Original Article

Increased Incidence of Parenteral Nutrition-Associated Cholestasis with Aminosyn PF Compared to Trophamine

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OBJECTIVE:

To compare the incidence of parenteral nutrition-associated cholestasis (PNAC) between two pediatric parenteral amino-acid formulations, Aminosyn PF (APF) and Trophamine (TA).

STUDY DESIGN:

Setting: Tertiary newborn intensive-care nursery. *Subjects*: A total of 661 neonates who received either TA or APF. *Design*: Retrospective. The incidence of PNAC was determined in three groups: Group I (TA, 8/19/97 to 8/19/98, $n = 335$), Group II (APF, 8/20/98 to 1/28/99, $n = 157$), and Group III (TA, 1/29/99 to 8/1/99, $n = 169$).

RESULTS:

No PNAC developed in any infant receiving parenteral nutrition (PN) for <3 weeks. Of 141 patients given PN for ≥ 21 days, 24 were diagnosed with PNAC: Group I (TA, 10/78, 12.8%), Group II (APF, 9/27, 33.3%), and Group III (TA, 5/36, 13.9%). The incidence of PNAC was significantly higher in infants who received APF ($p = 0.043$). Using logistic regression, only birth weight, duration of PN, and use of APF were significant risk factors for the development of PNAC. Despite an earlier initiation of enteral feedings, APF recipients developed PNAC sooner, had higher peak direct bilirubin levels, and remained jaundiced longer.

CONCLUSIONS:

The use of APF was temporally associated with a greater than two-fold increase in the incidence of PNAC compared to periods of exclusive TA use. In the absence of significant differences in parenteral nutrient or energy intake in neonates who developed PNAC, we speculate that possible differences between the amino-acid compositions of TA and APF may be responsible for the observed differences in the incidence of PNAC.
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INTRODUCTION

Since its original description by Peden et al.,[1] cholestasis has become a well-known complication of prolonged parenteral nutrition (PN) in neonates. Despite significant recent advances in the understanding of the physiology of bile formation,[2] the cause of parenteral nutrition-associated cholestasis (PNAC) remains unknown, and likely is multifactorial, involving a perpetuation of inflammatory and cholestatic conditions in a susceptible neonatal liver.[3] Many of the proposed risk factors for PNAC have been recently reviewed,[4,5] and include low birth weight, prematurity, duration of PN, lack of enteral intake, sepsis, enzyme deficiencies, genetic causes, quantity or quality of amino-acid intake, excess of nonprotein caloric intake, and trace mineral toxicity. Male gender,[6] perinatal depression or shock,[7] and more recently, phototoxicity of parenteral multivitamin supplements,[8] and toxicity from plant phytosterols[9] have also been implicated as potential risk factors for PNAC. Although several of these risk factors are unavoidable, research is still needed to define the optimal parenteral amino-acid solution for pediatric and neonatal patients,[10] one that would allow normal growth and development, result in normal serum amino-acid levels, and cause a minimum of unwanted side effects, such as cholestasis.

The first clinical trial using the pediatric amino-acid formulation, Trophamine™ (TA) (Kendall-McGaw Laboratories, Irvine, CA), reported an unexpectedly low incidence of cholestasis compared to historical controls.[11] Two subsequent studies comparing (TA) and another pediatric formulation, Aminosyn PF™ (APF) (Abbott Laboratories, North Chicago, IL), however, failed to demonstrate any differences in the incidence of cholestasis.[12,13] In August 1998, our pharmacy substituted APF as a lower-cost alternative to our usual parenteral amino-acid formulation, TA. After 6 months of APF usage, we suspected an increased incidence of cholestasis, and reverted to the exclusive use of TA. We subsequently undertook a retrospective study to

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determine if APF was associated with an increased incidence of PNAC.

METHODS

Of 1614 patients admitted to the Intensive-Care Nursery at the University of Tennessee Memorial Hospital (Knoxville, TN) from August 1997 until August 1999, 685 received PN for at least 24 hours. Babies were categorized into three groups based on time period and amino-acid formulation received. Infants were excluded from analysis if they were admitted at a postnatal age >72 hours ($n = 6$), or if they received both TA and APF ($n = 19$). The final study population ($n = 661$) included Group I (TA, 8/19/97 to 8/19/98, $n = 335$), Group II (APF, 8/20/98 to 1/28/99, $n = 157$), and Group III (TA, 1/29/99 to 8/1/99, $n = 169$). A retrospective chart review, approved by the Institutional Review Board at the University of Tennessee Medical Center at Knoxville, was then conducted. The primary outcome variable studied was the incidence of PNAC, defined as a direct serum bilirubin fraction of >2 mg/dl, occurring at least 14 days after the initiation of parenteral nutrition, in the absence of other identified etiologies. Fractionated serum bilirubin levels were routinely obtained at least twice per week during PN administration, and at least weekly thereafter in infants with persistent hyperbilirubinemia.

Gender, gestational age (using best obstetrical estimate), Apgar scores, and birth weight were recorded for each infant. Additional clinical variables reviewed included the incidence of necrotizing enterocolitis (diagnosed by unequivocal pneumatosis intestinalis or by laparotomy), sepsis (positive blood culture with associated clinical deterioration, bandemia, and/or elevated C-reactive protein), urinary tract infection (catheterized specimen with $>10^5$ organisms/ml), hypotension requiring pressor support, and duration of parenteral nutrition, assisted ventilation, and hospitalization. The typical evaluation for an infant with a persistently elevated direct bilirubin level included bacterial cultures of blood and urine, urine cytomegalovirus culture, acute hepatitis profile (including antibody testing for Hepatitis A, B, and C), an ultrasound of the liver and gall bladder, serum α-1 antitrypsin level and phenotype, quantitative serum amino-acid profile, and galactosemia screening. Selected infants also underwent DNA mutation analysis for cystic fibrosis.

For infants identified with PNAC, daily intakes (g/kg/d) of parenteral protein, carbohydrate, and fat, and daily enteral intake (ml/kg/d) of breast milk and/or formula were recorded, along with age at diagnosis of PNAC, age at initiation of PN, age at initiation of enteral feedings, age at first sepsis, proportion of total calories taken enterally while on PN, presence or absence of prolonged fasting (defined as ≥ 14 consecutive days with no enteral intake), duration of choleretic medications (ursodiol and/or phenobarbital), peak direct bilirubin concentration, and duration of cholestasis. PNAC was considered resolved when the direct serum bilirubin fraction fell to <2 mg/dl, or at hospital discharge or death, whichever occurred first. Likewise, duration of choleretic therapy was calculated based on actual days administered, or was considered discontinued at discharge or death, whichever happened first.

Parenteral nutrition (including lipids, electrolytes, pediatric multivitamins, and trace minerals) was typically initiated within 24 hours of birth. Prescribed parenteral nutrient intakes were consistent with those recommended by Heird and Gomez.[14] All infants, regardless of amino-acid formulation, received the same parenteral lipid emulsion, 20% Liposyn II™ (Abbott Laboratories, N. Chicago, IL). All parenteral nutrition solutions were supplemented with equivalent amounts of cysteine hydrochloride, and were shielded from light. Parenteral multivitamin dosages were calculated using a sliding scale based on daily body weights.

Statistical analysis was performed using SPSS for Windows 11.0.1 (© SPSS, Inc.). For continuous data, differences in means were calculated using Student's t-test. Differences in proportions were assessed using either the χ^2 or Fisher's exact test. For selected dichotomous variables, the Mantel–Haenszel common odds ratios and 95% confidence intervals were computed. A logistic regression analysis was performed on those infants receiving PN for ≥ 21 days to define which of the several risk factors were most significant for the development of PNAC. Results were considered significant at a p value <0.05.

RESULTS

Of the 661 study infants, 24 were diagnosed with PNAC (3.6%). Not surprisingly, infants diagnosed with PNAC were more premature and had lower birth weights. They required more days of hospitalization, assisted ventilation, and PN, and were also more likely to have sepsis, urinary tract infections, necrotizing enterocolitis, or require pressor support compared to infants who did not develop PNAC (Table 1). The likelihood of PNAC was highly dependent on the duration of PN. For those infants receiving PN for 14 to 30 days, the incidence of PNAC was 4.1% (5/123). For those given PN for 31 to 60, 61 to 90, 91 to 120, and 121 to 150 days, the incidence figures for PNAC were 14.7% (10/68), 35.7% (5/14), 75% (3/4), and 100% (1/1), respectively.

As no infant developed PNAC who received PN for less than 21 days, we next chose to analyze a more high-risk cohort, namely the 141 infants who received PN $\geq$ 21 days. The overall incidence of PNAC in these infants was 17% (24/141). Broken down by time period and amino-acid formulation used, the incidence of PNAC was 12.8% (10/78) in Group I (TA), 33.3% (9/27) in Group II (APF), and 13.9% (5/36) in Group III (TA). Group II infants, who received APF exclusively, were more likely to be diagnosed with PNAC than the TA recipients (Groups I and III) ($p = 0.043$ by χ^2). Table 2 compares infants with and without PNAC in the subset of 141 babies given ≥ 21 days of PN. Although infants with PNAC

Table 1 Risk Factors for PN-associated Cholestasis in 661 Infants Receiving PN

Variable	PNAC	Number	Mean ± SEM or number (%)	*p*
Birth weight (g)	No	637	2115 ± 32	<0.001
	Yes	24	1161 ± 94	
Gestational age (weeks)	No	637	33.7 ± 0.1	<0.001
	Yes	24	29.1 ± 0.7	
Length of stay (days)	No	637	31.6 ± 1.2	<0.001
	Yes	24	92.4 ± 5.8	
Discharge weight (g)	No	637	2627 ± 29	0.049
	Yes	24	2931 ± 159	
Days of ventilation	No	563	1.0 ± 0.1	<0.001
	Yes	11	3.5 ± 0.9	
Days of PN	No	637	13.0 ± 0.6	<0.001
	Yes	24	58.0 ± 6.0	
Male gender	No	637	355 (55.7%)	0.290
	Yes	24	16 (66.7%)	
Pressor support	No	637	44 (6.9%)	0.011
	Yes	24	5 (20.8%)	
5-minute apgar <6	No	633	25 (4.0%)	0.289
	Yes	24	2 (8.3%)	
Necrotizing enterocolitis	No	637	6 (0.9%)	<0.001
	Yes	24	4 (16.7%)	
Sepsis	No	637	74 (11.6%)	<0.001
	Yes	24	12 (50%)	
Urinary tract infection	No	637	29 (4.6%)	0.007
	Yes	24	4 (16.7%)	
Sepsis or urinary tract infection	No	637	92 (14.4%)	<0.001
	Yes	24	14 (58.3%)	
Received APF	No	637	148 (23.2%)	0.107
	Yes	24	9 (37.5%)	

were more likely to have had necrotizing enterocolitis, greater lengths of stay, and more days of PN than those without PNAC, they were also more likely to have received APF ($p = 0.012$). Expressed differently, the odds ratio for PNAC in APF recipients compared to those receiving TA was 3.3 (95% CI 1.26–8.68, $p = 0.016$). Using logistic regression, a model was created incorporating all the risk factors included in Table 2. Only birth weight ($p = 0.036$), duration of PN ($p < 0.001$), and use of APF ($p = 0.009$) remained as significant risk factors for the development of PNAC.

Finally, the 24 infants with PNAC were compared based on amino-acid solution received, APF versus TA. Demographic data are summarized in Table 3, while nutritional information is summarized in Table 4. The APF and TA patients with PNAC appeared to be well matched. One patient in each group had surgical necrotizing enterocolitis requiring bowel resection, one in each group was born with gastroschisis, and one in each group died. There were no significant differences in mean birth weight, gestational age, gender, length of stay, duration of assisted ventilation, weight gain, discharge weight, age at first sepsis, or incidence of infection, need for pressor support, low Apgar scores, or prolonged fasting. Neither group was different with regard to the mean age at initiation of PN, the mean duration of PN, the daily (or cumulative) parenteral nutrient or caloric intakes, or the mean nonprotein calorie/nitrogen ratios. The fraction of total calories taken enterally while on PN was similar for both the TA and APF patients.

While the mean values for peak direct bilirubin, age at diagnosis of PNAC, age at peak direct bilirubin, and age at resolution of PNAC were not statistically different, viewed graphically (Figure 1), some differences emerge. Whereas 10 of 15 (66.7%) TA patients had peak direct bilirubin levels <3.5 mg/dl, only one of nine (11.1%) of APF patients had peak direct bilirubin levels this low ($p = 0.013$). Although seven of nine (77.8%) APF patients were diagnosed with PNAC at <6 weeks of age, the majority of TA patients (11 of 15, 73.3%) were diagnosed with PNAC after 6 weeks of age ($p = 0.033$). The duration of PNAC was also more than 3 weeks longer on average in patients who received APF ($p = 0.035$). A trend toward longer use of choleretic medications (ursodiol and/or phenobarbital) in APF patients (59.7 days) versus TA patients (25.9 days) was observed, but did not achieve statistical significance ($p = 0.082$). A final, and surprising,

Table 2 Risk Factors for PN-associated Cholestasis in 141 Infants Receiving PN for ≥21 Days

	PNAC	*N*	Mean±SEM or number (%)	*p*
Birth weight (g)	No	117	1376±64	0.146
	Yes	24	1161±94	
Gestational age (weeks)	No	117	29.6±0.3	0.507
	Yes	24	29.1±0.7	
Length of stay (days)	No	117	74.8±3.3	0.025
	Yes	24	92.4±5.8	
Discharge weight (g)	No	117	2841±103	0.707
	Yes	24	2931±159	
Days of ventilation	No	58	2.3±0.3	0.131
	Yes	11	3.5±0.9	
Days of PN	No	117	37.8±1.5	<0.001
	Yes	24	58.0±6.0	
Male gender	No	117	58 (49.6%)	0.128
	Yes	24	16 (66.7%)	
Pressor support	No	117	14 (12%)	0.250
	Yes	24	5 (20.8%)	
5-minute apgar <6	No	116	4 (3.5%)	0.285
	Yes	24	2 (8.3%)	
Necrotizing enterocolitis	No	117	3 (2.6%)	0.004
	Yes	24	4 (16.7%)	
Sepsis	No	117	52 (44.4%)	0.621
	Yes	24	12 (50%)	
Urinary tract infection	No	117	14 (12%)	0.533
	Yes	24	4 (16.7%)	
Sepsis or urinary tract infection	No	117	58(49.6%)	0.438
	Yes	24	14 (58.3%)	
Received APF	No	117	18 (15.4%)	0.012
	Yes	24	9 (37.5%)	

difference between the APF and TA groups was the age at initiation of enteral feeds. APF infants, on average, began enteral feeding almost 1 week sooner (at a mean postnatal age of 4.3 days, compared to 10.9 days for TA patients, $p = 0.011$).

SIGNIFICANCE

From our initial study population of 661 infants who received PN for at least 24 hours, the 24 babies who were subsequently diagnosed with PNAC helped to reinforce previous associations of PNAC and low birth weight, prematurity, sepsis, necrotizing enterocolitis, and duration of PN. However, when refining our focus to the much higher-risk cohort of babies receiving PN for ≥21 days, a different pattern of risk became apparent. The observed incidences of PNAC in patients receiving parenteral protein exclusively from TA were very similar (12.8 and 13.9%, respectively) before and after an interim period of exclusive APF use, during which the incidence of PNAC was 33.3%, more than two times higher than either of the TA periods. Using logistic regression, only birth weight, duration of PN, and APF exposure were found to be significant risk factors for PNAC. When the 24 patients with PNAC were categorized by amino-acid formulation received, no differences in birth weight or duration of PN were found. Instead, APF recipients differed from TA recipients in only four ways. Despite an earlier initiation of enteral feedings, APF recipients were more likely to have PNAC diagnosed at a postnatal age <42 days, have a peak direct bilirubin ≥3.5 mg/dl, and have a longer duration with direct bilirubin ≥2 mg/dl.

Our data appear to implicate APF as a significant risk factor for the development of PNAC (when compared to TA) in infants receiving PN for ≥21 days. Previously published clinical studies involving TA are inconclusive. In 1987, Heird et al.[11] reported the clinical, nutritional, and biochemical effects of TA in an uncontrolled, unblinded, multicenter study involving 40 infants and children who received ~2.5 g/kg/day of protein from TA for periods ranging from 5 to 21 days. Instead of an expected incidence of cholestasis of 30 to 65%, only one of 31 patients receiving PN for at least 10 days developed cholestasis, prompting speculation that TA might decrease the incidence of PNAC. In 1991, Adamkin et al.[12] described a prospective, unblinded, multicenter comparison

Table 3 Demographic Comparison of 24 Neonates with PN-associated Cholestasis

Variable	Amino-acid solution	*N*	Mean±SEM or number (%)	*p*
Birth weight (g)	TA	15	1153±123	0.924
	APF	9	1173±154	
Gestational age at birth (weeks)	TA	15	29.2±0.9	0.834
	APF	9	28.9±1.2	
Length of stay (Days)	TA	15	95.5±6.4	0.510
	APF	9	87.3±11.5	
Discharge weight (g)	TA	15	2964±194	0.795
	APF	9	2876±286	
Days on ventilator	TA	6	4.3±1.3	0.352
	APF	5	2.6±1.2	
Male gender	TA	15	10 (66.7%)	1.000
	APF	9	6 (66.7%)	
Pressor support	TA	15	3 (20.0%)	0.902
	APF	9	2 (22.2%)	
5-minute Apgar < 6	TA	15	1 (6.7%)	0.718
	APF	9	1 (11.1%)	
Necrotizing enterocolitis	TA	15	2 (13.3%)	0.591
	APF	9	2 (22.2%)	
Sepsis	TA	15	6 (40.0%)	0.223
	APF	9	6 (66.7%)	
Urinary tract infection	TA	15	1 (6.7%)	0.097
	APF	9	3 (33.3%)	
Sepsis or urinary tract infection	TA	15	7 (46.7%)	0.147
	APF	9	7 (77.8%)	
Postnatal age at 1st infection (days)	TA	4	13.5±2.5	0.956
	APF	4	13.3±3.5	
Peak direct bilirubin (mg/dl)	TA	15	4.4±0.8	0.482
	APF	9	5.2±0.6	
Age at diagnosis of PNAC (days)	TA	15	48.0±3.1	0.144
	APF	9	38.9±5.8	
Age at peak direct bilirubin (days)	TA	15	68.8±5.8	0.691
	APF	9	65.1±6.8	
Age at resolution of PNAC (days)	TA	15	82.2±5.1	0.185
	APF	9	95.4±9.2	
Resolution of PNAC by discharge	TA	15	11 (73.3%)	0.818
	APF	9	7 (77.8%)	

of 44 preterm infants randomly chosen to receive either TA or APF. Each infant received ~2.5 g/kg/day of amino-acids for ~10 days. Although no differences in total bilirubin levels were observed between the groups, no direct bilirubin values were reported.

In 1995, Forchielli et al.[13] published a retrospective review of 70 infants aged <1 year who in 1990 received PN for ≥14 days. Of 33 patients who received only APF, six (18.2%) developed PNAC. Of 28 patients who received only TA, seven (25%) were diagnosed with PNAC. Although the mean duration of PN for TA recipients was 250 days, compared to 99 days for APF recipients, neither the incidence of PNAC nor the duration of PN was significantly different between the groups. APF recipients, however, were diagnosed with PNAC earlier (mean age 16 days) compared to TA recipients (mean age at diagnosis 35 days). The authors concluded that, although their data failed to show a protective effect of TA, their results could not be viewed as conclusive, as the number of subjects was small, and the patients were characterized by diverse severe medical and surgical conditions.

In contrast to the above studies, our data are drawn from a much larger, primarily nonsurgical, preterm population with an observation period spanning 2 years. Whereas the reports by Adamkin et al.[12] and Forchielli et al.[13] represent approximately 414 and 3770 patient days of PN, respectively, our study reflects 9651 patients days of PN (1976 PN days in 157 APF patients, 7675 PN days in 504 TA patients). Limited to those patients receiving PN for

Table 4 Nutritional Comparison of 24 Neonates with PN-associated Cholestasis

Variable	Amino-acid solution	*N*	Mean±SEM or number (%)	*p*
Days of PN	TA	15	61.9±8.6	0.406
	APF	9	51.4±7.0	
Duration of PNAC (day)	TA	15	34.2±5.4	0.035
	APF	9	56.6±9.3	
No enteral Intake for >14 consecutive days	TA	15	7 (46.7%)	0.111
	APF	8	1 (12.5%)	
Age when enteral feeds started (days)	TA	15	10.9±1.5	0.011
	APF	7	4.3±1.0	
Average weight gain (g/day)	TA	15	19.3±1.5	0.756
	APF	9	20.0±0.8	
Duration of choleretic medications (day)	TA	15	25.9±7.2	0.082
	APF	9	59.7±20.9	
Daily parenteral protein intake (g/kg/day)	TA	15	1.71±0.07	0.157
	APF	8	1.56±0.07	
Cumulative daily parenteral protein intake (g/kg)	TA	15	110.0±16.6	0.259
	APF	8	81.0±13.5	
Daily parenteral carbohydrate intake (g/kg/day)	TA	15	13.4±0.67	0.092
	APF	8	11.7±0.58	
Cumulative daily parenteral carbohydrate intake (g/kg)	TA	15	889±148	0.225
	APF	8	614±115	
Daily parenteral fat intake (g/kg/day)	TA	15	1.61±0.10	0.764
	APF	8	1.57±0.07	
Cumulative daily parenteral fat intake (g/kg)	TA	15	99.9±14.7	0.440
	APF	8	81.8±14.7	
Percent of total calories taken enterally while on PN	TA	15	21.5±2.1	0.480
	APF	8	24.3±3.6	
Cumulative parenteral caloric intake (kcal/kg)	TA	15	4462±661	0.234
	APF	8	3229±588	
Daily parenteral caloric intake (kcal/kg/day)	TA	15	68.7±2.2	0.058
	APF	8	61.5±2.6	
Daily enteral intake while on PN (kcal/kg/day)	TA	15	22.4±2.4	0.901
	APF	8	22.9±3.4	
Daily total caloric intake while on PN (kcal/kg/day)	TA	15	91.1±2.3	0.113
	APF	8	84.5±3.5	
Nonprotein calorie/nitrogen ratio while on PN (kcal/g/day)	TA	15	253±6.6	0.258
	APF	8	241±6.7	
Cumulative total caloric intake while on PN (kcal/kg)	TA	15	5852±800	0.247
	APF	8	4387±752	

$\geq$14 days, our data include 6978 patient days of PN (1369 PN days in 46 APF patients, 5609 PN days in 164 TA patients). In these patients, our incidence of PNAC for APF recipients was 19.6% (nine of 46), very comparable to the 18.2% reported by Forchielli et al.[13] However, our incidence for PNAC in patients receiving TA for $\geq$14 days was only 9.1% (15 of 164, $p = 0.05$), compared to the 25% reported by Forchielli et al.[13] A possible explanation for the different incidence of PNAC is the difference in duration of PN. The mean duration of PN in TA recipients as described by Forchielli et al.[13] was 250 days, compared to 34 days in our study (in the 164 infants who received TA for $\geq$14 days).

The mechanisms by which TA may be less likely to cause PNAC compared to APF remain speculative. Both products were designed with the intention of providing more physiological plasma aminograms compared to adult amino-acid formulations. Adamkin et al.[12] reported that both TA and APF, when infused for $\sim$10 days, resulted in plasma amino-acid levels that approximated reference standards for enterally fed preterm neonates. The subtle, but statistically significant, differences observed between group mean plasma amino-acid levels generally reflected the differences in individual amino-acid intakes provided by the two different formulations. The authors concluded that further studies were

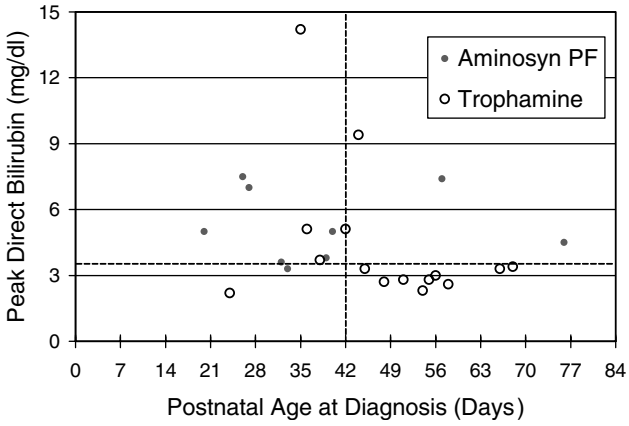

Figure 1. Peak direct bilirubin levels versus postnatal age at diagnosis of PN-associated cholestasis. Infants receiving APF were more likely to be diagnosed before 6 weeks of age or to have peak direct bilirubin levels >3.5 mg/dl.

needed to determine the ultimate disposition of amino acids during longer-term infusions. A recently published study by Suita et al.[15] concluded that PN-induced liver dysfunction was significantly associated not only with the duration of PN and presence of infection, but also the type of amino-acid solution administered (although neither TA nor APF was used in their study).

As both our study and that of Forchielli et al.[13] found that postnatal age at diagnosis of PNAC was younger for APF recipients compared to TA recipients, it is tempting to speculate that the PNAC was more likely the result of a possible toxicity, as opposed to a deficiency state, caused by APF. The strength of our conclusions is limited by our study design (retrospective) and sample size. Using the 141 patients who received PN for ≥ 21 days, the power to detect a proportion rate difference of 0.2 for PNAC (0.33 of 27 APF patients −0.13 of 114 TA patients) using a two-sided test with an α of 0.05 is 61% (SamplePower 2.0, SPSS, Inc.). Had we observed similar rate differences for PNAC in a sample of 140 patients divided equally (70 APF, 70 TA), our estimated power would increase to 81%. Although our study revealed a striking temporal association incriminating APF as more likely to result in PNAC compared to TA, only a larger, randomized, controlled clinical trial is likely to establish the true benefit, if any, of TA compared to APF.

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