

# Managing Bronchiolitis in Pediatric Patients: Current Evidence

Subhranshu Sekhar Dhal, Hiremath Sagar<sup>1</sup>

Department of Paediatrics, Mazumdar Shaw Medical Centre, Paediatric Intensive Care Unit, Narayana Health City, <sup>1</sup>Department of Paediatrics, Mazumdar Shaw Medical Centre, Narayana Health City, Bengaluru, Karnataka, India

## Abstract

**Background:** Acute bronchiolitis is an inflammatory process affecting small airways. Although most cases are self-limiting, it is still one of the most common causes of hospitalization below 24 months of age. Treatment is mainly supportive. The purpose of this narrative review was to look for recent evidence in the management of bronchiolitis. **Methods:** PubMed, EMBASE, Global Health, MEDLINE, SCOPUS, and Cochrane database searches were performed using keywords such as bronchiolitis, management, bronchodilators, nebulized epinephrine, corticosteroids, and hypertonic saline. Systematic reviews, original articles, and clinical practice guidelines with evidence for bronchiolitis management were included during our search. We excluded guidelines and clinical trials which solely focused on high-risk children, articles by a single author, and trials that are not part of a clinical practice guideline. **Discussion:** The safety and efficacy of various therapies for bronchiolitis such as bronchodilators, epinephrine, hypertonic saline, and corticosteroid were analyzed. Bronchodilators have not shown consistent benefits in bronchiolitis and may be tried in the selected population. Current evidence does not suggest routine use of nebulized epinephrine in bronchiolitis except as rescue therapy in selected cases. Hypertonic saline showed positive results in some studies but questions still remain regarding its effectiveness in all. Recent trials also do not support the use of systemic or inhaled corticosteroids in bronchiolitis. **Conclusion:** In conclusion, there is no strong evidence to routinely recommend the use of bronchodilator, epinephrine, hypertonic saline, or corticosteroids in acute bronchiolitis. Supportive care still remains the mainstay of therapy for bronchiolitis.

**Keywords:** Bronchiolitis, bronchodilator, epinephrine, hypertonic saline

## INTRODUCTION

Acute bronchiolitis is an inflammatory process affecting small airways of the lungs and predominantly affects children below 24 months of age. Although most cases are self-limiting, it still remains one of the most common causes of hospitalization in this age group. Respiratory syncytial virus (RSV) is the most common etiology of bronchiolitis with other viral etiologies being parainfluenza A and B, influenza A and B, human metapneumovirus, coronavirus, adenovirus, and rhinovirus.<sup>[1]</sup> RSV is quite common in India accounting for 30%–70% of cases of bronchiolitis as per various Indian studies.<sup>[2]</sup> RSV mainly peaks between the rainy and winter seasons, that is from September to March.<sup>[2,3]</sup>

The child with bronchiolitis initially develops cough and coryza followed by a fever that lasts for 1–3 days, later on progressing to severe respiratory distress in some cases. The time to peak symptoms is 4 days and is associated with the peak viral load; however, this may vary from infant to infant.<sup>[4]</sup> Physical findings in severe cases include poor feeding, tachypnea, chest

retractions, use of accessory muscles, hyperinflation of the chest, and reduced oxygen saturation. Increased respiratory rate is an important marker of disease severity while apnea is a red flag sign for impending respiratory failure.<sup>[5]</sup> The disease burden of bronchiolitis and its economic impact is also quite high. In 2019, globally 33 million RSV-associated lower respiratory tract infections were reported among which 3.6 million cases needed hospitalization with 26,300 deaths.<sup>[6]</sup> Each year, the number of admissions to hospitals is increasing. As per the study which collected data from the Australia and New Zealand Pediatric Intensive Care Registry, bronchiolitis admission rates per 1,00,000 population of <24 months

**Address for correspondence:** Dr. Hiremath Sagar, Room No – C 12, First Floor, Department of Pediatrics, Mazumdar Shaw Medical Centre, Narayana Health City, Bommasandra, Anekal Taluk, Bengaluru - 560 099, Karnataka, India.  
E-mail: docsagar2002@yahoo.co.in

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increased from 62.5 in 2002 to 208 in 2014.<sup>[7]</sup> Every year, managing children with bronchiolitis cost millions of dollars.<sup>[8]</sup>

Although bronchiolitis remains a cause of high admission rate and high economic burden, still the treatment remains mainly supportive with respiratory support ranging from nasal prong oxygen, high-flow nasal cannula oxygen to mechanical ventilation and maintenance of hydration.<sup>[9]</sup>

Many other treatment options such as bronchodilators, nebulized epinephrine, nebulized hypertonic saline, and steroids have been studied with varying results. The current review was to look for recent evidence in the treatment of bronchiolitis with these equivocal therapeutic options.

## METHODS

### Literature review

Literature databases such as PubMed, EMBASE, Global Health, MEDLINE, and SCOPUS were used during our evidence search. The area of focus was the management of bronchiolitis. Recent evidence was extracted over the past 20 years from the English-published literature. In addition to the Cochrane database of systematic reviews was included during our search.

### Search terms

The following keywords (including specific Medical Subject Headings): bronchiolitis, management, bronchodilators, nebulized epinephrine, hypertonic saline, and corticosteroids were used for searching publication.

### Eligibility criteria

Systematic reviews, original articles, and clinical practice guidelines with evidence for bronchiolitis management were included during our search. We excluded guidelines and clinical trial which are solely focusing on high-risk children, articles by a single author, and trials that are not part of a clinical practice guideline. Evidences were extracted by two independent reviewers, and later on, compiled into a single template, and disagreements were resolved with regard to eligibility criteria.

## DISCUSSION

### Bronchodilators

Many patients with bronchiolitis have wheeze and air trapping which has been considered a rationale for therapy with bronchodilators such as salbutamol and ipratropium bromide. Del Vecchio *et al.* in their retrospective study on the use of albuterol in young infants admitted with RSV bronchiolitis found that albuterol was not useful and in fact may be harmful with regard to increased supplemental oxygen used due to ventilation-perfusion mismatch.<sup>[10]</sup> Karadag *et al.* did a prospective double-blind placebo-controlled trial, wherein one group received nebulized salbutamol and ipratropium bromide and the other received a placebo. They concluded that in infants with first-time bronchiolitis severe enough to need

admission, bronchodilator therapy improved clinical scores and oxygenation during the first 24 h of disease onset but did not reduce the duration of hospitalization.<sup>[11]</sup> Patel *et al.* in their double-blind randomized control trial (RCT) compared oral albuterol with placebo with respect to the resolution of illness as the primary outcome. The study did not reveal any significant difference between the two groups.<sup>[12]</sup> Levin *et al.* in their prospective-blinded RCT showed no benefit in the bronchodilators arm rather pointed out significant tachycardia in the intervention group than placebo.<sup>[13]</sup>

Cochrane database systematic review by Gadomski and Scribani which included 30 trials and 1992 infants compared bronchodilators (other than epinephrine) with placebo. The authors concluded that bronchodilators are neither effective in routine management nor do they reduce the duration of hospitalization. The drawback of this review was the small sample sizes and the lack of a standardized study design.<sup>[14]</sup> Although many studies have shown no benefit of bronchodilators in bronchiolitis there is a possibility that it may be beneficial in a subgroup of patients with bronchiolitis. These subgroups would be infants with bronchiolitis above 6 months of age, bronchiolitis during nonpeak months, and infants with bronchiolitis and having atopic features or having a family history of asthma in first-degree relatives.<sup>[15,16]</sup>

The reason for variable results and nonresponsiveness of bronchodilators are due to the small sample size, different molecules used, and different causes of wheezing clubbed together and used in differing conditions. Furthermore, the pathophysiology of wheezing in bronchiolitis is complex and involves intraluminal blockage due to mucus plug, debris, and mucosal edema leading to unresponsiveness to bronchodilators. Hence, bronchodilators should not be used routinely in bronchiolitis patients, however, can be considered in the selected population as mentioned above. If there occurs a positive response in the form of improvement in respiratory status, it can be continued. On the other hand, if no response is noted to the bronchodilator, it should be discontinued.

### Epinephrine

Nebulized epinephrine has been used in bronchiolitis as it is not only a bronchodilator but also reduces mucosal edema. Hartling *et al.* in their systematic review and meta-analyses found epinephrine nebulization to reduce the admission on day 1 of illness but did not find any benefit in the inpatient group with respect to the length of hospital stay.<sup>[17]</sup> Wainwright *et al.* in their RCT of nebulized epinephrine in bronchiolitis did not find any significant reduction in length of hospital stay.<sup>[18]</sup> Another double-blind RCT conducted by Skjerven *et al.* which compared inhaled racemic epinephrine with inhaled saline did not show any significant difference in length of hospital stay.<sup>[19]</sup> The Canadian Bronchiolitis Epinephrine Steroid Trial compared hospitalization rates over 7 days. This study had four arms: nebulized epinephrine plus oral dexamethasone, nebulized epinephrine plus oral placebo, nebulized placebo plus oral dexamethasone, and nebulized

placebo plus oral placebo. Infants who received epinephrine with corticosteroids had a lower hospitalization rate by day 7 but the effect was statistically nonsignificant when adjusted for multiple variables.<sup>[20]</sup> A similar trial called BI-PED study is being carried out across 11 centers in Canada, Australia, and New Zealand with a sample size of around 1616 babies which may give further evidence on the use of nebulized epinephrine and oral steroid in combination.<sup>[21]</sup>

A recent case report of an otherwise healthy infant who developed unstable ventricular tachycardia after a single dose of nebulized epinephrine highlights the notion that no intervention is benign.<sup>[22]</sup> Gelbart *et al.* in a recent study showed oral prednisolone with nebulized epinephrine reduced the duration of positive pressure support (high-flow nasal prong oxygen, nasopharyngeal continuous positive airway pressure, or mechanical ventilation) as compared with placebo (26 h vs. 40 h,  $P=0.001$ ).<sup>[23]</sup> Current evidence does not support the routine use of nebulized epinephrine in bronchiolitis except as rescue therapy.

### Hypertonic saline

Hypertonic saline helps in bronchiolitis by hydrating airway surface liquid, reducing airway edema, and improving mucus clearance by mechanisms such as improving mucus rheology and increasing ciliary beat frequency.<sup>[24]</sup> Miraglia Del Giudice *et al.* in a randomized study compared 3% saline with 0.9% saline in addition to epinephrine nebulizations in both groups. The patients in the 3% saline group had a shorter length of stay in the hospital ( $4.9 \pm 1.3$  days vs.  $5.6 \pm 1.6$  days,  $P < 0.05$ ) and also had a better clinical response score.<sup>[25]</sup> Flores-González *et al.* compared 3% hypertonic saline with epinephrine and standalone 3% hypertonic saline and found that the combination reduced the length of stay in the hospital and also improved the clinical scores of severity from 3<sup>rd</sup> day of treatment.<sup>[26]</sup>

Wu *et al.* compared 3% saline with 0.9% saline in bronchiolitis patients attending the emergency department. They concluded that 3% saline reduced admission rates but did not significantly reduce the duration of hospital stay or Respiratory Distress Assessment Instrument score.<sup>[27]</sup> An RCT conducted by Sharma *et al.* which compared 3% saline versus 0.9% saline did not show any significant difference in duration of hospital stay or clinical severity scores.<sup>[28]</sup> In a prospective double-blind RCT, Silver *et al.* compared 3% saline with 0.9% saline in in-Patient bronchiolitis. Results were nonsignificant in terms of length of stay or day 7 readmission rates.<sup>[29]</sup> While most studies used 3% saline, Jacobs *et al.* used 7% saline and compared it with 0.9% saline. However, the study did not show any significant difference between bronchiolitis severity score which was the primary outcome, and secondary outcomes such as rate of hospitalization and length of emergency department or hospital stay.<sup>[30]</sup>

Cochrane review by Zhang *et al.* which included 28 trials and 4195 infants suggested hypertonic saline nebulizations may modestly reduce the duration of hospital stay and

improve clinical severity scores in infants admitted with bronchiolitis. It also suggested a reduction in the risk of hospitalization among outpatient and emergency department patients. However, the review also mentioned that the quality of evidence was low to moderate, thus routine use of hypertonic saline in infants with bronchiolitis could not be recommended.<sup>[31]</sup> Another recently updated meta-analysis on hypertonic saline in bronchiolitis concluded hypertonic saline should not be used and needs to be further studied in infants with bronchiolitis.<sup>[32]</sup> Trial sequential analysis was conducted by Harrison *et al.* to determine whether existing literature was sufficient to prove the effectiveness of hypertonic saline in bronchiolitis. The trial sequential analysis suggested the information or sample size available in the literature is far less than what would be needed to conclude the effectiveness of hypertonic saline in reducing the hospitalization rates and length of hospital stay. The authors concluded that the beneficial effect of hypertonic saline in bronchiolitis potentially represents type 1 error.<sup>[33]</sup>

Hence, the current evidence for use of hypertonic saline in bronchiolitis seems inconclusive and further studies with adequate sample sizes are needed to evaluate its efficacy.

### Corticosteroids

Bronchiolitis has significant airway inflammation which can be treated by corticosteroids through its anti-inflammatory effect and its ability to reduce airway edema and decrease mucus production. A study by Alansari *et al.*, in which oral dexamethasone was used showed shortened time to readiness for discharge; however, the patient population in this group had eczema and a family history of asthma in a first-degree relative.<sup>[34]</sup> The Canadian Bronchiolitis Epinephrine Trial mentioned in the epinephrine section suggested a combination of dexamethasone- and nebulized epinephrine-reduced hospitalization rate but the authors in conclusion mentioned that the result should be considered exploratory and need further study with adequate power to confirm the results.<sup>[20]</sup> One single-center and one large multicenter RCT by Mesquita *et al.* and Corneli *et al.* which studied a single dose of oral dexamethasone versus placebo in reducing the rate of hospitalization did not show any benefit with oral dexamethasone.<sup>[35,36]</sup>

The most recent Cochrane review by Fernandes *et al.* which included 17 RCT and 2596 patients showed no significant reduction in hospitalization rates and length of hospital stay by either inhaled or systemic glucocorticoids.<sup>[37]</sup> Kua and Lee in their systematic review on efficacy and safety of combined epinephrine and corticosteroid therapy concluded that the combination was ineffective in reducing the hospital admission and length of hospital stay.<sup>[38]</sup> Inhaled corticosteroids have also been used during and after bronchiolitis to study their effectiveness to prevent recurrent wheeze postbronchiolitis. However, none of the studies showed any benefit.<sup>[39-41]</sup> Summarizing all, current evidence does not support the use of systemic or inhaled corticosteroids in bronchiolitis.



## CONCLUSION

In conclusion, there is no new strong evidence to routinely recommend the use of bronchodilators, epinephrine, hypertonic saline, or corticosteroids in infants and children with acute bronchiolitis. However, bronchodilators may have a role in a selected population of bronchiolitis such as infants more than 6 months, bronchiolitis during nonpeak months, and infants having atopic features or having a family history of asthma in first-degree relatives. Further large studies are needed to decide the beneficence or nonbeneficence of these interventions in bronchiolitis. Till then supportive care will remain the mainstay of therapy for bronchiolitis.

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## Conflicts of interest

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