**Format for Mini-CAT (Rotation 5 week 1)**

**Clinical Question:**

1 y/o boy is brought to ED by mother with fever, cough, and difficulty breathing. Mother states that he has an URI 3 days ago. Temperature is 103F. Physical exam shows suprasternal and subcostal retraction. Auscultation of lung shows wheezing and crackles b/l.

**Search Question:**

Is nebulized hypertonic saline effective in treating acute bronchiolitis and reducing hospitalization in infants when comparing to placebo or normal saline?

**PICO Question:**

**Identify the PICO elements**

|  |  |  |  |
| --- | --- | --- | --- |
| **P** | **I** | **C** | **O** |
| Peds | Nebulized hypertonic saline | placebo | efficacy |
| Infants | Nebulized 3% saline | Standard care, supportive care | Rate of hospitalization |
| RSV | Inhalation hypertonic saline | Normal saline inhalation | Length of stay in hospital |
| Acute Bronchiolitis |  |  | Adverse events |
|  |  |  | Cost-effectiveness |
|  |  |  | Reduction in clinical severity |

**Search Strategy:**

Keywords used: “infants”, “acute bronchiolitis”, “hypertonic saline”, “normal saline”, “nebulized/inhaled”

Pubmed:

* Hypertonic saline/acute bronchiolitis/best match: 86 results
* Hypertonic saline/acute bronchiolitis/most recent: 85 results
* Hypertonic saline/acute bronchiolitis/best match/within 10 years/human/English/infants: 48 results

Cochrane library:

* Hypertonic saline/acute bronchiolitis: 2 results

CINAHL:

* Hypertonic saline/acute bronchiolitis: 36 results
* Hypertonic saline/acute bronchiolitis/within 10 years/English/infant: 30 results

**How do I narrow down my articles?**

Articles are narrowed down by having the key words in the title and abstract. Then articles of the most recent and higher level of evidence will be selected. The population of study, intervention and control, outcome of the study will also need to match my PICO question.

**Articles Chosen for Inclusion:**

[**Nebulized** **Hypertonic Saline** for **Acute** **Bronchiolitis**: A Systematic Review.](https://www.ncbi.nlm.nih.gov/pubmed/26416925)

Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C.

Pediatrics. 2015 Oct;136(4):687-701. doi: 10.1542/peds.2015-1914. Review. Erratum in: [Pediatrics. 2016 Apr;137(4):](https://www.ncbi.nlm.nih.gov/pubmed/27033109).

PMID: 26416925

### 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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[**Hypertonic saline** inhalations in **bronchiolitis**-A cumulative meta-analysis.](https://www.ncbi.nlm.nih.gov/pubmed/29266869)

Heikkilä P, Renko M, Korppi M.

Pediatr Pulmonol. 2018 Feb;53(2):233-242. doi: 10.1002/ppul.23928. Epub 2017 Dec 21. Review.

PMID:29266869

### Abstract

We undertook a cumulative meta-analysis for the efficacy of hypertonic saline (HS) compared to normal saline (NS) inhalations or no inhalations as controls in bronchiolitis. We performed literature searches from PubMed, Scopus, and by hand search until 20 June 2017. We accepted published randomized controlled trials of HS inhalations in children with bronchiolitis aged <24 months. We evaluated the differences between treatment group with HS and control group without HS inhalations for the length-of-stay in hospital (LOS) by cumulative mean difference (MD) and in hospitalization rate by cumulative risk ratio (RR). We identified 18 studies including 2102 children treated in hospital, and the cumulative MD in LOS was -0.471 days (95% confidence interval [CI] -0.765 to -0.177, Higgins heterogeneity test [I2 ] 72.9%). The cumulative MD reduced in more recently published papers. In studies with the upper age limit of 12 months, the cumulative MD was -0.408 days (95%CI -0.733 to -0.083) without any important heterogeneity (I2  = 0%). If only studies with a very low risk of bias were included, the cumulative MD was 0.034 (95%CI -0.361 to 0.293) without any important heterogeneity (I2  = 0%). We identified eight studies including 1834 children in the outpatient setting, and the cumulative risk ratio for hospitalization was 0.771 (95%CI 0.619-0.959, I2 55.8%). In conclusion, HS inhalations offered only limited clinical benefits, though the differences between HS and control groups were statistically significant. The heterogeneity between the studies was substantial. Further studies are warranted with consistent definitions of bronchiolitis and comparable research frames.

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[**Nebulized** **hypertonic** **saline** treatment reduces both rate and duration of hospitalization for **acute** **bronchiolitis** in infants: a meta-analysis.](https://www.ncbi.nlm.nih.gov/pubmed/24461195)

Chen YJ, Lee WL, Wang CM, Chou HH.

Pediatr Neonatol. 2014 Dec;55(6):431-8. doi: 10.1016/j.pedneo.2013.09.013. Epub 2014 Jan 21. Review.

PMID: 24461195

### Abstract

Nebulized hypertonic saline (HS) treatment reduced the length of hospitalization in infants with acute bronchiolitis in a previous meta-analysis. However, there was no reduction in the admission rate. We hypothesized that nebulized HS treatment might significantly decrease both the duration and the rate of hospitalization if more randomized controlled trials (RCTs) were included. We searched MEDLINE, PubMed, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) without a language restriction. A meta-analysis was performed based on the efficacy of nebulized HS treatment in infants with acute bronchiolitis. We used weighted mean difference (WMD) and risk ratio as effect size metrics. Eleven studies were identified that enrolled 1070 infants. Nebulized HS treatment significantly decreased the duration and rate of hospitalization compared with nebulized normal saline (NS) [duration of hospitalization: WMD = -0.96, 95% confidence interval (CI) = -1.38 to -0.54, p < 0.001; rate of hospitalization: risk ratio = 0.59, 95% CI = 0.37-0.93, p = 0.02]. Furthermore, nebulized HS treatment had a beneficial effect in reducing the clinical severity (CS) score of acute bronchiolitis infants post-treatment (Day 1: WMD = -0.77, 95% CI = -1.30 to -0.24, p = 0.005; Day 2: WMD = -0.85, 95% CI = -1.30 to -0.39, p < 0.001; Day 3: WMD = -1.14, 95% CI = -1.69 to -0.58, p < 0.001). There was no decrease in the rate of readmission (risk ratio = 1.08, 95% CI = 0.68-1.73, p = 0.74). Nebulized HS treatment significantly decreased both the rate and the duration of hospitalization. Due to the efficacy and cost-effectiveness, HS should be considered for the treatment of acute bronchiolitis in infants.

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[**Hypertonic saline** (HS) for acute **bronchiolitis**: **Systematic review** and meta-analysis.](https://www.ncbi.nlm.nih.gov/pubmed/26597174)

Maguire C, Cantrill H, Hind D, Bradburn M, Everard ML.

BMC Pulm Med. 2015 Nov 23;15:148. doi: 10.1186/s12890-015-0140-x. Review.

PMID: 26597174

Acute bronchiolitis is the commonest cause of hospitalization in infancy. Currently management consists of supportive care and oxygen. A Cochrane review concluded that, "nebulized 3 % saline may significantly reduce the length of hospital stay". We conducted a systematic review of controlled trials of nebulized hypertonic saline (HS) for infants hospitalized with primary acute bronchiolitis.

#### METHODS:

Searches to January 2015 involved: Cochrane Central Register of Controlled Trials; Ovid MEDLINE; Embase; Google Scholar; Web of Science; and, a variety of trials registers. We hand searched Chest, Pediatrics and Journal of Pediatrics on 14 January 2015. Reference lists of eligible trial publications were checked. Randomized or quasi-randomized trials which compared HS versus either normal saline (+/- adjunct treatment) or no treatment were included. Eligible studies involved children less than 2 years old hospitalized due to the first episode of acute bronchiolitis. Two reviewers extracted data to calculate mean differences (MD) and 95 % Confidence Intervals (CIs) for length of hospital stay (LoS-primary outcome), Clinical Severity Score (CSS) and Serious Adverse Events (SAEs). Meta-analysis was undertaken using a fixed effect model, supplemented with additional sensitivity analyses. We investigated statistical heterogeneity using I(2). Risk of bias, within and between studies, was assessed using the Cochrane tool, an outcome reporting bias checklist and a funnel plot.

#### RESULTS:

Fifteen trials were included in the systematic review (n = 1922), HS reduced mean LoS by 0.36, (95 % CI 0.50 to 0.22) days, but with considerable heterogeneity (I(2) = 78 %) and sensitivity to alternative analysis methods. A reduction in CSS was observed where assessed [n = 516; MD -1.36, CI -1.52, -1.20]. One trial reported one possible intervention related SAE, no other studies described intervention related SAEs.

#### CONCLUSIONS:

There is disparity between the overall combined effect on LoS as compared with the negative results from the largest and most precise trials. Together with high levels of heterogeneity, this means that neither individual trials nor pooled estimates provide a firm evidence-base for routine use of HS in inpatient acute bronchiolitis.

**Summary of the Evidence**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author (Date)** | **Level of Evidence** | **Sample/Setting**  **(# of subjects/ studies, cohort definition)** | **Outcome(s) studied** | **Key Findings** | **Limitations and Biases** |
| Article #1  Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C.  2015 Oct | Systematic review | 24 RCTs involving 3,209 patients | Length of stay in the hospital, post treatment clinical score, risk of hospitalization, adverse events | -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. | -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 article to infants with more severe bronchiolitis.  -The results for clinical score among inpatients may be biased because only 5 of 11 trials measuring this outcome were included in the analysis.  -1 trial with a relatively large sample size has contributed 43% of weight to the overall summary effects of hypertonic saline on reduction of risk of hospitalization |
| Article #2  Heikkilä P, Renko M, Korppi M.  2018 Feb | Meta-analysis | 18 RCTs with 2,102 children | Length of stay if patients treated in hospital, hospital admission rate if patients treated in ED or outpatient clinic | -Eight studies including 1834 children in the outpatient setting, and the cumulative risk ratio for hospitalization was 0.771 (95%CI 0.619-0.959, I2 55.8%).  -18 studies including 2102 children treated in hospital, and the cumulative MD in LOS was -0.471 days (95% confidence interval [CI] -0.765 to -0.177, Higgins heterogeneity test [I2 ] 72.9%). | -Patient with previous wheezing episodes were excluded from the trials.  - Patients with severe bronchiolitis, or on mechanical ventilation were excluded from trials. |
| Article #3  Chen YJ, Lee WL, Wang CM, Chou HH  2014 Dec | Meta-analysis | 11 RCTs with 1,070 infants | Duration and length of hospitalization, rate of hospitalization, clinical severity score post treatment, | -Nebulized HS treatment significantly decreased the duration and rate of hospitalization compared with nebulized normal saline (NS) [duration of hospitalization: WMD = -0.96, 95% confidence interval (CI) = -1.38 to -0.54, p < 0.001; rate of hospitalization: risk ratio = 0.59, 95% CI = 0.37-0.93, p = 0.02].  -Nebulized HS treatment had a beneficial effect in reducing the clinical severity (CS) score of acute bronchiolitis infants post-treatment (Day 1: WMD = -0.77, 95% CI = -1.30 to -0.24, p = 0.005; Day 2: WMD = -0.85, 95% CI = -1.30 to -0.39, p < 0.001; Day 3: WMD = -1.14, 95% CI = -1.69 to -0.58, p < 0.001).  -Nebulized HS treatment significantly decreased both the rate and the duration of hospitalization. | -Patients with severe bronchiolitis, oxygen saturation <80% or on mechanical ventilation were excluded from trials.  -Sample size of included trials was generally small.  -All trials are randomized, except in one which all patients were randomly assigned to one group according to the consecutive order of their admission to the short stay unit of ED, rather than by random number sequence generation. |
| Article #4  Maguire C, Cantrill H, Hind D, Bradburn M, Everard ML.  2015 Nov | Systematic review and meta-analysis | 15 RCTs with 1,922 patients | Length of stay, clinical severity score | -Hypertonic saline reduced mean length of stay by 0.36 (95% CI, 0.50 to 0.22) days, but considerable heterogeneity (I2=78%) and sensitivity to alternative analysis methods.  -A reduction in clinical severity score was observed when assessed. (n=5.16; MD -1.36, CI -1.52, -1.20) | -The definition of acute bronchiolitis differs between countries.  -There is variation among discharge criteria.  - Difference in practice also affects observed treatment effects. |

**Conclusion(s): Briefly summarize the conclusions of each article, then provide an overarching conclusion.**

Article #1: Nebulized hypertonic saline is associated with a mean reduction of 0.45 days in length of stay and a mean reduction of 20% in the risk of hospitalization. It also suggests that nebulized hypertonic saline is a safe treatment.

Article #2: Hypertonic saline was shown to have limited clinical benefits in treatment of bronchiolitis, though the difference between hypertonic saline and control groups were statically significant.

Article #3: Nebulized hypertonic therapy reduces the duration of hospitalization and decrease the rate of admission. Due to the efficacy and cost-effectiveness of the treatment, nebulized hypertonic saline should be considered in clinical practice.

Article #4: There is disparity between the overall combined effect on length of stay as compared with the negative results from the largest and most precise trials. Neither individual trials nor pooled estimates provide a firm evidence-base for routine use of hypertonic saline in acute bronchiolitis. The authors cannot rule out the possibility that inhale hypertonic saline offers symptomatic relief but have no data to support or deny this possibility.

Overall conclusion: The articles above present with different conclusions on the effectiveness of hypertonic saline in the treatment of acute bronchiolitis. #1 and #3 supports the use hypertonic saline in ways that reduce length of stay in the hospital and risk of hospitalization. On the other hand, #2 and #4 shows that there is limited clinical benefits and lack of a firm evidence-base for routine use of hypertonic saline.

**Clinical Bottom Line:**

In the treatment of acute bronchiolitis using nebulized hypertonic saline, it has the potential to reduce airway edema and improve clearance of mucus plugging. I have found four systematic review/meta-analysis to assess whether the use of nebulized hypertonic saline is effective and safe to manage acute bronchiolitis in infants. The 1st and 3rd articles both supports the use of nebulized hypertonic saline due to decrease risk and length of hospitalization, and reduce clinical severity. However, the 2nd and 4th article reveals that hypertonic saline has limit clinical benefit in treating acute bronchiolitis and lack of a firm evidence-base for routine use of hypertonic saline. In terms of strength, all the articles have the highest level of evidence that are published within the recent 10 years, and also include RCTs in the study. In terms of weakness, there is still lack of a fixed definition for acute bronchiolitis, and most trials excluded patients with severe bronchiolitis. Given to the controversy of the topic, additional well-designed and larger RCTs should be done in the future in assessing the effectiveness of hypertonic saline for the treatment of acute bronchiolitis when compare to normal saline. Unless additional high-quality studies show otherwise, nebulized hypertonic saline should not be fully recommended as a routine for treating acute bronchiolitis.