Pharmacological management of acute bronchiolitis

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Abstract: This article reviews the current knowledge base related to the pharmacological treatments for acute bronchiolitis. Bronchiolitis is a common lower respiratory illness affecting infants worldwide. The mainstays of therapy include airway support, supplemental oxygen, and support of fluids and nutrition. Frequently tried pharmacological interventions, such as ribavirin, nebulized bronchodilators, and systemic corticosteroids, have not been proven to benefit patients with bronchiolitis. Antibiotics do not improve the clinical course of patients with bronchiolitis, and should be used only in those patients with proven concurrent bacterial infection. Exogenous surfactant and heliox therapy also cannot be recommended for routine use, but surfactant replacement holds promise and should be further studied.

Keywords: bronchiolitis, respiratory syncytial virus, pharmacological, therapy, interventions

Introduction

Acute bronchiolitis is the most common lower respiratory tract illness in infants and young children, and is usually the result of viral infection. Respiratory syncytial virus (RSV) is the most frequent infecting agent (Wright et al 1989). This disease is characterized by inflammation, edema, and necrosis of the small airway epithelium with associated bronchospasm and increased mucous production. Bronchiolitis is a seasonal illness with the highest incidence between December and March in the Northern Hemisphere. However, there is significant regional variability in the timing and duration of RSV seasons throughout the US (Mullins et al 2003), and in tropical areas the virus is usually endemic and present in the community throughout the year.

Epidemiology

Acute bronchiolitis is a far reaching illness. Virtually all children have been infected with RSV by the age of 2 years, and nearly half of those will experience two infections (Glezen et al 1986). Of those infected, 40% will develop a lower respiratory tract infection (LRTI) (Bronchiolitis 2006). It is estimated that each year, as many as 126,000 infants are hospitalized in the US due to bronchiolitis (Shay et al 1999). While this represents a large burden, the numbers outside of the US are staggering. Worldwide, as many as 1/200 infants are hospitalized annually for treatment of LRTI, with a mortality rate as high as 5% (Davies et al 1996). In the US, RSV-associated mortality has declined from 4500 deaths in 1985 (Shay et al 2001) to 390 deaths in 1999 (Leader and Kohlhase 2003). The estimated annual cost of hospitalization for infants with bronchiolitis exceeds US $700 million (Stang et al 2001).

Etiology

Acute bronchiolitis is predominantly caused by viral infection, with RSV accounting for greater than 50% of cases. Other important viral causes include adenovirus, influenza virus, parainfluenza virus, human metapneumovirus, and rhinovirus. *Mycoplasma pneumoniae* may occasionally be associated with bronchiolitis.

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RSV is extremely contagious, with a 98% attack rate for first-time infection during epidemics. This decreases to a 75% attack rate for second infections (Henderson et al 1979). Transmission generally requires close contact, with exposure of the nasal mucosa or conjunctiva to infected secretions (Hall et al 1981). Thus, well implemented contact isolation precautions are effective in limiting spread of the infection.

Reinfection with RSV over an individual's lifetime is common; however, the first infection is generally the most severe and the most likely to involve the lower respiratory tract (Shay et al 1999). The second infection can also be quite severe, but after two RSV infections, the acquired immunity usually provides a significant reduction in the severity of a third and subsequent infections (Henderson et al 1979). Prematurely born children with chronic lung disease remain at risk for severe RSV infections for the first two years of life, and many forms of immune deficit and congenital heart disease represent a risk factor independent of age (MacDonald et al 1982; Hall et al 1986; Boyce et al 2000).

Pathophysiology

During the acute phase of bronchiolitis, the infecting virus precipitates an inflammatory response that results in edema, inflammatory cellular infiltration, and sloughing of the lower airway epithelium. This leads to bronchiolar plugging and hyperinflation, which is exacerbated by impaired ciliary clearance of mucous and cellular debris. After an early phase characterized by chemotaxis of polymorphonuclear leukocytes, the inflammatory infiltrates in infected airways become predominantly lympho-monocytic. In infants, the inflammation is generally limited to the small airways, sparing the alveoli (Simoes 1999), whereas later in life the infection is usually limited to the upper respiratory tract and large airways. The inflammatory response to RSV appears to be amplified and sustained by the peripheral nervous system via complex neuro-immune interactions primed by the virus.

In immunocompetent hosts, the infection with RSV is cleared within two weeks, whereas immunocompromised hosts can harbor and spread the virus for several months. Despite being a relatively short, self-limiting infection, RSV bronchiolitis is followed by chronic respiratory sequelae in a large proportion of children, particularly as recurrent episodes of wheezing that frequently lead to a diagnosis of asthma during the first decade of life.

Clinical features

The incubation period for RSV ranges from 2 to 8 days. Infants develop signs and symptoms of a mild upper respiratory tract infection within one week of exposure to an infected individual. This progresses to increased work of breathing, cough, wheezing, and irritability. The respiratory distress may range from mild to severe with nasal flaring, grunting, accessory muscle use and marked intercostal and subcostal retractions. Premature infants and newborns may present with decreased appetite, lethargy, and apnea after the upper respiratory tract infection prodrome.

Apnea is among the most common clinical manifestations of RSV infection in young infants, with an estimated incidence of 16%–25% (Sabogal et al 2005). A particularly high risk is associated with young age (<3 months) and prematurity. Interestingly, apnea can be the presenting sign of this infection preceding the onset of wheezing and other lower respiratory symptoms. This clinical observation and data obtained in animal models suggest that RSV can trigger apnea in as early as the nasal phase of the infection, before spreading to the lower airways. Because of its ability to interfere with ventilatory control, RSV infection has also been suggested as a precipitating factor in cases of sudden infant death.

Supportive care

The severity of bronchiolitis varies from mild to severe. Most infants endure a self-limited illness that can be treated in an outpatient setting, with close follow up to ensure that they have no respiratory distress, no supplemental oxygen requirement and remain well hydrated. Infants with moderate or severe disease characterized by poor feeding, tachypnea, nasal flaring or supplemental oxygen requirement should be admitted to the hospital for more aggressive management and monitoring. Regardless of the setting in which the patient is treated, the mainstay of therapy remains supportive care, which includes respiratory support and adequate fluid and nutrition management.

Children who are hypoxemic with oxygen saturations <90% should receive warm, humidified oxygen (Bronchiolitis 2006). Nasal obstruction is a common problem, and given that young infants are obligate nose breathers, may result in a significant increase in respiratory distress. Our experience has demonstrated that simple nasal toilet with saline drops and a suction bulb can significantly improve work of breathing and frequently abort the requirement for mechanical ventilatory support. Infants with hypoxemia refractory to supplemental oxygen, persistent respiratory distress or progressive respiratory failure usually require either non-invasive support with nasal continuous positive airway pressure (NCPAP) or endotracheal intubation.

Infants with bronchiolitis have decreased nutritional intake due to respiratory distress and tachypnea, which puts these patients at increased risk of aspiration and may therefore warrant the suspension of oral feeding. In addition, insensible losses are increased because of fever and elevated work of breathing. Adequate fluid intake and nutrition should be maintained with parenteral fluids or with placement of a nasogastric or orogastric feeding tube.

Pharmacological interventions

Bronchodilators

Bronchodilators are frequently tried in infants presenting with wheezing due to bronchiolitis because of its similarity to asthma. Their routine use is controversial. Despite many randomized, controlled trials (RCT), no consistent benefit has been demonstrated. It is probably sensible to give a brief trial of bronchodilators to patients with bronchiolitis while the effect is carefully monitored, but their use should be continued only if clinical improvement can be documented by objective endpoints.

Albuterol

A number of small RCTs have evaluated the effectiveness of albuterol in the treatment of acute bronchiolitis, with conflicting results. A double-blind, placebo-controlled trial evaluated the efficacy of nebulized albuterol in the treatment of infants aged 0–24 months with wheezing (Schweich et al 1992). Twenty-five infants were randomized to receive nebulized albuterol or saline placebo. The infants were assessed after each treatment for wheeze, retractions score, respiratory rate, heart rate, and pulse oximetry. In this study, the authors were able to demonstrate significant improvement in the wheeze and oxygenation scores of those infants that received albuterol, while no significant difference in the heart rate and respiratory rate were noted. These findings are supported by a Canadian double-blind, placebo-controlled trial that evaluated 40 infants between 6 weeks and 24 months of age with a first episode of wheezing and signs and symptoms of bronchiolitis (Schuh et al 1990). Improvements were demonstrated in oxygenation and work of breathing after two doses of albuterol. A criticism of both of these studies is that the patients were not followed over time, and no effect was demonstrated in improved resolution of symptoms or in length of stay (LOS). In fact, several other studies have shown opposite results, suggesting that albuterol offers no consistent improvement in patients with bronchiolitis.

Gadomski et al (1994) evaluated 88 infants with the first episode of wheezing in an emergency department setting. The subjects were randomized to receive two nebulized albuterol or nebulized placebo treatments 30 minutes apart or a single dose of oral albuterol or saline placebo. The investigators measured respiratory rate, heart rate, clinical scores, oxygen saturations and level of wakefulness. No significant difference was demonstrated among the four groups. Klassen et al (1991) demonstrated a short-term improvement in clinical scores 30 minutes after a single albuterol treatment; however no difference was demonstrated 60 minutes after the treatment. There was no difference between the two groups when oxygenation was compared.

Inpatient trials have also failed to demonstrate benefit in patients receiving nebulized albuterol. A small RCT evaluated 52 hospitalized infants with moderately severe acute viral bronchiolitis (Dobson et al 1998). There was no improvement in oxygenation, time to meet discharge criteria, or length of stay. A 1992 meta-analysis of 8 clinical trials examined several outcomes (Flores and Horwitz 1997). The analysis was unable to demonstrate any impact on the hospitalization rate or respiratory rate. The authors did find a statistically significant, but clinically insignificant, improvement in oxygen saturation and heart rate. They concluded that evidence for the efficacy of β2-agonist therapy in bronchiolitis is lacking.

In summary, albuterol has not been shown to consistently reduce the duration or severity of illness or length of hospital stay, and so cannot be recommended for routine care of the patient with bronchiolitis. A carefully monitored trial in individual patients may be warranted, with discontinuation of therapy if no improvement is noted. Animal model studies suggesting that single-isomer preparations like levalbuterol may have a better anti-inflammatory effect than racemic albuterol in RSV-infected airways (Auais et al 2005) have yet to be confirmed in clinical trials.

Racemic epinephrine

As with albuterol, the use of nebulized racemic epinephrine is controversial. No strong evidence exists to support its routine use; nevertheless, it is frequently used in wheezing infants with bronchiolitis. In a small, placebo-controlled, randomized trial, Kristjansson et al (1993) demonstrated an improvement in oxygen saturations at 30, 45 and 60 minutes after inhalation of nebulized epinephrine. However, the authors were unable to show that these responses improved the overall course. A small, non-controlled trial investigated the use of nebulized *l*-epinephrine in intubated infants with bronchiolitis, showing a significant reduction in airway resistance after treatment with nebulized epinephrine (Numa et al 2001). Despite this, there was no reduction in oxygen requirement.

More recently, a large RCT compared nebulized epinephrine with placebo in 194 infants hospitalized with bronchiolitis (Wainwright et al 2003). Patients were randomized to receive 3 doses of nebulized epinephrine or placebo, 4 hours apart. The authors evaluated length of stay, respiratory and heart rates, work of breathing, and length of oxygen therapy, and, again, found no significant reduction in the measured outcomes.

Several studies have compared the efficacy of nebulized albuterol against epinephrine. In one such study, Menon et al (1995) compared nebulized epinephrine to albuterol in an emergency department setting. Of those patients who received nebulized epinephrine, 33% required hospital admission compared with 81% of the albuterol group. In this study, the authors conclude that nebulized epinephrine is more effective than albuterol in preventing hospitalization of infants with bronchiolitis. In another evaluation of the efficacy of nebulized epinephrine versus albuterol, Hartling et al (2003) conducted a meta-analysis of 14 available studies. Among outpatients, epinephrine was more effective than albuterol or placebo in the reduction of clinical score, improvement in oxygenation and respiratory rates, and overall improvement. The measured outcomes also indicated that epinephrine was more effective in the inpatient setting, with improvements in clinical score and respiratory rate. However, in 2004 a Cochrane report of the available data found a lack of evidence to support the use of epinephrine in the inpatient setting (Hartling et al 2004). The report also determined that among outpatients, epinephrine may be more favorable than albuterol.

While no strong evidence exists to support the routine use of albuterol or epinephrine, the use of bronchodilators in select patients seems reasonable. When a bronchodilator trial is given, the available data supports the use of epinephrine over albuterol. If clinical improvement can be documented, then continued use is indicated. However, treatments should be discontinued if no improvement can be demonstrated. As epinephrine is typically not prescribed for use at home, albuterol may be a more appropriate choice for outpatient use.

Anticholinergic agents

Anticholinergic agents such as ipratropium bromide have not been demonstrated to be effective in the treatment of bronchiolitis. Several studies have evaluated ipratropium alone and with albuterol. While minor improvements in oxygenation have been reported, there is no consistent, significant benefit to the overall clinical course or outcome (Wang et al 1992; Chowdhury et al 1995; Schuh et al 2002).

Corticosteroids

Corticosteroids are commonly used in the treatment of bronchiolitis as anti-inflammatory agents; their use may be as high as 60% of inpatient therapy (Bronchiolitis 2006). Their appeal may be due to the similarities of bronchiolitis to asthma and to the role that corticosteroids play at many intracellular levels to reduce inflammation. In theory, corticosteroids should be of benefit in reducing the inflammatory response of the lower airways against viral infections, and for this reason they have been widely prescribed by physicians. But in reality, several studies and meta-analyses with corticosteroids have failed to show any significant benefit in acute or long-term clinical outcomes of virus-induced wheezing, whether administered systemically or inhaled.

Systemic corticosteroids

Bulow et al investigated the short and long term effects of systemic corticosteroids in infants admitted with RSV bronchiolitis (Bulow et al 1999). One hundred and forty-seven hospitalized infants were randomized to receive 2 mg/kg/day prednisolone or placebo for 5 days. Outcomes measured included length of stay and use of adjunctive medications and supportive therapies while hospitalized, as well as at 1 month and 1 year follow up. This study found no evidence that prednisolone effected any of the outcome measures. Schuh et al evaluated 70 children under the age of 2 years presenting to the emergency department with moderate or severe acute bronchiolitis (Schuh et al 2002). The patients were randomized to receive 1 mg/kg of oral dexamethasone vs placebo, and were evaluated hourly for 4 hours. Each group also received nebulized albuterol at 0, 30, 60, and 120 minutes. The authors demonstrated a greater rate of clinical improvement among the dexamethasone group, to such extent that there was a decrease in the admission rate (19% vs 44%) compared with the placebo group.

In a more recent study conducted in Thailand, Teeratakulpisarn et al (2007) evaluated 174 children hospitalized with acute bronchiolitis. The children were randomized to received 0.6 mg/kg of intramuscular dexamethasone or placebo. The authors evaluated the length of time to resolution of respiratory distress as the primary outcome. The duration of respiratory distress was decreased from 39 hours for the placebo group to 27.2 hours for the dexamethasone group, a difference of about 12 hours. The duration of oxygen was also reduced by 14.9 hours, and the hospital LOS was decreased by 13.4 hours.

Two meta-analyses are also available. Garrison et al (2000) evaluated 6 studies with a combined total of

347 subjects. The outcomes measured included LOS and impact on severity of symptoms. The authors reported statistically significant reductions in clinical symptom scores and a reduction in LOS of 0.43 hospital days/patient. These numbers are similar to those reported by Teeratakulpisarn et al. Although the reduction of hospitalization by half a day would not be clinically significant for the individual patient, the authors argue that approximately 51,000 hospital days could be saved annually by the routine use of corticosteroids.

Patel et al conducted a larger systematic review of 13 trials of glucocorticoid therapy in 1198 children with viral wheezing aged 0–30 months (Patel et al 2004). They found a similar decrease in LOS of 0.38 hospital days/patient, which however was not statistically significant. There was no difference in clinical scores, respiratory rate or oxygen saturation. For patients treated in the emergency department or clinic, there was no difference in admission rates. The authors do caution that significant heterogeneity of the included studies and results make the final analysis difficult to interpret with confidence, but concluded that this therapy lacks any significant clinical benefit compared to placebo and is not of benefit for this patient group.

In a more recent double blind, randomized trial, Corneli et al (2007) compared oral dexamethasone with placebo to study whether a single dose of oral dexamethasone (1 mg/kg) could reduce the need for hospitalization. Over a 3-year period, the authors enrolled 600 infants between the ages of 2 and 12 months presenting to the emergency department with first-time wheezing and a diagnosis of moderate-severe bronchiolitis. The primary outcome was hospital admission after 4 hours of emergency department observation. Secondary and later outcomes measured included: change in a respiratory assessment score, length of hospital admission, later medical visits or hospital admissions and adverse events. The authors found that a single dose of dexamethasone did not change the rate of hospital admission or the severity score of bronchiolitis after 4 hours. They also found no change in later outcomes.

Inhaled corticosteroids

Several studies have evaluated inhaled corticosteroids in patients with bronchiolitis, but no consistent benefit has been demonstrated (de Blic 2001; Chao et al 2003). A recent RCT compared 61 infants randomized to receive nebulized dexamethasone or saline; both groups also received nebulized epinephrine (Bentur et al 2005). In this study, no statistically significant difference was noted in clinical score or oxygen saturation. There was, however, a significant reduction in LOS in the dexamethasone group, especially among the subgroup of prematurely born infants (6.5 ± 1.7 days vs 9.1 ± 1.9 days).

In a Cochrane review of 5 studies with a total of 374 infants, Blom et al (2007) evaluated the use of inhaled corticosteroids to prevent post-bronchiolitic wheezing. This analysis demonstrated no reduction of wheezing, readmission rate, use of systemic corticosteroids or use of bronchodilators.

In general, young children without an atopic phenotype that wheeze in response to viral infections show a poor response to corticosteroids, and even children that will ultimately develop asthma are usually unresponsive to this therapy when they develop virus-induced wheezing during their first years of life. Another area of concern derives from safety considerations. In fact, severe RSV bronchiolitis typically occurs during the first year of life and coincides with a critical phase of rapid lung development. The safety of the therapeutic use of corticosteroids during this window, particularly at high doses and for prolonged periods, is virtually unknown and consequently no steroid has ever been approved by the US FDA for use in the first year of life.

We conclude that whether administered systemically or inhaled, corticosteroids should not be routinely used in the treatment of bronchiolitis. However, some specific patient populations may benefit from a trial of steroid therapy, particularly patients with family history (parental atopy or asthma) or medical history (atopic eczema) suggestive of atopic predisposition.

Ribavirin

Ribavirin is a synthetic nucleoside analog that demonstrates good *in vitro* activity against RSV. Several factors make its routine use controversial: it is expensive, difficult to administer, and possibly a teratogen. Furthermore, the available studies are all small, have inconsistent quality, and have produced conflicting results.

Early studies were encouraging. In 1983, Hall et al (1983) randomized 33 infants hospitalized with RSV to continuous aerosolized ribavirin for 3–6 days versus placebo. The ribavirin group demonstrated a greater improvement in severity score, lower respiratory tract signs, oxygen saturations and viral shedding compared to the placebo group. Rodriguez et al (1987) also demonstrated improved oxygenation and a greater rate of clinical improvement in patients receiving a short course of ribavirin, without evidence of adverse effects. Smith et al (1991) conducted a double-blind, placebo-controlled trial of continuously aerosolized ribavirin

in 28 mechanically ventilated infants with RSV infection, using nebulized sterile water as a control. This study reported a significant reduction in oxygen use and in the length of mechanical ventilation and hospitalization, especially among infants with no underlying illness, but these findings were criticized because bronchospasm associated with sterile water nebulization may artificially make ribavirin seem more effective (Moler et al 1991).

A subsequent, well-designed study evaluated ribavirin against nebulized saline in 42 mechanically ventilated patients with RSV bronchiolitis and respiratory failure (Guerguerian et al 1999). The authors found no significant improvement in the length of oxygen therapy, aerosol therapy, mechanical ventilation, PICU stay, or hospital stay. These findings were supported by a similar study performed by Meert et al (1994). Taber et al (1983) evaluated 26 infants randomized to receive ribavirin or placebo and found no difference in the rate of viral clearance between the two groups. In a longer outcome study, Everard et al (2001) followed patients treated with ribavirin for RSV bronchiolitis over 1 year and was unable to demonstrate any short-term improvement in the clinical course or long-term reduction in the use of inhaled bronchodilators or steroids.

In the early 1990s, the AAP endorsed ribavirin use for RSV bronchiolitis. This stance has since changed and the current recommendation is that ribavirin should not be used routinely to treat children with bronchiolitis. It should, however, be considered to treat RSV infection in immunocompromised hosts (Bronchiolitis 2006).

Antibiotics

It is not uncommon for infants with bronchiolitis to receive antibiotic therapy. It is estimated that antibiotics are used in 34%–99% of uncomplicated bronchiolitis (Kabir et al 2003; Vogel et al 2003). This therapy is frequently started because the patient is febrile, but fever per se cannot reliably differentiate viral from bacterial infections (Putto et al 1986). In fact, the risk of bacterial superinfection in infants with bronchiolitis and fever is quite low (0.2%), even when the temperature is $>$39 °C (Willwerth et al 2006). For intubated infants with severe bronchiolitis, the rate of secondary bacterial infection is much higher, and may be as high as 26% (Spurling et al 2007).

When a secondary bacterial infection (SBI) is diagnosed, the most common sites are the urinary tract and the middle ear (Andrade et al 1998; Purcell and Fergie 2004). In particular, infants with SBI are more likely to have a urinary tract infection than bacteremia or meningitis (12% vs 0.43%) (Purcell and Fergie 2004). Acute otitis media (AOM) is also seen as a complication of RSV infection (57%–67%), but its presence does not seem to influence the severity of fever, respiratory distress, or the overall clinical course of the disease (Shazberg et al 2000). In one series, evaluation of middle ear aspirates in children with bronchiolitis revealed RSV in 17 (71%) of 24 patients (Andrade et al 1998). In addition, all patients with acute otitis media had bacterial pathogens isolated, the most common being *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. If present, AOM should be managed according to current AAP recommendations (AOM 2004; Bronchiolitis 2006).

Several prospective RCTs have evaluated the clinical outcomes of infants who received antibiotics for the management of bronchiolitis. As early as 1966, a double blind RCT failed to demonstrate a benefit to treating bronchiolitis with antibiotics (Field et al 1966). Friis et al (1984) evaluated 136 children between the ages of 1 month and 6 years and found no difference in the course of the acute illness, fever relapse, or pulmonary complications in those patients with bronchiolitis who received antibiotics compared with those who did not (Friis et al 1984).

We conclude that antibiotics should be used in patients with bronchiolitis only when specific evidence of coexistent bacterial infection is present and confirmed bacterial infections should be managed no differently than in the absence of bronchiolitis.

Surfactant

Beyond its role of decreasing surface tension in alveoli and bronchioles, thereby improving alveolar and small airway patency, surfactant has protein components (A and D) that bind viral and bacterial surface markers and facilitate their immune-mediated elimination (Ventre et al 2006). In addition, surfactant protein D has been demonstrated to promote alveolar macrophage production of free radicals (LeVine et al 2004). In acute bronchiolitis, there is decreased production of these surfactant proteins, which return to normal levels with the resolution of the illness (Dargaville et al 1996).

Administration of exogenous surfactant to infants with severe respiratory failure due to bronchiolitis seems promising. Several small RCTs have been conducted to evaluate this therapy, with encouraging results. A recent meta-analysis by Ventre et al (2006) included 3 studies with a total of 79 patients. The authors identify decreases in duration of mechanical ventilation and PICU stay. There also seem to be improvements in pulmonary mechanics and gas exchange. It is important to note that the available studies are small

and underpowered, and that additional studies are required. However, exogenous surfactant therapy does appear to hold promise for use in patients with severe respiratory failure due to bronchiolitis.

Heliox

Medical helium for the treatment of upper airway obstruction and asthma was first described by Barach in the 1930s (Barach and Eckman 1936). Heliox is a mixture of helium and oxygen in a 70:30 or 80:20 ratio that maintains greater laminar flow and less turbulence through constricted airways than does nitrogen-oxygen mixtures. This reduces work of breathing and improves ventilation in patients with lower respiratory tract disease. Heliox has been studied in the treatment of bronchiolitis by several investigators, although most of these studies are quite small. Some of the authors have shown small improvements in clinical scores and decreased tachypnea and work of breathing (Hollman et al 1998; Martinon-Torres et al 2002; Cambonie et al 2006).

Liet et al (2005) evaluated rates of positive pressure ventilation in patients receiving heliox therapy vs standard nitrogen-oxygen air and found no difference between the two groups. When heliox therapy was evaluated in intubated children with bronchiolitis, Gross et al found no improvement in ventilation or oxygenation, regardless of the ratio of helium to oxygen employed (50:50, 60:40, or 70:30) (Gross et al 2000).

Heliox equipment is bulky and cumbersome and it can be problematic to administer. Furthermore, given that it is most effective at high helium to oxygen ratios, it is minimally effective in patients with higher oxygen requirements. In summary, the current evidence supporting heliox use for bronchiolitis is sparse, underpowered and conflicting, and therefore larger RCTs are required before it can be recommended for routine use.

Summary

Bronchiolitis is a common lower respiratory tract infection in infants caused by viral agents, the most common of which is RSV. Despite numerous attempts to identify pharmacological therapies to improve the clinical course and outcomes of this disease, the most effective therapy remains supportive care. Careful attention should be focused on maintaining patency of the infant's airway with gentle nasal and pulmonary toilet. Supplemental humidified oxygen is frequently required to maintain oxygen saturations above 92%. Patients should be monitored to ensure adequate fluid and nutrition intake, which may require supplementation with naso-gastric feeds or intravenous fluids. Bronchodilators are not consistently effective, but may have some benefit in selected patients. If given to patients with bronchiolitis, their use should only be continued if objective measures demonstrate improvement in the patients oxygenation or work of breathing. Corticosteroids have not been shown to be effective and are not recommended for routine use. Ribavirin is not recommended for routine use in patients with bronchiolitis, although it may be of benefit in immunocompromised patients. Antibiotics should only be used in the presence of a confirmed bacterial infection. Surfactant and heliox therapies may be tried for the treatment of severe respiratory failure, although additional studies are needed before they can be recommended for routine use.

Disclosures

None of the authors has any conflicts of interest to disclose.

References

Andrade MA, Hoberman A, Glustein J, et al. 1998. Acute otitis media in children with bronchiolitis. *Pediatrics*, 101:617–9.

Aom. 2004. Diagnosis and management of acute otitis media. *Pediatrics*, 113:1451–65.

Auais A, Wedde-Beer K, Piedimonte G. 2005. Anti-inflammatory effect of albuterol enantiomers during respiratory syncytial virus infection in rats. *Pediatr Pulmonol*, 40:228–34.

Barach AL, Eckman M. 1936. The effects of inhalation of helium mixed with oxygen on the mechanics of respiration. *J Clin Invest*, 15:47–61.

Bentur L, Shoseyov D, Feigenbaum D, et al. 2005. Dexamethasone inhalations in RSV bronchiolitis: a double-blind, placebo-controlled study. *Acta Paediatr*, 94:866–71.

Blom D, Ermers M, Bont L, et al. 2007. Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. *Cochrane Database Syst Rev*, CD004881.

Boyce TG, Mellen BG, Mitchel EF Jr, et al. 2000. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. *J Pediatr*, 137:865–70.

Bronchiolitis, AAP Subcommittee on the Diagnosis and Management of Bronchiolitis. (2006). Diagnosis and management of bronchiolitis. *Pediatrics*, 118:1774–93.

Bulow SM, Nir M, Levin E, et al. 1999. Prednisolone treatment of respiratory syncytial virus infection: a randomized controlled trial of 147 infants. *Pediatrics*, 104:e77.

Cambonie G, Milesi C, Fournier-Favre S, et al. 2006. Clinical effects of heliox administration for acute bronchiolitis in young infants. *Chest*, 129:676–82.

Chao LC, Lin YZ, Wu WF, et al. 2003. Efficacy of nebulized budesonide in hospitalized infants and children younger than 24 months with bronchiolitis. *Acta Paediatr Taiwan*, 44:332–5.

Chowdhury D, Al Howasi M, Khalil M, et al. 1995. The role of bronchodilators in the management of bronchiolitis: a clinical trial. *Ann Trop Paediatr*, 15:77–84.

Corneli HM, Zorc JJ, Majahan P, et al. 2007. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med*, 357:331–9.

Dargaville PA, South M, McDougall PN. 1996. Surfactant abnormalities in infants with severe viral bronchiolitis. *Arch Dis Child*, 75:133–6.

Davies HD, Matlow A, Petric M, et al. 1996. Prospective comparative study of viral, bacterial and atypical organisms identified in pneumonia and bronchiolitis in hospitalized Canadian infants. *Pediatr Infect Dis J*, 15:371–5.

De Blic J. 2001. [Use of corticoids in acute bronchiolitis in infants]. *Arch Pediatr*, 8(Suppl)1:49S–54S.

Dobson JV, Stephens-Groff SM, Mcmahon SR, et al. 1998. The use of albuterol in hospitalized infants with bronchiolitis. *Pediatrics*, 101:361–8.

Everard ML, Swarbrick A, Rigby AS, et al. 2001. The effect of ribavirin to treat previously healthy infants admitted with acute bronchiolitis on acute and chronic respiratory morbidity. *Respir Med*, 95:275–80.

Field CM, Connolly JH, Murtagh G, et al. 1966. Antibiotic treatment of epidemic bronchiolitis – a double-blind trial. *Br Med J*, 1:83–5.

Flores G, Horwitz RI. 1997. Efficacy of beta2-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics*, 100:233–9.

Friis B, Andersen P, Brenoe E, et al. 1984. Antibiotic treatment of pneumonia and bronchiolitis. A prospective randomised study. *Arch Dis Child*, 59:1038–45.

Gadomski AM, Lichenstein R, Horton L, et al. 1994. Efficacy of albuterol in the management of bronchiolitis. *Pediatrics*, 93:907–12.

Garrison MM, Christakis DA, Harvey E, et al. 2000. Systemic corticosteroids in infant bronchiolitis: A meta-analysis. *Pediatrics*, 105:E44.

Glezen WP, Taber LH, Frank AL, et al. 1986. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child*, 140:543–6.

Gross MF, Spear RM, Peterson BM. 2000. Helium-oxygen mixture does not improve gas exchange in mechanically ventilated children with bronchiolitis. *Crit Care*, 4:188–92.

Guerguerian AM, Gauthier M, Lebel MH, et al. 1999. Ribavirin in ventilated respiratory syncytial virus bronchiolitis. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med*, 160:829–34.

Hall CB, Douglas RG Jr, Schnabel KC, et al. 1981. Infectivity of respiratory syncytial virus by various routes of inoculation. *Infect Immun*, 33:779–83.

Hall CB, McBride JT, Walsh EE, et al. 1983. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. A randomized double-blind study. *N Engl J Med*, 308:1443–7.

Hall CB, Powell KR, MacDonald NE, et al. 1986. Respiratory syncytial viral infection in children with compromised immune function. *N Engl J Med*, 315:77–81.

Hartling L, Wiebe N, Russell K, et al. 2003. A meta-analysis of randomized controlled trials evaluating the efficacy of epinephrine for the treatment of acute viral bronchiolitis. *Arch Pediatr Adolesc Med*, 157:957–64.

Hartling L, Wiebe N, Russell K, et al. 2004. Epinephrine for bronchiolitis. *Cochrane Database Syst Rev*, CD003123.

Henderson FW, Collier AM, Clyde WA Jr, et al. 1979. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. *N Engl J Med*, 300:530–4.

Hollman G, Shen G, Zeng L, et al. 1998. Helium-oxygen improves Clinical Asthma Scores in children with acute bronchiolitis. *Crit Care Med*, 26:1731–6.

Kabir ML, Haq N, Hoque M, et al. 2003. Evaluation of hospitalized infants and young children with bronchiolitis – a multi centre study. *Mymensingh Med J*, 12:128–33.

Klassen TP, Rowe PC, Sutcliffe T, et al. 1991. Randomized trial of salbutamol in acute bronchiolitis. *J Pediatr*, 118:807–11.

Kristjansson S, Lodrup Carlsen KC, Wennergren G, et al. 1993. Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers. *Arch Dis Child*, 69:650–4.

Leader S, Kohlhase K. 2003. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*, 143: S127–32.

Levine AM, Elliott J, Whitsett JA, et al. 2004. Surfactant protein-d enhances phagocytosis and pulmonary clearance of respiratory syncytial virus. *Am J Respir Cell Mol Biol*, 31:193–9.

Liet JM, Millotte B, Tucci M, et al. 2005. Noninvasive therapy with helium-oxygen for severe bronchiolitis. *J Pediatr*, 147:812–7.

MacDonald NE, Hall CB, Suffin SC, et al. 1982. Respiratory syncytial viral infection in infants with congenital heart disease. *N Engl J Med*, 307:397–400.

Martinon-Torres F, Rodriguez-Nunez A, Martinon-Sanchez JM. 2002. Heliox therapy in infants with acute bronchiolitis. *Pediatrics*, 109:68–73.

Meert KL, Sarnaik AP, Gelmini MJ, et al. 1994. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double-blind, randomized trial. *Crit Care Med*, 22:566–72.

Menon K, Sutcliffe T, Klassen TP. 1995. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr*, 126:1004–7.

Moler FW, Bandy KP, Custer JR. 1991. Ribavirin therapy for acute bronchiolitis: need for appropriate controls. *J Pediatr*, 119:509–10.

Mullins JA, Lamonte AC, Bresee JS, et al. 2003. Substantial variability in community respiratory syncytial virus season timing. *Pediatr Infect Dis J*, 22:857–62.

Numa AH, Williams GD, Dakin CJ. 2001. The effect of nebulized epinephrine on respiratory mechanics and gas exchange in bronchiolitis. *Am J Respir Crit Care Med*, 164:86–91.

Patel H, Platt R, Lozano JM, et al. 2004. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev*, CD004878.

Purcell K, Fergie J. 2004. Concurrent serious bacterial infections in 912 infants and children hospitalized for treatment of respiratory syncytial virus lower respiratory tract infection. *Pediatr Infect Dis J*, 23, 267–9.

Putto A, Ruuskanen O, Meurman O. 1986. Fever in respiratory virus infections. *Am J Dis Child*, 140:1159–63.

Rodriguez WJ, Kim HW, Brandt CD, et al. 1987. Aerosolized ribavirin in the treatment of patients with respiratory syncytial virus disease. *Pediatr Infect Dis J*, 6:159–63.

Sabogal C, Auais A, Napchan G, et al. 2005. Effect of respiratory syncytial virus on apnea in weanling rats. *Pediatr Res*, 57:819–25.

Schuh S, Canny G, Reisman JJ, et al. 1990. Nebulized albuterol in acute bronchiolitis. *J Pediatr*, 117:633–7.

Schuh S, Coates AL, Binnie R, et al. 2002. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. *J Pediatr*, 140:27–32.

Schweich PJ, Hurt TL, Walkley EI, et al. 1992. The use of nebulized albuterol in wheezing infants. *Pediatr Emerg Care*, 8:184–8.

Shay DK, Holman RC, Newman RD, et al. 1999. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA*, 282:1440–6.

Shay DK, Holman RC, Roosevelt GE, et al. 2001. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979–1997. *J Infect Dis*, 183:16–22.

Shazberg G, Revel-Vilk S, Shoseyov D, et al. 2000. The clinical course of bronchiolitis associated with acute otitis media. *Arch Dis Child*, 83:317–9.

Simoes EA. 1999. Respiratory syncytial virus infection. *Lancet*, 354:847–52.

Smith DW, Frankel LR, Mathers LH, et al. 1991. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med*, 325:24–9.

Spurling GK, Fonseka K, Doust J, et al. 2007. Antibiotics for bronchiolitis in children. *Cochrane Database Syst Rev*, CD005189.

Stang P, Brandenburg N, Carter B. 2001. The economic burden of respiratory syncytial virus-associated bronchiolitis hospitalizations. *Arch Pediatr Adolesc Med*, 155:95–6.

Taber LH, Knight V, Gilbert BE, et al. 1983. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. *Pediatrics*, 72:613–8.

Teeratakulpisarn J, Limwattananon C, Tanupattarachai S, et al. 2007. Efficacy of dexamethasone injection for acute bronchiolitis in hospitalized children: a randomized, double-blind, placebo-controlled trial. *Pediatr Pulmonol*, 42:433–9.

Ventre K, Haroon M, Davison C. 2006. Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database Syst Rev*, 3, CD005150.

Vogel AM, Lennon DR, Harding JE, et al. 2003. Variations in bronchiolitis management between five New Zealand hospitals: can we do better? *J Paediatr Child Health*, 39:40–5.

Wainwright C, Altamirano L, Cheney M, et al. 2003. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med*, 349:27–35.

Wang EE, Milner R, Allen U, et al. 1992. Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial. *Arch Dis Child*, 67:289–93.

Willwerth BM, Harper MB, Greenes DS. 2006. Identifying hospitalized infants who have bronchiolitis and are at high risk for apnea. *Ann Emerg Med*, 48:441–7.

Wright AL, Taussig LM, Ray CG, et al. 1989. The Tucson Children's Respiratory Study. II. Lower respiratory tract illness in the first year of life. *Am J Epidemiol*, 129:1232–46.