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DEBATE

Current pharmacological treatments for bronchiolitis are useless
The case for the con's

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Summary Bronchiolitis is a recognized syndrome seen in infants following viral infections. The pattern is different in different countries related to the socio-economic conditions. A sequel that needs to be addressed is post-viral wheeze. Oxygen is the major beneficial pharmacological agent. Bronchodilators may be effective in some. There is a role for Palivizumab and Montelukast in selected infants. It is essential to define the right drug for the right patient at the right dose and the right time.

INTRODUCTION

Bronchiolitis is a recognized clinical syndrome occurring in 5–10% of infants, usually manifested by upper respiratory symptoms and mild fever followed by wheeze, crackles on auscultation and hyperinflation, with a small proportion (1 in 5–10) requiring hospital admission, increased 10 times with pre-existing conditions and a very few developing to apneic episodes and/or respiratory failure. Bronchiolitis in developing countries should be considered independently as the clinical pattern, therapy and outcomes are likely to be different to that in developed countries with a significantly greater (×4) risk of associated pneumonia and an increase (×8) of post bronchiolitis wheeze associated lower respiratory illness, possibly related to intensity of inoculation, poor nutritional status, pollution or secondary infection.

There is no diagnostic test for the condition and no universally accepted and validated scoring system to measure severity and response to treatment. Hence bronchiolitis means different thing to different people. Clearly, one size doesn't fit all.

To say that all pharmacological treatments are useless for bronchiolitis is to deny potential benefits to many suggested by clinical observation, just as we did in the 1970s when many, but not all, studies suggested that steroids were of no benefit for croup. Evaluation of pharmacological benefits need to consider the variations in presentation of the syndrome and the differences in timing of therapy, which may be preventive, treatment of the acute symptoms or minimizing long term sequelae.

Bronchiolitis is usually caused by RSV, but occasionally by adenovirus, Chlamydia, parainfluenza, influenza or rhinovirus. The infections and/or the host immunological cellular and mediator response to the virus infection leads to epithelial injury and mucus hypersecretion with infiltration of neutrophils and cytotoxic T cells and production of virus specific antibodies. There may be hypersensitization of nerve endings. This may explain the observed increased responsiveness to methacholine. Any of these components may be potentially susceptible to pharmacological therapy.

One group at risk for primary infection and moderate to severe acute viral bronchiolitis, often in the first 6 months in winter, are those with airway narrowing documented by low flow rates, those exposed to maternal smoking especially in utero, those who are preterm, with chronic neonatal lung disease, congenital heart disease, cystic fibrosis or immune deficiency. This group is at risk of recurrent wheezing illness in early childhood which ceases by 6 years.

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Another group in the first year are those with an atopic family or personal history who may already be sensitized to allergens in utero or neonatally, who then develop moderate to severe bronchiolitis on exposure to RSV. Some suggest that the viral infection may accelerate atopic sensitization in this group. This may be the group identified by Welliver and colleagues[1] who developed high levels of specific IgE and recurrent wheeze, but only in early childhood.

A third group, labelled bronchiolitis by some but not by others, is the group who wheeze with a viral illness in the second year of life. Many consider that this group, usually atopic, with recurrent wheeze associated viral illness is early onset asthma.

Further study is needed to elucidate the importance of the respective timing of allergen sensitization and RSV infection in presentation of the acute illness and sequelae. Recognition of these different patterns is essential in measuring outcomes to pharmacological interventions.

OXYGEN

Appropriate use of oxygen therapy requires that it be considered a pharmacological agent.[2] The use of supplemental oxygen has not been subjected to controlled trials, but it's use is essential to treat hypoxia. Some high risk infants may achieve slight benefit from using a helium oxygen mixture to reduce resistance and respiratory work.

ANTIBIOTICS

Antibiotics have little place in the management of bronchiolitis in developed countries and are only used in extremely ill infants, especially with radiographic evidence of alveolar disease, when secondary infection cannot be excluded. However, in developing countries the use of antibiotics according to WHO guidelines for possible pneumonia associated with the bronchiolitis has resulted in a 50% decrease in mortality.

BRONCHODILATORS

Randomized controlled trials of beta 2 agonists in viral bronchiolitis in the outpatient or inpatient setting have shown no clear or sustained benefit.[3] However, older infants, especially in the second year of life are more likely to respond. Similarly, Sanchez *et al.*[4] reported that those who had a sinusoidal wheeze as distinct from a complex wheeze on acoustic analysis showed a response to bronchodilator. This pattern and the older infant are likely to be early presentations of classical asthma.

Trials of epinephrine/adrenaline have generally shown a response in favour of the agent but this was rarely clinically significant. A randomized controlled trial of nebulized epinephrine/ adrenaline in acute bronchiolitis in the first 12 months of life did not demonstrate efficacy,[5] although another study did demonstrate reduced respiratory resistance while having no effect on oxygenation.[6] This appears to be an option to consider for some of the critically ill infants in the intensive care unit and for selected outpatients.[7] Further trials are needed.

Ipratropium bromide has not been shown to be useful in acute viral bronchiolitis.[8]

CORTICOSTEROIDS

Many studies, including a meta analysis of these, have failed to demonstrate efficacy of oral or inhaled steroids in viral bronchiolitis.[9] However, others have shown a reduced length of stay in hospital and better improvement in clinical score in those treated.[10] Many of these studies included infants up to 2 years and glucocorticoids may be considered in those likely to be in the asthma spectrum of the syndrome.

RIBAVIRIN

The use of Ribavirin, a guanosine analogue with antiviral (especially RSV) activity, is not supported generally by evidence of significant benefit.[11] There are associated problems related to administration with a small particle aerosol generator, staff safety concerns and cost. It does not reduce post bronchiolitis wheeze. However it is still considered in the immune suppressed and post transplant. There has been an argument for its benefit in combination with Montelukast in the critically ill by decreasing the inflammatory response to the viral infection.

IMMUNOGLOBULINS

Randomized controlled trials of intravenous immunoglobulins in children admitted to hospital with bronchiolitis showed no evidence of benefit.[12]

Respigam (RSV-IGIV) is prepared from the sera of adult humans and delivered as a monthly infusion was associated with reduced hospitalization in 'at risk' infants[13] but was costly, needed IV administration, was less potent than Palivizumab.

PALIVIZUMAB

Palivizumab is a human recombinant monoclonal antibody directed against a surface glycoprotein of RSV. It is administered monthly for 4 to 6 months over the RSV season. It is safe and there is more than 50% reduction in hospitalization and ICU admission rates in high risk infants, but no reduction in the rate of mechanical ventilation or length of stay in ICU.[14] Cost effectiveness has been questioned, but analysis is difficult. It's use appears to be justified in the most vulnerable infants, preterm with ongoing significant chronic lung disease and those with haemodynamically significant congenital heart disease.[15]

MONTELUKAST

Cysteinyl leukotrienes are produced with acute RSV infection and it is argued that administration of a leukotriene receptor antagonist may reduce the incidence and persistence of post infection wheeze. Bisgaard and colleagues[16] administered daily Montelukast from 3 days after admission with bronchiolitis for 28 days. The infants were aged 3 to 36 months with a mean age of 9 months. The post admission symptoms were high in the placebo group, but there was a significantly greater number of symptom free days and nights on Montelukast. There was no effect of age on the rate of response. This would suggest a potential benefit in a selected group of infants if those at risk could be identified. Further long term studies are necessary.

As mentioned, some argue a case for a combination of Ribavirin and Montelukast to reduce the viral load and the inflammatory response. No data are available.

CETIRIZINE

Although inconsistent, Cetirizine has been reported to reduce the onset of subsequent asthma symptoms in infants with atopic dermatitis.[17] A similar effect may be argued following acute viral bronchiolitis. This has yet to be tested.

OTHERS

Drugs trialled but shown not to be of benefit in acute bronchiolitis include Interferon, Vitamin A, Surfactant and DNAse.

CONCLUSIONS

Future pharmacological therapies are likely to be focused on immunomodulation prior to RSV exposure. In the meantime, those with mild viral bronchiolitis need only adequate fluids and observation with added oxygen if necessary. There is some evidence of potential effectiveness of a greater number of drugs than are available for many other conditions; they are not all useless, it is only a matter of defining the right drug for the right patient in the right dose at the right time.

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