Critical Asthma Mortality and Morbidity Planning Study

(The CAMMP Study)

CPCCRN Protocol Number 019

Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD)

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PROTOCOL TITLE:
Critical Asthma Mortality and Morbidity Planning Study

Short Title: The CAMMP Study
CPCCRN Protocol Number: 019

Lead Investigator and Author: Christopher Newth, MD, FRCPC
Children's Hospital of Los Angeles

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated.

I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Status asthmaticus is the most common medical emergency in children today[1] and is responsible for nearly half a million hospital admissions annually.[2, 3] Asthma affects more than 9 million children in the United States. Its prevalence has increased dramatically in recent years, rising by more than 50% among children aged 5-14 years of age from 1980 to the late 1990's. According to the Centers for Disease Control and Prevention, the prevalence of asthma among U.S. children was 5.8% in 2003. Despite evidence that asthma hospitalizations are decreasing, asthma mortality is not changing concomitantly. There is a subset of asthmatics with severe, acute exacerbations of disease, with a high incidence of morbidity and mortality. Characterization of this at risk population of children and adolescents has been difficult, and diversity of practice and disease management is common and may contribute to adverse outcomes.[4] In order to gain a better understanding of status asthmaticus, its treatment and its overall outcomes, each Pediatric Intensive Care Unit (PICU) research team within the Collaborative Pediatric Critical Care Research Network (CPCCRN) will examine its admissions records in detail for children aged from 1 year up to the 18th birthday over the last 5 years for any instances of deaths resulting from a diagnosis of asthma (fatal asthma). Postmortem data will be reviewed where available. In addition, the medical records for children intubated and mechanically ventilated for asthma (near-fatal asthma) will be analyzed. This review and abstraction will enable CPCCRN investigators to quantify the current variability of critical asthma treatment and will help us to identify additional medical problems, such as organ failure, that may have occurred during the patient's fatal or near-fatal illness. Data from this study will inform development of prospective studies investigating the management of critical asthma.

1 Study Summary

Following admission to the Pediatric Intensive Care Unit (PICU), some critically ill children with asthma require mechanical ventilation and/or progress to death. In order to gain a better understanding of status asthmaticus, its treatment and its overall outcomes, each PICU research team within the Collaborative Pediatric Critical Care Research Network (CPCCRN) will examine its admission records for children aged from 1 year up to the 18th birthday over the last 5 years for any deaths resulting from a diagnosis of asthma (fatal asthma). Autopsy reports will be reviewed where available. In addition, the admission records for any children intubated and mechanically

ventilated for asthma (near-fatal asthma) will be analyzed. The information obtained from careful analysis of risk factors and details surrounding the circumstances of the deaths and the management of the near-fatal cases, that can be extracted retrospectively, will better inform prospective studies on critical asthma assessment and therapeutic decision making (particularly pharmacologic) in the future.

1.1 Study Design

The CAMMP Study is a retrospective review of the medical records of patients who die or who require intubation and mechanical ventilation for an acute exacerbation of asthma or its complications.

1.2 Specific Aims

The specific aims of this study are:

Specific Aim 1. To describe, and where appropriate, to quantitate the clinical risk factors, course, and therapies used in the management of children who died with critical asthma in CPCCRN PICUs.

Specific Aim 2. To describe, and where appropriate, to quantitate the clinical risk factors, course, and therapies used in the management of children who were intubated and mechanically ventilated with critical asthma in CPCCRN PICUs and who survived.

1.3 Patient Eligibility

The CAMMP Study will include all patients who died or who required intubation and mechanical ventilation in CPCCRN PICUs with an acute exacerbation of asthma or status asthmaticus between 2005 and 2009, inclusive. For study purposes, a diagnosis of an acute exacerbation of asthma or status asthmaticus as a primary cause of admission to a PICU is defined as "critical asthma." Near-fatal asthma is defined as asthma requiring intubation and mechanical ventilation for the disease, irrespective of where the patients were intubated.

1.3.1 Inclusion Criteria

Critically ill children eligible for enrollment include:

- Admitted to the PICU between the years of 2005 and 2009; AND

- age greater than 1 and less than 18 years at the time of PICU admission; AND
- diagnosed with "critical asthma," defined as an acute exacerbation of asthma or status asthmaticus as a primary cause of admission to PICU; AND
- were treated for status asthmaticus or an acute exacerbation of asthma during the hospital stay; AND
- died in hospital OR survived but required intubation and mechanical ventilation at any point in their hospital stay.

1.3.2 Exclusion Criteria

Children are ineligible for enrollment if they had:

- Diagnosis of cystic fibrosis; OR
- diagnosis of bronchiolitis for current hospitalization.

1.4 Anticipated Recruitment and Study Duration

From the CPCCRN Core Data Registry, we estimate that 75-125 patients will meet study entry criteria per year across all CPCCRN sites, with anticipated total enrollment of 400-500 patients across the 5-year study period. Only a small percentage of these (<5%) are deaths. The study duration is anticipated to be 12 months, with at least 4 to 6 months required for medical record review and data extraction.

1.5 Human Subjects

Waiver of informed consent will be requested for this study because the scientific validity of the study, to determine the disease course and clinical care of patients admitted to the PICU with fatal or near-fatal critical asthma, requires 100% of eligible patients. The study fulfills regulatory requirements for a waiver, because there are no changes in clinical practice, no therapeutic interventions, only minimal risk to the patient's family (loss of privacy), and obtaining informed consent would threaten the scientific validity of the study.

2 Background and Significance

Asthma is the most common chronic childhood disease affecting more than 9 million children, resulting in nearly half a million hospital admissions annually. Status asthmaticus is the most common medical emergency in children.[1] Prevalence of asthma increased by more than 50% from 1980 until the late 1990's among children aged 5-14 years and is particularly high in the United States. According to the Centers for Disease Control and Prevention, the prevalence of asthma among U.S. children was 5.8% in 2003. According to the National Center for Health Statistics, asthma is the third leading cause of hospitalization among persons under 18 years of age in the United States, exceeded in frequency only by pneumonia and injuries.

Although there is evidence that asthma hospitalizations are decreasing in frequency, asthma mortality is not declining concomitantly. There remains a subset of asthmatics with severe disease and persistent morbidity prevalence and mortality incidence. Characterization of this population of children and adolescents has been difficult,[5] and diversity of practice and management is common.[4]

There appear to be two clinical subsets of children who die from status asthmaticus.[6] Some children with fatal asthma have a long history of poorly controlled, severe asthma, often with a previous history of respiratory failure (Type 1, or slow-onset, late arrival). This pattern of fatal asthma is responsible for the majority of asthma-related deaths and is generally considered preventable; death occurs secondary to acute respiratory failure and asphyxia or from complications associated with mechanical ventilation.[5, 7–11] Pathological examination in these cases demonstrates extensive bronchial mucus plugging, edema, and eosinophilic infiltration of the airways.

Alternatively, some children who present with only a mild history of asthma, and more often even with no history of asthma, experience a sudden onset of fulminant bronchospasm, and rapidly progress to cardiac arrest and death (Type 2, or fast-onset, asthma).[12–15] By contrast, pathologic examination of these Type 2 fatal cases shows empty airways devoid of mucus plugging with a greater proportion of neutrophils than eosinophils.[16] It can be anticipated from their pathology that, if recognized and managed early, these children would likely respond faster to beta-agonists and mechanical ventilator support compared with children with Type 1 fatal asthma whose airways are blocked.[17]

Robertson et al[18] reviewed 51 pediatric deaths from asthma in Australia between 1986 and 1999, and found that nearly one-third of these children were judged to have mild asthma with no prior hospitalizations for asthma.

1. History of previous attack with:
A. Severe, rapid progression of symptoms
B. Respiratory failure requiring endotracheal intubation or ventilator support
C. Seizures or loss of consciousness
D. Pediatric intensive care unit admission
2. Attacks precipitated by food allergy
3. Denial or failure to perceive the severity of illness
4. Noncompliance
5. Lack of social support network (dysfunctional family)
6. Associated psychiatric disorder, e.g. depression
7. Non-white children (especially African-American and Hispanic children)

Table 1: Risk factors for potentially fatal asthma

Sixty three percent experienced a sudden collapse within minutes of the onset of symptoms, and 75% died before reaching the hospital. In this series, only 25% had an acute progression of chronic, poorly controlled asthma that resulted in eventual death. The authors of this study concluded that about 39% of these deaths were preventable by earlier recognition and intervention.

Over a six-year period at The Hospital for Sick Children in Toronto, 89 children were admitted to the PICU for status asthmaticus. Three children died in the PICU from hypoxic-ischemic encephalopathy following out-of-hospital cardiac arrest.[19] Kravis and Kolski[20] reported a case series of 13 deaths secondary to asthma. Only one child died following admission to the hospital. Similarly, in two other studies, nearly 50% of asthmatic children died before reaching the hospital with the time from the onset of symptoms to death less than one hour in 21%, and less than 2 hours in 50% of these cases, respectively.[21, 22] This and other similar reports further underscore the need for early recognition for children at risk for Type 2 fast-onset, sudden asphyxial asthma. Accordingly, several authorities have attempted to define characteristics of risk factors of children who die of asthma (See Table 1).

Management of near-fatal and worsening asthma in pediatric intensive care units is not well-studied. Escalation of therapy in variable patterns is a common sequence of events in fatal and near fatal asthma. Figure 1 on the next page summarizes a conceptual framework (likely variable across PICUs) for understanding therapeutic escalation in these conditions.

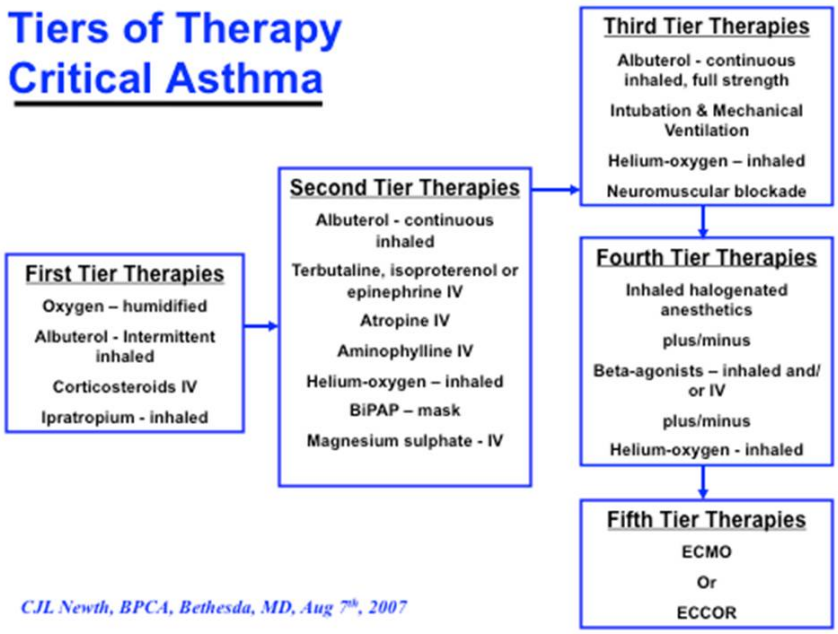

Figure 1: Tiers of therapy used to treat critical asthma

3 Study Design and Specific Aims

The CAMMP Study is a retrospective review of medical records of patients who die or who require intubation and mechanical ventilation for an acute exacerbation of asthma or its complications.

3.1 Specific Aims

The specific aims of this study are:

Specific Aim 1. To describe, and where appropriate, to quantitate the clinical risk factors, course, and therapies used in the management of children who died with critical asthma in CPCCRN PICUs.

Specific Aim 2. To describe, and where appropriate, to quantitate the clinical risk factors, course, and therapies used in the management of children who were intubated and mechanically ventilated with critical asthma in CPCCRN PICUs and who survived.

3.2 Patient Eligibility

The CAMMP Study will include all patients who died or who required intubation and mechanical ventilation in CPCCRN PICUs with an acute exacerbation of asthma or status asthmaticus between 2005 and 2009, inclusive. For study purposes, a diagnosis of an acute exacerbation of asthma or status asthmaticus as a primary cause of admission to a PICU is defined as "critical asthma." Near-fatal asthma is defined as asthma requiring intubation and mechanical ventilation for the disease, irrespective of where the patients were intubated.

3.2.1 Inclusion Criteria

Critically ill children eligible for enrollment include:

- Admitted to the PICU between the years of 2005 and 2009; AND
- age greater than 1 and less than 18 years at the time of PICU admission; AND
- diagnosed with "critical asthma," defined as an acute exacerbation of asthma or status asthmaticus as a primary cause of admission to PICU; AND
- were treated for status asthmaticus or an acute exacerbation of asthma during the hospital stay; AND
- died in hospital OR survived but required intubation and mechanical ventilation at any point in their hospital stay.

3.2.2 Exclusion Criteria

Children are ineligible for enrollment if they had:

- Diagnosis of cystic fibrosis; OR
- diagnosis of bronchiolitis for current hospitalization.

3.3 Inclusion of Children, Women and Minorities

3.3.1 Inclusion of Children in Research

All eligible subjects in this study are children.

3.3.2 Inclusion of Women in Research

All eligible subjects will be enrolled in the study regardless of gender.

3.3.3 Inclusion of Minorities in Research

All eligible subjects will be enrolled in the study regardless of race or ethnicity. The race and ethnicity breakdown of the study population is likely to differ from the overall population of PICU patients at each center because African American race and Hispanic ethnicity are associated with status asthmaticus.

4 Data Collection

Data will be collected for each asthma-related PICU admission meeting study entry criteria. If a patient is admitted to the hospital multiple times over the study period, the data collection should be completed for each qualifying PICU admission. If a patient is admitted to the PICU multiple times during one hospital stay, the data collection should be completed for the initial PICU admission.

The data elements to be collected include demographic and clinical variables, specifically:

4.1 Demographics

- Date of birth
- Gender
- Age at admission
- Weight (kg) at admission
- Height (cm) at admission
- Race

  American Indian or Alaska Native. A person having origins in any of the original peoples of North and South America, including Central America, and who maintains tribal affiliation or community attachment.

Asian. A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American. A person having origins in any of the black racial groups of Africa.

Native Hawaiian or Other Pacific Islander. A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White. A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Other. Provide text description.

Unknown.

- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Unknown
- Primary payer type
  - Commercial Insurance
  - Medicaid
  - Medicare
  - Other Governmental Insurance
  - Self pay
  - Worker's Compensation
  - Other
  - Unknown

4.2 History

- Hospital admissions for acute asthma in year prior to admission: Number or Unknown
- PICU admissions for acute asthma in year prior to admission: Number or Unknown

- This admission: New diagnosis of asthma, exacerbation of chronic asthma, or unknown?
- Known patient history of allergies (non-food)? Yes or No
- Known patient history of food allergy? Yes or No
  - If yes to either of the previous questions, was there a known allergic exposure precipitating this admission? Yes or No
- Known patient history of eczema? Yes or No
- Known patient history of any psychiatric or behavioral disorder? Yes or No
- Known patient history of any drug or alcohol abuse? Yes or No
- Known patient history of non-compliance with asthma therapy? Yes or No
- Family history of asthma? Yes, No, or Unknown
- Chronic asthma medications within 30 days prior to admission, specifically:
  - Short-acting inhaled beta-agonists: Yes, No, or Unknown
  - Long-acting inhaled beta-agonists: Yes, No, or Unknown
  - Inhaled antihistamine: Yes, No, or Unknown
  - Inhaled corticosteroids: Yes, No, or Unknown
  - Oral corticosteroids: Yes, No, or Unknown
  - Inhaled anticholinergics: Yes, No, or Unknown
  - Leukotriene-receptor antagonists: Yes, No, or Unknown
  - Monoclonal anti-IgE antibody: Yes, No, or Unknown
  - Methylxanthines: Yes, No, or Unknown
  - Home oxygen: Yes, No, or Unknown
  - Other (specify)
- Other known active medical conditions: Yes or No
  - If yes, specify condition(s) and medication(s), if any

4.3 Overview of Clinical Course

4.3.1 Hospital and PICU Admission

- Hospital admission and discharge dates
- PICU admission and discharge dates/times
- Source of admission to PICU: transfer from outside ED, admitted through study site ED, transfer from floor, transfer from another ICU, or unknown
- Mental status at time of PICU admission: alert, obtunded, sedated, or unknown
- Known cardiac arrest prior to arrival in PICU for this hospitalization? Yes or No
- Radiographic or clinical evidence of barotrauma (air leak) **prior to** PICU admission? Yes, No, or Unknown
  - If yes, check all that apply: pneumothorax, pneumomediastinum, pneumoperitoneum, pneumopericardium, subcutaneous emphysema
- Pulse oximetry and vital signs at first presentation to PICU:
  - S_pO_2
  - Temperature (°C)
  - Heart rate
  - Respiratory rate
  - Blood Pressure (mmHg)
  - Glasgow Coma Score (GCS) [collect only for patients not intubated prior to admission]
- Were any life-threatening arrhythmias, elevation of troponins, ECG evidence of ischemia, or other cardiac complications documented during the hospitalization? Yes or No
  - If yes, please describe:

4.3.2 Mechanical Ventilation

- Non-invasive ventilation prior to intubation? Yes or No
- Last blood gas prior to intubation. Collect:
  - Date
  - Time
  - pH
  - pCO_2
  - pO_2
  - Method of blood draw: arterial, venous, capillary
- Intubation, initiation location: PICU, referring hospital, transport team, ED, OR, floor, not intubated prior to death, unknown
- Intubation date and time
- Initial ventilator settings in ICU:
  - Mode (pressure control, pressure-regulated volume control, volume control, pressure support/PEEP, other [specify])
  - PIP
  - VT (mL)
  - PEEP
  - Ventilator rate
  - F_iO_2
  - Ti (sec)
- Final ventilator settings prior to extubation or death:
  - Mode (pressure control, pressure-regulated volume control, volume control, pressure support/PEEP, other [specify])
  - PEEP
  - F_iO_2
- Blood gas prior to extubation or death. Collect:
  - Date
  - Time

  - pH
  - pCO_2
  - pO_2
  - F_iO_2
  - Bicarbonate
  - S_pO_2
  - Method of blood draw: arterial, venous, capillary
- Extubation date and time
- Did the patient receive non-invasive ventilation after extubation? Yes, No, or Unknown
  - If yes, indicate:
    * Start: Date and time
    * Stop: Date and time

4.3.3 Inhalational Anesthesia

- Received inhalational anesthesia during the PICU stay? Yes, No, or Unknown
  - If yes, indicate drug(s) used:
    * Isoflurane
    * Sevoflurane
    * Halothane
    * Other(specify)
  - Start: Date and time
  - Stop: Date and time

4.3.4 Extracorporeal Membrane Oxygenation (ECMO)

- Patient treated with ECMO during the PICU stay (includes $ECCO_2R$)? Yes, No, or Unknown
  - If yes, indicate ECMO mode: VA, VV, or $ECCO_2R$ catheter
  - Start: Date and time
  - Stop: Date and time

- Were there any complications related to ECMO? (check all that apply or indicate none):
  - Hemorrhage
  - Thrombosis
  - Infection
  - Stroke
  - Other (specify)
  - None

4.3.5 Final Patient Status

- Patient status at PICU discharge: Survived with no known complications, survived with complications, or dead
  - If discharged with complications, were any of the following present?
    - Residual pulmonary barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum, pneumopericardium, subcutaneous emphysema)
    - Central nervous system deficits
    - Neuromyopathy
- Patient vital status at hospital discharge: alive or dead

4.4 Therapies and Interventions

The data elements below are to be collected for each of the following phases of care (if applicable):

1. **Prior to intubation**
2. **During invasive mechanical ventilation**
3. **During inhalational anesthesia (if applicable)**
4. **During ECMO (if applicable)**
5. **After extubation and prior to PICU discharge**

- Oxygen: Yes, No, or Unknown
- Bronchoscopy: Yes, No, or Unknown

- BiPAP/CPAP: Yes, No, or Unknown **(Prior to intubation and after extubation phases ONLY)**
- High-frequency oscillatory ventilation: Yes, No, or Unknown **(During invasive mechanical ventilation, inhalational anesthesia and ECMO phases ONLY)**
- Neuromuscular blockade while ventilated (excluding induction)? Yes, No, or Unknown **(During invasive mechanical ventilation phase ONLY)**
- Intermittent Albuterol - Inhaled: Yes, No, or Unknown
- Continuous Albuterol - Inhaled: Yes, No, or Unknown
- Terbutaline - Inhaled: Yes, No, or Unknown
- Terbutaline - IV: Yes, No, or Unknown
- Terbutaline - IM, SC: Yes, No, or Unknown
- Isoproterenol - IV: Yes, No, or Unknown
- Epinephrine - Inhaled: Yes, No, or Unknown
- Epinephrine - IV: Yes, No, or Unknown
- Epinephrine - IM, SC: Yes, No, or Unknown
- Corticosteroids - Inhaled: Yes, No, or Unknown
- Corticosteroids - IV, PO: Yes, No, or Unknown
- Ipratropium - Inhaled: Yes, No, or Unknown
- Atropine - IV: Yes, No, or Unknown
- Magnesium sulfate - IV: Yes, No, or Unknown
- Aminophylline/theophylline - IV, PO: Yes, No, or Unknown
- Helium-oxygen - Inhaled: Yes, No, or Unknown
- Ketamine - Infusion (excluding induction): Yes, No, or Unknown
- Nitric oxide: Yes, No, or Unknown **(During invasive mechanical ventilation, inhalational anesthesia and ECMO phases ONLY)**

- Mucolytics: Yes, No, or Unknown **(During invasive mechanical ventilation, inhalational anesthesia and ECMO phases ONLY)**

4.5 Death Information Form

- Date and time of death
- Moribund on arrival to CPCCRN PICU: Yes or No
- Mode of death:
  - Withdrawal of support/futility; OR
  - Brain death; OR
  - Failed CPR; OR
  - Other; OR
  - Unknown
- Causes of death (specify from copy of death certificate, if available, or medical record death note)
- Upload autopsy report, if available

5 Statistical Analysis Plan

The primary purpose of this study is to review the clinical course and risk factors for death in critically ill children admitted to the PICU with asthma as their primary diagnosis. The CAMMP Study will help CPCCRN investigators identify specific therapeutic decision points that have not been formally evaluated in the pediatric population. This will lead to development of potential observational studies and randomized trials of drugs used for treatment of critical asthma.

CPCCRN investigators will obtain medical records for eligible subjects and undertake detailed review and data point description. As these are intensive care admissions, the records are likely to be large and complex. Data from the chart abstractions in each site will be submitted to the DCC and summarized. In addition to providing detailed information about the clinical course of these children, information from this process will inform the draft definition of data elements for a prospective cohort study and provide preliminary data on patient treatment course and outcomes. Specific areas of interest include: (1) variability in the use and timing of agents at different

centers; (2) progression of treatment over the course of the acute illness; (3) trends or differences in practice over the five year study period; and (4) identification of key decision points in critical asthma care, in order to inform future trials and descriptive studies.

Appropriate statistical methods will be used to examine these and other questions of interest. We will use graphical methods including histograms and box plots to describe distributions of continuous variables. Variables that have approximately normal distributions will be reported using means and standard deviations, and any between-group comparisons performed using t-tests or standard analysis of variance. Substantially skewed distributions require using measures such as median and interquartile range, and between-group comparisons using the Wilcoxon rank-sum or Kruskal-Wallis test. Categorical measures will be described using rates or proportions, and associations between variables will be evaluated using the χ-square or Fisher's exact test, as appropriate. Since all analyses are exploratory and meant to inform planning for a future study, we will interpret any findings within this context and without formal adjustment for multiple endpoints or testing. Clinical relevance of the findings, in the context of existing knowledge in the field, will be of key importance rather than statistical significance.

5.1 Sample Size

There is no formal sample size calculation for this retrospective, observational planning study. The total anticipated enrollment across five years is 400-500 patients, as described in section 6. This will be the largest and most detailed cohort analysis to date for fatal and near-fatal asthma.

6 Anticipated Recruitment and Study Duration

From the CPCCRN Core Data Registry, we estimate that 75-125 patients will meet study entry criteria per year across all CPCCRN sites, with anticipated total enrollment of 400-500 patients across the 5-year study period. Only a small percentage of these (<5%) are deaths. The study duration is anticipated to be 12 months, with at least 4 to 6 months required for medical record review and data extraction.

7 Human Subjects

The Data Coordinator Center and each clinical site must obtain approval from their respective IRB prior to participating in the study. The DCC will track the IRB approval status at all participating centers.

7.1 Waiver of Consent

Waiver of informed consent will be requested for this study because the scientific validity of the study, to determine the disease course and clinical care of patients admitted to the PICU with fatal or near-fatal critical asthma, requires 100% of eligible patients. The study fulfills regulatory requirements for a waiver, because there are no changes in clinical practice, no therapeutic interventions, only minimal risk to the patient's family (loss of privacy), and obtaining informed consent would threaten the scientific validity of the study.

7.2 Study Population

All children who are admitted to the PICU with a diagnosis of critical asthma and who die or who require intubation and mechanical ventilation from this disease or its complications, as defined by the inclusion/exclusion criteria, are eligible for this study.

7.3 Research Materials

The research data obtained from enrolled subjects include details of past medical history, history leading to the current PICU admission, details of clinical management in the PICU, and use of asthma medications, anesthetic agents, mechanical ventilation and techniques of extracorporeal gas exchange. These data will be obtained by retrospective medical record review. The research data will be managed via a secure, HIPAA compliant, encrypted electronic data system at the Data Coordinating Center.

7.4 Potential Risks

This is a minimal risk study, and the only potential risk is loss of privacy. There are no interventions or clinical evaluations in this retrospective study. Data collection and storage will be handled securely at all times to maintain the privacy of the subjects.

7.5 Potential Benefits

There is no immediate direct benefit to subjects enrolled in this study. The potential benefit to future patients is that more effective strategies of critical asthma risk factor recognition and therapeutic maneuvers will be developed to lower the incidence of death and reduce morbidity from asthma in children. It is hoped that enhancement in the efficacious and accurate design of therapeutic trials will be a considerable benefit for all children, and eventually result in agents specifically labeled for pediatric use.

7.6 Patient Confidentiality

All evaluation forms and reports will be identified only by a coded number to maintain patient confidentiality. All records will be kept in a locked/password protected computer. All computer entry and networking programs will be done with coded numbers only.

8 Data Security

The Data Coordinating Center at the University of Utah has a dedicated, locked server room within its offices, and the building has 24 hour on-site security guards. The Data Coordinating Center has a state-of-the-art computer infrastructure and coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the Data Coordinating Center with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University.

Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. OpenClinica is the clinical trials software used at the Data Coordinating Center in Utah, and eRoom^{TM} is used for communications about the study. OpenClinica, eRoom^{TM} and other web applications use the SSL protocol to transmit data securely over the Internet.

Direct access to Data Coordinating Center computers is only available while physically located inside the Data Coordinating Center offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified

of intrusion alerts. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

The investigators and staff of the Data Coordinating Center are fully committed to the security and confidentiality of all data collected for CPC-CRN studies. All personnel at the Data Coordinating Center at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with Data Coordinating Center data systems have received Human Subjects Protection and HIPAA education.

9 Health Insurance Portability and Accountability Act

Registration of research subjects in the electronic data capture (EDC) system used by the DCC at the University of Utah requires a date of birth, race, ethnicity, and gender. These demographic data are held in database tables that are separate from coded research data (including clinical data). The demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

The Data Coordinating Center produces the de-identified research data sets that will be used for all analyses in this project. Since the raw data includes potential identifiers, such as dates of birth and admission, all CPC-CRN sites have been offered a Business Associate Agreement (BAA) with the University of Utah. Copies of executed Business Associate Agreements are maintained at the Data Coordinating Center in Utah.

All analyses will be conducted with de–identified data sets created by the Data Coordinating Center.

10 Record Retention

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include completion of all publications relating to the research.

All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

Bibliography

[1] Bohn D, Kissoon N. Acute asthma. Pediatr Crit Care Med. 2001 Apr;2(2):151–63.

[2] Dey AN, Bloom B. Summary health statistics for U.S. children: National Health Interview Survey, 2003. Vital Health Stat 10. 2005 Mar;(223):1–78.

[3] Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med. 2006 Nov;355(21):2226–35.

[4] Bratton SL, Odetola FO, McCollegan J, Cabana MD, Levy FH, Keenan HT. Regional variation in ICU care for pediatric patients with asthma. J Pediatr. 2005 Sep;147(3):355–61.

[5] Strunk RC. Death due to asthma. New insights into sudden unexpected deaths, but the focus remains on prevention. Am Rev Respir Dis. 1993 Sep;148(3):550–2.

[6] Papiris S, Kotanidou A, Malagari K, Roussos C. Clinical review: severe asthma. Crit Care. 2002 Feb;6(1):30–44.

[7] Benatar SR. Fatal asthma. N Engl J Med. 1986 Feb;314(7):423–9.

[8] McFadden ER Jr. Fatal and near-fatal asthma. N Engl J Med. 1991 Feb;324(6):409–11.

[9] McFadden ER Jr, Warren EL. Observations on asthma mortality. Ann Intern Med. 1997 Jul;127(2):142–7.

[10] Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. N Engl J Med. 1991 Jan;324(5):285–8.

[11] Death from asthma in two regions of England. British Thoracic Association. Br Med J (Clin Res Ed). 1982 Oct;285(6350):1251–5.

[12] DeNicola LK, Monem GF, Gayle MO, Kissoon N. Treatment of critical status asthmaticus in children. Pediatr Clin North Am. 1994 Dec;41(6):1293–324.

[13] Strunk RC. Identification of the fatality-prone subject with asthma. J Allergy Clin Immunol. 1989 Feb;83(2 Pt 1):477–85.

[14] Sur S, Crotty TB, Kephart GM, Hyma BA, Colby TV, Reed CE, et al. Sudden-onset fatal asthma. A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? Am Rev Respir Dis. 1993 Sep;148(3):713–9.

[15] Wasserfallen JB, Schaller MD, Feihl F, Perret CH. Sudden asphyxic asthma: a distinct entity? Am Rev Respir Dis. 1990 Jul;142(1):108–11.

[16] Reid LM. The presence or absence of bronchial mucus in fatal asthma. J Allergy Clin Immunol. 1987 Sep;80(3 Pt 2):415–6.

[17] Maffei FA, van der Jagt EW, Powers KS, Standage SW, Connolly HV, Harmon WG, et al. Duration of mechanical ventilation in life-threatening pediatric asthma: description of an acute asphyxial subgroup. Pediatrics. 2004 Sep;114(3):762–7.

[18] Robertson CF, Rubinfeld AR, Bowes G. Pediatric asthma deaths in Victoria: the mild are at risk. Pediatr Pulmonol. 1992 Jun;13(2):95–100.

[19] Stein R, Canny GJ, Bohn DJ, Reisman JJ, Levison H. Severe acute asthma in a pediatric intensive care unit: six years' experience. Pediatrics. 1989 Jun;83(6):1023–8.

[20] Kravis LP, Kolski GB. Unexpected death in childhood asthma. A review of 13 deaths in ambulatory patients. Am J Dis Child. 1985 Jun;139(6):558–63.

[21] Fletcher HJ, Ibrahim SA, Speight N. Survey of asthma deaths in the Northern region, 1970-85. Arch Dis Child. 1990 Feb;65(2):163–7.

[22] Matsui T, Baba M. Death from asthma in children. Acta Paediatr Jpn. 1990 Apr;32(2):205–8.