CURRENT TOPIC

Why do viruses make infants wheeze?

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Many infants wheeze whenever they have a cold. On average, preschool children and infants catch 6–8 colds per year, although they are certainly exposed to far more respiratory viruses. Even if the child becomes infected, he may remain asymptomatic and subclinical infections are likely to be common. If, on the other hand, the child becomes symptomatic, the illness and symptoms may be limited to the upper respiratory tract alone or a lower respiratory illness may develop as well (fig 1). The wheezing is a result of this lower respiratory illness and is associated with partial obstruction of the larger airways. It is not clear what determines the outcome, but the interaction between the competence of the host defence and the intrinsic pathogenicity of the virus is central to the process. This review considers how viruses cause wheezing together with the reasons why only certain infants wheeze.

Epidemiology

There is a striking temporal association between viral upper respiratory tract infection (URTI) and infant wheezing. All respiratory viruses have been implicated but in a review of over 20 studies, Pattemore *et al* showed that the principal ones involved were rhinovirus, respiratory syncytial virus (RSV), and parainfluenza virus.¹ The age of the children studied had the greatest influence on which viruses were isolated with RSV and

parainfluenza predominating in infancy. This picture may now be changing, however, and utilising newer techniques of RNA analysis,² it may be that rhinovirus will be shown to have a greater role in infant wheezing than previously suspected. It is not clear why these particular viruses are the ones usually associated with wheezing, but it is probably related to the frequency with which these viruses infect this age group. The large number of different rhinovirus serotypes also means new infections will continue throughout childhood due to lack of cross immunity. Finally, there may be some inherent property possessed by these viruses, the nature of which is still unknown.

The exact incidence of infant wheezing is difficult to determine. However, recent data from the longitudinal Tuscon Children's Respiratory Study have revealed that 20% of all children have at least one episode of a wheezing illness in their first year.³ They also estimate that over 40% of the children have wheezed at least once during the first three years of life.⁴

How viruses cause wheezing**(1) AIRWAY HYPERREACTIVITY**

Almost all respiratory viral infections can induce a state of bronchial hyperreactivity in normal individuals. If an underlying state of hyperreactivity is already present, as is the case in asthmatic children, then the additional insult of a viral infection will exacerbate this and lead to a greater degree of airway obstruction. Increased airway responsiveness to a number of agents has been demonstrated in both natural and experimental viral infections (reviewed by Bardin *et al*⁵) and the hyperreactivity may last as long as 6–7 weeks.⁶ Not all studies, however, have demonstrated this but different results are probably due to methodological discrepancies.

Bronchial hyperresponsiveness may result from direct viral injury to airway epithelium by a number of mechanisms, including increased permeability to antigen, changes in osmolarity of the epithelial lining fluid, and loss of proposed epithelial derived relaxant factors.⁷ Epithelial damage by the virus may also lead to exposure and sensitisation of cholinergic sensory nerve fibres normally protected by the epithelium.⁶ Repair of this damaged epithelium would account for the return to normal airway reactivity after six weeks. Recent

Figure 1 Relationship of viral infection to upper respiratory tract (URT) and lower respiratory tract (LRT) symptoms.

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interest has focused on the role of nitric oxide in airway reactivity. Initial work suggests a deficiency in endogenous nitric oxide production in airway epithelium after a viral infection may contribute to airway hyperresponsiveness.⁸

Overall, virus induced alteration in airway reactivity is probably not a major factor in infancy, although it certainly accounts for exacerbations in older children with established atopic asthma.

(2) DIMINISHED LUNG FUNCTION

Studies of normal adults with viral respiratory infections showed that viruses cause small airway obstruction, although the function of the large airways is unaltered (reviewed by Busse⁹). Although these changes may not be clinically apparent, the effect persisted in some of the subjects for up to eight weeks. Studies have also demonstrated alterations in lung function in infants hospitalised with acute bronchiolitis (reviewed by Stark and Busse¹⁰), as well as infants and children with acute URTI.¹¹ These alterations included lower flow rates, increased inspiratory and expiratory resistance, and increased thoracic gas volumes. Some of the changes persisted in the bronchiolitic infants for over a year, but lung function was normal in the infants with a simple URTI within one month.¹¹ It would seem therefore that respiratory viruses may transiently affect lung function in adults and children of all ages, but the effects usually remain subclinical. However, if lung function is already compromised, as it may be in those prone to wheezing (see later), then the effects of viruses may be more noticeable.

Altered β -adrenergic function may partly account for virus induced changes in lung function and several animal and in vitro studies support this idea. In particular, granulocytes taken from asthmatics responded less well to β -adrenergic stimulation than those taken from normal subjects and the response was further diminished during exacerbations caused by viral infection.¹² It has also been demonstrated that there are structural similarities between the cell surface receptors for certain viruses and β -adrenergic receptors that may account for the interaction between respiratory viruses and impaired β -adrenergic function.¹³

Viral damage to airway epithelium may also lead to bronchoconstriction by altering the metabolism of substance P, a neuropeptide that contributes to bronchomotor tone (reviewed by Stark and Busse¹⁰). Animal work has shown that destruction of airway epithelium by influenza virus reduced the enzymatic action of enkephalinase, a neutral endopeptidase that normally degrades substance P.¹⁴ It is possible that epithelial destruction and loss of neutral endopeptidase caused by viral infection may lead to bronchoconstriction and hyperresponsiveness, via the unchecked activity of substance P on the airways.¹⁴ It is not yet known whether similar effects are seen in humans after viral infections.

(3) AIRWAY INFLAMMATION

Release of bronchospastic and inflammatory mediators in the airways during viral infection may result in airway narrowing. As well as contraction of bronchial smooth muscle, the narrowing is due to a combination of vascular engorgement, cellular infiltration of airway walls, and mucosal and submucosal oedema. Numerous inflammatory cells have been implicated in this process; they may be recruited to the site by chemical messengers released by virally damaged cells. In turn the recruited cells release mediators that promote airway narrowing and further cell recruitment. Even if the infection is limited to the upper respiratory tract, inflammatory mediators produced locally in the nose may act on the lower airways to produce symptoms.

(A) Inflammatory cells

Mast cells may be central to the process as they release both histamine and leukotriene (LT) C₄; both these mediators have been shown to be raised in respiratory secretions of infants with viral wheeze.^{15 16} Furthermore, animal studies have shown that viral infection can lead to mast cell hyperplasia and increased activity with associated bronchial hyperresponsiveness.¹⁷

Neutrophils may play an important part in the transient airway hyperreactivity seen after viral infections, as they have a central role in viral airway inflammation. Markedly raised numbers of neutrophils have been found in nasal biopsy specimens of subjects with rhinovirus URTIs.¹⁸ Neutrophils were also the predominant inflammatory cell seen in bronchial secretions of children with lower respiratory tract infection due to RSV.¹⁹ Neutrophils have also been shown to display enhanced adhesion to airway epithelial cells infected with RSV or parainfluenza virus.²⁰ Finally, neutrophils release a number of toxic oxygen metabolites which are damaging to airway tissues and could lead to airway inflammation, obstruction, and hyperresponsiveness.

Eosinophils release a large number of mediators such as LTC₄ and platelet activating factor, but also release basic proteins such as major basic protein and eosinophilic cationic protein, which are toxic to airway epithelium. Release of major basic protein may also upregulate the contractile response of airway smooth muscle.²¹ Eosinophilic infiltration is a prominent feature of asthma and may also play a part in viral wheeze. In vitro work has shown that RSV activates human eosinophils and a study measuring the concentration of eosinophilic cationic protein in nasopharyngeal secretions of infants found significantly higher values in those with RSV induced wheezing compared with infants with URTI alone.²² Against the role of eosinophils, a recent study showed few present in bronchial lavage of infants with RSV bronchiolitis.¹⁹

Macrophages are abundant throughout the respiratory tract and alveolar macrophages are thought to be the first line of defence against both viral and bacterial infections. The

mechanism of the antiviral activity may be partly due to a direct effect on viral replication or the release of interferon and other cytokines. Infection of alveolar macrophages by RSV leads to increased secretion of tumour necrosis factor- α (TNF- α) as well as interleukin (IL)-6 and IL-8.^{23 24}

T lymphocytes have been found to have an increasingly important role in the pathogenesis of both adult and childhood asthma, particularly in terms of immunoregulation and cytokine production.^{25 26} Two types of T helper (Th) cells have been identified, defined by their cytokine secretion patterns; Th1 cells secrete IL-2, interferon gamma, and lymphotxin, whereas Th2 cells secrete IL-4, IL-5, IL-6, and IL-10, with several other cytokines secreted by both types (reviewed by Mosmann²⁷). Several features of the allergic asthmatic response are mediated by Th2 cytokines, particularly in relation to IgE production and eosinophil and mast cell activity. Although it is the Th1 response classically associated with antiviral immunity, the RSV G protein primarily promotes a Th2 like response which could account for some of the RSV lower airway symptomatology.²⁸

Basophils may have a role in the pathogenesis of viral wheezing but this is not yet fully established. However, IgE dependent histamine release is enhanced after incubation of human basophils with several respiratory viruses.^{29 30} This enhanced histamine release also occurred if the basophils were incubated with interferon, a product of virus infected cells, instead of the virus itself.²⁹ If these in vitro findings apply to the human airway during natural infection, then migration of basophils followed by enhanced mediator release may account for some of the bronchoconstriction seen in acute bronchiolitis.

(B) Inflammatory mediators

Production of inflammatory mediators may well be the key to viral wheezing, although it is unlikely any single mediator is the main culprit. It is worth briefly reviewing the more important mediators that have so far been implicated, but it should be stressed that finding raised levels of a particular mediator during episodes of viral wheezing does not necessarily imply cause, only association.

Histamine – raised concentrations have been measured in the nasopharyngeal secretions of infants with RSV infection¹⁵ and in bronchial secretions of animals infected with parainfluenza 3 virus.³¹ As well as local production, plasma concentrations of histamine have been found to be raised in infants with RSV bronchiolitis.³² Lack of therapeutic success with antihistamines, however, must throw doubt on the relevance of these findings.

Lipoxygenase products – the cysteinyl leukotrienes are a group of lipid inflammatory mediators derived from arachidonic acid via the 5-lipoxygenase pathway (reviewed by Henderson and Barnes *et al*^{33 34}). They are released by all the primary inflammatory cells that mediate lung inflammation as well as

pulmonary endothelial and epithelial cells. LTC₄ and LTD₄ are the most active compounds and are potent bronchoconstrictors, affecting both small and large airways. Leukotrienes have also been shown to increase vascular permeability and increase mucus production. Certain respiratory viruses (RSV, parainfluenza 3, and influenza A) have been shown to induce release of LTC₄ into nasopharyngeal secretions.³⁵ LTC₄ release was particularly enhanced during RSV infection and was detected more often and in higher concentrations in those infants who developed bronchiolitis with wheezing rather than upper respiratory symptoms alone.¹⁶ Treatment of RSV bronchiolitis with ribavirin led to a decline in leukotriene concentrations in the nasopharyngeal secretions over the first week in contrast to infants who received β -agonists only.³⁶ A more recent study measuring systemic leukotriene production found no alteration in urinary LTE₄ concentrations during acute episodes of viral wheezing in infants.³⁷ The large body of work on leukotrienes, particularly in adults, would seem to indicate that they do have an important role in wheezing conditions. It will be interesting to see whether leukotriene antagonists, which will soon be licensed for adult use, will find an eventual niche in the treatment of infant wheezing.

Cyclo-oxygenase products of arachidonic acid include the prostaglandins and thromboxane. Both prostaglandins D₂ and F_{2 α} are potent bronchoconstrictors. Plasma levels of the primary metabolite of PGF_{2 α} were shown to be raised in infants with RSV bronchiolitis; furthermore, those with recurrent wheezing after the infection had the highest initial values.³⁸ It has also been shown that RSV antibody complexes cause increased release of thromboxane, another bronchoconstrictor, from neutrophils.³⁹ Prostaglandin E₂, on the other hand, seems to have an inhibitory effect and may protect the airways from bronchoconstriction; it is suggested that viral damage of the epithelium may result in loss of these protective prostaglandins.⁷

Platelet activating factor, which is released by macrophages, eosinophils and neutrophils, can induce a sustained inflammatory response in the airway, similar to that found with viral infection. Platelet activating factor also stimulates airway mucus production, impairs mucociliary clearance, and increases pulmonary microvascular permeability.⁴⁰ In vitro work with mononuclear phagocytes has shown that RSV caused a sustained stimulation of platelet activating factor synthesis that paralleled viral replication and it has been suggested that production of platelet activating factor may have a critical role in the inflammatory response to RSV,⁴¹ although the evidence is still largely circumstantial.

Complement – C3a and C5a (the anaphylatoxins) have been shown to induce bronchoconstriction as well as induce release of histamine, prostaglandins, and leukotrienes; C5a is also chemotactic for several inflammatory cells.³⁴ The significance is that increases in

both C3a and C5a have been demonstrated in the upper airways during influenza A infection.⁴² Furthermore, RSV infected cells have been shown to activate complement, which increases adherence of neutrophils to the infected cells and enhances neutrophil mediated cytotoxicity (reviewed by Faden and Ogra⁴³).

Kinins – bradykinin and other related kinins are potent vasoactive peptides that can cause bronchoconstriction.³⁴ Studies with rhinovirus have shown a close association between symptoms of a cold and raised concentrations of bradykinin and lysylbradykinin in nasal secretions.⁴⁴ Similar infection of bronchial epithelium by rhinovirus could cause release of these kinins which might account for symptoms of cough and wheeze with enhanced bronchial hyperresponsiveness.⁵

(C) Cytokines

Cytokines are extracellular signalling proteins secreted by specific effector cells with the ability to modify the behaviour of other closely adjacent cells.⁴⁵ There are many different cytokines and new ones are being recognised and classified all the time. They interact through a complex network, influencing the inflammatory and immune responses, so the effects of combinations of cytokines cannot always be predicted based on knowledge of the action of individual ones. Many cytokines are involved with the airway inflammation found in asthma, mainly due to their influences on eosinophil activity and IgE synthesis.⁴⁶ Certain cytokines may also be involved in viral wheezing, although there is less direct evidence. These include IL-2, IL-6, IL-8, and IL-11.^{47–50} Two other cytokines are discussed in more detail as it is likely they have an important role.

TNF- α – viruses are capable of enhancing production of TNF- α and animal studies have shown that TNF- α can have adverse effects on lung function (reviewed by Kips *et al*⁵¹). TNF- α also induces an influx of inflammatory cells into tissues, mainly due to its ability to increase expression of adhesion molecules on endothelial cells. Recent work has shown that nasal TNF- α concentrations were significantly increased in infants during acute wheezy episodes associated with respiratory tract infections, and this was particularly associated with the presence of RSV.³⁷

As already mentioned, *interferon* enhances IgG mediated histamine release after exposure to several respiratory viruses.²⁹ The interaction between interferon and RSV infection is interesting. RSV has been shown to be acutely sensitive to both interferons alfa and gamma which inhibit its growth. Yet in vitro and clinical work has shown that interferon production seems to be suppressed by RSV, although this may return to normal in the recovery phase.⁵² The effect may be virus specific as nasal titres of interferon were detectable less often and at lower levels in children with RSV compared with influenza or parainfluenza infections.^{53 54} It has also been shown that a small group of wheezy infants

with recurrent URTIs consistently appeared unable to make interferon alfa during the acute episodes, although severity of illness was unaffected by interferon alfa production.⁵⁵

(D) Adhesion molecules

Adhesion molecules are receptors located on vascular endothelium and airway epithelium with the corresponding ligands located on circulating leucocytes. The endothelial expression of adhesion molecules at the site of inflammation mediates the cell mediated immune response.⁵⁶ Intercellular adhesion molecule-1 (ICAM-1) has been shown to act as a neutrophil and eosinophil receptor on airway epithelial cells⁵⁷ and induces antigen-induced bronchial hyperresponsiveness.⁵⁸ It has recently been shown by several investigators that the majority of rhinoviruses attach to the surface of cells via a receptor identified as ICAM-1 (reviewed by Johnston *et al*⁵⁹). If infection with rhinovirus leads to upregulation of ICAM-1 expression in the lower airways this may account for rhinovirus induced neutrophil influx, hyperresponsiveness, and wheeze. In vitro work has also shown that human bronchial and nasal epithelial cells infected with RSV or parainfluenza virus expressed increased concentrations of ICAM-1, which led to enhanced levels of eosinophil and neutrophil adhesion.^{60 61} Further evidence that ICAM-1 may have a role in modifying airway inflammation is provided by the fact that its expression is increased by several cytokines. As understanding of adhesion molecules increases, it is likely that they will be seen to have a part to play in the pathogenesis of airway inflammation and wheezing.

Why certain infants wheeze

(1) RISK FACTORS IN THE HOST

Viral responsiveness describes susceptibility to symptomatic viral infection and is one of the variables determining predisposition to wheeze. Several factors, both endogenous and exogenous, place some infants at a higher risk of developing viral wheeze. However, 20% of 3 year old wheezy children do not have any of the recognised major risk factors, so there must be other inherent factors that are as yet unknown.⁴

Age and sex – viral wheezing is commonest in young infants. Severe wheezing is unusual under 2 months and there is a sharp decline in incidence by 2 years. This is mainly due to immunological factors, although airway size may also be important. Wheezing due to RSV, parainfluenza 1 and 3, and adenovirus (but not rhinovirus) is far commoner in males; this may be related to differences in lung function and relative airway size.⁶²

Socioeconomic factors – the risk of serious RSV illness is much greater in infants from low income families, most likely related to crowded living conditions and large families. The presence of older siblings increases the risk of bronchiolitis mainly due to the introduction into the home of viruses that the older sibling

has picked up at nursery or school. For similar reasons, there is a greater risk of wheezing lower respiratory illness among children who attend day care centres. However, day care has a protective effect if the mother is a heavy smoker (over one pack of cigarettes per day).⁶³

Passive smoking – exposure to cigarette smoke leads to a fourfold increased risk of bronchiolitis and a threefold increased risk of any lower respiratory illness; these illnesses are also contracted at an earlier age.⁶³ The risk is related to maternal rather than paternal smoking and may be partly due to the longer time mothers generally spend with their infants. However, preliminary work has also suggested there are alterations in the developing lungs of the fetus due to mothers smoking during pregnancy that results in diminished lung function at birth and altered airway reactivity in the first 10 weeks of life.⁶⁴

Breast feeding – breast feeding seems to confer a degree of protection against wheezing lower respiratory illness and in particular RSV,⁶⁵ although the essential role is not the prevention of infections but reduction in severity of the illness. RSV neutralising activity has been detected in colostrum and is largely due to secretory IgA.⁶⁶ The RSV specific lymphoproliferative response may be suppressed in breast fed babies, which may account for why they are less severely affected.⁶⁷ This in turn may be due to serum interferon alfa which is found more often and at higher concentrations in breast fed babies and is associated with suppression of the lymphoproliferative response to RSV.⁶⁸

Atopy – studies that have examined the association of viral wheeze with atopy give conflicting results (reviewed by Skoner and Caligiuri⁶⁹). This is partly due to difficulties in defining and diagnosing atopy in the very young. It has been shown, however, that the risk of developing a wheezing illness in the first year of life was inversely related to the cord blood IgE concentrations.⁷⁰ No relationship was found in the second year, and by the third year of life the relationship had reversed so that the risk was directly related to the IgE concentrations.⁷¹ So although atopy might affect viral wheezing, it is unlikely it plays an important part in young infants. Interestingly, it is now emerging that early viral respiratory infections may actually have a protective role against the development of atopy in later life.⁷²

Pulmonary factors – the importance of baseline lung function as a risk factor for wheezing has been demonstrated in a study that measured lung function in infants before they had contracted any lower respiratory illnesses.⁷³ Infants with diminished airway conductance had a 3–6 times greater risk of wheezing in the first year of life. Furthermore, this risk of wheezing was still in evidence at three year follow up.⁷⁴ It would seem that narrower or smaller airways may be more likely to become obstructed when infected, leading to wheezing and hyperinflation. Early lung damage also increases the risk of lower respiratory illness and wheezing. Premature infants have a greater risk of wheezing, particularly if

they required mechanical ventilation and infants with bronchopulmonary dysplasia are at grave risk of developing life threatening bronchiolitis.⁷⁵ As well as this, some infants display enhanced airway reactivity, although the role in wheezing lower respiratory illness is unclear; it would seem, however, that underlying bronchial hyperresponsiveness is not a feature of infant wheezing.⁷⁶

(2) ALTERATIONS IN IMMUNE RESPONSE TO VIRUSES

There is increasing evidence that some infants have an immature or abnormal immune response to some respiratory viruses, and particularly RSV. Immune dysregulation could lead to an increased number of infections, but it is not clear whether wheezy infants are more susceptible to colds or whether colds are simply more noticeable in them due to additional symptoms of cough and wheeze. It is likely that both factors apply, however. One study has found that asthmatic children had a greater incidence of viral infection compared with their non-asthmatic siblings (due mainly to an increase in rhinovirus⁷⁷); another, however, showed that asthmatic children with rhinovirus have a higher incidence of symptoms than other children.⁷⁸ Immune dysregulation could also mean the microbe has a greater effect on the host. If defence is impaired the virus could cause greater damage, and this is particularly true of immunodeficient states – for example children on cytotoxic or immunosuppressive treatment may develop severe and often fatal infections with measles, chickenpox, RSV, influenza, and parainfluenza viruses. Equally, an exaggerated or exuberant immune response may also be harmful to the host.

(A) Cell mediated immunity

Cell mediated immunity (CMI) is important in antiviral defence but there is evidence it may also contribute to the pathological process.

Protective effect of CMI – children with impaired CMI show a prolonged shedding of RSV, 40–112 days compared with the usual mean of seven days.⁷⁹ These children also develop RSV pneumonia at an age when this is rather uncommon (over 3 years old). Although a 10 year prospective study did not find any evidence that CMI contributed significantly to the outcome of RSV infection,⁸⁰ virus specific cellular cytotoxic activity has been demonstrated in infants with acute RSV infection, usually within one week.⁸¹ The activity was age dependent with the response found in 65% of those aged 6–24 months but in only 35–38% of those aged 5 months or less; this may account for the severity of the disease in the younger age group.⁸² The reason for the relatively poor CMI response in the young may be immunological immaturity, but it is more likely that the greater response seen in older children is a reflection of previous RSV infection; the enhanced response may simply represent booster effects secondary to stimulation of

memory cells. Another possibility is that the CMI response in those under 6 months is inhibited by high levels of pre-existing maternally derived RSV antibody.

Pathological effect of CMI – studies on the relationship of the cellular response to RSV with age have not produced consistent findings. Using different methodology to that of Chiba *et al.*,⁸² other workers have found a significant CMI response in 78% of infants under 6 months compared with 46% over 6 months.⁸³ The greater CMI response in the age group most severely affected by RSV would indicate that CMI is involved in the pathogenesis of RSV. As well as this, exaggerated cellular responses were associated with severe pulmonary disease in infants with natural RSV infection who had previously been immunised with RSV vaccine.⁸⁴ It has also been shown that infants who developed RSV specific CMI within a few days of infection had a clinical illness characterised by bronchospasm⁸⁵; whereas CMI developed more gradually in those who developed upper respiratory illness or pneumonia. In addition, the infants with a high degree of RSV specific CMI activity 3–9 weeks after onset of infection were more prone to wheezing over the next six months. It seems that although a heightened T cell response is necessary to clear the virus, airway injury occurs as the virus is eradicated.¹⁰ CMI contributes to host defence against RSV at the same time as enhancing the pathological process.

(B) Humoral immunity

The humoral immune system has an important role against respiratory viruses, confirmed by the beneficial effect on incidence and severity of RSV bronchiolitis in children given prophylactic RSV immune globulin.⁸⁶

Effect of age – in a similar way to the CMI response, age has an important effect on humoral immunity. Infants under 6–8 months mount a poor antibody response to RSV infection compared with older infants, and there is often a failure to develop a protective secretory IgA or neutralising IgG response.⁸⁷ In particular, the effect of age is primarily on the response to the F (fusion) surface glycoprotein of RSV.⁸⁸ This poor antibody response is thought to be due to immaturity of the immune system, but while this may account for the general age distribution of the disease it does not account for the differences in disease severity seen among individuals of the same age.

Maternal antibodies – the presence of passively acquired maternal antibodies in the serum of young infants may have an immunosuppressive effect on the development of the infant's own immune response, although it is primarily the response to the G glycoprotein of RSV that is affected by maternal antibodies.⁸⁸ There is contrasting evidence as to whether these maternal antibodies are harmful or helpful. It has been hypothesised that due to lack of specific secretory IgA during the initial challenge with RSV, the maternal IgG could

diffuse to the lumen of the infant airways and form immune complexes.⁸⁹ Phagocytosis of these RSV:IgG immune complexes has been shown to stimulate release of inflammatory mediators by neutrophils which could contribute to the pathological process.⁹⁰ Conversely, there is evidence that maternal antibodies have a protective role. RSV infection is commonest under the age of 6 months when these antibody titres are at their highest. As well as this, infants with the highest titres of transplacentally acquired RSV specific IgG tend to develop less severe RSV pneumonia than those with lower titres and have significantly fewer infections.⁹¹

Serum IgG subclasses – there have been several reports of various IgG subclass abnormalities associated with infant wheezing, although the importance of these associations is not clear. One study found IgG₁ concentrations were significantly lower in the infants with bronchiolitis compared to healthy age matched controls.⁹² The other IgG subclasses did not differ between the two groups but 23% of the wheezy infants had IgG₁ deficiency. It was felt that the low IgG₁ concentrations might render the infants more susceptible to RSV infection as IgG₁ and IgG₃ are the predominant isotypes produced against RSV in children under 2 years. However, a recent study on 86 infants (median age 2 months) with RSV bronchiolitis found all the infants had normal subclass concentrations and there was no relation between the severity of RSV infection and immunoglobulin or IgG subclass concentrations.⁹³

As well as the various combinations of subclass deficiencies, there are reports of raised IgG₄ associated with atopy and wheezing.⁹⁴ The role of IgG₄ is uncertain, it has been proposed that it acts as a reagenic antibody on the surface of mast cells, but it has also been argued that it serves as a blocking or regulatory antibody. One study has shown that serum concentrations of virus specific IgG₄ were significantly higher in infants who wheezed with RSV than in those who had upper respiratory symptoms only, although it was not clear whether the IgG₄ contributed to the severity of the wheezing.⁹⁵

(C) Mucosal immunity

The common respiratory viral infections enter the host via the airways, and some will then progress distally to the parenchyma of the lung. It is for this reason that mucosal immunity has such an important role in the fight against these viruses, as it provides the host's first line of defence.

Local IgA production – IgA is the predominant immunoglobulin in respiratory secretions, where it is found in its dimeric form known as secretory IgA (sIgA). Concentrations of nasal sIgA may determine susceptibility to respiratory infection. It has been shown that infants who mount a greater nasal non-specific IgA response have fewer respiratory infections, although the frequency of infection was not associated with the baseline nasal IgA

Figure 2 Multifactorial association between respiratory viruses and wheezing.

concentrations.⁹⁶ However, a recent study has shown that wheezy infants mount a normal nasal IgA response to viral infection when compared to their non-wheezing siblings with simple URTIs.⁹⁷

Local IgE production – Welliver and his colleagues have implicated IgE in the pathogenesis of viral wheezing (reviewed by Stark and Busse¹⁰). They found significantly higher titres of RSV specific IgE in nasopharyngeal secretions in those who wheezed compared with those with non-wheezing RSV infection; similar results were found in parainfluenza infection. The original specific IgE response was found to be predictive of future wheezing at both four and seven to eight year follow up.⁹⁸ This work only proves an association between the production of RSV IgE and wheezing, although it is possible that virus specific IgE antibody becomes mast cell bound and interacts with viral antigen, leading to the release of vasoactive and inflammatory mediators which cause airway narrowing. The bronchoconstrictor mediator LTC₄, detected in the nasopharyngeal secretions of infants with RSV bronchiolitis, was positively correlated with RSV IgE titres.¹⁶

The reason why certain children are prone to a hyperactive IgE response may be related to abnormal T cell regulatory mechanisms. Welliver *et al* have shown a reduced number of OKT8 antigen positive cells (suppressor/cytotoxic T lymphocytes) during convalescence in those who wheezed with RSV compared with those with upper respiratory illness alone.⁹⁹ There was also an inverse correlation between RSV IgE in nasopharyngeal secretions and OKT8 positive cells in peripheral blood and it is suggested that these cells may include some that are responsible for suppression of IgE production. It is unknown whether this abnormal IgE regulation is virus induced or constitutionally

determined. Host factors which regulate the response of T lymphocytes to RSV may be critical in determining the clinical outcome of RSV infection.

Conclusions

Almost certainly the association between viruses and wheezing is multifactorial, as is the underlying predisposition to wheeze (fig 2). It is clear that the interaction between the immune system and the development of inflammation is extremely complex. Future work in molecular biology, particularly on the genetics and regulation of cytokine production, may establish whether some children have a predilection for excessive inflammation. Advances in viral detection will prove to be helpful and further progress in mucosal immunology may reveal a subtle deficiency in the way wheezy infants respond to respiratory viruses. Advances continue to be made from bronchial biopsy and lavage studies in adult asthma, but caution is warranted as many of the findings may not be applicable to infant wheezing. Our understanding will continue to be advanced by epidemiological research, particularly the long term study being undertaken in Tuscon.¹⁰⁰ Despite methodological difficulties, valuable insight can be gained from infant lung function studies and the value of clinical studies must also not be overlooked. Finally, a recent international workshop has gone a long way towards defining many of the questions related to infant wheezing that now need to be answered.¹⁰¹

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