

Treatment of Acute Viral Bronchiolitis

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Abstract: Acute viral bronchiolitis represents the most common lower respiratory tract infection in infants and young children and is associated with substantial morbidity and mortality. Respiratory syncytial virus is the most frequently identified virus, but many other viruses may also cause acute bronchiolitis. There is no common definition of acute viral bronchiolitis used internationally, and this may explain part of the confusion in the literature. Most children with bronchiolitis have a self limiting mild disease and can be safely managed at home with careful attention to feeding and respiratory status. Criteria for referral and admission vary between hospitals as do clinical practice in the management of acute viral bronchiolitis, and there is confusion and lack of evidence over the best treatment for this condition. Supportive care, including administration of oxygen and fluids, is the cornerstone of current treatment. The majority of infants and children with bronchiolitis do not require specific measures. Bronchodilators should not be routinely used in the management of acute viral bronchiolitis, but may be effective in some patients. Most of the commonly used management modalities have not been shown to have a clear beneficial effect on the course of the disease. For example, inhaled and systemic corticosteroids, leukotriene receptor antagonists, immunoglobulins and monoclonal antibodies, antibiotics, antiviral therapy, and chest physiotherapy should not be used routinely in the management of bronchiolitis. The potential effect of hypertonic saline on the course of the acute disease is promising, but further studies are required. In critically ill children with bronchiolitis, today there is little justification for the use of surfactant and heliox. Nasal continuous positive airway pressure may be beneficial in children with severe bronchiolitis but a large trial is needed to determine its value. Finally, very little is known on the effect of the various interventions on the development of post-bronchiolitic wheeze.

Keywords: Viral bronchiolitis, bronchodilators, corticosteroids, ribavirin, hypertonic saline.

INTRODUCTION

Clinical definitions of acute viral bronchiolitis vary between countries. While in many countries including the USA wheezing is fundamental for the diagnosis, in the U.K., Australia and New Zealand wheezing is not an obligatory diagnostic criterion [1, 2]. These differences in definition may account for part of the variability in study results; clearly, uniformity is needed to allow a comparison between studies performed in different parts of the world [3].

Acute viral bronchiolitis is the most common lower respiratory tract infection in infants and young children. Although only 2-3% of all children with bronchiolitis need hospitalisation, the disease is the leading cause of infant hospitalisation in the USA and has been associated with substantial morbidity in both inpatient and outpatient settings [4-7]. Respiratory syncytial virus (RSV) is the most frequently identified virus, but many respiratory viruses such as parainfluenza virus, influenza virus, rhinovirus and human metapneumovirus have been associated with acute viral bronchiolitis; further, young children with bronchiolitis often are infected with more than one virus, most commonly with RSV and either human metapneumovirus or rhinovirus [5, 7, 8].

While a relation between acute viral bronchiolitis and subsequent recurrent wheeze ("post-bronchiolitic wheeze") in later life has consistently been shown in clinical studies, there is no clear explanation for this association [5].

TREATMENT

Most children with acute viral bronchiolitis have a self limiting mild disease and can be safely managed at home with careful attention to feeding and respiratory status. Management mainly consists of good supportive care, and most infants do not require specific measures. Criteria for referral and admission may vary between hospitals. Generally, the decision to admit an infant with bronchiolitis to the hospital is based on the age of the patient, the phase of illness, the presence of risk factors, the severity of respiratory distress, the ability to take oral fluids, and social and local circumstances [8]. Clinical practice in the acute management of bronchiolitis varies widely even between centres in one country, and there is much controversy, confusion, and lack of evidence over the best treatment for this common, life-threatening condition [5].

Oxygen Supplementation

Treatment of hospitalised infants very often includes oxygen supplementation to maintain haemoglobin saturation $\geq 92\%$. There is, however, no evidence on which to base haemoglobin saturation limits for admission, during admission or for discharge from the emergency department or hos-

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pital. While the effect of supplemental oxygen on recovery from bronchiolitis is not known, oxygen supplementation is the prime determinant of the length of hospitalisation for infants with acute viral bronchiolitis [9]. Thus, the use of pulse oximetry has likely contributed to longer hospitalisations and greater use of health care resources [7]. In the most recent clinical practice guideline of the American Academy of Pediatrics (AAP) [1] the following options (options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to one approach over another) are presented:

Supplemental oxygen is indicated if haemoglobin saturation falls persistently below 90% in previously healthy infants. In this case, adequate supplemental oxygen should be used to maintain haemoglobin saturation at or above 90%. Oxygen may be discontinued if haemoglobin saturation is at or above 90% and the infant is feeding well and has minimal respiratory distress.

As the child's clinical course improves, continuous measurement of haemoglobin saturation is not routinely needed.

Nasogastric Vs. Intravenous Fluids

It is strongly recommended that clinicians should assess hydration and ability to take fluids orally [1]. Frequent small foods are often used but nasogastric or intravenous fluids may be required to maintain hydration. However, fluid replacement strategies have not been validated in randomised controlled trials (RCTs). A recent study comparing management of acute viral bronchiolitis between different centres in Australia and New Zealand concluded that practice is equally split between nasogastric and intravenous hydration, reflecting the current lack of evidence [10].

Bronchodilators (Beta 2 Agonists, Epinephrine)

As the contribution of airway smooth muscle constriction to airway obstruction in most cases is less than the one of mucus plugs, cellular debris and mucosal oedema, the rationale for treatment especially with beta 2 agonists is weak. Epinephrine by stimulating the alpha adrenoreceptor also causes vasoconstriction in the airway mucosa, and thus may result in a decrease of the mucosal oedema. Inhaled bronchodilators are widely used in the treatment of infants with acute viral bronchiolitis [5]; in emergency departments, especially nebulised epinephrine is frequently used [11]. Numerous clinical trials and systematic reviews of the literature examined the role of bronchodilators in the treatment of bronchiolitis. A recent meta-analysis of RCTs comparing bronchodilators (other than epinephrine) with placebo in the treatment of bronchiolitis including 1428 infants concluded that bronchodilators produce small short-term improvements in clinical scores but no significant improvement in oxygenation overall or in the rate of hospital admission [12]. Obviously, results of studies which employed a variety of therapies and outcome measures are difficult to compare, and pooling heterogeneous results from a number of studies may result in a significant difference of questionable clinical importance. Moreover, the inclusion of studies that enrolled

infants with recurrent wheezing may have biased the results in favour of bronchodilators [12]. Similarly, both a large RCT and a Cochrane review concluded that there is insufficient evidence to support the use of epinephrine in inpatients with bronchiolitis [13, 14]; however, there is some evidence to suggest that epinephrine may be favourable to salbutamol or placebo among outpatients, although admission rates were not significantly different [14].

With bronchodilators having no proven effect on the course of acute viral bronchiolitis, it is currently recommended that they should not be routinely used in the management of this disease [1, 3, 5]. A carefully monitored individual trial of nebulised alpha-adrenergic or beta-adrenergic medication may be justified, but inhaled bronchodilators should be discontinued unless a clear positive effect is documented [1, 3]. Epinephrine may be the preferred drug for such a trial.

Inhaled Corticosteroids (ICS)

In three studies, no effect of ICS was seen on clinical scores or length of hospitalisation [15-17]. ICS have also been used with the idea to prevent post-bronchiolitic wheezing. A recent systematic review of 5 studies involving 374 infants did not demonstrate an effect of ICS given during the acute phase of bronchiolitis in the prevention of recurrent wheezing following bronchiolitis. However, the small number of included participants and the inability to pool all clinical outcomes precluded the authors from making strong recommendations [18]. Very recently, another RCT in 243 infants with RSV related lower respiratory tract infection did not find an effect of early initiated, prolonged high dose inhaled corticosteroids on recurrent wheeze [19]. The authors thus concluded that the general use of inhaled corticosteroids during RSV bronchiolitis should not be advocated.

Systemic Corticosteroids (Oral, Intramuscular, Intravenous)

A meta-analysis performed on 13 RCTs involving 1198 patients (managed as outpatients or inpatients) found no positive effects of systemic corticosteroids on clinical scores, hospital admission rates, length of stay or readmission rates [20]. More recently, an RCT in previously healthy infants hospitalised for acute bronchiolitis (n=174) showed a modest benefit of a single intramuscular injection of dexamethasone on several outcomes, including length of hospital stay [21]. In contrast, a large RCT did not show any effect of a single oral dose of dexamethasone in 600 infants presenting with moderate-to-severe bronchiolitis at the emergency department [22]. Similarly to ICS, oral prednisolone during the acute phase of RSV bronchiolitis does not appear to be effective in preventing post-bronchiolitic wheezing or asthma [23]. Based on the data available, the current recommendation is that systemic corticosteroids should not be used routinely in the management of acute viral bronchiolitis, irrespective of the mode of application or the dose [1].

Combination of Epinephrine and Dexamethasone

Recently, an RCT involving 800 infants with acute viral bronchiolitis who were seen in the emergency department examined the effects of inhaled epinephrine, oral dexametha-

sone, and a combination of both, with hospital admission within seven days as the primary outcome [24]. In an unadjusted analysis, only the infants in the epinephrine-dexamethasone group were significantly less likely than those in the placebo group to be admitted by day 7. After adjustment for multiple comparisons, however, the difference did not reach statistical significance. If confirmed by a sufficiently powered study, the suggested moderate effect (11 infants would have to be treated to prevent one admission) due to the frequency of the disease could represent an important reduction in the number of hospitalisations. At present, however, this combination treatment cannot be recommended.

Leukotriene Receptor Antagonists

Cysteinyl leukotrienes are significantly increased in respiratory secretions from infants with acute viral bronchiolitis and remain so at short-term follow-up, suggesting a possible role of these substances in the pathogenesis of the disease [25]. An RCT compared montelukast, a specific cysteinyl leukotriene receptor antagonist, with placebo in infants with a first episode of bronchiolitis; treatment was given from hospital admission until discharge. Montelukast did not improve length of stay, clinical severity scores or cytokine levels in nasal lavage fluid [26]. Another RCT, serving as a pilot study, in 130 infants hospitalised with acute viral bronchiolitis showed that a 4-week-course of montelukast reduced respiratory symptoms subsequent to RSV bronchiolitis [27]. Subsequently, in a larger study infants hospitalised for a first or second episode of RSV bronchiolitis (n=979) were treated with montelukast for 24 weeks; in this study, montelukast did not improve respiratory symptoms of post-RSV bronchiolitis [28]. Similarly, a recent small RCT found that treatment with montelukast for three months after hospital admission for RSV bronchiolitis did not reduce respiratory symptoms during the treatment period and during a 9-month follow up period [29]. It follows that montelukast should not be used in acute viral bronchiolitis [3].

Immunoglobulins and Monoclonal Antibodies

A recent Cochrane systematic review assessing immunoglobulin treatment of RSV infection rather than its role as a prophylactic measure identified four RCTs of which none demonstrated a statistically significant benefit [30].

Palivizumab, a humanised monoclonal IgG1 antibody specifically directed to the RSV fusion protein has been shown to be efficacious in preventing serious RSV disease in high risk patients [31]. A phase I/II RCT was performed with palivizumab in previously healthy children hospitalised with acute RSV infection [32]. As this study, showing no significant differences in clinical outcomes, was not adequately powered, the efficacy of palivizumab as treatment of RSV infection remains unclear. The current recommendation is that neither immunoglobulins nor RSV monoclonal antibodies should be used in acute viral bronchiolitis [3].

Antibiotics

Bacteraemia is uncommon in children with RSV infection, unless they have nosocomial RSV infection, cyanotic

congenital heart disease, or require intensive care unit admission [33]. Several RCTs have studied the effect of antibiotics on the course of acute viral bronchiolitis. An old study investigating the effect of ampicillin in an outbreak of bronchiolitis reported no positive effect on the disease course [34]. This was the only trial that met the inclusion criteria of a systematic review on the use of antibiotics in children with bronchiolitis [35]. Not surprisingly, this review found no evidence to support the use of antibiotics. More recently, the authors of a very small study reported that clarithromycin was associated with a significant reduction in length of hospital stay and readmission to hospital [36]. In contrast, a larger trial in infants hospitalised with RSV bronchiolitis did not show a positive effect of azithromycin on duration of hospitalisation or resolution of symptoms [37]. The anti-inflammatory activity of macrolides should be studied in larger populations of both outpatients and inpatients. At present, it is recommended to limit the use of antibacterial medications to children with bronchiolitis who have specific indications of the coexistence of a bacterial infection [1, 3].

Antiviral Therapy

Ribavirin is a broad-spectrum antiviral agent approved for treatment of RSV infection, and is the only antiviral drug that has been studied in children with acute viral bronchiolitis. Its use, however, is controversial because of questions about its efficacy, safety concerns, and its high cost. A number of small studies, lacking sufficient power to provide reliable estimates of the effects, have been performed with ribavirin; these have been reviewed recently [38]. Ribavirin may reduce the duration of mechanical ventilation and days of hospitalisation, and may decrease the incidence of recurrent wheezing following bronchiolitis; however, in the absence of large RCTs, the effect of ribavirin remains unproven. Thus, at present ribavirin should not be used routinely in children with acute viral bronchiolitis [1, 3].

Hypertonic Saline

Airway oedema and mucus plugging are the predominant pathological features in acute viral bronchiolitis. Hypertonic saline decreases airway oedema, improves mucus rheologic properties and mucociliary clearance, and thus decreases airway obstruction [39]. Until 2007, four RCTs on the use of aerosolised 3% hypertonic saline solution in children with acute viral bronchiolitis were published [40-43]. One study was a multi-centre trial [43], the other three were conducted by the same group of investigators [40-42]. Outpatients were recruited in one trial [40] and inpatients in the other three trials [41-43]. Bronchodilators were added to the study solution in three studies [40-42]; in the multi-centre study, bronchodilators were added in a majority of the treatments by attending physicians [43]. A recent systematic review which included these four trials, involving 254 infants with acute viral bronchiolitis (189 inpatients and 65 outpatients), concluded that nebulised 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score [44]. Recently, another small RCT investigated the use of hypertonic saline in the emergency department setting, and the authors suggested that immediate clinical benefits may not be seen with nebulised hypertonic saline [45]. In

this study, there was a trend towards a reduction in hospitalisation rate with the use of hypertonic saline, but the study was not sufficiently powered for this outcome parameter. Very recently, an RCT found high volume normal saline to be as effective as 3% saline in children with very mild bronchiolitis in the emergency department, suggesting that the improvement in mucus clearance is not a function of the saline concentration but rather of the total mass of NaCl added to the airway surface [39, 46]. While there is a lack of strong evidence to support the routine use of aerosolised hypertonic saline solution in children with acute viral bronchiolitis, the lack of side effects and the limited cost of the treatment deserve consideration for a large RCT. The present recommendation is that hypertonic saline should probably be used in the treatment of acute viral bronchiolitis [3].

Furosemide

Inhaled furosemide has been reported to have a positive effect in a number of respiratory conditions. It acts only locally in the lung, but the precise mechanism of action is as yet unclear. In a small RCT, safety and the short and long term clinical effects of inhaled furosemide were evaluated in previously healthy children with acute viral bronchiolitis [47]. While inhaled furosemide appeared to be both feasible and safe, this pilot study did not show significant clinical effects in hospitalised infants with acute viral bronchiolitis.

Surfactant

Clinical and laboratory evidence suggests that severe viral bronchiolitis may result in secondary surfactant insufficiency [48]; thus, exogenous surfactant represents a potentially promising therapy. The efficacy of exogenous surfactant for the treatment of acute viral bronchiolitis in mechanically ventilated infants and children has been assessed in a meta-analysis, including three trials with a total of 79 patients [49]. Use of surfactant was associated with a non-significant decrease in duration of mechanical ventilation by 2.6 days and a borderline significant decrease in ICU length of stay by 3.3 days. In summary, presently available data on surfactant are not sufficient to provide reliable estimates of its effects in critically ill children with bronchiolitis.

Heliox

Acute viral bronchiolitis is characterised by airway obstruction, resulting in turbulent gas flow. Heliox, a mixture of oxygen and the inert gas helium, may improve gas flow through high-resistance airways and thus decrease the work of breathing. In a very recent meta-analysis, four trials involving 84 infants with RSV bronchiolitis who required paediatric intensive care unit hospitalisation were included [50]. The authors of this review concluded that heliox therapy in addition to standard medical care for acute viral bronchiolitis may significantly reduce respiratory distress in the first hour after starting treatment. However, there was no reduction in the rate of intubation, in the need for mechanical ventilation, or in the length of paediatric intensive care unit stay. Presently, the place for heliox in the therapeutic schedule for severe bronchiolitis is unclear.

Nasal Continuous Positive Airway Pressure

One RCT with a cross-over design compared nasal continuous positive airway pressure (CPAP) with standard treatment consisting of intravenous fluids and supplemental oxygen by nasal prongs or face mask in infants with bronchiolitis and hypercapnia [51]. When nasal CPAP was used first, the reduction in partial pressure of carbon dioxide in arterial blood was significantly greater than when CPAP was used second. Nasal CPAP was well tolerated with no complications identified. A large trial is needed to investigate whether nasal CPAP may reduce the need for invasive ventilation.

Chest Physiotherapy

The main goal of chest physiotherapy in paediatric respiratory diseases is to reduce airway resistance and thus the work of breathing, and to enhance gas exchange by assisting in the clearance of excessive respiratory secretions. A systematic review performed to determine the efficacy and safety of chest physiotherapy in infants with acute bronchiolitis included three RCTs [52]. The three studies employed vibration and percussion techniques with children in postural drainage positions compared to no intervention. The authors concluded that with the techniques applied, chest physiotherapy does not reduce length of hospital stay or oxygen requirements, or improve clinical severity scores in infants with acute viral bronchiolitis. The current recommendation is that chest physiotherapy should not be used routinely in children with acute viral bronchiolitis [1, 3].

CONCLUSIONS

In 1963, Reynolds and Cook stated that "... oxygen is vitally important in bronchiolitis and there is little convincing evidence that any other therapy is consistently or even occasionally useful ..." [53]. Now, almost fifty years later, supportive care including administration of oxygen and fluids still is the cornerstone of treatment of acute viral bronchiolitis, and there is no intervention that is of proven benefit on the course of the disease or the development of post-bronchiolitic wheeze. Bronchodilators may be effective in some patients and may thus be used on a trial-and-error basis. Preliminary evidence suggests a potential role for nebulised hypertonic saline, and in infants and children with severe disease the use of nasal CPAP appears to be beneficial. Some of the discussed treatments and promising combinations of therapies should be studied in further and larger RCTs.

CONFLICT OF INTEREST

In the past three years Ernst Eber has received travel expenses to attend scientific conferences and/or speaker's fees from Abbott, AstraZeneca, GlaxoSmithKline, Merck Sharp and Dohme, and Nycomed.

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