A Meta-analysis of Randomized Controlled Trials Evaluating the Efficacy of Epinephrine for the Treatment of Acute Viral Bronchiolitis

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Background: Controversy exists surrounding the use of bronchodilators for bronchiolitis. Epinephrine hydrochloride is being used with increasing frequency in this group; however, its efficacy has not been systematically reviewed.

Objective: To systematically review randomized controlled trials comparing inhaled or systemic epinephrine vs placebo or other bronchodilators.

Data Sources: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, primary authors, and reference lists.

Study Selection: Studies were included if they (1) were randomized, controlled trials; (2) involved children 2 years or younger with bronchiolitis; and (3) presented quantitative outcomes.

Data Extraction: Two reviewers independently extracted data and assessed study quality.

Data Synthesis: We included 14 studies (7 inpatient, 6 outpatient, and 1 patient status unknown). Thirteen of forty-five comparisons were significant. Among outpatients, results favored epinephrine compared with placebo for clinical score at 60 minutes (standardized mean difference [SMD], −0.81; 95% confidence interval [CI], −1.56 to −0.07), oxygen saturation at 30 minutes (weighted mean difference [WMD], 2.79; 95% CI, 1.50-4.08), respiratory rate at 30 minutes (WMD, −4.54; 95% CI, −8.89 to −0.19), and improvement (odds ratio, 25.06; 95% CI, 4.95-126.91); among inpatients, for clinical score at 60 minutes (SMD, −0.52; 95% CI, −1.00 to −0.03). Among outpatients, results favored epinephrine compared with albuterol sulfate (salbutamol) for oxygen saturation at 60 minutes (WMD, 1.91; 95% CI, 0.38-3.44), heart rate at 90 minutes (WMD, −14.00; 95% CI, −22.95 to −5.05), respiratory rate at 60 minutes (WMD, −7.76; 95% CI, −11.35 to −4.17), and improvement (odds ratio, 4.51; 95% CI, 1.93-10.53); among inpatients, respiratory rate at 30 minutes (WMD, −5.12; 95% CI, −6.83 to −3.41).

Conclusions: Epinephrine may be favorable compared with placebo and albuterol for short-term benefits among outpatients. There is insufficient evidence to support the use of epinephrine among inpatients. Large, multicentered trials are required before routine use among outpatients can be strongly recommended.


BRONCHIOLITIS, the most common lower respiratory tract infection in infants, is characterized by fever, coryza, cough, expiratory wheezing, and respiratory distress (ie, increased respiratory rate, chest wall indrawing, thoracoabdominal asynchrony). It is most commonly associated with viruses, with the leading cause being the respiratory syncytial virus. Overall, it is estimated that 11% to 12% of all infants are affected in the first year of life, with 1% to 2% requiring hospitalization. Because of the prevalence and morbidity associated with bronchiolitis, the economic burden placed on health care services is substantial. Despite the frequency of the condition, considerable controversy remains regarding its management. Historically, children have been offered supportive care, including oxygen and supplemental fluids. Recently, clinical trials have provided conflicting evidence regarding the benefit of pharmacological interventions. Much of the debate involves the role of bronchodilators.

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Although in common use, the efficacy of bronchodilators in this patient group has not been universally accepted. Two recent systematic reviews have found insufficient empirical support for widespread use of bronchodilators. Flores and Horwitz reviewed 8 randomized controlled trials (RCTs) to evaluate the efficacy of β2-agonists in bronchiolitis. Among 3 inpatient studies, the results were contradictory with respect to improved clinical scores, duration of hospital stay, and oxygen satu-
rator. Among the 5 outpatient studies, there was no bene-

fit in terms of hospitalization rate or respiratory rate. The
reviewers found a statistically significant improvement in 

oxygen saturation and heart rate, but the results were deemed to be not clinically significant.

Kellner and colleagues reviewed 20 RCTs, 18 of which 

examined β-agonists and 2, epinephrine hydrochloride. 

The review grouped all bronchodilators and compared these 

with placebo; they did not examine the relative efficacy of 

different bronchodilators. The reviewers found modest 

short-term improvements in clinical score among chil-

dren with mild and moderate bronchiolitis. The results for 

oxygen saturation were inconclusive owing to heteroge-

neity between studies. They found no significant improve-

ment in rate or duration of hospitalization. These authors 

concluded that bronchodilators could not be recom-

mended for routine management in first-time wheezers.

Although different nebulized bronchodilators such as 

albuterol sulfate (salbutamol), ipratropium bromide, and 

epinephrine are being used in the treatment of bronchiol-

itis, research to date supports epirolephrine as the broncho-

dilator of choice. Along with the β-adrenergic effects of 

bronchodilation, epinephrine adds α-adrenergic proper-

ties and is believed to offer the supplemental benefits of 

vasoconstriction in the bronchiolar vasculature. Along with 

others, Wohl and Chernick have suggested that this va-

soconstriction may reduce edema and mucous produc-

tion, hallmarks in the pathology of acute viral bronchi-

olitis. Because of the unique mechanism of action of 

epinephrine and its increasing use in infants with bron-

chiolitis, we chose to specifically investigate the efficacy of 

this drug in the treatment of bronchiolitis. Thus, the 

objective of this study was to review RCTs that compared 

the effects of inhaled or systemic epinephrine vs placebo or other 

bronchodilators in infants and young children (age, ≤2 

years) with bronchiolitis.

CRITERIA FOR INCLUDING STUDIES

All RCTs evaluating the efficacy of epinephrine vs placebo or of 

epinephrine vs other bronchodilators in the treatment of bron-

chiolitis were considered for inclusion, regardless of language 

or publication status. All studies involving infants and young chil-

dren 2 years or younger were eligible for inclusion. Bronchiol-

itis was defined as wheezing (with or without cough, tachy-

pnea, and increased respiratory effort) associated with clinical 

evidence of a viral infection (eg, coryza and fever). Studies of in-

patients and outpatients were included. Studies were included if 

they reported on at least 1 of the following outcome mea-

ures: clinical score, oxygen saturation (oximetry), admission to 

the hospital (rate of hospitalization), length of hospital stay, res-

piratory rate, heart rate, and results of pulmonary function tests.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches of MEDLINE (January 1966 through December 2000), 

EMBASE (January 1988 through December 2000), and The 

Cochrane Central Register of Controlled Trials were con-

ducted using the following terms: epinephrine, bronchilolitis, res-

piratory syncyntial viruses, respiratory syncyntial Pneumovirus, res-

piratory syncyntial virus, and adrenalin. The complete search 

strategies are available from the authors on request. We exam-

ined the reference lists of all selected articles for relevant stud-

ies. Primary authors of relevant trials were contacted for informa-

tion on additional trials. We searched PubMed at the end of 

the project (September 2002) to identify any recent studies.

STUDY SELECTION

The initial search of all of the databases and reference lists was 
screened independently by 2 of us (L.H. and K.R.) to identify 
citations with potential relevance. The full text of selected ar-

ticles was obtained. The 2 reviewers independently decided on 

trial inclusion using a standard form with predetermined eli-

gibility criteria. Disagreements were resolved by consensus 

reached after discussion.

QUALITY ASSESSMENT

Study quality for English-language studies was assessed independ-

ently by 2 of us (reviewers K.R., T.P.K., or L.H.); study quality 
of the Turkish reports was assessed by an independent reviewer.

Quality was assessed on the basis of published reports in peer-

reviewed journals when available; for 1 trial, quality assessment 

was based on the abstract and unpublished information from the 

author, as the manuscript was not yet available. Each study was 

evaluated using the Jadad 5-point scale to assess randomization 

(0-2 points), double blinding (0-2 points), and withdrawals and 

dropouts (0-1 point). The Jadad scale was chosen because it is 

the only quality assessment tool, to the best of our knowledge, 

that has been validated, and it incorporates components that are 
directly related to the control of bias. Concealment of allocation 
was assessed as adequate, inadequate, or unclear. Differences in 

quality ratings were resolved through discussion.

DATA EXTRACTION

Data from the English-language studies were extracted independ-

ently by 2 of us (L.H. and K.R.); data were extracted from the 

Turkish reports by a single individual. Additional data were re-

quested from authors as necessary. A standard form was used 

that described the following: characteristics of the study (de-

sign, method of randomization, and withdrawals/dropouts), par-

ticipants (age and sex), intervention (type, dose, route of ad-

ministration, timing and duration of therapy, and cointerventions), 

control (agent and dose), outcomes (types of outcome mea-

ures, timing of outcomes, complications, and adverse events), 

whether the study used an intention-to-treat protocol, funding 

source, and results. Data were entered into RevMan 4.1 (The 


and checked for accuracy by a second reviewer (L.H.).

Individual patient clinical score data were extracted from 

graphs for 1 study. Means were extracted from graphs for 4 stud-

ies, SDs for 1, and 95% confidence limits for 1. One trial 

used a crossover design; therefore, only data from the first phase 

were used in the meta-analysis. This same study included 2 pla-

cbeo groups; data from both groups were pooled. In some cases, 

variance was imputed from confidence intervals (CIs) and 

SEs. To calculate the variance of change in oximetry in 1 study, 

the end time-point SDs were substituted with the baseline SDs. 

Finally, for 1 study, the mean SDs from other studies were 

substituted for missing SDs for the clinical score outcomes.

DATA ANALYSIS

Analyses were performed using RevMan 4.1 (The Cochrane Col-

laboration, Oxford, England, 2000) and Splus 2000 (Insightful 

Corporation, Seattle, Wash, 1999). Separate analyses were con-

ducted for the 2 types of control groups (ie, placebo and nonepi-

nephrine bronchodilators) and patient status (ie, inpatient or 

outpatient). Dichotomous data (eg, improvement) were ex-
pressed as Mantel-Haenszel odds ratios, and a common Mantel-Haenszel odds ratio with 95% CIs was calculated. The number needed to treat was derived for significant results to help clarify the degree of possible benefit for the averaged (inverse-variance method) baseline rates. There were too few studies to check whether the relative risk was constant across different baseline rates; therefore the numbers needed to treat were not provided for a range of baseline rates. The changes in clinical score and oximetry were calculated using baseline and time-point data; a correlation of 0.5 was assumed. The clinical scores were converted to a standardized mean difference because the 14 studies used a total of 6 different clinical scores. An overall standardized mean difference was “the difference between 2 means divided by the estimate of the within-group standard deviation.” Other continuous data (eg, oximetry, heart rate, respiratory rate, and length of stay) were converted to the mean difference, and an overall weighted mean difference (with 95% CIs) was calculated. When mean differences (difference between treatment group means) are pooled by the inverse variance method, each mean difference is “the difference between 2 means divided by an estimate of the within-group standard deviation.” The Respiratory Distress Assessment Instrument; RDI, Respiratory Distress Index; RR, respiratory rate; SaO2, arterial oxygen percent saturation.

Abbreviations: HR, heart rate; LOS, length of stay; RACS, respiratory assessment change score; RDAI, Respiratory Distress Assessment Instrument; RDI, Respiratory Distress Index; RR, respiratory rate; SaO2, arterial oxygen percent saturation.

*Refers to study groups used in meta-analysis.
†Delivered via nebulizer in all studies except Lowell et al,9 in which delivery was subcutaneous.

### RESULTS

The results reported in this article differ slightly from those in a previously published abstract,20 as 5 trials were subsequently added.

### DESCRIPTION OF STUDIES

Seventy-six unique references were identified (the full list of references is available from the authors). Twenty-five studies were identified as being potentially relevant. Fourteen studies met the inclusion criteria,6,9,16,17,21-24; there was 100% agreement between the 2 reviewers with respect to study inclusion. The included studies are described in **Table 1**. The studies were generally small, but ranged in sample size from 30 to 194. Most studies (n = 12) were published in English, with 2 published in Turkish.10,21 The studies were conducted in a variety of primarily high-income countries.

A wide range of outcomes was reported. Table 1 describes the primary outcomes studied in each trial. Secondary outcomes included clinical score; oxygen saturation; respiratory rate; heart rate; blood pressure; activity status; time receiving oxygen; highest oxygen flow rates; need for supplemental parenteral fluids; transcutaneous oxygen and carbon dioxide tensions; time from admission to normal oxygenation, adequate intake, and minimal respiratory distress; pulmonary mechanics; duration of hospitalization; rate of hospitalization; and improvement as defined by the individual trials.

Although most studies measured clinical scores, a number of different scoring systems were used, and the scores were reported in different ways (Table 1 and **Table 2**). The Respiratory Distress Assessment Instru-

### Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. of Participants per Study Group*</th>
<th>Inpatient vs Outpatient</th>
<th>Clinical Score</th>
<th>Wheezing History</th>
<th>Primary Outcome</th>
<th>Type of Epinephrine†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboul-Ainine and Luyt11</td>
<td>England</td>
<td>19 Epinephrine hydrochloride; 19 placebo</td>
<td>In</td>
<td>RDAI</td>
<td>First time</td>
<td>RR, HR</td>
<td>L-epinephrine</td>
</tr>
<tr>
<td>Barlas et al25</td>
<td>Turkey</td>
<td>15 Epinephrine; 15 placebo; 14 albuterol</td>
<td>Out</td>
<td>Barlas et al25</td>
<td>Unknown</td>
<td>Clinical score</td>
<td>Racemic</td>
</tr>
<tr>
<td>Bertrand et al24</td>
<td>Chile</td>
<td>16 Epinephrine; 14 albuterol</td>
<td>In</td>
<td>Tal et al25</td>
<td>First time</td>
<td>Clinical score</td>
<td>L-epinephrine</td>
</tr>
<tr>
<td>Kristånnson et al15</td>
<td>Sweden/Norway</td>
<td>15 Epinephrine; 14 placebo</td>
<td>In</td>
<td>Kristånnson et al15</td>
<td>Mixed</td>
<td>Clinical score</td>
<td>Racemic</td>
</tr>
<tr>
<td>Hariprakash et al23</td>
<td>England</td>
<td>30 Epinephrine; 30 placebo</td>
<td>Out</td>
<td>RDAI</td>
<td>First time</td>
<td>Admission rate</td>
<td>L-epinephrine</td>
</tr>
<tr>
<td>Lowell et al26</td>
<td>United States</td>
<td>16 Epinephrine; 14 placebo</td>
<td>Out</td>
<td>RACS (RDAI)</td>
<td>First time</td>
<td>Clinical score</td>
<td>Racemic</td>
</tr>
<tr>
<td>Menon et al27</td>
<td>Canada</td>
<td>20 Epinephrine; 21 albuterol</td>
<td>Out</td>
<td>RDAI</td>
<td>First time</td>
<td>SaO2</td>
<td>L-epinephrine</td>
</tr>
<tr>
<td>Mull et al22</td>
<td>United States</td>
<td>30 Epinephrine; 32 albuterol</td>
<td>Unknown</td>
<td>RDAI</td>
<td>First time</td>
<td>Clinical score</td>
<td>Racemic</td>
</tr>
<tr>
<td>Okutan et al23</td>
<td>Turkey</td>
<td>16 Epinephrine; 19 albuterol; 19 placebo</td>
<td></td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al21</td>
<td>Canada</td>
<td>5 Epinephrine; 51 albuterol; 48 placebo</td>
<td></td>
<td>RDAI</td>
<td>First time</td>
<td>LOS</td>
<td>Racemic</td>
</tr>
<tr>
<td>Ray and Singh23</td>
<td>India</td>
<td>45 Epinephrine; 46 albuterol</td>
<td>Out</td>
<td>RDAI, Yale Observation Scale</td>
<td>Mixed</td>
<td>Clinical score</td>
<td>Racemic</td>
</tr>
<tr>
<td>Reijonen et al24</td>
<td>Finland</td>
<td>24 Epinephrine; 27 albuterol; 49 placebo</td>
<td></td>
<td>RDAI</td>
<td>First time</td>
<td>SaO2</td>
<td>L-epinephrine</td>
</tr>
<tr>
<td>Sanchez et al26</td>
<td>Canada</td>
<td>12 Epinephrine; 12 albuterol</td>
<td>In</td>
<td>Tal et al25</td>
<td>First time</td>
<td>Clinical score LOs, ready for discharge</td>
<td>Racemic</td>
</tr>
<tr>
<td>Wainwright et al25</td>
<td>Australia</td>
<td>99 Epinephrine; 99 placebo</td>
<td>In</td>
<td>None</td>
<td></td>
<td></td>
<td>L-epinephrine</td>
</tr>
</tbody>
</table>

Abbreviations: HR, heart rate; LOS, length of stay; RACS, respiratory assessment change score; RDAI, Respiratory Distress Assessment Instrument; RDI, Respiratory Distress Index; RR, respiratory rate; SaO2, arterial oxygen percent saturation.

*Refers to study groups used in meta-analysis.
†Delivered via nebulizer in all studies except Lowell et al,9 in which delivery was subcutaneous.
ment was the scoring system most commonly used. It was used in 7 studies, but in 2 of these studies, scores were not reported. In 1 study, the authors reported the mean time to a Respiratory Distress Assessment Instrument score of no greater than 4, and in another study, the authors reported only a P value for the mean change in score. The remaining studies used a variety of partially validated or unvalidated scales that measured different clinical features of bronchiolitis.

Most studies conducted short-term follow-up of up to 4 hours, whereas 3 studies followed up inpatients during their hospital stay (herein referred to as longer-term outcomes). In addition, 1 outpatient study evaluated 72-hour relapse rates, and 1 inpatient study asked general physicians to notify the study personnel of any deterioration in the patients’ condition during the 48-hour postdischarge period (no data presented).

**METHODOLOGICAL QUALITY OF INCLUDED STUDIES**

The methodological quality of studies is reported in Table 3. Three studies received pharmaceutical sponsorship, funding was received from other external sources in 6 trials, and the source of funding was not mentioned in 4 trials, and 2 studies received no funding. Two studies conducted an intention-to-treat analysis. Four studies reported withdrawals and excluded these from the analysis. Eight studies did not report any withdrawals.

**EPINEPHRINE VS PLACEBO**

Results were stratified by inpatient vs outpatient status. Five inpatient studies compared epinephrine and placebo. Only 1 of the 10 inpatient outcomes demonstrated a significant difference between treatment groups; change in clinical score at 60 minutes favored epinephrine.

Three studies compared epinephrine and placebo among outpatients. Five of 10 outcomes were significant. Change in clinical score at 60 minutes after treatment, change in oxygen saturation at 30 minutes after treatment, respiratory rate at 30 minutes after treatment (weighted mean difference [WMD], −4.54; 95% CI, −8.89 to −0.19), and improvement favored epinephrine. In 1 study, improvement was defined as a positive change in the respiratory assessment change score of at least 4 U, and in the other study, it was not defined. Heart rate at 60 minutes after treatment favored placebo. Admission rates (Figure 1), change in clinical score at 30 minutes after treatment, change in oxygen saturation at 60 minutes after treatment, and heart rate at 30 minutes after treatment were not significantly different between the treatment arms. Sensitivity analyses using fixed-effects models found 1 significant difference favoring epinephrine in change in clinical score at 30 minutes. One Turkish study did not indicate its inpatient/outpatient status. This study reported a significant change in clinical score at 60 minutes favoring epinephrine compared with placebo.

**EPINEPHRINE VS ALBUTEROL**

Table 5 presents the results of epinephrine vs albuterol. Four studies compared epinephrine with albuterol among inpatients. Only 1 of the 7 outcomes was statistically significant: respiratory rate at 30 minutes favored epinephrine compared with albuterol (WMD, −5.12; 95% CI, −6.83 to −3.41). The clinical scores, oxygen saturation, heart rate, and length of stay outcomes showed no significant difference.

Four outpatient studies reported on the epinephrine-albuterol comparison. Four of 16 outcomes showed the following statistically significant differences between treatment groups: change in oxygen saturation at 60 minutes, change in heart rate at 90 minutes (WMD, −14.00; 95% CI, −22.95 to −5.05), respiratory rate at 60 minutes (WMD, −7.76; 95% CI, −11.35 to −4.17), and improvement after treatment significantly favored epinephrine. Improvement in 1 study referred to patients in whom moderate and severe distress was converted to normal or mild distress after intervention; the other study did not define improvement. One outcome, the incidence of pallor at 30 minutes after treatment, favored albuterol. Sensitivity analyses using fixed-effects models found significant differences favoring epinephrine for change in clinical score at 60 minutes and admissions. In addition, fixed-effects analyses for heart rate at 60 minutes favored albuterol.

One Turkish study did not indicate its patient status (inpatients vs outpatients); neither of its 2 change-in-clinical-score outcomes was significant.

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Table 2. Description of Clinical Scores Used in the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Validated</th>
<th>Maximum Points</th>
<th>Retractions and Indrawing</th>
<th>Respiratory Rate</th>
<th>Wheezing</th>
<th>Cyanosis</th>
<th>Auscultatory Sounds</th>
<th>General Condition</th>
<th>Nostril Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDAI</td>
<td>Partially</td>
<td>17</td>
<td>0-9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RAS</td>
<td>Partially</td>
<td>*</td>
<td>*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RDI†</td>
<td>Unclear</td>
<td>9</td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kristánsson et al‡</td>
<td>No</td>
<td>10</td>
<td>0-2</td>
<td>0-2</td>
<td>NA</td>
<td>0-2</td>
<td>0-2</td>
<td>NA</td>
<td>0-3</td>
</tr>
<tr>
<td>Barlas et al¶</td>
<td>No</td>
<td>15</td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
<td>NA</td>
<td>NA</td>
<td>0-3</td>
<td>NA</td>
</tr>
<tr>
<td>Tal et al§ (modified from Bierman and Pierson)</td>
<td>Partially</td>
<td>12</td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not measured by the score; RACS, respiratory assessment change score; RDAI, Respiratory Distress Assessment Instrument; RDI, Respiratory Distress Index.

*Based on the RDAI; it is the sum of the change in each variable.

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Table 3. Description of Clinical Scores Used in the Included Studies

<table>
<thead>
<tr>
<th>Study Validated</th>
<th>Maximum Points</th>
<th>Retractions and Indrawing</th>
<th>Respiratory Rate</th>
<th>Wheezing</th>
<th>Cyanosis</th>
<th>Auscultatory Sounds</th>
<th>General Condition</th>
<th>Nostril Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partially</td>
<td>17</td>
<td>0-9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
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<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
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<td>10</td>
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<td>0-3</td>
<td>NA</td>
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<td>0-3</td>
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</tr>
<tr>
<td>Partially</td>
<td>12</td>
<td>0-3</td>
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<td>0-3</td>
<td>NA</td>
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</tr>
</tbody>
</table>
**OTHER OUTCOMES**

Only 1 study evaluated pulmonary mechanics among 24 patients randomized to receive epinephrine or albuterol. Significant differences between pretreatment and posttreatment values were noted in inspiratory, expiratory, and total pulmonary resistance in the epinephrine group, but not the albuterol group. There were no significant differences compared with baseline values in either group with respect to tidal volume, minute ventilation, dynamic compliance, or duration of inspiration as a fraction of total breath duration.

Because of the small number of studies that evaluated longer-term outcomes, some of these outcomes were not included in the meta-analysis. The largest trial, conducted by Wainwright et al, randomized 194 inpatients to epinephrine or placebo and found no differences between groups in length of stay or time ready for discharge. The second largest trial involved 149 inpatients randomized to epinephrine, albuterol, or placebo and found no significant difference between groups in length of stay or any secondary outcomes. Bertrand et al followed up 30 inpatients randomized to epinephrine or albuterol and found no statistically significant differences in length of stay or

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For a more detailed analysis, please refer to the original text.
duration of oxygen therapy, although the trend favored epinephrine. Mull et al\textsuperscript{6} assessed the relapse rate at 72 hours after treatment among 66 outpatients randomized to epinephrine or albuterol and found no significant difference.

Three studies reported on patient return to the hospital or emergency department after the study. Sanchez et al\textsuperscript{14} found that only 3 of 24 patients (treatment group not specified) were readmitted to the hospital for acute wheezing during a 6- to 10-month follow-up period; Bertrand et al\textsuperscript{21} found that no patients were readmitted in the 2 weeks after discharge from the hospital; and Patel et al\textsuperscript{24} reported that 93 of 149 infants (21 receiving epinephrine; 21, albuterol; and 25, placebo) had a medical visit in the week after discharge, that 8 of these visits (1 patient receiving epinephrine; 3, albuterol; and 4, placebo) were to the emergency department, and that 3 patients (receiving placebo) were readmitted. One study noted that children were sent home receiving oral medication but did not specify the type.\textsuperscript{23}

**COMMENT**

The objective of this study was to provide some resolution to the uncertainty in the literature regarding the use of epinephrine in the treatment of bronchiolitis. Some evi-

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**Table 5. Comparison of Epinephrine vs Albuterol by Inpatient/Outpatient Status**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Subjects</th>
<th>Summary Measure</th>
<th>Overall Effect Measure* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in clinical score 30 minutes after treatment</td>
<td>3</td>
<td>105</td>
<td>SMD</td>
<td>−0.43 (−1.01 to 0.16)</td>
</tr>
<tr>
<td>Change in clinical score 30 minutes after treatment after 24 h</td>
<td>1</td>
<td>30</td>
<td>SMD</td>
<td>0.11 (−0.61 to 0.83)</td>
</tr>
<tr>
<td>Change in clinical score 30 minutes after treatment after 36 h</td>
<td>1</td>
<td>30</td>
<td>SMD</td>
<td>0.55 (−0.18 to 1.29)</td>
</tr>
<tr>
<td>Change in oxygen saturation 30 minutes after treatment</td>
<td>2</td>
<td>75</td>
<td>WMD</td>
<td>0.21 (−0.73 to 1.14)</td>
</tr>
<tr>
<td>Length of stay, h</td>
<td>2</td>
<td>131</td>
<td>WMD</td>
<td>−3.96 (−25.55 to 17.62)</td>
</tr>
<tr>
<td><strong>Outpatients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in clinical score 30 minutes after treatment</td>
<td>2</td>
<td>107</td>
<td>SMD</td>
<td>−0.08 (−0.84 to 0.69)</td>
</tr>
<tr>
<td>Change in clinical score 60 minutes after treatment</td>
<td>4</td>
<td>228</td>
<td>SMD</td>
<td>−0.21 (−0.74 to 0.32)\textsuperscript{†}</td>
</tr>
<tr>
<td>Change in clinical score 90 minutes after treatment</td>
<td>2</td>
<td>107</td>
<td>SMD</td>
<td>−0.32 (−0.82 to 0.19)</td>
</tr>
<tr>
<td>Change in oxygen saturation 30 minutes after treatment</td>
<td>2</td>
<td>132</td>
<td>WMD</td>
<td>−1.31 (−3.15 to 5.76)</td>
</tr>
<tr>
<td>Change in oxygen saturation 60 minutes after treatment</td>
<td>3</td>
<td>162</td>
<td>WMD</td>
<td>1.91 (0.38 to 3.44)</td>
</tr>
<tr>
<td>Change in oxygen saturation 90 minutes after treatment</td>
<td>1</td>
<td>41</td>
<td>WMD</td>
<td>−0.68 (−2.39 to 1.03)</td>
</tr>
<tr>
<td>Improvement‡</td>
<td>2</td>
<td>120</td>
<td>OR</td>
<td>4.51 (1.93 to 10.53)</td>
</tr>
<tr>
<td>Admission rates</td>
<td>4</td>
<td>228</td>
<td>OR</td>
<td>6.00 (1.33 to 27.00)</td>
</tr>
<tr>
<td>Incidence of pallor 30 minutes after treatment</td>
<td>1</td>
<td>41</td>
<td>OR</td>
<td>2.78 (1.61 to 11.11)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NNT, number needed to treat; OR, odds ratio; SMD, standardized mean difference; WMD, weighted mean difference.

*Boldface results significantly favor epinephrine hydrochloride except where indicated.
†Significant with fixed-effect estimates and favors epinephrine.
‡Defined within the individual studies.
§Given an albuterol sulfate risk of 22% (95% CI, 11%-32%) for not improving.
‖Given an albuterol risk of 50% (95% CI, 38%-62%) for not being admitted.
dence supports the use of epinephrine among outpa-
tients. The combined results of the outpatient studies fa-
vored epinephrine compared with albuterol in terms of
oxygen saturation at 60 minutes, heart rate at 90 minutes,
respiratory rate at 60 minutes, and improvement. These re-
sults are based on a small number of studies of varying qual-
ity. Some evidence also suggests that epinephrine is favor-
able compared with placebo among outpatients in terms of
clinical score at 60 minutes after treatment, oxygen satu-
ration at 30 minutes after treatment, heart rate at 60 min-
utes after treatment, and overall improvement. None of the
studies reported any significant adverse effects resulting from
the administration of epinephrine, although 1 study re-
ported significantly less pallor at 30 minutes after treat-
ment in the albuterol group.

Because of the small number of studies for each com-
parison, we did not have the ability to examine the rela-
tive efficacy of epinephrine among other potentially im-
portant subgroups such as first-time vs recurrent wheezers,
severity of illness, specific viral etiology, age, and stage of
the disease. We also did not have the ability to assess dif-
f erent forms of delivery such as type of epinephrine, route
deivery, number of administrations, and dosage. We used a
more liberal definition of bronchiolitis, as is com-
mon in North America and parts of Europe. The results
should be interpreted in light of this.

Several factors may contribute to the lack of consis-
tency in the findings. First, there may be no differ-
ence between treatment with epinephrine vs treatment
with albuterol or placebo, and any significant findings
may have been spurious associations resulting from mul-
tiple comparisons.
The efficacy of the drug may be different for vari-
ous subgroups (eg, outpatients vs inpatients). The sub-
grouping of outpatients vs inpatients may be a proxy for
severity of illness, as those admitted may be more se-
verely affected, later in the course of the disease, or more
resistant to treatment. Continued focused evaluation
within these subgroups is warranted.

Six different scoring systems were used across the
component studies, which resulted in statistically signifi-
cant heterogeneity between studies. Multiple compar-
isons between clinical scores at different time points, among
different subgroups (outpatients and inpatients), and for
the different controls (albuterol and placebo) were per-
formed, and only 3 of 14 comparisons resulted in statis-
tically significant results. It is possible that these were spu-
rious findings. Alternatively, the scoring systems may not
be sensitive to clinically important differences. They may
not measure, or may measure differentially, the clinical
improvement in bronchiolitis. There is clearly a need to eval-
uate the clinical scores currently in use. Validation and
checking sensitivity of the scores used in individual trials
would facilitate comparisons between studies.

More than a dozen different outcome measures were
evaluated within the component trials. Because of the lack
of consistency in the outcomes reported, there were few
studies within each comparison. In primary studies, as in
meta-analyses, care needs to be taken to specify the
outcomes a priori to avoid bias that can arise if only those
outcomes with significant results are reported.

The quality of the trials was moderate, with a median
Jadad score of 3. All studies were described as random, but
only 4 studies described an appropriate method of ran-
donization. Twelve of the 14 studies were described as
double-blind, but only 5 studies described an appropriate
method of double blinding. Inadequate blinding can over-
estimate the effect, which could skew the results in favor
of either treatment, depending on the biases of the investi-
gators. Investigators should be aware that adequate blin-
ding is of particular concern in a study of epinephrine for 2
reasons. First, some investigators have noted reddish na-
sal discharge after administration of epinephrine. How-
however, in a large trial by Patel et al, no instances of red na-
sal discharge were reported; the investigators suggested that
this may be related to the age of the medication. Second,
perioral pallor results with nebulized epinephrine. This is
a concern in studies where a postmask assessment does not
allow sufficient time for the pallor to dissipate (eg, 30
minutes). This issue is of most importance in studies that
compare epinephrine with placebo vs those that compare
epinephrine with albuterol, since many of the short-term
adverse effects of albuterol are similar to those of epineph-
rine. Only 4 studies provided an adequate description of
withdrawals and dropouts. Six studies reported adequate
allocation concealment. Studies that do not properly con-
ceal treatment allocation can overestimate treatment ef-
fec t by as much as 40%.8

Figure 2. Metagraph of length of hospital stay (LOS) among inpatients. CI indicates confidence interval; WMD, weighted mean difference.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Epinephrine Group, No. of Inpatients/ Mean (SD) LOS</th>
<th>Control Group, No. of Inpatients/ Mean (SD) LOS</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine Hydrochloride vs Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al16</td>
<td>2002</td>
<td>50/59.8 (62)</td>
<td>48/63.3 (47)</td>
<td>–3.5 (–25.23 to 18.23)</td>
</tr>
<tr>
<td>Wainwright et al16 (In Press)</td>
<td></td>
<td>99/55.3 (40.61)</td>
<td>95/61.9 (42.77)</td>
<td>–6.6 (–13.35 to 5.15)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>–5.9 (–16.23 to 4.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine vs Albuterol Sulfate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertrand et al17</td>
<td>2001</td>
<td>16/98.4 (105.6)</td>
<td>14/124.8 (89.76)</td>
<td>–26.4 (–96.32 to 43.52)</td>
</tr>
<tr>
<td>Patel et al24</td>
<td>2002</td>
<td>50/59.8 (62)</td>
<td>51/61.4 (54)</td>
<td>–1.6 (–24.29 to 21.09)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>–3.96 (–25.55 to 17.62)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Much controversy has surrounded the use of bronchodilators for bronchiolitis. Recent evidence has suggested that epinephrine hydrochloride may offer some clinical benefit. Epinephrine is being used with increasing frequency in this group; however, its efficacy has not been systematically reviewed.

There is insufficient evidence to support the use of epinephrine for the treatment of bronchiolitis among inpatients. Some evidence suggests that epinephrine may be favorable compared with albuterol sulfate and placebo among outpatients. Further research needs include (1) a number of large, multicentered trials to examine the effectiveness of epinephrine compared with placebo and albuterol for infants presenting to the emergency department; and (2) development and validation of a reliable scoring system that is sensitive to important clinical changes in patients with bronchiolitis.

Finally, the meta-analysis may not have sufficient power to detect statistically significant differences between treatment groups. We calculated the power that the combined studies had to detect a simply pooled difference in the outcomes with largest combined sample size per comparison and patient status group. In a single trial with the same number of patients, there would have been only 7% to 57% power to detect a difference in these various comparisons. There would be less power for the other clinical score outcomes for which there were fewer studies and patients. The implication of this finding is that a number of large trials is needed to substantiate the relative efficacy of epinephrine in the treatment of bronchiolitis.

Some evidence suggests that epinephrine may be favorable compared with albuterol and placebo among outpatients. There is insufficient evidence to support the use of epinephrine for the treatment of bronchiolitis among inpatients. A validated, reliable scoring system is needed that is sensitive to important clinical changes in patients. The appropriateness of a scoring system may vary depending on the context in which it is used; eg, for acute changes, a clinical scoring system may be adequate, but for longer-term changes, inclusion of quality-of-life measures may be more appropriate (impact on feeding, family life, anxiety, difficulty breathing, etc). The use of a validated, reliable, and responsive scoring system would facilitate comparison of results across studies. A number of large, multicentered trials are required to examine the effectiveness of epinephrine compared with placebo and albuterol for infants presenting to the emergency department.

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This review has been registered with the Cochrane Collaboration. Regular updates will be available in the Cochrane Library.

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REFERENCES