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Management of bronchiolitis

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Abstract

Bronchiolitis is the commonest cause of hospital admission in infancy. Severity varies from mild and self-limiting through to respiratory failure requiring intensive care and ventilation. Many viruses cause bronchiolitis, the commonest being respiratory syncytial virus (RSV). Supportive care is the mainstay of treatment, with emphasis on fluid replacement and oxygen therapy. Agents with evidence of no benefit in acute bronchiolitis include β_2 agonists, ipratropium, montelukast, corticosteroids, antiviral agents such as ribavirin or RSV immunoglobulin, physiotherapy, nebulized deoxyribonuclease or antibiotics. It is possible that nebulized epinephrine has a small short-term effect, and that nebulized 3% hypertonic saline administered with a bronchodilator may decrease length of stay in hospital. Preventative strategies such as RSV immunoglobulin or the anti-RSV monoclonal antibody palivizumab can decrease disease severity.

Keywords bronchiolitis; bronchodilators; corticosteroids; hypertonic saline; RSV

Introduction

In 1963 EOR Reynolds concluded that 'oxygen therapy is vitally important in bronchiolitis and there is little convincing evidence that any other therapy is consistently or even occasionally useful'. It is arguable that there has been little progress in the subsequent 46 years. Treatments that might be effective include nebulized 3% hypertonic saline mixed with a bronchodilator, and ventilatory support for respiratory failure. For the majority of patients, however, supportive management is the mainstay, with emphasis on treating insufficient fluid intake and hypoxia.

Epidemiology

Bronchiolitis is the commonest cause of hospitalization in infancy. It usually affects infants aged 1–6 months, although it can occur up to 2 years of age, and is usually a mild self-limiting illness that does not require medical intervention. It is a clinical syndrome characterized initially by coryzal symptoms followed

by onset of harsh cough, tachypnoea and wheezing. On examination there may be chest hyperinflation with costal recession, and fine inspiratory crackles and polyphonic expiratory wheeze on auscultation.

A significant contributor to confusion over the management of bronchiolitis is the absence of an internationally agreed common definition. In the United Kingdom, Australasia, and parts of Europe, bronchiolitis is interpreted as the presence of tachypnoea, hyperinflation of the chest, and characteristically widespread fine end inspiratory crackles on auscultation. Wheeze is commonly but not invariably present. The pattern of illness is virtually always seen in the first year of life, most commonly in the first 6 months of life. In contrast, in North America and other parts of Europe, bronchiolitis is a term for any viral infection of the lower respiratory tract in the first 2 years of life, and may include children with recurrent wheeze. The confusion over definition is compounded by different types of study; many studies in inpatients will be closer to the UK and Australasian definition, while many studies in outpatients will include mostly children corresponding to the North American and European definition. Furthermore there is no widely accepted validated scoring system to measure illness severity, making comparisons between studies difficult. Commonly, outcome measures in interventional studies will include summation scores of symptoms and signs, oxygen saturations, respiratory rate, and length of stay in hospital.

Approximately 1–3% of infants will be hospitalized with bronchiolitis, of whom 1–2% will require ventilation for either respiratory failure or apnoeas. Hospitalization for bronchiolitis is commoner in boys and in lower socioeconomic groups. Preterm infants (less than 32 weeks) and infants with chronic lung disease, congenital cardiac abnormalities, or immune deficiencies are at higher risk of severe disease. Mortality rates in hospitalized infants are 0.5–1.7%. Respiratory syncytial virus (RSV) accounts for 50–90% of cases of bronchiolitis resulting in approximately 20000 UK admissions per year. Annual epidemics of RSV occur between late autumn and spring (October to March in the northern hemisphere). The virus rapidly infects the respiratory tract epithelium, causing epithelial necrosis and destruction of the cilia. There is a florid inflammatory response with neutrophil and lymphocytic cellular infiltration and oedema of the submucosa, and an imbalance in cytokines with an excess of TH type II over type I cytokines demonstrated by high interleukin 4 (IL4)/interferon γ ratio. There is increased mucus production from goblet cells which, in combination with the decimated epithelial cells, results in mucus plugging. Mucus plugging causes obstruction of bronchioles with resultant air trapping leading to areas of hyperinflation and airway collapse. As the respiratory epithelium regenerates, the new non-ciliated cells are poorly equipped to clear the inflammatory debris. Hypoxaemia is primarily due to ventilation/perfusion mismatch, and hypercapnoea is a relatively late phenomenon.

After RSV, the next most frequent cause is probably human metapneumovirus (hMPV) which causes a similar clinical picture as RSV, although dual infection with both RSV and hMPV may cause more severe disease. Rhinovirus may be a commoner cause in older infants, and less frequent causes include adenovirus, parainfluenza, influenza, coronavirus, and the more recently identified bocavirus. It is possible that bacterial superinfection is associated with increased severity of disease.

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Management

Interventions can be classed as supportive, therapeutic or preventative.

Supportive management

The current management of bronchiolitis is primarily supportive, concentrating on the major effects of the condition, namely inadequate feeding, respiratory distress and apnoeas. Inadequate feeding is usually secondary to respiratory distress and the consequent increased work of breathing. The infant will be tachypnoeic, may have bouts of coughing with increased upper airway secretions, and thus may struggle to feed adequately. Tachypnoea increases fluid loss, and so the infant can easily become dehydrated.

Infants with bronchiolitis are generally intolerant of interventions, and so minimal handling is recommended. For milder cases giving small volumes of feed at regular intervals may be sufficient. Administration of oxygen may be enough to decrease work of breathing, so allowing regular fluid intake. If this proves inadequate, a nasogastric tube can be passed to administer enteral fluids – initially bolus feeds, but if this worsens respiratory distress, by continuous feeding. Ultimately if the infant is unable to tolerate enteral feeds, fluids can be administered intravenously. RSV infection can result in inappropriate syndrome of inappropriate antidiuretic hormone secretion (SIADH), and so after determining serum electrolytes, intravenous fluids are usually restricted to 75% of maintenance requirements.

Respiratory support

The ventilation/perfusion mismatch characteristic of bronchiolitis results in hypoxia and increased work of breathing. Oxygen is the mainstay of treatment for respiratory distress, and is usually administered via head-box to minimize handling. For higher concentrations, a combination of head box and facemask or rebreathing bag may be used, although this usually implies significant respiratory failure and often precedes respiratory collapse. Increasing impairment of gas exchange will result in hypoxia unresponsive to head-box oxygen and hypercarbia, eventually leading to physical exhaustion and complete respiratory failure.

Ventilatory support

Between 2% and 5% of bronchiolitis admissions will have respiratory failure, and increasingly non-invasive ventilation is used to offer continuous positive airway pressure (CPAP) support, usually via nasal prongs to decrease the need for intubation and sedation. It is thought that the action of CPAP is through prevention of airway collapse during the respiratory cycle, so preserving ventilation and decreasing ventilation/perfusion mismatch. Observational studies suggest that in bronchiolitis CPAP decreases the respiratory rate, pulse rate, and partial pressure of carbon dioxide, and so decreases the intubation rate and consequently the rate of ventilator-associated pneumonia. CPAP does not appear to affect length of hospital stay or duration of ventilation. A controlled study demonstrated that if initiated early, nasal CPAP resulted in a significant decrease in PCO_2 and was well tolerated without any significant complications, suggesting that earlier intervention would improve outcome. If respiratory failure continues despite nasal CPAP, full intubation and ventilation is

warranted. In those that are mechanically ventilated, administration of exogenous surfactant may decrease duration of mechanical ventilation. If mechanical ventilation is ineffective, there may be a role for extracorporeal membrane oxygenation (ECMO).

Therapeutic interventions

Bronchodilators

Interpretation of the evidence for the efficacy of bronchodilators in bronchiolitis is hampered by the heterogeneity of the inclusion criteria in different studies. Many studies, particularly if outpatient-based, will include infants up to 2 years old with recurrent wheeze, and it is arguable that many of these infants may have an asthma phenotype. Three classes of bronchodilators have been trialled in bronchiolitis: β_2 agonists, ipratropium, and adrenergic agents, all of which have shown benefit in asthmatics.

β_2 agonists

Bronchodilators are the treatment of choice for acute asthma in older children and adults, and there is some evidence that bronchodilators may produce short-term improvement in clinical scores in outpatient-based studies of bronchiolitis. An earlier meta-analysis by Flores and Horwitz concluded that β_2 agonists had a statistically significant but clinically insignificant effect on oxygen saturations and heart rate when used in milder cases in an outpatient setting, but had no significant effect on hospitalizations. A later systematic review of all pharmacological treatments concluded that β_2 agonists had no significant beneficial effects. The most recent Cochrane review of 22 trials involving 1428 infants with bronchiolitis who received inhaled bronchodilators (including β_2 agonists, ipratropium and adrenergic agents) reported a significant improvement in overall average clinical score, but had no effect on either pulse oximetry measurements or on risk of hospitalization. However, the inclusion criteria for many of the studies allowed children with recurrent wheezing up to 24 months of age, and subgroup analysis suggested that benefit was primarily in outpatient studies of shorter duration, suggesting that many of those who showed benefit may have had recurrent wheeze rather than isolated bronchiolitis.

Ipratropium

An earlier systematic review identified four studies assessing the use of nebulized ipratropium bromide in bronchiolitis and concluded that there was no significant benefit. A subsequent Cochrane analysis reached similar conclusions. It is likely that ipratropium has a role in young infants with recurrent wheeze.

Adrenergic agents

Adrenergic agents such as epinephrine appear attractive as they combine the β -adrenergic effects of bronchodilation with the α -adrenergic effects of vasoconstriction of the bronchiolar vasculature. The vasoconstrictive action in particular could potentially decrease the characteristic mucosal oedema and mucus hyper-secretion. A meta-analysis of 14 studies concluded that nebulized epinephrine had beneficial effects compared to either placebo or salbutamol, but the effects were short-term. In studies of inpatients, when compared to placebo epinephrine resulted in a significantly better clinical score at 60 minutes, and when compared to salbutamol resulted in a significantly lower respiratory

rate after 30 minutes. Short-term benefits were more pronounced in outpatient studies, but the benefits lasted less than 60 minutes and had no effect on hospitalization rates.

Thus in summary there is very little evidence of benefit for any bronchodilators in bronchiolitis. What evidence there is of very short-term benefit from epinephrine, mostly in the outpatient setting, which may reflect benefit in infants with recurrent wheeze phenotypes.

Montelukast

The leukotriene receptor antagonist montelukast may be beneficial in young children and infants when started early in acute (mostly virus-induced) asthma/wheezing. However, a recent placebo-controlled study of montelukast in 53 infants with a first episode of bronchiolitis demonstrated absence of benefit, with no significant differences in length of hospitalization, clinical severity score, or inflammatory mediators between the two groups.

Corticosteroids

Corticosteroids would appear to be an attractive therapy for bronchiolitis; bronchiolitis is characterized by a florid inflammatory response, and the anti-inflammatory actions of corticosteroids are beneficial in older children and adults with asthma. Unfortunately there is a large body of evidence for their lack of benefit in bronchiolitis. The most recent Cochrane review of 13 trials included nearly 1200 children aged 0–30 months who had received the equivalent of 0.5–10 mg/kg of systemic prednisone for 2–7 days. Although the length of hospitalization was 0.38 days shorter in the steroid-treated group, the difference was not significant, and there was a similar lack of significant differences in respiratory rate, oxygen saturations, need for supplemental oxygen, need for supportive fluids, and need for bronchodilators. Furthermore corticosteroids showed no significant benefits even in subgroup analyses of infants who were less than 12 months of age, had confirmed respiratory syncytial virus (RSV) infection, or had no previous history of wheezing. It is interesting to note that a recent large trial of oral corticosteroids in older preschool children with acute wheeze also demonstrated no benefit.

Hypertonic saline

The mode of action of hypertonic saline (HS) in bronchiolitis is unclear. *In vitro*, HS increases the airway surface liquid (ASL) height in an epithelial cell line model, and *in vivo* HS increases the mucociliary clearance of radiolabelled aerosol in both normal controls and asthmatics. Hypertonic saline is increasingly utilized in cystic fibrosis (CF) where it increases mucociliary clearance for at least 8 hours in a dose-dependent manner, and increases sputum expectoration. In a randomized placebo-controlled study 4 ml of 7% HS administered twice daily via a nebulizer resulted in significant decreases in the number of both mild and severe respiratory exacerbations, in the days antibiotics received per year; and in the number of days absent from work or school. HS can induce bronchospasm even in normal adults, and so in CF it is recommended that HS is only administered after a bronchodilator.

There is increasing evidence that disease pathogenesis in CF is due to increased sodium absorption from the airway surface, leading to airway dehydration and subsequent loss of the normal ASL volume and thus decreased ciliary clearance. Administration of HS is thought to attract water into the airway, so increasing

ASL volume and ciliary clearance. Other agents that attract water into the airway, such as the sugar alcohol mannitol, have similar effects. It is unclear whether a similar mode of action is applicable to bronchiolitis, and other postulated modes of action include breakdown of ionic bonds within airway mucus, resulting in decreased mucus viscosity and so easing clearance of airway secretions, and increased prostaglandin E₂ release which stimulates ciliary beat frequency; or possibly HS simply induces coughing, even in normal subjects, and so some of its action could be simply through its tussive effect.

A Cochrane review of four trials of HS in 254 infants with bronchiolitis demonstrated significantly decreased duration of hospitalization. Three trials were from the same group of investigators, and used a similar treatment protocol of administering 4 ml of 3% HS every 8 hours, mixed with either 1.5 mg of epinephrine or 5 mg of terbutaline. Although administration of a bronchodilator was not essential in the other trial, the majority of subjects concomitantly received a bronchodilator. The pooled data suggested that 3% HS decreased the median duration of stay by 0.94 days (95% confidence Interval: –1.48 to –0.4, $P = 0.0006$) compared to nebulized 0.9% saline, although there was no significant effect on hospitalization rate.

Antiviral agents

A controlled trial of the antiviral agent ribavirin via aerosol in infants receiving mechanical ventilation for severe RSV infection initially showed significant benefit, although there were concerns over the choice of aerosolized water as the control. A repeat study using aerosolized saline as control demonstrated no benefit, and a subsequent meta-analysis of all controlled trials concluded that there was no significant benefit from aerosolized ribavirin, although there may be a slight reduction in the duration of mechanical ventilation. There may however be a role for intravenous ribavirin in severe disease in immunocompromised patients. Intravenous RSV immune globulin is ineffective in the acute treatment of RSV lower respiratory tract infection.

Other treatments

Other treatments that have shown no benefit in acute bronchiolitis include nebulized deoxyribonuclease, chest physiotherapy, and antibiotics.

Prevention

Infants known to be at risk of severe bronchiolitis can receive passive immunization against RSV, either with RSV immunoglobulin (RSVIG) by monthly intravenous injections or with monthly intramuscular injections of the humanized monoclonal antibody palivizumab. Neither has any risk of RSV transmission, and neither interferes with the routine childhood vaccination schedule.

RSV immunoglobulin

The PREVENT study was a randomized double-blind comparison of RSV immunoglobulin prophylaxis every 30 days versus placebo in over 500 premature infants and infants with bronchopulmonary dysplasia; it demonstrated a significant reduction of hospitalization for RSV and duration of hospitalization, but demonstrated no significant effect on the need for mechanical ventilation, days on intensive care, or mortality. RSVIG is no longer

used because of the need for monthly intravenous infusions and the small theoretical risk of viral transmission.

Humanized monoclonal antibody

There is probably no agent that divides neonatologists and respiratory paediatricians as much as palivizumab. Palivizumab is a humanized immunoglobulin G1 that binds to the RSV fusion protein, and in the cotton rat model it is 50–100 more potent than RSV immunoglobulin. It prevents entry of RSV into the cells lining the respiratory tract, and when administered intramuscularly has a half life of 18–20 days. It is administered by monthly intramuscular injections during the RSV season, and is currently licensed for use in preterm infants (less than 35 weeks' gestation) who are less than 6 months old at the start of the bronchiolitis season, any child under 2 years of age who has received treatment for bronchopulmonary dysplasia in the previous 6 months, or in children with haemodynamically significant heart disease.

The Impact study was a placebo-controlled trial of intramuscular palivizumab every 30 days in over 1500 high-risk infants; the infants were either born at or earlier than 35 weeks' gestation and were less than 6 months of age, or were less than 2 years of age and had had a clinical diagnosis of bronchopulmonary dysplasia which required treatment (oxygen, corticosteroids, bronchodilators or diuretics) in the preceding 6 months. Palivizumab significantly decreased the risk of hospitalization, duration of hospitalization, and the need for intensive care, although it had no significant effect on either the need for ventilation or death.

Although the relative effect was striking, the absolute effect was much less so, and the calculated number needed to treat (NNT) was 17. Due to its high cost, its economic value has been questioned, with an estimated cost of preventing one hospital admission of £43,000. In 2005 the Joint Committee for Vaccinations and Immunizations (JCVI) recommended that palivizumab should be given to all children less than 2 years of age who had previously been treated with home oxygen for chronic lung disease, or those with haemodynamically significant congenital heart disease, pulmonary hypertension, or severe congenital immune deficiency. Despite these recommendations, the use of Palivizumab varies greatly in different areas of the UK.

Vaccination

At present there is no effective vaccine for bronchiolitis. Attempts have been made to develop a vaccine against RSV; however, when this vaccine was entered into clinical trials patients given the vaccine went on to develop more severe symptoms than those not vaccinated. Current efforts to develop a vaccine suitable for human trials focus on using non-animal-derived materials to obtain viral plasmid DNA; at present the efficiency of viral recovery is 30–100%.

Conclusions

Fluids and oxygen are the mainstays of management. There is increasing evidence for the role of nebulized 3% hypertonic saline administered with a bronchodilator. CPAP and if necessary mechanical ventilation are effective for respiratory failure. Palivizumab decreases the risk of hospitalizations in high-risk infants, although there is controversy over its benefits. ♦

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Practice points

- Although for most infants bronchiolitis is a mild, self limiting illness, it is nevertheless the commonest cause of hospital admission in infancy – 1–3% of infants will be hospitalized
- It is a clinical syndrome characterized by coryzal symptoms followed by onset of harsh cough, tachypnoea and

wheezing with chest hyperinflation with costal recession on examination, and fine inspiratory crackles and polyphonic expiratory wheeze on auscultation

- RSV accounts for 50–90% of cases of bronchiolitis – other causative agents include Human Metapneumovirus (hMPV), rhinovirus and less frequently adenovirus, parainfluenza, influenza, coronavirus and the more recently identified bocavirus
- Management of bronchiolitis is primarily supportive, concentrating on the major complications of inadequate feeding, respiratory distress and apnoeas. Fluids (either

enteral or parenteral) and Oxygen are the mainstays, although CPAP or mechanical ventilation are effective for respiratory failure

- There is no role for bronchodilators, corticosteroids, antiviral agents, physiotherapy, nebulized DNase or antibiotics, but nebulized 3% hypertonic saline administered with a bronchodilator may decrease length of stay in hospital
- Preventative strategies such as RSV immunoglobulin or the anti-RSV monoclonal antibody palivuzimab can decrease disease severity and need for hospitalization, although there is controversy over their benefits