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Evaluation of Time to Resolution of Medical Necrotizing Enterocolitis Using Severity-Guided Management in a Neonatal Intensive Care Unit

Katelyn E. Bull, PharmD; Andrew B. Gainey, PharmD; Christina L. Cox, PharmD; Anna-Kathryn Burch, MD; Martin Durkin, MD, MPH; and Robert Daniels, PharmD

OBJECTIVE No studies, to our knowledge, have determined the relationship between symptom resolution and timing of antimicrobial discontinuation in necrotizing enterocolitis (NEC). Our study seeks to determine the period to NEC resolution by using severity-guided management, based on surrogate markers used in the diagnosis of NEC.

METHODS This retrospective, observational review included patients in our NICU with NEC from June 1, 2012, to June 1, 2018. Patients were excluded for surgical NEC, a positive blood culture or transfer from an outside institution at the time of NEC, presence of a peritoneal drain, or death prior to NEC resolution. The primary outcome was time to resolution of NEC, measured by return to baseline of surrogate markers used in the diagnosis of NEC.

RESULTS The median times to resolution in days, based on our institution's NEC severity group, were as follows: mild 3 (range, 1–4); moderate 4 (range, 1–17); severe 9 (range, 5–21). No difference in NEC recurrence was found based on antibiotic duration (OR 0.803; 95% CI, 0.142–4.225).

CONCLUSIONS Time to resolution of NEC differs by severity group, suggesting a need for different treatment durations. Recurrence of NEC did not differ between groups, suggesting that shorter antibiotic durations do not lead to an increased incidence of NEC recurrence. Further exploration of the optimal antimicrobial treatment duration for NEC is warranted.

ABBREVIATIONS CBC, complete blood count; CI, confidence interval; HR, hazard ratio; IDSA, Infectious Diseases Society of America; IQR, interquartile range; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; OR, odds ratio; SD, standard deviation; SIS, Surgical Infection Society; WSES, World Society of Emergency Surgery

KEYWORDS antimicrobial stewardship; necrotizing enterocolitis; neonate

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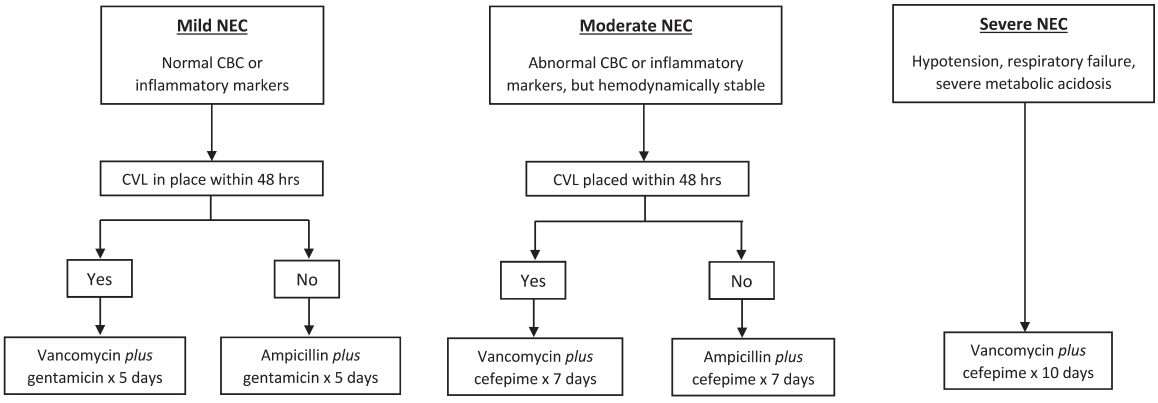
Introduction

Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies observed in NICUs.[1] It is estimated that 2% to 5% of all infants admitted to a NICU will develop NEC and of those, 20% to 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% to 35%.[3] Consequences of NEC can include short bowel syndrome, prolonged neonatal hospitalization, 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 continued 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 to 14 days, and antimicrobials used can vary widely. Duration of treatment may depend on the severity of NEC, as classified by Bell Staging and Modified Bell Staging.[4,5] Although treatment durations for NEC have remained constant for many years, no studies, to our knowledge, have sought to see when it may be safe to stop antibiotics based on symptom resolution. Infectious Diseases Society of America (IDSA) and World Society of Emergency Surgery (WSES) guidelines recommend treatment durations of 4 to 7 days

Figure 1. Institutional NEC treatment protocol.*



CVL, central venous line; NEC, necrotizing enterocolitis.
* See Table 1 for definitions of abnormal markers

for complicated intra-abdominal infection but do not differentiate neonatal intra-abdominal infections.[6,7] The 2017 Surgical Infection Society (SIS) guidelines state to "[u]se a 7-10 day course of antimicrobial therapy in pediatric patients less than one month of age, particularly for those with necrotizing enterocolitis."[8] From recommended antibiotic durations ranging from 4 to 10 days, our institution implemented a new protocol for the treatment of NEC (Figure 1), which uses more objective markers for risk stratification than Bell Staging Criteria, and shorter durations of antibiotics than previously used. This study sought to determine the true period when NEC resolves, based on surrogate markers used in the diagnosis of NEC, in hopes of decreasing antibiotic exposure in our neonatal population. Secondarily, because our institution changed its NEC protocol to shorter treatment durations, this study also sought to identify whether shorter antibiotic durations in NEC are appropriate, in hopes of decreasing antibiotic exposure in our neonatal population.

Materials and Methods

Study Design and Setting. This retrospective, observational study was approved via expedited review by our institution's institutional review board. Informed consent was not required by the institutional review board. Patients with a diagnosis of medical necrotizing enterocolitis admitted from June 1, 2012, to June 1, 2018, were included in the study. Patients were identified through the Vermont Oxford Network, ICD-9/10 codes, and antimicrobial stewardship records. Patients with intestinal perforations were also identified, and pathology reports along with surgery notes were reviewed to determine if the patient should have been diagnosed with NEC. Patients were categorized as on protocol vs non-protocol on the basis of severity markers and duration of treatment (Figure 1). Patients were excluded for the following: surgical NEC, positive blood culture at the time of NEC, presence of a drain, outside transfer, or death prior to resolution of NEC.

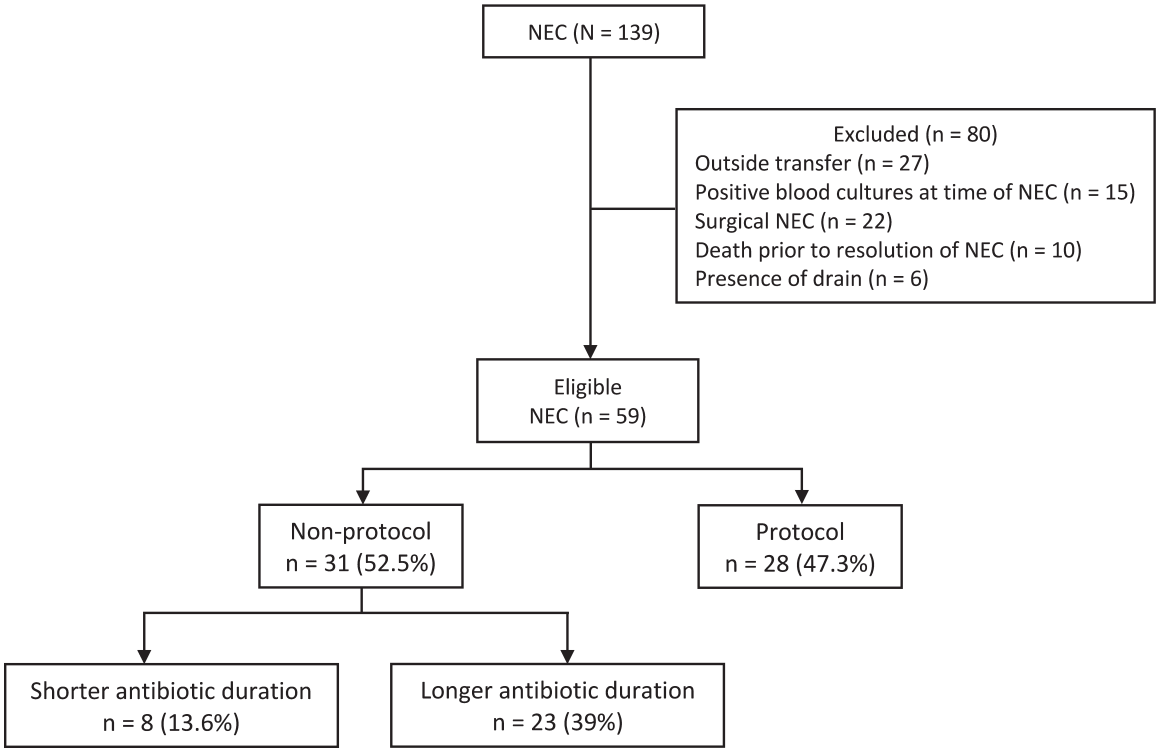
Outcome Measures and Definitions. The primary objective of this study was to determine the time to resolution of mild, moderate, and severe NEC at a regional perinatal center. Time to resolution was defined as the return to baseline or normal values of surrogate markers following NEC diagnosis (Table 1). Secondary objectives were resolution of NEC based on antibiotic duration, incidence of NEC recurrence based on antibiotic duration and protocol use, time to return to baseline feeds, and antibiotic discontinuation prior to resolution of NEC. Protocol use was defined as a duration of antibiotics consistent with the duration recommended in the protocol. Patients who did not follow the protocol were split into 2 other categories:

Table 1. Data Points

Vasopressor Requirement (Excluding Dopamine ≤5 mcg/kg/min)*	FiO_2 Requirements and Mode of Ventilation*	I:T Ratio <0.2 (1-mo-old) or Band Count >13 (≥1-mo-old)
Pneumatosis	Portal venous gas	Metabolic acidosis
Bloody stool	Procalcitonin†	C-reactive protein†

I:T ratio, immature to total neutrophil ratio
* Return to baseline defined as value 48 hr prior to diagnosis.
† Return to baseline defined as decrease by 80% of peak value.

Figure 2. Patient selection.



NEC, necrotizing enterocolitis.

antibiotics for any duration shorter than protocol recommended or antibiotics for any duration longer than protocol recommended.

NEC recurrence was defined as confirmed NEC diagnosis following a successfully treated episode of NEC and return to baseline feeding. Time to return to baseline feeding was defined as returning to the volume and caloric density that was tolerated within the 48 hours prior to NEC diagnosis.

Data Collection. Data were collected starting 48 hours prior to NEC diagnosis. Markers used to determine NEC resolution (Table 1) were monitored until the marker normalized. Once the final marker leading to NEC diagnosis had resolved, the time (in days) for this to occur was recorded as the time to resolution of NEC. Only markers that were abnormal at diagnosis needed to normalize in order to record this as the time to resolution of NEC. Daily progress notes were then used to determine when the patient returned to full feeds, and if the patient had an episode of NEC recurrence. Other data points collected for exploratory analysis included number of central line days from NEC diagnosis to discharge, and total parenteral nutrition use for >90 days.

Statistical Analysis. Data were summarized by using either medians and IQR or mean and SD for continuous variables. Frequency and percentage were used for categorical variables. Our primary objective was assessed by using Kaplan-Meier curves and log-rank test. Time to resolution of NEC, based on antibiotic duration and time to return to baseline feeds, was assessed with Cox regression models. Incidence of NEC recurrence, based on antibiotic duration and protocol used, was assessed by using Goodman-Kruskal gamma and Fisher exact test, respectively. All analyses were conducted by using R Core Team 2018 (R Foundation for Statistical Computing, Vienna, Austria), with 2-sided p values <0.05 considered statistically significant.

Results

Patient Characteristics. One hundred thirty-nine patients were identified as having NEC during the study period. Fifty-nine patients were included in the dataset. Most patients were excluded for outside transfer (Figure 2); 50.8% of patients were male and 62.7% were African American. The mean ± SD gestational age was 30.1 ± 3.33 weeks and the median day of life when NEC occurred was 15 (IQR, 10–25) days. Based on institutional staging, 62.7% of patients were classified as having moderate medical NEC. There was no difference in NEC severity based on institutional staging between those who followed protocol and those who did not (p = 0.194) (Table 2). Most of the neonates in this study were low

Table 2. Baseline Characteristics

	All Subjects (N = 59)	Non-Protocol (n = 31)	Protocol (n = 28)	p value
Gestational age, mean ± SD, wk	30.11 ± 3.33	29.71 ± 3.11	30.81 ± 3.43	0.198*
Birth weight, n (%), kg				
≥2.5	1 (1.7)	0 (0)	1 (3.6)	0.531†
1.5–2.49	20 (33.9)	10 (32.3)	10 (35.7)	
1–1.49	22 (37.3)	12 (38.7)	10 (35.7)	
<1	16 (27.1)	9 (29)	7 (25)	
Male, n (%)	30 (50.8)	17 (54.8)	13 (46.4)	0.519‡
Race, n (%)				
African American	37 (62.7)	19 (61.3)	18 (64.3)	>0.999§
Caucasian	17 (28.8)	9 (29)	8 (28.6)	
Asian	2 (3.4)	1 (3.2)	1 (3.6)	
Unknown	3 (5.1)	2 (6.5)	1 (3.6)	
NEC day of life, median (IQR)	15 (14)	15 (12.5)	14.5 (12.25)	0.543¶
Bell staging, n (%)				
Ia	2 (3.4)	2 (6.5)	0 (0)	0.739†
Ib	6 (10.2)	3 (9.7)	3 (10.7)	
IIa	38 (64.4)	19 (61.3)	19 (67.9)	
IIb	7 (11.9)	4 (12.9)	3 (10.7)	
IIIa	6 (10.2)	3 (9.7)	3 (10.7)	
IIIb	0 (0)	0 (0)	0 (0)	
Institutional staging, n (%)				
Mild medical	11 (18.6)	9 (29)	2 (7.1)	0.194†
Moderate medical	37 (62.7)	16 (51.6)	21 (75)	
Severe medical	11 (18.6)	6 (19.4)	5 (17.9)	

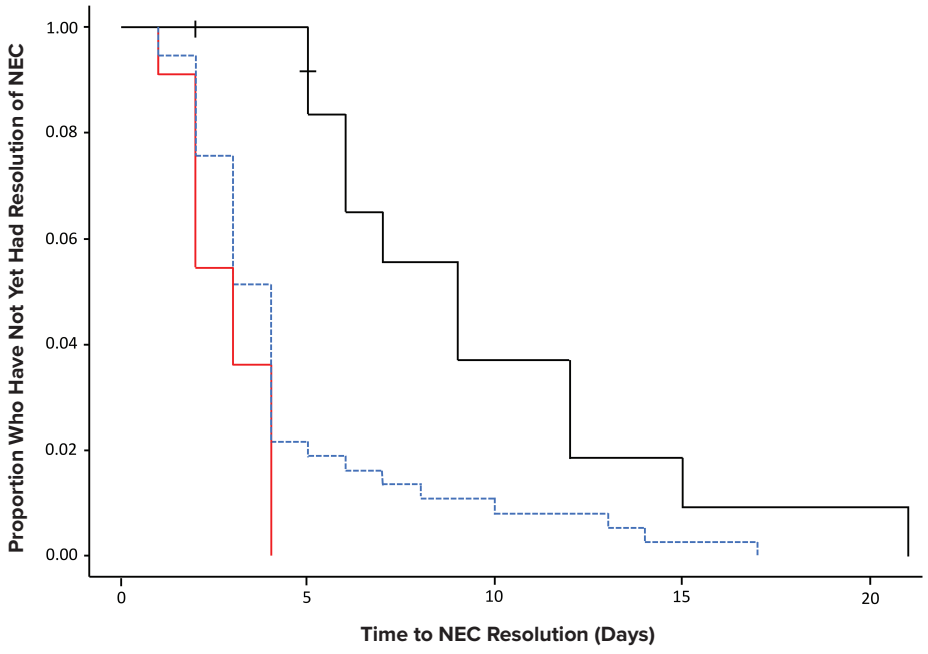
NEC, necrotizing enterocolitis
* *t* test (equal variance); descriptive statistics are mean (SD).
† Goodman-Kruskal gamma test; descriptive statistics are count (percentage).
‡ Chi-square test; descriptive statistics are count (percentage).
§ Fisher exact test; descriptive statistics are count (percentage).
¶ Wilcoxon rank sum test; descriptive statistics are median (IQR).

or very low birth weight premature neonates (Table 2).

Primary Outcome. The median time to NEC resolution for all patients, regardless of whether they followed protocol, was 4 (IQR, 3–8; range, 1–21) days. The median time to NEC resolution based on NEC severity was as follows: mild NEC, 3 (IQR, 2–4; range, 1–4) days; moderate NEC, 4 (IQR, 3–4; range, 1–17) days; and severe NEC, 9 (IQR, 6–12; range, 2–21) days. A difference in time to resolution existed between mild, moderate, and severe medical NEC groups, regardless of whether they followed protocol, when all 3 were compared ($p < 0.001$) (Figure 3). When comparing specific severity groups to each other instead of all groups, no difference in time to resolution existed between mild and moderate medical NEC ($p = 0.092$). However, a difference in time to resolution existed between mild and severe NEC ($p < 0.001$) and moderate and severe NEC ($p = 0.002$) groups.

Secondary Outcomes. ***Resolution of NEC Based on Antibiotic Duration.*** Twenty-eight patients (47.5%) followed institutional protocol–recommended antibiotic durations (Figure 1). Patients with shorter durations of antibiotics than per protocol were more likely to experience resolution at any time than those who followed protocol (hazard ratio [HR] 4.242; 95% CI, 1.769–10.172) when controlling for severity group (Table 3). Patients with moderate or severe NEC were less likely to experience resolution than those with mild NEC (HR 0.258 [95% CI, 0.116–0.574] and HR 0.106 [95% CI, 0.040–0.281]), respectively). The median antibiotic duration for all patients was 7 (IQR, 7–11; range, 5–14) days. The slowest marker to resolve was C-reactive

Figure 3. Kaplan-Meir curve for time to resolution by severity of NEC.



NEC, necrotizing enterocolitis.
Logrank p value < 0.001
— Mild; --- Moderate; — Severe

protein, while imaging findings and blood in the stool were the quickest markers to resolve (Table 4).

NEC Recurrence. Nine patients (15.3%) had NEC recurrence. The median for recurrence was 15 (IQR, 11–21; range, 1–49) days. No difference in NEC recurrence existed in patients who followed protocol (OR 0.803; 95% CI, 0.142–4.225) (Table 5). Eight patients (13.6%) had antibiotic therapy stopped prior to the resolution of NEC. Of those 8 patients, 5 (62.5%) followed protocol and 3 (37.5%) received antibiotics for a longer duration than per protocol. Twenty-five percent (2/8) of patients with antibiotic therapy stopped prior to resolution had NEC recurrence. Both of the patients with NEC recurrence received antibiotics for a longer duration than per protocol.

Time to Return to Baseline Feeds. Patients with severe NEC were less likely to return to baseline feeds at any time than those with mild NEC (HR 0.192; 95% CI, 0.075–0.490). Patients who received shorter durations of antibiotics than per protocol were more likely to have returned to feeds at any time than those who followed protocol (HR 2.508; 95% CI, 1.073–5.864) (Table 6). No patients received total parenteral nutrition for >90 days.

Other Outcomes. Thirty (50.8%) patients had a central line after NEC diagnosis for a median duration of 5 days. There was no difference in central line use between those who followed protocol (57%) and those who did not (46.7%). Patients with a longer duration of antibiotics than recommended in the protocol had a longer median duration of central line use than those who followed protocol (40 days vs 17.5 days). Although we did not analyze antibiotic agent used, ampicillin, gentamicin, and vancomycin were the most used agents in our study (Figure 4).

Discussion

NEC accounts for significant morbidity and mortality

Table 3. Time to Resolution of NEC by Protocol*

Protocol Use	Median, days (IQR)	HR (95% CI)
Protocol (n = 28)	4 (3–5.25)	
Non-protocol short (n = 8)	2 (2–3)	4.242 (1.769–10.172)
Non-protocol long (n = 23)	4 (3–8)	0.592 (0.326–1.073)

HR, hazard ratio; NEC, necrotizing enterocolitis
* Cox regression model, controlled for severity, with time to resolution as the outcome and duration of treatment as predictors

Table 4. Time to Resolution of Markers

Marker	Days to Resolution, median (IQR)
C-reactive protein	6 (3.5–8)
Ventilation	5 (3.25–11.25)
Vasopressor	4 (3–4)
Procalcitonin	3 (3–4)
Acidosis	3 (1.5–3.5)
FiO_2%	2.5 (2–3)
I:T ratio or band count	2 (2–4.75)
Imaging	2 (2–3)
Blood in stool	1 (1–3)
Portal venous gas	1 (1–1.25)

I:T ratio, immature to total neutrophil ratio

in the neonatal population.[1–3] Much data surrounding NEC focuses on pathogenesis, prevention, and outcomes. However, the optimal treatment duration and time to resolution of NEC has yet to be established. When a patient is diagnosed with NEC, they are exposed to broad spectrum antibiotics that may be continued for their treatment course. 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 risk for subsequent infections and antibiotic resistance. Recent studies have also linked early antibiotic use during infancy to the development of asthma and obesity later in life.[9,10] Prolonged antibiotic courses also lead to a need for intravenous access. Recently published IDSA and WSES guidelines recommend treatment durations of 4 to 7 days for complicated intra-abdominal infection but do not differentiate neonatal intra-abdominal infections.[6,7] The 2017 SIS guidelines state to "[u]se a 7-10 day course of antimicrobial therapy in pediatric patients less than one month of age, particularly for those with necrotizing enterocolitis"; however, this recommendation is based on weak evidence and is focused on patients with known intestinal perforations.[8] Based on recommended antibiotic durations ranging from 4 to 10 days, our institution implemented a new protocol for the treatment of NEC (Figure 1) that uses more objective markers for risk stratification than Bell Staging and Modified Bell Staging Criteria, and shorter durations of antibiotics than previously used.[4,5]

In this single center, retrospective review of neonates with a diagnosis of NEC, the time to resolution, based on severity group, was shorter than currently recommended antibiotic durations in the literature for NEC. These results were derived from our institution's own unique protocol and staging of patients with NEC (Figure 1). About 50% of patients included in the study did not follow our institution's unique protocol. This protocol was not officially launched at our institution until 2018, which could explain why most patients fell in the non-protocol group. However, owing to the retrospective nature of this study, if a patient's severity group and treatment duration aligned with the current protocol during all included years, they were "on protocol." Patients who followed protocol with shorter durations of antibiotics were not at a higher risk for NEC recurrence than those with longer durations of antibiotics. If antibiotics were stopped prior to resolution of NEC, the risk of NEC recurrence did increase. However, all patients with this occurrence continued antibiotics for longer durations than per protocol. Treatment duration did not affect time to return to baseline feeds; however, longer treatment durations did lead to more central line days.

For mild, moderate, and severe NEC, time to resolution fell within the recommended antibiotic duration in our institution's protocol. Several surrogate markers could be influenced by other neonatal disease states, such as ventilation status, and inflammatory markers. In our study population, we did have outliers in severity groups that could have increased time to resolution for the population. Patients with shorter durations of antibiotics had a shorter time to NEC resolution, which is expected and shows that providers were treating patients by symptom resolution.

NEC recurrence rates in the literature range from 4% to 10%, which is lower than the recurrence rate of 15.3% we found in our population.[11,12] Although incidence of recurrence did not differ by duration of antibiotics, there was a trend towards higher recurrence rates in those with longer durations of antibiotics. Those patients with longer treatment durations were likely critically ill, based on severity staging. This high recurrence rate prompted us to look individually at all patients with recurrence. We found that 4 of 9 patients with NEC recurrence had a complicated abdominal history outside of their NEC diagnosis. Examples of diagnoses in these patients include colonic strictures, gastroschisis, and spontaneous intestinal perforation prior to NEC diagnosis.

Table 5. Recurrence by Protocol Use

Protocol Use	Recurrence, n (%)	No Recurrence, n (%)	OR (95% CI)
Protocol (n = 28)	4 (14.3)	24 (85.7)	0.803 (0.142–4.225)
Non-protocol short (n = 8)	1 (12.5)	7 (87.5)	
Non-protocol long (n = 23)	4 (17.4)	19 (82.6)	

OR, odds ratio

Table 6. Time to Return to Baseline Feeds by Treatment Duration (Controlled for Gestational Age)

Protocol Use	Median, days (IQR)	HR (95% CI)
Protocol	14 (3.25)	
Non-protocol short	13.5 (1.75)	2.508 (1.073–5.864)
Non-protocol long	18 (10.5)	0.692 (0.352–1.362)

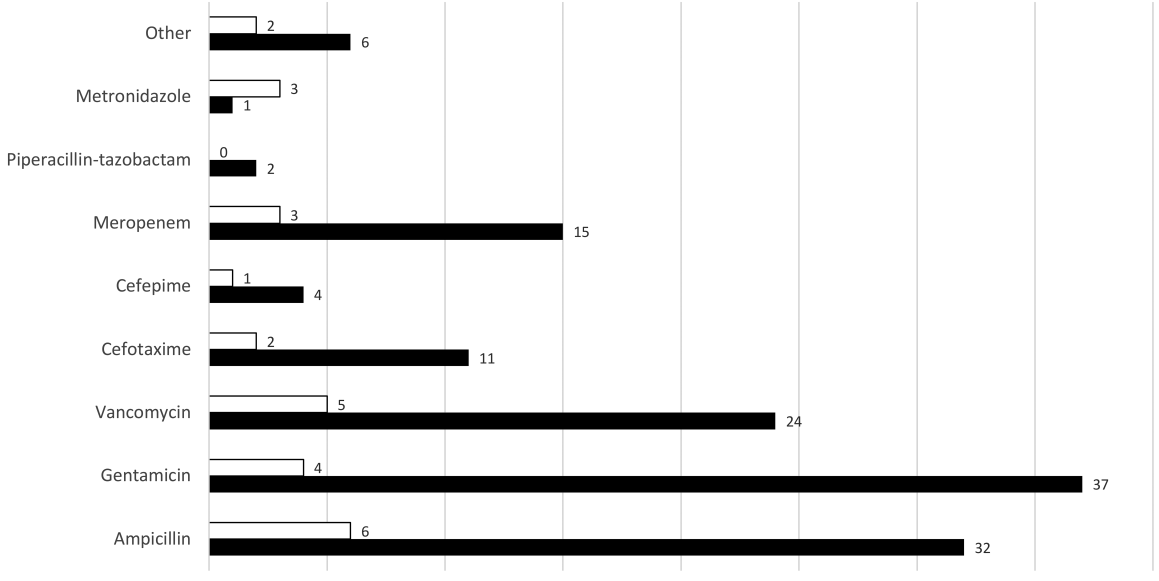
HR, hazard ratio

Furthermore, another patient was found to have closed over perforations and strictures when they underwent surgery for NEC recurrence. This suggests that this patient should have been treated as a surgical NEC case from the start, which could have led to the episode of recurrence. If these patients are excluded from the recurrence rate, the latter decreased to 8.5% (5/59 patients), which is more consistent with recurrence rates in the literature. Of these complicated patients, all received antibiotics for longer than the duration stated in the protocol. Therefore, we assume that duration of antibiotics may not play as large of a role in risk of NEC recurrence as other comorbidities do.

Patients with longer durations of antibiotics had more central line days, which can predispose patients to more complications such as infections and thrombosis. Following protocol-suggested antibiotic durations did not cause harm to patients and did offer benefits such as decreased central line use. We did find that harm may be caused by increasing the risk of recurrence if antibiotics are stopped prior to resolution. This highlights the importance of personalized antibiotic treatment durations in patients who are not showing symptom resolution as expected.

Several limitations to this study exist and must be factored into the results. While NEC recurrence rates were higher in our population than previously published rates, the actual number of patients with recurrence was small. This makes it hard to infer what may put a patient at risk of recurrence. There are many confounding factors in the NICU such as ventilator weaning, different radiologists reading films, and concomitant disease states that may affect resolution of NEC. Two factors that affected results in our population were return to ventilation and vasopressors. This study used a very conservative definition of resolution by requiring all markers to return to baseline. In clinical practice, if a patient requires prolonged ventilation, a provider could assess other reasons outside of NEC for this situation; however, we were unable to determine this, so time to resolution of NEC reflected in this study could be longer than the actual clinical time to resolution of NEC. Another major limitation is that we did not analyze the antibiotic agent used, which could affect time to resolution, complications of NEC, and recurrence rates.[6]

Figure 4. Antibiotic Agent Used.



NEC, necrotizing enterocolitis.
□ NEC Recurrence; ■ No NEC Recurrence

Conclusions

Despite these limitations, this study demonstrated that the median time to resolution of NEC differs by severity group. Because of this, antibiotic durations may need to be tailored to a patient's severity group. This study also found that shorter antibiotic durations than previously recommended (ranging from 5–10 days based on severity) did not lead to increased NEC recurrence and may be appropriate for patients with medical NEC. This study provides background information and development of research questions for larger prospective trials. Future, larger studies should evaluate the antibiotic agents used, as well as duration of treatment, and incorporate more outcomes of decreasing antibiotic use.

Article Information

Affiliations. Department of Pharmacy (KEB, ABG, CLC, RD), Department of Pediatrics (A-KB), Department of Clinical Research and Operations (MD), Prisma Health Children's Hospital–Midlands, Columbia, SC; Department of Clinical Sciences and Outcome Pharmacy (CLC), University of South Carolina College of Pharmacy, Columbia, SC; Department of Pediatrics (AKB), University of South Carolina School of Medicine, Columbia, SC.

Correspondence. Katelyn E. Bull, PharmD; Katelyn.Rasmussen@PrismaHealth.org

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