**Mini-CAT Final Name: Sierra Teegarden**

**Clinical Question:**

While on my Pediatric Rotation, an 18-month-old child presented to the Pediatric Emergency Room with her mother who stated her child has been congested with increased breathing difficulty for the past 3 days. Upon physical exam the patient was in no acute distress with stable vital signs, but auscultation of the lungs revealed diffuse wheezing. The child was diagnosed with bronchiolitis and prescribed albuterol nebulizer treatments along with supportive care. The mother asked if the albuterol would improve her child’s breathing and the Pediatrician advised that there is no consensus on whether or not to use bronchodilators for bronchiolitis, but he recommends a trial of it to see if there is improvement.

**PICO Question:** In children under two, how effective are bronchodilators like albuterol compared to placebo in improving respiratory status for bronchiolitis?

**PICO search terms:**

|  |  |  |  |
| --- | --- | --- | --- |
| **P** | **I** | **C** | **O** |
| Children under two | Bronchodilator | Placebo | Bronchiolitis improvement |
| Pediatric | Albuterol | Supportive care only | Bronchiolitis respiratory status |
| Toddlers | SABA |  | Bronchiolitis recovery |
| Peds | Ventolin |  | Bronchiolitis breathing |
| Kids | Salbutamol |  |  |

**Search tools and strategy used:**

|  |  |  |  |
| --- | --- | --- | --- |
| Database | Terms | Filter | Articles |
| Cochrane Library | Bronchiolitis Bronchodilator | Search Terms in Title Abstract Keywords | 10 |
| Scopus | Enhanced Recovery After Colorectal Surgery | Article  Review  Last 5 Years  Keyword: Colorectal Surgery  Open Access | 56 |
| Wiley Online Library | Bronchiolitis Bronchodilator | Journal Articles / Search terms in Title | 8 |
| PubMed | Bronchiolitis bronchodilator  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Bronchiolitis albuterol | Text availability: Free full Text  Article Type: case reports, clinical study, clinical trial, comparative study, controlled clinical trial, meta-analysis, observational study, randomized control trial, systematic review  Publication date: From 2000-2022 | 92  31 |
| UpToDate | Searched for “Bronchodilator treatment for bronchiolitis pediatric” and visited the “Bronchiolitis in infants and children: Treatment, outcome, and prevention” page | I selected “Interventions that are not routinely recommended.” From the outline tab and evaluated several citations related to bronchodilator use. | 3 |
| JAMA | Bronchiolitis Bronchodilator | Search All | 74 |
| TRIP Database | PICO Format: P: Pediatrics  I: Bronchodilator  C: Placebo  O: Bronchiolitis improvement | Order by Quality | 43 |
| ScienceDirect | Bronchiolitis albuterol | Article Type: Research Articles  Years: 2000-2022  Publication Title: The Journal of Pediatrics & Clinical Pediatric Emergency Medicine | 41 |
| Google Scholar | Bronchiolitis Albuterol | All search terms in title  Years: 2010-2022  Sort by Relevance | 20 |

**Results found:** 378

**Explain how you narrow your choices to the few selected articles.**

Amongst the hundreds of articles returned, only a few of them were useful in answering my research question. I started each search by broadly searching the terms “bronchiolitis bronchodilator” or “bronchiolitis albuterol” which was then further narrowed down by selecting articles with those terms directly in the title, abstract, or keywords. If results were still too wide set then I would apply additional filters such as date ranges, sorting by relevance, and selecting specific journals or types of studies. I found six articles initially for inclusion but two of the articles required access to medical journals with monetary subscriptions and therefore, were excluded since only the abstracts could be obtained. The resulting four articles met the criteria of being accessible, providing high levels of evidence, relevant patient populations, and directly answered my research question.

**Articles Chosen:**

|  |  |
| --- | --- |
| **CITATION** | Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev*. 2014;2014(6):CD001266. Published 2014 Jun 17. doi:10.1002/14651858.CD001266.pub4 |
| **ABSTRACT** | **Background** Bronchiolitis is an acute, viral lower respiratory tract infection affecting infants and is sometimes treated with bronchodilators. **Objectives** To assess the effects of bronchodilators on clinical outcomes in infants (0 to 12 months) with acute bronchiolitis. **Search methods** We searched CENTRAL 2013, Issue 12, MEDLINE (1966 to January Week 2, 2014) and EMBASE (1998 to January 2014). **Selection criteria** Randomized controlled trials (RCTs) comparing bronchodilators (other than epinephrine) with placebo for bronchiolitis. **Data collection and analysis** Two authors assessed trial quality and extracted data. We obtained unpublished data from trial authors. **Main results** We included 30 trials (35 data sets) representing 1992 infants with bronchiolitis. In 11 inpatient and 10 outpatient studies, oxygen saturation did not improve with bronchodilators (mean difference (MD) ‐0.43, 95% confidence interval (CI) ‐0.92 to 0.06, n = 1242). Outpatient bronchodilator treatment did not reduce the rate of hospitalization (11.9% in bronchodilator group versus 15.9% in placebo group, odds ratio (OR) 0.75, 95% CI 0.46 to 1.21, n = 710). Inpatient bronchodilator treatment did not reduce the duration of hospitalization (MD 0.06, 95% CI ‐0.27 to 0.39, n = 349).  Effect estimates for inpatients (MD ‐0.62, 95% CI ‐1.40 to 0.16) were slightly larger than for outpatients (MD ‐0.25, 95% CI ‐0.61 to 0.11) for oximetry. Oximetry outcomes showed significant heterogeneity (I2 statistic = 81%). Including only studies with low risk of bias had little impact on the overall effect size of oximetry (MD ‐0.38, 95% CI ‐0.75 to 0.00) but results were close to statistical significance.  In eight inpatient studies, there was no change in average clinical score (standardized MD (SMD) ‐0.14, 95% CI ‐0.41 to 0.12) with bronchodilators. In nine outpatient studies, the average clinical score decreased slightly with bronchodilators (SMD ‐0.42, 95% CI ‐0.79 to ‐0.06), a statistically significant finding of questionable clinical importance. The clinical score outcome showed significant heterogeneity (I2 statistic = 73%). Including only studies with low risk of bias reduced the heterogeneity but had little impact on the overall effect size of average clinical score (SMD ‐0.22, 95% CI ‐0.41 to ‐0.03).  Sub‐analyses limited to nebulized albuterol or salbutamol among outpatients (nine studies) showed no effect on oxygen saturation (MD ‐0.19, 95% CI ‐0.59 to 0.21, n = 572), average clinical score (SMD ‐0.36, 95% CI ‐0.83 to 0.11, n = 532) or hospital admission after treatment (OR 0.77, 95% CI 0.44 to 1.33, n = 404).  Adverse effects included tachycardia, oxygen desaturation and tremors. **Authors' conclusions** Bronchodilators such as albuterol or salbutamol do not improve oxygen saturation, do not reduce hospital admission after outpatient treatment, do not shorten the duration of hospitalization and do not reduce the time to resolution of illness at home. Given the adverse side effects and the expense associated with these treatments, bronchodilators are not effective in the routine management of bronchiolitis. This meta‐analysis continues to be limited by the small sample sizes and the lack of standardized study design and validated outcomes across the studies. Future trials with large sample sizes, standardized methodology across clinical sites and consistent assessment methods are needed to answer completely the question of efficacy. |
| **LINK/PDF** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7055016/ |

|  |  |
| --- | --- |
| **CITATION** | Cai Z, Lin Y, Liang J. Efficacy of salbutamol in the treatment of infants with bronchiolitis: A meta-analysis of 13 studies. *Medicine (Baltimore)*. 2020;99(4):e18657. doi:10.1097/MD.0000000000018657 |
| **ABSTRACT** | **Background:** To systematically evaluate the clinical efficacy of salbutamol treatment in infants with bronchiolitis. **Methods:** A systematic review and meta-analysis of randomized controlled trials (RCTs) investigating the use of salbutamol in infants with bronchiolitis was performed. The Cochrane Risk of Bias Assessment Tool was used to evaluate the quality of RCTs. Data were extracted and meta-analyzed using STATA version 12.0 (StataCorp, College Station, TX). **Results:** Thirteen RCTs, including a total of 977 participants, were assessed in the present meta-analysis. Results indicated that salbutamol therapy for bronchiolitis in infants led to an increase in respiratory rate (weighted mean difference [WMD] 2.26 [95% confidence interval {CI} 0.36–4.16]) and higher heart rate (WMD 12.15 [95% CI 9.24–15.07]). However, as a selective β2-agonist, salbutamol did not improve the clinical severity score of infants with bronchiolitis (WMD –0.11 [95% CI –0.26 to 0.03]), length of hospital stay (WMD 0.12 [95% CI –0.32 to 0.56]), or oxygen saturation (WMD 0.20 [95% CI –0.35 to 0.75]). **Conclusion:** Based on the results of this systematic review, the use of salbutamol had no effect on bronchiolitis in children <24 months of age. Moreover, the treatment can also lead to side effects, such as high heart rate. As such, salbutamol should not be recommended for treatment of bronchiolitis in infants. |
| **LINK/PDF** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004745/ |

|  |  |
| --- | --- |
| **CITATION** | Condella A, Mansbach JM, Hasegawa K, et al. Multicenter Study of Albuterol Use Among Infants Hospitalized with Bronchiolitis. *West J Emerg Med*. 2018;19(3):475-483. doi:10.5811/westjem.2018.3.35837 |
| **ABSTRACT** | **Introduction** Although bronchiolitis is a common reason for infant hospitalization, significant heterogeneity persists in its management. The American Academy of Pediatrics currently recommends that inhaled albuterol not be used in routine care of children with bronchiolitis. Our objective was to identify factors associated with pre-admission (e.g., emergency department or primary care) use of albuterol among infants hospitalized for bronchiolitis. **Methods** We analyzed data from a 17-center observational study of 1,016 infants (age <1 year) hospitalized with bronchiolitis between 2011–2014. Pre-admission albuterol use was ascertained by chart review, and data were available for 1,008 (99%) infants. We used multivariable logistic regression to identify infant characteristics independently associated with pre-admission albuterol use. **Results** Half of the infants (n=508) received at least one albuterol treatment before admission. Across the 17 hospitals, pre-admission albuterol use ranged from 23–84%. In adjusted analysis, independent predictors of albuterol use were the following: age ≥2 months (age 2.0–5.9 months [odds ratio (OR) 2.09, 95% confidence interval (CI) {1.45–3.01}] and age 6.0–11.9 months [OR 2.89, 95% CI {1.99–4.19}]); prior use of a bronchodilator (OR 1.89, 95% CI [1.24–2.90]); and presence of wheezing documented in pre-admission chart (OR 3.94, 95% CI [2.61–5.93]). By contrast, albuterol use was less likely among those with ≥7 days since the start of breathing problem (OR 0.66, 95% CI [0.44–1.00]) and parent-reported fever (OR 0.75, 95% CI [0.58–0.96]). **Conclusion** Variation in pre-admission albuterol use suggests that local practice had a strong influence on use, but that patient characteristics also influenced the decision. While we agree with current guidelines in recommending against albuterol for all infants with bronchiolitis, our understanding of possible subgroups of responders may improve through investigation of infants with the identified characteristics. |
| **LINK/PDF** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5942012/ |

|  |  |
| --- | --- |
| **CITATION** | Hartling L, Fernandes RM, Bialy L, et al. Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. *BMJ*. 2011;342:d1714. Published 2011 Apr 6. doi:10.1136/bmj.d1714 |
| **ABSTRACT** | **Objective** To evaluate and compare the efficacy and safety of bronchodilators and steroids, alone or combined, for the acute management of bronchiolitis in children aged less than 2 years.  **Design** Systematic review and meta-analysis.  **Data sources** Medline, Embase, Central, Scopus, PubMed, LILACS, IranMedEx, conference proceedings, and trial registers.  **Inclusion criteria** Randomised controlled trials of children aged 24 months or less with a first episode of bronchiolitis with wheezing comparing any bronchodilator or steroid, alone or combined, with placebo or another intervention (other bronchodilator, other steroid, standard care).  **Review methods** Two reviewers assessed studies for inclusion and risk of bias and extracted data. Primary outcomes were selected by clinicians a priori based on clinical relevance: rate of admission for outpatients (day 1 and up to day 7) and length of stay for inpatients. Direct meta-analyses were carried out using random effects models. A mixed treatment comparison using a Bayesian network model was used to compare all interventions simultaneously.  **Results** 48 trials (4897 patients, 13 comparisons) were included. Risk of bias was low in 17% (n=8), unclear in 52% (n=25), and high in 31% (n=15). Only adrenaline (epinephrine) reduced admissions on day 1 (compared with placebo: pooled risk ratio 0.67, 95% confidence interval 0.50 to 0.89; number needed to treat 15, 95% confidence interval 10 to 45 for a baseline risk of 20%; 920 patients). Unadjusted results from a single large trial with low risk of bias showed that combined dexamethasone and adrenaline reduced admissions on day 7 (risk ratio 0.65, 0.44 to 0.95; number needed to treat 11, 7 to 76 for a baseline risk of 26%; 400 patients). A mixed treatment comparison supported adrenaline alone or combined with steroids as the preferred treatments for outpatients (probability of being the best treatment based on admissions at day 1 were 45% and 39%, respectively). The incidence of reported harms did not differ. None of the interventions examined showed clear efficacy for length of stay among inpatients.  **Conclusions** Evidence shows the effectiveness and superiority of adrenaline for outcomes of most clinical relevance among outpatients with acute bronchiolitis, and evidence from a single precise trial for combined adrenaline and dexamethasone. |
| **LINK/PDF** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3071611/ |

**Summary of the Evidence**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Author (Date) | Level of Evidence | Sample/Setting  (# of subjects/ studies, cohort definition etc. ) | Outcome(s) studied | Key Findings | Limitations and Biases |
| Gadomski AM, Scribani MB. June 17 2014 | Systematic Review of 30 randomized controlled trials | -Authors searched CENTRAL, MEDLINE, and EMBASE for RCTs.  -11 inpatient studies with 495 participants and 10 outpatient studies with 747 participants were included  -Total of 1242 participants  Inclusion criteria:  -Randomized, placebo-controlled trials of bronchodilators for bronchiolitis  -Infants and young children up to 24 months with bronchiolitis  -Intervention with bronchodilator therapy including albuterol, salbutamol, terbutaline, ipratropium bromide, and adrenergic agents.  Exclusion criteria  -Interventions with inhaled corticosteroids and epinephrine.  -No placebo group  -Research protocol only without patient outcome data  -Not a randomized controlled trial  -Abstract only  -Criteria for diagnosis unclear  -Results did not meet outcomes of inclusion criteria  - RCTs included (Author Name, Year):  Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Can 1998; Chevallier 1995; Chowdhury 1995; Dobson 1998; Gadomski 1994a ‐ neb; Gadomski 1994b ‐ neb; Goh 1997; Gupta 2008; Gurkan 2004; Ho 1991; Karadag 2008; Klassen 1991; Levin 2008; Lines 1990; Lines 1992; Patel 2002; Patel 2003; Ralston 2005; Schuh 1990; Tinsa 2009; Totapally 2002; Wang 1992). | -Outcomes measured oxygen saturation by pulse oximetry, clinical score, admission to hospital, duration of hospital stay, PFTs, and time to resolution of illness. | -There was no effect of bronchodilators on oxygen saturation or clinical scores. [MD -0.43] [95% CI -0.92 to 0.06]  -Infants hospitalized for bronchiolitis showed no significant benefit of bronchodilator treatment.  -Bronchodilators do not reduce the need for hospitalization, shorten the length of stay in hospital [OR 0.75] [95% CI 0.46 to 1.21], or shorten the length of the illness at home.  -Inpatient bronchodilator treatment did not reduce the duration of hospitalization [MD 0.06] [95% CI -0.27 to 0.39, n=349]  -Side effects of bronchodilators include rapid heartbeat, decrease in oxygen and shakiness. | -The studies were generally of small size.  -Inability to identify participants who were first‐time wheezers versus recurrent wheezers in the older studies.  -There was lack of standardized methods for outcome evaluation (timing of assessments, clinical scoring systems used) and lack of standardized intervention (various bronchodilators, drug dosages, routes of administration and nebulization delivery systems) used across the studies. |
| Cai Z, Lin Y, Liang J. Jan 24 2020. | Meta-analysis of 13 randomized controlled trials | -The authors searched PubMed, EMBASE, Web of Science, CBM, and CNKI databases for relevant articles published before 1/1/2019 without any language restrictions.  -Search terms “Salbutamol or albuterol” and “infants with bronchiolitis” were adopted in the meta-analysis  -13 articles were selected  -Total of 977 participants  -Inclusion criteria  -RCTs fulfilling the following criteria: <24 months of age with acute bronchiolitis; sufficient data to calculate weighted mean differences and corresponding 95% confidence intervals; and the correlation between salbutamol treatment and children with acute bronchiolitis was estimated.  -No limitations on sex, ethnicity, disease course, or severity of disease  Exclusion criteria:  -Case reports, systematic reviews, and letters to the editor  -RCTs included  Gadomski, 1994  Cengizlier, 1997  Patel, 2002  Totapally, 2002  Patel, 2003  Khashabi, 2005  Gupta, 2008  Karadag, 2008  Aril, 2010  Ipek, 2011  Scarlett, 2012  Bawazeer, 2014  Zamani, 2015 | -Length of hospitalization  -Clinical severity score  -Oxygen saturation  -Heart rate  -Respiratory rate | -Salbutamol therapy for bronchiolitis in infants led to an increase in respiratory rate  [WMD 2.26%] [95% CI]  -Salbutamol did not improve the clinical severity score of infants with bronchiolitis [WMD -11] [95% CI -0.26 to 0.03], length of hospital stay [WMD 0.12] [95% CI -0.32 to 0.56], or oxygen saturation [WMD 20] [95% CI -0.35 to 0.75] | -Although all included RCTs included investigated bronchiolitis in infants, overestimation, and underestimation cannot be excluded due to differences in the severity of bronchiolitis.  -Many articles were eliminated due to insufficient data to calculate the WMD and corresponding 95% CI, which may have biased the conclusions.  -Characteristic information from the studies was possibly incomplete. |
| Condella A, Mansbach J, Kohei H, Dayan P, Sullivan A, Espinola J, Camargo C, May 19 2018 | Multicenter Prospective Cohort Study | -Infants were enrolled for three consecutive fall/winter seasons from 2011-2014  -1,061 enrolled participants (infants with bronchiolitis)  -17 hospitals participated spread across 14 U.S. states  -Inclusion criteria  An attending physician’s diagnosis of bronchiolitis, age < 1 year, parent/guardian able to give informed consent within 24 hours of admission, complete contact information  -Exclusion Criteria  Transfer to a participating hospital >48 hours after original admission, >24 hours since transferring to a participating hospital, a parent/guardian refusing collection or future use of biospecimens, insurmountable language barrier, certain chronic conditions, gestational age <32 weeks, the patient had met the primary endpoint of the initial five-year grant at the time of enrollment | -To identify infant characteristics independently associated with pre-admission albuterol use | -Half of the infants (n=508) received at least one albuterol treatment before admission.  -Across the 17 hospitals, pre-admission albuterol use ranged from 23–84%.  -In adjusted analysis, independent predictors of albuterol use were the following: age ≥2 months (age 2.0–5.9 months [odds ratio (OR) 2.09, 95% confidence interval (CI) {1.45–3.01}] and age 6.0–11.9 months [OR 2.89, 95% CI {1.99–4.19}]); prior use of a bronchodilator (OR 1.89, 95% CI [1.24–2.90]); and presence of wheezing documented in pre-admission chart (OR 3.94, 95% CI [2.61–5.93]).  -By contrast, albuterol use was less likely among those with ≥7 days since the start of breathing problem (OR 0.66, 95% CI [0.44–1.00]) and parent-reported fever (OR 0.75, 95% CI [0.58–0.96]). | Factors associated with pre-admission albuterol use were predominately limited to those collected during a single intake visit, including a parent interview, and could not account for all possible sources of demographic and clinical variation in pre-admission albuterol use.  -Data was not collected on the presence of clinical decision support or local quality improvement efforts, and thus, were unable to address how these may have affected hospital-specific rates of albuterol use.  -The study did not include patients who presented with bronchiolitis to the ED or another pre-hospital setting but were not later admitted to the hospital.  -The study was not designed to address clinical outcomes of albuterol use, as there is no objective clinical measurement for improvement in the pre-admission setting. |
| Hartling L, Fernandes R, Bialy L, Milne A, Johnson D, Plint A, Klassen T, Vandermeer B, April 6 2011 | Systematic Review and Meta-analysis | The authors searched Medline, Embase, Central Scopus, PubMed, LILACS, IranMedEx, conference proceedings, and trial registers  -48 RCTs were included with a total of 2897 participants  Inclusion Criteria  Randomized controlled trials of children aged 24 months or less with a first episode of bronchiolitis with wheezing comparing any bronchodilator or steroid, alone or combined, with placebo or another intervention (other bronchodilator, other steroid, standard care).  Exclusion criteria  -Studies in which any participants had a history of wheezing, respiratory distress, or a formal diagnosis of asthma.  -Studies in the intensive care setting or with intubated or ventilated participants  -Studies assessing longer courses of steroids started during the acute phase of bronchiolitis for the prevention of post-bronchiolitic wheezing.  Studies included  Abu-Shukair, 2001  Abu-Ainine, 2002  Barlas, 1998  Beek, 2007  Bentur, 2005  Berger, 1998  Bertrand, 2001  Bilan, 2007  Cade, 2000  Can 1998  Cengizlier, 1997  Chevallier, 1995  Chowdhury, 1995  Corneli, 2007  De Boeck, 1997  Gadomski, 1994  Gadomski, 1994  Goebel, 2000  Goh, 1997  Gomez-y-Lopez 2007,  Gupta, 2008  Ho, 1991  John, 2006  Karadag, 2008  Khashabi, 2005  Klassen, 1991  Klassen, 1997  Kuyucu, 2004  Menon, 1995  Mesquita, 2009  Mull, 2004  Okutan, 1998  Patel, 2003  Patel, 2002  Plint, 2009  Ralston, 2005  Richter, 1998  Roosevelt, 1996  Sanchez, 1993  Schuh, 1990  Schuh, 2002  Schuh, 1992  Teeratakulpisarn, 2007  Tinsa, 2009  Totapally, 2002  Uyan, 2002  Wainwright, 2003  Zhang, 2003 | Primary outcomes: rate of admission at day 1 and day 7 for outpatient studies and length of stay in the hospital for inpatient studies  Secondary outcomes: change in clinical score, oxygen saturation, respiratory rate, and heart rate; readmissions (for inpatients); return visits to the emergency department or any healthcare provider; and harms or adverse events | -Only adrenaline (epinephrine) reduced admissions on day 1 (compared with placebo: pooled risk ratio 0.67, 95% confidence interval 0.50 to 0.89; number needed to treat 15, 95% confidence interval 10 to 45 for a baseline risk of 20%; 920 patients).  -Unadjusted results from a single large trial with low risk of bias showed that combined dexamethasone and adrenaline reduced admissions on day 7 (risk ratio 0.65, 0.44 to 0.95; number needed to treat 11, 7 to 76 for a baseline risk of 26%; 400 patients).  -A mixed treatment comparison supported adrenaline alone or combined with steroids as the preferred treatments for outpatients (probability of being the best treatment based on admissions at day 1 were 45% and 39%, respectively).  -The incidence of reported harms did not differ.  -None of the interventions examined showed clear efficacy for length of stay among inpatients. | -Potential risk of bias in the included studies and sparsity of data for many of the outcomes and comparisons, which resulted in imprecise estimates and unknown consistency of estimates across studies.  -Risk of bias was high due to potential selective outcome reporting, incomplete outcome data, and lack of blinding.  -Reporting of sequence generation and allocation concealment was often unclear.  -Sparsity of data was a result of few studies making the same comparisons as well as variability in the choice of outcomes and timing of outcome assessments. |

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

Gadomski AM, Scribani MB. (Jun 17 2014): **Bronchodilators such as albuterol or salbutamol do not improve oxygen saturation, do not reduce hospital admission after outpatient treatment, do not shorten the duration of hospitalization and do not reduce the time to resolution of illness at home.** Given the adverse side effects and the expense associated with these treatments, bronchodilators are not effective in the routine management of bronchiolitis.

Cai Z, Lin Y, Liang J. (Jan 24 2020): **The use of salbutamol had no effect on bronchiolitis in children <24 months of age.** When considering the treatment side effects, such as high heart rate, salbutamol should not be recommended for treatment of bronchiolitis in infants.

Condella A, Mansbach J, Kohei H, Dayan P, Sullivan A, Espinola J, Camargo C (May 19 2018): This study of >1,000 infants hospitalized for bronchiolitis showed more than three-fold variation across hospitals in the use of albuterol as a pre-admission treatment. Several other factors were shown to be associated with albuterol use, including age, presence of wheezing documented in pre-admission chart, and previous use of a bronchodilator. **Factors that were associated with pre-admission albuterol use** – based on clinical data, and supported by recent cluster analyses – **suggest a promising area for future investigation of the targeted use of pre-admission albuterol among a subset of infants with bronchiolitis.**

Hartling L, Fernandes R, Bialy L, Milne A, Johnson D, Plint A, Klassen T, Vandermeer B (Apr 6 201): This systematic review shows a benefit of epinephrine in reducing day 1 admission rates from the emergency department. Evidence suggests a benefit of combined adrenaline and dexamethasone for reducing admission rates seven days after the emergency department visit. For inpatients, none of the interventions examined showed clear benefits for length of stay; however, **limited evidence suggests some benefits on clinical score for adrenaline as well as for steroids and salbutamol compared with placebo.**

**Clinical Bottom Line:**

Please include an assessment of the following:

- Weight of the evidence – summarize the weaknesses/strengths of the articles and explain how they factored into your clinical bottom line (this may recap what you discussed in the criteria for choosing the articles)

- Magnitude of any effects

- Clinical significance (not just statistical significance)

- Any other considerations important in weighing this evidence to guide practice - If the evidence you retrieved was not enough to conclude an answer to the question, **discuss what aspects still need to be explored and what the next studies will have to answer/provide (e.g. larger number, higher level of evidence, answer which sub-group benefits, etc)**

PICO Question: In children under two, how effective are bronchodilators like albuterol compared to placebo in improving respiratory status for bronchiolitis?

Clinical Bottom Line: Based on the highest quality of evidence found, Bronchodilators such as albuterol should not be used in the treatment of bronchiolitis based on no observed clinical benefit and potential side effects.

Weight of the Evidence (With Rank (**bolded number**) and Explanation):

**1.** Gadomski AM, Scribani MB. (Jun 17 2014): This study is a systematic review of 30 RCTs including 11 in patient studies and 10 outpatient studies with a total of 1242 participants. The relatively larger sample size compared to other studies and the inclusion of both inpatient and outpatient populations expands the clinical significance of the findings. Additionally, this study was published within the last 8 years meaning that the evidence is still current. The study’s objective “to assess the effects of bronchodilators on clinical outcomes in infants (0 to 12 months) with bronchiolitis” directly answers my PICO question. The inclusion and exclusion criteria were clearly defined and reflected a setting similar to my patient population. The study clearly described the sign and methodological quality features of each individual study as well. The analysis compared bronchodilators to placebo for treatment of acute bronchiolitis with outcomes measured clearly defined. The main limitation of this study was the inability to identify participants who were first-time wheezers verses recurrent wheezers in some of the studies which may have skewed the results.

**2.** Cai Z, Lin Y, Liang J. (Jan 24 2020): This study is a meta-analysis of 13 RCTs with a total of 977 participants. This study ranks second because it has less trials and a smaller sample size than Gadomski & Scribani, 2014. However, this student is the most recent, published in 2020. The study objective “to systematically evaluate the clinical efficacy of salbutamol treatment in infants with bronchiolitis” directly answers my PICO question. The inclusion criteria was very well defined but the exclusion criteria was not as well defined as Gadomski & Scribani, 2014. The analysis clearly measured the intervention of bronchodilator use with clinical outcomes such as improvement in clinical severity scores and vital signs. This study had two main limitations. First, there may have been overestimation and underestimation of outcomes. Second, the conclusion may have been biased by the elimination of many articles because of their insufficient data.

**3.** Hartling L, Fernandes R, Bialy L, Milne A, Johnson D, Plint A, Klassen T, Vandermeer B (Apr 6 2011): This study is a systematic review & meta-analysis of 48 RCTs totaling 2897 participants. Studies were a mix of inpatient and outpatient management. While this study includes more individual studies and the largest sample size of all four studies, I am ranking the level of evidence as third because a large amount of the individual studies focuses on steroid use alone or in combination with bronchodilators rather than strictly analyzing bronchodilator use. Additionally, this study excludes patients in the intensive care setting which may skew results of the overall benefit but eliminating patients of different disease severities since my original question is not limited to less severe disease states. Both the inclusion and exclusion criteria were clearly defined in this study. The analysis clearly measured steroids and bronchodilators alone and in combination with one another. There were to main limitations of this study. First, potential bias from sparsity of data on outcomes and comparisons. Second, there was a risk of bias from potential selective outcome reporting, incomplete outcome data, and black of blinding.

**4.** Condella A, Mansbach J, Kohei H, Dayan P, Sullivan A, Espinola J, Camargo C (May 19 2018): This study is ranked the lowest level of evidence because it is a prospective, cohort study while all other levels of evidence presented are systematic reviews and/or meta-analysis of randomized controlled trials. There were 17 hospitals participating across 14 U.S. states with a total of 1,061 enrolled participants making it a relatively large individual study considering this sample size is comparable to some of the systematic reviews with multiple studies combined. While this study is relevant to my PICO question, it is the least specific of all the studies. It has clear inclusion and exclusion criteria and the exclusion criteria addresses eliminating patients with potential underlying lung pathology that may skew results such as those born less than 32 weeks gestation. Limitations of this prospective, cohort study include data not collected on the presence of clinical decision support or local quality improvement efforts, no inclusion of patients who presented with bronchiolitis to the ED but were not later admitted to the hospital, and lack of design to address clinical outcomes of albuterol use since there was no objective clinical measurement for improvement in the pre-admission setting.

Magnitude of Effects:

**1.** Gadomski AM, Scribani MB. (Jun 17 2014): **Bronchodilator recipients did not show a significant improvement in oxygen saturation as measured by pulse oximetry compared to placebo**, mean difference (MD) ‐0.43, 95% confidence interval (CI) ‐0.92 to 0.06. **Improvement in clinical scores In seven trials (five inpatient and two outpatient), the clinical score of 64% of those infants treated with bronchodilators improved compared to 27% with placebo** (odds ratio (OR) for no improvement = 0.18, 95% CI 0.06 to 0.50, n = 365). The improvement in overall average clinical score was statistically significant (standardized MD (SMD) ‐0.30, 95% CI ‐0.54 to ‐0.05) but **the small magnitude of this change limits its clinical significance. Admission to hospital The rate of hospitalization was not significantly reduced in bronchodilator recipients compared with placebo recipients in outpatient studies** (11.9% versus 15.9%; OR 0.75, 95% CI 0.46 to 1.21) **Rate of hospitalization was not significantly different between oral bronchodilator or placebo groups followed in longer‐term home‐based** studies (4.5% versus 5.2%; OR 0.86, 95% CI 0.28 to 2.64). **There was no difference between bronchodilator and placebo groups in the length of hospital stay** (MD 0.06 days, 95% CI ‐0.27 to 0.39). **There is no difference between bronchodilator and placebo groups with respect to time to resolution of illness** (MD 0.29, 95% CI ‐0.43 to 1.00, n = 269). However, only two studies examined this outcome.

**2.** Cai Z, Lin Y, Liang J. (Jan 24 2020): **Salbutamol therapy for bronchiolitis in infants led to an increase in respiratory rate** (weighted mean difference [WMD] 2.26 [95% confidence interval {CI} 0.36–4.16]) and **higher heart rate** (WMD 12.15 [95% CI 9.24–15.07]). **Salbutamol did not improve the clinical severity score of infants with bronchiolitis** (WMD –0.11 [95% CI –0.26 to 0.03]), **length of hospital stay** (WMD 0.12 [95% CI –0.32 to 0.56]), or **oxygen saturation** (WMD 0.20 [95% CI –0.35 to 0.75]).

**3.** Hartling L, Fernandes R, Bialy L, Milne A, Johnson D, Plint A, Klassen T, Vandermeer B (Apr 6 2011): **Steroids with use of bronchodilators** (adrenaline or salbutamol) that followed a protocol compared with placebo and bronchodilators **showed a similar magnitude of effect (**32%) **but did not reach statistical significance** (pooled risk ratio 0.68, 95% confidence interval 0.44 to 1.05; P=0.08). Mixed treatment comparison for admissions up to day 7 identified steroids with bronchodilators as the interventions with the highest probability of being most effective.

**4.** Condella A, Mansbach J, Kohei H, Dayan P, Sullivan A, Espinola J, Camargo C (May 19 2018):

**Independent predictors of albuterol use were the following: age ≥2 months** (age 2.0–5.9 months [odds ratio (OR) 2.09, 95% confidence interval (CI) {1.45–3.01}] and age 6.0–11.9 months [OR 2.89, 95% CI {1.99–4.19}]); **prior use of a bronchodilator** (OR 1.89, 95% CI [1.24–2.90]); and **presence of wheezing documented in pre-admission chart** (OR 3.94, 95% CI [2.61–5.93]). By contrast, **albuterol use was less likely among those with ≥7 days since the start of breathing problem** (OR 0.66, 95% CI [0.44–1.00]) **and parent-reported fever** (OR 0.75, 95% CI [0.58–0.96]).

Clinical Significance:

In conclusion, children <24 months of age with bronchiolitis should not be treated with bronchodilators such as albuterol. Bronchodilators were not found to improve clinical severity scores, decrease length of hospital stay, prevent hospital admission, improve respiratory rate or oxygen saturation. In addition to no clinical benefit, bronchodilators such as short acting beta-2 agonists were found to cause side effects such as tachycardia in this patient population. Considering lack of efficacy and risk of side effects, bronchodilators have no role in the management of bronchiolitis.

Other Considerations:

The prospective, cohort trial by Condella, et. al 2018 identified a subgroup of potential responders to early generalized trials of albuterol – future research should consider further identifying this subgroup and observed clinical benefit to see if a statistically significant subgroup of patients may benefit from this therapy. Future search should also focus on areas where there is suggestion of benefit but low strength in evidence to see if the confidence in the results is altered. Last, standardized methodology across individual studies and clinical sites is needed to better determine efficacy of trials.