Use of β_2-agonists for viral bronchiolitis

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Abstract

Question A 9-month-old baby presented to my rural emergency department with 2 days of cough and congestion and 1 day of breathing difficulties in the month of February. An auscultation examination of the lungs indicated there were scattered, faint wheezes and coarse sounds. Based on the baby's age, symptomatology, and the winter season, the likely diagnosis was bronchiolitis. Are inhaled β_2-agonists an appropriate treatment for this patient?

Answer The use of inhaled β_2-agonists in children younger than 2 years of age with bronchiolitis is not indicated. Wheezing is most commonly part of the diagnosis of bronchiolitis, a lower respiratory viral infection in young children. Unlike with asthma, smooth muscle constriction in the lungs is not a symptom of bronchiolitis. Treatment of bronchiolitis requires supportive care, but pharmaceutical interventions such as β_2-agonists, steroids, and antibiotics have not been shown to decrease length of illness, illness severity, or hospitalization rates. There may be a subgroup of infants with bronchiolitis who respond to β_2-agonists treatment; however, this group has not been fully identified in the literature to date.

Bronchiolitis, an inflammation and obstruction of the lower airways, affects children younger than 2 years of age and is almost always secondary to a viral infection. It commonly starts with upper respiratory symptoms including cough, congestion, and rhinorrhea. Owing to collection of mucus, sloughing of epithelial cells, and inflammation in the lower airways, the condition may progress to respiratory distress and hypoxemia. Auscultation examinations of the lungs frequently indicate wheezing or coarse sounds, and infants with more severe illness may present with respiratory distress. Human respiratory syncytial virus (HRSV) is the most common trigger for bronchiolitis, accounting for up to 80% of cases.[1,2] Bronchiolitis is one of the most common reasons infants seek medical care and the most common cause of hospitalizations in children younger than 12 months of age in Canada and around the world.[2,3] Accepted standard of care for bronchiolitis is supportive care, including hydration, gentle suctioning of secretions, and oxygen administration for those with hypoxia.[1,3]

Racemic epinephrine, antibiotics, β_2-agonists, and corticosteroids have all been studied for the treatment of bronchiolitis in inpatient and outpatient settings. Yet, none of these therapies are indicated in the treatment of acute bronchiolitis. In a recent meta-analysis[4] of 150 randomized controlled trials (RCTs) with nebulized treatments or placebo for bronchiolitis, 76% of more than 19,000 patients had moderate bronchiolitis, as determined by either narrative statements or clinical scores (19% did not list illness severity). Hospital admission rates after initial visits to the emergency department were significantly lower among those treated with a combination of nebulized hypertonic saline and β_2-agonists (odds ratio [OR]=0.44, 95% CI 0.23 to 0.84) and among those treated with nebulized epinephrine alone (OR=0.64, 95% CI 0.44 to 0.93) compared with those receiving nebulized placebo. Infants had shorter lengths of stay in hospital when they received nebulized hypertonic saline alone (mean difference [MD]=-0.63 days, 95% CI -1.02 to -0.25) or when combined with nebulized epinephrine (MD=-0.91 days, 95% CI -1.42 to -0.39) compared with nebulized placebo. Notably, the investigators had low confidence in the supporting evidence for all treatments because of both imprecision in estimating effect sizes and risk of bias based on an assessment using the Cochrane Collaboration risk-of-bias tool.[4]

Interestingly, House et al[5] considered the utility of nebulized saline as a placebo for bronchiolitis studies, as nebulized saline may itself have some impact on the course of illness. The authors reviewed 29 studies that used respiratory rate, oxygen saturation, and respiratory scores to analyze the efficacy of nebulized saline in bronchiolitis. The Respiratory Distress Assessment Instrument was used in 14 of the studies and the Wang Respiratory Score was used in 4 of the studies. Overall, the authors found that nebulized saline improved respiratory scores but not oxygenation status, but the quality of the evidence was weak. The authors concluded that nebulized saline may be an active treatment for bronchiolitis and future RCTs are needed to better assess its use as a placebo.[5]

Treatment with β_2-agonists

Since one hallmark symptom of bronchiolitis is wheezing, clinicians have long trialed β_2-agonists as a treatment.[6] β_2-Agonists induce bronchodilation, resulting in the relaxation of smooth muscles, and they are an effective treatment for asthma, where smooth muscle constriction in the lungs causes respiratory distress.[7-9]

The use of β_2-agonists in children with viral bronchiolitis has been of interest for a long time. A 2014 Cochrane review[6] included 30 randomized placebo-controlled trials examining the efficacy of bronchodilators in bronchiolitis by measuring oxygen saturation, hospital admission, and duration of hospitalization in patients who received inhaled β_2-agonists versus placebo. There was no significant difference in oxygen saturation (MD=-0.43, 95% CI -0.92 to 0.06) and no significant differences in hospital admission rates (11.9% versus 15.9%; OR=0.75; 95% CI 0.46 to 1.21) or duration of hospitalization (MD=0.06 days, 95% CI -0.27 to 0.39).[6]

In recent viral bronchiolitis guidelines, the American Academy of Pediatrics recommended against the use of β_2-agonists in bronchiolitis, advising there was no improvement in the clinical course of infants. Furthermore, the guideline advised against future attempts to study this treatment, suggesting that transient changes in the course of illness and lack of an accepted clinical scoring criteria may subvert attempts to document true improvement due to bronchodilators.[1] This view is also reflected by Canadian Paediatric Society,[3] National Institute for Health and Care Excellence,[10] and Australasian bronchiolitis guidelines.[11]

Furthermore, β_2-agonists may cause tachycardia, irritability, flushing, nausea, vomiting, headache, decreased oxygen saturation, and tremors.[1,6,7,12] Although the current generation of β_2-agonists carries a reduced risk of adverse effects compared with that of older generations, trials of β_2-agonists are not indicated in bronchiolitis.

While evidence against the use of β_2-agonists is compelling, there remains a small subgroup of infants with bronchiolitis who may respond to inhaled therapies. Those infected with rhinovirus, rather than HRSV, might respond to β_2-agonists given T helper 2 cells and cytokine profiles (nuclear factor–κB, and interleukins 4 and 13) may potentiate airway smooth muscle constriction. In contrast, in HRSV infections, T helper 1 cells and type 2 and type 17 cytokines are thought to be more prominent and less β_2-agonist–responsive. Children with bronchiolitis caused by rhinovirus also tend to be older and are more likely to have a history of atopy compared with those infected with HRSV, and they are therefore more likely to respond to inhaled β_2-agonists.[13] To date, studies have failed to distill this subgroup fully and future RCTs are needed.

Despite agreement that β_2-agonists are not indicated for treatment of bronchiolitis, they are frequently administered to young children. In a prospective cohort study from the United States of 1016 enrolled patients younger than 1 year of age across 17 hospitals, 508 (50%) received salbutamol before hospital admission.[14] Another multicentre retrospective observational study across 7 sites in Australia and New Zealand reported that among the 3546 charts reviewed, between 13.2% and 35.2% of patients received β_2-agonists while admitted to the hospital, though it depended on the study site.[15] Some clinicians believe the intervention is warranted and have advocated for a trial treatment of β_2-agonists in all infants with bronchiolitis, based on the idea that some will be β_2-agonist–responsive.[16] In a survey of 57 pediatricians treating bronchiolitis, De Brasi et al found that 21 (37%) prescribed β_2-agonists because of detection of improvement after administration, 13 prescribed them (23%) because of the clinical severity of illness, and 1 (2%) wished "just to do something" because of perceived parental pressure to administer treatment.[17]

Conclusion

Infants with seasonal viral bronchiolitis should not receive inhaled β_2-agonists. Treatments should focus on supportive care with hydration and gentle nasal suctioning. Patients with signs of respiratory distress, dehydration, or hypoxia should be referred to the emergency department for further evaluation and escalation of care. Future RCTs are needed to determine whether there is a subgroup of infants who should be treated with inhaled β_2-agonists.

Competing interests
None declared

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