The Effectiveness of Dexamethasone as Adjunctive Therapy to Racemic Epinephrine for a Pediatric Patient With Bronchiolitis

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The Effectiveness of Dexamethasone as Adjunctive Therapy to Racemic Epinephrine for a Pediatric Patient With Bronchiolitis

Abstract
Background: Bronchiolitis is a lower respiratory tract infection that is most common in the pediatric population, and is the major cause of hospitalizations for patients in their first year of life. Despite the prevalence of this disease, a consensus for optimal treatment is elusive. Although numerous studies have addressed dexamethasone or epinephrine alone, the combination is not well established. The optimal therapeutic management of bronchiolitis is still controversial. The objective of this literature review is to determine the effectiveness of the combination of dexamethasone and epinephrine in pediatric patients with bronchiolitis.

Methods: A systematic review from 1990 to the present of English-language published literature was conducted using MEDLINE, CINAHL, and ISI Web of Science, Evidence Based Medicine Reviews Multifile, and Google Scholar using keywords bronchiolitis, and dexamethasone, and epinephrine. Articles of original research examining outcomes of the management of bronchiolitis with dexamethasone and epinephrine versus placebo and epinephrine versus placebo. Meta-analyses and case reports or series were excluded. Fifteen studies, three of which compared combination therapy of dexamethasone and epinephrine therapy to placebo were retrieved and analyzed for quality and significant results.

Results: The three studies that were reviewed indicate that there is a significant positive effect of the combination therapy of dexamethasone and epinephrine in the management of bronchiolitis. There is a synergistic effect between dexamethasone and epinephrine that has been shown to decrease the rate of hospital admission and length of hospital stay in the three studies included in this systematic review.

Discussion: Current guidelines suggest tailoring the treatment of bronchiolitis based on the presentation of symptoms. Although the American Academy of Pediatrics has produced a manuscript for the diagnosis and management of bronchiolitis, it gives an overview of available treatment modalities without a consensus on optimal treatment. Additional prospective research efforts, perhaps even larger, multi-center, randomized placebo-controlled trials, are needed to quantify and qualify possible risks of combination therapy of dexamethasone with epinephrine in the pediatric population. Such work should be on large population with a broader age range (2 months to 5 years), and should include patients who are both first-time wheezers, and recurrent wheezers. Lastly, research should be performed on the long-term effects of corticosteroid therapy in the pediatric population.

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The Effectiveness of Dexamethasone as Adjunctive Therapy to Racemic Epinephrine for a Pediatric Patient With Bronchiolitis

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A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Rob Rosenow, PharmD, OD
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

[Redacted for privacy]
Abstract

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**Keywords:** Dexamethasone, Epinephrine, Bronchiolitis
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List of Abbreviations

AAP……………………………………………………………………American Academy of Pediatrics

RDAI.............................................................................................Respiratory Distress Assessment Index

RCT………………………………………...……………………….…….Randomized Controlled Trials

SEM……………………………………….………………………………..……Standard Error of Mean
The Effectiveness of Dexamethasone as Adjunctive Therapy to Racemic Epinephrine in the Pediatric Patient with Bronchiolitis

BACKGROUND

Overview

Bronchiolitis is the most prevalent lower respiratory tract infection in childhood, although most children experience it only in its mild forms.{{51 Lieberthal, Allan S. 2006}} It most often has a viral etiology, with the leading virus being respiratory syncytial virus (RSV), which is most prevalent during the winter and fall seasons.{{65 Piedra, Pedro 2009}} The diagnosis is made by patient history and physical examination. It is characterized, by most clinicians, as a constellation of symptoms: viral upper respiratory prodrome followed by increased respiratory effort and wheezing, fever, coryza, cough, expiratory wheezing, and respiratory distress{{65 Piedra, Pedro 2009}} {{51 Lieberthal, Allan S. 2006}}. Severe disease is characterized by persistently increased respiratory effort (increased respiratory rate and decreased pulse oximetry), apnea, or the need for medical interventions such as fluid therapy, supplemental oxygen, or mechanical ventilation. {{51 Lieberthal, Allan S. 2006}} {{66 Glover, Mark L}} A viral nasal wash via nasopharyngeal swab and ELISA may be performed to identify the causative pathogen; however, generally, this does not change the treatment or management course.{{51 Lieberthal, Allan S. 2006}}

Bronchiolitis is an infectious disease that affects the muco-epithelial lining of the bronchiole.{{66 Glover, Mark L; 51 Lieberthal, Allan S. 2006}} This causes pathophysiological changes such as local edema, a large amount of thick secretions in the airway lumen, mucous plugging, and increased intraluminal pressure, making it difficult to breathe. In adults bronchiolitis is a mild viral infection that induces inflammation of the bronchioles with minimal effect. What is merely a mild infection in adults, is more critical in the Pediatric population, inducing a more severe disease of the airway lining. The respiratory distress assessment index (RDAI), is a clinical assessment tool that is
used in most bronchiolitis studies to assess the severity of the disease. It rates wheezing and respiratory distress on a scale from 0-17, with higher scores indicating more severe illness.\{48 Plint,Amy C. 2009\}

Epidemiology

Bronchiolitis is the most common lower respiratory tract infection, afflicting 11-12% of the pediatric population within the first year of life \{43 Shay,D.K. 1999\}. Approximately 1-2% of affected infants under the age of one may require hospitalization.\{43 Shay,D.K. 1999\} According to a study published by the Journal of the American Medical Association, during a 17-year study period, an estimated 1.65 million hospitalizations for bronchiolitis occurred among children under five years, accounting for 7 million inpatient stays. \{43 Shay,D.K. 1999\} In previously healthy infants who are older than six months and require hospitalization for the management of bronchiolitis, the average length of hospitalization is three days \{43 Shay,D.K. 1999\}. Despite the high prevalence of bronchiolitis, there is a lack of consensus regarding the treatment and management of the disease. In addition to morbidity and mortality during the acute course of bronchiolitis, infants hospitalized with bronchiolitis are more likely to have respiratory issues as older children, wheezing in particular, when compared to those who did not have severe disease. \{46 Kajosaari,M. 2000\} \{64 Martinez,F.D. 2003\}\{Treatment for bronchiolitis is generally supportive, antipyretics, supplementary oxygen, and fluid therapy. The optimal treatment for acute bronchiolitis still remains controversial.

Current Treatment of Bronchiolitis

Supportive care

Treatments for and management of bronchiolitis can be divided into two categories, either specific or symptomatic. Specific treatment refers to an antiviral therapy for positive RSV bronchiolitis.\{54 Bordley,W.C. 2004\} Symptomatic treatment with antipyretics, supplemental oxygen, fluid therapy, and close monitoring are the most common.\{59 Abul-Ainine,A. 2002\}
Supportive care in both the inpatient and outpatient settings, includes respiratory support and appropriate fluid maintenance.\{66 Glover, Mark L\} \{59 Abul-Ainine, A. 2002\} Respiratory support may be administered based on patient’s need, in order to maintain arterial oxygen saturation above 90-92%. \{51 Lieberthal, Allan S. 2006; 32 Mallory, Michael D. 2003; 61 Milner, A.D. 1989\} The American Academy of Pediatrics (AAP) guidelines recommends oxygen supplement in oxygen saturation readings of less than 90% \{51 Lieberthal, Allan S. 2006\}. Fluid resuscitation via the parenteral route may also be necessary to avoid dehydration. Patients with bronchiolitis have increased metabolic demand related to fever, tachypnea, and respiratory distress, and therefore, electrolyte status should also be monitored.\{66 Glover, Mark L; 51 Lieberthal, Allan S. 2006\} Along with supportive care, repeated clinical assessment (patient monitoring) should be done to assess the patient’s respiratory status. Hospitalized patients should have continuous monitoring of basic vital signs including but not limited to, respiratory rate, heart rate, and oxygen saturation.

**Bronchodilators**

Studies performed on inpatients with bronchiolitis, have not shown positive clinical progress that would recommend for routine albuterol. \{37 Klassen, T.P. 1997; 42 Schuh, S. 2002\} Several studies have compared epinephrine to albuterol (salbutamol) or epinephrine to placebo.\{58 Patel, H. 2002; 49 Walsh, Paul 2008\} Clinically, racemic epinephrine has been shown to be slightly more effective than albuterol, and it may be postulated that the improvement is related to the α effect of the medication. \{51 Lieberthal, Allan S. 2006\} In a meta-analysis studying the effectiveness of epinephrine by Hartling et al\{56 Hartling, L. 2003\}, it was concluded that “[t]here is insufficient evidence to support the use of epinephrine for the treatment of bronchiolitis among inpatients. There is some evidence to suggest epinephrine may be favorable to salbutamol and placebo among outpatients.” Epinephrine is an effective, fast-acting bronchodilator that stimulates α and β1 and β2 receptors. It may be injected subcutaneously or inhaled. Sympathomimetics such as epinephrine relax the airway smooth
muscle and inhibit release of bronchoconstricting mediators from mast cells. {{58 Patel, H. 2002}} Additionally, they may also inhibit microvascular leakage and increase mucociliary transport by increasing ciliary activity. There are a few adverse side effects that may occur because of the adrenoreceptor agonist mechanism of action. Maximum effect of bronchodilation, is seen after 15 minutes of therapy and lasts 60-90 minutes. {{65 Piedra, Pedro 2009}}

Although bronchodilators have not shown to be clinically useful in viral bronchiolitis, it is also difficult to distinguish between a patient with a propensity to develop asthma, and a patient with viral bronchiolitis. Both of these have disease courses present similarly with wheezing and respiratory distress. Therefore, it may be necessary to do a trial of inhaled bronchodilators, which may be continued if there is clinical improvement by objective standards. Selective adrenoreceptor agonist drugs from the β-2 selective class, predominantly albuterol, are structurally different than epinephrine in having a larger substitution on the amino group and in the position of the hydroxyl groups on the aromatic ring. {{66 Glover, Mark L}} {{65 Piedra, Pedro 2009}} They are effective after inhaled or orally administered and have a long duration of action. Maximum effect of bronchodilation, is within 15-30 minutes of therapy and lasts for 3-4 hours. {{66 Glover, Mark L}} The clinical AAP guidelines state that bronchodilators should not be used routinely in the management of bronchiolitis {{51 Lieberthal, Allan S. 2006}}.

Corticosteroids

Inhaled dexamethasone, prednisolone, budesonide, which belong to the class of glucocorticoids, alone are not used routinely in the management of bronchiolitis. {{51 Lieberthal, Allan S. 2006}} Corticosteroids are effective anti-inflammatory drugs that have proven to clinically improve asthma, however, the effectiveness in bronchiolitis is not well established. {{62 Roosevelt, Genie 1996}} A randomized trial of nebulized budesonide versus placebo in 161 infants hospitalized with RSV bronchiolitis did not demonstrate any significant decrease in morbidity or length of disease
course between the two treatment groups. {{47 Cade,A. 2000}} Dexamethasone sodium is freely soluble in water, slightly soluble in lipid, and is a strong anti-inflammatory agent. {{66 Glover, Mark L}}

**Purpose of Study**

Although bronchiolitis is not a major cause of mortality in the pediatric population, RSV bronchiolitis may have a correlation with subsequent bronchial hyper-reactivity, recurrent obstructive bronchitis, and asthma symptoms. {{46 Kajosaari,M. 2000}} Pathophysiologically, the combination of the innately smaller airways, and the obstruction due to inflammatory mediators, indicates that systemic corticosteroids may play a role in the management of acute bronchiolitis and shorten the disease process. Currently, the effectiveness of dexamethasone and epinephrine combination therapy has not yet been identified as a standard of treatment for acute bronchiolitis. The purpose of this paper is to perform a systematic review and determine whether or not dexamethasone as adjunctive therapy to racemic epinephrine, is effective in pediatric bronchiolitis patients by looking at the decrease in the rate of hospital admission and the length of hospital stay. The basis of treatment is generally case by case, therefore it is important for providers to stay updated on the most recent clinical studies regarding bronchiolitis treatment and management.

**Clinical Question**

The question of the effectiveness of dexamethasone as adjunctive therapy to epinephrine is an important one because the lack of information regarding the success. There is no standard therapy for the management of bronchiolitis. Recommendations have been graded and printed in a manuscript by the American Academy of Pediatrics, but the question of the effectiveness of this combination therapy still remains.
METHODS

Search Strategy

In order to design a detailed and thorough search of scientific literature, more than three search engines were used. An exhaustive literature search was performed using MEDLINE, CINAHL, ISI Web of Science, Evidence Based Medicine Reviews Multifile, and Google Scholar using keywords bronchiolitis, dexamethasone, and epinephrine. Articles of original research examining outcomes of the management of bronchiolitis with dexamethasone and epinephrine versus placebo and epinephrine versus placebo were included in the research. Meta-analyses and case reports or series were excluded. Fifteen studies were reviewed from the entire systematic review. Three of the fifteen studies met the inclusion criteria, by comparing dexamethasone and racemic epinephrine versus placebo, and, were retrieved and analyzed for quality and significant results. Subsequently, an analysis of bibliographic entries from the three articles, generated additional studies for consideration.

Inclusion/Exclusion Criteria

The search was also limited to English-language published studies of the pediatric population after 1990. Only randomized controlled studies were included. Studies of pharmaceutical therapy other than dexamethasone or epinephrine were excluded. Taking into account these exclusions, three articles were appraised using the Jadad scoring guideline. The Jadad scoring guideline was used as a guideline for quality and validity of each article. Articles that received a score greater than three were included in this review. As such, all three articles remained valid by score. See Table 1 for a description of the Jadad criteria.

RESULTS

After an extensive search, a total of three articles which met all of the inclusion and exclusion criteria were examined (See Tables 1 and 2 for summary of articles reviewed. The sample sizes of the
studies are 800 infants, 69 infants, and 61 infants. Ages of the patients ranged from 2 months- 21 months. All studies that are included in this review are randomized controlled trials. All studies were also double-blinded, and compared the combination therapy of dexamethasone with epinephrine versus placebo. Each study measured outcome with various objective measuring standards, and each utilized the respiratory distress assessment index (RDAI) score value. {{51 Lieberthal, Allan S. 2006}} The RDAI is the most widely used score and is reliable with respect to scoring, but it has not been validated for clinically predictive value in bronchiolitis. {{51 Lieberthal, Allan S. 2006}} {{49 Walsh, Paul 2008}} The shortest study was 5 days in length, and the longest study was over 3 months. Bronchiolitis was defined as the first episode of wheezing associated with signs of an upper respiratory tract infection during the peak RSV season in Kuyucu et al{{40 Kuyucu, S. 2004}} and Plint et al.{{48 Plint, Amy C. 2009}}

In a study of 69 infants published by *Pediatrics International*, Kuyucu et al{{40 Kuyucu, S. 2004}}, conducted a study in a pediatric outpatient clinic and the emergency department at Mersin University during the winter months to determine the additive effects of dexamethasone in L-epinephrine or salbutamol therapy in patients with bronchiolitis. Bronchiolitis is defined by the study as first time wheezing associated with clinical evidence of a viral infection in infants. This was a randomized, double-blind, placebo-controlled study. This study received a Jadad score of 5. Patients were eligible for the study if they were aged between 2-21 months, admitted for a first episode of wheezing, clinical findings compatible with diagnosis of acute bronchiolitis, and a RDAI score of ≥ 4. Patients were excluded from the study if they had a personal history of wheezing, a previous treatment with bronchodilators, a previous diagnosis of asthma or allergic bronchitis, a personal history of atopic dermatitis or allergic rhinitis, any chronic cardiac or pulmonary disease, any steroid treatment within the previous 2 weeks, signs of severe respiratory disease (pulse rate ≥ 200 beats/min, respiratory rate ≥ 100 breaths/min, RDAI score of ≥ 15, profound lethargy, clinical and/or radiological evidence of
bacterial infection, and family or parental history of asthma or atopic disease. A thorough history was taken and a complete physical examination was performed.\cite{Kuyucu2004}

Eligible patients were divided into three groups. Group 1 was treated with 3 mg of nebulized L-Epinephrine and fifteen minutes following the nebulized L-Epinephrine, participants in group 1 received dexamethasone 0.6 mg/kg intramuscularly. Group 2 received salbutamol 0.15 mg/kg, and fifteen minutes following the treatment, participants received dexamethasone 0.6 mg/kg intramuscularly. Group 3 received nebulized L-epinephrine and placebo whereas group 4 received salbutamol and placebo. The clinical outcome measures were heart rate, respiratory rate, and RDAI score. Clinical assessments were taken at 30, 60, 90, and 120 minutes after the first treatment. If patients did not improve their RDAI score by 4 points by 120 minutes, an additional treatment of the same medication was administered. Patients were also followed up at 24 hours and finally finished at 5 days post-treatment. Patients were then followed up in 2 months to determine the prevalence of respiratory complaints such as development of exercise induced wheezing and continued wheezing.\cite{Kuyucu2004}

Kuyucu et al.\cite{Kuyucu2004} concluded that a single dose of intramuscular dexamethasone in addition to L-epinephrine or salbutamol therapies did result in better outcome measures than placebo in the late phase (fifth day) of mild to moderate bronchiolitis attack. At day 5, in groups 1 and 2, both groups that received intramuscular dexamethasone, patients demonstrated a significantly lower RDAI score when compared to groups 3 and 4 who had received placebo. Fifth day RDAI score in group 1 was significantly lower than group 3 and group 4 (P = 0.01 and P = 0.00). The fifth day score of group 2 was also appreciably lower than group 4 (P = 0.01), but not statistically significant when compared to group 3 (P = 0.09). The fifth day RDAI scores between groups 1 and 2 were not statistically significant, which established that there was no difference in clinical outcome between epinephrine and salbutamol. With these results, this study concludes that a single dose of
dexamethasone added to either nebulized L-epinephrine or salbutamol treatments, resulted in a better clinical outcome measures than treatment with bronchodilators alone, on the fifth day after treatment of mild to moderate bronchiolitis.\{40 Kuyucu,S. 2004\}

Bentur et al\{52 Bentur,L. 2005\} studied 61 infants aged 3 to 12 months with bronchiolitis. The patients were similar in demographics, except for six infants in group 1 and seven infants in group 2 who were born prematurely. Prematurity was defined at gestational age < 32 weeks. There were no other significant differences between the groups in age, demographic data, breastfeeding, weight, oxygen saturation, and clinical score at admission. The study was a double-blinded, placebo-controlled study. This study received a Jadad score of 4 because there was no explanation of patient withdrawal or drop out (if any). In Table 1 of this article, there is a description of the number of infants enrolled in the study, however the 3 month follow-up is expressed as ± SEM, yet they are not accounted for. Patients were included in they had a first episode of wheezing and dyspnea, positive RSV antigen detected by ELISA, and parental signature of informed consent. Patients were excluded from the study if they had a previous treatment with systemic steroids, inhaled β2 agonist or inhaled steroids prior to admission, or if they suffered from bronchopulmonary dysplasia, cystic fibrosis, and congenital heart disease.\{52 Bentur,L. 2005\}

There were two study groups. Group 1 was treated with 0.25mg inhaled dexamethasone with 1mL epinephrine, and group 2 was treated with 0.5 mL 0.9% saline with 1mL epinephrine. The therapy was administered through a face mask every six hours, and continued until the patient was discharged. The clinical outcome was measured by objective variables including: respiratory rate, heart rate, oxygen saturation, and clinical status every 8 hours. Each variable was given a point value to establish a point system similar to RDAI. Supplemental oxygen therapy was provided, during intervals for a patient who had an oxygen saturation of < 92%, given by pulse oximetry. Additionally, if the respiratory rate was > 60 breaths/minute, oral feeding was stopped and intravenous fluid was
started. The clinical outcome was measured by the length of in-patient hospital stay.{{52 Bentur,L. 2005}}

The result of this study found that the difference in the length of hospitalization was especially notable among infants from group 1 who were born prematurely. This particular patient group had a shorter hospitalization period (6.5 ± 1.7d, mean ± SEM) compared with the prematurely born children in group 2 (9.1 ± 1.9) (p < 0.018). An analysis of full-term infants demonstrated the same trend. The cumulative proportion of in-patient stay of full term and pre-term infants was lower in the dexamethasone group than in the placebo group, most noticeably in days 5 and 6 post-hospitalization (p < 0.038). This study concluded from these values that inhaled dexamethasone therapy in addition to inhaled epinephrine, may decrease the overall length of in-patient hospital stay, especially in the subset of prematurely born infants.{{52 Bentur,L. 2005}}

The last study was the largest study, and was conducted by Plint et al.{{48 Plint,Amy C. 2009}}. Plint et al.{{48 Plint,Amy C. 2009}} studied the effectiveness of combining nebulized epinephrine with corticosteroids. The study design was a multi-center, double-blind, placebo-controlled trial that included 800 infants (6 weeks to 12 months of age) with bronchiolitis, who were seen in the pediatric emergency department. This study received a Jadad score of 5. Patients were recruited December through April, during the bronchiolitis season, at eight Canadian pediatric emergency departments, for a total of 3 years. Bronchiolitis, was defined in this study, as the first episode of wheezing associated with signs of upper respiratory tract infection during the peak RSV season and was diagnosed by a physician. Once the diagnosis was made, an RSV nasal pharyngeal sample was taken for testing. Participants qualified for the study if: they had a score of 4-15 according to the RDAI. Participants were excluded from the study if: they received bronchodilator therapy in the ED before being assessed by the research nurse, infants had received oral or inhaled corticosteroids within the previous 2 weeks, infants had a previous episode of wheezing or diagnosis of asthma, they
had previous bronchodilator use, they had any chronic cardiopulmonary disease or immunodeficiency, and infants who were in severe respiratory distress. Additionally, infants who were born before 37 weeks gestational age with a corrected age of less than 6 weeks at presentation were also excluded. Finally, patients were excluded if there was a severe insurmountable obstruction to communication with parents or guardians. Prior to the treatment if patients had an oxygen saturation of < 92% at room air they received supplemental oxygen, and any child with a fever (rectal temperature > 38°C) received acetaminophen (15 mg/kg).{{48 Plint,Amy C. 2009}}

Patients were then randomly divided into four separate study groups. Group 1 received nebulized epinephrine plus oral dexamethasone, group 2 received nebulized epinephrine plus oral placebo, group 3 received nebulized placebo plus oral dexamethasone, and group 4 received nebulized placebo plus oral placebo. The patients were given two nebulization treatments at 30 minutes apart, with a suspension of 3ml of generic epinephrine in a 1:1000 solution or an equivalent volume of saline (placebo). The oral treatments of dexamethasone were based on a study by Schuh et al, {{48 Plint,Amy C. 2009}} {{42 Schuh,S. 2002}} and consisted of 1.0 mg of dexamethasone per kilogram of body weight (maximum dose of 10mg) or placebo, given after the first nebulized treatment in the emergency department, followed by five once-daily doses of dexamethasone (0.6 mg/kg; maximum daily dose, 10mg) or placebo.{{48 Plint,Amy C. 2009}}

Throughout the study, the patient’s RDAI score, respiratory rate, heart rate, and oxygen saturation at room air, were documented. These measurements were taken between the two nebulizations and again at 30, 60, 90, 120, 180, and 240 minutes. Patients were followed up to 22 days past enrollment. The primary outcome of this study was hospital admission up to 7 days after enrollment, which was determined through telephone follow-up and chart review. Secondary outcomes were changes in heart rate, respiratory rate, RDAI score, and oxygen saturation from baseline, and
measured at 30, 60, 90, 120, and 240 minutes. Secondary outcomes of the duration and severity of bronchiolitis were determined by telephone follow-up. {{48 Plint,Amy C. 2009}}

The results of this study demonstrated that the relative risk of admission by day 7 in group 1 (epinephrine and dexamethasone) and group 4 (placebo) was 0.65 (95% confidence interval, 0.45 to 0.95; p = 0.02 and p = 0.07 for the unadjusted and adjusted analyses, respectively). From these values, it can be calculated that 11 infants would need to be treated in order to prevent one hospital admission (NNT). Additionally, this study demonstrates that epinephrine or dexamethasone treatment alone (groups 2 and 3), do not reduce the rate of hospital admission in comparison to placebo (p = 0.87 and p = 0.52, respectively for the unadjusted analyses.

This study concluded that there was an unexpected synergy between dexamethasone and epinephrine such that this combined therapy, when compared to placebo, reduced the rate of hospital admission in the 7 days after study enrollment by 9 percentage points, with a relative risk reduction of 35%. These results were modified by RSV status, presence or absence by history of atopy, or the severity or the duration of illness. The outcome of combining dexamethasone and epinephrine is most apparent in the first 3 days after study enrollment. Secondary outcomes were also improved by the combination therapy. Infants in group 1 were discharged earlier from medical care and resumed quiet breathing and normal feeding sooner than infants in group 4. {{48 Plint,Amy C. 2009}}

**DISCUSSION**

The main goal of this literature review is to examine, by evaluating and appraising the most relevant and current medical literature, the effectiveness of the combination therapy of dexamethasone and epinephrine, in decreasing hospital admission rates or length of hospital stay in pediatric patients with bronchiolitis. Of the three articles that were appraised in this literature review, the evidence was conclusive that there is a statistically significant relationship between dexamethasone with epinephrine
therapy in decreasing the rate of hospital admission and the length of hospital stay.\{{52 Bentur,L. 2005; 40 Kuyucu,S. 2004; 48 Plint,Amy C. 2009}\}} All three articles shared a common quality; they were randomized controlled studies that compared the combination therapy of dexamethasone and epinephrine with placebo. Furthermore, all three studies used the RDAI score as either, part of the clinical assessment, or as the clinical outcome measurement.

Currently, there is no standard of care for the treatment of bronchiolitis. Infants with bronchiolitis have been treated with corticosteroids because this class is well known for anti-inflammatory effects on multiple cellular levels.\{{66 Glover, Mark L}\}} Health care providers have used corticosteroids in infants in part, because of their effective therapy in the pediatric population for asthma and croup. The studies that are reviewed in this paper address the use of corticosteroids in decreasing the morbidity due to bronchiolitis. Patients in each study group had similar baseline characteristics (age, demographics, RDAI scores), and were otherwise healthy infants ranging from 2 months to 21 months. \{{52 Bentur,L. 2005; 40 Kuyucu,S. 2004; 48 Plint,Amy C. 2009}\}} Bentur et al\{{52 Bentur,L. 2005}\}}, was the only exception because this study included pre-term infants (< 32 weeks gestational age) in the sample population. Further limitations of each study are discussed below.

**Limitations of Study**

The results of this systematic literature review should be interpreted in light of several limitations. In Kuyucu et al\{{40 Kuyucu,S. 2004}\}}, one of the limitations is that it was a small study (69 participants), with a small number of patients in the placebo groups. This study, however, did take into account the social history of the child, tobacco exposure, sibling history, and duration of illness. No RSV swab was taken to identify the causative agent. The diagnosis of bronchiolitis was made clinically, with no distinction between asthmatic wheezer and bronchiolitis.\{{40 Kuyucu,S. 2004}\}} Bentur et al\{{52 Bentur,L. 2005}\}} was also limited by having a small study with only 61 participants. Bentur et al\{{52 Bentur,L. 2005}\}} did take a RSV antigen swab detected by ELISA; each participant
did have a positive RSV antigen. Consequently, this study is specifically studying RSV bronchiolitis. In the Plint et al{{48 Plint,Amy C. 2009}} study, an RSV antigen swab was not taken.

These studies defined bronchiolitis as an episode of first time wheezing associated with clinical evidence of a viral infection. It is difficult to distinguish the etiology of wheezing as either intrinsic or triggered by a myriad other assaults. Accordingly, effective treatments for infants with bronchiolitis have proven to be elusive.

The studies by Plint et al{{48 Plint,Amy C. 2009}} and Kuyucu et al{{40 Kuyucu,S. 2004}} were conducted during the winter season which is peak RSV season, whereas Bentur et al{{52 Bentur,L. 2005}} was done continuously from September 2002-March 2003 and, as part of the inclusion criteria, all participants were tested for a positive RSV antigen via ELISA nasopharyngeal swab.

In general, the articles that are included in this review used similar research methods in obtaining their sample population, however treatment modalities varied slightly. Kuyucu et al{{40 Kuyucu,S. 2004}} administered one single intramuscular dose of dexamethasone added to nebulized L-epinephrine, whereas Bentur et al{{52 Bentur,L. 2005}} administered 0.25mg dexamethasone with 1ml epinephrine via nebulizer every six hours until discharge. The study participants of Plint et al{{48 Plint,Amy C. 2009}} received two treatments of nebulized epinephrine, which consisted of 3ml of epinephrine in a 1:1000 solution per treatment, and a total of six oral doses of dexamethasone (1.0mg/kg of body weight in the emergency department and 0.6 mg/kg for an additional five days).

Although the conclusion of these three articles is that there is a statistically significant relationship between the combination therapy (dexamethasone and epinephrine) and decreasing hospital admission rates and/or the length of inpatient hospital stay, the outcome measurements varied in each study. The variability in dosing and administration of dexamethasone together with the variability in outcome measurements makes comparing these studies more complicated.
None of these studies address other confounding factors such as the decision to hospitalize a child. Beyond a recommendation from the infant’s pediatrician, the decision to hospitalize a child is multifaceted. For example, the distance to the hospital or the ability of the guardian to provide adequate care for the child, are among the factors that influence the decision for parents to hospitalize their child.

**Further Studies**

In order to improve the validity of the effectiveness between dexamethasone and epinephrine, more research is warranted. Based on the studies that have been appraised here, it is noted that two of the three studies have small sample populations. A sufficient study sample is necessary in order to draw statistically significant conclusions, and would magnify all the small changes in the patients’ outcomes. Larger, multi-center studies including acute bronchiolitis cases, with varying degrees of severity, and a larger age range, are needed in order to determine the effects of corticosteroids. As Bentur et al. found, the pre-term subgroup had better outcomes with the dexamethasone and epinephrine therapy. A look into the subgroups of infants who respond better to corticosteroids, for possible biomarkers, that may include virus identification techniques, may prove invaluable. Although, there were no serious short-term adverse events among the infants that were involved in the reviewed studies, there is a need for more long-term research or follow-up to determine, if the study treatment may cause adrenal suppression, arrest of somatic growth, or neurodevelopmental delay. Adrenal suppression from exogenous corticosteroids is still a risk, however, in a short term course of corticosteroids, this type of suppression is likely to be only temporary. 

One of the weaknesses in bronchiolitis literature, is the lack of validated clinical scoring scales that are objective, replicable, and can be easily carried out in a variety of settings. Future studies should choose to evaluate clinically relevant outcomes. Most of the outcomes in this literature focus on short-term measurements such as oxygen saturation or respiratory rate returning to baseline after treatment.
Investigators should focus more on the outcomes that matter to parents, clinicians, and health systems by measuring hospital admission or readmission rates, duration of hospital stay, costs of care, the level of parental satisfaction with treatment, and the development of future respiratory symptoms in the patient.

Additional research can follow the direction of Kuyucu et al{{40 Kuyucu,S. 2004}}, Bentur et al{{52 Bentur,L. 2005}}, and Plint et al{{48 Plint,Amy C. 2009}}, in determining a standardized dosing and administration of dexamethasone with epinephrine. A future study should also follow a more consistent follow-up protocol, clear and precise documentation, and standardized outcome measurements.

CONCLUSION

Emerging from the literature, there is evidence to suggest a positive synergistic effect between the combination therapy of dexamethasone with epinephrine in the treatment of bronchiolitis, and the decrease in morbidity, resulting in a shortened disease process. However, there is still insufficient evidence to support the use of this combination therapy until a larger, multi-centered trial is conducted. Although Plint et al{{48 Plint,Amy C. 2009}} was a large, multi-centered, randomized, placebo controlled trial, it did not expect to discover a relationship between dexamethasone and epinephrine which would effect the morbidity of bronchiolitis, and therefore, should be considered exploratory. Although, further studies are warranted, it is established that supportive care and close monitoring is valuable for children who present with an initial episode of wheezing. Therefore, confirmation of Plint et al{{48 Plint,Amy C. 2009}}, and the two smaller studies by Bentur et al{{52 Bentur,L. 2005}} and Kucuyu et al{{40 Kuyucu,S. 2004}}, by a study that is specifically designed to compare combined dexamethasone and epinephrine therapy with placebo is needed in order to definitively ascertain the differential effects of therapy as applied to the severity and phase of bronchiolitis.
### Table 1. JADAD Score Calculation

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study described as randomized (this includes words such as randomly, random, randomization)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method used to generate the sequence of randomization and appropriate (table of random numbers, computer-generated, etc)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the study described as double-blind?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was there a description of withdrawals and dropouts?</td>
<td>0/1</td>
</tr>
<tr>
<td>Deduct one point if the method used to generate the sequence of randomization was described and it was appropriate (patients were allocated alternately, or according to date of birth, hospital number, etc)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs. injection with no double dummy).</td>
<td>0/1</td>
</tr>
</tbody>
</table>

### Table 2. Summary of Reviewed Articles

<table>
<thead>
<tr>
<th>Author/Title/Year/Journal</th>
<th>Year Published</th>
<th>Patients/Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study Type</th>
<th>Score (of 5)/Comments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plint et al. {48 Plint, Amy C. 2009}</td>
<td>2009</td>
<td>800 infants (6 weeks to 12 months) with bronchiolitis</td>
<td>1. Nebulized EPI + oral DEX</td>
<td>Placebo Hospital admission within 7 days of enrollment (the initial visit to the ED)</td>
<td>Multi-center, double blind, RCT/placebo-controlled trial, with 22 day follow up 2004-2007.</td>
<td>5/5.</td>
<td>Combined therapy with DEX and EPI may significantly reduce hospital admissions.</td>
<td></td>
</tr>
<tr>
<td>Bentur et al. {52 Bentur, L. 2005}</td>
<td>2005</td>
<td>61 infants with bronchiolitis (3-12 months)</td>
<td>0.25 mg DEX with 1 ml EPI nebulization q 6 hours</td>
<td>Placebo (0.5 ml Nebulized 0.9% saline) and 1ml EPI</td>
<td>Length of inpatient hospital stay</td>
<td>RCT. Double-blind, placebo controlled study, with 3 months follow up. Sept 2002-</td>
<td>4/5.</td>
<td>No description of withdrawals Or dropouts. Inhaled DEX may reduce the length of hospitalization in combination with EPI nebulization.</td>
</tr>
</tbody>
</table>
Kuyucu et al. {{40
Kuyucu, S. 2004}}

<table>
<thead>
<tr>
<th>Yr.</th>
<th>Infants</th>
<th>Epi and Dex</th>
<th>Outcome Measures</th>
<th>March 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>69 infants with bronchiolitis, outpatient setting. (2-21 months)</td>
<td>1. Salbutamol + placebo 2. Epi + placebo</td>
<td>Heart rate, respiratory rate, RDAI.</td>
<td>5/5.</td>
</tr>
</tbody>
</table>

EPI: Epinephrine; DEX: Dexamethasone; RCT: Randomized Controlled Trial; ED: Emergency Department; RDAI: Respiratory Distress Assessment Instrument; RACS: Respiratory Assessment Change Score

<table>
<thead>
<tr>
<th>Table 3. RDAI (Respiratory Distress Assessment Index)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>Expiratory Wheezing</td>
</tr>
<tr>
<td>Inspiratory Wheezing</td>
</tr>
<tr>
<td>Location of Wheeze</td>
</tr>
<tr>
<td>Supraclavicular retraction</td>
</tr>
<tr>
<td>Intercostal retraction</td>
</tr>
<tr>
<td>Subcostal retraction</td>
</tr>
</tbody>
</table>

A single dose of IM DEX with nebulized L-EPI resulted in better outcome measures than bronchodilators alone in the late phase (5th day).