Current therapy for bronchiolitis

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ABSTRACT

Bronchiolitis is a common, self-limiting, seasonal viral respiratory tract infection in infancy accounting for the majority of hospital admissions in this age group. Supportive care is the mainstay of treatment, concentrating on fluid replacement, gentle suctioning of nasal secretions, prone position (if in hospital), oxygen therapy and respiratory support if necessary. There is a long history of pharmacological agents offering no benefit in acute bronchiolitis. More recently, nebulised epinephrine has been demonstrated to offer short term benefits, while two stratagems have shown promise in decreasing risk of hospitalisation and length of hospital stay. The combination of oral dexamethasone with nebulised epinephrine potentially decreases the need for hospitalisation, while nebulised 3% hypertonic saline mixed with a bronchodilator decreases the length of hospitalisation. Although both stratagems appear safe and well tolerated, their role in clinical practice remains unclear.

INTRODUCTION

It is nearly 50 years since Reynolds and Cook wrote that “oxygen therapy is vitally important in bronchiolitis and there is little convincing evidence that any other therapy is consistently or even occasionally useful”. The mainstays of treatment remain oxygen, fluids and, if necessary, respiratory support. More recently, the combination of nebulised epinephrine and dexamethasone, or nebulised epinephrine and dexamethasone, or nebulised hypertonic saline with a bronchodilator have emerged as potential therapeutic strategies.

The Scottish Intercollegiate Guidelines Network defines bronchiolitis as “a seasonal viral illness characterised by fever, nasal discharge and dry wheezy cough. Examination of the chest reveals crepitations and/or wheeze”. In contrast, the American Academy of Pediatrics subcommittee defines bronchiolitis as “a disorder most commonly caused in infants by viral LRTI; it is the most common lower respiratory infection in this age group and is characterised by acute inflammation, oedema and necrosis of epithelial cells lining small airways, increased mucus production and bronchospasm”. These definitions reflect differences in the interpretation of the disease – in North America bronchiolitis may encompass children up to 2 years of age with a first episode of multi-trigger wheeze. These differences may also limit the generalisability of some studies.

Bronchiolitis is the most common cause for lower respiratory tract infection (LRTI) during the first year of life, and even allowing for differences in definition, accounts for majority of hospital admissions during this period in the UK and the USA. Between 2% and 3% of all infants are hospitalised in their first 12 months of life with bronchiolitis, imposing a significant burden on the healthcare system. Although many viruses may cause the constellation of symptoms and signs that characterise bronchiolitis, 60–85% of cases are caused by respiratory syncytial virus (RSV). Every year between 152 000 and 172 000 children less than 5 years of age are hospitalised in the USA with RSV infections.

The natural history of bronchiolitis is of a self-limiting disease that usually lasts 3–7 days, and management is thus primarily supportive, concentrating on the major consequences of the condition– inadequate feeding, respiratory distress and apnoeas. The majority of children with bronchiolitis will have mild disease and are usually managed at home with support from primary care. Indications for hospitalisation include poor feeding, lethargy, history of apnoea, respiratory rate >70/min, presence of nasal flaring and/or grunting, severe chest wall recession or oxygen saturation less than 95%. Supportive care in the form of assisted feeding, minimal handling, nursing prone (only in hospital), gentle nasal suctioning and oxygen therapy are the mainstay of treatment for the majority of hospitalised infants. A small minority of infants, especially those with associated co-morbidities, may require mechanical ventilation – early recognition of impending respiratory failure is key to the management of these infants. This review will consider supportive and therapeutic pharmacological interventions but will not discuss preventive interventions such as palivizumab.

SUPPORTIVE INTERVENTIONS

Feeding and fluids

Inadequate feeding is usually due to respiratory distress and the resulting increased work of breathing. The combination of tachypnoea, bouts of coughing and increased upper airway secretions can result in inadequate fluid intake. Furthermore, tachypnoea increases fluid loss, potentially hastening dehydration.

Infants with bronchiolitis are generally intolerant of interventions, and minimal handling is recommended. For milder cases giving small volume
frequent feeds should be encouraged, and breast feeding should be supported. Administration of oxygen may be sufficient to decrease the work of breathing to allow regular fluid intake. Nasogastric feeding may be needed for those with more significant respiratory distress, initially with bolus feeds, but if this worsens respiratory distress, by continuous feeding. If the infant is unable to tolerate enteral feeding, fluids should be administered intravenously. RSV infection can result in inappropriate antidiuretic hormone hypersecretion and so after serum electrolytes are determined, intravenous fluids are usually restricted to two thirds of maintenance requirements.

Respiratory support
Bronchiolitis is associated with increased mucus secretion and airway oedema, resulting in small airway obstruction and dynamic collapse during expiration leading to air trapping. Decreased ventilation in affected areas with increased lung resistance results in a ventilation/perfusion mismatch with hypoxia and increased work of breathing. Respiratory support includes oxygen to treat hypoxia and decrease work of breathing; heliox to improve gas flow through obstructed airways; airway support either through continuous positive airway pressure (CPAP) or heated humidified high flow nasal cannulae (HHHFNC) therapy to prevent dynamic airway collapse and thus improve gas exchange; or for a minority, intubation and mechanical ventilation. Although advocated in some countries, neither chest physiotherapy nor steam inhalation appear effective in bronchiolitis.

Oxygen
Oxygen is the mainstay of treatment for respiratory distress, and is usually administered via nasal cannulae or a head box to minimise handling. Infants with copious secretions should receive nasal suctioning. Nursing in the prone position can improve oxygenation, possibly through improved diaphragmatic function. A combination of head box and facemask or re-breathing bag may be used to administer higher concentrations, although this is usually a sign of worsening respiratory failure, and warrants consideration of CPAP.

A recent Cochrane Review of oxygen therapy for LRTI in children between 3 months and 15 years of age identified no studies comparing oxygen with no oxygen. Although conventional management is to administer supplemental oxygen, there is significant variation in the indication for therapy based on the infant’s transcutaneous oxygen saturations. In the UK, supplemental oxygen therapy is usually administered for oxygen saturations of less than 95% in air, while the American Academy of Pediatrics recommends its use only if oxygen saturations fall persistently below 90% in previously healthy infants. In the USA, the introduction of routine measurement of oxygen saturations was associated with a 2.5-fold increase in hospitalisations for bronchiolitis without any significant change in mortality, and it is arguable that there is little to be gained in administering oxygen to infants with oxygen saturations of greater than 90% in the absence of respiratory distress. Accepting lower oxygen saturation thresholds before administering supplemental oxygen might decrease the rate and length of hospital stay, and a multi-centre Bronchiolitis of Infancy Discharge Study is currently underway.

Airway support
It is likely that CPAP improves work of breathing by preventing dynamic airway collapse during the respiratory cycle, thereby reducing air trapping and improving gas exchange. Indications for CPAP would include severe respiratory distress, a requirement for FiO2>0.5 or in infants with apnoeas. A recent systematic review identified eight trials of CPAP in bronchiolitis – one crossover randomised controlled trial, four before–after studies, and three of CPAP with heliox (see below). Use of CPAP was associated with a mean decrease in PCO2 of between 6.9 and 1.7 mm Hg (p<0.015) and in respiratory rate of between 12 and 16 breaths/min after 2 h (p<0.01). The review concluded that the studies were of poor methodological quality, and no study was powered to determine whether CPAP reduces the need for mechanical ventilation. Nevertheless, clinical practice suggests that CPAP decreases the need for mechanical ventilation, and that the benefits are greatest if instituted early. In a recent study, oxygen requirement at admission to the hospital was the single most significant clinical predictor for CPAP requirement. A potential alternative might be HHHFNC therapy, which is suggested to offer better tolerability and potentially decreased need for mechanical ventilation.

Heliox
Heliox is a mixture of helium and oxygen. Due to the low density of helium compared to air, heliox has improved gas flow through high-resistance airways, so potentially decreasing the work of breathing. A Cochrane Review identified four trials involving 84 children aged less than 2 years with RSV positive bronchiolitis. Use of heliox resulted in a reduction in a clinical respiratory score in the first hour after starting treatment, but no reduction in need for intubation or mechanical ventilation. Use of CPAP with heliox is associated with additional improvements in PCO2 and respiratory rate compared to CPAP alone, but again no significant change in need for intubation or mechanical ventilation.

Mechanical ventilation
Mechanical ventilation for bronchiolitis was first described in the 1960s and was reported to decrease the mortality due to respiratory failure in bronchiolitis. In those who require mechanical ventilation, administration of exogenous surfactant is associated with significantly decreased duration of mechanical ventilation and intensive care length of stay. A very small minority who deteriorate despite mechanical ventilation, most commonly those with pre-existing bronchopulmonary dysplasia, may benefit from extracorporeal membrane oxygenation.

PHARMACOLOGICAL INTERVENTIONS
One or more therapeutic agents including antibiotics are used in as many as 50–80% of infants admitted with bronchiolitis in the USA and other countries. Yet the evidence for the use of the majority of therapeutic agents is minimal at best – among the agents demonstrated to have little beneficial effect are salbutamol, ipratropium bromide, inhaled and systemic corticosteroids, antibiotics, antivirals, DNase and montelukast. The exceptions to date are the combination of nebulised epinephrine with dexamethasone; and nebulised hypertonic saline (virtually always with added bronchodilator). It is worth re-iterating that the different definitions of bronchiolitis means that the results of studies performed in North America (particularly for those performed in emergency departments) and Europe may not be easily transferrable to each other.

Bronchodilators
Three classes of nebulised bronchodilators have been trialled in bronchiolitis – β2 agonists (salbutamol), anticholinergic agents...
(ipratropium bromide) and adrenergic agents (epinephrine), all of which have at some time shown modest, short term benefit, although the short term benefits of epinephrine appear greater. A meta-analysis in 1997 and subsequent Cochrane Review of 22 trials of inhaled bronchodilators both reported a small short term improvement in clinical score for salbutamol, but no effect on risk of hospitalisation. A Cochrane Review of nebulised ipratropium concluded that ipratropium (particularly when combined with β2 agonists) might have minor short term effects, but again no effect on risk of hospitalisation.

Epinephrine has theoretical benefits due to its combination of α and β adrenergic properties, and thus potentially greater vasoconstrictor effects and reduction of oedema. A Cochrane Review of 19 studies of children up to 2 years of age concluded that compared to placebo, nebulised epinephrine significantly reduced the risk of admission on day 1 (RR 0.67; 95% CI 0.50 to 0.95) but that there was no effect on length of hospital stay. The review found no evidence to recommend use of epinephrine for inpatient management. A subsequent systematic review and meta-analysis utilising a mixed treatment comparison using a Bayesian network model again concluded that epinephrine was beneficial in reducing day 1 admission rates from emergency departments, with a single study showing additional benefits with dexamethasone (see below).

Corticosteroids

There are now over 17 trials involving over 2500 participants, including one large multi-centre study of 600 infants, which demonstrate that neither inhaled nor systemic steroids significantly reduce the duration of hospital stay or severity of symptoms.

Bronchodilator and corticosteroid combination therapy

Three studies have utilised the combination of a nebulised bronchodilator and systemic corticosteroids. The largest study in Canadian emergency departments using a combination of nebulised epinephrine and 6 days of oral dexamethasone decreased the hospitalisation risk by the 7th day by 9.3% compared to placebo (RR 0.65; 95% CI 0.45 to 0.95, p=0.02; number needed to treat 11). There were additional benefits in earlier discharge from medical care (4.6 vs 5.3 days; mean ratio 0.83, 95% CI 0.50 to 0.80, p=0.02). Concerns have been raised over the relatively high dose of steroids administered, although there were no serious adverse events, and the applicability of the study to European practice.

Antibiotics or antiviral agents

A Cochrane Review of five studies involving 543 infants concluded that there was minimal evidence to support the use of antibiotics in bronchiolitis, although their use might be warranted in those who require mechanical ventilation. Antiviral drugs such as ribavirin are of no benefit in acute bronchiolitis.

Hypertonic saline

Nebulised hypertonic saline is believed to improve airway hydration resulting in altered mucus rheology and subsequent improvement in mucociliary clearance of airway secretions. A recent Cochrane Review of seven trials including 581 infants with mild to moderate acute viral bronchiolitis concluded that infants treated with nebulised 3% saline at least every 8 h had a significantly shorter mean length of hospital stay compared to those treated with nebulised 0.9% saline (mean difference –1.16 days, 95% CI –1.55 to –0.77, p<0.00001). This equated to a reduction in duration of hospitalisation of approximately 25%. There were similar improvements in clinical severity scores over the first 3 days of therapy.

No significant adverse events were reported, but in six of the seven studies the administered hypertonic saline was mixed with a bronchodilator – three added epinephrine, two added a β2 agonist, and one epinephrine plus a β2 agonist. In the one study that did not mandate the addition of a bronchodilator, over half the infants received one concomitantly. Thus, 3% hypertonic saline appears efficacious and safe if administered with a bronchodilator. A large controlled trial underway in the UK (SABRE) is likely to provide further insights into its use in bronchiolitis (http://clinicaltrials.gov/ct2/show/NCT01469845).

Other agents

Neither nebulised DNase nor montelukast are of use in the management of bronchiolitis. Caffeine is used by some clinicians in apnoea associated with bronchiolitis, usually in very young ex-preterm infants, although the evidence is limited.

CONCLUSIONS

Supportive interventions remain the mainstay of management, but there is evidence for administration of nebulised epinephrine in combination with either oral dexamethasone or mixed with nebulised 3% hypertonic saline. Both strategies use a short acting agent (usually nebulised epinephrine) to decrease acute symptoms in combination with a potentially disease modifying agent – dexamethasone to decrease risk of hospitalisation or hypertonic saline to decrease hospital length of stay. However, there remain uncertainties over the optimal treatment strategy due to differences in the definition of bronchiolitis in clinical trials. It is noteworthy that Reynolds and Cook’s seminal review on bronchiolitis concluded that “carefully controlled trials of various regimens certainly need to be done”.

Contributors PN and ID contributed equally to the design and writing of the manuscript.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

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Arch Dis Child published online June 25, 2012
doi: 10.1136/archdischild-2011-301579

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Published online June 25, 2012 in advance of the print journal.

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