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Epidemiology of infections and development of asthma

Jenny Resiliac, BA and

Division of Allergy and Immunology; 700 Children's Drive; Columbus, OH 43205; Biomedical Sciences Graduate Program, The Ohio State University College of Medicine; Center for Translational and Clinical Research, The Research Institute at Nationwide Children's Hospital; Division of Allergy and Immunology, Department of Pediatrics, The Ohio State University College of Medicine

Mitchell H. Grayson, MD

Biomedical Sciences Graduate Program, The Ohio State University College of Medicine; Center for Translational and Clinical Research, The Research Institute at Nationwide Children's Hospital; Division of Allergy and Immunology, Department of Pediatrics, The Ohio State University College of Medicine

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Introduction

Asthma is a common chronic condition affecting both children and adults, and is characterized by chronic airway inflammation leading to bronchial hyper-responsiveness and mucous hypersecretion. Asthma can be triggered by a variety of stimuli, leading to recurrent and reversible episodes of wheezing, shortness of breath, chest tightness, and coughing[1]. Asthma prevalence has increased dramatically both in the United States (US) and worldwide. Recent statistics from the National Health Interview Surveys (NHIS) and the US Centers for Disease Control and Prevention (CDC) estimated that 26.5 million people in the US, including 6.1 million children, have asthma[2]. Globally, about 235 million people suffer from asthma[3]. Implicated in the development of asthma are respiratory viral infections and infections with atypical bacteria (such as mycoplasma and/or chlamydia). Infectious agents have not only been associated with the inception of disease in asthma, they have also been involved in its exacerbations. In fact, in 2015 more than 11.5 million people with asthma, including nearly 3 million children, had one or more exacerbations of their asthma[4]. The burden of asthma is significant, both in terms of financial expenses and lost productivity, and in many situations, it is an infectious agent that initiates an asthma

Corresponding Author: Mitchell H. Grayson, MD, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, Tel: 614-722-4404, wheeze@allergist.com.

exacerbation. This review will discuss the epidemiology of respiratory infections (figure 1) in the development of asthma, as well as potential mechanisms that may translate these respiratory infections into asthma.

Epidemiology of infections and asthma

The role of early-life infections in the development of asthma results from complex interactions between pathogens, genetics, and environmental factors such as tobacco smoke. Acute respiratory infections are common in asthmatic patients. While controversial, some investigators believe there may be an increased risk of infection among atopic patients caused by opportunistic infections, especially in patients with severe atopic diseases[5]. For instance, viral or bacterial infections were observed in 70% of adult inpatients with an asthma exacerbation[6] and clinical studies report that asthma onset after an acute respiratory illness is exceedingly common (up to 45% of adult-onset asthma cases)[7]. Of course, this just supports the idea that respiratory infections can exacerbate asthma, but does not prove that patients with asthma are more likely to have a respiratory infection. A study comparing over eleven thousand individuals, reported increased risk of developing asthma in individuals who had any infection independent of their smoking history[8]. Individuals with early asthma who never smoked had significantly increased risk of any infection (hazard ratio 1.65; 95% confidence interval 1.40–1.94), pneumonia (2.44; 1.92–3.11) or any non-respiratory tract infection (1.36; 1.11–1.67); results were similar in smokers with early asthma. The researchers also found that asthma history was not limited to early disease as individuals who never smoked but had *any* history of asthma during their lifetime also had significantly increased risk of infection (1.44; 1.24–1.66) and pneumonia (1.99; 1.62–2.44) [8]. However, there remains the issue of bias – those with asthma are more likely to have *clinically* significant infections. Finally, not surprisingly, early infections but not smoking history were best indicators for the development of asthma.

Viral infections and development of asthma

As mentioned, evidence supports the role of early-life viral infections in the development of asthma. Viral infections are common during early childhood development. Infant respiratory viral infection and childhood asthma are the most common acute and chronic diseases of childhood, respectively[9]. So, it is not surprising that these two illnesses overlap. Bronchiolitis and early wheezing are frequently seen in children, usually as a result of a viral infection (regardless of presence of asthma). Respiratory viruses often are detected in first-time wheezing children, and may associate with the development of atopic disease[10]. Studies have shown that one-third of all children suffer from infection-induced wheezing during the first 3 years of life[11, 12]. Up to half of all children have acute wheezing at least once before school age, and amongst these children, 30% to 40% develop recurrent wheezing[11]. Moreover, viral respiratory infections have been implicated in up to 80% of wheezing episodes and asthma exacerbations[13]. These studies demonstrate the relationship of viral infections and development or wheezing and/or exacerbation of asthma.

Respiratory syncytial virus (RSV), rhinovirus (RV) and parainfluenza viruses (parainfluenza virus 1 and 2) are most commonly detected in asthma exacerbations in children, but they have been associated as well in the development of the disease – especially with severe

infections by these viruses early in life[14–17]. Wheezing illnesses in infancy and early childhood caused by viral infection of RV, RSV, and parainfluenza strongly correlate with asthma development later in life[18–20]. While RSV and RV appear to be the viruses most associated with asthma development, a larger group of pathogens have been identified in asthma exacerbations (Figure 1). Within the range of these respiratory viral pathogens, the most common viruses identified during an asthma exacerbation are RV (44-88%), RSV (2-20%), and PIV (2-11%)[21]. Other viruses associated with asthma exacerbations (usually less than 5% of the time) include Adenovirus, Enterovirus (non-RV), Influenza, Metapneumovirus, Bocavirus, and Coronovirus[22, 23]. It is also important to note that around 10% of these cases have a co-infection with more than one virus – usually with RV being the other virus identified[24].

RSV and development of asthma

The initial studies linking respiratory viral infections with development of asthma focused on RSV, which is one of the most common infections in children and infants. RSV is also known as one of the leading causes of severe respiratory infection in infants and several studies have strongly suggested a causal role for RSV in the development of asthma and allergen sensitization[24–27]. A cohort study by El Saleeby, *et al,* found that high levels of RSV titer were associated with more severe respiratory viral disease outcomes. In this study previously healthy RSV-infected children under 2 years old who had significantly higher viral titers had increased requirements for intensive medical care and were more prone to respiratory failure when compared to those with lower titers[28]. Asthma outcomes were similarly affected as demonstrated by a multi-center cohort study in the US and Finland conducted by Hasegawa, *et al,* determining the relationship between viral load in RSV infected children and clinical symptoms of asthma. Out of the 2,612 children in the study, 67% developed RSV bronchiolitis, but most interestingly, children with higher RSV titer had higher risk for severe bronchiolitis[29]. Taken together, these studies demonstrate the relevance of severe RSV infections in the development of asthma and asthma symptoms.

Enteroviruses and asthma

Enteroviruses (EV) are RNA viruses of the family *Picornaviridae*, of which the most common is RV, which has been associated with asthma development and exacerbation[30]. The Childhood Origins of ASThma (COAST) cohort study followed children from birth and identified RV as the viral etiology of 90% of wheezing illnesses by age 3 years; RV was identified as the major risk factor for asthma at 6 years of age[21]. While RV is associated with asthma development, the COAST investigators used mathematical modeling to demonstrate that RV infection likely followed the development of atopy. This raises a question as to whether respiratory RV infections drive development of asthma, or simply uncover an existing predisposition for the disease.

RV can be divided into three clades, RV-A, RV-B, and RV-C. Of these three, RV-C has been found to most strongly correlate with severity of asthma exacerbations[23]. A recent study from China further verified that RV-C is associated most often with both inpatient and outpatient asthma exacerbations, but also demonstrated that high titer of RV-A also could

lead to significant exacerbation of disease[24]. Clearly RV is a major component of asthma disease burden, even if it is not causative of disease development.

In addition to RV, other EV have been identified in patients undergoing an asthma exacerbation, and these viruses may play a role in the inception of asthma. Many studies have reported an association with increased incidence of EV infections and asthma development[31–34]. One study retrospectively compared patients over a decade (January 2000-December 2011) and examined the relationship between EV infection and asthma. The incidence of asthma was 1.48-fold higher in patients (≤ 5 years old) who had an EV infection compared to those who did not[35]. Although the results were intriguing, it is important to note that this was a retrospective study depending upon claims data.

Influenza and asthma

Influenza circulates both as a seasonal infection and occasional pandemic. The seasonal variety clearly causes asthma exacerbations, but appears to be a minor contributor to the overall burden of asthma disease development. During the 2009 influenza pandemic (pH1N1), asthma was the most common co-morbidity among patients, accounting for 22-29% of all hospitalized patients with influenza[36–39]. Children with asthma accounted for 44% of hospitalized children with influenza although the major differences between the pandemic influenza and seasonal influenza was that pH1N1 was associated with higher incidence of pneumonia (46% versus 40%, pH1N1 versus seasonal, $p = 0.04$) and a greater need for intensive care (22% versus 16%, $p = 0.01$)[40]. Another study analyzed data from 12 different Canadian pediatrics hospitals during the pH1N1 pandemic and compared them with data from children hospitalized with seasonal influenza A. The results from that study revealed that pre-existing asthma was overrepresented in pH1N1 infected relative to seasonal influenza A infections[41]. Further, pH1N1 seemed to cause more disease in older children, with the median age for these pH1N1 patients being 4.8 years old, while the median age for seasonal influenza A patients was 1.7 years[41]. Data from 272 patients hospitalized for at least 24 hours with an influenza-like illness and a positive H1N1 polymerase chain reaction test, demonstrated that 73% of the patients had at least one underlying medical condition; these conditions included asthma, diabetes, pregnancy, and other heart, lung, and neurologic diseases[36]. Although asthma was over-represented in patients hospitalized with pH1N1, at least one study found that having asthma led to a more rapid recovery from the viral infection[42]. Supporting the idea that asthma might have a protective advantage in the recovery from pH1N1, a retrospective chart review of two case-series found that those with asthma who were hospitalized with pH1N1 were less likely to have pneumonia, need mechanical ventilation, or die compared to those admitted without asthma [42]. So, while influenza may be associated with asthma exacerbations, it also appears that asthma *may* protect against pandemic influenza mediated morbidity and mortality.

The mechanisms linking respiratory viral infections to development of asthma and its exacerbation are actively being studied. Some links relate to the role of innate lymphoid cells (ILCs) translating RSV infection into atopic disease. ILCs can be classified based on their transcriptional regulation and cytokine production into ILC1, ILC2, and ILC3 cells, which largely emulate the adaptive $CD4^+$ T helper 1 (Th1), Th2, and Th17 cells,

respectively. ILC2s produce high levels of interleukin 13 (IL-13) and interleukin 5 (IL-5), two cytokines known to play important roles in asthma. IL-5 is a required cytokine for eosinophil development, and several new asthma treatments have been developed to block its effects[43]. IL-13 has been implicated in IgE synthesis, mucus hypersecretion, airway hyperresponsiveness (AHR), and fibrosis[44]. In a murine model, RSV induced robust IL-13 production from ILC2 during the early phase of the infection[45]. This increased production of IL-13 was found to depend upon thymic stromal lymphopeitein (TSLP) signaling. Neutralizing TSLP resulted in significant reduction of IL-13, and the post-viral airway disease[45].

We have utilized the murine parainfluenza virus, Sendai virus (SeV), to explore the translation of a respiratory viral infection into asthma. Mice infected with SeV develop post-viral airway hyper-reactivity and mucous cell metaplasia after clearance of the virus. The mechanistic pathway depends upon the initial recruitment of a subset of CD49d expressing neutrophils, which require cysteinyl leukotrienes for their survival. These neutrophils induce expression of the high-affinity receptor for IgE, FcεRI, on lung conventional dendritic cells (DC). At the same time the mouse makes IgE against SeV, and this leads to crosslinking of FcεRI on the DC. This crosslinking of DC FcεRI induces production of CCL28, a chemokine that recruits IL-13 producing lymphocytes to the lung. The IL-13 then drives subsequent development of post-viral airway disease[46]. Interestingly, exposure to a non-viral antigen during the antiviral immune response is sufficient to drive allergic disease against the non-viral antigen. Thus, this model translates a respiratory viral infection into atopy and asthma. Importantly, components of this pathway are present in the human. We demonstrated CD49d expressing neutrophils in the nasal lavage of humans, and expression of the cysteinyl leukotriene receptor on these cells[47]. Human conventional DC express FcεRI, and the level of expression is increased during a respiratory viral infection[48]. Crosslinking DC FcεRI leads to release of CCL28, and humans make IgE against viruses, such as RSV and RV[49–54]. Whether this pathway does indeed translate a respiratory viral infection to asthma in human infants remains to be fully determined.

Atypical bacterial infection and development of asthma

Infections with atypical bacteria also appear to play a role in the induction and exacerbation of asthma in both children and adults. Several studies suggest that atypical respiratory pathogens such as *Chlamydophila pneumoniae* (CP) and *Mycoplasma pneumoniae* (MP) and fungi like *Aspergillosis* may contribute to the pathogenesis of asthma[55–59]. Chronic CP infections are more frequent in asthmatic patients and have been associated with poor asthma control[60, 61]. Von, *et al,* investigated the relationship between severity of asthma, CP titers, and antibodies specific for CP's heat shock protein (chsp60), and their association with asthma. Patients (n = 116) were categorized into three groups based on the severity of their asthma (mild, moderate, or severe). Although antibodies against chsp60 were elevated in the asthmatic group compared to the controls, the difference did not reach statistical significance. However, severe and moderate asthma were significantly associated with the presence of elevated anti-chsp60 IgA, suggesting chronic infection in these more severe asthma patients[62]. An additional study reported that IgE against CP strongly and positively associated with asthma severity, suggesting a role of anti-CP IgE (and by

extension, CP) in the pathogenesis of asthma[63]. While MP's role in asthma has been less intensively investigated than CP, MP has been associated with recurrent wheeze and may be present as a co-infection with respiratory viruses. Children with asthma were more likely to have MP-specific IgM than those without asthma (39% vs 0%)[64], suggesting increased exposure/colonization of MP in those with asthma.

In addition to CP and MP, emerging data suggest species of the *Streptococcus, Moraxella,* and *Haemophilus* genera also associate with respiratory illnesses and asthma development[65, 66]. Hypopharyngeal colonization with *S. pneumoniae, H. influenza,* or *M. catarrhalis* in neonates was reported to increase the risk for recurrent wheeze and asthma early in life[67]. In neonates, colonization with *H. influenza* or *M. catarrhalis* (or both) significantly associated with persistent wheeze (hazard ratio, 2.40 (CI: 1.45 to 3.99)), acute severe exacerbation of wheeze (hazard ratio, 2.99 (CI: 1.66 to 5.39)), and hospitalization for wheeze (hazard ratio, 3.85 (CI: 1.90 to 7.79))[67]. In fact, children colonized by these bacteria as neonates had a higher prevalence of asthma by 5 years of age, as well as increased beta-agonist reversibility compared to those children not colonized as neonates with these organisms. Other bacteria such as *Helicobacter pylori (H. pylori)* and *Bordetella pertussis (B. Pertussis)* have been associated with asthma, as well. In subjects under 40 years of age, *H. pylori* infection (as documented by IgG against *H. pylori* in the peripheral blood) appears to protect against asthma (OR 0.503), but not other allergic diseases[68]. *B. Pertussis* has not been associated with development of asthma, but may infect asthma patients more frequently. Following a pertussis outbreak in California and Minnesota, Capili and colleagues conducted a population-based, case-control study to determine the prevalence of pertussis and its association with asthma[69]. They reported an increased risk of *B. pertussis* infection among subjects with asthma (adjusted OR for *B. pertussis* infection with pre-existing asthma, 1.73; (CI: 1.12 - 2.67); p = 0.013). Interestingly, the majority of this risk was attributable to children (OR 1.92 (1.2 – 3.09); p = 0.007) not adults (OR 1.14 (0.37 – 3.55); p = 0.820). These authors calculated the population attributable risk of asthma for pertussis infection at 17%[69]. Thus, bacterial infections can have implications beyond just the development and/or exacerbation of asthma.

Similar to viral infections, the mechanisms by which atypical bacterial drive inception of asthma are being studied. Early infection with CP or MP leads to a higher risk for asthma through induction of type 2 airway inflammation, mucus cell metaplasia, and airway hyperreactivity -- all hallmarks of asthma. For instance, CP infection was shown to induce a Th2 immune response, as well as both airway eosinophilia and neutrophilia leading to permanent alteration of lung structure and function[70]. Using a mouse model, it was shown that infection with a chlamydia species (*C. muridarum*) during allergen sensitization (using ovalbumin) led to a neutrophilic inflammatory response in the lung associated with a Th1/Th17 response, but an inhibited Th2 response[71]. This model is reminiscent of the human neutrophilic asthma phenotype. If CP and MP do cause asthma, then treatment with macrolide antibiotics (for which CP and MP are sensitive) should prevent or ameliorate asthma. In fact, treatment with a macrolide antibiotic *in vitro,* did block CP induced mucin production in cultured human airway cells[72]. A larger clinical study found macrolide treatment reduced the severity of respiratory tract infections, but had no impact on the

symptom scores or the use of albuterol[73]. Therefore, it remains unclear how important atypical bacterial infections are to the pathogenesis of asthma.

Conclusion

This review has discussed the association between various respiratory pathogens and the development and exacerbation of asthma. Viral respiratory infections are common causes of acute illnesses in both adults and children, and are strongly associated with inception and exacerbation of asthma. As discussed, several other pathogens, such as atypical bacteria like CP and MP, also have been linked to the onset and exacerbation of asthma. Some microorganisms (like *H. pylori)* have a protective effect against the development of asthma. Further studies are required to better outline the complex interaction between human hosts and pathogens that lead to (or prevent) asthma development. These studies will require multidisciplinary approaches including epidemiological studies with longitudinal cohorts and mechanistic mouse models. These future investigations will increase our knowledge of the pathological process during infections that lead to the development of asthma, and will enable us to identify new therapeutic targets. These future interventions hopefully will reduce and maybe eliminate development and exacerbations of asthma.

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Key points:

1. Respiratory RNA viral infections have been correlated with the development and exacerbation of asthma (and possibly allergies).
2. Atypical bacteria and some typical bacteria have also been associated with asthma development.
3. The mechanisms linking these organisms to development and exacerbation of asthma are areas actively being explored.

Synopsis

Asthma and allergic diseases have become more prevalent, although the reasons for this increase in disease burden are not known. Understanding why these diseases have become more common requires knowledge of the disease pathogenesis. Multiple studies have identified respiratory viral infections and atypical bacteria as potential etiologic agents underlying the development of asthma (and possibly allergies). This review will discuss the epidemiology and potential mechanistic studies that provide links between these infectious agents and the development (and exacerbation) of asthma. These studies provide insight into the increase in disease prevalence and have identified potential targets for future therapeutic intervention.

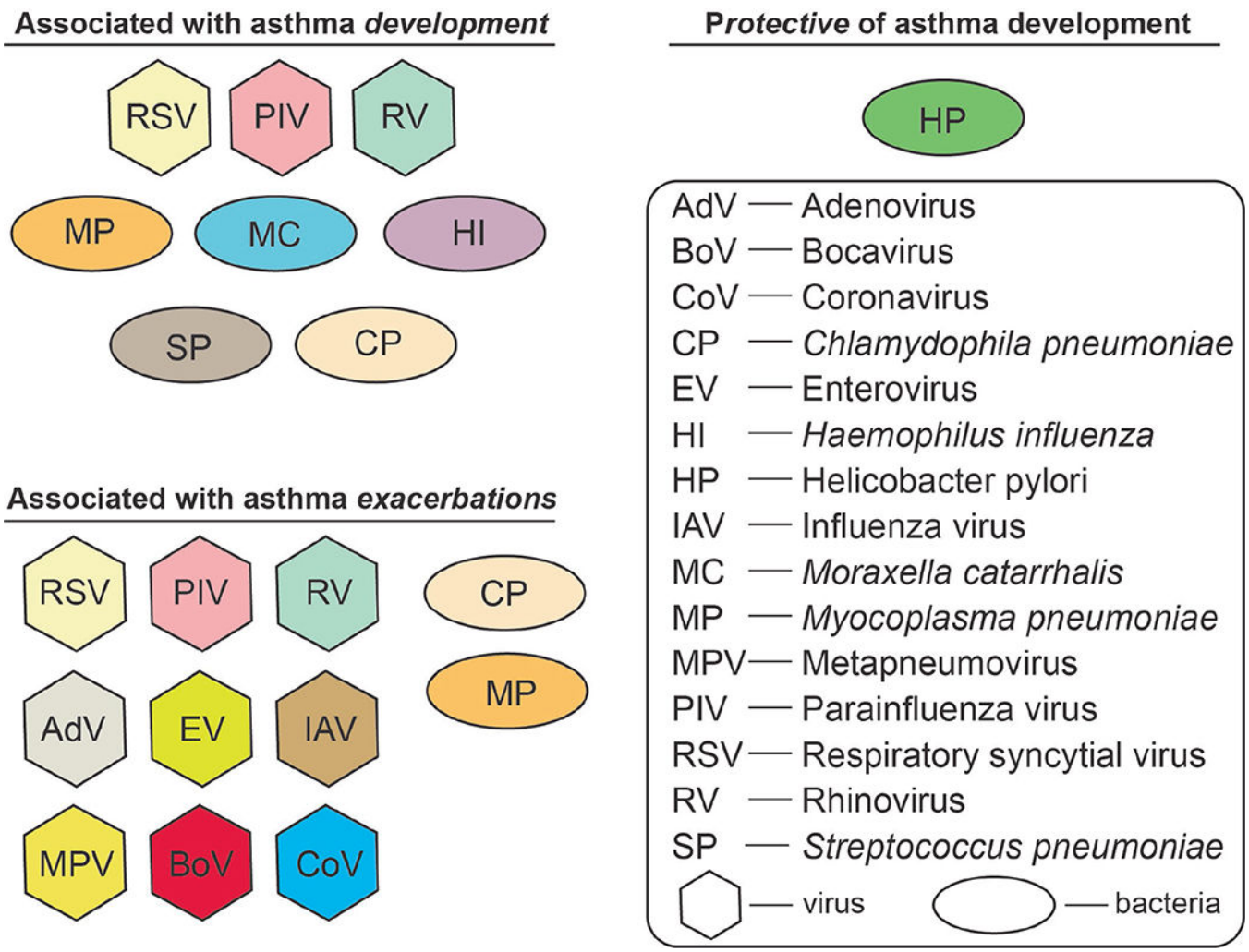

Figure 1. Pathogens associated with asthma development and exacerbation.

Early life infections play a role in the development of asthma and disease exacerbation. This figure lists the pathogens that have been associated with asthma development (upper left) and asthma exacerbations (bottom left). *H. pylori* has been shown to be protective of asthma development (upper right). Abbreviations are explained in the box; viruses are shown in hexagrams, while bacteria are in ovals. See text for more details.