VIRAL EXACERBATIONS OF ACUTE LUNG DISEASE IN CHILDREN

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ABSTRACT

Viral respiratory tract infections are a common aetiology of respiratory illness in children. This is especially true for patients with chronic lung disease such as asthma or cystic fibrosis (CF). They are also a frequent cause of morbidity and hospitalisation in young children. Respiratory viral infections are thought to be associated with an increased risk of asthma. This stems from the high rate of asthma in children where there has been a history of severe viral lower respiratory tract infections during infancy. Although respiratory syncytial virus has been traditionally implicated, it is becoming clear that rhinovirus is more important, especially rhinovirus type C. Although it is clear that children who wheeze with respiratory viruses during infancy may go on to develop asthma, many outgrow the problem. However, whether symptomatic viral infections of the lower respiratory tract are causal in the development of asthma, or simply a predisposition, still remains controversial. The role of viral respiratory exacerbations in chronic lung disease, especially CF, should also not be forgotten. Viruses are important contributors to deterioration in lung function, morbidity and chronic respiratory symptoms. Therefore, annual influenza vaccination is recommended in these patients.

INTRODUCTION

Viral respiratory illnesses are extremely common during early life. Approximately 20% of children wheeze in infancy and 70% of these cases are associated with viruses. Viral infections therefore remain a frequent cause of morbidity and hospitalisation in young children. The most common viruses identified are respiratory syncytial virus (RSV) and human rhinovirus (HRV). Less common causes are included in Table I. Table II lists those viruses that exacerbate wheezy illnesses.

Table I. Prevalence of common respiratory viral infections (common cold)

- Rhinoviruses
- Coronaviruses (winter)
- Parainfluenza viruses
- Enteroviruses (summer)
- Influenza A, B, C (winter)
- Respiratory syncytial virus (winter)
- Metapneumoviruses (winter)
- Bocavirus (winter)

Table II. Viruses that elicit wheeze in infants

- Respiratory syncytial virus (winter)
- Rhinoviruses
- Metapneumoviruses (winter)
- Coronaviruses
- Parainfluenza viruses
- Influenza viruses
- Adenoviruses
- Bocavirus (winter)

RSV is seasonal, with peak infection during the winter. Children hospitalised with RSV tend to be younger than children hospitalised for other respiratory viral infections. In contrast, HRV infections occur throughout the year. In comparison with RSV, children hospitalised for HRV tend to be older and are more likely to have wheezed previously.[1] They also have more atopic risk factors or characteristics, including eczema, allergic sensitisation and parental asthma. Traditionally, HRVs have been divided into two groups (A and B). Recently, a newly identified group (C) has been implicated in upper and lower respiratory tract illnesses, frequently including illnesses severe enough to lead to hospitalisation.

Respiratory viral infections are thought to be associated with an increased risk of asthma. The aetiology of asthma is thought to stem from both genetic factors and potentially modifiable environmental factors, such as viral infections. Although it is unclear whether respiratory viral infections cause asthma, observational studies have shown that a high rate of asthma in children occurs where there has been a history of severe viral lower respiratory tract infections (LRTIs) during infancy. Also, viruses are associated with the majority of asthma exacerbations among both children and adults. When discussing viral exacerbations of acute lung disease, it is therefore important to examine the different roles of important respiratory viral infections in childhood asthma.

THE ROLE OF RSV IN ASTHMA

RSV lower respiratory tract illnesses, particularly those severe enough to lead to hospitalisation, are associated with an increased risk of asthma at school age.[2,3] This is supported by a study by Wu *et al.*[4] who were able to demonstrate that children born 120 days prior to the peak of the RSV season had the greatest risk of asthma between 4 and 5.5 years of age.

Some argue that this does not necessarily mean that RSV has a causal relationship with asthma. Rather, the predisposing factors leading to asthma and severe RSV are potentially common. This is suggested by a large Danish twin registry which assessed the relationship between severe RSV and asthma development.[5,6] It is postulated that early RSV wheeze may lead to a recurrent wheezy phenotype but not lifelong asthma. This argument is strengthened by the weakening association of RSV and asthma over time. Renato *et al.*[7]

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demonstrated that RSV lower respiratory tract illnesses are associated with wheezing at 11 years but not at 13 years of age.

THE ROLE OF HRV IN ASTHMA

Recently, several studies have shown that children with a history of LRTI with viruses other than RSV may have as high, or even higher, risk of subsequent wheezing.[8,9] In fact, wheezing illnesses caused by HRV are potentially a more robust predictor of asthma development than RSV. Kotaniemi *et al.*[8] revealed that children under 2 years of age, hospitalised for HRV bronchiolitis, were four times more likely to develop asthma, as compared with other viral infections. The COAST study uncovered the fact that, although HRV wheezing illnesses were an independent risk factor for the development of asthma, the group most at risk were those who had aeroallergen sensitisation during infancy as well.[9]

Although it is clear that children who wheeze with respiratory virus illness during infancy may go on to develop asthma, many outgrow the problem. But when examining children with asthma at school age, most are found to have begun wheezing during the first several years of life.[10] Whether symptomatic viral infections of the lower respiratory tract are causal in the development of asthma, or simply a predisposition, remains controversial. There may be a critical time period in the development of a child, in which target organs such as the lungs are particularly vulnerable to environmental influences, such as respiratory tract infections. This is further complicated by genetic and other influences.

THE ROLE OF VIRAL INFECTIONS IN ASTHMA EXACERBATIONS

Viruses are the most important triggers of asthma exacerbations. They are detected, using polymerase chain reaction (PCR), in up to 85% of children with asthma exacerbations.[11] These exacerbations are more frequently due to HRV infection.[11] A number of factors have been postulated to explain the role of rhinovirus in asthma exacerbations:[12]

- HRVs are able to reach and replicate in epithelial cells of the lower airways. Activation of these cells follows with production of pro-inflammatory mediators.
- HRVs can also become cytotoxic to the epithelium, having a cytopathic effect.
- Atopic asthmatics have a decreased immune response to HRV, producing less interferon-γ and more interleukin (IL)-10 than normal subjects in response to HRV.
- HRV infection induces an inflammatory response in bronchial epithelium, with the release of cytokines such as IL-6 and IL-8.
- Asthmatics have a defective T-helper 1 response to HRV if atopic. Antiviral immune responses are usually dominated by type 1 cytokines.

Viral bronchiolitis

Viral respiratory tract infections are commonly self-limiting and benign events. However, in young children, asthmatics and other high-risk groups, viral infections can result in serious LRTIs requiring hospitalisation. It is therefore important to identify patients at risk of developing serious viral exacerbations. The South African guideline for the diagnosis, management and prevention of acute viral bronchiolitis in children, has clearly defined which patients are at risk of severe bronchiolitis (Table III).[13]

Table III. Risk factors for severe viral infections[13]

Environmental factors
Poverty
Passive smoke exposure
Pollution
Overcrowding
Day care attendance
Host factors
Prematurity
Congenital heart disease
Chronic lung disease of prematurity
Neurological disease
Infants <6 months of age
Immunodeficiency
Lack of breastfeeding

Although, HRV is now being identified as equally important, RSV is still identified as one of the commonest causes of bronchiolitis in children under 2 years of age. Specific RSV monoclonal antibody, palivizumab, is available for children at risk of severe bronchiolitis. It reduces RSV hospitalisations by 45% (p=0.003), total days of RSV hospitalisation (p=0.003) and RSV hospital days requiring supplemental oxygen (p=0.014). This has been demonstrated in a randomised, double-blind, placebo-controlled trial including 1 287 children with congenital heart disease (CHD) randomly assigned to receive 5-monthly intramuscular injections of 15 mg/kg palivizumab or placebo.[14] The highest reduction in hospitalisation rate was seen in premature infants of gestational age 32-35 weeks. RSV prophylaxis with palivizumab reduced hospitalisations by 80% (p=0.002). The indications for RSV prophylaxis are reflected in Table IV.[13]

Table IV. Indications for RSV prophylaxis[13]

1. Premature infants of gestational age <32 weeks at birth
   Prophylaxis should be continued until the earlier of:
   - 6 months of chronological age, or
   - the end of the RSV season (last dose in July).
2. Premature infants of gestational age 32-36 weeks at birth
   Prophylaxis should be continued until the earlier of:
   - 3 months of chronological age, or
   - the end of the RSV season (last dose in July).
3. Children of any gestation who are <24 months of age at the start of the RSV season with any of the following:
   - Chronic lung disease of prematurity
   - Chronic lung disease
   - Primary immunodeficiency
   - Cyanotic congenital heart disease.

   Prophylaxis should be used for 5 months beginning in February in most areas of South Africa except for KwaZulu-Natal, where it should be started in December.
4. High-risk premature infants should commence their prophylaxis while still in hospital.

Influenza

Influenza is another important viral infection that among healthy children is generally an acute, self-limited and uncomplicated disease. However, it is associated rarely with severe morbidity and mortality in certain groups of children (Table V).

Table V. Risk factors for complicated influenza[15]

- Children <2 years
- Chronic pulmonary disease (including asthma)
- Chronic cardiovascular, renal, hepatic, haematological, neuromuscular and neurodevelopmental disorders
- Immunosuppression

Prevention of influenza[15]

Annual influenza vaccination is the most effective strategy for preventing influenza. There are two types of influenza vaccines:

- Trivalent inactivated influenza vaccine (TIV), administered intramuscularly
- Trivalent live-attenuated, cold-adapted influenza vaccine (LAIV), administered intranasally

According to several studies in children,[16,17] LAIV may be more efficacious than TIV, and may provide greater immunity against mismatched strains, immediate protection during an outbreak, better T-cell responses and longer-standing protection than TIV. In studies comparing TIV and LAIV in children, children who received LAIV had 32-55% fewer cases of culture-confirmed influenza than children who received TIV.[18] In a case-control study of 1 155 children and adults with acute respiratory illness early in the 2012-2013 influenza season, the Centers for Disease Control and Prevention (CDC) estimate that the effectiveness of 2012-2013 seasonal influenza vaccine in preventing laboratory confirmed influenza is 62% (95% confidence interval (CI) 51-71%).[19] Effectiveness against influenza A was 55% (95% CI 39-67%) and against influenza B was 70% (95% CI 56-80%). Given the moderate effectiveness of the vaccine, influenza infection will occur in some individuals who receive the influenza vaccine.[20] Nevertheless, the American Academy of Pediatrics (AAP) recommends influenza vaccination for all children > 6 months.[21]

The choice of vaccine for an individual child depends upon age and risk factors for severe or complicated influenza. The following groups should receive TIV rather than LAIV:[22]

- Children ≥6 through 23 months of age
- Children (of any age) with asthma and children 2-4 years of age with a history of recurrent wheezing
- Children with medical conditions that increase the risk for severe or complicated influenza infection
- Children who are close contacts of severely immunocompromised individuals (e.g. haematopoietic stem cell transplant recipients).

Treatment of influenza

Two classes of antiviral drugs are available for the prevention and treatment of influenza in children: neuraminidase inhibitors and adamantanes (M2 inhibitors).[19] Antiviral drug resistance has spread widely throughout the world, particularly against the adamantanes.[23]

Decisions regarding treatment of influenza in children must consider underlying conditions, disease severity and duration of symptoms. The CDC and AAP provide the following indications for antiviral treatment:[19,21]

- Any child hospitalised with presumed influenza
- Children with confirmed or suspected influenza who have severe, complicated, or progressive illness
- Influenza infection of any severity in children at high risk for complications (see above), regardless of influenza-immunisation status
- Any otherwise healthy child with influenza infection for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her provider (if treatment can be initiated within 48 hours of illness onset).

VIRAL EXACERBATIONS IN CHRONIC LUNG DISEASE

Chronic lung disease in children is an important risk factor for serious viral LRTI. This includes chronic lung disease of prematurity, cystic fibrosis (CF), non-CF bronchiectasis and chronic aspiration syndromes. However it is unclear what proportion of exacerbations are triggered by a viral infection. The frequency of exacerbations is higher in more severe lung disease[24] and unmanaged disease.[25] Limiting respiratory exacerbations is an important long-term goal in these patients. This prevents further lung damage, preserves lung function and improves quality of life.

THE ROLE OF VIRAL EXACERBATIONS IN CF

Viruses are implicated as an aetiology of respiratory exacerbations in CF, in up to 18% of cases.[26] RSV is implicated in up to half of these,[27] and HRV in 16% of episodes.[28] However, non-rhinovirus respiratory exacerbations are characterised by more severe morbidity, decline in lung function, mechanical ventilation and chronic respiratory signs requiring prolonged oxygen therapy.[27] Viral exacerbations in CF are more likely to occur in association with:[29]

- Lower Shwachman scores (scoring system used in CF to assess disease severity)[30]
- Lower ideal weight for height
- Lower forced expiratory volume in 1 second (FEV_1)
- Duration of hospitalisation for respiratory exacerbations.

These data suggest that viral infections are associated with severe exacerbations in patients with CF. Therefore viral infections should always be considered, when CF patients present with a respiratory exacerbation. For this reason, annual influenza vaccination is recommended to patients with CF over the age of 6 months.[31] There are however, no current recommendations for palivizumab in CF as a prophylactic measure for RSV.[31]

CONCLUSION

Viral respiratory tract infections are a common aetiology for respiratory illness and exacerbations in children. This is especially true for patients with chronic lung disease such as CF. They are also a frequent cause of morbidity and hospitalisation in young children.

Respiratory viral infections are thought to be associated with an increased risk of asthma. This stems from the high rate of asthma in children with a history of severe viral LRTIs during infancy. Although it is clear that children who wheeze with respiratory viruses during infancy may go on to develop asthma, many outgrow the problem. However, whether symptomatic viral infections of the lower respiratory tract are causal in the development of asthma, or simply a predisposition, still remains controversial.

Declaration of conflict of interest

The author declares no conflict of interest.

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