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ORIGINAL ARTICLE

Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease

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Background: Prolonged use of parenteral nutrition (PN) in neonates can lead to parenteral nutrition-associated liver disease (PNALD), manifested by elevated direct bilirubin concentrations, and in some cases progressing to hepatic failure. When new potential means of preventing PNALD in the neonatal intensive care unit (NICU), such as Omegaven usage, are tested in clinical trials, the studies should enroll neonates at a very high risk of developing PNALD. However, it is not always clear, in the first days of life, which neonates are most likely to develop PNALD. Therefore, preparatory to devising studies of prophylaxis against PNALD, we conducted an evaluation of all NICU patients who received PN for $\geqslant$14 day, assessing their likelihood of developing PNALD.

Methods: We performed an historic cohort analysis of all neonates in the Intermountain Healthcare system, receiving PN for 14 days or more during their stay, with dates of birth between 1 January, 2002 and 30 June, 2006.

Results: During the 4½-year period, 9861 neonates were cared for in the Intermountain Healthcare NICUs. Of these, 9547 (96.8%) survived for at least 28 days, and of these 6543 (68.5%) received PN. Twenty-one percent (1366 patients) of those receiving PN, received it for $\geqslant$14 days. PNALD was ascertained in this group by a direct bilirubin $\geqslant$2.0 mg/dl. Neonates receiving PN for 14–28 days had a 14% incidence of PNALD, those receiving PN for 29–56 days had a 43% incidence, those receiving PN for 57–100 days had a 72% incidence and those receiving PN for >100 days had a 85% incidence. Groups of patients identifiable on the first day of life as having the highest risk of developing PNALD were birth weight <500 g (odds ratio (OR), 30.7), birth weight 500–749 g (OR, 13.1), gastrochisis (OR, 20.3) and jejunal atresia (OR, 24.0). Among 357 patients who developed PNALD, the highest direct bilirubin concentrations correlated with the highest serum alkaline phosphatase and transaminase concentrations. Deaths after 28 days were much more common in those with the highest direct bilirubin and transaminase concentrations (P<0.0001).

Conclusions: In the first days of life, certain NICU patients can be identified as being at very high risk for developing PNALD. These are patients <750 g birth weight, those with gastrochisis and those with jejunal atresia. We speculate that these groups would be reasonable subjects for including in a PNALD prophylaxis trial, testing new preventative strategies such as Omegaven usage.
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Introduction

Parenteral nutrition (PN) is an integral aspect of neonatal intensive care, and can be life saving for critically ill neonates who are unable to receive adequate nourishment enterally.[1,2] However, PN can lead to the untoward outcome of PN-associated liver disease (PNALD), particularly when it is administered for many weeks.[3,4]

Reducing the incidence or severity of PNALD would be an advance in neonatal intensive care. However, to date, studies testing prophylactic strategies have not identified a consistently successful method, other than discontinuing the PN, which frequently is not a feasible option. Those studies included prophylactic administration of taurosusodeoxycholic acid,[5] cholecystokinin-octapeptide,[6,7] taurine,[8] phenobarbitol[9] and removing copper and manganese from the PN.[10,11]

One problem inherent in any prophylactic strategy in the NICU is accurately predicting which neonates are at highest risk for developing the adverse outcome, so that high-risk patients can be eligible for study while low-risk patients can be excluded. Indeed, in the first days of life, when a prophylactic treatment to prevent PNALD might be started, it is not clear how to identify the neonates receiving PN who are at highest risk of developing PNALD. One problem in devising risk-assessment tools for PNALD is that in any given NICU, PNALD is rare. Therefore, for a series of patients to be sufficiently large to devise a meaningful risk assessment, single institutions must report their incidence of PNALD over decades.

However, changes over time, in PN constituents, concomitant medications, equipment and other aspects of NICU care, can confound the interpretation of long-term chronological reports.

We sought to assess the occurrence of PNALD in a contemporary group of neonates cared for within Intermountain Healthcare, a large healthcare delivery system in the western United States. We studied all neonates in this system with dates of birth from 1 January, 2002 through 30 June, 2006, who received at least 14 days of PN. We hypothesized that this information would help us focus new experimental strategies for preventing PNALD, such as Omegaven use,[12–16] on patients at highest risk for developing PNALD.

Methods

Data were collected as a deidentified limited data set from archived Intermountain Healthcare records. The information collected was limited to the information displayed in the tables and figures of this report. Data were obtained for patients admitted to the NICU at McKay-Dee Hospital (Ogden, UT, USA), LDS Hospital (Salt Lake City, UT, USA), Primary Children's Medical Center (Salt Lake City, UT, USA), and Utah Valley Regional Medical Center (Provo, UT, USA) with a date of birth from 1 January, 2002 through 30 June, 2006. We studied only patients who received 14 days or more of PN and who survived at least 28 days or were discharged home before 28 days. PN was defined as an amino acid containing, multivitamin containing, intravenous solution ordered on the Intermountain Healthcare 'Parenteral Nutrition Program' and prepared by the hospital pharmacy PN team.

The program used for data collection was a modified subsystem of 'clinical workstation'. 3M Company (Minneapolis, MN, USA) approved the structure and definitions of all data points for use within the program. Data were collected from the electronic medical record, case mix, pharmacy and laboratory systems. Trained and designated clinical personnel enter and access data. Medical records (paper charts) were reviewed for all patients who received PN for 14 days or more and subsequently died. Evidence of PNALD was sought from autopsy findings[17,18] and from death summaries. In each death of a patient where a direct bilirubin >2.0 mg/dl was found, we also determined whether the direct bilirubin was increasing or decreasing in the weeks immediately preceding death. The Intermountain Healthcare Institutional Review Board approved the study.

Descriptive statistics were calculated using Statit (Corvallis, OR, USA). A logistic regression model was developed in Statit to calculate ORs. It calculates maximum likelihood fitting of regression where the response is a binomial variable, using the logistic (logit) model. Parameter estimates are presented on the anti-logarithmic scale. Proportions were compared between groups using χ^2 tests with Yate's continuity correction or, when counts were small, Fisher's exact test. Two-tailed tests were used, and for all tests α was set at 0.05.

Results

Between 1 January, 2002 and 30 June, 2006, 9861 neonates were cared for in four Intermountain Healthcare NICUs. Of these, 9547 (96.8%) were alive 28 days after birth or were discharged home before that day. Of these 9547 'survivors', 6543 (68.5%) received PN. The number of days PN was administered to each of these patients is shown in Figure 1. Seventy-nine percent of those receiving PN received it for 13 days or fewer; conversely, 21% (1366 patients) of those receiving PN received it for 14 days or more. These 1366 patients, shown in Figure 1b, are the basis of this report. These patients generally received intravenous lipid preparation up to 3 g/kg/day as part of the PN. One hundred and forty-seven patients (2.2 %) received PN for 50 days or more and 14 patients (0.2%) received PN for 100 days or more. One received PN for 179 days.

Table 1 categorizes the 1366 patients who received PN for $\geqslant 14$ days according to their birth weight and whether they had surgery or extracorporeal membrane oxygenation. The majority (75%, 1022/1366) of those who received PN for $\geqslant 14$ days were neonates $\geqslant 750$ g who did not have surgery. However, the groups with the highest probability of receiving PN for >28 days were neonates <750 g (66%; 111/167), those with necrotizing enterocolitis (NEC) who underwent surgery (75%; 9/12), those with omphalocoele (54%; 6/11), jejunal atresia (59%; 13/22) or treated with extracorporeal membrane oxygenation (67%; 20/30). The groups with the highest probability of receiving PN for over 8 weeks (56 days) were those with NEC treated with laparotory (33%; 3/9), those with jejunal atresia (32%; 7/22), preterm infants <750 g birth weightt (19%; 32/167) and those with gastrochisis (15%; 13/86). We found no effect of gender or race on likelihood of developing PNALD.

The great majority (93%) of the neonates who received PN for $\geqslant 14$ days had multiple direct bilirubin values recorded. Twenty-eight percent (357/1266) had one or more direct bilirubin measurements $\geqslant 2.0$ mg/dl. Table 2 shows the percentage of patients who developed a direct bilirubin $\geqslant 2.0$ mg/dl as related to the categories in Table 1. As the number of days on PN increased, the incidence of a direct bilirubin $\geqslant 2.0$ mg/dl increased. When all patient groups were considered together, those who received PN for 14–28 days had a 14% incidence (125/894) of developing a high direct bilirubin, those receiving PN for 29–56 days had a 43% incidence (164/382), those receiving PN for 57–100 days had a 72% incidence (68/94) and those receiving PN for >100 days had a 86% incidence (12/14). The duration of the direct hyperbilirubinemia (Figure 2) ranged from fewer than 10 days to more than 440 days.

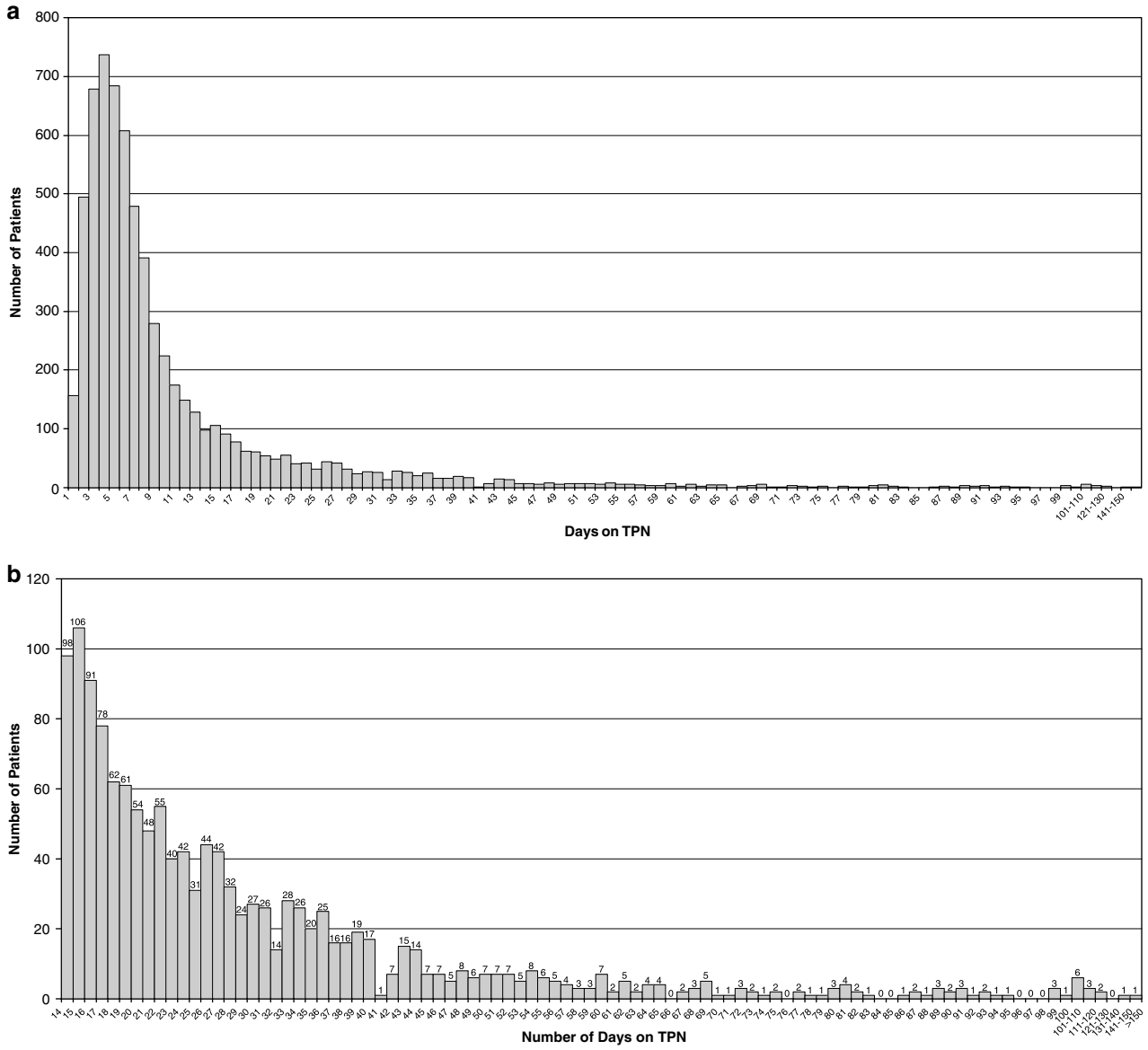

Figure 1 Number of days PN was administered. (**a**) The number of days is shown for each of 6543 NICU patients received PN. (**b**) More details of the 1366 patients who received PN for 14 days or more. Only patients who survived at least 28 days are included.

Outcomes of the 1366 neonates who received PN for $\geqslant$14 days and survived at least 28 days are shown in Table 3. Patient groups with the highest direct bilirubin concentrations also had the highest alkaline phosphatase, the highest serum glutamic pyruvic transaminase and the highest serum glutamic oxaloacetic transaminase values recorded. Patients who received PN for $\geqslant$14 days but whose direct bilirubin never exceeded 0.9 mg/dl had a mortality rate of 3%. However, those whose direct bilirubin was $\geqslant$1.0 mg/dl had a 9% mortality rate ($P<0.00001$). Those with a direct bilirubin $\geqslant$11 mg/dl had a 26% mortality rate ($P<0.00001$ vs those with a bilirubin $<$11 mg/dl).

Seventy-one patients received PN for $\geqslant$14 days and subsequently died 28 days later. We sought to determine whether any of these 71 had PNALD, and if so whether it was improving or progressing (worsening) immediately before their death. Thirty patients who died had no evidence of PNALD, as they had no direct bilirubin measurement in excess of 2.0 mg/dl (Table 3). The remaining 41 all had a direct bilirubin exceeding 2.0 mg/dl. None of these 41 had PNALD listed as the sole cause of death in the autopsy report or death summary. However, 32 of the 41 (73%) had PNALD identified as an active, progressing problem at the time of death.

Estimates of the odds of developing PNALD, depending on birth weight and surgical condition, are shown in Table 4. The highest odds occurred among those weighing $<$750 g at birth, those who developed NEC and subsequently received surgery (either

Table 1 Classification of 1366 NICU patients who received PN for 14 days or more

	N[a]	*PN for 14–28 days*	*PN for 29–56 days*	*PN for 57–100 days*	*PN for >100 days*
Neonates having no surgery[b]					
>1500 g	466	365	83	17	1
1000–1499 g	340	249	77	10	4
750–999 g	216	126	77	11	2
500–749 g	150	53	68	27	2
<500 g	17	3	11	3	0
Neonates having surgery or ECMO					
NEC with laparotomy	9	3	3	3	0
NEC with surgical drain[c]	3	0	3	0	0
Gastrochisis	86	49	24	10	3
Omphalocele	11	5	5	1	0
Diaphragmatic hernia	39	21	15	3	0
Jejunal atresia	22	10	6	5	2
ECMO	30	10	16	4	0

Abbreviations: ECMO, extracorporeal membrane oxygenation; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PN, parenteral nutrition.
Only patients who survived at least 28 days after birth are included.
[a]Number of patients in this category who were alive 28 days after birth.
[b]Excluding patent ductus arteriosus ligation, inguinal hernia repair, retinopathy of prematurity surgery, and other 'minor' surgeries.
[c]No laparotomy.

Table 2 Percent of patients receiving PN for >14 days who developed a direct bilirubin >2.0 mg/dl

	PN for 14–28 days (%)	*PN for 29–56 days (%)*	*PN for 57–100 days (%)*	*PN for >100 days (%)*
Neonates having no surgery[a]				
⩾1500 g	15	46	71	100
1000–1499 g	8	40	60	50
750–999 g	12	43	64	100
500–749 g	21	35	67	100
<500 g	—	55	100	—
Neonates having surgery or ecmo				
NEC with laparotomy	33	33	100	—
NEC with surgical drain[b]	—	67	—	—
Gastrochisis	18	63	100	100
Omphalocele	20	60	100	—
Diaphragmatic hernia	14	33	33	—
Jejunal atresia	33	67	100	100
ECMO	20	25	25	—

Abbreviations: ECMO, extracorporeal membrane oxygenation; NEC, necrotizing enterocolitis; PN, parenteral nutrition.
The percent of patients who developed a direct bilirubin concentration ⩾2.0 mg/dl is shown, as related to birth weight, surgical condition and days PN was administered. Data are given only for NICU patients who survived at least 28 days after birth.
[a]Excluding patent ductus arteriosus ligation, inguinal hernia repair, retinopathy of prematurity surgery, and other 'minor' surgeries.
[b]No laparotomy.

laparotomy or drain) and those with gastrochisis or jejunal atresia. When examined from the standpoint of which groups of patients, identifiable on the first day of life, were most likely to develop PNALD if they survived for >28 days, the following risks were calculated: (1) patients weighting <750 g birth weight had a 39% likelihood of developing PNALD, (2) patients with gastrochisis had a 43% likelihood of developing PNALD and (3) patients with jejunal atresia had a 64% likelihood of developing PNALD.

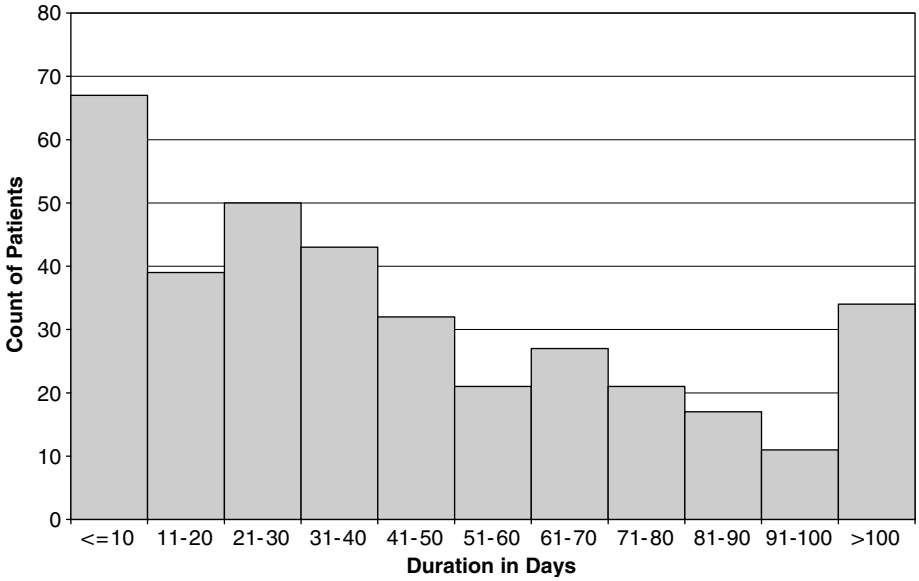

Figure 2 Duration of the direct hyperbilirubinemia. The number of days is shown between the first detection of an elevated direct bilirubin (>2.0 mg/dl) and the decrease to <1.0 mg/dl. Included are NICU patients who were treated for >14 days with PN and survived at least 28 days after birth.

Table 3 Survival rates of NICU patients who received PN for ⩾14 days, as related to their highest recorded direct bilirubin concentration

Highest direct bilirubin recorded (mg/dl)	N	*Highest alkaline phosphatase recorded*[a] *(U/l)*	*Highest SGPT recorded*[a] *(U/l)*	*Highest SGOT recorded*[a] *(U/l)*	*Highest GGTP recorded*[a] *(U/l)*	*Died after 28 days (N and %)*	*Those who died where PNALD was a problem at the time of death*[b]
<1.0	586	397±264	87±77	43±69	111±122	15 (3%)	0/15 (0%)
1.0–1.9	274	441±243	145±379	52±88	154±169	15 (6%)	0/15 (0%)
2.0–3.9	156	564±560	119±107	77±119	151±141	15 (10%)	6/15 (40%)
4.0–6.9	147	621±288	252±330	143±138	192±202	11 (8%)	8/11 (73%)
7.0–10.9	60	649±226	384±349	224±309	209±230	4 (7%)	3/4 (75%)
11.0–15.0	22	741±362	783±883	385±534	287±274	6 (27%)	2/6 (33%)
⩾15.0	20	809±418	1916±298	523±587	127±152	5 (25%)	3/5 (60%)

Abbreviations: GGTP, gamma-glutamyl-transpeptidase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; PNALD, parenteral nutrition-associated liver disease.
The highest direct bilirubin recorded corresponded with the highest alkaline phosphatase, SGPT, SGOT and GGPT recorded.
[a]Mean±s.d.
[b]Number (and percentage) of deaths where PNALD was listed as an active problem at the time of death; information obtained from autopsy reports and/or death summaries.

Discussion

When a neonate receives PN for many weeks, PNALD commonly develops. Kobuta *et al.*[19] reported that, in their experience all neonates receiving PN for over 8 weeks develop PNALD; defining PNALD as a direct bilirubin ⩾2.0 mg/dl. In the present study we observed a slightly lower incidence, of 76%, among 108 neonates who received PN for 8 weeks or more.

PNALD can be a lethal complication. Wales *et al.*[20] reported that PNALD has a disease-associated mortality rate of 3–13%. Various other reports indicate that the mortality rate of neonates with PNALD approaches 100%, if they are unable to be weaned off PN or if they fail to receive a liver/small bowel transplant.[17,18] We observed that among 71 neonates who received PN for ⩾14 days and subsequently had a late (>28 days) death PNALD was generally a problem and remained so at the time of death. However, it is not clear to what extent the PNALD actually contributed to the mortality. Certainly, the incidence of late death was higher among those with the highest direct bilirubin concentrations.

It has been postulated that PNALD is due, at least in part, to the lipid portion of PN, and that a lipid product high in omega-3 fatty

Table 4 Logistic regression analysis, deriving odds ratios for developing PNALD, using the birth weight categories and surgical conditions as independent variables

Independent variable	*Odds ratio estimate*	*95% confidence interval*	P-*value*
Birth weight 1000–1499 g	2.8	2.1–3.7	0.000
Birth weight 750–999 g	8.2	6.0–11.2	0.000
Birth weight 500–749 g	13.1	9.4–18.3	0.000
Birth weight <500 g	30.7	9.5–56.2	0.000
NEC with laparotomy	11.7	10.0–13.6	0.001
NEC with drain	23.6	5.3–105.0	0.000
Gastrochisis	20.3	4.9–83.9	0.000
Omphalocele	3.1	1.9–4.9	0.043
Diaphragmatic hernia	4.0	1.1–15.0	0.002
Jejunal atresia	24.0	9.0–64.1	0.000
ECMO	4.3	1.5–12.5	0.003

Abbreviations: ECMO, extracorporeal membrane oxygenation; NEC, necrotizing enterocolitis; PNALD, parenteral nutrition-associated liver disease.

acids produced from fish oil rather than soybean oil would lead to a lower incidence.[14,15,21] One such product, Omegaven (Fresenius Kabi AG, Bad Homburg, Germany), has been administered to two neonatal patients with PNALD, in a recent report, with excellent success in reversing the process.[14] Gura *et al.*[14] in reporting this encouraging experience called for randomized controlled trials testing lipid preparations that are high in omega-3 vs standard lipid preparations, as a means of preventing PNALD. We agree with this suggestion, adding that some of these prevention trials should focus on NICU patients who are at a very high risk of developing PNALD. In this way, neonates eligible for the study would be those with the most to gain from participating, whereas those with the least to gain would be excluded and therefore not be exposed to any potentially harmful effects of the test preparation.

It is challenging to predict, on the first day of life, which NICU patients will go on to develop PNALD. Nevertheless, attempting to identify these high-risk patients prospectively would be very useful. Our present data suggest that groups at highest risk are those born weighing <750 g and those with gastrochisis or jejunal atresia. Certainly, neonates with a variety of surgical conditions including midgut volvulus are at risk for developing PNALD, but perhaps not quite at as high a risk as those in the three groups mentioned.

Certain neonatal patients, not identifiable on the first day of life might also be good candidates for studying fish oil-based intravenous emulsions later during their hospital course. These groups would include patients who develop surgical NEC and are left with short remnant bowel length, because their odds of developing PNALD are very high.[20] On the basis of the findings of the present study, we suggest that randomized trials to evaluate Omegaven or other potential means of preventing PNALD, where enrollment is to begin in the first days of life, should seek to enroll patients <750 g birth weight, or with gastrochisis or jejunal atresia. It appears that these groups are the most likely identifiable on the first day of life, to go on to develop PNALD. Therefore these patients are likely to accrue the benefits of successful PNALD prevention trials.

Abbreviations

NICU, neonatal intensive care unit; PN, parenteral nutrition; PNALD, parenteral nutrition-associated liver disease.

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