Study Protocol

Steroid Use for the Treatment of Non-RSV Bronchiolitis

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Scientific background: Bronchiolitis is the most common viral lower respiratory tract infection experienced by children < 24 months. The most common pathogen causing bronchiolitis is RSV, with the highest incidence of infection occurring throughout late winter/spring. Signs and symptoms include nasal congestion, cough, tachypnea, wheeze, and rales, and may progress to symptoms of respiratory distress (accessory muscle use, nasal flaring, head bobbing). While RSV is the predominant virus associated with bronchiolitis (up to 40% of cases), other viruses including rhinovirus, influenza, human metapneumovirus, and parainfluenza virus are also common causes. The second most common viral etiology of bronchiolitis is rhinovirus, which may account for up to 25%-40% of cases.

Bronchiolitis is one of the leading causes of hospitalization for young children. In 2002, it was estimated that bronchiolitis hospitalization costs totaled $543 million, with a mean length of stay of 3.3 days. One study in 2013 indicated that although the incidence of hospitalizations for bronchiolitis decreased in the early 2000s, national healthcare utilization costs increased from $1.34 billion to $1.73 billion (a 30% increase). Due to the prevalence of bronchiolitis and high utilization cost, the American Academy of Pediatrics (AAP) issued an update in 2014 of the 2006 guidelines for the diagnosis, management, and prevention of bronchiolitis. These guidelines indicate that bronchiolitis should be diagnosed clinically and treated with supportive care, such as nasal suctioning, intravenous fluid administration, and supplemental oxygen if required. These guidelines specifically recommend against the use of bronchodilators, nebulized hypertonic saline, systemic corticosteroids, and antibacterials. Since these guidelines have been published, studies show that there has been on overall decrease in both healthcare utilization costs and length of admission, but that there has not been a significant impact on all-cause 7-day readmission rates.

While the treatment and management of RSV bronchiolitis has been extensively studied and validated, there is significantly less evidence to support similar management in children with non-RSV bronchiolitis. We conducted a literature review of over 120 articles related to the treatment of bronchiolitis with steroids. Many articles, including the AAP 2014 revised guidelines, discuss the limited use of steroids in the treatment of bronchiolitis. A 2007 PECARN multicenter study also showed no significant difference in hospitalization rate or re-admission rate with steroid use. These studies, however, do not differentiate between RSV and non-RSV bronchiolitis.

Studies evaluating the immune response to different viral etiologies of bronchiolitis indicate that there may be a significant difference in the pathophysiology of disease. For example, RSV bronchiolitis causes an increased expression of β glucocorticoid receptors (GR) with no increase in α-GR, leading to a lower ratio of α/β receptors, which has been associated with an insensitivity response to glucocorticosteroids. In contrast, human rhinovirus-associated bronchiolitis has been associated with a higher Th2 helper cell response leading to more histamine release than RSV, which causes a Th1 predominant response. Additionally, a meta-analysis from 2017 suggested that infection with rhinovirus leading to wheezing before the age of 36 months is associated with increased risk of developing asthma later in life, possibly through airway remodeling, epithelial release of cytokines, and upregulated expression of genes predisposing to asthma. The mechanism of action of corticosteroids revolves around the inhibition of initial inflammatory

responses such as vasodilation and chemotaxis of leukocytes to sites of inflammation. Since rhinovirus appears to have a different pathophysiology of immune response, it is possible that bronchiolitis secondary to other non-RSV viruses may respond to different immunomodulators, specifically steroids. This pilot study will contribute knowledge about the utility of steroid use in non-RSV bronchiolitis both clinically in terms of patient outcomes, and economically in terms of hospital utilization. If the proposed aims are achieved, this contribution will be significant because there may be reason to re-evaluate the current AAP Guidelines for diagnosis and management of bronchiolitis. We hypothesize that steroid use in this cohort will reduce length of stay, and subsequently reduce hospital costs through reduction of both 7-day same cause re-admission rate and escalation of care (transfer to ICU).
In the short term, our work will address the feasibility of conducting a clinical trial assessing the utility and safety of steroid use in non-RSV bronchiolitis in the inpatient setting. Moreover, the work proposed here will develop a platform for a larger, multi-center double-blinded randomized control trial addressing the same question. This pilot study will establish expected target enrollment rates, adherence and drop-out rates, expected length of stay, and expected severity of disease assessed with the Kristjansson score at time of discharge for use in sample size and power calculations for future phase II/III trials. Thus, this work will be a foundational resource providing a research strategy and protocol for a larger scale trial.

Objectives: The long-term objective of this research is to improve the clinical course and outcomes of children diagnosed with non-RSV bronchiolitis. The objective of this proposal is to determine the efficacy of steroid use as a treatment modality in children < 24 months diagnosed with non-RSV bronchiolitis. The central hypothesis is that the use of standard airway- dose steroids (0.6mg/kg dexamethasone) will improve the clinical outcome of children hospitalized for non-RSV bronchiolitis, which will be evident by decreased length of stay. The central hypothesis was formulated based on data showing an interleukin response to rhinovirus that is dampened by steroid administration. The rationale underlying this proposal is that the completion of this research will identify a new treatment option for non-RSV bronchiolitis. The proposed work may change the currently accepted practice guidelines for diagnosis and management of bronchiolitis. The central hypothesis will be tested by pursuing these specific aims:
1) To determine the extent to which steroid administration reduces hospital length of stay for clinical non-RSV bronchiolitis.
Hypothesis: Steroid administration will decrease duration of admission from time of admission from the emergency department (ED) to time of discharge instructions being printed.
2) To determine the extent to which steroid administration reduces the severity of bronchiolitis by using the Modified Tal Score to assess patients at admission, enrollment (if differs from admission time), 24 hours after administration of intervention, and discharge.
Hypothesis: Steroid administration will reduce the severity of bronchiolitis, which will be evident by a lower Modified Tal Score at 24 hours after medication administration.

Design/Methods: The study is a double-blind, randomized control trial. All participants will be treated with standard of care for viral bronchiolitis, including supportive care. All participants will also have had some form of viral testing confirming they do not have RSV or influenza. In

addition, half the participants will receive standard airway dosing of dexamethasone (0.6mg/kg) orally, and the other half will received placebo (sugar water 0.6mL/kg).

Eligibility Criteria:

Inclusion criteria:
1. Less than or equal to 24 months
2. First episode of wheezing or a clinical diagnosis of bronchiolitis
3. Admitted to the general pediatric service at UPMC Children's Hospital of Pittsburgh
4. Between 2/1/20 and 12/31/22
5. Ability of a parent or guardian to understand and comply with the study procedures
6. Signed written informed consent by parent or guardian
7. Respiratory viral testing obtained within 24 hours of admission

Exclusion Criteria
1. Preterm birth < 35 weeks
2. Presence of underlying cardiopulmonary, neuromuscular, or other complex disease
3. Admission to the PICU
4. Coinfection with influenza infection, RSV, acute COVID-19, or concomitant bacterial infection (such as pneumonia) as documented within the past 72 hours (per chart review)
5. History of allergy or reaction to steroids
6. History of an underlying chronic medical condition -including chronic heart disease, chronic lung disease (except asthma),congenital anomalies of the airways or lung, cystic fibrosis, chronic renal disease including nephrotic syndrome, protein losing enteropathy of any cause, severe malnutrition, glaucoma, neurocognitive disorders, metabolic disorders (including phenylketonuria, diabetes mellitus), or genetic disorders (note: genetic syndromes such as Down syndrome and Edwards Syndrome are excluded; however, children with genetic disorders (e.g., hemophilia) but who do not have a genetic syndrome may not satisfy this particular exclusion criterion; it is important that children with such genetic disorders do not have symptoms and/or comorbidities that would pose additional risk to them nor jeopardize the adequacy of study assessments.")
7. History of a condition that compromises the immune system -HIV infection, primary immunodeficiency, anatomic or functional asplenia; receipt of a hematopoietic stem cell or solid organ transplant at any time; receipt of immunosuppressive therapy including chemotherapeutic agents, biologic agents, antimetabolites or radiation therapy during the past 12 months; or daily use of systemic corticosteroids for more than 7 consecutive days during the past 14 days.
8. Any other condition that in the judgment of the investigator precludes participation because it could affect the safety of the subject
9. Any patient admitted to the inpatient general pediatrics teams from 4pm-9pm, as patients are to be enrolled in the study within 10 hours of admission and medication distribution cannot be complete until 7am.
10. Any patient who has previously received a dose of steroids medication in the emergency department within 24 hours prior to admission

Statistical Considerations: We will compare mean duration of hospital stay in the two treatment groups using the student T-test. As a secondary outcome we will compare mean scores on the Kristjansson scale (range 0 to 9) at each time point using generalized estimating equations

between the two treatment groups. Because this is a pilot study we will be underpowered, however, this study will provide data that will allow us to estimate the sample size needed for a future study. The number of time points to be used for the generalized estimating equation can be determined ad hoc to include a reasonably balanced sample to make the comparison valid.