Controversies in the treatment of bronchiolitis

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Purpose of review

Bronchiolitis is a very common and potentially serious respiratory disease of young children. To date, there is not a single, widely practiced, evidence-driven treatment approach. This review summarizes important recently published studies on the treatment of acute bronchiolitis for both outpatients and hospitalized children.

Recent findings

Bronchodilators, epinephrine, and corticosteroids have all been used in the treatment of bronchiolitis. As with older studies, most recently published randomized clinical trials have failed to demonstrate clinical efficacy in the use of these medications to treat either outpatients or infants hospitalized with bronchiolitis. Further, several meta-analyses and systematic reviews on this subject have been published in the last year or 2. Once again, most fail to provide convincing evidence to support the routine use of these medications to treat bronchiolitis.

Summary

The routine and repetitive use of bronchodilators, epinephrine, or corticosteroids to treat bronchiolitis in the absence of demonstrated clinical benefits for individual patients is not justified.

Keywords

bronchiolitis, bronchodilators, epinephrine, corticosteroids

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Introduction

Bronchiolitis is a significant health problem among young children and is the leading cause of hospitalization in infants [1••,2•]. In the United States between 1997 and 2000, there were more than 700,000 emergency department visits by infants with lower respiratory infection diagnoses during the RSV season, and 29% were admitted [1••]. Costs of these emergency department visits were more than $200 million, and hospital charges were more than $2.5 billion [1••].

Clinicians have various treatment options at their disposal, including supplemental oxygen, fluids, bronchodilators, epinephrine, and corticosteroids, and there is wide variation in treatment practices [3•]. The Agency for Healthcare Research and Quality recently reviewed the efficacy of these and other therapies. The only treatments classified as having "clear evidence for effectiveness" were supportive care and supplemental oxygen [4]. Optimal management beyond that remains elusive because research results have led to conflicting recommendations.

Bronchodilators

For the purposes of this discussion, *bronchodilators* are defined as pure β-agonists; epinephrine is discussed separately. There is considerable debate and disagreement about the role of bronchodilators to treat bronchiolitis. Some believe that airway obstruction is caused primarily by cellular debris in the bronchioles and, as such, bronchodilators have little effect on clinical course. Others believe that the use of bronchodilators does improve expiratory flow [5] or cite anecdotal experience of clinical benefits. There have been few recent studies on this topic, and most of the older studies failed to show a clinical benefit [6–8]. This article reviews the largest and best-designed older randomized trials, presents the results of the most recent clinical study, and discusses the results of a recent systematic review.

In two similar studies, Gadomski *et al.* [6,7] assessed both treatment effects and route of administration by randomizing emergency department patients to one of four treatment arms: nebulized albuterol, saline placebo, oral albuterol, or placebo. In each trial, there were no appreciable differences in any of the main study outcomes. Of interest is that, in the second study, 41 children with a history of recurrent wheezing were treated with nebu-

lized albuterol and compared with 128 children wheezing for the first time [7]. Those with a previous history of wheezing had a significantly greater degree of improvement in clinical score (8 *vs* 4 points) at 60 minutes. Based on these data, the authors recommended albuterol only for those infants with a previous history of wheezing.

Another group of investigators assessed the efficacy of sustained bronchodilator therapy for hospitalized infants [8]. Subjects were treated with nebulized bronchodilators every 2 hours for the first 24 hours and then every 4 hours for the next 48 hours. Once again, there were no significant differences between the two groups in any outcome measure including oxygen saturation, time to reach discharge criteria, or length of stay. These authors stated that the routine use of albuterol in the hospital setting was not supported.

Most published trials among outpatients have assessed the efficacy of aerosolized bronchodilators in preventing the need for hospitalization. However, in 2004, Patel *et al.* [9••] studied the use of oral albuterol versus placebo among children discharged home after an emergency department visit. By parental report, there were no differences between the two groups in time to symptom resolution or any secondary outcome measure. Of note is that, on average, symptom resolution took 9 days, underscoring the prolonged duration of symptoms for many children. Most clinicians who use bronchodilators to treat infants with bronchiolitis choose aerosolized therapy. Compared with systemic bronchodilator therapy, aerosolized therapy has a more rapid onset of action and fewer adverse effects.

A systematic review published in 2004 found that among seven studies assessing the need for or length of hospitalization, none showed a bronchodilator benefit [10••]. Similarly, just three of 12 studies demonstrated a short-term benefit to the use of nebulized bronchodilator compared with placebo [10••]. These results were similar to those of a meta-analysis that included 251 outpatients and "revealed that short-term beta-agonist therapy had no impact on the hospitalization rate or respiratory rate, and had a statistically significant but clinically insignificant impact on oxygen saturation and heart rate" [11].

Epinephrine

Epinephrine causes decreased airway mucosal edema via its α-adrenergic effects and bronchodilation by way of β-adrenergic activity. Some investigators have described better outcomes for infants hospitalized with bronchiolitis treated with epinephrine compared with treatment with selective β-agonists [12,13]. Menon *et al.* [14] conducted a randomized, blind trial comparing epinephrine with salbutamol in the treatment of 41 emergency department patients. Those treated with epinephrine had a significantly lower admission rate (33% *vs* 81%). However, it is difficult to account for this markedly lower hospitalization rate. There were no significant differences between the two groups in respiratory distress scores or respiratory rates at any time. Also, although epinephrine-treated infants had higher mean oxygen saturation after 60 minutes, this was not sustained at 90 minutes.

Since 2002, there have been six published randomized trials assessing the use of epinephrine in the treatment of bronchiolitis, and most have failed to duplicate the findings of Menon *et al.* [14] (Table 1). Patel *et al.* [15] treated hospitalized infants with epinephrine, albuterol, or placebo. Infants treated with either epinephrine or albuterol fared no better than those treated with placebo, and these authors recommended not using either drug for infants hospitalized with bronchiolitis. Of note is that infants received nebulizations every 1 to 6 hours, but the frequency was not standardized. That infants could potentially receive less effective therapy more frequently would tend to drive the results to the null hypothesis. Also, study children were assessed only twice daily; perhaps more frequent assessments would have provided more accurate data on time that criteria for discharge were met. This study had an 80% power to demonstrate a 30-hour difference in length of stay. Thus, smaller but clinically important length of stay differences might have been missed.

Two recent studies of similar design had conflicting results [16,17••]. A study from India demonstrated a benefit of epinephrine compared with salbutamol among children in the emergency department [16]. After three doses of study drugs, all outcome measures assessed, except heart rate, favored the use of epinephrine. However, investigators were not blind to treatment assignments. Also, there may have been some children with asthma enrolled in this study, because children with one previous episode of wheezing were not excluded, and children as old as 24 months were enrolled. In contrast, Mull *et al.* [17••] did not demonstrate a clear epinephrine benefit compared with albuterol among children in the emergency department treated with three nebulizations. These investigators were blind, and enrollment criteria were stringent enough to exclude infants without bronchiolitis. These authors used a high dose of racemic epinephrine, so it is not likely that the lack of an epinephrine benefit was caused by underdosing. In a recently published randomized, placebo-controlled trial, the administration of two doses of nebulized epinephrine did not result in a decreased need for hospitalization among infants in the emergency department with bronchiolitis [18•].

No benefit of epinephrine over placebo was demonstrated in a small study of inpatients [19]. Finally, a multicenter trial of 194 hospitalized infants compared epinephrine with placebo in a randomized, blind fashion

Table 1. Epinephrine in the treatment of bronchiolitis

Author, year	Design	Number	Population	Comparison	Findings
Patel, et al., 2002 [15]	Double-blind, placebo-controlled RCT	149	Inpatients	Epinephrine and albuterol and placebo	• No differences in length of stay • No differences in any secondary outcome measure
Ray and Singh, 2002 [16]	Unblinded RCT	91	ED patients	Epinephrine and salbutamol	• Epinephrine group had a lower hospitalization rate, lower mean respiratory rate, and greater improvements in clincial score and oxygen saturation
Mull, et al 2004 [17••]	Double-blind RCT	66	ED patients	Epinephrine and albuterol	• No differences in hospitalization rate, mean clincial scores, mean respiratory rates, or mean oxygen satruation • Epinephrine group met ED discharge criteria sooner
Hariprakash, et al., 2003 [18•]	Double-blind, placebo-controlled	75	ED patients	Epinephrine and placebo	• No differences in hospitalization rate, mean clinical scores, mean respiratory rates, or mean oxygen saturation
Bul-Ainine, et al., 2002 [19]	Double-blind, placebo-controlled RCT	38	Inpatients	Epinephrine and placebo	• No differences in mean clinical scores, mean respiratory or heart rates, or mean oxygen saturation
Wainwright, et al., 2003 [20••]	Double-blind, placebo-controlled RCT	196	Inpatients	Epinephrine and placebo	• No differences in length of stay, time ready for discharge, admission to the intensive care unit, or need for mechanical ventilation

RCT = randomized controlled trial.

[20••]. This study design improved on that of previous work by assessing a large sample size, including only those who had wheezed previously, and standardizing the postadmission management by use of a clinical pathway. The treatment group received three 4-mg doses of nebulized epinephrine at 4-hour intervals. These authors found no epinephrine benefits in any of the study outcomes. They concluded that epinephrine does not produce a clinically relevant improvement in clinical status among infants hospitalized with bronchiolitis.

In 2004, a systematic review of the use of epinephrine in bronchiolitis included eight randomized controlled trials and 660 children [10••]. These authors concluded that "few results favoring nebulized epinephrine emerged, and most outcomes reported were short-term" [10••]. The sum total of these data cast doubt on the efficacy of epinephrine for the treatment of bronchiolitis in either the emergency department or the inpatient setting. Additionally, those managing outpatients with bronchiolitis must use nebulized epinephrine with caution. Clinicians should be concerned that patients may experience transient clinical benefits, be discharged home, and then worsen as the effect of epinephrine wanes. Because the epinephrine therapy cannot be provided at home, caretakers would not be able to duplicate the benefits that had been achieved earlier.

Corticosteroids

Once infants with bronchiolitis become symptomatic, the inflammatory cascade is well-established [21•], raising doubt that anti-inflammatory agents like corticosteroids could influence clinical course. In fact, until very recently, there had been little evidence to support the use of corticosteroids in the treatment of infants with bronchiolitis [22–24].

More recently, 70 children younger than 2 years and presenting to the emergency department with bronchiolitis were studied [25]. Those with moderate or severe symptoms were randomized to receive either 1 mg/kg oral dexamethasone or placebo, along with nebulized albuterol. The dexamethasone-treated children experienced significantly better outcomes within 4 hours as measured by bronchiolitis scores and a hospitalization rate that was less than half that of placebo-treated children. A critique of this work reveals that the dose of dexamethasone chosen for this study was equivalent to approximately 5 mg/kg prednisone, considerably higher than the 2 mg/kg recommended by the National Institutes of Health for children with acute asthma. A concern of administering such a high dose to large numbers of sick infants is an increased risk of bacterial superinfection [26]. Additionally, the corticosteroid benefit may have been nonspecific; the antipyretic effect of dexamethasone may have led to less tachypnea and improved clinical scores [26].

Csonka *et al.* [27•] randomized 230 children 6 to 35 months old with viral-induced wheezing to receive either prednisone or placebo. In this study from Finland, prednisone-treated children had better outcomes, although they did not have lower hospitalization rates. However, fully 59% of enrolled subjects had wheezed previously; it

should not be surprising that a prednisone benefit was demonstrated among those who may have early reactive airway disease.

An earlier meta-analysis in which the results of six small studies were pooled demonstrated a statistically significant but qualitatively small corticosteroid benefit [28]. A careful assessment of these data suggests that the results may have been driven by benefits to children who were ventilated or who had wheezed previously. Two separate systematic reviews were published in 2004 [10••,29••]. King *et al.* [10••] found that "the preponderance of evidence does not favor the use of corticosteroids to decrease hospitalization." Separately, studies using inhaled corticosteroids "did not demonstrate a benefit for either hospitalization or most symptom scores" [10••]. The review by Patel *et al.* [29••] included 13 trials and 1198 children. They found "no benefits in either length of stay or clinical scores" and "no differences in respiratory rate, hemoglobin oxygen saturation, hospital revisit, or readmission rates" in children treated with systemic glucocorticoids [29••].

Conclusion

It is fairly remarkable to consider that even though bronchiolitis is the most common cause of wheezing in infants and even though infants with bronchiolitis have been enrolled in scores of published studies, fundamental disagreements regarding appropriate initial treatment remain. Randomized controlled trials, meta-analyses, and systematic reviews have failed to demonstrate a clear and consistently reproducible benefit to treatment with bronchodilators, epinephrine, or corticosteroids. This is true independent of route of medication delivery or dose and is true for infants presenting for emergency department care and the subset of children ill enough to require hospitalization.

The studies discussed in this review would seem to support a clinical practice guideline that was developed for the treatment of infants hospitalized with bronchiolitis [30]. Key aspects of these guidelines, as they relate to treatment with medications, are summarized in Table 2. Three years after implementation of the guidelines, the researchers noted significant reductions in hospital length of stay, the use of β-agonist inhalations, and mean costs, without a corresponding increase in readmission rates [31].

Table 2. Bronchiolitis Guideline Highlights

- The routine use of bronchodilator aerosol therapy is not recommended
- Steroids by inhalation are not recommended
- Epinephrine by inhalation may be considered in selected patients
  - If within 60 minutes of a trial inhalation therapy there is not significant improvement, it is recommended that the therapy not be repeated

In contrast with asthma, the lack of proven efficacy of these therapies in bronchiolitis may be a result of the underlying pathophysiology of the disease. Alternatively, there may be other, yet to be determined, factors at play that remain areas in which future research may be focused. Increased respiratory rates, short inspiratory time, and low tidal volumes make delivery of aerosolized medication to infants extremely inefficient. It is difficult to assess young infants, because clinical scores only approximate clinical status. Also, what impact, if any, that phase of illness has on the likelihood of response to treatment is not well studied.

Given the costs, side effects, and unproven benefit of medications traditionally used to treat bronchiolitis, their routine and repetitive use for all patients is not justified. However, it is not unreasonable to initiate a trial with a bronchodilator and/or epinephrine on an individualized basis. If the therapy is judged to be ineffective, it should be discontinued. The subset of children with more severe disease or risk factors for adverse outcomes such as very young age or prematurity need to be hospitalized for hydration, oxygenation, and supportive care.

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- • Of special interest
- •• Of outstanding interest

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