**Paediatric asthma – viruses and bacteria**

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**AIMS**

This presentation will provide an overview of the roles played by respiratory viral infections and bacteria resident in the upper airways in early life in the risk of developing childhood asthma. Specific areas to be addressed include:

- Does asthma cause respiratory viral infections?
- Do viruses cause asthma?
- Viral : allergen interactions in asthma
- Do bacteria cause asthma?
- Viral : Bacterial interactions
- Viral triggering of existing asthma

**SUMMARY**

The association between respiratory viral infections in the first few years of life and subsequent asthma has been studied for decades. The initial focus was on RSV bronchiolitis leading to asthma and more recently on wheezing illnesses with human rhinovirus (hRV) increasing the risk of subsequent asthma markedly. However, to a very real extent, the question as to whether viral infections cause asthma or whether wheezing with respiratory viruses simply marks the susceptible host has not been resolved.

There are a number of ways in which being destined to develop asthma could increase the risk of more severe viral infections and wheeze. Firstly, longitudinal studies show that, as a group, asthmatics have lower lung function than non-asthmatics. This deficit in lung function is seen as early as it is measured raising the possibility that low lung function is a primary risk factor for asthma. A child with lower lung function is more likely to wheeze and to develop a more severe LRI when infected with a respiratory virus.

Secondly, the way an asthmatic responds when they are infected by a respiratory virus has been reported to be different from healthy controls in some, but not all studies. A respiratory virus first infects the nasal mucosa and, in the presence of a robust anti-viral defence, is usually confined to the upper airway resulting in cold symptoms. When nasal epithelial cells are infected they mount an anti-viral defence by secreting interferon (IFN)β, then IFNλ, and subsequently IL-8 to “call in the inflammatory cavalry”. Both IFN-dependent and INF-independent anti-viral mechanisms are engaged to cause apoptosis of infected cells and limit viral spread. Airway epithelial cells (AECs) from asthmatics have been shown to produce less IFNβ and IFNλ in response to infection with hRV, a virus that appears particularly susceptible to IFN-dependent defence. However, RSV actively suppresses the ability of AECs to produce IFNs and it and human metapneumo virus are more suppressed by INF-independent anti-viral defences. These mechanisms have been less well studied in asthmatics. Infections with different respiratory viruses may have different implications for subsequent asthma.
In addition, overlap in the genetic susceptibility for asthma and for wheezing with respiratory viral infections has recently been shown in several birth cohorts. Consistent with the premise that those predestined to get asthma are more likely to wheeze with respiratory viral infections.

The other side to this question is whether respiratory viral infections can “damage” the lungs, reduce lung function growth and trigger the airway remodelling characteristic of persistent asthma. Certainly severe viral pneumonia can result in permanent lung damage and recurrent or persistent respiratory symptoms, but this is not asthma. One way in which respiratory viral infections could induce airway remodelling is via wheeze. Recent data from atopic adult asthmatics has shown that bronchoconstriction per se can induce secretion of pro-fibrotic cytokines and deposition of collagen under the airway basement membrane. Whether this same phenomenon occurs in children or in the non-atopic and what implications this has for developing persistent asthma are unknown.

Epidemiological data has shown a clear association between allergic sensitization in early life and viral LRI in increasing the risk of persistent asthma. Data from both the Wisconsin COAST study and the Australian Childhood Asthma Study (CAS), two birth cohorts of high risk children, shows strong evidence that the interaction between these two factors is what produces the highest risk for subsequent asthma. The data from CAS are particularly striking in that the risk of subsequent asthma at both 5 and 10 years of age was only seen in children with allergic sensitization by 5 years of age. The precise mechanism is not known but lessons from what occurs during acute asthma suggest interactions between type 1 IFNs, the high affinity IgE receptor on myeloid lineage cells and IgE antibodies, as will be discussed later.

The potential role played by bacteria resident in the upper airway in increasing or decreasing asthma risk has received considerable recent attention. Data from the COPSAC study, a cohort of children born to asthmatic mothers, suggested that hypopharyngeal colonization with *S. pneumoniae, M. catarrhalis* or *H. influenzae* (but not with *S. aureus*) at 4 weeks of age, using culture-based techniques, increased the risk of wheeze and asthma. Data from the CAS, using non-culture-dependent methodology, showed that the initial pharyngeal microbiome in infancy was very simple with 4 or 5 common geneses. Respiratory health was associated with a microbiome dominated by *Staphylococcus, Corynebacterium* or *Alloiococcus* whereas with viral infections *Streptococcus, Moraxella* and *Haemophilus* were more commonly seen. Early asymptomatic colonization with *S. pneumoniae* was associated with earlier and more severe LRI in infancy and an increased risk of asthma at 5 years of age. Data from other cohort studies in Australia suggest that it is not so much the bacteria that are present at the times of respiratory viral infections but the way the immune system responds to them that determines disease risk. There is still much to learn in this field!

Studying the immune response of children during an acute exacerbation of asthma and following recovery has been illuminating. During an acute exacerbation requiring presentation to hospital, children in Perth, Australia where typically infected with a respiratory virus, especially hRV type C and >90% had high levels of HDM-specific IgE antibodies. Flow cytometry showed an increased proportion of myeloid lineage cells with up-regulation of the high affinity IgE receptor in their peripheral blood. The proposed mechanism includes the following steps:

- Secretion of type 1 IFN from infected AECs
- Up-regulation of the high affinity IgE receptor on monocyte derived macrophages and myeloid dendritic cells
- Cross-linking of IgE receptors by IgE antibodies with secretion of type 2 cytokines (IL-5, IL-4, IL-13)
- Circulating IL-5 acts on the bone marrow to recruit more myeloid-lineage cells expressing IgE receptor which circulate to the lungs and keep the cycle going long after the initiating virus has been cleared.
In summary, knowledge of the roles played by respiratory viruses and bacteria and how they are recognized by the immune system modifies risk of subsequent asthma has increased markedly. However, much remains to be understood, especially if targeting these mechanisms to prevent asthma.

SUGGESTED READING


