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Predictors of Development and Diagnostic Delay of Post-Necrotizing Enterocolitis Strictures

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Abstract

Objectives: To evaluate predictors of post-Necrotizing Enterocolitis (NEC) stricture development and explore the incidence, location, and time to diagnosis of post-NEC strictures at a major pediatric teaching hospital.

Methods: A retrospective review of infants from 2003-2013 was performed. Data collected included demographics, treatment type, NEC stage, time to presentation and diagnosis of strictures, and laboratory values (C-reactive protein, minimum platelet count, duration of thrombocytopenia, and pH). Univariate, Multivariate and Wilcoxon-Rank Sum testing was used to evaluate the association between variables and stricture development.

Results: A total of 175 infants with NEC were identified, of which 35 (20%) developed post-NEC strictures. Univariate analysis revealed that patients receiving laparotomy ($p<0.01$), with higher NEC stage ($p=0.013$), elevated CRP (<0.01), lower platelet counts ($p=0.018$), greater duration of thrombocytopenia ($p=0.011$) and lower blood pH ($p=0.028$) were at significant risk of stricture development. After multivariate analysis, however, only elevated CRP values were found to be predictive of stricture development ($p<0.047$). Additionally, patients with small bowel strictures took significantly longer (35 days) to present with symptoms of obstruction than those with strictures in the large bowel (18.5 days; $p=0.037$). There was a trend towards delay in diagnosis of small bowel strictures, however, this difference did not achieve statistical significance ($p=0.09$).

Conclusions: A higher index of suspicion should be maintained for intestinal strictures in patients with advanced NEC and elevated inflammatory markers. Symptoms of obstruction may take longer to manifest in infants with small bowel strictures.

Keywords: Antibiotics; Necrotizing Enterocolitis; Post-NEC Stricture; Surgery

Introduction

Necrotizing Enterocolitis (NEC), a common gastrointestinal complication in newborn infants, is characterized by variable damage to the intestinal tract, ranging from mucosal injury to full-thickness necrosis and perforation. NEC occurs in 1 to 3 per 1000 live births and 1 to 7.7 percent of admissions to neonatal intensive care units. Although early recognition and aggressive treatment of this disorder has improved clinical outcomes, NEC accounts for substantial long-term morbidity in survivors of neonatal intensive care, particularly in premature very low birth weight (BW) infants (<1500 g). The mortality rate (15%-25%) for affected infants has not changed appreciably in 30 years [1,2]. The optimal treatment of NEC, via medical intervention, peritoneal drainage, or laparotomy is also controversial. Many infants with NEC recover uneventfully with medical therapy and have long-term outcomes similar to unaffected infants of matched gestational age. Infants with progressive disease requiring peritoneal drainage and/or surgical intervention suffer almost all of the mortality and morbidity. Of these, approximately 30%-40% will die of their disease and most

of the remainder will develop long-term neurodevelopmental and gastrointestinal morbidity [2].

Current work is focusing on developing a better understanding of the pathogenesis and improving means to identify which infants are at greatest risk of disease progression and complications. This includes, post-NEC intestinal strictures, which affect up to one third of patients and are a major driver of severe prolonged morbidity. Intestinal strictures promote bacterial overgrowth in the small bowel, often leading to repeated infections, bloody stools, failure to thrive, and bowel obstruction [3]. Although the incidence of strictures is high, its risk factors are not well studied. One prospective observational study reported abnormal values of C-Reactive Protein (CRP) in both stage II and stage III NEC. CRP returned to normal at a mean of 9 days after initiation of appropriate medical management except in those who developed complications such as stricture or abscess formation [4]. In another retrospective study, the mean maximum CRP concentration during acute phase was significantly higher in infants who developed stricture ($p<0.001$), as was the mean duration of the elevation of CRP levels ($p<0.001$) [5]. Various other laboratory parameters, including full blood count, platelet count, duration of thrombocytopenia and pH have been studied, however, none have consistently been shown to predict the development of post-NEC strictures [5-11]. There is also a lack of studies on the impact of stricture location (i.e. small versus large bowel) on the time to presentation and diagnosis of post-NEC intestinal obstruction.

In this study, we aimed to define the incidence and location of post-NEC strictures in infants who underwent peritoneal drainage, laparotomy or medical management at a single major pediatric teaching hospital. We also evaluated potential predictors of post-NEC stricture development and explored the time to presentation and diagnosis of strictures in infants with NEC.

Methods

We performed a retrospective study of infants with a diagnosis of NEC who were treated at the Hospital for Sick Children (Toronto, Ontario, Canada) from 2003-2013. Infants who died within the first month of life were excluded.

We conducted a comprehensive chart review and collected demographic data, including BW and gestational age (GA). Clinical data including the presence and location of post-NEC strictures, delay in presentation and diagnosis of stricture (days), type of treatment (medical management, peritoneal drainage, surgery), and Bell's NEC stage (I, IIA, IIB, III) was also obtained. Infants with stage I NEC, or suspected disease, were excluded from analysis. Stage IIA and IIB NEC was defined as mild and moderate disease respectively. Infants with stage IIA NEC presented with systemic signs including apnea, bradycardia and lethargy, in addition to grossly bloody stool, absent bowel sounds, and pneumatosis intestinal is on radiographs. Stage IIB was diagnosed if an infant presented with the abovementioned signs and symptoms, plus definite abdominal tenderness, right lower quadrant mass and/or ascites. Infants with Stage III NEC generally presented with all of the above in addition to severe systemic deterioration consisting of marked acidosis, hypotension, apnea, disseminated intravascular coagulation and neutropenia. Medical treatment generally consisted of feeding cessation with broad-spectrum antibiotics, the maintenance of vital hemodynamic and respiratory function, analgesia and parenteral nutrition. Peritoneal drainage, performed under local anesthesia, involved the placement of a drainage catheter in the abdominal cavity. Finally, the surgical protocol used involved exploratory laparotomy with detailed examination of the entire small and large bowel and identification of perforations, excision of non-viable bowel with primary anastomosis or stoma creation. We also collected laboratory data including maximum CRP levels, minimum platelet count, duration of thrombocytopenia (days), and ph.

Univariate analyses were then completed to assess for associations between the independent variables described above and stricture development. The results of our univariate analysis were used to identify variables to be studied using a multivariate model. This included birth weight, intervention, NEC stage, maximum CRP values, duration of thrombocytopenia and blood ph. GA and minimum platelet count were found to be co-linear with BW and duration of thrombocytopenia respectively, and thus, were excluded from the multivariate model.

Our secondary analysis consisted of evaluating differences in location of stricture and its impact on time to presentation of symptoms of obstruction and diagnosis of stricture. Time to presentation of symptoms was defined as the time period between cessation of treatment for NEC and onset of symptoms such as distention, vomiting, and obstipation. Time to diagnosis was defined as the period between onset of symptoms to confirmation of post-NEC stricture on contrast study. Since time to presentation of symptoms and diagnosis were both non-normally distributed variables, we used median values and non-parametric Wilcoxon-Rank Sum testing for our comparative analysis.

For all analyses, p-values ≤ 0.05 were considered significant. All statistical analyses were conducted with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The study protocol was approved by the Hospital for Sick Children Research Ethics Board prior to study initiation.

Results

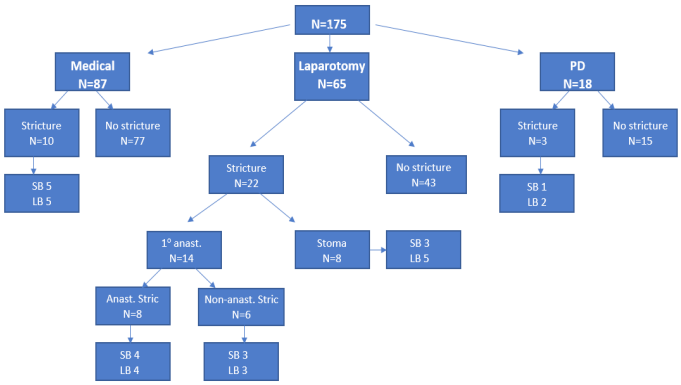
A total of 175 infants, 94 males and 81 females, with NEC were included in the primary analysis. Table 1 details the demographic characteristics of the patient cohort. The mean GA and

BW was 31.8 weeks and 1743.8 grams respectively. A total of 87 (50%), 65 (37%) and, 18 (10%) patients were treated with medical management, laparotomy and, peritoneal drain respectively. Nearly half (51%) of the population had Stage IIA disease at the time of diagnosis. A total of 14 (8%) and 72 (41%) infants were diagnosis with stage IIB and stage III disease, respectively (Table 1).

Variable	N=175
Sex, n (%)	
Male	94 (54)
Female	81 (46)
Gestational Age, mean (SD)	31.8 weeks (4.8)
Birth Weight, mean (SD)	1743.8 grams (931.7)
Interventions, n (%)	
Peritoneal Drain	18 (10)
Laparotomy	65 (37)
Medical	87 (50)
NEC stage, n (%)	
IIA	89 (51)
IIB	14 (8)
III	72 (41)

Table 1: Baseline Characteristics.

35 (20%) patients developed post-NEC strictures (Figure 1). Univariate analysis revealed several predictors of post-NEC stricture development (Table 2). Infants treated surgically, with laparotomy and resection, were significantly more likely to develop intestinal strictures ($p<0.01$). A majority of these patients (63%) underwent resection and primary anastomosis, of which about 57% developed strictures at the anastomotic suture line. Likewise, infants with higher NEC stage ($p=0.013$), CRP elevation ($p<0.01$), greater duration of thrombocytopenia ($p=0.011$), lower platelet counts ($p=0.018$), and academia ($p=0.028$) were at higher risk of developing post-NEC strictures (Table 2). After multivariate analysis, however, only elevation in CRP was shown to be predictive of stricture occurrence ($p<0.047$; OR 1.01; Table 3).



Abbreviations: Peritoneal Drain (PD); Small Bowel (SB); Large Bowel (LB)

Figure 1: Incidence of post-NEC strictures stratified by intervention.

Variable	No Stricture (n=140)	Stricture (n=35)	p
Sex, n (%)			
Male	78 (55.7)	16 (45.7)	
Female	62 (44.3)	19 (54.3)	0.289
Gestational Age, mean (SD)	31.24 (4.67)	31.4 (4.01)	0.855
Birth Weight, mean (SD)	1608.21 (835.06)	1698.54 (802.10)	0.565
Intervention, n (%)			
Peritoneal Drain	15 (10.7)	3 (8.6)	
Laparotomy	43 (34.3)	22 (62.9)	**<0.01**
Medical	77 (55.0)	10 (28.6)	
NEC stage, n (%)			
IIA	79 (56.4)	10 (28.6)	
IIB	10 (7.1)	4 (11.4)	**0.013**
III	51 (36.4)	21 (60.0)	

CRP (mg/L), mean (SD)	80.04 (84.67)	130.69 (64.41)	**<0.01**
Minimum Platelet Count, mean (SD)	125.78 (104.78)	80.74 (78.30)	**0.018**
Duration of Thrombocytopenia* (d), mean (SD)	9.17(16.84)	18.40(26.32)	**0.011**
pH, mean (SD)	7.27 (0.10)	7.23(0.12)	**0.028**
*Platelet count < $100x10^9$/L			

Table 2: Univariate Predictors of Stricture Development.

Variable	Odds Ratio	95% CI	p
Birth Weight	1	1.00-1.01	0.328
Intervention			
Peritoneal Drain	1.22	0.21-7.10	0.824
Laparotomy	1.53	0.42-5.55	0.517
Medical (Reference Group)	1		
NEC stage			
IIA (Reference Group)	1		
IIB	2.39	0.58-9.84	0.229
III	1.39	0.39-4.84	0.61
CRP (mg/L)	1.01	1.00-1.01	**<0.047**
Thrombocytopenia*	1.06	0.39-2.89	0.908
pH, mean (SD)	0.11	0.00-12.08	0.365
*Platelet count < $100x10^9$/L			

Table 3: Multivariate Predictors of Stricture Development.

Notably, patients with strictures in the small bowel took significantly longer to present with symptoms of obstruction after cessation of therapy, compared to those with colonic strictures (35 days vs. 19 days; p=0.037; (Table 4A). The former cohort also experienced a relative delay (21 days vs. 12 days) in definitive diagnosis after onset of symptoms. This difference however, did not achieve statistical significance (p=0.09; Table 4B).

All Patients (33/35)	Large Bowel Stricture	Small Bowel Stricture	p
Median delay to symptoms in days (IQR)	18.5 (7.5-32.5)	35 (15.0-85.0)	**0.037**
Patients post-peritoneal drainage (3)			
Median delay to symptoms in days (IQR)	8.5 (0-)	120.0 (120.0-120.0)	0.22
Patients post-laparotomy (20)			
Median delay to symptoms in days (IQR)	30.0 (14.0-50.0)	70.0 (32.5-102.5)	**0.01**
Patients managed medically (10)			
Median delay to symptoms in days (IQR)	6.0 (2.0-19.5)	17.0 (2.0-31.5)	0.69
Abbreviations: IQR (Interquartile Range)			

Table 4A: Delay to Symptoms in NEC infants with large versus small bowel strictures.

All Patients (35)	Large Bowel Stricture	Small Bowel Stricture	p
Median delay to diagnosis in days (IQR)	12.0 (8.0-21.0)	21 (14.0-41.5)	0.09
Patients post-peritoneal drainage (3)			
Median delay to diagnosis in days (IQR)	13.0 (12.0-)	40.0 (40.0-40.0)	0.22
Patients post-laparotomy (22)			
Median delay to diagnosis in days (IQR)	11.0 (8.0-46.3)	23.5 (14.0-46.5)	0.197
Patients managed medically (10)			
Median delay to diagnosis in days (IQR)	8.0 (2.0-15.0)	12.0 (4.0-16.0)	0.421
Abbreviations: IQR (Interquartile Range)			

Table 4B: Delay to diagnosis in NEC infants with large versus small bowel strictures.

Discussion

This retrospective chart review reports the incidence, risk factors and time to presentation and diagnosis of post-NEC strictures in a cohort of 175 infants treated with medical management, peritoneal drainage or laparotomy. Our initial

analysis revealed 35 infants (20%) with post-NEC strictures. After multivariate analysis, solely the CRP value was found to be an independent predictor of post-NEC stricture development. For everyone increase in CRP, there was a 1.01 increased odds of post-NEC stricture development. Infants with small bowel strictures also experienced a significantly longer median time to presentation of symptoms of obstruction (35 days) than those with strictures in the large bowel (18.5 days). While there was a trend towards delay in diagnosis, this difference was not statistically significant.

We report a 20% rate of post-NEC strictures in the overall study population. This rate is relatively lower than that reported in the recent literature [5, 7, 12]. For instance, Gaudin et al. reviewed 60 cases of NEC at a single tertiary center and reported a stricture rate of up to 57% [5]. It is important to note that in most of these studies, contrast study was routinely performed to screen for strictures. At our institution, however, patients are only investigated upon presenting with symptoms of obstruction or stricture. Screening for strictures in asymptomatic patients can increase reported rate of strictures from 17% to 36% [13] and may explain the difference in incidence of strictures observed in other reports compared to ours. Though screening with contrast study might prevent complications such as septicemia, perforation, and severe intestinal obstruction, we believe that this practice exposes infants to unnecessary radiation since most asymptomatic patients with strictures do not require intervention. In fact, systemic screening with contrast study is often performed early in the disease process. Histological evidence suggests that this practice is more likely to reveal strictures as it detects inflammatory lesions that tend to regress naturally [13]. Therefore, some suggest contrast study should only be performed at or after 6 weeks, followed by cautious re-feeding [14-16].

We observed a similar rate of stricture in NEC cases treated with laparotomy (34%) in comparison to other published reports [12]. As far as surgical treatment is concerned, the techniques used are numerous and vary from center to center [17, 18]. In our hospital, the surgical treatment of choice in most cases was laparotomy with resection of the necrotic zones and primary anastomosis. Necrotic regions were left un-resected in palliative patients with end-stage disease or in advanced cases that warranted a planned second look surgery after allowing the bowel to demarcate with hopes of minimizing the amount of bowel requiring resection. Resection during the acute phase allows the digestive tract to be better conserved since the disappearance of necrotic lesions leads to a decrease in the inflammatory and infectious phenomena that promotes the spreading of lesions [5]. This technique however, may promote the formation of intestinal strictures due to scarring and subsequent narrowing at the anastomotic suture line. Alternatively, a primary anastomosis may leak, leading to further inflammation and infection in the region causing the area to heal with an intestinal stricture. This phenomenon is reflected in our patient cohort, as patients treated with laparotomy and primary anastomosis were at increased risk of developing intestinal strictures, nearly 60% (8/14) of which occurred at the anastomotic suture line. Some authors propose proximal diversion, without resection of necrotic regions of the bowel. While this technique is thought to reduce the extent of resection and to increase the final length of the digestive tract, it may necessitate secondary resection of necrotic zones that undergo stricture at a later time [5].

One of our primary objectives was to study the risk factors that may predict the development of post-NEC strictures. In our study, having advanced disease (i.e. stage III) correlated significantly with the occurrence of post-NEC strictures. Our findings are consistent with other reports in which infants with Bell's stage I or II disease as well as non-specific intestinal dilatation were significantly less likely to develop a stricture [12]. In addition to being a marker of extensive disease, a high Bell's stage also represents a heightened immune mediator response and therefore, is a biologically plausible risk factor for the development of intestinal strictures. Similarly, a marked elevation of CRP levels, $\geq$ 49.5 mg/L, was significantly correlated with the occurrence of post-NEC strictures. After multivariate analysis, CRP elevation was the only variable that predicted the risk of post-NEC strictures in our patient cohort. These findings correlate with other reports of a potential relationship between the severity of the inflammatory syndrome and the chance of developing an intestinal stricture. A recent retrospective study demonstrated that the mean maximum CRP concentration and the mean duration of CRP elevation was significantly higher in infants who developed post-NEC strictures [5]. Likewise, in their prospective observational study, Pourcyrous et al. concluded that in infants with suspected NEC, normal CRP values should prompt abortion of antibiotic therapy and resumption of feeds. Furthermore, they observed that the CRP values of infants with stage II NEC returned to normal at a mean of 9 days except in those who developed complications including stricture formation. Persistent elevation of CRP levels, therefore, was related to the occurrence of post-NEC strictures requiring surgical intervention [4]. Our results confirm the prognostic relevance of CRP, a sensitive marker of systemic inflammation, to the risk of developing post-NEC intestinal strictures. In the future, one may also investigate the utility of other markers of inflammation, such as fecal calprotectin, interleukin-6 and pro-calcitonin in the development of post-NEC strictures [19].

Furthermore, in our cohort of 175 infants, we identified 35 infants (20%) with small bowel strictures and 33 infants (19%) with large bowel strictures. In contrast to these findings, several studies in the literature have reported a relatively higher incidence of strictures in the colon than in the small bowel [5,12, 20-23]. The most common site of post-NEC strictures is thought to be the left colon, especially around the vascular watershed region of the splenic flexure [23]. However, our findings indicate that in addition

to colonic strictures, physicians and surgeons must also maintain a high index of suspicion for strictures in the small intestine. In our study, infants with small bowel strictures took significantly longer to present with symptoms of obstruction after cessation of treatment than those with strictures in the large bowel. This delay in presentation was accompanied by a subsequent delay in establishing a definitive diagnosis in this subgroup of patients. To our knowledge, this is the first study to evaluate the difference in time to presentation and diagnosis of small and large bowel post-NEC strictures. We postulate that the difference in diagnosis is likely due to the inability of the contrast medium to penetrate the far reaches of small bowel, especially in areas near the mid-small bowel and proximal ileum. Re-absorption of the contrast medium prior to reaching these areas can lead to missed and/or delayed diagnoses, which further complicates the care of infants with NEC. There have been reports of patients with intestinal obstruction from small bowel strictures despite normal contrast study [13]. One may mitigate this problem with innovative imaging modalities, such as the ones being used in the management of stricturing Crohn's disease [24, 25]. Future studies must be aimed at studying their clinical utility in comparison to traditional imaging options such as contrast enema and small bowel follow through, in the timely diagnosis and treatment of small bowel strictures.

The results of our study are limited by the retrospective, single center study design. Regular monitoring of CRP and other laboratory markers also did not become common practice at our center until 2013, leaving a large proportion of patients with limited data and eventual exclusion from the study. There may be additional risk factors, such as the degree of leukocytosis or length of resected bowel [12], for the development of post-NEC strictures that were present in our patient population but not studied. Lastly, ours is a tertiary/ quaternary pediatric facility with referrals from other neonatal units for surgical evaluation. These cases may represent the severe end of the NEC spectrum; our results therefore, may not apply to other perinatal settings that manage infants with milder cases of NEC.

Physicians must maintain a lower threshold for the development of intestinal strictures in patients with advanced NEC, elevated inflammatory markers and need for surgical intervention. Prospective studies are required to validate these risk factors and develop a predictive model for post-NEC strictures. Our findings also suggest that obstructive symptoms from small bowel strictures may take longer to manifest clinically; this warrants further study of innovative imaging modalities to enable timely diagnosis of strictures in this vulnerable patient population.

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Conflicts of Interest

None.

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