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A.S.P.E.N. Clinical Guidelines: Support of Pediatric Patients With Intestinal Failure at Risk of Parenteral Nutrition–Associated Liver Disease

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Abstract

Background: Children with severe intestinal failure and prolonged dependence on parenteral nutrition are susceptible to the development of parenteral nutrition–associated liver disease (PNALD). The purpose of this clinical guideline is to develop recommendations for the care of children with PN-dependent intestinal failure that have the potential to prevent PNALD or improve its treatment. *Method*: A systematic review of the best available evidence to answer a series of questions regarding clinical management of children with intestinal failure receiving parenteral or enteral nutrition was undertaken and evaluated using concepts adopted from the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group. A consensus process was used to develop the clinical guideline recommendations prior to external and internal review and approval by the American Society for Parenteral and Enteral Nutrition Board of Directors. *Questions*: (1) Is ethanol lock effective in preventing bloodstream infection and catheter removal in children at risk of PNALD? (2) What fat emulsion strategies can be used in pediatric patients with intestinal failure to reduce the risk of or treat PNALD? (3) Can enteral ursodeoxycholic acid improve the treatment of PNALD in pediatric patients with intestinal failure? (4) Are PNALD outcomes improved when patients are managed by a multidisciplinary intestinal rehabilitation team? (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords

pediatrics; life cycle; parenteral nutrition; nutrition; home nutrition support; lipids

Background

Parenteral nutrition–associated liver disease (PNALD), also known as intestinal failure–associated liver disease (IFALD), is a feared and life-threatening complication associated with parenteral nutrition (PN) dependence. The incidence of short bowel syndrome in neonates is 24.5 per 100,000 live births with a case fatality rate of 37.5%.[1] Two-thirds of patients with intestinal failure will develop PNALD, and traditionally, 25% would advance to end-stage liver disease. While the long-term survival is 70%–90%,[2-6] the prevention of PNALD stands to improve the quality of life of children and their families. There is no standardized definition of PNALD, and there is no agreed upon clinical threshold by which to make the diagnosis. PNALD is cholestatic in nature, and there is a spectrum of disease moving from mild cholestasis through cirrhosis and liver failure with death unless transplantation is performed.[6,7] For practical reasons, PNALD is most often described by hyperbilirubinemia (direct or total). At other times, different liver biochemistry measures such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), or alkaline phosphatase are used. When liver biopsies have been used as an end point, they typically depict a picture of cholestasis and varying degrees of fibrosis. Liver biopsy is invasive and not practical for routine care. It is also prone to sampling error.

PNALD is multifactorial and has been associated with PN. All components of PN may promote cholestasis. Most of the recent interest has been with soy-based fat emulsions (SOEs)

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available in North America. SOEs have been thought to promote cholestasis as they contain predominantly ω-6 long-chain polyunsaturated fatty acids and phytosterols and have a relatively low antioxidant content.

Several clinical factors increase the risk of PNALD. Premature babies have increased risk for PNALD.[7] Premature infants have immature livers with incompletely expressed enzymatic activity. There is also inadequate bile salt uptake and excretion, as well as inadequate production of glutathione. Recurrent sepsis, from bacterial translocation or related to central venous catheters, has been shown to be a risk factor for cholestasis. Endotoxin from sepsis acts directly or indirectly through production of inflammatory cytokines on bile transport proteins, impairing biliary excretion.[8] Patients with intestinal failure commonly are unable to tolerate substantial enteral nutrient stimulation. Lack of enteral feeding impairs the enterohepatic circulation and bile acid secretion/absorption, thus leading to mucosal atrophy, and increases the risk of bacterial translocation.

Since liver failure is the most common cause of death in patients with PNALD, the goal of therapy has been to optimize intestinal function and promote gut adaptation before the development of irreversible liver complications. With the control of liver dysfunction, patients can be provided with a prolonged period to allow intestinal adaptation to occur. Much of the improvement in patient outcomes over the past decade has been related to controlling the progression of PNALD. These guidelines focus on 4 therapeutic interventions of interest in the care of patients with intestinal failure.

Children with PN-dependent intestinal failure require central venous catheters to permit delivery of needed nutrients. These catheters are susceptible to catheter-related bloodstream infections (CLABSIs), which are associated with an increased risk of PNALD when they occur frequently.[9,10] CLABSI is diagnosed when a common pathogen is cultured from both peripheral blood and the catheter. Children with intestinal failure are also at risk of these infections because they often have feeding enterostomies, stomas, and overgrowth of intestinal bacteria that may result in translocation to the bloodstream.[11] Thus, the prevention of CLABSI is one strategy that has been proposed to reduce the risk of PNALD. The instillation of 70% ethanol as a lock solution into the PN catheter has been examined as a strategy to prevent CLABSI.[12] In laboratory studies, ethanol has been shown to be effective in penetrating and breaking down biofilm when the ethanol concentration was ≥30%; however, in vivo, the greatest efficacy has been shown with higher concentrations of ethanol (70%) with dwell times of 2 hours or more.[13] Both silicone and polyurethane catheters have been tested in the laboratory, but only silicone catheters have been tested with ethanol lock therapy in children.[11]

Doses of intravenous (IV) SOE ≥1 g/kg/d have also been associated with increased risk of PNALD in mixed adult and pediatric home PN (HPN) cohorts[14] and examined more recently in children.[15,16] Young children with PN, however, require a larger dose of fat emulsion per kilogram body weight to provide for their energy requirements to promote growth, provide neurological development, and prevent essential fatty acid deficiency (EFAD). Reduced doses of SOE, the addition of fish oil emulsion (FOE), and fat emulsions designed with a mixture of soy oil, medium-chain triglycerides, olive oil, and fish oil (SMOF) have been considered as potential therapies in children with HPN who develop PNALD.

Ursodeoxycholic acid (UDCA) is a bile acid that has been given orally to treat cholestatic liver disease in adults.[17] While the mechanism of UDCA's effects is not fully established, the treatment may correct bile acid deficiency, improve bile flow, displace cytotoxic bile acids, or provide immunomodulatory protection.[17] However, less is known about such treatment in children, particularly in children with PN-dependent intestinal failure as absorption of UDCA may be limited.

Over the past few years, multidisciplinary nutrition support teams or intestinal rehabilitation programs have been developed to optimize the management of children with intestinal failure who require HPN. The impact of these programs on PNALD outcomes has been examined.

The purpose of this clinical guideline is to develop recommendations for the care of children with PN-dependent intestinal failure that have the potential to prevent PNALD or improve its treatment.

Method

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization composed of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of clinical nutrition and metabolism. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. These Clinical Guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing Clinical Guidelines since 1986.[18-28]

These A.S.P.E.N. Clinical Guidelines are based on general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Since guidelines cannot account for every variation in circumstances, the practitioner must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

The A.S.P.E.N. Clinical Guidelines process has adopted concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.[29-32] A full description of the methodology has been published.[33] Briefly, specific clinical questions where nutrition support is a relevant mode of therapy are developed and key clinical outcomes are identified. A rigorous search of the published literature is conducted, and each included study is assessed for research quality, tables of findings are developed, and the body of evidence for the question is evaluated. A recommendation for clinical practice that is based on both the best available evidence and the risks and benefits to patients is developed by consensus. Strong recommendations are made when the evidence is graded high and/or net benefits outweigh harms. Weak recommendations are made when evidence is graded low or if there are important trade-offs to the patient. When limited research is available to answer a question, no recommendation can be made.

A.S.P.E.N. Clinical Guidelines undergo peer review by clinical content experts both internal and external to the organization. The author and reviewer teams for this guideline include members of each of the professional groups that could play a role in the use of such a guideline (dietetics, nursing, medicine, pharmacy, research), as well as by the A.S.P.E.N. Board of Directors. After the author response to the initial reviews, the guideline was reviewed and approved by the A.S.P.E.N. Board of Directors and their legal consultant.

Results

Four questions were developed to be addressed by this guideline. The questions and recommendations are summarized in Table 1. For the current Clinical Guideline, the following terms were used to search PubMed and CINAHL until May 2013: *intestinal failure, short bowel syndrome, clinical outcomes, lipid, bloodstream infection, team, multidisciplinary team, parenteral nutrition*, and *enteral nutrition*. The searches were limited to studies that included pediatric subjects, English-language publications, randomized controlled trials (RCTs), controlled observational studies, and uncontrolled case series. A total of 16 RCTs, 13 controlled observational studies, and 23 uncontrolled case series met the inclusion criteria and were abstracted for the tables below. A revision of this guideline is planned for 2018.

> *Question 1*. Is ethanol lock effective in preventing bloodstream infection and catheter removal in children at risk of PNALD? (Tables 2, 3)

Recommendation: A suggestion is made to use ethanol lock to prevent CLABSI and to reduce catheter replacements in children at risk of PNALD.

Evidence: Low and very low

Recommendation Grade: Weak

Rationale: The evidence for decreased CLABSI and catheter removal is low and very low, respectively. The desirable effect of both decreased infection and catheter removal has to be interpreted in light of the unknown effects of increased thrombus formation and disruption of catheter structure integrity.

The Oliveira et al[34] meta-analysis of observational studies that are summarized in Table 2 includes low-quality evidence that shows a very strong association favoring of the use of ethanol lock for the prevention of CLABSI. However, the size of the study cohort is very small. Further research is likely to change the estimate of the effect.

Catheter replacement was not a primary outcome of the included studies. The desirable effect of decreased catheter replacement has to be interpreted in light of the unknown effects of increased thrombus formation and disruption of catheter structure integrity.[35] The Oliveira et al[34] meta-analysis of observational studies includes low-quality evidence that shows a strong association with the use of ethanol lock and the reduction of catheter replacements. However, one of the included studies reports the superiority of heparin lock to decrease catheter replacements. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

No recommendation can be made regarding the risk of catheter thrombosis due to ethanol lock therapy secondary to small sample sizes in observational studies, variable days of lock therapy, broad differences in observation time, and lack of clarity about the procedure with regard to ethanol concentration and withdrawal vs instillation of the ethanol solution after the dwell time. All research reports, however, were in cohorts of HPN patients. Further research is likely to change our confidence in the risk of catheter thrombosis with regard to ethanol lock.

Research is needed in a number of key areas. Data are needed to define more clearly the most effective concentration of ethanol in the lock, the number of days per week and the optimum duration of instillation of flush, and whether the best practice is flushing the ethanol through the catheter or withdrawing it after the instillation time. Whether silicone catheters are the only ones that should be used for ethanol lock is also important to consider systematically. Future clinical trials that use thrombosis and maintenance of catheter structural integrity as outcomes are needed and might change our confidence in the efficacy of this therapy.[36]

> *Question 2*. What fat emulsion strategies can be used in pediatric patients with intestinal failure to reduce the risk of or treat PNALD? (Tables 4, 5)

Recommendation: Since the only IV fat emulsion available for use in the United States is SOE, a suggestion is made to reduce the dose of SOE to ≤1 g/kg/d to treat cholestasis in children with PNALD. The quality of evidence supporting this recommendation is very low. Most studies are small observational studies. The desirable effect of reduction of liver indices has to

Table 1. Nutrition Support Clinical Guideline Recommendations in Pediatric Patients With Intestinal Failure.

Question	Recommendation	Grade
1. Is ethanol lock effective in preventing bloodstream infection and catheter removal in children at risk of parenteral nutrition–associated liver disease (PNALD)?	A suggestion is made to use ethanol lock to prevent catheter-related bloodstream infection (CLABSI) and to reduce catheter replacements in children at risk of PNALD. The evidence for decreased CLABSI and catheter removal is low and very low, respectively. The desirable effect of both decreased infection and catheter removal has to be interpreted in light of the unknown effects of increased thrombus formation and disruption of catheter structure integrity.	Evidence: Low, very low Recommendation: Weak
2. What fat emulsion strategies can be used in pediatric patients with intestinal failure to reduce the risk of or treat PNALD?	Since the only fat emulsion in the United States is soy oil fat emulsion (SOE), a suggestion is made to reduce the dose of SOE to ≤1 g/kg/d to treat cholestasis in children with PNALD. The quality of evidence supporting this recommendation is very low. Most studies are small observational studies. The desirable effect of the reduction of liver indices has to be considered in light of the unknown effects of poor growth and development when lipids are restricted.	Evidence: Very low Recommendation: Weak
	Fish oil fat emulsion (FOE) is available in the United States under a compassionate use protocol. Until it is approved by the Food and Drug Administration, no recommendation can be made for use in the United States. The evidence supporting the use of FOE is very low quality. Included studies are small observational studies that are confounded by concurrent SOE dose reduction and advancement of enteral feedings. The desirable effect of the reduction of liver indices has to be considered in light of the unknown effects of poor growth and development when lipids are restricted.	Evidence: Further research needed Recommendation: No recommendation
	Fat emulsion with soy oil, medium-chain triglycerides, olive oil, and fish oil (SMOF) is not available in the United States. Until it is approved for use, no recommendation can be made for use in the United States. If available, the evidence supporting the use of SMOF for the treatment of cholestasis is very low quality. The randomized controlled trials are primarily safety and efficacy studies in preterm infants with the primary outcome variable of plasma phospholipid levels and safety.	Evidence: Further research needed Recommendation: No recommendation
	Fat emulsion that contains a blend of refined olive and soy oil has been approved for adults receiving PN. It is not approved for infants or children. Until it is approved for use in children, no recommendation can be made for use in the United States.	Evidence: Further research needed Recommendation: No recommendation
3. Can enteral ursodeoxycholic acid (UDCA) improve the treatment of PNALD in pediatric patients with intestinal failure?	A suggestion is made to use UDCA for the treatment of elevated liver enzymes in children with PNALD. The evidence is of very low quality and is confounded by the presence of enteral feedings along with treatment with UDCA. In the included studies, no harm from this treatment was reported. The desirable effect of the reduction of liver indices has to be weighed against the unknown efficacy of the treatment and the fact that in most cases, the study participants did not have primary intestinal pathology.	Evidence: Very low Recommendation: Weak
4. Are PNALD outcomes improved when patients are managed by a multidisciplinary intestinal rehabilitation team?	A suggestion is made to refer patients with PN-dependent intestinal failure to multidisciplinary intestinal rehabilitation programs. The evidence on this topic is of very low quality, but the improvement in survival is compelling, and the risk to the child of treatment with multidisciplinary practice is not increased.	Evidence: Very low Recommendation: Weak

be considered in light of the unknown effects of poor growth and development when lipids are restricted.

Evidence: Very Low

Recommendation Grade: Weak

FOE is available in the United States under a compassionate use protocol. Until it is approved by the U.S. Food and Drug Administration (FDA), no recommendation can be made for use in the United States. The evidence supporting the use of FOE is very low quality. Included studies are small observational studies that are confounded by concurrent lipid dose reduction and advancement of enteral feedings. The desirable effect of improved cholestasis has to be considered in light of the unknown effects of poor growth and development when lipids are restricted.

Table 2. Evidence Summary Question 1: Is Ethanol Lock Effective in Preventing Bloodstream Infection and Catheter Removal in Children at Risk of PNALD?

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
			Ethanol Lock Solution		
Pieroni, 2013[53]	Retrospective case series	HPN patients, N = 14	Assess CLABSI prior to and after 70% ethanol lock therapy over 2 hours once weekly	**Prior to ethanol lock:** CLABSI = 9.8/1000 CVC days CVC removal = 4.3/1000 CVC days **During ethanol lock:** CLABSI = 2.7/1000 CVC days CVC removal = 1/1000 CVC days No CVC thrombosis after 690 days of observation One case of facial flushing that resolved with reduced volume of lock	Total of 87 CLABSIs through entire time, 803 preethanol lock + 690 postethanol lock catheter days
Wong et al, 2012[54]	Retrospective case series	HPN patients, N = 4	Report case series of catheter complications after use of 70% ethanol lock 3 times weekly	Thrombosis in line when ethanol withdrawn at 413 days (n = 1), at 168 days (n = 1), at 9 days (n = 1), and CVC occlusion at 3 days (n = 1). The occlusion cleared after stopping ethanol lock.	
Wales et al, 2011[55]	Retrospective case series	HPN patients with at least 1 previous CLABSI. N = 10 Median age 44 months (range, 31–129 months) Body weight: 5 kg for single lumen; 9 kg for double-lumen CVC	Assess incidence of CLABSI and CVC replacements after initiation of 70% ethanol lock therapy daily	With ethanol lock, CLABSI fell from 10.2 ± 6.2 to 0.9 ± 1.8/1000 CVC days (*P* = .005) CVC replacements fell from 5.6 to 0.3/1000 CVC days (*P* = .038) Ethanol lock discontinued in 2 of 10 patients due to CVC thrombosis, occurred 227 ± 64 days after lock started	Small sample size Minimum dwell time 4 hours
Cober et al, 2011[15]	Retrospective case series	HPN patients with silicone-based CVC, weight ≥5 kg, high risk for CLABSI (>2 CVC replaced due to CLABSI, 2 CLABSIs not cleared, loss of CVC access sites) N = 15 Mean age: 5.6 ± 6.9 years Mean weight: 19.9 kg	Evaluate outcomes of outpatient daily ethanol lock therapy on CLABSI incidence, types of organisms, and complications of daily ethanol lock therapy	With ethanol lock, mean CLABSI fell from 8.0 ± 5.4 to 1.3 ± 3.0/1000 CVC days (*P* < .01) Four patients experienced 5 episodes of CLABSI with *Staphylococcus* species Adverse events included deep vein thrombosis (n = 1), CVC occlusion (n = 3), and repair of CVC for leakage/tear (n = 20) Adverse events rose from 3.1 ± 5.2 to 6.4 ± 10.0/1000 CVC days (*P* = .20)	Small sample size Minimum dwell time 2 hours Ethanol withdrawn and discarded at the end of dwell time
Jones et al, 2010 [56]	Retrospective case series	HPN patients aged 3 months to 18 years, weight >5 kg, with at least 1 prior CLABSI in silicone-based CVC or PICC N = 23	Assess incidence of CLABSI after 70% ethanol lock 3 times weekly	CLABSI decreased from median (IQR) of 9.9 (4.4–16) to 2.1 (0–4.7)/1000 CVC days, *P* = .03 Eighteen of 23 patients had decreased CLABSI rate; 5 of 23 (patients with motility disorders) had increased rate No adverse events over 22 months	
Mouw et al, 2008[57]	Retrospective case series	HPN patients with silicone-based CVC, N = 10	Evaluate incidence rates of CLABSI, CVC removal, and adverse events after daily 70% ethanol lock therapy	Ten patients had 26 CVC, 3556 total CVC days, 3018 ethanol lock days CLABSI in 5 patients decreased from 11.4 to 2.07/1000 CVC days CLABSI rate for patients with no ethanol-lock free period (n = 5) was 1.99/1000 catheter days CVC thrombosis after 630 days of lock therapy, n = 1 Disseminated intravascular coagulation, 2 events in 1 patient	No statistical analysis due to small sample size Dwell time 4–14 hours Ethanol instilled through the catheter lumen at the end of dwell time

CLABSI, catheter-related bloodstream infection; CVC, central venous catheter; HPN, home parenteral nutrition; IQR, interquartile range; PICC, peripherally inserted central catheter; PNALD, parenteral nutrition–associated liver disease.

Table 3. GRADE Table Question 1: Is Ethanol Lock Effective in Preventing Bloodstream Infection and Catheter Removal in Children at Risk of PNALD?

Quality Assessment						No. of Patients		Effect			
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Ethanol Locks	Heparin Locks	Relative (95% CI)	Absolute	Quality	Importance
CRBSI rate (follow-up 215–3018 days; measured with average rate per 1000 catheter days; range of scores, 6.7–9.3; better indicated by lower values)											
4	Observational studies	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	0[b]	—	—	MD 7.46 higher (5.87–9.47 higher)	Low	Critical
Catheter replacement (follow-up 215–3018 days; measured with average rate per 1000 catheter days; range of scores, –1.46 to 8.2; better indicated by higher values)											
3	Observational studies	No serious risk of bias[a,c]	Serious[d]	No serious indirectness	No serious imprecision	0[3]	—	—	MD 5.07 higher (1.12–9.03 higher)	Low	Critical

CI, confidence interval; CLABSI, catheter-related bloodstream infection; MD, mean difference; PNALD, parenteral nutrition–associated liver disease.

[a] Used the Newcastle-Ottawa scale for cohort studies.

[b] The number of participants in either the intervention or control group was provided in the meta-analysis.

[c] Two criteria for bias were not reported or met in all studies. It was not reported if the outcome of interest was absent at the start of the study, and 1 study poorly reported a description of excluded patients. The other 3 studies did not report on excluded patients.

[d] Mouw et al[57] favored heparin lock, while the other 2 studies favored ethanol locks. Heterogeneity is high; the I^2 statistic = 70%.

Table 4. Evidence Summary Question 2: What Fat Emulsion Strategies Can Be Used in Pediatric Patients With Intestinal Failure to Reduce the Risk of or Treat PNALD?

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Soy Fat Emulsion Dose					
Rollins et al, 2013[16]	RCT—pilot	Infants ≥26 weeks' gestation with >50% daily energy intake from PN for at least 4 weeks SOE 1 g/kg/d with mean GIR at 10.7 mg/kg/min, n = 15 SOE 3 g/kg/d with mean GIR at 8.8 mg/kg/min, n = 13 N = 28	Demonstrate the feasibility of performing a study to compare reduced dose (1 g/kg/d) vs standard dose (3 g/kg/d) of SOE	**Conjugated bilirubin (change from baseline):** • 0 vs 1.3 mg/dL, 1 vs 3 g/kg/d, $P = .04$ No difference in ALT, AST, GGT, alkaline phosphatase **Triene to tetraene ratio:** • 0.016 ± 0.004 vs 0.012 ± 0.002, 1 vs 3 g/kg/d, $P = .03$ **Weight z score (change from baseline):** • –0.36 vs 0.01, 1 vs 3 g/kg/d, $P = .006$ **Head circumference z score (change from baseline):** • –0.05 vs +0.005, 1 vs 3 g/kg/d, $P = .09$	Cholestasis markers rose less rapidly, no EFAD, less growth, and trend to lower head circumference with 1 g/kg/d
Nehra et al, 2013[58]	Retrospective review of case series	All neonates admitted to ICU 2007–2011 with surgical condition necessitating PN support for ≥21 days Patients with SOE at 1 g/kg/d, n = 29 Patients with SOE at 2–3 g/kg/d, n = 32 N = 53	Determine whether provision of SOE at 1 g/kg/d prevents the development of cholestasis Compare incidence of cholestasis in neonates with SOE at 1 g/kg/d with those with 2–3 g/kg/d	No difference in conjugated or unconjugated bilirubin, ALT, or alkaline phosphatase at baseline by SOE dose group **Incidence of cholestasis:** • 1 g/kg/d, 51.7% • 2–3 g/kg/d, 43.8%, not significantly different **Time to cholestasis:** • 1 g/kg/d, 32.6 ± 24.1 d • 2–3 g/kg/d, 27.7 ± 10.6 d, not significantly different	Small sample Retrospective data with no information about why some patients were selected for 1-g/kg/d dosing
Cober et al 2012[41]	Prospective controlled cohort observation	Surgical patients with chronic PN (≥2 weeks) typically providing SOE 3 g/kg/d and with cholestasis (conjugated bilirubin ≥2.5 mg/dL); SOE, n = 31 Dose reduced to 1 g/kg/d SOE, n = 31	Evaluate efficacy of reduced SOE dose on bilirubin levels, growth, incidence of EFA deficiency, and mortality	**Total bilirubin change from baseline:** • SOE= 0.39 mg/dL/wk, $P = .027$ • Dose-reduced SOE = –0.73 mg/dL/wk, $P = .009$ • Dose reduced, controlled for septic episodes, slope = –0.09 mg/dL/d, $P = .049$ **Growth, control vs dose reduced:** • Weight gain = 13.25 ± 13.81 g vs 13.55 ± 12.38 g • Weight-for-length z scores = –0.89 ± 1.38 vs –0.6 ± 1.52 • Head circumference z scores = –0.99 ± 0.22 vs –0.64 ± 1.26 **EFAD:** • Mild deficiency in 8 of 13 dose-reduced patients • No severe or clinical deficiency signs	Drop in bilirubin with no difference in growth parameters
Diamond et al, 2011[9]	Retrospective review of case series	All infants with gastrointestinal surgery and PN, N = 152; including 22 with increased conjugated bilirubin	Analysis of factors associated with increased conjugated bilirubin	Days of SOE >2.5 g/kg/d associated with elevated bilirubin	Number of septic episodes, days with amino acid >2.5 g/kg/d also predict elevated bilirubin

(continued)

Table 4. (continued)

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Rollins et al, 2010[39]	Retrospective review of case series	Infants with short bowel syndrome and PN for at least 6 months' duration, N = 26	Is elimination of SOE associated with decrease in cholestasis in individual patients?	Twenty-three of 26 developed cholestasis Elimination of SOE in 6 patients resolved cholestasis	Small sample Enteral fish oil provided to 4 patients
Shin et al, 2008[40]	Retrospective review of case series	Low-birth-weight neonates with PN: With cholestasis, n = 22 Without cholestasis, n = 22	Define factors associated with cholestasis	Cumulative SOE dose-independent risk factor for cholestasis: OR, 1.17 (95% CI, 1.007–1.369, $P = .041$)	Days with no EN, parenteral amino acid dose, days on antibiotics also associated
Colomb et al, 2000[38]	Retrospective review of case series	Children in HPN program 1989–1999, total N = 183 Children with cholestasis, n = 10 with 23 episodes of cholestasis	Evaluate role SOE in cholestasis development	**Total bilirubin:** • 50–330 µmol/L **Liver biopsy:** • In 9 children, all abnormal with varied levels of fibrosis and cholestasis, no cirrhosis **Lipid dose:** • In 15 of 23 episodes of cholestasis, lipid dose had been increased from 0.94 ± 0.89 to 2.2 ± 0.41 g/kg/d • In 17 of 23 episodes where lipid dose was stopped, total bilirubin dropped within 1–3 months • Essential fatty acid deficiency in 3 children measured after 3 months without fat emulsion • Cholestasis episodes occurred 5.7 ± 3.8 years after PN initiation	Authors propose guidelines of: • Maximal daily SOE 2–2.5 g/kg/d, with maximal infusion rate of 150 mg/kg/h, no more than 5 infusions weekly, and maximal lipid-to-energy ratio of 25% • Monitor liver function tests and platelets
FOE vs SOE Fat Emulsion					
Calkins et al, 2013[59]	Prospective observation of case series	Children ages 2 weeks to 18 years with PNALD on SOE n = 10 patients treated with FOE at 1 g/kg/d for 24 weeks Historic controls, n = 20	Describe reversal of cholestasis (conjugated bilirubin <2 mg/dL) as primary outcome; secondary outcomes of death, transplant, and full enteral feeds; safety measures of growth, EFAD, and laboratory markers of bleeding risk	**Time to resolution of cholestasis:** • 11.5 (range 2.4–18) weeks vs 24 (range 5.4–24) weeks in FOE vs SOE groups, $P < .0001$ **Mortality:** • 2 (20%) vs 2 (10%) in FOE vs SOE **Transplant:** • 1 (10%) vs 2 (10%) in FOE vs SOE **Full enteral feeds:** • 1 (10%) vs 3 (15%) in FOE vs SOE **Safety:** • No difference in platelet concentrations or INR • No difference in weight or head circumference z scores • Change in length z score = –0.9 ± 0.3 vs –1.8 ± 0.4 in FOE vs baseline value, $P = .03$ **EFAD:** • None in either group, range of triene to tetraene ratios 0.01 to 0.03	Small sample with historical control Concurrent FOE, fat emulsion dose reduction, and enteral feeds

(continued)

Table 4. (continued)

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Premkumar et al, 2013[60]	Prospective observation of case series	Infants <6 months of age with PN-associated cholestasis, N = 57	Describe the clinical correlates associated with resolution of cholestasis after treatment with FO at 1 g/kg/d	**Summary:** • Preconjugated bilirubin, 7.5 mg/dL (2.1–25) • Survivors, 5 (2.1–2.5) • Nonsurvivors, 10.7 (3.6–14.3) • Survival to discharge in 82.5% • Median time to resolution of cholestasis 35 (range 7–129) days • Time to resolution inversely correlated with gestational age at birth ($r^2 = 0.12$, $P = .03$) **Characteristics of survivors vs nonsurvivors:** • Less premature at birth, 29.1 vs 25.9 weeks ($P = .056$)	
Le et al, 2011[43]	Retrospective review of case series	Pediatric patients with cholestasis while treated with SOE in 2004–2009 in single center, N = 79 Changed to FOE at 1 g/kg/d ≥1 month Diet initiated and advanced as tolerated concurrent with FOE	Describe changes in fatty acid and lipid profiles of children with PN-cholestasis treated with FOE	**Total bilirubin (median, IQR):** • Pre- vs post-FOE, 7.9 (5.0–13.0) vs 0.5 (0.3–1.3), $P < .0001$ **Conjugated bilirubin (median, IQR):** • Pre- vs post-FOE, 5.4 (3.5–8.5) vs 0.2 (0.1–0.6), $P < .0001$ **Triglyceride (median, IQR):** • Pre- vs post-FOE, 147 (100–223) vs 71 (50–108), $P < .0001$ **Cholesterol:** • Pre- vs post-FOE, 138.7 ± 56.1 vs 114.2 ± 33.8, $P < .001$ **LDL:** • Pre- vs post-FOE, 83.4 ± 44.6 vs 63.6 ± 32.7, $P < .001$ **VLDL:** • Pre- vs post-FOE, 31.7 ± 16.1 vs 63.6 ± 32.7, 16.5 ± 9.7, $P < .001$	Dose of FOE 1 g/kg/d vs SOE 1–4 g/kg/d No liver biopsies No randomization to treatment arm
Le et al, 2010[61]	Retrospective review of case series	Of infants with cholestasis during PN with SOE in single center between April 2005 and February 2009, SOE discontinued and FOE given as single source for at least 1 month, N = 10	Does parenteral FOE improve lipid profile and bilirubin?	**Cholestasis reversal:** 6 of 10 (60%) resolved 2 of 10 (20%) improved	Limited EN Dose of FOE 1 g/kg/d vs historic SOE 1–4 g/kg/d No liver biopsies No randomization to treatment arm

(continued)

Table 4. (continued)

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
de Meijer et al, 2010[62]	Prospective cohort analysis No control	Infants with cholestasis during PN with SOE, N = 10	Does parenteral FOE protect against EFAD?	Neither clinical nor biochemical evidence of EFAD **Conjugated bilirubin:** • Pre- vs post-FOE, 6.8 (range, 2.5–12.8) mg/dL vs 0.9 (range, 0.1–9.6) mg/dL, *P* < .009)	Limited EN Dose of FOE 1 g/kg/d vs SOE 1–4 g/kg/d No liver biopsies No randomization to treatment arm
Diamond et al, 2009[63]	Retrospective review of case series No control	Infants with SBS and cholestasis, FOE, N = 12	Define effect of use of parenteral FOE	**Cholestasis reversal:** 9 of 12 (75%) 3 required transplant	One patient had prior liver transplant
Lee et al, 2009[64]	Prospective case series Contemporary historical controls	Infants with cholestasis during PN with SOE, treated with FOE, n = 18 SOE, n = 59	Reversal of cholestasis and serum triglyceride levels	**Cholestasis reversal:** • FOE, 16 of 18 (89%) • SOE 28 of 59 (47%)	Dose of FOE 1 g/kg/d vs SOE 1–4 g/kg/d No liver biopsies No randomization to treatment arm
Puder et al, 2009[44]	Prospective case series Historical controls	Infants with cholestasis (conjugated bilirubin >2 mg/dL) during PN with SOE, changed to FOE FOE, n = 42 SOE, n = 49	Safety and efficacy measured by improvement in bilirubin and ALT	**Cholestasis reversal:** • FOE, 19 of 38 (50%) • SOE, 2 of 36 (6%)	Dose of FOE 1 g/kg/d vs SOE 1–4 g/kg/d No liver biopsies No randomization to treatment arm
Gura et al, 2008[42]	Prospective case series Historical controls	Infants with cholestasis during PN with SOE, changed to FOE FOE, n = 18 SOE, n = 21	Reversal of cholestasis	**Time to cholestasis reversal:** • FOE 9.4 [IQR 7.6–10.9] weeks • SOE 44.1 [IQR 10.9–45.6] weeks (*P* = .001)	Dose of FOE 1 g/kg/d vs SOE 1–4 g/kg/d No liver biopsies No randomization to treatment arm
SMOF vs SOE Fat Emulsion					
Rayyan et al, 2012[49]	RCT	Premature neonates in single hospital, n = 53 Randomized to PN, including SMOF, n = 26 vs SOE, n = 27 over 7 days with dose escalation from 1–3.3 g/kg/d in both groups Enteral feeds stared when able	Determine safety and tolerance of SMOF vs SOE	**Primary outcomes:** No difference in triglyceride, growth parameters, or SAE in SMOF vs SOE **Secondary outcomes from per protocol analysis:** *Total bilirubin (change from baseline)*: • SMOF –50.3 ± 45.8 vs • SOE –18.6 ± 54.2 μmol/L, *P* < .05 *Conjugated bilirubin (change from baseline)*: • SMOF –2.2 ± 8.89 vs • SOE 4.79 ± 8.38 μmol/L, *P* < .05	Course of PN <3 weeks

(continued)

Table 4. (continued)

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Tomsits et al, 2010[48]	RCT	Premature neonates, day of life 3–7, on PN SMOF, n = 30 SOE, n = 30 Fat emulsion dose initiated at 0.5 g/kg/d and advanced to 2 g/kg/d by day 14 Enteral feeds started when able	Evaluate safety, efficacy, and tolerability of SMOF vs SOE	No difference in SAE, lipid profile, growth parameters, and total bilirubin **GGT:** • SMOF, pre vs post, 125 ± 0.3 vs 107.78 ± 81.71 IU/L • SOE, pre vs post, 118.03 ± 98.81 vs 188.79 ± 176.73 IU/L, *P* < .05	
Skouroliakou et al, 2010[47]	RCT	Premature infants with PN randomized on day of life 0 to initiate fat emulsion on day 2 with SMOF, n = 14 SOE, n = 18 Fat emulsion dose advanced gradually to maximum of 3 g/kg/d Enteral feeding started as soon as possible	Evaluate the effect of SMOF on antioxidant status	Total antioxidant potential increased in SMOF, not SOE group	
Goulet et al, 2010[46]	RCT	PN-dependent patients aged 5 months to 11 years (mean age, 30–39 months), randomized to 4 weeks of SMOF, n = 15 SOE, n = 13 IVFE dosage up to 2 g/kg/d in both groups	Compare safety by growth, blood pressure, electrolytes, transaminases, EFA profile, lipid profile, and lipid peroxidation	No significant difference in total adverse events, ALT, AST, GGT, growth, and lipid profile **Total bilirubin:** SMOF 9.07 ± 10.04 to 7.58 ± 8.83 IU/L vs SOE 8.75 ± 6.25 to 11.08 ± 6.63, *P* < .01	Heterogeneous population but well matched in groups

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; EFA, essential fatty acid; EFAD, essential fatty acid deficiency; EN, enteral nutrition; FO, fish oil; FOE, fish oil fat emulsion; GIR, glucose infusion rate; GGT, γ-glutamyl transpeptidase; HPN, home parenteral nutrition; ICU, intensive care unit; INR, international normalized ratio; IVFE, intravenous fat emulsion; LDL, low-density lipoprotein; OR, odds ratio; PN, parenteral nutrition; PNALD, parenteral nutrition–associated liver disease; RCT, randomized controlled trial; SAE, serious adverse event; SBS, short bowel syndrome; SOE, soy oil fat emulsion; SMOF, soy oil, medium-chain triglycerides, olive oil, and fish oil; VLDL, very low-density lipoprotein.

Table 5. GRADE Table Question 2: What Fat Emulsion Strategies Can Be Used in Pediatric Patients With Intestinal Failure to Reduce the Risk of or Treat PNALD?

Quality Assessment[a]								
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality	Importance
Cholestasis improvement (assessed with either total or conjugated bilirubin[b])								
SOE—dose reduction								
6	Observational studies	No serious risk of bias[b]	Serious[c]	No serious indirectness	Very serious[d]	None	Very low	Critical
FOE and dose reduction vs SOE								
9	Observational studies	No serious risk of bias[b]	Serious[c]	No serious indirectness	Serious[d]	None	Very low	Critical
SMOF vs SOE								
4	Randomized trials	No serious risk of bias[e]	Serious[c]	Serious[f]	Serious[e]	None	Very low	Critical

FOE, fish oil fat emulsion; PNALD, parenteral nutrition–associated liver disease; SMOF, soy oil, medium-chain triglycerides, olive oil, and fish oil; SOE, soy oil fat emulsion.

[a] SOE: Rollins et al,[16] Cober et al,[41] Diamond et al,[9] Rollins et al,[39] Shin et al,[40] and Colomb et al.[38] FOE: Calkins et al,[59] Premkumar et al,[60] Le et al,[43] Le et al,[65] de Meijer et al,[66] Diamond et al,[63] Lee et al,[64] Puder et al,[44] and Gura et al.[42] SMOF: Rayyan et al,[49] Tomsits et al,[48] Skouroliakou et al,[47] and Goulet et al.[46]

[b] The studies report bilirubin in many ways; total, conjugated, and change in bilirubin. When possible, changes in serum conjugated bilirubin will be considered.

[c] Observation studies start with a GRADE of low quality due to the bias attributed to the study design. Will not decrease for bias at this time.

[d] Unable to assess precision of reported values.

[e] At least 1 study used per protocol analysis.

[f] For most studies, bilirubin determination was not the primary outcome; safety parameters, such as serum blood lipids and measurement of antioxidant factors, were primary outcomes.

Evidence: Further research needed
Recommendation: No recommendation

SMOF is not available in the United States. Until it is approved for use, no recommendation can be made for use in the United States. If available, the evidence supporting the use of SMOF for the treatment of cholestasis is very low quality. The RCTs are primarily safety and efficacy studies in preterm infants with the primary outcome of plasma phospholipid profiles and adverse events.

Evidence: Further research needed
Recommendation: No recommendation

Fat emulsions that contain a blend of refined olive and soybean oil have been approved for adults receiving PN. It is not approved for infants or children.[37] Until it is approved for use in children, no recommendation can be made for use in the United States.

Rationale: This is an emerging area of study; until larger RCTs with indicators of cholestasis are reported, strong recommendations are difficult to make. New research, if performed, will change our confidence in the estimate of effect of manipulating fat emulsion dose and/or type to prevent or resolve liver disease in those who require PN.

Higher doses of SOE have been associated with cholestasis, at increasing prevalence rates with longer duration of SOE therapy. Several studies prospectively, in a nonrandomized fashion, have demonstrated that reduction in the amount of SOE results in decreased severity or incidence of PNALD. The precise breakpoint in the reduction is not clear, as studies have varied from complete stoppage of SOE[38,39] to reduction of either SOE[16] or change from SOE to reduced-dose FOE. There is no adequately powered RCT that tests whether dose reduction of SOE provides similar improvement in cholestasis to complete stoppage or SOE vs FOE as monotherapy. Practically, such a trial may be difficult to complete as the rate of cholestasis in any of these lipid restriction groups would be expected to be low. Delivery of 1.2 g/kg/d SOE did not result in cholestasis in low-birth-weight neonates compared with a very high dose (>4 g/kg/d) in the cholestasis group.[40] In terms of safety, Cober et al[41] identified mild EFAD based on declines of linoleic and α-linolenic acids with 1 g/kg given twice a week, which were reversed if given at 1 g/kg 3 times a week. In an RCT of SOE dosed conventionally (3 g/kg/d) compared with lipid restriction (1 g/kg/d) designed as a cholestasis prevention trial, the results favored dose reduction for preservation of hepatic function.[16] However, the dose restriction group demonstrated a statistically significant decrease in weight gain at trial completion, and there was a trend to impaired growth in head circumference as well. The implications for neurodevelopmental changes or longer term growth with reduced SOE dose have not been studied.

No well-performed prospective RCT has been reported to date testing the ability of FOE to prevent or treat cholestasis.

The data suggest that the use of FOE as a substitute for SOE, along with a reduction in the dosage of SOE to 1 g/kg/d and advancement of enteral feedings, results in a progressive decline in the conjugated bilirubin levels. Most studies used this regimen and were retrospective cohort studies.[9,42-44]

The safety of FOE to prevent EFAD is not yet clear. In a report of 10 infants receiving FOE over a 10-week period, the authors concluded that no EFAD occurred.[45] However, a detailed examination of their data showed that 8 of the 10 infants had a decline (at times >2- to 3-fold) in linoleic and α-linolenic acid. No normative ranges for these values were reported in this study. Based on the fact that the Mayo Clinic performed the fatty acid analyses, the normal range (around the time this study was published) was 1000–3300 µmol/L for linoleic acid and 10–190 µmol/L for α-linolenic acid. While no child had a deficiency of α-linolenic acid, 5 had values below the lower limit of normal. Furthermore, if this trend continued, major and mixed (linoleic and α-linolenic) fatty acid deficiencies would be anticipated. Since levels of both of these fatty acids declined, dependence on a triene to tetraene ratio cannot be used to diagnose EFAD. Thus, the use of FOE will need further examination to determine long-term safety. In the study by Le et al,[43] a similar and significant decline in α-linolenic and linoleic acid was identified in a larger cohort of patients. While the mean values were above the lower limit of normal, the standard deviation for these would indicate that approximately 15% were deficient in linoleic acid. The implications for neurodevelopmental changes with use of FOE have not been studied. Further research is likely to have an important impact on our confidence in the safety of FOE.

The available studies evaluating SMOF are limited by evaluation of cholestasis as a secondary outcome, small sample size, short observation time, and studies in premature patients rather than patients with longer term PN-dependent intestinal failure. The Goulet et al[46] RCT was high quality, but only 28 children were studied, with 13 and 15 children in each group. While bilirubin levels were not the primary measure, these values declined significantly more in the SMOF group than in the SOE group over 29 days. Conjugated bilirubin is not reported, and GGT did not decline significantly. Linoleic acid declined slightly but not significantly in the SMOF group compared with the SOE group, where α-linolenic levels increased over the 29 days. In 2 RCTs in premature infants, there was no significant difference in bilirubin between SMOF and SOE groups after 2 weeks of treatment.[47,48] However, GGT declined significantly in the SMOF group[48], despite it not showing any difference in the Goulet[46] et al study. In a third RCT of premature neonates with 7 days of observation, total and conjugated bilirubin levels declined significantly in the SMOF group.[49] The safety of SMOF has been shown; however, data testing neurodevelopmental outcomes and long-term therapy effects on EFAD are still needed.[47-49]

A fat emulsion with a blend of refined olive and soy oil was approved by the FDA for use in PN for adult patients. However, it was not approved for infants or children.[37] The caution from the FDA actually carries a warning about the risk of death in preterm infants and states that the amount of essential fatty acids may be inadequate for the nutrition needs of children. References that included PNALD as an outcome were not found. However, in view of the FDA guidance, the product should not be used in premature infants or children.

Several important issues remain to be clarified about the use of IV fat emulsion in children with PN-dependent intestinal failure. Will a long-term reduction in SOE dose to ≤1 g/kg/d result in adequate growth and neurological development, and will EFAD be prevented? Is FOE more effective than equivalently dosed SOE at preventing PNALD, promoting neurological development? What is the incidence of EFAD if the low dose is given over a long duration, and how should EFAD be tracked in these individuals? Is SMOF given at conventional lipid doses effective at preventing the development of PNALD while optimizing growth and development over the long term? In addition, at this stage, it may be unethical to design a trial evaluating novel lipid strategies (dose restriction or FOE) in the setting of rescue therapy for children with advanced PNALD as these children traditionally have a high mortality and will die without transplantation. The focus of future trials, therefore, should be on PNALD prevention with short-term hepatic and longer term growth and developmental outcomes. Obstacles to progress include no standard definition of PNALD, determination of the appropriate study clinical end point, individual clinician bias and perception of “advanced PNALD,” access to novel lipid products, and lack of robust prospective, multicenter clinical trials in pediatric intestinal failure.

Question 3. Can enteral ursodeoxycholic acid (UDCA) improve the treatment of PNALD in pediatric patients with intestinal failure? (Tables 6, 7)

Recommendation: A suggestion is made to use UDCA for the treatment of elevated liver enzymes in children with PNALD. The evidence is of very low quality and confounded with the presence of enteral feeding in conjunction with treatment with UDCA. In addition, the patients studied tend to be premature infants with an intact intestinal tract; therefore, the efficacy of UDCA may not be generalizable to patients with established intestinal failure. In the included studies, no harm from this treatment was reported. The desirable effect of the reduction of liver indices has to be weighed against the unknown efficacy of the treatment and the fact that in most cases, the study participants did not have primary intestinal pathology.

Evidence: Very low

Recommendation: Weak

Table 6. Evidence Summary Question 3: Can Enteral Ursodeoxycholic Acid Improve the Treatment of PNALD in Pediatric Patients With Intestinal Failure?

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Gokmen et al, 2012[67] Prevention study	RCT testing UDCA vs erythromycin vs placebo Computer randomized, blinded	Preterm Turkish infants 27–28 weeks gestational age, weight ~1000 g, needing PN at least 12 days Had to be tolerating enteral feeds at 75 mL/kg/d UDCA, n = 24 Erythromycin, n = 24 Placebo, n = 23	Compare the efficacy of erythromycin, UDCA, or placebo in minimizing PNALD (GGT >120 as secondary outcome) and feeding intolerance (time to full enteral feeding as primary outcome) in VLBW infants	**Incidence GGT >120:** UDCA, 5 of 24 (20.8%) Erythromycin, 10 of 24 (41.7%) Placebo, 14 of 23 (60.9%) *P* = .04 **Feeding intolerance (days to full enteral feeds):** UDCA, 24.08 ± 3.05 Erythromycin, 22.46 ± 3.4 Placebo, 27.0 ± 5.8 *P* = .004	Significantly fewer GGT elevations with UDCA than with placebo Infants were on PN a range of 15–28 days
Arslanoglu et al, 2008[68] Prevention study	RCT testing UDCA vs placebo No information on randomization or blinding Small sample	Preterm Italian infants ≤900 g needing PN UDCA, n = 15 Placebo, n = 14	Evaluate time to full enteral feedings (primary outcome), fat excretion, biomarkers of liver disease (secondary outcomes)	**Primary outcome** *Feeding tolerance (days to full EN)*: UDCA, 18.6 ± 5.8 Placebo, 20.4 ± 8.6, not significantly different **Secondary outcomes** *GGT*: UDCA: baseline (PN only), 102.7 ± 79.1 Weeks 3–4 (EN initiated + PN), 72.4 ± 54.3 Week 6 (EN only), 56.1 ± 36 *P* < .05 vs placebo Placebo: Baseline (PN only), 83.7 ± 50.5 Weeks 3–4 (EN initiated + PN), 90.0 ± 60.5 Week 6 (EN only), 71.9 ± 29.1	UDCA safe, well tolerated No liver biopsies
De Marco et al, 2006[69] Treatment study	Open-label trial of UDCA No control Small sample	PN-dependent Italian infants with PNALD SBS, n = 7 Non-SBS, n = 5	Evaluate results of UDCA therapy on liver enzymes at baseline and 6 months	**GGT** *Patients with SBS*: Pre-UDCA, 350 Post-UDCA, 5 *Patients without SBS*: Pre-UDCA, 100 Post-UDCA, 80 **ALT** *Patients with SBS*: Pre-UDCA, 175 Post-UDCA, 50 *Patients without SBS*: Pre-UDCA, 90 Post-UDCA, 50 **Conjugated bilirubin** *Patients with SBS*: Pre-UDCA, 3 Post-UDCA, <1 *Patients without SBS*: Pre-UDCA, 1 Post-UDCA, 0.2	Patients with SBS had higher liver enzymes than those without SBS at baseline No liver biopsies

(continued)

Table 6. (continued)

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Al-Hathlol et al, 2006[51] Treatment study	Open-label trial of UDCA No control Fat emulsion was a MCT/LCT mixture Small samples	PN-dependent Saudi infants with BW <1500 g with PNALD that persisted after stopping PN n = 13	Evaluate results of UDCA therapy on cholestasis	**GGT (U/L):** Pre-UDCA, 284 ± 57 Post-UDCA, 231 ± 52 $P = .48$ **Total bilirubin (μmol/L):** Pre-UDCA,244 ± 38 Post-UDCA, 16 ± 2 $P = .0001$ **Conjugated bilirubin (μmol/L):** Pre-UDCA, 202 ± 32 Post-UDCA, 10 ± 2 $P = .0001$ **AST (U/L):** Pre-UDCA, 185 ± 22 Post-UDCA, 80 ± 14 $P = .001$	Not HPN patients
Chen et al, 2004[70] Treatment study	Open-label trial of UDCA vs no treatment control No placebo control Small sample	PN-dependent Taiwanese VLBW infants with PNAC UDCA, n = 10 Control, n = 18	Evaluate the effect of UDCA on preterm infants with PNALD	**Initial conjugated bilirubin (μmol/L):** UDCA, 4.2 ± 0.4 Control, 3.9 ± 0.6 **Peak conjugated bilirubin (μmol/L):** UDCA, 4.9 ± 0.4 Control, 9.8 ± 1.8 $P = .023$ **Duration of cholestasis:** UDCA, 62.8 d Control, 92.4 d $P = .006$	Small sample Not HPN patients Retrospective Open-label study with no placebo control Excluded patients with abdominal surgery
Heubi et al, 2002[50] Prevention and treatment study	Open-label trial of TUDCA vs no treatment control No placebo control Small sample	Infants l with PN-dependence >2 weeks and total bilirubin <2 μmol/L TUDCA, n = 22 Control, n = 30	Evaluate whether TUDCA would prevent or ameliorate liver injury in neonates treated with PN	No difference in liver injury (conjugated bilirubin, ALT, alkaline phosphatase, or bile acid) levels over 120 days of PN therapy in TUDCA vs control	Due to slow enrollment, IRB permitted study to change to open-label treatment with control patients whose parents refused study participation Enrolled after surgery, surgery not described. Poorly reported study
Spagnuolo et al, 1996[71] Treatment study	Open-label case series of UDCA No control Small sample	PN-dependent children, NPO with PN n = 7	Evaluate UCDA as treatment for PNALD	Liver enzymes improved on UDCA, increased when UDCA withdrawn	

AST, aspartate aminotransferase; BW, birth weight; EN, enteral nutrition; GGT, γ-glutamyl transaminase; HPN, home parenteral nutrition; IRB, institutional review board; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; NPO, nil per os; PN, parenteral nutrition; PNAC, PN-associated cholestasis; PNALD, PN-associated liver disease; RCT, randomized controlled trial; SBS, short bowel syndrome; TUDCA, tauroursodeoxycholate; UDCA, ursodeoxycholate; VLBW, very low birth weight.

Table 7. GRADE Table Question 3: Can Enteral Ursodeoxycholic Acid Improve the Treatment of PNALD in Pediatric Patients With Intestinal Failure?

Quality Assessment[a]								
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality	Importance
Prevention of PNALD								
2	Randomized trials	No serious risk of bias	Serious[b]	No serious indirectness	Serious[c]	None	Low	Critical
Change in liver enzymes (better indicated by lower values)								
2	Observational studies	Serious[d]	No serious inconsistency[b]	No serious indirectness	Serious[e]	None	Very low	Critical

PNALD, parenteral nutrition–associated liver disease.

[a] Gokmen et al,[67] Arslanoglu et al,[68] Chen et al,[70] and Heubi et al.[50]

[b] Time to full feeds was evaluated in both studies. Day of life (DOL) ursodeoxycholic acid (UDCA) was started varied, on DOL 3 in one study and DOL 14 in the other. All received enteral nutrition; difficult to know if it was the EN or the UDCA that had the treatment effect.

[c] Small number of participants in 2 studies. Confidence levels are wide.

[d] Open-label trials.

[e] Knew participants to whom treatment was administered.

Rationale: The review by San Luis and Btaiche[17] suggests that UDCA may be effective at reducing biochemical signs of PNALD. While the existing reports of UDCA use do not suggest significant infant intolerance to the treatment, the total number of patients treated with UDCA and reported in the 2 RCT prevention studies included here is only 39. One study using a related bile acid, tauroursodeoxycholic acid, for the prevention of cholestasis is included,[50] where the drug was administered at the start of PN therapy.[50] No difference in conjugated bilirubin was seen while children received PN for a duration of about 4 months.

Four studies were reviewed for the treatment of PNALD, defined as elevated total or conjugated bilirubin with UDCA. Al-Hathlol et al[51] provide a retrospective report on 13 children with necrotizing enterocolitis (NEC) and intestinal atresia with persistent direct hyperbilirubinemia, but off PN and on full enteral feeding. Since one would expect the liver biochemistry to resolve over several months after PN is discontinued, the treatment benefit of UDCA is likely confounded by recovered gut function. The other 3 studies were in children who had not had intestinal resections and thus were not at risk for the consequences of the interruption of the enterohepatic circulation of bile acids. Patients with established intestinal failure of any etiology may not tolerate or absorb UDCA, and the proposed treatment benefits of UDCA from these other children may not translate to the intestinal failure population.

Research is needed about dose, timing, duration of therapy, and long-term outcomes in patients with PN-dependent intestinal failure. Trials focusing on patients with established intestinal failure would make the results more applicable. Further research is likely to change our confidence in the effectiveness of UDCA to improve cholestasis.

Question 4. Are PNALD outcomes improved when patients are managed by a multidisciplinary intestinal rehabilitation team? (Tables 8, 9)

Recommendation: A suggestion is made to refer patients with PN-dependent intestinal failure to multidisciplinary intestinal rehabilitation programs. The evidence on this topic is of very low quality, but the improvement in survival is compelling, and the risk to the child of treatment with multidisciplinary practice is not increased.

Evidence: Very low

Recommendation: Weak

Rationale: The data supporting this recommendation are based on comparisons of clinical outcomes after the establishment of multidisciplinary intestinal rehabilitation programs relative to historical controls in the same 3 sites and with a total of 133 children included. In a meta-analysis of these 3 studies by Stanger et al,[52] the relative risk of survival from intestinal failure was 1.22 (95% confidence interval [CI], 1.06–1.40), favoring the post-multidisciplinary team practice; however, these findings may also be influenced by factors other than the multidisciplinary team practice that have changed over the same window in time. The Stanger et al article found another 12 articles that were descriptive in design outlining clinical improvement in patients with intestinal failure after initiation of an intestinal rehabilitation program, but no control group was included. In addition, interpretation of the literature is made difficult due to heterogeneity of patient populations, the intestinal rehabilitation program construct at different institutions, variable treatment protocols, and inconsistent definitions of key clinical outcomes. The literature would be improved if investigators could reach consensus on definitions of specific outcomes such as short bowel

Table 8. Evidence Summary Question 4: Are PNALD Outcomes Improved When Patients Are Managed by a Multidisciplinary Intestinal Rehabilitation Team?

Author, Year, Reference No.	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Sigalet et al, 2009[6]	Retrospective medical record review	Infants referred for surgical and nutrition care in 1998–2006, n = 33 vs 2006–2009, n = 22	Compare outcomes of early conventional approach to team-based aggressive care to prevent PNALD	**Treatments that were increased in later cohort:** • Rotating antibiotics • Fat emulsion dose reduction • FOE • STEP procedure **Survival:** • 1998–2006, 24 of 33 (73%) • 2006–2009, 22 of 22 (100%), $P = .01$ **PNALD:** • 1998–2006, 0 of 33 • 2006–2009, 0 of 22 **Months of follow-up:** • 1998–2006, 75 ± 15 • 2006–2009, 15.4 ± 8.0, $P = .01$	
Modi et al, 2008[5]	Retrospective medical record review	All patients with SBS after multidisciplinary team in 1999–2006, n = 54, vs historical control in 1986–1998, n = 30	Does multidisciplinary team management improve outcomes?	**Survival:** • 1986–1998, 22 of 30 (73%) • 1999–2006, 49 of 54 (89%), $P < .05$ **PNALD:** • 1986–1998, 1 of 30 (3%) • 1999–2006, 5 of 54 (9%)	Small sample size
Diamond et al, 2007[4]	Retrospective medical record review	All patients with SBS after multidisciplinary team in 2003–2005, n = 54, vs historical control in 1997–1999, n = 40	Describe outcome from multidisciplinary team management	**Overall survival:** • 1997–1999, 28 of 40 (70%) • 2003–2005, 42 of 54 (78%) **Mortality from liver failure:** • 1997–1999, 22.2% • 1999–2006, 11.1%, $P = .14$ **Sepsis episodes (median/month):** • 1997–1999, 0.5 • 1999–2006, 0.3, $P = .01$	Small sample size

FOE, fish oil fat emulsion; PNALD, parenteral nutrition–associated liver disease; SBS, short bowel syndrome; STEP, serial transverse enteroplasty procedure.

syndrome/intestinal failure, cholestasis, liver failure, sepsis, and PN independence. Further research is likely to change this recommendation.

A number of related questions remain to be answered. What characteristics of nutrition supportive care employed by these programs are associated with improved clinical outcomes? Can key practice protocols derived from these groups be translated broadly to improve the care of children who are not able to access a multidisciplinary program? What is the prevalence of other chronic health concerns, such as metabolic bone disease, in long-term survivors of intestinal failure? Now that mortality risk has diminished with establishment of intestinal rehabilitation programs, future research should address the impact of other comorbidities on outcome, long-term neurodevelopmental outcomes, quality of life of patients receiving chronic PN and after intestinal transplantation, and economic evaluation of intestinal rehabilitation programs.

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Table 9. GRADE Table Question 4: Are PNALD Outcomes Improved When Patients Are Managed by a Multidisciplinary Intestinal Rehabilitation Team?

Quality Assessment[a]							No. of Patients		Effect			
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Multidisciplinary IRP, No. (%)	Control, No. (%)	Relative Risk (95% CI)	Absolute	Quality	Importance
Survival from intestinal failure (follow-up 7–22 months)												
3	Observational studies	Serious[b]	No serious inconsistency[b,c]	No serious indirectness	No serious imprecision	None	113/130 (86.9)	74/103 (71.8)[d]	1.22 (1.06–1.40)	158 more per 1000 (from 43–287 more)	Very low	Critical
Overall survival (follow-up 7–22 months)												
3	Observational studies	Serious[b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	106/130 (81.5)	70/103 (68)	1.22 (1.09–1.41)	150 more per 1000 (from 61–279 more)	Very low	Critical
Development of liver failure (follow-up 7–22 months)												
2	Observational studies	Serious[b]	Serious[e]	Serious[f]	Serious	None	13/76 (17.1)	34/73 (46.6)	0.2 (0–17.25)	373 fewer per 1000 (from 466 fewer to 1000 more)	Very low	Critical
Enteral autonomy (follow-up 7–22 months)												
3	Observational studies	Serious[b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	89/130 (68.5)	69/103 (67)	1.05 (0.88–1.25)	33 more per 1000 (from 80 fewer to 167 more)	Very low	Critical

CI, confidence interval; IRP, intestinal rehabilitation programs; PNALD, parenteral nutrition–associated liver disease.

[a] Sigalet et al,[6] Modi et al,[5] and Diamond et al.[4]

[b] The risk ratio of the median risk of the 3 studies is equivalent to the mean risk ratio and is not reported.

[c] By design, the findings are associative.

[d] Selection bias is likely. Tertiary centers are likely to have children with shorter bowel length than children treated at nonreferral centers with smaller geographic coverage.

[e] Heterogeneity is very high for this outcome. The I^2 statistic is 90%.

[f] Wide confidence intervals and zero events in some groups decrease the precision in the size of the effect.

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