

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Systemic Corticosteroids in Infant Bronchiolitis: A Meta-analysis

Michelle M. Garrison, Dimitri A. Christakis, Eric Harvey, Peter Cummings and
Robert L. Davis

Pediatrics 2000;105:e44

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/105/4/e44.full.html>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2000 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Systemic Corticosteroids in Infant Bronchiolitis: A Meta-analysis

Michelle M. Garrison, MPH*§; Dimitri A. Christakis, MD, MPH†§; Eric Harvey, PharmD, MBA§; Peter Cummings, MD, MPH*; and Robert L. Davis, MD, MPH*†§

ABSTRACT. *Objective.* To determine whether corticosteroids are efficacious in treating bronchiolitis in hospitalized infants.

Methods. Online bibliographic databases (Medline, Embase, and Cochrane Clinical Trials Registry) were searched for: 1) bronchiolitis or respiratory syncytial virus, and 2) corticosteroid or glucocorticoid or steroidal antiinflammatory agents or adrenal cortex hormones. Reference lists from all selected articles were also examined. Randomized, placebo-controlled trials of systemic corticosteroids in treatment of infants hospitalized with bronchiolitis were selected by 2 investigators. Of 12 relevant publications identified in the literature search, 6 met the selection criteria and had relevant data available. Investigators independently extracted data for 3 outcomes: length of stay (LOS), duration of symptoms (DOS), and clinical scores.

Results. In the pooled analysis, infants who received corticosteroids had a mean LOS or DOS that was .43 days less than those who received the placebo treatment (95% confidence interval: -.81 to -.05 days). The effect size for mean clinical score was -1.60 (95% confidence interval: -1.92 to -1.28), favoring treatment. Secondary analyses of mean LOS or DOS were performed on 5 trials that had clearly identified methods of randomization, 5 trials that measured LOS, and 4 trials that clearly excluded infants with previous wheezing. The estimates of effect were similar to the primary analysis but were not statistically significant.

Conclusions. Combined, published reports of the effect of systemic corticosteroids on the course of bronchiolitis suggest a statistically significant improvement in clinical symptoms, LOS, and DOS. *Pediatrics* 2000;105(4). URL: <http://www.pediatrics.org/cgi/content/full/105/4/e44>; *bronchiolitis, corticosteroid, anti-inflammatory agents, steroidal, meta-analysis, infant.*

ABBREVIATIONS. RSV, respiratory syncytial virus; LOS, length of stay; DOS, duration of symptoms; CI, confidence interval.

Bronchiolitis is an acute lower respiratory tract infection, generally characterized by rhinorrhea, cough, expiratory wheezing, and respiratory distress, that has most commonly been associated with respiratory syncytial virus (RSV). Based on data from the National Hospital Discharge Survey, it

is estimated that ~120 000 infants are hospitalized with bronchiolitis each year in the United States.¹

Therapies currently used in the treatment of infant bronchiolitis include bronchodilators,^{2,3} ribavirin,⁴⁻⁷ corticosteroids, immune globulin,⁸⁻¹⁰ interferon- α 2a,^{11,12} and vitamin A.¹³ Although bronchodilators and corticosteroids are among the most commonly used treatments, clinical trials have not shown clear evidence of efficacy for either therapy. Two recent meta-analyses concluded that bronchodilators may have a minimal effect on the clinical features of bronchiolitis but did not have a clinically important or statistically significant effect on the likelihood of hospital admission or the average length of stay (LOS).^{2,3}

Both animal studies and pathophysiological theory suggest that the antiinflammatory action of corticosteroids might alleviate the symptoms of bronchiolitis and expedite recovery,¹⁴⁻¹⁶ but the majority of clinical trials have failed to demonstrate this. Although many authors have used this lack of proven benefit to advocate against the use of steroids in bronchiolitis,¹⁷⁻¹⁹ the studies performed to date have been based on relatively small samples and may have been underpowered to detect possible beneficial effects. Therefore, we conducted a meta-analysis of systemic steroids in the treatment of bronchiolitis to answer 2 primary questions. First, is systemic steroid therapy for infants hospitalized with bronchiolitis associated with a decreased length of hospital stay? Second, does such therapy provide symptomatic relief?

METHODS

Study Identification and Assessment of Quality

Searches were conducted on the following computerized bibliographic databases: Medline database (January 1966 to January 1999), the Cochrane Clinical Trials Registry (as of January 1999), and Embase (January 1990 to January 1999). The search terms were: 1) bronchiolitis (MeSH or text) or respiratory syncytial viruses (MeSH) or RSV (text), and 2) adrenal cortex hormones (MeSH or text) or corticosteroid (text) or glucocorticoid (MeSH or text) or antiinflammatory agents, steroidal (MeSH). In addition, the bibliographies of review articles¹⁷⁻²¹ and all selected articles were examined. Study titles and abstracts were evaluated, and prospective, placebo-controlled trials of systemic corticosteroids in infant bronchiolitis were selected for further review.

The remaining articles were independently reviewed by 2 of us (D.A.C. and E.H.). At this stage, the investigators were blinded to the results of the studies, as well as to the journal and author names. For inclusion in the meta-analysis, articles had to meet the following criteria: 1) random allocation of infants to either placebo or systemic corticosteroid treatment, 2) concealment of allocation, 3) no reported differences among the groups in the interventions used other than administration of corticosteroids, and 4) collection of data on LOS, duration of symptoms, and/or clinical scores.²² To

From the *Department of Epidemiology and †Division of General Pediatrics, University of Washington; and §Child Health Institute, Seattle, Washington.

Received for publication Sep 16, 1999; accepted Nov 19, 1999.
Reprint requests to (D.A.C.) Child Health Institute, 146 N Canal St, Suite 300, Seattle WA 98103. E-mail: dachris@u.washington.edu
PEDIATRICS (ISSN 0031 4005). Copyright © 2000 by the American Academy of Pediatrics.

increase homogeneity of the sample, only data concerning hospitalized patients who did not require mechanical ventilation were included. Disagreements were resolved through discussion, and consensus was achieved in the selection of articles for analysis. Data were then independently abstracted by 3 of us (M.M.G., D.A.C., and E.H.) using a standardized reporting form and disagreements were resolved by consensus. Attempts were made to contact authors for unpublished data if needed.

Outcome Measures

Length of hospital stay, duration of symptoms (DOS), clinical scores, and oxygen saturation (oximetry) were chosen as our a priori outcome measures. Because all included studies were conducted using hospitalized patients, we considered LOS and DOS to be proxies of each other and these were combined into 1 measure (LOS-DOS). These 2 measures were also analyzed independently in a subanalysis. Clinical score and oxygen saturation data were analyzed for 24 and 72 hours after initial treatment.

The primary analysis included all trials with available outcome data that passed the quality review. Five additional prestated subanalyses were performed: studies for which methods of randomization were clearly specified; studies stratified by total drug exposure, daily dose, route of administration; and studies that clearly excluded patients with a previous history of wheezing.

Statistical Methods

For the outcome measures in which the same units and scales were used in all trials (LOS, DOS, and oxygen saturation), the pooled mean differences between treatment and placebo groups were calculated. The mean differences were calculated for each study, and the variances for each difference was calculated as:

$$[(SD_1^2)/N_1] + [(SD_2^2)/N_2].$$

The mean differences were then weighted by the inverse of their variances and a pooled mean difference was calculated using these weights:

$$[(\sum(\text{weight} * \text{mean})) / (\sum \text{weight})].$$

Two-tailed *P* values of <.05 were used as the level of statistical significance, and 95% confidence intervals (CIs) were also calculated.^{23,24}

For clinical scores, however, the studies used different scales. Therefore, we calculated the mean difference in clinical score for each study and standardized each difference by dividing it by its standard deviation.²⁵ Heterogeneity was tested for using the *Q*-statistic for pooled effect sizes.²³ Linear regression analyses of daily and total dose on LOS-DOS were also performed to determine whether there was a significant dose-response relationship. The potential for publication bias was investigated using the test of Begg and Mazumdar,²⁶ using a continuity correction for ties.²⁷

All statistical analyses were performed using Stata 6.0 (Stata Corporation, College Station, TX) and Microsoft Excel 97 (Microsoft, Redmond, WA), and results were calculated using both random- and fixed-effects models. Fixed-effects models assume that the true effects of treatment are the same in all studies, whereas random-effects models allow for the possibility that the true effects of treatment might differ between trials.²³ The 2 models resulted in the same point estimates and CIs for the primary analyses and all but 1 subanalysis (the LOS only analysis). Because there was heterogeneity in this 1 subanalysis, we decided to present only the results for the random-effects model for all analyses.

RESULTS

Study Selection

The literature search returned 238 articles, of which 12 were clinical trials of corticosteroid therapy in infant bronchiolitis. After review, 3 trials were excluded because they were not randomized,²⁸⁻³⁰ 1 trial was excluded because it did not include our primary outcome measures,³¹ and 1 trial was excluded because the subjects were randomized before hospital admission and not all patients were subse-

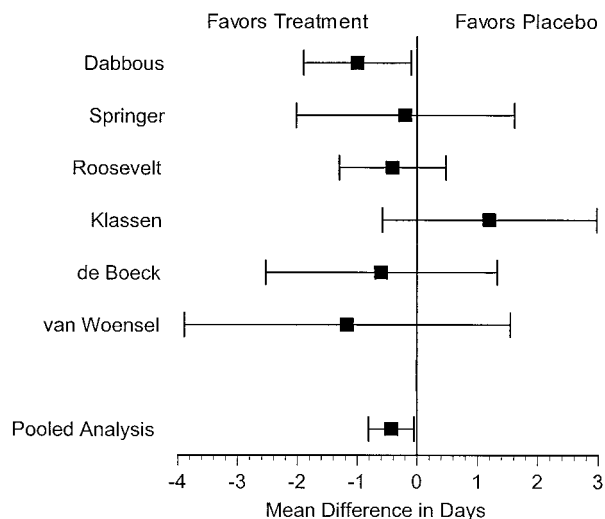


Fig 1. Analysis of mean difference in LOS or DOS in trials comparing systemic corticosteroids with placebo.

quently hospitalized, leading to a nonrandom distribution of hospitalized patients.³² One additional trial, now 30 years old, was later excluded because of inconsistencies in the data that could not be resolved despite attempts at contacting the authors.³³ One of the studies included patients on mechanical ventilation—these patients were excluded from our primary analysis and are discussed separately in the “Discussion” section.³⁴ The Begg and Mazumdar test²⁶ showed no statistical evidence of publication bias (*P* = 1.0) among the 6 trials that remained.

For the outcome of LOS-DOS, 5 trials measured LOS and 1 additional trial measured DOS (Table 1). In the 1 trial that measured DOS, hospital discharge was a priori dependent on the resolution of symptoms, ensuring that virtually all days with symptoms were captured (verified via personal communication with author).³⁵ For the outcome of clinical scores, all 6 trials reported data but only 3 of the trials measured clinical scores at 24 hours and the data at 72 hours were too heterogeneous for analysis (*P* < .001). For the outcome of oxygen saturation, 3 trials reported data, but there was a large degree of heterogeneity in the timepoints at which measurements occurred, making combination inappropriate.

Four of the included trials had clearly adequate methods of randomization specified either in the article or in personal communications, rather than merely stating that patients were randomized.³⁴⁻³⁷ In addition, 4 authors of included trials kindly supplied supplemental data on request.³⁵⁻³⁸

Characteristics of Individual Trials

A total of 347 subjects in 6 studies were included, of which 181 received corticosteroid therapy (Table 1). All study subjects were younger than 24 months old, and 2 studies were limited to infants younger than 12 months old.^{35,38} The most common exclusion criteria used were previous wheezing and chronic cardiorespiratory disease. Two of the studies included only infants with positive laboratory test results for RSV.^{34,36}

TABLE 1. Characteristics of Studies Comparing Corticosteroid Treatment of Bronchiolitis With a Placebo

Study	Number of Patients		Age Range	Study Criteria		Drug, Route†	Outcomes Measured§
	Treated	Control		Inclusion*	Exclusion†		
Dabbous et al ³⁹	22	22	1.5–18 mo		?	Methylprednisone, IM	LOS, CS, CO ₂
Springer et al ³⁸	25	25	1.5–11 mo		PW	Hydrocortisone, IV, then prednisone, PO	LOS, CS, PFT
Roosevelt et al ³⁵	65	53	1–12 mo		PW, CCD, ICU	Dexamethasone, IM	DOS, CS, DO ₂ , O ₂
Klassen et al ³⁷	35	32	1.5–15 mo		PW, CCD, SU	Dexamethasone, PO	LOS, CS, O ₂
de Boeck et al ³⁶	14	15	<24 mo	RSV	PW, CCD, PI	Dexamethasone, IV	LOS, CS, O ₂ , PFT
van Woensel et al ³⁴	20	19	<24 mo	RSV	SU	Prednisolone, PO	LOS, CS

* RSV indicates only patients with positive RSV laboratory results included.

† PW indicates previous wheezing; CCD, chronic cardiorespiratory disease; ICU, admitted to intensive care unit; SU, recent corticosteroid use; PI, premature infants.

‡ IM indicates intramuscular; IV, intravenous; PO, oral.

§ CS indicates clinical score; CO₂, carbon dioxide retention; PFT, pulmonary function testing; DO₂, duration of oxygen therapy; O₂, oxygen saturation.

The corticosteroids used in the trials included prednisone,³⁸ prednisolone,³⁴ methylprednisone,³⁹ hydrocortisone,³⁸ and dexamethasone.^{35–37} To allow comparability of dosage and types of corticosteroids used in the different studies, we converted both average daily doses and average total exposure to mg/kg prednisone equivalents.⁴⁰ Average daily doses ranged from .6 to 6.3 mg/kg and average total exposures from 3.0 to 18.9 mg/kg. Routes of drug administration included oral, intramuscular, and intravenous. None of the studies reported adverse effects associated with corticosteroid treatment.

Analysis of Pooled Data

Mean LOS ranged from 2.8 to 8.3 days in the placebo groups and from 3.2 to 7.1 in the treatment groups (Table 2). The pooled mean LOS-DOS among patients treated with corticosteroids was less than that of the children in the placebo group: mean difference $-.43$ days (95% CI: $-.81$ to $-.05$; Fig 1). Combining LOS and DOS measures increased the homogeneity of the data (the Q-test *P* value for LOS alone was .30, compared with .56 for LOS-DOS). The point estimate for the mean difference was the same for the LOS and LOS-DOS measures (Table 3). Adequate data were not available or were too heterogeneous, to perform the subanalyses regarding dosage and drug administration. The pooled estimates of the other subanalyses had point estimates similar to that of the primary analysis. The linear regression of mean difference in LOS-DOS on mean daily dose and total drug exposure showed no statistically significant relationships (for daily dose, $\beta = -.07$; 95%

CI: $-.57$ to $.44$; for total exposure, $\beta = -.01$; 95% CI: $-.16$ to $.13$).

Only 3 studies had useable data for clinical scores (Table 2). Symptoms that were included in the calculation of clinical scores of these studies were wheezing, oxygen saturation, accessory muscle use, and respiratory rate. In all the clinical scales, higher scores indicated worse or more symptoms. The pooled estimate of the standardized mean difference in clinical scores at 24 hours after the initial treatment was lower by 1.60 (95% CI: 1.92–1.28) among those who received steroids compared with those who received the placebo.

DISCUSSION

This meta-analysis has shown that the use of corticosteroids in the treatment of bronchiolitis in infants may be more effective than previously acknowledged. In this meta-analysis, corticosteroid therapy was associated with a statistically significant reduction in both clinical symptom scores and length of hospital stay. A conclusion about the effect of corticosteroids on oxygen saturation levels was not possible given the available data. The clinical relevance of oxygen saturation levels in such studies has been debated, and at most, they may serve as a surrogate endpoint for other outcomes, such as LOS.

The difference in clinical scores between corticosteroid and placebo groups indicates that corticosteroid therapy provides significant symptomatic relief within 24 hours of treatment. None of the studies reported results for individual symptoms, so we could not assess whether corticosteroid treatment

TABLE 2. Results for Trials Examining LOS, DOS, and Clinical Scores, Mean (Standard Deviation)

Study	LOS or DOS			Clinical Scores*		
	Steroid	Placebo	Difference	Steroid	Placebo	Difference
Dabbous et al ³⁹	4.16 (1.52)	5.16 (1.53)	-1.00 (.46)	NA	NA	NA
Springer et al ³⁸	5.00 (1.20)	5.20 (1.70)	$-.20$ (.41)	7.92 (1.38)	8.54 (1.54)	$-.62$ (1.50)
Roosevelt et al ³⁵	3.18 (1.56)	3.59 (1.58)	$-.41$ (.28)	1.90 (.98)	2.20 (.89)	$-.30$ (.17)
Klassen et al ³⁷	3.98 (5.11)	2.78 (2.78)	1.20 (.99)	NA	NA	NA
de Boeck et al ³⁶	6.00 (2.62)	6.60 (1.16)	$-.60$ (.76)	6.00 (2.19)	6.92 (1.65)	$-.92$ (.72)
van Woensel et al ³⁴	7.13 (5.37)	8.30 (3.92)	-1.17 (1.50)	NA	NA	NA

NA indicates not applicable.

* Clinical scores in de Boeck and Springer were scaled from 0 to 12, and in Roosevelt from 0 to 6, with higher scores indicating greater disease severity.

TABLE 3. Pooled Mean Difference (Treatment Minus Placebo) in LOS and DOS

Analysis Performed	Mean*	Lower CI	Upper CI	P Value	Number of Studies	Included
All studies, pooling LOS and DOS	-.43 d	-.81	-.05	.03	6	Dabbous, de Boeck, Klassen, Roosevelt, Springer, van Woensel
Only studies for which randomization methods were clearly identified	-.35 d	-.84	.14	.17	4	de Boeck, Klassen, Roosevelt, van Woensel
Studies which measure LOS only	-.43 d	-1.05	.18	.17	5	Dabbous, de Boeck, Klassen, Springer, van Woensel
Only studies which clearly exclude patients with previous wheezing	-.29 d	-.71	.13	.18	4	de Boeck, Klassen, Roosevelt, Springer

* A negative mean favors treatment; a positive mean favors the placebo.

more effectively ameliorates some symptoms than others. The difference in the LOS-DOS measure also lends support to a quicker resolution of symptoms in patients treated with corticosteroids, because we presume resolution of symptoms to be strongly correlated with discharge from the hospital.

At a population level, the benefits of systemic steroids could be substantial. For example, with a mean reduction in LOS of .43 days per patient, ~51 600 hospital days could potentially be saved through the use of inpatient corticosteroid treatment. The relative safety and ease of administration associated with corticosteroids only enhances the potential benefit. Moreover, this mean reduction of stay is based on all hospitalized patients, ignoring the possibility that steroids may be more beneficial for some patients than others.

In fact, this meta-analysis raises some interesting questions regarding the possibility that the benefits of corticosteroids might depend on disease severity and timing of therapy initiation. It is possible that corticosteroids may have a greater efficacy in treating infants with severe rather than mild bronchiolitis. In 1 study in this meta-analysis, patients treated while on mechanical ventilation had a mean LOS that was 6 days (95% CI: -10.2 to -1.8) shorter than the placebo group on mechanical ventilation, as opposed to a difference of 1 day (95% CI: -4.1 to 2.2) in the nonventilated groups.³⁴ This study also found that among nonventilated patients, those who had higher symptom scores at entry were more likely to respond to the treatment. The potential implications of this are twofold. First, if the findings of this meta-analysis were primarily driven by the more severe cases, these results may not be generalizable to the outpatient setting. Second, if more severely affected patients do benefit more from systemic steroid treatment, then this may be a subgroup to target for either this treatment or for further studies.

It is also possible that the timing of treatment may impact the effectiveness of corticosteroid treatment. In all these studies, treatment was initiated at least several days into the course of the disease. Corticosteroid therapy might be more or less effective if initiated at the onset of symptoms. In 1 study that enrolled patients at emergency department visits, there were no significant differences between treated and placebo patients in clinical scores, oxygen saturation levels, or respiratory rates.³² The relatively small sample size of this study, however, limits the conclusions that can be drawn from it. If corticoste-

roid treatment is efficacious in the early stages of bronchiolitis, its use in the outpatient setting may reduce both morbidity and hospitalization rates.

The potential long-term benefits of more aggressive treatment of bronchiolitis are unknown. One trial of ribavirin in infants with RSV bronchiolitis showed in a follow-up that treated infants had significantly better pulmonary function test results and less wheezing, reactive airway disease, and pneumonia than the placebo group.⁴¹ The 1 study in our meta-analysis that assessed the prevalence of chronic respiratory symptoms 2 years after recovery from bronchiolitis found no difference between the corticosteroid and placebo groups.³² However, several cohort studies have observed associations between severe acute bronchiolitis infections in infancy and later diagnosis with asthma.⁴² One prospective cohort study found that 23% of the infants with a history of bronchiolitis developed asthma by 3 years old, compared with 1% of the matched control infants (odds ratio: 28; 95% CI: 4-1235).⁴³

Although it is not clear whether this merely reflects the fact that bronchiolitis may be more likely to occur in children predisposed to asthma, if infant bronchiolitis is causally related to asthma, successful treatment with corticosteroids might reduce the prevalence of childhood asthma in treated children. In contrast, if bronchiolitis is more common or severe in children predisposed to developing asthma, corticosteroid therapy might be more effective in these infants than in those who are not so predisposed. It may be that this predisposition drives the effectiveness of steroids for bronchiolitis, just as it might in the use of bronchodilators for bronchiolitis.² Because this predisposition cannot be identified a priori, it may still be prudent to use systemic steroids to treat all infants hospitalized with bronchiolitis so as to benefit the susceptible fraction of them.

There are some limitations to our analysis. First, publication bias is always a potential problem in meta-analyses. Although we did not attempt to locate unpublished data for our analysis, the fact that the majority of the published studies were negative decreases the possibility that publication bias could account for our results. Moreover, our analysis failed to detect any suggestion of such bias. Second, we used a standardized mean difference in clinical scores to pool the results of different clinical scales. Although this method is commonly used for meta-analysis,²⁵ others have shown that this method can produce spurious results.⁴⁴ Unfortunately, we know

of no suitable alternative method when outcome scales differ. Third, although combining the data for LOS and DOS seemed appropriate for our purposes, they may not be as reflective of one another as we hypothesized. However, given the facts that homogeneity tests showed that the data were comparable enough to pool and that the point estimates for the LOS and LOS-DOS measures were equal, this combination did not seem to be detrimental to our analysis.

A large, well-designed, randomized, controlled trial of corticosteroids and bronchiolitis could resolve many of the questions left unanswered here, particularly because large clinical trials do not always agree.⁴⁵ Such a trial could confirm or refute of our findings while providing additional statistical power for more refined subanalyses. If the true effect size is .43 days in LOS-DOS and the distribution of the outcome followed a pattern similar to that in the studies published to date, a future randomized, controlled trial would need 728 subjects (364 in each arm) to achieve 80% power at an α -level of .05.

Including infants with a broad range of disease severity would allow investigators to analyze whether corticosteroids have a differential effect that corresponds to disease severity, although this would necessitate a larger sample size. Using objective outcome measures such as LOS would allow greater comparability among studies, and standardized discharge criteria could enhance the objectivity of this measure. Other suggestions include the use of a moderate dose of steroids, performing stratified analyses by initial severity of illness, and monitoring of adverse events. Long-term follow-up could assess which children in the study are later diagnosed with asthma. Although further study is clearly needed, the long history of systemic steroid use in inpatient asthma therapy and its acceptable safety profile lead us to conclude that they should be considered in the therapy of infants with bronchiolitis.

ACKNOWLEDGMENTS

This work was supported, in part, by a grant from the Packard Foundation.

Dr Christakis is a Robert Wood Johnson Generalist Faculty Physician Scholar.

We thank Dr Frederick Rivara for his thoughtful critique of this manuscript.

REFERENCES

- Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA*. 1999;282:1440–1446
- Kellner JD, Ohlsson A, Gadomski AM, Wang EE. Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis. *Arch Pediatr Adolesc Med*. 1996;150:1166–1172
- Flores G, Horwitz RI. Efficacy of β_2 -agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics*. 1997;100:233–239
- Janai HK, Stutman HR, Zaleska M, et al. Ribavirin effect on pulmonary function in young infants with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J*. 1993;12:214–218
- Barry W, Cockburn F, Cornall R, Price JF, Sutherland G, Vardag A. Ribavirin aerosol for acute bronchiolitis. *Arch Dis Child*. 1986;61:593–597
- Stutman HR, Rub B, Janaim HK. New data on clinical efficacy of ribavirin. *Pediatr Infect Dis J*. 1990;9:S79–S82
- Taber LH, Knight V, Gilbert BE, et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. *Pediatrics*. 1983;72:613–618
- Rimensberger PC, Burek-Kozłowska A, Morell A, et al. Aerosolized immunoglobulin treatment of respiratory syncytial virus infection in infants. *Pediatr Infect Dis J*. 1996;15:209–216
- Rodriguez WJ, Gruber WC, Welliver RC, et al. Respiratory syncytial virus (RSV) immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infections. Respiratory Syncytial Virus Immune Globulin Study Group. *Pediatrics*. 1997;99:454–461
- Rodriguez WJ, Gruber WC, Groothuis JR, et al. Respiratory syncytial virus immune globulin treatment of RSV lower respiratory tract infection in previously healthy children. *Pediatrics*. 1997;100:937–942
- Sung RY, Yin J, Oppenheimer SJ, Tam JS, Lau J. Treatment of respiratory syncytial virus infection with recombinant interferon α -2a. *Arch Dis Child*. 1993;69:440–442
- Chippes BE, Sullivan WF, Portnoy JM. α -2A-interferon for treatment of bronchiolitis caused by respiratory syncytial virus. *Pediatr Infect Dis J*. 1993;12:653–658
- Kjolhede CL, Chew FJ, Gadomski AM, Marroquin DP. Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr*. 1995;126:807–812
- Bunch C, Hoffman R. Prednisone drugdex drug evaluation. *Micromedex Healthcare Ser*. 1998;100
- Katzung BG. *Basic and Clinical Pharmacology*. Stamford, CT: Appleton & Lange; 1998
- Thomas LH, Stott EJ, Collins AP, Crouch S, Jebbett J. Infection of gnotobiotic calves with a bovine and human isolate of respiratory syncytial virus: modification of the response by dexamethasone. *Arch Virol*. 1984;79:67–77
- Klassen TP. Recent advances in the treatment of bronchiolitis and laryngitis. *Pediatr Clin North Am*. 1997;44:249–261
- Levy BT, Graber MA. Respiratory syncytial virus infection in infants and young children. *J Fam Pract*. 1997;45:473–481
- Welliver RC. Therapy for bronchiolitis: help wanted. *J Pediatr*. 1997;130:170–172. Editorial
- Jeng MJ, Lemen RJ. Respiratory syncytial virus bronchiolitis. *Am Fam Physician*. 1997;55:1139–1146,1149–1150
- DeVincenzo J. Prevention and treatment of respiratory syncytial virus infections for advances in pediatric infectious diseases. *Adv Pediatr Infect Dis*. 1997;13:1–47
- Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412
- Petitti DB. *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. New York, NY: Oxford University Press; 1994:116
- Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res*. 1993;2:121–145
- Petitti DB. *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. New York, NY: Oxford University Press; 1994:119–123
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–1101
- Steichen TJ. Tests for publication bias in meta-analysis. *Stata Tech Bull*. 1998;41
- Dennis JL. Steroids in the treatment of obstructive bronchiolitis. *South Med J*. 1963;56:1436
- Oski FA. Steroid therapy in bronchiolitis: a double-blind study. *Am J Dis Child*. 1961;102:759
- Sussman S. Dexamethasone in obstructive respiratory tract infections in children: a controlled study. *Pediatrics*. 1964;85:1–855
- Leer JA Jr, Green JL, Heimlich EM, et al. Corticosteroid treatment in bronchiolitis: a controlled, collaborative study in 297 infants and children. *Am J Dis Child*. 1969;117:495–503
- Berger I, Argaman Z, Schwartz SB, et al. Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up. *Pediatr Pulmonol*. 1998;26:162–166
- Connolly JH, Field CM, Glasgow JF, Slattery CM, MacLynn DM. A double blind trial of prednisolone in epidemic bronchiolitis due to respiratory syncytial virus. *Acta Paediatr Scand*. 1969;58:116–120
- Van Woensel JB, Wolfs TF, van Aalderen WM, Brand PL, Kimpen JL. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax*. 1997;52:634–637
- Roosevelt G, Sheehan K, Grupp-Phelan J, Tanz RR, Listernick R. Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet*. 1996;348:292–295
- De Boeck K, van der Aa N, van Lierde S, Corbeel L, Eeckels R. Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone ef-

- ficacy study. *J Pediatr.* 1997;131:919–921
37. Klassen TP, Sutcliffe T, Watters LK, Wells GA, Allen UD, Li MM. Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized, controlled trial. *J Pediatr.* 1997;130:191–196
 38. Springer C, Bar-Yishay E, Uwayyed K, Avital A, Vilozni D, Godfrey S. Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis. *Pediatr Pulmonol.* 1990;9:181–185
 39. Dabbous IA, Tkachyk JS, Stamm SJ. A double blind study on the effects of corticosteroids in the treatment of bronchiolitis. *Pediatrics.* 1966;37:477–484
 40. McLeod DC, Finkelstein E. Corticosteroids—comparison of potencies and properties. *Micromedex Healthcare Ser.* 1999;101
 41. Rodriguez WJ, Arrobio J, Fink R, Kim HW, Milburn C. Prospective follow-up and pulmonary functions from a placebo-controlled randomized trial of ribavirin therapy in respiratory syncytial virus bronchiolitis. Ribavirin Study Group. *Arch Pediatr Adolesc Med.* 1999;153:469–474
 42. Wang SZ, Forsyth KD. Asthma and respiratory syncytial virus infection in infancy: is there a link? *Clin Exp Allergy.* 1998;28:927–935
 43. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics.* 1995;95:500–505
 44. Greenland S, Schlesselman JJ, Criqui MH. The fallacy of employing standardized regression coefficients and correlations as measures of effect. *Am J Epidemiol.* 1986;123:203–208
 45. Cappelleri JC, Ioannidis JP, Schmid CH, et al. Large trials vs meta-analysis of smaller trials: how do their results compare? *JAMA.* 1996;276:1332–1338

Systemic Corticosteroids in Infant Bronchiolitis: A Meta-analysis
Michelle M. Garrison, Dimitri A. Christakis, Eric Harvey, Peter Cummings and
Robert L. Davis
Pediatrics 2000;105:e44

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/105/4/e44.full.html
References	This article cites 37 articles, 10 of which can be accessed free at: http://pediatrics.aappublications.org/content/105/4/e44.full.html#ref-list-1
Citations	This article has been cited by 9 HighWire-hosted articles: http://pediatrics.aappublications.org/content/105/4/e44.full.html#related-urls
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://pediatrics.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://pediatrics.aappublications.org/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2000 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

