Practice Variability in Antibiotic Use for Necrotizing Enterocolitis:
A Retrospective Descriptive Analysis

Study Purpose and Rationale

Necrotizing enterocolitis is a common serious pathophysiologic entity in neonatal ICUs. Mortality rates are estimated between 20-50%, and morbidity includes development of strictures, adhesions and short bowel syndrome because of necrosis of bowel. A major risk factor for NEC is prematurity, with 90% of cases occurring in premature infants. The tissue damage that occurs is thought to be because of an immature mucosal barrier in premature infants, which can lead to bacterial stasis, overgrowth and translocation. The way by which enteral feeds are introduced and advanced can also affect the mucosal barrier and lead to NEC.

Common bacteria isolated from neonates with the disease include gram-negative rods, like *Klebsiella* spp., *Escherichia coli, Enterobacter* spp. and *Pseudomonas* spp., as well as *Clostridium difficile*, *Staphylococcus epidermidis*, coronaviruses and rotaviruses. Although positive blood cultures are rarely associated with NEC and it is unclear whether the bacteria are a cause or a byproduct of the pathophysiology of the disease, broad-spectrum antibiotics are generally accepted as first-line treatment for NEC, as well as nasogastric decompression, cessation of feeds, and close monitoring of fluid and respiratory status.

Despite multiple advances in the field of neonatology, NEC continues to have high rates of morbidity and mortality, and there is limited evidence about the efficacy of various antibiotic regimens in preventing progression and sequelae of this disease. This retrospective chart review will provide a descriptive analysis of outcomes associated with different antibiotic regimens.

Study Design and Procedure

A retrospective multicenter chart review will be done to evaluate differences in outcomes for different antibiotic regimens. Current variability in antibiotic prescribing practices include use of anaerobic coverage, use of vancomycin, use of cephalosporin, and the use of optimal Gram-negative coverage. Patients will be grouped into these categories based on treatment received.

Outcome measures will include length of hospital stay (continuous) and progression to surgery or mortality (categorical). The incidence of death ranges from 0-20% at the various sites; we estimate an incidence of progression to death or surgery at 30% based on our site with the largest numbers.

Statistical Analysis

This study will primarily be a descriptive analysis for many reasons. There will be overlap amongst the various groups because monotherapy is not a standard of care for patients with NEC. In addition, our sample size is small because the incidence of NEC in our database is 4%, lower than the actual incidence rate at each institution and in the network, because not all infants are able to be captured. Also, with large rates of progression to surgery and death,

it will be difficult to show statistically significant changes in rates, especially with the small sample size available.

All of the data will be analyzed in a nonparametric fashion because it is not normally distributed. For length of hospital stay, a linear regression analysis would be done to account for multiple covariates associated with this outcome. Similarly, a logistic regression analysis would allow us to evaluate our composite categorical outcome, progression to surgery or death.

If we were to assume a fixed sample size with equal distribution amongst the different antibiotic practicing regimens and no overlap between these distinct groups, we would be able to calculate a minimal detectable risk for each outcome with power of 80%. Let us assume that n = 33 in each distinct group. With respect to length of hospital stay, we would need a change of 0.7*SD for one practice to be statistically different from another. In terms of progression to surgery and mortality, because our sample size is small, we would need a reduction to 2.3% or an increase to 66% for one group to be statistically significant from the other group.

Study Drugs

Broad-spectrum antibiotics are first-line of management in treatment of neonates with NEC. Metronidazole provides coverage against anaerobic bacteria. Most Gram-positive bacteria are susceptible to penicillins, like ampicillin. Vancomycin is targeted towards Gram-positive bacteria, and is unique because it is effective against Methicillin-Resistance Staphylococcus Aureus (MRSA). Cephalosporins are a type of beta-lactam antibiotic. First generation cephalosporins are effective mainly against Gram-positive bacteria, and subsequent generations have increasing efficacy against Gram-negative bacteria. Optimal Gram-negative coverage refers to double coverage against Gram-negative pathogens. All antibiotics that will be included in this analysis are part of standard care in neonatal intensive care units.

Medical Device
No medical devices will be used in this study.

Study Questionnaires
No questionnaires will be used in this study.

Study Subjects

The study will include all very low birth weight (VLBW, 700g-1499g) preterm infants < 32 weeks gestational age who have been diagnosed with necrotizing enterocolitis based on chart review of clinical signs as well as laboratory and radiologic data. Based on analysis of three sites so far, we estimate this will include approximately 100 subjects.

Recruitment of Subjects

The subjects will be drawn from the Interdisciplinary NICU Antimicrobial Prescribing Study (iNAP) database. This is a pre-existing multicenter database of patients from neonatal ICUs at four different sites.

Confidentiality of Study Data

Study data is secure and will only be accessible to the investigators involved in the study. Subjects will be give unique identifiers. All identifying information is coded to protect confidentiality.

Potential Conflict of Interest
No conflict of interest.

Location of the Study

The multicenter database includes patients from the neonatal intensive care units at the Children's Hospital of Philadelphia, Cornell University Medical Center and Christiana Hospital. Data analysis will take place at Columbia University Medical Center.

Potential Risks

Given that this is a retrospective descriptive analysis of variability in the use of antibiotic regimens that are already part of current practice, there are no potential risks for the patients based on this study alone.

Potential Benefits

An analysis of various antibiotic practices will provide further information on which regimens are associated with the most favorable outcomes.

Alternative Therapies
N/A

Compensation to Subjects
No compensation has been provided to the subjects involved.

Costs to Subjects
No additional costs to subjects will be incurred based on this study.

Minors as Research Subjects
All subjects received treatments that are standard of care at their individual institutions.

Radiation or Radioactive Substances
N/A