Viruses in asthma

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Current evidence suggests that the overall load of infectious agents, including respiratory viruses, encountered early in life is an important factor influencing maturation of the immune system from a type 2 bias at birth towards predominantly type 1 responses, thus avoiding atopic diseases. The 'hygiene hypothesis' proposes that the relatively sterile environment present in industrialised Western countries has contributed to the recent epidemic of asthma and atopy. Whether specific infections are of greater or lesser protective value is an important question if strategies are to be derived to mimic the beneficial effects of childhood infection whilst avoiding morbidity and potential mortality of the natural pathogens.

Infection by respiratory viruses is a major trigger of wheezing in infants and of exacerbations of asthma in older children. Viruses are detected in up to 85% of such episodes. Rhinovirus is common in all age groups; respiratory syncytial virus (RSV) is most important in infants and young children. Knowledge of the immunopathogenetic mechanisms of virus infection in the asthmatic airway will lead to the development of new treatments for virus-induced asthma.

Asthma is a disease of major importance affecting 20–33% of children in the UK[1]. The health costs of this condition are enormous in terms of time off school, GP consultations, hospital admissions and mortality. Asthma is a multifaceted syndrome involving atopy, bronchial hyper-reactivity and IgE and non-IgE mediated acute and chronic immune responses. The asthmatic airway is characterised by an infiltrate of eosinophils and of T lymphocytes expressing the type 2 cytokines (IL-4, IL-5 and IL-13). Trigger factors associated with acute exacerbations of asthma include exposure to environmental allergens, especially animals, moulds, pollens and mites, cold, exercise, air pollution and drugs. Infection, especially by respiratory viruses, is a major trigger of wheezing in infants and of asthma in children. Viruses have also been implicated in the aetiology of asthma and atopic disease. This area is complex and exposure to infectious agents may increase or decrease the risk of developing these diseases.

This review will begin by discussing the role of infection in the aetiology of asthma. We will then go on to discuss the role of viruses in precipitating wheezing episodes in infants and young children, and exacerbations of asthma in older children. Finally we will discuss treatment of virus-induced wheezing and asthma.

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The role of infectious agents in the aetiology of asthma

The prevalence of asthma varies from country to country. The ISAAC study[2] is a world-wide, questionnaire-based, multicentre study of the prevalence of asthma, allergic rhinitis and atopic dermatitis in 463,801 children aged 13–14 years from 155 centres in 56 countries. The countries with the highest prevalence of asthma symptoms are the UK, Australia, New Zealand and the Republic of Ireland, followed by North, Central and South America; the lowest prevalences are found in Eastern Europe, Indonesia, Greece, China, Taiwan, Uzbekistan, India and Ethiopia. There was a 20-fold difference (1.6–36.8%) reported between centres with the highest and lowest rates and an 8-fold variation between the 10th and 90th centiles (3.9–30.6%).

In general, asthma is most common in the industrialised nations with a 'Western' life-style. von Mutius has studied the role of cultural and environmental differences in disease prevalence in East and West Germany following re-unification in 1989[3]. Children living in East Germany had a lower prevalence of asthma and hayfever despite being exposed to higher levels of atmospheric pollution, but higher rates of bronchitis. By the mid 1990s, the prevalence of hayfever and atopic sensitisation had increased whilst the prevalence of asthma had remained stable[4].

The reasons for such differences are not clear. Possible factors in the aetiology of asthma include ethnic origin, childhood respiratory diseases, allergen exposure, diet and socio-economic differences. It has been suggested that improved hygiene in the Western world has resulted in a different exposure to infectious diseases with one consequence being an increased tendency to atopic responses to environmental allergens[5].

A protective effect of early exposure to infection

The recent epidemic of atopic disease and asthma may have occurred as a consequence of a decline in certain childhood infections or a more general lack of exposure to a broad range of infectious agents in the first years of life. This idea is supported by studies of children in environments that would be expected to lead to increases in viral infections. Ball *et al*[6] investigated 1035 children as part of the Tucson Children's Respiratory Study. Children with older siblings at home or who attended day care and, therefore, were more likely to be exposed to respiratory virus infections, were more likely to have frequent wheezing (more than 3 episodes in the preceding year) at age 2 years, but were less likely to have frequent wheezing from ages 6–13 years (Fig. 1). Such children have a reduced risk of atopic sensitisation and asthma at school age[7].

Illi[8] and other members of the Multicentre Allergy Study (MAS) Group have shown that, in German children, repeated upper respiratory

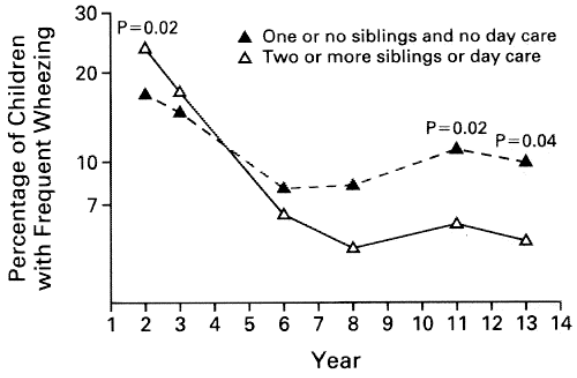

Fig. 1 Prevalence of frequent wheezing among children who had two or more older siblings or who attended day care during the first 6 months of life and among children with less exposure to other children. Children with less exposure to other children were those who had one or no older siblings and who did not attend day care during the first 6 months of life. *P* values are for the comparisons between the two groups of children. [Figure 2 from Ball *et al*,*N Engl J Med* 2000; **343**: 538–43[6] © 2000 Massachusetts Medical Society. All rights reserved.]

tract infection and infection with non-respiratory viruses such as herpes simplex in infancy may reduce the risk of asthma developing up to school age.

Measles infection appears to inhibit atopic disease. Amongst children in Guinea-Bissau, Shaheen *et al* have shown that those who have recovered from natural measles infection have half the incidence of atopy and positive responses to house dust compared to children who have been vaccinated[9]. In a study of Scottish schoolchildren, Bodner *et al*[10] have also shown a reduction in atopic disease, in this case allergic rhinitis in those children with a history of measles. In contrast, a study by Paunio *et al*[11] from Finland found a positive association between measles infection and atopy. Children with established atopic diseases may demonstrate remission of disease during measles infection with recurrence of symptoms following recovery.

Matricardi *et al*[12] have shown that respiratory allergy in Italian air force cadets is less frequent after heavy exposure to orofaecal and foodborne microbes as demonstrated by positive serology for *Toxoplasma gondii*, *Helicobacter pylori* and hepatitis A. A Westernised, semisterile diet may facilitate atopy by influencing the overall pattern of commensals and pathogens that stimulate the gut-associated lymphoid tissue.

A number of additional possible non-viral protective infectious influences have been proposed[13]. These include prenatal or perinatal bacterial infections, exposure to endotoxin[14] and differences in intestinal microflora. Children of farmers in rural areas have a lower prevalence of symptoms of allergic rhinitis and of allergen specific IgE than those in non-farming

families[15,16]. Children with tuberculin test evidence for natural exposure to tuberculosis have fewer symptoms of asthma, eczema, and rhinitis[17].

Hopkin[18] has shown that treatment with oral antibiotics before the age of 2 years is associated with subsequent atopic disease. The mechanism of this effect is unclear, but it may be that antibiotics are associated with a disruption of the normal bowel flora necessary for maturation of the immune system. Alternatively, eliminating a pathogen by antibiotic therapy may limit the beneficial effects on maturation of the immune system of that infection.

It has been suggested that exposure to viruses and other infectious agents in early life is protective against the development of atopy and asthma. Of course such infections are themselves associated with significant morbidity and mortality, and this has been dramatically reduced by preventive strategies such as improvements in public health and measles vaccination. It is possible that some infections help the immune system to mature from an early predominantly Th2-biased state[19] towards a Th1-biased state and that in their absence, in individuals predisposed by genetic or additional environmental factors such as allergen exposure or maternal cigarette smoking, that this fails to happen. The consequence is atopic disease, including asthma, characterised by inflammation with a Th2 phenotype. The use of immunomodulatory drugs[20] to inhibit Th2 cell function may help to deviate the immune system away from a state where atopic disease and asthma are likely to develop. Such a strategy would require the identification of individuals at high risk and treatment in early life. There are significant ethical problems in human trials of such drugs in infants and young children, and the possible harmful effects of immune deviation are unknown.

Acute wheezing illness in infancy

In spite of the possible protective influence of a wide range of infectious agents (including some of the respiratory viruses) on the subsequent development of atopy and asthma, infection by respiratory viruses is a common cause of wheezing episodes in infancy and, as discussed below, of exacerbations in asthmatic children. Some 70% of wheezing episodes in the first year are associated with viral respiratory infection[21]. Respiratory syncytial virus (RSV), rhinovirus and influenza B are the most frequently cultured[22]. In some children, RSV causes bronchiolitis, a potentially serious lower respiratory tract illness with a significant mortality.

Of the respiratory viruses, RSV has most often been associated with subsequent asthma. Sigurs *et al* reported that infants suffering wheezing RSV infections requiring hospitalisation were more likely than prospectively identified control subjects to have allergen-specific IgE and

asthma by the age of 3 years[23]. Other studies have failed to demonstrate a relationship between RSV infection and asthma[24,25].

Martinez and colleagues[26] have studied the relationship between childhood respiratory disorders, their prognosis and the development of asthma in the Tucson Children's Respiratory Study. A total of 1246 newborn babies were recruited and studied in the first 6 years of life. Those children who suffered wheezing early in life before age 3 years could be divided into two groups. Persistent wheezers (those who still had episodes of wheezing at age 6 years) had higher levels of IgE, higher prevalence of atopic dermatitis and a higher prevalence of maternal asthma. Transient wheezers (those without wheezing by age 6 years) were more likely to have small airways and impaired lung function at birth rather than factors associated with atopy. Differences were observed between these two groups in the response at the time of the first infective wheezing episode, which occurred at around 1 year and which was due to RSV in two-thirds of episodes. Persistent wheezers showed an increase in serum IgE not seen in transient wheezers. Eosinopenia was observed in transient wheezers and in children with lower respiratory tract illness without wheezing; eosinophil counts were maintained in persistent wheezers. Such episodes were also observed to be more severe in persistent wheezers. It has been suggested that persistent wheezers will, therefore, be over-represented in studies of children hospitalised with RSV infection, and this may explain why such studies show such a strong association with subsequent asthma[27].

Stein[28] further examined the relationship between lower respiratory tract illness before the age of 3 years and the prevalence of childhood atopy and wheeze in the Tuscon cohort. Those children with lower respiratory tract infection due to RSV had an increased risk of wheezing in the first 6 years, but this increased risk had disappeared by age 11 years. Similar increased risk was observed with other pathogens and indeed with lower respiratory tract infection with negative tests (which in this study may indicate rhinovirus infection since sensitive methods for detection were not included). No association was found between infection by RSV or other pathogens and the subsequent development of atopy.

Whether respiratory viruses actually cause subsequent asthma is unclear. Infants and young children who wheeze with acute respiratory virus infection appear to be at risk of wheeze later in childhood. This may be because such children have other factors such as small airways or deficient type 1 immunity which predispose them to wheeze during virus infections in both early and late childhood and may also predispose them to develop subsequent asthma. Roman[29] has shown low IL-4 and IFN-γ responses and significantly lower IFN-γ/IL-4 ratios in PBMC from children hospitalised with RSV relative to PBMC from control children. Respiratory viruses may simply identify predisposed

children in infancy since they respond to infection by wheezing. They may or may not influence the development of asthma or the progression of asthmatic airway disease.

Respiratory viruses as triggers of asthma exacerbations in older children

The link between respiratory infection and asthma exacerbations is well established although incompletely understood. In the 1950s, this association was attributed to bacterial allergy[30], but it is now clear that the majority of exacerbations are due to viral rather than bacterial infection.

Epidemiology

The viruses implicated in causing primarily respiratory disease include influenza, parainfluenza, enteroviruses, adenovirus, respiratory syncytial virus (RSV), rhinovirus and coronavirus. These viruses were first isolated between 1933 (influenza)[31] and the early 1960s (rhinoviruses[32,33] and coronaviruses[34,35]). It is likely that additional viruses exist, but have not yet been identified. A recent study of children in The Netherlands has identified a new human metapneumovirus[36] causing symptoms similar to RSV ranging from upper respiratory tract disease to severe bronchiolitis and pneumonia. Serology demonstrated that human metapneumovirus has been circulating in humans for at least 50 years and that virtually all children in The Netherlands have been exposed to this virus.

Viral respiratory tract infections are a major cause of wheezing in infants and children. Their role may have been underestimated in early epidemiological studies because of difficulties in isolation and identification[37]. Studies carried out in the 1970s and 1980s were limited to viral culture and serology, and did not always include sensitive methods for detection of rhinoviruses and coronaviruses. The introduction of molecular biology techniques (RT-PCR) to such studies has implicated viral infection in the majority of asthma exacerbations.

Apart from the method of detection used, study design also influences the frequency of detection of respiratory viruses. Asthma exacerbations often occur following a preceding history of common cold symptoms. If clinical sampling is delayed until the child is brought to the GP or accident and emergency department, then samples will be taken at a time when virus shedding is falling and isolation becomes more difficult. In an early study, it was found that 33% of specimens obtained in the first 5 days of illness were positive, but this fell to 18% if specimens were not taken until after the first 5 days[38]. The highest rates of virus

detection are found in prospective studies where children are followed closely and samples are taken as soon as symptoms commence.

Indirect evidence from population studies has established a significant correlation between the seasonal variation in wheezing episodes in young children and peaks of virus identification[39]. In a study of schoolchildren in Southampton, UK, specimens were obtained during respiratory infection or when there was a drop in peak expiratory flow rate. Seasonal patterns of identification of respiratory viruses in this cohort were associated with peaks in local hospital admissions for children with asthma indicating a role for such infections in severe asthma attacks[40].

Direct evidence implicating viral infection in asthma exacerbations has been provided by studies showing an increased rate of virus detection in individuals suffering asthma attacks. Such studies fall into two main types: cross-sectional studies[22,38,41–52] and prospective studies[39,46,53–59]. Viruses have been identified in 10–85% of asthma exacerbations in children.

The highest rates of identification are in those studies where subjects are followed prospectively allowing collection of clinical specimens early in the course of the illness, where PCR-based methods of diagnosis are used in addition to serology and culture, and where the methodology used allows for detection of rhinoviruses.

In Southampton[55], 108 children aged 9–11 years were identified by questionnaire as suffering symptoms of asthma. These children were then followed prospectively over a period of 13 months. Diary cards and peak flow monitoring were used to identify episodes of fall in peak flow, upper respiratory symptoms, cough or wheeze. Nasal samples were taken early during such episodes. A combination of culture and RT-PCR detected viruses in 85% of episodes, the most frequent being rhinovirus.

Rakes *et al*[42] have recently reported the results of a cross-sectional study of 70 infants and children with severe wheezing attending the emergency department in Virginia, USA. This study used both RT-PCR and viral culture to detect a range of viruses including rhinovirus, RSV, coronavirus, enterovirus, influenza and adenovirus in nasal wash samples. Respiratory viruses were detected in 82% of wheezing infants below the age of 2 years and in 83% of older wheezing children. The predominant pathogens were RSV in infants (68%) and rhinovirus in older children (71%). After the age of 2 years, wheezing was most frequent in those with a positive RT-PCR for rhinovirus together with a positive serum RAST for aero-allergens, nasal eosinophilia or elevated nasal ECP.

Freymuth *et al*[52] have similarly used a mixture of conventional and molecular methods for detection of rhinovirus, enterovirus, RSV, adenovirus, coronavirus, influenza, parainfluenza, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in nasal aspirates from 75 infants and children hospitalised for a severe attack of asthma. Overall, a pathogen was detected in 81.8% of those studied, the most frequently identified

being rhinovirus (46.9%) and RSV (21.2%). The use of RT-PCR in this study increased the detection rates for rhinovirus and RSV 5.8-fold and 1.6-fold, respectively.

The rate of detection of viruses between exacerbations when individuals are asymptomatic is only of the order of 3–12%[60]. In contrast, a study of transtracheal aspirates in adult asthmatics during exacerbations[61] yielded sparse bacterial cultures with no correlation to clinical illness and no difference from those of normal subjects. In almost all studies of asthmatics, the predominant viruses are rhinoviruses, RSV and parainfluenza viruses. Rhinoviruses alone are detected in around 50% of virus-induced asthma attacks. Adenoviruses, enteroviruses and coronaviruses are also detected but less frequently. Influenza is only found during annual epidemics.

If a child with asthma develops an infection in which a rhinovirus, coronavirus or RSV is cultured, the likelihood of an associated asthma attack is around 50–70% in prospective studies[37].

The mechanisms of virus-induced wheezing and exacerbation of asthma

This is a complex area that has been reviewed by a number of authors[62–64] and will only be considered briefly here. As yet, our knowledge remains incomplete. Much of the data concerning the mechanisms of virus-induced wheezing and asthma are derived from experimental virus infection in mild adult asthmatics, usually with specific serotypes of rhinovirus, from *in vitro* work on virus infection in epithelial cell culture systems or from animal studies. These data may or may not be relevant to virus-induced wheezing in infants and children.

Whereas other respiratory viruses (such as influenza, parainfluenza, RSV and adenovirus) are well recognised causes of lower airway syndromes such as pneumonia and bronchiolitis and are capable of replication in the lower airway, there has been uncertainty as to whether rhinovirus infection occurred in the lower airway as well as in the upper respiratory tract. Although the possibility of nasopharyngeal contamination cannot be ruled out, rhinovirus has been detected in lower airway clinical specimens such as sputum[49], tracheal brushings[65], and BAL[66] by both RT-PCR and culture. Rhinovirus has been cultured in cell lines of bronchial epithelial cell origin[67] and replication has been demonstrated in primary cultures of bronchial epithelial cells[68,69]. Finally, the use of *in situ* hybridisation has demonstrated rhinovirus in bronchial biopsies of subjects following experimental infection[68]. These data confirm that rhinovirus infection of the lower airway does occur and directly implicate lower airway infection in the pathogenesis of asthma exacerbations.

The interaction of respiratory virus infection and chronic asthmatic airway inflammation results in respiratory symptoms that are more severe than those suffered by non-asthmatic individuals. The detailed immunological mechanisms underlying this interaction are currently unclear. The disease syndrome following infection by virus is a consequence both of direct harmful effects of the virus itself and of immunopathology resulting from the host immune response, some of which may be unavoidable if the virus is to be eliminated. In an asthmatic individual, exacerbation may occur because of functional interaction between viral pathology and asthmatic pathology (*i.e.* through different mechanisms with the same end effect on function), or by sharing the same pathogenetic mechanism in an additive or even in a synergistic fashion. Pre-existing asthmatic inflammation might interfere with an effective antiviral response and thus allow the virus itself to cause increased airway damage. Alternatively, virus infection might increase the sensitivity of the asthmatic airway to trigger factors such as allergen exposure. In fact, it is likely that virus-induced asthma exacerbations occur because of a combination of these four types of interaction.

The virally infected epithelial cell is an important component of the antiviral immune response, producing cytokines and chemokines (IL-6, IL-8, RANTES, IL-11, IL-1β, MCP-1, MIP-1α) capable of activating and recruiting a variety of other cells including lymphocytes, eosinophils and neutrophils. Efficient clearance of virus is orchestrated by antibodies and by T-cells producing type 1 cytokines. The asthmatic airway is rich in type 2 cytokines and this may result in virus-specific T cells with type 2 or mixed type 1/type 2 character. If this is the case, then virus infection could be followed by both an inefficient antiviral immune response with delayed viral clearance and by amplification of on-going asthmatic inflammation; the consequence of this interaction is severe, often prolonged viral illness and exacerbation of asthma.

Treatment for virus-induced asthma exacerbations

The success of vaccination to prevent respiratory virus infections has been limited by significant variation within the major virus types causing disease. There are 102 serotypes of rhinovirus and no effective vaccine has been introduced. The influenza viruses display antigenic shift and drift. New vaccines must be developed every 2–3 years to cover the strains prevalent at the time. When a new pandemic strain arises, there is a delay before sufficient quantities of vaccine can be made available. Vaccination against RSV experienced a major setback in the 1960s when the use of formalin inactivated virus in young babies resulted in increased disease severity following subsequent virus infection[70]. Of

vaccinated children, 80% required hospitalisation when subsequently infected with RSV, as compared to 5% of controls. The lungs of two vaccinated children who died contained eosinophilic infiltrates. It has been suggested that formalin inactivation may have modified epitopes within the RSV G and F surface glycoproteins, resulting in a modified immune response to subsequent infection with enhanced immunopathology[71]. Vaccinated individuals demonstrate a number of differences from individuals who have suffered natural RSV infection including a lack of specific mucosal antibodies and deficient neutralising and fusion-inhibiting serum antibodies[72]. There are also differences in the cell-mediated immune response with some vaccinated individuals demonstrating peripheral eosinophilia and exaggerated lymphocytic proliferative responses to RSV[73]. To protect against RSV infection, a successful vaccine would need to provide more effective protection than natural infection, which is itself frequently followed by re-infection[74], and would have to be administered early in infancy to have an effect on infant bronchiolitis.

There are two main approaches to therapy for a viral exacerbation. The first is to use antiviral agents with direct actions against the virus itself. Because of the large number of viruses producing similar clinical syndromes, the use of specific antiviral drugs requires rapid accurate diagnostic methods such as PCR.

An alternative approach is to treat virus-induced inflammation, perhaps by strategies that promote type 1 responses in individuals with excessive type 2 responses. Understanding the complexities of the antiviral immune response, in particular how it may be altered in the context of pre-existing chronic airway diseases such as asthma, is an essential first step. Further work is needed to elucidate the important sites of interaction between the immunological networks of asthma and of virus infection. Greater knowledge is required if we are to identify key targets for therapeutic intervention, the aim of which will be to minimise immunopathology whilst maintaining or enhancing the host antiviral immune response.

Currently, much of the treatment of infective exacerbations of asthma is symptomatic, consisting of increased bronchodilators, or supportive in the form of oxygen and, in severe cases, non-invasive or invasive ventilatory measures. Corticosteroids are widely used in inhaled or oral form for their anti-inflammatory actions and have a major role in asthma. The effects of corticosteroids are the result of actions at many points in various inflammatory cascades[75]. Whilst this undoubtedly contributes to their beneficial effects, it also results in significant side-effects, in particular if systemic steroid treatment is prolonged or frequent. In addition, systemic steroids may interfere with the antiviral immune response resulting in reduced viral clearance[76].

Specific antiviral agents exist for the influenza viruses including amantidine, rimantidine and the more recently developed neuraminidase inhibitors, zanamivir and oseltamivir. Their use is currently restricted to

adults. Influenza is a relatively unusual cause of asthma exacerbations in children, especially outside epidemics.

Ribavirin is a nucleoside analogue, active against RSV *in vivo* and also against influenza *in vitro*. Nebulised ribavirin therapy is licensed for use in hospitalised infants and children in the first 3 days of RSV bronchiolitis. It is, however, expensive and of unproven benefit on clinical outcome.

RSV-enriched immunoglobulin is effective as prophylaxis for infants at high risk of RSV bronchiolitis[77], and trials with RSV neutralising monoclonal antibodies are in progress.

Rhinoviruses are a major target for drug treatment. It has been estimated that rhinoviruses result in 6–10 colds per year in young children As yet, no effective agent is available for clinical use. Capsid binding/canyon inhibitors block the binding of rhinoviruses to their host cell receptor (ICAM-1 in the case of the major group). One example in phase 3 clinical trials is pleconaril (Picovir). These drugs can be extremely potent, but their clinical usefulness is often limited by serotype specificity and the rapid development of resistance. Alternative targets include soluble ICAM-1 which inhibits major rhinovirus infection *in vitro* and conserved viral enzymes such as protein 3D, the RNA-dependent RNA transcriptase, protein 2C, the associated ATP-helicase, and the cysteine protease 3C.

Conclusions and Summary

The role of infection in the aetiology of asthma is complex. Current evidence suggests that the overall load of infectious agents, including respiratory viruses, encountered early in life is an important factor influencing maturation of the immune system from a type 2 bias at birth towards predominantly type 1 responses, thus avoiding atopic diseases. The 'hygiene hypothesis' is that the relatively sterile environment present in industrialised Western countries has, therefore, contributed to the recent epidemic of asthma and atopy.

Whether specific infections are of greater or lesser protective value is unclear. This is an important question if strategies are to be derived to mimic the beneficial effects of childhood infection whilst avoiding morbidity and potential mortality of the natural pathogens[78].

There is no convincing evidence that specific infections cause atopy or asthma. There is, however, a strong association between severe wheezing episodes in infancy (commonly due to virus infection, in particular RSV) and subsequent wheezing or asthma later in life, particularly in those children with features of atopy.

Infection by respiratory viruses is a common trigger of wheezing in infants and of exacerbations of asthma in older children. Viruses are detected in up to 85% of such episodes. Rhinovirus is common in all age

groups, RSV is most important in infants and young children. Our knowledge of the immunopathogenetic mechanisms involved remains incomplete.

Current therapy for virus-induced exacerbations of asthma relies on increased treatment of pre-existing disease. Corticosteroids form the major anti-inflammatory component of such therapy, but their use can be associated with significant side-effects, especially if used systemically and in high doses. Antiviral agents do exist, in particular for influenza viruses, but the effective use of such drugs in asthma requires viral diagnosis and commencement of treatment early in the course of an exacerbation or the targeting of high-risk groups for prophylaxis. Clinically effective broad spectrum agents are not yet available for the rhinoviruses which are the commonest cause of exacerbations. Alternative strategies for drug development may involve the identification of key factors common to exacerbations induced by a range of different viruses. Increased knowledge of the host–virus interaction is required to design treatments that will increase virus clearance and minimise immunopathology.

Key points for clinical practise

- The vast majority of asthma exacerbations in school-age children are precipitated by acute respiratory viral infection
- The failure to develop adequate type 1 immunity is associated with an increased risk of development of atopy and asthma
- A high overall load of infectious disease early in life (including viral upper respiratory tract infections) protects against atopy and asthma, presumably by augmenting type 1 immunity
- Unnecessary use of antibiotics in the first years of life should be avoided for this reason
- Individual severe viral infections (such as RSV) in those at increased risk (with relatively deficient type 1 immunity) are associated with wheeze in early life and the later development of atopy and asthma

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References

1 Kaur B, Anderson HR, Austin J *et al*. Prevalence of asthma symptoms, diagnosis, and treatment in 12–14 year old children across Great Britain (International Study of Asthma and Allergies in Childhood, ISAAC UK). *BMJ* 1998; **316**: 118–24

2 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; **351**: 1225–32

3 von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994; **149**: 358–64
4 von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998; **351**: 862–6
5 Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259–60
6 Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000; **343**: 538–43
7 Strachan DP. Allergy and family size: a riddle worth solving. *Clin Exp Allergy* 1997; **27**: 235–6
8 Illi S, von Mutius E, Lau S *et al*. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001; **322**: 390–5
9 Shaheen SO, Aaby P, Hall AJ *et al*. Measles and atopy in Guinea-Bissau. *Lancet* 1996; **347**: 1792–6
10 Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. The Aberdeen WHEASE Group. *Thorax* 1998; **53**: 28–32
11 Paunio M, Heinonen OP, Virtanen M, Leinikki P, Patja A, Peltola H. Measles history and atopic diseases: a population-based cross-sectional study. *JAMA* 2000; **283**: 343–6
12 Matricardi PM, Rosmini F, Riondino S *et al*. Exposure to foodborne and orofaecal microbes *versus* airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; **320**: 412–7
13 Wahn U, von Mutius E. Childhood risk factors for atopy and the importance of early intervention. *J Allergy Clin Immunol* 2001; **107**: 567–74
14 von Mutius E, Braun-Fahrlander C, Schierl R *et al*. Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; **30**: 1230–4
15 Braun-Fahrlander C. Allergic diseases in farmers' children. *Pediatr Allergy Immunol* 2000; **11** (**Suppl 13**): 19–22
16 Braun-Fahrlander C, Gassner M, Grize L *et al*. Prevalence of hay fever and allergic sensitization in farmers' children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. *Clin Exp Allergy* 1999; **29**: 28–34
17 Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; **275**: 77–9
18 Hopkin JM. Early life receipt of antibiotics and atopic disorder. *Clin Exp Allergy* 1999; **29**: 733–4
19 Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 1999; **353**: 196–200
20 Holt PG, Sly PD. Prevention of adult asthma by early intervention during childhood: potential value of new generation immunomodulatory drugs. *Thorax* 2000; **55**: 700–3
21 Wright AL, Holberg CJ, Martinez FD, Morgan WJ, Taussig LM. Breast feeding and lower respiratory tract illness in the first year of life. Group Health Medical Associates. *BMJ* 1989; **299**: 946–9
22 Duff AL, Pomeranz ES, Gelber LE *et al*. Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. *Pediatrics* 1993; **92**: 535–40
23 Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995; **95**: 500–5
24 Cogswell JJ, Halliday DF, Alexander JR. Respiratory infections in the first year of life in children at risk of developing atopy. *BMJ* 1982; **284**: 1011–3
25 Welliver RC. RSV and chronic asthma. *Lancet* 1995; **346**: 789–90
26 Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; **319**: 1112–7
27 Martinez FD. Viruses and atopic sensitization in the first years of life. *Am J Respir Crit Care Med* 2000; **162**: S95–9
28 Stein RT, Sherrill D, Morgan WJ *et al*. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; **354**: 541–5
29 Roman M, Calhoun WJ, Hinton KL *et al*. Respiratory syncytial virus infection in infants is associated with predominant Th-2-like response. *Am J Respir Crit Care Med* 1997; **156**: 190–5
30 Stevens FA. Acute asthmatic episodes in children caused by upper respiratory bacteria during colds, with and without bacterial sensitization. *J Allergy* 1953; **24**: 221–6

31 Smith W, Andrewes CH, Laidlaw PP. A virus obtained from influenza patients. *Lancet* 1933; **II**: 66–8

32 Tyrrell DAJ, Parsons R. Some virus isolations from common colds. III Cytopathic effects in tissue cultures. *Lancet* 1960; **I**: 235–8

33 Taylor-Robinson D. Laboratory and volunteer studies on some viruses isolated from common colds (rhinoviruses). *Am Rev Respir Dis* 1963; **88**: 262–8

34 Tyrrell DAJ, Bynoe ML. Cultivation of a novel type of common cold virus in organ cultures. *BMJ* 1965; **1**: 1467–70

35 Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. *Proc Soc Exp Biol Med* 1966; **121**: 190–3

36 van den Hoogen BG, de Jong JC, Groen J *et al*. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001; **7**: 719–24

37 Pattemore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. *Clin Exp Allergy* 1992; **22**: 325–36

38 Horn ME, Brain E, Gregg I, Yealland SJ, Inglis JM. Respiratory viral infection in childhood. A survey in general practice, Roehampton 1967–1972. *J Hygiene* 1975; **74**: 157–68

39 McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *J Pediatr* 1973; **82**: 578–90

40 Johnston SL, Pattemore PK, Sanderson G *et al*. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am J Respir Crit Care Med* 1996; **154**: 654–60

41 Rylander E, Eriksson M, Pershagen G, Nordvall L, Ehrnst A, Ziegler T. Wheezing bronchitis in children. Incidence, viral infections, and other risk factors in a defined population. *Pediatr Allergy Immunol* 1996; **7**: 6–11

42 Rakes GP, Arruda E, Ingram JM *et al*. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. *Am J Respir Crit Care Med* 1999; **159**: 785–90

43 Tyrrell DAJ. A collaborative study of the aetiology of acute respiratory infections in Britain, 1961–4. *BMJ* 1965; **2**: 319–26

44 Disney ME, Matthews R, Williams JD. The role of infection in the morbidity of asthmatic children admitted to hospital. *Clin Allergy* 1971; **1**: 399–406

45 Glezen WP, Loda FA, Clyde WAJ *et al*. Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *J Pediatr* 1971; **78**: 397–406

46 Mitchell I, Inglis JM, Simpson H. Viral infection as a precipitant of wheeze in children. Combined home and hospital study. *Arch Dis Child* 1978; **53**: 106–11

47 Henderson FW, Clyde WAJ, Collier AM *et al*. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J Pediatr* 1979; **95**: 183–90

48 Horn ME, Brain EA, Gregg I, Inglis JM, Yealland SJ, Taylor P. Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* 1979; **34**: 23–8

49 Horn ME, Reed SE, Taylor P. Role of viruses and bacteria in acute wheezy bronchitis in childhood: a study of sputum. *Arch Dis Child* 1979; **54**: 587–92

50 Carlsen KH, Orstavik I, Leegaard J, Hoeg H. Respiratory virus infections and aeroallergens in acute bronchial asthma. *Arch Dis Child* 1984; **59**: 310–5

51 Jennings LC, Barns G, Dawson KP. The association of viruses with acute asthma. *N Z Med J* 1987; **100**: 488–90

52 Freymuth F, Vabret A, Brouard J *et al*. Detection of viral, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections in exacerbations of asthma in children. *J Clin Virol* 1999; **13**: 131–9

53 Mertsola J, Ziegler T, Ruuskanen O, Vanto T, Koivikko A, Halonen P. Recurrent wheezy bronchitis and viral respiratory infections. *Arch Dis Child* 1991; **66**: 124–9

54 Roldaan AC, Masural N. Viral respiratory infections in asthmatic children staying in a mountain resort. *Eur J Respir Dis* 1982; **63**: 140–50

55 Johnston SL, Pattemore PK, Sanderson G *et al*. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; **310**: 1225–9

56 Berkovich S, Millian SJ, Snyder RD. The association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. *Ann Allergy* 1970; **28**: 43–9

57 Lambert HP, Stern H. Infective factors in exacerbations of bronchitis and asthma. *BMJ* 1972; **3**: 323–7

58 Minor TE, Dick EC, DeMeo AN, Ouellette JJ, Cohen M, Reed CE. Viruses as precipitants of asthmatic attacks in children. *JAMA* 1974; **227**: 292–8

59 Minor TE, Dick EC, Baker JW, Ouellette JJ, Cohen M, Reed CE. Rhinovirus and influenza type A infections as precipitants of asthma. *Am Rev Respir Dis* 1976; **113**: 149–53

60 Johnston SL. Viruses and asthma. *Allergy* 1998; **53**: 922–32

61 Berman SZ, Mathison DA, Stevenson DD, Tan EM, Vaughan JH. Transtracheal aspiration studies in asthmatic patients in relapse with 'infective' asthma and in subjects without respiratory disease. *J Allergy Clin Immunol* 1975; **56**: 206–14

62 Papadopoulos NG, Johnston SL. The acute exacerbation of asthma. Pathogenesis. In: Holgate ST, Boushey HA, Fabbri LM. (eds) *Difficult Asthma*. London: Martin Dunnitz, 1999; 183–204

63 Corne JM, Holgate ST. Mechanisms of virus induced exacerbations of asthma. *Thorax* 1997; **52**: 380–9

64 Folkerts G, Busse WW, Nijkamp FP, Sorkness R, Gern JE. Virus-induced airway hyperresponsiveness and asthma. *Am J Respir Crit Care Med* 1998; **157**: 1708–20

65 Halperin SA, Eggleston PA, Hendley JO, Suratt PM, Groschel DH, Gwaltney Jr JM. Pathogenesis of lower respiratory tract symptoms in experimental rhinovirus infection. *Am Rev Respir Dis* 1983; **128**: 806–10

66 Gern JE, Galagan DM, Jarjour NN, Dick EC, Busse WW. Detection of rhinovirus RNA in lower airway cells during experimentally induced infection. *Am J Respir Crit Care Med* 1997; **155**: 1159–61

67 Subauste MC, Jacoby DB, Richards SM, Proud D. Infection of a human respiratory epithelial cell line with rhinovirus. Induction of cytokine release and modulation of susceptibility to infection by cytokine exposure. *J Clin Invest* 1995; **96**: 549–57

68 Papadopoulos NG, Bates PJ, Bardin PG *et al*. Rhinoviruses infect the lower airways. *J Infect Dis* 2000; **181**: 1875–84

69 Schroth MK, Grimm E, Frindt P *et al*. Rhinovirus replication causes RANTES production in primary bronchial epithelial cells. *Am J Respir Cell Mol Biol* 1999; **20**: 1220–8

70 Kim HW, Canchola JG, Brandt CD *et al*. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am J Epidemiol* 1969; **89**: 422–34

71 Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med* 2001; **344**: 1917–28

72 Murphy BR, Prince GA, Walsh EE *et al*. Dissociation between serum neutralizing and glycoprotein antibody responses of infants and children who received inactivated respiratory syncytial virus vaccine. *J Clin Microbiol* 1986; **24**: 197–202

73 Kim HW, Leikin SL, Arrobio J, Brandt CD, Chanock RM, Parrott RH. Cell-mediated immunity to respiratory syncytial virus induced by inactivated vaccine or by infection. *Pediatr Res* 1976; **10**: 75–8

74 Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and re-infection with respiratory syncytial virus. *Am J Dis Child* 1986; **140**: 543–6

75 Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin Sci* 1998; **94**: 557–72

76 Gustafson LM, Proud D, Hendley JO, Hayden FG, Gwaltney Jr JM. Oral prednisone therapy in experimental rhinovirus infections. *J Allergy Clin Immunol* 1996; **97**: 1009–14

77 Rodriguez WJ, Gruber WC, Welliver RC *et al*. Respiratory syncytial virus (RSV) immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infections: Respiratory Syncytial Virus Immune Globulin Study Group. *Pediatrics* 1997; **99**: 454–61

78 Johnston SL, Openshaw PJ. The protective effect of childhood infections. *BMJ* 2001; **322**: 376–7