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Effect of Nebulized Hypertonic Saline Treatment in Emergency Departments on the Hospitalization Rate for Acute Bronchiolitis
A Randomized Clinical Trial

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IMPORTANCE Acute bronchiolitis is the leading cause of hospitalization among infants. Previous studies, underpowered to examine hospital admission, have found a limited benefit of nebulized hypertonic saline (HS) treatment in the pediatric emergency department (ED).

OBJECTIVE To examine whether HS nebulization treatment would decrease the hospital admission rate among infants with a first episode of acute bronchiolitis.

DESIGN, SETTING, AND PARTICIPANTS The Efficacy of 3% Hypertonic Saline in Acute Viral Bronchiolitis (GUERANDE) study was a multicenter, double-blind randomized clinical trial on 2 parallel groups conducted during 2 bronchiolitis seasons (October through March) from October 15, 2012, through April 15, 2014, at 24 French pediatric EDs. Among the 2445 infants (6 weeks to 12 months of age) assessed for inclusion, 777 with a first episode of acute bronchiolitis with respiratory distress and no chronic medical condition were included.

INTERVENTIONS Two 20-minute nebulization treatments of 4 mL of HS, 3%, or 4 mL of normal saline (NS), 0.9%, given 20 minutes apart.

MAIN OUTCOMES AND MEASURES Hospital admission rate in the 24 hours after enrollment.

RESULTS Of the 777 infants included in the study (median age, 3 months; interquartile range, 2-5 months; 468 [60.2%] male), 385 (49.5%) were randomized to the HS group and 387 (49.8%) to the NS group (5 patients did not receive treatment). By 24 hours, 185 of 385 infants (48.1%) in the HS group were admitted compared with 202 of 387 infants (52.2%) in the NS group. The risk difference for hospitalizations was not significant according to the mixed-effects regression model (adjusted risk difference, −3.2%; 95% CI, −8.7% to 2.2%; $P = .25$). The mean (SD) Respiratory Distress Assessment Instrument score improvement was greater in the HS group (−3.1 [3.2]) than in the NS group (−2.4 [3.3]) (adjusted difference, −0.7; 95% CI, −1.2 to −0.2; $P = .006$) and similarly for the Respiratory Assessment Change Score. Mild adverse events, such as worsening of cough, occurred more frequently among children in the HS group (35 of 392 [8.9%]) than among those in the NS group (15 of 384 [3.9%]) (risk difference, 5.0%; 95% CI, 1.6%-8.4%; $P = .005$), with no serious adverse events.

CONCLUSIONS AND RELEVANCE Nebulized HS treatment did not significantly reduce the rate of hospital admissions among infants with a first episode of acute moderate to severe bronchiolitis who were admitted to the pediatric ED relative to NS, but mild adverse events were more frequent in the HS group.

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Editorial
Supplemental content

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The burden of bronchiolitis has remained high for the past 20 years. Each year, 1 in 5 infants has a respiratory infection caused by respiratory syncytial virus (RSV).[1] In the United States, an estimated 280 000 visits to emergency departments (EDs) for bronchiolitis occur annually.[2,3] Each year, 150 000 infants are hospitalized, with an estimated cost of more than $1.7 billion in 2009.[4,5] Bronchiolitis is the first cause of hospitalization among infants younger than 1 year.[5]

As stated by the American Academy of Pediatrics in 2014, treatment is mostly supportive, such as oxygen supplementation and hydration, because most drugs and curative therapies, such as antibiotics, have proved to be ineffective.[6-9] Nebulized hypertonic saline (HS) treatment has been proposed for bronchiolitis to reduce the length of hospital stay, with mostly mild adverse events reported.[10,11] The debate concerning the mechanism of action of nebulized HS for bronchiolitis continues, but it is supposed to reduce airway edema, decrease mucous plugging, and improve clearance of mucus.[12] However, the latest analyses have cast doubt over the true efficacy of HS treatment for admitted infants to reduce the length of hospital stay.[13,14] Thus, efficacy of HS treatment in the ED to reduce the number of hospital admissions also remains unclear.[10] Analysis of 7 randomized clinical trials comprising a total of 951 infants with a first episode of bronchiolitis admitted in the pediatric ED suggested that nebulized HS treatment reduced the risk of hospitalization by 20% (pooled relative risk, 0.80; 95% CI, 0.67-0.96; $P = .01$) relative to normal saline (NS) treatment, with evidence of moderate quality.[10] Only one study,[15] which included 408 infants in 2 Californian pediatric EDs, found a statistically significant reduction in admission rates (adjusted odds ratio, 0.49; 95% CI, 0.28-0.86; $P = .01$) with the use of albuterol plus HS vs albuterol plus NS. However, no follow-up was performed in this study to verify the evolution of the patients discharged from the ED.[15] We conducted a large multicenter trial (Efficacy of 3% Hypertonic Saline in Acute Viral Bronchiolitis [GUERANDE]) to evaluate the efficacy of nebulized HS relative to NS on the admission rate among previously healthy infants visiting a pediatric ED for a first episode of moderate to severe acute bronchiolitis to address the limitation of previous studies (lack of follow-up, uncertainty of results, and small number of included patients) and the risk of potential adverse events with nebulized HS treatment, such as bronchospasm and desaturation.[10,16]

Key Points

Question What is the effect of treatment with nebulized hypertonic saline, 3%, vs normal saline, 0.9%, on the admission rate among infants with acute moderate to severe bronchiolitis in the emergency department?

Findings In this randomized clinical trial of 777 healthy infants, the hospital admission rate in the hypertonic saline group was 48.1% compared with 52.2% in the normal saline group. Mild adverse events, such as worsening of cough, occurred more frequently among children in the hypertonic saline group.

Meaning Nebulized hypertonic saline treatment did not significantly reduce the hospital admission rate among infants with a first episode of acute bronchiolitis admitted to the pediatric emergency department.

Methods

Trial Design

GUERANDE was a multicenter, double-blind randomized clinical trial conducted in 24 French pediatric EDs during 2 bronchiolitis seasons (October through March) from October 15, 2012, through April 15, 2014. Patients were randomized into 2 parallel groups to receive 3% HS or 0.9% NS nebulization treatment. The full study protocol, including trial sites, can be found in Supplement 1. The Saint Germain en Laye Ethics Committee approved the study.

Participants

Infants 6 weeks to 12 months old who were seen at participating pediatric EDs with a first episode of moderate to severe bronchiolitis were eligible for the study.[17] Bronchiolitis was diagnosed by a history of viral upper respiratory tract infection plus wheezing and/or crackles on chest auscultation with respiratory distress. Respiratory distress was diagnosed if at least 2 of the following conditions were met: (1) altered general condition and/or reduced alimentary intake, (2) respiratory rate greater than 50/min, (3) oxygen saturation less than 95% while awake, and (4) at least 1 severe or 2 moderate retraction signs according to the Respiratory Distress Assessment Instrument (RDAI) score (see Supplement 1 for more details about the RDAI score).[18] Infants were not eligible if they had any of the following: premature birth (defined as birth before 37 weeks of gestation); immunologic, cardiac, or chronic pulmonary disease; bone malformation of the chest; previous use of nebulized HS; or inability to communicate with the family (a language barrier or lack of telephone on the part of the parent or guardian). Critically ill infants defined by the need of admission to a pediatric intensive care unit (PICU) were also not eligible.

Potential participants were identified and screened at admission by trained study physicians present in the pediatric ED. Children were enrolled in the study if attending personnel (research nurse and physician) were available (40 hours per week, mostly between 8 AM and 8 PM Monday through Friday) in the pediatric ED. After written informed consent was obtained from a parent or legal guardian, children underwent randomization and the assigned study medication was administered. The baseline characteristics of the children were obtained at admission and were recorded on a patient case report form. The assessment included a physician-guided structured interview of one or both parents.

Interventions

Patients received 2 nebulizations according to their randomization group: 4 mL of HS, 3% (MucoClear 3%; PARI Pharma GmbH), or 4 mL of NS, 0.9% (sodium chloride, 0.9%; Unither Pharmaceuticals), lasting 20 minutes and given 20 minutes apart. The study medication was delivered using a jet nebulizer (PARI LC SPRINT SP Baby; PARI Pharma GmbH) through

a firmly applied face mask with an oxygen flow rate of 6 L/min. The preparations were packaged in identical clear plastic vials labeled only with the randomization numbers. Both HS and NS were clear and odorless and were thus indistinguishable in the syringe and nebulization chamber. Additional therapies were ordered in accordance with routine care at the discretion of the treating physician. A nasopharyngeal aspiration sample was obtained for viral testing using polymerase chain reaction. In case of hospitalization, the study did not plan to pursue further nebulizations.

Assessment

Study physicians and research nurses performed respiratory scoring at baseline, between the 2 nebulizations, and after 20 minutes. Any adverse effects were recorded throughout the observation period in the pediatric ED. All patients received assessments by a study physician 20 minutes after the end of the second nebulization. The decision to admit or discharge the infant from the pediatric ED was made at the discretion of the attending physician. The research nurse obtained data regarding hospital admissions and infant's feeding, breathing, and coughing 3, 8, 15, and 28 days after the ED visit by using a standardized telephone follow-up procedure.

Outcome Measures

The primary end point of the study was hospital admission up to 24 hours after enrollment in the study, which was determined through medical record review and telephone follow-up. We evaluated hospital admission up to 24 hours to avoid transient improvement, which could delay hospitalization by a few hours without clinical pertinence.[19] Secondary outcomes were admission within 28 days, changes in the RDAI score,[18] duration of symptoms, length of hospital stay for hospitalized infants, and adverse events, such as bronchospasm, desaturation, excessive coughing, apnea, and cyanosis, which were recorded using a standardized medical record abstraction form. The study physicians performing the clinical scoring were trained on site at investigator meetings by one of the authors (V.G.) and local primary investigators. Interrater reliability was not tested.

Randomization

A random allocation sequence using a 1:1 ratio and permutation blocks with a block size of 4, stratified according to center, was computer generated. Randomization was performed electronically using a secure internet platform (https://cleanweb.aphp.fr). Block size was not mentioned to the physicians involved in patient recruitment. The investigational pharmacy prepared the study drugs in sequentially numbered, visually identical packets to conceal the allocation sequence. All pediatric department staff, parents, and guardians were masked to the treatment assignment. Randomization codes were kept secure until data entry was complete. Thus, those involved in the evaluation of the primary outcome were masked to the group assignment.

Statistical Analysis

We determined the sample size using the hospitalization rates for bronchiolitis recorded in study hospitals during previous years. We estimated that a total of 349 infants per group would be needed to detect a difference between groups, using a 2-tailed α of .05 and a (1 − β) of .80, for a comparison of 2 independent proportions if there was an absolute decrease in the hospitalization rate of 10%. We planned to include an additional 15% of patients to ensure that we had sufficient participants for analysis (because of potential study dropouts or consent withdrawals). We therefore planned to enroll 800 infants in this trial.

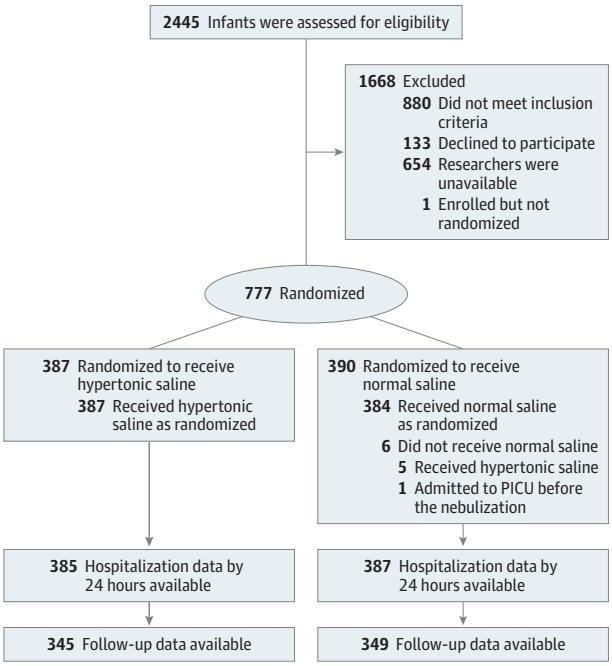
Our primary analysis was conducted using an intent-to-treat approach and therefore included all randomized infants. Baseline characteristics of patients in the 2 treatment groups were reported using frequency distributions and descriptive statistics, including measures of central tendency and dispersion. In the framework mixed-effects regression models, the difference between treatment groups was estimated using odds ratios and risk differences with 95% CIs. We performed mixed-effects model analyses to account for the correlation among measurements in the same center.[20] Every model was adjusted for potential clinical relevant covariates, such as age, RSV infection status, duration of symptoms before enrollment, previous use of systemic corticosteroids, feeding, heart rate, oxygen saturation, and initial RDAI score. A per-protocol analysis using a linear regression model was used to compare adverse events between the HS and NS groups. All analyses were conducted using Stata software, version 13.1 (StataCorp). *P* values were calculated using multieffect or linear regression models, and $P < .05$ was considered statistically significant.

Results

Recruitment and Baseline Characteristics

Of the 2445 infants who met the criteria for enrollment, 778 were enrolled (**Figure**). One family withdrew their consent before randomization. Of the 777 infants included in the study (median age, 3 months; interquartile range, 2-5 months; 468 [60.2%] male), 385 (49.5%) were randomized to the HS group and 387 (49.8%) to the NS group (**Table 1**). Of the 390 infants assigned to the NS group, 1 patient in the NS group was admitted to the PICU before administration of the study drug; 5 received HS rather than the allocated treatment. In these 5 patients, because of a human error, the patients did not receive the treatment contained in the packet corresponding to their randomization numbers but received the treatment of a packet corresponding to another randomization number. Five infants were unavailable for follow-up after discharge from the pediatric ED before day 3 (2 in the HS group and 3 in the NS group). Clinical and sociodemographic characteristics were similar in both groups (Table 1). The prevalence of RSV infection was high in both groups (84% in the HS group and 88% in the NS group). Patients in both groups had received prior treatment with bronchodilators (78 [20.3%] in the HS group and 71 [18.4%] in the NS group) and systemic corticosteroids (75 [19.5%] in the HS group and 43 [11.1%] in the NS group) for the same episode in the previous days.

Figure. Eligibility, Randomization, and Follow-up of the Study Participants



Data were available for 772 infants for the primary outcome of hospital admission by 24 hours after enrollment. PICU indicates pediatric intensive care unit.

Hospital Admissions

We found no significant difference between the study groups with respect to hospitalization. By 24 hours, 185 of the 385 infants (48.1%) in the HS group were admitted compared with 202 of the 387 infants (52.2%) in the NS group. The difference in hospitalization rates between the HS and NS groups was not significant according to the mixed-effects regression model using the center as the random effect (risk difference, -3.2%; 95% CI, -8.7% to 2.2%; *P* = .25) (**Table 2** and **Table 3**).

Secondary Outcomes

Subgroup analyses comparing the admission rates among infants younger than 3 months revealed no significant difference between the HS and NS groups. with admission rates of 54.8% (121 of 221 infants) in the HS group and 57.4% (132 of 230 infants) in the NS group (*P* = .58). The mean (SD) length of stay for all admitted infants was 3.7 (2.7) days, with no difference between groups: 3.8 (2.5) days for the HS group and 3.7 (3.0) days for the NS group (adjusted difference, -0.1; 95% CI, -0.6 to 0.4; *P* = .71). By day 28, 209 of the 378 infants (55.3%) in the HS group and 226 of the 383 infants (59.0%) in the NS group had been admitted to the hospital. Among hospitalized infants, 28 were admitted to a PICU (15 from the HS group and 13 from the NS group). Admission rates varied among the 24 centers from 31.6% to 83.3% (mean [SD], 53.0% [15.0%]). Additional therapies received by the children during their stay in the pediatric ED are described in the eTable in Supplement 2.

Table 1. Baseline Characteristics of the Patients[a]

Characteristic	Hypertonic Saline Group (n = 387)	Normal Saline Group (n = 390)
Age, median (IQR), mo	3 (2-5)	3 (2-5)
Male sex	229 (59.2)	239 (61.3)
RDAI score, mean (SD)	8.0 (3.2)	7.7 (3.4)
Respiratory rate, mean (SD), /min	56.1 (10.6)	57.0 (11.0)
Heart rate, mean (SD), /min	154.4 (17.3)	155.1 (17.7)
Oxygen saturation, mean (SD), %	97.0 (2.7)	97.2 (2.5)
Temperature, mean (SD), C°	37.3 (0.6)	37.4 (0.6)
Reduced feeding	323 (83.5)	329 (84.4)
Duration of symptoms before enrollment, median (IQR), d	3 (2-4)	3 (2-5)
Atopy		
Personal history	42 (10.9)	47 (12.2)
Family history	215 (56.3)	208 (53.9)
Smokers in home	94 (24.5)	102 (26.6)
Day care	111 (29.1)	87 (22.6)
No. of siblings		
0	113 (29.5)	105 (27.1)
1	174 (45.4)	175 (45.2)
2	60 (15.7)	74 (19.1)
≥3	36 (9.4)	33 (8.5)
Previous treatment for current illness		
Bronchodilators	78 (20.3)	71 (18.4)
Systemic corticosteroids	75 (19.5)	43 (11.1)
Antibiotics	53 (13.8)	43 (11.1)
RSV status		
Positive	327 (84.5)	344 (88.2)
Negative	48 (12.4)	37 (9.5)
No viral testing	12 (3.1)	9 (2.3)

Abbreviations: IQR, interquartile range; RDAI, Respiratory Distress Assessment Instrument; RSV, respiratory syncytial virus.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Clinical Measures

The RDAI score improved in both groups (Table 2), with a greater mean (SD) change in the HS group of -3.1 (3.2) compared with -2.4 (3.3) in the NS group (adjusted difference, -0.7; 95% CI, -1.2 to -0.2; *P* = .006), and similarly for the Respiratory Assessment Change Score (RACS) (Table 2).

Adverse Events

Although no serious adverse events were reported, mild adverse events were more frequent in the HS group. Adverse events occurred 57 times among 50 infants: in 35 of 392 children (8.9%) in the HS group vs 15 of 384 (3.9%) in the NS group (risk difference, 5.0%; 95% CI, 1.6%-8.4%; *P* = .005) (**Table 4**). One adverse event occurred in an infant randomized to the NS group who was admitted to the PICU before administration of the study medication (Table 4). Cough without respiratory distress was the most frequent adverse event observed and occurred 30 times among 26 children in the HS group and 4 times among 3 children in the NS group.

Table 2. Hospital Admission Rates by Hour 24 and Day 28[a]

Characteristics	Hypertonic Saline Group (n = 385)	Normal Saline Group (n = 387)	Risk Difference, %[b] (95% CI)	*P* Value
Admission by hour 24	185 (48.1)	202 (52.2)	-3.2 (-8.7 to 2.2)	.25
Direct admission	169 (43.9)	188 (48.6)	-3.8 (-9.2 to 1.6)	.17
Secondary admission	16/216 (7.4)	14/199 (7.0)	0.1 (-3.1 to 5.1)	.63
Admission by day 28[c]	209/378 (55.3)	226/383 (59.0)	-2.7 (-8.7 to 3.3)	.37
Admission rate by age group				
<3 mo	121/221 (54.8)	132/230 (57.4)	-1.8 (-8.1 to 4.5)	.58
≥3 mo	64/164 (39.0)	70/157 (44.6)	-4.6 (-13.4 to 4.2)	.31
PICU admission	15/209 (7.2)	13/226 (5.8)	1.6 (-2.7 to 5.9)	.47
Length of stay, mean (SD), d[d]	3.8 (2.5)	3.7 (3.0)	-0.1[e] (-0.6 to 0.4)	.71
RDAI score after nebulization, mean (SD)[f]	4.9 (3.2)	5.3 (3.4)	-0.5[e] (-0.9 to -0.1)	.02
Change in RDAI before and after nebulization, mean (SD)[g]	-3.1 (3.2)	-2.4 (3.3)	-0.7[e] (-1.2 to -0.2)	.006
RACS, mean (SD)[h]	-4.4 (4.9)	-3.4 (4.8)	-0.1[e] (-1.7 to -0.3)	.006

Abbreviations: PICU, pediatric intensive care unit; RACS, Respiratory Assessment Change Score; RDAI, Respiratory Distress Assessment Instrument.

[a] Data are presented as number/total number (percentage) of patients unless otherwise indicated.

[b] Differences with 95% CIs were calculated using linear mixed-effects regression models accounting for the random effect for the center. Every model was adjusted for potential clinical relevant covariates, such as age, respiratory syncytial virus infection status, duration of symptoms before enrollment, previous use of systemic corticosteroids, feeding, heart rate, oxygen saturation, and initial RDAI score. $P < .001$ of the likelihood ratio test comparing the linear mixed-effects regression model with an ordinary linear regression model in all cases, which is highly significant, meaning ordinary regression was to be rejected.

[c] Denominators were calculated by adding patients with complete follow-up and patients with a known hospitalization before being unavailable for follow-up.

[d] n = 185 in the hypertonic saline group; n = 202 in the normal saline group.

[e] Risk differences adjusted for age, respiratory syncytial virus infection status, duration of symptoms before enrollment, previous use of systemic corticosteroids, feeding, heart rate, oxygen saturation, and initial RDAI score.

[f] n = 379 in the hypertonic saline group; n = 378 in the normal saline group.

[g] n = 379 in the hypertonic saline group; n = 375 in the normal saline group.

[h] n = 377 in the hypertonic saline group; n = 374 in the normal saline group. The RACS was calculated by adding changes in RDAI score before and after treatment plus a point for each 10% change in respiratory rate above 5% (eg, −1 for a decrease of 6%-15% and −2 for a decrease of 16%-25%; negative values signify improvement).[18]

Discussion

Our multicenter, double-blind randomized clinical trial of 777 infants with moderate to severe acute bronchiolitis in the pediatric ED found no significant difference in hospital admission rates after 24 hours whether the infants received nebulized HS or NS (risk difference, -3.2%; 95% CI, -8.7% to 2.2%; $P = .25$). We also did not find any difference between the HS and NS groups for PICU admission, admission by day 28, or admission among infants younger than 3 months. To our knowledge, this randomized clinical trial is the largest to evaluate the efficacy of nebulized HS treatment in pediatric ED outpatient management of bronchiolitis. Our results contrast those from a recent meta-analysis[10] that included 7 studies[15,17,19,21-24] and 951 infants in outpatient settings that found a moderate benefit with the HS treatment on admission rates (relative risk, 0.80; 95% CI, 0.67-0.96; $P = .01$).

Our study of 2 saline nebulizations was sufficiently powered to allow the detection of a 10% decrease in the hospitalization rate. Because the lower limit of the 95% CI for the adjusted risk difference in the mixed-effects regression model was −8.7%, our study rules out the possibility that HS treatment can reduce hospitalizations by at least 10 percentage points.

We found only mild adverse events and no serious adverse events, in agreement with a meta-analysis[10] of 24 previous trials of a total of 1557 infants receiving nebulized HS treatment. However, infants in the HS group experienced adverse events significantly more often than those in the NS group (8.9% vs 3.9%; risk difference, 5.0%; 95% CI, 1.6%-8.4%; $P = .005$). Because of the low benefit of HS nebulization and the higher risk of adverse events, our results strongly argue against the use of HS treatment for infants with a first episode of bronchiolitis in pediatric EDs.

In our study, the mean length of stay of admitted infants was 3.7 days, which is similar to the 3.6 days described in a recent review,[13] and did not differ between the HS and NS groups. Likewise, hospitalization between hour 24 and day 28 applies to only 24 children in each group, indicating that we included infants with typical acute bronchiolitis. The 24 participating centers were spread throughout the country, allowing a nationally representative patient cohort. The overall hospitalization rate was 50%, which appears to be representative of infants with acute bronchiolitis in pediatric EDs because infants with milder forms with no respiratory distress were not eligible. Previous studies[21,23,24] performed in pediatric EDs were heterogeneous; some studies[15,19] included infants with a milder form of bronchiolitis, whereas other studies, such as the study by Florin et al[22] and our study, included infants with moderate to severe bronchiolitis. The hospitalization rates in these 3 studies[15,19,22] varied from 36% to 68%, whereas hospitalization rates varied among centers from 31.6% to 83.3% in our study. The study was managed according to national

guidelines, and the baseline characteristics were similar in both groups. Despite our efforts to limit the effect of practice variability, our results seemed to reveal that the propensity to admit infants with bronchiolitis varies markedly regardless of objective measures of illness. This outcome is evident in Table 3 in the large estimated variance of the random effect for center. The variance is 0.23 (95% CI, 0.08-0.70), which means the SD of the random effect is 0.48. To put this magnitude in context, the log of the estimated odds for the age of 1 to 3 months is log(1.85) = 0.62. Thus, the SD of the center random effect is almost as large as the association between young age and admission.

Although our study failed to find any significant difference in hospital admission rate between the HS and NS groups, we found a greater improvement in the RDAI score and RACS in the HS group. This finding suggests that HS treatment can help to alleviate symptoms in the short term, even though it does not prevent hospitalization. As reported previously, an association between RDAI score and hospital admission seems to exist but at a moderate magnitude.[25] In fact, the study by Wu et al[15] found inverse results, with a decrease in hospital admissions in the HS group compared with the NS group but no difference in the decrease of RDAI score and RACS between the HS and NS groups.

Table 3. Mixed-Effects Logistic Regression Model for Hospitalization Admission, Taking Into Account the Random Effect for the Center[a]

Variable	Adjusted OR[b] (95% CI)	*P* Value
Hypertonic saline treatment	0.87 (0.63-1.20)	.38
Age 1-3 mo	1.85 (1.31-2.60)	<.001
Duration of symptoms before enrollment	0.98 (0.93-1.04)	.59
Previous systemic corticosteroids	1.15 (0.75-1.77)	.52
Reduced feeding	2.35 (1.48-3.75)	<.001
Heart rate >160 /min	2.12 (1.50-2.99)	<.001
Oxygen saturation <95%	9.29 (4.90-17.60)	<.001
Initial RDAI score >8	1.81 (1.28-2.57)	<.001
RSV infection	2.17 (1.25-3.78)	.005

Abbreviations: OR, odds ratio; RDAI, Respiratory Distress Assessment Instrument; RSV, respiratory syncytial virus.

[a] Center was included as a random effect (variance, 0.23; 95% CI, 0.08-0.70). *P* < .001 for the likelihood ratio test comparing the mixed-effects model with an ordinary logistic regression, which is highly significant, meaning ordinary logistic regression was to be rejected.

[b] A total of 750 observations were included in the mixed-effects model.

Limitations

The study has some limitations. Infants with the most severe form of acute bronchitis who required direct PICU admission and patients with milder forms of acute bronchiolitis were not eligible. We cannot exclude that nebulized HS could have efficacy in these populations. Similarly, our results cannot be extrapolated to preterm infants. The use of thresholds for respiratory rate and oxygen saturation to define respiratory distress as an inclusion criterion is a limitation because these factors vary across conditions.[25] Normal saline treatment is a control intervention and not a placebo and thus may have had an effect, such as on the RDAI score. However, the use of NS allowed the trial to be double-blind.[12] Attending personnel, research nurses, and physicians were not available 24 hours per day 7 days per week, which could have limited the representativeness of our population. We performed 2 nebulizations in the pediatric ED and cannot exclude that a different regimen could have a different effect. Socioeconomic status has not been recorded in our study and has not been included in our models, although it may have an important effect on the decision to admit a patient.

We used a 3% concentration of HS, which is the most commonly studied, but the HS concentration was higher in a few studies,[10,19] up to 7%. We used HS and NS alone, whereas a meta-analysis[10] found that most previous studies used a study medication that combined saline solution with a bronchodilator, such as epinephrine, albuterol, or terbutaline. The theory behind the additional use of a bronchodilator with HS was to prevent bronchospasm rather than to improve efficacy.[16] There was no evidence of benefit for any of these mixed solutions vs HS solution alone for efficacy or safety.[10,16]

As for most of previous studies, we included only infants with a first episode of bronchiolitis; infants with recurrent wheezing were not included.[10] The high percentage of RSV (86%) is another factor that indicates that we recruited infants with typical acute bronchiolitis.

Table 4. Per-Protocol Adverse Events

Adverse Event	No. (%) of Events or Infants			
	Hypertonic Saline Adverse Events	Infants Involved (n = 392)	Normal Saline Adverse Events	Infants Involved (n = 384)
Worsening of cough with respiratory distress	2	2 (0.5)	5	5 (1.3)
Worsening of cough without respiratory distress	30	26 (6.6)	4	3 (0.8)
Bronchospasm	0	0	3	3 (0.8)
Fainting	0	0	1	1 (0.3)
Desaturation	1	1 (0.3)	2	2 (0.5)
Tachycardia	1	1 (0.3)	1	1 (0.3)
Eruption	2	2 (0.5)	0	0
Vomiting	4	3 (0.8)	0	0
Total	40	35 (8.9)[a]	16	15 (3.9)[a]

[a] Risk difference between both groups was 5.0% (95% CI, 1.6%-8.4%; *P* = .005) calculated using a linear regression model.

Conclusions

Although short-term improvements in the RDAI score and RACS were greater in the HS group, overall admission rates were not improved. Our study failed to demonstrate superiority of nebulized HS treatment compared with NS treatment in reducing the hospitalization rate of infants with acute bronchiolitis in the pediatric ED. Although no serious adverse events occurred, mild adverse events were more frequently experienced by infants in the HS group. The use of HS treatment for infants with a first episode of acute bronchiolitis in the pediatric ED cannot be recommended.

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REFERENCES

1. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360(6):588-598.

2. Johnson LW, Robles J, Hudgins A, Osburn S, Martin D, Thompson A. Management of bronchiolitis in the emergency department: impact of evidence-based guidelines? *Pediatrics*. 2013;131 (suppl 1):S103-S109.

3. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr. Temporal trends in emergency department visits for bronchiolitis in the United States, 2006 to 2010. *Pediatr Infect Dis J*. 2014;33(1):11-18.

4. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. *Pediatrics*. 2013;132(1):28-36.

5. Pelletier AJ, Mansbach JM, Camargo CA Jr. Direct medical costs of bronchiolitis hospitalizations in the United States. *Pediatrics*. 2006;118(6):2418-2423.

6. Meissner HC. Viral bronchiolitis in children. *N Engl J Med*. 2016;374(1):62-72.

7. Ralston SL, Lieberthal AS, Meissner HC, et al; American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474-e1502.

8. Gajdos V, Katsahian S, Beydon N, et al. Effectiveness of chest physiotherapy in infants hospitalized with acute bronchiolitis: a multicenter, randomized, controlled trial. *PLoS Med*. 2010;7(9):e1000345.

9. Farley R, Spurling GK, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age. *Cochrane Database Syst Rev*. 2014;(10):CD005189.

10. Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C. Nebulized hypertonic saline for acute bronchiolitis: a systematic review. *Pediatrics*. 2015;136(4):687-701.

11. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev*. 2013;(7):CD006458.

12. Mandelberg A, Amirav I. Hypertonic saline or high volume normal saline for viral bronchiolitis: mechanisms and rationale. *Pediatr Pulmonol*. 2010;45(1):36-40.

13. Brooks CG, Harrison WN, Ralston SL. Association between hypertonic saline and hospital length of stay in acute viral bronchiolitis: a reanalysis of 2 meta-analyses. *JAMA Pediatr*. 2016;170(6):577-584.

14. Zhang L. Hypertonic saline for bronchiolitis: a meta-analysis reanalysis. *J Pediatr*. 2016;176:221-224.

15. Wu S, Baker C, Lang ME, et al. Nebulized hypertonic saline for bronchiolitis: a randomized clinical trial. *JAMA Pediatr*. 2014;168(7):657-663.

16. Ralston S, Hill V, Martinez M. Nebulized hypertonic saline without adjunctive bronchodilators for children with bronchiolitis. *Pediatrics*. 2010;126(3):e520-e525.

17. Grewal S, Ali S, McConnell DW, Vandermeer B, Klassen TP. A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. *Arch Pediatr Adolesc Med*. 2009;163 (11):1007-1012.

18. Lowell DI, Lister G, Von Koss H, McCarthy P. Wheezing in infants: the response to epinephrine. *Pediatrics*. 1987;79(6):939-945.

19. Jacobs JD, Foster M, Wan J, Pershad J. 7% Hypertonic saline in acute bronchiolitis: a randomized controlled trial. *Pediatrics*. 2014;133 (1):e8-e13.

20. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974.

21. Anil AB, Anil M, Saglam AB, Cetin N, Bal A, Aksu N. High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. *Pediatr Pulmonol*. 2010;45(1):41-47.

22. Florin TA, Shaw KN, Kittick M, Yakscoe S, Zorc JJ. Nebulized hypertonic saline for bronchiolitis in the emergency department: a randomized clinical trial. *JAMA Pediatr*. 2014;168(7):664-670.

23. Ipek IO, Yalcin EU, Sezer RG, Bozaykut A. The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis. *Pulm Pharmacol Ther*. 2011;24(6):633-637.

24. Sarrell EM, Tal G, Witzling M, et al. Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. *Chest*. 2002;122(6):2015-2020.

25. Fernandes RM, Plint AC, Terwee CB, et al. Validity of bronchiolitis outcome measures. *Pediatrics*. 2015;135(6):e1399-e1408.