Systemic Corticosteroids in Infant Bronchiolitis: A Meta-analysis

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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-α2a,[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 articles[17–21] 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

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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:

$$[(\Sigma(weight*mean))/(\Sigma weight)].$$

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 subsequently 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 test[26] showed no statistical evidence of publication bias ($P = 1.0$) among the 6 trials that remained.

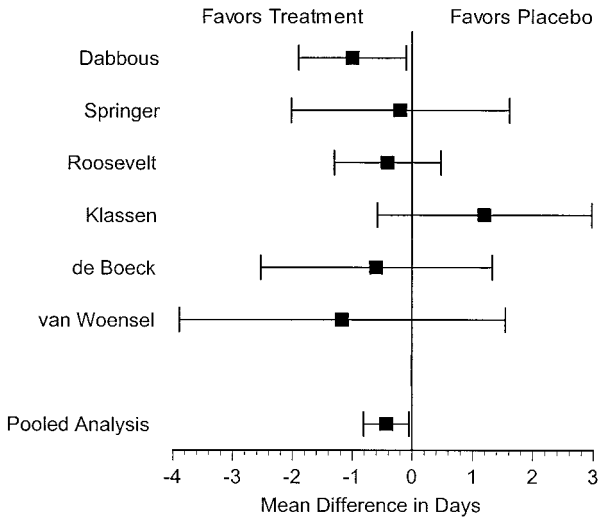

Fig 1. Analysis of mean difference in LOS or DOS in trials comparing systemic corticosteroids with placebo.

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; CO_2, carbon dioxide retention; PFT, pulmonary function testing; DO_2, duration of oxygen therapy; O_2, 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 corticosteroid 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 scoresto 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.

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Systemic Corticosteroids in Infant Bronchiolitis: A Meta-analysis

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