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Original article

Cholestasis affects enteral tolerance and prospective weight gain in the NICU☆

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SUMMARY

Background: Intestinal Failure-Associated Liver Disease is characterized by cholestasis and hepatic dysfunction due to parenteral nutrition (PN) therapy. We described key features of cholestatic infants receiving PN to assess overall outcomes in this population at our institution.
Methods: This is a retrospective single center study of 163 neonates grouped into cholestatic (n = 63) and non-cholestatic (n = 100) as defined by peak conjugated bilirubin of ≥2.0 mg/dL or < 0.8 mg/dL, respectively. Univariate and multiple regression models were used to study associations between variables and outcomes of interest.
Results: Lower Apgar scores (4 ± 3 vs. 6 ± 3, p-value = <0.005 at 1 min; 6 ± 2 vs. 7 ± 2, p < 0.005 at 5 min) and lower birth weight (adj β [SE] = 0.62 [0.27], p-value = 0.024) were risk factors for developing cholestasis. Cholestatic infants were more likely to have had gastrointestinal surgery (31 [49%] vs. 15 [15%], p-value <0.005), received PN for a longer duration (40 ± 39 days vs. 11 ± 7 days, p-value <0.005), and started enteral feeds later in life (86 ± 23 days vs. 79 ± 20 days, p-value <0.005) when compared to non-cholestatic infants. Weight percentiles in cholestatic infants were lower both at hospital discharge (14 ± 19 vs. 24 ± 22, p-value <0.005) and at 6 months of age (24 ± 28 vs. 36 ± 31, p-value = 0.05).
Conclusions: Cholestasis in the NICU is a multifactorial process, but it has a long lasting effect on prospective weight gain in infants who receive PN in the NICU. This finding highlights the importance of follow-up for adequate growth and the potential benefit from aggressive nutritional support.

1. Introduction

Parenteral nutrition (PN) is commonly used as a critical life-saving nutritional supplement in the neonatal intensive care unit (NICU) until the immature neonatal gut can tolerate enteral nutrition [1]. Many NICU patients receiving PN have a diagnosis associated with intestinal failure [2], and are therefore unable to tolerate enteral nutrition [3]. Intestinal failure-associated liver disease (IFALD) is a complication of PN therapy that presents with early cholestasis (defined as conjugated bilirubin ≥2.0 mg/dL [4]), progresses to hepatic dysfunction, and sometimes leads to liver transplantation [2,5,6].

Infants who develop cholestasis can progress to cirrhosis within as little as 3–5 months [6]. Cholestasis has been shown to be most severe in low birth weight (BW) and premature patients [7–10]. Clinical studies have shown up to a 50% risk of developing cholestasis in infants with BW of <1000 g [8], and an incidence of approximately 70% in premature infants [11]. Duration of PN is also associated with cholestasis [12], with as high as an 80% risk of cholestasis in patients receiving PN for >60 days [8].

Abbreviations: PN, parenteral nutrition; NICU, neonatal intensive care unit; IFALD, intestinal failure-associated liver disease nutrition-associated liver disease; BW, birth weight; UVa, University of Virginia; GA, gestational age; WHO, World Health Organization; BLCS, blood cultures; SD, standard deviation; SE, standard error; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; INR, International Normalized Ratio; IV, intravenous.

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IFALD is a multi-factorial process, and various strategies have been studied to alleviate PN-associated hepatotoxicity [2]. The best way to improve IFALD is early PN discontinuation [2,13] however, this is often not possible in the NICU population due to gut immaturity and enteral feeding intolerance. Other strategies include use of trophic feeds [14–16], PN cycling [17], use of fish oil based lipids [18–22], and ursodiol therapy [23,24], which have all been shown to independently improve cholestasis and liver function [25].

In this work, we aimed to 1) describe key features of cholestatic versus non-cholestatic neonates receiving PN at our center, 2) investigate variables associated with weight and enteral tolerance in cholestatic neonates, and 3) identify findings that could inform a quality improvement initiative to improve growth and enteral tolerance in our NICU.

2. Methods

2.1. Study population

A retrospective review was performed of the medical records of 163 neonates admitted to our hospital's NICU between 2014 and 2017. Patients were included if they met the following criteria: 1) admission to the NICU, including patients born at an outside hospital who were immediately admitted to our NICU after stabilization; 2) use of PN, defined as receiving total parenteral nutrition for ≥5 consecutive days. We further categorized our patient sample into two groups: 1) non-cholestatic group: peak conjugated bilirubin of <0.8 mg/dL during NICU stay; 2) cholestatic group: peak conjugated bilirubin of ≥2.0 mg/dL during NICU stay. Patients with peak conjugated bilirubin of 0.8–2.0 mg/dL were excluded as these values are sometimes considered cholestatic in some studies and not in others [4]. Patients were excluded if they had 1) received care at an outside hospital before admission to our hospital's NICU (not including patients who were born at an outside hospital and transferred immediately to our NICU), or 2) were transferred to an outside hospital NICU.

Subjects were identified by a search of the clinical data repository at our institute, a locally developed, enterprise-wide data warehouse that contains longitudinal data on over 1.5 million patients [26,27]. The study protocol was approved by our institutional review board (IRB-HSR #20116).

2.2. Data collection and interpretation

Our initial search identified 80 patients as cholestatic and 593 patients as non-cholestatic. After a chart review, 63 cholestatic patients met our inclusion criteria, and 100 non-cholestatic patients were chosen randomly for the non-cholestatic group. Demographic variables (i.e. gestational age, gender), and baseline characteristics (i.e. surgical history, length of NICU stay, inpatient gastroenterology consult) are described in Table 1. Primary gastrointestinal diagnosis was identified by review of patient notes, and included the following: gastroschisis, omphalocele, atresia, malrotation, necrotizing enterocolitis (defined as the presence of both bloody stools and suggestive X-ray findings at our center), congenital diaphragmatic hernia (data not shown). Weight percentiles were reported using Fenton growth curves [28] up to 50 weeks gestation, and Centers for Disease Control (CDC) growth curves [29] beyond 50 weeks gestation. Corrected gestational age (GA) percentiles [28] were reported for premature infants. Six month weight percentile was reported if it was measured between 5 and 7 months of age. Generally, weights are recorded daily at our institution, with exceptions only in the first week of life for <32 week premature babies and for long term patients with a more complex care individualized patient care model. The following definitions were used: 1) age achieving full enteral tolerance: the first day the patient was receiving all nutrition enterally, 2) cycling of PN: any mention of PN cycling in review of daily progress notes throughout the duration of the patient's NICU stay. At our center, PN is cycled when conjugate bilirubin is rising (with >2 g/dL as a minimum) and when there is no advancement of feeds within one week. This is only done for infants who weigh more than 1250 g. Dextrose, protein and lipids are usually cycled over 20 h, initially decreasing the glucose-infusion rate with dextrose-containing fluid for 4 h, and weaning down to eventually running only normal saline at a minimal rate while cycling (i.e. achieving a true cycle phase). All other variables were reported as seen in Table 1.

The following continuous variables were converted to categorical variables for inclusion in our linear regression model analysis. GA was reported as a categorical variable according to the World Health Organization (WHO) definitions [30] of 1) term, ≥37 weeks; 2) late preterm, 32–37 weeks; 3) very preterm, 28–32 weeks; and 4) extremely preterm, <28 weeks. BW was reported as 1) ≥2500 g or 2) <2500 g according to the WHO definition of low BW [31]. Length of small bowel resected was reported as either 1) 0 cm or 2) >0 cm. Total number of positive blood cultures (BLCS) during hospitalization was reported as either 1) 0 or 2) ≥1.

2.3. Statistical analysis

All statistical analyses were performed using R version 3.3.3 [32]. Descriptive statistics were calculated for all variables and were reported as mean ± standard deviation (SD) for continuous variables and "n" (%) for categorical variables. Differences between non-cholestatic and cholestatic groups were calculated using unpaired 2-sample t tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Non-normally distributed variables were log transformed prior to analysis.

We were interested in examining the relationship of the following primary outcomes with cholestasis: 1) 6-month weight percentile and 2) age achieving full enteral tolerance. We performed simple linear regression (Supplementary Table 1) to examine the association of each primary outcome with the other measured variables (reported as β [SE]). In addition, the Pearson correlation coefficient was calculated and reported. We then performed multivariable linear regression (Table 2) with each primary outcome as the dependent variable (reported as Adjβ [SE]). Independent variables included in the model were chosen based on clinical and biological relevance, as seen in Fig. 1.

3. Results

3.1. Patient demographics and characteristics

Cholestatic and non-cholestatic groups were not significantly different for GA (32 ± 6 weeks vs. 33 ± 4 weeks, p-value = 0.33), BW (1.9 ± 1.1 kg vs. 2.0 ± 0.9 kg, p-value = 0.57), or gender (40 [64%] males vs. 58 [58%] males, p-value = 0.59). Cholestatic infants had significantly lower Apgar scores at 1 and 5 min (4 ± 3 vs. 6 ± 3, p-value <0.005; and 6 ± 2 vs. 7 ± 2, p-value <0.005, respectively), and were more likely to have had gastrointestinal surgery (31 [49%] vs. 15 [15%], p-value <0.005).

Cholestatic infants were more likely to have had resections of small bowel (3.1 ± 12 cm vs. 0 ± 0 cm, p-value = 0.04), and less likely to have their entire large bowel (57 [91%] not resected vs. 100 [100%] not resected, p-value <0.005), and/or ileocecal valve (60 [95%] intact ileocecal valve vs. 100 [100%] intact ileocecal valve, p-value = 0.06) resected. Ten patients had small bowel resections, with resection length ranging from 2 to 83 cm, and five patients had

Table 1
Patient, nutrition, cholestasis, and management characteristics of cholestatic and non-cholestatic groups.

	Cholestatic[a] (Mean (SD)/n (%))	Non-Cholestatic[b] (Mean (SD)/n (%))	p-value[c]
Patient Characteristics			
Gestational age (weeks) *(c = 63, nc = 100)*	32 (6)	33 (4)	0.33
Birth weight (grams) *(c = 63, nc = 100)*	1876 (1130)	1971 (883)	0.57
Male gender *(c = 63, nc = 100)*	40 (64%)	58 (58%)	0.59
Apgar score at 1 min *(c = 61, nc = 98)*	4 (3)	6 (3)	<0.005
Apgar score at 5 min *(c = 62, nc = 99)*	6 (2)	7 (2)	<0.005
History of gastrointestinal surgery *(c = 63, nc = 100)*	31 (49%)	15 (15%)	<0.005
Length of small bowel resected (cm) *(c = 10, nc = 0)*	3 (12)	0 (0)	0.04
Length of colon resected: *(c = 63, nc = 100)*			
None	57 (91%)	100 (100%)	
Partial	6 (10%)	0 (0%)	<0.005
Presence of ileocecal valve *(c = 63, nc = 100)*	60 (95%)	100 (100%)	0.06
Total # of positive BLCS during hospitalization *(c = 63, nc = 100)*	0.4 (0.8)	0.1 (0.4)	0.01
NICU length of stay (days) *(c = 63, nc = 100)*	78 (63)	39 (35)	<0.005
Inpatient gastroenterology consult for cholestasis *(c = 63, nc = 100)*	23 (37%)	0 (0%)	<0.005
Gastroenterology follow-up within 2 months of discharge *(c = 57, nc = 98)*	33 (58%)	2 (2%)	<0.005
Growth Characteristics			
Birth weight percentile *(c = 61, nc = 100)*	47 (31)	50 (28)	0.58
4 week weight percentile *(c = 56, nc = 64)*	27 (25)	22 (18)	0.29
8 week weight percentile *(c = 43, nc = 27)*	17 (22)	17 (16)	0.88
Discharge weight percentile *(c = 56, nc = 97)*	14 (19)	24 (22)	<0.005
6 month weight percentile *(c = 47, nc = 60)*	24 (28)	36 (31)	0.05
g/day gained during NICU stay *(c = 61, nc = 100)*	17 (9)	21 (60)	0.48
Bilirubin Values			
Peak conjugated bilirubin (mg/dL) *(c = 62, nc = 98)*	7 (6)	0.5 (0.1)	<0.005
Peak total bilirubin (mg/dL) *(c = 63, nc = 100)*	12 (9)	9 [4	0.01
Liver Biomarkers			
Peak AST (U/L) *(c = 62, nc = 91)*	250 (161)	60 (125)	<0.005
Peak ALT (U/L) *(c = 61, nc = 90)*	133 (106)	30 (52)	<0.005
Peak ALP (U/L) *(c = 63, nc = 99)*	544 (296)	322 (157)	<0.005
Peak INR *(c = 45, nc = 35)*	2 (0.6)	1.5 (0.4)[d]	0.01
Minimum Albumin (g/dL) *(c = 63, nc = 99)*	2 (0.4)	3 (0.5)	<0.005
Nutritional Characteristics			
Use of soy-based lipid *(c = 63, nc = 100)*	62 (98%)	100 (100%)	0.39
Cycling of PN *(c = 63, nc = 100)*	25 (40%)	3 (3%)	<0.005
Use of trophic feeds *(c = 63, nc = 99)*	56 (89%)	75 (76%)	0.06
Ursodiol treatment *(c = 63, nc = 100)*	42 (67%)	0 (0%)	<0.005
Total time on PN (days) *(c = 63, nc = 100)*	40 (39)	11 (7)	<0.005
Age of onset of enteral feeding (days) *(c = 59, nc = 99)*	9 (10)	4 (5)	<0.005

Note: # = Number; BLCS = Blood Cultures; NICU = Neonatal Intensive Care Unit; PN = Parenteral Nutrition; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; ALP = Alkaline Phosphatase; INR = International Normalized Ratio.
[a] Peak Conjugated bilirubin during hospitalization ≥2.0 mg/dL; n = 63.
[b] Peak Conjugated bilirubin during hospitalization <0.8 mg/dL; n = 100.
[c] Calculated using t-test or Chi Square/Fisher's Exact test; the n for each category is stated as c = cholestatic & nc = non-cholestatic.
[d] This value was left to one decimal place as rounding to the nearest whole figure resulted in the mean values in the two groups to look identical.

large bowel resections. Additionally, cholestatic infants received PN for a significantly longer duration (40 ± 39 days vs. 11 ± 7 days, p-value <0.005), and were also significantly more likely to start enteral feeds later in life (9 ± 10 days vs. 4 ± 5 days, p-value <0.005). These patients were receiving PN for a variety of reasons, including intestinal abnormalities such as gastroschisis, critical congenital heart disease, sepsis, and immaturity of the gut secondary to prematurity.

Weight percentiles between the groups did not differ at birth (47 ± 31 vs. 50 ± 28, p-value = 0.58), 4 weeks (27 ± 25 vs. 22 ± 18, p-value = 0.29) or 8 weeks (17 ± 22 vs. 17 ± 16, p-value = 0.88), but were significantly lower at discharge for the cholestatic group (14 ± 19 vs. 24 ± 22, p-value <0.005, n = 47 cholestatic, n = 60 non-cholestatic). This effect persisted through age 6 months (24 ± 28 vs. 36 ± 31, p-value = 0.05). Weight percentiles were available for 97% of patients at birth, 89% at 4 weeks, 68% at 8 weeks, 75% at 6 months, and 89% at discharge. Furthermore, cholestatic infants had significantly longer NICU stays (78 ± 63 days vs. 39 ± 35 days, p-value <0.005). A pediatric gastroenterology consult was obtained for 23 (37%) of the cholestatic infants, and 33 (58%) were seen in the pediatric gastroenterology follow-up clinic. At our center, obtaining a pediatric gastroenterology consultation is at the discretion of the primary physician, and there is no clear pathway through which patients were scheduled for follow up in gastroenterology clinic on discharge.

3.2. Laboratory evaluation of cholestasis and liver function

Cholestatic infants exhibited significantly higher peak conjugated bilirubin (7 ± 6 mg/dL vs. 0.5 ± 0.1 mg/dL, p-value <0.005) and total bilirubin (12 ± 9 mg/dL vs. 9 ± 4 mg/dL, p-value 0.01). Of patients who had a bilirubin measured within 2 days of discharge (28 patients), 89% remained cholestatic at discharge. Their liver biomarkers were also significantly higher, with higher transaminases (Aspartate Aminotransferase [AST] 250 ± 161 U/L vs. 60 ± 125 U/L; Alanine Aminotransferase [ALT] 133 ± 106 U/L vs. 30 ± 52 U/L, p-value <0.005), higher alkaline phosphatase (ALP) (544 ± 296 IU/L vs. 322 ± 157 IU/L, p-value <0.005), higher International Normalized Ratio (INR) (2 ± 0.6 vs. 1.5 ± 0.4, p-value 0.01) and lower albumin (2 ± 0.4 g/dL vs. 3 ± 0.5 g/dL, p-value <0.005).

3.3. Interventions to ameliorate cholestasis

Soy-based intravenous (IV) lipid emulsion (standard of care at our institution) was used in the PN for all non-cholestatic patients, and in all but one of the cholestatic patients; one cholestatic patient

Table 2
Multivariate associations for six month weight percentile and age at which full enteral tolerance was achieved among cholestatic (direct bilirubin >2.0 mg/dL) neonates.

	Beta (SE)	Adjusted Beta (SE)	p-value
With 6 month weight percentile[a]			
Gestational age	0.11 (0.25)	−0.3 (0.36)	0.406
Birth weight	0.49 (0.67)	1.28 (0.84)	0.136
APGAR score at 1 min	−0.37 (0.37)	−0.84 (0.40)	0.045[c]
History of gastrointestinal surgery	−1.30 (0.62)	−0.85 (0.71)	0.243
Length of small bowel resected	−0.92 (0.76)	2.17 (1.00)	0.036[c]
Total # positive BLCS during hospitalization	−1.41 (0.66)	0.52 (0.77)	0.501
Peak conjugated bilirubin	−1.00 (0.54)	0.09 (0.60)	0.886
Age of onset of enteral feeding	−0.09 (0.29)	0.31 (0.31)	0.321
Peak AST	−0.57 (0.35)	−0.7 (0.45)	0.132
Minimum Albumin	4.63 (1.56)	6.39 (2.06)	0.004[c]
With age at which full enteral tolerance achieved[b]			
Gestational age	−0.25 (0.09)	−0.28 (0.10)	0.007[c]
Birth weight	−0.37 (0.27)	0.07 (0.25)	0.779
History of gastrointestinal surgery	1.15 (0.21)	0.48 (0.22)	0.031[c]
Length of small bowel resected	0.95 (0.33)	−0.07 (0.27)	0.803
Length of colon resected	1.05 (0.43)	0.65 (0.29)	0.029[c]
Total # positive BLCS during hospitalization	0.72 (0.28)	0.14 (0.19)	0.475
Age of onset of enteral feeding	0.25 (0.11)	0.10 (0.09)	0.289
Cycling of PN	1.25 (0.20)	0.69 (0.22)	0.004[c]
Use of trophic feeds	1.61 (0.40)	1.15 (0.33)	0.001[c]
Ursodiol treatment	0.11 (0.28)	−0.24 (0.19)	0.207
Phenobarbital treatment	−1.09 (0.32)	0.07 (0.26)	0.775

Note: SE = Standard Error; # = Number; BLCS = Blood Cultures; PN = Parenteral Nutrition; AST = Aspartate Aminotransferase.
[a] Model constructed as follows: $Y = \beta_0 + \beta_1 X1 + \beta_2 X_2 \ldots \beta_n X_n$ where Y represents 6 month weight percentile and X_n represents one of several independent predictor variables. Variables were chosen based on clinical relevance and all variables included in the model are displayed in the table.
[b] Model constructed as follows: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \ldots \beta_n X_n$ where Y represents age at which full enteral tolerance achieved and X_n represents one of several independent predictor variables. Variables were chosen based on clinical relevance and all variables included in the model are displayed in the table.
[c] Significant values.

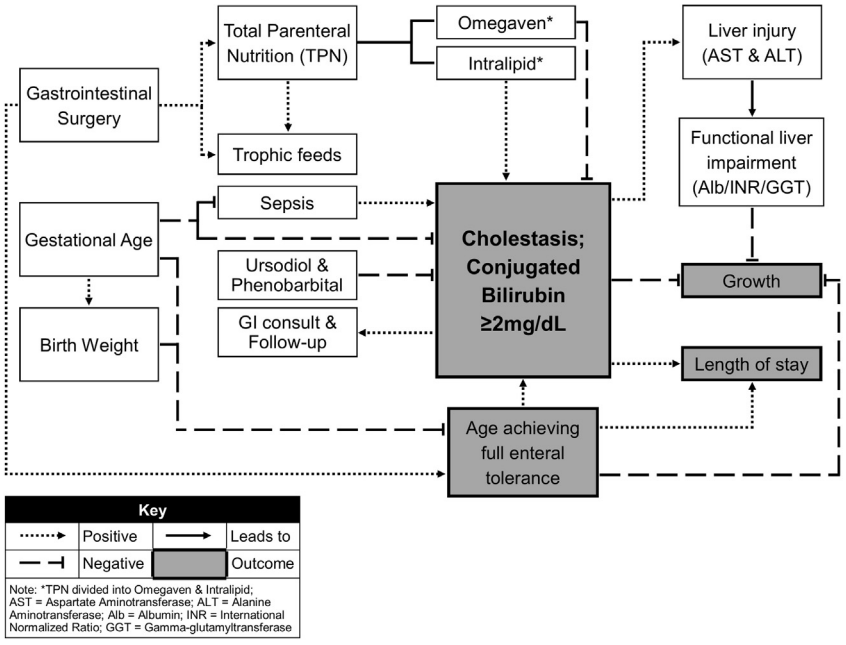

Fig. 1. Hypothesized associations for Intestinal Failure-Associated Liver Disease.

received Omegaven, a fish oil-based IV lipid emulsion that can be obtained at our institution via a compassionate drug use protocol for patients with severe liver dysfunction or PN- associated cholestasis (IRB-HSR #17770). PN was cycled in 25 (40%) of the cholestatic patients and 3 (3%) of the non-cholestatic patients. The cholestatic group was also significantly more likely to have received ursodiol (42 [67%] vs. 0 [0%], p-value <0.005).

3.4. 6-Month weight percentile in cholestasis group

Univariate analysis was notable for a significant association between 6-month weight percentile and history of gastrointestinal surgery (−1.30 [0.62], p-value = 0.043), length of colon resected (−2.42 [0.88], p-value = 0.009), presence of ileocecal valve (3.00 [1.22], p-value = 0.018), duration of PN (−0.69 [0.28], p-

value = 0.016), PN cycling (−1.44 [0.60], p-value = 0.020), number of positive BLCS during hospitalization (−1.41 [0.66], p-value = 0.039), peak INR (−3.73 [0.95], p-value <0.001), and minimum albumin (4.63 [1.56], p-value = 0.005). In multivariable analysis, Apgar score at 1 min (−0.84 [0.40], p-value = 0.045), length of small bowel resected (2.17 [1.00], p-value = 0.036), and minimum albumin (6.39 [2.06], p-value = 0.004) were independently predictive of 6-month weight percentile.

3.5. Achieving full enteral tolerance in cholestasis group

In the cholestatic group, in univariate analyses, GA (−0.25 [0.09], p-value = 0.009), history of gastrointestinal surgery (1.15 [0.21], p-value <0.001), length of small bowel resected (0.95 [0.33], p-value = 0.005), length of colon resected (1.05 [0.43], p-value = 0.018), type of intestinal abnormality (0.16 [0.04], p-value <0.001), PN duration (0.83 [0.06], p-value <0.001), PN cycling (1.25 [0.20], p-value <0.001), trophic feed use (1.61 [0.40], p-value <0.001), age of onset of enteral feeds (0.25 [0.11], p-value = 0.034), volume of enteral feeds when first off PN (1.90 [0.47], p-value <0.001), phenobarbital therapy (−1.09 [0.32], p-value = 0.001), number of positive BLCS during hospitalization (0.72 [0.28], p-value = 0.014), peak ALT (0.41 [0.13], p-value = 0.003), peak ALP (0.86 [0.20], p-value <0.001), and minimum albumin (−2.89 [0.55], p-value <0.001) were significantly associated with age achieving full enteral tolerance. In multivariate analysis, GA (−0.28 [0.10], p-value = 0.007), history of gastrointestinal surgery (0.48 [0.22], p-value = 0.031), length of colon resected (0.65 [0.29], p-value = 0.029), PN cycling (0.69 [0.22], p-value = 0.004), and trophic feed use (1.15 [0.33], p-value = 0.001) were independently predictive of the age achieving full enteral tolerance.

4. Discussion

The present study investigated key features of cholestatic and non-cholestatic neonates receiving PN at our institution's NICU. We aimed to report our center's experience, and to investigate variables associated with weight percentiles and age achieving enteral tolerance in the cholestatic group. Additionally, we have used these data in informing further quality improvement interventions at our institution currently underway. Notable findings include: 1) decreased weight gain of cholestatic infants at discharge and 6 months of age, 2) length of colon resected independently predicts a delay in achieving enteral tolerance, and 3) lower Apgar scores, lower BW, and increased duration of PN therapy are risk factors for developing cholestasis.

NICU infants receive PN in order to meet metabolic demands for growth and illness [33,34], and IFALD is a common and significant complication that can negatively impact outcomes. Identification of risk factors for cholestasis and study of the impact of treatment are important steps in improving outcomes both at our center and at others across the world. Several studies have aimed to identify risk factors for PN cholestasis in the NICU [7–9,35,36]. In our study, cholestatic infants were significantly more likely to have lower Apgar scores, but not lower GA or BW when compared to non-cholestatic counterparts. This suggests that any notable differences in outcomes described in this work between cholestatic and non-cholestatic infants cannot be fully explained by differences in BW or GA among the two groups, as these variables were not significantly different between these two groups.

A significantly higher proportion of cholestatic infants had a history of gastrointestinal surgery and/or small bowel, colon, or ileocecal valve resection when compared to non-cholestatic controls. Surgical manipulation of the normal gastrointestinal anatomy can lead to development of cholestasis by several mechanisms. Gastrointestinal surgery can increase the need for prolonged PN, thus increasing the risk of developing IFALD [37]. Post-operative gastrointestinal dysmotility impairs bile acid elimination by slowing transit time and increasing biliary enterohepatic circulation. Additionally, children without ileocecal valves take longer to wean from PN [38,39] and are at higher risk of developing bloodstream infections [40], which are independently associated with developing cholestasis [41]. Furthermore, surgery itself is a risk factor for infection, compounding the risk of infection-associated cholestasis in this population.

Cycling of PN, use of trophic feeds, and ursodiol treatment have been shown to mitigate IFALD [16,17,23,24]. In our study, cholestatic patients were significantly more likely to have PN cycling and ursodiol treatment. Additionally, a majority (88.9%) received trophic feeds at some point during hospitalization. Later achievement of enteral tolerance was associated with PN cycling and trophic feed use in our multivariable analysis, indicating the higher likelihood of these interventions to be employed in patients who are on PN for a longer duration. There is some data to suggest that cycling PN earlier in the course can decrease the risk of cholestasis in neonates [17,42], and perhaps this is an area that can be further improved with quality improvement methodology in the future. Data have shown a clear benefit of SMOF and Omegaven lipid formulations in ameliorating PN associated cholestasis [20,21,43,44]. Given these data, a quality improvement initiative is underway to add both SMOF and Omegaven to our clinical formulary (currently available only for select patients via a compassionate use protocol) as well as to develop institution-specific guidelines and protocols to guide use.

Despite these interventions, cholestatic patients in our study were significantly more likely to exhibit signs of hepatic dysfunction, as demonstrated by abnormalities in markers of liver injury and synthetic function. However, average levels of liver biomarkers were disproportionately high when compared with time on PN, suggesting the presence of other concurrent hepatoxic processes. Many patients in our NICU have other reasons to have liver injury, such as septic shock or heart failure, which could contribute to exaggerated elevations in liver biomarkers.

Malnutrition is associated with abnormal brain development [45] and optimizing early nutrition has been associated with improved neurocognitive outcomes [46,47]. The most important finding in our study is that infants with cholestasis have a decreased weight percentile at discharge and 6 months compared to non-cholestatic infants. The reasons for this difference are likely the same as those that contribute to development of IFALD: bowel surgery with resultant short bowel syndrome, recurrent infections, and the need for prolonged parenteral nutrition. Our study indicates that small bowel resection is a risk for lower weight percentile at 6 months and, although we did not define these children as having short bowel syndrome, some did meet that definition. Fat malabsorption from decreased bile acid secretion in children with cholestasis likely contributes in part to the observed difference in weight gain [4]. Additionally, IFALD itself has been associated with intestinal dysbiosis, which may play a role in enteric maturation and ultimately enteral feeding tolerance [5]. This is echoed by our study, in which older age at onset of enteral feeds independently predicted lower discharge weight. Although some patients in the cholestatic group remained cholestatic at discharge, a majority had already had normalization of bilirubin by this point, suggesting the impact of cholestasis on prospective weight gain even after resolution of hyperbilirubinemia. Our findings highlight the importance of diligent follow-up and continued aggressive nutrition assessment and therapy in this population.

In studying variables associated with cholestasis at our center, we uncovered several important areas for improvement of our

practice. For example, only 37% of patients were seen by a gastroenterology consultant while in the NICU. Multidisciplinary team approaches are known to positively impact outcomes in healthcare settings [48–51], and patients who develop PN associated cholestasis could benefit from this care model as well. After this study ended, our center started a weekly multidisciplinary round-table discussion that included neonatologists, gastroenterologists, surgeons, radiologists, nurses, nutritionists, and pharmacists. This team discusses all patients, thus giving each patient the benefit of an informal gastroenterology consultation. Further directions for quality improvement also include standardization of the PN cycling protocol, trophic feed use, and ursodiol treatment regimens. Further exploration of the subgroup of patients who did not have PN cycling, trophic feed use, and/or ursodiol treatment could yield valuable insights into the nature of practice at our center. By employing QI methodology with PDSA cycles, we aim to uncover inconsistencies in care and to improve practice for all patients via the implementation of a standardized parenteral nutrition protocol in our NICU. This can then be used to evaluate the effect of multidisciplinary, standardized care on outcomes in these vulnerable infants, and can be applied to care models at other institutions.

Strengths of our study included: 1) cross-sectional design with longitudinal data collection time points; 2) use of non-cholestatic controls to better describe management of cholestasis independently of other factors; 3) assessment of growth at various ages; and 4) use of multivariable regression to characterize variables that independently predicted outcomes. Limitations included: 1) small sample size; 2) retrospective data collection; and 3) fairly lenient inclusion criteria which ultimately contributed to a rather heterogeneous study population. Stratification of groups based on principal diagnosis and an evaluation of neurocognitive outcomes in this population would be useful in future studies, which would require a much larger sample size and longer study duration.

In summary, we describe our experience at a tertiary care center in caring for NICU patients with cholestasis and IFALD. While several of our findings (low Apgar scores, gastrointestinal surgery, longer duration of PN are all risk factors for cholestasis) reiterate previous data, our work also suggests that cholestasis itself is associated with worse growth. This significant and long lasting negative effect on weight in cholestatic infants highlights the need for increased nutritional support for this population.

Statement of authorship

SS, BDV, and JPM contributed in the conception and design of the study; MN contributed towards the design the study; MN and SS completed the acquisition, interpretation, and analysis of data; MN and MNK drafted the manuscript; MNK and SS critically revised the manuscript; all authors contributed towards the final review before submission.

Conflict of interest and funding

The authors have no conflicts of interest to declare, and confirm that this work is their own. No funding was obtained to complete this work.

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Appendix A. Supplementary data

Supplementary data to this chapter can be found online at https://doi.org/10.1016/j.clnesp.2019.01.006.

References

[1] Puntis JW. Nutritional support in the premature newborn. Postgrad Med J 2006;82(965):192–8.
[2] Orso G, Mandato C, Veropalumbo C, Cecchi N, Garzi A, Vajro P. Pediatric parenteral nutrition-associated liver disease and cholestasis: novel advances in pathomechanisms-based prevention and treatment. Dig Liver Dis 2016;48(3):215–22.
[3] Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R, Parenteral Nutrition Guidelines Working G. Guidelines on paediatric parenteral nutrition of the European society of paediatric gastroenterology, hepatology and nutrition (ESPGHAN) and the European society for clinical nutrition and metabolism (ESPEN), supported by the European society of paediatric research (ESPR). J Pediatr Gastroenterol Nutr 2005;41(Suppl. 2):S1–87.
[4] Feldman AG, Sokol RJ. Neonatal cholestasis. Neoreviews 2013;14(2).
[5] Cahova M, Bratova M, Wohl P. Parenteral nutrition-associated liver disease: the role of the gut microbiota. Nutrients 2017;9(9).
[6] Cohen C, Olsen MM. Pediatric total parenteral nutrition. Liver histopathology. Arch Pathol Lab Med 1981;105(3):152–6.
[7] Alkharfy TM, Ba-Abbad R, Hadi A, Sobaih BH, AlFaleh KM. Total parenteral nutrition-associated cholestasis and risk factors in preterm infants. Saudi J Gastroenterol 2014;20(5):293–6.
[8] Beale EF, Nelson RM, Bucciarelli RL, Donnelly WH, Eitzman DV. Intrahepatic cholestasis associated with parenteral nutrition in premature infants. Pediatrics 1979;64(3):342–7.
[9] Beath SV, Davies P, Papadopoulou A, Khan AR, Buick RG, Corkery JJ, et al. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. J Pediatr Surg 1996;31(4):604–6.
[10] Tufano M, Nicastro E, Giliberti P, Vegnente A, Raimondi F, Iorio R. Cholestasis in neonatal intensive care unit: incidence, aetiology and management. Acta Paediatr 2009;98(11):1756–61.
[11] Moss RL, Das JB, Raffensperger JG. Total parenteral nutrition-associated cholestasis: clinical and histopathologic correlation. J Pediatr Surg 1993;28(10):1270–4. Discussion 4–5.
[12] Kumpf VJ. Parenteral nutrition-associated liver disease in adult and pediatric patients. Nutr Clin Pract 2006;21(3):279–90.
[13] Blackmer AB, Btaiche IF, Arnold MA, Teitelbaum DH. Parenteral nutrition-associated liver disease in pediatric patients: strategies for treatment and prevention. In: Murray KF, Horslen S, editors. Diseases of the liver in children: evaluation and management. New York, NY: Springer New York; 2014. p. 327–49.
[14] Le HD, Fallon EM, de Meijer VE, Malkan AD, Puder M, Gura KM. Innovative parenteral and enteral nutrition therapy for intestinal failure. Semin Pediatr Surg 2010;19(1):27–34.
[15] Veenstra M, Danielson L, Brownie E, Saba M, Natarajan G, Klein M. Enteral nutrition and total parenteral nutrition components in the course of total parenteral nutrition-associated cholestasis in neonatal necrotizing enterocolitis. Surgery 2014;156(3):578–83.
[16] Slagle TA, Gross SJ. Effect of early low-volume enteral substrate on subsequent feeding tolerance in very low birth weight infants. J Pediatr 1988;113(3):526–31.
[17] Jensen AR, Goldin AB, Koopmeiners JS, Stevens J, Waldhausen JH, Kim SS. The association of cyclic parenteral nutrition and decreased incidence of cholestatic liver disease in patients with gastroschisis. J Pediatr Surg 2009;44(1):183–9.
[18] Puder M, Valim C, Meisel JA, Le HD, de Meijer VE, Robinson EM, et al. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Ann Surg 2009;250(3):395–402.
[19] Gura KM, Lee S, Valim C, Zhou J, Kim S, Modi BP, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 2008;121(3):e678–86.
[20] Gura KM, Duggan CP, Collier SB, Jennings RW, Folkman J, Bistrian BR, et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics 2006;118(1):e197–201.
[21] Diamond IR, Sterescu A, Pencharz PB, Kim JH, Wales PW. Changing the paradigm: omegaven for the treatment of liver failure in pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr 2009;48(2):209–15.
[22] Cheung HM, Lam HS, Tam YH, Lee KH, Ng PC. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. Clin Nutr 2009;28(2):209–12.
[23] Luis VAS, Btaiche IF. Drug information rounds: ursodiol in patients with parenteral nutrition–associated cholestasis. Ann Pharmacother 2007;41(11):1867–72.
[24] Simic D, Milojevic I, Bogicevic D, Milenovic M, Radlovic V, Draskovic B, et al. Preventive effect of ursodeoxycholic acid on parenteral nutrition-associated liver disease in infants. Srp Arh Celok Lek 2014;142(3–4):184–8.

[25] Kelly DA. Intestinal failure-associated liver disease: what do we know today? Gastroenterology 2006;130(2 Suppl 1):S70–7.
[26] Einbinder JS, Scully KW, Pates RD, Schubart JR, Reynolds RE. Case study: a data warehouse for an academic medical center. J Healthc Inf Manag 2001;15(2):165–75.
[27] Scully KW, Pates RD, Desper GS, Connors AF, Harrell FE, Pieper KS, et al. Development of an enterprise-wide clinical data repository: merging multiple legacy databases. In: Proceedings of the AMIA annual fall symposium; 1997. p. 32–6.
[28] Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
[29] Centers for Disease Control and Prevention. National Center for Health Statistics. Clinical Growth Charts. Available from: https://www.cdc.gov/growthcharts/clinical_charts.htm.
[30] World Health Organization. Fact Sheets 2018. Preterm Birth: Key Facts [updated 2/19/2018. Available from: https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth.
[31] World Health Organization. Definitions and metadata: Newborns with low birth weight (%), Available from: https://www.who.int/whosis/whostat2006NewbornsLowBirthWeight.pdf.
[32] Team RC. R: a language and environment for statistical computing. 2013. Available from: http://www.R-project.org/.
[33] Hans DM, Pylipow M, Long JD, Thureen PJ, Georgieff MK. Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey. Pediatrics 2009;123(1):51–7.
[34] Thureen PJ. Early aggressive nutrition in the neonate. Pediatr Rev 1999;20(9):e45–55.
[35] Christensen RD, Henry E, Wiedmeier SE, Burnett J, Lambert DK. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. J Perinatol 2007;27(5):284–90.
[36] Lacaille F, Gupte G, Colomb V, D'Antiga L, Hartman C, Hojsak I, et al. Intestinal failure-associated liver disease: a position paper of the ESPGHAN working group of intestinal failure and intestinal transplantation. J Pediatr Gastroenterol Nutr 2015;60(2):272–83.
[37] Calkins KL, Venick RS, Devaskar SU. Complications associated with parenteral nutrition in the neonate. Clin Perinatol 2014;41(2):331–45.
[38] Georgeson KE, Breaux Jr CW. Outcome and intestinal adaptation in neonatal short-bowel syndrome. J Pediatr Surg 1992;27(3):344–8. Discussion 8–50.
[39] Spencer AU, Neaga A, West B, Safran J, Brown P, Btaiche I, et al. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg 2005;242(3):403–9. Discussion 9–12.
[40] Dibaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. Clin Gastroenterol Hepatol 2006;4(1):11–20.
[41] Chand N, Sanyal AJ. Sepsis-induced cholestasis. Hepatology 2007;45(1):230–41.
[42] Collier S, Crough J, Hendricks K, Caballero B. Use of cyclic parenteral nutrition in infants less than 6 months of age. Nutr Clin Pract 1994;9(2):65–8.
[43] Tomsits E, Pataki M, Tolgyesi A, Fekete G, Rischak K, Szollar L. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition. J Pediatr Gastroenterol Nutr 2010;51(4):514–21.
[44] Goulet O, Antebi H, Wolf C, Talbotec C, Alcindor LG, Corriol O, et al. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr 2010;34(5):485–95.
[45] Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev 2014;72(4):267–84.
[46] Uhing MR, Das UG. Optimizing growth in the preterm infant. Clin Perinatol 2009;36(1):165–76.
[47] Su BH. Optimizing nutrition in preterm infants. Pediatr Neonatol 2014;55(1):5–13.
[48] Section on Hematology/Oncology Committee on G, American Academy of P. Health supervision for children with sickle cell disease. Pediatrics 2002;109(3):526–35.
[49] Ajarmeh S, Er L, Brin G, Djurdjev O, Dionne JM. The effect of a multidisciplinary care clinic on the outcomes in pediatric chronic kidney disease. Pediatr Nephrol 2012;27(10):1921–7.
[50] Modi BP, Langer M, Ching YA, Valim C, Waterford SD, Iglesias J, et al. Improved survival in a multidisciplinary short bowel syndrome program. J Pediatr Surg 2008;43(1):20–4.
[51] Schechter MS, Margolis P. Improving subspecialty healthcare: lessons from cystic fibrosis. J Pediatr 2005;147(3):295–301.