *C. pneumoniae* and the optimal dose and duration of therapy in various patient populations.[135]

7. Conclusion

Although the number of pathogens suspected to be associated with acute or chronic asthma pathogenesis in childhood is increasing, the number of options for specific therapies available now or in the near future is also increasing. Thus, before starting a therapy it is strongly recommended that clinicians perform a rapid clinical and laboratory diagnosis accompanied by a detailed history. Thereafter, a specific and individual therapy regimen should be considered in order to avoid the development of resistance and to minimize drug-specific adverse effects or unnecessary drug interactions. In this manner, treatment may avoid acute and/or chronic asthma in the affected patient.

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