Nebulized Hypertonic Saline for Acute Bronchiolitis: A Systematic Review

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abstract

BACKGROUND AND OBJECTIVE: The mainstay of treatment for acute bronchiolitis remains supportive care. The objective of this study was to assess the efficacy and safety of nebulized hypertonic saline (HS) in infants with acute bronchiolitis.

METHODS: Data sources included PubMed and the Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information up to May 2015. Studies selected were randomized or quasi-randomized controlled trials comparing nebulized HS with 0.9% saline or standard treatment.

RESULTS: We included 24 trials involving 3209 patients, 1706 of whom received HS. Hospitalized patients treated with nebulized HS had a significantly shorter length of stay compared with those receiving 0.9% saline or standard care (15 trials involving 1956 patients; mean difference [MD] −0.45 days, 95% confidence interval [CI] −0.82 to −0.08). The HS group also had a significantly lower posttreatment clinical score in the first 3 days of admission (5 trials involving 404 inpatients; day 1: MD −0.99, 95% CI −1.48 to −0.50; day 2: MD −1.45, 95% CI −2.06 to −0.85; day 3: MD −1.44, 95% CI −1.78 to −1.11). Nebulized HS reduced the risk of hospitalization by 20% compared with 0.9% saline among outpatients (7 trials involving 951 patients; risk ratio 0.80, 95% CI 0.67–0.96). No significant adverse events related to HS inhalation were reported. The quality of evidence is moderate due to inconsistency in results between trials and study limitations (risk of bias).

CONCLUSIONS: Nebulized HS is a safe and potentially effective treatment of infants with acute bronchiolitis.

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Dr Zhang conceptualized and designed the study, participated in trial selection, quality assessment, data collection and data analysis, and drafted the protocol and the review article; Dr Mendoza-Sassi provided input for study design, critically reviewed the protocol and the review article, and participated in trial selection, quality assessment, and data collection; Drs Klassen and Wainwright provided input for study design, and critically reviewed the protocol and review article; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Acute bronchiolitis in infancy, mainly caused by respiratory syncytial virus (RSV), is the most common lower respiratory infection and the leading cause of hospitalization in children younger than 2 years. In the United States, acute bronchiolitis in infancy is responsible for ~150 000 hospitalizations each year at an estimated cost of $500 million.[1,2] From 1992 to 2000, bronchiolitis accounted for ~1 868 000 emergency department (ED) visits for children younger than 2 years.[3] In the United Kingdom, hospital admissions for acute bronchiolitis increased from 21 330 in 2004 and 2005 to 33 472 in 2010 and 2011.[4]

Globally, it has been estimated that, in 2005, at least 33.8 million episodes of RSV-associated acute lower respiratory infections (ALRIs) occurred in children younger than 5 years, with incidence in developing countries more than twice that of industrialized countries.[5] In the same year, RSV-associated severe ALRIs were responsible for ~3.4 million hospitalizations and 66 000 to 199 000 deaths in young children worldwide, with 99% of these deaths occurring in developing countries.

Despite its high incidence and morbidity, there are few effective therapies for acute bronchiolitis in infancy, and the mainstay of treatment remains supportive care.[6,7] Given the theoretical effects of hypertonic saline (HS) in reducing airway edema, unblocking mucus plugging, and improving mucociliary clearance, HS administered via nebulizer has been proposed as a potentially effective therapy for acute bronchiolitis in infants.[8] The first randomized trial, published in 2002, showed a significant effect of nebulized 3% saline solution in improving symptom scores among 65 outpatients with acute bronchiolitis, as compared with 0.9% normal saline (NS).[9] Over the past decades, a growing number of randomized trials have been undertaken to assess the effects and safety of nebulized HS in infants with acute bronchiolitis.[10–19] The Cochrane review published in 2013 including 11 randomized trials shows that nebulized 3% saline may significantly reduce the length of stay (LOS) in hospitalized infants with acute bronchiolitis and improve the clinical severity score (CSS) in both outpatient and inpatient populations.[20] Since then, new trials with conflicting results have been published, and an updated synthesis of the literature is needed.[21] We decided to conduct a new systematic review of currently available randomized trials to assess the efficacy and safety of nebulized HS in infants with acute bronchiolitis and to explore possible reasons for inconsistent results across trials. We hypothesize that nebulized HS may be less effective than previously claimed for acute bronchiolitis and effect size of HS may mainly depend on diagnostic accuracy of bronchiolitis and the treatment regimen.

METHODS

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for writing this systematic review and meta-analysis.[22] The full review protocol is available in the supplementary material. We used different data sources, search strategy, and statistical techniques than that used in the 2013 Cochrane review.[20]

Data Sources and Search Strategy

We searched PubMed and the Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information (BIREME), which contains Medline, CENTRAL, LILACS, IBECS, and >20 other databases (www.bireme.br). All databases were searched from inception until May 2015. The search strategy on PubMed was as follows: (bronchiolitis OR "acute wheezing" OR "respiratory syncytial virus" OR RSV OR "parainfluenza virus") AND ("hypertonic saline" OR "saline solution" OR 3% saline OR 5% saline OR saline). We used the limits of study type: clinical trial, randomized controlled trial (RCT). The search strategy on the Virtual Health Library of BIREME was as follows: bronchiolitis AND "hypertonic saline." There was no restriction on language of publication. We also conducted a search of the ClinicalTrials.gov trials registry to identify completed but unpublished trials. We checked reference lists of all primary studies and review articles for additional relevant trials.

Study Selection

To be included in this review, studies had to meet all of the following criteria: (1) study design: RCTs or quasi-RCTs; (2) participants: infants up to 24 months of age with diagnosis of acute bronchiolitis; we classified participants into "inpatients" who were admitted to the hospital and "outpatients" who attended at an ambulatory care unit or ED; (3) interventions and comparisons: nebulized HS (≥3%) alone or mixed with bronchodilator, compared with nebulized NS alone or mixed with same bronchodilator, or standard treatment; (4) outcome measures: primary outcomes included LOS in hospital for inpatients defined as time to actual discharge or time taken to be ready for discharge, and admission rate for outpatients, and secondary outcomes included CSSs, rate of readmission to hospital or ED, oxygen saturation, respiratory rate, heart rate, time for the resolution of symptoms/signs, duration of oxygen supplementation, results of pulmonary function tests, radiologic findings, and adverse events (AEs). We excluded studies that included patients who had had recurrent wheezing or were intubated and ventilated, and studies that assessed pulmonary function alone.

Two review authors (RM and LZ) independently assessed the titles and abstracts of all citations identified by the searches. We obtained the full articles when they appeared to meet the inclusion criteria or there were insufficient data in the title and abstract to make a clear decision for their inclusion. The definitive inclusion of trials was made after reviewing the full-text articles. We resolved any disagreements between the 2 review authors about study inclusion by discussion and consensus.

Data Extraction and Management

One review author (LZ) extracted study details from the included trials by using a standardized data extraction form. These were checked by another review author (RM). We resolved any disagreements by discussion and consensus. We extracted the following data: (1) study characteristics: year of publication, and country and setting of study; (2) methods: study design, methods of random sequence generation, allocation concealment and blinding, and description of withdrawal; (3) participants: sample size, age, gender, and inclusion and exclusion criteria; (4) interventions and controls: concentration and volume of saline, type of nebulizer, interval of administration, treatment duration, and cointerventions; (5) outcomes: primary and secondary outcomes as described previously. For continuous outcomes, we extracted sample size, mean (median) and precision of measurements (SD, SE, 95% confidence interval [CI], or interquartile range) of each treatment arm. For dichotomous outcomes, we extracted number of events and total number of participants of each treatment arm. We contacted the principal investigators of 5 trials[10,12,18,23,24] for methodological details and additional trial data, of whom 3[10,12,18] provided the requested data. We used Engauge digitizing software (digitizer.sourceforge.net) to extract the 25th and 75th percentiles of LOS in hospital from the figure of 1 paper.[24] For 2 trials,[24,25] we estimated mean and SD from median and interquartile range of LOS in hospital by using the method described by Wan et al.[26] When the trial recruited multiple groups, we combined them into HS and NS groups.[14,15,17,24,27]

Assessment of Risk of Bias

Two reviewers (RM and LZ) independently assessed the risk of bias in included trials by examining the 6 key domains according to the recommendations of the Cochrane Collaboration.[28] We graded each potential source of bias as yes, no, or unclear, relating to whether the potential for bias was low, high, or unknown. We resolved any disagreements between the 2 review authors by discussion and consensus.

Data Synthesis and Statistical Analysis

We performed meta-analysis for quantitative data synthesis whenever there were available data from the primary studies. For continuous outcomes, we used weighted mean difference (MD) between treatment groups and 95% CI as the metrics of effect size. Dichotomous data were synthesized by using risk ratios (RR) and 95% CIs as the effect measures. We used the random-effects model for meta-analyses.

We assessed heterogeneity in results between studies by using the Cochrane Q test ($P < .1$ considered significant) and the I^2 statistic. The I^2 statistic ranges from 0% to 100% and measures the degree of inconsistency across studies, with values of 25%, 50%, and 75% corresponding to low, moderate, and high heterogeneity, respectively.[29]

We conducted a priori subgroup analysis based on the treatment regimen. We also conducted post hoc subgroup analyses according to diagnosis criteria for bronchiolitis (presence of wheeze as essential diagnostic criteria and availability of virological testing) and risk of bias in the trials. We performed post hoc sensitivity analyses excluding open trials, trials in which mean and SD were estimated from median and interquartile range, trials with high risk of attrition bias (withdrawal rate >20% or data obtained from a part of study sample), and trials that did not

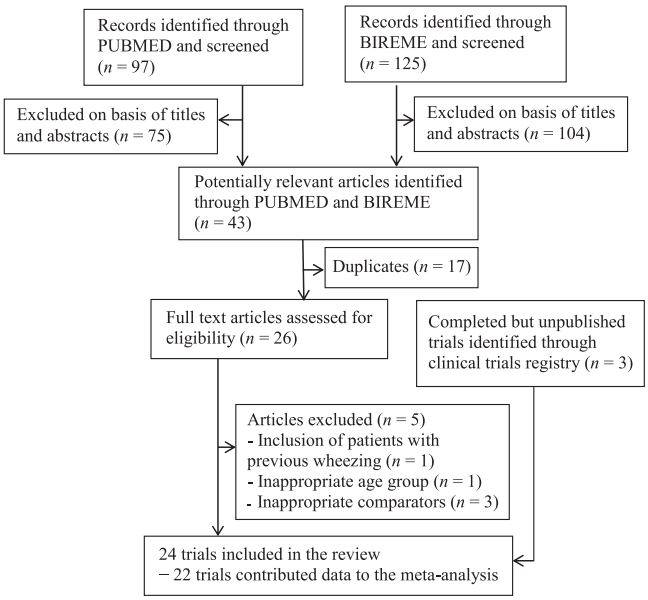

FIGURE 1
Flow diagram of study selection.

TABLE 1 Characteristics of Included Trials

Study ID and Country	Setting	Inclusion Criteria of Participants	RSV Positivity	Intervention and Control	Treatment Regimen	Outcomes
Al-Ansari 2010,[14] Qatar	Outpatient (ED)	Infants ≤18 mo with moderate to severe bronchiolitis, defined as a prodromal history of viral RTI followed by wheezing and/or crackles and Wang CSS of ≥4.	56.1% (96/171)	−5 mL 3% saline + 1.5 mg epinephrine (*n* = 58) −5 mL 5% saline + 1.5 mg epinephrine (*n* = 57) −5 mL 0.9% saline + 1.5 mg epinephrine (*n* = 56)	Saline solutions given on enrollment and every 4 h thereafter.	- Primary: Wang CSS at 48 h. - Secondary: Wang CSS at 24 and 72 h, LOS in ED, revisit to ED, AEs.
Anil 2010,[15] Turkey	Outpatient (ED)	Infants 6 wk to 24 mo with first episode of bronchiolitis, defined by symptoms of upper RTI and presence of bilateral wheezing and/or crackles on auscultation and Wang CSS between 1 and 9.	NA	−4 mL 3% saline + 1.5 mg epinephrine (*n* = 39) −4 mL 0.9% saline + 1.5 mg epinephrine (*n* = 38) −3% saline + 2.5 mg salbutamol (*n* = 36) −4 mL 0.9% saline + 2.5 mg salbutamol (*n* = 36) −4 mL 0.9% saline (*n* = 37)	Saline solutions given at 0 and 30 min.	- Primary: Wang CSS at 0, 30, 60, 120 min. - Secondary: SAO_2 in room air and heart rate at 0, 30, 60 and 120 min, AEs.
Everard 2014,[4] England and Wales	Inpatient	Children <12 mo with diagnosis of bronchiolitis defined as apparent viral RTI with airway obstruction (hyperinflation, tachypnea, and subcostal recession) and widespread crepitations, needing O_2 with SaO_2 <92%.	84% (179/212)	−4 mL 3% saline + standard care (*n* = 142) - Standard care (*n* = 149)	HS given every 6 h until primary outcome achieved.	- Primary: fit for discharge (75% of usual intake and SaO_2 ≥92% for 6 h at room air). - Secondary: actual time to discharge, readmission within 28 d from randomization, healthcare usage, duration of respiratory symptoms postdischarge, ITQoL, AEs.
Florin 2014,[31] USA	Outpatient (ED)	Children <24 mo with first episode of bronchiolitis, defined as first episode of wheezing associated with signs and symptoms of upper RTI and respiratory distress measured by RDAI score between 4 and 15.	NA	−4 mL 3% saline (*n* = 31) −4 mL 0.9% saline (*n* = 31)	One dose of saline solutions given at 0 min.	- Primary: RACS at 1 h after inhalation. - Secondary outcomes: vital signs, SaO_2, hospitalization rate, physician clinical impression, parental assessment, AEs.
Grewal 2009,[13] Canada	Outpatient (ED)	Children 6 wk to 12 mo with diagnosis of bronchiolitis, defined as first episode of wheezing and symptoms of viral RTI, initial SAO_2 85%–96% and initial RDAI score ≥4.	82.2% (37/45)	−2.5 mL 3% saline + 0.5 mL 2.25% racemic epinephrine (*n* = 24) −2.5 mL 0.9% saline + 0.5 mL 2.25% racemic epinephrine (*n* = 24)	One dose saline solutions given at 0 min.	- Primary: RACS 0–120 min, change in SAO_2 0–120 min. - Secondary: admission to hospital, return to ED, AEs.
Ipek 2011,[17] Turkey	Outpatient (ED)	Children <2 y with history of preceding viral upper RTI followed by wheezing and crackles on auscultation and Wang CSS between 4 and 8.	NA	−4 mL 3% saline + 0.15 mg /kg salbutamol (*n* = 30) −4 mL 0.9% saline + 0.15 mg /kg salbutamol (*n* = 30) −4 mL 3% saline (*n* = 30) −4 mL 0.9% saline (*n* = 30)	Saline solutions given at 0, 20, 40 min.	- Primary: Wang CSS, use of corticosteroid, hospitalization, clinical assessment 48–72 h. - Secondary: SAO_2, respiratory rate, heart rate.

TABLE 1 Continued

Study ID and Country	Setting	Inclusion Criteria of Participants	RSV Positivity	Intervention and Control	Treatment Regimen	Outcomes
Jacobs 2014,[32] USA	Outpatient (ED)	Children 6 wk to < 18 mo with bronchiolitis defined as viral RTI and first episode of wheezing, Wang CSS ≥4 and SaO_2 >85%.	60.3% (41/68)	−3 mL 7% saline + 0.5 mL 2.25% racemic epinephrine (*n* = 52) −3 mL 0.9% saline + 0.5 mL 2.25% racemic epinephrine (*n* = 49)	One dose of saline solutions given at 0 min.	- Primary: Wang CSS before and after treatment and at disposition. - Secondary: hospitalization rate, proportion of admitted patients discharged at 23 h, LOS, AEs.
Kuzik 2007,[12] Abu Dhabi and Canada	Inpatient	Children ≤18 mo with history of preceding viral upper RTI, wheezing or crackles on chest auscultation, plus either SaO_2 of 94% in room air or significant respiratory distress as measured by RDAI score ≥4.	68.8% (55/80)	−4 mL 3% saline (*n* = 47) −4 mL 0.9% saline (*n* = 49)	3 doses given every 2 h, followed by every 4 h for 5 doses, followed by every 6 h until discharge.	- Primary: LOS defined as time between study entry and time at which the infant either reached protocol-defined discharge criteria (RDAI score < 4 and SaO_2 ≥95% in room air for 4 h) or discharged by attending physician, whichever came first. - Secondary: AEs.
Li 2014,[35] China	Outpatient (Ambulatory care unit)	Children 2–18 mo with first episode of bronchiolitis (Wang CSS ≥4).	NA	−2 mL 3% saline (*n* = 42) −2 mL 5% saline (*n* = 40) −2 mL 0.9% saline (*n* = 42)	Saline solutions given twice daily for 3 d.	- Primary: Wang CSS 24, 48, 72 h after treatment. - Secondary: AEs.
Luo 2010,[18] China	Inpatient	Wheezing infants with mild to moderate viral bronchiolitis, measured by Wang CSS.	69.9% (65/93)	−4 mL 3% saline + 2.5 mg salbutamol (*n* = 50) −4 mL 0.9% saline + 2.5 mg salbutamol (*n* = 43)	Saline solutions given every 8 h until discharge.	LOS (discharge decided by attending physician), time for resolution of wheezing, cough, pulmonary moist and crackles, Wang CSS, AEs.
Luo 2011,[19] China	Inpatient	Children <24 mo with first episode of wheezing diagnosed as moderate to severe bronchiolitis according Wang CSS.	73.2% (82/112)	−4 mL 3% saline (*n* = 57) −4 mL 0.9% saline (*n* = 55)	3 doses given every 2 h, followed by every 4 h for 5 doses, followed by every 6 h until discharge.	LOS (discharge decided by attending physician), time for resolution of wheezing, cough, pulmonary moist and crackles, Wang CSS, AEs.
Mandelberg 2003,[10] Israel	Inpatient	Children ≤12 mo with clinical presentation of viral bronchiolitis, temperature >38°C and SaO_2 ≥85%.	87% (47/52)	−4 mL 3% saline + 1.5 mg epinephrine (*n* = 27) −4 mL 0.9% saline + 1.5 mg epinephrine (*n* = 25)	Saline solutions given every 8 h until discharge.	- Primary: LOS (discharge decided by attending physician), Wang CSS. - Secondary: radiograph score, AEs.
Miraglia 2012,[16] Italy	Inpatient	Children under 24 mo with diagnosis of bronchiolitis, defined as first episode of wheezing and clinical symptoms of viral RTI, SAO_2 <94% in room air and significant respiratory distress measured by Wang CSS.	82.1% (87/106)	- ? mL 3% saline + 1.5 mg epinephrine (*n* = 52) - ? mL 0·9% saline + 1.5 mg epinephrine (*n* = 54)	Saline solutions given every 6 h.	- Primary: LOS defined as time between study entry and time of discharge. - Secondary: Wang CSS on each treatment day.

TABLE 1 Continued

Study ID and Country	Setting	Inclusion Criteria of Participants	RSV Positivity	Intervention and Control	Treatment Regimen	Outcomes
Ojha 2014,[33] Nepal	Inpatient	Children >6 wk to <24 mo with first episode of bronchiolitis defined as wheezing associated with upper RTI, tachypnea, increased respiratory effort, clinical scoring of respiratory distress ≥4 and SaO_2 ≥85%.	NA	−4 mL 3% saline (n = 36)	Saline solutions given every 8 h until discharge.	- Primary: LOS calculated from time of entry to time of discharge (no supplemental O_2, feeding adequately, minimal or absent of wheezing, crackles, and retractions, S_aO_2 ≥95% at room air for 4 h and severity score was < 4).
				−4 mL 0.9% saline (n = 36)		- Secondary: duration of supplemental O_2, clinical scores.
Pandit 2013,[34] India	Inpatient	Children 2–12 mo with acute bronchiolitis defined as short history of cough with or without fever <7 d and first episode of wheezing.	NA	−4 mL 3% saline + 1 mL adrenaline (n = 51)	3 doses given every 1 h, followed by every 6 h until discharge.	- Primary: LOS (discharge criteria: respiratory rate <60/min, without retractions and wheezing).
				−4 mL 0.9% saline + 1 mL adrenaline (n = 49)		- Secondary: improvement in RDAI score, respiratory rate, SaO_2, heart rate, number of add on treatment, AEs.
Sarrel 2002,[9] Israel	Outpatient (Ambulatory care unit)	Children ≤24 mo with clinical presentation of mild to moderate bronchiolitis and SaO2 <96%.	80% (52/65)	−2 mL 3% saline + 5 mg terbutaline (n = 33)	Saline solutions given every 8 h for 5 d.	- Primary: hospitalization rate, Wang CSS.
				−2 mL 0.9% saline + 5 mg terbutaline (n = 32)		- Secondary: radiograph score, AEs.
Sharma 2012,[23] India	Inpatient	Children 1–24 mo with moderate (Wang CSS 3–6) acute bronchiolitis defined as first episode of wheezing with prodrome of upper RTI.	NA	−4 mL 3% saline + 2.5 mg salbutamol (n = 125)	Saline solutions given every 4 h until discharge.	- Primary outcome: LOS defined as time from admission to Wang CSS < 3.
				−4 mL 0.9% saline + 2.5 mg salbutamol (n = 123)		- Secondary: Wang CSS, AEs.
Tal 2006,[11] Israel	Inpatient	Children ≤12 mo with clinical presentation of viral bronchiolitis leading to hospitalization and SaO_2 ≥85%.	80% (33/41)	−4 mL 3% saline + 1.5 mg epinephrine (n = 21)	Saline solutions given every 8 h until discharge.	- Primary: LOS (discharge decided by attending physician), Wang CSS.
				−4 mL 0.9% saline + 1.5 mg epinephrine (n = 20)		- Secondary: radiograph score, AEs.
Teunissen 2013,[24] The Netherlands	Inpatient	Children 0–24 mo with moderate to severe (Wang CSS ≥3) bronchiolitis defined as upper RTI with wheezing, tachypnea, and dyspnea.	88% (212/241)	−4 mL 3% saline + 2.5 mg salbutamol (n = 84)	Saline solutions given every 8 h until discharge.	- Primary outcome: LOS defined as time between the first dose of medications and clinical decision to discharge (protocol-defined discharge criteria: no supplemental O_2, no tube-feeding or intravenous fluids).
				−4 mL 6% saline + 2.5 mg salbutamol (n = 83)		- Secondary: transfer to ICU, duration of supplemental O_2 or tube-feeding, AEs.
				−4 mL 0.9% saline + .·5 mg salbutamol (n = 80)		

TABLE 1 Continued

Study ID and Country	Setting	Inclusion Criteria of Participants	RSV Positivity	Intervention and Control	Treatment Regimen	Outcomes
Tinsa 2014,[27] Tunis	Inpatient	Children 1 to 12 mo with diagnosis of bronchiolitis, defined as first episode of wheezing associated with acute RTI and Wang score ≥3.	NA	−4 mL 5% saline (n = 31) −2 mL 5% saline + 2 mL epinephrine (n = 37)	Saline solutions given every 4 h until discharge.	- Primary: Wang CSS at 30, 60 and 120 min. - Secondary:. LOS (discharge criteria: no supplemental O_2, adequate fluid intake, Wang CSS <3), AEs.
Wu 2014,[30] USA	Outpatient (ED)	Children <24 mo with first episode of bronchiolitis during bronchiolitis season.	62·2% (84/135)	−4 mL 0.9% saline (n = 26) −4 mL 3% saline (n = 211) −4 mL 0.9% saline (n = 197)	Saline solutions given every 20 min to a maximum of 3 doses. Admitted patients: every 8 h until discharge.	- Primary: admission rate, LOS. - Secondary: RDAI score, need for supplemental therapy, AEs.
NCT01276821,[36] Nepal	Outpatient (ED)	Children 6 wk to 2 y with bronchiolitis defined as first episode of wheezing and Wang CSS between 1 and 9.	NA	−4 mL 3% saline + 1.5 mg epinephrine (n = 50) −4 mL 0.9% saline + 1.5 mg epinephrine (n = 50)	Saline solutions given at 0, 30 min.	- Primary: Wang CSS at 30, 60, 120 min. - Secondary: S_aO_2, respiratory rate, heart rate at 30, 60, 120 min, transfer to ICU, discharge rate after 120 min, revisit to ED within 1 wk, AEs.
NCT01488448,[25] USA	Inpatient	Children 0–12 mo admitted to hospital with a diagnosis of bronchiolitis.	NA	−4 mL 3% saline (n = 93) −4 mL 0.9% saline (n = 97)	Saline solutions given every 4 h until discharge.	- Primary: LOS. - Secondary: readmission within 30 d, transfer to ICU, AEs.
NCT01238848,[37] Argentina	Inpatient	Children 1–24 mo hospitalized for first episode of bronchiolitis, with severity score ≥5 and oxygen saturation ≥97%.	NA	−3 mL 3% saline + albuterol 0·25 mg/kg/day (n = 37) −3 mL 0.9% saline + albuterol 0.25 mg/kg/day (n = 45)		- Primary: LOS. - Secondary: duration of supplemental O_2, AEs.

ITQoL, Infant Toddler Quality of Life; NA, not applicable; RACS, Respiratory Assessment Change Score; RTI, respiratory tract infection; SaO_2, oxygen saturation.

use 0.9% saline as the control. All meta-analyses were performed by using Stata version 11.0 (Stata Corp, College Station, TX).

RESULTS

Literature Search and Study Selection

The search strategy identified 97 unique records from PubMed and 125 records from BIREME. After screening the titles and abstracts, we retrieved 26 potentially relevant full-text articles for further evaluation. Five articles were excluded for reasons shown in Fig 1. We obtained the data from clinical trials registry (ClinicalTrials.gov) to assess the eligibility of 3 completed but unpublished trials and all met the inclusion criteria. No additional trials were found by checking the reference lists of primary studies and review articles. Thus, a total of 24 trials[4,9–19,23–25,27,30–37] involving 3209 patients were included in the review. All but 2 trials[14,35] contributed data to the meta-analyses.

Study Characteristics and Risk of Bias

Table 1 summarizes the characteristics of the 24 included trials. All studies were parallel-group RCTs except 1 that was a quasi-RCT.[17] The criteria for diagnosis of bronchiolitis were clearly defined by 19 trials. Eighteen trials[12–19,23,24,27,31–37] defined bronchiolitis as the first episode of wheezing associated with viral respiratory infection in children <2 years of age. In 1 trial,[4] bronchiolitis was defined as an apparent viral respiratory tract infection associated with airways obstruction manifest by hyperinflation, tachypnea, and subcostal recession with widespread crepitations on auscultation. Virological investigation was available in 13 trials[4,9–14,16,18,19,24,30,32] and the positive rate for RSV varied

from 56% to 88%. The concentration of HS was defined at 3% in all but 5 trials, in which 5%[14,27,35] (n = 165), 6%[24] (n = 83), and 7%[32] saline (n = 52) was used. Treatment regimen of nebulized HS varied across studies, especially outpatient trials (Table 1).

All trials were double-blind except 3 open trials,[4,34,37] in which performance bias and detection bias might occur (Supplemental Table 5). All trials but 1[17] were stated as randomized; however, 11 trials[9–12,15,16,18,25,30,35,37] did not describe the methods for random sequence generation and/or allocation concealment. Attribution bias might occur in 3 trials[25,32,37] because of high and unbalanced withdrawal rate after randomization.

Efficacy of Nebulized HS in Inpatients

LOS in Hospital

Among 14 inpatient trials, 13[9–12,16,18,19,23–25,33,34,37] used LOS as the primary outcome and 1[27] used LOS as the secondary outcome. One ED trial[30] involving 408 patients provided the data of LOS among 145 hospitalized patients. We included the data of these 145 inpatients in the meta-analysis. The pooled results of 15 trials with a total of 1956 inpatients showed a statistically significant shorter mean LOS among infants treated with HS compared with those treated with 0.9% saline or standard care (MD of −0.45 days, 95% CI −0.82 to −0.08, P = .01) (Fig 2). There was significant heterogeneity in results between studies (I^2 statistic = 82%). The data were suitable for conducting 5 subgroup analyses (Table 2). Nine trials[4,10–12,16,18,19,24,30] in which virological investigation was available showed significant effects of HS on reducing LOS, whereas 6 trials[23,25,27,33,34,37] in which such testing was not available did not show significant benefits (P = .02 for subgroup comparison). The effect size of HS on LOS appeared to be greater in trials[10–12,16,18,25,30,37] with unclear or high risk of selection bias, compared with trials[4,19,23–25,27,33] with low risk of selection bias.

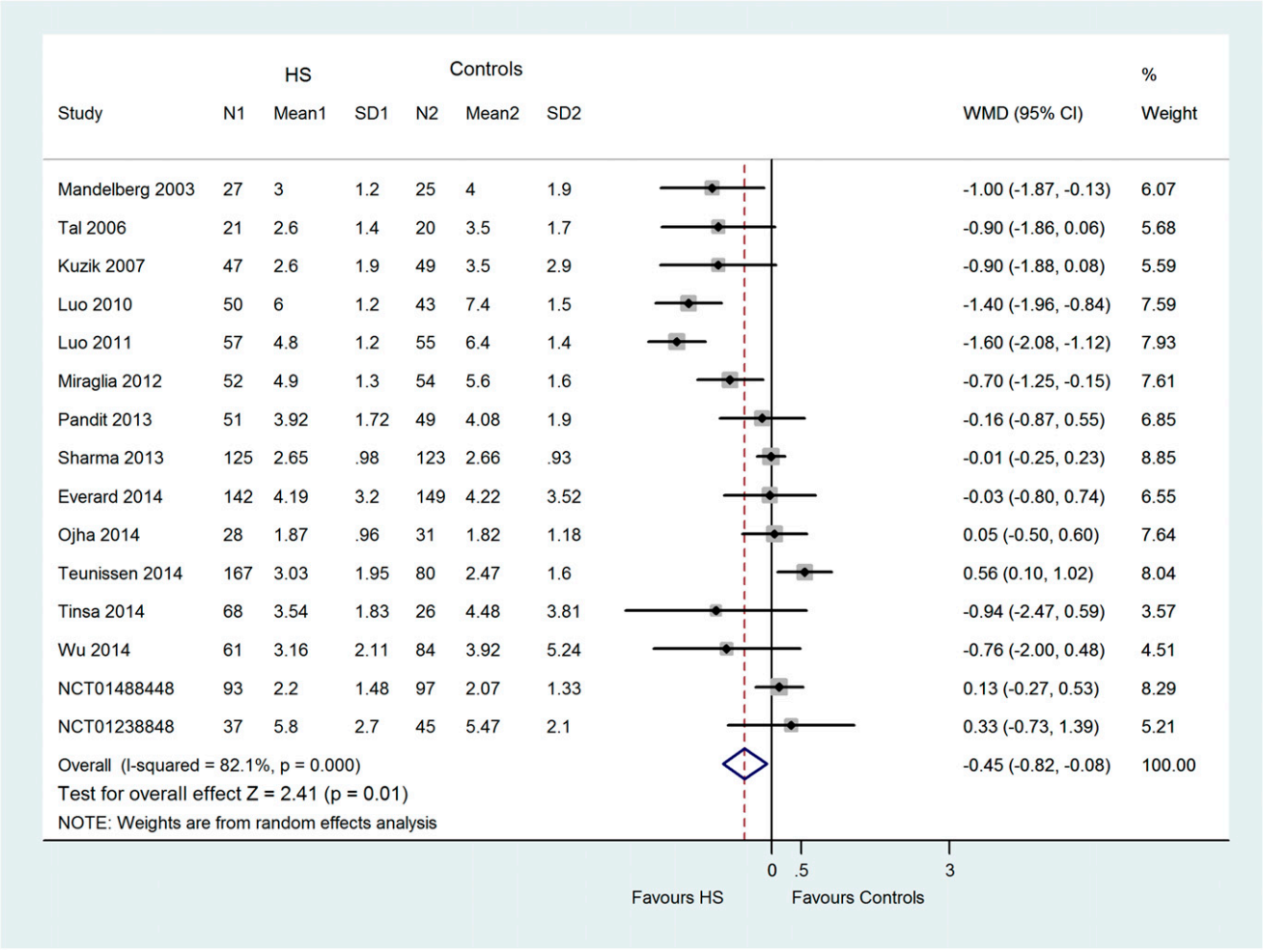

FIGURE 2
Effects of nebulized HS on reduction of LOS among inpatients.

TABLE 2 Subgroup Analyses on LOS (Inpatients) and Admission Rate (Outpatients)

Subgroups	LOS, d				Admission rate, %			
	Trial, *n*	Patients, *n*	Effect Size: MD (95% CI)	Subgroup Comparison,[a] *P* Value	Trial, *n*	Patients, *n*	Effect Size: RR (95% CI)	Subgroup Comparison,[a] *P* Value
Virological investigation				.02				.06
Available	9	1183	−0.74 (−1.32 to −0.16)		4	620	0.71 (0.58–0.88)	
Not available	6	773	0.01 (−0.17–0.19)		3	331	1·04 (0.75–1.44)	
Wheeze as diagnostic criteria				.42				—
Yes	11	1427	−0.40 (−0.84–0.04)		5	478	0.92 (0.72–1.16)	
No	1	291	−0.03 (−0.80–0.74)		0	0	—	
HS mixed with bronchodilator[b]				.80				.71
Yes	9	1019	−0.42 (−0.89–0.05)		5	481	0.76 (0.55–1.06)	
No	7	937	−0.52 (−1.18–0.14)		2	470	0.85 (0.52–1.40)	
Treatment regimen[c]				.79				.07
A	6	840	−0.52 (−1.14–0.09)		4	358	0.93 (0.73–1.20)	
B	9	1116	−0.41 (−0.93–0.10)		3	593	0.67 (0.52–0.87)	
Selection bias				.31				.13
Low	7	1151	−0.26 (−0.82–0.30)		3	209	0.91 (0.68–1.23)	
Unclear/high	8	805	−0.65 (−1.14 to −0.15)		4	742	0.68 (0.52–0.87)	

[a] Subgroup comparison using χ^2 test (degrees of freedom = 1) with $P < .1$ considered as statistically significant.
[b] One trial had 2 interventions compared with NS: HS mixed with epinephrine and HS alone. We included 2 comparisons, splitting the number of NS group in half for each comparison.
[c] For inpatients: regimen A, every 4 h or 3 initial doses given every 1–2 h followed by every 4–6 h; regimen B, every 6–8 h. For outpatients: regimen A, 1 to 2 doses; regimen B, multiple doses (≥3).

However, the difference between subgroups was not statistically significant.

Four sensitivity analyses, excluding 2 trials[24,25] with estimated mean and SD of LOS, 3 trials[25,33,37] with high risk of attrition bias, 2 open trials,[4,34] and 1 trial[4] that did not use 0.9% saline as the control, did not significantly affect the results of the meta-analysis.

Improvement in CSSs

Eleven inpatient trials used bronchiolitis severity scores as outcome measure. Two trials[12,34] used Respiratory Distress Assessment Instrument (RDAI)[38] scores based on wheezing and retractions, but 1[12] did not report the results and the other[34] reported RDAI scores only on day 1 of admission. One trial[33] used a clinical score based on respiratory rate, wheezing, retractions, and oxygen saturation. This trial did not find a significant difference between HS and NS groups in clinical scores through day 1 to day 4 of admission. All the remaining 8 trials used Wang's clinical scores,[39] grading respiratory rate, wheezing, retractions, and general condition from 0 to 3. However, only 5 trials[10,11,16,18,19] with a total of 404 patients provided suitable data for the meta-analysis, showing a significant effect of HS in improving clinical scores on day 1 (MD of −0.99, 95% CI −1.48 to −0.50, $P < .0001$, I^2 statistic = 67%), day 2 (MD of −1.45, 95% CI −2.06 to −0.85, $P < .0001$, I^2 statistic = 79%), and day 3 of admission (MD of −1.44, 95% CI −1.78 to −1.11, $P < .0001$, I^2 statistic = 53%).

Other Efficacy Outcomes

Three trials[24,33,37] used duration of in-hospital oxygen supplementation as efficacy outcome. Other efficacy outcomes used by at least 1 trial included duration of tube feeding, time for the resolution of respiratory symptoms and signs, radiograph scores, measurement of respiratory rate, heart rate and oxygen saturation, readmission within 28 days from randomization, and infant and parental quality-of-life questionnaire. Two trials[18,19] reported a shorter duration of respiratory symptoms and signs (cough, wheezing, and crackles) in patients treated with HS compared with those receiving NS. None of the trials showed significant effects of HS on other previously mentioned outcomes.

Efficacy of Nebulized HS in Outpatients

Admission Rate

Seven outpatient trials with a total of 951 patients assessed the efficacy of nebulized 3% saline on reducing the risk of hospitalization. The pooled RR was 0.80 (95% CI 0.67–0.96, $P = .01$) (Fig 3). There was no significant heterogeneity in results between studies (I^2 statistic = 2%). The data were available for conducting 4 subgroup analyses (Table 2). The effect size of HS on the risk of hospitalization was significantly greater in trials[9,13,30,32] in which virological investigation was available and in trials[9,17,30] in which multiple doses (≥3) of saline solutions were administered, compared with trials[15,17,31] in which virological testing was not available and trials[13,15,31,32] by using only 1 to 2 doses of saline solutions, respectively. Four trials[9,15,17,30] with unclear or high risk of selection bias showed

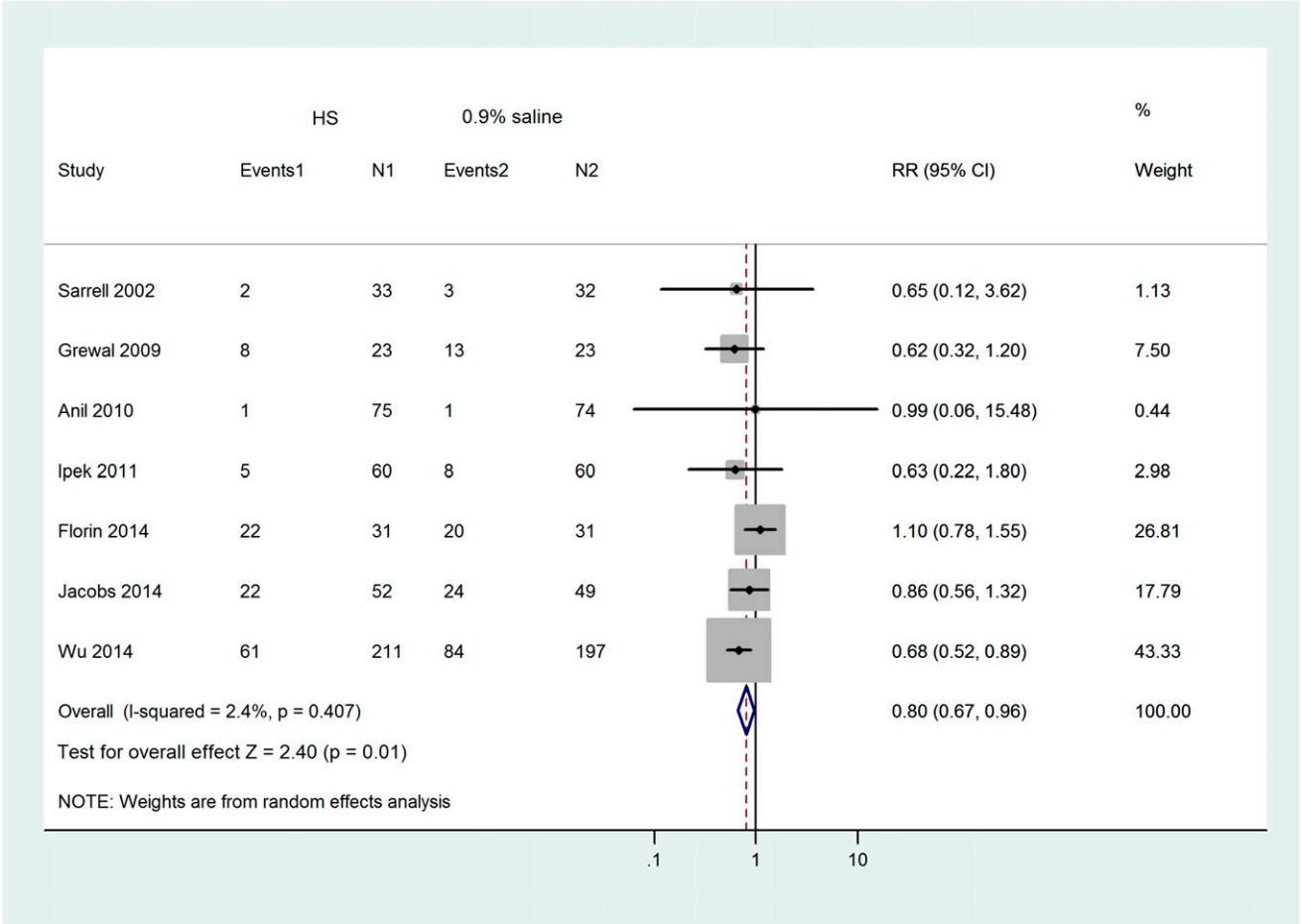

FIGURE 3
Effects of nebulized HS on reducing the risk of hospitalization among outpatients.

significant effects of HS on reducing the risk of hospitalization, whereas 3 trials[13,31,32] with low risk of selection bias did not show significant benefits of HS; however, the difference between subgroups was not statistically significant.

Improvement in CSSs

All 10 outpatient trials used bronchiolitis severity scores as the outcome measure. Variation in scoring methods and time points of assessment makes it inappropriate to conduct meta-analyses. Thus, we narratively summarized the main results of 9 trials in terms of effects of HS on improving clinical scores (Table 3). These trials did not show significant effects of nebulized HS in improving clinical scores, except 3 of the trials. One[9] showed significant benefits of 3% saline compared with NS on each of 3 treatment days, the second[14] showed consistent trend favoring 5% saline compared with 3% and 0.9% saline solutions from 8 to 72 hours after randomization, and the third[34] showed the superiority of both 5% and 3% saline solutions over NS on each of 3 treatment days, but no significant difference was found between 5% and 3% saline groups.

Rate of Readmission to Hospital or ED

Five outpatient trials reported the rate of readmission to hospital and/or the ED 24 hours to 1 week after discharge. The meta-analysis did not show significant effects of HS in reducing the risk of readmission to hospital (4 trials[13–15,31] with 428 patients, RR of 1.45, 95% CI 0.67–3.14, P = .34, I^2 statistic = 1%) and to ED (5 trials[13–15,31,36] with 523 patients, RR of 0.78, 95% CI 0.46–1.32, P = .36, I^2 statistic = 29%).

Other Efficacy Outcomes

Oxygen saturation was used as an efficacy outcome by 4 trials.[13,15,17,31] Other efficacy outcomes used by at least 1 trial included duration of oxygen supplementation, measurement of respiratory rate and heart rate, radiograph scores, and parental perception of improvement. None of the trials showed beneficial effects of HS on previously mentioned outcomes.

Safety of Nebulized HS

Of 24 trials included in this review, 21 reported safety data among 2897 participants, 1557 of whom received HS (3% saline: n = 1257; 5% saline:

TABLE 3 Narrative Summary of the Main Findings of 10 Outpatient Trials in Terms of Effects of HS on Improving Clinical Scores

Trial	Scoring Methods	Main Findings
Al-Ansari 2010[14]	Wang score	- Mean scores (SD) 24 h after randomization: 5% saline vs 0.9% saline: 3.75 (1.27) vs 3.97 (1.40), $P > .05$; 3% saline vs 0.9% saline: 4.0 (0.98) vs 3.75 (1.27), $P > .05$. - Mean scores (SD) 48 h after randomization: 5% saline vs 0.9% saline: 3.69 (1.09) vs 4.12 (1.11), $P = .04$; 3% saline vs 0.9% saline: 4.0 (1.22) vs 4.12 (1.11), $P > .05$. - Consistent trend favoring 5% saline from 8 to 72 h after randomization.
Anil 2010[15]	Wang score	There was no significant difference between 3% and 0·9% saline groups in terms of clinical scores at 30, 60, and 120 min of assessment.
Florin 2014[31]	RDAI score	- Mean RDAI scores (95% CI) 1 h after saline administration: 3% saline vs 0.9% saline: 6.6 (5.5–7.6) vs 5.1 (4.1–6.2), $P = .05$. - Mean RACS scores (95% CI) 1 h after saline administration: 3% saline vs 0.9% saline: −1.5 (−3.1–0.2) vs −4.0 (−5.3 to −2.7), $P = .01$.
Grewal 2009[13]	RDAI score	Mean RACS scores (95% CI) from 0 to 120 min: 3% saline vs 0.9% saline: 4.39 (2.64–6.13) vs 5.13 (3.71–6.55), $P > .05$.
Ipek 2011[17]	Wang score	There was no significant difference between 3% and 0.9% saline groups in terms of clinical scores at 60 min of assessment.
Jacobs 2014[32]	Wang score	- Mean change in scores (SD) at ED disposition: 7% saline vs 0.9% saline: 2.6 (1.9) vs 2.4 (2.3), $P = .21$. - Mean change in scores (SD) after first nebulization in ED disposition: 7% saline vs 0.9% saline: 2.06 (1.7) vs 2.0 (1.9), $P = .06$.
Li 2014[35]	Wang score	Median scores (interquartile range): 5%, 3% vs 0.9% saline. −24 h after treatment: 6 (1), 6 (1) vs 7 (1); $P < .05$ (5% vs 0.9%; 3% vs 0.9%). −48 h after treatment: 5 (1), 5 (1) vs 6 (0.2), $P < .05$ (5% vs 0.9%). −72 h after treatment: 3.5 (1), 4 (1) vs 7 (0), $P < 0·05$ (5% vs 0.9%; 3% vs 0.9%).
Sarrell 2002[9]	Wang score	Mean scores differed significantly, in favor of 3% saline compared with 0.9% saline, on each of the treatment days.
Wu 2014[30]	RDAI score	Mean scores (SD): 3% saline vs 0.9% saline: 5.32 (3.14) vs 4.88 (2.95), $P > .05$.
NCT 01276821[36]	Wang score	Mean change in scores (SD) after 2 sessions of nebulization: 3% saline vs 0.9% saline: 3.52 (1.41) vs 2.26 (1.15)

n = 165; 6% saline: n = 83; 7% saline: n = 52). Fourteen trials[9–11,14,15,18,23,25,27,31,32,34,36,37] did not find any significant AEs among a total of 1548 participants, of whom 828 received nebulized HS (mixture with bronchodilators: n = 673, 81.3%; HS alone: n = 155, 18.7%). In the remaining 7 trials[4,12,13,19,24,30,35] involving 1324 participants of whom 729 received nebulized HS (mixture with bronchodilators: n = 190, 26%; HS alone: n = 539, 74%), at least 1 AE was reported. Variation in reporting and in outcomes precluded the possibility of conducting meta-analysis of safety data. We narratively summarized the safety data of 7 trials (Table 4). Various AEs were reported in both HS and control groups. In most of cases, AEs were mild and resolved spontaneously. Only 1 inpatient trial[4] involving 142 patients receiving 3% saline alone without bronchodilator reported 1 serious AE (bradycardia and desaturation) possibly related to HS inhalation but resolved the following day.

DISCUSSION

This new systematic review and meta-analysis shows a modest but statistically significant benefit of nebulized 3% saline in reducing LOS in infants hospitalized for acute bronchiolitis. The review also shows that nebulized HS could reduce the risk of hospitalization by 20% compared with normal saline among outpatients with bronchiolitis.

The results of this new review confirmed our hypothesis that nebulized HS may be less effective than previously claimed for infants with acute bronchiolitis. The effect size of nebulized HS on reducing LOS in hospitalized patients shown by the present review is only approximately one-third of that shown by the 2013 Cochrane review,[20] which included 6 inpatient trials involving 500 patients (MD −1.15 days, 95% CI −1.49 to −0.82 days). It is interesting to note that all 8 trials[4,23–25,27,30,33,34] published in 2013 and thereafter, including 2 European multicenter studies[4,24] with relatively large sample size, did not find significant effects of nebulized HS on LOS among inpatients with bronchiolitis. For outpatients, this new review showed a 20% reduction on the risk of hospitalization associated with nebulized HS in contrast with a 37% non–statistically significant reduction shown by the 2013 Cochrane review,[20] which included 4 outpatient trials involving 380 participants (RR 0.63, 95% CI 0.37–1.07).

We conducted subgroup analyses to explore potential effect modifiers and sources of heterogeneity in the results across studies. We found that trials in which virological investigation was available showed a significantly greater effect size of nebulized HS than trials without such testing in both inpatients and outpatients, measured by reduction of LOS and risk of hospitalization. These data suggest that diagnostic accuracy of bronchiolitis may affect the treatment outcomes with HS. The number and frequency of saline

TABLE 4 Narrative Summary of AEs of Treatment Reported by 7 Trials

Trial	HS (*n*) vs Controls (*n*)	Main Findings
Everard 2014[4]	3% saline (*n* = 142) vs standard care (*n* = 143)	Six AEs were possibly related to saline treatment, including 1 serious AE (SAE), bradycardia and desaturation, which resolved the following day. The remaining 5 non-SAEs were bradycardia (self-correcting), desaturation, coughing fit, and increased respiratory rate (all of which were resolved within 1 d), and a chest infection that resolved after 6 d.
Grewal 2009[13]	3% saline + epinephrine (*n* = 23) vs 0.9% saline + epinephrine (*n* = 23)	AEs were noted in 4 infants (vomiting, 3; diarrhea, 1); all were enrolled in the HS group. No additional bronchodilators were given to any enrolled patient during the study period.
Kuzik 2007[12]	3% saline (*n* = 47) vs 0.9% saline (*n* = 49)	No infants were withdrawn by the medical staff due to AEs, although 5 infants were withdrawn at parents' request because of perceived AEs, only 2 from the HS group, of whom 1 presented with vigorous crying and another with agitation.
Li 2014[35]	5% saline (*n* = 40), 3% saline (*n* = 42) vs 0.9% saline (*n* = 42)	No AEs were observed in the 3% and 0.9% saline groups. Four patients from the 5% saline group presented with paroxysmal cough during saline inhalation.
Luo 2011[19]	3% saline (*n* = 57) vs 0.9% saline (*n* = 55)	No infants were withdrawn by the medical staff because of AEs. Coughing and wheezing never worsened during saline inhalation, although 5 infants had hoarse voices, only 2 from the HS group, and the symptom disappeared after 3–4 d.
Teunissen 2014[24]	3%, 6% saline + salbutamol (*n* = 167) vs 0.9% + salbutamol (*n* = 80)	A substantial number of AEs (eg, cough, bronchospasm, agitation, desaturation) were noted in all treatment groups. Except for cough, which occurred significantly more in the HS groups ($P = .03$), no differences were found between groups. Withdrawals due to AEs did not differ between groups (4.3%, 6.1% and 7.9% in the 3%, 6% and 0.9% saline groups, respectively, $P = .59$).
Wu 2014[30]	3% saline (*n* = 211) vs 0.9% saline (*n* = 197)	Three patients in the NS group and 4 in the HS group withdrew owing to parent request. Of these parent requests, 1 in the NS group and 2 in the HS group were attributed to worsening cough. For these 3 patients, pretreatment and posttreatment vital signs and RDAI score were the same or improved, and no intervention or additional treatment was necessary.

inhalations may also appear to influence the effect size of HS. Trials undertaken in an outpatient setting in which multiple doses (≥3) of saline solutions were administrated showed a significantly greater reduction on the risk of hospitalization compared with trials that used 1 to 2 doses of saline solutions. However, for inpatients, no significant difference was observed in reduction of LOS between trials that used more frequent saline inhalations (3 initial doses given every 1–2 hours, followed by every 4–6 hours) and those in which saline solutions were given every 6 to 8 hours. Another factor that could possibly influence the effect size of HS was risk of selection bias. Trials with unclear or high risk of selection bias showed significant effects of HS on reducing LOS and risk of hospitalization, whereas trials with low risk of selection bias did not show significant benefits of HS on these outcomes. This does cast some doubt on the overall effect estimates of HS; however, the difference between subgroups was not statistically significant. A tight seal between the mask and the infant's face is crucial for an effective drug delivery with nebulizer.[40] The performance of the nebulizer may also affect drug delivery.[41] Thus, variability in drug delivery could be considered one of the potential sources of heterogeneity across studies; however, lack of data from primary studies did not allow us to include this important factor for subgroup analyses.

Clinical score is generally considered a relatively objective measure to assess the severity of illness. Eleven inpatient trials used bronchiolitis severity scores as the efficacy outcome, but only 5 trials that used Wang's clinical scores provided suitable data for meta-analysis. The pooled results of these 5 trials showed a significant effect of HS in improving clinical scores through day 1 to day 3 of admission. However, the inability to include another 6 inpatient trials in the meta-analysis may have affected the results of the analysis. Seven of 10 outpatient trials did not show significant effects of nebulized HS in improving clinical scores.

Potential adverse effects of intervention with nebulized HS, such as acute bronchospasm, remain a potential concern. In this review, there were 14 trials involving 828 patients receiving nebulized HS that did not report any significant AEs. In 81.3% of these patients, saline solutions were mixed with bronchodilators. In contrast, there

were 7 trials involving 729 patients treated with nebulized HS of which 74% received HS alone and reported at least 1 AE. Most AEs were mild and resolved spontaneously. These results suggest that nebulized HS is a safe treatment in infants with bronchiolitis, especially when administered in conjunction with a bronchodilator.

This systematic review included trials conducted in both high-income and low-income countries and in different settings (inpatient, ambulatory care unit, and ED). Thus, evidence derived from the review may have a wide applicability. However, the quality of evidence could be graded only as moderate, mainly due to inconsistency in the results between studies and risk of bias in some trials, according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria.[42] Moreover, all but 3 trials excluded patients requiring mechanical ventilation, intensive care, or having an oxygen saturation reading <85% on room air, so caution should be taken when extrapolating the findings of this review to infants with more severe bronchiolitis. The underlying airway pathologic changes may vary between infants with different severity of bronchiolitis, so different responses to treatments with HS may be expected in more severe cases. The results of meta-analysis for effects of HS on clinical scores among inpatients may be biased because only 5 of 11 trials measuring this outcome were included in the analysis. The number of trials and patients in outpatient settings is limited, and 1 trial[30] with a relatively large sample size has contributed 43% of weight to the overall summary estimate of effects of HS on reduction of risk of hospitalization. All but 1 trial[4] used NS as the comparison. The use of NS allows the trial to be double-blind; however, NS is not technically a placebo, as high-volume NS inhalation could potentially have physiologic effects by improving airway mucociliary clearance, which may have beneficial effects on acute bronchiolitis.[8] Use of NS as the control may tend to minimize the effect size of HS.

In conclusion, this new systematic review shows that nebulized HS is associated with a mean reduction of 0.45 days (~11 hours) in LOS among infants admitted for acute bronchiolitis and a mean reduction of 20% in the risk of hospitalization among outpatients. This review also suggests that nebulized HS is a safe treatment in infants with bronchiolitis, especially when administered in conjunction with a bronchodilator. Given the high prevalence of bronchiolitis in infants and huge burden on health care systems throughout the world, benefits of nebulized HS shown by this review, even though smaller than previously estimated, may still be considered clinically relevant. Moreover, good safety profile and low cost make nebulized HS a potential attractive therapeutic modality for bronchiolitis in infants. However, further large multicenter trials are still warranted to confirm benefits of nebulized HS in both inpatients and outpatients with bronchiolitis, given the limited number of available trials, the small sample sizes of most previous trials, and conflicting results across studies. Further trials should use the most widely accepted clinical criteria and virological investigation for diagnosis of bronchiolitis. When LOS in hospital and admission rate are used as the primary efficacy outcomes, well-defined admission and discharge criteria should be used. Multiple doses of saline inhalations should be administered in outpatients; however, the optimal treatment regimen of nebulized HS for infants with bronchiolitis remains to be determined by further trials in both inpatients and outpatients.

ABBREVIATIONS

AEs: adverse events
ALRIs: acute lower respiratory infections
BIREME: Latin American and Caribbean Center on Health Sciences Information
CI: confidence interval
CSS: clinical severity score
ED: emergency department
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
HS: hypertonic saline
LOS: length of stay
MD: mean difference
NS: normal saline
RACS: respiratory assessment change score
RCTs: randomized controlled trials
RDAI: respiratory distress assessment instrument
RR: risk ratio
RSV: respiratory syncytial virus
RTI: respiratory tract infection

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BACON FROM THE SEA: *Recently, a friend prepared lunch for me. He toasted some bread and then layered tomatoes, lettuce, and some dried leaves he had briefly pan fried. The sandwich was delicious, but what really surprised me was that the sandwich tasted just like a bacon, lettuce, and tomato sandwich – without any bacon. When I asked him what gave the sandwich the bacon flavor, he responded with a smile, "seaweed".*

As reported in Bon Appetit *(Test Kitchen: July 30, 2015), the type of seaweed my friend was referring to is called "dulse." Dulse is an edible seaweed, much like nori and kelp, which looks like leafy red lettuce and is packed with fiber, protein, and minerals. It grows wild on the northern Atlantic and Pacific coasts, and is harvested at low tide from early summer to early fall. Dulse is usually immediately dried and sold either in whole leaf or powder form. Fresh dulse tastes a bit salty and has mineral overtones suggestive of the ocean from which it came, while dried dulse can take on a variety of flavors. However, when pan-fried, whole-leaf dulse becomes smoky and savory, and tastes remarkably similar to bacon.*

I like to cook with bacon, and will have to try pan-fried dulse in some of my tomato-based dishes to see if I can get the same undertones without the fat of bacon.

Noted by WVR, MD

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