Final Comprehensive Report

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I. Introduction

A. Nature of the research problem

Bronchiolitis is the most common lower respiratory infection in infants, and the respiratory condition leading to the most hospital admissions in young children. In this disease, viral infection of the small airways, or bronchioles, leads to breathing problems. Bronchiolitis is seen most commonly in the first two years of life, and recurs annually throughout the world in winter epidemics. In the US, the cost of hospitalization alone was estimated some years ago at $700 million, and the rate of hospitalization is known to be increasing. Despite this, research does not provide consistent evidence to guide the treatment of this common serious condition.

Because bronchiolitis produces airway changes similar to those of asthma, physicians often use asthma medicines, such as albuterol or corticosteroids, for bronchiolitis. Corticosteroids especially have been the subject of recent research. Although some studies have found positive benefits, others have not.

Most prior studies of corticosteroid use had been small. They examined different populations and different outcomes. Against this background, a clearly defined and carefully conducted trial (see literature review, below) appeared in 2002 with the finding that dexamethasone, a corticosteroid, appeared to markedly decrease admission rates and respiratory scores in infants and toddlers with first-time attacks of bronchiolitis. Although positive, this study was small in size and conducted under idealized conditions at a single center. Experts felt that before the results were widely adopted, with the treatment of potentially millions of infants worldwide, a larger trial was needed. Government panels, reviewers, editorials, and specialty committees therefore called for multi-center, placebo-controlled, randomized trials of dexamethasone for bronchiolitis.

B. Purpose, scope, and methods of the investigation

We set out to conduct such a study: a multi-center, randomized, controlled trial (RCT) in a large sample of infants treated in emergency departments (EDs) to assess the effectiveness of a single dose of oral dexamethasone for acute, moderate-to-severe, outpatient bronchiolitis against outcomes including hospitalization and respiratory scores after 4 hours of observation, as well as later outcomes.

C. Nature of the findings

After careful data collection and analysis, there were no significant differences between the treatment and placebo groups for any outcome.

II. Review of the Literature

As many as 3% of infants are hospitalized for bronchiolitis in the first year of life.(1) Bronchiolitis admissions have increased substantially. In a study(2) from the Centers for Disease Control of children younger than 1 year, bronchiolitis hospitalization rates increased 2.4-fold between 1980 and 1996. Among all infant hospitalizations in this period, the proportion due to bronchiolitis more than tripled from 5% to 16%. The

authors noted that over 100,000 infants are hospitalized for bronchiolitis in the US annually, and the yearly costs of hospitalization alone are estimated at $700 million.

The effectiveness for bronchiolitis of the common bronchodilator medications used for asthma appears at best inconsistent.[3-6] Anti-inflammatory corticosteroids are increasingly recognized as central to effective treatment of asthma. Although bronchiolitis is also known to involve extensive inflammation of the airways, a number of studies had found corticosteroids ineffective in treating bronchiolitis.[7-10] Expert reviews had suggested that corticosteroids were not indicated for bronchiolitis.[11] This remained controversial, though, as other studies[12-18] suggested a benefit of corticosteroids in bronchiolitis.

Then a small, carefully conducted trial by Schuh and colleagues in 2002[19] found that dexamethasone, after 4 hours' observation, reduced admissions among infants with moderate-to-severe bronchiolitis by more than half, from 44% in the placebo group to 19% in the dexamethasone group. This study appeared likely to affect clinical practice and increase the already substantial use of corticosteroids for this condition (see below).

Despite these results, the effectiveness of corticosteroids was considered an open question. Many calls for further study were issued. These ranged from editorials in major journals,[20] and Cochrane Collaboration reviews,[21] to an Evidence Report sponsored by the federal Agency for Healthcare Research and Quality (AHRQ) in 2003,[22] and a recent clinical practice guideline from the American Academy of Pediatrics.[23] This guideline, a 2006 review of the available evidence, acknowledged that prior evidence was unclear, and specifically anticipated the results of our study to help resolve this area of controversy.

The 2003 AHRQ report, under Priorities for Further Research, noted that for the treatments studied, including corticosteroids, "*data are simply insufficient to exclude them as possible effective treatments. The treatment studies we reviewed were almost universally underpowered and as such do not give clinicians adequate guidance for management of bronchiolitis…. The following interventions, in particular, should be studied with a well-designed, rigorously conducted RCT, preferably with placebo control… (d) Oral corticosteroids, preferably dexamethasone.*"

This combination of conflicting prior evidence, a plausible mechanism of action, and the need to be certain of effectiveness in a disease affecting millions of children around the world created a situation in which further study seemed urgently needed, and in which clinical equipoise was clearly present.

III. Study Design and Methods

A. Study design

In line with the calls for research, this study was designed as a large, multi-center, randomized placebo-controlled trial. Expert panels had suggested that study outcomes in such trials be chosen to be important to parents and physicians. Hospital admission meets this definition, and has major impact on health care costs, missed days of work, hospital crowding, and other societal impacts. Respiratory scores were studied to see whether changes in breathing could be detected even in centers where admission had different criteria, and whether the benefits, if they existed, did result from changes in respiration rather than, for example, simple fever reduction or a feeling of well-being, known to be nonspecific effects of corticosteroids. Length of hospital stay and later doctor visits were

also studied. Adverse events were studied to determine, first, whether the treatment itself had risks, and second, to detect other possible benefits, if, for example, adverse events were reduced in the corticosteroid group.

B. Population studied

The multi-center design of the study was achieved through the participation of 20 EDs in the Pediatric Emergency Care Applied Research Network (PECARN), a unique research partnership created by the Emergency Medical Services for Children (EMSC) program and the Maternal and Child Health Bureau (MCHB) of the Health Resources and Services Administration (HRSA).

The study population was chosen to be similar to that in the small, positive trial described above. We conducted the study during bronchiolitis season (November through April) over a 3-year period from January, 2004 through April, 2006. For both scientific reasons (treatment of "pure" bronchiolitis) and ethical reasons (to avoid withholding dexamethasone from possible asthmatics, in whom it is known to work) we included only infants 2 to 12 months of age presenting with a first-time episode of bronchiolitis, defined as wheezing within the first 7 days of symptoms. In addition, to exclude children who ethically might not need treatment, or scientifically might not qualify for admission in any event, the episode was required to be moderate or severe. To enhance safety and validity, we excluded children with other illness (e.g., chronic lung disease) who might be at more risk and more likely to be admitted regardless of treatment response.

All centers approved the study at their IRB (human subjects committee). Informed consent was obtained from the parents of all study patients.

C. Sample selection

This was a convenience sample with careful screening. Patients were screened for eligibility during times when a research assistant and participating clinician were available. Because patients were blindly randomized to treatment groups, no attempt was made to study all patients, but records were kept on all screened patients, including those declining informed consent and those not meeting inclusion criteria.

D. Instruments used

Standard vital signs and oxygen saturation were recorded. Respiratory status was scored using the Respiratory Distress Assessment Instrument (RDAI), a standard respiratory score used extensively in prior research on bronchiolitis and asthma. Trained clinicians recorded RDAI scores at enrollment and at 1 hour and 4 hours after study treatment. Groups were compared using the Respiratory Assessment Change Score (RACS), calculated as the sum of the RDAI change plus a standardized score for respiratory rate percentage change, with a reduction of 1 unit for a decrease in rate >5% but ≤15%, 2 units for a decrease of 15–25%, and so on. Thus, negative values signify improvement.

E. Statistical techniques employed

The primary analysis was performed according to the principle of intention-to-treat, with all patients included in their assigned treatment group. A secondary per-protocol analysis examined patients according to the treatment actually received. Hospital admission was compared between treatment arms using the Pearson chi-squared statistic. The RACS outcome was assessed using a two-sample t-test. Adjusted measures and subgroup effects for admission and RACS were analyzed using logistic and linear regression, respectively.

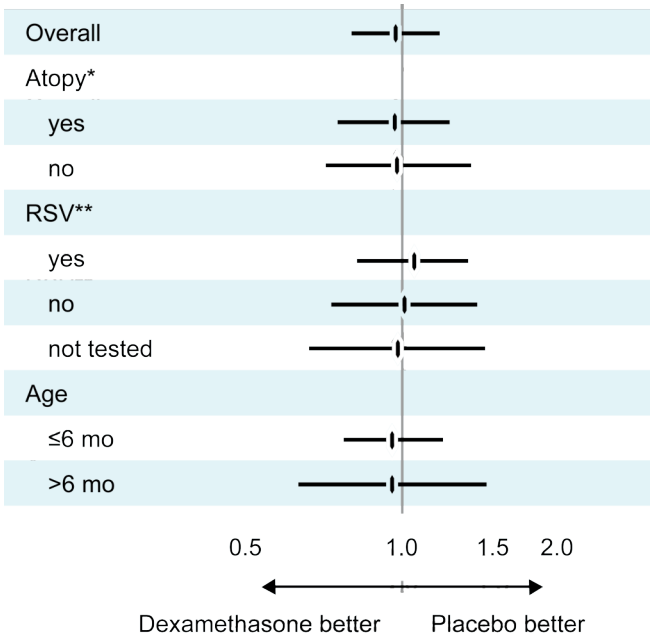
Changes in clinical variables after 4 hours' observation were regressed against baseline values and treatment group as predictors. Length-of-stay measures were compared using the two-sample Wilcoxon test.

IV. Detailed Findings

A total of 8,686 infants were screened; in the end, 600 patients were randomized. Among patients not meeting inclusion criteria, two-thirds had either prior wheezing (41%) or a mild case of bronchiolitis (25%). Among studied patients, 305 were randomly assigned to receive dexamethasone and 295 to receive placebo. The two treatment groups were statistically similar in their baseline demographic and clinical characteristics.

Of the 305 patients in the dexamethasone group, 121 (39.7%) were admitted, compared to 121 (41.0%) of the 295 patients in the placebo group. This difference was not statistically significant (absolute difference, −1.3%; 95% confidence interval [CI], −9.2 to 6.5; p = .74).

There was no significant difference when admission was analyzed in a pre-specified subgroup with eczema or a family history of asthma (difference 1.3%; 95% CI -8.5%, 11.1%). There was also no significant difference when admission was analyzed in the subgroups of positive and negative patients tested for RSV. Subgroup analyses are shown in the following figure.



Estimated risk ratios (risk of hospitalization in the dexamethasone group as compared to the placebo group) are shown for the overall data set and for specific subgroups evaluated in bivariate analysis. The horizontal lines represent the 95 percent confidence intervals. Risk ratios <1 favor dexamethasone; the value 1.0 represents equivalence between the two groups. A statistically significant result would appear as a horizontal line that lay entirely to the left or the right of the centerline at 1.0.

The respiratory status of both treatment groups improved during ED treatment and observation, but mean improvement in RACS did not differ significantly between the treatment groups. There was also no significant difference when RACS was analyzed in

the subgroup with eczema or a family history of asthma, or in the RSV-positive versus RSV-negative subgroups. There were small differences between the groups in temperature, heart rate, and oxygen saturation, but these were so small (0.4° C, 8 beats per minute, 0.6%) as to have no clinical usefulness. These differences (placebo value minus dexamethasone value) are summarized here:

	Treatment group				
Variable	Dexamethasone	Placebo	Difference	95% CI	p-value
RACS	–5.3 ± 4.7	–4.8 ± 4.6	0.5	(–0.3, 1.3)	.21
RDAI score	–4.4 ± 3.1	–3.9 ± 3.2	0.5	(0.1, 1.0)	.03
RR (breaths/min)	–8 ± 15	–7 ± 14	1	(–1, 3)	.39
SaO_2 (%)	0.3 ± 3.3	0.9 ± 3.2	0.6	(0.1, 1.0)	.02
HR (beats/min)	–13 ± 24	–5 ± 25	8	(5, 12)	<.001
Temperature (°C)	–0.6 ± 0.9	–0.2 ± 1.0	0.4	(0.3, 0.6)	<.001

RR = respiratory rate; HR = heart rate; plus-minus values are means ± SDs

There was no significant difference in later outcomes. The mean length of stay for hospitalized patients was 2.55 days in the dexamethasone group and 2.27 days in the placebo group (p = .10). Subsequent hospital admissions were reported for 12 (4%) of 284 children in the dexamethasone group and 10 (4%) of 265 children in the placebo group.

Adverse events did not differ significantly between the treatment groups. Vomiting within 20 minutes of drug administration occurred in 5% of each group. No patients developed gastrointestinal bleeding, hypertension, or complicated varicella. Pneumonia was diagnosed in three patients; two were in the placebo group, and one of these developed a more complicated chest infection (empyema).

V. Discussion and Interpretation of Findings

A. Conclusions to be drawn from findings

Our study of 600 infants from 2 to 12 months of age with moderate-to-severe bronchiolitis conducted in 20 EDs found that 1 mg/kg of oral dexamethasone did not significantly alter their rate of hospital admission or their respiratory condition after 4 hours` observation. Likewise, it did not affect hospital length of stay, later admission, later unscheduled medical visits, or other adverse events.

After 4 hours of observation, neither hospital admission nor clinical variables differed between treatment and placebo groups in any meaningful way, nor was there any evidence that a history of eczema or family history of asthma, viral test results, or age could help physicians select a subgroup of patients who would be more likely to be helped by dexamethasone.

When a study finds no statistically significant difference between treatment groups, we should ask if it included a large enough sample size to statistically exclude a difference of such size as to be useful or interesting. This is the problem of study power. This study was designed to have more than 80% power to detect a true difference between treatment groups as small as 12.5%. (Recall that the Schuh study found a 25% difference in admission rates.) The observed confidence limits in our study for the treatment effect on

hospitalization imply that even at our upper limit of uncertainty, 11 patients would require treatment with dexamethasone to prevent one admission. Thus, this study, with 95% statistical confidence, can exclude scenarios in which even as few as 10% of treated patients would benefit. We cannot exclude small differences beyond this limit.

The absence of outcome differences for changes in respiratory scores and related biologic variables also suggests that clinically useful differences between treatment groups were not likely missed in this study. The study's large size, designed to detect a difference in admission outcomes, would have much more power to detect a clinically important difference in respiratory improvement. Previous researchers have felt, for example, that a change of 2 points in the RACS would be the minimum that would make a difference to parents or doctors; the observed RACS difference in this study of 0.5 had 95% confidence limits of -0.3, 1.3, meaning that a 2-point difference can be statistically excluded.

B. Explanation of study limitations

One important issue in testing asthma treatments for bronchiolitis is that some children with bronchiolitis develop later asthma. When bronchiolitis recurs, it may be that those with recurrent attacks increasingly represent patients with asthma, and thus their response to asthma medication may not be reflective of its effect in first-time, or pure, bronchiolitis. Some prior studies did not distinguish children with first attacks from those with recurrent attacks of bronchiolitis or potential asthma. Likewise, some studies focused only on bronchiolitis caused by the respiratory syncytial virus (RSV), the most common cause of bronchiolitis, although in fact other viruses or a mixture of viruses cause up to 30 to 50% of bronchiolitis cases.

We studied the effects of the possible tendency to develop asthma, and of viral type, by performing subgroup analyses. Because the response to corticosteroids might differ in children with potential allergy or asthma, our pre-specified subgroup examined patients with eczema or a family history of asthma. Because bronchiolitis is a clinical syndrome caused by several viruses, we also examined subgroups positive and negative for RSV. No significant difference was found in these analyses.

For both ethical and scientific reasons, however, we tried to exclude children with likely asthma who might benefit from dexamethasone. We therefore studied only infants 2 to 12 months of age with first time wheezing. As noted, it is possible that older children or those with recurrent wheezing might respond differently to dexamethasone. Clinicians who suspect clinical asthma may want to continue to use corticosteroids, as their effectiveness in that disease is clear.

We studied a single large, 1 mg/kg oral dose of dexamethasone. This makes it unlikely that a larger dose would be effective. Oral administration and 4 hours' observation were chosen to duplicate the methods used by Schuh and colleagues. Their findings suggested a significant reduction in admissions with this dose and observation interval. Given those results, and the fact that theirs was the best-designed study on the topic, we felt it was important to select these parameters. Furthermore, their study and ours were predicated on extensive evidence that oral corticosteroids are effective within 4 hours in asthma and croup, other common childhood diseases involving airway inflammation. Evidence from our study makes it unlikely that we missed a later benefit of dexamethasone. We carefully collected later outcomes including hospital length-of-stay, later admissions or unscheduled medical visits, and adverse events (due to bronchiolitis as well as study

drug) in both treatment groups. If dexamethasone were effective later than 4 hours, this should have appeared in one or more of these later outcomes. No such effect was observed.

C. Comparison with findings of other studies

Our findings are consistent with prior studies that failed to demonstrate the efficacy of corticosteroids in bronchiolitis.[7, 9, 23-25] Many of those studies were small, however, and they involved a variety of endpoints. A systematic review published by the Cochrane Collaboration analyzed 13 studies of corticosteroids for acute bronchiolitis.[21] Their analysis found no statistical difference in respiratory rates, oxygen saturation, hospital admission, length of stay, later visits, or readmission rates. The AHRQ report cited above[22] analyzed five placebo-controlled studies of oral corticosteroids, including dexamethasone, and two of parenteral dexamethasone. Only one study[19] found a statistically significant difference between groups. A subcommittee of the American Academy of Pediatrics recently reviewed the existing evidence of prior studies and recommended against routine corticosteroid use for bronchiolitis.[23] All of these reviews, however, noted the inconclusive nature of the existing evidence.

Some prior studies[12, 14-16, 26] had suggested a benefit of corticosteroids; their size, methods, and findings have been carefully reviewed.[21, 22] A meta-analysis[13] examining six trials of systemic corticosteroids in infant bronchiolitis also found an apparent small benefit in the corticosteroid groups if length-of-stay was combined as an outcome with days-of-symptoms, but this effect was small and did not persist when these outcomes were analyzed separately, or when only studies of first-time wheezing were examined.

The findings of our study differ from those of Schuh and colleagues.[19] By design, we studied the same 1 mg/kg dose of oral dexamethasone, 4 hours of ED observation, and endpoints of hospitalization and RACS. There were several differences, however, between the two studies. The Schuh study continued oral dexamethasone (0.6 mg/kg) or placebo for 5 days in patients discharged home. This would not, however, affect their main positive outcomes, hospitalization and RACS after 4 hours' ED observation. We limited enrollment to infants in the first year of life while their study included children up to 24 months of age. It is possible that older children could behave differently, especially if they were more likely wheezing due to asthma, which does respond to corticosteroids. By chance, the dexamethasone group in their study had a significantly higher proportion of patients with family histories of atopy than did the placebo group. Our study groups were balanced in this regard. In their study, a research nurse assigned respiratory scores, while in ours the treating physicians did so. Their study was substantially smaller and conducted at a single institution where all patients were treated with a standardized bronchodilator regimen using an ultra-nebulizer. Given the current wide variability in the use of bronchodilators[27, 28] and uncertainty regarding their effectiveness,[21, 22] we did not seek to control bronchodilator use. We did, however, confirm that equal types and numbers of bronchodilator treatments were administered in the dexamethasone and placebo groups.

D. Possible application of findings to actual MCH health care delivery situations (including recommendations when appropriate)

As mentioned, bronchiolitis is the most common lower respiratory infection in infants, and the respiratory condition leading to the most hospital admissions in young children.

Thus it is likely to be seen in every US community clinic, pediatric and family medicine practice, and emergency department, and to have important consequences for children, their parents, and healthcare spending. Bronchiolitis is also currently one of the most common serious illnesses of childhood lacking evidence-based treatment. Little clear evidence had emerged in repeated trials to guide therapy. The results of multiple studies had been conflicting, and many studies suffered from small size, creating a lack of power to detect treatment differences if they did, in fact, exist.

Therefore, the results of this large, randomized, carefully controlled study should help clinicians treating infants choose appropriate therapy for this common condition. Without these results, evidence and experience suggest that corticosteroid use, already fairly common, might increase. The 2003 AHRQ report noted that, "There is substantial evidence that clinicians commonly use several interventions such as…corticosteroids" for bronchiolitis. Even before the Schuh study had a chance to change practice, evidence suggested that corticosteroids were commonly used for bronchiolitis. A 1998 study[29] of practice patterns in Europe, the United States, and Australia found a median of 17% of 1,563 patients received corticosteroids. In a 2001 study of ten US children's hospitals, an average of 27% of children with bronchiolitis received corticosteroids; in one hospital, this percentage was 61%.[28] A 2005 study[27] of 30 US hospitals also found an average of 25% of patients receiving corticosteroids for bronchiolitis. Since the time these results were collected, it is possible that the positive findings of the Schuh study have tended to further increase the use of corticosteroids for bronchiolitis.

Thus, the results of our study should allow a rational approach to the management of bronchiolitis in infancy. Although corticosteroid medicines are usually well-tolerated in short-term use, any medication has costs and possible side effects, and any costs and side effects occasioned by corticosteroid use in first-time bronchiolitis could be avoided using this rational approach.

Evidence also suggests that therapy for bronchiolitis varies widely among different physicians, health centers, and regions. The results of this study should allow for more uniformity and consistency of care, widely recognized as important.

E. Policy implications

The results of this study have sufficient statistical power that they could alter clinical care nationwide, but they do not rise to the level of policy-making. It will be useful to integrate these results with ongoing work by government agencies such as the MCHB, AHRQ, and others to define practice models and best-practice benchmarks. It is also anticipated that not only hospitals and clinics, but also organizations such as the American Academy of Pediatrics, American Academy of Family Physicians, American College of Emergency Physicians, and others may find these results useful as they develop clinical care guidelines.

F. Suggestions for further research

Further research may be directed to the role of corticosteroids in older children with bronchiolitis, and especially those with recurrent wheezing. As such patients were specifically excluded from this study for both ethical and scientific reasons, we can draw no conclusions regarding their care. Such research would require ethical design considerations to avoid withholding appropriate therapy for patients who actually have asthma. Likewise, unless such patients were handled carefully, their presence would tend

to decrease the valid utility of the findings; it is not in question that asthma medications are effective in patients with asthma.

For these reasons, research on recurring bronchiolitis will be challenging. Clinicians may be required to continue to try to distinguish between asthma and recurrent bronchiolitis on clinical grounds. Thus, a biologic marker (such as, perhaps, IgE or leukotriene levels, or some other indicator) that tended to predict the presence of asthma (or, on the other hand, to detect infection-induced wheezing) could be useful. Eventually, genetics and molecular biology may make this possible. Clinical research has already shown that certain risk factors (e.g., premature birth before 37 weeks' gestation) increase the risk from bronchiolitis. Clinical work should go on to help predict more precisely which infants are at risk for bronchiolitis, severe bronchiolitis, or recurrence.

It is possible that dexamethasone might affect the response to bronchodilator medications in bronchiolitis. Little evidence exists on this question. Our study was not powered to examine possible interactions between bronchodilators and dexamethasone. This could be done in further research, but would require a very large sample.

Why would anti-inflammatory medication such as dexamethasone not be effective in bronchiolitis? Basic science could be pursued in this area. Some hints from current evidence suggest that inflammation may play a role in limiting the spread of virus infection in the airways.

Other anti-inflammatory medications (e.g., antileukotriene agents) may work differently from corticosteroids, and are being tested in bronchiolitis. Early evidence suggests these might be effective for persistent or recurrent symptoms, a considerable source of morbidity, parent anxiety, and presumably missed work and decreased productivity, but this needs further exploration. Their role in the acute disease state remains unclear.

Work on an improved vaccine against RSV is progressing, and may be promising. Vaccination in early infancy is affected by the presence of maternal antibodies. Work on maternal vaccines is underway. Because a number of other viruses also cause bronchiolitis, other vaccines (e.g., against influenza and parainfluenza viruses) may be important. Better understanding of the virology and pathophysiology of bronchiolitis is important.

Further research using the dataset generated in this study is planned in the PECARN network. This work is nearing completions as of early 2008.

VI. List of products

1. Corneli HM, Zorc JJ, Mahajan P et al: Dexamethasone for bronchiolitis, a randomized controlled trial. (abstract, presented before the American Academy of Pediatrics Section on Pediatric Emergency Medicine, Atlanta GA October 6, 2006)
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