Intermittent versus continuous pulse oximetry monitoring of infants admitted for bronchiolitis

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3. Christus Santa Rosa Children's Hospital, San Antonio, TX

Protocol Version: (*2.0)* **Protocol Date: 10/30/2013**

1. STUDY OBJECTIVES/HYPOTHESIS

Primary Objective(s)

1. To assess the impact of intermittent versus continuous pulse oximetry monitoring on length of stay of children admitted for bronchiolitis.

    a. Hypothesis: Children who undergo intermittent pulse oximetry monitoring will have a significantly decreased length of stay than children hospitalized for bronchiolitis who are continuously monitored by pulse oximetry.

Secondary Objectives:

1. To assess the difference of intermittent versus continuous pulse oximetry monitoring in the number and types of medical interventions received by patients admitted for bronchiolitis

2. To calculate the estimated difference in cost of stay for patients receiving intermittent versus continuous pulse oximetry.

2. BACKGROUND

Bronchiolitis describes a lower respiratory tract infection (LRTI) syndrome that can be caused by multiple viruses in infants. It is the most common LRTI in children less than 24 months old, and accounts for an estimated 90,000 hospitalizations annually at a cost of more than $700 million in children less than 12 months of age1. Despite the widespread nature of this illness, practitioners vary greatly in how they diagnose and manage children with bronchiolitis2. In 2006 the American Academy of Pediatrics (AAP), in conjunction with the American Academy of Family Practice, AHRQ and others, developed and released evidence-based guidelines on bronchiolitis diagnosis and treatment in an effort to standardize management of this illness among practitioners3. As part of these recommendations, patients admitted to the hospital were recommended to receive supplemental oxygen if deemed clinically necessary. This level has been set as a transcutaneously-measured peripheral oxygen concentration (SpO2) of 90%. However, this recommendation is based on expert opinion.

Physiologic data based on the oxyhemoglobin dissociation curve demonstrates that small increases in arterial partial pressure of oxygen (PaO2) are associated with marked improvement in SpO2 when the latter is less than 90%; with SpO2 readings greater than 90% it takes very large elevations in PaO2 to effect further increases. In the case of bronchiolitis, no data exists to suggest such increases result in any clinically significant difference in physiologic function, patient symptoms, or clinical outcomes. The 2006 guidelines suggest a SpO2 persistently less than 90% as criteria for supplemental oxygen therapy or possible hospital admission in children with bronchiolitis. However, there is scant evidence regarding the appropriate SpO2 level for which to initiate therapy or to proceed with hospitalization in otherwise healthy children.

No studies directly address the impact of transient hypoxia on long-term outcomes for patients who have had bronchiolitis. However, previous data shows that healthy infants will experience multiple episodes of SpO2 less than 90% while sleeping4. Additionally, no causation has been proven for cognitive impairment in children who experience repeat episodes of transient hypoxia from asthma exacerbations5. Given that, unlike asthma, children with bronchiolitis do not generally suffer multiple, repeated, or prolonged episodes of hypoxia during the course of their illness as well as the fact that bronchiolitis is a self-limited disease, it is quite likely these patients would be at an even smaller risk for any long-term cognitive sequelae. Despite this, pulse oximetry monitoring has contributed to significant changes in clinical practice.

Since the advent of widespread pulse oximeter use in the emergency department and on inpatient pediatric units, hospitalization rates have increased by over 250%6. Additionally, some studies suggest close monitoring of oxygenation for children admitted with bronchiolitis increases length of stay for children who otherwise clinically would meet discharge criteria7. Continuous monitoring of pulse oximetry in children not receiving supplemental oxygen is also discouraged under the 2006 guidelines (recommendation 7b). Despite these recommendations, continuous monitoring of infants with bronchiolitis often occurs throughout the entire hospitalization. To date there has

never been a prospective, randomized trial to fully elucidate the effect of removing continuous pulse oximetry monitoring from care of bronchiolitis patients.
This section should describe what is known about your disease/condition of interest in relation to your research question. Summarize the available clinical study data (published and available unpublished data) with relevance to the protocol – if none available, include a statement that there is no available clinical research data to date.

3. RATIONALE

Intermittent pulse oximetry measurement of children admitted for bronchiolitis but not requiring supplemental oxygen may result in decreased length of stay in the hospital. This could result in significant cost savings for parents/guardians as well as decreasing the nosocomial and iatrogenic illness risks associated with hospitalization.

4. STUDY DESIGN

This is a randomized trial with two study arms: (1) children who receive continuous transdermal pulse oximetry monitoring throughout admission; and (2) children who receive intermittent pulse oximetry monitoring when oxygen saturations remain above 90%. Both groups will receive continuous pulse oximetry monitoring while receiving supplemental oxygen for hypoxia as detailed below.

Randomization Procedure and Control:
The two treatment groups in this protocol will be randomized within each participating institution. Patients who are eligible for randomization will be entered sequentially starting with the lowest random number at that institution. A faxed report from the affiliate sites detailing the sequential number and study arm will be faxed to the Children's Mercy (primary) study site to allow for close monitoring of enrollment progress. Study enrollment will occur within 24 hours of hospital admission for bronchiolitis. The study will not be blinded due to the obvious differences in monitoring that will be apparent to healthcare providers, research personnel, patients, and families.

5. Each patient will undergo randomization via computer-generated random allocation. Randomization will occur in separate batches at each study site. Each center will label gathered data with sequential subject ID codes. Upon entering the study, each new patient will be entered sequentially starting with the ID number available at that center.

6. TARGET STUDY POPLUATION SPECIFICS

Inclusion Criteria

- Children less than or equal to 24 months old with a history of term delivery (gestational age ≥37 weeks) admitted with a presumptive diagnosis of bronchiolitis

- Bronchiolitis will be defined as an episode of wheezing or increased work of breathing associated with signs of an upper respiratory tract infection experienced by a patient

- Enrollment within 24 hours of admission

Exclusion Criteria

- History of severe cardiac or pulmonary illness, including but not limited to bronchopulmonary dysplasia, chronic lung disease, asthma/reactive airway disease, congenital heart disease, heart failure, and cardiothoracic surgery

- History of home albuterol use for asthma or reactive airway disease

- History of use of bronchodilator with successful patient response to the medication prior to study enrollment

- Use of corticosteroids within the past two weeks up to day of admission

- Use of antibiotics after admission for suspected pneumonia or similar pulmonary disease

- History of premature birth (<37 weeks gestation)

- History of receiving palivizumab (anti-RSV antibody)

- Diagnosis of chronic immune deficiency, hematologic dyscrasia, or cancer

- Chronic treatment with immunosuppressants

- Parents/guardians unable to give informed consent in English

- Need for PICU transfer at any point during illness

- Transfer from an outside institution where patient was hospitalized for ≥12 hours

- Previous enrollment in this study

- Pediatric care team refuses to comply with study protocol. List specific clinical contraindications.

7. STUDY CONDUCT

Inpatient pulse oximetry monitoring

a) Inpatient treatments common to both groups:

All patients will receive vital sign evaluations per nursing routine and as needed throughout the admission. Superficial nasal suctioning via suction catheter or bulb will be conducted as needed. Nasopharyngeal suctioning with catheter may also be

performed depending on local practice at each study site and discretion of the primary medical team. Upon enrollment patients will receive one dose of nebulized albuterol with monitoring for improvement in respiratory function if deemed clinically indicated by the admitting physician team. The remainder of evaluation and management measures will be based on clinical assessment and adherence to the 2006 AAP bronchiolitis guidelines as well as local practice guidelines where applicable.

b) Continuous pulse oximetry monitoring group

Patients will be placed on continuous pulse oximetry from admission until discharge. Management of oxygenation status will be as outlined below.

c) Intermittent pulse oximetry monitoring group

Patients with SpO2 of ≥90% will undergo pulse oximetry monitoring only when vital signs are being evaluated as scheduled or if clinically significant deterioration is suspected by healthcare personnel or upon parental/guardian request. If the patient is found to be <90% on spot check, they will then be monitored continuously for five minutes to determine if hypoxia is transient. This observation period is waived if oxygenation drops below 80%. This SpO2 level is used because 80% is near the inflection point of the oxyhemoglobin dissociation curve and represents a transition to markedly decreased available arterial oxygen (PaO2) and markedly increased tissue hypoxia. Persistent hypoxia will result in initiation of supplemental oxygen and initiation of continuous monitoring while on oxygen. Once the patient has been off supplemental oxygen for 1 hour, the continuous oximetry monitoring will be stopped and spot checks resumed for those children randomized to intermittent monitoring.

d) Weaning of supplemental oxygen

Supplemental oxygen will be initiated for an initial goal SpO2 ≥92%. This will be supplied by nasal canula. Pulse oximetry will be monitored continuously in both groups as detailed above. Oxygen rate may be weaned when SpO2 remains >92% for 1 hour.

Patients who are less than 10kg body weight will be weaned by 0.25 liters per minute (LPM) every hour if SpO2 is consistently greater than 92%.

Patients who are ≥10kg will be weaned 0.5 LPM every hour if SpO2 is consistently >92%.

4. Patients transferred to the PICU at any time will exit the study

5. Patient safety and data monitoring board (DSMB)

a) This will be comprised of 2-3 faculty members within the Department of Pediatrics and who are not members of the division of hospital medicine or pediatric infectious disease.

b) The committee will be tasked with reviewing the data and determining if either the study endpoint is met early (i.e. significant differences between the two groups are found at an interim analysis), or if significant differences in adverse outcomes is detected.

c) The committee will review patient outcomes at each interim analysis which will occur after enrollment of 50 subjects (performed), 100 subjects (performed), 150 subjects, 200 subjects, and study completion. Outcomes considered will be rates of transfer to higher levels of care, readmissions for the same episode of illness, and mortality. The study will be suspended if significant differences in the rate of adverse outcomes (patient mortality or clinical deterioration requiring transfer to higher level of care) between the two groups.

d) The previous data safety monitoring board will be disbanded at Hasbro Children's Hospital and a new one convened at Children's Mercy Hospital due to the change of primary study site to Children's Mercy Hospital.

e) In review of previous DSMB reports there have been no safety issues identified nor has the primary study endpoint been met early.

8. DATA COLLECTION

Data Collection Procedures

Screening prior to study enrollment
Study personnel at each site will obtain admissions data and screen for possible participants as outlined above.

Data collected while participant is admitted
Study data will be gathered after the patient has been discharged and completed the intervention.

Chart Review Data
Data will be collected by review of patient charts in the Section of Pediatric Infectious Disease office. Electronic records will be reviewed using secure computers within the Section of Pediatric Infectious Diseases.

Data to be collected include: length of stay, age at diagnosis, gender, referral location (if any), diagnostic testing completed, therapeutic measures undertaken including medications, respiratory therapies, and nursing therapies. Also data on cost of stay, complications, transfer to the intensive care unit, readmission for same illness, and mortality will be collected.

Data will be analyzed between control and intervention groups. Also, length of stay data will be compared with the previous year's length of stay data. Data from each study site will be analyzed at the primary site (Children's Mercy Hospital). Data from the Hasbro Children's Hospital and Christus Santa Rosa study sites will be transmitted to the primary site as described below.

Records to be kept

Initial screening data will be stored in a hard-copy log that contains the patient name, location, and medical record number (attached). At the end of each day this screening log will have relevant information transferred to the final screening log and the enrolled

subject logs as detailed below and then will be destroyed using confidential shredding services.

Final screening data detailing the number of patients screened, the number of patients consented, and the number and reasons for refusal to participate in the study will be kept in a separate log (attached). No personal identifiers will be kept in this log.

No personal identifiers are included in the study database but linked identifiers will exist separately in a hardcopy log (attached). The codes in this log will be stored in a locked cabinet in an office accessible only by authorized study personnel at each respective study site. This log will be destroyed at the end of the study after all relevant data has been abstracted from the patient's medical record.

The study is minimal risk and data collected are not sensitive in nature. No personal identifiers are included in the electronic database, but such identifiers are linked by patient code to the hardcopy log described above. Data will first be abstracted to a study worksheet before being entered into the electronic study database (attached). The database will be stored on a secure network drive for the Section of Pediatric Infectious Disease and accessible by password. After all data are transferred to the electronic database, the paper worksheet will be destroyed using confidential shredding services.

Aggregate data from each study site will be analyzed without exchanging the hardcopy log information in order to prevent unauthorized sharing of personal identifiers between study sites.

Database data, which will contain no personal identifiers, will be transmitted to the primary study site from collaborating sites via facsimile transmission of de-identified patient data to the Section of Pediatric Infectious Diseases office at Children's Mercy Hospital. This machine is approved for receipt of confidential information, is located in an office continuously monitored during the day and secured behind a locked door after-hours. Once this data is received at the primary study site it will be transferred to a secure drive for the Section of Pediatric Infectious Diseases as noted above.

Secure Storage of Data

The research record generated will consist of an Access database which will be housed in the Pediatric Infectious Diseases network drive on the CMH internal network. Only the data points listed in the attached data collection sheet will be entered into the research record. Security measures include: storage of the Access database on a password protected computer in a restricted assess departmental folder limited to only listed study personnel and storage of data collection worksheets in a locked cabinet within a locked office and prompt destruction of the paper worksheet after data entry into the Access database.

Study personnel responsible for data safety and integrity:

1. Dr. Russell McCulloh, primary study investigator and principal investigator at the primary study site, will serve as study personnel responsible for data security per Children's Mercy Hospital policies and as described above.

2. Dr. Michael Koster, principal investigator at the Hasbro Children's Hospital study site, will serve as study personnel responsible for data security and transmission in accordance with Hasbro Children's Hospital (part of Lifespan Healthcare) policy and this protocol.

3. Dr. Vanessa Hill, principal investigator at the Christus Santa Rosa Children's Hospital site, will serve as study personnel responsible for data security and transmission in accordance with Baylor University and Christus Santa Rosa policy and this protocol.

9. STUDY DURATION/STUDY TIMELINE

This is an ongoing study that is in the final phase of conduct initially approved at Rhode Island Hospital. Subject enrollment has been ongoing since 2009 and will complete spring of 2014. The remaining timeline is as follows:

1. Subject enrollment (October 2013-May 2014)
2. Completion of medical record review/data collection: June 2014
3. Presentation and publication: October 2014
4. Study end date and conversion of database to data repository (estimated): December 2014.

10. STATISTICAL CONSIDERATIONS

Measures

Primary measure: length of stay, in hours

Secondary measures:

Number of times a patient undergoes deep nasal suctioning
Number of patients transferred to the PICU
Total cost of hospitalization, in dollars

General Design Issues

The primary objective is to compare the length of stay in children undergoing intermittent or continuous pulse oximetry monitoring, thus are measurement of hours hospitalized is consistent with the primary objective.

Secondary objectives relate to both safety of the intervention and cost-effectiveness related to the two monitoring strategies and so the outlined measures are consistent with these objectives.

Sample size determination

Average length of stay for healthy children with bronchiolitis: approx. 62.45 hours

Expected difference between control and intervention groups: 12 hours, or approximately 20%

For a study with 80 percent probability of detecting a 20 percent difference in outcome with a 95 percent confidence interval, investigators will need to enroll 266 patients into the study (133 patients into each study arm). This will utilize a paired t-test to evaluate the hypothesis regarding length of stay. To date the study has enrolled 112 subjects. We estimate that we will have to screen an additional 300 subjects to enroll the additional 154 subjects study-wide.

Data Analyses

Length of stay will be analyzed using pair t-testing with a 2-sided p-value of significance being <0.05. Rates of invasive suctioning and PICU admission will be compared using Chi-square analysis with significance being assigned as $p<0.05$. Costs of care will also be assessed using t-testing with a 2-sided p-value of significance being $p<0.05$.

The randomized study design will help account for unmeasured confounders. Additionally, we will collect supplemental data regarding the patient's hospital course, including diagnostic testing and medications given that will be assessed for potential association/confounding of the outcomes of interest.

11. HUMAN SUBJECTS (Note the text in this section are examples only)

Institutional Review Board (IRB) Review and Informed Consent

IRB of record:
This protocol, and any subsequent modifications, will be reviewed and approved by the Pediatric IRB at The Children's Mercy Hospital & Clinics.

Both the Hasbro Children's Hospital and Christus Santa Rosa Children's Hospital sites will utilize their own institutional IRBS to obtain study approval.

Informed consent procedure
We will obtain a preparatory-to-research approval to review medical information of admitted patients for inclusion and exclusion criteria prior to approaching the subject's parent or guardian. The Hasbro Children's Hospital and Christus Santa Rosa Children's Hospital sites will maintain similar permissions from their respective Institutional Review Boards which have been previously granted. Admissions to each study site will be screened daily for potential subjects and those subjects will be entered into the initial screening log as outlined above.

Parents of patients will be approached and provided information regarding the study in the patient's hospital room. A copy of the consent document will be provided the parent(s) for their review and initial questions will be answered. The parent(s) will be given ample time to individually review the consent documents and to have their questions answered by study staff prior to performing any other procedures related to this study.

Subject Confidentiality

No personal identifiers are included in the study database but linked identifiers will exist separately in a hardcopy log. The codes in this log are stored in a locked cabinet in an office accessible only by authorized study personnel at each respective study site. There are no patient identifiers recorded in the research record. All computer entry and networking programs will be done using study identification only. All data will be entered into a computer that is password protected. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the Sponsor, or the Sponsor's designee. All paper records will be kept in a locked file cabinet of the investigators and maintained for a minimum of three years after the completion of the study.

Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the Sponsor, the OHRP, the FDA or other Government agencies as part of their duties to ensure that research subjects are protected.

12. PUBLICATION OF RESEARCH FINDINGS

Interim analysis data were presented at IDWeek October 2012 in San Diego, CA, Eastern Society for Pediatric Research March 2013 in Philadelphia, PA, and Pediatric Hospital Medicine August 2013 in New Orleans, LA.

Final results are planned to be submitted to IDWeek 2014 and for publication in a major academic medical journal such as *Pediatrics* or *JAMA Pediatrics*.

13. REFERENCES

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