

# Nebulized epinephrine for young children with bronchiolitis

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## Abstract

**Question** Every winter I see infants with flulike symptoms and wheezing. I frequently diagnose them with bronchiolitis based on their presenting symptoms. Would it be prudent to send those infants to the nearest emergency department for treatment with nebulized epinephrine?

**Answer** Nebulized epinephrine should not be routinely used in infants with bronchiolitis. It is an option to consider in those with severe symptoms. If it is given and there are no signs of improvement, further doses are discouraged. Ongoing studies of epinephrine combined with other agents (eg, hypertonic saline, oral dexamethasone) are needed to confirm their benefit.



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**B**ronchiolitis is an acute inflammation of the bronchioles that leads to small airway edema, necrosis, and increased mucus production.<sup>1</sup> It is triggered by viral infections, most commonly respiratory syncytial virus,<sup>2</sup> and affects children younger than age 2.<sup>3</sup> Peak incidence of bronchiolitis is between December and March in North America.<sup>4</sup> Common presenting symptoms include rhinorrhea and cough, followed by tachypnea, nasal flaring, accessory muscles use, and, in some children, crackles and wheezing.<sup>5</sup> The diagnosis is based on history and physical examination. Blood sampling and chest radiography are rarely needed.<sup>1</sup>

Treatment of bronchiolitis is mostly supportive and includes suctioning of secretions, encouraging feeding, and maintaining hydration. Other treatments include bronchodilators, corticosteroids, and nebulized hypertonic saline. However, according to guidelines by the American Academy of Pediatrics<sup>1</sup> and the Canadian Paediatric Society,<sup>6</sup> albuterol or salbutamol and systemic corticosteroids should not be prescribed to infants with bronchiolitis. Although nebulized hypertonic saline is not recommended in the emergency setting, it might be considered in hospitalized infants with bronchiolitis.<sup>7</sup> Supplemental oxygen is recommended for children who present with an oxygen saturation of less than 90%.<sup>1,6</sup> Hand washing has been identified as the most important measure to prevent dissemination of the disease.

## Nebulized epinephrine for inpatients

Epinephrine is a mixed  $\alpha$ - and  $\beta$ -adrenergic agonist. The  $\alpha$ -adrenergic action is responsible for vasoconstriction

and reduction of airway edema,<sup>8</sup> hence its potential role in treatment of acute bronchiolitis.

Patel and colleagues<sup>9</sup> from Canada assessed length of hospital stay in 149 term and healthy infants up to 12 months of age who were admitted with a first episode of acute respiratory tract infection and wheezing. Infants receiving nebulized epinephrine (2.25% solution), albuterol (5 mg/mL solution), or saline placebo (0.9% sodium chloride) had similar lengths of stay (mean [SD] number of hours was 59.8 [62] for epinephrine, 61.4 [54] for albuterol, and 63.3 [47] for placebo;  $P=.95$ ). Similar findings were reported by Wainwright et al<sup>10</sup> from Australia. After administration of nebulized epinephrine or placebo, there was no difference found in length of hospital stay ( $P=.16$ ) among 194 healthy infants with a first episode of wheezing and a clinical diagnosis of bronchiolitis. These 2 studies were included in a systematic review,<sup>11</sup> which concluded that nebulized epinephrine and saline placebo had similar effects on admission length (mean difference  $-0.35$  days; 95% CI  $-0.87$  to  $0.17$  days).

A following study from Norway<sup>12</sup> confirmed the lack of epinephrine effect on length of hospital stay among 404 infants with moderate to severe bronchiolitis (racemic epinephrine dissolved in 0.9% saline vs 0.9% saline alone;  $P>.43$ ). Hospital admission was longer if inhaled epinephrine was given on a “fixed” schedule compared with an “on demand” schedule (61.3 hours, 95% CI 45.4 to 77.2 hours vs 47.6 hours, 95% CI 30.6 to 64.6 hours;  $P=.01$ ).

## Combined epinephrine and hypertonic saline

Evidence on the effect of nebulized hypertonic saline

in infants with bronchiolitis is conflicting,<sup>13</sup> and some research suggests it might reduce length of hospital stay for children hospitalized for more than 3 days.<sup>7</sup> It was suggested that a combination of epinephrine and hypertonic saline might be of benefit to admitted children.

Among 185 term and healthy infants (younger than age 24 months) with moderate bronchiolitis admitted to a Spanish hospital, investigators administered nebulized 3% hypertonic saline with either a 3-mL epinephrine or 3-mL placebo (ie, sterile water) combination.<sup>14</sup> Infants improved significantly earlier in the epinephrine group ( $P=.029$  and  $P=.036$  on days 3 and 5, respectively), and length of hospital stay was significantly shorter in the epinephrine group compared with those receiving placebo (mean [SD] of 3.9 [1.9] vs 4.8 [2.3] days;  $P=.011$ ). On the contrary, in a small study from Tunisia<sup>15</sup> with 94 term infants (up to 12 months old) with a first episode of moderate acute bronchiolitis, length of hospital stay in infants who received a combination of 2 mL of epinephrine and 2 mL of 5% hypertonic saline every 4 hours was similar to those who received hypertonic saline alone or with saline placebo (mean [SD] of 3.5 [2.0], 3.6 [1.7], and 4.5 [3.8] days, respectively;  $P=.316$ ).

While the Spanish study provides a compelling argument to use a combination of epinephrine and hypertonic saline, it is premature to recommend such treatment, and larger studies repeating these findings are needed to endorse such therapy.

### Nebulized epinephrine for outpatients

While findings among admitted infants show a lack of sufficient response to nebulized epinephrine, emergency department (ED) research investigated the benefit of early epinephrine therapy in the ED. A Cochrane review<sup>11</sup> included 5 studies<sup>16–20</sup> with 995 children who received nebulized epinephrine versus saline placebo. Cumulative evidence documented a significantly lower admission rate at day 1 after the ED visit among those receiving epinephrine (relative risk [RR] of 0.67; 95% CI 0.50 to 0.89), a benefit lost by day 7 after the ED visit (RR=0.81; 95% CI 0.63 to 1.03). Out of those 5 studies, 2<sup>19,20</sup> declared admission rate as a primary outcome while the other studies used clinical score as the primary outcome and admission rate as the secondary outcome.

When nebulized racemic epinephrine was compared with albuterol and saline placebo in the treatment of bronchiolitis in an American urgent care clinic,<sup>19</sup> 65 term and healthy infants aged 6 weeks to 24 months with a diagnosis of bronchiolitis were randomized to receive 5 mg of nebulized racemic epinephrine, 5 mg of albuterol, or an equivalent volume of saline placebo (3 doses at 0, 30, and 60 minutes). Admission to the hospital was needed in 10 of 17 infants in the epinephrine group and 16 of 25 infants in the saline placebo group ( $P>.05$ ).

In another large Canadian study, 20 800 term and healthy infants (6 weeks to 12 months of age) with moderate bronchiolitis who visited 8 pediatric EDs during the peak respiratory syncytial virus season received nebulized epinephrine and oral dexamethasone (group 1), nebulized epinephrine with oral placebo (group 2), nebulized placebo with oral dexamethasone (group 3), or nebulized placebo with oral placebo (group 4). The 2 nebulized treatments administered 30 minutes apart consisted of 3 mL of 1:1000 epinephrine or saline. The oral treatment consisted of 1 mg/kg of dexamethasone (maximum 10 mg) or placebo given after the first nebulized treatment in the ED, followed by once-daily doses of dexamethasone (0.6 mg/kg) or placebo for 5 days. Infants receiving epinephrine and dexamethasone had lower ED admission rates compared with those receiving placebo by day 7 (RR=0.65; 95% CI 0.45 to 0.95;  $P=.02$ ; unadjusted analysis). However, after adjusted analysis owing to multiple comparisons, the RR of ED admission by day 7 in the group receiving epinephrine with dexamethasone compared with the group receiving placebo was no longer significant (95% CI 0.41 to 1.04;  $P=.07$ ). Nebulized epinephrine or oral dexamethasone alone did not reduce the rate of admission compared with placebo in both unadjusted and adjusted analysis. Nebulized epinephrine seems to have only a transient effect on preventing ED admission. Further studies are needed to confirm this result.

### Conclusion

Nebulized epinephrine should not be used in hospitalized children except if used as a rescue agent for severe disease—markedly increased respiratory rate, retractions, and decreased oxygen saturation. For children seen in the ED, evidence does not support the effectiveness of nebulized epinephrine in infants with bronchiolitis. For children with severe illness, providers can administer a dose of epinephrine and carefully monitor for possible improvement. If there are no signs of improvement, further doses are discouraged. The combination of epinephrine with other agents (eg, hypertonic saline or oral dexamethasone) needs further research in order to confirm any benefit.

#### Competing interests

None declared

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