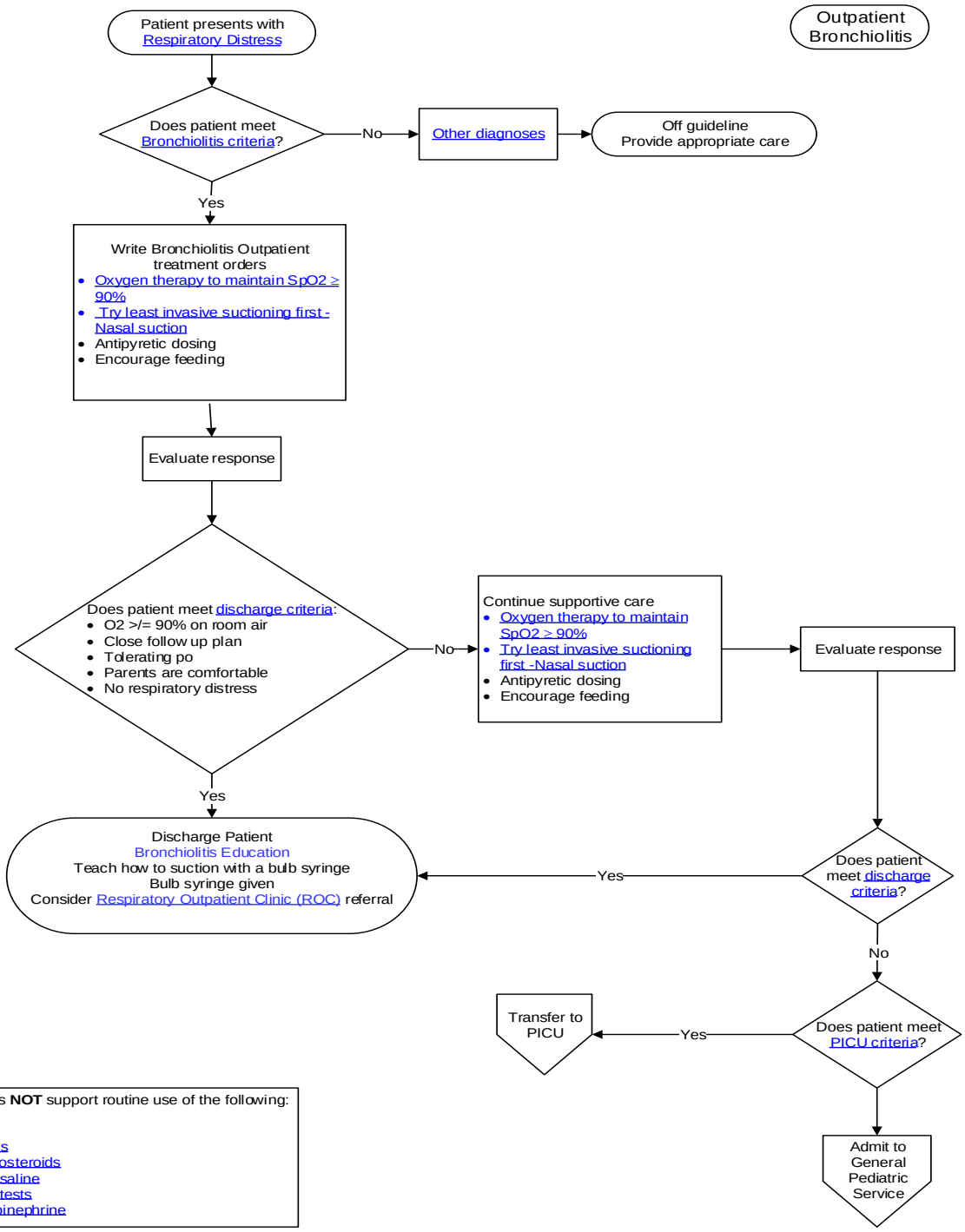
Children's Mercy Hospitals and Clinics
Evidence Based Practice Clinical Practice Guide

Bronchiolitis 2016

Outpatient



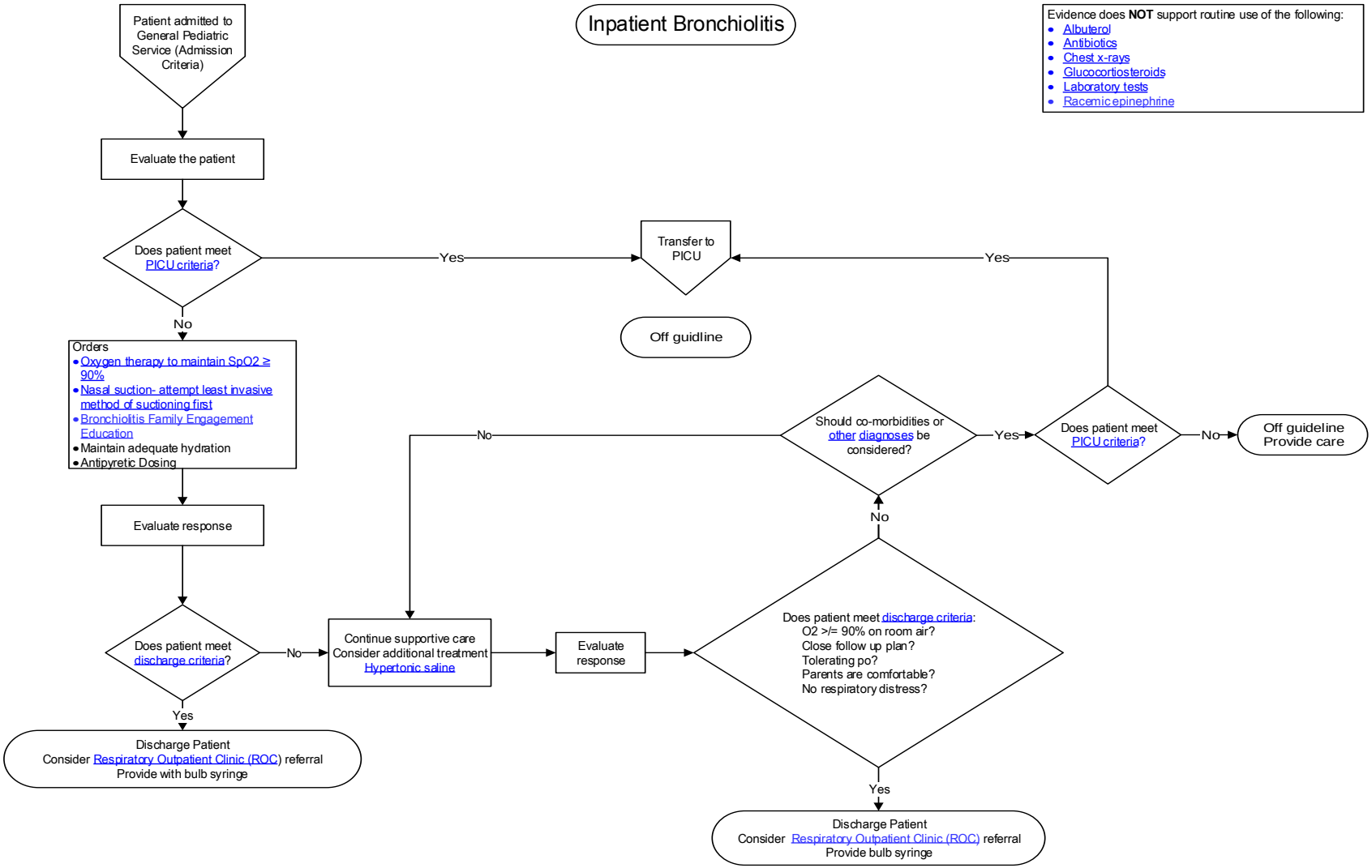
Evidence does **NOT** support routine use of the following:
- Albuterol
- Antibiotics
- Chest x-rays
- Glucocorticosteroids
- Hypertonic saline
- Laboratory tests
- Racemic epinephrine

If you have questions regarding this Clinical Practice Guideline – please contact jkjberg@cmh.edu, anedved@cmh.edu, or jmichael@cmh.edu

Children's Mercy

Inpatient

Inpatient Bronchiolitis



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Epidemiology: Bronchiolitis is the most common lower respiratory tract infection in infants. There is no specific diagnostic test for bronchiolitis. It is a viral disease whose causative agents include most prominently RSV, human meta-pneumovirus, adenovirus and parainfluenza virus, although other viruses have been implicated.

Diagnosis of bronchiolitis is made by a typical history and physical examination in the appropriate age group (infants and toddlers). It typically begins as an apparent upper respiratory tract infection with sneezing, cough and congestion.

There may be diminished appetite and fever. This is followed by the gradual onset of respiratory distress frequently including paroxysmal cough, wheezing, and tachypnea. Findings on physical examination often include wheezing and may include crackles, retractions, nasal flaring, grunting and a prolonged-expiratory phase.

Objective of Guideline: To standardize the care of children who present for the first time with symptoms typical of bronchiolitis.

Target Users: Emergency Department/ Urgent Care Center (ED/UCC) physicians, General Pediatricians, Pediatric Nurse Practitioners

Guideline Inclusion Criteria: The guideline includes infants who are 2-24months of age presenting with the typical bronchiolitis presentation.

Guideline Exclusion Criteria: This guideline excludes infants with:

- Asthma
- Pneumonia
- Airway compromise from foreign body or anatomic stricture or laxity (vascular rings, tracheo- or bronchomalacia)
- Congestive heart failure
- Pertussis
- GERD
- Chronic aspiration
- Inhalation injury
- Cystic Fibrosis
- Chronic lung disease
- History of lower airway surgery
- Immunodeficiency

Clinical Questions Answered by Guideline:

1. For the child being treated for the symptoms of bronchiolitis, what is the goal oxygen saturation that should be maintained?
2. **Updated October 2016**-For the patient who presents with the symptoms of bronchiolitis should inhaled hypertonic saline be used (see Appendix A)
3. For the child with bronchiolitis when should nasal suctioning (with a bulb tip) or nasopharyngeal suctioning (with a catheter) be used to clear secretions (see Appendix B)
4. **Updated October 2016**-For the child who presents with the symptoms of bronchiolitis should high flow, high humidity nasal cannula be used (see Appendix C)
5. **Updated October 2016**- For the child who presents with the symptoms of bronchiolitis should inhaled racemic epinephrine be used in the inpatient or outpatient settings (see Appendix D)
6. For the child who presents with the symptoms of bronchiolitis should glucocorticoids be used in the inpatient or outpatient settings (see Appendix E)
7. For the child who presents with the symptoms of bronchiolitis should short acting beta agonists be used in the inpatient or outpatient settings (see Appendix F)
8. For the child who presents with the symptoms of bronchiolitis should antibiotics be used in the inpatient or outpatient settings (see Appendix G)
9. For the child with bronchiolitis should laboratory tests and/or chest x-rays be obtained

Differential Diagnosis:

- Asthma
- Pneumonia
- Congestive heart failure
- Pertussis
- Congestive heart failure
- GERD
- Chronic aspiration
- Inhalation injury
- Cystic fibrosis
- Chronic lung disease
- History of lower airway surgery
- Immunodeficiency (specifically lymphocytes < 2,500)
- Obstructions involving large airways
    - Foreign body in trachea or bronchus
    - Vocal cord dysfunction
    - Vascular rings
    - Tracheomalacia, bronchomalacia

Practice Recommendations:

Physical Exam: The physical exam of a child presenting with suspected bronchiolitis focuses on respiratory symptoms including tachypnea, intercostal retractions and sub-costal retractions. An expiratory wheeze and crackles, both coarse and fine may be heard on auscultation (Piedra & Stark, 2012). Oxygen saturation may be < 95%. Upper respiratory congestion will be present.

Diagnostics: Bronchiolitis is diagnosed on the basis of the history and physical examination. There is no gold standard for diagnosing the disease. Although the viral etiology may be identified (e.g. by viral culture, nucleic amplification testing, or rapid antigen testing), there is no specific test that confirms the diagnosis of bronchiolitis itself. RSV rapid antigen testing, chest x-ray, complete blood counts, and basic metabolic panels may be indicated in specific clinical situations, though there is no evidence for routinely obtaining these tests (Ralston et al., 2014).

Treatment:

- Inpatient and Outpatient
    - Oxygen therapy to maintain oxygen saturation above 90%
    - Suction- try least invasive technique first
    - Antipyretic dosing
    - Maintain hydration
    - Topical anesthetic prior to needle procedure
- Inpatient
    - Nebulized hypertonic (3%) saline as therapy for children who have increased need for mucociliary clearance. Discuss with the Respiratory Therapist to follow the Respiratory Care Services Policy and Procedure to administer inhaled hypertonic saline
- Outpatient
    - A recommendation to use or not use racemic epinephrine cannot be made at this time
- Inpatient or Outpatient
    - Evidence does not support routine use of the following, for either the inpatient or outpatient management of bronchiolitis:
        - Glucocorticoids
        - Antibiotics
        - Laboratory tests
        - Chest x-rays

- PICU Criteria: non-resolution or worsening of symptoms
    - Recurrent apnea requiring close monitoring
    - Severe respiratory distress
    - Respiratory failure
    - Hypoxemia (oxygen saturation < 90%) refractory to therapies that can provided on the inpatient units
- Discharge Criteria**:** Resolution of respiratory distress and infrequent respiratory care needs:
    - Respiratory rate for the infant is near 60 breaths per minute or less
        - There is minimal to no increased work of breathing
        - Stable without the need for nasopharyngeal suctioning for an adequate length of time
    - Nutrition:
        - The patient is able to maintain adequate hydration with oral feedings.
    - Medication/Durable medical equipment:
        - If the patient is receiving intravenous medications, convert to oral medications if the child will be going home on the medications
        - Bulb syringe
    - Social/Education:
        - Parental comfort with discharge plans
        - Family or caregiver has the resources to care for the child
        - Parent education on:
            - How to use a bulb syringe with or without nasal saline
            - The expected course of illness - the course may be variable many children will have up to six weeks of cough and/or nasal congestion
            - The signs and symptoms of respiratory distress - increased respiratory rate or labored breathing (including abdominal breathing, retractions, tracheal tug or nasal flaring)
            - Home intervention when distress occurs - suctioning, fever control
            - The signs and symptoms of dehydration - dry mouth, no tears, cool extremities, infrequent or small voids
        - On admission, review Family Engagement handout
        - Before discharge review the following KidsHealth material
            - Bronchiolitis
            - Bulb Syringe
            - Fever
        - Consider a referral to the Respiratory Outpatient Clinic (ROC Clinic) if the patient meets the clinic's criteria.
        - Contact the primary care physician about the discharge plans and arrange for follow up evaluation.

Measures:

Outcome:

% of bronchiolitis patients undergoing/receiving 1 or more of the Process Measures, below

Process measure:

% of patients diagnosed with bronchiolitis for which the provider ordered bronchiolitis education

% use of bronchiolitis power plan for patients diagnosed with bronchiolitis

% of bronchiolitis patients undergoing rapid RSV

% of bronchiolitis patients undergoing respiratory panel PCR

% of bronchiolitis patients undergoing CBC
% of bronchiolitis patients undergoing blood culture
% of bronchiolitis patients undergoing chest x-ray
% of bronchiolitis patients receiving albuterol
% of bronchiolitis patients receiving systemic steroids
% of bronchiolitis patients antibiotic(s)

Balancing measure:

Length of stay
Readmissions within 72 hours
Cost

Potential Cost Implications:

- Potential cost savings with decreased use of medication and lab utilization.

Potential Organizational Barriers:

Training of staff on new procedures

- Use of hypertonic saline (inhaled) on inpatient units
- Change to nasal suction to preferred method, with nasopharyngeal as backup method to clear secretions
- New lower limit of oxygen saturation level for use of oxygen therapy
- Intermittent pulse oximetry after oxygen is discontinued on inpatient units

Clinical Questions Answered:

For all clinical questions, the Bronchiolitis Clinical Practice Guideline of the American Academy of Pediatrics (AAP) was adopted as our "parent" guideline. The Guideline as assessed using the AGREE II Tool by three reviewers. For each domain contains three to eight questions, that are answered on a numeric scale, range [1-7], higher is better.

Table 1.

AGREE II Tool Score

Domain	Percent Agreement
Domain 1 - SCOPE AND PURPOSE	100%
Domain 2 - STAKEHOLDER INVOLVEMENT	87%
Domain 3 - RIGOR OF DEVELOPMENT	96%
Domain 4 - CLARITY AND PRESENTIATION	87%
Domain 5 - APPLICABILITY	53%
Domain 6 - EDITORIAL INDEPENDENCE	96%
Overall Guideline Assessment	90%

Question 1: For the child being treated for the symptoms of bronchiolitis, what is the goal oxygen saturation that should be maintained?

Bronchiolitis Team Recommendation:
Outpatient and Inpatient
The Bronchiolitis Team recommends using supplemental oxygen to maintain an oxygen saturation ≥ 90%, based on the AAP statement for the care of the patient with bronchiolitis (Ralston et al., 2014). Per the AAP statement, tolerance of oxygen saturation in the low 90% is influenced by acidosis, some hemoglobinopathies, correct position of the O2 saturation probe, temporal relation to the last nasal clearance of secretions, and the infant's work of breathing. Oxygen supplementation may be administered when SaO2 is greater than 90% if any of these factors are present. We placed a high value on assuring the comfort of the patient.

Question 2. Updated October 2016- For the patient who presents with the symptoms of bronchiolitis should inhaled saline be used?

Bronchiolitis Team Recommendation:
We concur with the Clinical Practice Guideline of AAP that makes a moderate recommendation that 3% nebulized hypertonic saline should not be administered to infants and children in the Emergency Department, and further makes a weak recommendation that 3% nebulized hypertonic saline may be administered to infants and children who are in the hospital (Ralston et al., 2014). Further research is likely to have an important influence on our confidence in these recommnedations.

Literature (See Appendix A) supporting this recommendation: Twenty citations are included to answer this question. Sixteen are blinded RCT, and four are open label RCT. All studies included in the AAP Guideline (Ralston et al. 2014) and studies published after the AAP Guideline literature search are included.

Question 3: For the child with bronchiolitis, when should nasal suctioning (with a bulb tip) or nasopharyngeal suctioning (with a catheter) be used to clear secretions?

Bronchiolitis Team Recommendation:
Outpatient and Inpatient
Based on low quality evidence, the Bronchiolitis CPG Team recommends the use of nasal suctioning/nasal aspiration as the primary route for removing respiratory secretions. Nasopharyngeal (NP) suctioning may be used if signs of labored breathing continue after nasal suctioning. We placed high value on amelioration of labored breathing and decreasing potential adverse effects of deep suctioning. One low quality study reports reduction in visible and audible secretions with NP suctioning. However, a QI project completed at Children's Mercy Kansas by Jarvis et al (2012) showed similar hospital readmission rates, admissions to the PICU, parental satisfaction, and average length of stay when nasal suctioning increased by 13% and NP suctioning decreased by 15% over two bronchiolitis seasons. This recommendation may change when higher quality evidence becomes available.

Literature (See Appendix B) supporting this recommendation: No citations were found on searches of PubMed or CINAHL on bronchiolitis and deep suctioning. However, 13 citations were located when searching CINAHL searching on just Bronchiolitis and suctioning. Of these articles, two articles are included in this review. Additionally, a QI project conducted at Children's Mercy Kansas informed this review.

Question 4: Updated October 2016- For the child who presents with the symptoms of bronchiolitis should high flow, high humidity nasal cannula be used?

Bronchiolitis Team Recommendation:
We concur with the recommendation from the AAP Bronchiolitis Guideline, and cannot make a specific recommendation to use or not use HFNC. This is in agreement with the Canadian Pediatric Society (Friedman et al., 2014), and the NICE Guidelines (NICE), 2015) as well. Further research on the efficacy of HFNC, either in the PICU or on an inpatient unit is likely to have important influence on our confidence in making a recommendation.

Literature (See Appendix C) supporting this recommendation
Five publications are included for this topic. Guidelines from the AAP, the Canadian Pediatric Society, and the NICE Guidelines (Ralston et al., 2014; Friedman et al., 2014;& NICE, 2015) along with a recent Cochrane Review (Beggs et al., 2014), and pre-post retrospective study (Riese, Firece, Riese, & Alverson, 2015)

Question 5: Updated October 2016- For the child who presents with the symptoms of bronchiolitis should inhaled racemic epinephrine be used in the inpatient or outpatient settings?

Bronchiolitis Team Recommendation
The AAP guideline recommends against the routine use of inhaled racemic epinephrine to treat acute bronchiolitis in both the inpatient and outpatient settings (Ralston et al., 2014). However, the Bronchiolitis CPG Team concludes the evidence is insufficient at this time to make a recommendation for against using racemic epinephrine.

Literature (See Appendix D) supporting this recommendation:
The meta-analysis by Hartling et al., (2011) was analyzed using GRADEprofiler (GRADEpro). The evidence is GRADED as Moderate to Low quality. Risk of bias, specifically poorly reported allocation concealment and blinding were detected in the included studies. Studies were also inconsistent, which decreases confidence in the pooled results. However for the following outcomes there was no difference in the following outcomes

- Length of stay: (N= 292) Mean difference = 0.35 days, (0.35 hours shorter to 0.17 hours longer)
- Admission at from first outpatient encounter to within 24 hours: (N= 995) *RR=* 0.67, 95% CI [0.5, 0.89]
- Admission overall, up to 7 days: (N= 835) *RR=* 0.81, 95% CI [0.63, 1.03]

Hartling et al., (2011) conclude that the evidence shows some reduction in hospital admission when children with bronchiolitis are treated with epinephrine. However, the short term of medication effect and the differences in timing of outcome measurements limit the quality of the evidence. There is no evidence to support the use of racemic epinephrine in the inpatient setting.

In a series of studies (Skjerven et al., 2013, 2015) report on the same group of subjects who received either inhaled racemic epinephrine versus normal saline for acute bronchiolitis in the inpatient setting. In the first study, (Skjerven et al., 2013) LOS was not significantly between the two groups. In the second study (Skjerven et al., 2015), the same subjects were evaluated approximately 2 years later. For those who received racemic epinephrine at the acute bronchiolitis visit, a comparison was made between and went on to develop either recurrent bronchial obstruction, atopic eczema, or allergic sensitization and those who did not develop these conditions. The outcome was the LOS at the acute bronchiolitis visit. There was no difference in LOS between those who went on to develop atopic symptoms and those who did not.

Question 6: For the child who presents for the symptoms of bronchiolitis should glucocorticosteriods be used in the inpatient or outpatient settings?

Bronchiolitis Team Recommendation:
Outpatient
Based on high quality evidence, the Bronchiolitis CPG Team recommends against the use of glucocorticoid steroids for the outpatient treatment of the child who presents for the first time with the symptoms of bronchiolitis. We placed high value on avoiding exposure to a medication without evidence to support its use. This recommendation can apply to most patients in most circumstances. Ten studies, summarized in a Cochrane Review (Fernandes et al., 2010) showed that when glucocorticoids were given, hospitalization from the outpatient setting was not decreased. Children who received steroids and were then admitted to the hospital did not have a shorter length of stay. However, there is an exploratory report from a large, high quality trial that suggests combining systematic glucocorticoids (specifically dexamethasone) with epinephrine may significantly reduce hospital admissions. No short-term adverse effects noted, and the trial was not designed to evaluate long-term effects. Further research is likely to change our confidence in the estimate of the effect.

Inpatient
Based on high quality evidence, the Bronchiolitis CPG Team recommends against the use of glucocorticoid steroids for inpatient treatment of the child who presents for the first time with the symptoms of bronchiolitis. We placed high value on avoiding exposure to a medication without evidence to support its use. This recommendation can apply to most patients in most circumstances. Further research is likely to change our confidence in the estimate of the effect.

Literature (See Appendix E) supporting this recommendation:
Sixty-four citations were found from the literature search. One Cochrane Database of Systematic Reviews (CDSR) paper is included (Fernandes et al., 2010). Single studies identified in by the Bronchiolitis Team are included in the Fernandes 2010 CDSR, and are not reported upon separately.

Question 7: For the child who presents with the symptoms of bronchiolitis should short acting beta agonists be used in the inpatient or outpatient settings?

Bronchiolitis Team Recommendation:
Outpatient
Based on moderate to low quality evidence, the Bronchiolitis CPG Team recommends against the use of SABA for the outpatient treatment of the child who presents for the first time with the symptoms of bronchiolitis. We placed high value on avoiding exposure to a medication without evidence to support its use. This recommendation can apply to most patients in most circumstances. The Gadomski and Brower (2010) CDSR (included 15 low to moderate quality studies) reported that the use of bronchodilators did not improve oxygen saturation as measured by pulse oximetry, clinical score, decrease length of stay, or decrease time to resolution of illness

Inpatient
Based on high quality evidence, Bronchiolitis CPG Team recommends against the use of SABA for the inpatient treatment of the child who presents for the first time with the symptoms of bronchiolitis. We placed high value on avoiding exposure to a medication without evidence to support its use. This recommendation can apply to most patients in most circumstances. All studies identified by this CPG team were included in the Gadomski and Brower (2010) CDSR. Gadomski and Brower (2010) reported from seven moderate quality studies that clinical score did not improve with the use of beta-agonists. From 5 moderate quality inpatient studies, use of beta agonists did not decrease length of stay and from two moderate quality studies, use of beta agonists did not affect time to resolution of illness, measured in days.

Literature (See Appendix F) supporting this recommendation: Twenty one citations were found from the literature search. One CDSR paper is included (Gadomski and Brower, 2010). Single studies identified in by the Bronchiolitis Team are included in the CDSR, and are not reported upon separately.

Question 8: For the child who presents with the symptoms of bronchiolitis, should antibiotics be used in the inpatient or outpatient settings?

Bronchiolitis Team Recommendation:
Outpatient and Inpatient
Based on high quality evidence, the Bronchiolitis CPG Team recommends against the routine use of antibiotics for the child who presents for the first time with the symptoms of bronchiolitis. The presence of secondary infection should be treated appropriately. The recommendation is based on the CDSR by Spruling, Doust, Del Mar and Eriksson (2011). It included five studies- two high quality and three of moderate quality. The use of antibiotics did not affect duration of symptoms, (at three days) length of stay for inpatients, re-admission rate or deaths.

Literature (see Appendix G) supporting this recommendation: Ninety-five studies were identified by the PubMed search, no unique articles were added by the CINAHL search and one CDSR was located. The CDSR by Spruling, Doust, Del Mar and Eriksson (2011) is included in this review. No single studies published since the CDSR were identified that answered this question.

Question 9: For the child with bronchiolitis should laboratory tests and /or chest x-ray be obtained?

Bronchiolitis Team Recommendation:
Outpatient and Inpatient
The Bronchiolitis CPG Team recommends against obtaining laboratory tests such as CBC & Diff w/platelets, Basic Metabolic Panel, Blood Culture, RSV antigen detection, Flu A & B antigen, or chest x-ray for the infant who is presenting for the first time with symptoms of bronchiolitis. The recommendation concurs with the AAP (2014) and Scottish Intercollegiate Guidelines Network (SIGN, 2009) bronchiolitis guidelines. RSV antigen testing maybe obtained if applied to cohorting infants on inpatient units to prevent the spread of RSV. Bronchiolitis is diagnosed based on history and physical examination (AAP, 2014). We placed high value on avoiding unnecessary medical testing and reduction of discomfort to the patient.

Supporting Tools
Education Handouts:

- Family Engagement Handout
- KidsHealth- Bronchiolitis
- KidsHealth- Bulb Syringe
- KidsHealth- Fever

Procedures:

Nebulized 3% Hypertonic Saline for Bronchiolitis, CMH Respiratory Care Policy and Procedure
High Humidity/High Flow Nasal Cannula Administration, CMH Respiratory Care Policy and Procedure

Guideline Preparation: This guideline was prepared by The Office of Evidence Based Practice (EBP) in collaboration with content experts at Children's Mercy Hospitals and Clinics. Development of this guideline supports the Department of Clinical Effectiveness's initiative to promote care standardization that builds a culture of quality and safety that is evidenced by measured outcomes. If a conflict of interest is identified the conflict will be disclosed next to the team members name.

Bronchiolitis Clinical Practice Guideline Team Members:

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Guideline development funded by:
No external funding was obtained in the development of this guideline.

Development Process:
The review summary documents the following steps:

1. Review of existing internal and external guidelines and standards

a. Internal guidelines: CMH Bronchiolitis Clinical Practice Guideline (2013)
b. External guidelines:
    i. Ralston, S. L., Lieberthal, A. S., Meissner, H. C., Alverson, B. K., Baley, J. E., Gadomski, A. M., . . . American Academy of Pediatrics. (2014). Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics, 134*(5), e1474-1502. doi:10.1542/peds.2014-2742
    ii. National Institute for Health and Care Excellence (NICE), (2015). *Bronchiolitis in children: Diagnosis and management*. London: NICE.
    iii. Friedman, J. N., Rieder, M. J., & Walton, J. M. (2014). Bronchiolitis: Recommendations for diagnosis, monitoring and management of children one to 24 months of age. *Paediatric Child Health, 19*(9).
    iv. Scottish Intercollegiate Guidelines Network. (2009). *Bronchiolitis in children.* (ISBN 1 (10) 905813 01 5 Retrieved from http://www,sign.ac.uk
    v. Texas Children's Hospital. (2010). *Bronchiolitis Clinical Guideline.* Houston, Texas, USA: TCH Evidenced-Based Outcomes Center.

2. Review preparation
    a. PICOT (***P***atient, ***I***ntervention, ***C***omparison, ***O***utcome, ***T***ype of question) questions established
    b. Team leaders confirmed search terms employed by the Health Science Medical librarians, reviewed article titles and abstracts from the search, and identified articles to be read and synthesized by the Evidence Based Practice Scholars.
3. Databases searched
    a. AHRQ National Guideline Clearinghouse
    b. Medline
    c. CDSR
    d. CINAHL
4. Critically analyze the evidence
    a. Guidelines
        i. AGREE II criteria were used to analyze published clinical guidelines
    b. Literature
        i. For single studies, the EBP Scholars used the Cochrane Collaborative's electronic software, RevMan, to produce systematic reviews of the evidence of the effects of healthcare and delivered these documents to the team for review. RevMan allowed the EBP Scholars to build the tables of study characteristics, tables of study biases, and analyze study data in a meta-analysis.
        ii. When a meta-analysis was found in the literature search, or created in RevMan, the GRADE criteria evaluated the literature using GRADEpro to assesses the meta-analysis for:
            a. Limitations in study design and execution
            b. Inconsistency between studies
            c. Indirectness of study outcomes
            d. Imprecision
            e. Publication bias
            f. The balance between desirable and undesirable effects
            g. Patient values and preferences
            h. Resource utilization
    c. Table 2 defines how the quality of the evidence is rated and how the recommendation is established based on the type of evidence.

Table 2. Grading of CPG Recommendations

Grade of Recommendation	Confidence in Clarity of Benefits vs Harms, Burden, and Cost	Quality of Supporting Evidence	Implications
Strong recommendation High quality evidence	Desirable effects clearly outweigh undesirable effects or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect
Strong recommendation Moderate-quality evidence	Desirable effects clearly outweigh undesirable effect or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important effect on our confidence in the estimate of effect and may change the estimate.
Strong recommendation Low-quality evidence	Desirable effects clearly outweigh undesirable effect or vice versa	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation Very-low-quality evidence (Very rarely applicable)	Desirable effects clearly outweigh undesirable effect or vice versa	Evidence for at least 1 of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect, for at least 1 critical outcome, is uncertain.
Recommended High-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ, depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Recommended Moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important influence on our confidence in the estimate of effect and may change the estimate.
Recommended Low-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Further research is likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate.
Recommended Very-low-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is uncertain.

Adapted from: Schunemann, H. J., Vist, G. E., Jaeschke, R., Kunz, R., Cook, D. J., & Guyatt, G. (2002). Advanced topics in moving from evidence to action: Grading recommendations. In Guyatt, G., Rennie, D., Meade, M. O., & Cook, D. J.(Ed.), *Users' guides to the medical literature: A manual for evidence-based clinical practice* (pp 679-701). New York, NY:McGraw-Hill.

5. Recommendations for the guideline were developed by a consensus process incorporating the three principles of EBP (current literature, content experts, and patient and family preference, when possible).

Approval Process:

The original guideline was reviewed and approved by internal and external expert reviewers, the Content Expert Team, the Office of EBP, and other appropriate hospital committees as deemed suitable for the guidelines intended use. This guideline update (October 2016) was reviewed and approved by the Content Expert Team, the Office of EBP, and other appropriate hospital committees as deemed suitable for the guidelines intended use.

Disclaimer:

The content experts and the Office of EBP are aware of the controversies surrounding the Bronchiolitis Clinical Practice Guideline. When evidence is lacking or inconclusive, options in care are provided in the guideline and the power plans that accompany the guideline.

These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time.

It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly these guidelines should guide care with the understanding that departures from them may be required at times.

Appendix A

Question 2. Updated October 2016- For the patient who presents with the symptoms of bronchiolitis should inhaled hypertonic saline be used?

Literature Summary:

Inpatient Length of Stay

Since the publication of the current AAP Guideline, two randomized control trails have been published that report on the outcome Inpatient Length of Stay (LOS) (Everard et al., 2014; Silver et al., 2015). The results of the studies show no difference in inpatient hospitalization when infants and children with bronchiolitis were treated with hypertonic saline versus those who received standard treatment, Mean Difference (MD) = 0.10, 95% CI [-0.26, 0.45] (See Figure 2).

Studies above were pooled with studies prior to the AAP Guideline and analyzed using GRADE (Atkins et al., 2004).

1) Based on very low quality evidence hypertonic saline resulted in shorter inpatient LOS compared to standard care, MD = -0.53, 95% CI [-0.91, -0.14] (See Figure 3).
   a) However, when the studies are placed in subgroups based on the risk of selection bias (did they blind participants, personnel, and outcome assessors and did they conceal the group to which subjects would be allocated?) Eight of the thirteen studies have low risk of selection bias, and five studies have high risk of selection bias.
      i) When studies with low risk of selection bias are analyzed as a subgroup, the mean difference in inpatient LOS for the same comparison was not significant, MD = -0.37, 95% CI [-0.84, 0.09]. The included studies are graded as low quality evidence.
      ii) When studies with unclear or high risk of selection bias are analyzed as a subgroup, the mean difference in inpatient LOS was significant, MD= -0.82, 95% CI [-1.32, -0.32]. The included studies are graded as very low quality evidence.
   b) There is inconsistency among the studies. The I^2 statistic is 81% and less than 50% is desired for this measure. The I2 statistic is a measure of heterogeneity, it describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance). (Higgins & Green, 2011).

Interpreting the I2 Statistic	
Value	Interpretation
0% to 40%	Might not be important
30% to 60%	May represent moderate heterogeneity*
50% to 90%	May represent substantial heterogeneity*
75%-100%	Considerable heterogeneity

Note: * the importance of the observed I2 depends on (a) the magnitude and direction of effects and (d) strength of evidence for heterogeneity, either or the P value from the chi-square test, or a confidence interval for I2. (Higgins & Green, 2011).

2) Based on moderate quality evidence hypertonic saline resulted in lower odds of hospitalization, OR = 0.63, 95% CI [0.45, 0.87] (See Figure 4). The studies are graded down for imprecision, there are low number of events and the confidence intervals are wide. The I^2 statistic is 0, which is desired (Higgins & Green, 2011). Note the estimate of the effect is driven by one recent study, Wu et al. (2014). At this time the Bronchiolitis CPG team is concurring with the AAP CPG that hypertonic saline should not be administered to infants with the diagnosis of bronchiolitis in the emergency department (Ralston et al, 2014). Further research is likely to have an important influence on our confidence in the estimate of the effect and may change the estimate.

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Search Strategy and Results:

((("Bronchiolitis, Viral/drug therapy"[Majr] OR "Bronchiolitis, Viral/prevention and control"[Majr] OR "Bronchiolitis, Viral/therapy"[Majr]) AND ("Respiratory Syncytial Virus Infections"[Mesh] OR "Respiratory Syncytial Virus, Human"[Mesh]) AND ((Humans[Mesh]) AND (English[lang]) AND (Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Consensus Development Conference[ptyp] OR Guideline[ptyp]) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))) AND "2015/06/13 15.00"[MHDA]:"2015/07/18 15.00"[MHDA]) Search performed on July 18 2015. One study identified, and excluded, does not answer the question.
And

Sent on: Mon Apr 11 11:30:46 2016
Search: ("Saline Solution, Hypertonic"[Mesh] AND ("Administration, Inhalation"[Mesh] OR "Nebulizers and Vaporizers"[Mesh])) AND ("Bronchiolitis/therapy"[Mesh] OR "Respiratory Syncytial Virus Infections/therapy"[Mesh]) Filters: From 2013/01/01 to 2015/12/31
22 articles identified- the Zhang, L., Mendoza-Sassi, R. A., Klassen, T. P., and Wainwright, C. (2015) systematic review was selected, as other articles identified in the search that answered the question are included in the systematic review.

Sent on Monday April 11 2016 10:48 AM
Search for bronchospasm as an adverse event of inhaled hypertonic saline
Search: (("Saline Solution, Hypertonic"[Mesh] OR "hypertonic saline") AND ("Administration, Inhalation"[Mesh] OR "Nebulizers and Vaporizers"[Mesh] OR "inhaled" OR "nebulized")) AND ("Bronchial Spasm"[Mesh] OR "bronchospasm")
17 articles returned, all excluded based on title and abstract.

Studies included in this review

Includes the following studies from Zhang 2013 Cochrane Review:

Al-Ansari, K., Sakran, M., Davidson, B. L., El Sayyed, R., Mahjoub, H., & Ibrahim, K. (2010). Nebulized 5% or 3% hypertonic or 0.9% saline for treating acute bronchiolitis in infants. *J Pediatr, 157*(4), 630-634, 634 e631. doi:10.1016/j.jpeds.2010.04.074

Anil, A. B., Anil, M., Saglam, A. B., Cetin, N., Bal, A., & Aksu, N. (2010). High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. *Pediatr Pulmonol, 45*(1), 41-47. doi:10.1002/ppul.21108

Grewal, S., Ali, S., McConnell, D. W., Vandermeer, B., & Klassen, T. P. (2009). A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. *Arch Pediatr Adolesc Med, 163*(11), 1007-1012. doi:10.1001/archpediatrics.2009.196

Ipek, I. O., Yalcin, E. U., Sezer, R. G., & Bozaykut, A. (2011). The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis. *Pulm Pharmacol Ther, 24*(6), 633-637. doi:10.1016/j.pupt.2011.09.004

Luo, Z., Fu, Z., Liu, E., Xu, X., Fu, X., Peng, D., . . . Yang, X. (2011). Nebulized hypertonic saline treatment in hospitalized children with moderate to severe viral bronchiolitis. *Clin Microbiol Infect, 17*(12), 1829-1833. doi:10.1111/j.1469-0691.2010.03304.x

Luo, Z., Liu, E., Luo, J., Li, S., Zeng, F., Yang, X., & Fu, Z. (2010). Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. *Pediatr Int, 52*(2), 199-202. doi:10.1111/j.1442-200X.2009.02941.x

Mandelberg, A., Tal, G., Witzling, M., Someck, E., Houri, S., Balin, A., & Priel, I. E. (2003). Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. *Chest, 123*(2), 481-487.Everard, M. L., Hind, D., Ugonna, K., Freeman, J., Bradburn, M., Cooper, C. L., . . . Team, S. S. (2014). SABRE: a multicentre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. *Thorax, 69*(12), 1105-1112. doi:10.1136/thoraxjnl-2014-205953

Miraglia Del Giudice, M., Saitta, F., Leonardi, S., Capasso, M., Niglio, B., Chinellato, I., . . . Peroni, D. (2012). Effectiveness of nebulized hypertonic saline and epinephrine in hospitalized infants with bronchiolitis. *Int J Immunopathol Pharmacol, 25*(2), 485-491Grewal, S., Ali, S., McConnell, D. W., Vandermeer, B., & Klassen, T. P. (2009). A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. *Arch Pediatr Adolesc Med, 163*(11), 1007-1012. doi:10.1001/archpediatrics.2009.196

Ipek, I. O., Yalcin, E. U., Sezer, R. G., & Bozaykut, A. (2011). The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis. *Pulm Pharmacol Ther, 24*(6), 633-637. doi:10.1016/j.pupt.2011.09.004

Kuzik, B. A., Al-Qadhi, S. A., Kent, S., Flavin, M. P., Hopman, W., Hotte, S., & Gander, S. (2007). Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *J Pediatr, 151*(3), 266-270, 270 e261. doi:10.1016/j.jpeds.2007.04.010

Sarrell, E. M., Tal, G., Witzling, M., Someck, E., Houri, S., Cohen, H. A., & Mandelberg, A. (2002). Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. *Chest, 122*(6), 2015-2020.

Tal, G., Cesar, K., Oron, A., Houri, S., Ballin, A., & Mandelberg, A. (2006). Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. *Isr Med Assoc J, 8*(3), 169-173.

Studies added in the update:

Everard, M. L., Hind, D., Ugonna, K., Freeman, J., Bradburn, M., Cooper, C. L., . . . Team, S. S. (2014). SABRE: a multicentre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. *Thorax, 69*(12), 1105-1112. doi:10.1136/thoraxjnl-2014-205953

Florin, T. A., Shaw, K. N., Kittick, M., Yakscoe, S., & Zorc, J. J. (2014). Nebulized hypertonic saline for bronchiolitis in the emergency department: a randomized clinical trial. *JAMA Pediatr, 168*(7), 664-670. doi:10.1001/jamapediatrics.2013.5306

Jacobs, J. D., Foster, M., Wan, J., & Pershad, J. (2014). 7% Hypertonic saline in acute bronchiolitis: a randomized controlled trial. *Pediatrics, 133*(1), e8-13. doi:10.1542/peds.2013-1646

Ojha, A. R., Mathema, S., Sah, S., & Aryal, U. R. (2014). A comparative study on use of 3% saline versus 0.9% saline nebulization in children with bronchiolitis. *J Nepal Health Res Counc, 12*(26), 39-43.

Pandit, S., Dhawan, N., & Deepak, T. (2013). Utility of Hypertonic Saline in the Management of Acute Bronchiolitis in Infants: A Randomised Controlled Study. *International Journal of Clinical Pediatrics, 2*(1), 24-29. doi:doi: http://dx.doi.org/10.4021/ijcp96w

Silver, A. H., Esteban-Cruciani, N., Azzarone, G., Douglas, L. C., Lee, D. S., Liewehr, S., . . . O'Connor, K. (2015). 3% Hypertonic Saline Versus Normal Saline in Inpatient Bronchiolitis: A Randomized Controlled Trial. *Pediatrics, 136*(6), 1036-1043. doi:10.1542/peds.2015-1037

Wu, S., Baker, C., Lang, M. E., Schrager, S. M., Liley, F. F., Papa, C., . . . Mason, W. H. (2014). Nebulized hypertonic saline for bronchiolitis: a randomized clinical trial. *JAMA Pediatr, 168*(7), 657-663. doi:10.1001/jamapediatrics.2014.301

Zhang, L., Mendoza-Sassi, R. A., Wainwright, C., & Klassen, T. P. (2013). Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database of Systematic Reviews*(7). doi:10.1002/14651858.CD006458.pub3

Studies not included in this review with rationale for exclusion:

Study	Reason for Exclusion
(Canty & Colomb-Lippa, 2014)	Clinicaltrial.gov; no results as of Aug 5 2016
(Jacobs, Foster, Wan, & Pershad, 2014)	Compared 7% saline to normal saline inhaled
(Legg & Cunningham, 2015)	Case study
(Li & Zhao, 2014)	All subjects were pretreated with ipratropium and budesonide X 2 then treated with 5% hypertonic saline or normal saline
(S. Ralston, Hill, & Martinez, 2010)	Retrospective cohort, looking for adverse events when used without SABAs
(Tinsa et al., 2014)	Does not answer this question; compares 5% saline to 5% saline with epinephrine

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5) was used to synthesize the included studies (Higgins & Green, 2011).
AGREE II (Brouwers et al., 2010) was used to assess the quality of AAP Guideline (Ralston et al., 2014).
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) web based tool, The GDT, was used to grade the quality of the included studies

Updated August 5, 2016, August 9 2016, Sept 16 2016

Included Studies:

Total Number: 20 RCT

Blinded: 16 RCT

Non-blinded: 4 RCT

Quality Assessment of Included Studies:

Bias risk assessment factors: randomization concealment, patient selection, adequacy of blinding, and duration of follow-up

Number of Independent reviewers: 2

GRADE Analysis:

Number of independent reviewers: 2

GRADE of the Included Studies for the Comparison, Nebulized Saline versus Control
Date: August 5, 2016
Question: Hypertonic Saline compared to Controls for Bronchiolitis

Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006458. DOI: 10.1002/14651858.CD006458.pub2.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirect-ness**	**Imprecision**	**Other considera-tions**	**Hypertonic Saline**	**Con-trols**	**Relative (95% CI)**	**Absolute (95% CI)**		
Inpatient LOS												
13	randomized trials	serious [1]	very serious [2]	not serious	not serious	none	791	824	-	MD **0.53 lower** (0.91 lower to 0.14 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Inpatient LOS - Low risk of selection bias												
8	randomized trials	not serious	very serious [3]	not serious	not serious	none	604	637	-	MD **0.37 lower** (0.84 lower to 0.09 higher)	⊕⊕◯◯ LOW	CRITICAL
Inpatient LOS - High or unclear risk of selection bias												
5	randomized trials	serious [4]	very serious [5]	not serious	serious [6]	none	187	187	-	MD **0.82 lower** (1.32 lower to 0.32 lower)	⊕◯◯◯ VERY LOW	
Odds of hospitalization from the ED												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirect-ness**	**Imprecision**	**Other considera-tions**	**Hypertonic Saline**	**Con-trols**	**Relative (95% CI)**	**Absolute (95% CI)**		
7	randomized trials	not serious	not serious	not serious	serious [6]	none	121/455 (26.6%)	148/473 (31.3%)	**OR 0.66** (0.48 to 0.90)	**82 fewer per 1,000** (from 22 fewer to 134 fewer)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

1. For all thirteen studies, 5 (38%) have high or unclear risk for selection bias. Studies were either not randomized or allocation concealment was not performed.
2. The means and standard deviations have poor overlap. For all of the included studies the I2 statistic is 81%. Less than 50% is desired.
3. The means and standard deviations of individual studies have poor overlap. For this group of studies, the I2 statistic is 83%. Less than 50% is desired
4. This group of studies are all high or unclear risk of selection bias. Either they were not randomized or, allocation concealment was not performed or reported
5. The means and standard deviations of individual studies have poor overlap, although the I2 statistic is 54%.
6. The confidence intervals are wide.

Characteristics of Studies Tables

(Anil et al., 2010)

Methods	Prospective, randomized, double blind controlled trial Emergency Department
Participants	**Setting:** ED, recruitment from November 1 2005 to March 31 2006 **Number randomized:** 190 enrolled, 4 excluded prior to treatment, 186 were treated. **Number completed:** N= 186 **Gender:** 24% Male **Age:** 9.5 months **Inclusion criteria:** Clinical severity (CS) score between 1-9 (range 0-12, lower is better) also known as the Wang score **Exclusion criteria:** administration of study drug was delayed by 10 minutes or more (a protocol deviation),or if clinical deterioration mandated withdrawal **Power analysis:** for the detection of the difference of 1 using in the CS between the five treatment groups with an alpha of 0.05 and power of 80%, 30 subjects were needed per group, or 150 subjects total.
Interventions	All treatments were administered at 0 and 30 minutes using a facemask with continuous flow of 100% oxygen at 6 L/min Treatment 1: 1.5 mg epinephrine in 4 ml of 0.9% saline n= 38 Treatment 2: 1.5 mg epinephrine in 4 ml of 3% saline n= 39 Treatment 3: 2.5 mg salbutamol in 4 ml of 0.9% saline n=36 Treatment 4: 2.5 mg salbutamol in 4 ml of 3% saline n= 36 Control: 4 ml 0.9% saline n= 37
Outcomes	Change in clinical severity score taken at 0, 30, 60 and 120 minutes. Change in room air oxygen saturation, Heart rate Adverse Events- heart rate > 200, tremor, withdrawal from the study due to worsening clinical status, discontinuation of medication due to side effects
Notes	

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The investigators used a random number table in the sequence generation process

Allocation concealment (selection bias)	Low risk	Participants and investigators enrolling participants could not foresee assignment because only the study coordinator was aware of allocation. Study solutions were identical in appearance and color.
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. Study solutions were identical in appearance and color. Identity of solutions was blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment ensured. Intra-observer agreement for clinical severity scores was tested.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Other bias	Low risk	The study appears to be free of all other sources of bias

(Everard et al., 2014)

Methods	SABRE study, multicenter, parallel-group RCT
Participants	**Setting:** 10 Pediatric wards and assessment units in England and Wales **Randomized into study:** N=317 • Group 1: nebulized 3% HS group n=158 • Group 2: standard supportive bronchiolitis care n=159 **Completed study:** • Group 1: n=149 • Group 2: n=141 **Age:** Infants less than 12 months • Group 1: mean 3.4 months, SD 2.8 • Group 2: mean 3.3 months, SD 2.6 **Gender, males:** • Group 1: 85 (57%) • Group 2: 73 (51.4%) **Inclusion Criteria:** • Previously healthy infants less than 1 year of age. • Admitted to hospital with a clinical diagnosis of acute bronchiolitis • Requiring supplemental oxygen therapy on admission • Consented and randomized within 4 hours of admission **Exclusion Criteria:** • Had wheezy bronchitis or asthma • Had gastro-esophageal reflux (if investigated and diagnosed in hospital) • Had previous lower respiratory tract infections (which required assessment in hospital).

	• Had risk factors for severe disease (gestation of < 32 weeks, immunodeficiency, neurological and cardiac conditions, chronic lung disease). • Subjects for whom the carer's English was not fluent and translational services were not available. • Required admission to HDUs or ICUs at the time of recruitment • involved in other research studies and this question was asked during the informed consent process, and for whom the investigating team felt that it would have been inappropriate to include them in the study **Power analysis:** 139 patients per group at a two-sided alpha-level of 5% **Location:** United Kingdom
Interventions	**Group 1:** standard supportive care plus nebulized 3% HS solution, 4ml q 6 hours-oxygen as required, fluid administration **Group 2:** Standard supportive bronchiolitis care- oxygen as required , minimal handling and fluid administration as appropriate
Outcomes	**Primary outcomes:** • time to patient fit for discharge • PICU admission • Readmission within 28 days of discharge **Safety outcome:** • adverse events

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	use of central web-based randomization service
Allocation concealment (selection bias)	Low risk	Randomization not revealed to anyone involved in patient recruitment/care
Blinding of participants and personnel (performance bias)	High risk	Did not blind
Blinding of outcome assessment (detection bias)	Low risk	No member of the study team had access to unblinded data sets or the unblinded reports until the final analyses
Incomplete outcome data (attrition bias)	High risk	There were some post randomization exclusions that are not defined. They did a sensitivity analysis and the results were the similar • Group 1: 16 exclusions • Group 2: 10 exclusions
Selective reporting (reporting bias)	Low risk	all outcomes (primary and secondary) have been reported
Other bias	Unclear risk	

(Florin, Shaw, Kittick, Yakscoe, & Zorc, 2014)

Methods	Randomized clinical trial ED
Participants	**Setting:** urban, tertiary care emergency department within a freestanding children's hospital **Randomized into study:** N = 62 • **Group 1:** nebulized 3% hypertonic saline = 31 • **Group 2:** normal saline = 31 **Completed study:** N = 62 **Gender, males:** • **Group 1:** 15 • **Group 2:** 13 **Age, mean in months:** • **Group 1:** 7.2 • **Group 2:** 6.1 **Inclusion Criteria:** • Children aged 2 to less than 24 months • Presenting to emergency department (ED) with first episode of acute bronchiolitis • Respiratory Distress Assessment Instrument (RDAI) score of 4 to 15, after albuterol treatment and no intention for further respiratory therapy by ED physician in first hour after assessment **Exclusion Criteria:** Infants with: • History of wheezing or asthma • Bronchodilator therapy prior to the current illness • Chronic lung or heart disease • Critical illness • Inability to receive nebulized medications • Non-English-speaking guardians due to inability to provide fully informed consent within study time constraints **Power Analysis:** 30 infants in each group to detect a mean change of 3 on the RACS between the groups, assuming α = .05 and ß = .2 (80% power)
Interventions	• **Group 1:** 4mL of 3% HS (hypertonic saline) • **Group 2:** 4 mL of NS (normal saline) 1. All participants prior to confirmation of eligibility received standard therapy for bronchiolitis per the ED bronchiolitis pathway, to include nasal suctioning and trial of single dose of nebulized albuterol 2. Study medications were delivered using a jet nebulizer with an oxygen flow rate of 8 L/min 3. Medication administration occurred within 90 minutes after albuterol administration 4. Respiratory scoring occurred at 1 and 2 hours after the study treatment 5. Brief parental surveys were performed at 1 and 2 hours after study treatment to gather information on respiratory distress, ability to feed, and a medical history form was completed

Outcomes	**Primary Outcomes:** • Difference in mean RACS 1 hour after treatment demonstrated significantly less improvement in the HS group compared with the NS group. • No significant difference in the RDAI score at 1 hour between the 2 groups. • No significant difference in RACS at 2 hours between the 2 groups. **Secondary Outcomes:** • No significant difference at 1 hour in change in heart rate or oxygen saturation between groups • No significant difference between groups in rate of hospitalization or parental perception of child's breathing or feeding status • **No adverse events occurred during the study.**

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Use of computer-generated random permuted block randomization
Allocation concealment (selection bias)	Low risk	Central allocation (pharmacy-based) utilized
Blinding of participants and personnel (performance bias)	Low risk	No study personnel, parents or guardians were aware of group assignments; both HS and NS are clear and odorless so indistinguishable in syringe and nebulization chamber
Blinding of outcome assessment (detection bias)	Low risk	Study clinicians performing scoring were unaware of group assignments
Incomplete outcome data (attrition bias)	Low risk	Intention to treat principle was used in data analysis of primary outcome
Selective reporting (reporting bias)	Low risk	Protocol is available and all pre-specified outcomes were reported on
Other bias	Low risk	

(Grewal, Ali, McConnell, Vandermeer, & Klassen, 2009)

Methods	RCT ED
Participants	Infants 6 weeks to 12 months- mild to moderate bronchiolitis Initial Respiratory Distress Assessment Instrument (RDAI) score was ≥4
Interventions	**Control group**--2.5-mL aliquots of 0.9% normal saline+0.5mL of 2.25% racemic epinephrine --> total mixture of 3 mL was given to the patient by nebulization.

	Treatment group-- and 2.5-mL aliquots indistinguishable solution of 3% hypertonic saline + total mixture of 3 mL was given to the patient by nebulization. Each treatment was given by nebulizer with continuous flow of oxygen at 6 L/min.
Outcomes	**Primary outcome:** change in respiratory distress as measured by the Respiratory Assessment Change Score (RACS), from baseline to 120 minutes. Change in oxygen saturation **Secondary outcome:** rate of hospital admission, return to emergency department.
Notes	Exclusion criteria were preexisting cardiac or pulmonary disease, previous diagnosis of asthma by a physician, any previous use of bronchodilators (except for treatment of the current illness), severe disease requiring resuscitation room care, inability to take medication using a nebulizer, inability to obtain informed consent secondary to a language barrier, or no phone access for follow-up.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Patients were randomized into blocks of 4. The randomization scheme was generated by the pharmacy using the Web site Randomization.com
Allocation concealment (selection bias)	Low risk	The randomization process was determined by the pharmacy. Physicians, house staff, nurses, study personnel, and patients remained blinded to treatment allocation throughout the study.
Blinding of participants and personnel (performance bias)	Low risk	The solutions were similar in appearance and smell, stored in identical syringes, labeled only by a code number, The randomization list was concealed by the pharmacy until completion of the study
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Unclear risk	Used intention to treat analysis reported. One subject withdrew, from each group
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Power analysis based on the ability to detect a change of 3 points in the RACS score.

(Ipek, Yalcin, Sezer, & Bozaykut, 2011)

Methods	RCT
Participants	**Setting:** the short-stay unit of the Pediatric Emergency Department or a training research hospital; October 2009-March 2010 **Number randomized:** 120 infants **Number completed:** 120 infants Age

	Gender **Inclusion criteria:** • < 2 years of age • history of viral respiratory infection followed by wheezing and crackles on auscultation • CBSS (severity score) of 4-8 (range 0-12, lower is better), also known as the Wang score **Exclusion criteria:** • CBBS < 4 or > 8 • oxygen saturation < 85% on room air • chronic cardiac illness • premature birth • low birth weight < 2500 g • severe immune deficiency • severe neurological disease • < 1 month or > 2 years • consolidation or atelectasis on chest x-ray **Power analysis:** not reported **Location:** Turkey
Interventions	Supportive care, oxygen supplementation, aspiration, and hydration was provided to all as needed **Group 1**: 4 ml of solution containing 0.15 mg/kg salbutamol plus normal saline **Group 2:** 4 ml of solution containing 0.15 mg/kg salbutamol plus 3% saline **Group 3:** 4 ml of solution containing only 3% saline G**roup 4:** 4 ml of solution containing normal saline
Outcomes	**Primary:** Change in CBBS score **Secondary:** Corticosteroid need- when CBSS deteriorated and/or sao2< 85% on room air after the treatment Hospitalization ratios Clinical assessment at 48-72 hours

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	High risk	Patients were assigned to groups in a consecutive manner. The first patient went to Group 1, the second to Group 2 etc.
Allocation concealment (selection bias)	High risk	Allocation was not concealed
Blinding of participants and personnel (performance bias)	Low risk	

Blinding of outcome assessment (detection bias)	Low risk	Physician doing follow up was blinded to study treatment
Incomplete outcome data (attrition bias)	Low risk	All completed
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

(Kuzik et al., 2007)

Methods	RCT multi-center study
Participants	**Setting:** multi-center study December 2003 to April 2006 **Number randomized:** 96 **Number completed:** 96 **Age:** Mean age 4.7 +/- 4.2 months, range [10 days to 18 months] **Gender:** 57% male in the hypertonic saline group and 61% male in the normal saline group **Inclusion criteria:** • Moderately severe bronchiolitis • History of viral upper respiratory infection • Wheezing or crackles on chest auscultation • Either an oxygen saturation (SaO_2) < 94% or a severity score (RDAI, range 0-17, lower is better) of >/= 4. **Exclusion criteria:** • Previous episode of wheezing • Chronic cardiopulmonary disease • Immunodeficiency • Illness that requires admission to the intensive care unit • Use of nebulized hypertonic saline within previous 12 hours • Premature birth (</= 34 weeks gestational age) **Power analysis:** A reduction of LOS by one day was determined to be clinically significant. Sample size was calculated to be 46 subjects per arm for 80% power to show a p-value </= to 0.05 **Location:** Canada and United Arab Emirates
Interventions	Supportive care was provided to both groups, supplemental oxygen, aspiration, fluid administration **Treatment:** 4 ml of 3% saline NEB every 2 hours for three doses, followed by every 4 hours for five doses, followed by every 6 hours until discharge **Control:** 4 ml of normal saline NEB every 2 hours for three doses, followed by every 4 hours for five doses, followed by every 6 hours until discharge

Outcomes	**Primary**: length of stay (definition- time from study entry to protocol- defined discharge criteria were met or independent clinical grounds by the attending physician. The protocol defined discharge criteria included an RDAI score < 4 and an SaO2 of >/= 95% on room air for 4 hours.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer-based randomization program
Allocation concealment (selection bias)	Low risk	Double-blinded
Blinding of participants and personnel (performance bias)	Low risk	Double-blinded
Blinding of outcome assessment (detection bias)	Low risk	Study solutions were prepared by a research pharmacist and were identical in appearance and odor.
Incomplete outcome data (attrition bias)	Unclear risk	ITT, outcome data was reported
Selective reporting (reporting bias)	Low risk	All specified outcomes were reported
Other bias	Low risk	

(Luo et al., 2011)

Methods	RCT
Participants	93 infants <24 months of age with viral bronchiolitis for the first time, China
Interventions	**Treatment:** 2.5 mg salbutamol dissolved in 4.0 ml hypertonic (3%) saline **Control:** 2.5 mg salbutamol dissolved in 4.0 ml normal (0.9%) saline
Outcomes	Wheezing remission time, cough remission time, pulmonary moist crackles and hospital time

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	States random, but the randomization is not described

Allocation concealment (selection bias)	High risk	The method of concealment is not described
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants and key study personnel ensured. Identities of therapeutic packaging were not available to investigators or attending physicians
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment ensured. Identities of therapeutic packaging were not available to nursing or medical staff
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category
Other bias	Low risk	

Luo 2011

Methods	RCT
Participants	**Setting:** teaching hospital **Number randomized:** 135 subjects **Number completed:** 112 subjects, n= 57 in 3% saline group and n= 55 in the normal saline group **Age:** range 1.5-10.1 month **Gender:** 56% male **Inclusion criteria:** • < 24 months • first episode of wheezing • moderate to severe bronchiolitis by internal respiratory score **Exclusion criteria:** • > 24 months • previous episode of wheezing • chronic cardiac and pulmonary disease • immunodeficiency • accompanying respiratory failure • require mechanical ventilation • inhaling the nebulized 3% hypertonic saline 12 hours before this treatment • prematurity (birth at < 34 weeks gestation) **Power analysis:** not reported **Location:** China
Interventions	Supportive care was provided to both groups, supplemental oxygen, aspiration, fluid administration **Treatment:** 4 ml of 3% saline NEB every 2 hours for three doses, followed by every 4 hours for five doses, followed by every 6 hours until discharge

	Control: 4 ml of normal saline NEB every 2 hours for three doses, followed by every 4 hours for five doses, followed by every 6 hours until discharge
Outcomes	Symptom relief LOS Clinical severity score

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Concealed in an opaque sealed envelope
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	Seven patients in each group were discharged within 12 hours after enrollment, and not included in the analysis. Including the subjects does not change the overall effect, only the confidence interval changes by a small degree
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

(Mandelberg et al., 2003)

Methods	Randomized, double-blind, controlled-trial
Participants	**Setting:** Edith Wolfson Medical Center (Israel) **Randomized into study:** n = 53 **Completed study:** n = 52 • Group 1: 0.9% NS + Epi = 25 • Group 2: 3% NS + Epi = 27 **Gender, males (%):** • Group 1: 15 (60%) • Group 2: 15 (55%) **Age in months (mean):**

	• Group 1: 2.6 • Group 2: 3 **Inclusion criteria:** clinical presentation of bronchiolitis with temp > 30C who were admitted to hospital (specific diagnosis criteria for bronchiolitis were not discussed) **Exclusion criteria:** cardiac ds, chronic respiratory disease, previous wheezing episode, age > 12 months of age, oxygen saturation < 85% on room air, obtunded consciousness, and/or progressive respiratory failure requiring mechanical ventilation **Power analysis:** not reported
Interventions	**Group 1:** 0.9% Saline + 1.5 mg Epinephrine via nebulizer q8hr **Group 2:** 3% Saline + 1.5 mg Epinephrine via nebulizer q8hr
Outcomes	Improvement in Clinical Severity Scores Length of Stay
Notes	• Percent of infants positive for RSV was not significantly different between groups • Eight eligible patients were excluded because their parents did not agree to sign informed consent (3 intended for 3% group and 5 for 0.9% group) - randomized prior to consent???

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	randomized in a "blinded manner" but no specifics on how this was accomplished
Allocation concealment (selection bias)	Unclear risk	subjects "randomly assigned to one of two groups" but no specifics provided
Blinding of participants and personnel (performance bias)	Low risk	attending physician responsible for discharging patient was blinded to treatment
Blinding of outcome assessment (detection bias)	Low risk	no blinding of outcome assessment (length of stay - objective data)
Incomplete outcome data (attrition bias)	Low risk	outcomes reported on all subjects; 1 subject excluded due to clinical deterioration
Selective reporting (reporting bias)	Low risk	pre-specified outcomes were reported as expected
Other bias	Unclear risk	it appears subjects were randomized prior to consent as authors reported 8 subjects were excluded (3 intended for 3% group and 5 intended for 0.9% groups) because parents did not sign consent; when a sensitivity analysis was done with and without the subjects in the denominators, it did not impact the statistical significance of length of stay findings but is noteworthy none-the-less

(Miraglia Del Giudice et al., 2012)

Methods	RCT
Participants	**Setting:** Inpatients, less than 2 years with a clinical diagnosis of bronchiolitis. **Number randomized:** 109 enrolled **Number completed:** 106 completed. Three withdrew after randomization, and before treatment **Age:** 4.5 months **Gender:** 65% male **Inclusion criteria:** Clinical diagnosis • first episode of wheezing • symptoms of a viral respiratory infection • Oxygen saturation < 94% in room air • significant respiratory distress using the CSS (Wang) score (range 0-12, lower is better) **Exclusion criteria:** • pre-existing cardiac or pulmonary diseases • premature birth < 36 weeks of gestational age • previous diagnosis of asthma • initial oxygen saturation of </= 85% • respiratory distress severe enough to require resuscitation **Power analysis:** Not reported **Location:** Italy
Interventions	All nebulized treatments included and oxygen and fluid therapy, as needed **Treatment group:** nebulized 3% hypertonic saline with aerosolized epinephrine (1.5 mg) **Control group:** nebulized 0.9% saline

Outcomes	**Primary:** Hospital length of stay CSS score from baseline CSS after epinephrine administration

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	Three who were randomized did not complete the study
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

NTC01238848

Methods	RCT
Participants	**Setting-** Inpatient **Number randomized:** N= 100 ; n= 50 in each group **Number completed:** Total n= 82; n= 37 in the Treatment group and n= 45 in the control group **Gender:** 50% male **Age:** only reported as 1-24 months **Inclusion criteria:** Infants aged 1-24 months, hospitalized for first episode of bronchiolitis , severity score >/= 5 and oxygen saturation >/= 97% **Exclusion criteria:** chronic respiratory or cardiovascular disease **Location:** Argentina
Interventions	**Treatment:** 3% hypertonic saline 3 ml nebulized + albuterol 0.25 mg/kg/d four times a day (QID), 5 days **Control:** Normal saline,+ albuterol 0.25 mg/kg/d four times a day (QID), 5 days

Outcomes	**Primary:** Hospitalization days **Secondary:** length of oxygen use

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	High risk	18% did not complete the study. 26% in the treatment group and 10% in the control group
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

(*Ojha, Mathema, Sah, & Aryal, 2014)*

Methods	Double-blind RCT
Participants	**Setting:** Pediatric department of Kathmandu Medical College, Sinamangal, Kathmandu **Randomized into Study:** Treatment Group (0.9% Saline) n = 36; Control Group (3% Saline) n = 36 **Completed Study:** Treatment Group N = 31; Control Group N = 28 **Mean Age:** Treatment = 8.51 months +/- 4.24; Control = 8.61 months +/- 5.742 **Gender:** 74% male **Inclusion Criteria:** • Children older than 6 weeks and below 24 months • Clinical presentation of bronchiolitis for first time **Exclusion Criteria:** • Previous episodes of wheezing • Chronic cardiac and pulmonary disease • Immunodeficiency • Accompanying respiratory failure requiring mechanical ventilation • Inhalation of nebulized 3% hypertonic saline solution and salbutamol 12 hours before treatment

	• Premature infants born at less than 34 weeks gestation • Those with oxygen saturation below 85% on room air **Power Analysis:** PS-Power and Sample Size Calculator Version 3.0.43 was used to determine number of subjects in each group. For this study "72:36 in case and control group" were needed.
Interventions	All patients were enrolled into the study within 24 hours of admission to hospital. Patients in each group received the following: • A minimum of 3 nebulization each day delivered at 8 hour intervals until discharge • Additional nebulization or other treatment was left to the decision of the treating physician who was blinded to the groups • Supplemental oxygen was given when oxygen saturation fell below 92% on room air • Clinical scores were obtained at treatment time and 30 minutes before the beginning of each inhalation session **Treatment Group:** received inhalation of 4ml normal saline (0.9%) **Control Group:** received inhalation of 4 ml hypertonic saline (3%)
Outcomes	• A clinical score was recorded and included the following parameters: respiratory rate, wheezing, retraction, and oxygen saturation • Length of hospital stay (calculated from time of entry into study to time of discharge) • Duration of oxygen supplementation • Time period required for clinical score to fall below 4 (Score range- 0-12, lower is better)

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Reported use of computer generated random number
Allocation concealment (selection bias)	Low risk	Numbers were kept in sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk	0.9% and 3% saline were both kept in identical containers and labeled A and B. Labeling was done by a person not associated with the study. Solutions were similar in appearance and smell
Blinding of outcome assessment (detection bias)	Low risk	Randomization list was concealed until completion of study. Solution containers labeled A and B.
Incomplete outcome data (attrition bias)	High risk	Thirty-six were required in each group, for a total of 72 subjects. 59/72 (82%) completed the study and are included in the report.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Treatment and control groups appear to be reversed as defined in the Figure 1, although the article reports on outcomes as defined in figure.

(Pandit, Kim, Song, & Jeon, 2013)

Methods	A Prospective, randomized controlled, non-blinded study.
Participants	**Setting:** 100 consecutive patients attending Paediatrics Emergency at a Government Multi Specialty Hospital Sector 16, India during period from 1/11/2009 to 1/05/2011 (19 months) **Randomized into study:** 100 consecutive patients attending Paediatrics Emergency at a GMSH between the age groups of 2 to 12 months and admitted with clinical diagnosis of acute bronchiolitis were enrolled in the study. Criteria for clinical diagnosis of acute bronchiolitis were short history of cough with or without fever of less than seven days duration and wheezing on examination and with first attack of wheezing. **Completed Study:** • **Group A:** 51 patients • **Group B:** 49 patients **Gender, males:** not reported **Age in months (range):** 2 to 12 months **Inclusion Criteria:** Clinical diagnosis of acute bronchiolitis. • Short history of cough with or without fever of less than seven days duration • Wheezing on examination • First attack of wheezing. **Exclusion Criteria:** • Patient with recurrent episodes of wheezing, one or more episodes of respiratory distress in the past • Patients with family history of asthma, atopy • Presence of congenital heart disease • History of prematurity or mechanical ventilation in newborn period • Very sick patients with shock, seizures, heart rate >100/min and adjudged to be in incipient respiratory failure. • Grade III and IV PEM (PEM is not defined in the paper) • Consolidation lung on X-ray chest • No child to be included in the study twice. **Power Analysis:** Based on the results of Kudzik et al., 2007, for the outcome length of stay, sample size of 100 subjects to detect a difference with 80% power and an alpha of 0.05.
Interventions	• **Group A:** Hypertonic saline group, 4 mL of 3% hypertonic saline and 1 mL of 1,000 adrenaline was given as nebulization with oxygen flow of 6-8 liter/min. • **Group B:** (normal saline group), 4 mL of normal saline (0.9%) and 1 mL of 1:1,000 adrenaline was given as nebulization. The nebulization was given three times over three hours • Assessment done before first treatment and after third treatment • Respiratory rate • Respiratory Distress Assessment Instrument (RDAI) score, • Heart rate • Oxygen saturation was done

	Thereafter, nebulization was given every six hours to patients in each group until discharge and were assessed before and half an hour after nebulization for their respiratory rate, RDAI, heart rate, oxygen saturation Discharge criteria- respiratory rate less than 60/min, without any retractions and wheezing.
Outcomes	**Primary outcomes**: • Length of hospital stay **Secondary outcomes**: • Improvement in RDAI score • Respiratory rate • Hemoglobin saturation • heart rate • Number of add on treatment • Adverse events (defined as tachycardia, pallor, tremor, nausea, vomiting) **Group A:** Hospital stay ranged from 1 to 10 days with mean stay of 3.9 days **Group B:** Hospital stay ranged from 1 to 12 days with mean stay of 4.0 days.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Low risk	Opaque envelopes for concealment, opened and then assigned to group
Blinding of participants and personnel (performance bias)	High risk	Non-blinded study design Inpatients only
Blinding of outcome assessment (detection bias)	High risk	Non-blinded
Incomplete outcome data (attrition bias)	Low risk	No drop outs
Selective reporting (reporting bias)	Low risk	authors reported on outcomes
Other bias	Low risk	

(Sarrell et al., 2002)

Methods	Randomized, double-blind, controlled trial

Participants	65 ambulatory infants with viral bronchiolitis
Interventions	**Treatment:** 0.5 ml (5mg) terbutaline in 2 ml of 3% saline solution **Control:** 0.5 ml (5mg) terbutaline in 2 ml of 0.9% saline solution
Outcomes	Clinical Severity score (CS) described by Wang et al, Radiograph Assessment (RA) score described by Nasr et al
Notes	Israel

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Study states patients were randomly assigned to 1 of 2 groups; does not describe methodology.
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described.
Blinding of participants and personnel (performance bias)	Low risk	A code was placed on each "therapeutic package" which indicated control versus experimental. This code was only available to the statistician.
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. The code on the therapeutic package was not available to the investigator or medical personnel.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across groups. Authors performed intent to treat analysis which they report was not different from reported per protocol results.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'.
Other bias	Low risk	

(Sharma, Thakur, Joshi, & Kulkarni, 2014)

Methods	Randomized, Double-blind study of Hypertonic (3%) Saline vs. 0.9% Saline Nebulization for Acute Viral Bronchiolitis
Participants	**Setting:** Tertiary care teaching hospital in India from Sept 2009-Dec 2010 **Randomized into study:** n = 250 Group 1: 0.9% Saline (NS) n = 125 Group 2: Hypertonic 3% Saline (HS) n = 125 **Completed study:** 248 Group 1: NS n = 123 Group 2: HS n = 125 **Gender,** males (%):

	Group 1: NS 92 (75) Group 2: HS 97 (78) **Age,** years (SD): Group 1: NS 4.18 (4.24) Group 2: HS 4.93 (4.31) **Inclusion Criteria:** Infants aged 1-24 months hospitalized with acute bronchiolitis (viral presentation) of moderate severity (clinical severity score 3-6). Bronchiolitis was defined as first episode of wheezing along with upper rep tract infection including rhinorrhea, cough, $\pm$ low grade fever **Exclusion Criteria:** children with obtunded consciousness, cardiac disease, chronic respiratory disease, previous wheezing episode, progressive respiratory distress requiring respiratory support other than supplemental oxygen, and those having received nebulized saline within the previous 12 hours **Power Analysis:** Reduction in length of hospital stay of 1 day was previously proposed as being clinically significant. It was anticipated that this would require a sample size of 113 patients in each arm.
Interventions	**Group 1:** 4 mL 0.9% saline + 2.5 mg salbutamol q4hr via conventional jet nebulizer with tight-fitting face mask **Group 2:** 4 mL 3% saline + 2.5 mg salbutamol q4hr via conventional jet nebulizer with tight-fitting face mask
Outcomes	**Primary Outcome:** length of hospital stay defined as time from admission to reach clinical severity score < 3 Secondary Outcome: improvement in clinical severity scores at 12 hour intervals until discharge **Safety Outcome:** no specific outcomes reported
Notes	Method of determining "clinical severity score" not defined in this study but references Wang, et al 1992 No adverse events related to nebulized therapy were reported by the parents, caregivers, or treating medical attendants in in both groups

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	"Computer generated random numbers were used for enrollment in in consecutive manner"
Allocation concealment (selection bias)	Low risk	"Combination code of therapeutic package was not available to investigator or treating staff"
Blinding of participants and personnel (performance bias)	Low risk	"No detectable difference in color, smell, or other physical properties between 0.9% saline and 3% hypertonic saline"
Blinding of outcome assessment (detection bias)	High risk	Outcomes were not blinded to the investigators completing the assessments; since the method of determining the clinical severity score was not defined in this article it is unclear whether Outcomes were subjective and therefore susceptible to considerable bias
Incomplete outcome data (attrition bias)	Low risk	Primary and secondary outcomes were reported as anticipated Two patients were lost in final analysis but article does not elaborate; however, this is unlikely to affect results

Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes were reported; however the difference in clinical severity scores was reported only as not statistically significant (data reported in line chart but individual scores not specified)
Other bias	Unclear risk	No funding or competing interests were reported

(Silver et al., 2015)

Methods	Randomized control trial
Participants	**Setting:** Urban tertiary care children's hospital, November 2011 to June 2014 **Number randomized:** 227 randomized **Number completed:** 190 completed the study **Gender:** 64% male I**nclusion criteria:** • Physician diagnosis of bronchiolitis • < 12 months old **Exclusion criteria:** • Treatment of asthma (corticosteroids or bronchodilators) • Chronic cardiopulmonary disease such as bronchopulmonary dysplasia, cystic fibrosis • Previous nebulized hypertonic saline < 12 hours before presentation • Non-English, non-Spanish speaker • Enrollment assessment> 12 hours after admission • Patients previously enrolled within 72 hours of presentation **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	**Treatment group:** 4 ml of nebulized 3% hypertonic saline every four hours from enrollment until hospital discharge **Control group:** 4 ml of normal saline every four hours from enrollment until hospital discharge All patients could receive study treatment every 2 hours pro re nata (PRN) with a maximum of 2 PRN dosages per 24 hour period
Outcomes	**Primary:** length of stay defined as the time from the first study treatment to the time of hospital discharge or meeting discharge criteria **Secondary:** Adverse events • Seven-day readmission rates • 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 **Exit criteria:** • 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) • Provider initiated bronchodilators or glucocorticosteriods (n=8)

	• Transfer to PICU • Parent or guardian request
Notes	They included subjects with prematurity in both the treatment and control arms.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Investigational Drug Pharmacy was responsible of allocation
Blinding of participants and personnel (performance bias)	Low risk	Study medications were indistinguishable from each other
Blinding of outcome assessment (detection bias)	Low risk	
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. The numbers in the flow diagram do not add up. They say they did a per protocol analysis, but go on to report an intention to treat analysis for the LOS outcome. For the per protocol analysis, they did not meet power.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

(Tal et al., 2006)

Methods	Double blind randomized control trial
Participants	Forty-four infants (< 12 months) hospitalized for acute viral bronchiolitis during the winter 2001-2002. There were 3 drop-outs, 41 subjects were included in the analysis.
Interventions	**Control Group:** Inhalation of 1.5mg epinephrine in 4mL of 0.9% (NS) every 8 hours during admission. N=20 **Treatment Group**: Inhalation of 1.5mg epinephrine in 4mL of hypertonic (3%) saline every 8 hours during admission. N=21.
Outcomes	1. Duration of hospitalization 2. Change in clinical score at the end of each day
Notes	The authors reported their own pooled data from previous study comparing hypertonic saline/epi compared to NS/epi treatments. Both groups of participants were reported to have similar clinical characteristics and variables at baseline. The authors report statistically significant data for duration of hospitalization and improved clinical scores after inhalation therapy.

	However, the treatments in the first study were administered by a different nebulizer which has shown to be less effective than nebulizer used in follow up study.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Authors do not report how the double-blind randomization was achieved
Allocation concealment (selection bias)	Low risk	Volume, look, and smell of inhalation treatments were identical. Code was deposited by the statistician.
Blinding of participants and personnel (performance bias)	Low risk	Therapeutic modality not disclosed to medical personnel or investigator examining the participants on admission and each subsequent day.
Blinding of outcome assessment (detection bias)	Low risk	Decision to discharge patients made by attending physician each morning on rounds. Physicians blinded to treatment modality
Incomplete outcome data (attrition bias)	Low risk	Three participants not included in data analysis because 1) deterioration immediately after first treatment. 2) Subject refused admission. 3) Subject required steroid treatment due to low cortisol levels. Subjects who withdrew are not included in the analysis, and it is not clear to which group(s) they were assigned.
Selective reporting (reporting bias)	Low risk	Reported on outcomes described. They added a short report on the pooled results from the similar study they conducted the previous bronchiolitis season. Results from both cohorts were pooled- description of the previous year study is not included, except it was "similar".
Other bias	Low risk	

(Wu et al., 2014)

Methods	Double-blind randomized clinical trial
Participants	**Setting**: ED at 2 tertiary free-standing urban children's hospitals in California. Oakland and Los Angeles during bronchiolitis season (November through April) March 1, 2008- April 30, 2011. **Number randomized**: Hypertonic saline (HS) N= 211 and Normal saline (NS) N= 197 **Number who completed the study**: HS N=204 NS N=190 **Gender**= HS male=58.9% NS male=54.6% **Age**: Younger than 24 months **Inclusion criteria**: • Primary diagnosis of viral bronchiolitis during bronchiolitis season **Exclusion criteria**: • prior illness with wheezing or bronchodilator use • Premature - Born at less than 34 weeks • cyanotic congenital heart disease

	• chronic lung disease • tracheostomy
Interventions	**Intervention**: 2.5 mg of nebulized albuterol sulfate, followed by 4 mL of hypertonic saline via a small-volume wall nebulizer **Control**:2.5 mg of nebulized albuterol sulfate, followed by 4 mL of normal 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 • Admitted patients continued receiving study medication at a dosage of 4 mL every 8 hours until discharge
Outcomes	• **Admission rate** was calculated as the number of patients requiring inpatient hospitalization divided by the total number of patients randomized. • **Length of stay** was calculated as an integer value by subtracting the admission date from the discharge date. • **The Respiratory Distress Assessment Instrument** (RDAI) score was assigned by a study investigator before and 30 minutes after each treatment in the ED and once each morning of hospitalization This score was converted into the Respiratory Assessment Change Score, which is calculated by adding together the change in RDAI score from before to after treatment, plus a point for each 10% change in respiratory rate above 5% (e.g., −1 for a decrease of 6%-15% and −2 for a decrease of 16%-25%; negative values signify improvement). Previous studies have determined a change in RDAI of 4 points or greater or a change in Respiratory Assessment Change Score of 2 points or greater to be clinically significant.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer-generated random number table stratified by site
Allocation concealment (selection bias)	Low risk	Allocated by simple randomization to the HS or the NS group by the investigational pharmacy
Blinding of participants and personnel (performance bias)	Low risk	Families, clinical staff, and study personnel were blinded to treatment allocation. Study medication was identical in color, odor, and labeling.
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcome data explained
Selective reporting (reporting bias)	Low risk	Full protocol available
Other bias	Low risk	Study appears to be free of bias

Figures

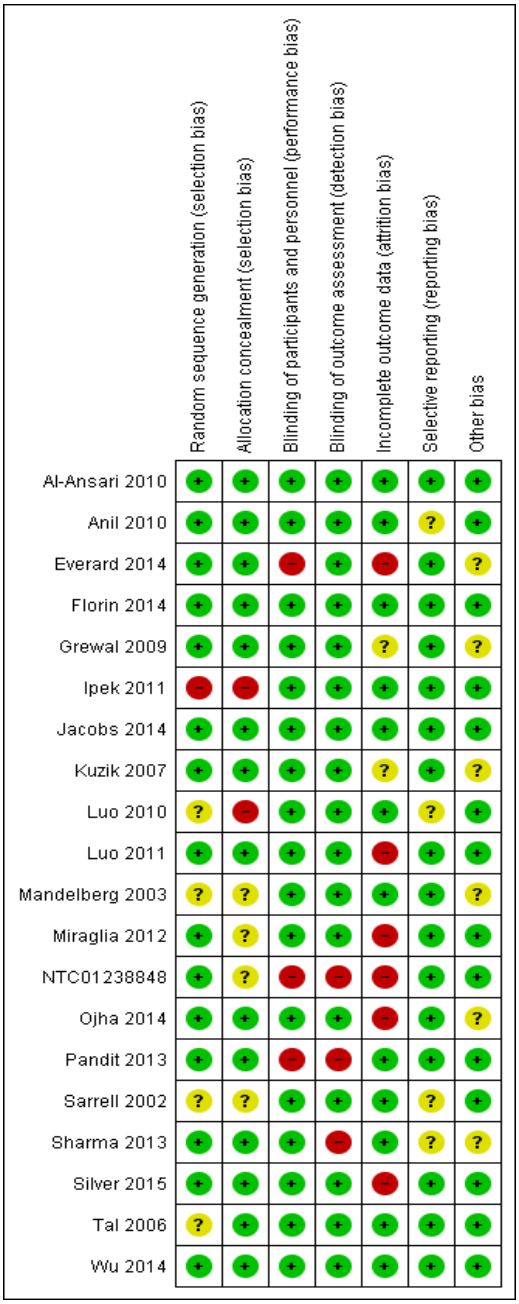

Figure 1. Risk of bias summary: Evidence Based Scholars' judgments about each risk of bias item for each included study for hypertonic saline administration

Note: Includes the following studies from Zhang 2013 Cochrane Review: (Al-Ansari et al., 2010); (Anil et al., 2010); (Grewal, Ali, McConnell, Vandermeer, & Klassen, 2009) (Ipek, Yalcin, Sezer, & Bozaykut, 2011); (Kuzik et al., 2007); (Luo et al., 2010); (Luo et al., 2011) (Mandelberg et al., 2003); (Sarrell et al., 2002); (Tal et al., 2006).

The following studies, published since Zhang were added to the meta-analysis (Everard et al., 2014); (Florin, Shaw, Kittick, Yakscoe, & Zorc, 2014); (Jacobs, Foster, Wan, & Pershad, 2014); (Miraglia Del Giudice et al., 2012); NTCO1238848; (Ojha, Mathema, Sah, & Aryal, 2014); (Pandit, Dhawan, & Deepak, 2013; Silver et al., 2015); and (Wu et al., 2014).

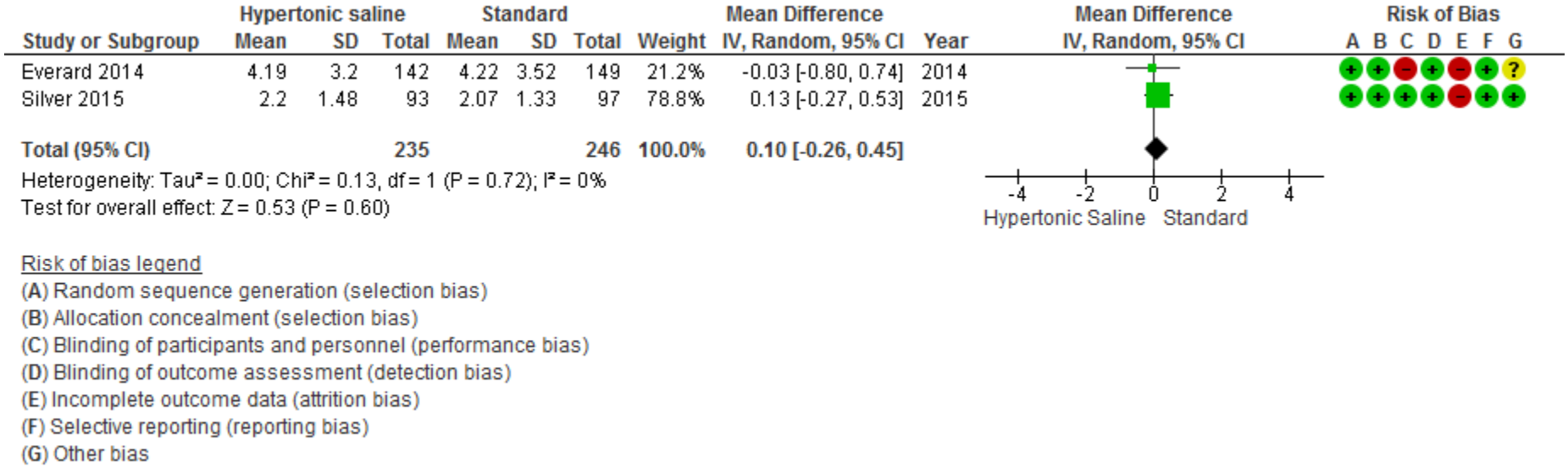

Figure 2. Hypertonic Saline vs. Control, Studies since the publication of Ralston et al. (2014), Outcome: Inpatient Length of Stay.

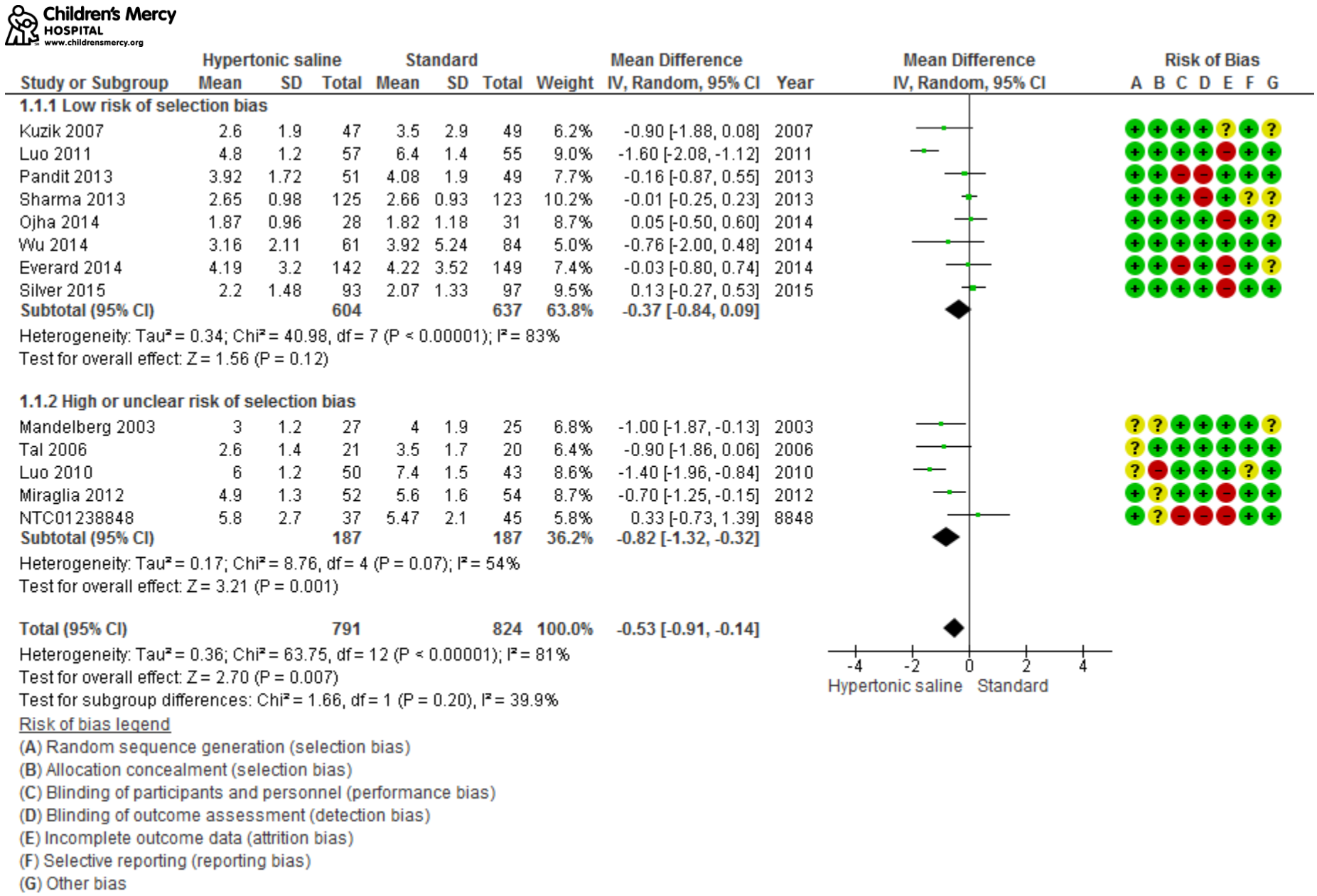

Figure 3. Hypertonic Saline vs. Control, All studies, Outcome: Inpatient Length of Stay.

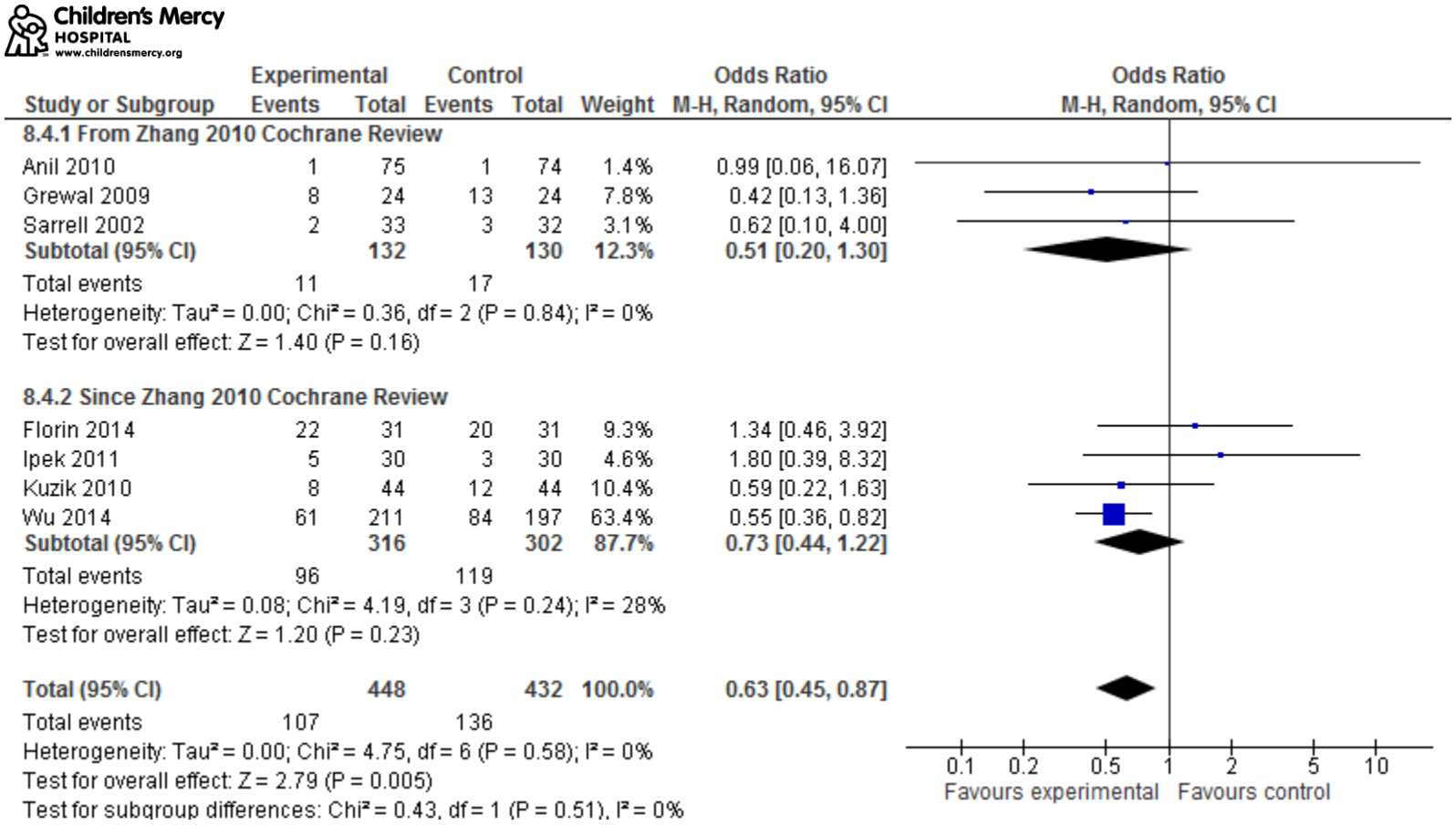

Figure 4. Hypertonic Saline vs. Control, Outcome: Odds of Hospitalization from the ED.

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Appendix B

Question 3: **For the child with bronchiolitis, when should nasal suctioning (with a bulb tip) or nasopharyngeal suctioning (with a catheter) be used to clear secretions?**

Critically Appraised Topic (CAT)

Synthesis of relevant studies:

<table>
<tr><th>Author, date, country, and industry of funding</th><th>Patient Group</th><th>Level of Evidence (Oxford) /</th><th>Research design</th><th>Significant results</th><th>Limitations</th></tr>
<tr><td>Conway-2004</td><td>Guideline Infants <= to 1 yr. old with first-time admits of Bronchiolitis</td><td>Differential Diagnosis/ Symptom prevalence 4 study.</td><td>QI report</td><td>Guideline Implementation: Respiratory Care for patients was considered "Perfect" if bronchodilator administration was PRECEDED by nasal suctioning and the post-suctioning score was >/= 3 on an internal scoring tool (scoring range 0-8)
Prior to guide-line implementation only 2% of the patients received "perfect" respiratory care—following guideline implementation "perfect care" increased to 19%.
14% of the time SUCTIONING lowered the Respiratory Score from >/= 3 to <3.</td><td>Only infants </= to one year old – first time episode of uncomplicated bronchiolitis.
Exceptions patients with history of cystic fibrosis, immunodeficiency, CHD, BPD, congenital airway issues, or need for mechanical ventilation or other intensive therapies warrant of PICU admission.
Premature infants are included as long as they had not underlying exceptions stated above.</td></tr>
<tr><td>Jarvis, K., 2012 USA</td><td>Comparison of suctioning practices before and after the implementation of a suctioning protocol</td><td>4</td><td>QI report</td><td>
<table>
<tr><th>Measures</th><th>2010-2011 Season</th><th>2011-2012 Season</th></tr>
<tr><td># Patients</td><td>894</td><td>483</td></tr>
<tr><td>% NP suction</td><td>30</td><td>16.6</td></tr>
<tr><td>% times nasal suction</td><td>70</td><td>83.4</td></tr>
<tr><td>Readmit rate</td><td>4.28</td><td>3.93</td></tr>
<tr><td>% pts on IV fluid</td><td>46.5</td><td>35.1</td></tr>
</table>
</td><td>Number of patients in each group varied due to a light bronchiolitis season 2011-2012.
Retrospective
Compliance to protocol use was not measured.
Quality project.</td></tr>
</table>

				Admission to PICU	2	2	
				Parental satisfaction (range 0-3, 3 best)	2.94	2.94	
				Avg. LOS (d)	3.39	3.29	
Mallory, 2003 USA	None	Decision analysis level 5	Survey completed by 519 physicians who are members of the AAP Section of Emergency Medicine and living in the US. Survey contained 1 of 4 vignettes of an infant with moderately severe bronchiolitis followed by 17 questions about the physician's diagnostic and treatment preferences and perceptions of the importance of potential treatments. Vignettes were identical except for given Spo_2 (94% or 92%) and RR (50/min or 65/min).	Use of Therapeutic Options: ○ 96% of respondents would treat with a bronchodilator. Variation in vignette Spo_2 or RR did not significantly affect this decision. ○ 82% would attempt to remove nasal secretions for therapeutic reasons. Variation in vignette Spo_2 or RR did not significantly affect this decision. ○ 57% would administer supplemental oxygen. Decision to administer oxygen was more likely with the lower Spo_2 (92%) and the higher RR (65). ○ 9% would treat with a decongestant. Variation in vignette Spo_2 or RR did not significantly affect this decision. ○ 8% would treat with a corticosteroid. ○ 9% would treat with an antibiotic. Comparison of Therapeutic Options – respondents were asked to rank the given therapeutic options from 1 to 6, 1 having the highest expected potential for positive clinical effect. ○ Nasal suction received the greatest number of first-place rankings ○ Bronchodilators 2nd place ○ Supplemental oxygen 3rd place Laboratory Tests: ○ 61% of respondents would order a CXR ○ 47% would order an RSV test ○ 11% would order a CBC		○ A survey is not an assessment of actual clinical practice ○ Subjects received no incentive for participation

				○ 5% would order a blood gas analysis ○ 4% would order a blood culture ○ 4% would order serum electrolytes ○ 3% would order a urinalysis ○ 2% would order a urine culture ○ 29% would not order any tests ○ Respondents who received a vignette with Spo2 of 92% were slightly more likely to order tests than those who received a vignette with Spo2 of 94%. Admission: ○ 67% of all respondents indicated that they would recommend admission. ○ Respondents who received a vignette with Spo_2 of 92% were much more likely to recommend admission. ○ Respiratory rate was significantly associated with admission preference only when the vignette Spo_2 was 94% but not when the Spo_2 was 92%.	

Synthesis Author(s): EBP Scholars (Menown, J., Thompson, L., & Tobin, T.)
Date: 2012-05-03

CINAHL Search Strategy performed
AARC GUIDELINE: NASOTRACHEAL SUCTIONING
NTS 5.0 CONTRAINDICATIONS:
Listed contraindications are relative unless marked as absolute.
5.1 Occluded nasal passages1,6
5.2 Nasal bleeding1
5.3 Epiglottitis or croup (absolute)1,6
5.4 Acute head, facial, or neck injury1,2,6
5.5 Coagulopathy or bleeding disorder1,3,6
5.6 Laryngospasm1,3,6
5.7 Irritable airway1
5.8 Upper respiratory tract infection1
5.9 Tracheal surgery6
5.10 Gastric surgery with high anastomosis6
5.11 Myocardial infarction6
5.12 Bronchospasm2

Appendix C

Question: Updated October 2016- For the child who presents with the symptoms of bronchiolitis should high flow, high humidity nasal cannula be used?

Plain Language Summary from the Office of Evidence Based Practice:

Acute bronchiolitis is a common cause of visits to the Emergency Department and hospitalization of infants less than 2 years old. Symptoms of a common cold, such as runny nose and congestion get worse, secretions increase, the child has difficulty breathing, coughs, and wheezes. The usual treatment is providing supplemental oxygen, suctioning to remove nasal secretions, and providing fluids if dehydration is present. Recently, supplying oxygen at a higher flow rate and adding humidity (high flow nasal cannula) has been suggested as a treatment to improve the child's breathing. This review compares the effects of high flow nasal cannula with standard oxygen administration in the care of the child with bronchiolitis.

Two very low quality studies were identified that made the comparison of HFNC versus standard oxygen delivery and measured how long the child stayed in the hospital. The results of the studies contradict each other. One study found no reduction in length of stay, while the other stated children treated with HFNC had shorter time in the hospital.

Clinical Bottom Line:

There is insufficient evidence to determine the effectiveness of HFNC for the treatment of bronchiolitis in children < 2 years of age. This concurs with the recommendations from the AAP (Ralston et al., 2014), the Canadian Pediatric Society (Friedman et al., 2014), and the NICE Guidelines (NICE, 2015). Further research on the efficacy of HFNC, either in the PICU or on an inpatient unit is likely to have important influence on our confidence in making a recommendation.

Literature Summary

The primary treatment for children who are admitted with bronchiolitis continues to be providing supplemental oxygen, suctioning to remove secretions, and encouraging feedings. Conventionally, oxygen is delivered via low-flow nasal prongs. High flow nasal cannula allows the delivery of a heated, humidified air/oxygen blend and oxygen at higher flows, which may improve ventilation. Flow rates of > 1 L/min to 5 L/min for infants and up to 8 L/min in older children can be administered.

The Bronchiolitis Clinical Practice Guideline (CPG) of the AAP was adopted as the parent guideline of the Children's Mercy Bronchiolitis CPG. Application of the AGREE II tool to assess the AAP CPG yielded an overall agreement with the guideline of 90%. (See Table 1.) The AAP Guideline states without completed RCTs on the efficacy of HFNC, they are unable to make a recommendation to use or not use the therapy (Ralston et al., 2014).

LOS

Since the publication of the AAP guideline, a Cochrane Review has been published (Beggs, Wong, Kaul, Ogden, & Walters, 2014). It includes one very low quality study, Hilliard et al. (2012) a non-blinded RCT pilot study, that compared HFNC to oxygen therapy via an oxygen hood. The other included study is a pre- post retrospective study (Riese, Fierce, Riese & Alverson, 2015). Both of the included studies reported on the outcome length of stay (LOS). No harms were identified in either study.

The included evidence is very low quality. Hilliard et al. (2012) reports no difference in LOS between the treatment groups (n= 19) for the comparison HFNC versus standard care (median time for HFNC 162 hours, range [96, 300) vs. hood oxygen 164 hours, range [84-233] p= 0.7. Riese et al. (2015) report a significant difference ($p < 0.001$) in LOS comparing median, days, [IQR] of before the use of HFNC Median 4 [IQR 3, 5] versus post the use of HFNC
Median 3 [IQR 2, 4).

Characteristics of Included Studies

(Beggs et al., 2014)

Methods	Cochrane Review
Participants	Included one RCT- Hilliard 2012 Inclusion criteria • RCTs or quasi -RCTs (quasi allocation method such as date of birth would be accepted) • Abstract reports ok • Included infants < 24 months of age with a clinical diagnosis of bronchiolitis Exclusion criteria • Studies include infants with cardiorespiratory disease
Interventions	HFNC was defined as oxygen or oxygen/room air blend at flow rates > 4L/min via nasal cannula HFNC compared with other forms of respiratory support • Clinical and oxygen saturation monitoring • Oxygen delivered by head box, mask or tent • Oxygen delivered by low-flow nasal cannula (flow rate equal to or less than 4L/min • Invasive intermittent positive pressure ventilation (IPPV)
Outcomes	**Primary** • Need for IPPV or CPAP • Length of time in the hospital or time until ready for discharge **Secondary** • Clinical severity score • Duration of oxygen therapy or other form of respiratory support • Oxygen saturation • Respiratory rate

	• Heart rate • Adverse events
Notes	See description below

(Hilliard et al., 2012)

Methods	Prospective, randomized, open pilot study
Participants	**Number included:** N= 19 Gender: not reported Age: median age 3 months, range [0.3-11.3] Inclusion criteria: clinical diagnosis of moderately severe bronchiolitis Exclusion criteria: not reported Power analysis: not reported
Interventions	**Both groups:** Oxygen concentration adjusted to achieve target pulse oximeter oxygen saturation (SpO_2) of 92-96% **Treatment group:** HFNC, n= 11 • Vapotherm 2000i at 4lpm with 100% oxygen and increased up to 8 lpm if tolerated. • Continued for at least 24 hours then flow rate decreased sequentially and switched to dry oxygen once 2lpm. **Control group:** oxygen hood : n=7
Outcomes	Primary outcomes • SpO2 at 8 hours post randomization • LOS, or time until ready for discharge •
Notes	Only study included in the Beggs et al., (2014) a Cochrane SR/MA. The search strategy included records published until May 15 2013.

Risk of Bias Table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Method to generate the sequence was not described

Allocation concealment (selection bias)	High risk	Authors did not disclose
Blinding of participants and personnel (performance bias)	High risk	There was no attempt made to blind
Blinding of outcome assessment (detection bias)	High risk	There was no attempt made to blind
Incomplete outcome data (attrition bias)	Low risk	All subjects completed the study
Selective reporting (reporting bias)	Low risk	Not evident
Other bias	High risk	The weaning protocols for the two treatments were different. The HFNC protocol had a slower wean than did the head box oxygen protocol.

(Riese et al, 2015)

Methods	Retrospective, nonrandomized, pre-intervention vs post-intervention by chart review
Participants	**Setting:** USA, large urban children's hospital **Number Randomized:** NOT randomized, but included total group size N= 290 1. infants <24 months of age 2. admitted to the PICU between April 1, 2010 and March 31, 2014 3. diagnosis of bronchiolitis by ICD9 1. 466.19 (not RSV bronchiolitis) 2. 466.11 (RSV bronchiolitis) 3. 786.03 (apnea) 4. 465.9 (acute upper respiratory infection) 5. V73.99 (unspecified viral illness) 4. n = 120 (24 months *prior* to protocol implementation) 5. n = 170 (24 months *post* protocol implementation) **Inclusion criteria:** • initially admitted to the PICU and received HFNC **Exclusion criteria:** • greater than 24 months of age (to reduce inclusion of non-bronchiolitis acute respiratory infections) • hospitalizations greater than 21 days (to reduce inclusion of more complex cases) • infant's with gestation of less than 37 weeks • specific diagnosis of chronic lung disease • asthma

	• chromosomal abnormalities • heart disease • neurological disease
Interventions	Application of HFNC by a prescribed HFNC protocol
Outcomes	**Primary:** • Length of stay after initiation of HFNC protocol **Secondary:** • Total hospital charges • Intubation rates • 30 day readmission
Notes	HFNC defined as a flow >2 LPM and using a heated humidification device **<u>Intervention Outcome Measures (Median and IQR interquartile range)</u>** Median Total LOS (days) Before: 4 (IQR 3-5) After: 3 (IQR 2-4) *p <0.001* Median Total Hospital Charges Before: $12,257 (IQR 8,365-17,226) After: $9,337 (IQR 6,882-12,624) *p <0.001* Intubation (Adverse Outcome) Before: 9/120 (7.5%) After: 11/170 (6.5%) *p*= 0 .73 30-d Readmission (Adverse Outcome) Before: 11/120 (9.2%) After: 13/170 (7.7%) *p*= 0.64

Appendix D

Question 5: Updated October 2016- For the child who presents with the symptoms of bronchiolitis should inhaled racemic epinephrine be used in the inpatient or outpatient settings?

Bronchiolitis Team Recommendation

The AAP guideline recommends against the routine use of inhaled racemic epinephrine to treat acute bronchiolitis in both the inpatient and outpatient settings (Ralston et al., 2014). However, the Bronchiolitis CPG Team concludes the evidence is insufficient at this time to make a recommendation for against using racemic epinephrine.

The meta-analysis by Hartling et al., (2011) was analyzed using GRADEprofiler (GRADEpro). The evidence is GRADED as Moderate to Low quality. Risk of bias, specifically poorly reported allocation concealment and blinding were detected in the included studies. Studies were also inconsistent, which decreases confidence in the pooled results. Hartling et al., (2011) conclude that the evidence shows some reduction in hospital admission when children with bronchiolitis are treated with epinephrine. However, the short term of medication effect and the differences in timing of outcome measurements limit the quality of the evidence. There is no evidence to support the use of racemic epinephrine in the inpatient setting. See the GRADE table below.

In a series of studies (Skjerven et al., 2013, 2015) report on the same group of subjects who received either inhaled racemic epinephrine versus normal saline for acute bronchiolitis in the inpatient setting. In the first study, (Skjerven et al., 2013) LOS was not significantly between the two groups. In the second study (Skjerven et al., 2015), the same subjects were evaluated approximately 2 years later. For those who received racemic epinephrine at the acute bronchiolitis visit, a comparison was made between and went on to develop either recurrent bronchial obstruction, atopic eczema, or allergic sensitization and those who did not develop these conditions. The outcome was the LOS at the acute bronchiolitis visit. There was no difference in LOS between those who went on to develop atopic symptoms and those who did not.

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GRADEpro Table:

Quality assessment (Hartling et al., 2011)							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Epinephrine vs placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Length of Stay (inpatients only) (range of scores: 2.45-2.9; Better indicated by lower values)												
2	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	149	143	-	MD 0.35 lower (0.87 lower to 0.17 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Admission at enrollment or <24 hours (outpatient only (assessed with: Count)												
6	randomized trials	serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/493 (12.6%)	93/502 (18.5%)[4]	RR 0.67 (0.5 to 0.89)	61 fewer per 1000 (from 20 fewer to 93 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Admissions overall up to 7 days (outpatient only) (assessed with: Count)												
3	randomized trials	no serious risk of bias	serious[5]	no serious indirectness	serious[6]	none	88/437 (20.1%)	110/438 (25.1%)	RR 0.81 (0.63 to 1.03)	48 fewer per 1000 (from 93 fewer to 8 more)	⨁⨁◯◯ LOW	CRITICAL
Outpatient clinical score at 60 minutes (Better indicated by lower values)												
6	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	490	485	-	MD 0.73 lower (1.13 to 0.33 lower)	⨁⨁⨁⨁ HIGH	CRITICAL

[1] One study had high risk for selective reporting bias.
[2] Poorly reported allocation concealment
[3] Poorly reported blinding technique
[4] Chose the mean baseline risk as the variation in risk was similar across studies (~20%), except one study where it was 75%. (Ralston 2005a)
[5] One study varied the saline concentration of the epinephrine carrier as well
[6] Low number of events

(Skjerven, et al, 2013)

Methods	An eight center, randomized double blind trial with a 2 by 2 factorial design; inpatients
Participants	**Setting:** Eight centers in Norway **Number randomized:** N= 404; n= 203 in the treatment group and n= 201 in the control group Enrollment only occurred as long as a physician and nurse were available. **Number completed:** N=321; n= 167 in the treatment group and n= 154 in the control group **Gender:** 59% male **Inclusion criteria:** moderate bronchiolitis (score of 4 or greater on a scale of 0-10, lower is better); less than 12 months old; **Exclusion criteria:** any serious cardiac, immunologic, neurologic, or oncologic disease; serious respiratory disease other than bronchiolitis; more than one previous episode of obstructive airway disease; symptoms of lower airway disease (i.e. coughing) for more than 4 weeks; treated with glucocorticosteriod within the previous 4 weeks **Power analysis:** 176 subjects in each medication group would provide a power of 80% at an alpha level of 0.05
Interventions	**Treatment group:** Weight based - 10 ml of racemic adrenaline dissolved in 0.9% saline to form a solution of 20 mg per mL • < 5 kg- 0.10 mL • 5 to 6.9 kg 0.15 mL • 7 to 9.9 kg, 0.20 mL • 10 kg or more 0.25 mL **Control group:** 0.9% saline alone
Outcomes	**Primary:** LOS- definition time from the first study inhalation until discharge from the hospital **Secondary:** clinical score 30 minutes after the first inhalation, use of nasogastric feeding,
Notes	Cannot enter data into data table. The difference in LOS in children who received RE (n=203) = 63.6 hours, Range [46.2-81.0[; while the range of those who received normal saline was 64.1 hours, range [49.8, 86.4]. The Difference = 4.5, 95% CI [-6.5-15.5] and is not significant p= 0.42 There was a significant difference between subjects who received either treatment on a "On Demand" schedule vs. a "Fixed" schedule. Here the Difference = 13.7, 95% CI [2.9, 2424].

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block of eight, assignment to one of four study groups- randomization occured at a central site 1. RE scheduled 2. Placebo scheduled 3. RE intermittent

		4. Placebo intermittent
Allocation concealment (selection bias)	Low risk	Used a list of study number for use for consecutive assignment
Blinding of participants and personnel (performance bias)	Low risk	All treatments were prepared in an off-site pharmacy
Blinding of outcome assessment (detection bias)	Unclear risk	Author did not disclose
Incomplete outcome data (attrition bias)	Low risk	20% did not complete the study for various reasons, but the analyzed the primary outcome with intention to treat analysis
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

(Skjerven et al., 2015)

Methods	This is a follow up study of Skjerven 2013. Looking at the treatment response in infancy was different when subjects were ~ 2 years of age and had recurrent bronchial obstruction, atopic eczema, or allergic sensitization. It is an eight center, randomized double blind trial with a 2 by 2 factorial design; inpatients
Participants	**Setting:** Eight centers in Norway **Number randomized:** N= 404; n= 203 in the treatment group and n= 201 in the control group Enrollment only occurred as long as a physician and nurse were available. **Number completed:** N=321; n= 167 in the treatment group and n= 154 in the control group **Gender:** 59% male **Inclusion criteria:** moderate bronchiolitis (score of 4 or greater on a scale of 0-10, lower is better); less than 12 months old; **Exclusion criteria:** any serious cardiac, immunologic, neurologic, or oncologic disease; serious respiratory disease other than bronchiolitis; more than one previous episode of obstructive airway disease; symptoms of lower airway disease (i.e. coughing) for more than 4 weeks; treated with glucocorticosteriod within the previous 4 weeks **Power analysis:** 176 subjects in each medication group would provide a power of 80% at an alpha level of 0.05
Interventions	**Treatment group:** Weight based - 10 ml of racemic adrenaline dissolved in 0.9% saline to form a solution of 20 mg per mL • < 5 kg- 0.10 mL • 5 to 6.9 kg 0.15 mL • 7 to 9.9 kg, 0.20 mL • 10 kg or more 0.25 mL **Control group:** 0.9% saline alone

Outcomes	**Primary:** LOS- definition time from the first study inhalation until discharge from the hospital, strafifed by subgroups identified 2 years later. Sub groups were patients with and without recurrent bronchial obstruction, atopic eczema, or allergic sensitization by 2 years of age
Notes	Cannot enter data into data table. When the data was re analyzed (~ 2 years) after the subjects could be separated into subgroups of those who had recurrent bronchial obstruction, atopic eczema, or allergic sensitization, no effect was seen in the LOS between those who developed atopic disease and received RE or not.

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Figures:

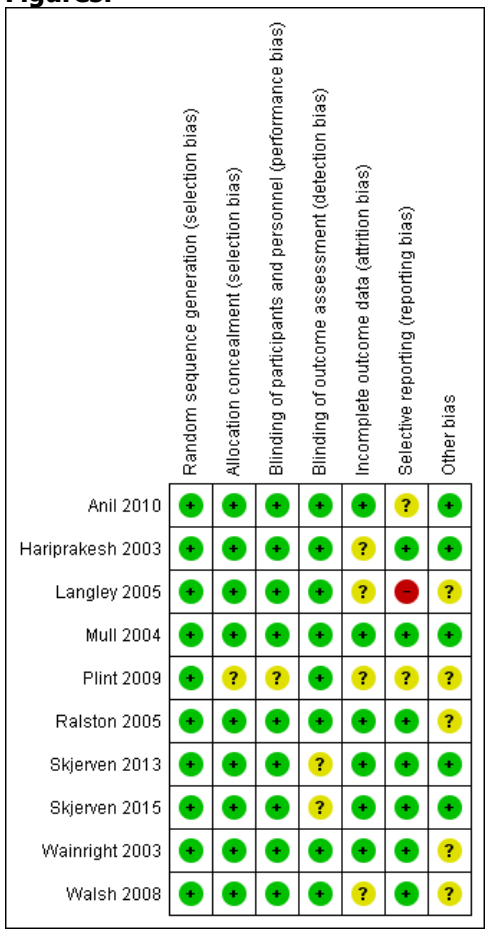

Figure: Risk of Bias Summary for included studies for racemic epinephrine and bronchiolitis.

Note: includes the following studies from Hartling, Wiebe, Russell, Patel and Klassen (2011) – Anil, 2010; Hariprakash 2003; Langley 2005; Mull 2004; Plint 2009; Ralston 2005: Wainright 2003; Walsh 2008. Skjerven 2013 and Skjerven 2015 were added to the meta-analysis for this guideline.

Synthesis Authors:
EBP Scholars: Menown, J., Pirvu, D., Shubat, S. J., Tobin, T.
Office of EBP: Allen, N. H.,
Date: October 5 2016

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Appendix E

Question 6: For the child who presents for the symptoms of bronchiolitis should glucocorticoids be used in the inpatient or outpatient settings?

GRADEpro Table:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucocorticoids (systemic and inhaled)	Control	Relative (95% CI)	Absolute		
Outpatient- Admission by day 1 (follow-up mean 1 days; assessed with: count)												
10	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	205/907 (22.6%)	20%	RR 0.92 (0.78 to 1.08)	16 fewer per 1000 (from 44 fewer to 16 more)	⨁⨁⨁◯ HIGH	CRITICAL
Outpatient- Admission by day 7 (follow-up 7 days; assessed with: count)												
6	randomized trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	231/787 (29.4%)	251/743 (33.8%)	RR 0.86 (0.7 to 1.06)	47 fewer per 1000 (from 101 fewer to 20 more)	⨁⨁⨁◯ HIGH	CRITICAL
Inpatient- Length of stay (follow-up 0.6-7 days; measured with: days; range of scores: 0.5-7; Better indicated by lower values)												
8	randomized trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	322	311	-	MD 1.08 lower (0.39 lower to 0.04 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

[1] Two of the studies (inclusive of ~ 7% of the subjects) did not report on all outcomes.

[2] Two of the studies for this outcome (inclusive of ~ 16% of subjects) did not report on all outcomes.

[3] Three of the eight studies had risk of bias (inclusive of ~36% of subjects)

Appendix F

Question 7: **For the child who presents with the symptoms of bronchiolitis should short acting beta agonists be used in the inpatient or outpatient settings?**

GRADEProTable:

Quality assessment Gadomski, & Brower (2010)							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Short acting bronchodilators**	**Control**	**Relative (95% CI)**	**Absolute**		
Oxygen Saturation by pulse oximetry inpatient and outpatient (follow-up 40-2880 Minutes[1]; measured with: SpO2; range of scores: 88.54-98.8; Better indicated by higher values)												
15	randomized trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	636	546	-	MD 0.45 lower (0.96 lower to 0.05 higher)	⨁◯◯◯ LOW	CRITICAL
Oxygen saturation by pulse oximetry, inpatients only (follow-up 40-2880 minutes; measured with: SpO2; range of scores: 93-97.2; Better indicated by higher values)												
10	randomized trials	serious[1]	serious	no serious indirectness	no serious imprecision	none	230	208	-	MD 0.29 lower (1.1 lower to 0.51 higher)	⨁◯◯◯ LOW	CRITICAL
Oxygen saturation by pulse oximetry in outpatients (follow-up 60-120 minutes[4]; measured with: SpO2; Better indicated by lower values)												
9	randomized trials	serious	serious[2,4]	no serious indirectness	very serious[3]	none	406	350	-	MD 0.57 lower (1.13 lower to 0 higher)	⨁◯◯◯ VERY LOW	CRITICAL

No improvement in clinical score inpatient (measured with: improvement in clinical score; range of scores: 0.58-6.17; Better indicated by lower values)												
7	randomized trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	239	157	-	SMD 0.20 lower (0.43 lower to 0.03 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of hospitalization (follow-up 4.5-2.17 days; measured with: hours; range of scores: 2.17-4.5; Better indicated by lower values)												
5	randomized trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	220	129	-	MD 0.06 higher (0.27 lower to 0.39 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Time to resolution of illness (measured with: days; range of scores: 5-8.9; Better indicated by lower values)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	134	135	-	MD 0.29 higher (0.43 lower to 1 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

[1] Six of ten inpatient studies gave the time outcomes were assessed.
[2] Wide range of time to assessment, varying intervals between doses, different doses
[3] There is greater precision in the inpatient studies than in the outpatient studies. Confidence intervals are wider in the outpatient studies.
[4] Only two outpatient studies described length of follow up
[5] Only two studies, low number of subjects

Search Results: A Cochrane Systematic Review Gadomski, & Brower (2010) is the source of evidence for this question
Synthesis Author(s): EBP Scholar, (Allen, N. H)
Date: 2012-06-20

Appendix G

Question 8: **For the child who presents with the symptoms of bronchiolitis, should antibiotics be used in the inpatient or outpatient settings?**

GRADEPro Table

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**Control**	**Relative (95% CI)**	**Absolute**		
Duration of symptoms (follow-up 3-10 days; measured with: days; range of scores: 4.62-9.7; Better indicated by lower values)												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	63	-	MD 0.32 higher (1.14 lower to 1.78 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Length of stay (follow-up 2-6 days; measured with: days; range of scores: 2.13-5.82; Better indicated by lower values)												
3	randomized trials	serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	143	145	-	MD 0.34 higher (0.71 lower to 1.38 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Re-admissions (follow-up 3 weeks; assessed with: Count)												
1	randomized trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/12 (8.3%)	4/9 (44.4%)	OR 0.11 (0.01 to 1.29)	364 fewer per 1000 (from 437 fewer to 63 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Deaths (assessed with: Count)												
5	randomized trials	serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/331 (0%)	212/0 (0%)	-[5]	-	⨁⨁⨁◯ MODERATE	CRITICAL
										-		

Synthesis Author(s) EBP Scholars (Allen, N. H.)
Date: 2012-12-02

Search Strategy performed:
(((((("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents"[Pharmacological Action]) OR "Macrolides"[Majr]) OR "Penicillins"[Mesh]) OR "Tetracyclines"[Mesh]) OR "Cephalosporins"[Majr]) AND ("Bronchiolitis"[Mesh] OR "Bronchiolitis, Viral"[Mesh]) AND ("child"[MeSH Terms] OR "child"[All Fields])

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