



Impact of hypertonic saline on hospitalization rate in infants with acute bronchiolitis: A meta-analysis

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Abstract

Aim: This meta-analysis aimed to assess the efficacy of nebulized hypertonic saline (HS) on the rate of hospitalization in infants with acute bronchiolitis in the Emergency Department (ED) setting.

Method: We searched PubMed, Virtual Health Library-BVS and Cochrane CENTRAL from inception until January 31, 2018. We selected randomized trials that compared nebulized HS with normal saline (NS) or standard care in children up to 24 months of age with acute bronchiolitis in the ED setting. We conducted random-effects meta-analyses to estimate the risk ratio (RR) and 95% confidence interval (CI).

Results: A total of 293 records were screened and 8 trials involving 1708 patients were included. The meta-analysis showed a 16% reduction in the risk of hospitalization among patients treated with HS compared to NS (risk ratio [RR]: 0.84, 95% confidence interval [CI]: 0.71-0.98, $P = 0.03$). A significant effect of HS in reducing the risk of hospitalization was found only in the subgroup analyses of trials in which HS was mixed with bronchodilators, multiple doses (≥ 3) were given, and risk of bias was low.

Conclusions: Nebulized hypertonic saline may potentially reduce the risk of hospitalization in infants with acute bronchiolitis in the ED setting. Quality of evidence is moderate due to substantial clinical heterogeneity between studies and large multicenter trials are still warranted.

KEY WORDS

bronchiolitis, emergency department, hospitalization rate, hypertonic saline, meta-analysis, normal saline, systematic review

1 | INTRODUCTION

Despite the high burden of disease, no effective treatment is currently available for acute bronchiolitis in infants. Hypertonic saline (HS) is believed to hydrate airway mucus, improve mucociliary clearance, and reduce airway wall edema which may be beneficial to infants with

acute bronchiolitis.¹ However, some of recent trials, especially those published in 2013 and thereafter,²⁻⁴ have not confirmed previously reported effects of nebulized HS in reducing length of stay among patients hospitalized with bronchiolitis. The reasons for conflicting results between earlier and later inpatient trials have not yet been fully elucidated.⁵

Many infants with acute bronchiolitis are treated in the emergency department (ED). It is estimated that, between 2006 and 2010, there were approximately 1 435 110 ED visits with bronchiolitis in children under 2 years of age in the USA.⁶ There are only a few trials that assess

Abbreviations: BVS, virtual health library; ED, emergency department; HS, hypertonic saline; LILACS, latin american and caribbean center on health sciences information; NS, normal saline; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

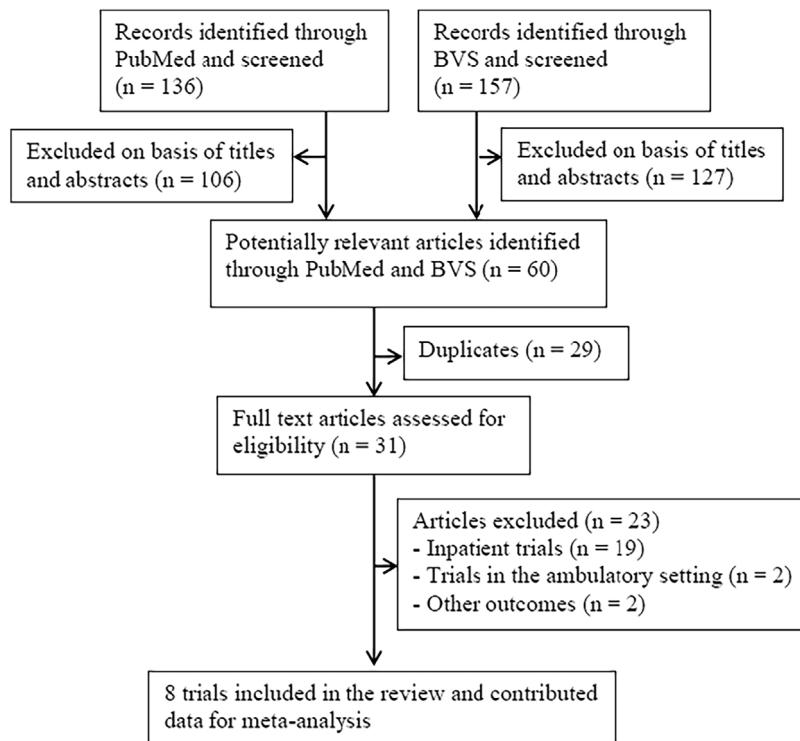


FIGURE 1 PRISMA flow diagram of study selection/a flow diagram describes the process of identification, screening, assessment for eligibility, and inclusion of studies

the effects of nebulized HS on the risk of hospitalization in infants with acute bronchiolitis in the ED. Two most recent meta-analyses have showed a statistically significant reduction in the risk of hospitalization related to nebulized HS,^{7,8} however, they included trials conducted in both ambulatory (outpatient) and ED settings. Infants attending the ED may have more severe bronchiolitis than those seen at ambulatory care service or outpatient clinic. On the other hand, they present at an earlier disease stage compared to inpatients. Thus, infants with acute bronchiolitis treated at the ED may have a more favourable response to nebulized HS. We conducted this meta-analysis to assess especially the effects of nebulized HS on the risk of hospitalization in infants with acute bronchiolitis in the ED setting. We also assessed the influence of several factors on the effect size of HS.

2 | METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to conduct and report this review.⁹ The review protocol has been approved by the Institutional Review Board at Faculty of Medicine of Federal University of Rio Grande. We did not register the review protocol, but it is available when required.

We searched PubMed and the Virtual Health Library (BVS) (<http://bvsalud.org>) which contains MEDLINE, LILACS (Latin American and Caribbean Center on Health Sciences Information) and more than 20 other databases. All databases were searched from inception until January 31, 2018, using the following search strategy: bronchiolitis AND ("hypertonic saline" OR "3% saline" OR "5% saline" OR "7% saline"). We

also searched Cochrane CENTRAL and checked reference lists of retrieved original studies and systematic reviews for additional trials.

We included randomized trials that compared the effects of nebulized HS ($\geq 3\%$) with normal saline (NS) or standard care on the rate of hospitalization in children up to 24 months of age with acute bronchiolitis in the ED setting. We excluded studies that included patients with history of previous episode of wheezing and there were no separate data for patients with the first episode of wheezing.

Two authors (CBG, OSF) independently assessed the titles and abstracts of all citations identified by the searches. We obtained the full articles when they met the inclusion criteria or there were insufficient data in the title and abstract for assessment of eligibility. The definitive inclusion of trials was made after reviewing the full-text articles.

One author (LZ) extracted trial data using a standardized form. These were checked by another author (CBG). We extracted the following data: 1) Trial identification: first author, year of publication, country of study; 2) Methods: study design, methods of random sequence generation, allocation concealment and blinding, description of withdrawal; 3) Participants: age, gender, sample size, inclusion, and exclusion criteria; 4) Interventions and controls: concentration of saline, volume of saline, number and interval of administration, co-interventions; and 5) Outcomes: rate of hospitalization (the number of patients requiring inpatient hospitalization/the total number of patients randomized) in each treatment group, criteria for hospital admission.

Two authors (OSF, LZ) independently assessed the risk of bias in included trials by examining the six key domains according to the Cochrane Handbook¹⁰: allocation sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome

TABLE 1 Characteristics of included trials

Study ID and country	Participants	Intervention and control	Criteria for hospital admission
Grewal et al ¹² Canada	Inclusion criteria: infants aged 6 weeks to 12 months with mild to moderate bronchiolitis, defined as first episode of wheezing and symptoms of viral RTI, S_aO_2 85-96% and RDAI score four or higher.RSV positivity: 82.2% (37/45). Mean age (months): 5.6 HS group; 4.4 NS group	2.5 mL 3% HS + 0.5 mL 2.25% racemic epinephrine (n = 24); 2.5 mL NS + 0.5 mL 2.25% racemic epinephrine (n = 24). Single dose given at 0 min, but a second dose could be added as needed. The quantity of N_aCL : 75-150 mg HS group, 22.5-45 mg (NS group).	Not reported
Anil et al ¹³ Turkey	Inclusion criteria: infants aged 6 weeks to 24 months with first episode of bronchiolitis, defined by symptoms of upper RTI, and bilateral wheezing and/or crackles on auscultation and Wang CSS between one and nine.RSV positivity: test not available.Mean age (months): 9.4-9.7 HS groups; 9.1-10.4 NS groups.	4 mL 3% HS + 1.5 mg epinephrine (n = 39); 4 mL NS + 1.5 mg epinephrine (n = 38); 4 mL 3% HS + 2.5 mg salbutamol (n = 36); 4 mL NS + 2.5 mg salbutamol (n = 36); 4 mL NS (n = 37). Two doses given at 0 and 30 min.The quantity of N_aCL : 240 mg HS group, 72 mg (NS group)	Decision made by attending physician, according to AAP guidelines.
Kuzik et al ¹⁴ Canada	Inclusion criteria: children aged up to 24 months presenting with moderately severe viral bronchiolitis, defined by history of preceding viral upper RTI, wheezing or crackles on chest auscultation, and an S_aO_2 : $\leq 94\%$ on room air or RDAI ≥ 4 . RSV positivity: 46.6% (21/45).Mean age (months): 8.6 HS group; 9.2 NS group.	4 mL 3% HS + 1 mg salbutamol (n = 29); 4 mL NS + 1 mg salbutamol (n = 21). Three doses given over a 1 h period. The quantity of N_aCL : 360 mg HS group, 108 mg (NS group)	Decision made by attending physician, but no details reported.
Ipek et al ¹⁵ Turkey	Inclusion criteria: children <2 years with history of preceding viral upper RTI followed by wheezing and crackles on auscultation and Wang CSS between four and eight. RSV positivity: test not available. Mean age (months): 7.9-8.4 HS groups; 7.4-8.1 NS groups.	4 mL 3% HS + 0.15 mg/kg salbutamol (n = 30); 4 mL NS + 0.15 mg/kg salbutamol (n = 30); 4 mL 3% HS (n = 30); 4 mL NS (n = 30). Three doses given at 0, 20, and 40 min.The quantity of N_aCL : 360 mg HS group, 108 mg (NS group)	CSS deteriorated and/or S_aO_2 $< 85\%$ on room air.
Florin et al ¹⁶ USA	Inclusion criteria: children <24 months with moderate to severe bronchiolitis, defined as first episode of wheezing associated with signs and symptoms of upper RTI and RDAI score between four and 15. RSV positivity: test not available. Mean age (months): 7.2 HS group; 6.1 NS group.	4 mL 3% HS (n = 31); 4 mL NS (n = 31). Single dose given at 0 min. The quantity of N_aCL : 120 mg HS group, 36 mg (NS group)	Decision made by attending physician, but no details reported.
Jacobs et al ¹⁷ USA	Inclusion criteria: infants aged 6 weeks to <18 months with moderate to severe bronchiolitis, defined as viral RTI and first episode of wheezing, Wang CSS ≥ 4 and $S_aO_2 > 85\%$. RSV positivity: 60.2% (41/68). Mean age (months): 6.0 HS group; 5.6 NS group.	3 mL 7% HS + 0.5 mL 2.25% racemic epinephrine (n = 52); 3 mL NS + 0.5 mL 2.25% racemic epinephrine (n = 49). Single dose given at 0 min.The quantity of N_aCL : 210 mg HS group, 27 mg (NS group)	Decision made by attending physician, but no details reported.
Wu et al ¹⁸ USA	Inclusion criteria: children <24 months with first episode of bronchiolitis during bronchiolitis season.RSV positivity: 62.2% (84/135). Mean age (months): 6.5 HS group; 6.4 NS group.	4 mL 3% HS (n = 211); 4 mL NS (n = 197). One dose given at enrolment, but two additional doses could be given every 20 min. The quantity of N_aCL : 120-360 mg HS group, 36-108 mg (NS group)	Decision made by attending physician ($S_aO_2 < 92\%$, increased work of breathing or inadequate oral intake).
Angoulvant et al ¹⁹ France	Inclusion criteria: infants aged 6 weeks to 12 months with first episode bronchiolitis, defined as viral upper RTI plus wheezing and/or crackles on chest auscultation with respiratory distress. RSV positivity: 88.7% (671/756). Median age (months): 3.0 HS group; 3.0 NS group.	4 mL 3% HS (n = 387); 4 mL NS (n = 390). Two doses given at 0 and 20 min.The quantity of N_aCL : 240 mg HS group, 72 mg (NS group)	Decision made by attending physician, but no details reported.

AAP, American Academy of Pediatrics; CSS, clinical severity score; HS, hypertonic saline; NS, normal saline; RDAI, respiratory distress assessment instrument; RTI, respiratory tract infection; S_aO_2 : oxygen saturation.

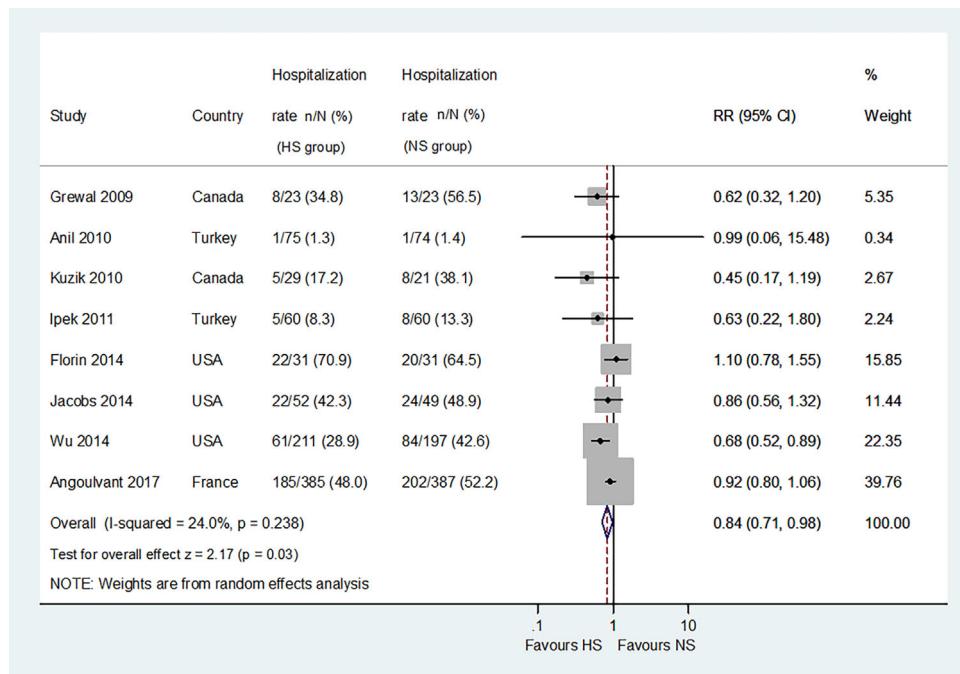


FIGURE 2 Effects of nebulized HS on the reduction of risk of hospitalization/black dot represents point estimate of risk ratio, horizontal line represents 95%CIs, and grey square area represents the weight of each trial. Diamond represents overall effect size and 95%CI

reporting, and other sources of bias. We graded each potential source of bias as yes, no or unclear, relating to whether the potential for bias was low, high, or unknown. The same two authors independently assessed the quality of evidence of this review using the GRADE approach recommended by Cochrane Handbook.

The effect measure was risk ratio (RR) and 95% confidence interval (CI). We used the random-effects method for meta-analysis which incorporates an estimate of between study variation (heterogeneity) into the calculation of the common effect. The random-effects method and the fixed-effect method will yield identical results when there is no significant

heterogeneity across studies. Otherwise, the random-effects method is more conservative than the fixed-effects method and provides estimates with wider CI.¹⁰

We assessed heterogeneity in results between studies using the Cochrane Q-test ($P < 0.1$ considered significant) and the I^2 statistic. The I^2 statistic ranges from 0% to 100% and measures the degree of inconsistency across studies.¹¹ An I^2 value greater than 50% was considered to indicate substantial heterogeneity.

We conducted a priori subgroup analyses based on patient's upper age limits, number of doses of saline solution, concomitant use of

TABLE 2 Subgroup analyses of the effects of HS on risk of hospitalization in infants with acute bronchiolitis

Subgroups	Trials (n)	Patients (n)	Effect size (RR, 95%CI)	P-value	I^2 (%)
Upper age limits					
Up to 12 months	2	818	0.86, 0.64-1.15	0.31	26
Up to 18-24 months	6	890	0.80, 0.62-1.02	0.08	27
HS mixed with bronchodilator					
Yes	5	466	0.72, 0.52-0.99	0.04	0
No	3	1242	0.87, 0.68-1.11	0.27	66
Number of nebulization					
1-2 doses	5	1130	0.92, 0.81-1.04	0.21	0
Multiple-doses (≥ 3)	3	578	0.65, 0.51-0.84	0.01	0
Sample size					
<200	6	528	0.86, 0.66-1.11	0.24	8
≥ 200	2	1180	0.81, 0.59-1.09	0.16	75
Risk of bias					
Low	6	1439	0.83, 0.69-1.00	0.05	43
Unclear/high	2	269	0.66, 0.24-1.78	0.41	0

bronchodilator, sample size, and risk of bias in the trials. We conducted a post hoc sensitivity analysis excluding trials with very low (<20%) or very high (>80%) rate of hospitalization in the NS group. The hospitalization rate in the control group may reflect illness severity and criteria for hospital admission. We assessed publication bias using a funnel plot and Egger's test.

All meta-analyses were performed using Stata version 11.0 (Stata-Corp, College Station, TX).

3 | RESULTS

The search strategy identified 293 records from PubMed and BVS. After screening the titles and abstracts, we retrieved 31 potentially relevant full text articles for further evaluation. Twenty-three trials were excluded (19 inpatient trials, two trials in the ambulatory setting, and two trials used other outcomes). No additional trials were found from other sources. Thus, eight ED trials^{12–19} involving 1708 participants (866 HS, 842 NS) were included in the meta-analysis (Figure 1). We contacted the two trialists^{13,18} for unpublished data regarding allocation concealment, and one of them provided detailed information.¹⁸ Table 1 summarizes the characteristics of eight randomized, parallel-group, double-blind, controlled trials.

All but two trials had low risk of bias (Supplementary E-Table S1). One trial had high risk of selection bias due to inappropriate randomization and allocation concealment.¹⁵ Another trial used adequate methods for random sequence generation, but did not report allocation concealment which makes it impossible to assess the potential risk of selection bias.¹³

The meta-analysis of eight trials showed a relative reduction of 16% in the risk of hospitalization among patients treated with HS compared to NS (RR 0.84, 95%CI 0.71–0.98, $P = 0.03$, $I^2 = 24\%$) (Figure 2). The sensitivity analysis excluding two trials^{13,15} with hospitalization rate <20% in the NS group did not significantly change the results of the meta-analysis (RR 0.83, 95%CI 0.69–1.00, $P = 0.05$, $I^2 = 43\%$).

Table 2 shows the results of subgroup analyses. A significant effect of HS in reducing the risk of hospitalization was found only in the pooled analyses of trials in which HS was mixed with bronchodilators,^{12–15,17} multiple doses (≥ 3) were given,^{14,15,18} and risk of bias was low.^{12,14,16–19}

All but one trial¹⁵ presented safety data. No serious adverse events (AEs) were reported. Three trials reported at least one event,^{12,18,19} and worsening of cough was the most frequently reported minor AEs which occurred in 6.6% of patients treated with HS and 0.8% of patients treated with NS.¹⁹

Funnel plot and Egger's-test did not suggest a major publication bias ($P = 0.27$ for Egger's-test) (Supplementary E-Figure S1). There were no serious concerns on four domains of GRADE approach (risk of bias in most included trials, indirectness, imprecision, and publication bias). Despite no statistical heterogeneity found across studies, we downgraded the quality of evidence to moderate due to substantial clinical heterogeneity between

studies regarding patient's characteristics, treatment regimen, and outcome measures (criteria for hospital admission).

4 | DISCUSSION

This meta-analysis of eight randomized trials revealed a statistically significant effect of nebulized HS in reducing the risk of hospitalization among infants with acute bronchiolitis in the ED setting. A relative reduction of 16% in the risk of hospitalization should be considered potentially clinically relevant given the large number of ED visits and significant burden of hospitalization for acute bronchiolitis in infants.^{6,20}

Two most recent meta-analyses have showed that nebulized HS could significantly reduce hospitalization rate in infants with acute bronchiolitis. The first was an updated Cochrane review including 28 trials, of which seven were conducted at the ED and one was conducted at ambulatory department.⁷ The pooled analysis of eight ED/outpatient trials revealed a RR of 0.86 (95%CI 0.76–0.98) for hospitalization. The second was a cumulative meta-analysis including 18 inpatient trials and eight outpatient trials (seven at the ED and one at the ED and outpatient department).⁸ The pooled analysis of eight ED/outpatient trials showed a cumulative RR of 0.77 (95%CI 0.61–0.95) for hospitalization. Both previous meta-analyses excluded one ED trial¹⁴ that recruited patients with history of previous episode of wheezing, but there were separate data for those with the first episode of wheezing. We included this trial in the review, but only the data of patients with the first episode of wheezing were used for analysis. The current meta-analysis of eight ED trials showed a RR of 0.84 (95%CI 0.71–0.98), almost identical to the results of the updated Cochrane review.⁷

Two large trials^{18,19} contributed 62% to the weight of the current meta-analysis, but they presented inconsistent results. Both trials were generally well-designed and conducted. One trial involving 408 patients from two pediatric EDs in the USA reported a relative reduction of 51% in the risk of hospitalization among patients treated with up to three doses of 3% HS compared to NS.¹⁸ The major weakness of this trial is the use of convenience sampling, and only one third (1254/3447) of the target population were assessed for eligibility. This may limit the representativity of study sample, but it could be expected to affect both treatment groups equally. In contrast, another multicenter trial involving 777 patients from 24 French pediatric EDs did not find significant benefits of two doses of 3% HS on hospitalization rate compared to NS.¹⁹ The hospitalization rates varied remarkably among 24 participating centers (31.6–83.3%) which may reflect substantial heterogeneity of patients and/or outcome measures across study sites given that no clearly-defined criteria were used for hospital admission in this trial.

We conducted subgroup analyses to assess the influence of several factors on the effects of HS. A significant effect of HS in reducing the risk of hospitalization was found only in the pooled analyses of trials in which HS was mixed with bronchodilators, multiple doses (≥ 3) were given, and risk of bias was low. However, cautions are

needed when interpreting the results of indirect comparisons through subgroup analyses.

As shown by previous systematic reviews^{5,7} and this meta-analysis, nebulized HS has good safety profile with minor adverse effects in infants with acute bronchiolitis. Worsening of cough was the most frequently reported adverse event, but it is generally mild and self-limiting, and no intervention or additional treatment is necessary. It has been proposed that HS inhalation can cause sputum induction and cough, which can help to clear the sputum from the airways and thus improve airway obstruction.¹ From this point of view, increased coughing should be considered an expected, and therapeutic response but not an adverse effect.

The substantial variation of hospitalization rate between studies (from 1.4% to 64.5% in the NS group and from 1.3% to 70.9% in the HS group) is one of the main limitations of this review. Two trials^{13,15} with very low hospitalization rates in both treatment arms have mainly contributed to such a variation. However, the sensitivity analysis excluding the two trials did not significantly change the results of the meta-analysis. All but one trial¹⁷ used 3% hypertonic saline, however, the delivered quantity of NaCl in both HS and NS groups varied substantially between studies, and this may be one of the sources of heterogeneity. Another limitation is relatively small number of included trials and small sample size in the majority of included trials which led to a relatively low statistical power of this review, especially for some subgroup analyses, and sensitivity analysis.

In the same issue where the French multicenter trial was published, Ralston SL²¹ presented an interesting editorial entitled "Could this be the last word on hypertonic saline?" There are at least two arguments that justify further trials in the ED setting. Firstly, no individual trial could definitively confirm or deny the potential benefits of HS. Secondly, the body of evidence provided by this meta-analysis shows a potentially clinically relevant effect of HS in reducing the risk of hospitalization among infants with acute bronchiolitis in the ED. However, the quality of evidence is at best moderate which needs to be verified by further studies. If a relative reduction of 16% on the risk of hospitalization would be confirmed by further trials and the treatment is used in a population with 40-50% hospitalization rates, it can be expected to decrease the rates to 34-42%. This corresponds to a number needed to treat of 12-16. The treatment of 12-16 infants with up to three doses of nebulized HS within one hour in the ED setting to prevent one hospitalization seems to be cost-effective given the mean cost of \$3799 per hospitalization related to bronchiolitis,²⁰ and significant emotional and social burden related to hospitalization.

Several major challenges must be faced in conducting clinical trials in infants with acute bronchiolitis. There is no consensus on the clinical definition of acute viral bronchiolitis. The current most frequently used definition "the first episode of wheezing in an infant" may include a heterogeneous group of patients with different underlying pathologies.²² Therefore, the development of valid diagnostic criteria for acute bronchiolitis in infants is urgently needed. Selection of reliable and clinically meaningful outcomes is another crucial issue. The hospitalization rate is an important clinical outcome for ED trials, but well-defined criteria for hospital admission should be established. Clinical

severity score, length of stay, need for intensive care, and rate of re-admission to hospital may also be considered as clinically relevant outcome measures. NS has been widely used as a comparator in bronchiolitis trials. NS may make double-blinding more feasible, however, a large mass of NaCl delivered as high volume NS inhalations could be sufficient to cause significant improvement in infants with acute bronchiolitis,¹ and this may attenuate the difference of effects between NS and HS groups. Selection of the appropriate control group is a challenge for future research, and use of standard support care may be an option. Saline solutions are usually given via an oxygen driven nebulizer. A good seal between mask and face is essential for an effective drug delivery in infants.²³ Adequacy of delivery system and inhalation technique should be taken into account when conducting new trials. Further trials should have sufficient statistical power to detect clinically relevant effects of the intervention.

In conclusion, moderate evidence suggests that nebulized hypertonic saline may potentially reduce the risk of hospitalization in infants with acute bronchiolitis in the ED setting. Large multicenter trials are still warranted.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

AUTHORS' CONTRIBUTIONS

LZ conceptualized and designed the study, participated in trial selection, quality assessment, data collection and data analysis, drafted the protocol, and the review article. CB Gunther provided input for study design, participated in trial selection, quality assessment and data collection, and critically reviewed the manuscript. OSF provided input for study design, participated in trial selection, quality assessment and data collection, and critically reviewed the manuscript. TPK provided input for study design and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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