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Risk Factors for Parenteral Nutrition–associated Liver Disease Following Surgical Therapy for Necrotizing Enterocolitis

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Abstract

Objective—The aim of the study was to prospectively determine risk factors for the development of parenteral nutrition–associated liver disease (PNALD) in infants who underwent surgery for necrotizing enterocolitis (NEC), the most common cause of intestinal failure in children.

Patients and Methods—From February 2004 to February 2007, we diagnosed 464 infants with NEC, of whom 180 had surgery. One hundred twenty-seven patients were available for full analysis. PNALD was defined as serum direct bilirubin ≥ 2 mg/dL or ALT $\geq 2 \times$ the upper limit of normal in the absence of sepsis after ≥ 14 days of exposure to PN. Median

Results—Median gestational age was 26 weeks and 68% were boys. Seventy percent of the cohort developed PNALD and the incidence of PNALD varied significantly across the 6 study sites, ranging from 56% to 85% ($P=0.05$). Multivariable logistic regression analysis identified small-bowel resection or creation of jejunostomy (odds ratio [OR] 4.96, 95% confidence interval [CI] 1.97–12.51, $P=0.0007$) and duration of PN in weeks (OR 2.37, 95% CI 1.56–3.60, $P<0.0001$) as independent risk factors for PNALD. Preoperative exposure to PN was also associated with the development of PNALD; the risk of PNALD was 2.6 (95% CI 1.5–4.7; $P=0.001$) times greater in patients with ≥ 4 weeks of preoperative PN compared with those with less preoperative PN use. Breast milk feedings, episodes of infection, and gestational age were not related to the development of PNALD.

Conclusions—The incidence of PNALD is high in infants with NEC undergoing surgical treatment. Risk factors for PNALD are related to signs of NEC severity, including the need for small-bowel resection or proximal jejunostomy, as well as longer exposure to PN. Identification of these and other risk factors can help in the design of clinical trials for the prevention and treatment of PNALD and for clinical assessment of patients with NEC and prolonged PN dependence.

Keywords

intestinal failure; jejunostomy; necrotizing enterocolitis; parenteral nutrition–associated liver disease; short-bowel syndrome

Parenteral nutrition (PN) is a lifesaving therapy for patients with intestinal failure, and since its development, mortality due to dehydration and malnutrition essentially has been eliminated (1). This critical therapy, however, has been plagued by the recognition that patients with prolonged dependence on PN commonly develop hepatic dysfunction, also known as parenteral nutrition–associated liver disease (PNALD). PNALD is characterized by cholestasis, steatosis, and mixed inflammatory changes and can progress to fibrosis and cirrhosis (2,3). PNALD is especially common in infants and children with intestinal failure (IF), occurring in 40% to 60% of pediatric patients receiving prolonged courses of PN (4,5).

Recent data have confirmed that the presence of liver disease in patients receiving PN is strongly associated with a high mortality rate. In a cohort study of 78 children with IF, the mortality rate among those with cholestasis (direct bilirubin concentration ≥ 2 mg/dL) was close to 80% compared with 20% in those without cholestasis (6). These data confirmed a previously reported mortality rate of 90% among infants with IF and cholestatic liver disease who were unable to be weaned from PN (7). With advanced liver disease in the setting of prolonged dependence on PN, liver and intestinal transplantation is sometimes required (8).

Multiple risk factors for the development of PNALD have been identified and include premature birth, disruption of the enterohepatic circulation of bile acids, intestinal stasis with subsequent bacterial overgrowth, ischemia or decreased blood flow from reduced portal venous return causing inflammation and intestinal necrosis, early and/or recurrent central venous catheter–related sepsis, excessive glucose intake leading to hyperinsulinism and subsequent steatosis, and high parenteral protein, fat, and/or energy intake (7,9–12). No unifying theory, however, has been put forward to explain all of the features of PNALD, and previous studies to evaluate epidemiologic risk factors for its occurrence have been limited by retrospective, single-center designs (7,12,13).

We conducted a prospective, multicenter cohort study to identify clinical, demographic, and disease-specific risk factors for the progression of necrotizing enterocolitis (NEC) (14). The aim of the present analysis was to determine risk factors for the occurrence of PNALD in a subset of patients who underwent surgical treatment for NEC.

PATIENTS AND METHODS

The subjects in this analysis were drawn from an observational, prospective cohort study of infants with NEC conducted at 6 academic medical centers in the United States. The design and primary results of the main cohort study have been reported (14). A total of 464 patients meeting the protocol definition for NEC were enrolled between February 2004 and February 2007. Entry criteria for this study were those commonly used to identify infants with suspected or confirmed NEC (15). Patients were enrolled on the day they met these criteria, which included having at least 1 finding from each of a prespecified set of historical factors, physical examination findings, and radiographic findings. Historical factors included feeding

intolerance, apneic/bradycardic episodes, oxygen desaturation, or grossly blood stools. Physical examination findings included abdominal distension, capillary refill time >2 seconds, abdominal wall discoloration, or abdominal tenderness. Radiographic findings included pneumatosis intestinalis, dilated bowel, portal venous gas, ileus, pneumoperitoneum, air/fluid levels, thickened bowel walls, ascites, peritoneal fluid, free intraperitoneal air, or abnormal bowel gas pattern. Subjects were excluded if they had any major gastrointestinal anomalies or had undergone abdominal surgery before enrollment. The protocol was approved by the institutional review board at each site, and informed consent was obtained when required; consent waivers were granted at some sites.

For the purposes of this analysis and because liver biopsies were not routinely performed in these settings, PNALD was defined as abnormal liver biochemical testing (either serum direct bilirubin ≥ 2 mg/dL or alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal [ULN]). In addition, subjects had to have at least 14 days of PN exposure at the time of liver disease diagnosis and no concurrent positive blood cultures to explain the abnormal biochemical tests. Full enteral feeding was defined as the provision of ≥ 100 kcal/kg/day from enteral nutrition (EN) and demonstrating a mean weight gain of ≥ 15 g/day for 7 days, or being discharged after discontinuing PN. Patients were ineligible for this analysis if they had no liver biochemical testing after 14 days of PN exposure, had evidence of abnormal liver biochemical testing before surgery, were being treated with intravenous omega-3 fatty acids or ursodeoxycholic acid, or had incomplete follow-up. Surgical therapy was defined as either exploratory laparotomy (with or without intestinal resection) or surgical placement of peritoneal drains.

Demographic, maternal, prenatal, and intrapartum data, and medication history (for both mother and child) and newborn history before study entry were abstracted from medical records. Data collected daily during the week before diagnosis of NEC included mode of feeding (PN or EN), method (bolus or continuous), type of EN (breast milk, formula, or a combination), volume of formula, and weight of the infant. After study entry, detailed clinical data were collected prospectively on a daily basis until subjects underwent surgery. Because bilirubin and ALT test results were collected routinely only for surgical patients and values before surgery were not recorded uniformly, we limited our analysis to surgical patients and considered only postoperative test results as outcomes. Surgical findings and data on postoperative course were collected weekly. Data collected included medications, laboratory and imaging evaluations, ventilation status, fluid/hemodynamic status, and blood culture results.

The use of PN was recorded up to 1 week before NEC diagnosis and then daily from the time of diagnosis until surgical intervention. If PN was not recorded for 5 or more consecutive days when it was known that enteral nutrition was withheld, then daily PN was assumed. After surgery, PN use was documented weekly. For the purposes of analysis, this day was considered representative of the week's PN exposure. Volumes of dextrose, protein, and fat were recorded over the same time intervals as for PN. Each nutrient was expressed in grams per kilogram per day and kilocalories per kilogram per day, and then summed over all of the days to obtain cumulative exposure.

Statistical Analysis

Our study endpoint was the development of PNALD. Summary statistics for continuous variables were expressed as median (quartiles). Categorical variables were summarized with frequency distributions. Tests of group differences were made using the Wilcoxon rank sum test and the Pearson chi-square test or the Fisher exact test. Associations between pairs of predictors were investigated using the Spearman rank correlation coefficient.

The determination of predictors for PNALD was made using multiple logistic regression analysis. Except where noted otherwise, we used information that would be known at the time of surgery (or immediately after) as candidate predictors. Candidate postoperative correlates of PNALD were also considered, but only data from days 1 to 28 after surgery were used to define the predictors to minimize the use of exposure information to predict an event that may have occurred before the exposure. For surgical information, this included data from subjects who had second surgical procedures within 28 days of the first. All of the patients who underwent jejunostomy developed PNALD, preventing us from including a variable noting the creation of a jejunostomy in a predictive model. We therefore created a clinically relevant composite variable by combining jejunostomy with the presence of any small bowel resection because each variable was highly significant by itself, the 2 were correlated with each other, and both surgical interventions render part of the small bowel nonfunctional. The fit of the final model was assessed using the Hosmer-Lemeshow goodness-of-fit test (16).

A product-limit estimate of the survivor function was used to examine the time from surgery to PNALD, defined as the time from surgery until either serum direct bilirubin ≥ 2 mg/dL or ALT $\geq 2 \times$ ULN, with a minimum of 14 days' PN exposure and no concurrent positive blood cultures to explain the abnormal biochemical tests. This duration was censored at the time of the last laboratory report for those who did not develop PNALD, including those who later died. Patients not requiring surgical intervention were excluded from this analysis because markers of liver dysfunction were not routinely obtained in patients who did not undergo surgery. Group comparisons were made using proportional hazards regression. Because not all of the patients had accumulated 14 days of PN exposure before surgery, an adjustment was made in all of the time-to-PNALD analyses to allow these patients to be considered at risk for PNALD at the appropriate time (17).

All tests of significance were 2-sided with a type I error rate of 0.05. All of the data analysis was performed using SAS/STAT software, version 9.1 of the SAS System for Windows (SAS Institute, Cary, NC).

RESULTS

Of 464 subjects, 180 (39%) underwent surgical intervention for NEC (Fig. 1). In all, 127 surgical patients had ≥ 14 days of PN exposure and were available for analysis, of whom 70% developed PNALD. The rate of PNALD varied significantly across the 6 study sites, ranging from 56% to 85% ($P=0.05$). Among the 89 subjects with PNALD, 56 subjects met the criteria for liver disease due to both direct bilirubin >2 mg/dL and ALT $>2 \times$ ULN, 31 due to direct bilirubin >2 mg/dL alone, and only 2 subjects due to ALT $>2 \times$ ULN alone.

Two-thirds of all of the patients were boys (Table 1) and 63% were white, with a median gestational age of 26 weeks. Age at diagnosis of NEC ranged from 1 to 74 days (median 11 days), with 32% diagnosed within 1 week of birth and 65% within 2 weeks. Fifty-seven percent of the infants weighed <1000 g at birth. Sixtythree percent of all of the patients had surgery for NEC within 48 hours of diagnosis, and 84% of the patients had surgery within 1 week. Twenty-two (17%) patients required a second surgery within 28 days of the first, usually within the first week. Among the 127 enrolled patients, 23 (18%) patients died at a median age of 10 weeks (interquartile range 6–25). Additional patient characteristics are shown in Table 1.

One hundred (79%) patients received EN before or on the day of diagnosis of NEC, whereas 14 (11%) received enteral feeds after diagnosis and before surgery for NEC. Days of PN use

before surgery ranged from 1 to 70 days (median 10 days), with daily dependence on PN from birth until surgery in 38 (30%) patients.

Initial surgical intervention for NEC included peritoneal drainage (n=29, 23%) or exploratory laparotomy (n=98, 77%). Among the 29 patients who underwent peritoneal drainage, 6 required surgical resection. Sixteen (55%) of the 29 patients developed PNALD, as compared with 100% among 17 patients requiring jejunostomy and 76% among 80 patients requiring some type of surgical resection. Findings during laparotomy prompted small-bowel resection (n = 65, 66%), creation of diverting ileostomy (n = 57, 58%), large-bowel resection (n = 30, 31%), and ileocecal valve resection (n = 23, 23%). Multiple surgical interventions were common, with 50 (39%) patients undergoing 2 of these operative procedures. Resection of the small bowel ranged from 0.8 to 80.0 cm (median 12.0 cm) among those 45 patients whose resected bowel length was recorded. Unadjusted comparison of patients with PNALD versus those without is shown in Table 2. Abdominal wall discoloration and pneumoperitoneum were less frequently reported in patients progressing to PNALD, whereas any EN by the time of diagnosis, ileocecal valve resection, jejunostomy, and small-bowel resection were more frequent in patients who developed PNALD ($P < 0.05$ for each). Abdominal distension, pneumatosis intestinalis, portal venous gas, ventilation on the day of diagnosis, and any PN use by the day of NEC diagnosis were marginally statistically significant ($P < 0.10$), with each more prevalent among patients with PNALD. Statistically significant effects were not found for any other demographic characteristics, maternal and birth information, medical and feeding histories, or surgical interventions (Table 2).

Independent predictors of PNALD are shown in Table 3. PN exposure measured in days proved more predictive than when measured as kilocalories per kilogram per day and summed over days. The 2 were highly correlated (Spearman correlation 0.81, $P < 0.0001$) and either by itself was highly significant. Furthermore, once total PN exposure was included in the model, the addition of any of the 3 specific parenteral macronutrients (carbohydrates, fat, or protein) was not significant. In preliminary models, we accumulated PN exposure days separately before and after surgery; each variable was significant when adjusted for the other ($P = 0.001$ for each) and had similar coefficients (test of equality, $P = 0.38$). We therefore combined the 2 into a single variable. Overall, the odds of PNALD increased 2.4-fold for each additional week of PN exposure. Patients with small-bowel resection or jejunostomy had odds of PNALD nearly 5 times that of patients without these interventions ($P = 0.001$), even when taking into consideration length of PN exposure. The independent effects of abdominal discoloration, prediagnosis EN, and other surgical interventions were not statistically significant after adjustment for the aforementioned independent predictors.

Figure 2 displays time from surgery for NEC until PNALD for patients with ≥ 4 weeks of PN before surgery (n = 16) compared with those with < 4 weeks of preoperative PN (n = 105). The probability of PNALD was consistently greater in the PN ≥ 4 weeks group. The median time to develop PNALD was 9 days for patients with ≥ 4 weeks of preoperative PN use compared with 21 days in the PN < 4 weeks group. Overall, the risk of PNALD was 2.6 (95% CI 1.5 to 4.7; $P = 0.001$) times greater in the ≥ 4 weeks of PN group.

DISCUSSION

PNALD encompasses a variety of injuries in the liver (18) and is associated with a high mortality rate among children with intestinal failure (7). Our prospective multicenter study identified 2 independent and strong predictors of PNALD: pre- and postoperative exposure to PN, and the creation of a proximal jejunostomy or small-bowel resection for NEC.

Overall, 70% of the cohort developed PNALD, making it a common morbidity of infants undergoing surgical therapy for NEC. To our knowledge, our study is unique because it prospectively determined risk factors for PNALD in a large cohort of patients with NEC and quantified the risk of its occurrence, a 2.4-fold increase for each additional week of PN exposure and a nearly 5-fold higher risk for patients who undergo small-bowel resection or the creation of a jejunostomy.

Our data do not support the hypothesis that a particular parenteral macronutrient (protein, fat, and/or carbohydrate) (7,9–12) is responsible for the development of PNALD (12,19). We evaluated whether exposure to higher amounts of these macronutrients was related to the occurrence of PNALD and found that once the total PN exposure days was included in the model, the total energy from PN or from any of the 3 specific macronutrients did not significantly improve the fit of this model. Similarly, the percentages of energy from each macronutrient were not statistically related to the occurrence of PNALD. Instead, our data suggest that total PN exposure days is the primary nutrition-related risk factor for PNALD. Prospective trials of newer forms of parenteral macronutrients in the prevention of PNALD, including omega-3-fatty acids (20), are under way and will help evaluate these findings.

Exposure to enteral feeds, either breast milk or formula, was also not predictive of PNALD. A previous retrospective study (7) found that the use of protein-hydrolysate formula was associated with a lower incidence of PNALD in a group of intestinal-failure patients, but our prospective data did not support this relation in patients with NEC. Univariate analysis suggested that any EN on or before the day of diagnosis of NEC was associated with PNALD ($P=0.01$, Table 2). Similarly, in our recent analysis (21) from this cohort we found that exposure to enteral feeds before the diagnosis of NEC was associated with subsequent need for PN for >90 days. Continued feeding during this period of disrupted intestinal integrity may potentiate the local inflammatory response and in turn increase the severity of NEC, the need for prolonged PN, and the risk for cholestatic liver disease.

We also found several factors to be associated with the development of PNALD in the univariate analysis (Table 2) that did not remain significant predictors in the final multivariate model. Nevertheless, these results may provide clues about the etiology of this condition. Collectively, these risk factors (abdominal distension, pneumatosis intestinalis, portal venous gas, mechanical ventilation on the day of diagnosis) are associated with increased severity of NEC and consequently require prolonged duration of PN. Among the surgical factors analyzed, ileocecal valve resection was a significant univariate risk factor for the development of PNALD. This finding has not been previously reported in the literature, although 1 retrospective case series (22) found that absence of an ileocecal valve leads to prolonged PN exposure. It is possible that resection of the ileocecal valve predisposes patients to less efficient enterohepatic bile salt recirculation and subsequently more cholestasis. Similar physiologic mechanisms may underlie our observed association between PNALD and small-bowel resection or the creation of a jejunostomy.

The variation in PNALD incidence across the 6 university referral centers (56%–85%, $P=0.05$) is interesting and may reflect differences in patient characteristics and in surgical, medical, or nutrition-management practices. In addition, variation in referral patterns could lead to overrepresentation of the most severe NEC cases at some centers and underrepresentation at others.

Although our study is one of the few prospective, multicenter reports on the incidence of PNALD in infants with NEC, it still has important limitations. Because of the design of the parent study, our analysis was limited to patients who underwent surgery for NEC. The incidence of PNALD among medical patients with NEC, however, is likely to be lower,

owing to their much shorter duration of PN use (21). In our analysis of predictors of prolonged PN dependence, for instance, we found that 42% of surgical patients with NEC had PN exposure ≥ 90 days versus only 2% in medical patients with NEC ($P < 0.001$) (21).

In summary, PNALD is a common morbidity among patients undergoing surgery for NEC. To our knowledge, this is the first prospective multicenter effort to report data concerning the incidence and risk factors for this severe condition and to provide a quantifiable estimate of disease risk. In patients with PNALD, both the high likelihood of developing end-stage liver disease requiring liver transplantation and the high mortality rate (6,8) highlight the importance of identifying, in advance, patients who are likely to develop this condition. Identification of risk factors may allow the development of strategies for the prevention of PNALD and/or to offer treatment options early in the course of disease that can ultimately minimize the high rate of morbidity and mortality.

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FIGURE 1.
Study cohort enrolled from February 2004 through February 2007.

FIGURE 2.

Cumulative probability of PNALD showing a higher risk of PNALD over time among patients with ≥ 28 days of preoperative PN use compared with those with < 28 days of PN (hazard ratio 2.64; $P = 0.001$). PNALD Parenteral nutrition–associated liver disease.

TABLE 1

Characteristics of the study population (NU127)

Demographic characteristics (%)	
Male sex	86/127 (68)
Gestational age, wk, median (Q1–Q3)	26 (25–31)
Birth weight, g, median (Q1–Q3)	898 (674–1315)
Birth length, cm, median (Q1–Q3)	35 (32–40)
Birth head circumference, cm, median (Q1–Q3)	24 (23–27)
Maternal information	
Age of mother at delivery, y, median (Q1–Q3)	28 (21–33)
Prenatal steroid use (%)	97/119 (82)
History of gestational hypertension (%)	26/118 (22)
History of gestational diabetes (%)	10/116 (9)
Birth information	
Intubation at delivery (%)	82/127 (65)
Vaginal delivery (%)	44/127 (35)
Resuscitation drugs used at delivery (%)	18/127 (14)
Medical history	
Antibiotic use on the day of diagnosis of NEC (%)	115/126 (91)
Ventilator use on the day of diagnosis of NEC (%)	95/127 (75)
Surfactant use before diagnosis of NEC (%)	90/123 (73)
PDA confirmed by echocardiography before diagnosis of NEC* (%)	53/93 (57)
Steroid use before diagnosis (%)	18/123 (15)
Feeding history	
Received PN before diagnosis of NEC (%)	117/127 (92)
Received EN before diagnosis of NEC (%)	100/127 (79)
Breast milk only (%)	36/100 (36)
Formula only (%)	25/100 (25)
Both breast milk and formula (%)	32/100 (32)
Type of EN unknown (%)	7/100 (7)
Labs	

Metabolic acidosis (pH <7.3 or HCO₃ <16 mEq/L) on the day of diagnosis (%) 88/111 (79)

Positive blood culture within 5 d of diagnosis of NEC[‡] (%) 39/104 (38)

EN=enteral nutrition; NEC= necrotizing enterocolitis; PDA=patent ductus arteriosis; PN=parenteral nutrition; Q=quarter.

* n=93 patients with an echocardiogram before diagnosis of NEC.

[‡] Blood cultures obtained for 104 patients.

TABLE 2

Risk factors for PNALD, unadjusted (N=127)

	PNALD (n=89)	No PNALD (n=38)	P *
Demographic characteristics			
Male sex (%)	62/89 (70)	24/38 (63)	0.47
Gestational age, wk, median (Q1–Q3)	26 (25–30)	26 (25–32)	0.92
Birth weight, g, median (Q1–Q3)	916 (668–1315)	825 (697–1362)	0.95
Birth length, cm, median (Q1–Q3)	35 (31–40)	35 (32–39)	0.84
Maternal information			
Prenatal steroid use (%)	68/85 (80)	29/34 (85)	0.50
History of gestational hypertension (%)	19/82 (23)	7/36 (19)	0.65
History of gestational diabetes (%)	8/81 (10)	2/35 (6)	0.72
Birth information			
Intubation at delivery (%)	56/89 (63)	26/38 (68)	0.55
Vaginal delivery (%)	34/89 (38)	10/38 (26)	0.20
Medical history			
PDA confirmed by echocardiography before diagnosis of NEC [†] (%)	36/65 (55)	17/28 (61)	0.63
Abdominal wall discoloration (%)	19/89 (21)	18/38 (47)	0.003
Abdominal distension (%)	83/89 (93)	31/38 (82)	0.06
Grossly bloody stools (%)	21/88 (24)	8/38 (21)	0.73
Pneumoperitoneum (%)	5/89 (6)	7/38 (18)	0.04
Pneumatoxis intestinalis (%)	40/89 (45)	10/38 (26)	0.05
Portal venous gas (%)	16/89 (18)	2/38 (5)	0.06
Feeding intolerance (%)	50/88 (57)	21/38 (55)	0.87
Acidosis on the day of diagnosis (%)	64/77 (83)	24/34 (71)	0.13
Antibiotic use on the day of diagnosis (%)	81/88 (92)	34/38 (89)	0.73
Vasopressor use on the day of diagnosis (%)	28/88 (32)	13/38 (34)	0.79
Ventilator use on the day of diagnosis (%)	71/89 (80)	24/38 (63)	0.05
Platelets <100 K/μL on the day of diagnosis (%)	16/83 (19)	4/35 (11)	0.30
WBC >12.0×10 ³ on the day of diagnosis (%)	35/82 (43)	16/35 (46)	0.76
Ever sepsis before surgery for NEC (%)	26/89 (29)	10/38 (26)	0.74

	PNALD (n=89)	No PNALD (n=38)	P *
Ever Gram-negative culture before surgery for NEC (%)	15/79 (19)	2/32 (6)	0.14
Feeding history			
Days of PN before surgery for NEC, median (Q1–Q3)	12.0 (7.0–22.0)	8.0 (5.0–11.0)	0.007
Received EN on or before day of diagnosis (%)	76/89 (85)	24/38 (63)	0.01
Received breast milk on or before day of diagnosis [†] (%)	53/71 (75)	15/22 (68)	0.55
Received formula on or before the day of diagnosis [‡] (%)	44/71 (62)	13/22 (59)	0.81
% of presurgery kcal/kg/day from parenteral carbohydrates	54.2 (49.5–63.0)	55.7 (46.0–61.7)	0.71
% of presurgery kcal/kg/day from parenteral fat	28.5 (18.4–32.7)	27.2 (20.3–36.5)	0.40
% of presurgery kcal/kg/day from parenteral protein	15.4 (13.6–20.2)	15.3 (12.1–19.5)	0.38
Surgical interventions [§] (%)			
Exploratory laparotomy	73/89 (82)	25/38 (66)	0.05
Ileocecal valve resection	23/89 (26)	2/38 (5)	0.008
Jejunostomy	17/89 (19)	0/38 (0)	0.004
Large-bowel resection	26/89 (29)	9/38 (24)	0.52
Small-bowel resection	59/89 (66)	13/38 (34)	0.001
Small-bowel resection or jejunostomy	61/89 (69)	13/38 (34)	0.0003

EN=enteral nutrition; NEC=necrotizing enterocolitis; PDA=patent ductus arteriosus; PN=parenteral nutrition; PNALD=parenteral nutrition-associated liver disease.

* P value from Wilcoxon rank-sum test, Pearson chi-square test, or Fisher exact test.

[†] n=93 patients with an echocardiogram before diagnosis of NEC.

[‡] Some patients may have received both breast milk and formula. n=100 patients received EN before or on the day of diagnosis; however, the type of nutrition (breast milk, formula) was recorded in 93 of these patients.

[§] Includes second surgeries (in 19 patients) that occurred up to 28 days after the first surgery.

TABLE 3

Independent predictors of PNALD (N=127)

	Odds ratio (95% CI)	P
Weeks of PN [*]	2.37 (1.56–3.60)	<0.0001
Small-bowel resection or jejunostomy	4.96 (1.97–12.51)	0.0007

CI=confidence interval; PN=parenteral nutrition; PNALD=parenteral nutrition–associated liver disease.

* Cumulative exposure from birth through 4 weeks after surgery.