Children's Mercy KANSAS CITY
Evidence Based Practice

# *Critically Appraised Topic (CAT): Bronchiolitis- Hypertonic Saline*

**Specific Care Question**
For hospitalized children ≤ 24 months of age with bronchiolitis, does use of nebulized 3% hypertonic saline (HS) impact patient outcomes?

**Recommendations from the Bronchiolitis CPG Committee Based on Current Literature (Best Evidence) Only**

*A conditional recommendation is made against use of nebulized 3% HS, based on the GRADE Evidence to Decision instrument[a] the Summary of Findings Table[a]. The overall certainty in the evidence is very low[a]. Eleven randomized control trials showed a shorter length of stay for patients receiving treatment with HS, MD = -6.47 hours, 95% CI [-12.72, -0.22], p = .04. There was no difference in the need for oxygen supplementation, duration of oxygen supplementation, or improvement of clinical severity scores for patients receiving treatment with HS when compared to no treatment with HS. The potential for shorter length of stay was balanced against the associated costs (monetary and otherwise). See Summary by Outcome for substantiation of recommendations.*

**Recommendations from the Bronchiolitis CPG Committee**

*Following a review of additional considerations using the GRADE Evidence to Decision instrument[a] (see Appendix), a conditional recommendation is made against use of nebulized 3% HS based on evidence showing the limited benefits of treatment are outweighed by the cost of treatment and burden on hospital staff. Additional considerations should be taken for patients with history of prematurity or comorbidities for whom HS may be of higher value.*

**Literature Summary**

***Background***

Bronchiolitis is a common illness in patients less than 2 years of age and is one of the most frequent causes of hospital admission for patients less than 12 months of age (Ralston et al., 2014). Patients with bronchiolitis experience mucus production caused by inflammation of the bronchioles, which may result in mucus plugging. Nebulized 3% hypertonic saline (HS) is used to improve mucociliary clearance, though there is no direct evidence to show significant improvement of patient outcomes (Ralston et al., 2010). The most recent AAP guideline makes a weak recommendation for HS use in the inpatient setting for patients whose admission exceeds 3 days, however, the average admission for bronchiolitis in the U.S. is 2.4 days (Ralston et al., 2014). This recommendation is based on evidence published prior to 2014. The search dates were determined based on the publication date of the current AAP guideline (Raltson et al., 2014) and one year previous to publication was selected to include studies that may not have been identified otherwise. This review will summarize identified literature to answer the specific care question.

**Study characteristics**. The search for suitable studies was completed on January 26, 2023. Jeremy Beyer, MD and Shautonja Woods, BS, RRT-NPS reviewed the 53 titles and/or abstracts found in the search and identified[b] 20 single studies, one systematic review, and three meta-analyses believed to answer the question. After an in-depth review of the single studies[b], 10 studies answered the question. After an in-depth review of the systematic review and four meta-analyses[b], five single studies met the timeframe criteria designated in the original search strategy and answered the question.

**Race/Ethnicity**

Race and ethnicity as defined by the individual authors were reviewed in the literature. Of the studies that reported on race and ethnicity, 11-35% of participants were Black and 63-71% were Hispanic.

**Question Answered. For hospitalized children ≤ 24 months of age with bronchiolitis does use of nebulized 3% hypertonic saline (HS) impact patient outcomes?**

Alatwani et al. (2021) completed a randomized control trial (RCT) comparing hospitalized patients up to 18 months of age with moderate or severe bronchiolitis (*N* = 159). Patients were randomized to receive either 4 mL of 3% HS via nebulizer upon admission and then every 6 hours (*n* = 83) or conventional treatment as ordered by a physician (*n* = 76).

Everard et al. (2014) completed an RCT comparing patients less than 12 months of age hospitalized with acute bronchiolitis (*N* = 317). All patients received standard supportive care (oxygen as required and fluid administration as appropriate). Patients were randomized to receive either treatment with 4 mL nebulized 3% HS every 6 hours in addition to standard care (oxygen and fluids as needed) (*n* = 158) or standard care without nebulized HS (*n* = 159).

Flores-González et al. (2019) completed an RCT comparing patients less than 12 months of age hospitalized with acute bronchiolitis (*N* = 68). Following the initial treatment with deep nasal suctioning of 0.9% nasal saline drops and nebulization of 1.25 mg salbutamol in 3 mL of 0.9% normal saline (NS), patients were randomized to receive treatment every 6 hours with either 3 mL of nebulized 3% HS with 1.25 mg salbutamol (*n* = 33) or 3 mL of nebulized NS with 1.25 mg salbutamol.

Hmar et al. (2021) completed an RCT comparing patients aged 3 months to 2 years hospitalized with acute bronchiolitis (*N* = 158). Patients were randomized to receive treatment every 6 hours with either 3 mL of nebulized 3% HS with salbutamol or nebulized 3 mL of NS with salbutamol.

Islam et al. (2018) completed an RCT comparing patients 1 month to 2 years of age hospitalized with symptoms of bronchiolitis (*N* = 90). Patients were randomized to receive treatment every 8 hours with either 4 mL nebulized 3% HS (*n* = 45) or 4 mL nebulized NS (*n* = 45).

Jaquet-Pilloud et al. (2020) completed an RCT comparing patients aged 6 weeks to 2 years of age hospitalized with acute bronchiolitis (*N* = 120). All patients received standard supportive care (nasal suctioning, fluids, and supplemental oxygen as needed). Patients were randomized to receive either 4 mL of nebulized 3% HS every 6 hours (*n* = 61) or standard care without nebulized saline (*n* = 59).

Köse et al. (2016) completed an RCT comparing patients aged 1 to 24 months hospitalized with bronchiolitis (*N* = 104). Patients were randomized to receive either treatment twice upon admission at 30 minute intervals and then every 6 hours with either 2.5 mL nebulized NS with 0.15 mg salbutamol (*n* = 34), 2.5 mL nebulized 3% HS with 0.15 mg salbutamol (*n* = 35), or 2.5 mL nebulized 7% HS with 0.15 mg salbutamol (*n* = 35).

Mahesh Kumar et al. (2013) completed an RCT comparing patients less than 2 years of age hospitalized with a lower respiratory tract infection (*N* = 40). Patients were randomized to receive treatment every 6 hours with either 3 mL nebulized 3% HS with 0.15 mg salbutamol (*n* = 20) or 3 mL nebulized NS with 0.15 mg salbutamol (*n* = 20).

Morikawa et al. (2018) completed an RCT comparing patients less than 12 months of age hospitalized with acute bronchiolitis due to respiratory syncytial virus (RSV) (*N* = 128). All patients received oxygen supplementation, bronchodilators, intravenous fluids, deep nasal suction, and antibiotics as needed at the discretion of the attending physicians. Patients were randomized to receive treatment six times daily with either 2 mL nebulized 3% HS with 0.1 mL of 0.5% salbutamol (*n* = 63) or 2 mL nebulized NS with 0.1 mL 0.5% salbutamol (*n* = 65).

Ojha et al. (2014) completed an RCT comparing patients between 6 weeks and 24 months of age hospitalized with bronchiolitis (*N* = 72). All patients received supplemental oxygen as needed. Patients were randomized to receive treatment every 8 hours (or more often at the discretion of the physician) with either 4 mL of nebulized 3% hypertonic saline (*n* = 36) or 4 mL nebulized 0.9% saline (*n* = 36).

Pandit et al. (2013) completed an RCT comparing patients aged 2 to 12 months hospitalized with acute bronchiolitis (*N* = 100). Patients were randomized to receive treatment with either 4 mL of nebulized 3% hypertonic saline with 1 mL of 1:1,000 adrenaline (*n* = 51) or 4 mL nebulized 0.9% saline with 1 mL of 1:1,000 adrenaline (*n* = 49). Patients initially received three treatments over the first 3 hours after admission, then received treatment every 6 hours thereafter.

Sharma et al. (2013) completed an RCT comparing patients aged 1 to 24 months hospitalized with acute bronchiolitis (*N* = 250). Patients were randomized to receive treatment every 4 hours with either 4 mL nebulized 3% hypertonic saline with 2.5 mg salbutamol (*n* = 125) or 4 mL nebulized 0.9% saline with 2.5 mg salbutamol (*n* = 123).

Silver et al. (2015) completed an RCT comparing patients less than 12 months of age hospitalized with bronchiolitis (*N* = 227). Patients were randomized to receive treatment every 4 hours with either 4 mL of nebulized 3% hypertonic saline (*n* = 113) or 4 mL of nebulized 0.9% saline (*n* = 114). An additional two treatments could be administered every 24 hours at the discretion of the physician.

Teunissen et al. (2014) completed an RCT comparing patients 0 to 24 months of age hospitalized with mild to severe viral bronchiolitis (*N* = 247). All patients received oxygen supplementation as needed. Patients were randomized to receive treatment every 8 hours with either 4 mL nebulized 3% hypertonic saline with 2.5 mg salbutamol (*n* = 97), 4 mL nebulized 6% hypertonic saline with 2.5 mg salbutamol (*n* = 102), or 4 mL nebulized 0.9% saline with 2.5 mg salbutamol (*n* = 93).

Wu et al. (2014) completed an RCT comparing patients less than 24 months of age hospitalized with viral bronchiolitis (*N* = 408). Patients were randomized to receive treatment with either 4 mL nebulized 3% hypertonic saline with 2.5 mg albuterol sulfate (*n* = 211) or 4 mL nebulized 0.9% saline with 2.5 mg albuterol sulfate (*n* = 197). Patients may have received up to three treatments every 20 minutes in the emergency department, and once admitted, received treatments every 8 hours.

**Data Summary by Outcome (rationale for evidence certainty rating[a] provided for each outcome)**

***Length of Stay (LOS)***

Eleven RCT studies (Everard, 2014; Flores-González, 2016; Hmar, 2021; Islam, 2018; Jaquet-Pilloud, 2019; Mahesh Kumar, 2013; Morikawa, 2018; Ojha, 2014; Pandit, 2013; Sharma, 2013; Wu, 2014) reported the mean (SD) LOS, (*n* = 1,449). For the outcome of LOS, the *MD* = -6.47 hours, 95% CI [-12.72, -0.22], *p* = .04, indicated the LOS was shorter for patients that received treatment with 3% HS versus no treatment with 3% HS (see Figure 2 & Table 1).

> **Certainty Of The Evidence For LOS.** The certainty of the body of evidence was low. The body of evidence was found to not have serious inconsistency or imprecision, however, serious risk of bias and serious indirectness were found. Risk of bias was serious due to lack of blinding of study personnel. Indirectness was serious due to the variability of the control used in each study (normal saline versus standard care), addition of a beta agonist to the nebulized treatments, and variation in the frequency of administration of HS treatments.

***LOS: Low risk of bias***

A subgroup analysis was performed for the four studies with low risk of bias (*n* = 431) (see Figure 3 & Table 1). In the subgroup of the four studies with low risk of bias, there was no difference in LOS for patients treated with 3% HS compared to patients not treated with 3% HS, *MD* = -7.17, 95% CI [-20.40, 6.07], *p* = 0.29.

**Certainty Of The Evidence For LOS: Low risk of bias.** The certainty of the evidence was low. The body of evidence was found to not have serious risk of bias or inconsistency, however, serious indirectness and serious imprecision were found. Indirectness was serious due to the variability of the control used

in each study (normal saline versus standard care), addition of a beta agonist to the nebulized treatments, and variation in the frequency of administration of HS treatments. Imprecision was due to the low number of participants and the wide CI.

***LOS: High risk of bias***

A subgroup analysis was performed for the four studies with high or unclear risk of bias (*n* = 1018) (see Figure 3 & Table 1). In the subgroup of the seven studies with high or unclear risk of bias, there was no difference in LOS for patients treated with 3% HS compared to patients not treated with 3% HS *MD* = -6.00, 95% CI [-13.49, 1.50], *p* = 0.12. The certainty of the evidence is very low.

> **Certainty Of The Evidence For LOS: High risk of bias.** The certainty of the body of evidence was low. The body of evidence was found to not have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Risk of bias was serious due to the lack of blinding of study personnel. Indirectness was serious due to the variability of the control used in each study (normal saline versus standard care), addition of a beta agonist to the nebulized treatments, and variation in the frequency of administration of HS treatments. Imprecision was due to the wide CI.

***LOS: HS versus standard care (SC)***

A subgroup analysis was performed for the two studies (*N* = 413) that compared treatment with nebulized 3% HS versus standard care (no nebulized treatment) (see Figure 4 & Table 1). In the subgroup of the two studies that compared treatment with 3% HS versus standard care, there was no difference in LOS for patients that received treatment with 3% HS compared to patients that did not received treatment with 3% HS, *MD* = -2.43, 95% CI [-13.41, 8.54], *p* = .66.

> **Certainty of the Evidence for LOS: HS versus SC.** The certainty of the evidence was low. The body of evidence was found to not have serious inconsistency or indirectness, however, serious risk of bias and serious imprecision were found. Serious risk of bias was due to the lack of blinding of study personnel. Serious imprecision was due to the low number of participants and the wide CI.

***LOS: HS versus NS***

A subgroup analysis was performed for the nine studies that compared treatment with nebulized 3% HS versus treatment with nebulized NS (*N* = 1036) (see Figure 4 & Table 1). In the subgroup of the nine studies that compared treatment with 3% HS versus NS, there was no difference in LOS for patients that received treatment with 3% HS compared to patients that did not received treatment with 3% HS, *MD* = -7.29, 95% CI [-14.78, 0.20], *p* = .06.

> **Certainty of the Evidence for LOS: HS versus NS.** The certainty of the evidence was very low. The body of evidence was found to have serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision. Serious risk of bias was due to the lack of blinding of study personnel. Serious inconsistency was due to unexplained heterogeneity. Serious indirectness was due to addition of a beta agonist to nebulized treatments and variation in the frequency of administration of HS treatments. Serious imprecision was due to the wide CI.

***LOS: HS with a beta agonist or adrenaline***

A subgroup analysis was performed for the seven studies that included a beta agonist or epinephrine with nebulized treatment (*N* = 887) (see Figure 5 & Table 1). In the subgroup of the two studies that included a beta agonist or adrenaline with nebulized treatment, there was no difference in LOS for patients treated with 3% HS compared to patients not treated with 3% HS, *MD* = -6.86, 95% CI [-16.11, 2.40], *p* = .15.

> **Certainty of the Evidence for LOS: HS with a beta agonist or adrenaline.** The certainty of the evidence was very low. The body of evidence was found to have serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision. Serious risk of bias was due to the lack

of blinding of study personnel. Serious inconsistency was due to unexplained heterogeneity. Serious indirectness was due to the variation of use of a beta agonist or adrenaline. Serious imprecision was due to the low number of participants and the wide CI.

***LOS: HS with no beta agonist or adrenaline***
A subgroup analysis was performed for the four studies that did not include a beta agonist or epinephrine with nebulized treatment (*n* = 562) (see Figure 5 & Table 1). In the subgroup of the two studies that did not include a beta agonist or epinephrine with nebulized treatment, there was no difference in LOS for patients treated with 3% HS compared to patients not treated with 3% HS, *MD* = -6.04, 95% CI [-15.19, 3.12], *p* = .13.

**Certainty of the Evidence for LOS: HS** with no beta agonist or adrenaline. The certainty of the evidence is very low. The body of evidence was found to not have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Serious risk of bias was due to the lack of blinding of study personnel. Serious indirectness was due to the variation of the frequency of administration of HS treatments. Serious imprecision was due to the low number of participants and the wide CI.

***LOS: HS administered every 4 hours***
A subgroup analysis was performed for the two studies that administered nebulized treatment with 3% HS every 4 hours (*N* = 376) (see Figure 6 & Table 1). In the subgroup of the two studies that administered treatment every 4 hours, there was no difference in LOS for patients treated with 3% HS compared to the patients not treated with 3% HS, *MD* = 0.22, 95% CI [-5.22, 5.66], *p* = .94.

**Certainty of the Evidence for LOS: HS administered every 4 hours.** The certainty of the evidence was very low. The body of evidence was not found to have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Serious risk of bias was due to the lack of blinding of study personnel. Serious indirectness was due to the variation of use of a beta agonist or adrenaline. Serious imprecision was due to the low number of participants and the wide CI.

***LOS: HS administered every 6 hours***
A subgroup analysis was performed for the six studies that administered nebulized treatment with 3% HS every 6 hours (*N* = 779) (see Figure 6 & Table 1). In the subgroup of the six studies that administered treatment every 6 hours, there was no difference in LOS for patients treated with 3% HS compared to the patients not treated with 3% HS, *MD* = -8.52, 95% CI [-17.23, 0.19], *p* = .06.

**Certainty of the Evidence for LOS: HS administered every 6 hours.** The certainty of the evidence is very low. The body of evidence was not found to have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Serious risk of bias was due to the lack of blinding of study personnel. Serious indirectness was due to the variation of use of a beta agonist or adrenaline. Serious imprecision was due to the low number of participants and the wide CI.

***LOS: HS administered every 8 hours***
A subgroup analysis was performed for the three studies that administered nebulized treatment with 3% HS every 8 hours (*N* = 294) (see Figure 6 & Table 1). In the subgroup of the three studies that administered treatment every 8 hours, there was no difference in LOS for patiens treated with 3% HS compared to the patients no treated with 3% HS, *MD* = -9.9, 95% CI [-23.49, 3.68], *p* = .15.

**Certainty of the Evidence for LOS: HS administered every 8 hours.** The certainty of the evidence is very low. The certainty of the evidence is very low. The body of evidence was not found to have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were

found. Serious risk of bias was due to the lack of blinding of study personnel. Serious indirectness was due to the variation of use of a beta agonist or adrenaline. Serious imprecision was due to the low number of participants and the wide CI.

***LOS: Studies not included in meta-analysis***

Alatwani et al. (2021) reported the mean LOS without SD and found a shorter LOS in the group that received treatment with HS (3.38 days) compared to the group that received treatment with nebulized NS (4.67 days), a reduction of 1.3 days (27.8%), $p$ = .001.

Kose et al. (2016) reported the mean (min – max) LOS and found that the LOS was not different for the groups that received nebulized 3% HS (64 hours), NS (72 hours), or 7% HS (60 hours), $p$ = .76.

Silver et al., (2015) found that the median (IQR) LOS in days was not different for the group that received nebulized 3% HS (2.1 (1.2 – 4.6)) compared to the group that received nebulized NS (2.1 (1.2 – 3.8)), $p$ = .73.

Teunissen et al. (2014) reported the median (IQR) LOS in hours and did not find a difference between the group that received nebulized 3% HS (69 (57)), NS (53 (53)), and nebulized 6% HS (70 (69)), $p$ = .29.

**Certainty of the Evidence for LOS: Qualitative analysis.** The certainty of the evidence was very low. The body of evidence was found to have serious risk of bias, serious indirectness, and serious imprecision. Serious risk of bias was found due to lack of blinding of study personnel. Serious indirectness was found due to use of beta-agonists and variation of frequency of nebulization. Serious imprecision was found due to a low number of participants. As results were unable to be pooled inconsistency was not assessed.

***Need for Supplemental Oxygen***

Four studies (Flores-González, 2016; Islam, 2018; Ojha, 2014; Teunissen, 2014) reported the need for supplemental oxygen ($n$ = 430). For the outcome of need for supplemental oxygen, the $OR$ = 0.88, 95% CI [0.57, 1.34], $p$ = .54, indicating there was no difference between the intervention of treatment with nebulized 3% HS compared to the intervention of no treatment with nebulized 3% HS. (see Figure 10 & Table 1).

**Certainty of the Evidence for Need for Supplemental Oxygen**. The certainty of the body of evidence was very low. The body of evidence was found to not have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Serious risk of bias was due to lack of blinding of study personnel. Serious indirectness was due to the variation of hospitals' criteria for administration of supplemental oxygen and variation in the use of beta agonists or adrenaline. Serious imprecision was due to the low number of study participants.

***Duration of Supplemental Oxygen***

Five studies (Flores-González, 2016; Islam, 2018; Jaquet-Pilloud, 2019; Morikawa, 2018; Ojha, 2014) reported the duration of supplemental oxygen in hours ($n$ = 346). For the outcome of duration of supplemental oxygen, the $MD$ = -5.84, 95% CI [-11.41, -0.28], $p$ = <.05, indicating the intervention of treatment with nebulized 3% HS was favorable to the intervention of no treatment with 3% HS.

**Certainty of the Evidence for Duration of Supplemental Oxygen**. The certainty of the body of evidence was very low. The body of evidence was found to not have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Serious risk of blinding was due to the lack of blinding of study personnel. Serious indirectness was due to the variation of use of nebulized NS versus standard care as the control. Serious imprecision was due to the low number of study participants.

***Clinical Severity Scores (CSS) Following 1 Day of Treatment***

Three studies (Flores-González, 2016; Hmar, 2021; Kose, 2016) reported the mean (SD) CSS (as described by Wang et al., 1992) following 1 day of treatment ($n$ = 296). For the outcome of improvement of CSS, the $MD$ = -0.76, 95% CI [-1.07, -.046], $p$ = <.05, indicating the treatment with nebulized 3% HS was favorable compared to the intervention of no treatment with 3% HS. (see Figure 7 & Table 1).

**Certainty Of The Evidence For CSS Following 1 Day of Treatment.** The certainty of the body of evidence was very low. The body of evidence was found to not have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Serious risk of bias was assessed to lack of blinding of study personnel. Serious indirectness was due to the variation in the ranges of CSS. Serious imprecision was due to a low number of study participants.

***Clinical Severity Scores (CSS) Following 2 Days of Treatment***

Two studies (Flores-González, 2016; Hmar, 2021) reported the mean (SD) CSS (as described by Wang et al., 1992) following 2 days of treatment ($n$ = 226). For the outcome of improvement of CSS, the $MD$ = -0.54, 95% CI [-0.79, -.028], $p$ = <.05, indicating the intervention of treatment with nebulized 3% HS was favorable compared to the intervention of no treatment with 3% HS. (see Figure 8 & Table 1).

**Certainty Of The Evidence For CSS Following 2 Days of Treatment.** The certainty of the body of evidence was very low. The body of evidence was found not to have serious inconsistency, however, serious risk of bias, serious indirectness, and serious imprecision were found. Serious risk of bias was assessed due to lack of blinding of study personnel. Serious indirectness was due to the variation in the baseline CSS. Serious imprecision was due to a low number of study participants.

***Clinical Severity Scores (CSS) Following 3 Days of Treatment***

Two studies (Flores-González, 2016; Islam, 2018) reported the mean (SD) CSS (as described by Wang et al., 1992) following 3 days of treatment ($n$ = 296). For the outcome of improvement of CSS, the $MD$ = -1.19, 95% CI [-1.67, -.071], $p$ = <.05, indicating the treatment with nebulized 3% HS was favorable compared to the intervention of no treatment with 3% HS. (see Figure 9 & Table 1).

**Certainty Of The Evidence For CSS Following 3 Days of Treatment.** The certainty of the body of evidence was very low. The body of evidence was found to not have serious risk of bias, however, serious inconsistency, serious indirectness, and serious imprecision were found. Serious inconsistency was assessed due to unexplained heterogeneity. Serious indirectness was due to the variation in the ranges of CSS. Serious imprecision was due to a low number of study participants.

**Identification of Studies**

**Search Strategy and Results** (see Figure 1)

1) 'bronchiolitis'/exp OR bronchiolitis:ti,ab,kw
2) inhaled:ti,ab,kw OR inhalation:ti,ab,kw OR nebulized:ti,ab,kw OR nebulize:ti,ab,kw OR 'metered dose inhaler'/exp OR 'inhalational drug administration'/exp OR 'nebulizer'/exp
3) 'hypertonic saline':ti,ab,kw
4) #2 AND #3
5) #1 AND #4
6) #1 AND #4 AND (2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py) AND ([infant]/lim OR [newborn]/lim OR [preschool]/lim) AND ('article'/it OR 'article in press'/it) NOT ('case report'/de OR 'case study'/de OR 'human cell'/de)

Search Dates: 2013–Current.
Records identified through database searching *n* = 53
Additional records identified through other sources *n* = 10

*Studies Included in this Review*

| Citation | Study Type |
|---|---|
| Alatwani et al. (2021) | RCT |
| Everard et al. (2014) | RCT |
| Flores et al. (2016) | RCT |
| Hmar et al. (2021) | RCT |
| Islam et al. (2018) | RCT |
| Jaquet-Pilloud et al. (2019) | RCT |
| Kose et al. (2016) | RCT |
| Mahesh Kumar et al. (2013) | RCT |
| Morikawa et al. (2018) | RCT |
| Ojha et al. (2014) | RCT |
| Pandit et al. (2013) | RCT |
| Sharma et al. (2013) | RCT |
| Silver et al. (2015) | RCT |
| Teunissen et al. (2014) | RCT |
| Wu et al. (2014) | RCT |

*Studies Not Included in this Review with Exclusion Rationale*

| Citation | Reason for exclusion |
|---|---|
| Angoulvant et al. (2017) | Does not include hospitalized patients |
| Brooks et al. (2016) | Meta-analysis including studies published prior to 2013 |
| Canty & Colomb-Lippa (2014) | Narrative review |
| Everard et al. (2015) | Re-analysis of previous study |
| Faten et al. (2015) | Does not include intervention of 3% HS |
| Florin (2015) | Use of beta agonist in control patients only |
| Heikkilä et al. (2018) | Meta-analysis including interventions other than 3% HS |
| Jacobs et al. (2014) | Does not include intervention of 3% HS |
| Li & Zhao (2014) | Not available in English |
| Lin et al. (2022) | Not available in English |
| Liu & Li (2014) | Not available in English |
| Nenna & Costantino (2013) | Does not include intervention of 3% HS |
| Pandit et al. (2014) | Use of beta agonist in control patients only |
| Shahid et al. (2022) | Does not include hospitalized patients |
| Tinsa et al. (2014) | Does not include intervention of 3% HS |
| Wang (2014) | Not available in English |

| | |
|---|---|
| Yu et al. (2022) | Meta-analysis including studies published prior to 2013 |
| Zhang et al. (2018) | Meta-analysis includes non-hospitalized patients |

**Methods Used for Appraisal and Synthesis**

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings (SOF) table(s) for this analysis. Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[d]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Page et al., 2021).

**References to Appraisal and Synthesis Methods**

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[d]Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. International journal of surgery, 88, 105906. **For more information, visit www.prisma-statement.org.**

**Question Originator**

A. Nedved, MD

Findings from this review were presented with the question originator and S. Woods, BHS, RRT, J. Hartley, DO, and M. Collins, MD, MPH on April 24, 2023.

**Medical Librarian Responsible for the Search Strategy**

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*Acronyms Used in this Document*

| Acronym | Explanation |
|---|---|
| CAT | Critically Appraised Topic |
| CSS | Clinical severity score |
| EBP | Evidence Based Practice |
| HS | Hypertonic saline |
| LOS | Length of stay |
| NS | Normal saline |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| SC | Standard care |

*Statistical Acronyms Used in this Document*

| Statistical Acronym | Explanation |
|---|---|
| CI | Confidence Interval |
| *M* or $\bar{X}$ | Mean |
| *Mdn* | Median |
| *n* | Number of cases in a subsample |
| *N* | Total number in sample |
| *OR* | Odds Ratio |
| *P or p* | Probability of success in a binary trial |
| RCT | Randomized controlled trial |
| *SD* | Standard deviation |
| SR | Systematic Review |

**Figure 1**

*Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)*[d]

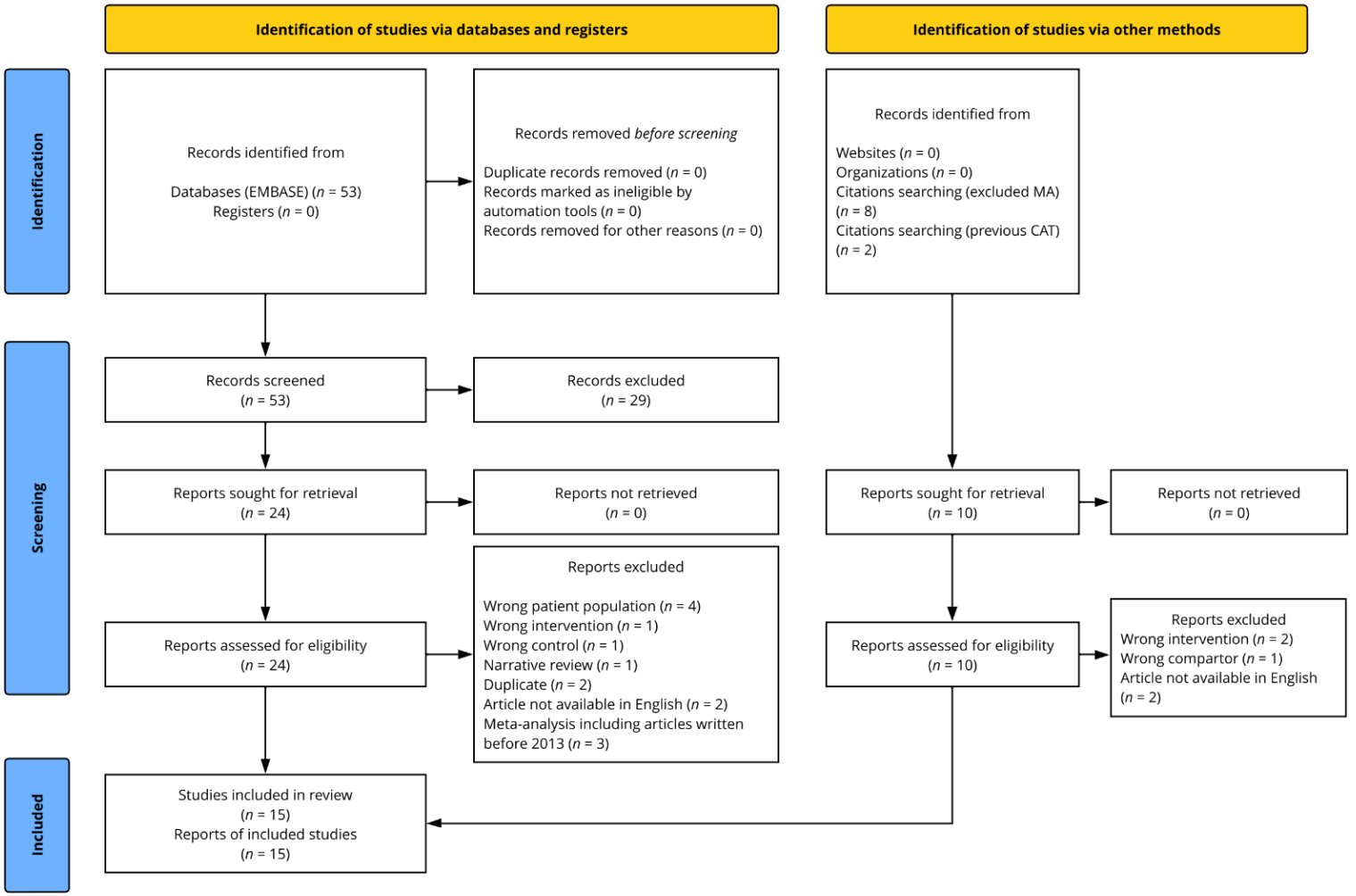
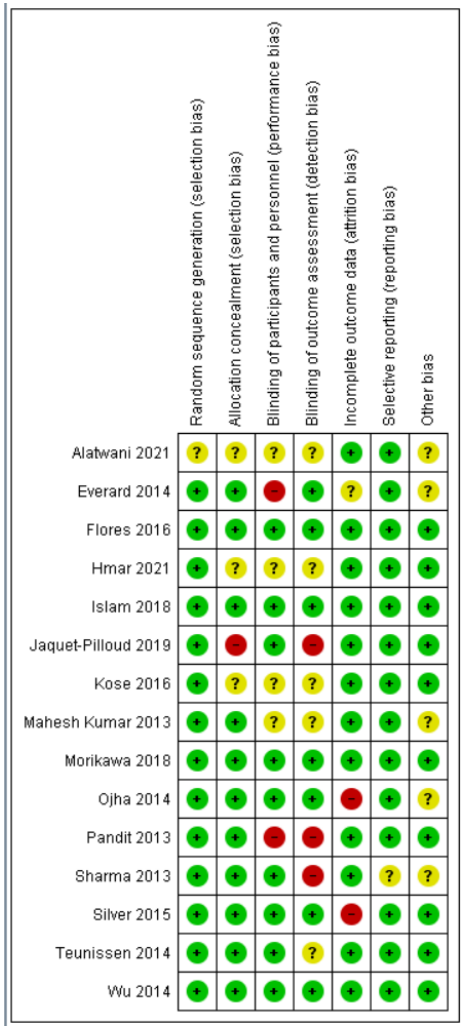


**Figure 1**

*Risk of Bias Summary*



**Summary of Findings Table**
**Table 1**
***Summary of Findings Table[a]: Bronchiolitis- Hypertonic Saline***

| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Risk difference with nebulized 3% hypertonic saline |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | With no nebulized 3% hypertonic saline | With nebulized 3% hypertonic saline | | |
| **LOS (hours)** | | | | | | | | | | |
| 1449 (11 RCTs) | serious[a] | not serious | serious[b,c,d] | not serious | none | ⊕⊕◯◯ Low | 741 | 708 | - | MD **6.47 lower** (12.72 lower to 0.22 lower) |
| **LOS (hours) subgroup: High or unclear risk of bias** | | | | | | | | | | |
| 1018 (7 RCTs) | serious[a] | not serious | serious[b,c,d] | serious[e] | none | ⊕◯◯◯ Very low | 512 | 506 | - | MD **6 lower** (13.49 lower to 1.5 higher) |
| **LOS (hours) sub group: Low risk of bias** | | | | | | | | | | |
| 431 (4 RCTs) | not serious | not serious | serious[b,c,d] | serious[f] | none | ⊕⊕◯◯ Low | 229 | 202 | - | MD **7.17 lower** (20.4 lower to 6.07 higher) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **LOS (hours) subgroup: HS vs SC** | | | | | | | | | | |
| 413 (2 RCTs) | serious[a] | not serious | not serious | serious[f] | none | ⊕⊕◯◯ Low | 210 | 203 | - | MD **2.43 lower** (13.41 lower to 8.54 higher) |
| **LOS (hours) subgroup: HS vs NS** | | | | | | | | | | |
| 1036 (9 RCTs) | serious[a] | serious[g] | serious[c,d] | serious[e] | none | ⊕◯◯◯ Very low | 531 | 505 | - | MD **7.29 lower** (14.78 lower to 0.2 higher) |
| **LOS (hours) subgroup: No beta agonist or adrenaline included in nebulization** | | | | | | | | | | |
| 562 (4 RCTs) | serious[a] | not serious | serious[d] | serious[f] | none | ⊕◯◯◯ Very low | 286 | 276 | - | MD **6.04 lower** (15.19 lower to 3.12 higher) |
| **LOS (hours) subgroup: Beta agonist or adrenaline included in nebulization** | | | | | | | | | | |
| 887 (7 RCTs) | serious[a] | serious[g] | serious[c] | serious[f] | none | ⊕◯◯◯ Very low | 455 | 432 | - | MD **6.86 lower** (16.11 lower to 2.4 higher) |

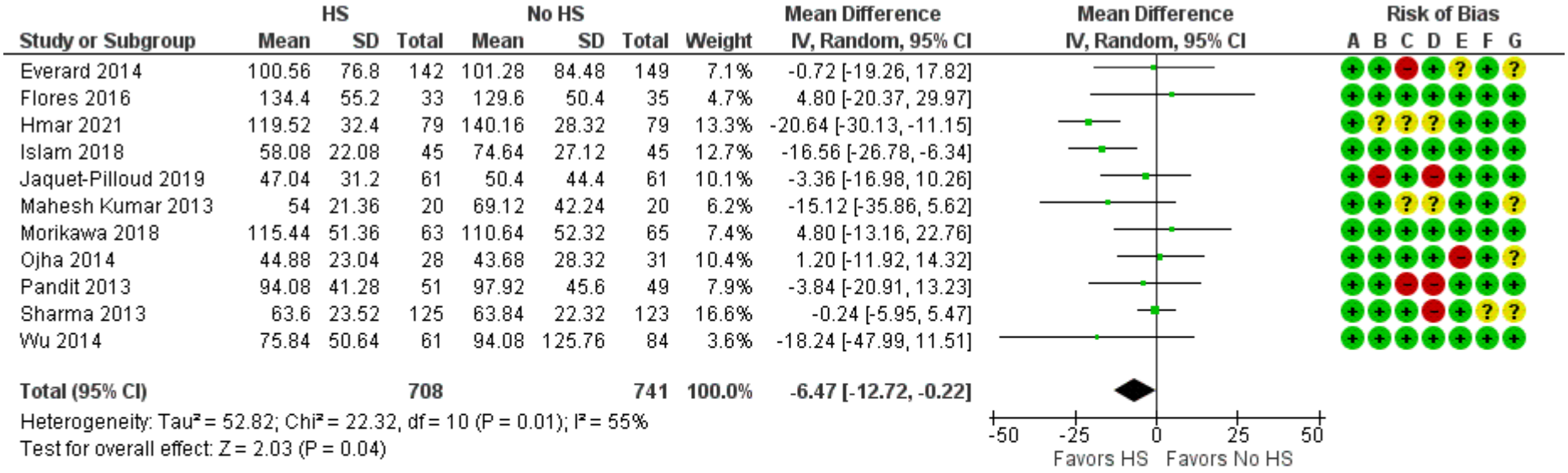
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **LOS (hours) subgroup: Treatment administered every 4 hours** | | | | | | | | | | |
| 376 (2 RCTs) | serious[a] | not serious | serious[c] | serious[f] | none | ⊕◯◯◯ Very low | 188 | 188 | - | MD **0.22 higher** (5.22 lower to 5.66 higher) |
| **LOS (hours) subgroup: Treatment administered every 6 hours** | | | | | | | | | | |
| 779 (6 RCTs) | serious[a] | not serious | serious[d] | serious[f] | none | ⊕◯◯◯ Very low | 393 | 386 | - | MD **8.52 lower** (17.23 lower to 0.19 higher) |
| **LOS (hours) subgroup: Treatment administered every 8 hours** | | | | | | | | | | |
| 294 (3 RCTs) | serious[a] | not serious | serious[c] | serious[f] | none | ⊕◯◯◯ Very low | 160 | 134 | - | MD **9.9 lower** (23.49 lower to 3.68 higher) |
| **LOS (hours): Studies not included in meta-analysis** | | | | | | | | | | |
| 418 (3 RCTs) | serious[a] | not serious | serious[c,d] | serious[h] | none | ⊕◯◯◯ Very low | 203 | 215 | - | not pooled |
| **Wang CSS following 1 day of treatment** | | | | | | | | | | |
| 296 (3 RCTs) | serious[a] | not serious | serious[i] | serious[h] | none | ⊕◯◯◯ Very low | 149 | 147 | - | MD **0.76 lower** (1.07 lower to 0.46 lower) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Wang CSS following 2 days of treatment** | | | | | | | | | | |
| 226 (2 RCTs) | serious[a] | not serious | serious[i] | serious[h] | none | ⊕◯◯◯ Very low | 114 | 112 | - | MD **0.54 lower** (0.79 lower to 0.28 lower) |
| **Wang CSS following 3 days of treatment** | | | | | | | | | | |
| 168 (2 RCTs) | not serious | serious[g] | serious[i] | serious[h] | none | ⊕◯◯◯ Very low | 85 | 83 | - | MD **1.19 lower** (1.67 lower to 0.71 lower) |
| **Need for Supplemental O2** | | | | | | | | | | |
| 430 (4 RCTs) | serious[a,j] | not serious | serious[k] | serious[h] | none | ⊕◯◯◯ Very low | 97/214 (45.3%) | 92/216 (42.6%) | **OR 0.88** (0.57 to 1.34) | **31 fewer per 1,000** (from 132 fewer to 73 more) |
| **Duration of Supplemental O2 (hours)** | | | | | | | | | | |
| 346 (5 RCTs) | serious[a] | not serious | serious[c,k] | serious[f] | none | ⊕◯◯◯ Very low | 173 | 173 | - | MD **5.84 lower** (11.41 lower to 0.28 lower) |

***Explanations***

a. Lack of blinding or unclear description of blinding
b. Control varied among studies as either nebulized NS or no nebulized treatment
c. Variation in administration of beta agonist or adrenaline
d. Variation in frequency of administration of nebulized HS
e. Wide CI
f. Low number of participants, wide CI
g. Unexplained heterogeneity
h. Low number of participants
i. Variation in baseline CSS scores
j. Attrition bias
k. Variation in hospital criteria for O2 requirement

**Meta-analysis(es)**
**Figure 2**
Comparison: HS versus no HS, Outcome: LOS (hours)




Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

**Figure 3**
Comparison: HS versus no HS, Outcome: LOS (hours), Subgroups: High or unclear risk of bias versus low risk of bias

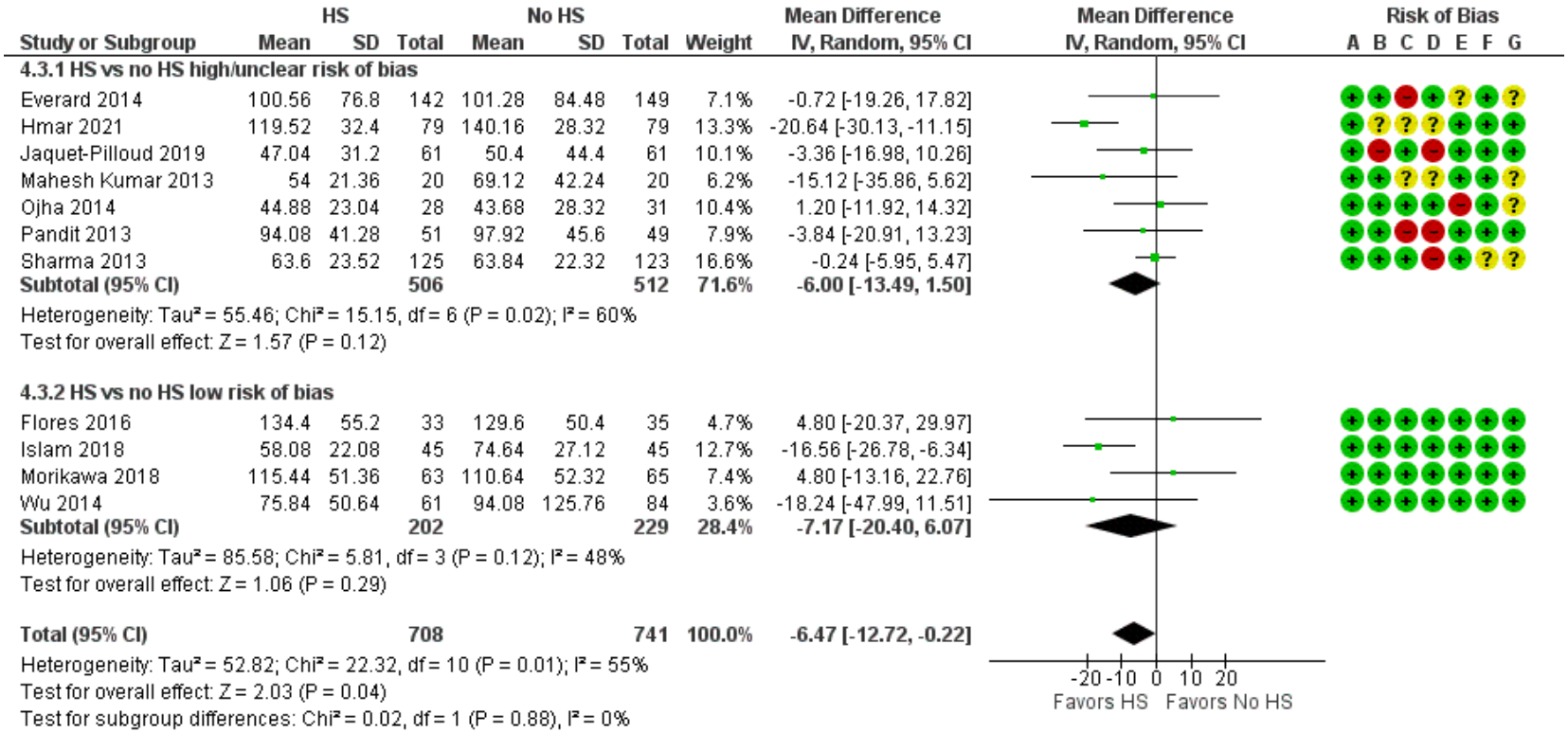


**Figure 4**
Comparison: HS versus no HS, Outcome: LOS (hours), Subgroups: HS versus NS, HS versus standard care (SC)

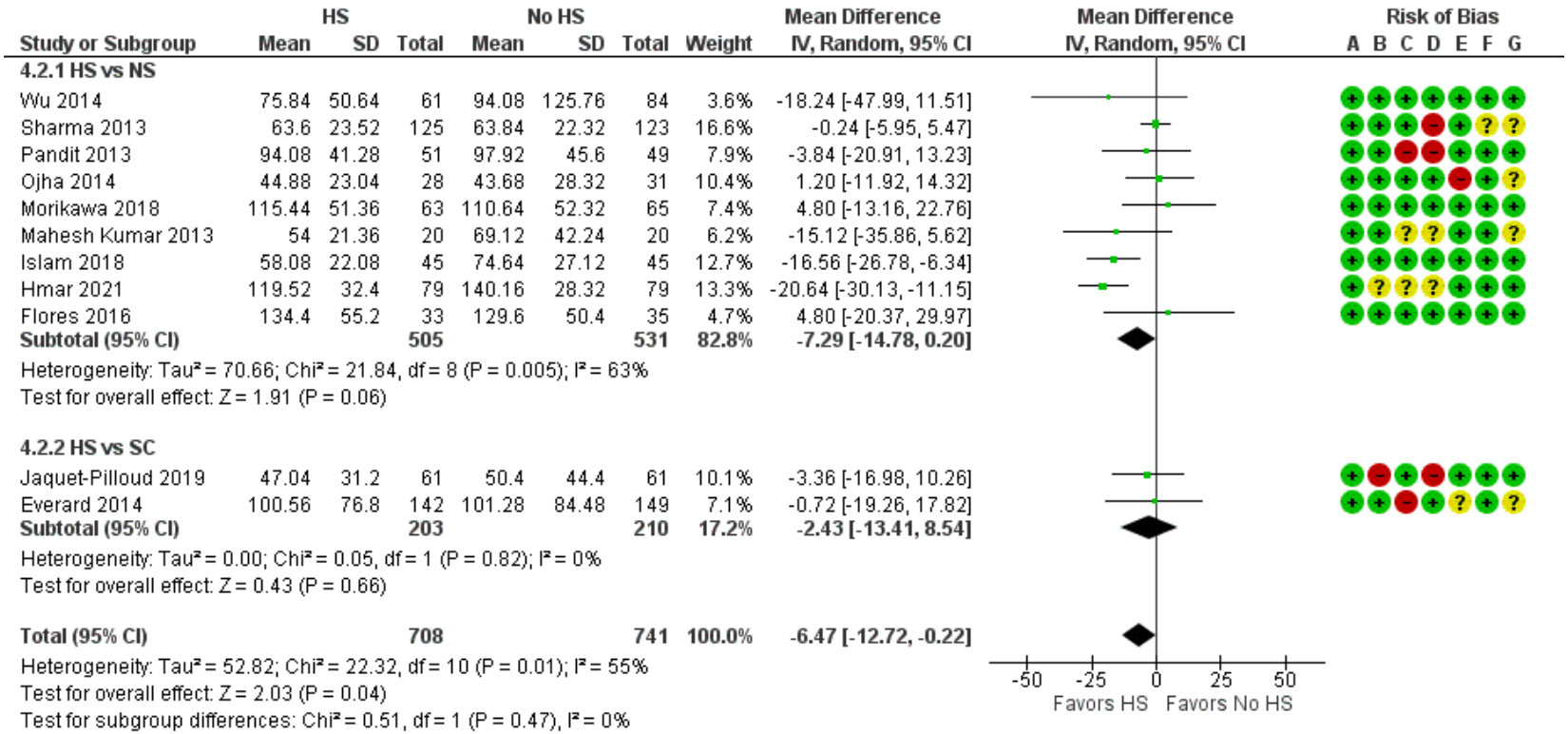


**Figure 5**
Comparison: HS versus no HS, Outcome: LOS (hours), Subgroups: HS with beta agonist or adrenaline versus NS or SC with beta agonist (BA) or adrenaline, HS without BA or adrenaline versus NS or SC without BA or adrenaline

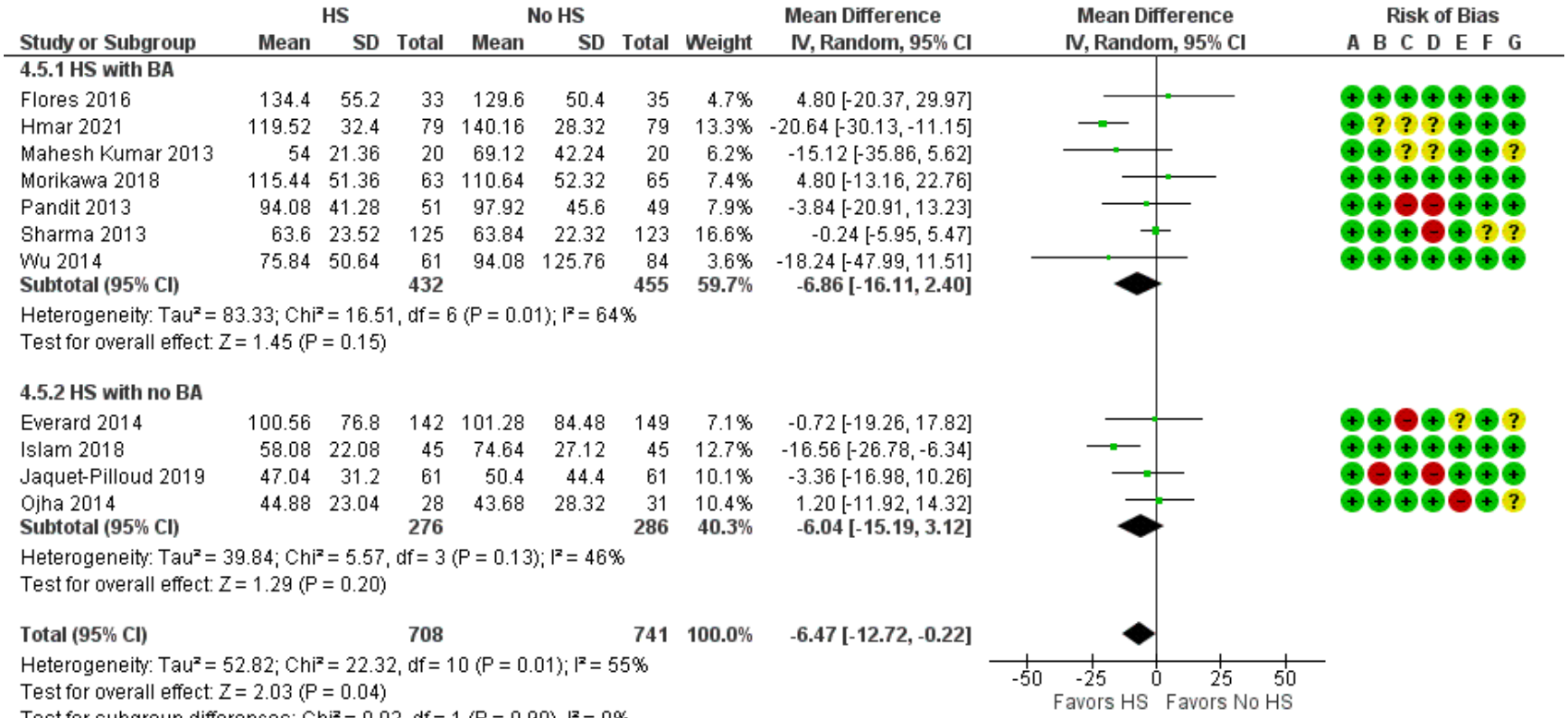


**Figure 6**

Comparison: HS versus no HS, Outcome: LOS (hours), Subgroups: HS administered every 4 hours, HS administered every 6 hours, HS administered every 8 hours

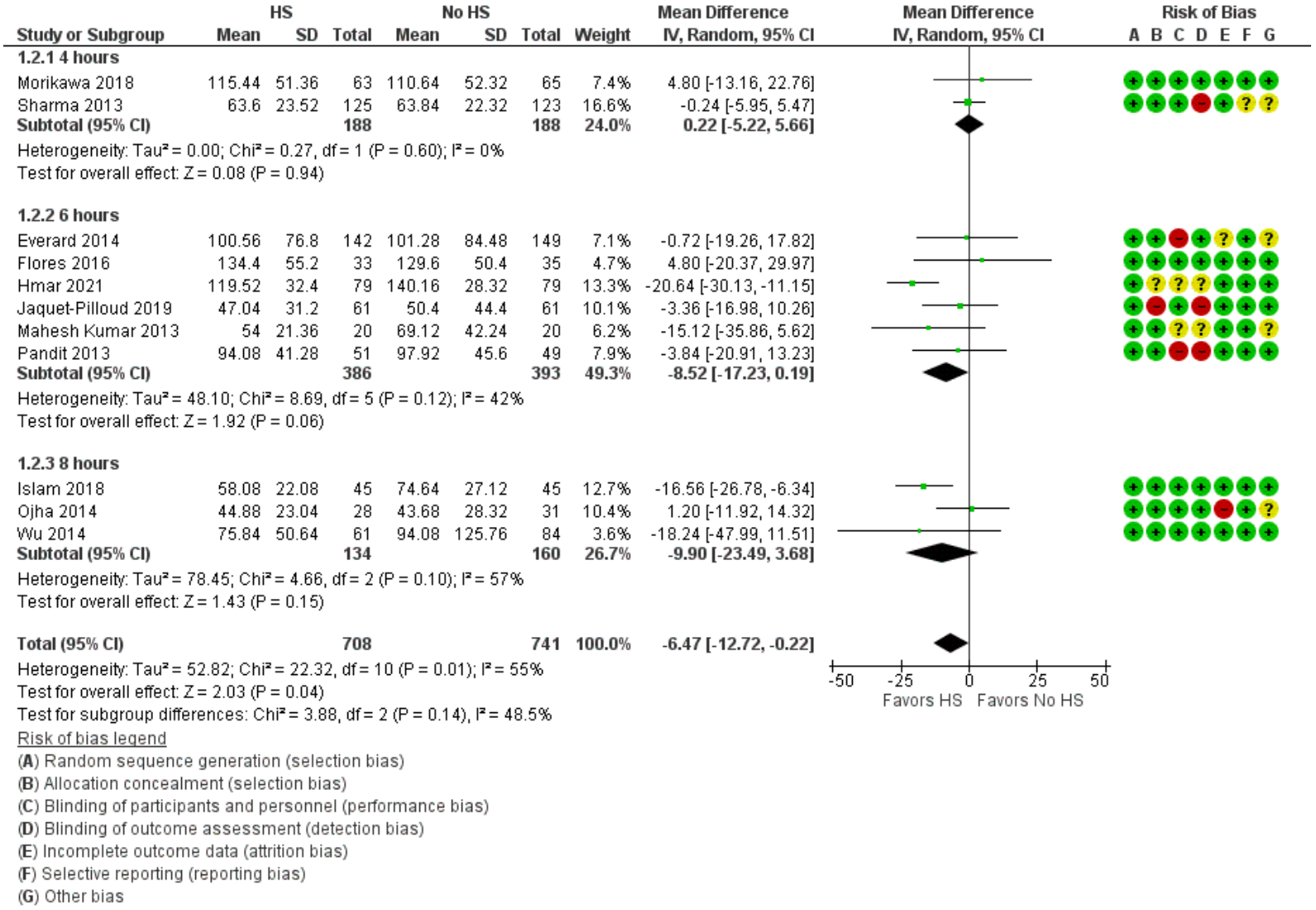
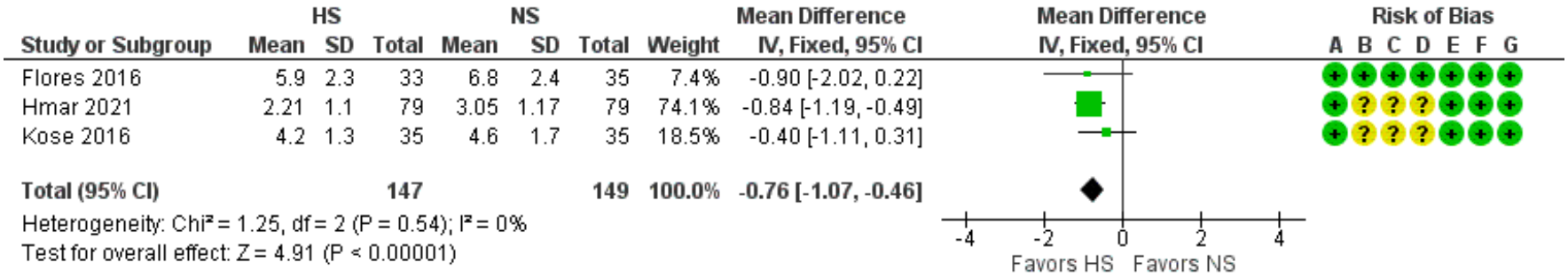
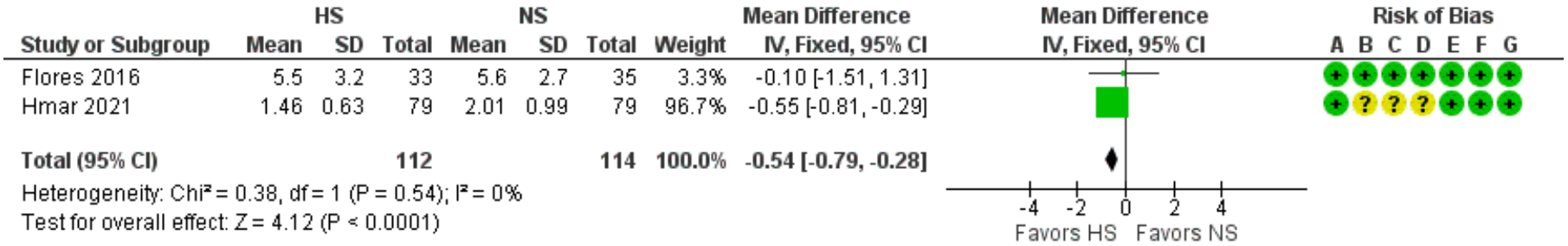


**Figure 7**
Comparison: HS versus no HS, Outcome: CSS following 1 day of treatment



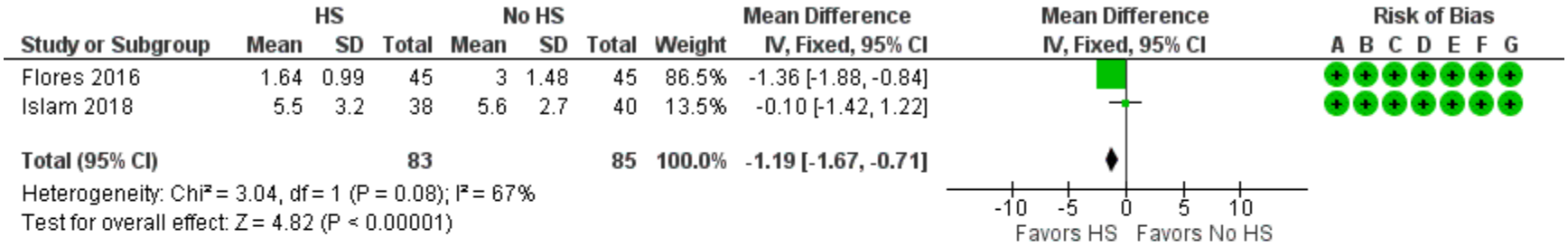

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

**Figure 8**
Comparison: HS versus no HS, Outcome: CSS following 2 days of treatment



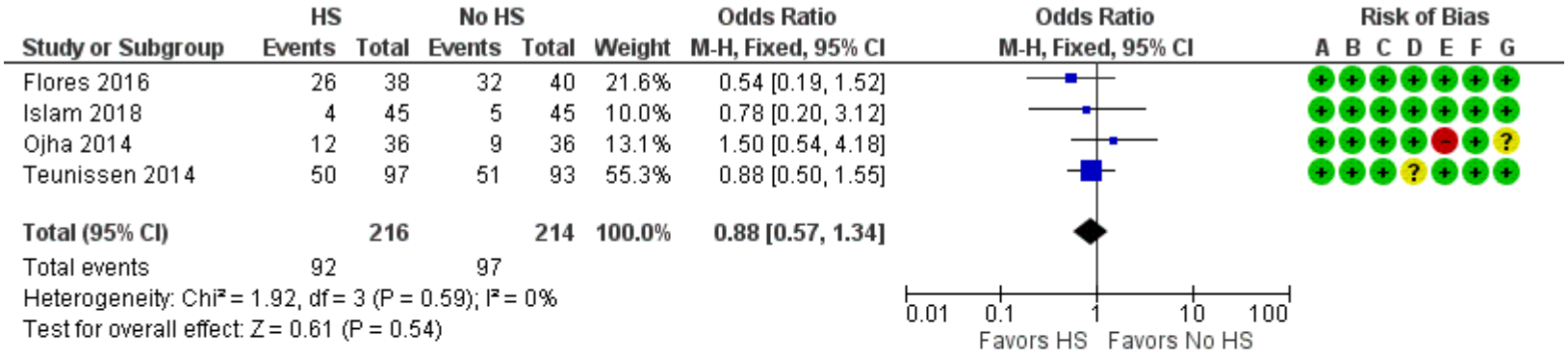

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

**Figure 9**
Comparison: HS versus no HS, Outcome: CSS following 3 days of treatment




Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

**Figure 10**
Comparison: HS versus no HS, Outcome: Need for Supplemental Oxygen




Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Children's Mercy KANSAS CITY
Evidence Based Practice

# *Critically Appraised Topic (CAT): Bronchiolitis- Hypertonic Saline*

*Characteristics of Intervention Studies*
**Alatwani et al., (2021)**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children < 18 months of age with moderate or severe bronchiolitis from November 1, 2016 through January 30, 2018<br>**Setting:** Teaching hospital in Karbala<br>**Randomized into study:** *N* = 161<br>• **Group 1, 4mL of 3% hypertonic saline nebulizer*:** *n* = 83<br>• **Group 2, conventional treatment as ordered by physician:** *n* = 78<br><br>**Completed Study:** *N* = 159<br>• **Group 1:** *n* = 83<br>• **Group 2:** *n* = 76<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 45 (54%)<br>• **Group 2:** *n* = 41 (53%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months, (Frassanito et al.)**<br>• **Group 1:** 6.37 (17 days to 18 months)<br>• **Group 2:** 6.21 (17 days to 18 months)<br>**Inclusion Criteria:**<br>• Children < 18 months of age with severe or moderate bronchiolitis admitted to the hospital<br>• History of upper respiratory viral infection which included:<br>  ○ Wheezing<br>  ○ Crackles in chest<br>  ○ Oxygen saturation levels < 94%<br>  ○ Respiratory distress measured by Respiratory Distress Assessment Instrument (RDAI) score > 4 (scoring determined based on respiratory rate, use of accessory muscles, pallor, and auscultatory findings)<br>**Exclusion Criteria:**<br>• Children with a reported recent episode of wheezing<br>• Children with history of chronic cardiopulmonary disease or immunodeficiency<br>• Children who were critically ill on presentation<br>• Children who were referred to the intensive care unit<br>**Power Analysis:** Not reported |
| **Interventions** | **Both:** Inhaled therapies were used by infants considered to be in stable condition. A tight-fitting mask or head box was used to administer. Clinical response was determined by using the RDAI and oxygen saturation levels at the beginning of the study and three times a day during the study.<br>• **Group 1, *4mL of 3% hypertonic saline nebulizer*:** Received nebulized solution a few hours after admission, then every 6 hours<br>• **Group 2, *conventional treatment as ordered by physician*:** Conventional treatment was not specified |
| **Outcomes** | **Primary outcome(s):**<br>• Length of hospital stay*<br>• Oxygen saturation levels*<br>**Secondary outcome(s)**<br>• Not reported<br>**Safety outcome(s):**<br>• Not reported<br>*Outcomes of interest to the CMH CPG or CAT development team |

**Notes**

**Results:**

- The two patients from the control group were unable to complete due to condition deterioration, both were in the control group
- Children between the ages of 0-6 months (56%) were more likely to require hospitalization when comparing to children between the ages of 7-12 months or 13-18 months (44%).
- Improvement in oxygen saturation within the first two days of treatment was most rapid in the intervention group when compared to the control group (*see table*)
- Mean hospital length of stay in days was shorter for the hypertonic saline group (3.38) versus the normal saline group (4.67), a reduction of 1.3 days (27.8%), $p$ = .001.
- Majority of the children included in the study were < 12 months of age, of which 57% ($n$ = 47) in the intervention group and 55% ($n$ = 43) in the control group were between the ages of 0-6 months.

**Length of Stay, *n* (%)**

| Days | 3% HS ($n$ = 83) | Conventional Treatment ($n$ = 78) |
|---|---|---|
| 3 days | 44 (53%) | 36 (46%) |
| 3-6 days | 39 (47%) | 22 (28%) |
| > 6 days | 0 (0%) | 20 (26%) |

**Limitations:**
Not reported

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Unclear risk | The study did not report how children were randomized into the study |
| **Allocation concealment (selection bias)** | Unclear risk | The study did not report on how children were allocated to intervention groups |
| **Blinding of participants and personnel (performance bias)** | Unclear risk | The study did not report on how personnel were blinded for the study |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | Hospital length of stay and oxygen saturation levels were the outcomes assessed. It is unclear of the parameters established for hospital discharge which may have impacted length of stay |
| **Incomplete outcome data (attrition bias)** | Low risk | Outcomes for the total number of participants were reported |
| **Selective reporting (reporting bias)** | Low risk | All pre-determined outcomes were reported |
| **Other bias** | Unclear risk | Conflict of interest, funding not reported |

**Everard et al., 2014**

| | |
|---|---|
| **Methods** | **Randomized Control Trial** |
| **Participants** | **Participants:** Healthy infants under 1 year of age needing supplementary oxygen for oxygen saturations of <92% when admitted to the hospital with a diagnosis of acute bronchiolitis, between October of 2011 and December 2013.<br>**Setting:** United Kingdom, ten sites in England and Wales, including teaching hospitals and district general hospitals.<br>**Randomized into study:** *N* = 317<br>• **Group 1,** Standard supportive care (SC): *n* = 159<br>• **Group 2,** SC and nebulized 3% hypertonic saline (HS): *n* = 158<br>**Completed Study:** *N* = 290<br>• **Group 1:** *n* = 149<br>• **Group 2:** *n* = 142<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 85 (57.0%)<br>• **Group 2:** *n* = 73 (51.4%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, *mean* (SD) / *median* (IQR) in months**<br>• **Group 1:** 3.4 (2.8) / 2.5 (0.3 to 11.5)<br>• **Group 2:** 3.3 (2.6) / 2.3 (0.3 to 11.5)<br>**Inclusion Criteria:**<br>• Healthy infants under 1 year of age<br>• Apparent viral respiratory tract infection<br>• Associated with airway obstruction, as indicated by<br>  ○ Hyperinflation<br>  ○ Tachypnea<br>  ○ Subcostal recession<br>  ○ Widespread crepitations on auscultation<br>• Supplemental oxygen therapy required at admission<br>**Exclusion Criteria:**<br>• History of<br>  ○ Wheezy bronchitis<br>  ○ Asthma<br>  ○ Gastroesophageal reflux<br>  ○ Previous lower respiratory tract infections<br>• Risk factors for severe disease<br>• Caregiver lacking fluent English in the absence of translational services.<br>• Patients requiring admission to high dependency or intensive care units (HDU/ICU) at presentation.<br>**Power Analysis:** Not reported |
| **Interventions** | **Both:** All study participants received SC which includes supplemental oxygen as required, minimal handling to avoid exhaustion and fluid administration. Discontinuation of previously prescribed antibiotics was encouraged but were permissible for suspected secondary bacterial infection as per United Kingdom guidance.<br>• **Group 1:** SC only<br>• **Group 2:** SC plus HS, administered every six hours by a nurse, via the PARI Sprint nebulizer with appropriate face mask. |
| **Outcomes** | **Primary outcome(s):**<br>• Length of time until the infant was assessed at fit for discharge, defined as<br>  ○ Adequate feeding, taking >75% of their usual intake.<br>  ○ Tolerating room air with an oxygen saturation of at least 92% for six hours. |

| | |
|---|---|
| | **Secondary outcome(s)**<br>• Time to actual discharge*<br>• Readmission within 28 days from randomization<br>• Adverse events*<br>• Healthcare usage<br>• Duration of respiratory symptoms post discharge.<br>**Safety outcome(s):**<br>• Not reported<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• There was no difference between the infants receiving standard supportive care plus nebulized 3% hypertonic saline and the infants that received standard care alone. Nebulized HS does not reduce the length of stay or the length of time until being declared fit for discharge in infants hospitalized with acute bronchiolitis.<br>• Adverse events:<br>○ Six adverse events were possibly related to HS treatment, including one serious adverse event (SAE), bradycardia and desaturation during administration of the nebulizer, which resolved the following day.<br>○ The remaining five non-SAEs were:<br>▪ Bradycardia (self-correcting)<br>▪ Desaturation (resolved in one day)<br>▪ Coughing fit (resolved in one day)<br>▪ Increased respiratory rate (resolved in one day)<br>▪ Chest infection (resolved after six days)<br>○ Although one infant in the HS group developed bradycardia with desaturation, there were no statistically significant differences in the incidence of adverse events between the control group and intervention group.<br>• As per the study authors, this study does not support the use of HS in the treatment of acute bronchiolitis.<br>**Limitations:**<br>• A potential limitation of the study is the absence of blinding, but the study authors propose no blinding as a strength, because it removes potential confounders due to other nebulized interventions.<br>• Restrictive time window within which it was permissible to randomize, limited inclusion of otherwise eligible infants.<br>• The definition of acute bronchiolitis varies from country to country. The standard British definition is more restrictive and may have influenced study outcomes (p. 1110).<br>• The study was not powered for secondary outcomes. |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Infants were randomized using a centralized web-based randomization system with a computer generated algorithm generated by Sheffield Clinical Trials Research Unit. Randomization was conducted in randomly ordered blocks of size two, four and six stratified by hospital. |
| **Allocation concealment (selection bias)** | Low risk | See selection bias note. |
| **Blinding of participants and personnel (performance bias)** | High risk | There was no blinding due to the study design. However, the data was collected at ten sites, using measurable, routinely recorded clinical information, obtained by nurses caring for patients. The authors argue that, "It is extremely unlikely that any systematic view of the potential benefits or harm would influence the many dozens of medical staff involved in the care of these infants." |
| **Blinding of outcome assessment (detection bias)** | Low risk | Outcome measurement is unlikely to be influenced by a lack of blinding. |
| **Incomplete outcome data (attrition bias)** | Unclear risk | The study authors account for all missing outcome data including lack of recorded date and time of fit for discharge for a group of patients and five patients that did not receive treatment as scheduled and noted that the missing data was unlikely to have impacted the outcome. |
| **Selective reporting (reporting bias)** | Low risk | The study protocol is well described and outcomes have been reported in a pre-specified way. |
| **Other bias** | Unclear risk | The study notes that the funder was not involved in the study design, patient recruitment, data collection, analysis, interpretation, writing or publication of the report. |

**Flores-González et al., 2016**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Infants aged less than 12 months with acute bronchiolitis.<br>**Setting:** Pediatric department of a general urban hospital in Lisbon, Portugal<br>**Randomized into study:** *N* = 78<br>• **Group 1, 3% Hypertonic saline:** *n* = 38<br>• **Group 2, 0.9% Saline:** *n* = 40<br>**Completed Study:** *N* = 68<br>• **Group 1:** *n* = 33<br>• **Group 2:** *n* = 35<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 18 (54.4%)<br>• **Group 2:** *n* = 18 (51.4%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months, (+/- SD):**<br>• Group 1: 3.3 (+/- 2.4 months)<br>• Group 2: 3.8 (+/- 2.5 months)<br>**Inclusion Criteria:**<br>• Infants < 12 months of age.<br>• Diagnosis of acute viral bronchiolitis (defined as an apparent viral respiratory tract infection diagnosed in an infant with nasal discharge and wheezy cough, in the presence of fine inspiratory crackles and/or high pitched expiratory wheeze, in which apnea could be a presenting feature).<br>**Exclusion Criteria:**<br>• Previous episodes of wheezing.<br>• Personal history of prematurity (gestational age <34 weeks).<br>• Physician diagnosis of eczema, or food allergy.<br>• Physician diagnosis of chronic disease (cardiac, respiratory, immunological, neurological, or metabolic).<br>• High severity criteria (coma, respiratory rate >80 breaths/minute, oxygen saturation on <88% on room air or need for assisted ventilation).<br>• Refused to participate.<br>**Power Analysis:**<br>• For hospital days with admission for bronchiolitis, the study needs a sample size of 31 infants in each group for an alpha of 0.05 and a power of 90%<br>• For a clinically significant change in severity score, the study needs a sample size of 33 infants in each group for an alpha of 0.05 and a power of 90%. |
| **Interventions** | **Both:** Prior to enrollment, all infants underwent deep nasal suctioning with nasal 0.9% saline drops, and a trial nebulization of salbutamol (1.25 mg in 3 ml of NS). After randomization 0.25 ml (1.25 mg) of salbutamol was added to each 3 ml aliquot of saline.<br>• **Group 1:** 3% hypertonic saline via nebulization<br>• **Group 2:** 0.9% normal saline via nebulization |
| **Outcomes** | **Primary outcome(s):**<br>• Efficacy of inhaled hypertonic saline vs normal saline on length of stay*<br>• Efficacy of inhaled hypertonic saline vs normal saline on severity scores (Wang) in infants with acute viral bronchiolitis*<br>**Secondary outcome(s)**<br>• Need for supplemental oxygen*<br>• Need for tube feeding<br>• Need for add-on therapies (further doses of salbutamol, nebulized epinephrine, systemic corticosteroids, antibiotics, or diuretics) |

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| | **Safety outcome(s):**<br>• Not reported<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• No difference was found in time until patients were fit for discharge, time until discharge, severity scores, need for supplemental oxygen, need for tube feeding, or need for add on medications.<br>**Limitations:**<br>• Could not reliably rule out other causes of infant wheezing (like asthma)<br>• Local practices of diagnosis and treatment may have differed.<br>• Average length of stay is higher in study country compared to USA, Israel, and the Netherlands.<br>• The study was not powered for secondary outcomes. |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Used a computer random number generator. |
| **Allocation concealment (selection bias)** | Low risk | The randomization list was concealed by the Pharmacy. |
| **Blinding of participants and personnel (performance bias)** | Low risk | Both solutions were similar in appearance and smell, stored in identical syringes, labeled only by a code number, and stored in the same refrigerator. |
| **Blinding of outcome assessment (detection bias)** | Low risk | Patients were clinically evaluated from study inclusion until discharge by the same investigator. |
| **Incomplete outcome data (attrition bias)** | Low risk | Patients who were excluded during the study were accounted for (clinical deterioration with need for ICU). |
| **Selective reporting (reporting bias)** | Low risk | All primary outcomes reported. |
| **Other bias** | Low risk | No conflict of interest or funding source concerns. |

**Hmar et al., (2021)**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children between the ages of 3 months and 2 years with acute bronchiolitis admitted between September 2016 through August 2018<br>**Setting:** Pediatric ward or Regional Institute of Medial Sciences, Imphal, Manipur (India)<br>**Randomized into study:** *N* = 158<br>• **Group 1, 3% hypertonic saline (HS):** *n* = 79<br>• **Group 2, 0.9% normal saline (NS):** *n* = 79<br>**Completed Study:** *N* = 158<br>• **Group 1:** *n* = 79<br>• **Group 2:** *n* = 79<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 42 (53.2%)<br>• **Group 2:** *n* = 48 (61%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months, (SD)**<br>• **Group 1:** 10.02 ± 5.45<br>• **Group 2:** 8.45 ± 4.88<br>**Inclusion Criteria:**<br>• Children between the ages of 3 months to 2 years of age<br>• Children with features of acute bronchiolitis<br>**Exclusion Criteria:**<br>• Children diagnosed with:<br>  ○ Bacterial or aspiration pneumonia<br>  ○ Previous wheezing episodes<br>  ○ Oxygen saturation < 92% in room air<br>  ○ Cyanosis<br>  ○ Obtunded consciousness<br>  ○ Progressive respiratory failure<br>  ○ Requiring mechanical ventilation<br>  ○ Foreign body inhalation<br>  ○ Cardiac disease<br>  ○ Congenital malformations<br>• Parents refusing consent<br>**Power Analysis:** 80% and 5% error (95% CI) |
| **Interventions** | **Both:** Nebulization was completed using the Apex Eco-Plus nebulizer made by Apex Medical Corp, France. All patients were enrolled with 24 hours of hospital admission, examined, and re-examined every day at treatment time. Patients in each group received four treatments each day of their hospital stay which were delivered every 6 hours until ready for discharge (absence of fever and respiratory distress, breathing room air comfortably with saturation > 96%, and tolerating oral feeds). Any additional inhalations were recorded and calculated as an add-on therapy. Clinical parameters were measured and recorded using a CS score (Wang et al., 1992). Antibiotics were used in the presence of fever, leukocytosis, and chest x-ray infiltrations.<br>• **Group 1, 3% HS:** Received salbutamol inhalation in 3 mL of 3% saline solution<br>• **Group 2, 0.9% NS:** Received inhalation of salbutamol in 3 mL of 0.9% saline solution |
| **Outcomes** | **Primary outcome(s):**<br>• Improvement in respiratory distress-clinical severity (CS)*<br>• Length of hospital stay (LOS)*<br>**Secondary outcome(s)**<br>• Not reported |

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| | **Safety outcome(s):**<br>• Adverse effects or worsening of symptoms<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• The maximum number of cases occurred in the > 6-12 months age group (HS, *n* = 46 (58.2%); NS, *n* = 36 (45.6%))<br>• Nebulized salbutamol diluted with 3% HS produced a clinically significant reduction (*p* = < 0.001) in the CS scores as compared to treatment with NS as a diluent following treatment on both the second day of admission (2.21 ± 1.10 (HS); 3.05 ± 1.17 (NS)) and the third day of admission (1.46 ± 0.63 (HS); 2.01 ± 0.99 (NS))<br>• The mean LOS was significantly lower (*p* = < 0.0001) and one day shorter in the HS group (4.98 ± 1.35 days) than the NS group (5.84 ± 1.18 days).<br>• There were no reported adverse effects or worsening of symptoms between groups<br><br>**Mean (SD) Clinical Severity Scores**<br>Day of Admission \| HS Group \| NS Group \| *p - value*<br>Admission \| 3.98 ± 1.20 \| 3.75 ± 1.06 \| 0.209<br>Second Day \| 2.21 ± 1.10 \| 3.05 ± 1.17 \| < 0.001<br>Third Day \| 1.46 ± 0.63 \| 2.01 ± 0.99 \| < 0.001<br><br>**Limitations:**<br>• Diagnosis of bronchiolitis was based on clinical considerations as virological diagnostic facilities were not available<br>• Generalizations of findings are limited due to the reduced number of participants and single study site.<br>• The study was not powered for secondary outcomes. |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Standard randomization table used |
| **Allocation concealment (selection bias)** | Unclear risk | Participant selection procedures were not described in the study. There was insufficient information to permit judgement of low or high risk. |
| **Blinding of participants and personnel (performance bias)** | Unclear risk | Participant and personnel blinding mechanisms were not reported. There was insufficient information to permit judgement of low or high risk. |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | The methods for collecting and analyzing data were not clearly described in the study. There was insufficient information to permit judgement of low or high risk. |
| **Incomplete outcome data (attrition bias)** | Low risk | All individuals randomized within the study were analyzed |
| **Selective reporting (reporting bias)** | Low risk | Data was presented for all study outcomes identified |
| **Other bias** | Low risk | There were no concerns for other bias. |

**Islam et al., 2018**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children one month to two years of age presenting with symptoms of bronchiolitis between January 2013 to December 2013<br>**Setting:** Dhaka Medical College Hospital, department of pediatrics<br>**Randomized into study:** *N* = 90<br>• **Group 1, 3% hypertonic saline (HS) nebulization:** *n* = 45<br>• **Group 2, 0.9% normal saline (NS) nebulization:** *n* = 45<br>**Completed Study:** *N* = 90<br>• **Group 1:** *n* = 45<br>• **Group 2:** *n* = 45<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 25 (55.5%)<br>• **Group 2:** *n* = 26 (57.7%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months, (standard deviation or SD)**<br>• **Group 1:** 5.2 ± 3.2<br>• **Group 2:** 5.5 ± 3.0<br>**Inclusion Criteria:**<br>• Children between one month and two years of age<br>• Children presenting with:<br>  ○ Preceding or existing runny nose<br>  ○ Cough<br>  ○ Breathing difficulty<br>  ○ Chest in-drawing (increased work of breathing) and rhonchi (airway sounds) on auscultation<br>• Children admitted between January 2013 to December 2013<br>**Exclusion Criteria:**<br>• None reported<br>**Power Analysis:** Not reported |
| **Interventions** | **Both:** Relevant history and physical examination findings were recorded via a pre-tested, semi-structured questionnaire. Clinical severity scores were obtained using the respiratory distress assessment instrument. Oxygen saturation in room air was measured using a pulse oximeter and recorded on admission. Each group received the same supportive measures (propped up positioning, suction when needed, fluid, feeding, oxygen therapy (when oxygen saturation < 90%), paracetamol for fever, and counseling.<br>• **Group 1, 3% HS nebulization:** Received 4 mL of 3% hypertonic saline nebulization three times daily at 8 hour intervals until appropriate for discharge<br>• **Group 2, 0.9% NS nebulization:** Received 4 mL of 0.9% normal saline nebulization three times daily at 8 hour intervals until appropriate for discharge |
| **Outcomes** | **Primary outcome(s):**<br>• Clinical severity score measured using the Respiratory Distress Assessment Instrument (RDAI; Wang et al., 1992)*<br>• Length of hospital stay*<br>• Oxygen saturation in room air<br>• Duration of oxygen supplementation*<br>**Secondary outcome(s)**<br>• None reported<br>**Safety outcome(s):**<br>• Adverse event (Side effect of medications)<br>*Outcomes of interest to the CMH CPG or CAT development team |

**Notes**

**Results:**

- Difference between groups regarding age ($p$ = .82) and sex ($p$ = .50) were not significant
- All children in both groups presented with runny nose, cough, breathing difficulty, chest in-drawing, and lung sounds. However, feeding difficulty was a presenting feature in 55.5% of the children in the 3% HS group and 57.7% of the children in the 0.9% NS group
- Clinical severity score of both treatment groups reduced. However, reduction was more significant in children who received 3% HS (*see table*)
- Of those requiring oxygen therapy, children in the 3% HS group required 15 hours on average, whereas children in the 0.9% NS group required 26.4 hours on average. The duration of oxygen between groups was significantly reduced in the 3% HS intervention group (*see table*)
- Forty-two (93.3%) of the children in the 3% HS group recovered and discharged within 72 hours, whereas 26 (57.8%) of the children in the 0.9% NS group recovered and discharged within the same time period.
- When comparing interventions, length of stay was significantly less ($p$ = .001) in the 3% HS group
- No adverse events were identified in either the 3% HS group, nor the 0.9% NS group

**Clinical Severity Score**

| Timeframe | 3% HS ($n$ = 45) | 0.9% NS ($n$ = 45) | $p$-value |
|---|---|---|---|
| Baseline | 9.0 ± 1.0 | 9.3 ± 1.8 | 0.943 |
| 12 hours | 8.2 | 9.0 | Not reported |
| 24 hours | 5.3 | 7.8 | Not reported |
| 36 hours | 4.3 | 6.1 | Not reported |
| 48 hours | 2.6 | 4.3 | Not reported |
| 60 hours | 2.9 | 4.5 | Not reported |

**Duration of Oxygen Therapy**

| Duration of Oxygen Therapy | 3% HS ($n$ = 4) | 0.9% NS ($n$ = 5) | $p$-value |
|---|---|---|---|
| Mean ± SD | 15.0 ± 6.0 | 26.4 ± 5.4 | 0.02 |

**Limitations:**

- Study occurred at a single site with a small sample size

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomization was completed by lottery method. The parents or caregivers were given a chance to select a sealed encoded envelope from a box containing eight envelopes (four sealed envelopes designated for each intervention). |
| Allocation concealment (selection bias) | Low risk | The intervention allocation was randomized using a lottery method of which sealed encoded envelopes were used. |
| Blinding of participants and personnel (performance bias) | Low risk | While not overtly addressed, it appears the participants may have been blinded through mention of the following statement, "there was no detectable difference in color, smell, or other physical properties existed between 0.9% saline solution and 3% saline solution" |
| Blinding of outcome assessment (detection bias) | Low risk | No blinding of outcome assessment. However, the review author judges that the outcome measurement is not likely to be influenced by lack of blinding |
| Incomplete outcome data (attrition bias) | Low risk | There is no missing outcome data |
| Selective reporting (reporting bias) | Low risk | The report includes all expected outcomes |
| Other bias | Low risk | The study appears to be free of other sources of bias |

**Jaquet-Pilloud et al., 2019**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children, aged 6 weeks to 2 years, with acute bronchiolitis presenting to the Emergency Department (ED), between April 2013 and March 2016<br>**Setting:** Switzerland, One secondary care center and tertiary care hospital<br>**Randomized into study:** *N* = 122<br>• **Group 1, Nebulized 3% hypertonic saline in addition to supportive care:** *n* = 61<br>• **Group 2, Standard supportive care:** *n* = 61<br>**Completed Study:** *N* = 120<br>• **Group 1:** *n* = 61<br>• **Group 2:** *n* = 59<br>**Gender, female/male:**<br>• **Group 1:** *n* = 22 (36%)<br>• **Group 2:** *n* = 22 (37.3%)<br>*Reporting by author does not specify gender is provided<br>**Race / ethnicity or nationality:**<br>• Not reported<br>**Age, median in months, (range)**<br>• **Group 1:** 6.3 (1.4 to 21.4)<br>• **Group 2:** 6.1 (1.4 - 21.9)<br>**Inclusion Criteria:**<br>• Children aged 2 weeks to 24 months<br>• First episode of acute bronchiolitis (defined as symptoms of upper respiratory tract infection in addition to tachypnea, wheezing and widespread crackles breath sounds)<br>• Wang Score of 5 - 12 (moderate to severe) on arrival<br>**Exclusion Criteria:**<br>• Mild bronchiolitis (Wang Score < 5)<br>• Previous episodes of wheezing, cardiac or chronic respiratory disease<br>• Immunocompromised children<br>• Gestation age < 34 weeks<br>• Critical illness requiring immediate admission to Intensive Care Unit (ICU)<br>• RSV immunoglobulin therapy or corticosteroid therapy in previous 2 weeks<br>• Bronchodilator use 24 hours prior to presentation<br>**Power Analysis:** With a sample size of 60 in each arm there would be a power of 80% to detect a significant difference ($p < .05$) |
| **Interventions** | **Both:** Suctioning nasal secretions, water-electrolyte balance, supplemental oxygen, if needed. Nebulized epinephrine 4mg if signs of respiratory failure<br>• **Group 1:** 4 mL of NaCl 3% nebulized every 6 hours until discharge<br>• **Group 2:** No additional interventions |
| **Outcomes** | **Primary outcome(s):**<br>• Length of stay*<br>**Secondary outcome(s)**<br>• Duration of oxygen therapy*<br>• Need for nebulized epinephrine<br>• Transfer to ICU*<br>• Adverse events<br>• Readmission within 7 days of discharge<br>**Safety outcome(s):**<br>• Not reported<br>*Outcomes of interest to the CMH CPG or CAT development team |

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|---|---|
| **Notes** | **Results**<br>• There was no significant difference for mean length of stay in hours between the nebulized saline group (47) and the standard care group (50.4), difference of -3.4, 95% CI [-17.05, 10.25].<br>• No significant differences between groups for mean duration of oxygen therapy, a difference of -1.6 hours, 95% CI [-13.15, 9.95]<br>• No significant differences between groups for racemic epinephrine rescue therapy, transfer to pediatric intensive care unit, or readmission within 7 days after discharge.<br>**Limitations**<br>• Absence of blinding<br>• No use of active comparator (placebo)<br>• Not controlled for duration of illness prior to hospitalization<br>• Low statistical power for secondary outcomes and completion of sensitivity analysis<br>**Additional Information**<br>• Reported results as intention to treat but did not include all patients randomized into study (61 in each arm). Analysis did not include two subjects that were excluded following randomization. In the flow chart in Figure 1, it appears that one subject in each arm was excluded, however in the results section and Tables 1 and 2, it appears that both excluded subjects were from the group receiving only supportive care. Following our sensitivity analysis, we determined this would not have a significant effect on the results of the study.<br>• Ten participants did not receive treatment as expected.<br>• Five patients were admitted to hospital again within 7 days after discharge. Two patients in each group were readmitted for persisting symptoms of bronchiolitis (cough, nasal obstruction) and one patient had gastroenteritis. |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Randomly allocated on a 1:1 basis using a computer-generated randomization program in blocks of 10 |
| **Allocation concealment (selection bias)** | High risk | Allocation did not appear to be concealed |
| **Blinding of participants and personnel (performance bias)** | Low risk | Blinding of participants and personnel not possible due to nature of intervention (use of nebulized saline vs. no use of nebulized saline) and lack of use of placebo in protocol, but lack of blinding of participants and personnel not likely to affect outcome |
| **Blinding of outcome assessment (detection bias)** | High risk | Physicians in charge of the ward assessed the Wang Score and did not appear to be blinded. As this is subjective, bias is possible. Equipment for 3% hypertonic saline may be in the patient's room. |
| **Incomplete outcome data (attrition bias)** | Low risk | Statistical analysis claimed to follow intention to treat principle but did not include two patients in standard care arm excluded after randomization. However, our sensitivity analysis showed that including these patients in analysis did not affect results. |
| **Selective reporting (reporting bias)** | Low risk | All outcomes defined a priori were reported. |
| **Other bias** | Low risk | The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. No competing interests declared |

**Kose et al., 2016**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Infants, age 1 - 24 months<br>**Setting:** Pediatric hospital setting between January 2014 and May 2014<br>**Randomized into study:** *N* = 104<br>• **Group A,** Salbutamol 0.15 mg/kg plus 2.5mL 0.9% saline *n* = 35<br>• **Group B,** Salbutamol 0.15 mg/kg plus 2.5mL 3% saline: *n* = 35<br>• **Group C,** Salbutamol 0.15 mg/kg plus 2.5mL 7% saline: *n* = 34<br><br>**Gender, males:**<br>• **Group A:** *n* = 14 (66.67%)<br>• **Group B:** *n* = 14 (66.67%)<br>• **Group C:** *n* = 14 (70%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, Median in months (min - max):**<br>• **Group A:** 7.6 (1 - 18)<br>• **Group B:** 7.6 (2 - 23)<br>• **Group C:** 7.7 (1 - 24)<br>**Inclusion Criteria:**<br>• Age 1 - 24 months<br>• History of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation<br>• First wheezing episode<br>• Clinical severity score (CSS) of ≥ 4<br>**Exclusion Criteria:**<br>• Infants with CSS < 4<br>• Oxygen saturation < 80% in room air<br>• Chronic cardiopulmonary or neurological disease<br>• Premature birth<br>• Birth weight < 2500 g<br>• History of recurrent wheezing episodes<br>• Proven immune deficiency<br>• Age < 1 month or > 2 years<br>• Proven or suspected acute bacterial infection<br>• Previous treatment with bronchodilators or corticosteroids<br>• Presence of symptoms > 7 days<br>• Consolidation or atelectasis on a chest roentgenogram<br>**Power Analysis:** The power of the study was 50% (no further information given as to number needed for power) |
| **Interventions** | • **Both:** All patients received inhalation of 0.15 mg/kg salbutamol plus 2.5 mL of either 0.9%, 3% or 7% saline solution, twice upon admission at 30 minute intervals and then every 6 hours until discharge<br>• **Group A:** 0.9% inhaled saline<br>• **Group B:** 3% inhaled saline<br>• **Group C:** 7% inhaled saline |
| **Outcomes** | **Primary outcome(s):**<br>• Effect of study drugs on the length of hospital stay (LOS)<br>**Secondary outcome(s)**<br>• Safety and efficacy in reducing the clinical severity score (CSS) at the 24 hours of the study<br>**Safety outcome(s):** |

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|---|---|
| | • Side effects of study drugs including tachycardia, tremor, bronchospasm and cough<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• Median LOS in hours (min - max) was not significantly different in the group receiving 0.9% saline (72.0, (20 - 288)) vs. 3% saline (64.0, (12 - 168)) vs. 7% saline (60.0, (12 - 264)), $p$ = .760<br>• CSS scores were not significantly different between groups at 0 hours, $p$ = .778, 1 hour, $p$ = .271, or 24 hours, $p$ = .165.<br>• In the group receiving 7% saline, bronchospasm was observed in two patients, cough during nebulization was observed in two patients, and both bronchospasm and cough during nebulization were observed in one additional patient. |

**Length of Stay**

| | Group A $n$ = 35 | Group B $n$ = 35 | Group C $n$ = 34 | $p$ |
|---|---|---|---|---|
| LOS in hours (min - max) | 72.0 (20 - 288) | 64.0 (12 - 168) | 60.0 (12 - 264) | 0.760 |

**Clinical Severity Scores (CSS)**

| | Group A $n$ = 35 | Group B $n$ = 35 | Group C $n$ = 34 | $p$ |
|---|---|---|---|---|
| CSS at 0 hours | 7.0 ± 1.7 | 7.2 ± 1.9 | 7.3 ± 1.7 | 0.778 |
| CSS at 1 hour | 5.8 ± 1.9 | 6.2 ± 1.8 | 6.6 ± 2.0 | 0.271 |
| CSS at 24 hours | 4.6 ± 1.7 | 4.2 ± 1.3 | 4.7 ± 1.1 | 0.165 |

**Limitations:**
- Limited number of study participants
- No standardized dosage or volume of 7% inhaled saline
- Hypernatremia as side effect of inhaled saline treatment not evaluated

**Additional Information**
- 1 mg/kg steroid were administered for 3 days to all patients with CSS $\geq$ 10 after 1 hour of initial treatment
- Two patients in group C subsequently withdrawn because of deteriorated clinical status.
- Patients discharged if CSS <4, oxygen saturation >92% in room air for 4 hours, and no feeding difficulty

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | The randomization of the given drug was performed according to the age, sex and CCS distributions of the patients with a computer program. |
| **Allocation concealment (selection bias)** | Unclear risk | No description of drug containers was given to know whether they were identical in appearance or had features that would allow differentiation between groups, though it does state that the treating providers did not know which drug was given |
| **Blinding of participants and personnel (performance bias)** | Unclear risk | Though this study states it is double-blinded, it does not explicitly state that participants and personnel are blinded to the treatment |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | The outcome is assessed by researchers other than the primary providers treating the patients and administering treatment. Though the study states that it is double-blinded, it does not explicitly state that the outcome assessors are blinded to treatment. |
| **Incomplete outcome data (attrition bias)** | Low risk | Two patients in Group C withdrew due to deteriorated clinical status but were included in analysis and unlikely to affect outcome of study. |
| **Selective reporting (reporting bias)** | Low risk | All pre-determined outcomes were reported. |
| **Other bias** | Low risk | Study reports no conflict of interest or financial support. |

**Mahesh Kumar et al., 2013**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children < 2 years of age, admitted with first episode of lower respiratory tract infection during the winter months from October 2007 to March 2009.<br>**Setting:** India, Bengalore, M S Ramaiah Medical College and Hospital, Department of Pediatrics<br>**Randomized into study:** *N* = 40<br>• **Group 1, 3% hypertonic saline (HS):** *n* = 20<br>• **Group 2, normal saline (NS):** *n* = 20<br>**Completed Study:** *N* = 40<br>• **Group 1:** *n* = 20<br>• **Group 2:** *n* = 20<br>**Gender, male ratio (as defined by researchers):**<br>• **All patients randomized into study:** 1.6 : 1<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months, (range):**<br>• **All patients randomized into study:** 5.93 ± 3.83 (2 - 12 months)<br>**Inclusion Criteria:**<br>• Children < 2 years of age<br>• Admitted with first episode of lower respiratory tract infection<br>• Present with wheeze and moderate respiratory distress<br>• Clinical score between 4 and 8<br>**Exclusion Criteria:**<br>• Pre-existing cardiac disease<br>• Previous wheezing episodes<br>• Severe disease (clinical score > 8)<br>• Need for mechanical ventilation<br>  ○ Oxygen saturation < 85% on room air<br>  ○ Cyanosis<br>  ○ Obtunded consciousness<br>  ○ Progression to respiratory failure<br>**Power Analysis:** Not reported |
| **Interventions** | **Both:** All patients received humidified oxygen, intravenous (IV) fluids, and a calculated dose of salbutamol (0.15 mg/kg/dose) for nebulization. The volume of nebulized saline was 3mL for both groups. Nebulized medications were administered every six hours until discharge, using identical nebulizer set-ups.<br>• **Group 1:** 3% saline (HS)<br>• **Group 2:** normal saline (NS) |
| **Outcomes** | **Primary outcome(s):**<br>• Improvement in respiratory distress as indicated by clinical score*<br>• Duration of hospital stay (LOS)*<br>**Secondary outcome(s)**<br>• Number of add-on nebulized treaments required<br>• Failure rate, defined as children who showed a worsening of clinical scores during the course of stay<br>**Safety outcome(s):**<br>• Not reported<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• Patients in the HS arm of the study demonstrated slightly more reduction in clinical severity (1.8 ± 0.83) than the NS arm (1.7 ± 0.86), *p* = .712 |

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| | • Patients in the HS arm had a 24% reduction in LOS, with mean LOS in the HS arm of 2.25 ± 0.89 days vs. in the NS arm of 2.88 ± 1.76 days, *MD* 0.63 ± 0.87, $p$ = .165<br>• Patients in the HS arm had fewer add-on nebulized treatments (1.7 ± 1.75) vs the NS arm (2.4 ± 4.1)<br>• Patients in the HS arm had no treatment failures, as opposed to four failures in the NS group, which was clinically significant $p$ = .03<br>• All findings except the number of treatment failures were statistically insignificant.<br>**Limitations:**<br>• Small sample size<br>• Younger age of the study population<br>• Relatively low clinical scores |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Randomized into two groups using a computer generated random numbers. The eligible patients were recruited sequentially and randomized in a double-blind manner |
| **Allocation concealment (selection bias)** | Low risk | The eligible patients were recruited sequentially and randomized in a double-blind manner |
| **Blinding of participants and personnel (performance bias)** | Unclear risk | The authors did not report if there were any distinguishable differences between the HS and NS solutions including appearance, labels or packaging. Although the authors noted the randomization was done in a double-blind manner, no other information was reported regarding blinding of participants and personnel. While the risk of performance bias is likely low, the authors do not specifically speak to this concern. Insufficient information to permit judgment of low risk or high risk. |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | Insufficient information to permit judgment of low risk or high risk. |
| **Incomplete outcome data (attrition bias)** | Low risk | All randomized subjects were included in analysis. |
| **Selective reporting (reporting bias)** | Low risk | The published report contains all expected outcomes |
| **Other bias** | Unclear risk | The authors did not disclose study funding or provide a declaration of competing interests. |

**Morikawa et al., 2018**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Infants < 12 months of age hospitalized for acute bronchiolitis due to respiratory syncytial virus (RSV) from November 2008 to March 2013<br>**Setting:** Two tertiary children's hospitals and three general hospitals in Tokyo, Japan<br>**Randomized into study:** *N* = 128<br>• **Group 1, 3% nebulized saline (HS):** *n* = 63<br>• **Group 2, 0.9% nebulized saline (NS):** *n* = 65<br>**Completed Study:** *N* = 128<br>• **Group 1:** *n* = 63<br>• **Group 2:** *n* = 65<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 36 (57%)<br>• **Group 2:** *n* = 42 (65%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months, (SD):**<br>• **Group 1:** 4.4 ± 3.1<br>• **Group 2:** 4.2 ± 3.0<br>**Inclusion Criteria:**<br>• Hospitalized infants < 12 months of age<br>• Infants diagnosed with acute bronchiolitis due to RSV<br>**Exclusion Criteria:**<br>• Infants with<br>○ $pCO_2$ >60 mm Hg<br>○ Oxygen saturation < 95% on oxygen<br>○ Episodes of apnea<br>○ Previous history of wheezing episodes<br>○ History of cerebral palsy, congenital heart disease, lung disease, muscular disorder, malformation syndrome, immune deficiency disorder<br>○ History of preterm birth (gestational age < 36 weeks)<br>○ Progressive respiratory failure requiring mechanical ventilation<br>○ Previous administration of palivizumab<br>**Power Analysis:** 80% ($p$ = < 0.05, two-sided). The hazard ratio of the NS group to HS group was assumed to be 0.6. All analyses were based on intention-to-treat principle. |
| **Interventions** | **Both:** The patients in each group were treated four times daily during their hospital stay until they met discharge criteria (maintenance of axillary temperature below 37.5°C for 24 hours, no need for supplemental oxygen for 24 hours, adequate feeding defined as more than 100 mL/kg/day of milk or meals equal to or more than 70% of the preadmission volume as gauged by the physician and the parents). Additional nebulizations using the solutions were permitted. All nebulization therapies were delivered via standard oxygen-driven hospital nebulizers. The nebulizers used were the Cirrus™ nebulizer with a flow rate of 5 L/min, the PARI LC PLUS® with a flow rate of 5L/min, the Compressor Nebulizer NE-C29 with a flow rate of 10L/min, the Millicon Cube nebulizer with a flow rate of 10L/min, and the Millicon Cube nebulizer KN-80S with a flow rate of 10L/min. Oxygen was administered if the patient's oxygen saturation level remained below 95%. Once oxygenation of 94% was achieved, the oxygen supply was reduced, then stopped by the nurses. Additional therapies such as bronchodilators, intravenous fluids, deep nasal suction, and antibiotics were permitted at the discretion of the attending physicians. The use of steroids and/or theophylline was not allowed. Upon admission, Clinical Severity Scores (CSS), blood $CO_2$ levels, and a chest x-ray were obtained. RSV was diagnosed using one of three test kits. Nurses monitored the patients' oxygen saturation levels and for any adverse events occurring throughout the hospitalization. Body weight was recorded upon admission. Axillary temperature was |

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| | obtained three times daily. Feeding status was monitored every morning. Follow-up was performed in the outpatient department on Day 7 after discharge.<br>• **Group 1, 3% HS:** Received 0.1 mL of 0.5% salbutamol in 2 mL of 3% HS<br>• **Group 2, 0.9% NS:** Received nebulized 0.1 mL of 0.5% salbutamol in 2 mL of 0.9% NS |
| **Outcomes** | **Primary outcome(s):**<br>• Length of hospital stay* (defined as the time from admission until discharge criteria met)<br>**Secondary outcome(s):**<br>• Change in CSS between the time of admission and 72 hours later*<br>• Duration of oxygen administration<br>**Safety outcome(s):**<br>• Adverse events defined in accordance with the Common Terminology Criteria for Adverse Events (CTCAE)<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• One patient in the HS group received the treatment designed for the other group once and was included in the intention-to-treat group<br>• Two patients who received hydrocortisone were included in the intention-to-treat group<br>• Two patients were discharged before they fulfilled discharge criteria and were censored (lost to follow-up) at discharge.<br>• The mean LOS was 4.71 ± 2.15 days for the study population (4.81 ± 2.14 days (HS); 4.61 ± 2.18 days (NS))<br>• There was not a significant difference ($p$ = .60) between groups in overall LOS.<br>• The mean duration of oxygen administration was not significant ($p$ = .55) between groups (2.77 ± 2.68 days (HS); 2.50 ± 2.50 days (NS)<br>• The proportion of patients receiving oxygen was not significant ($p$ = .61) between groups, consisting of 71.4% in the HS group and 75.4% in the NS group.<br>• The CSS at baseline was not significant ($p$ = .56) between groups (5.63 ± 2.09 (HS); 5.40 ± 2.47 (NS)<br>• Improvement in the CSS from baseline to 72 hours was not significant ($p$ = .91) between groups (-3.63 ± 2.30 (HS); -3.58 ± 2.56 (NS)<br>• Two patients in the HS group required hospital readmittance (one for acute otitis media, the other for pneumonia)<br>• No patients required mechanical ventilation following admission<br>**Limitations:**<br>• The study was open label presenting potential biases in LOS, the primary endpoint, and additional therapies.<br>• Variability was reported in nebulizer types and administration methods<br>• Lacked power to detect smaller effects than assumed ($HR$ = 0.6)<br>• Participants in the study were restricted to Japanese infants with RSV infection<br>•<br>• The study was not powered for secondary outcomes. |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Used data from the University Hospital Medical Information Network (UMIN) and the Internet Data and Information Center for Medical Research (INDICE). |
| **Allocation concealment (selection bias)** | Low risk | Dynamic (minimization) allocation was used to assign patients randomly to groups in a 1:1 ratio by stratification according to age (< 60 vs ≥ 60 days) and institute. |
| **Blinding of participants and personnel (performance bias)** | Low risk | The allocation status was disclosed at registration. The patients and treating physicians were not masked to assignment. The study reported the open-label nature as a potential for bias, though was able to predefine criteria which should not have been influenced due to lack of blinding. |
| **Blinding of outcome assessment (detection bias)** | Low risk | Biostatisticians were blinded to the allocation during the trial and analysis |
| **Incomplete outcome data (attrition bias)** | Low risk | Intention-to-treat analysis completed |
| **Selective reporting (reporting bias)** | Low risk | The study included reports of all outcomes |
| **Other bias** | Low risk | The study appears to be free of other risks of bias |

**Ojha et al., 2014**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children 6 weeks - 24 months with diagnosis of bronchiolitis<br>**Setting:** Kathmandu, Nepal; hospital department of pediatrics, July 2012-August 2013<br>**Randomized into study:** *N* = 72<br>• **Group 1, Nebulized 3% saline (Solution B):** *n* = 36<br>• **Group 2, Nebulized 0.9% saline (Solution A):** *n* = 36<br>**Completed Study:** *N* = 59<br>• **Group 1:** *n* = 28<br>• **Group 2:** *n* = 31<br>**Gender, males**: *N* = 53 (74%)<br>• **Group 1:** *n* = (%) not reported; see notes<br>• **Group 2:** *n* = (%) not reported; see notes<br>**Race / ethnicity or nationality:**<br>• Not specified<br>**Age: months, mean (+/- SD)**<br>• **Group 1:** 8.61 (5.742)<br>• **Group 2:** 8.51 (4.24)<br>**Inclusion Criteria**:<br>• Children older than 6 weeks and below 24 months<br>• Clinical presentation of bronchiolitis for the first time<br>○ Bronchiolitis was defined as the first episode of wheezing associated with tachypnea, increased respiratory effort, and an upper respiratory tract infection<br>• Clinical scoring of respiratory distress $\geq$ 4<br>**Exclusion Criteria**:<br>• Previous episode of wheezing<br>• Chronic cardiac and pulmonary disease<br>• Immunodeficiency<br>• Accompanying respiratory failure requiring mechanical ventilation<br>• Inhalation of nebulized 3% hypertonic saline solution and salbutamol in the 12 hours before treatment<br>• Premature infants born at less than 34 weeks gestation<br>• Children with oxygen saturation < 85% on room air<br>**Power Analysis**: The sample size for this study was 72:36 in case and control group. This was calculated using PS-Power and Sample Size Calculator Version 3.0.43. |
| **Interventions** | **Both:**<br>• At least three nebulized saline treatments on each day of hospitalization, 8 hours apart<br>• Clinical scoring tool was used 30 minutes before and immediately after treatment<br>• Parameters measured using the clinical score: respiratory rate, wheezing, retractions, oxygen saturation<br>• **Group 1:** 4ml nebulized 3% saline<br>• **Group 2:** 4ml nebulized 0.9% saline |
| **Outcomes** | Primary outcome(s):<br>• Length of stay*<br>• Need for supplemental oxygen (defined as oxygen saturation below 92% on room air)<br>• Duration of supplemental oxygen<br>• CSS improvement<br>*Outcomes of interest to the CMH CPG or CAT development team |

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| **Notes** | **Results:**<br>• Length of stay<br>  ○ The difference in average duration of hospital stay was not statistically significant ($p$ = .86)<br>• Need for oxygen supplementation<br>  ○ Out of 72 children, 21 required oxygen supplementation. Twelve of these patients were in the 3% saline group and the remaining 9 were in the 0.9% saline group.<br>• Duration of oxygen supplementation<br>  ○ The difference in mean duration of oxygen supplementation was not statistically significant ($p$ = .85)<br>• CSS improvement:<br>  ○ Both groups had a decrease in clinical severity score after commencement of the treatment; however, the decrease was not statistically significant according to the authors ($p$ value not reported)<br>  ○ Children who received 3% saline and 0.9% saline took 36.79 (±19.53) hours and 38.34 (±26.67) hours respectively to have their clinical score fall below a score of 4; however, this difference was again not statistically significant ($p$ = .80)<br>**Limitations:**<br>• Authors state that 53 (74%) of study participants were male but do not state how many were in each group<br>• All participants received nebulized saline **at least** 3 times per day, more saline treatments could be done at the discretion of the treating physician<br>• Authors report difficulty in asserting the diagnosis of bronchiolitis, as a diagnostic tool to identify the virus was not available<br>• Difficult to distinguish between wheezing due to bronchiolitis vs. possible first episode of asthma |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Random number generator was used. |
| **Allocation concealment (selection bias)** | Low risk | Random numbers kept in a sealed envelope, labeling was done by sister who was not involved in patient care. |
| **Blinding of participants and personnel (performance bias)** | Low risk | Emergency physicians, house staff, nurses, study personnel, and patients were blinded to treatment allocation throughout the study. |
| **Blinding of outcome assessment (detection bias)** | Low risk | Study personnel were blinded to treatment throughout the study. |
| **Incomplete outcome data (attrition bias)** | High risk | Several children in both groups did not finish at parental request, either by leaving early against medical advice, being discharged at parent's request, or because parent wanted to discontinue study. The original power was for 36 participants in both groups, 5 were excluded in group 2 and 8 from group 1. |
| **Selective reporting (reporting bias)** | Low risk | Pre-specified outcomes reported as expected. |
| **Other bias** | Unclear risk | See limitations. In addition, this study does not address potential conflict of interest. |

**Pandit et al., 2013**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children between the ages of 2 to 12 months admitted with clinical diagnosis of acute bronchiolitis.<br>**Setting:** Paediatrics Emergency at Government Multi Specialty Hospital (GMSH), Sector-16, Chandigarh, India.<br>**Randomized into study:** *N* = 100<br>• **Group 1, Group A: Hypertonic Saline:** *n* = 51<br>• **Group 2, Group B: Normal Saline***:* *n* = 49<br>**Completed Study:** *N* = 100<br>• **Group 1:** *n* = 51<br>• **Group 2:** *n* = 49<br>**Gender, males (as defined by researchers):**<br>• Not detailed in article. Noted in results section that groups had comparable demographic data.<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not detailed in article. Noted in results section that groups had comparable demographic data.<br>**Age, mean/median in months/years, (range/IQR):** not detailed in article. Noted in results section that groups had comparable demographic data.<br>**Inclusion Criteria:**<br>• Children ages 2 to 12 months<br>• Clinical diagnosis of acute bronchiolitis (short history of cough with or without fever of less than seven days duration and wheezing on examination and with the first attack of wheezing)<br>**Exclusion Criteria:**<br>• Patient with recurrent episodes of wheezing, one or more episodes of respiratory distress in the past.<br>• Patients with family history of asthma, atopy<br>• Presence of congenital heart disease<br>• History of prematurity or mechanical ventilation in newborn period<br>• Very sick patients with shock, seizures, heart rate > 180/minute and adjudged to be in incipient respiratory failure<br>• Grade III and IV PEM<br>• Consolidation lung on x-ray chest<br>• No child included in the study twice<br>**Power Analysis:** The calculated sample size was 100 for 80% power and a 95% confidence interval |
| **Interventions** | **Both:** Nebulization given three times upon admission with an interval of one hour between two nebulization, and every 6 hours thereafter<br>Assessment of respiratory rate, respiratory distress assessment instrument (RDAI) score, heart rate, oxygen saturation was done on admission before the nebulization and half an hour after third nebulization.<br>Nebulization given every 6 hours with respective saline and adrenaline daily until discharge.<br>• **Group 1:** 4mL of 3% hypertonic saline and 1mL of 1:1,000 adrenaline was given as nebulization with oxygen flow of 6-8 L/minute.<br>• **Group 2:** 4mL of normal saline (0.9%) and 1mL of 1:1,000 adrenaline was given as nebulization. |
| **Outcomes** | **Primary outcome(s):**<br>• Length of stay*<br>**Secondary outcome(s)**<br>• Improvement in RDAI score<br>• Respiratory rate |

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| | • Oxygen saturation<br>• Heart rate<br>• Number of add on treatments<br>• Adverse events*<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• Found no significant difference between the two groups in relation to length of stay ($p$ = .67).<br>• Length of stay significantly higher in patients who received add on treatments ($p$ < .05)<br>• Secondary outcomes<br>  ○ No significant difference in clinical parameters between group 1 and group 2 on day 1 and day 2 of admission. ($p$ > .05)<br>  ○ Significant improvement in clinical parameters from pre to post nebulization within both groups on day 1 and day 2 of admission. ($p$ < 0.05)<br>• Adverse events<br>  ○ Side effects (vomiting, diarrhea) noted in 4% of participants; all enrolled in group 2.<br>  ○ No adverse effects such as tremors or paleness in any participant.<br>**Limitations:**<br>• Non-blinded study design; introducing some bias during evaluation.<br>• Only included hospitalized children ≤ 12 months of age<br>• Enrolled based upon clinical diagnosis and not confirmed by viral studies<br>• Exact duration of hypertonic saline effect and its continuing impact on clinical parameter is unknown |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Utilized a computer generated program for random assignment between groups |
| **Allocation concealment (selection bias)** | Unclear risk | Concealed in an opaque envelope |
| **Blinding of participants and personnel (performance bias)** | High risk | Non-blinded study. Staff were aware of participants' treatment groups. |
| **Blinding of outcome assessment (detection bias)** | High risk | Non-blinded study design; assessment could be influenced by knowing treatment prescribed |
| **Incomplete outcome data (attrition bias)** | Low risk | All participants completed study. |
| **Selective reporting (reporting bias)** | Low risk | All results were reported out. |
| **Other bias** | Low risk | Reported no conflicts of interest, no financial sponsorships |

**Sharma et al., 2013**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Hospitalized children (age 1 - 24 months) with acute bronchiolitis of moderate severity<br>**Setting:** Tertiary care teaching hospital. No additional setting information was provided.<br>**Randomized into study:** *N* = 250<br>• **Group 1, Hypertonic Saline (HS) Group:** *n* = 125<br>• **Group 2, Normal Saline (NS) Group:** *n* = 125<br>**Completed Study:** *N* = 248<br>• **Group 1:** *n* = 125<br>• **Group 2:** *n* = 123<br>**Gender, % males:**<br>• **Group 1:** *n* = 77.6%<br>• **Group 2:** *n* = 74.8%<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months (SD)**<br>• **Group 1:** 4.93 $\pm$ 4.31<br>• **Group 2:** 4.18 $\pm$ 4.24<br>**Inclusion Criteria:**<br>• Hospitalized infants and children aged 1 to 24 months.<br>• Clinical presentation of viral bronchiolitis of moderate severity, with a clinical severity score of 3-6.<br>**Exclusion Criteria:**<br>• Obtunded consciousness<br>• Cardiac disease<br>• Chronic respiratory disease<br>• Previous wheezing episode<br>• Progressive respiratory distress requiring respiratory support other than supplemental oxygen<br>• Received nebulized hypertonic saline within the previous 12 hours<br>**Power Analysis:** Not reported |
| **Interventions** | **Both:** Both groups received 2.5 mg salbutamol. All medications were administered by nebulizer every 4 hours, six times daily till the patient was ready for discharge, using a conventional jet nebulizer, tight fitting face mask, and oxygen flow rate of 7L/minute.<br>• **Group 1:** 4 mL 3% HS<br>• **Group 2:** 4 mL 0.9% NS |
| **Outcomes** | **Primary outcome(s):**<br>• To compare the length of hospital stay (time taken to reach clinical severity score <3).*<br>**Secondary outcome(s)**<br>• To compare the improvement in clinical severity scores in hospitalized children with acute bronchiolitis nebulized with 3% HS and NS.*<br>**Safety outcome(s):**<br>• Not reported<br>*Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results:**<br>• There was no significant difference in Clinical Severity (CS) score at enrollment and at reassessment every 12 hours until discharge (values not given, shown in graph as median CSS over time after admission) |

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| | • There was also no difference in mean length of hospital stay in hours for the group receiving HS (63.51 ± 21.27) vs. the group receiving NS (63.93 ± 22.43), $p$ = .878.<br>**Limitations:**<br>• The authors noted the median CS score at time 0 was based on 125 subjects, whereas the data at 132 hours was only based on two patients (due to timing of hospital discharge)<br>• The study was not powered for secondary outcomes. |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | **Low risk** | Computer generated random numbers were used for enrolment in consecutive manner and patients were randomly assigned to a treatment arm |
| **Allocation concealment (selection bias)** | **Low risk** | HS and NS solutions had no detectable differences in color, smell, or other physical properties. The combination code of the therapeutic package was not available to the investigator or treating medical staff (only the statistician). Solutions were administered to patients using identical equipment, method and interval |
| **Blinding of participants and personnel (performance bias)** | **Low risk** | All participants and study personnel were appropriately blinded and it is unlikely that the blinding could have been broken |
| **Blinding of outcome assessment (detection bias)** | **Low risk** | Blinding of outcome assessment was ensured. Investigators performing assessments were unaware of treatment arm assignment |
| **Incomplete outcome data (attrition bias)** | **Low risk** | 125 participants were assigned to the NS group and 123 were analyzed. The authors do not address the two patients that were not included in the analysis. However, the required sample size in each arm was 113 patients and the difference in sample size between the HS and NS groups was negligible, making it unlikely that the two missing patients are enough to introduce clinically relevant bias |
| **Selective reporting (reporting bias)** | **Low risk** | Published reports include the expected outcomes. |
| **Other bias** | **Low risk** | They reported there was no funding for this study and no competing interests. |

**Silver et al., 2015**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Patients < 12 months of age hospitalized with bronchiolitis<br>**Setting:** Urban tertiary care children's hospital, November 2011 to June 2014, United States<br>**Randomized into study:** *N* = 227<br>• **Group 1, nebulized 3% hypertonic saline (HS):** *n* = 113<br>• **Group 2, nebulized 0.9% normal saline (NS)** *n* = 114<br>**Completed Study:** *N* = 190<br>• **Group 1:** *n* = 93<br>• **Group 2:** *n* = 97<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 62 (67%)<br>• **Group 2:** *n* = 60 (62%)<br>**Race / ethnicity or nationality (as defined by researchers), *n* (%):**<br><br>**HS** / **NS**<br>Black: 24 (26) / 35 (36)<br>White: 17 (18) / 17 (18)<br>Other: 48 (52) / 41 (42)<br>Missing: 4 (4) / 4 (4)<br>Hispanic ethnicity: 71 (76) / 71 (73)<br><br>**Age, mean in months, (SD)**<br>• **Group 1:** 3.9 ± 3.0<br>• **Group 2:** 4.4 ± 3.0<br>**Inclusion Criteria:**<br>• Physician diagnosis of bronchiolitis<br>• < 12 months old<br>**Exclusion Criteria:**<br>• Treatment of asthma (corticosteroids or bronchodilators)<br>• Chronic cardiopulmonary disease such as bronchopulmonary dysplasia, cystic fibrosis<br>• Previous nebulized hypertonic saline < 12 hours before presentation<br>• Non-English, non-Spanish speaker<br>• Enrollment assessment> 12 hours after admission<br>• Patients previously enrolled within 72 hours of presentation<br>**Power Analysis:** 105 subjects were needed in each arm to identify a 0.6 day change in length of stay, with 80% power with a 2-tailed test. Alpha = 0.05. |
| **Interventions** | **Both:** In addition to treatment every 4 hours, all patients could receive study treatment every 2 hours prn with a maximum of 2 PRN doses per 24 hour period<br>• **Group 1:** 4 mL of nebulized 3% HS every 4 hours from enrollment until hospital discharge<br>• **Group 2:** 4 mL of NS every 4 hours from enrollment until hospital discharge |
| **Outcomes** | **Primary outcome(s):**<br>• Length of stay defined as the time from the first study treatment to the time of hospital discharge or meeting discharge criteria<br>**Secondary outcome(s)**<br>• Adverse events<br>• Seven-day readmission rates<br>• Clinical worsening- transfer to PICU or bronchospasm within 30 minutes of a nebulized study treatment, as indicated by a RDAI score worsening by >/= to 4<br>**Safety outcome(s):**<br>• Not reported |

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| | *Outcomes of interest to the CMH CPG or CAT development team |
| **Notes** | **Results**<br>• No difference in median (IQR) length of stay between the group receiving HS (2.1 days, (1.2 - 4.6)) and the group receiving NS (2.1 days, (1.2 - 3.8)), *p* = .73.<br>• No difference in total adverse events between the group receiving HS, *n* = 14 (15%) and the group receiving NS, *n* = 12 (12%), *p* = .67.<br>• No difference in readmissions between the group receiving HS, *n* = 4 (4%) and the group receiving NS, *n* = 3 (3%), *p* = .77.<br>• No difference in clinical worsening between the group receiving HS, *n* = 10 (9%) and the group receiving NS, *n* = 9 (8%), *p* = .97.<br>**Limitations**<br>• Use of NS as control instead of placebo<br>• Single-center study raises question of generalizability of results<br>• Enrollment within 12 hour window of time of admission could influence duration of patients' participation in study<br>• No minimum severity score for eligibility<br>• Variability in approach to nebulized treatment administration in infants resisting and crying infants<br>• The study was not powered for secondary outcomes.<br>**Additional Information**<br>• Patients with prematurity were included in both treatment and control arms<br>• Exit criteria:<br>○ Respiratory Distress Assessment Instrument (RDAI) before and 30 minutes after the first study treatment as a safety measure. An increase of >/= 4 points the patient received a bronchodilator and withdrawn from the study (*n* = 1)<br>○ Provider initiated bronchodilators or corticosteriods (*n* = 8)<br>○ Transfer to PICU<br>○ Parent or guardian request |

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Computer-generated block randomization |
| **Allocation concealment (selection bias)** | Low risk | Allocation concealed and administered by Investigational Drug Services |
| **Blinding of participants and personnel (performance bias)** | Low risk | Study medications were indistinguishable from one another |
| **Blinding of outcome assessment (detection bias)** | Low risk | Outcome assessors were blinded to the treatment given |
| **Incomplete outcome data (attrition bias)** | High risk | Thirty-seven subjects did not complete the study, 20 from the treatment arm and 17 from the control arm. Only per-protocol analysis was completed. For the per protocol analysis, they did not meet power. |
| **Selective reporting (reporting bias)** | Low risk | All pre-identified outcomes were reported |
| **Other bias** | Low risk | No potential conflicts of interest, funding, or financial relationships reported |

**Teunissen et al., 2014**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children, 0 - 24 months, admitted for mild to severe viral bronchiolitis with a Wang score of >2, from November 2009 to May 2011<br>**Setting:** Eleven general hospitals and one tertiary medical center in the Netherlands<br>**Randomized into study:** *N* = 292<br>• **Group 1, 3% hypertonic saline (3% HS):** *n* = 97<br>• **Group 2, 6% hypertonic saline (6% HS):** *n* = 102<br>• **Group 3, Control (0.9% NS):** *n = 93*<br>**Completed Study:** *N = 247*<br>• **Group 1:** *n = 80*<br>• **Group 2:** *n = 84*<br>• **Group 3:** *n = 83*<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 44 (52.4%)<br>• **Group 2:** *n = 48* (57.8%)<br>• **Group 3:** *n = 49* (61.3%)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean in months, (IQR):**<br>• **Group 1:** 3.6 (5.2)<br>• **Group 2:** 3.4 (3.8)<br>• **Group 3:** 3.5 (5.0)<br>**Inclusion Criteria:**<br>• Hospitalized children 0 - 24 months of age<br>• Diagnosis of mild to severe viral bronchiolitis, by nasal swab<br>• Wang score of > 2 at presentation<br>**Exclusion Criteria:**<br>• Wang score improvement of at least 2 points after 2.5 mg salbutamol inhalation<br>• Hemodynamically important congenital heart disease<br>• Chronic pre-existing lung disease<br>• T-cell immunodeficiency<br>• Treatment with corticosteroids<br>• Previous wheezing<br>• Allergy (food) or eczema<br>**Power Analysis:** 65 patients per trial arm required for the current study to achieve a power of 90% (p <.05) |
| **Interventions** | **Both:** The patients in each group were treated every 8 hours until discharge. Treatment given with a constant oxygen flow of 6–8 L/min from a wall outlet in combination with a HOT Top Plus Nebulizer (Intersurgical, Uden, The Netherlands), Mass Median Aerodynamic Diameter (MMAD) 4 mm, via a tight-fitting face mask and were administered until empty. Evaluation twice daily by pediatrician on duty, based on physical examination, Wang score, heart rate, saturation, respiratory rate, need for supplemental oxygen, and tube feeding. Supplemental oxygen was initiated with a room air saturation of 93%, or lower, during > 10 min or acute desaturation of <85%. This was stopped when saturation was consistently >93%. The indication for starting and stopping tube feeding was a minimal intake calculated as 75% of normal intake. Fluid loss because of dehydration or diarrhea was compensated by the addition of lost fluid to the minimal intake. Additional medication and other supportive care were given according to hospital guidelines. All additional medication, time and quantity of supplemental oxygen and tube feeding were recorded in the case record form. Protocol-defined discharge criteria included no need for supplemental oxygen, tube-feeding or intravenous fluids, according to the responsible pediatrician. |

<table>
<tr><td></td><td>

- **Group 1:** 3% HS: Received 2.5 mg Salbutamol and 3% sodium chloride, total volume of 4ml
- **Group 2:** 6% HS: Received 2.5 mg Salbutamol and 6% sodium chloride, total volume of 4 ml
- **Group 3:** 0.9% NS: Received 2.5 mg Salbutamol and 0.9% sodium chloride, total volume of 4ml

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<tr><td>Outcomes</td><td>

**Primary outcome(s):**

- Length of hospital stay (LOS)* (calculated as the number of hours between the first dose of study medication and the clinical decision to discharge)

**Secondary outcome(s)**

- Transfer to Pediatric Intensive Care Unit (PICU) because of respiratory insufficiency, need and duration of supplemental oxygen or tube feeding.
- Wang Clinical Severity Score (CSS)

**Safety outcome(s):**

- Registration of adverse events

*Outcomes of interest to the CMH CPG or CAT development team

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<tr><td>Notes</td><td>

**Results:**

- A substantial number of adverse effects were noted in all treatment groups, withdrawal because of adverse events did not differ between groups ($p$ = .59)
- No significant difference ($p$ = .26) between groups in overall LOS
- No significant difference ($p$ = .7) between groups in supplemental oxygen need, median duration of 54, 54, and 40 hours
- Wang CSS improved at discharge for all groups without significant difference between groups ($p$ = .8)
- Cough occurred significantly more in both HS groups ($p$ = .03)

**Length of Hospital Stay**

| **Timeframe** | **3% HS Group** (n = 84) | **6% HS Group** (n = 83) | **NS Group** (n = 80) | ***p* - value** |
|---|---|---|---|---|
| Hours, median (IQR) | 69 (57) | 70 (69) | 53 (53) | .29 |

**Limitations:**

- Participants in the study restricted to children in the Netherlands with viral bronchiolitis
- Exclusion of children with a rapid response to single dose salbutamol; 14% screened for inclusion had to be excluded due to positive response to salbutamol
- The study not designed to examine subgroups with different disease severity
- Study only considered nebulized therapy, not non-nebulized therapy
- The study was not powered for secondary outcomes.

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</table>

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Nico Oldenhof (VieCuri Medical Centre, Venlo, The Netherlands) created the randomization procedure. Randomization was done per center and clustered in blocks of six patients. |
| **Allocation concealment (selection bias)** | Low risk | Each patient received a consecutively randomized number that corresponded to identical 20 mL vials, which contained the different sodium chloride solutions |
| **Blinding of participants and personnel (performance bias)** | Low risk | All participants, care givers and medical staff were blinded to the composition of the study solutions, which were identical in vial packaging, color, smell and other physical characteristics |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | Before the start of the study all participating medical staff were trained how to evaluate the patients and classify the Wang clinical severity scoring system in order to improve inter-observer agreement |
| **Incomplete outcome data (attrition bias)** | Low risk | Analyses were done according to the intention-to-treat and per protocol principles. Differences between included and excluded patients, with respect to patient characteristics, were evaluated by means of independent t-test (age) and Chi-squared test (sex and intervention). |
| **Selective reporting (reporting bias)** | Low risk | The study included reports of all outcomes |
| **Other bias** | Low risk | Financial support disclosed and conflicts of interest disclosed |

**Wu et al., 2014**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children younger than 24 months with primary diagnosis of viral bronchiolitis during bronchiolitis season.<br>**Setting:** Emergency department at 2 tertiary free-standing urban children's hospitals in California.<br>**Randomized into study:** *N* = 447<br>• **Group 1, 0.9% Normal Saline (NS):** *n* = 216<br>• **Group 2, 3% Hypertonic Saline (HS):** *n* = 231<br>**Completed Study:** *N* = 394<br>• **Group 1:** *n* = 190<br>• **Group 2:** *n* = 204<br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 118 (54.6%)<br>• **Group 2:** *n* = 136 (58.9%)<br>**Race / ethnicity:**<br><br>**Age, mean (SD) in months:**<br>• **Group 1:** 6.40 (5.33)<br>• **Group 2:** 6.57 (5.17)<br>**Inclusion Criteria:**<br>• Younger than 24 months with a primary diagnosis of viral bronchiolitis during bronchiolitis season (November - April)<br>**Exclusion Criteria:**<br>• Prior illness with wheezing or bronchodilator use<br>• Premature (gestational age, <34 weeks)<br>• Cyanotic congenital heart disease<br>• Chronic lung disease<br>• Tracheostomy<br>**Power Analysis:** For length of stay, 124 patients in each arm would yield 80% power to detect a significant difference ($p < .05$) |
| **Interventions** | **Both:** Patients in the emergency department received 2.5 mg of nebulized albuterol sulfate, followed by 4 mL of nebulized HS or NS. ED physicians could order up to 2 additional treatments every 20 minutes. Other care given at discretion of physician. Admitted patients continued receiving nebulized HS or NS with albuterol every 8 hours until discharge.<br>• **Group 1:** 4 mL of NS<br>• **Group 2:** 4 mL of HS |
| **Outcomes** | **Primary outcome(s):**<br>• Admission rate<br>• Length of stay*<br>• Respiratory Distress Assessment Instrument (RDAI) score<br>• Supplemental Therapies<br>**Safety outcome(s):**<br>• Adverse Events*<br>*Outcomes of interest to the CMH CPG or CAT development team |

| Group 1 n (%) | Group 2 n (%) |
|---|---|
| White | 21 (9.7) | 13 (5.6) |
| African American | 25 (11.6) | 43 (18.6) |
| Latino/Hispanic | 142 (65.7) | 147 (63.6) |
| Asian | 7 (3.2) | 10 (4.3) |
| Other | 21 (9.7) | 18 (7.8) |

| Notes | **Results:**<br>• Hypertonic saline given to children with bronchiolitis in the ED decreased hospital admissions.<br>• No significant difference in RDAI score or LOS between groups.<br>• Found a significant difference between sites for mean LOS.<br>• Found no difference between the mean (SD) Respiratory Assessment Change Score for the NS and HS groups. Found no sigificant change when adjusting for the baseline RDAI score.<br>• No significant difference was found in supplemental treatment use between groups.<br>• Six patients in the NS group and 4 in the HS group required transfer to the PICU or NICU.<br>**Limitations:**<br>• Failure to achieve planned sample size of 350 in each arm<br>• Only 145 patients underwent analysis for LOS, which is underpowered to detect differences in LOS of < 1 day<br>• The study was not powered for secondary outcomes. |
|---|---|

**Risk of bias table**

| Bias | Judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Patients were allocated by simple randomization to the HS or the NS group by the investigational pharmacy, using a computer-generated random number table stratified by site. |
| Allocation concealment (selection bias) | Low risk | Families, clinical staff, and study personnel were blinded to treatment allocation. |
| Blinding of participants and personnel (performance bias) | Low risk | Study medication was identical in color, odor, and labeling. |
| Blinding of outcome assessment (detection bias) | Low risk | Patients enrolled in the ED received 2.5 mg of nebulized albuterol sulfate, followed by 4 mL of normal saline or hypertonic saline via a small-volume wall nebulizer. The ED physicians could order 2 additional treatments every 20 minutes to a maximum of 3 inhaled doses. |
| Incomplete outcome data (attrition bias) | Low risk | No missing outcome data. |
| Selective reporting (reporting bias) | Low risk | Reports include all expected outcome data. |
| Other bias | Low risk | No conflicts of interest were reported. Funding was provided by a grant but the funding sources had no role in the study. |

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Children's Mercy KANSAS CITY
Evidence Based Practice

# *Critically Appraised Topic (CAT): Bronchiolitis- Hypertonic Saline*

**Appendix**

Evidence to Decision Assessment for Use of Nebulized 3% Hypertonic Saline

QUESTION

| **Should nebulized 3% hypertonic saline vs. no nebulized 3% hypertonic saline be used for treatment of hospitalized patients with bronchiolitis?** | |
|---|---|
| **POPULATION:** | Hospitalized patients with bronchiolitis |
| **INTERVENTION:** | Nebulized 3% hypertonic saline |
| **COMPARISON:** | No nebulized 3% hypertonic saline |
| **MAIN OUTCOMES:** | LOS (hours); LOS (hours) subgroup: High or unclear risk of bias; LOS (hours) subgroup: Risk of bias: Low risk of bias; LOS (hours) subgroup: HS vs SC; LOS (hours) subgroup: HS vs NS; LOS (hours) subgroup: No beta agonist or adrenaline included in nebulization; LOS (hours) subgroup: Beta agonist or adrenaline included in nebulization; LOS (hours) subgroup: Treatment administered every 4 hours; LOS (hours) subgroup: Treatment administered every 6 hours; LOS (hours) subgroup: Treatment administered every 8 hours; LOS (hours): Studies not included in meta-analysis; Wang CSS following 1 day of treatment; Wang CSS following 2 days of treatment; Wang CSS following 3 days of treatment; Need for Supplemental O2; Duration of Supplemental O2 (hours); |

ASSESSMENT

**Problem**
Is the problem a priority?

| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Bronchiolitis is a common illness in patients less than 2 years of age and is one of the most frequent causes of hospital admission for patients less than 12 months of age (Ralston et al., 2014). Mucus production is caused by inflammation of the bronchioles and may result in mucus plugging. Nebulized hypertonic saline (HS) is used to improve mucociliary clearance, though there is currently no direct evidence to show significant improvement (Ralston et al., 2010). The most recent AAP guideline makes a weak recommendation for use in the inpatient setting for patients whose admission exceeds 3 days, however, the average admission for bronchiolitis in the U.S. is 2.4 days (Ralston et al., 2014). This recommendation is based on evidence published prior to 2014. | Increased use of HS treatments increases the number of respiratory therapy (RT) staff needed each shift, while RT is currently experiencing staffing issues. |

| **Desirable Effects**<br>How substantial are the desirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | ***Length of Stay (LOS)***<br>Eleven RCT studies (Everard et al., (2014), Flores-González et al. (2016), Hmar et al., (2021), Islam et al., (2018), Jaquet-Pilloud et al., (2019), Mahesh Kumar et al., (2013), Morikawa et al., (2018), Ojha et al., (2014), Pandit et al., (2013), Sharma et al., (2013), Wu et al., (2014)) reported the mean (SD) LOS, ($n$ = 1,449). For the outcome of LOS, the $MD$ = -6.47 hours, 95% CI [-12.72, -0.22], $p$ = .04, indicated the LOS was shorter for patients that received treatment with 3% HS versus no treatment with 3% HS (see Figure 2 & Table 1).<br>***Length of Stay (LOS): Qualitative analysis***<br>Alatwani et al. (2021) reported the mean LOS without SD and found a shorter LOS in the group that received treatment with HS (3.38 days) compared to the group that received treatment with nebulized NS (4.67 days), a reduction of 1.3 days (27.8%), $p$ = .001.<br>Kose et al. (2016) reported the mean (min – max) LOS and found that the LOS was not different for the groups that received nebulized 3% HS (64 hours), NS (72 hours), or 7% HS (60 hours), $p$ = .76.<br>Silver et al., (2015) found that the median (IQR) LOS in days was not different for the group that received nebulized 3% HS (2.1 (1.2 – 4.6)) compared to the group that received nebulized NS (2.1 (1.2 – 3.8)), $p$ = .73.<br>Teunissen et al. (2014) reported the median (IQR) LOS in hours and did not find a difference between the group that received nebulized 3% HS (69 (57)), NS (53 (53)), and nebulized 6% HS (70 (69)), $p$ = .29.<br>***Need for Supplemental Oxygen***<br>Four studies (Flores-González et al. (2016), Islam et al., (2018), Ojha et al., (2014), Teunissen et al., (2014)) reported the need for supplemental oxygen ($n$ = 430). For the outcome of need for supplemental oxygen, the $OR$ = 0.88, 95% CI [0.57, 1.34], $p$ = .54, indicating there was no difference between the intervention of treatment with nebulized 3% HS compared to the intervention of no treatment with nebulized 3% HS. (see Figure 10 & Table 1).<br>***Duration of Supplemental Oxygen***<br>Five studies (Flores-González et al. (2016), Islam et al., (2018), Jaquet-Pilloud et al., (2019), Morikawa et al., (2018), Ojha et al., (2014)) reported the duration of supplemental oxygen in hours ($n$ = 346). For the outcome of duration of supplemental oxygen, the $MD$ = -5.84, 95% | |

| | | |
|---|---|---|
| | CI [-11.41, -0.28], *p* = <.05, indicating the intervention of treatment with nebulized 3% HS was favorable to the intervention of no treatment with 3% HS.<br>***Clinical Severity Scores (CSS) Following 1 Day of Treatment***<br>Three studies (Flores-González et al. (2016), Hmar et al., (2021), Kose et al., (2016)) reported the mean (SD) CSS (as described by Wang et al., (1992)) following 1 day of treatment (*n* = 296). For the outcome of improvement of CSS, the *MD* = -0.76, 95% CI [-1.07, -.046], *p* = <.05, indicating the treatment with nebulized 3% HS was favorable compared to the intervention of no treatment with 3% HS. (see Figure 7 & Table 1).<br>***Clinical Severity Scores (CSS) Following 2 Days of Treatment***<br>Two studies (Flores-González et al. (2016), Hmar et al., (2021)) reported the mean (SD) CSS (as described by Wang et al., (1992)) following 2 days of treatment (*n* = 226). For the outcome of improvement of CSS, the *MD* = -0.54, 95% CI [-0.79, -.028], *p* = <.05, indicating the intervention of treatment with nebulized 3% HS was favorable compared to the intervention of no treatment with 3% HS. (see Figure 8 & Table 1).<br>***Clinical Severity Scores (CSS) Following 3 Days of Treatment***<br>Two studies (Flores-González et al. (2016), Islam et al., (2018)) reported the mean (SD) CSS (as described by Wang et al., (1992)) following 3 days of treatment (*n* = 296). For the outcome of improvement of CSS, the *MD* = -1.19, 95% CI [-1.67, -.071], *p* = <.05, indicating the treatment with nebulized 3% HS was favorable compared to the intervention of no treatment with 3% HS. (see Figure 9 & Table 1). | |

| **Undesirable Effect**<br>How substantial are the undesirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Trivial<br>○ Small<br>● Moderate<br>○ Large<br>○ Varies<br>○ Don't know | Adverse events include bronchospasm, increased coughing, tachycardia, apnea, infection, cyanosis, and tremor. Seven studies reported adverse events (*N* = 1436). There was no difference in the number of adverse events between the patients treated with 3% HS compared to the group not treated with 3% HS, OR = 1.1, 95% CI [0.59, 2.05], *p* = .76. | Treatments with HS incur cost to the hospital and patient through medication cost and staff time to administer treatment.<br><br>Patients may experience distress or discomfort during treatment<br><br>Misrepresentation of the benefits of treatment to patients' families may lead to requests for nebulizers and treatment at home after discharge.<br><br>Use of HS treatments may drive use of other overutilized treatments such as albuterol |
| **Certainty of evidence**<br>What is the overall certainty of the evidence of effects? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Overall certainty of the evidence is very low due to serious risk of bias (lack of or unclear description of blinding of study personnel), serious indirectness (use of beta agonist/adrenaline in some studies, frequency/timing of treatment, use of NS or standard care as control), and serious imprecision (wide confidence interval). | |

| **Values**<br>Is there important uncertainty about or variability in how much people value the main outcomes? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | | There is possible variation in the value placed on length of stay, cost of treatment, staff usage to administer treatment, and value placed on treatment by patients' families.<br><br>The definition of clinically significant differences in length of stay is uncertain. |
| **Balance of effects**<br>Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ● Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | The evidence shows a shorter length of stay for patients receiving treatment with HS versus patients not receiving treatment with HS, but shows no difference for need for oxygen supplementation, duration of oxygen supplementation, or clinical severity scores following treatment. | Treatment with HS may increase cost to the patient and hospital, use of hospital staff, and patient discomfort without necessarily improving the care of the patient with routine bronchiolitis.<br><br>The shorter length of stay for patients receiving treatment with HS was not deemed likely to be clinically significant when considering the range of the CI. |

| **Resources required**<br>How large are the resource requirements (costs)?" | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Large costs<br>● Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | | The resources required for the intervention (HS) includes the cost to the patient for treatment ($218 charge for RT visit plus medication charges), cost of RT time (estimated to be wages of $36/hour and 30 minutes per treatment), and use of hospital staff to administer treatment. |
| **Certainty of evidence of required resources**<br>What is the certainty of the evidence of resource requirements (costs)? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Very low<br>○ Low<br>● Moderate<br>○ High<br>○ No included studies | The average length of stay for hospitalized patients with bronchiolitis in the U.S. is 2.4 days (Ralston et al., 2014) and the geometric mean of direct cost of hospitalization in 2016 in the US was $3724, 95% CI [3572, 3876] for patients with primary diagnosis of bronchiolitis without other complex chronic conditions (Fujiogi et al., 2019). | Evidence exists for cost of length of stay for bronchiolitis but not for direct cost of HS treatment. Resource costs provided by CMH. |
| **Cost effectiveness**<br>Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ No included studies | | The cost of resources for treatment with HS is likely higher than a minimal reduction in length of stay. |

| **Equity**<br>What would be the impact on health equity? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>● Don't know | | No evidence found to address inequities with treatment with HS.<br><br>Inequities exist for effect of increased/decreased length of stay for those experiencing barriers related to transportation, healthcare access, health literacy and other social determinants of health.<br><br>Inequities exist for effect of treatment cost on those with lower income. |
| **Acceptability**<br>Is the intervention acceptable to key stakeholders? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>● Varies<br>○ Don't know | | Variation of acceptability exists for providers and respiratory therapists when administering treatment that may not have evidence-based benefits. |

| **Feasibility**<br>Is the intervention feasible to implement? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | | Feasibility may be affected by staffing availability to administer treatments, patients experiencing distress and parent dissatisfaction.<br><br>Supplies needed for treatment are generally readily available with infrequent supply unavailability. |

SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | **Small** | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Trivial | Small | **Moderate** | Large | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE** | **Very low** | Low | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | **Favors the comparison** | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | **Moderate** | High | | | No included studies |
| **COST EFFECTIVENESS** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | No included studies |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **ACCEPTABILITY** | No | Probably no | Probably yes | Yes | | **Varies** | Don't know |

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |

TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |