A Randomized Trial of Nebulized 3% Hypertonic Saline With Salbutamol in the Treatment of Acute Bronchiolitis in Hospitalized Infants

Pedro Flores, MD, PhD,* Ana Luisa Mendes, MD, and Ana S. Neto, MD, PhD

Summary. Objective: Acute bronchiolitis is a common disorder of infants that often results in hospitalization. Apart from supportive care, no therapy has been shown to influence the course of the disease, except for a possible effect of nebulized hypertonic saline (HS). To determine whether this does have beneficial effects on length of stay in hospital or on severity scores, we undertook a double-blind, randomized, controlled trial in a pediatric department of a Portuguese hospital. Methods: Previously healthy infants, younger than 12 months, hospitalized with mild-to-moderate acute viral bronchiolitis were randomized to receive either nebulized 3% (hypertonic, HS) or 0.9% (normal, NS) saline during their entire hospital stay. Primary endpoints were: length of hospital stay and severity scores on each day of hospitalization. Need for supplemental oxygen, further add-on medications and adverse effects were also analyzed. Results: Sixty-eight patients completed the study (HS: 33; NS: 35). The median length of hospital stay did not differ between groups: HS: 5.6 ± 2.3 days; NS: 5.4 ± 2.1 days ($P = 0.747$). We found no difference between groups in severity scores from day 1 to day 4. There were no differences in need for supplemental oxygen or add-on medications. Patients in HS group had significantly more cough (46% vs. 20%, $P = 0.025$) and rhinorrhoe (58% vs. 31%, $P = 0.30$). Conclusion: This study does not support the use of nebulized HS over NS in therapy of hospitalized children with mild-to-moderate acute viral bronchiolitis. **Pediatr Pulmonol.**

Key words: Pneumonia; TB; viral; evidence-based medicine & outcomes; asthma & early wheeze.

INTRODUCTION

Acute bronchiolitis is an infection of the lower respiratory tract, typical of infants, most commonly caused by respiratory syncytial virus (RSV).[1] It is the leading cause of hospitalization for respiratory disease in infants, with an estimated 80,000 cases and 10,000 hospital days in Portugal each year, constituting a significant burden in health expenditure.[2–9]

Since wheeze is sometimes a feature of bronchiolitis, asthma treatments are frequently used. Nevertheless, pathophysiology of bronchiolitis is quite different: it affects the bronchiolar epithelium, with necrosis and sloughing of epithelial cells, edema, increased secretion of mucus, and peribronchiolar cell infiltration. These changes obstruct large and small airways, leading to wheezing, atelectasis, and hyperinflation.[9,10]

Beta-agonists, corticosteroids, and diuretics are generally considered ineffective for bronchiolitis. In spite of some therapeutic benefit of nebulized epinephrine, the mainstay of treatment of acute bronchiolitis remains hydration, supplemental oxygen, and tube feeding, when necessary.[1,9–11]

Inhaled hypertonic saline (HS) has recently been shown to be a promising therapy, because of its ability to draw fluid from the submucosa and adventitial spaces, decreasing airway edema.[10–13] In cystic fibrosis and bronchiectasis, studies have found significant improvement of broncho-pulmonary and rhino-sinusal mucous rheologic properties, which could be relevant in infants with acute bronchiolitis.[11–14] Immunomodulator effects of HS have also been suggested.[15,16]

It has been demonstrated that nebulized HS is associated with decreasing hospital admissions,[2,16,17] its length,[14,18–21] and severity scores,[15,18,20,21] in patients

Hospital Cuf Descobertas, Lisboa, Portugal.

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*Correspondence to: P. Flores, PhD, Hospital Cuf Descobertas, Rua Goncalves Zarco 21, 2ºA, Lisboa 1400-033, Portugal.
E-mail: pedro.flores@sapo.pt

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with acute viral bronchiolitis. A recent Cochrane metanalysis recommends use of nebulized HS in these patients.[10]

The objective of this study was to compare the efficacy of inhaled HS vs normal saline (NS), on length of stay and severity scores in infants with acute viral bronchiolitis. Secondary outcomes were: need for supplemental oxygen, tube feeding, and add-on therapies. Safety of HS was also evaluated.

PATIENTS AND METHODS

Settings

We conducted a randomized, double-blind controlled trial in a pediatric department of a general urban hospital (Hospital CUF Descobertas—Lisbon, Portugal), comparing 3% hypertonic saline (HS group) with 0.9% normal saline (NS group). Patients were evaluated in the Emergency Department (ED) and admitted to the Pediatric Ward of the same Hospital. The study was conducted during two winter seasons (2012–2013 and 2013–2014, from November 1st to April 30th).

Patients

We included 68 infants, admitted with the diagnosis of acute viral bronchiolitis, defined as an apparent viral respiratory tract infection diagnosed in an infant with nasal discharge and wheezy cough, in the presence of fine inspiratory crackles and/or high pitched expiratory wheeze, in which apnoe could be a presenting feature.[22,23]

Inclusion criterion was: infants aged less than 12-months with acute bronchiolitis. Exclusion criteria were: previous episodes of wheezing; personal history of prematurity (gestational age <34 weeks); physician diagnosis of eczema, food allergy, or chronic (cardiac, respiratory, immunological, neurological, or metabolic) disease; high severity criteria (coma, respiratory rate >80 breaths/minute, oxygen saturation $<88\%$ on room air or need for assisted ventilation).

Study Design

Physicians working in the ED performed a standard history and physical examination on all patients and assessed them for study eligibility.

Patients were randomized by the Hospital Pharmacy before inclusion, using a computer random number generator (Excel for Windows™ v. 2013). The randomization list was concealed by the Pharmacy until completion of the study. Physicians, nurses, study personnel and patients' families remained blinded to treatment allocation throughout the trial.

The same staff prepared the study solutions as described: 3% hypertonic saline resulted of mixing, in sterile environment, 11 ml of 20% NaCl with 89 ml of 0.9% NaCl. The homogenized mixture was divided in 3 ml aliquots, that were preserved in the ED refrigerator between 2 and 8°C. They would be usable for a period of 7 days. Commercial preparation of normal saline (0.9%) were similarly homogenized, divided, and preserved in the same refrigerator. Both solutions were similar in appearance and smell, stored in identical syringes, and labelled only by a code number. Procedures followed national legislation and hospital good practices. Pharmacy is certified by national quality board but has no formal certificate for preparation of trial medications.

To each 3 ml aliquot, nurses added 0.25 ml (1.25 mg) of salbutamol. The mixture was given to the patient by nebulization.[19,24] When salbutamol solution was added, actual concentration of NaCl lowered from 3% to 2.77% in HS and from 0.9% to 0.83% in NS.

Infants received the same code treatment every 6 h until discharge. After deep nasal suctioning, it was delivered through a tight fixing face mask (Pediatric Ecolite™ Aerosol Mask, Wokingham, Berkshire, United Kingdom), from a standard oxygen-driven nebulizer (Cirrus 2 Nebuliser™, Wokingham, Berkshire, United Kingdom), connected to a source of pressurized oxygen from the wall, set to a flow rate of 6 L/min, until empty. Mass median aerodynamic diameter (MMAD) of nebulized particles was 3.9 μm.

All patients were enrolled within 24 hr of admission. Data on age, sex, gestational age, family history of atopic disease (eczema, rhinitis, or asthma in mother, father, or sibling), tobacco smoke exposure (if cohabitants regularly smoked during pregnancy or after birth), and breastfeeding (current or exclusive until 3 months) was recorded. Medication received before trial enrolment was also registered, including normal saline. At ED, all patients received a trial of nebulized salbutamol, according to hospital guidelines. Infants with favorable response were not excluded.

Patients were clinically evaluated at study inclusion and every day (less than 60 min after a scheduled morning nebulization) until discharge, by the same investigator (PF or ALM). The following parameters were recorded, using the clinical score proposed by Wang[25]: respiratory rate, wheezing, retraction and general condition. This scoring system assigns a number of 0–3 to each variable with increased severity receiving a higher score—maximum of 12 (Table 1).

Three times a day, the hospital personnel on duty registered the following data in a standardized sheet: general condition, respiratory rate, presence of wheezing, costal retractions, oxygen saturation, need for supplemental oxygen or tube feeding. Twice a week, the investigators scheduled meetings with the medical staff, in order to uniformize criteria between observers, namely for administration of add-on medications.

Additional inhalations of 1.25 mg salbutamol diluted in NaCl 0.9% or non-diluted 1 ml 1:1000 epinephrine or other

TABLE 1— Wang Severity Score (Wang et al. 1992)

Punctuation	0	1	2	3
Respiratory rate (breaths/min)	<30	31–45	46–60	>60
Costal retractions	None	Intercostal only	Tracheosternal	Severe with nasal flaring
Wheezing	None	Terminal expiration or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiratory and expiratory without stethoscope
General condition	Normal			Irritable, lethargic, poor feeding

medications (antibiotics, corticosteroids, or diuretics) were given as needed, according to hospital guidelines.

Hemoglobin oxygen saturation was determined by Nellcore Oximax™ N-560 with Oxiprobe™ BM-201 disposable sensor, Tyco Health Care, United Kingdom.

Each child had nasal secretions collected for Respiratory Syncytial Virus (RSV) antigen detection, using a commercial immunochromatographic assay (RSV Respi-Strip™, Coris Bioconcept, Gemloux, Belgium). The sensitivity of the test is 80–90%.

Decisions to request additional tests, provide intravenous fluids, supplemental oxygen or tube feeding were taken by attending physicians, based on clinical grounds and hospital guidelines. Supplemental oxygen was started in infants with a room air saturation of 93% or lower, and stopped when higher than 93% for 8 hr including a period of sleep. Tube feeding was initiated when infants could not get at least 75% of their usual intake by mouth and stopped when the reverse was true. IV fluids were given to compensate for fluid loss in clinically dehydrated infants, or those with vomit or diarrhoe.

Symptoms previously described as adverse effects of HS were also recorded[11,18,26]: sudden bronchial constriction, apnoe, cyanosis, exacerbation of cough, rhinorrhoe, saturation dips, tachycardia >200 cpm, agitation, and vomiting.

Patients were excluded from the study in cases of clinical deterioration requiring intensive care (at least non-invasive ventilation) or if parents withhold their consent.

Infants were considered "fit for discharge" when they did not need supplemental oxygen for 8 hr including a period of sleep, had minimal or no chest retraction, and fed adequately at least 75% of their usual intake with no need for tube feeding or intravenous fluids. Time of "actual discharge" was also recorded. The latter was influenced by social or administrative factors. Wang score at discharge was recorded but a minimum value was not mandatory.

Measurement of Treatment Effect

We compared the two groups (HS vs. NS), considering two major outcomes:

a) Length of hospitalization, in days ("Fit to discharge" and "Actual discharge").
b) Severity scores on day 1, 2, and 3.

Minor outcomes were:

a) Need for supplemental oxygen and tube feeding and their duration.
b) Other treatments (further doses of salbutamol, nebulized epinephrine, systemic corticosteroids, antibiotics, or diuretics).
c) Symptoms attributable to side effects of trial solutions.

Ethics

The study was approved by the Hospital's Ethics Committee. Informed written consent was obtained from a parent of each child, before enrolment.

Statistical Analysis

Sample Size Justification

For the first major outcome (hospitalization days), we found, in previous (non published) studies conducted in our hospital, and data from other southern European countries,[2,4,7,15,20,21] a mean value of 5.4 days (standard deviation of 1.2). We considered as clinically significant a reduction of 1 day. Assuming a α of 0.05 and a power of 90%, we required a sample size of 31 infants in each group to be able to detect such a difference.

Previous measurements of severity score in infants with bronchiolitis showed that an expectable mean of 6.0 on 12 points (standard deviation of 1.3). To detect a clinically significant change of at least one point in the severity score,[14,15,18,20,21] and assuming a α of 0.05 and a power of 90%, a sample size of 33 in each group was necessary.

Data Analysis

A database was created using SPSS 21 for Windows™. Following descriptive analyses for the entire sample, HS and NS groups were compared, using independent samples *t*-test for normally distributed continuous data, Mann–Whitney tests for non-normal continuous variables, and Fisher or Pearson χ^2 test, as appropriate, for categorical data. P value < 0.05 was considered statistically significant.

RESULTS

Participants' Flow and Baseline Data

Ninety-eight patients with mild-to-moderate bronchiolitis were enrolled, and 68 completed the whole study (Fig. 1).

There were no significant differences between groups (HS vs. NS) in baseline characteristics (Table 2).

Excluded patients (that refused to participate or had clinical deterioration), had similar baseline characteristics as included subjects (data not shown).

Prior to enrolment, in ED, all patients had deep nasal suctioning, received nasal 0.9% saline drops, and a trial nebulization of salbutamol (1.25 mg in 3 ml of NS). Before arriving to hospital, nineteen had received paracetamol (HS: 9; NS: 10), sixteen nasal phenylephrine (HS: 6; NS: 10), five inhaled salbutamol (HS: 2; NS: 3), and two anti-hystaminic syrup (HS: 1; NS: 1).

Outcomes of Therapeutic Effects

Major Outcomes

In Table 3, major outcomes (length of stay and severity scores from day 1 to day 3), are showed:

Minor Outcomes

In Table 4, the following outcomes are presented: need for supplemental oxygen, tube feeding, and corresponding durations, and added medications. Use of antibiotics was justified by concomitant acute otitis media or radiographic chest infiltrates. No significant differences were found between groups.

In Table 5, possible adverse effect of trial medication are enumerated. Except for excessive cough and rhinorrhoe that occurred more often in Group I (HS), no differences were found between groups. No child was withdrawn from the study because of these symptoms.

DISCUSSION

This prospective double blind controlled trial comparing effects of nebulized 3% hypertonic saline (HS) with 0.9% normal saline (NS) in hospitalized infants with mild-to-moderate acute bronchiolitis showed no significant difference in length of stay in hospital, severity scores, need for supplemental oxygen, tube feeding, or add-on medications. In addition to this lack of apparent benefit of the use of HS, we found increased morbidity (evidenced by higher incidence of cough and rhinorrhoe), which argues against the use of HS in the management of acute bronchiolitis.

From eight previously published studies that analysed length of stay as a primary outcome, four demonstrated a benefit in reducing average length of stay in hospital (1.0–1.6 less days in HS group when compared to NS group)[14,15,20,21] and six did not show such a difference.[11–13,18,19,27] Study populations included children younger than 24 months in most trials, except three, with up to 12 months-old patients.[14,18,27] We believe that selecting younger patients would allow us to include children with acute viral bronchiolitis, although we could not reliably exclude other causes of infant wheezing, such as infant asthma. Our effort to exclude patients with medical diagnosis of eczema and food allergy, in addition to similar distribution, in both groups, of patients with family history of atopic disease, and absence of improvement after salbutamol trial in ED, lowered but did not eliminate bias associated with inclusion of patients wheezing by other causes.[10–18]

Differences in study populations are unlikely to explain the contradictory results. Our population was comparable to others in respect to size, age, tobacco smoke exposure, breastfeeding, clinical severity, and RSV identification.[1,3,11–21] Time of illness before admission was 2.5 days, similar to that found by Anil,[17] but lower than

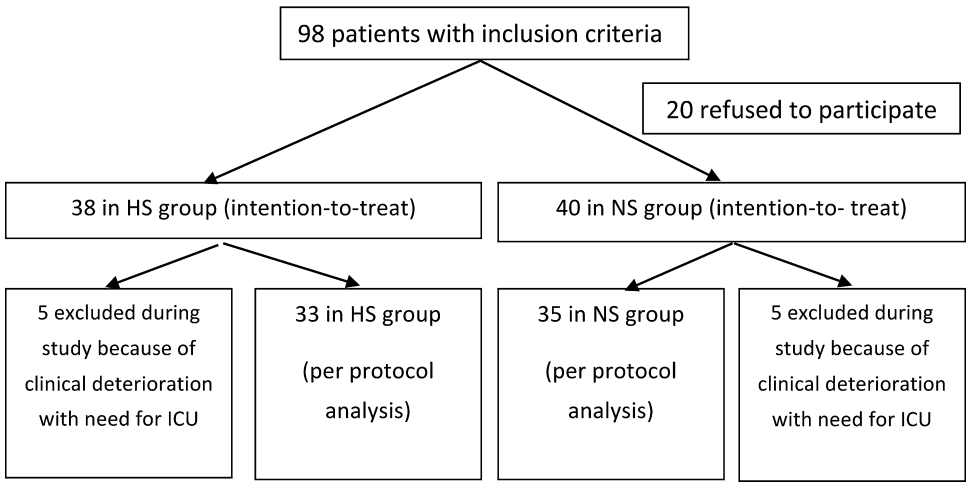

Fig. 1. Flow of patients through the study.

TABLE 2— Patient Demographic Characteristics and Illness Status at Baseline (HS vs. NS)

Characteristic	Hypertonic saline Group I (HS) N = 33	Normal saline Group II (NS) N = 35	*P* value
Mean (± SD) age, months	3.3 ± 2.4	3.8 ± 2.5	0.303
Male N (%)	18 (54.5)	18 (51.4)	0.797
Days of illness before hospitalization (mean ± SD)	2.3 ± 1.0	2.4 ± 1.0	0.677
Mean (± SD) severity score on admission	5.7 ± 1.9	6.1 ± 1.6	0.306
Family history of atopy N (%)	10 (30.3)	12 (34.3)	0.726
Tobacco smoke exposure N (%)	7 (21.2)	6 (17.1)	0.670
Breastfeeding N (%)	20 (60.6)	18 (51.4)	0.446
RSV N (%)	29 (87.9)	29 (82.9)	0.559
Positive response to salbutamol trial (N)	0	0	
Supplemental oxygen at study entry N (%)	16 (48.5)	21 (60.0)	0.465
Tube feeding at study entry N (%)	9 (27.3)	8 (22.9)	0.782

other studies (average between 3 and 5 days).[11,14,15,18–21,26–30] Local practices of diagnosis and treatment may have influenced our results.

Generalization of length-of-stay findings between different trials should be undertaken with caution. In the United States,[13,26] Israel,[14,18,27] or the Netherlands,[11] for instance, average length of stay of bronchiolitis patients is 1 to 2 days shorter than in Southern Europe[2,4,5,7,10] or East Asia.[15,20] Such disparity may, in part, be attributed to different clinical guidelines and healthcare systems, as well as medical efficiency, family, transport, social, or administrative issues. We did not find differences between groups in time until patients were "fit for discharge" nor actual times for discharge. Again, possible bias introduced by local practices cannot be excluded. These findings need to be confirmed by a multicenter trial, planned for in the near future.

We found no difference between HS and NS group, regarding severity scores. Among six previous studies addressing this topic, conclusions were conflicting: four studies demonstrated a slight benefit of score in HS group,[15,19–21] with an average reduction of 1.15 points on day 1, 1.32 on day 2 and 1.32 on day 3; two studies showed no difference in any considered day of treatment.[11,14] In our study, both groups had similar severity scores. A difference of 0.9 points, in day 2, did not reach statistical significance. We used Wang scoring system as we considered it the best available validated classification and would allow comparison with other authors.[10–21,25] We question, however, the clinical significance of a one-point drop of severity, found by other authors.[10,15,18,20] Better instruments to measure clinical outcomes of acute bronchiolitis are needed. Jacobs, in a recent study, used a different scoring system, including oxygen saturation and consolability, allowing a more detailed stratification of patients.[26]

Comparing to admission, we found a higher severity scores on day 1 and 2. Patients were admitted on average during the third day of illness, earlier than referred by others.[11,14,15,18–21,26,28–30] Concerning the natural history of bronchiolitis and the absence of specific therapies, we believe that that readiness could, at least, explain clinical worsening of patients during hospitalization, with higher Wang scores and need for supplemental oxygen or tube feeding.[2,4,5,7,22,23]

TABLE 3— Major Outcomes for the Two Intervention Groups

	Hypertonic saline Group I (HS) N = 33	Normal saline Group II (NS) N = 35	*P* value
Days until "fit to discharge" (mean ± SD)	4.9 ± 2.4	4.7 ± 2.3	0.621
Days until discharge (mean ± SD)	5.6 ± 2.3	5.4 ± 2.1	0.747
Severity score D1 (33, 35)[1]	5.8 ± 2.1	6.3 ± 1.7	0.286
Severity score D2 (33,34)[1]	5.9 ± 2.3	6.8 ± 2.4	0.099
Severity score D3 (29,31)[1]	5.5 ± 3.2	5.6 ± 2.7	0.865
Severity score when "fit to discharge" (33,35)[1]	1.3 ± 1.4	1.5 ± 1.3	0.575

[1](N Group I, N Group II).

TABLE 4— Minor Outcomes for the Two Intervention Groups

	Hypertonic saline Group I (HS) N = 33	Normal saline Group II (NS) N = 35	*P* value
Supplemental oxygen			
Patients N (%)	26 (78.8)	32 (91.4)	0.181
Duration (hours)[1]	91 ± 39	86 ± 40	0.640
Need for tube feeding			
Patients N (%)	14 (42.4)	14 (40.0)	0.837
Duration (hours)[1]	79 ± 35	67 ± 34	0.353
Further doses of salbutamol	17 (51.5)	23 (65.7)	0.234
Nebulized epinephrine	9 (27.3)	5 (14.3)	0.186
Systemic corticosteroids	8 (24.2)	10 (28.6)	0.686
Antibiotics	18 (54.5)	13 (37.1)	0.150
Diuretics	4 (12.1)	2 (5.7)	0.352

[1]Patients without oxygen, respectively tube fed, were excluded for analyses.

Our nebulizers and oxygen flow was similar to others.[3,10,11,14,17,18,26,28–30] Several non-controlled factors (tidal volumes, crying, cough, combativeness, or sleepiness) influence deposition of particles in lower airways. These would justify further assessment. Frequency of inhaled medication in our study should not justify differences as it was similar to others, which have used 4,[28] 6,[12,21] or 8 hr intervals.[11,13–16,18,20,21]

Difference between concentration of NaCl in HS (2.77%) and NS (0.83%) given three times a day, was low and could contribute for the lack of effect found in our study. Studies with different concentrations (5%, 6%, or 7% HS) and frequency of nebulizations, leading to higher total dosis of sodium chloride have been conducted, with conflicting results.[11,26,29] Normal saline may not be merely a placebo, as discussed by other authors.[11–13,26] The fact that acute bronchiolitis tends to remit spontaneously, regardless of treatment, makes it important to optimize measures of effect of medical interventions.

We associated salbutamol to nebulized HS or NS, aiming to prevent bronchospasm, potentially associated to hypertonic solutions.[10–13,15,20] Others have used different bronchodilators such as terbutaline[16] or epinephrine.[14,18,21] In order not to reduce concentration of NaCl, we used lower doses of salbutamol,[11,15,20] without significant differences.

We did not evaluate patients before and after nebulization, and so we could not find differences in immediate effects of therapy. Others have done so, mainly in studies conducted in ED environment, and found immediate relief provided by HS, obviously an important result.[3,10,13,16,17,26]

Other minor outcomes were evaluated in our study: need for supplemental oxygen, tube feeding and add-on medications. We did not find differences between HS and NS groups concerning these indirect markers of severity. A great variability was found, possibly related to age of patients and airway calibre. Add-on medication depended upon physician decisions, and was mostly administered without formal indication from guidelines. These attitudes may have introduced a non-quantified bias to our trial,[1,6,9,10,22] that was possibly distributed evenly between HS and NS groups. As a clinical trial team, we scheduled meetings with hospital pediatricians, in order to uniformize indications for medications.

TABLE 5— Adverse Effects Noted in Each Group N(%)

Symptom	Hypertonic saline Group I (HS) N = 33	Normal saline Group II (NS) N = 35	*P* value
Sudden bronchial constriction	2 (6.1)	2 (5.7)	0.952
Apnoe	0	0	
Cyanosis	0	0	
Exacerbation of coughing	15 (45.5)	7 (20.0)	0.025
Excessive rhinorrhoe	19 (57.6)	11 (31.4)	0.030
Saturation dips	0	0	
Tachycardia >200 cpm	0	0	
Agitation	9 (27.3)	12 (34.3)	0.532
Vomiting	0	0	

One of the strengths in our study was a detailed record of adverse effects potentially attributable to HS. It was difficult to blame medication for symptoms that could largely be due to acute bronchiolitis itself. Excessive rhinorrhoe and coughing was more prevalent in HS group, as recently described by Teunissen.[14] We believe that exacerbation of rhinorrhoe and cough could be explained by physiological effects of HS and should not be considered a negative effect. HS solutions diminish mucosal edema, and stimulate mechanical cleansing of secretions, increasing intrabronchiolar water and mucous, with subsequent cough and nasal discharge. These changes, as well as possible immune modifications associated with sodium chloride are still not completely understood in bronchiolitis.[11–13,24,26,28,30]

In conclusion, we showed that, in children younger than 12 months old that were hospitalized with acute viral bronchiolitis, nebulized 3% HS, when compared to 0.9% NS, although safe, did not reduce duration of hospital stay, clinical severity score, need for supplemental oxygen, tube feeding, or add-on medications. Our results do not support the routine use of HS in infants with bronchiolitis.

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