ORIGINAL RESEARCH

Intestinal Resection is More Likely to be Effective in Necrotizing Enterocolitis Extending to Colon than in Disease Limited to the Small Intestine

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Abstract

Background: The prognosis in surgical necrotizing enterocolitis (NEC) has focused on the total length of the resected bowel; the relative impact of small intestinal vs colonic resection is not well studied.

Objective: We hypothesized that intestinal resections may reduce mortality and length of hospital stay (LOS) more likely in infants who have NEC extending into the colon than in those with disease limited to the small intestine. We also investigated the relationship between gestational maturation and NEC-related mortality.

Methods: A retrospective study of 153 patients compared demographic, clinical, and histopathological information in infants who had NEC limited to the small intestine vs disease with colonic involvement.

Results: Our 153 infants had a mean (±standard deviation) gestational age of 27.4 ± 3.4 weeks and a birth weight of 987 ± 505 g. NEC was limited to the small intestine in 103 (67.3%) infants and extended into the colon in 50 (32.7%). Infants with small intestinal NEC needed shorter bowel resections of 28 ± 31.9 cm than 42.2 ± 40.7 cm in those with colonic involvement ($p = 0.02$). The LOS was longer in NEC limited to the small intestine than in disease with colonic lesions (96 ± 88.1 vs 69.7 ± 19.1 days; $p < 0.05$). In small intestinal NEC, mortality decreased to <50% beyond a gestational age (GA) >37 weeks. In contrast, infants with NEC that involved the colon had mortality <50% mortality beyond 27.3 weeks' GA ($p = 0.008$).

Conclusions: Bowel resections may be more likely associated with shorter LOS in surgical NEC that involves both the small bowel and colon, even when longer segments of the gastrointestinal tract are removed, than in disease limited to the small intestine.

Keywords: Necrotizing enterocolitis, Neonatology, Newborn.

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Introduction

Necrotizing enterocolitis (NEC) is an inflammatory bowel necrosis seen in premature and critically ill neonates,[1] particularly in those born at gestational ages of 22–28 weeks with birth weights less than 1500 g.[1,2] The incidence of NEC has shown some encouraging reduction in recent years.[3,4] However, in affected infants, it remains a life-threatening illness requiring close monitoring and intensive care.[5] About half of all infants with confirmed NEC need surgical intervention. Regardless of gestational age and birth weight, infants with advanced disease typically have extended hospital stays and at least 30% mortality.[6]

The pathogenesis of NEC is unclear. Early diagnosis is difficult and rests on suggestive clinical and radiological signs in at-risk infants. At onset, the clinical features are nonspecific and may include abdominal distension, gastric stasis or emesis, and gastrointestinal bleeding.[7] The pathognomonic sign, *pneumatosis intestinalis*, is the radiological (or intraoperative) observation of intramural cysts that are known to contain gaseous products of bacterial fermentation, and is seen in about half of all patients.[4,7] NEC is treated with bowel rest, antibiotics, and in advanced disease, with surgical resection of the diseased bowel and anastomosis or exteriorization of the healthier parts of the intestine.[5,8–10] The typical histopathological findings of NEC are coagulative necrosis, inflammation, interstitial hemorrhages, pneumatosis, and in some foci, reparative changes.[2–6] The postoperative period may be marked by feeding difficulties, surgical wound complications, infections, cholestasis, and in some infants, short bowel syndrome.[3,8,9,11–14]

In infants with surgical NEC, increasing length of the diseased/resected intestine is usually viewed with a pessimistic outlook, as associated with a lower likelihood of postoperative rehabilitation

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and survival.[10,15,16] However, most studies of prognosis in surgical NEC have focused on the total length of the resected bowel; the relative impact of small intestinal vs colonic resection is not well documented. We hypothesized that surgical resection for NEC that extends into the colon may be more effective in reducing mortality and the length of hospital stay (LOS) than in disease limited to the small intestine. We posited that bowel resections extending into the colon, even if longer, might not be as harmful because of potentially greater reductions in the total load and transmural translocation of luminal bacteria, and consequently, in intestinal and systemic inflammation.

We performed this study using a retrospective design but made an extensive effort to record all possible clinical information. A major difficulty in studying surgical NEC is to find accurate data from an optimum number of patients. We are fortunate that the incidence of NEC is relatively limited at 3–5% of very-low-birth-weight (VLBW) infants, but these low numbers also bring challenges in finding a statistically adequate cohort for clinical studies. Among infants with confirmed NEC, 30% need surgery, and 30% of these patients may have postoperative mortality. Therefore, to detect a 50% difference in mortality due to surgical NEC involving the colon vs disease limited to the small intestine, we needed at least 150 patients. Even though University of Mississippi Medical Center (UMMC) is a major regional facility for surgical treatment of NEC, prospective enrollment of this large number of eligible patients was difficult within a reasonable period. A multicenter format was an alternative, but there were major differences in medical records and in the thresholds for surgical intervention at other regional centers. Again, considering the relatively low incidence of surgical NEC, a retrospective study format seemed reasonable provided we could carefully record information from all possible medical, surgical, and nursing records. We have recently described 90 infants who were treated at UMMC for surgical NEC during the years 2000–2015,[5,17] and an extension of the study period to 2018 provided an adequate number of patients (as described in methods). As may be evident in the tables, we reviewed clinical records and histopathology sections from all infants, and gross pathology specimens from most patients.

Methods

This retrospective study was conducted at the University of Mississippi Medical Center (UMMC) at Jackson, Mississippi, which is a regional referral center for surgical NEC, after approval by the Institutional Review Board. A detailed review of medical records identified 193 patients who had undergone exploratory laparotomy and other surgical procedures for advanced NEC during the period between January 2000 and December 2018. After excluding 15 infants who were missing clinical data and 25 for confounding congenital anomalies involving the gastrointestinal tract or multiple systems, we identified 153 eligible infants (Flowchart 1).

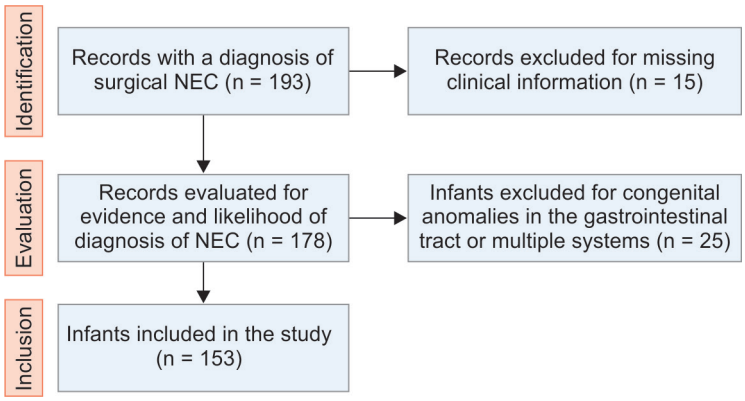
Clinical Information

We recorded prenatal factors such as pregnancy-induced hypertension (PIH), chorioamnionitis, and antenatal steroids. Demographic data included gestational age, birth weight, small-for-gestational age (SGA) status, ethnicity, gender, and outborn status. Clinical information included Apgar scores ≤6 at 5 minutes, age at initiation of feedings, culture-proven sepsis prior to NEC, central line use, assisted ventilation, patent ductus arteriosus (PDA), and its medical/surgical treatment. The age at onset of NEC, its clinical presentation (abdominal distension, bloody stools, and emesis), and length of the resected intestine were noted. Our two primary clinical outcomes of NEC were mortality and the LOS. Other postoperative data included hemodynamic instability, duration of paralytic ileus, need for pressor support for ≥24 hours after surgery, days of antibiotic treatment, days on parenteral nutrition, and the number of days to reach full enteral feedings (120 mL/kg/day). We also recorded late-onset sepsis, surgical wound dehiscence or infection, strictures, and short bowel syndrome (SBS; need for parenteral nutrition ≥3 months following bowel resection).[18]

Pathology

Two blinded pathologists evaluated hematoxylin and eosin (H&E)-stained intestinal sections for histopathological evidence of NEC, including coagulative necrosis, inflammation, hemorrhages, and reparative changes. Coagulative necrosis was defined by the loss of nuclear staining and diminished eosinophilic staining of the cytoplasm, but with relatively preserved "ghost-like" crypt-villus histoarchitecture. Inflammation was marked by leukocyte infiltration; these white blood cells were also enumerated per high-power field (HPF). Hemorrhages were noted in various intestinal regions and layers. The severity of NEC was assessed by the depth to which these histopathological changes were seen; grade I was limited to the mucosa, grade II extended to the submucosa, grade III to the *muscularis*, and grade IV was transmural. Reparative changes included neovascularization, epithelial regeneration, and increase in fibroblasts and/or myofibroblasts.

Flowchart 1: Enrollment of patients in the study



Statistical Information

Descriptive, categorical data were summarized as frequencies (absolute and relative) and tested for differences using Chi-square tests. Continuous data, when symmetric, were recorded as averages, with both standard deviations (SD) and standard error of the mean (SEM) as indices of variability. In studies of premature infants, concomitant presentation of SDs and SEMs is useful;[5] SDs are familiar, accurate descriptors of variability, whereas SEMs can convey the precision with which inferences drawn from the relatively limited, disease-specific cohorts of preterm infants can be extrapolated to the larger universe of these infants.[19] If data were skewed, we used medians (with ranges) for presentation. *T*-values were used to compute the size of the difference relative to the variation in the sample data. Data were evaluated for normality using Shapiro-Wilk and Kolmogorov-Smirnov tests. Two or multiple groups with continuous, parametric data were compared using a Student's *t* or analysis of variance, respectively. For nonparametric data, we used the Mann-Whitney *U* or Kruskal-Wallis *H* tests. Kaplan-Meier survival curves were plotted with 95% confidence intervals against gestational age, birth weights, postnatal age, and lengths of the small intestine and the colon. These curves were compared using the log-rank (Mantel-Cox) and Gehan-Breslow-Wilcoxon tests.[20] Statistical analysis was done using the software programs STATA 15 (Stata Software, College Station, Texas) and GraphPad Prism (San Diego, California). Statistical significance was accepted at *p*-values below 0.05.

Results

Clinical Information

We reviewed the medical records of 153 infants with surgical NEC (Flowchart 1) for their demographic data, clinical course, and outcomes (Table 1). In this group, 90 infants have been previously described.[17] The 153 infants included in this study had an average gestational age (mean ± SD; ± SEM) of 27.4 ± 3.4 weeks (±0.3 weeks SEM) and a birth weight of 987 ± 505 g (±40.8 g SEM). Eighty-seven (56.8%) were outborn. There were 96 (62.7%) males and 57 (37.3%) females. One hundred and nineteen (77.8%) infants were African American, 28 (18.3%) were Caucasian, 3 (2%) were Latino, and 3 (2%) were of mixed ancestry.

NEC occurred on 22.4 ± 20.1 days (±1.6 days SEM); 139 (90.2%) presented with abdominal distension, 8 (5.2%) with feeding intolerance, and 7 (4.5%) had bloody stools. All enrolled infants had some radiological evidence of NEC such as *pneumatosis*, mucosal thickening, bowel loop dilatation, ascites, and/or pneumoperitoneum. These patients underwent an exploratory laparotomy if they had evidence of peritonitis with worsening abdominal distention, hypotension, thrombocytopenia, anemia, or metabolic acidosis. The diagnosis of NEC was confirmed by intraoperative inspection and pathological examination of the resected bowel.

After surgery, 51 (33.3%) infants needed hemodynamic support with intravenous fluid boluses and pressor support for >24 hours. Postoperative ileus lasted for 17.3 ± 14.5 days (±6.6 days SEM). Enteral feedings were initiated on 18 ± 14.5 days SD (±1.2 days SEM), and full feeding volumes were achieved on 72.4 ± 44.2 days (±3.6 days SEM). Parenteral nutrition was given for 91.1 ± 53.8 (±1.2 days SEM). Forty-six (30.1%) patients died at a postnatal age of 84.2 ± 84.9 days (±6.8 days SEM). Survivors were discharged after

Table 1: Demographic and clinical summary

		n = 153
Prenatal information		
1	Pregnancy-induced hypertension, *n* (%)	37 (24.1%)
2	Chorioamnionitis, *n* (%)	12 (7.8%)
3	Antenatal steroids, *n* (%)	90 (58.8%)
Infant demographics		
5	Gestational age (weeks; mean ± SD)	27.4 ± 3.4
6	Birth weight (g; mean ± SD)	987 ± 505
7	Male gender, *n* (%)	96 (62.7%)
8	Ethnicity	
	a Caucasian	28 (18.3%)
	b Latino	3 (2%)
	c Mixed	3 (2%)
	d African American	119 (77.8%)
9	Small for gestational age, *n* (%)	40 (26.1%)
10	Mode of delivery	
11	C-section	65 (42.4%)
12	Vaginal	88 (57.5%)
13	Outborn, *n* (%)	87 (56.8%)
Infant medical information prior to NEC		
14	Apgar score <6 at 5 minutes	39 (25.4%)
15	Patent ductus arteriosus, *n* (%)	88 (57.5%)
16	Patent ductus arteriosus, indomethacin treated, *n* (%)	25 (16.3%)
17	Patent ductus arteriosus, surgically ligated, *n* (%)	5 (3.3%)
NEC disease features		
18	Age at NEC onset (days; mean ± SD)	22.1 ± 20.6
19	Corrected gestational age at NEC onset (weeks; mean ± SD)	30.4 ± 4.2
20	Clinical presentation	
	a Abdominal distension, *n* (%)	139 (90%)
	b Bloody stools, *n* (%)	7 (4.5%)
	c Feeding Intolerance, *n* (%)	8 (5.2%)
21	Radiological findings	
	a Pneumatosis, *n* (%)	57 (37.2%)
	b Pneumoperitoneum, *n* (%)	43 (28.1%)
	c Portal venous gas, *n* (%)	10 (6.5%)
22	Length of bowel resected (cm; mean ± SD)	26.6 ± 28.7
Postoperative systemic course		
23	Assisted ventilation (intubated), *n* (%)	138 (90.1%)
24	Pressor support >24 hours, *n* (%)	51 (33.3%)
25	Blood culture positive sepsis, *n* (%)	41 (26.7%)
Postoperative nutrition		
26	Postoperative ileus [days; *n* (%)]	17.3 ± 14.4
27	Surgical wound infection, *n* (%)	21 (13.7%)
28	Surgical wound dehiscence	13 (8.4%)
29	Postoperative day at starting enteral feedings (days; mean ± SD)	18 ± 14.5
30	Feeding at start	
31	Mother's own/donor milk, *n* (%)	41 (26.7%)
32	Infant formula, *n* (%)	63 (41.1%)

33	Mixed	21 (13.1%)
34	Day of attainment of full enteral feedings (120 mL/kg; mean ± SD)	73.5 ± 44.1
35	Duration of parenteral nutrition (days; mean ± SD)	92.8 ± 53.5
36	Intestinal adhesions, *n* (%)	28 (18.3%)
37	Intestinal strictures, *n* (%)	15 (9.8%)
38	Short bowel syndrome, *n* (%)	43 (28.8%)
Discharge		
39	Length of stay (days; mean ± SD)	133.9 ± 81.9
40	All deaths, *n* (%)	46 (30%)

154.8 ± 71.1 days (±6.9 days SEM). The average hospital stay was 133.6 ± 81.9 days (±6.6 days SEM).

Pathological Findings

Intestinal specimens from all 153 patients showed histopathological signs of NEC (Table 2). The average grading for necrosis was 2.3 ± 1.4 (±0.2 SEM), and it correlated with inflammation ($r = 0.38$, $p < 0.001$) and hemorrhages ($r = 0.37$, $p < 0.001$). The length of the resected intestine was 14.9 ± 2.4 cm (±0.3 cm SEM). Inflammation was graded at 3 ± 1 (±0.3 SEM), with 88.3 ± 12 WBCs/hpf (±3.8 WBCs/hpf SEM). Hemorrhages were seen in all infants, with a grade of 3.3 ± 0.9 (±0.2 SEM). Reparative changes were prominent in histopathological sections from 25 (16.3%) patients and were graded 0.6 ± 1 (±0.3 SEM).

NEC lesions were limited to the small intestine in 103 (67.3%) patients and extended into the colon in 50 (32.7%). The two groups had similar gestational ages of 27.2 ± 4 weeks (±0.3 weeks SEM) and 26.9 ± 3.5 weeks (±0.5 weeks SEM), and birth weights of 935 ± 471 g (±46.4 g SEM) and 961 ± 559 g (±77.9 g SEM), respectively. Infants who had NEC in only their small intestine needed a bowel resection of 28 ± 31.9 cm (±2.1 cm SEM), which was significantly shorter than 42.2 ± 40.7 cm (±2.2 cm SEM) in those with colonic involvement ($p = 0.02$). The length of the resected small intestines in the two groups was not different and measured 20 ± 23 cm (±2.3 cm SEM) and 18.7 ± 26.7 cm (±3.8 cm SEM). The second group had colonic involvement of 16.4 ± 11.6 cm (±1.6 cm SEM). Ninety-seven (94.2%) infants with small intestinal NEC had an intact ileocecal valve, whereas only 10 (20%) in the second group had one ($p < 0.001$). Finally, there were 46 (30%) deaths; 32/103 (31.1%) infants who had NEC lesions only in the small intestine died, whereas 14/50 (28%) had lesions extending into the colon. This trend was not statistically significant. Table 3 shows the demographic data, clinical course, and pathological findings in the resected intestine in these two subgroups.

Clinical Outcomes of NEC that was Limited to the Small Intestine or Extended into the Colon

We performed linear regression to identify factors that determined the localization of NEC to the small intestine or its extension into the colon. Birth weight, gender, and indomethacin use were identified to be significant (Supplemental Table 1, section a). However, r^2, the goodness-of-fit measure, was modest at 0.11.

We next investigated for the determinants of mortality in NEC that was limited to the small intestine or extended to the colon (Supplemental Table 1, sections b and c). In small intestinal NEC, gestational age and the length of resected bowel were significant determinants of mortality in the entire groups. In NEC extending into the colon, gestational age remained significant, but a history of PDA and the age at onset of NEC were also important. Finally, we looked for predictors of LOS (Supplemental Table 1, sections d and e). The important clinical determinants in small intestinal disease were gestational age, death, age of onset of NEC, and the length of bowel resection. In disease extending into the colon, gestational age and death were significant predictors of LOS. Considering the importance of gestational age as a key determinant in most comparisons, we focused further analysis on the relationship between gestational maturation and outcomes of NEC.

Gestational Age and NEC Region Involvement

We next plotted Kaplan-Meier curves for mortality against gestational age (Flowchart 1) both for NEC that was limited to the small intestine (blue lines) or extended into the colon (red lines). The 95% confidence intervals (CIs) are shown with dotted, similarly colored lines. Summated data from the entire cohort are depicted with a magenta line and a similarly shaded 95% CIs. In infants with small intestinal NEC, mortality decreased to less than 50% after 37 weeks' gestation. In contrast, NEC extending into the colon showed <50% mortality beyond a gestational age of 27.3 weeks (Fig. 1; $p = 0.008$). The number of deaths prior to and beyond the gestational age thresholds in both groups showed statistically significant differences (Table 4). In all infants studied together, mortality dropped to levels less than 50% beyond 31.3 weeks' gestation (Supplemental Table 2). The clinical information of infants born prior to and beyond these gestational age thresholds is shown in Table 4.

To understand the impact of intestinal maturation on NEC-related mortality, we plotted Kaplan-Meier curves for mortality against the post-menstrual age (PMA). In NEC limited to the small intestine, mortality decreased to less than 50% beyond 38.2 weeks PMA ($p = 0.015$). In contrast, mortality in NEC with colonic involvement dropped below 50% at 33 weeks' PMA. In the entire cohort, mortality decreased to less than 50% at a PMA of 37.3 weeks (Fig. 1; Supplemental Table 3).

In other analyses, we did not find a difference in NEC-related mortality against the birth weights in these two groups ($p = 0.54$; Supplemental Figure 1). The postnatal age at onset of NEC was also not a predictor of its being restricted to the small intestine or extension into the colon ($p = 0.33$; Supplemental Figure 2). The length of the resected small intestine was similar in the two groups ($p = 0.6$). However, infants with NEC involving both the small intestine and the colon had a median survival at a resection of 58 cm, which was significantly longer than those who had to undergo removal of small intestinal disease (median 30 cm, $p = 0.02$; Supplemental Figure 3). Supplemental Figure 4 shows the relationship between survival and the length of colonic resection.

We also developed prediction models for LOS; Supplemental Table 1, sections d and e). In NEC limited to the small intestine ($r^2 = 0.58$), LOS was associated with gestational age, age at onset of NEC, death, and the length of resected bowel. The intercept was significant ($|t| = 3.7$, $p < 0.001$), indicating that the some determinants of small intestinal NEC remain to be discovered. The prediction models for LOS were less robust in infants who had colonic lesions ($r^2 = 0.35$); gestational age and death remained significant. The intercept remained important ($|t| = 4.1$, $p < 0.001$), again emphasizing the importance of hitherto undetermined elements.

Table 2: Pathological changes in resected intestinal tissue

Gross pathological changes in available tissue samples										
		Specimens available from patients with NEC lesions only in the small intestine (n = 40)			*Specimens available from patients with NEC extending into the colon (n = 20)*			*Combined (n = 60)*		
		Total (40)	*Alive (32)*	*Dead (8)*	*Total (20)*	*Alive (17)*	*Dead (3)*	*Total (60)*	*Alive (49)*	*Dead (11)*
Acute changes	Necrosis, *n* (%)	10 (25%)	6 (18.8%)	4 (50%)	7 (35%)	6 (35.3%)	1 (33.3%)	17 (28.3%)	12 (24.5%)	5 (45.5%)
	Dusky, *n* (%)	10 (25%)	8 (25%)	2 (25%)	9 (45%)	7 (41.2%)	2 (66.7%)	19 (31.6%)	15 (30.6%)	4 (36.4%)
	Erythema, *n* (%)	2 (5%)	2 (6.3%)	0	1 (5%)	0	1 (33.3%)	3 (5%)	2 (4.1%)	1 (9.1%)
	Hemorrhage, *n* (%)	9 (22.5%)	6 (18.8%)	3 (37.5%)	6 (30%)	5 (29.4%)	1 (33.3%)	15 (25%)	11 (22.4%)	4 (36.4%)
	Defect/perforation, *n* (%)	20 (50%)	14 (43.8%)	6 (75%)	9 (45%)	8 (47.1%)	1 (33.3%)	29 (48.3%)	22 (44.9%)	7 (63.6%)
Subacute changes	Thinning, *n* (%)	6 (15%)	5 (15.6%)	1 (12.5%)	5 (25%)	4 (23.5%)	1 (33.3%)	11 (18.3%)	9 (18.4%)	2 (18.2%)
	Stricture, *n* (%)	2 (5%)	1 (3.1%)	1 (12.5%)	2 (10%)	2 (11.8%)	0	4 (6.6%)	3 (6.1%)	1 (9.1%)
	Friable, *n* (%)	8 (20%)	7 (21.9%)	1 (12.5%)	7 (35%)	5 (29.4%)	2 (66.7%)	15 (25%)	12 (24.5%)	3 (27.3%)
	Adhesions, *n* (%)	20 (50%)	14 (43.8%)	6 (75%)	9 (45%)	8 (47.1%)	1 (33.3%)	29 (48.3%)	22 (44.9%)	7 (63.6%)
Histopathological changes										
		NEC lesions only in the small intestine (n = 103)			*NEC extending into the colon (n = 50)*			*Combined (n = 153)*		
		Total (103)	*Alive (75; 72.8%)*	*Dead (28; 27.2%)*	*Total (50)*	*Alive (32; 64%)*	*Dead (18; 36%)*	*Total (153)*	*Alive (107; 69.9%)*	*Dead (46; 30.1%)*
Histopathological changes	Necrosis (mean ± SD)	2.3 ± 1.4	2.4 ± 1.5	2 ± 1.1	2.2 ± 1.4	2.4 ± 1.4	2 ± 1.4	2.3 ± 1.4	2.4 ± 1.4	1.9 ± 1.2
	Inflammation (mean ± SD)	3.08 ± 1.05	3.1 ± 1.1	2.9 ± 0.84	2.9 ± 0.99	3.1 ± 0.9	2.5 ± 1.0	3.0 ± 1.0	3.15 ± 1.0	2.7 ± 0.91
	Hemorrhage (mean ± SD)	3.3 ± 0.97	3.3 ± 1.0	3.4 ± 0.88	3.3 ± 1.0	3.5 ± 0.9	3.0 ± 1.1	3.3 ± ± 0.9	3.4 ± 0.98	3.2 ± 1
	Reparative changes (mean ± SD)	0.72 ± 1.4	0.67 ± 1.1	0.8 ± 1.2	0.3 ± 0.6*	0.38 ± 0.76	0.30 ± 0.75	0.6 ± 1.0	0.6 ± 1.03	0.61 ± 1.1

*$p < 0.05$

Table 3: Demographic data and clinical outcomes in infants with small intestinal NEC and those with colonic disease and variable small intestinal involvement

		NEC lesions only in the small intestine			*NEC extending into the colon*			*Combined*		
		n = 103	*75 (72.8%)*	*28 (27.2%)*	*n = 50*	*32 (64%)*	*18 (36%)*	*n = 153*	*107 (69.9%)*	*46 (30%)*
		Total	*Alive*	*Dead*	*Total*	*Alive*	*Dead*	*Total*	*Alive*	*Dead*
Prenatal information										
1	Pregnancy-induced hypertension, *n* (%)	25 (24.2%)	18 (24%)	7 (25%)	12 (24%)	7 (21.8%)	5 (27.7%)	37 (24.1%)	25 (23.3%)	12 (26%)
2	Chorioamnionitis, *n* (%)	9 (8.7%)	7 (9.3%)	2 (7.1%)	3 (6%)	2 (6.2%)	1 (5.5%)	12 (7.8%)	9 (8.4%)	3 (6.5%)
3	Antenatal steroids, *n* (%)	60 (58.2%)	48 (64%)	12 (42.8%)	30 (60%)	19 (59.3%)	11 (61.1%)	90 (58.8%)	67 (62.6%)	23 (50%)
Infant demographics										
5	Gestational age (weeks; mean ± SD)	27.2 ± 4	27.2 ± 3.2	25.8 ± 3	26.9 ± 3.5	27.9 ± 3.8	27.1 ± 3.0	27.4 ± 3.4	27.7 ± 4.1	26.4 ± 3.1
6	Birth weight (g; mean ± SD)	935 ± 471	981 ± 510	812 ± 290	961 ± 559	1134 ± 575	1038 ± 527	987 ± 505	1024 ± 538	900 ± 400
7	Male gender, *n* (%)	69 (66.9%)	60 (80%)	9 (32.1%)	27 (54%)	15 (46.8%)	8 (44.4%)	96 (62.7%)	79 (73.8%)	17 (36.9%)
8	Ethnicity									
	a Caucasian	19 (18.4%)	13 (17.3%)	6 (21.4%)	9 (18%)	7 (21.8%)	2 (11.1%)	28 (18.3%)	16 (15%)	12 (26%)
	b Latino	2 (1.9%)	2 (2.7%)	0	1 (2%)	1 (3.1%)	0	3 (2%)	3 (2.8%)	0
	c Mixed	3 (2.9%)	2 (2.6%)	1 (3.5%)	0	0	0	3 (2%)	3 (2.8%)	0
	d African American	79 (77.8%)	62 (82.7%)	21 (75%)	40 (80%)	29 (90.6%)	11 (61.1%)	119 (77.8%)	91 (85%)	28 (60.9%)
9	Small for gestational age, *n* (%)	28 (27.1%)	21 (28%)	7 (25%)	12 (24%)	7 (21.8%)	5 (27.7%)	40 (26.1%)	28 (26.1%)	12 (26%)
10	Mode of delivery									
11	C-section	40 (38.8%)	28 (37.3%)	12 (42.8%)	25 (50%)	16 (50%)	9 (50%)	65 (42.4%)	44 (41.1%)	21 (45.6%)
12	Vaginal	63 (61.2%)	47 (62.6%)	16 (57.1%)	25 (50%)	16 (50%)	9 (50%)	88 (57.5%)	63 (58.8%)	25 (54.3%)
13	Outborn, *n* (%)	58 (56.3%)	48 (64%)	10 (35.7%)	29 (58%)	20 (62.5%)	9 (50%)	87 (56.8%)	68 (63.5%)	19 (41.3%)
Infant medical information prior to NEC										
14	Apgar score <6 at 5 minutes	30 (29.1%)	21 (28%)	9 (32.1%)	9 (18%)	5 (15.6%)	4 (22.2%)	39 (25.4%)	26 (24.2%)	13 (28.2%)
15	Patent ductus arteriosus, *n* (%)	63 (61.1%)	46 (61.3%)	17 (60.7%)	25 (50%)	19 (59.3%)	6 (33.3%)	88 (57.5%)	65 (60.7%)	23 (50%)
16	Patent ductus arteriosus, indomethacin treated, *n* (%)	21 (20.3%)	13 (17.3%)	8 (28.5%)	4 (8%)*	3 (9.3%)	1 (5.5%)	25 (16.3%)	16 (14.9%)	9 (19.5%)
17	Patent ductus arteriosus, surgically ligated, *n* (%)	4 (3.8%)	4 (5.2%)	0	1 (2%)	1 (3.1%)	0	5 (3.3%)	5 (4.6%)	0
NEC disease features										
18	Age at NEC onset (days; mean ± SD)	21.5 ± 21.3	18.5 ± 16.7	29.6 ± 29.4	23.5 ± 17.04	27.1 ± 19.1	18.7 ± 12.1	22.1 ± 20.6	21.1 ± 17.8	25.2 ± 24.4
19	Corrected gestational age at NEC onset (weeks; mean ± SD)	30 ± 4.2	30.2 ± 4.4	30 ± 4.2	29.6 ± 2.9	31.7 ± 4.2	29.8 ± 2.9	30.4 ± 4.2	30.6 ± 4.4	29.9 ± 3.7
20	Clinical presentation									
	a Abdominal distension, *n* (%)	99 (96.1%)	72 (96%)	27 (96.4%)	40 (80%)	25 (78.1%)	15 (83.3%)	139 (90%)	98 (91.5%)	41 (89.1%)
	b Bloody stools, *n* (%)	2 (1.9%)	2 (2.6%)	0	5 (10%)*	3 (9.3%)	2 (11.1%)	7 (4.5%)	5 (4.6%)	2 (4.3%)
	c Feeding Intolerance, *n* (%)	3 (2.9%)	2 (2.6%)	1 (3.5%)	5 (10%)*	4 (12.5%)	2 (11.1%)	8 (5.2%)	5 (4.6%)	3 (6.5%)
21	Radiological findings									
	a Pneumatosis, *n* (%)	46	41 (54.6%)	5 (17.8%)	24 (48%)	17 (53.1%)	7 (38.8%)	57 (37.2%)	43 (40.1%)	14 (30.4%)
	b Pneumoperitoneum, *n* (%)	26	23 (30.6%)	3 (10.7%)	29 (58%)	18 (56.2%)	11 (61.1%)	43 (28.1%)	31 (28.9%)	12 (26%)
	c Portal venous gas, *n* (%)	14	10 (13%)	4 (14.2%)	3 (6%)	2 (6.2%)	1 (5.5%)	10 (6.5%)	3 (2.8%)	7 (15.2%)

(Contd...)

Table 3: *(Contd...)*

		NEC lesions only in the small intestine			*NEC extending into the colon*			*Combined*		
		n = 103	*75 (72.8%)*	*28 (27.2%)*	*n = 50*	*32 (64%)*	*18 (36%)*	*n = 153*	*107 (69.9%)*	*46 (30%)*
		Total	*Alive*	*Dead*	*Total*	*Alive*	*Dead*	*Total*	*Alive*	*Dead*
22	Length of bowel resected (cm; mean ± SD)	28 ± 31.9	17.1 ± 15.2	28 ± 31.9	42.2 ± 40.7**	37.9 ± 34.4	41.7 ± 39.6	26.6 ± 28.7	23.3 ± 24.5	33.8 ± 35.3
Postoperative systemic course										
23	Assisted ventilation (intubated), *n* (%)	95 (92.2%)	73 (97.3%)	22 (78.5%)	48 (96%)	32 (100%)	16 (88.8%)	138 (90.1%)	100 (93.4%)	38 (82.6%)
24	Pressor support >24 hours, *n* (%)	38 (36.9%)	26 (34.7%)	12 (42.9%)	20 (40%)	7 (21.9%)	3 (16.7%)	51 (33.3%)	36 (33.6%)	15 (32.6%)
25	Blood culture positive sepsis, *n* (%)	26 (25.2%)	22 (29.3%)	4 (14.2%)	15 (30%)	10 (31.2%)	5 (27.7%)	41 (26.7%)	36 (33.6%)	5 (10.8%)
Postoperative nutrition										
26	Postoperative ileus [days; mean ± SD)	14.6 ± 8.9	18.1 ± 17.1	14.6 ± 8.9	18.5 ± 13.6	16.2 ± 9.3	18.5 ± 13.6	17.3 ± 14.4	17.6 ± 15.4	16.1 ± 10.9
27	Surgical wound infection, *n* (%)	14 (13.5%)	10 (13.3%)	4 (14.2%)	5 (10%)	2 (6.2%)	5 (27.7%)	21 (13.7%)	12 (11.2%)	9 (19.5%)
28	Surgical wound dehiscence	9 (8.7%)	9 (12%)	0	8 (16%)	4 (12.4%)	1 (5.5%)	13 (8.4%)	12 (11.2%)	1 (2.1%)
29	Postoperative day at starting enteral feedings (days; mean ± SD)	15.6 ± 8.9	18.8 ± 17.1	15.5 ± 8.9	18.7 ± 13.5	16.8 ± 9.2	18.7 ± 13.4	18 ± 14.5	18.2 ± 15.4	16.8 ± 10.8
30	Feeding after surgery									
31	Mother's own/donor milk, *n* (%)	31 (30.0%)	16 (21.3%)	15 (53.5%)	25 (50%)	19 (59.3%)	6 (33.3%)	41 (26.7%)	41 (38.3%)	0
32	Infant formula, *n* (%)	41 (39.8%)	38 (50.6%)	3 (10.7%)	25 (50%)	22 (68.7%)	3 (16.6%)	63 (41.1%)	54 (50.4%)	9 (19.5%)
33	Mixed	13 (12.6%)	11 (14.6%)	2 (7.1%)	10 (20%)	2 (6.2%)	8 (44.4%)	21 (13.1%)	20 (18.6%)	1 (2.1%)
34	Day of attainment of full enteral feedings (120 mL/kg; mean ± SD)	51.9 ± 33.1	79.4 ± 46.1	51.8 ± 33.1	58 ± 40.7***	63 ± 40.1	58 ± 40.7	73.5 ± 44.1	75.1 ± 44.9	54.4 ± 34.8
35	Duration of parenteral nutrition (days; mean ± SD)	60.5 ± 44.6	103.2 ± 46.2	60.5 ± 44.6	83.6 ± 69.8*	93.4 ± 60.8	78.4 ± 70.5	92.8 ± 53.5		68 ± 56.8
36	Intestinal adhesions, *n* (%)	22 (21.3%)	20 (26.6%)	2 (7.1%)	6 (12%)	4 (12.5%)	3 (16.6%)	28 (18.3%)	23 (21.4%)	5 (10.8%)
37	Intestinal strictures, *n* (%)	9 (8.7%)	8 (10.6%)	1 (3.5%)	5 (10%)	3 (9.3%)	2 (11.1%)	15 (9.8%)	12 (11.2%)	3 (6.5%)
38	Short Bowel syndrome, *n* (%)	27 (26.2)	26 (34.6%)	1 (3.5%)	22 (44%)	13 (40.6%)	9 (50%)	43 (28.8%)	42 (39.2%)	1 (2.1%)
Discharge										
39	Length of stay (days; mean ± SD)	96.04 ± 88.1	152 ± 61.6	96 ± 88.1	69.7 ± 19.1*	161 ± 90	65.8 ± 78.4	133.9 ± 81.9	154 ± 71.0	84.2 ± 84.9
40	All deaths, *n* (%)	32 (31.1%)			14 (28%)			46 (30.1%)		

*p <0.05, **p <0.01, ***p <0.001

Table 4: Demographic data and clinical outcomes of infants with small intestinal NEC, colonic disease, and combined data, above and below the gestational age thresholds for 50% mortality

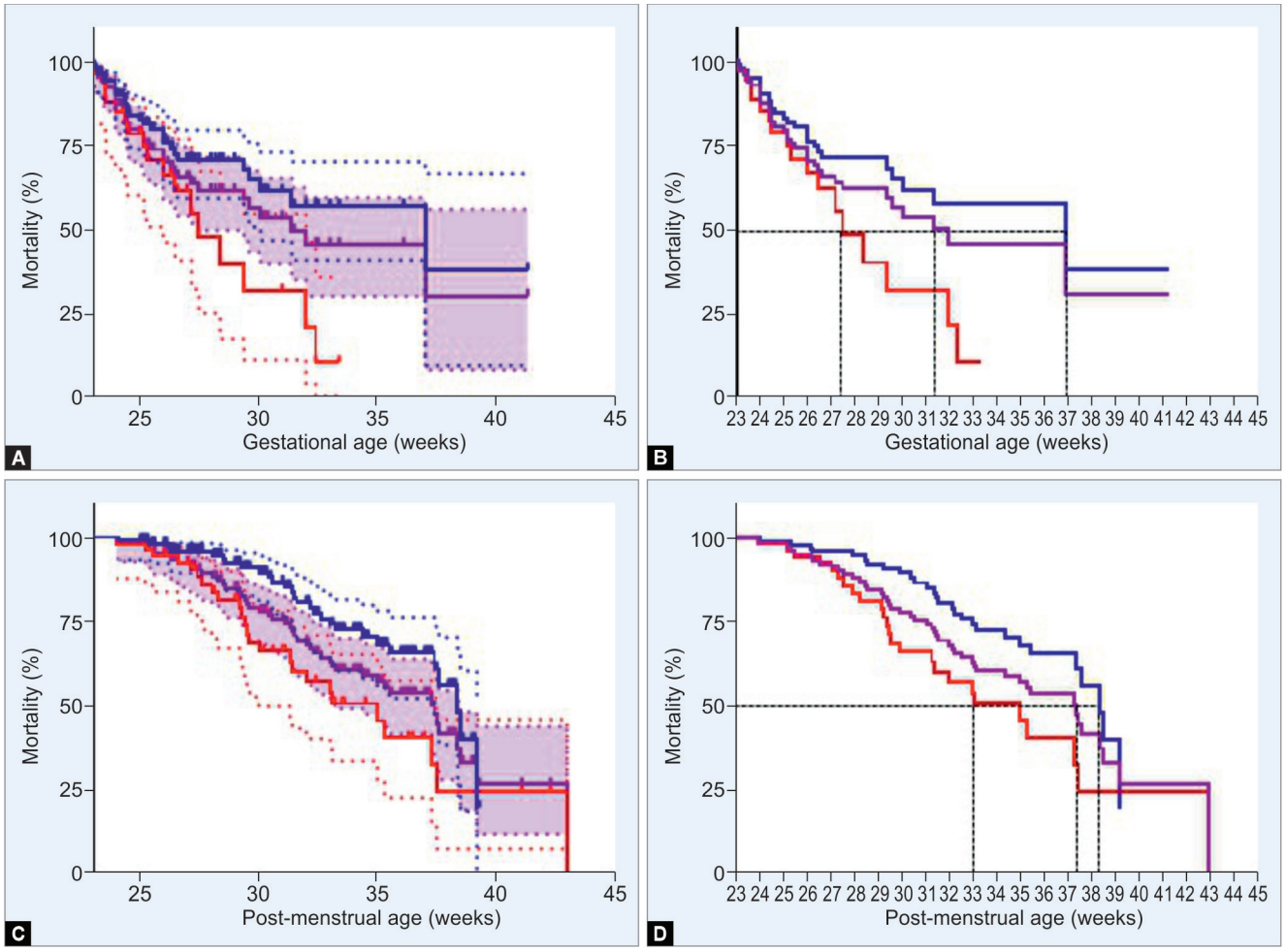
	NEC lesions only in the small intestine <37 weeks, n = 99	*NEC lesions only in the small intestine >37 weeks, n = 4*	*NEC extending into the colon <27.3 weeks, n = 28*	*NEC extending into the colon >27.3 weeks, n = 22*	*Combined <31 weeks, n = 126*	*Combined >31 weeks, n = 27*
	Mortality >50%	*Mortality <50%*	*Mortality >50%*	*Mortality <50%*	*Mortality >50%*	*Mortality <50%*
Prenatal information						
1 Pregnancy-induced hypertension, *n* (%)	26 (26.2)	1 (25%)	3 (10.7%)	9 (40.9%)*	29 (23%)	8 (29.6%)
2 Chorioamnionitis, *n* (%)	9 (9%)	0	3 (10.7%)	0	12 (9.5%)	0*
3 Antenatal steroids, *n* (%)	60 (60.6%)	1 (25%)	18 (64.2%)	12 (54.5%)	78 (61.9%)	12 (44.4%)*
Infant demographics						
5 Gestational age (weeks; mean ± SD)	26.6 ± 2.9	40.4 ± 4.3***	25.1 ± 1.3	29.5 ± 2.8***	25.9 ± 2.0	34 ± 3.4***
6 Birth weight (g; mean ± SD)	922 ± 446	1130 ± 973	758 ± 185	1527 ± 569***	816 ± 265	1809 ± 576***
7 Male gender, *n* (%)	35 (35.4%)	0	16 (57.1%)	7 (31.8%)*	51 (40%)	6 (22.2%)*
8 Ethnicity						
a White	19 (19.2%)	1 (25%)	4 (14.3%)	4 (18.2%)	24 (19%)	4 (14.8%)
b Latino	1 (1%)	0	1 (3.5%)	1 (4.5%)	3 (2.4%)	0
c Mixed	3 (3%)	0	0	0	3 (2.4%)	0
d African American	80 (80.8%)	3 (75%)	19 (67.8%)	17 (77.2%)	96 (76.2%)	23 (85.1%)
9 Small for gestational age, *n* (%)	27 (27.2%)	1 (25%)	4 (14.2%)	8 (36.3%)*	33 (26.1%)	7 (25.9%)
10 Mode of delivery						
11 C-section, *n* (%)	38 (38.3%)	2 (50%)	13 (46.4%)	12 (54.5%)	53 (42%)	12 (44.4%)
12 Vaginal, *n* (%)	61 (61.6%)	2 (50%)	15 (53.5%)	10 (45%)	73 (57.9%)	15 (55.5%)
Infant medical information prior to NEC						
13 Apgar score <6 at 5 mins	29 (29.2%)	1 (25%)	8 (28.5%)	1 (4.5%)*	34 (26.9%)	5 (18.5%)
14 Patent ductus arteriosus, *n* (%)	60 (62.6%)	1 (25%)	17 (60.7%)	8 (36.3%)*	77 (61.1%)	11 (40.7%)*
15 Patent ductus arteriosus, indomethacin treated, *n* (%)	20 (20.2%)	0	4 (14.2%)	0	24 (19%)	1 (3.7%)*
16 Patent ductus arteriosus, surgically ligated, *n* (%)	4 (4.0%)	0	1 (3.5%)	0	5 (3.9%)	0
NEC disease features						
17 Age at NEC onset (days; mean ± SD)	22.2 ± 21.4	4.7 ± 3.2	25.4 ± 18.5	21.6 ± 14.7	24.4 ± 20.8	12.3 ± 11.4**
18 Corrected gestational age at NEC onset (weeks; mean ± SD)	29.7 ± 3.7	29.9 ± 4.2	28.7 ± 2.9	33.8 ± 3.5***	29.3 ± 3.48	35.6 ± 3.5***
19 Clinical presentation						
a Abdominal distension, *n* (%)	96 (96.9%)	4 (100%)	23 (82.1%)	17 (77.2%)	118 (94.4%)	22 (81.4%)*
b Bloody stools, *n* (%)	3 (3.0%)	0	1 (3.5%)	4 (18.1%)	3 (2.3%)	5 (18.5%)***
c Feeding Intolerance, *n* (%)	1 (1%)	0	4 (16%)	1 (4.5%)	6 (4.7%)	0
20 Radiological findings						
a Pneumatosis, *n* (%)	44 (44.4%)	2 (50%)	10 (35%)	14 (63.6%)	54 (42.8%)	16 (59.2%)
b Pneumoperitoneum, *n* (%)	24 (24.2%)	2 (50%)	18 (64.2%)	11 (50%)	40 (31.7%)	15 (55.5%)**
c Portal venous gas, *n* (%)	13 (13.1%)	1 (25%)	2 (7%)	1 (4.5%)	15 (11.9%)	2 (7.4%)

(Contd...)

Table 4: (*Contd...*)

	NEC lesions only in the small intestine <37 weeks, n = 99	*NEC lesions only in the small intestine >37 weeks, n = 4*	*NEC extending into the colon <27.3 weeks, n = 28*	*NEC extending into the colon >27.3 weeks, n = 22*	*Combined <31 weeks, n = 126*	*Combined >31 weeks, n = 27*
	Mortality >50%	*Mortality <50%*	*Mortality >50%*	*Mortality <50%*	*Mortality >50%*	*Mortality <50%*
21 Length of bowel resected (cm; mean ± SD)	19.1 ± 20.0	20.0 ± 21.2	36 ± 38.3	46.6 ± 34.7	24.4 ± 28.6	35.3 ± 26.4*
Postoperative systemic course						
22 Assisted ventilation (intubated), *n* (%)	84	4 (100%)	28 (100%)	20 (90%)	112 (88.8%)	24 (88.8%)
23 Pressor support >24 hours, *n* (%)	39 (39.4%)	0	6 (21.4%)	7 (31.8%)	40 (31.7%)	8 (29.6%)
24 Blood culture positive sepsis, *n* (%)	25 (25.2%)	1 (25%)	11 (39.2%)	4 (18.1%)	34 (26.9%)	7 (25.9%)
Postoperative nutrition						
25 Postoperative ileus [days; *n* (%)]	17.6 ± 16.1	12.5 ± 7.4	14.7 ± 6.0	18.1 ± 12.5	17.7 ± 15.3	15.5 ± 10.1
26 Postoperative day at starting enteral feedings (days; mean ± SEM)	18.4 ± 16.1	13.3 ± 8.5	15.2 ± 6.1	19.3 ± 12.4	18.4 ± 15.4	16.2 ± 10.2
27 Surgical wound infection, *n* (%)	13 (13.1%)	1 (25%)	3 (10.7%)	4 (18.1%)	16 (12.6%)	5 (18.5%)
28 Surgical wound dehiscence	7 (7%)	1 (25%)	4 (14.2%)	1 (4.5%)	11 (8.7%)	2 (7.4%)
29 Intestinal adhesions, *n* (%)	21 (21.2%)	0	3 (10.7%)	4 (18.1%)	25 (19.8%)	3 (11.1%)
30 Intestinal strictures, *n* (%)	10 (10.1%)	0	4 (14.2%)	1 (4.5%)	14 (11.1%)	1 (3.7%)
31 Feeding at start						
32 Mother's own/donor milk, *n* (%)	16 (16.1%)	0	11 (39.2%)	14 (63.6%)	24 (19.0%)	17 (62.9%)
33 Infant formula, *n* (%)	36 (36.3%)	2 (50%)	13 (46.4%)	12 (54.5%)	46 (36.5%)	17 (62.9%)
34 Mixed	9 (9%)	2 (50%)	8 (28.5%)	2 (9.0%)	19 (15.0%)	2 (7.4%)
35 Day of attainment of full enteral feedings (120 mL/kg; mean ± SD)	77.6 ± 45.8	41.5 ± 0.7	67.2 ± 50.9	62.8 ± 29.9	76.5 ± 46.5	55.8 ± 28.5*
36 Duration of parenteral nutrition (days; mean ± SD)	94.1 ± 48.6	64.7 ± 58.6	99 ± 69.9	85 ± 61.9	93.0 ± 53.6	82.5 ± 54.9
37 Short Bowel syndrome, *n* (%)	17 (17.1%)	4 (100%)	15 (53.5%)	7 (31.8%)	33 (26.1%)	10 (37%)
Discharge						
38 Length of stay (days; mean ± SD)	139.3 ± 73.4	74.2 ± 59.2*	144 ± 109	107 ± 82.6	142.3 ± 83.1	93.1 ± 62.9**
39 Death, *n* (%)	29 (29.3%)	3 (25%)*	11 (39.3%)	3 (13.6%)*	40 (31.7%)	6 (22.2%)

*p <0.05, **p <0.01, ***p <0.001



Figs 1A to D: (A) Kaplan-Meier curves for mortality against gestational age (weeks). Blue line shows infants with NEC limited to the small intestine ($n = 103$), red shows patients with NEC extending into the colon ($n = 50$), and magenta shows the entire cohort ($n = 103 + 50 = 153$). The 95% confidence intervals (CIs) are shown with dotted, similarly colored lines. The magenta-shaded zone shows 95% confidence zone for the entire cohort; (B) Kaplan-Meier curves similar to panel A, where dotted black lines show the convergence of 50% mortality with gestational age in NEC limited to the small intestine, disease extending into the colon, and in the entire cohort; (C) Kaplan-Meier curves for mortality against the corrected gestational age (weeks). Color coding of the curves, dotted lines, and the combined zone as in panel A; (D) Kaplan-Meier curves similar to panel C, where dotted black lines show the convergence of 50% mortality with PMA in NEC limited to the small intestine, disease extending into the colon, and in the entire cohort

Discussion

We studied 153 infants with a clinical profile typical for surgical NEC, with an average (±SD) gestational age of 27.3 ± 3.9 weeks and a birth weight of 986.9 ± 505 g. NEC occurred on postnatal day 22.4 ± 20.1 with usual presenting features of abdominal distension, feeding intolerance, and/or bloody stools. Abdominal surgery was done within 24 hours of disease onset. Postoperatively, ileus lasted 17.3 ± 14.5 days; enteral feedings were started on 18 ± 14.5 days, and full volumes were achieved on 72.4 ± 44.2 days. Parenteral nutrition was given for 91.1 ± 53.8 days. Forty-six (30.1%) infants died. The average hospital stay was 133.6 ± 81.9 days.

The findings in this study support our hypothesis that surgical resections may be more likely associated with better outcomes in NEC that extends into the colon than in disease limited to the small intestine. In our cohort, 103 infants had small intestinal NEC, whereas the other 50 had colonic involvement. The two groups had comparable gestational ages and birth weights and, except for some minor differences, had generally similar clinical courses prior to and after surgery for NEC. In the resected tissues, the gross and microscopic pathological changes of NEC, and their severity, were similar except for the relative prominence of reparative changes in some infants with colonic involvement (Table 2). There were significant differences in the LOS of the two groups, and a trend toward significance in mortality (Table 3). The application of Kaplan-Meier statistics, when mortality data were plotted against the gestational age at birth or the corrected gestational age at onset of NEC, showed important differences in the clinical trajectories of the two groups. These results once again emphasize the need for cautious analysis in numerically limited clinical samples.[21] Despite longer bowel resections, infants who had NEC involving the colon were quicker to reach full-volume enteral feedings and had shorter hospital stays. Their mortality rates dropped below 50% at 27.3 weeks' gestation, which was much earlier than the 37 weeks' threshold we noted in NEC limited to the small intestine. The reasons for these differences in the gestational age thresholds for mortality are not clear. Prior to 28 weeks' gestation, the mid-gestation colon is still undergoing histomorphological and functional differentiation and resembles the small intestine in many ways.[22,23] Its mucosa displays villus-like structures that express

digestive enzymes such as sucrose-isomaltase, aminopeptidase, and alkaline peptidase; hormones such as glucagon, somatostatin, and pancreatic polypeptide; absorb glucose, alanine, and methionine; and synthesize apolipoproteins. Interestingly, the two subgroups show major differences in mortality only beyond 28 weeks' gestation. One possibility that needs further investigation is whether the two subgroups could have temporal differences in colonic differentiation of the distal intestine.

We found no difference in the average gestational age of infants who developed NEC exclusively in their small intestine vs others who had disease extending into the colon. These findings contrast with existing information that colonic NEC lesions may occur more frequently in infants born at gestational ages closer to term than in very premature ones.[7,24] One possible explanation for this observed concordance in the gestational age and PMA between the two studied subgroups is that developmentally regulated changes in intestinal structure or function, or predisposing genetics, may have a relatively strong impact on the onset of NEC.[5,25] After surgery, infants with NEC involving the colon had improved survival at a significantly earlier gestational age and PMA. As hypothesized, these differences in survival rates may reflect the greater impact of surgical resections in reducing gut microbial loads, bacterial translocation across the diseased bowel, and consequent local and systemic inflammation. These possibilities merit further investigation. Finally, the two groups developed NEC at a similar postnatal age. This temporal convergence could possibly be rooted in one or more postnatal factors. Increasing evidence emphasizes the role of postnatal exposures such as enteric dysbiosis and overgrowth of gram-negative bacteria, to potentially injurious components of artificial feedings, and the limitations of mucosal antimicrobial defenses such as immature Paneth cells. We also have some information on point triggers of NEC during intensive care, such as hypoxia and hypothermia, ischemia and reperfusion, severe anemia and blood transfusions, and enteral exposure to immunological stimuli.[26–32]

We confirmed the diagnosis, severity, and the anatomic localization of NEC in surgically resected intestines (Table 2). Gross pathological specimens were available from 60 infants, and all showed findings of NEC. Acute changes included gangrenous areas, dusky discoloration suggesting altered perfusion, hemorrhages, and in some samples, perforations. Some samples showed subacute changes such as bowel wall thinning, friability, strictures, and adhesions. Histopathological sections of the resected intestine were available from all 153 patients. All showed findings of NEC, including necrosis, inflammation, and hemorrhages, and some showed regenerative changes. Consistent with our earlier observations,[17] necrosis, inflammatory changes, and hemorrhages correlated with each other. Pneumatosis was seen in about 30% of the sections. Tissue reparative changes were more prominent in mild-moderate NEC than in severe disease.[7] Finally, bowel resections had clean margins in only about 35% of all sections. The rest showed some necrosis in the resected edges, possibly pointing to both the surgeons' efforts to minimize the removal of the intestines and to some difficulty in visually differentiating completely vs partially necrosed bowel. We have recently shown that incomplete resections of necrotic bowel may increase mortality in NEC.[17] There may be some justification for on-site, rapid histopathological screening of the resected tissues to prevent excessive removal of segments that could possibly recover in time, but also to ensure that all clearly necrotic patches have been removed.

The demographic and clinical features of infants who had NEC limited to the small intestines were generally similar to those with colonic involvement (Table 3). Infants in both groups had comparable gestational ages and birth weights. They developed NEC at a similar postnatal age. Infants who developed small intestinal NEC had a more frequent history of symptomatic PDA than those with colonic NEC. These infants also had a higher frequency of feeding intolerance and bloody stools as presentations of NEC. Small intestinal NEC led to shorter bowel resections, but resulted in longer periods to reach full enteral feedings and longer hospital stays. The reasons for these clinical differences are unclear. They could have had a higher incidence of intestinal dysmotility or subclinical strictures, but these data are not available and need further investigation. Their clinical course was likely complicated as their Kaplan-Meier estimates for the gestational age at 50% mortality were much more delayed than in those with NEC extending into the colon (37 vs 27.3 weeks, Table 4).

In our entire cohort, the gestational age threshold for 50% mortality was at 31.3 weeks (Table 4). Infants born prior to this maturational cutoff were more often exposed to chorioamnionitis and had less frequent treatment with antenatal steroids. Their average gestational ages and birth weights were lower, and they were more often male. They had a higher incidence of PDA, developed NEC at an earlier PMA but a later chronological age, developed abdominal distension and bloody stools more frequently at the time of presentation with NEC, and developed pneumoperitoneum more frequently. Many of these differences were also noted across the comparison thresholds in small intestinal NEC or in disease that extended into the colon, although some differences did not reach statistical significance because of the smaller numbers.

African American infants constituted a large proportion of our cohort. Several large studies have now shown the impact of ethnic and genetic influences in the pathogenesis of NEC, but the underlying reasons are still unclear.[33,34] In a recent study, Janevic et al.[35] reported increased risk of NEC in African American [adjusted relative risk (RR) 1.39, 95% CI, 1.00–1.93]. In another study at the Pediatrix medical group, 8,796 (7%) patients were identified to have NEC in a cohort of 126,089 infants.[33] NEC was frequent in African Americans [adjusted odds ratios (AOR) 1.31, 95% CI 1.24–1.39]. The mortality was also higher in these infants than in Caucasians (AORs 1.35, 95% CI 1.15–1.58). These health disparities need further investigation, possibly focusing on environmental exposures and genetic variants associated with NEC.[25]

To conclude, we present novel information suggesting that surgical resections may be more likely associated with better outcomes in NEC involving the colon than in disease limited to the small intestine. There may also be other exciting opportunities; infants who developed NEC extending into their colon had an average time gap of nearly 6 weeks between the gestational age at birth and the PMA at onset of NEC. This interval may provide an opportunity, at least in some infants, for intensive clinical monitoring, risk stratification with analysis of the microbiome or other parameters, or focused interventions with nutritional, pharmacological, or probiotic-based supplementation. Our study had limitations in its single-center design, limited sample size, and the retrospective design, which increase the risk of bias. There is a need to validate these results in a larger, prospectively enrolled, and multicentric cohort, which may also allow the evaluation of additional clinical/laboratory predictors in the statistical models.[36–39]

AM and PMG designed the study, PMG, JLP, MZ, KL, NV, CM, MM and AA collected and analyzed the data. AM and PMG wrote the study. All the authors contributed to and approved the manuscript.

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Supplementary Material

All the supplementary figures and tables are available online on the website of www.newbornjournal.org.

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