Asthma is a common, chronic disease of the airways. Asthmatics can suffer exacerbations (worsening symptoms) due to a range of environmental and occupational factors. At least half of all asthma exacerbations are caused by respiratory viruses. In this article we examine some of the microbiological causes of asthma development and exacerbations.

What is asthma?

Asthma is a chronic inflammatory condition of the airways. It is a heterogeneous disease with several clinical phenotypes described as mild, moderate or severe, although definition can be difficult. Asthma is often difficult to diagnose as the symptoms (wheeze, difficulty breathing) are common to other illnesses such as respiratory tract infections and obesity. ‘Viral-induced wheeze’ and cough are common in young children with respiratory infections, but are not necessarily caused by asthma. The disease is characterised by episodes of wheezing, breathlessness and chest tightness due to widespread narrowing of the airways in the lungs, known as exacerbations. Exacerbations can vary from mild to severe and result in periods of incapacity, emergency hospital admissions and, rarely, death.

Exacerbations can be triggered by a number of environmental and occupational allergens including:

- viral infections (which cause the majority of exacerbations in children and adults)
- exercise
- cold weather
- exposure to specific allergens such as:
  - house dust mites
  - pollens
  - mould spores
  - animal dander
- irritants such as:
  - tobacco smoke
  - pollution (such as nitrogen dioxide (NO₂) from the combustion of natural gas and motor fuel)
  - some food additives
- occupational exposure to:
  - specific allergens
  - irritants including dust and fumes.

One in 10 Australians suffer from asthma. The prevalence of asthma in Australian children increased between 1982 and 1992, but has now declined in children since 2001 and is stabilised in adults. Asthma is a significant health problem in Australia, and in 2006–2007 the number of Australians hospitalised due to this disease reached well over 36,000 people. It has been predicted that over the next two decades, asthma will continue to rank as one of the major causes of disease burden in Australia. With this there is also great cost. The most recent data show that from 2004–2005 $606 million was spent on asthma (1.2% of all health expenditure in that year).

While there is currently no cure for asthma, inhaled corticosteroids and other medications are available to control the disease and prevent exacerbations. The underlying causes of asthma are not yet well understood, but it appears that a combination of predisposing genetic factors and certain environmental factors cause an individual to develop chronic asthma.

Asthma and respiratory viruses

Respiratory viruses cause up to 90% of asthma exacerbations in children. The most common viruses responsible are human rhinoviruses (HRVs), respiratory syncytial virus (RSV), human metapneumovirus (hMPV) and influenza viruses (Table 1).
HRVs are the most frequently detected respiratory pathogen, and typically cause the common cold\textsuperscript{12,13}. Annually, HRVs infect billions of people worldwide\textsuperscript{14} and cost billions in healthcare dollars\textsuperscript{15}. HRVs were discovered as the common cold pathogen over 50 years ago, with the first classical strain discovered in 1956\textsuperscript{16,17}. There are approximately 160 types and together they cause a wide range of clinical outcomes infecting both upper and lower respiratory tracts\textsuperscript{13–15}. In addition to the common cold, infections with HRV can be asymptomatic but can also cause severe lower respiratory illnesses such as exacerbations of asthma and even pneumonia\textsuperscript{14}. HRVs are a large group of genetically diverse RNA viruses and are classified into three different species (A, B and C). The classical serotypes are found within species A and B with another 50 additional strains recently identified as being part of species C\textsuperscript{13,14}. They are part of the Picornaviridae family, have a 7200-nucleotide mRNA positive sense genome and are classified due to their sequence variations with HRV-C showing substantial sequence divergence from the other classified species\textsuperscript{13,18,19}. The development of more sensitive molecular techniques has enabled scientists to detect more HRVs and other respiratory virus infections\textsuperscript{20} and gain a greater appreciation of the broad range of clinical illnesses caused by HRVs\textsuperscript{13,14}. By using these techniques, viral respiratory infections have been detected in up to 85\% of asthma exacerbations in children\textsuperscript{13,21} and approximately 50\% in adults\textsuperscript{13}. Of these infections, approximately two-thirds are caused by HRVs. Of the three species, HRV-A and HRV-C are more common in infections and exacerbations. Miller \textit{et al.} showed that almost half of all hospitalisations due to HRV infections were associated with HRV-C suggesting that this group causes a substantial burden of paediatric disease\textsuperscript{21}. Multiple strains of HRV circulate at any one time during a season\textsuperscript{23,22}, with children having several HRV infections per year\textsuperscript{23}. HRVs are present year-round with all three species (HRV-A, HRV-B and HRV-C) being represented\textsuperscript{21,25}. In temperate climates there are peaks of HRV infections in autumn and spring, coinciding with return to school after holidays. This is known as ‘the back-to-school effect’ and it is seen globally\textsuperscript{23}. Exacerbations of asthma and hospital admissions for asthma also show distinct peaks in autumn and

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
<th>Importance in asthma</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Human rhinoviruses (HRVs)</td>
<td>‘Common cold’. Rarely complications.</td>
<td>Most common virus associated with asthma exacerbations. HRV-A and HRV-C associated with more severe effects. HRV-C associated with worse exacerbations. HRV-A associated with longer duration of symptoms.</td>
<td>\textsuperscript{26}</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td>Upper respiratory tract infections (URTIs) but can cause pneumonia/bronchiolitis in young children (inflammation of the bronchioles making breathing difficult)</td>
<td>Commonly associated with asthma and wheezing in children (~20% of viral-induced wheeze in young children is caused by RSV)</td>
<td>\textsuperscript{11}</td>
</tr>
<tr>
<td>Influenza viruses</td>
<td>URTI</td>
<td>Influenza viruses are more often associated with asthma exacerbations in adults (20–25%) than in children (4%). Recent evidence on H1N1 2009 and asthma showed people with asthma had reduced ICU stay and hospitalisation compared with non-asthmatics. Probably due to prior corticosteroid use and earlier hospital admission.</td>
<td>\textsuperscript{27,28}</td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>Similar to RSV and indicated in URTI, severe bronchiolitis and pneumonia in children</td>
<td>Has been detected in a small number of asthma exacerbations in young children</td>
<td>\textsuperscript{29–32}</td>
</tr>
<tr>
<td>Parainfluenza viruses</td>
<td>Can cause lower respiratory tract infection in young children</td>
<td>Recent systematic review failed to find an association between parainfluenza and asthma exacerbations</td>
<td>\textsuperscript{33}</td>
</tr>
<tr>
<td>Human coronavirus</td>
<td>URTI</td>
<td>Seems to be more important in adult asthma exacerbations, but probably plays only a minor role overall</td>
<td>\textsuperscript{33}</td>
</tr>
<tr>
<td>Human bocavirus</td>
<td>Clinical relevance unknown. More common as co-infections with other respiratory viruses.</td>
<td>Has been detected in a small number of exacerbations in asthmatic children that were negative for other respiratory viruses</td>
<td>\textsuperscript{26,34}</td>
</tr>
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spring, suggesting that viral infections could be major contributors to seasonal asthma morbidity\textsuperscript{13}. The seasonal prevalence of different HRV subtypes has also been examined with the proportion of respiratory infections in which HRV-B and HRV-C were detected being the lowest in summer, and more common in autumn\textsuperscript{21,25}. It also appears that with this seasonal variation, HRV-C seems to exchange its dominance with HRV-A.

**Evidence for early life viral infections and development of asthma**

Approximately one-third of infants who have an acute viral wheezing illness will go on to develop more common wheezing events\textsuperscript{13}; however, most wheezing illnesses in infancy will resolve with no long-term effects. A number of birth cohort studies have shown that viral respiratory illnesses early on in life might promote asthma in some children\textsuperscript{13}.

Sigurs \textit{et al.}\textsuperscript{35} studied 47 children hospitalised due to RSV infection in their first year of life, and 93 age- and gender-matched controls, prospectively for 18 years. The cohort infected with RSV had high prevalence of early onset allergy-associated wheeze, increased airway hyper-responsiveness (AHR) and reduced airway function at 18 years of age\textsuperscript{35}. The RSV group had a higher incidence of parental asthma/atopy compared with the control group (indicating the children were at ‘high-risk’ of developing asthma), but the difference was not significant.

Jackson \textit{et al.}\textsuperscript{11}, in genetically ‘high-risk’ children at birth into the NIH-funded Childhood Origins of Asthma study (COAST) based on one or both of their parents having asthma/allergies. Children who had a wheezing respiratory illness caused by HRV in the first 3 years of life had a 10-fold increase in asthma risk at age 6 years. HRV infection without wheeze was not associated with an increased asthma diagnosis at age 6 years. RSV wheezing illness was associated with a smaller increase in asthma risk at 6 years. An Australian birth cohort study has also found that more wheezing illness in infants is caused by HRV than RSV\textsuperscript{36}.

But do early life infections with HRV or RSV necessarily cause asthma? It is the age-old question: Which came first, the chicken or the egg? Whether it is causal or genetic factors linking HRV and RSV to asthma later in life is still not known and much debated. Kuehni and colleagues\textsuperscript{57} argued that existing evidence shows it is more likely that a genetic predisposition for asthma renders an individual more susceptible to worse illness caused by RSV in early life, rather than RSV being the cause of asthma development. It might be that, as hypothesised by Jackson \textit{et al.}\textsuperscript{11}, in genetically high-risk individuals, HRV and RSV infections cause pathological changes in the lungs that have lasting effects and lead to asthma. However, not all infants who wheeze with a viral infection will go on to develop asthma. Further studies are needed to resolve this question.

**Asthma and other microorganisms**

Respiratory viruses are important in children with asthma, but bacteria and fungi can also cause exacerbations of asthma and are more important in older children and adults\textsuperscript{1}.

Recent studies of \textit{Mycoplasma pneumoniae}, \textit{Chlamydia pneumoniae} and \textit{Legionella pneumophila} have looked at the associations of these atypical bacteria with both acute exacerbations and chronic cases of asthma\textsuperscript{26}. Evidence from human studies have linked both \textit{M. pneumoniae} and \textit{C. pneumoniae} to cases of prevalent asthma and even new cases of wheezing indicating they could play possible roles in promoting airway inflammation\textsuperscript{58}. Gil \textit{et al.} found that \textit{M. pneumoniae} colonised at a higher rate in patients with asthma (24.7%) than those without (5.7%), possibly inducing the wheezing events\textsuperscript{39}. Qasem and colleagues, in a study of both asthmatic and non-asthmatic patients, found that \textit{M. pneumoniae} was more common in asthmatic patients and was also related to the exacerbation of asthma symptoms (patients with suspected viral infections were excluded from this study)\textsuperscript{38}. In a study conducted in France of children with known asthma and children with a new diagnosis of asthma, Biscardi \textit{et al.} found that \textit{M. pneumoniae} and \textit{C. pneumoniae} were found in both groups of children, but at higher infection rates in those children with newly diagnosed asthma (50% of newly diagnosed patients had \textit{M. pneumoniae} infection compared with 5.2% of stable asthma patients). Along with the different bacteria, respiratory viruses were tested for within the participants; however, major comparisons were not made and coinfections were not looked at\textsuperscript{40}. Further to this, of those children infected with both bacteria and who were experiencing their first attack, 62% had asthma recurrences compared with only 27% who were not infected\textsuperscript{40}.

Some individuals with asthma (approximately 2.5\%\textsuperscript{41}) can become chronically infected with the fungus \textit{Aspergillus fumigatus}, causing the diseases allergic bronchopulmonary aspergillosis (ABPA). ABPA can cause bronchiectasis (chronic inflammation of the airways, decreased mucus clearance, leading to chronic lung infection) and sometimes death. \textit{A. fumigatus} acts as an allergen and pathogen and also sensitises the sufferer to several other fungal pathogens.

**Conclusions**

Clinical data now indicate microorganisms are the main cause of asthma exacerbations, with many cases of wheeze in children
<1 year linked to asthma later in life. However, many aspects of the interaction between asthma and microorganisms are still not well understood. Why do some children with wheezing HRV/RSV infections go on to develop asthma and some do not? Why do some children with viral respiratory infections have more severe exacerbations of their asthma (leading to hospitalisations) and some do not? Further studies are needed on the severity of these infections and resulting impact on asthma symptoms. The likely benefits of such studies are enormous in terms of reducing the clinical impact of asthma.

References


Christiana Willenborg is a Research Assistant in the Virology Research Laboratory at Prince of Wales Hospital. Her current research involves examining the respiratory viruses that infect children at risk of an asthma exacerbation and how these viruses affect their asthma. The aim is to learn why colds and flu make asthma worse and to use the information to reduce or prevent exacerbations.

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