

Pediatric Emergency Care Applied Research Network (PECARN)

**The effectiveness of oral dexamethasone for acute bronchiolitis:
A multicenter randomized controlled trial (Version 4, 9/20/05)**

Principal investigators:

Howard M. Corneli, MD*
Kathy N. Shaw, MD, MSCE**
Joseph J. Zorc, MD**
Prashant Mahajan, MD†

This study originates at the University of Utah College of Medicine and Primary Children's Medical Center, Salt Lake City, Utah

Participating PECARN institutions and investigators:

***University of Utah College of
Medicine
Salt Lake City UT**
Howard M. Corneli, MD
Jeff E. Schunk, MD

****Children's Hospital of Philadelphia
Philadelphia PA**
Joseph J. Zorc, MD
Kathy N. Shaw, MD, MSCE

**†Children's Hospital of Michigan
Detroit MI**
Prashant Mahajan, MD

**Washington University / St. Louis
Children's Hospital
St. Louis MO**
Kyle Nelson, MD
Dave Jaffe, MD

**Children's Hospital Medical Center
Cincinnati OH**
Scott Reeves, MD
Rich Ruddy, MD

**Children's National Medical Center
Washington DC**
Kathleen Brown, MD

**Johns Hopkins University
Baltimore, MD**
Mitch Goldstein, MD
Allen Walker, MD

**DeVos Children's Hospital / Spectrum
Health
Grand Rapids, MI**
Matt Denenberg, MD
John Hoyle, MD

**Boston Children's Hospital – Harvard
Boston, MA**
Mark Baskin, MD

**Howard County General Hospital
Columbia MD**
David Monroe, MD

**Strong Memorial Hospital / University
of Rochester
Rochester NY**
Lynn Cimpello, MD

**University of Maryland
Baltimore, MD**
Getachew Teshome, MD

**Bellevue Hospital Center
New York NY**
Mike Tunik, MD

**Hurley Medical Center
Flint MI**
Dominic Borgialli, MD

**Children's Hospital New York /
Columbia University
New York NY**
Joan Bregstein, MD
Peter Dayan, MD

**Upstate Medical College
Syracuse, NY**
James Callahan, MD

**Children's Hospital of Buffalo
Buffalo, NY**
Kathleen Lillis, MD

**Central Data Management and
Coordinating Center
University of Utah
Salt Lake City, Utah**
Rich Holubkov, PhD

ABSTRACT

Bronchiolitis is the most common lower respiratory infection in infants. It is associated with rapidly increasing hospital admission rates in young children. It may also be the most common serious illness of childhood lacking evidence-based treatment. A 2003 report from the Agency for Healthcare Research and Quality (AHRQ) found “no evidence that any single agent can be recommended for treatment of bronchiolitis,” and called for randomized controlled trials. A recent small study has suggested that oral dexamethasone in a single dose of 1 mg/kg could markedly decrease the need for hospital admission, and the AHRQ report urged a trial of this medication.

This study will compare a single dose of oral dexamethasone to placebo in a multicenter, randomized, double blind trial, with a primary outcome of hospital admission. The study is powered to detect an effect size less than half of that seen in the previous study mentioned, and will seek to enroll 400 patients in each group. Patients will be drawn from the emergency departments at participating medical centers in the Pediatric Emergency Care Applied Research Network, created by the Emergency Medical Services for Children program and the Maternal and Child Health Bureau of the Health Resources and Services Administration to study health problems of high acuity and high incidence in children.

Study participation will require four hours of observation in the Emergency Department, but will not incur any additional charges, other treatment, or testing. A single follow-up telephone call will be placed after 7 to 10 days.

Dexamethasone in similar doses has been used in young children for many years for related conditions such as croup and asthma. Further, the side effects of dexamethasone are very few and the drug is almost always well tolerated. After review, the Food and Drug Administration has determined that this study is exempt from Investigational New Drug requirements.

This is a research question with a high priority and clinical equipoise. Extensive safeguards are described to ensure informed consent, patient safety, and privacy.

BACKGROUND AND INTRODUCTION

Bronchiolitis is the most common lower respiratory infection in infants,¹ and the respiratory condition leading to the most hospital admissions in young children.² It is also probably the most common serious illness of childhood lacking evidence-based treatment. A 2003 report¹ on evidence-based treatment of bronchiolitis from the Agency for Healthcare Research and Quality (AHRQ) finds that, “No evidence that any single agent can be recommended for treatment of bronchiolitis was identified,” and concludes, “At present, evidence is insufficient to recommend any of the treatments studied.”

As many as 90% of children will be infected with the respiratory syncytial virus (RSV), the most common cause of bronchiolitis, during their first two years of life.³ Although many can be treated as outpatients, bronchiolitis admissions are increasing. In a recent study from the Centers for Disease Control² of children younger than 1 year, bronchiolitis hospitalization rates increased 2.4-fold between 1980 and 1996, while overall admissions for lower respiratory illness in this age held steady. Among all infant hospitalizations, the proportion due to bronchiolitis more than tripled, from 5% to 16%. Well over 100,000 infants are hospitalized for bronchiolitis in the US annually, and the yearly costs of hospitalization alone have been estimated at \$700 million.

Control measures for bronchiolitis including vaccination have had limited impact.⁴ Even worse, it has been difficult to demonstrate the effectiveness of the commonly used bronchodilator medications.⁵⁻⁸

Interest, therefore, has focused on anti-inflammatory treatment. Bronchiolitis shares features with asthma, a condition in which anti-inflammatory corticosteroid medication is increasingly recognized as central to effective treatment.⁹ Although bronchiolitis is known to also involve extensive inflammation of the bronchi and bronchioles, a number of studies¹⁰⁻¹³ have found corticosteroids ineffective in bronchiolitis. Expert reviews have concluded that corticosteroids are not indicated for bronchiolitis.¹⁴ Only a few studies^{15, 16} have suggested a benefit of corticosteroids. On the other hand, many prior studies have been small, lacked power, and assessed the course of bronchiolitis once hospitalized, rather than the effect on hospitalization. A meta-analysis published in 2000¹⁷ combined evidence from these small studies, and suggested corticosteroids might be more effective in acute bronchiolitis than previously thought.

Recently, a small but well-conducted randomized controlled trial (RCT) from established Canadian researchers on respiratory illness¹⁸ found striking reductions in respiratory scores and admission rates with the use of 1 mg/kg of oral dexamethasone in moderate to severe bronchiolitis. In this study, 19% of children treated with dexamethasone were hospitalized compared to 44% in the placebo group ($p = .039$). Respiratory scores were also significantly lower in patients receiving dexamethasone. This study was small, however, and was conducted in a single center under idealized conditions. Before widespread adoption of dexamethasone treatment for bronchiolitis, which might affect hundreds of thousands of children, it is vital to confirm these findings in a larger sample, assess whether they can be generalized, and analyze the effectiveness of dexamethasone under the varying clinical practices that typify bronchiolitis treatment.

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 creates a situation in which further study is urgently needed, and in which clinical equipoise can readily be seen to exist. In fact, the authors of the AHRQ report¹ cited

above identify specific treatments which “should be studied with well-designed, rigorously conducted RCTs, preferably with placebo control,” and that these include “oral corticosteroids, preferably dexamethasone.”

Dexamethasone has several advantages. Almost all adverse effects of dexamethasone occur after long-term use.¹⁹ In doses of 0.6 to 1 mg/kg, dexamethasone has been widely used for many years in the treatment of croup.^{20, 21} More recently, it has also been used in similar doses for treatment of acute asthma.⁹ Oral administration is found to be equally effective as intramuscular administration.^{21, 22} Fortunately, too, oral administration is effective within 4 hours.²³ In addition to having a longer duration of action and being more effective on a milligram basis than other corticosteroids such as prednisone or prednisolone, oral dexamethasone seems to cause a lower incidence of vomiting.⁹ In all these studies it appears highly effective and well accepted by patients and parents with a very low rate of side effects or complications.

The use and formulation of dexamethasone in this study have been reviewed by the Center for Drug Evaluation and Research of the US Food and Drug Administration (see Appendix A) and found exempt from the regulations regarding Investigational New Drugs under the requisites of 21 CFR 312.2(b)(1).

OBJECTIVES AND HYPOTHESES

Our *objective* is to assess the effectiveness of oral dexamethasone for acute moderate-to-severe outpatient bronchiolitis in a multicenter randomized controlled trial, both as regards the need for hospital admission (primary outcome) and as regards severity, measured by respiratory scores, and duration of disease (secondary outcomes). The primary *hypothesis* is that dexamethasone will be more effective than placebo in preventing hospital admission. The secondary hypotheses are that dexamethasone will decrease respiratory scores and possibly the duration of the disease when compared to placebo, and that dexamethasone will be as safe and as well tolerated as placebo.

Outcome measures have been chosen in accord with the recommendations of the AHRQ study that, “Investigators should concentrate on measuring outcomes that are of interest to parents, clinicians, and health systems.”

DESIGN AND METHODOLOGY

This will be a double blind, randomized, controlled trial with one treatment arm receiving dexamethasone and the other placebo. This one-time administration of the study drug will be the only difference in treatment. Randomization will be stratified by center, and performed to generate equal-sized treatment and placebo groups. Patient assignment will be performed by an automated computer system via a telephone connection with the Cooperative Studies Coordinating Center in Perry Point, Maryland. The study will be conducted during the winter bronchiolitis season between December 2003 and April 2006, inclusive. All follow-up patient contact will be completed within 2 weeks.

Patient selection criteria

Patients will be recruited by research assistants working for this project in the Emergency Departments (EDs) at participating medical centers in the Pediatric Emergency Care Applied Research Network (PECARN), created by the Emergency Medical Services for Children program and the Maternal and Child Health Bureau

(MCHB) of the Health Resources and Services Administration (HRSA) to study health problems of high acuity and high incidence in children.

To avoid withholding corticosteroids from children who may have asthma, bronchiolitis will be defined as a *first time* attack of wheezing in a child under the age of 12 months. Because risk, and the decision to admit, is often based on factors other than severity prior to 2 months of age, this age group will also be excluded. Other exclusion criteria will include a prior adverse reaction to dexamethasone, known heart disease or lung disease (eg, cystic fibrosis, bronchopulmonary dysplasia), premature birth at less than 36 weeks gestation, a history of prior asthma or bronchodilator use, immune suppression or deficiency, treatment with corticosteroids within the past 14 days, active varicella, or known exposure to varicella within 21 days. Patients with life-threatening complications of bronchiolitis, including apnea, respiratory failure, or the clinical appearance of sepsis or shock, will be excluded from the study. In addition, cases meeting the criteria for mild bronchiolitis not requiring treatment will be excluded from this protocol. For this study, these criteria comprise a Respiratory Distress Assessment Instrument (RDAI) score less than 6.

To standardize patient consent and follow-up documents and ensure clear informed consent, participating parents will only include those whose primary language is English or Spanish. For the latter, Spanish-language materials will be prepared, and Spanish translation will be provided. Patients will otherwise be included regardless of ethnicity, sex, or economic background. As the study involves only infants, no issues arise of mental handicap, pregnancy, or patient assent.

Study Procedures

Parents will be offered information about the study and informed consent obtained. After informed consent, patients will be randomized to receive a single dose of oral dexamethasone, 1 mg/kg, or an equal volume of placebo designed to have the same appearance, odor, and taste. A pharmacy will have prepared medication and placebo in numbered vials. All personnel and parents will be blinded to whether medication or placebo is given. If the medication is vomited within 20 minutes, vomiting will be recorded in the study results, but no further medication will be administered. A maximum dose of 12 mg will be set, as children up to 12 months of age typically do not weigh more than 12 kg.

Study Medication

The dexamethasone oral formulation will be prepared from dexamethasone injection solution as in the recent Canadian study¹⁸ showing high efficacy, which also used a dose of 1 mg/kg. Although dexamethasone oral formulations are available, we will use an oral formulation made from dexamethasone phosphate injection solution for several reasons.

Most importantly, the standard oral solution is only available in a concentration of 0.1 mg/ml. In this concentration, a dose of 1 mg/kg for a 10-kg child would require administration of 100 cc. The elixir (also 0.1 mg/ml) and concentrate (Intensol™ — 1 mg/ml) contain 30% alcohol, which is undesirable in children. Further, experience suggests these formulations are associated with poor palatability and a high incidence of vomiting at the time of administration.

To avoid these issues, some hospitals use dexamethasone tablets crushed extemporaneously at the time of administration and mixed with flavored pharmaceutical syrup. This approach is avoided here, however, as it creates problems not only with standardized preparation, but also with dosage measuring, in that the tablets are of 4 mg size, and rounding off of doses or estimating of volumes necessarily create dosing imprecision.

Fortunately, an oral solution made from dexamethasone phosphate injection solution was well tolerated in the Canadian study¹⁸ and can be dosed very precisely. Further, such a solution has been shown to be stable for at least 90 days at room temperature,²⁴ which will enhance validity, practicability, and patient safety. The stability study prepared this solution with a 1:1 mixture of Ora-Sweet and Ora-Plus (Paddock Laboratories Inc., Minneapolis, Minnesota), which are, respectively, commercially available sweetening and suspending agents.

The use of dexamethasone in this study and our central pharmacy's formulation of oral dexamethasone from the injection solution have been reviewed by the Center for Drug Evaluation and Research of the U.S. Food and Drug Administration (FDA) and found exempt from the regulations regarding Investigational New Drugs under the requisites of 21 CFR 312.2(b)(1). The California Board of Pharmacy and the FDA have also approved the compounding and distribution for research of this medication from our central pharmacy. If required by local or state regulations, an identical preparation scheme is followed by hospital pharmacies.

Drug formulation details

Following published methods,²⁴ a suspension of commercially dexamethasone sodium phosphate 4 mg/ml injection solution will be prepared in a 1:1 mixture of Ora-Sweet and Ora-Plus (Paddock Laboratories Inc., Minneapolis, Minnesota) to a final concentration of 1mg/ml. This will be measured into vials containing 12 ml (the specified maximum dose).

Placebo solution will be prepared simply as the 1:1 mixture of Ora-Sweet and Ora-Plus, considered by experts as an ideal, safe, and established placebo indistinguishable in taste, color, and appearance from the active formulation.²⁵ Again, this will be measured into vials containing 12 ml (the specified maximum dose).

Vials will be numbered after randomization. Randomization will be stratified by participating center. Randomization records will be maintained at the central pharmacy, secured from all investigators and study personnel, but accessible 24 hours a day, every day, in case it becomes necessary to break the code and determine whether an individual child received study drug or placebo. (See DSMB section, below.)

Because this is a single-dose study, no provision needs to be made for discontinuing further use of the drug.

Other treatment

The AHRQ report¹ calling for rigorously designed, adequately sized trials suggested that, "...all subjects must be given standard supportive care." To study the effectiveness of dexamethasone in actual practice, and to avoid changing current standards of care, any use of bronchodilator therapy will be determined by local protocol and individualized for each patient based on response. Patients who receive

bronchodilator therapy will be enrolled and assigned to therapeutic subgroups, which will be analyzed. Because inhaled albuterol is a typical standard treatment tried in most centers,²⁶ and because dexamethasone may work to some extent by potentiating adrenergic bronchodilation, some participating centers will be those using at least one to two albuterol inhalations for moderate-to-severe bronchiolitis. Other centers may prefer to use racemic epinephrine.²⁷⁻³² Still others may prefer to avoid any bronchodilator in some cases.^{33, 34} Clinicians would determine “standard supportive care” based on local practice and patient response. To prevent any withholding of therapy, patients are allowed to have received bronchodilators for the current episode within 1 week, including treatments given prior to arrival at the ED. Patients who respond to bronchodilators may receive additional treatments within the 4-hour observation period. Bronchodilator administration would be recorded and used in subgroup analysis.

Diagnostic testing

The AHRQ researchers found that, “...existing data do not support the usefulness” of testing to diagnose bronchiolitis. Diagnostic testing, if performed, will be done in accordance with current standard ED practice at each institution. No additional studies will be required or suggested for this protocol, and no added financial charges will accrue to patients. If a viral diagnostic study or chest radiography is obtained by standard practice, results will be recorded for analysis. Because these results may not be available during the ED visit, they can be extracted at chart review.

Other procedures

Study medication will be given as soon as practical after enrollment. Patients will be observed in the ED for 4 hours after treatment with study medication. Permanent ED staff (faculty, fellows, physician’s assistants, nurse practitioners, or respiratory therapists) will record baseline, 1-hour and 4-hour respiratory rates, and RDAI scores. In addition, oximetry readings at these times will be made with patients awake and upright.

Participating clinicians will have reviewed a PowerPoint@program with training on the RDAI score. Clinicians will also perform their usual clinical assessments that may examine variables including oximetry, respiratory rate, respiratory effort, severity of wheezing, other auscultatory findings, and the patient’s state of comfort (attention, affect, activity, feeding, sleeping, etc.). The decision to admit or discharge the patient will be made according to standard current practice at each institution based on clinical assessment after observation.

Any patients worsening to require intubation or intensive care admission during 4-hour observation will be exempted from further observation. To maintain validity under intention-to-treat, however, these patients will remain in the study for analysis. Bronchiolitis is a disease in which clinical state may change rapidly; for example, apnea may develop without regard to baseline symptoms or severity. Likewise, all prior evidence suggests that dexamethasone would be extremely unlikely to provoke rapid respiratory deterioration. Such events will, however, be collected and analyzed as serious adverse events (see section on DSMB and adverse event reporting) even if not likely related to the study drug.

Research assistants will make a telephone call to parents 7 to 10 days after the ED visit to answer a standardized questionnaire about adverse events, duration of

hospitalization if admitted, any later admission for hospital care, return ED visits, visits to other physicians or providers, any subsequent use of corticosteroid medication, and parental satisfaction. Any adverse events will be recorded and analyzed as discussed below.

STATISTICAL METHODS, DATA ANALYSIS, AND POWER

Simple hypotheses will be tested using bivariate methods (t-test or Mann-Whitney test, and Chi-squared or exact tests, as appropriate). Outcomes involving rates and proportions will be analyzed by multivariate log-linear and logistic regression methods. Changes in respiratory scores over the period of observation will be compared, taking as covariates treatment center, age, duration of symptoms, and baseline RDAI scores. The effect of these covariates on the probability of admission will be analyzed by logistic regression.

Power

The AHRQ report¹ recommends, “Studies should be powered to detect meaningful differences in clinically relevant outcomes.” In research following previous negative studies, it is important to avoid Type II error, the failure to detect a true difference if it exists. Therefore, 90% power has been set as a target rather than the more typical 80%. With an alpha of 0.05, this would require 343 patients *in each group* to detect a true difference between a 40% admission rate (the approximate current rate for moderate to severe bronchiolitis) in one group and 28% in the other. At this absolute rate reduction of 12%, a number-needed-to-treat analysis suggests that 8.3 patients would require dexamethasone treatment to prevent one hospitalization. This appears a reasonable minimum treatment effect to attempt to detect. At this size, the study would have sufficient power to detect a reduction in admission rates less than half that noted in the study cited above.¹⁸ This study, which involved just 70 children, showed an absolute rate reduction of 25%. Even allowing for 15% loss to follow-up, approximately 400 patients in each group should be enrolled. Even if as few as 300 patients were analyzed in each group, the study would retain greater than 85% power to detect a 12% absolute difference in admission rates.

Subgroup analysis

Analysis of excessive subgroups and multiple outcomes is to be avoided in an initial study to avoid statistical problems associated with multiple comparisons.¹ Two particular subgroups are of interest, however.

As noted above, one goal of this study is to assess effectiveness in real-world treatment groups, given that “different treatment modalities have been in practice for some years.”¹ As noted, many patients will receive albuterol as part of routine treatment. To achieve 80% power to detect a true difference at least as large as that between 21% and 42% admission rates, subgroups receiving racemic epinephrine or no adrenergic medication would require at least 200 patients in each subgroup (100 each in treatment and placebo arms). Preliminary surveys of practice patterns at participating centers suggest that this should be achievable for racemic epinephrine. Approximately 90% of patients, however, currently receive at least a trial of adrenergic therapy. It is, therefore, unclear whether complete avoidance of adrenergic medication in 200 patients is

practicable under current practice patterns, and this might have to be pursued in future studies. The fact that 90 to 100% of patients currently receive adrenergic medications, however, combined with the fact that adrenergics were used in 100% of patients in the Canadian study,¹⁸ suggests that this trial will be able to meet its goal of assessing real-world effectiveness.

The other subgroup of interest is RSV-associated bronchiolitis. Evidence suggests bronchiolitis is RSV-positive in only 40 to 70% of cases.³⁵ It is possible that corticosteroids could work differently in this group, although evidence of this is lacking. Preliminary work in our network suggests that viral testing is currently performed in at least half of all cases of bronchiolitis. Thus subgroups at least as large as those mentioned above should be available.

Safety analysis

Any adverse events will be reported to local IRBs as per regulations and requirements. All adverse events noted during ED treatment or in phone follow-up (per study protocol) will be reported to the CDMCC (data center) and analyzed. Serious adverse events will be reported to the site investigator and to the study coordinator at the CDMCC. Unexpected serious adverse events will be reported immediately to the site investigator, the study coordinator, and the Data Safety and Monitoring Board (DSMB). The site investigator will then obtain any additional details needed and complete an adverse events report to be faxed to the head of the DSMB. (See DSMB section, below.) The data center (CDMCC) will tabulate adverse events and report these to the DSMB.

Even at 300 patients per group, the study is powered to detect adverse events such that if none should occur, the resulting 95% confidence interval would be as small as (0, 0.01). In other words, even with just 300 patients per group, we have at minimum a 95% chance of observing at least one occurrence of an outcome with a true population rate of 1% or greater.

Capture rates

To ascertain capture rates at each center, RAs will record age and inclusion criteria on a face sheet for all patients with bronchiolitis seen during the hours of convenience sampling. The total numbers of patients with bronchiolitis during the study period will be extracted from computer records. Two resulting calculations will be available. To calculate the percentage of patients with bronchiolitis seen during hours of convenience sampling, the number seen with bronchiolitis will be divided by the total number of all patients seen during these hours. To calculate the percentage of bronchiolitis patients meeting inclusion criteria and the number successfully enrolled, the number of eligible patients will be counted and compared to the patients offered enrollment and those accepting enrollment.

Follow-up rates

As noted, follow-up in each case consists of a single phone call. To maximize validity, high follow-up rates are needed. Emergency department patients are known to have somewhat fragmentary and incomplete contact information and a risk for loss to follow-up. Therefore the research assistant will obtain extensive contact information for each family. This information will be treated as privileged health information, and kept separate from the clinical data on each patient. As detailed below, none of this contact

information will be shared with the central data repository or other sites and investigators. Prior experience in this research network suggests it is reasonable to expect follow-up rates over 80%.

PATIENT SAFETY AND CONFIDENTIALITY

Rationale

This is a research area in which clinical equipoise supports a larger, multicenter, blinded, placebo-controlled randomized clinical trial. All subjects, including the placebo group, will receive treatment consistent with the standard of care. The exclusion from the study of the critically ill, very young patients, and those with immunity problems, heart disease, lung disease, or premature birth will protect patients with high-risk and unpredictable courses of bronchiolitis. These same exclusion criteria will enhance validity, as these factors typically create an *a priori* reason for admission in children with bronchiolitis. The exclusion of mild cases will prevent unnecessary treatment and inconvenience for patients who would not be expected to benefit from a possible reduction in hospital admission rates.

Risk and inconvenience

As noted above, extensive experience with other childhood diseases suggests dexamethasone is well tolerated with very low toxicity and high safety. Extensive safety and effectiveness experience exists with this drug given in doses of 0.6 to 1 mg/kg for both asthma⁹ and croup^{20, 21, 36-41} in children, including children of the age group we propose to study. Doses as large as 1 mg/kg or larger have been used safely not only in the Canadian study mentioned, but in previous studies of croup⁴² and bronchiolitis.^{11, 12} Unlike our study, many studies have used multiple doses. Infants down to 3 months of age have been included in previous studies.^{21, 22, 36} Moreover, although corticosteroids have obvious adverse effects in long-term use, their short-term use in children has been remarkably safe. Dexamethasone seems to be particularly well tolerated, with a very low incidence even of immediate vomiting, the most common side effect of other oral corticosteroids such as prednisone or prednisolone.⁹ We have been able to discover only one adverse event reported since 1966, a case of croup complicated by *Candida* infection after prolonged administration in combination with antibiotics.⁴³

Patient discomfort is minimized by oral administration. Although dexamethasone appears extremely well-tolerated, possible short-term side effects might include vomiting at the time of administration, temporary immune suppression (hence concern about varicella), or possible mood change, typically a very mild euphoria or enhanced sense of well-being.¹⁹ Mild euphoria or increased activity might interfere with sleep.

Well known long-term steroid side effects such as adrenal suppression, thinning of skin, or alteration in body appearance are not to be expected from short-term (single-dose) treatment.

Rare, serious, short-term side effects of steroid medications may include hypertension, agitated behavior, and gastric bleeding or ulceration. These are very uncommon in extensive experience with parallel childhood disease and dosing, and would be expected to be even more rare (and brief in duration — no more than several days) with the single dose involved in this study.

Allergy to any medication is possible, but steroid medications seldom cause allergic reactions and in fact are used to treat them.

Parental inconvenience is minimized by a single follow-up phone call. Although remaining in the ED for 4 hours of observation may be inconvenient, this much observation time or more is common at present. Further, other inconvenience such as hospital admission and follow-up visits would be reduced if this study confirmed that dexamethasone has a beneficial effect on hospital admission rates or the subsequent course of bronchiolitis. This is also an area of equipoise.

Privacy, confidentiality, and federal regulatory compliance

A multicenter trial is clearly required to achieve sufficient sample size and power. Moreover, a multicenter trial will enhance study validity by providing geographic, ethnic, and cultural diversity. It will also obviate concerns that criteria for admission, the primary outcome, vary from center to center. Finally, it will allow an assessment of real-world effectiveness, rather than idealized efficacy, under realistically variable treatment protocols, and will allow insight into which of these treatments may interact in their effect with dexamethasone.

A multicenter trial will, however, require extra steps to ensure patient confidentiality. Data will be recorded on pre-formatted data sheets (Appendix C). Completed sheets will be dropped into a locked box in the emergency department. Research assistants or the site investigator will transfer these sheets to a double-locked drawer in the investigator's office. At all times, only the research assistants and investigator will have access to the data sheets. Data sheets at each center will be maintained under double lock for six years as required by federal regulations. Research assistants will electronically enter data. This will be transferred to the PECARN data center (see below) via an encrypted secure point-to-point connection provided by VPN (Virtual Private Network) or SSL (Secured Socket Layer) technology. At centers where secure electronic data transfer is not possible, data will be entered in a database on a computer locked in the local investigator's office, encrypted using state-of-the-art 128-bit software, written onto a CD-ROM, and shipped to the CDMCC via a secure delivery service with full package tracking and signature delivery.

The patient's eligibility criteria including age (date of birth) will be transferred via telephone to the Cooperative Studies Coordinating Center in Perry Point, Maryland for randomization purposes. The patient will not be identifiable from the data transferred, and the randomization center will not know the location of the participating sites, which will be identified only by site number. Thus this data will not compromise patient privacy.

As noted, exhaustive safeguards of privacy, security, and confidentiality are already in place at the data center. Despite this security, patient identifiers such as name, phone numbers, medical record number, and phone numbers, which will be required at each site to allow record completion and follow-up, will only be kept and used locally. No names, addresses, medical record numbers, or phone numbers will be sent to the data center. The date of birth and date of visit, used to calculate age, and the times used in calculations such as time of treatment and duration of visit, are the only personal data sent to the data center.

Data management and patient privacy

PECARN's Central Data Management and Coordinating Center (CDMCC), based at the University of Utah, works under a separate cooperative agreement with HRSA/MCHB to manage data generated from PECARN and oversee data quality control measures for the network. The CDMCC has substantial experience with research data transmission, security and encryption. The CDMCC will insure the confidentiality of the data at all times, as dictated under HIPAA.

Confidentiality

All data collected during the study will be treated as confidential medical information by all involved staff at each local center and the CDMCC. All research staff and personnel must maintain patient confidentiality, and all personnel at the CDMCC sign specific confidentiality agreements as a condition of employment at the University of Utah.

At each clinical center, the local investigator will store data forms in a secure locked file cabinet. The data sheet containing patient identifier information that will allow the follow-up phone call and act as a key to the unique identifier number will be separated from the clinical data forms and stored in a separate locked cabinet. HIPAA-sensitive Personal Health Information (PHI) will not be reused or disclosed to any other person or entity, except as required by regulation and law or for authorized oversight of the research project.

Data security

The CDMCC is housed in a state-of-the-art building with a dedicated, highly secure server facility containing sufficient hardware to handle several thousand simultaneous connections. These resources amply serve the information systems requirements of PECARN in implementing the proposed study.

Facilities include a dedicated, separately locked, on-site computer server room with a computer-safe fire suppression system, industry-grade air conditioning, and separate air filtration. Its physical and electronic security is coordinated with the University of Utah. The main firewall hardware is a redundant NetScreen-500, capable of 700 Mbps firewall throughput, supporting up to 10,000 IPsec (IP Security protocol) tunnels, and allowing 250,000 concurrent sessions. To assure high performance virtual private networks (VPN) as used by CDMCC, the network infrastructure includes a Cisco VPN 3030 Concentrator, which supports 1,500 simultaneous VPN sessions with hardware-based encryption at 50 Mbps throughput. The concentrator uses the IPsec encapsulating security payload (ESP) with 3DES (168-bit) encryption, tunneled with the IPsec tunneling protocol. Internal network speed within IICRC is 100 Mbps. Network equipment includes two HP Procurve 4000 M high-speed switches. User authentication is centralized in the IICRC with two Windows Active Directory servers. There are five servers with aggregate storage in excess of 300 gigabytes; four of these servers are equipped with RAID configurations that assure rapid recovery of data in the event of hardware failure. Servers are backed up daily using three DLT tape backup systems. Tapes are stored in a fireproof safe inside the server room.

There is a receptionist at the only entrance to the CDMCC during all hours that the entrance is unlocked; the servers are contained in a dedicated server room within the

CDMCC and this server room has a separate lock. Keys to the server room are available only to the two full-time data managers and the center's director (J. Michael Dean, MD). Research access into the CDMCC from outside the firewall is established with VPN software, requires user authentication at the security gateway, and requires separate user authentication on the CDMCC domain servers. These security arrangements meet all requirements of the Health Insurance Portability and Accountability Act (HIPAA), as well as other Federal regulatory requirements.

Additional CDMCC functions

The CDMCC will help coordinate and oversee the training of PECARN physicians and research assistants in the Manual of Operations for the study, and provide electronic (computer-based) instruction as well. Statisticians at the CDMCC will assist with and validate the analysis of data for this study in collaboration with the principal investigators and other PECARN statisticians.

MONITORING AND QUALITY ASSURANCE

Monitoring

As noted, this study is exempt from the specific monitoring required under Investigational New Drug regulations. Training, monitoring, and auditing are planned, however, to ensure scientific validity and patient safety.

A detailed Manual of Operations will be designed and updated at the CDMCC and distributed to each study center. The CDMCC has designed a monitoring and audit scheme to be followed throughout the study.

Site monitoring proved very helpful in the first year. More comprehensive monitoring is now conducted as our grant application has been funded. Trained site monitors from the network will visit each participating site to assure scientific validity and patient safety. A monitor will conduct site visits in three phases: an initiation visit, a mid-study visit, and a seasonal closeout visit. The focus of the initiation visit will be to audit for study requirements and review prior training on study procedures. Mid-study visits will include a comprehensive review of patient records, verification of source documents, informed consent, and any protocol deviations or adverse events. The closeout visit will examine these issues in addition to the completion of data entry. The monitor will provide each site with a written report and sites will be required to follow up on any deficiencies. Additional visits will be made to sites found to have significant protocol violations or any safety issues.

Quality assurance

To assess internal data validity, the medical charts of ten already-entered patients will be selected by the CDMCC for re-abstraction by the research assistant at one month. To assess cross-observer validity, five additional charts will be selected for review by the local investigator.

The CDMCC will monitor data from each site as it arrives at the data center. Data consistency and completeness will be audited using standard techniques. Missing and inconsistent data will be called to the attention of the site investigator (without unblinding) to allow real-time correction and thus enhance validity.

Data safety and monitoring board (DSMB)

A DSMB will be formed from PECARN personnel not participating in this trial. This board will include a senior scientist, an ethicist, a researcher familiar with respiratory disease, and a community representative. To maintain blinding of all investigators, and to monitor for safety problems while maintaining blinding, adverse events will be reported to the DSMB. Because of the short period of data collection, because the projected sample size will be required to study subgroups even if overall statistical confidence should be achieved with fewer patients as the study progresses, and because of enrollment caps in place for the entire study and for individual centers, no interim data analysis or stopping rule analysis is planned.

The primary responsibility of the DSMB is to ensure the safety of the patients. None of the members will be investigators in the study. The DSMB will appoint a study monitor who will act as coordinator for DSMB activities.

The DSMB may meet in person or by telephone conference. Routine business may also be addressed via email. The work of the DSMB, however, will be conducted in complete isolation from any of the investigators of this study. Breaches of this confidence by any member of the DSMB that might impair investigator blinding will be strictly avoided.

The proceedings of any DSMB meeting will be recorded in minutes. These minutes will be isolated from the investigators until after the trial database has been locked and the study has been unblinded.

The randomization code of study medication will be kept by the DSMB at the University of California, Davis, where randomization will be coordinated. In the event of an adverse event, the DSMB may break the randomization code and unblind itself.

In keeping with FDA guidelines and Good Clinical Practices, adverse events are defined as any untoward occurrence in a study patient following administration of study drug, whether or not related to the study. Serious adverse events are defined as any that lead to death, life-threatening complications, hospitalization, prolongation of existing hospitalization, or significant disability. . Unexpected serious adverse events are those whose nature and severity are not in keeping with the study protocol and informed consent documents. Examples might include death, operations, or sepsis. All adverse events will be collected on standard data forms and reported to the CDMCC (data center). Serious adverse events (SAEs) will be reviewed by the site PI, analyzed, and reported to the data center, which in turn reports to the DSMB. Because hospital admission is expected in at least 40% of patients coming to an ED with bronchiolitis of this severity, it will be reported to the DSMB as part of their routine data analysis rather than in separate SAE reports.

The local investigator must report to the data center study coordinator and to the DSMB study monitor by fax or telephone within 24 hours any unexpected serious adverse event at any time during the clinical study or within 7days (ie, 5 half-lives) of a patient's receiving the study medication, whether or not related to the study drug. Investigators should not wait for other information before notifying the study monitor of an unexpected serious adverse event. This telephone report should be followed by a full written report. Pertinent medical records should be reviewed. In the event of any potential safety concern, the head of the DSMB will contact the Principal Investigator to recommend any needed modification or even cessation of the study.

POTENTIAL RISKS AND BENEFITS

Potential risks, adverse effects, and parental inconvenience are discussed above under Risk and Inconvenience. There are no direct potential benefits of taking part in this study, unless the study drug proves effective, and then these would only occur in those randomized to receive the drug. Indirect benefits might include the knowledge that this study will increase knowledge about this disease. The alternative treatment for parents who do not want to participate will be standard bronchiolitis care without randomization, study drug, or placebo.

A parent compensation fee of \$15 per patient will be authorized to offset the potential inconvenience of 4-hour observation and a single follow-up telephone call. Note that each site will arrange how to offer this compensation (meal voucher, taxi voucher, phone voucher, cash, etc.) according to local needs and *only* in accord with local IRB approval.

A fiscal offset for additional time and effort of \$25 per patient will be authorized to be paid to the clinical department or division employing the participating clinicians and PI taking part in the study. This will only be paid after patient enrollment is completed for the season, and its use will be governed by pertinent institutional rules and regulations.

COSTS TO SUBJECTS

There will be no costs to subjects taking part in this study.

FUNDING AND CONFLICT OF INTEREST

This study is funded using the internal resources of PECARN and MCHB Grant no. R40MC04298-01-00. No funds will accrue to any of the investigators. No funding is sought or exists from commercial sources. No relationship exists or is sought with any commercial company. The study drug is long since out of patent in the US, and the results of this study are not expected to lead to any changes of marketing, advertising, or profitability regarding this drug.

CONTRACTUAL AGREEMENTS

This research protocol originates at the University of Utah College of Medicine. Participating centers take part in this study under already-existing agreements within PECARN. Grant funding contracts are already in place between participating institutions and their PECARN regional nodal centers.

PECARN sites and personnel

This research will be conducted at sites in PECARN, a network including academic as well as community medical centers. The principal investigator for this project is:

Howard M. Corneli, MD

Professor, Department of Pediatrics
Division of Emergency Medicine
University of Utah College of Medicine
Primary Children's Medical Center
100 North Medical Drive

Salt Lake City, UT 84113

Co-principal investigators for this project are:

**Kathy N. Shaw, MD, MSCE and
Joseph J. Zorc, MD**

Department of Emergency Medicine
Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard
Philadelphia, PA 19104

Prashant Mahajan, MD, MPH

Assistant Professor
Department of Emergency Medicine
Children's Hospital of Michigan
3901 Beaubien — Emergency Department
Detroit, Michigan 48201-2196

Other co-investigators are listed on the cover page of this protocol,

REFERENCES

1. Management of Bronchiolitis in Infants and Children. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
2. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA* 1999;282(15):1440-1446.
3. Levy BT, Graber MA. Respiratory syncytial virus infection in infants and young children. *J Fam Pract* 1997;45(6):473-481.
4. Englund JA. Prevention strategies for respiratory syncytial virus: passive and active immunization. *J Pediatr* 1999;135(2 Pt 2):38-44.
5. Schuh S, Johnson D, Canny G, Reisman J, Shields M, Kovesi T, et al. Efficacy of adding nebulized ipratropium bromide to nebulized albuterol therapy in acute bronchiolitis. *Pediatrics* 1992;90(6):920-923.
6. Gadomski AM, Lichenstein R, Horton L, King J, Keane V, Permutt T. Efficacy of albuterol in the management of bronchiolitis [see comments]. *Pediatrics* 1994;93(6 Pt 1):907-912.
7. Ho L, Collis G, Landau LI, Le Souef PN. Effect of salbutamol on oxygen saturation in bronchiolitis. *Arch Dis Child* 1991;66(9):1061-1064.
8. Lugo RA, Salyer JW, Dean JM. Albuterol in acute bronchiolitis--continued therapy despite poor response? *Pharmacotherapy* 1998;18(1):198-202.
9. Qureshi F, Zaritsky A, Poirier MP. Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma. *J Pediatr* 2001;139(1):20-26.
10. 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(3):181-185.
11. Roosevelt G, Sheehan K, Grupp-Phelan J, Tanz RR, Listernick R. Dexamethasone in bronchiolitis: a randomised controlled trial [see comments]. *Lancet* 1996;348(9023):292-295.
12. Klassen TP, Sutcliffe T, Watters LK, Wells GA, Allen UD, Li MM. Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized, controlled trial [see comments]. *J Pediatr* 1997;130(2):191-196.
13. Berger I, Argaman Z, Schwartz SB, Segal E, Kiderman A, Branski D, et al. Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up. *Pediatr Pulmonol* 1998;26(3):162-166.
14. Klassen TP. Recent advances in the treatment of bronchiolitis and laryngitis. *Pediatr Clin North Am* 1997;44(1):249-261.

15. 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 [see comments]. *Thorax* 1997;52(7):634-637.
16. Goebel J, Estrada B, Quinonez J, Nagji N, Sanford D, Boerth RC. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clin Pediatr (Phila)* 2000;39(4):213-220.
17. Garrison MM, Christakis DA, Harvey E, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: A meta-analysis. *Pediatrics* 2000;105(4):E44.
18. Schuh S, Coates AL, Binnie R, Allin T, Goia C, Corey M, et al. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. *J Pediatr* 2002;140(1):27-32.
19. . Physician's Desk Reference. Montvale, NJ: Medical Economics; 2002. p. 1780-1782.
20. Jaffe DM. The treatment of croup with glucocorticoids. *N Engl J Med* 1998;339(8):553-555.
21. Rittichier KK, Ledwith CA. Outpatient treatment of moderate croup with dexamethasone: intramuscular versus oral dosing. *Pediatrics* 2000;106(6):1344-1348.
22. Kunkel NC, Baker MD. Use of racemic epinephrine, dexamethasone, and mist in the outpatient management of croup. *Pediatr Emerg Care* 1996;12(3):156-159.
23. Scarfone RJ, Loiselle JM, Wiley JF, 2nd, Decker JM, Henretig FM, Joffe MD. Nebulized dexamethasone versus oral prednisone in the emergency treatment of asthmatic children. *Ann Emerg Med* 1995;26(4):480-486.
24. Chou J, D D, Dumont R, Ensom M. Stability of dexamethasone in extemporaneously prepared oral suspensions. *Can J Hosp Pharm* 2001;54(2):96-101.
25. Ward R. In: Corneli H, editor; 2003.
26. Nahata MC, Schad PA. Pattern of drug usage in bronchiolitis. *J Clin Pharm Ther* 1994;19(2):117-118.
27. Bertrand P, Aranibar H, Castro E, Sanchez I. Efficacy of nebulized epinephrine versus salbutamol in hospitalized infants with bronchiolitis. *Pediatr Pulmonol* 2001;31(4):284-288.
28. Numa AH, Williams GD, Dakin CJ. The effect of nebulized epinephrine on respiratory mechanics and gas exchange in bronchiolitis. *Am J Respir Crit Care Med* 2001;164(1):86-91.
29. Barr FE, Patel NR, Newth CJ. The pharmacologic mechanism by which inhaled epinephrine reduces airway obstruction in respiratory syncytial virus-associated bronchiolitis. *J Pediatr* 2000;136(5):699-700.

30. Reijonen T, Korppi M, Pitkakangas S, Tenhola S, Remes K. The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995;149(6):686-692.
31. Menon K, Sutcliffe T, Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis [see comments]. *J Pediatr* 1995;126(6):1004-1007.
32. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis [see comments]. *J Pediatr* 1993;122(1):145-151.
33. Perlstein PH, Kotagal UR, Bolling C, Steele R, Schoettker PJ, Atherton HD, et al. Evaluation of an evidence-based guideline for bronchiolitis [In Process Citation]. *Pediatrics* 1999;104(6):1334-1341.
34. Gadowski AM, Aref GH, el Din OB, el Sawy IH, Khallaf N, Black RE. Oral versus nebulized albuterol in the management of bronchiolitis in Egypt. *J Pediatr* 1994;124(1):131-138.
35. Schlesinger C, Koss MN. Bronchiolitis: update 2001. *Curr Opin Pulm Med* 2002;8(2):112-116.
36. Donaldson D, Poleski D, Knipple E, Filips K, Reetz L, Pascual RG, et al. Intramuscular versus oral dexamethasone for the treatment of moderate-to-severe croup: a randomized, double-blind trial. *Acad Emerg Med* 2003;10(1):16-21.
37. Luria JW, Gonzalez-del-Rey JA, DiGiulio GA, McAnaney CM, Olson JJ, Ruddy RM. Effectiveness of oral or nebulized dexamethasone for children with mild croup. *Arch Pediatr Adolesc Med* 2001;155(12):1340-1345.
38. Ausejo M, Saenz A, Pham B, Kellner JD, Johnson DW, Moher D, et al. The effectiveness of glucocorticoids in treating croup: meta-analysis. *BMJ* 1999;319(7210):595-600.
39. Skolnik NS. Treatment of croup. A critical review. *Am J Dis Child* 1989;143(9):1045-1049.
40. Leipzig B, Oski FA, Cummings CW, Stockman JA, Swender P. A prospective randomized study to determine the efficacy of steroids in treatment of croup. *J Pediatr* 1979;94(2):194-196.
41. Eden AN, Kaufman A, Yu R. Corticosteroids and croup. Controlled double-blind study. *JAMA* 1967;200(5):403-404.
42. Postma DS, Jones RO, Pillsbury HC, 3rd. Severe hospitalized croup: treatment trends and prognosis. *Laryngoscope* 1984;94(9):1170-1175.
43. Burton DM, Seid AB, Kearns DB, Pransky SM. Candida laryngotracheitis: a complication of combined steroid and antibiotic usage in croup. *Int J Pediatr Otorhinolaryngol* 1992;23(2):171-175.