

Proposed title: Evaluation of time to resolution of and treatment duration for necrotizing enterocolitis in a neonatal intensive care unit

Katelyn Bull, PharmD¹; Andrew Gainey, PharmD¹; Christina Cox, PharmD^{1,2}; Anna-Kathryn Burch, MD^{1,3}, Martin Durkin, MD,MPH ¹; Robert Daniels, PharmD¹

¹Palmetto Health Children's Hospital, Columbia, SC, USA

²University of South Carolina College of Pharmacy, Columbia, SC, USA

³Department of Pediatrics, University of South Carolina School of Medicine, Columbia, SC, USA

Corresponding author:

Katelyn Bull, PharmD

700 Woodrow St. Unit 102

Columbia, SC 29205

(803) 434-3040

Pending IRB submission and approval: **Pro00081545**

Evaluation of time to resolution of and treatment duration for necrotizing enterocolitis in a neonatal intensive care unit

1) Background / Justification For Study

Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies observed in neonatal intensive care units (NICU).¹ It is estimated that 2-5% of all infants admitted to a NICU will develop NEC, and of those 20-40% may require surgical intervention.² NEC remains one of the leading causes of morbidity and mortality in the neonatal population with mortality ranging from 20-35%.³ Consequences of NEC can include short gut syndrome, increased central line days, and exposure to broad spectrum antibiotic use.

Ample research has been conducted to understand the pathophysiology and etiology of NEC, however it appears to be multifactorial and the exact pathogenesis is still unknown. The goal of treating NEC is to prevent continuing injury to the mucosal lining of the gastrointestinal tract, stop disease progression, and treat any infection that may be present.² Treatment typically includes withholding all enteral feedings, administering intravenous antibiotics and supportive care. While much research has focused on understanding NEC, there are controversies in the care of infants with NEC, and guidelines have been based off expert opinion and institutional preference.

The standard duration of therapy for NEC ranges from 7-14 days, and antimicrobials used can vary widely. Duration of treatment may depend on the severity of NEC, as classified by Modified Bell Staging. Although treatment durations for NEC have remained constant for many years, no studies, to our knowledge, have sought to see when symptoms of NEC resolve, and when it may be safe to stop antimicrobials. Antibiotic use is necessary for the treatment of NEC, but use can alter a neonate's developing microbiome and immune system. These alterations can increase their risk for subsequent infections and antibiotic resistance. Recent studies have linked antibiotic use with obesity and asthma.^{4, 5} Antibiotic use is not benign, which is why antibiotic exposure should be limited. Our study seeks to determine the true time period when NEC resolves, based on surrogate markers used in the diagnosis of NEC, in hopes of decreasing antibiotic exposure in our neonatal population.

2) Objectives / Research Aims:

Primary objective:

What is the time to resolution of mild, moderate, and severe necrotizing enterocolitis (NEC) in a level IIIB medical and surgical neonatal intensive care unit (NICU)?

Secondary objectives:

- Is the time to resolution of NEC longer in patients who received shorter durations of antibiotics?
- Is the incidence of NEC recurrence greater in patients who receive shorter durations of antibiotics?
- Is the time to return to baseline feeds different based on treatment duration

For the above questions, treatment durations are stratified as followed:

- Mild Medical NEC: 5 days vs 7 days
 - Moderate Medical NEC: 7 days vs 10 days
 - Severe Medical NEC: 10 days vs 14 days
 - Surgical NEC: 7 days vs 14 days
- Is there a difference in the incidence of NEC recurrence between patients who followed institutional recommended antibiotic durations and those who did not?
 - Are antibiotics discontinued in patients prior to the resolution of NEC?

Hypothesis: We hypothesize that the time to resolution of necrotizing enterocolitis will be less than 7 days. We also hypothesize that there is no difference between the incidence of NEC recurrence or time to baseline feeds based on duration of treatment.

Evaluation of time to resolution of and treatment duration for necrotizing enterocolitis in a neonatal intensive care unit

3) Setting: Research will be conducted at Palmetto Health Children's Hospital

4) Study Design

This study is a retrospective, observational review including patients in the neonatal intensive care unit at Palmetto Health Richland with a diagnosis of necrotizing enterocolitis from June 1st 2012-June 1st 2018.

Patients will be identified through the Vermont Oxford Network and patient medical records will be accessed using the medical record number (MRN) assigned to each patient.

a) Inclusion and Exclusion Criteria

Inclusion criteria: All patients admitted to Palmetto Health Richland's neonatal intensive care unit during the study period with a diagnosis of necrotizing enterocolitis.

Exclusion criteria: Positive blood culture at the time of NEC, presence of a drain, transfer from an outside institution at the time of NEC

b) Number of Subjects

We expect to collect data on approximately 180 patients. This number is based on previous diagnosis rates. We anticipate approximately 7-11 patients to have recurrence of NEC based on published literature.⁶

c) Study Endpoints

The primary endpoint of this study is the time to return to baseline (value 48 hours prior to NEC diagnosis) or normal values of the following markers following NEC diagnosis: (assuming markers are elevated at diagnosis)

- I:T ratio in patients <1 month old, bands in patients \geq 1 month old
- Portal venous gas on imaging
- Vasopressor requirement (excluding renal dopamine dosing, defined as \leq 5 mcg/kg/min)
- Inflammatory markers (C-reactive protein, erythromycin sedimentation rate, procalcitonin)
- Metabolic acidosis
- Bloody stool
- Pneumatosis on abdominal imaging
- Oxygen requirements and mode of ventilation
-

For all of the above values, data will be collected starting 48 hours prior to NEC, and will be followed until the marker has normalized. Once the final marker that led to a NEC diagnosis has resolved, the duration of time (in days) this took to occur will be recorded as the time to resolution of NEC.

Secondary endpoints:

- Time to recurrence of NEC
 - o Recurrence is defined as confirmed NEC (Bell Stage II or III) following a successfully treated episode of NEC. Successful treatment is defined by resolution of symptoms related to NEC as listed above, and return to baseline feeding.⁷
- Central line days
- Time to return to baseline feeding (baseline feeding defined as volume and caloric density 48 hours prior to NEC diagnosis)

Evaluation of time to resolution of and treatment duration for necrotizing enterocolitis in a neonatal intensive care unit

d) Statistical Analysis

To determine the time to resolution of NEC, patients will be separated into five different groups, since duration of therapy depends on severity of NEC. Patients will be divided into mild medical, moderate medical, severe medical, moderate surgical, or severe surgical NEC.

Primary objective:

What is the time to resolution of mild, moderate, and severe necrotizing enterocolitis (NEC) in a level IIIB medical and surgical neonatal intensive care unit (NICU)?

Kaplan-Meier curves will be constructed for all five severity groups and they will be compared with a log-rank test. Patients who die prior to resolution of NEC will be censored at the time of death.

Secondary objectives:

- Is the time to resolution of NEC longer in patients who received shorter durations of antibiotics?

Whether the patient received shorter versus longer duration for treatment (as detailed below) will be entered into a Cox regression model with time to resolution as the outcome, group (five levels) and duration of treatment (dichotomous) as predictors.

- Is the incidence of NEC recurrence greater in patients who receive shorter durations of antibiotics?

A 2x2 table will be constructed with recurrence as the column variable and treatment duration as the row variable. The proportion of patients with recurrence will be computed for both duration groups. If the number of patients with recurrent NEC is sufficiently large, an odds ratio with 95% confidence interval will be computed.

- Is the time to return to baseline feeds different based on treatment duration

Whether the patient received shorter versus longer duration for treatment (as detailed below) will be entered into a Cox regression model with time to return to baseline feeds as the outcome, and group (five levels), duration of treatment (dichotomous), and gestational age as predictors.

- For the above questions, treatment durations (short vs long) are defined as followed:

- Mild Medical NEC: 5 days vs 7 days
- Moderate Medical NEC: 7 days vs 10 days
- Severe Medical NEC: 10 days vs 14 days
- Surgical NEC: 7 days vs 14 days

- Is there a difference in the incidence of NEC recurrence between patients who followed institutional recommended antibiotic durations and those who did not?

A 2x2 table will be constructed with recurrence as the column variable and whether institutional recommended antibiotic durations were followed as the row variable. The proportion of patients with recurrence will be computed for both groups. If the number of patients with recurrent NEC is

Evaluation of time to resolution of and treatment duration for necrotizing enterocolitis in a neonatal intensive care unit

sufficiently large, an odds ratio with 95% confidence interval will be computed.

- Are antibiotics discontinued in patients prior to the resolution of NEC?

The proportion of patient where antibiotics were discontinued prior to the resolution of NEC will be computed, along with a 95% confidence interval.

e) Procedures/Data Banking

This study will be conducted as a retrospective, single-center study. Data will be collected using electronic chart review (Cerner Medication Manager and Powerchart® systems). Data to be collected is presented in Appendix A.

f) Data Management and Confidentiality

Data collected will be unlinked from patient identifiers (MRN) at the time of data collection. PHI will be stored in a secure location, on a password-protected network, with a password protected file. Only necessary members of the research team will have access to this information. Electronic data collection sheets will be housed on RedCap.

5) Risks to Subjects

This is a retrospective review that will evaluate various outcomes of NEC after treatment. No intervention is being made and we will not be directly involved with the study subjects, therefore there is minimal risk. Data being collected is already a part of Palmetto Health's electronic medical record and is documented as part of the standard of care. Data will be reported as a summary to minimize any potential privacy disclosures.

6) Consent Process

This study will utilize a waiver of the consent process. A waiver (instead of written authorization) is needed to conduct the research because of the nature of a retrospective review. Data will be collected after patient discharge, therefore contacting patients/families poses a greater risk of interfering with their privacy.

7) Bibliographic References

1. Blackwood BP, Hunter CJ, Grabowski J. Variability in Antibiotic Regimens for Surgical Necrotizing Enterocolitis Highlights the Need for New Guidelines. *Surgical Infections*. 2017; 18(2):215-20.
2. Shah D, Sinn JKH. Antibiotic regimens for the empirical treatment of newborn infants with necrotizing enterocolitis. *Cochrane Database of Systematic Reviews*. 2012, Issue 8. Art. No.: CD007448.
3. Rich BS, Dolgin SE. Necrotizing Enterocolitis. *Pediatrics in Review*. 2017;38(12):552-559.
4. Cotton CM. Adverse consequences of neonatal antibiotic exposure. *Curr Opin Pediatr*. 2016;28:141-149.
5. Scott FI, Horton DB, Mamtani R, Haynes K et al. Administration of Antibiotics to Children Before Age 2 Years Increases Risk for Childhood Obesity. *Gastroenterology*. 2016;151(1):120-129.
6. Downward CD, Renaud E, St. Peter SD, Abdullah F, Islam S, et al. Treatment of necrotizing enterocolitis: An American Pediatric Surgical Association Outcomes and Clinical Trial Committee systematic review. *Journal of Pediatric Surgery*.
7. Thyoka M, Eaton S, Hall NJ, Drake D, Kiely E, Curry J, Cross K, de Coppi P, Pierro A. Advanced Necrotizing Enterocolitis Part 2: Recurrence of Necrotizing Enterocolitis. *Eur J Pediatr Surg*. 2012;22:13-16.