Clinic Rev Allerg Immunol (2015) 48:104–113
DOI 10.1007/s12016-014-8435-x

Infection in Severe Asthma Exacerbations and Critical Asthma Syndrome

Christian E. Sandrock · Andrew Norris

Published online: 2 July 2014

Abstract In chronic persistent asthma and severe acute exacerbations of bronchial asthma, infectious agents are the predominant triggers that drive disease and airway pathobiology. In acute exacerbations of bronchial asthma (AEBA) including near fatal and fatal asthma, viral agents, particularly human rhinovirus-C, respiratory syncytial virus and influenza A appear to be the more prevalent and recurring threats. Both viral, and to a lesser extent bacterial agents, can play a role, and co-infection may also be present and worsen prognosis in hospitalized patients, placing a portion at risk for critical asthma syndrome. During severe acute exacerbations, infectious agents must be treated empirically, but the initial treatment regimens can vary and viral coverage may also vary based on seasonality and patient age. Early treatment with ceftriaxone and azithromycin, along with oseltamivir in winter months, should be initiated with all cases of severe exacerbations where infection is suspected, and definitely in critical asthma syndrome until infection is excluded by appropriate diagnostic testing. In this manuscript we will outline the impact of the major viral agents on severe asthma including the data from the 2009 H1N1 influenza pandemic. The role of bacterial infections in acute exacerbations of asthma will also be reviewed as well as the benefit of empiric antibiotics and the role of macrolides in both acute and chronic asthma.

Keywords Acute Exacerbation of Bronchial Asthma (AEBA) · Critical asthma syndrome · Community acquired pneumonia · Viral pneumonitis

C. E. Sandrock (✉) · A. Norris
Division of Pulmonary, Critical Care, and Sleep Medicine, University of California, Davis, School of Medicine, 4150 V Street, Suite 3400, Sacramento, CA 95817, USA
e-mail: cesandrock@ucdavis.edu

Introduction

The role of respiratory infections in wheezing illnesses, including COPD and asthma, has been established for some time. Both bacterial and viral respiratory infections in acute exacerbations of bronchial asthma (AEBA) in children and adults have become increasingly important given the significant morbidity and mortality associated with these diseases. Particularly important is critical asthma syndrome which is defined as a severe and sudden respiratory condition, i.e. critical asthma, status asthmaticus, near fatal asthma that, although needing aggressive and urgent treatment, has not progressed to irreversible hypoxia and cardiopulmonary arrest. During severe acute exacerbations, infectious agents must be treated quickly and empirically, but the initial treatment regimens can vary widely and include bacterial, atypical and viral depending on regional epidemiology. Antibiotics in particular may offer additional benefit, e.g. anti-inflammatory and thus alter the course of the disease independent of their antimicrobial effect. We examine the impact of the major viral and bacterial agents on severe asthma including data from the 2009 H1N1 influenza pandemic. The additional benefit of empiric antibiotics and the role of macrolides in both acute and chronic asthma will also be reviewed.

The Role of Viral Infections in Acute Exacerbation of Bronchial Asthma (AEBA)

Epidemiology of Viral Infections in AEBA

Viruses are the most common cause of upper respiratory infections (URI's) and lower respiratory tract infections (LTRI's) in both children and adults. URI's occur frequently in children and most adults experience 2–4 URI's per year [1]. The role of viral infections in acute exacerbations of asthma is

well known with approximately 85 % to 95 % of acute exacerbation of bronchial asthma (AEBA) in children caused by viral infections [2] and up to 60 % of asthma exacerbations in adults related to upper respiratory tract infections [3]. Recent advances in the detection of viral DNA and RNA, e.g., viral respiratory panel, have helped to confirm this data with a significant increase in the weighted average of viral identification noted in patients of all ages with asthma exacerbation [4]. The main features of viruses that may impact asthma are listed in Table 1.

A strong relationship between the seasonal incidence of asthma exacerbations and viral infection has also been established, and viral infections were found to be the major identifiable risk factor for autumn and winter asthma exacerbations [5, 6]. The absence of a correlation between pollen or spore counts and asthma exacerbations additionally highlights the role of viral infections as the cause of AEBA [5]. For critical asthma syndrome, e.g., near-fatal asthma, viral infections also are the predominant associated trigger. Tan et al. detected viral nucleic acids in 59 % (10 out of 17 patients) with near-fatal asthma (picornavirus and adenovirus) [7]. Thus, from mild AEBA to critical asthma syndrome and fatal asthma, viral pathogens are the most commonly associated risk factor.

Viral-Induced Changes in Airway Biology

The role of viral infections in changes in airway biology continues to evolve, but a few associations have been established. Patients with asthma experience a similar number of URI's as their healthy cohabitants [8]. However, people with asthma have a twofold greater risk of developing lower airway infections and they tend to have more severe symptoms and symptoms for a greater duration than their healthy counterparts. This suggests that asthmatics have an inability to contain and remove the virus or limit the initial upper airway response to the virus. Several mechanisms for the viral-induced changes in the airway have been proposed, including airway inflammation, mucus hypersecretion, and bronchial hyperresponsiveness.

The majority of research examining viral-induced changes in airway biology has been completed with human rhinovirus. Wark et al. demonstrated that the viral RNA expression and release of viruses was increased in epithelial cells of asthmatic patient when compared to controls [9]. Rhinovirus has been shown to increase the number of inflammatory cells including neutrophils, lymphocytes, and eosinophils in the airway during acute infection [10]. Rhinovirus increases the plasma histamine content during infection [11] as well as the sensitivity of bronchial cells to histamine [12] leading to increased airway inflammation. Additionally, rhinovirus increases nitric oxide (NO) production. Sanders, et al. demonstrated a significant increase in both nasal and lower airway exhaled NO (eNO) in healthy volunteers infected with human rhinovirus 16 (HRV-16) [13]. In patients with bronchial asthma, infection with experimental rhinovirus also increased the NO concentrations and the authors suggested viral induced cytokine release causing increased iNOS (inducible NO synthase) activity by alveolar macrophages and epithelial cells as the source of the increased NO [12]. High concentrations of NO in the airway likely have a proinflammatory effect. However, NO may play a dual role in the airway by both reducing hyperresponsiveness and helping to resolve cold symptoms [12, 13].

The role of mast cell degranulation in innate host defense against bacterial infections has been established and it may also play a role in in the defense against viral pathogens leading to mucosal inflammation and edema [14]. Extensive mass cell degranulation has been demonstrated in calves infected with bovine respiratory syncytial virus [15] and activation of mast cells by H5N1 both in vivo and in vitro has been demonstrated in mice leading to severe inflammatory response [16].

Additional mechanisms by which viral infections may alter airway biology include mucosal edema and increased smooth muscle contraction in the airway. Influenza virus has been demonstrated to increase the vascular endothelial permeability in mouse lungs by increasing IL-1β, IL-6, TNF-α, and trypsin [17]. Influenza can lead to damage of the respiratory epithelium and denuded airways, even in asthmatic patients with good symptom control [18]. Denuded airways can be associated with vascular leak and cellular inflammation further contributing to airway edema, particularly in severe AEBA. In regards to smooth muscle contraction and viral infection, Hakonarson et al. found direct effects of rhinovirus infection on airway smooth muscle [19]. They showed that in isolated rabbit and human airway smooth muscle (ASM) inoculated with human rhinovirus (serotype 16), there was an increase in ASM tissue constrictor responsiveness to acetylcholine and attenuated dose-dependent relaxation of ASM to β-adrenoreceptor stimulation with isoproterenol. Interestingly, the same response was not demonstrated with adenovirus implying that this may occur with all upper respiratory viral pathogens.

Rhinovirus

Human rhinovirus (HRV) has been well established as the most commonly associated virus in upper respiratory infections as well as in acute asthma exacerbations in children [20]. It is the most common cause of wheezing in children in the community [2]. The studies of HRV in adults are less robust, but the frequency of cause in wheezing appears to be similar to children. In one North American study, 29 % of acute asthma exacerbations in adults were noted to be associated with HRV [21]. HRV was detected in 28 % of adults requiring

Table 1 Main features of viruses that may impact asthma

	Seasonal influenza	Avian influenza	RSV	Adenovirus	hMPV	Rhinovirus
Virus family	Orthomyxo-virdae	Orthomyxo-virdae	Paramyxo-virdae	Adenovirus	Paramyxo-virdae	
Usual clinical syndrome	Influenza	Conjunctivitis, pneumonia	URI	URI	URI	URI
High risk groups for severe asthma	Infants and adolescents	All groups	infants	Institution, immuno-compromised	Immuno-compromised	Asthma and children
Epidemiological link	Winter season or travel	Contact with sick, dead birds and poultry	Winter season	Military camps, mental health facilities	None known	Winter, schools
Mode of transmission	Droplet	Droplet, contact	Droplet, contact	Droplet, contact	Unknown, but droplet and contact suspected	Droplet
Isolation required	Droplet	Airborne and contact initially, droplet possible	Droplet and contact	Droplet and contact	Droplet	none
Diagnostic testing	Antigen assay, viral culture, PCR	Viral culture and PCR	Antigen immunoassay, viral culture, PCR	Viral culture, PCR, antigen assay	PCR	PCR
Treatment	Oseltamivir, zanamivir	Oseltamivir, zanamivir	Ribaviron	Supportive	Supportive	Supportive
Mandatory public health notification	No	Yes	No	No	No	No
	Seasonal influenza	Avian influenza	RSV	Adenovirus	hMPV	Rhinovirus
Virus family	Orthomyxo-virdae	Orthomyxo-virdae	Paramyxo-virdae	Adenovirus	Paramyxo-virdae	
Usual clinical syndrome	Influenza	Conjunctivitis, pneumonia	URI	URI	URI	URI
High risk groups for severe asthma	Infants and adolecents	All groups	infants	Institution, immuno-compromised	Immuno-compromised	Asthma and children
Epidemiological link	Winter season or travel	Contact with sick, dead birds and poultry	Winter season	Military camps, mental health facilities	None known	Winter, schools
Mode of transmission	Droplet	Droplet, contact	Droplet, contact	Droplet, contact	Unknown, but droplet and contact suspected	Droplet
Isolation required	Droplet	Airborne and contact initially, droplet possible	Droplet and contact	Droplet and contact	Droplet	none
Diagnostic testing	Antigen assay, viral culture, PCR	Viral culture and PCR	Antigen immunoassay, viral culture, PCR	Viral culture, PCR, antigen assay	PCR	PCR
Treatment	Oseltamivir, zanamivir	Oseltamivir, Zanamivir	Ribaviron	Supportive	Supportive	Supportive
Mandatory public health notification	No	Yes	No	No	No	No

ILI = Influenza like illness

URI = Upper respiratory tract infection

PCR = polymerase chain reaction

hospitalization for acute asthma exacerbation and in 47 % of adults hospitalized for critical asthma syndrome, i.e., near-fatal asthma requiring mechanical ventilation [7].

The severity of HRV infection is also affected by multiple factors including age, presence of chronic respiratory disease such as asthma, male sex, and reduced lung function [22]. Additionally, species and subtype seems to play a role in the severity of illness. Lee et al. evaluated the species and types of HRV from nasal lavages in infants from birth to 12 months at both scheduled well visits and during episodes of respiratory symptoms [23]. They found that subtypes HRV-A (odd ratio, 8.2) and HRV-C (odds ratio 7.6) were more likely to cause moderate to severe illness (MSI) and that HRV infections were five- to tenfold more likely to cause MSI in winter months. Additionally, in children deemed more susceptible to HRV-induced MSI (based on parental history), the risk of at least one HRV MSI was much higher when compared to low risk and average risk children. HRV-C has been shown to account for the majority of asthma attacks in children presenting to hospital for severe asthma exacerbations and was associated with more severe consequences than other HRV groups and other viruses [24]. HRV-C has also been linked to hospital admission for AEBA [25].

HRV causes an infiltration of neutrophils, lymphocytes and eosinophils in the nasal and bronchial mucosa. Increase in pro-inflammatory substances in lung cells including IL-1α, IL-6, IL-8, IL-11, and TNF-α caused by rhinovirus infection has also been demonstrated [10]. A mild increase in inflammatory changes in the bronchial wall was also demonstrated in patients with asthma infected with RV16 [26]. This increase in inflammation, viral production, and cytokine release is seen clinically in AEBA and probably critical asthma syndrome. In a large longitudinal cohort study, RV infections were also found to be associated with declines in lung function in asthmatics when compared to normal subjects with decline occurring within 2 days after infection with rhinovirus [8].

Respiratory Syncytial Virus (RSV)

The most common and important cause of acute bronchiolitis and acute pneumonia in children is RSV. Infants and children who develop RSV bronchiolitis have an increased frequency of wheezing episodes and the likelihood of asthma diagnosis later in life, although this effect diminishes with increasing age (no definitive age for cutoff but appears to be less than 2 years of age. Do not have definitive study to quote here). RSV is more common in children less than 2 years old although it is sometimes detected in older children during wheezing episodes [27].

Despite the risk of asthma later in life, the role of RSV in acute severe AEBA is not clear. Earlier studies on the incidence of RSV in adults with acute exacerbations of asthma found a low prevalence [28]. A prospective study of 79 adults with acute severe exacerbations of asthma who required hospitalization over a 12-month period only implicated RSV in one of 29 cases of asthmatic patients with evidence of recent respiratory tract infection confirmed by serologic testing or culture [28]. Influenza A and Rhinovirus were the most commonly isolated viral organisms in the study. However, some studies suggest RSV may play a greater role in AEBA. Simpson et al. compared sputum production combined with reverse-transcription polymerase chain reaction (RT-PCR) to serology and immunofluorescent antigen (IFA) testing in adults with acute exacerbation of asthma. RSV was detected in 37 % and 20 % of samples, respectively, suggesting a greater role for RSV in acute exacerbations of asthma [29]. Falsey et al. showed that when compared to healthy adults, patients at high risk for respiratory complications, including patients with asthma, were more likely to require hospitalization when infected with RSV [30].

Adenovirus

Adenovirus seems to play a limited role in adults with AEBA. The frequency of adenovirus in asthma exacerbations appears to be low, reported as the cause in 0.7 % to 2.5 % of cases [21, 28]. However, adenovirus may play a more important and unique role in near-fatal asthma exacerbations. In one study, adenovirus was found in 24 % of adult patients who were hospitalized for acute severe asthma exacerbations that required mechanical ventilation which defines critical asthma syndrome [7].

Prior studies have suggested a role for adenovirus in airway remodeling in patients with COPD [31]. But this role has not been clear in asthma. Adenovirus DNA was found in 78.4 % of asthmatic children during symptom free periods compared to 5 % of healthy control subjects [32]. Additionally, shedding of adenovirus appears to be prolonged with adenovirus identified by bronchoalveolar lavage (BAL) in children with asthma up to 12 months or more after acute infection [33]. Yet this impact of adenovirus presence has not been correlated with a specific pathogenic or clinical change in asthmatics. The role of adenovirus in adults with asthma remains under further investigation but epidemiologic studies suggest it may have a major role in severe, but not mild to moderate, acute exacerbations of asthma.

Human Metapneumovirus

Human metapneumovirus (hMPV) and its role in respiratory disease in children have been established, and it has been suggested to be a cause of AEBA in children. Papadopoulos et al. reported the detection of hMPV in 4 % to 8 % of children hospitalized with acute exacerbations of asthma [34]. The role of hMPV in adults with AEBA is less clear as the incidence in adults remains low. One study collected nasal wash specimens

at admission and 3 months after discharge and tested for hMPV with real time reverse transcription polymerase chain reactions assays. hMPV detected in 6.9 % at hospitalization and in 1.3 % at follow up [35]. This study suggests that hMPV plays a direct role in AEBA but at a significantly lower incidence compared to other viruses.

Influenza Virus and the 2009 H1N1 Pandemic

Influenza virus (Type A, Type B and subtypes, e.g., H1N1) has previously been established as a dangerous trigger for AEBA in children but the overall prevalence appears low, ranging from close to zero to 7 % [2, 36]. Influenza has also been shown to significantly reduce the FEV1 by as much as 30 % in children with asthma during acute infection. In contrast, the prevalence of influenza in adults during acute exacerbation of asthma appears to be higher, with several studies of patients in the emergency department and hospitalized patients having influenza identified in 20 % to 25 % of cases [34]. A review of adults hospitalized from 2005 to 2008 who were positive for influenza found that 27 % of adults ages 18 to 49 years had underlying asthma suggesting adult asthmatics are more prone to infection with influenza [37].

The 2009 H1N1 influenza pandemic is of particular interest as the number of acute asthma exacerbations associated with influenza as well as the severity of those exacerbations was increased. These influenza A virus strains are categorized according to two proteins found on the surface of the virus: hemagglutinin (H) and neuraminidase (N). All influenza A viruses contain hemagglutinin and neuraminidase, but the structure of these proteins differ from strain to strain due to rapid genetic mutation in the viral genome.

Influenza A virus strains are assigned an H number (H for hemagglutinin) and an N number (N for neuraminidase) based on which forms of these two proteins the strain contains. Hemagglutinin binds the virus to the respiratory cell it is infecting whereas neuraminidase allows the virus to be released from host carrier cell to promote another round of infection. There are 16 H and 9 N subtypes known in birds, but only H 1, 2, and 3, and N 1 and 2 are commonly found in humans.

During the pandemic 2009 H1N1 influenza season, children with asthma were infected with H1N1 almost as twice as much when compared to other respiratory viruses. This was a new or noval influenza “Swine Flu” virus classified as Influenza A, Novel H1N1/09. This H1N1/09 virus was a mutation combining human, swine and bird flu genes. Additionally, the severity of cold symptoms and acute exacerbations was much higher in children infected with H1N1 compared to other viruses [38]. Infection rates in adults with asthma appeared to be similar to previous seasons, with one study of hospitalized adults between September and October 2009 who were positive for pH1N1 by PCR revealed 25 % to have underlying asthma [39]. However, those infected with H1N1 had a significantly higher risk of admission, mechanical ventilation, and death when compared to cohorts infected with seasonal influenza stains. In a global risk analysis, asthma was found to increase the relative risk of both hospitalization and death following pH1N1 infection, but less so than other chronic conditions such as diabetes, cardiac disease, and liver disease. However, among patients with asthma who were hospitalized, survival was comparative to other conditions [40]. Early retroviral therapy (within 48 h of symptom onset) reduced severe outcomes (critical asthma syndrome or death) in adults with asthma who were hospitalized with H1N1 [41, 42]. Of interest, the vaccination rate among adults with asthma ages 25 to 64 was poor at only 25.5 % by one study [43]. The 2009 H1N1 virus was a novel, triple reassortment virus for which most asthmatics did not have a pre-existing immunity. Thus, the trigger of a cellular response was initiated, with a higher rate of wheezing, severe asthma, and prolonged symptoms that placed patients at risk for critical asthma syndrome.

The Role of Bacterial Infections in Asthma and AEBA

When compared to viral respiratory infections, bacterial infections play a smaller and less significant role. Studies in children reveal that bacterial infections only seem to play a small role in acute asthma exacerbations with only a slightly increased incidence in adult populations. In patients suffering from an AEBA, only 27 % had bacteria isolated in their sputum, with *Streptoccoccus pneumoniae*, *Streptoccoccus aureus*, and *Moraxella cattarhalis* being the most commonly isolated organisms [44]. A more recent study looking for *Mycoplasma pneumoniae* as an etiology of AEBA found positive sputum cultures in 53 % of patients with acute asthma exacerbations with *S. pneumoniae*, *S. aureus*, and *M. pneumoniae* found in decreasing order of prevalence [45]. However, results of how often bacteria were isolated in controls (subjects with asthma, not exacerbation) were not provided.

S. pneumoniae, *Haemophilus influenzae*, and *M. catarrhalis* in AEBA

S. pneumoniae, *Haemophilus flu*, and *M. catarrhalis* are common inhabitants of the upper respiratory tract and cause frequent extrapulmonary infections in children including otitis media and sinusitis. Their role as a pathogen in acute asthma exacerbations is much less clear. A large study by Nagayama et al. assessed bacterial colonization in children with recurrent wheezing, children with acute wheezing and children with no history of wheezing [46]. They found no statistical difference in dominant amounts of bacterial colonization between the

groups. Interestingly, the presence of bacterial colonization of the lower airways is common in patients with chronic severe asthma and has been linked to the duration of asthma and having had exacerbations in past year [47].

Asthma has been shown to be a risk factor for invasive pneumococcal disease. Talbot et al. conducted a nested case–control study to examine the association between asthma and invasive pneumococcal disease. They found among a total of 635 persons with invasive pneumococcal disease, 114 (18 %) had underlying asthma. This was statistically significant when compared to the control group, 6,350 controls with 516 (8.1 %) having underlying asthma [48]. Another study found the risk of invasive pneumococcal infection to be higher among working age adults with asthma when compared to controls [49].

H. influenzae has not been directly correlated in AEBA but has been found to be one the most commonly isolated bacteria in neutrophilic asthma and its role in the development of corticosteroid-resistant neutrophilic asthma has recently been implicated [50]. Like *H. influenzae*, *M. catarrhalis* in AEBA is not clear, but it has been more frequently isolated in asymptomatic and acutely wheezy asthmatics (70 and 75 % respectively) when compared to normal children (33 % colonized). However, this impact in acute exacerbations remains unclear [51]. *M. catarrhalis* also seems to be almost always associated with concomitant viral infection, and as such, it may be difficult to isolate the impact of this bacterial infection alone in AEBA or critical asthma syndrome [52].

Role of *Chlamydia pneumonia* and *M. pneumonia* in AEBA

Both *C. pneumonia* and *M. pneumonia* have been shown to be the cause of URIs, pneumonia, and acute exacerbations of chronic bronchitis. Their role in AEBA and critical asthma syndrome has not been definitively established. Lieberman et al. demonstrated evidence of acute infection with *M. pneumoniae* in 18 patients (18 %) hospitalized for AEBA compared with 3 % in control group. In 10 of these patients, however, there was evidence of infection with at least one additional pathogen (7 viral pathogens), thus their impact is confounded by this co-infection [53].

Several other studies have implicated chlamydia infection in more serious AEBA. *C. pneumoniae* (CP) has been identified as a single agent in 19 of 58 patients with acute exacerbation of asthma [54] and the presence of CP IgG or IgA titers was fourfold higher in patients with acute asthma when compared to controls [55]. The severity of AEBA has also been shown to be much more severe with *C. pneumoniae* and *M. pneumoniae*. Functional impairment on hospital admission, persistent reduction in FEV_1, and the proportion of patients with severe AEBA were greater in the group with atypical infections compared to groups without atypical infections (15/22 vs. 12/36, $p=0.01$; OR 4.29) [54]. None of the patients in this study met criteria for critical asthma syndrome.

The role of *C. pneumonia* and *M. pneumonia* in chronic asthma is also an area of interest and may provide insight into its role in AEBA. The link between *C. pneumonia* and *M. pneumonia* in new-onset wheezing, exacerbations of prevalent asthma, and long-term decrements in lung function appears complicated [56]. In animal models of acute and chronic infection showing *C. pneumonia* and *M. pneumonia*, the ability to modulate allergic sensitization and pulmonary immune response to an allergen challenge appears altered and increased and thus may play a role in long term control of asthma that may increase the impact of allergens in acute severe asthma.

Role of *Bordetella pertussis* in AEBA and chronic asthma

The role of *B. pertussis* in AEBA and chronic asthma is also not clear. A large cross-sectional study by Nagel et al. examined the role of pertussis and measles infection with asthma and allergic sensitization [57]. They found that pertussis infection was associated with increased likelihood of wheezing and rhinoconjunctivitis. They also found measles to be associated with increased likelihood of wheezing. Interestingly, they found no association with skin prick test (SPT) positivity suggesting that association between pertussis and measles with wheezing was no allergically mediated. A longitudinal study examining the risk of asthma and childhood infections was also recently published [58]. They found that pertussis was actually negatively associated with asthma persisting to age 13 (adjusted OR [aOR], 0.53; 95 % CI, 0.28–1.00). However, pertussis was associated with increased incidence of preadolescent incident asthma (adjusted hazard ratio [aHR], 1.80; 95 % CI, 1.10–2.96).

Fungal Infections and Acute Exacerbations of Bronchial Asthma

The role of fungi and mold in AEBA is much less clear than viral and bacterial infections. It has been shown that fungal sensitization increases the risk of having more severe asthma [59] and the risk of dying in asthma patients increases with increased spore exposure [60]. Additionally, fungal sensitivity to *Aspergillus* and *Clasdosporium* species increases the risk of adult-onset asthma [61]. The term severe asthma associated with fungal sensitization (SAFS) has been previously coined to describe patients with fungal sensitivity and persistent severe asthma who have some improvement with antifungal therapy [62]. Denning et al. demonstrated a significant improvement in quality of life in patients with SAFS who were treated with oral itraconazole for 8 months [63]. More specifically, sensitivity to *Aspergillus fumigatus* has been directly

linked to severe persistent asthma in adults and is the cause of allergic bronchopulmonary aspergillosis (ABPA). Both oral corticosteroids and antifungal therapies have been shown to be partially successful in controlling symptoms of ABPA including improving asthma related symptoms.

Inhaled Corticosteroids (ICS) and Infections in Asthma

The increased risk of pneumonia with inhaled corticosteroids (ICS) in patients with COPD has been previously established [64, 65]. Although ICS are a staple in the treatment of asthma, their roll in increasing risk of pneumonia is much less established. A recent cohort study of patients with asthma evaluated the association between the dose and type of inhaled corticosteroid and risk of pneumonia or lower respiratory tract infection (LRTI) when compared to age and sex-matched controls [66]. They found a dose response relationship between strength of dose and risk of pneumonia or LRTI with people receiving the highest doses having the highest increase in risk. Further studies are needed.

The role of ICS in increasing risk of viral infections is also not clear. It is well established that common colds are frequent triggers of asthma. As noted previously, patients with asthma experience the same number of URI's per year as healthy counterparts, but typically have more severe symptoms. However, it has not been established that ICS use increases asthmatic patients risk of URI or other viral infections [8]. Until further investigation has been completed, we recommend reducing inhaled corticosteroid doses to lowest effective dosage to conceivably reduce the risk of increased viral and bacterial infections.

The Role of Antibiotics in Severe Asthma Exacerbations and Critical Asthma Syndrome

The role of antibiotics in acute severe AEBA and critical asthma syndrome is very limited. One study evaluating the value of anti-bacterial antibiotics in 60 adults with AEBA found no difference in length of hospital stay, time taken for 50 % improvement in symptoms and symptoms and respiratory function at the time of discharge [67]. Another study in children admitted with status asthmaticus or critical asthma syndrome without signs of bacterial infection found no benefit in hospital course, complications or duration of hospital stay [68]. However, the additional benefits of antibiotics may play a role that underlies their direct antibacterial effect.

Macrolide antibiotics have anti-inflammatory effects as well as anti-microbial properties and the use of macrolide antibiotics in acute asthma exacerbations has become an area of interest. An open labeled, randomized, prospective study including 40 children with intermittent or mild persistent asthma with AEBA was recently completed. This study demonstrated that children in clarithromycin group had significantly more symptom free days and less total number of periods with loss of control during the follow up period compared to controls [69]. A double-blind, randomized, placebo-controlled study in adults with telithromcyin was conducted by Johnston et al. [70] with 278 adults with documented asthma enrolled within 24 h of acute exacerbation were randomized to receive 10 days of oral telithromcyin or placebo. The primary endpoints were a change from baseline over the treatment period in symptoms (as reported by the patients) and in the peak expiratory flow in the morning at home. A significant reduction in asthma symptoms compared to placebo was noted but no change in morning PEF rate was seen. Although 61 % of patients had evidence of *C. pneumoniae*, *M. pneumoniae*, or both, no relationship between bacteriologic status and response to treatment was seen.

The role of macrolide antibiotics in chronic asthma has also been investigated. A Cochrane database review was completed in 2005 and included seven studies with 416 participants [71]. Studies included macrolide treatment for at least 4 weeks in adult and pediatric patients treated for chronic asthma. Four studies had positive effect on symptoms in different types of asthmatic patients. However, no significant difference in FEV1 for either parallel or crossover trials was seen. One large parallel group trial reported a significant difference in peak flow but the benefit abated within 6 months of treatment. A recent randomized double-bind placebo-controlled trial examined the benefit of azithromycin in prevention of exacerbations in severe asthma (AZISAST) [72]. Patients with exacerbation-prone severe asthma received either low-dose azithromycin or placebo as an add-on treatment to combination therapy of inhaled corticosteroids and long-acting β_2 agonists for 6 months. No significant reduction in primary end points (rate of severe exacerbations and LRTI requiring treatment with antibiotics during 26 week treatment phase) in the treatment arm. In a predefined subgroup analysis according to the inflammatory phenotype, a significant reduction in PEP was seen in patients with non-eosinophilic severe persistent asthma.

Overall, the role of empiric antibiotic therapy without clear evidence of a bacterial trigger for an acute severe asthma exacerbation and critical asthma syndrome is unclear. Bacterial pathogens play a lesser role when compared to viral agents, but both typical and atypical bacteria are found with relative frequency. During the initial management moments of an acute severe exacerbation or critical asthma syndrome, the etiology, particularly an infectious one, may not be clearly evident. An approach to the use of antibiotics and antiviral therapy in severe AEBA is shown in Fig. 1.

Antibacterial and Antiviral Approach to a Patient with Severe AEBA or Critical Asthma Syndrome

Early empiric therapy in both bacterial and viral pneumonia has been shown to reduce morality, especially when initiated

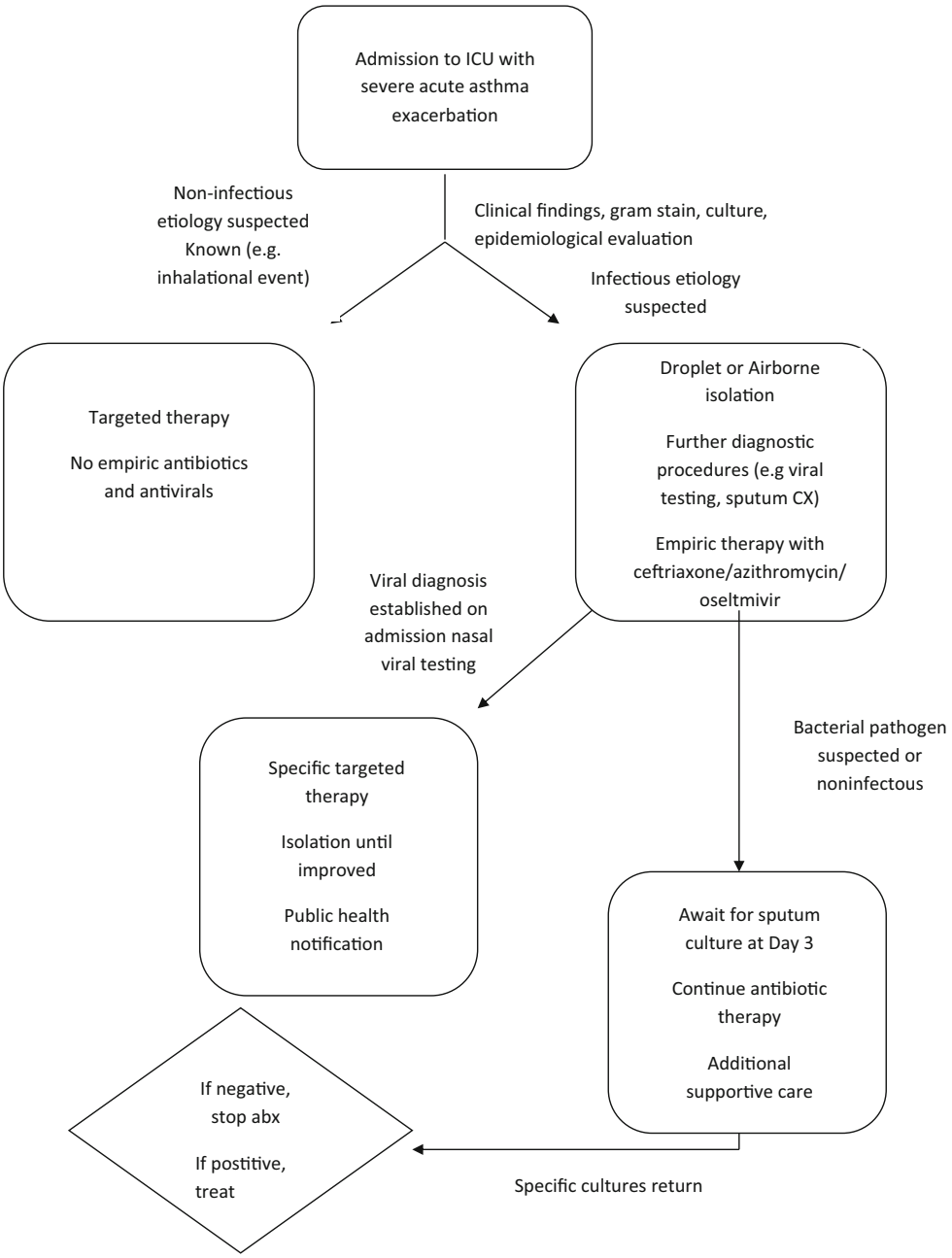

Fig. 1 The use of antibiotics and antiviral therapy in severe AEBA

within 12 h [55]. Additionally, acute exacerbations of asthma predominately have an infectious trigger, most particularly viral, but their early treatment in AEBA does not correlate with the similar outcomes of community acquired pneumonia [67]. However, given the immediate need for care, we recommend an approach of early empiric therapy with aggressive de-escalation.

All patients presenting with severe acute asthma exacerbation and at risk for critical asthma syndrome should have a microbiologic work up that consists of standard sputum culture and a viral respiratory panel, regardless of presenting symptoms or apparent triggers. Once microbiologic testing is performed, antibacterial therapy geared towards the agents of community-acquired pneumonia (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, *C. pneumoniae*, and *M. pneumoniae*). A cephalosporin, e.g., ceftriaxone with a macrolide, e.g. azithromycin is the preferred therapy over a fluoroquninolone given its anti-inflammatory properties in asthma. However, there is no clinical data to support this choice over a fluoroquinolone. In the Fall and Winter months, anti-influenza therapy with oseltamivir should be administered at 150 mg twice daily. Antibacterial and antiviral agents should be continued for at least 48 h until an alternative trigger is determine and cultures return without a specific agent. If

microbiologic studies return with an agent, therapy should be tailored to that agent only.

Conclusion

In chronic persistent asthma and acute exacerbations of bronchial asthma, infectious agents are the predominant triggers that drive disease and airway pathobiology. In acute exacerbations of bronchial asthma, viral agents, particularly HRV-C, RSV, and influenza A appear to be the more prevalent and recurring threats. Both viral and to a lesser extent bacterial agents can play a role, and co-infection may also be present and worsen prognosis in hospitalized patients. Early treatment with ceftriaxone and azithromycin, along with oseltamivir in winter months, should be initiated with all cases of severe exacerbations where infection is suspected and definitely in critical asthma syndrome until infection is excluded by appropriate diagnostic testing.

References

1. Monto AS, Sullivan KM (1993) *Acute respiratory illness in the community*. Frequency of illness and the agents involved. Epidemiol Infect 110(1):145–160
2. Johnston SL et al (1995) Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 310(6989):1225–1229
3. Johnston SL et al (1996) The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. Am J Respir Crit Care Med 154(3 Pt 1):654–660
4. MacDowell AL, Bacharier LB (2005) Infectious triggers of asthma. Immunol Allergy Clin North Am 25(1):45–66
5. Carlsen KH et al (1984) Respiratory virus infections and aeroallergens in acute bronchial asthma. Arch Dis Child 59(4):310–315
6. Dales RE et al (1996) Respiratory infections and the autumn increase in asthma morbidity. Eur Respir J 9(1):72–77
7. Tan WC et al (2003) Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease. Am J Med 115(4):272–277
8. Corne JM et al (2002) Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. Lancet 359(9309):831–834
9. Wark PA et al (2005) Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 201(6):937–947
10. Yamaya M (2012) Virus infection-induced bronchial asthma exacerbation. Pulm Med 2012:834826
11. Calhoun WJ et al (1991) Experimental rhinovirus 16 infection potentiates histamine release after antigen bronchoprovocation in allergic subjects. Am Rev Respir Dis 144(6):1267–1273
12. de Gouw HW et al (1998) Relationship between exhaled nitric oxide and airway hyperresponsiveness following experimental rhinovirus infection in asthmatic subjects. Eur Respir J 11(1):126–132
13. Sanders SP et al (2004) Role of nasal nitric oxide in the resolution of experimental rhinovirus infection. J Allergy Clin Immunol 113(4):697–702
14. Marshall JS, King CA, McCurdy JD (2003) Mast cell cytokine and chemokine responses to bacterial and viral infection. Curr Pharm Des 9(1):11–24
15. Jolly S, Detilleux J, Desmecht D (2004) Extensive mast cell degranulation in bovine respiratory syncytial virus-associated paroxystic respiratory distress syndrome. Vet Immunol Immunopathol 97(3–4):125–136
16. Hu Y et al (2012) Mast cell-induced lung injury in mice infected with H5N1 influenza virus. J Virol 86(6):3347–3356
17. Wang S et al (2010) Influenza virus-cytokine-protease cycle in the pathogenesis of vascular hyperpermeability in severe influenza. J Infect Dis 202(7):991–1001
18. Guilbert TW, Denlinger LC (2010) Role of infection in the development and exacerbation of asthma. Expert Rev Respir Med 4(1):71–83
19. Hakonarson H et al (1998) Mechanism of rhinovirus-induced changes in airway smooth muscle responsiveness. J Clin Invest 102(9):1732–1741
20. Makela MJ et al (1998) Viruses and bacteria in the etiology of the common cold. J Clin Microbiol 36(2):539–542
21. Atmar RL et al (1998) Respiratory tract viral infections in inner-city asthmatic adults. Arch Intern Med 158(22):2453–2459
22. Gern JE (2010) The ABCs of rhinoviruses, wheezing, and asthma. J Virol 84(15):7418–7426
23. Lee WM et al (2012) Human rhinovirus species and season of infection determine illness severity. Am J Respir Crit Care Med 186(9):886–891
24. Bizzintino J et al (2011) Association between human rhinovirus C and severity of acute asthma in children. Eur Respir J 37(5):1037–1042
25. Cox DW et al (2013) HRV-C infection in young children with acute wheeze is associated with increased acute respiratory hospital admissions. Am J Respir Crit Care Med 188:1358–64
26. Grunberg K et al (2001) Rhinovirus-induced airway inflammation in asthma: effect of treatment with inhaled corticosteroids before and during experimental infection. Am J Respir Crit Care Med 164(10 Pt 1):1816–1822
27. Rakes GP et al (1999) Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. Am J Respir Crit Care Med 159(3):785–790
28. Teichtahl H, Buckmaster N, Pertnikovs E (1997) The incidence of respiratory tract infection in adults requiring hospitalization for asthma. Chest 112(3):591–596
29. Simpson JL et al (2003) Use of induced sputum for the diagnosis of influenza and infections in asthma: a comparison of diagnostic techniques. J Clin Virol 26(3):339–346
30. Falsey AR et al (2005) Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 352(17):1749–1759
31. Hayashi S, Hogg JC (2007) Adenovirus infections and lung disease. Curr Opin Pharmacol 7(3):237–243
32. Marin J et al (2000) Persistence of viruses in upper respiratory tract of children with asthma. J Infect 41(1):69–72
33. Macek V et al (1994) Persistent adenoviral infection and chronic airway obstruction in children. Am J Respir Crit Care Med 150(1):7–10
34. Papadopoulos NG et al (2011) Viruses and bacteria in acute asthma exacerbations—a GA(2) LEN-DARE systematic review. Allergy 66(4):458–468
35. Williams JV et al (2005) Human metapneumovirus infection plays an etiologic role in acute asthma exacerbations requiring hospitalization in adults. J Infect Dis 192(7):1149–1153
36. Khetsuriani N et al (2007) Prevalence of viral respiratory tract infections in children with asthma. J Allergy Clin Immunol 119(2):314–321

37. Dao CN et al (2010) Adult hospitalizations for laboratory-positive influenza during the 2005–2006 through 2007–2008 seasons in the United States. J Infect Dis 202(6):881–888
38. Kloepfer KM et al (2012) Increased H1N1 infection rate in children with asthma. Am J Respir Crit Care Med 185(12):1275–1279
39. Skarbinski J et al (2011) Hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in the United States—September-October 2009. Clin Infect Dis 52(Suppl 1):S50–S59
40. Van Kerkhove MD et al (2011) Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med 8(7):e1001053
41. Mortensen E. et al (2013) Epidemiology and outcomes of adults with asthma who were hospitalized or died with 2009 pandemic influenza A (H1N1)—California, 2009. Influenza Other Respi Viruses
42. Jain S et al (2009) Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 361(20):1935–1944
43. Lu PJ et al (2011) A Influenza (H1N1) 2009 monovalent vaccination among adults with asthma, U.S., 2010. Am J Prev Med 41(6):619–626
44. Cazzola M, Matera MG, Rossi F (1991) Bronchial hyperresponsiveness and bacterial respiratory infections. Clin Ther 13(1):157–171
45. El Sayed Zaki M, Raafat D, El Metaal AA (2009) Relevance of serology for Mycoplasma pneumoniae diagnosis compared with PCR and culture in acute exacerbation of bronchial asthma. Am J Clin Pathol 131(1):74–80
46. Nagayama Y et al (2007) Bacterial colonization in respiratory secretions from acute and recurrent wheezing infants and children. Pediatr Allergy Immunol 18(2):110–117
47. Zhang Q et al (2012) Bacteria in sputum of stable severe asthma and increased airway wall thickness. Respir Res 13:35
48. Talbot TR et al (2005) Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med 352(20):2082–2090
49. Klemets P et al (2010) Risk of invasive pneumococcal infections among working age adults with asthma. Thorax 65(8):698–702
50. Essilfie AT et al (2012) Combined Haemophilus influenzae respiratory infection and allergic airways disease drives chronic infection and features of neutrophilic asthma. Thorax 67(7):588–599
51. Seddon PC et al (1992) Branhamella catarrhalis colonization in preschool asthmatics. Pediatr Pulmonol 13(3):133–135
52. Lehtinen P et al (2006) Bacterial coinfections in children with viral wheezing. Eur J Clin Microbiol Infect Dis 25(7):463–469
53. Lieberman D et al (2003) Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. Am J Respir Crit Care Med 167(3):406–410
54. Cosentini R et al (2008) Severe asthma exacerbation: role of acute Chlamydophila pneumoniae and Mycoplasma pneumoniae infection. Respir Res 9:48
55. Wark PA et al (2002) Chlamydia pneumoniae immunoglobulin A reactivation and airway inflammation in acute asthma. Eur Respir J 20(4):834–840
56. Sutherland ER, Martin RJ (2007) Asthma and atypical bacterial infection. Chest 132(6):1962–1966
57. Nagel G et al (2012) Association of pertussis and measles infections and immunizations with asthma and allergic sensitization in ISAAC Phase Two. Pediatr Allergy Immunol 23(8):737–746
58. Burgess JA et al (2012) Childhood infections and the risk of asthma: a longitudinal study over 37 years. Chest 142(3):647–654
59. Denning DW et al (2006) The link between fungi and severe asthma: a summary of the evidence. Eur Respir J 27(3):615–626
60. Targonski PV, Persky VW, Ramekrishnan V (1995) Effect of environmental molds on risk of death from asthma during the pollen season. J Allergy Clin Immunol 95(5 Pt 1):955–961
61. Jaakkola MS, Ieromnimon A, Jaakkola JJ (2006) Are atopy and specific IgE to mites and molds important for adult asthma? J Allergy Clin Immunol 117(3):642–648
62. Knutsen AP et al (2012) Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol 129(2):280–291, quiz 292–3
63. Denning DW et al (2009) Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: The Fungal Asthma Sensitization Trial (FAST) study. Am J Respir Crit Care Med 179(1):11–18
64. Crim C et al (2009) Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J 34(3):641–647
65. Rodrigo GJ, Castro-Rodriguez JA, Plaza V (2009) Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. Chest 136(4):1029–1038
66. McKeever T et al (2013) Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case control study. Chest 144:1788–1794
67. Graham VA et al (1982) Routine antibiotics in hospital management of acute asthma. Lancet 1(8269):418–420
68. Shapiro GG et al (1974) Double-blind study of the effectiveness of a broad spectrum antibiotic in status asthmaticus. Pediatrics 53(6):867–872
69. Koutsoubari I et al (2012) Effect of clarithromycin on acute asthma exacerbations in children: an open randomized study. Pediatr Allergy Immunol 23(4):385–390
70. Johnston SL et al (2006) The effect of telithromycin in acute exacerbations of asthma. N Engl J Med 354(15):1589–1600
71. Richeldi L et al (2005) Macrolides for chronic asthma. Cochrane Database Syst Rev 4:CD002997
72. Brusselle GG et al (2013) Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 68(4):322–329