

## Original Investigation

# Nebulized Hypertonic Saline for Bronchiolitis in the Emergency Department

## A Randomized Clinical Trial

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**IMPORTANCE** Acute bronchiolitis is the most frequent lower respiratory tract infection in infants, yet there are no effective therapies available. Current evidence is unclear about the role of hypertonic saline (HS) for the acute treatment of bronchiolitis.

**OBJECTIVE** To determine whether nebulized 3% HS compared with normal saline (NS) improves respiratory distress in infants with bronchiolitis not responding to standard treatments in the emergency department.

**DESIGN, SETTING, AND PARTICIPANTS** A randomized clinical trial with blinding of investigators, health care providers, and parents was conducted at a single urban pediatric ED. The participants included children aged 2 to less than 24 months with their first episode of bronchiolitis and a Respiratory Distress Assessment Instrument score of 4 to 15 after nasal suctioning and a trial of nebulized albuterol.

**INTERVENTIONS** Patients were randomized to receive either nebulized 3% HS (HS group) or NS (NS group).

**MAIN OUTCOMES AND MEASURES** The primary outcome was change in respiratory distress at 1 hour after the intervention, as measured by the Respiratory Assessment Change Score (a decrease indicates improvement). Secondary outcomes included vital signs, oxygen saturation, hospitalization, physician clinical impression, parental assessment, and adverse events.

**RESULTS** The 31 patients enrolled in each treatment arm had similar baseline demographic and clinical characteristics. At 1 hour after the intervention, the HS group demonstrated significantly less improvement in the median Respiratory Assessment Change Score compared with the NS group (HS,  $-1$  [interquartile range,  $-5$  to  $1$ ] vs NS,  $-5$  [interquartile range,  $-6$  to  $-2$ ];  $P = .01$ ). There were no significant differences in heart rate, oxygen saturation, hospitalization rate, or other outcomes. There were no adverse events.

**CONCLUSIONS AND RELEVANCE** Infants with bronchiolitis and persistent respiratory distress after standard treatment in the emergency department had less improvement after receiving 3% HS compared with those who received NS. Based on these results and the existing evidence, administration of a single dose of 3% HS does not appear to be indicated to treat bronchiolitis in the acute care setting.

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Acute bronchiolitis is the most frequent lower respiratory infection and the most frequent cause of hospitalization in infants.<sup>1-3</sup> During the past 3 decades, hospitalization rates for infants with bronchiolitis have more than doubled in the United States,<sup>4</sup> at a cost of more than \$500 million annually.<sup>5</sup> Despite its widespread prevalence, there are no proven effective therapies for bronchiolitis beyond routine supportive care.

Nebulized hypertonic saline (HS) has been shown to increase mucociliary clearance in healthy individuals and in those with asthma, cystic fibrosis, and bronchiectasis.<sup>6-11</sup> Hypertonic saline is thought to have this effect by lowering the viscosity of mucus secretions, stimulating ciliary beat, and reducing airway edema.<sup>12-16</sup> Several studies<sup>14,15,17-19</sup> have suggested that nebulized 3% HS may reduce the length of hospital stay and lessen the clinical severity in infants hospitalized with bronchiolitis. Two studies<sup>20,21</sup> conducted in emergency departments (EDs) found no significant effect of HS on respiratory distress scores; however, they identified nonsignificant trends toward lower hospitalization rates with HS. Both of these studies combined HS with a bronchodilator, making it difficult to assess the independent effects of HS because the peak effects of both medications occurred simultaneously. Emergency department providers often administer a bronchodilator trial for bronchiolitis, despite mixed evidence for efficacy, and nebulized HS could be considered for infants who do not respond to bronchodilators. The objective of our study was to determine whether nebulized 3% HS, compared with normal saline (NS), improves respiratory distress in infants presenting to the ED with acute bronchiolitis and persistent distress after a trial of nasal suctioning and nebulized albuterol sulfate.

## Methods

### Study Design

This was a randomized clinical trial of nebulized 3% HS compared with NS in children aged 2 to less than 24 months who presented to the ED with acute bronchiolitis, with respiratory distress persisting after a trial of nebulized albuterol and nasal suctioning. Investigators, health care providers, and parents were blinded to study intervention. The study was conducted at a single urban, tertiary care ED within a freestanding children's hospital during 2 consecutive bronchiolitis seasons, from November 1 to April 30 of 2010 and 2011. The institutional review board of The Children's Hospital of Philadelphia approved the study, and written informed consent was obtained from the parent or guardian of every infant enrolled. Participants received financial compensation.

### Participants and Baseline Measures

Eligible patients included children aged 2 to less than 24 months presenting to the ED with a first episode of acute bronchiolitis, defined as their first episode of wheezing associated with signs and symptoms of respiratory distress and upper respiratory infection. Further inclusion criteria were a Respiratory Distress Assessment Instrument<sup>22</sup> (RDAI) score of 4 to 15 (moderate to severe) obtained after albuterol treatment and no in-

tention for further respiratory therapy by the ED physician during the first hour after assessment. We excluded infants with a history of wheezing or asthma, bronchodilator therapy prior to the current illness, chronic lung or heart disease, critical illness, and inability to receive nebulized medications. Infants with non-English-speaking guardians were excluded because of the inability to provide fully informed consent within the study time constraints.

Potential participants were identified and screened by trained research staff present in the ED from 7 AM to 12 AM daily. All infants received standard therapy for bronchiolitis per our ED's bronchiolitis pathway, including nasal suctioning and a trial of a single dose of nebulized albuterol (2.5 mg for infants weighing <10 kg, 3.75 mg for those 10-20 kg, and 5 mg for those >20 kg; all doses were diluted with 3 mL of NS) before enrollment. Within 90 minutes after albuterol treatment and suctioning, a pediatric emergency medicine physician trained in score determination assigned an RDAI score. No RDAI was conducted before administration of albuterol. If the RDAI score was between 4 and 15, eligibility was confirmed, and the family was approached to obtain informed consent.

### Randomization

Research pharmacists prepared study medications according to a randomization list generated by the investigational pharmacy using computer-generated random permuted block randomization (<http://www.randomization.com>). All investigators, ED and research staff, parents, and guardians were unaware of group assignments.

### Interventions

Patients were randomized to receive 4 mL of 3% HS (HS group) or 4 mL of NS (NS group). The investigational pharmacy prepared the study medications, which were stored in sequentially numbered envelopes with blinded syringes labeled only with the study number to ensure allocation concealment. The study medication was delivered using a jet nebulizer with an oxygen flow rate of 8 L/min. Both HS and NS are clear and odorless, and thus were indistinguishable in the syringe and nebulization chamber. Study medication administration occurred within 90 minutes after albuterol administration. Additional therapies were ordered at the discretion of the treating physician.

### Outcome Measures

Study clinicians performed respiratory scoring at 1 and 2 hours after the study treatment. All patients received assessments at 1 hour after study treatment. All patients being discharged home were assessed at 2 hours after the study treatment to observe for adverse effects after the peak effect of HS. For hospitalized patients, the 2-hour assessment was performed if the patient was still in the ED at that time, as study constraints prevented research staff from leaving the ED to perform this assessment. Disposition decisions were made by treating clinicians independent of study procedures. Research assistants performed brief parental surveys designed for this trial before physician assessment at 1 and 2 hours after the study treatment that asked about the patient's respiratory distress and ability to feed, and a standard medical history form was com-

Table 1. Respiratory Distress Assessment Instrument<sup>a</sup>

Variable	Points				
	0	1	2	3	4
Wheezing					
Inspiration	None	Part	All		
Expiration	None	End	1/2	3/4	All
Lung fields	None	≤2 of 4	≥3 of 4		
Retractions					
Supraclavicular	None	Mild	Moderate	Marked	
Intercostal	None	Mild	Moderate	Marked	
Subcostal	None	Mild	Moderate	Marked	

<sup>a</sup> Adapted from Lowell et al.<sup>22</sup>

pleted for all participants by treating clinicians. A research assistant performed a telephone interview with the parents or guardians approximately 7 days after the ED visit. The interview, which was designed for this trial, included questions about hospitalizations, return ED visits, and unscheduled visits to primary care physicians.

The primary end point of the study was the Respiratory Assessment Change Score (RACS), which was measured 1 hour after the study intervention. The RACS assesses the alteration in respiratory status using the change in the RDAI score and a standardized change in respiratory rate, with points being assigned by change increments of 10%.<sup>22</sup> For example, a change in respiratory rate of 5% or less from baseline is counted as a change of 0 units, and a decrease or increase of 6% to 15% is counted as improvement or deterioration of 1 unit. The RDAI assigns up to 8 points for wheezing and 9 points for retractions, depending on their location and severity (Table 1).<sup>22</sup> The overall RACS is the arithmetic sum of the RDAI score change and the standardized respiratory rate change between assessments, with a decrease in RACS signifying improvement. Internal reliability and responsiveness of the RACS as a measure of respiratory distress in infants has been previously demonstrated,<sup>22-26</sup> and it correlates well with other measures of respiratory distress.<sup>22</sup>

The secondary end points included changes in heart rate and respiratory rate, changes in oxygen saturation, hospitalization, physician clinical impression (ie, overall rating of clinical severity, categorized as mild, moderate, or severe), parental perception of improvement in breathing and feeding (ie, improved, worse, or unchanged), and adverse events. Physician clinical impression was included in addition to objective severity outcomes to account for the effect of the physician's impression of severity on assessment and treatment decisions.<sup>27</sup> Adverse events, such as bronchospasm, excessive coughing, apnea, and cyanosis, were recorded using a standardized medical record abstraction form. Follow-up measures included parental perception of improvement of the child's symptoms and need for an unscheduled primary care provider or ED visit or hospitalization.

### Statistical Analysis

Based on prior studies<sup>20</sup> and expert opinion, the study was designed to detect a clinically significant difference, defined as a mean change of 3, in the RACS between the groups. The

sample size required to detect this difference, assuming  $\alpha = .05$  and  $\beta = .2$  (80% power), was estimated to be 30 infants in each group. Data for the primary outcome were analyzed using the intention-to-treat principle.

Prior literature<sup>26</sup> demonstrated that the RDAI score had not been normally distributed; therefore, nonparametric analyses were planned a priori. Because the RDAI data in the present study were normally distributed, both parametric and nonparametric analyses were conducted. The difference in mean RACS and RDAI values between the HS and NS groups was assessed using a 2-sample *t* test. Similarly, the difference in median RACS and RDAI values was examined using the Mann-Whitney test. We performed a subgroup analysis to assess the effect of severity using the median baseline RDAI score to define severity groups.  $P < .05$  was considered significant. All analyses were performed using Stata, version 12.1 (StataCorp).

## Results

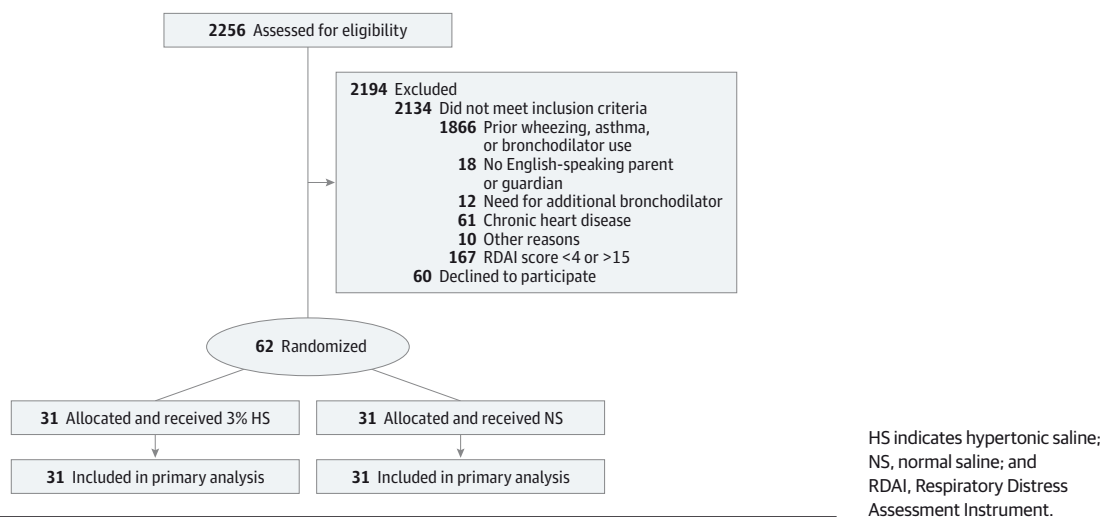
### Patient Characteristics

A total of 2256 infants were screened for eligibility. Of the 2134 ineligible infants, most (1866 [87%]) had prior wheezing, asthma, or bronchodilator use. Of the 122 eligible patients, 60 parents or guardians (49%) declined to participate. Sixty-two patients with bronchiolitis were randomized, enrolled, and had RDAI assessments conducted 1 hour after study treatment (Figure 1). There were 31 patients in each treatment group. Baseline demographic and clinical characteristics were similar between the HS and NS groups (Table 2).

### Respiratory Assessment Change Score

Using a RACS of -3 as a clinically significant improvement, the NS group demonstrated improvement in respiratory status 1 hour after treatment, and the HS group did not substantially improve (Figure 2). The difference in both the median and mean RACS 1 hour after treatment demonstrated significantly less improvement in the HS group compared with the NS group (Table 3). When the individual components of the RACS were examined, there was no significant difference in the RDAI score at 1 hour between the 2 groups. Furthermore, there was no significant difference

Figure 1. Consolidated Standards for Reporting of Trials Study Flow Diagram



found between the individual components of the RDAI score between groups. There was a greater decrease in respiratory rate in the NS group, with a difference of 8 breaths/min in the respiratory rate change from baseline to 1 hour. There was no significant difference in the RACS at 2 hours after study treatment between the 2 groups (mean [SD] RACS: HS, -3.4 [3.7]; NS, -3.5 [4.1];  $P = .94$ ); however, these results were limited by missing data (23 per group).

For severity subgroup analyses, the subgroups were divided based on the median baseline RDAI score of 7, with a value of 7 or less considered moderate severity and an RDAI score of 8 or more indicating high severity. In the group of patients with moderate baseline severity based on the RADI ( $n = 34$ ), there was significant improvement in the RACS 1 hour after treatment in the NS group (median RACS, -4; 95% CI, -6 to -1) that was not seen in the HS group (median RACS, 0; 95% CI, -2 to 2). The difference in RACS at 1 hour was significant between the HS and NS groups (difference in median RACS, 4;  $P = .02$ ). Of the patients with high baseline severity ( $n = 28$ ), clinical improvement occurred in both the HS (median RACS, -3; 95% CI, -5 to -1) and NS (median RACS, -5; 95% CI, -6 to -2) groups; however, there was no significant difference in the RACS at 1 hour between the 2 groups (difference in median RACS, 2;  $P = .43$ ).

### Secondary Outcomes

There were no significant differences in the 1-hour change in heart rate or oxygen saturation between the 2 groups (Table 3). There also was no significant difference between the 2 groups in the rate of hospitalization or the parental perception of the child's breathing or feeding status. No adverse events occurred during the study.

### Patient Follow-up

Follow-up telephone calls were completed in 90% of the participants. There was no significant difference between the groups in the parental perception of the study treatment im-

Table 2. Baseline Characteristics

Characteristic	Saline	
	3% HS ( $n = 31$ )	NS ( $n = 31$ )
Female sex, No. (%)	16 (52)	18 (58)
Age, mean (SD), mo	7.2 (5.1)	6.1 (3.6)
Eczema history, No. (%)	8 (26)	7 (23)
Family history of atopy, No. (%)	22 (71)	24 (77)
African American race, No. (%)	24 (77)	23 (74)
Days of symptoms, mean (SD)	3.4 (3.7)	3.4 (2.4)
Smokers present in household, No. (%)	17 (55)	13 (42)
Intensive care unit history, No. (%) <sup>a</sup>	6 (19)	4 (13)
RDAI score		
Mean (SD)	7.8 (2.6)	7.4 (2.5)
Median (IQR)	7 (6-10)	7 (5-9)
Respiratory rate, mean (SD), breaths/min	49.6 (12.4)	52.4 (12.4)
Heart rate, mean (SD), beats/min	153.4 (18.4)	159.3 (21.9)
Oxygen saturation, mean (SD), No. (%)	95.4 (3.8)	96.3 (3.7)
Physician clinical impression, No. (%) <sup>b</sup>		
Mild	9 (30)	11 (35)
Moderate	21 (70)	20 (65)

Abbreviations: HS, hypertonic saline; IQR, interquartile range; NS, normal saline; RDAI, Respiratory Distress Assessment Instrument.

<sup>a</sup> Includes neonatal intensive care unit and pediatric intensive care unit.

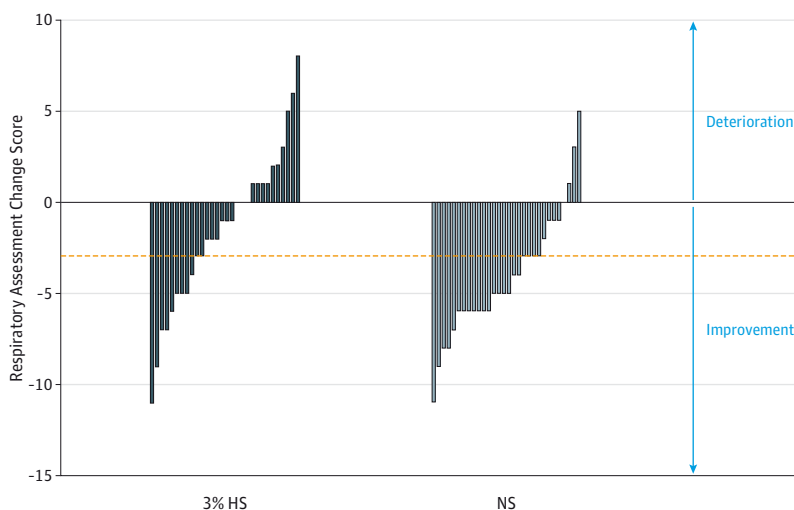
<sup>b</sup> Data were not completed on 1 infant in the 3% HS group.

proving their child's symptoms (HS, 77% [20] vs NS, 74% [20];  $P = .70$ ), unscheduled pediatrician (HS, 31% [8] vs NS, 32% [9];  $P = .91$ ) or ED (HS, 8% [2] vs NS, 0% [0];  $P = .13$ ) visits after the initial ED visit, or hospitalization after initially being discharged from the ED (HS, 15% [4] vs NS, 4% [1];  $P = .15$ ).

### Discussion

This randomized clinical trial of infants with acute bronchiolitis demonstrated that patients with persistent distress af-

Figure 2. Respiratory Assessment Change Score (RACS) Values 1 Hour After HS and NS Administration



Each bar represents an infant's RACS 1 hour after administration of study medication. Lower numbers indicate improvement in respiratory symptoms. The dashed line represents a clinically significant improvement. HS indicates hypertonic saline; NS, normal saline.

Table 3. Outcomes 1 Hour After Saline Administration

Characteristic	Saline		Difference	P Value
	3% HS (n = 31)	NS (n = 31)		
<b>RACS</b>				
Mean (95% CI)	-1.5 (-3.1 to 0.2)	-4 (-5.3 to -2.7)	2.5 (0.5 to 4.6)	.01
Median (IQR)	-1 (-5 to 1)	-5 (-6 to -2)	4	.01
<b>RDAI score</b>				
Mean (95% CI)	6.6 (5.5 to 7.6)	5.1 (4.1 to 6.2)	1.5 (-0.02 to 2.9)	.05
Median (IQR)	6 (4 to 9)	5 (3 to 8)	1	.06
Respiratory rate change, mean (95% CI), breaths/min <sup>a</sup>	-1.8 (-6.5 to 2.8)	-9.8 (-14.6 to -4.9)	8 (1.4 to 14.5)	.02
Heart rate change, mean (95% CI), beats/min <sup>a</sup>	3.4 (-5 to 11.8)	-2.6 (-11.2 to 6)	6 (-5.7 to 17.8)	.31
Oxygen saturation change, mean (95% CI), % <sup>a</sup>	1.1 (-0.4 to 2.6)	0.1 (-1.6 to 1.8)	1 (-1.2 to 3.2)	.36
<b>Physician clinical impression, No. (%)</b>				
Mild	15 (48)	21 (68)	-6 (-20)	
Moderate	16 (52)	9 (29)	7 (23)	.14
Severe	0	1 (3)	-1 (3)	
Hospitalization, No. (%)	22 (71)	20 (65)	2 (6)	.86
<b>Parental perception of improvement, No. (%)</b>				
Breathing	15 (50)	17 (55)	-2 (-5)	.62
Feeding	8 (27)	6 (19)	2 (8)	.51

Abbreviations: HS, hypertonic saline; IQR, interquartile range; NS, normal saline; RACS, Respiratory Assessment Change Score; RDAI, Respiratory Distress Assessment Instrument.  
<sup>a</sup> Change from baseline to 1 hour after saline administration.

ter nasal suctioning and a trial of albuterol who received a single dose of nebulized 3% HS in the ED had less improvement in respiratory distress compared with those receiving NS. Based on prior literature,<sup>20</sup> a RACS of at least -3 indicated a clinically significant improvement in respiratory status. Using this threshold, the NS group showed clinical improvement, which was not observed in the HS group. The decrease in RACS appears to be driven by the greater decrease in respiratory rate in the NS group 1 hour after treatment.

The lack of significant benefit of HS compared with NS that we observed in the ED is consistent with the findings of prior studies. Grewal and colleagues<sup>20</sup> found that 1 to 2 doses of 3%

HS mixed with racemic epinephrine was no more effective than NS mixed with racemic epinephrine in the ED treatment of bronchiolitis, as measured by the RACS. Another ED study<sup>21</sup> performed at 4 centers compared 3 doses of 3% HS mixed with albuterol with 3 doses of NS mixed with albuterol and found no statistically significant difference in the RACS. A Turkish single-center study<sup>28</sup> examining the effects of HS independently and mixed with salbutamol found no difference. These studies administered HS concomitantly with a bronchodilator. Our results add to this evidence by demonstrating that patients with persistent moderate respiratory distress after receiving albuterol do not improve clinically after a single dose

of HS. In the previous studies, the lack of improvement with HS could have been affected by concomitant effects of bronchodilators, because the peak effects of both interventions occurred simultaneously. Here, in a group of patients with persistent respiratory distress after bronchodilator treatment, we found no benefit and, in fact, an apparent short-term worsening in distress associated with HS administration. These results are in contrast to those of studies<sup>19</sup> examining the use of HS repeatedly over time, which generally show a decreased length of stay in hospitalized infants or improved clinical severity in outpatients.

Several potential mechanisms may explain the lack of benefit in the ED compared with other settings. Hypertonic saline may cause a transient increase in secretions that may induce cough and have a beneficial effect on pulmonary toilet over time. In the ED, when patients are generally at the peak of their illness, such an effect may result in increased symptoms and a transient ventilation-perfusion mismatch, leading to a temporary increase in distress associated with HS.<sup>29,30</sup> The same is true of albuterol, and the effects may have been additive. Consistent with other bronchiolitis studies,<sup>20,26</sup> our study population had a high rate of atopic family history. This predisposition may explain the lack of improvement with HS because of potentially worsening bronchial reactivity. It is not feasible to perform a truly blinded study of HS in bronchiolitis, and thus to be consistent with prior studies, we used NS as the comparison group. Normal saline is not a true placebo, because it adds water and sodium chloride to the airway surface liquid. Therefore, another possible explanation of our results is not that HS is ineffective but that NS is more effective in the short period after administration than HS, given the substantial improvement 1 hour after treatment in the NS group compared with the HS group. Prior clinical trials<sup>20,25,26</sup> of various interventions for bronchiolitis in the ED have also found that patients improve over the time in the ED, regardless of the intervention. Therefore, the improvement seen could also be the result of nasal suctioning and other supportive care, nebulized solutions, or a combination of these and other factors.

Our study has several limitations. It was conducted at a single center, so the results may not be generalizable. Consistent with prior studies,<sup>15,21,31</sup> we enrolled infants aged 2 to less than 24 months. Although this may result in including children with reactive airways, we limited our population to the first episode of wheezing. In addition, the median age in our study was 5 months, with an interquartile range of 3 to 9 months. We assessed a single dose of 3% HS, which is a relatively low concentration of HS, and results may differ with in-

creasing concentrations or repeated doses.<sup>32</sup> We intended to separate the delivery of albuterol and HS so that our primary outcome was assessed soon after the peak effect of HS and well after the peak effect of albuterol. It is possible that there were residual effects of albuterol at the time of assessment; however, this evaluation occurred much longer after the peak effect of albuterol. Overall, our population represented infants with wide-ranging disease severity. To address this, we performed a subgroup analysis by severity and found that although patients with moderate baseline severity had a significant difference in improvement between those treated with HS compared with NS, there was no trend toward greater improvement in those with more severe disease. Although it is difficult to draw definitive conclusions in a subgroup analysis with a small sample size, we found statistically and clinically significant results that generate hypotheses about which patients may be most likely to be affected by HS. Finally, although the RACS is reliable and responsive, we applied it as a short-term outcome and a proxy for other outcomes such as need for hospitalization. Emergency department and primary care providers make disposition and treatment decisions based on short-term outcomes, making this a relevant choice given our practice environment. In addition, previous studies<sup>11,33</sup> have demonstrated the peak effect of HS to occur within 10 to 20 minutes after inhalation, with clearance completed by 90 minutes. To provide adequate power to assess hospitalization as an outcome would require a much larger study. Before proceeding to a large, costly study, we believe that trials examining clinical response to treatment are the first step. Given the lack of improvement in respiratory status after HS treatment observed in the present study and other ED studies, enrolling a larger cohort in a trial of a single dose of HS in the ED setting alone does not appear to be indicated. Future work should focus on longer-term effects of this agent and determining whether patients with bronchiolitis would benefit from repeated doses of HS.

## Conclusions

Our study demonstrates that HS results in less improvement 1 hour after treatment in the ED compared with NS in infants with bronchiolitis who had persistent distress after albuterol and nasal suctioning. Based on the results of this and other studies, the administration of a single dose of 3% HS in the acute care setting does not appear to be more effective than NS in improving short-term respiratory distress in bronchiolitis.

### ARTICLE INFORMATION

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**Study concept and design:** Florin, Shaw, Zorc.

**Acquisition, analysis, or interpretation of data:** Florin, Kittick, Yakscoe, Zorc.

**Drafting of the manuscript:** Florin.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Florin.

**Obtained funding:** Florin.

**Administrative, technical, or material support:** Shaw, Kittick, Yakscoe.

**Study supervision:** Shaw, Zorc.

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