Variability in Antibiotic Regimens for Surgical Necrotizing Enterocolitis Highlights the Need for New Guidelines

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Abstract

Background: Necrotizing enterocolitis or NEC is the most common gastrointestinal emergency in the newborn. The etiology of NEC remains unknown, and treatment consists of antibiotic therapy and supportive care with the addition of surgical intervention as necessary. Unlike most surgical diseases, clear guidelines for the type and duration of peri-operative antibiotic therapy have not been established. Our aim was to review the antibiotic regimen(s) applied to surgical patients with NEC within a single neonatal intensive care unit (NICU) and to evaluate outcomes and help develop guidelines for antibiotic administration in this patient population.

Patients and Methods: A single-center retrospective review was performed of all patients who underwent surgical intervention for NEC from August 1, 2005 through August 1, 2015. Relevant data were extracted including gestational age, age at diagnosis, gender, pre-operative antibiotic treatment, post-operative antibiotic treatment, development of stricture, and mortality. Patients were excluded if there was incomplete data documentation.

Results: A total of 90 patients were identified who met inclusion criteria. There were 56 male patients and 34 female patients. The average gestational age was 30 5/7 wks and average age of diagnosis 16.7 d. A total of 22 different pre-operative antibiotic regimens were identified with an average duration of 10.6 d. The most common pre-operative regimen was ampicillin, gentamicin, and metronidazole for 14 d. A total of 15 different post-operative antibiotic regimens were identified with an average duration of 6.6 d. The most common post-operative regimen was ampicillin, gentamicin, and metronidazole for two days. There were 26 strictures and 15 deaths. No regimen or duration proved superior.

Conclusion: We found that there is a high degree of variability in the antibiotic regimen for the treatment of NEC, even within a single NICU, with no regimen appearing superior over another. As data emerge that demonstrate the adverse effects of antibiotic overuse, our findings highlight the need for guidelines in the antibiotic treatment of NEC and suggest that an abbreviated course of post-operative antibiotics may be safe.

NECROTIZING ENTEROCOLITIS, or NEC, is a devastating inflammatory intestinal disease of premature infants and is the most common gastrointestinal emergency observed in the neonatal intensive care unit (NICU) [1,2]. Mortality rates are estimated to be approximately 15%–30% with increased mortalities observed in lower birth weight and patients requiring surgery [1,3–5]. Furthermore, those patients who do survive the disease can go on to have significant morbidities [6–9]. Despite decades of research, the etiology and pathophysiology behind the disease remain elusive [10].

Necrotizing enterocolitis is associated with an immature intestine and the presence of bacteria [2]. Initial treatment consists primarily of supportive care and antibiotic therapy [11]. When NEC is suspected or diagnosed, enteral feedings are held, gastric decompression is performed, and broad-spectrum antibiotics are started. Patients are observed closely for any signs of progression of the disease or decompensation. If there is clinical deterioration, or a concern for full-thickness intestinal ischemia or perforation, surgical intervention is warranted [11–13]. Post-operatively, supportive care and antibiotics are

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continued while observing these patients for clinical improvement before eventual return of enteral feeding.

Unlike many surgical diseases, no formal guidelines for the type of peri-operative antibiotics or the duration of therapy have been established for NEC. Recent reviews of the literature have shown that there is a lack of data from which to make formal antibiotic recommendations [14,15]. Our aim was to review the antibiotic regimens applied to surgical NEC patients in a single neonatal intensive care unit (NICU). We hypothesized that there would be high variability in the antibiotic regimens observed because of the lack of set guidelines. Using the outcomes data collected we would then be able to develop a prospective comparative effectiveness research study of specific peri-operative antibiotic regimens.

Patients and Methods

A single-center retrospective review was performed of all patients who underwent surgical intervention via laparotomy for NEC from August 1, 2005 through August 1, 2015. Relevant data were extracted including gestational age, age at diagnosis, gender, pre-operative abdominal drain placement, pre-operative antibiotic treatment, post-operative antibiotic treatment, development of stricture, and mortality. Patients were followed until their initial hospital discharge.

Antibiotic regimen data were identified by searching individual patient charts. Physician notes from each hospital day were read and cross-referenced with the medication administration record [16]. These daily antibiotic regimens were then compiled into either pre-operative or post-operative regimens with respect to the date of surgical intervention. Patients were excluded if there was incomplete data documentation on the antibiotics regimens that were administered. The pre-operative and the post-operative antibiotic regimens for each patient had to be documented clearly, otherwise, the patient was excluded. Patients who received drains but no laparotomy were not included.

Results

Initial chart review identified 166 potential study patients. However, 76 patients were excluded because there were insufficient data to analyze completely either the pre-operative or post-operative antibiotic regimens. A total of 90 patients were identified who met inclusion criteria. There were 56 male patients and 34 female patients. The average gestational age was 30 5/7 (22 6/7 to 38 5/7) wks and average age at diagnosis 16.7 (1–84) d. Twenty-one patients (23.3%) had undergone placement of a temporizing abdominal drain prior to laparotomy. There were 15 mortalities (Table 1).

The neonatologists managing the patients' care were responsible for choosing the pre-operative antibiotics given. There were 10 individual medications used in 22 different combinations pre-operatively (Table 2). The surgeons who operated on the patients were responsible for choosing the post-operative antibiotics given. There were eight individual medications used in 15 different combinations post-operatively (Table 3). The medications used most frequently in pre-operative regimens were gentamicin (14 regimens), metronidazole (10 regimens), ampicillin (eight regimens), and cefotaxime (eight regimens) (Fig. 1). The medications used most frequently in the post-operative antibiotic regimens were ampicillin (seven regimens), gentamicin (seven

TABLE 1. A RETROSPECTIVE REVIEW OF NINETY PATIENTS WITH SURGICAL NECROTIZING ENTEROCOLITIS: PATIENT DEMOGRAPHICS

<i>Patient characteristics (n=90)</i>	
Gender	
Male	56 (62.2%)
Female	34 (37.8%)
Average gestational age (weeks)	30 5/7 (22 6/7–38 5/7)
Average age at diagnosis of NEC (days)	16.7 (1–84)
Pre-operative drain placement	21 (23.3%)
Mortalities	15 (16.6%)

NEC = necrotizing enterocolitis.

regimens), metronidazole (six regimens), and cefotaxime (five regimens) (Fig. 1).

The 22 different pre-operative antibiotic regimens had an average duration of 10.6 d and a mode duration of 14 d (Fig. 2). The most common pre-operative regimen was ampicillin, gentamicin, and metronidazole for 14 d. The 15 different post-operative antibiotic regimens had an average duration of 6.6 d and a mode duration of two days (Fig. 2). The most common post-operative regimen was ampicillin, gentamicin, and metronidazole for two days. There were 26 strictures and 15 deaths. The degree of variability did not correlate with the service managing the patient, whether it was the neonatology service or the surgical service. Also, no clear pattern was identified when looking at the variability of the antibiotics over time. Ampicillin, gentamicin, and metronidazole was the most common regimen both in 2005 and in 2015. No regimen or duration was superior when it came to outcome analysis.

Discussion

Necrotizing enterocolitis is heterogeneous in terms of presentation and severity. Bell's staging has been used for decades to classify patients with NEC and highlights the heterogeneity of the disease [16]. Antibiotics, however, are the mainstay of treatment for all patients with NEC. They are used in those patients who are managed medically and those who undergo surgical intervention. Because of the high variability in the disease, we chose to focus our study only on patients who developed surgical NEC. An absolute indication for surgical intervention is pneumoperitoneum. Additionally, neonates with worsening pneumatosis, acidosis, sustained platelet drop, and hypotension have been shown to be high risk for requiring operative intervention [13,17,18]. Given the specific indications for surgical intervention in NEC, we felt that analyzing these patients would give us a more uniform and homogenous study population [11–13].

Even after focusing on the subset of surgical NEC patients, the data collected from our single institutional review demonstrate highly variable treatment and the need for antibiotic guidelines. After careful review of these 90 surgical NEC patients, we identified a total of 22 different pre-operative antibiotic combinations and 15 post-operative antibiotic combinations (Tables 1 and 2).

Interestingly, there has been little research investigating the optimal type of peri-operative antibiotics and their durations for NEC. A recent survey questioned 80 surgeons

TABLE 2. A RETROSPECTIVE REVIEW OF NINETY PATIENTS WITH SURGICAL NECROTIZING ENTEROCOLITIS: PRE-OPERATIVE ANTIBIOTICS USED

<i>Pre-operative antibiotic combinations</i>										
<i>Combinations</i>	<i>Ampicillin</i>	<i>Gentamicin</i>	<i>Metronidazole</i>	<i>Cefotaxime</i>	<i>Vancomycin</i>	<i>Cefoxitin</i>	<i>Ceftazidime</i>	<i>Clindamycin</i>	<i>Meropenem</i>	<i>Fluconazole</i>
1	x	x								
2	x	x	x							
3	x	x		x						
4		x	x		x					
5			x	x	x					
6		x	x		x					x
7	x		x							
8			x	x	x					x
9	x	x	x	x						
10	x			x						
11	x	x	x				x			
12										
13		x			x					
14		x						x		
15	x	x				x		x		
16										
17				x						
18		x		x						
19		x		x	x				x	
20										
21		x						x		
22		x	x				x			

There was a total of 10 different medications used pre-operatively in 22 different combinations.

TABLE 3. A RETROSPECTIVE REVIEW OF NINETY PATIENTS WITH SURGICAL NECROTIZING ENTEROCOLITIS: POST-OPERATIVE ANTIBIOTICS USED

<i>Post-operative antibiotic combinations</i>							
<i>Combinations</i>	<i>Ampicillin</i>	<i>Gentamicin</i>	<i>Metronidazole</i>	<i>Cefotaxime</i>	<i>Vancomycin</i>	<i>Cefazidime</i>	<i>Clindamycin</i>
1							
2	X		X	X			
3	X	X	X				
4			X	X			
5	X		X		X		
6			X	X			
7							
8	X						
9		X	X		X		
10	X	X		X			
11	X	X					
12		X			X		
13	X						
14		X					
15		X					

There was a total of eight different medications used postoperatively in 15 different combinations. Of note, although cefoxitin and ceftazidime were used pre-operatively, they were not found in any post-operative regimens.

FIG. 1. The medications used most frequently in pre-operative regimens were gentamicin (14 regimens), metronidazole (10 regimens), ampicillin (eight regimens), and cefotaxime (eight regimens). The medications used most frequently in the post-operative antibiotic regimens were ampicillin (seven regimens), gentamicin (seven regimens), metronidazole (six regimens), and cefotaxime (five regimens)

FIG. 2. The 22 different pre-operative antibiotic regimens had an average duration of 10.6 d and a mode duration of 14 d. The 15 different post-operative antibiotic regimens had an average duration of 6.6 d and a mode duration of two days.

from 29 different countries on their management of NEC. In this survey, Zani et al. [19] found that 51% of the surgeons routinely used a combination of two different antibiotics whereas 48% used a combination of three different antibiotics in the treatment of NEC. However, the specific antibiotics were not given. There were a limited number of randomized controlled trials in the 1980s that tried to assess the use of specific antibiotics in the treatment of NEC. One study looked at the use of ampicillin and gentamicin with or without enteral gentamicin and found no significant difference in outcomes [20]. Another randomized controlled trial compared the use of intravenous ampicillin and gentamicin to the use of ampicillin, gentamicin, and clindamycin [21]. Although there was no substantial difference in mortality or perforation rates, this study found that there may be an increased risk of intestinal stricture with the use of clindamycin. A third study compared retrospectively patients who received ampicillin and gentamicin versus patients who received cefotaxime and vancomycin [22]. This study found that lower weight neonates had better outcomes when given cefotaxime and vancomycin.

On the basis of these older studies the World Health Organization (WHO) has recommended the use of ampicillin, gentamicin, and metronidazole for 10 d when medical NEC is diagnosed [23,24]. However, more recently a Cochrane Database Systematic Review along with a separate American Pediatric Surgical Association Outcomes and Clinical Trials Committee Systematic Review have both come to the conclusion that there is insufficient evidence to make specific recommendations on the type and duration of antibiotics to be used in patients with NEC [14,15]. No guidelines exist to aid in the management of surgical NEC patients. These studies have highlighted the paucity of data on antibiotic use in NEC. Our data then show the resulting problems observed clinically.

No adverse outcomes were observed in those patients who received shorter durations of post-operative antibiotics. As a result, our data indicate that a shorter post-operative course of antibiotics might be worth future study efforts. In the current medical environment there are multiple problems resulting from the unrestrained use of antibiotics and prolonged central venous access, both issues that occur in the treatment of NEC. *Clostridium difficile* infection is the classic example of an adverse effect from the use of antibiotics and is the most commonly reported pathogen in hospital-associated infections [25]. However, the growing number of antibiotic-resistant organisms may be the most concerning result of the way in which medical professionals have utilized antibiotics. In the United States, the U.S. Centers for Disease Control and Prevention (CDC) estimate that two million people require hospitalization annually for bacterial infections that are resistant to one or more antibiotics, and as many as 23,000 people die each year from these infections [26]. Furthermore, treatment of these infections has become costly [26]. One study examined only 188 patients with antibiotic-resistant infections and estimated societal costs of these patients to be anywhere from \$13 to \$18 million [27].

There has been an increased recognition in the medical community of the importance of the naturally occurring microbiome when it comes to infant and childhood development and immunity [28,29]. There is a growing body of evidence showing that antibiotics can disrupt the normal microbiome [30,31]. Children who have been exposed to antibiotics have

been shown to have not only less stable but also less diverse microbial communities [32]. Whereas the true impact of these findings may not be appreciated completely as of yet, studies have begun to identify consequences of disrupting the natural microbiota of developing infants and children. In just two examples there is evidence linking microbiome disruption to the development of obesity and asthma [33,34]. These data highlight yet another reason why it is important to have clear guidelines for antibiotic use in neonates with NEC.

Some may argue that NEC is too variable in its presentation to develop clear guidelines for antibiotic therapy. However, clear benefits have been observed in the standardization of treatment in other surgical disease with variable presentations. Appendicitis and diverticulitis are just two examples of surgical diseases that have had improved outcomes with more standardized care and specific guidelines for treatment [35–37]. With regards to appendicitis, standardization of care and the use of antibiotics has resulted in decreased antibiotic duration, costs, and re-admissions [35,37]. Similarly evidence-based guidelines in the management of diverticulitis have also resulted in a reduction in the use of antibiotics [36].

Our data highlight a problem in the antibiotic management of NEC. Without specific antibiotic guidelines, patients are likely to receive different antibiotic regimens depending on the institution and physician treating them at any given time. To date there have been only a few randomized controlled trials concerning antibiotics and NEC and none of these being recent studies. A limitation of our study is that it is a retrospective review, with the inherent biases in terms of reporting. Because of high degree of variability in the antibiotic regimens identified in our retrospective study, we are unable to identify a superior antibiotic regimen but our data suggest that a shortened post-operative antibiotic course may be safe and may be the basis for an initial prospective study.

Conclusion

We show that there is a high degree of variability in the perioperative antibiotic regimen for the treatment of surgical NEC, even within a single NICU, with no one regimen appearing to be superior. As data continue to show that antibiotic overuse is problematic, our study highlights the need for specific guidelines in the antibiotic treatment of NEC and suggests that an abbreviated course of post-operative antibiotics is worth further study.

Author Disclosure Statement

No competing financial interests exist.

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