# Breast Milk Is Better Than Formula Milk in Preventing Parenteral Nutrition–Associated Liver Disease in Infants Receiving Prolonged Parenteral Nutrition

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## ABSTRACT

**Background and Aim:** Breast milk has been shown to be associated with greater success with regard to weaning children with intestinal failure off parenteral nutrition (PN). There are only a few studies investigating the role of breast milk in decreasing PN-associated liver disease (PNALD). The aim of our study was to determine whether breast milk is better than formula milk in preventing PNALD in infants receiving PN for >4 weeks.

**Methods:** We conducted a retrospective analysis of newborns requiring prolonged parenteral nutrition. We divided the sample into 3 different groups (exclusive breast-feeding, exclusive formula-feeding, and mixed feeding. We compared baseline characteristics, feeding profiles and liver function tests, and liver enzymes among the 3 groups.

**Results:** Among infants receiving PN for >4 weeks, we found that infants who were fed only breast milk were significantly less likely to develop PNALD (34.6%) compared with those who were fed only formula milk (72.7%; $P = 0.008$). The mean maximum conjugated bilirubin ($P = 0.03$) and the mean maximum aspartate aminotransferase were significantly lower in the breast-fed group ($P = 0.04$) compared with the formula-fed group. Among the mixed-feeding group, infants who received a higher percentage of breast milk showed a significant negative correlation with the mean maximum conjugated bilirubin. (Pearson correlation −0.517, $P = 0.027$). The mean number of days receiving PN and the average daily lipid intake in the 2 groups was not significantly different.

**Conclusions:** As a modality for early enteral nutrition, breast milk is protective against the development of PNALD in infants receiving PN for >4 weeks.


**Key Words:** alanine aminotransferase, aspartate aminotransferase, breast milk, enteral nutrition, parenteral nutrition, parenteral nutrition–associated liver disease

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Parenteral nutrition (PN) is an important component of intestinal rehabilitation. The endpoint of intestinal rehabilitation is to make the transition from PN to full enteral nutrition (EN); however, intestinal rehabilitation runs the risk of PN-associated liver disease (PNALD), which is reported in 40% to 60% of patients receiving prolonged PN (1,2). PNALD can have a wide spectrum of signs and symptoms, ranging from abnormal liver function tests and liver enzymes to cirrhosis and liver failure (3,4). Liver failure is reported in 3% to 19% of these patients (4–6). Factors involved in the pathogenesis of PNALD include low birth weight, prematurity, duration of PN, sepsis, and bacterial overgrowth; however, the exact pathogenesis of this condition is not fully understood. The treatment of this complication is a combined liver and intestinal transplant. The morbidity and mortality associated with this procedure is high. Hence, the prevention of PNALD has become an important part of managing these children.

Early EN, fish oil–based intralipids, intravenous lipid minimization, limiting the glucose infusion rate, addition of carnitine or glutamine, and preventing sepsis (antibiotic and ethanol lock therapy) are some of the modalities that have been tried to prevent PNALD (7,8). Early enteral feeding has been shown to decrease incidence of PNALD (9–11). The nutrients in the feedings (especially short-chain fatty acids) are believed to stimulate the colonic mucosa and lead to intestinal adaptation. This further helps in achieving enteral autonomy, which is the goal of intestinal rehabilitation. There are conflicting reports on whether the composition of the enteral feeds affects the development of PNALD. A previous study has suggested that breast milk or an amino acid–based formula can decrease the risk of PNALD by improving intestinal adaptation (3); however, in another study involving newborns exposed to prolonged PN found that administration of a particular composition of enteral feeds (breast milk or formula milk) was not predictive of PNALD (2). In summarizing proceedings of a recent symposium on intestinal rehabilitation and transplantation, Mazariegos et al (8) concluded that breast milk is a preferred modality of early EN. Breast milk is believed to lead to intestinal adaptation and shorter duration of PN.

There are only a few studies investigating the effect of different modalities of early EN on the development of PNALD. Hence, we decided to investigate this cause–effect relation. The aim of our study was to determine whether breast milk is better than formula milk in preventing PNALD in infants receiving PN for >4 weeks.

## METHODS

We conducted a retrospective chart review in the neonatal intensive care unit of a free-standing children's hospital in South Florida. The primary analysis included neonatal intensive care unit admissions from January 2010 to December 2011. Among the above, only the infants who received PN for >4 weeks were included in the study (12). A further subanalysis of the data using

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the infants who received PN for >2 weeks and the infants who received PN for >6 weeks was performed.

In our study, a total of 79 infants received PN for >2 weeks, 67 infants received PN for >4 weeks, and 40 infants received PN for >6 weeks. We then recorded the gestational age, birth weight, length, diagnosis, and episodes of sepsis (positive blood, urine, or cerebrospinal fluid [CSF] cultures). We recorded nutritional data from the nutritional flow sheets. These data included parameters such as the number of days while receiving PN, the day of starting enteral feeds while receiving PN, the number of days nil per os, the composition of PN (average daily intake of intralipids, amino acids, and dextrose), and the type of early enteral feeds. Based on these data, infants were then divided into 3 groups: breast-feeding (BF), mixed-feeding (MF), and formula-feeding (FF). Weekly liver function tests and liver enzymes for all of the patients during the period that they were receiving PN were recorded. The highest conjugated bilirubin, highest alanine aminotransferase enzyme (ALT), highest aspartate aminotransferase enzyme (AST), highest AST:ALT ratio, highest alkaline phosphatase (ALP), and lowest albumin were noted for each case. We also noted the highest C-reactive protein (CRP) value.

We defined episodes of feed intolerance as either vomiting >3 times per day or diarrhea with a stool output of >40 mL · $kg^{-1}$ · $day^{-1}$ and an acidic stool pH (<5.5) or the presence of reducing substances or presence of macroscopic blood in stools and gastric residuals with ≥50% of the previous feed volume (13,14).

In the cases of MFs (BF and FF), we calculated the percentage of days on a single modality of feeding as shown below:

$$\text{Percentage of days on BF} = \text{total number of days with BF/total number of days the infant received EN while receiving PN} \times 100$$

The primary outcome measured was the development of PNALD. PNALD was defined as the presence of at least 2 of the following 3 parameters: conjugated bilirubin >2 mg/dL (normal 0.05–0.2 mg/dL), AST and ALT >65 U/L (normal 5–40 U/L) for >2 weeks; and the absence of an alternative explanation for abnormal liver function tests (2,12,15). The week of onset of PNALD was also noted. We also compared the mean maximums of direct bilirubin, ALT, AST, ALP, and the mean minimum albumin for the 2 groups.

The data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, IL). We compared categorical data using the $\chi^2$ test or the Fisher exact test. We compared numerical data using the *t* test. We used the Pearson correlation analysis for the subanalysis of the MF group. A Kaplan-Meier curve evaluating the time to cholestasis based on the type of feeds was constructed. In all of the above, we considered *P* values <0.05 as being significant.

## RESULTS

Of the 67 newborns included in the primary analysis, 26 were in the BF group, 19 in the MF group, and 22 in the FF group. The mean number of days while receiving PN in the 3 groups combined was 55.82 days (range 28–340 days). The baseline characteristics among the 3 groups are shown in Table 1. We found no significant difference in the sex, gestational age, and birth weight among the groups. In our study, the newborns received PN for a variety of diagnoses. The majority (55.2% [37/67]) of the newborns had necrotizing enterocolitis. Other diagnoses included intestinal atresia, gastroschisis, tracheoesophageal fistula, intestinal pseudo obstruction, congenital diaphragmatic hernia, and extremely sick newborns having congenital heart defects or persistent pulmonary hypertension of the newborn. We divided the infants into 4 groups based on the diagnosis: specifically, necrotizing enterocolitis, dysmotility (eg, Hirschsprung disease, pseudoobstruction), congenital defects of the gastrointestinal tract (eg, jejunal atresia, tracheoesophageal fistula, congenital diaphragmatic hernia), and miscellaneous serious medical conditions (eg, persistent pulmonary hypertension, congenital heart defects) that caused the enteral feeds to be stopped for a prolonged duration. There was no significant difference in the proportion of infants in each of the above groups among the BF, FF, and MF groups (Table 1). There was a higher proportion of infants who underwent surgery for 1 of the above etiologies in the FF group; however, the difference was not statistically significant (BF 15.4% vs FF 31.8%; $P = 0.302$).

All of the infants in our study received soy-based intravenous lipids while receiving PN. The summary of the feeding characteristics for the 3 groups is shown in Table 2. There was no significant difference in the number of days while receiving PN among the 3 groups. There was also no significant difference in the number of episodes of feeding intolerance among the 3 groups. The infants in the BF group started receiving EN significantly earlier compared with the children in the FF group by approximately 5.8 days ($P = 0.03$). There was no difference in the number of days of being on nil per os status among the 3 groups. There was no significant difference in the average daily intravenous lipid intake between the BF (2.46 g · $kg^{-1}$ · $day^{-1}$, 95% confidence interval [CI] 2.32–2.57 g · $kg^{-1}$ · $day^{-1}$) and the FF group (2.41 g · $kg^{-1}$ · $day^{-1}$, 95% CI 2.25–2.57 g · $kg^{-1}$ · $day^{-1}$; $P = 0.634$); however, the average daily dextrose intake was significantly higher in the BF group (14.5 mg · $kg^{-1}$ · $min^{-1}$, 95% CI 13.9–15.1 mg · $kg^{-1}$ · $min^{-1}$) compared with

TABLE 1. Comparison of baseline characteristics among the 3 groups

| Characteristics | BF, mean (95% CI) | MF, mean (95% CI) | FF, mean (95% CI) | *P* (BF vs FF)/ (MF vs FF) |
|---|---|---|---|---|
| Sex (M:F) | 14:12 | 13:6 | 13:9 | 0.715/0.54 |
| Birth weight, g | 1371.1 (1106–1636) | 1266 (891–1641) | 1652.8 (1150–2155) | 0.31/0.21 |
| Gestational age, wk | 29.8 (28.1–31.5) | 28.4 (25.9–30.9) | 30.1 (27.8–32.5) | 0.82/0.07 |
| Diagnosis group 1 (NEC) (%) | 14 (38.5) | 13 (68.4) | 10 (45.5) | 0.77/0.25 |
| Diagnosis group 2 (congenital disorders) (%) | 3 (11.5) | 1 (5.3) | 2 (9.1) | 0.78/0.64 |
| Diagnosis group 3 (dysmotility) (%) | 0 (0) | 2 (10.6) | 1 (4.5) | 0.93/0.90 |
| Diagnosis group 4 (miscellaneous) (%) | 9 (34.6) | 3 (15.7) | 9 (40.9) | 0.84/0.41 |
| Surgery (%) | 4 (15.4) | 9 (47.3) | 7 (31.8) | 0.302/0.31 |
| Total | 26 | 19 | 22 | |

BF = breast-feeding group; CI = confidence interval; FF = formula-feeding group; MF = mixed-feeding group; NEC = necrotizing enterocolitis.

TABLE 2. Comparison of feeding characteristics among the 3 groups

| Characteristics | BF, mean (95% CI) | MF, mean (95% CI) | FF, mean (95% CI) | *P* (BF vs FF)/(MF vs FF) |
|---|---|---|---|---|
| Feed intolerance episodes | 1.23 (0.67–1.79) | 2.05 (1.15–2.95) | 1.08 (0.64–1.5) | 0.665/0.114 |
| Day of onset enteral nutrition | 13.2 (14.6–25.2) | 16.4 (11.6–21.1) | 19.9 (14.05–27.8) | 0.04/0.33 |
| PN, days | 45.4 (38.1–52.8) | 77.7 (44.3–111.1) | 49.3 (41.8–56.8) | 0.45/0.09 |
| Days NPO | 22.4 (18.4–26.4) | 31.1 (22.4–39.8) | 28.1 (22.2–34) | 0.77/0.554 |
| Average daily lipids, $g \cdot kg^{-1} \cdot day^{-1}$ | 2.46 (2.32–2.57) | 2.5 (2.3–2.7) | 2.41 (2.25–2.57) | 0.63/0.65 |
| Average daily dextrose, $mg \cdot kg^{-1} \cdot min^{-1}$ | 14.5 (13.9–15.1) | 14.3 (13.6–15.0) | 13.4 (12.7–14.1) | 0.02/0.06 |
| Average daily amino acid, $g \cdot kg^{-1} \cdot day^{-1}$ | 3.3 (3.2–3.4) | 3.2 (3.02–3.38) | 3 (2.8–3.2) | 0.004/0.07 |
| Total | 26 | 19 | 22 | |

BF = breast-feeding group; CI = confidence interval; FF = formula-feeding group; MF = mixed-feeding group; NPO = nil per os; PN = enteral nutrition.

that of the FF groups (13.4 $mg \cdot kg^{-1} \cdot min^{-1}$, 95% CI 12.7–14.1 $mg \cdot kg^{-1} \cdot min^{-1}$; $P = 0.017$). The average daily amino acid intake was significantly higher in the BF group (3.3 $g \cdot kg^{-1} \cdot day^{-1}$, 95% CI 3.2–3.4 $g \cdot kg^{-1} \cdot day^{-1}$) compared with the FF group (3.0 $g \cdot kg^{-1} \cdot day^{-1}$, 95% CI 2.8–3.2 $g \cdot kg^{-1} \cdot day^{-1}$; $P = 0.004$). There was no significant difference in the average daily intake of intravenous lipid, dextrose, and amino acids between the MF and FF groups. Similarly, there was no significant difference in the average daily intake of intravenous lipids, dextrose, and amino acids between the MF and the BF groups. We performed binary logistic regression to study the effects of delayed onset of enteral feeds on the development of PNALD. We used the development of PNALD as the dependent binary variable and the type of feeds and the days of onset of the enteral feeds as the covariate variables. The type of feeds was significantly associated with development of PNALD (Exp. B = 2.021, 95% CI 1.066–3.831; $P = 0.031$), whereas the day of onset of enteral feeds was not significantly associated with the development of PNALD (Exp. B = 1.044, 95% CI 0.972–1.122; $P = 0.240$).

In our study, we found that the prevalence of PNALD among infants in the FF group (72.7%) was significantly higher than among infants in the BF group (34.6%; $P = 0.008$; odds ratio 5.03 [1.46–17.37]; Fig. 1); however, there was no significant difference in the weeks of the onset of PNALD between the 2 groups (5 [95% CI 4.1–5.9] vs 6.8 weeks [95% CI 5.8–7.8], respectively; $P = 0.08$).

The prevalence of PNALD among infants in the MF group (52.7%) was not significantly lower than that for the infants in the FF group (72.7%; $P = 0.19$). Additionally, there was no significant difference in the weeks of onset of PNALD between these 2 groups (5 vs 6.2 weeks, respectively; $P = 0.277$). The newborns that received a higher percentage of breast milk showed a significant negative correlation with the mean maximum conjugated bilirubin ($R = -0.517$; $P = 0.027$) (Fig. 2).

We found that the prevalence of PNALD among infants in the BF group (34.6%) was not significantly lower than that for the infants in the MF group (52.7%; $P = 0.249$). Additionally, there was no significant difference in the weeks of onset of PNALD between these 2 groups (6.2 vs 6.8 weeks, respectively; $P = 0.34$). The mean maximum conjugated bilirubin was significantly higher in the FF group (4.7, 95% CI 3.1–6.3) compared with the BF group (2.6, 95% CI 1.4–3.8; $P = 0.03$) (Table 3). The mean maximum AST was significantly higher in the FF group (186.5, 95% CI 127.3–245.7) compared with that of the BF group (100.2, 95% CI 55.9–135.5; $P = 0.04$; Table 3). There was no significant difference between the mean maximum ALT and mean minimum albumin in the 2 groups; however, we did see a trend toward lower ALT values in the BF group compared with the FF group (Table 3). There was no significant difference in the mean maximum AST:ALT ratio in the 2 groups (BF 5.08 vs FF 5.66, $P = 0.452$). The mean maximum CRP levels were significantly lower in the BF group (3.2, 95% CI

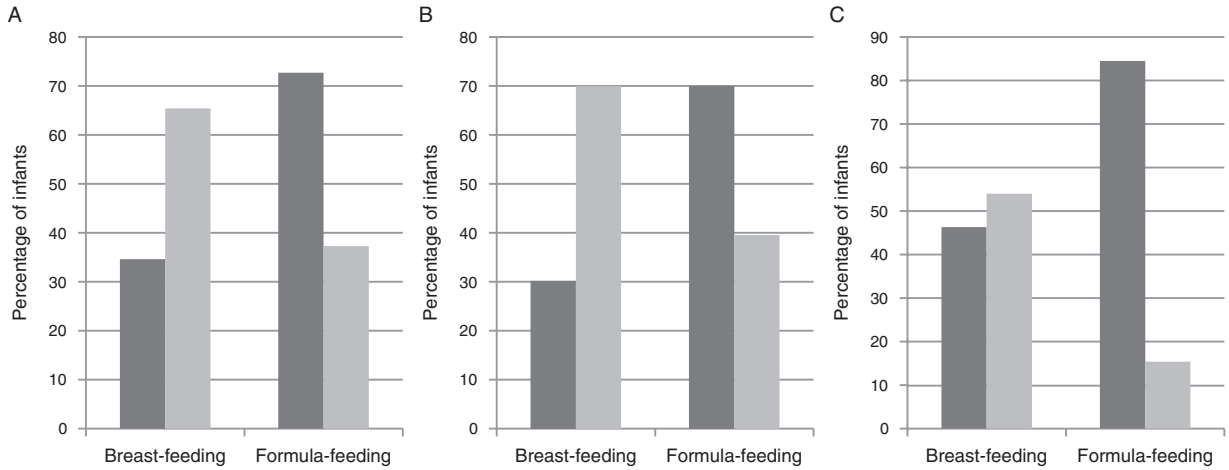


**FIGURE 1.** Proportion of newborns with parenteral nutrition–associated liver disease (PNALD) among the breast-feeding and formula-feeding group at 4 weeks (A), 2 weeks (B), and 6 weeks (C). Bars on the left represent infants with PNALD, whereas bars on the right represent infants without PNALD.

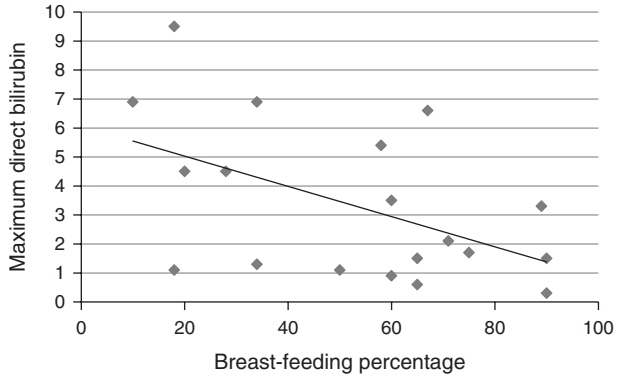


**FIGURE 2.** XY scatter and line of best fit showing the relation between the percentage of breast-feeding days in the mixed-feeding group and the direct bilirubin.

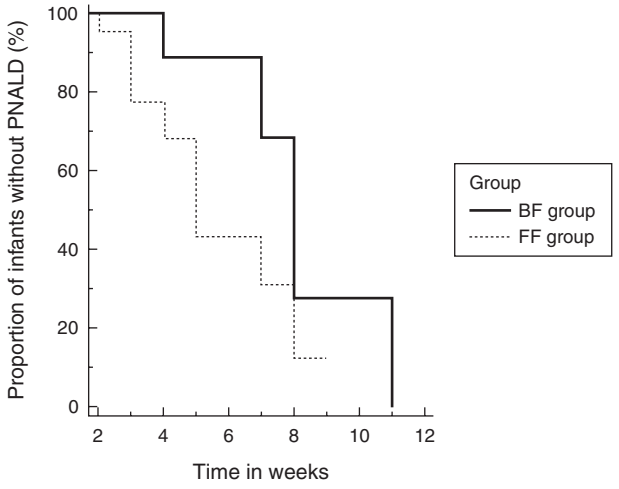


**FIGURE 3.** Kaplan-Meier curve studying the time to cholestasis based on the type of feeds showing that infants in the formula-feeding group reached the primary endpoint (development of PNALD) significantly earlier than infants in the breast-feeding group (hazard ratio 2.46 [95% CI 1.1–5.44]; $P = 0.009$).

0.9–5.5) compared with that of the FF group (8.1, 95% CI 4.9–11.2; $P = 0.01$). There was no difference between the number of episodes of sepsis (positive blood, urine, or CSF cultures) between the BF and the FF groups.

There were no significant differences among the mean maximum bilirubin, mean maximum ALT, mean maximum AST, mean maximum AST:ALT ratio, mean minimum albumin, and mean maximum ALP between the MF and FF groups. Similarly, there were no significant differences among the mean maximum bilirubin, mean maximum ALT, mean maximum AST, mean maximum AST:ALT ratio, mean minimum albumin, and mean maximum CRP between the MF and BF groups (Table 3).

A Kaplan-Meier curve evaluating the time to cholestasis based on the type of feeds is shown in Figure 3. The infants in the BF group reached the primary endpoint (development of PNALD) at a mean of 7.9 weeks (95% CI 6.7–9.0 weeks), whereas infants in the FF group reached the primary endpoint at 5.7 weeks (95% CI 4.7–6.7 weeks). Infants in the FF group reached the primary endpoint significantly earlier than the infants in the BF group (hazard ratio 2.46 [95% CI 1.1–5.44]; $P = 0.009$).

The subanalysis of infants who were receiving PN for >2 weeks revealed that the prevalence of PNALD was significantly lower in the BF group (30%) compared with that of the FF group (70.4%; $P = 0.005$). Of the liver function tests and liver enzymes, the mean maximum conjugated bilirubin ($P = 0.03$) and mean maximum AST ($P = 0.04$) were significantly lower in the BF group compared with those of the FF group (Fig. 1).

On the contrary, in infants who were receiving PN for >6 weeks, there was no significant difference in the prevalence of PNALD between the BF (46.1%) and FF groups (84.6%; $P = 0.097$; Fig. 1). Additionally, there were no significant differences among the mean maximum conjugated bilirubin, mean maximum ALT, mean maximum AST, mean maximum AST:ALT ratio, mean minimum albumin, and mean maximum among the 3 groups.

## DISCUSSION

The results of our study indicate that breast milk is better than formula milk in preventing PNALD in infants receiving PN for >4 weeks, irrespective of the duration of PN. Despite having been exposed to a similar average daily intravenous lipid intake and a higher average daily dextrose and amino acid intake, the prevalence of PNALD in the BF group was significantly lower than that observed in the FF group. Additionally, the infants who received breast milk had significantly less liver damage compared with the infants who received formula milk, as indicated by the significantly lower mean maximum conjugated bilirubin, mean maximum AST,

TABLE 3. Comparison of laboratory parameters among the 3 groups

| Characteristics | BF, mean (95% CI) | MF, mean (95% CI) | FF, mean (95% CI) | *P* (BF vs FF)/(MF vs FF) |
|---|---|---|---|---|
| Direct bilirubin, mg/dL | 2.6 (1.4–3.8) | 3.33 (2.04–4.62) | 4.7 (3.06–6.34) | 0.03/0.17 |
| ALT, U/L | 70.5 (35.1–105.9) | 76.7 (41.6–111.8) | 105.3 (75.1–135.5) | 0.13/0.17 |
| AST, U/L | 100.2 (55.9–144.5) | 122.9 (75.4–170.4) | 186.5 (127.3–245.7) | 0.02/0.09 |
| Albumin, mg/dL | 2.02 (1.88–2.16) | 2 (1.8–2.2) | 1.9 (1.72–2.08) | 0.31/0.46 |
| ALP, U/L | 721.6 (569.6–873.6) | 631.2 (501.2–761.2) | 701.8 (542.5–861.2) | 0.78/0.49 |
| CRP, mg/dL | 3.2 (0.9–5.5) | 6.9 (3.5–10.3) | 8.1 (4.9–11.2) | 0.01/0.59 |
| Episodes of sepsis | 7 (26.9%) | 5 (26.3%) | 7 (31.8%) | 0.71/0.7 |
| LD onset, wk | 6.8 (5.8–7.8) | 6.2 (4.5–7.9) | 5 (4.1–5.9) | 0.08/0.34 |
| Total | 26 | 19 | 22 | |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BF = breast-feeding group; CI = confidence interval; CRP = C-reactive protein; FF = formula-feeding group; LD = liver disease; MF = mixed-feeding group; NPO = nil per os.

and a trend toward a lower mean maximum ALT. There was no significant difference in the other liver function tests. Although abnormalities in liver function tests and liver enzymes are frequently observed in PNALD, the levels of bilirubin, AST, and ALT do not correlate well with the severity of liver histology in PNALD (16–18).

The infants in the FF group started receiving enteral feeds significantly later compared with the BF group. Hence, the benefits of early EN were delayed in the FF group. Using binary logistic regression, we found that the type of feeds was significantly associated with the development of PNALD ($P = 0.031$), whereas day of onset of enteral feeds was not significantly associated with development of PNALD ($P = 0.240$). The mean maximum CRP was significantly lower in the BF group compared with the FF group. While comparing the 2 groups, we did not find any difference in the severity of the primary disease. Although the percentage of infants undergoing surgery for various reasons in the BF group was lower than the percentage of infants undergoing surgery in the FF group, this difference was not significant. The results of our study indicate that breast milk is better than formula milk in preventing PNALD, irrespective of the duration of PN in infants receiving PN >2 and 4 weeks, but not in infants receiving PN for >6 weeks. One of the possible explanations for this finding could be that the benefits of BF are ill-sustained beyond 6 weeks of receiving PN. The number of infants included in the analysis decreased from 79 at 2 weeks to 67 at 4 weeks and 40 at 6 weeks. Hence, the power of the study decreased, and this could represent a type II statistical error.

A previous study had shown that the use of breast milk or amino acid–based formula was associated with a shorter duration of PN and improved intestinal adaptation (3). In our study, the newborns in the BF group had significantly lower prevalence of PNALD, even though the total days of receiving PN were not significantly different between the 2 groups.

The beneficial effects of breast milk can be explained by its ability to decrease intestinal bacterial overgrowth, bacterial translocation, and sepsis (19–24). Endotoxin resulting from bacterial translocation contributes to cholestasis by downregulating the bile acid secretory proteins in the canalicular membrane (25). In our study, there was no significant difference in the prevalence of sepsis (positive blood, urine, or CSF cultures) in the 3 groups; however, the mean maximum CRP was significantly lower in the BF group than that of the FF group. Another hypothesis is that breast milk leads to an increased enterohepatic circulation of bile acids (26,27). An increase in the enterohepatic circulation of bile acids has been shown to stimulate farsenoid X receptor in the liver. This receptor decreases the de novo production of hepatotoxic lipophobic bile acids (28–31).

The retrospective data collection is the chief drawback of our study. At best, it simply generates the hypothesis that breast milk is better than formula milk in preventing PNALD. Further prospective studies are required to confirm the hypothesis. Only 40 infants received PN for >6 weeks. Hence, the study does not have sufficient power to draw conclusions about this subgroup of infants.

In conclusion, the use of breast milk as early EN along with other preventive factors (eg, fish oil–based PN, prevention of sepsis) may help to prevent this life-threatening complication in infants receiving prolonged PN (32). The benefits of breast milk in preventing PNALD may also translate to infants with intestinal failure. Another important question would be to investigate the reason behind the protective properties of breast milk against the development of PNALD. This may further help us to fill the gaps in understanding the pathogenesis of PNALD.

## REFERENCES


1. LaRosa C, Baluarte HJ, Meyers KE, et al. Outcomes in pediatric solid-organ transplantation. *Pediatr Transplant* 2011;15:128–41.
2. Duro D, Mitchell PD, Kalish LA, et al. Risk factors for parenteral nutrition-associated liver disease following surgical therapy for necrotizing enterocolitis: a Glaser Pediatric Research Network Study. *J Pediatr Gastroenterol Nutr* 2011;52:595–600.
3. Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. *J Pediatr* 2001;139:27–33.
4. Glover JJ, Caniano DA, Balint J. Ethical challenges in the care of infants with intestinal failure and lifelong total parenteral nutrition. *Semin Pediatr Surg* 2001;10:230–6.
5. Sondheimer JM, Asturias E, Cadnapaphornchai M. Infection and cholestasis in neonates with intestinal resection and long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr* 1998;27:131–7.
6. Merritt RJ. Cholestasis associated with total parenteral nutrition. *J Pediatr Gastroenterol Nutr* 1986;5:9–22.
7. Venick RS, Callins K. The impact of intravenous fish oil emulsions on pediatric intestinal failure-associated liver disease. *Curr Opin Organ Transplant* 2011;16:306–11.
8. Mazaeiegos GV, Superina R, Rudolph J, et al. Current status of pediatric intestinal failure, rehabilitation, and transplantation: summary of a colloquium. *Transplantation* 2011;92:1173–80.
9. Takahashi M, Sawaguchi S, Okhawa H, et al. Hepatobiliary dysfunction in neonates associated with total parenteral nutrition. *Acta Neonat Jpn* 2011;19:333–41.
10. Drongowski RA, Coran AG. An analysis of factors contributing to the development of total parenteral nutrition-induced cholestasis. *J Parenteral Enteral Nutr* 1989;13:586–9.
11. Rager R, Finegold MJ. Cholestasis in immature newborn infants: is parenteral alimentation responsible? *J Pediatr* 1975;86:264–9.
12. Bishay M, Pichler J, Horn V, et al. Intestinal failure-associated liver disease in surgical infants requiring long-term parenteral nutrition. *J Pediatr Surg* 2012;47:359–62.
13. Vanderhoof JA. Short bowel syndrome and intestinal adaptation. In: Walker WA, Goulet O, Kleinman RE, et al. *Pediatric Gastrointestinal Diseases*. 4th ed. Hamilton, Canada: BC Decker; 2004:747–60.
14. Rojas MA, Lozano JM, Rojas MX, et al. Prophylactic probiotics to prevent death and nosocomial infection in preterm infants. *Pediatrics* 2012;130:e1113–20.
15. Kurvinen A, Nissinen MJ, Anderrson S, et al. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. *J Pediatr Gastroenterol Nutr* 2012;54:803–11.
16. Kaufman SS. Prevention of parenteral nutrition-associated liver disease in children. *Pediatr Transplant* 2002;6:37–42.
17. Dahms BB, Haplin TC. Serial liver biopsies in parenteral nutrition associated liver disease in children: natural history and prognosis. *Gastroenterology* 1981;81:136–44.
18. Sax HC, Talamini MA, Brackett K, et al. Hepatic steatosis in total parenteral nutrition: failure of fatty infiltration to correlate with abnormal serum hepatic enzyme levels. *Surgery* 1984;100:697–704.
19. Rangel SJ, Calkins CM, Cowles RA, et al. Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. *J Pediatr* 2012;47:225–40.
20. Haskel Y, Udassin R, Freund HR, et al. Liquid enteral diets induce bacterial translocation by increasing cecal flora without changing intestinal motility. *J Parenteral Enteral Nutr* 2001;25:60–4.
21. Cole CR, Frem JC, Gewirtz AT, et al. The rate of bloodstream infection is high in infants with short bowel syndrome: relationship with small bowel bacterial overgrowth, enteral feeding, and inflammatory and immune responses. *J Pediatr* 2010;156:941–947.e1.
22. Li J, Gong YM, Wu J, et al. Anti-tumor necrosis factor-alpha monoclonal antibody alleviates parenteral nutrition-associated liver disease in mice. *J Parenteral Enteral Nutr* 2012;36:219–25.
23. Aprahamian CJ, Chen M, Yang Y, et al. Two-hit rat model of short bowel syndrome and sepsis: independent of total parenteral nutrition, short bowel syndrome is proinflammatory and injurious to the liver. *J Pediatr Surg* 2007;42:992–7.

24. Sherman MP. New concepts of microbial translocation in the neonatal intestines: mechanisms and prevention. *Clin Perinatol* 2010;37:565–79.
25. Elfrink MG, Olinga P, Draaisma AL, et al. LPS-induced downregulation of MRP2 and BSEP in human liver due to a posttranscriptional process. *Am J Physiol Gastrointest Liver Physiol* 2004;287:G1008–16.
26. Yamada M, Tazawa Y, Nakagawa M, et al. Alterations of serum bile acid profile in breast-fed infants with prolonged jaundice. *J Pediatr Gastroenterol Nutr* 1985;4:741–5.
27. Abrahamse E, Minekus M, van Aken GA, et al. Development of the digestive system-experimental challenges and approaches of infant lipid digestion. *Food Dig* 2012;3:63–77.
28. Jain AK, Stoll B, Burin DG, et al. Enteral bile acid treatment improves parenteral nutrition-related liver disease and intestinal mucosal atrophy in neonatal pigs. *Am J Physiol Gastrointest Liver Physiol* 2012;302: G218–24.
29. Inagaki T, Choi M, Moschetta A, et al. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab* 2005;2:217–25.
30. Fu L, John LM, Adams SH, et al. Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes. *Endocrinology* 2004;145:2594–603.
31. Modica S, Gadaleta R, Moschetta A, et al. Deciphering the nuclear bile acid receptor FXR paradigm. *Nucl Recept Signal* 2010;8: e005.
32. Fishbein TM, Matsumoto CS. Intestinal replacement therapy: timing and indications for referral of patients to an intestinal rehabilitation and transplant program. *Gastroenterology* 2006;130(2 Suppl 1): S147–51.

## Failure to Thrive

. . . not only the good women (midwives) but also most physicians attribute the source of this disorder to incantation or fascination because they can discover no other manifest causes of it. Some in general call it macies; but to give a more reasonable account of its causes, they may be reduced to the following heads in general: because the patients take little or no nourishment; although they take it in great plenty, yet they dissipate it more abundantly; the combination of both these causes. The existence of the disorder is discovered at first sight. But its causes are more difficult and hidden because to investigate them, the infant's state should be examined . . .*

Jean Astruc (1684–1766), *A General and Complete Treatise on all Diseases incident to Children, from their Birth to the Age of Fifteen with particular Instruction to tender Mothers prudent Midwives and Careful Nurses.* 1746

*Astruc emphasized the inadequacy of the perfunctory, complaint-focused or organ-focused examinations doctors usually made, such as an abdominal examination, for a complaint of stomach pain. He insisted that a careful and complete physical examination of the patient be made. He dismissed superstitious causes of diseases, and championed logical and sequential thought regarding etiology. As in the example above, he analyzed basic mechanisms when considering failure to thrive from malnutrition; either the patient did not eat, or food was malabsorbed, or a combination of both factors were the cause.

—Submitted by Angel R. Colón, MD